Adenocarcinoma of the Esophagogastric Junction

From Barrett's Esophagus to Cancer

Simone Giacopuzzi
Andrea Zanoni
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Preface

Esophagogastric junction (EGJ) cancer is, among solid cancers, the fastest growing tumor in terms of incidence in Western countries, and due to the lifestyle changes in developing and newly industrialized countries, this trend is expected to intensify worldwide. EGJ adenocarcinoma, however, is poorly defined: first because it is not an "organ disease" but a "zone disease," and also because among EGJ cancers there can be included different diseases with different etiology and different biology. Eastern countries, led by Japan, taught us the correct management of gastric cancer and provided us guidelines for the treatment of esophageal squamous cell carcinoma. However when we talk about EGJ adenocarcinoma, it is a separate entity and is more properly a Western reality; therefore, Western countries should systematize and give answers to the relevant issues this cancer raises, along the road to standardization. Europe has been leading the evolution of thought on EGJ carcinoma, especially thanks to Siewert and the German school, which created the classification that still is used as a guide by clinicians in therapeutic strategy planning. With the introduction of the latest version of the TNM, all EGJ cancers were defined as esophageal cancers, suggesting the possibility of a uniform treatment. In the era of tailored treatment and targeted therapy, we may wonder if what we already have is enough or if we need to go further on, especially considering the lack of homogeneity in the choice of multimodal treatments according only to topography.

I then decided that it was still necessary to concentrate just on this difficult cancer and, together with my co-workers Simone Giacopuzzi and Andrea Zanoni, I decided to write a book, which we hope will shed a little light on such a complex and current topic. To make this book more international, I invited to participate, in order to give their significant key to interpretation, also some surgeons of renowned importance in the field. I would like to thank them all deeply for their contributions.

Based on the experience of the Italian Research Group for Gastric Cancer (GIRCG) and the European Chapter of IGCA, we hope that this collaboration will start to build an even closer international cooperation with the opportunity to create a European network on EGJ adenocarcinoma.

Verona, Italy

Simone Giacopuzzi
Andrea Zanoni
Giovanni de Manzoni

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Epidemiology and Risk Factors

1

Giuseppe Verlato and Giovanni De Manzoni

1.1 Methodological Issues

The definition of esophagogastric junction (EGJ) is still debated in the current literature. For instance, the landmark for the border between the esophagus and the stomach is the proximal margin of the gastric folds according to the Prague C&M criteria, while the distal limit of the lower esophageal longitudinal or palisade vessels is mainly used in the Japanese criteria [1].

Also, the definition of EGJ or cardia cancer gave rise to many discrepancies. In most European countries, a code for cardia cancer was introduced only in the late 1970s, and a consensus on the definition of gastric cardia cancer was achieved only at the end of the 1990s [2]. As a consequence, true cardia cancer incidence, occurring between 1989 and 1994 in Sweden, could have been up to 45 % higher or 15 % lower than that reported by the Swedish Cancer Registry [2].

Of note, two studies were recently performed in the United States on the same database (SEER = Surveillance, Epidemiology, and End Results cancer registry program) over about the same period. The studies reported different trends in EGJ adenocarcinoma from 1973 to 2008 [3] and in gastric cardia carcinoma from 1978 to 2005 [4]. The World Health Organization seems to include both carcinomas in EGJ carcinomas, which are defined as tumors "*that cross the oesophagogastric junction… regardless of where the bulk of the tumours lies*" [5]. In this chapter, the term adenocarcinoma of the "esophagogastric junction (EGJ)" will be preferentially used. However, the term "cardia" cancer or "gastric cardia" cancer will also be adopted when used by the authors cited.

1.2 General Overview of Cancers from the Upper Gastrointestinal Tract

In Western countries, the decrease in the incidence of esophageal squamous cell cancer (SCC) and noncardia gastric cancers parallels a concomitant increase in the incidence of distal esophageal adenocarcinoma (AC) and EGJ/"gastric cardia" cancer. As a consequence, upper gastrointestinal tumors are decreasing overall, but concentrating around the gastroesophageal junction.

In detail, the incidence of esophageal AC has been markedly increasing in the last decades in most European regions [6] and in the United States, especially among white American men [7, 8]. On

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the contrary, the incidence of esophageal SCC is decreasing in both sexes and in all ethnic groups in the United States [7, 8], as well as in men living in Southern and Western Europe, while being on the rise in men from Northern Europe and in women from all European regions [6]. In the rest of the world, the incidence of esophageal SCC has been relatively stable or slightly decreasing [9].

Similarly, the increase in EGJ adenocarcinoma [3] and gastric cardia carcinoma [4] was more prominent in American white men and less pronounced among women and black people. In Norway, age-adjusted rates for distal gastric tumors decreased in both sexes between 1958 and 1992, while the rates of proximal gastric cancer were stable in men and decreased only slightly in females [10].

In Eastern Asia, the rise in esophageal adenocarcinoma has not occurred, despite a recent increase in the prevalence of gastroesophageal reflux disease (GERD), especially in urbanized areas. Chinese, Koreans, and Japanese seem to be more predisposed to esophageal SCC [9]. Nevertheless, the proportion of cardia cancer on overall gastric cancer has been reported to be on the rise also in Japan [11] and China [12, 13].

1.3 Incidence of EGJ Adenocarcinoma

1.3.1 Geographic Variability

Incidence of gastric cardia adenocarcinoma presents large variations among countries. According to the Five-Continent database [14], the cumulative incidence between 0 and 74 years was the lowest (about 0 %) among women in Concordia (Argentina) and the highest among Dutch men (0.52 %).

Cumulative incidence varied substantially by ethnicity, even within the same country; for instance, in the United States, cumulative incidence between 0 and 74 years was 0.37 % (95 % CI 0.35–0.39 %) among Whites and 0.25 % (0.19–0.31 %) among Blacks. An even larger discrepancy was observed in Singapore, where 0–74 years cumulative incidence was sixfold higher among Chinese men (0.29 %, 0.22–0.36 %) than among Malay men (0.05 %) [14]. Conversely, significant differences were observed even within the same ethnic group, when living in different countries; for instance, cumulative incidence doubled from Indians living in the mainland (0.08 %, 0.06–0.10 %) to Indians migrated to Singapore (0.15 %, 0.01–0.29 %) [14].

In the United States, ethnic differences are mainly restricted to men, while women present approximately the same incidence of the disease. During 1996–1998, age-adjusted incidence rate per 100,000 person-years was 3.4 among Caucasian men while being 1.9–2.1 among Hispanics, Blacks, and Asians/Pacific Islanders [15]. Among women, incidence rates ranged between 0.6 and 0.7 per 100,000 person-years among these ethnicities. At variance, Native Americans had a very low incidence, both in men and in women (0.9 and 0.2 per 100,000 person-years, respectively) [15].

1.3.2 Age and Sex Distribution

As regards sex and age distribution, in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, cardia adenocarcinoma was more common among men (37 % of all gastric adenocarcinoma) than among women (18 %), while an opposite pattern was recorded for noncardia adenocarcinoma (58 % among women vs. 41 % among men) [16]. Much higher male to female ratios were found in Spanish (6:1) [17] and British (4:1) [18] patients with gastric cardia cancer, and in American patients with gastric cardia adenocarcinoma (5:1) [19].

Age at onset did not differ between gastric cardia (63.8 ± 7.4 years, mean ± SD) and noncardia adenocarcinoma (62.5 ± 8.5 years) according to the EPIC study [16]. Likewise, median age at onset was similar in adenocarcinoma of the gastric cardia (69.3 years) and esophagus (69.6 years) in the Netherlands [20]. Of note, 75 % of gastric cardia adenocarcinomas were diagnosed after 60 years of age in the Netherlands [20], and also in the United States most patients with gastric cardia adenocarcinoma were older than 60 years at diagnosis [19].

1.3.3 Proportion of Gastric Cancer Arising from the Cardia

According to the EPIC study, cardia adenocarcinomas represent 29.4 % of all gastric adenocarcinomas in Europe. The proportion of cardia cancer was higher in Northern countries (35 %) than in Mediterranean countries (18 %) [16] (Fig. 1.1). Of note, these proportions become even higher (43.8 % and 24.7 %, respectively) if one excludes cancers from unknown site.

In the United States, the proportion of cardia cancer was 24.1 % in the SEER database from 1978 to 2005 [4], and this proportion increased to 34.2 % after excluding overlapping and nonspecified sites.

The proportion of cardia cancer was rather low in South Korea (6.9 %) [21] and Japan (10 %) [11], while in China it was comparable to that recorded in Northern Europe (33.6 %) [12] (Fig. 1.1). The proportion of proximal gastric carcinomas among small carcinomas (<=2 cm) was even higher, peaking at 45 % in 2011 in a Chinese hospital series [13].

1.3.4 Trends in Cardia Cancer

EGJ/cardia cancer reportedly increased in Western countries until the 1990s, remaining stable or declining thereafter (Table 1.1). The incidence of cardia cancer more than doubled in England [18] and Spain [17], it increased by 3.9 % every year in Sweden [26]. Interestingly in the American SEER database, the incidence of EGJ adenocarcinoma nearly doubled [3], while the incidence of cardia cancer increased only by 23 % [4].

During the 1990s, the increasing trend persisted in British Columbia, Canada [25], but in most countries it leveled off (Spain [17], the United States [3, 19, 23]), or turned into a declining trend (The Netherlands [20], Switzerland [24], Sweden [26]).

Moreover it should be reminded that gastric cancer from unspecified site also markedly decreased in the last decades, and this pattern could have amplified the rising trend in cardia cancer [18].

The increase in cardia cancer, combined with the simultaneous decrease in noncardia gastric adenocarcinoma, caused a remarkable increase in the proportion of gastric cancers arising from the cardia. In the Connecticut Tumor Registry [23], the ratio of cardia/noncardia tumors increased from 0.2 in 65–69 to 0.6 in 2003–2007. In a large Japanese series [11], the overall proportion of EGJ adenocarcinoma increased from 2.3 % (1962–1965) to 10.0 % (2001–2005). Likewise in the Gansu province of China, the proportion of cardia cancers increased from 29.6 % in 1993 to 37.1 % in 2004 [12]. Accordingly in a Chinese

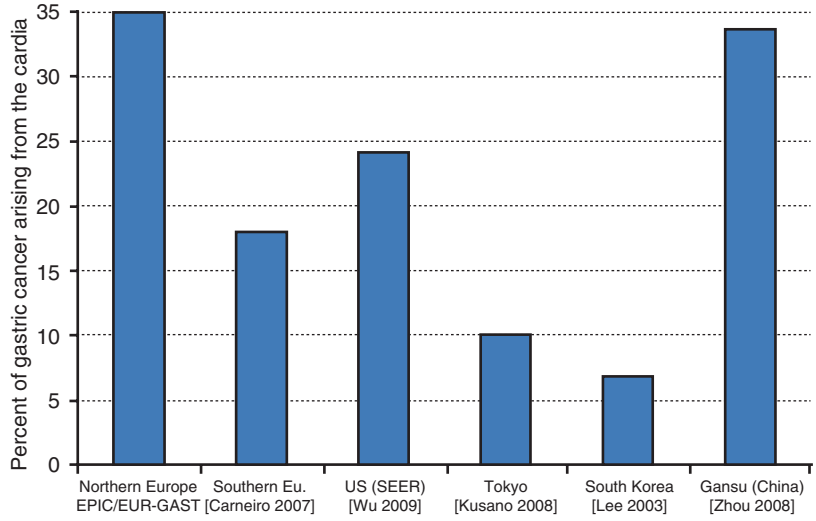

Fig. 1.1 Proportion of gastric adenocarcinomas arising from the cardia

Table 1.1 Incidence (per 100.000 person-years) of adenocarcinoma of gastroesophageal junction (GEJ) and cardia

I Author	Country		Incidence (per 100,000 pyrs)		
			Start	Middle	Final
Newnham	England	Men	**2.0 in 1971**		**5.4 in 1991**
2003 [18][a]	(cardia ca.)	Women	**0.6**		**1.4**
Crane	Olmsted	EGJ AC	**0.6 in 1971–1980**		**2.2 in 1991–2000**
2007 [22][e]	Minnesota	Cardia AC	0.9 in 1971-1980		0.8 in 1991–2000
Abrams	Connecticut	Cardia	**2.4 in 1965–1969**	**3.7 in 1988–1992**	3.4 in 2003–2007
2013 [23][d]	USA	Cancer			
Wu 2009 [4][d]	SEER USA	Gastric cardia	**1.8 in 1978–1983**	**2.2 in 1996–2000**	2.1 in 2001–2005
Buas	SEER USA	White men	**2.48 in 1973–1978**	**4.10 in 1991–1996**	3.78 in 2003–2008
2013 [3][d]	(EGJ AC)	White women	**0.40**	**0.71**	0.80
		Black men	**1.35 in 1973–1978**	**2.05 in 1991–1996**	2.01 in 2003–2008
		Black women	**0.34**	**0.68**	0.55
Aragones	Spain	Men	**1.13 in 1980–1984**	**2.71 in 1990–1994**	2.76 in 2000–2004
2010 [17][d]	(cardia ca.)	Women	**0.26**	**0.56**	0.48
El-Serag 2002 [19][c]	SEER USA	Cardia adenocarcinoma	3.3 in 1987–1991		3.1 in 1992–1996
Dikken	NL	Men	**5.7 in 1989**	**(–1.2 %/year)**	**4.4 in 2008**
2012 [20][a]	(cardia AC)	Women	1.2	(–0.2 %/year)	1.0
Schmass-	Switzerland	Men	**7.5 in 1982–1985**		**4.3 in 2006–2007**
mann 09[a] [24]	(cardia AC)	Women	**2.4**		**1.8**

I Author	Country		Start	% variation/yr	End
Bashash	British	Men	**From 1990**	**+3.8**	**To1999**
2008 [25]	Columbia (cardia ca.)	Women		**+9.2**	
Lagergren	Sweden	Cardia	**From 1970**	**+3.9 (3.2 –4.7)**	**To1990**
2011 [26][b]		adenocarcinoma	**From 1990**	**–1.0 (–1.6 – –0.3)**	**To 2008**

Significant/remarkable changes are highlighted in bold and increasing trend is further highlighted with a gray background

AC adenocarcinoma, SEER Surveillance, Epidemiology, and End Results cancer registry program in the United States
Age-standardized using [a]the European standardized population, [b]the 1989 Swedish population, [c]the 1970 US population, [d]the 2000 US standard population, [e]the 2000 US white standard population, [f]the 1996 Canadian population

series [13], the proportion of small gastric carcinomas (<=2 cm), located within 3 cm below the EGJ, increased from 16 % in 2004 to 45 % in 2011. At variance, in South Korea the proportion of gastric cardia cancer did not change from 1991 to 1995 to 1996–2000, being 6.2 % and 6.9 %, respectively [21].

The increase in cardia cancer was mainly due to an increase in the incidence of Siewert type II cancer and reflux-related subtype. In a Japanese series [11], the proportion of Siewert type II rose from 28.5 % (1962–1965) to 57.3 % (2001–2005), while that of type I remained at around 1 %. According to the Connecticut Tumor Registry [23], the reflux-related subtype markedly increased during the last 50 years, from 0.3 per 100,000 person-years in 1955–1959 to 2.4 in 2003–2007. On the contrary, *Helicobacter pylori*-related cardia cancer markedly declined during the same period, from 3.7 to 1.0 per 100,000 person-years.

1.4 Stage and Survival

As regards stage, in a national Dutch study [20] about 45 % of gastric cardia cancers, diagnosed in 2004–2008, were classified as M0, 40 % as M1, while in 15 % stage was unknown. In a multicentric US study [27], T stage was more advanced in gastric cardia adenocarcinoma than in noncardia subtype: indeed the proportion of AJCC T3-T4 tumors was, respectively, 71.8 % vs. 59.2 %. At variance, no significance difference was detected as regards the proportion of patients with nodal metastases, which was, respectively, 60.3 % and 59.2 % in gastric cardia and noncardia adenocarcinoma.

Prognosis is still poor in Western countries. In Dutch patients diagnosed with gastric cardia adenocarcinoma in 2004–2008, relative survival was 20.6 % (95 % CI 17.7–23.8 %) at 5 years in M0 patients, while it dropped to 6 % (4.6–7.7 %) at 2 years in M+ patients [20]. Likewise in the American SEER database, 5-year survival was 17 % in patients diagnosed from 1997 to 2008 [3]. Survival was substantially higher in patients undergoing surgery with curative intent, being 32.5 % 5 years after surgery in a US multicentric study [27] and 40.2 % after 3 years in an Italian series [28].

A much better 5-year survival (58.7 %) was recorded in a Japanese series [29].

Five-year survival in patients with EGJ adenocarcinoma doubled in the United States from 1973–1984 to 1997–2008 [3], and this improvement was attributed to both diagnostic anticipation and better treatment. At variance, the prognosis of gastric cardia adenocarcinoma did not improve from 1989 to 2008 in the Netherlands [20]. The authors pointed out that centralization of surgery and adoption of multimodal treatment allowed to improve prognosis in esophageal cancers, and the same interventions should be adopted also in cardia cancer treatment.

1.5 Risk Factors

According to the main risk factor involved, two distinct subtypes of cardia cancer have been identified: reflux-related and *H. pylori*-related [8, 23]. Of note, gastroesophageal reflux is the main risk factor for esophageal adenocarcinoma, while *H. pylori* infection is the main risk factor for gastric noncardia adenocarcinoma [30]. Reflux-related subtype presents an intestinal histotype, while *H. pylori*-related subtype is associated with severe atrophic gastritis and can present both an intestinal and a diffuse histotype. According to the Connecticut Tumor Registry [23], the *H. pylori*-related subtype was more common in 1955–1959 (3.7 vs. 0.3 per 100,000 person-years), while in 2003–2007 the reflux-related subtype has become predominant (2.4 vs. 1.0 per 100,000 person-years). Recent studies reported that *H. pylori* infection, one of the most important risk factors in noncardia cancer, could be even protective in cardia cancer [31].

Discrepancy exists on whether the adverse effect of gastroesophageal reflux is larger as regards the risk of adenocarcinoma of the esophagus [32] or gastric cardia [33]. In addition to gastroesophageal reflux, adenocarcinoma of the gastric cardia shares several risk factors with esophageal adenocarcinoma: obesity [34, 35],

meat and fat consumption [36], smoking [37], body posture, and occupational activities [32] (Table 1.2).

In particular, recent meta-analyses performed by the International Barrett's and Esophageal Adenocarcinoma (BEACON) consortium found that the OR associated with a BMI of >=40 relative to a BMI of <25 was 3.07 (95 % CI: 1.89–4.99) [34], while the OR of EGJ adenocarcinoma in smokers with respect to nonsmokers was 2.18 (95 % CI 1.84–2.58) [37]. Smoking was not only harmful per se but also amplified the carcinogenic effect of GERD [43].

At variance, abdominal obesity, alcohol drinking, and dietary antioxidant intake, which are strong predictors of esophageal adenocarcinoma, do not affect EGJ adenocarcinoma. Indeed, in a prospective cohort study [44], increasing waist-to-hip ratio increased the risk of esophageal but not EGJ adenocarcinoma. Another meta-analysis by the BEACON consortium reported that the OR for 7 drinks/day was 0.77 (95 % CI: 0.54–1.10) with respect to nondrinkers [45]. Moderate intake (0.5–>1 drink/day) was even protective (OR 0.78, 95 % CI: 0.62–0.99). Another meta-analysis found that dietary antioxidant intake (vitamin C, vitamin E, or beta-carotene/vitamin A) is protective against esophageal adenocarcinoma, while no consistent association has been found between antioxidant intake and the risk of cardiac carcinoma [46].

In summary, gastroesophageal reflux, obesity, and smoking may account for almost 70 % of EGJ adenocarcinoma [47]. The risk profile of

Table 1.2 Summary of risk factors for cardia cancer

Risk factor	Type of association	Study country
Demographic factors		
Gender, sexual hormones	Reduced risk in a male cohort treated with estrogens for prostate cancer	Sweden [38]
Ethnicity	Higher incidence in white men compared with the other ethnic groups studied both in England and in the United States	England [39], United States [15]
Socioeconomic factors		
Education	Higher education was associated with a reduced risk of gastric cardia cancer (HR: 0.42, 95 % CI: 0.20–0.89)	EPIC [40]
Occupation	Increased risk in gardeners, transport workers, bricklayers, and chemical process workers among men	Sweden [41]
Lifestyle factors		
Physical activity	Regular physical activity may be protective against noncardia cancer, and to a lower extent, cardia cancer	NL [42]
Meat and fat consumption	A diet high in processed meat, red meat, sweets, and high-fat dairy nearly double the risk of EGJ adenocarcinoma relative to a diet low in these foods	Sweden [36]
Obesity	OR of 3.07 (95 % CI: 1.89–4.99) associated with a BMI of >=40 relative to a BMI of <25	BEACON meta-analysis [34]
	Increased body mass index increases the risk of esophageal adenocarcinoma, and to a lower extent, the risk of cardia cancer	US [35]
Smoking	OR 2.18 (95 % CI 1.84–2.58) in smokers vs. nonsmokers	BEACON meta-analysis [37]
Pathologic factors		
Gastroesophageal reflux disease	More important role in the pathogenesis of esophageal adenocarcinoma	NL [32]
	More important role in the pathogenesis of gastric cardia adenocarcinoma	Minnesota [33]
H. pylori infection	*H. pylori* infection enhances the risk of noncardia gastric cancer but reduces the risk of cardia cancer	Finland [31]

cardia cancer is somewhat different from the risk profile of both esophageal adenocarcinoma and gastric noncardia adenocarcinoma.

1.5.1 Genetic Factors

EGJ adenocarcinoma has been associated with genes involved in DNA repair or inflammatory response. TP53 mutations were the most common abnormality, being detected in 42 % of gastroesophageal junction carcinomas [48]. Also, genes involved in Interleukin 2 and 4 metabolism were associated with gastric cardia cancer [49].

In a Japanese series of patients with Siewert type II adenocarcinoma, 18.2 % had HER2-positive tumors, which were also more prone to liver recurrence (23.7 % in HER2-positive patients vs. 7.6 % in HER2-negative patients [29].

Conclusions

The incidence of adenocarcinoma of the esophagogastric junction (EGJ)/cardia has increased in Western countries in the 1970s and 1980s, and then has either remained stable or slightly declined. In Eastern Asia, the rise in cardia cancer has been much smaller and somewhat delayed. Nowadays, cardia adenocarcinoma represents one third of all gastric cancer in Europe and in some areas of China. Prognosis is still poor in Europe and in the United States, 5-year survival being less than 20 %.

The rise in EGJ cancer during the last 50 years mainly reflected an increase in the subtype related to gastroesophageal reflux, while the *H. pylori*-related subtype declined over the same period. In addition to gastroesophageal reflux, adenocarcinoma of the EGJ shares several risk factors with esophageal adenocarcinoma: obesity, meat and fat consumption, smoking, body posture, and occupational activities. Nevertheless, the risk profile of EGJ/cardia cancer is somewhat different from the risk profile of both esophageal adenocarcinoma and gastric noncardia adenocarcinoma.

References

1. Ishimura N, Amano Y, Sollano JD et al, for the IGICS Study Group (2012) Questionnaire-based survey conducted in 2011 concerning endoscopic management of Barrett's esophagus in East Asian countries. Digestion 86(2):136–146
2. Ekstrom AM, Signorello LB, Hansson LE et al (1999) Evaluating gastric cancer misclassification: a potential explanation for the rise in cardia cancer incidence. J Natl Cancer Inst 91(9):786–790
3. Buas MF, Vaughan TL (2013) Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. Semin Radiat Oncol 23(1):3–9
4. Wu HY, Rusiecki JA, Zhu KM et al (2009) Stomach carcinoma incidence patterns in the United States by histologic type and anatomic site. Cancer Epidemiol Biomarkers Prev 18(7):1945–1952
5. Odze RD, Flejou JF, Boffetta P et al (2010) Adenocarcinoma of the oesophgogastric junction. In: Bosman FT, Carneiro F, Hruban RH, Theise ND (eds) WHO classification of tumours of the digestive system. World Health Organization Classification of Tumours. IARC Press, Lyon, pp 39–44
6. Steevens J, Botterweck AAM, Dirx MJM et al (2010) Trends in incidence of oesophageal and stomach cancer subtypes in Europe. Eur J Gastroenterol Hepatol 22:669–678
7. Trivers KF, Sabatino SA, Stewart SL (2008) Trends in esophageal cancer incidence by histology, United States, 1998–2003. Int J Cancer 123:1422–1428
8. Cook MB, Chow WH, Devesa SS (2009) Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977–2005. Br J Cancer 101:855–859
9. Hongo M, Nagasaki Y, Shoji T (2009) Epidemiology of esophageal cancer: orient to occident. Effects of chronology, geography and ethnicity. J Gastroenterol Hepatol 24(5):729–735
10. Hansen S, Wiig JN, Giercksky KE, Tretli S (1997) Esophageal and gastric carcinoma in Norway 1958–1992: incidence time trend variability according to morphological subtypes and organ subsites. Int J Cancer 71:340–344
11. Kusano C, Gotoda T, Khor CJ et al (2008) Changing trends in the proportion of adenocarcinoma of the esophagogastric junction in a large tertiary referral center in Japan. J Gastroenterol Hepatol 23(11):1662–1665
12. Zhou Y, Zhang Z, Zhang Z et al (2008) A rising trend of gastric cardia cancer in Gansu Province of China. Cancer Lett 269:18–25
13. Shi J, Sun Q, Xu BY et al (2014) Changing trends in the proportions of small (<= 2 cm) proximal and non-proximal gastric carcinomas treated at a high-volume tertiary medical center in China. J Dig Dis 15(7):359–366
14. Corley DA, Buffler PA (2001) Oesophageal and gastric cardia adenocarcinomas: analysis of regional

variation using the Cancer Incidence in Five Continents database. Int J Epidemiol 30:1415–1425
15. Kubo A, Corley DA (2004) Marked multi-ethnic variation of esophageal and gastric cardia carcinomas within the United States. Am J Gastroenterol 99:582–588
16. Carneiro F, Moutinho C, Pera G et al (2007) Pathology findings and validation of gastric and esophageal cancer cases in a European cohort (EPIC/EUR-GAST). Scand J Gastroenterol 42(5):618–627
17. Aragones N, Izarzugaza MI, Ramos M et al, for the Oesophago-gastric Cancer Working Group (2010) Trends in oesophago-gastric cancer incidence in Spain: analysis by subsite and histology. Ann Oncol 21(Suppl. 3):iii69–iii75
18. Newnham A, Quinn MJ, Babb P et al (2003) Trends in the subsite and morphology of oesophageal and gastric cancer in England and Wales 1971–1998. Aliment Pharmacol Ther 17:665–676
19. El-Serag HB, Mason AC, Petersen N et al (2002) Epidemiological differences between adenocarcinoma of the oesophagus and adenocarcinoma of the gastric cardia in the USA. Gut 50:368–372
20. Dikken JL, Lemmens VE, Wouters MWJM et al (2012) Increased incidence and survival for oesophageal cancer but not for gastric cardia cancer in the Netherlands. Eur J Cancer 48(11):1624–1632
21. Lee JY, Kim HY, Kim KH, Jang HJ, Kim JB, Lee JH et al (2003) No changing trends in incidence of gastric cardia cancer in Korea. J Korean Med Sci 18:53–57
22. Crane SJ, Locke GR 3rd, Harmsen WS et al (2007) The changing incidence of oesophageal and gastric adenocarcinoma by anatomic sub-site. Aliment Pharmacol Ther 25:447–453
23. Abrams JA, Gonsalves L, Neugut AI (2013) Diverging trends in the incidence of reflux-related and helicobacter pylori-related gastric cardia cancer. J Clin Gastroenterol 47(4):322–327
24. Schmassmann A, Oldendorf MG, Gebbers JO (2009) Changing incidence of gastric and oesophageal cancer subtypes in central Switzerland between 1982 and 2007. Eur J Epidemiol 24:603–609
25. Bashash M, Shah A, Hislop G et al (2008) Incidence and survival for gastric and esophageal cancer diagnosed in British Columbia, 1990 to 1999. Can J Gastroenterol 22:143–148
26. Lagergren J, Mattsson F (2011) No further increase in the incidence of esophageal adenocarcinoma in Sweden. Int J Cancer 129:513–516
27. Amini N, Spolverato G, Kim Y et al (2015) Clinicopathological features and prognosis of gastric cardia sdenocarcinoma: a multi-institutional US study. J Surg Oncol 111(3):285–292
28. de Manzoni G, Pedrazzani C, Verlato G et al (2004) Comparison of old and new TNM systems for nodal staging in adenocarcinoma of the gastro-oesophageal junction. Br J Surg 91(3):296–303
29. Katai H, Ishida M, Yamashita H et al (2014) HER2 Expression in carcinomas of the true cardia (Siewert Type II Esophagogastric Junction Carcinoma). World J Surg 38(2):426–430
30. de Martel C, Forman D, Plummer M (2013) Gastric cancer epidemiology and risk factors. Gastroenterol Clin North Am 42(2):219–240
31. Kamangar F, Dawsey SM, Blaser MJ et al (2006) Opposing risks of gastric cardia and noncardia gastric adenocarcinomas associated with Helicobacter pylori seropositivity. J Natl Cancer Inst 98:1445–1452
32. Jonge PJF, Wolters LMM, Steyerberg EW et al (2007) Environmental risk factors in the development of adenocarcinoma of the oesophagus or gastric cardia: a cross-sectional study in a Dutch cohort. Aliment Pharmacol Ther 26(1):31–39
33. Crane SJ, Locke GR, Harmsen WS et al (2007) Subsite-specific risk factors for esophageal and gastric adenocarcinoma. Am J Gastroenterol 102(8):1596–1602
34. Hoyo C, Cook MB, Kamangar F et al (2012) Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the international BEACON consortium. Int J Epidemiol 41(6):1706–1718
35. Olefson S, Moss SF (2015) Obesity and related risk factors in gastric cardia adenocarcinoma. Gastric Cancer 18(1):23–32
36. Bahmanyar S, Ye W (2006) Dietary patterns and risk of squamous-cell carcinoma and adenocarcinoma of the esophagus and adenocarcinoma of the gastric cardia: a population-based case–control study in Sweden. Nutr Cancer 54:171–178
37. Cook MB, Kamangar F, Whiteman DC et al (2010) Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. J Natl Cancer Inst 102:1344–1353
38. Lindblad M, Ye WM, Rubio C, Lagergren J (2004) Estrogen and risk of gastric cancer: a protective effect in a nationwide cohort study of patients with prostate cancer in Sweden. Cancer Epidemiol Biomarkers Prev 13(12):2203–2207
39. Coupland VH, Lagergren J, Konfortion J et al (2012) Ethnicity in relation to incidence of oesophageal and gastric cancer in England. Br J Cancer 107(11):1908–1914
40. Nagel G, Linseisen J, Boshuizen HC et al (2007) Socioeconomic position and the risk of gastric and overphageal cancer in the European Prospective into Cancer and Nutrition (EPIC-EURGAST). Int J Epidemiol 36(1):66–76
41. Ji JG, Hemminki K (2006) Socio-economic and occupational risk factors for gastric cancer: a cohort study in Sweden. Eur J Cancer Prev 15(5):391–397
42. Abioye AI, Odesanya MO, Abioye AI, Ibrahim NA (2015) Physical activity and risk of gastric cancer: a meta-analysis of observational studies. Br J Sports Med 49(4):224–233
43. Pandeya N, Webb PM, Sadeghi S et al (2010) Gastro-oesophageal reflux symptoms and the risks of oesoph-

ageal cancer: are the effects modified by smoking, NSAIDs or acid suppressants? Gut 59:31–38
44. O'Doherty MG, Freedman ND, Hollenbeck AR et al (2012) A prospective cohort study of obesity and risk of oesophageal and gastric adenocarcinoma in the NIH-AARP Diet and Health Study. Gut 61:1261–1268
45. Freedman ND, Murray LJ, Kamangar F et al (2011) Alcohol intake and risk of oesophageal adenocarcinoma: a pooled analysis from the BEACON consortium. Gut 60:1029–1037
46. Kubo A, Corley DA (2007) Meta-analysis of antioxidant intake and the risk of esophageal and gastric cardia adenocarcinoma. Am J Gastroenterol 102(10):2323–2330
47. Olsen CM, Pandeya N, Green AC et al (2011) Population attributable fractions of adenocarcinoma of the esophagus and gastroesophageal junction. Am J Epidemiol 174:582–590
48. Li-Chang HH, Kasaian K, Ng Y et al (2015) Retrospective review using targeted deep sequencing reveals mutational differences between gastroesophageal junction and gastric carcinomas. BMC Cancer (15):32
49. Wu J, Lu Y, Ding YB et al (2009) Promoter polymorphisms of IL2, IL4, and risk of gastric cancer in a high-risk Chinese population. Mol Carcinog 48(7):626–632

Barrett's Esophagus: Pathogenesis and Prevention

2

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2.1 Pathogenesis

As outlined in the previous chapter, risk factors for the development of Barrett's esophagus include male sex, increasing age, high BMI at a young, age and increased hip to waist ratio [1].

The development of Barrett's esophagus involves metaplasia of the normal squamous esophageal epithelium to mucus-secreting columnar epithelium. It has been proposed that this represents a two-step process, whereby the initial transformation from squamous to columnar mucosa occurs relatively quickly, over a few years, while the second step, which involves the development of goblet cells, which are indicative of intestinal metaplasia, occurs relatively slowly – over 5–10 years [2]. This cellular change occurs in response to chronic esophageal injury due mainly to gastroesophageal reflux disease (GERD), particularly in genetically susceptible individuals [3]. One case series suggested that >60 % of patients with Barrett's developed it as a result of chronic reflux; other causes of chronic lower esophageal inflammation included chemotherapy, NSAIDs, and viral infection [4].

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The exact cellular process by which this occurs in humans is not known. Animal models are not great determinants of human disease [5]. Key molecular events in man are inherited genomic alterations leading to alterations in somatic mutations, growth factor expression [6] and cell adhesion molecule activity [7].

Theories suggested for the development of Barrett's esophagus in humans revolve around reflux-induced squamous mucosal damage, which leads to alterations of the expression of developmental transcription factors. This altered expression pattern is postulated to cause either mature esophageal squamous cells to change into columnar cells, a process known as trans-differentiation, or immature esophageal progenitor cells to undergo differentiation to columnar cells rather than squamous – trans-commitment [8–10].

It has also been suggested that the presence of chronic reflux will affect the intestinal microbiome of the lower esophagus and that this disruption may lead to an increase in esophageal inflammation. Further analysis of the microbiome found that esophagitis and Barrett's patients contain significantly fewer gram-positive bacteria and an increase in the numbers of gram-negative bacteria. Gram-negative bacteria contain lipopolysaccharides (LPSs) in their outer membrane. LPS has been shown to upregulate gene expression of pro-inflammatory cytokines and can furthermore cause relaxation of the lower

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esophageal sphincter by induction of nitric oxide synthase [11].

Hereditable factors which influence Barrett's development include male sex and white ethnicity, while one of the major risk factors for developing esophageal malignancy is aging, implying that the accumulation of somatic mutations is key to the pathogenesis of esophageal malignancy. However, the relationship between Barrett's and age is not clear; this is mainly because the diagnosis of Barrett's esophagus requires an endoscopy, often prompted by reflux symptoms, but as many as 40 % of patients with malignancy on a background of Barrett's esophagus deny having had significant reflux symptoms [12]. This makes it difficult to elucidate how much of Barrett's esophagus is due to hereditary factors and how much is due to sporadic/somatic mutations in response to factors such as diet and behavior. Barrett's is usually diagnosed in the 6th or 7th decade while diagnosis is very rare in infants and children [13]. It may well be that Barrett's has been present for decades prior to diagnosis and simply not been detected due to the fewer numbers of endoscopies performed in young adults [3].

Familial studies into Barrett's esophagus have shown mixed results. One study offered upper endoscopy to first-degree relatives of patients with proven long-segment Barrett's. They found that risk factors for developing Barrett's esophagus included advancing age, male sex, and prolonged reflux symptoms. They also found that first-degree relatives were twice as likely to have Barrett's esophagus compared to the control group, even adjusting for the three major risk factors. The first-degree relatives of Barrett's patients who denied any reflux symptoms were found to be three times more likely to have evidence of reflux esophagitis on endoscopy [14]. This suggests a familial predisposition to Barrett's esophagus and GERD, be it genetic, environmental, or a combination of both.

Two large genome-wide collaboratives, EAGLE, a UK and north European cohort, and BEACON, a worldwide cohort, are currently reporting the final stage of their findings. A collaboration of the two studies, ~8000 patients and 18,000 controls, has identified two genetic regions which confer hereditary predisposition to esophageal cancer – both are single-nucleotide polymorphisms and are located on 6p and 16q [15].

Other studies into biomarkers potentially implicated in the malignant progression from Barrett's to cancer due to a variety of different mechanisms including, cell cycle damage, apoptosis, invasion, and abnormal growth signaling. These include inactivation of p16 located on chromosome 9p due to loss of heterozygosity (LOH) and mutations. This results in abnormal cells which can be selected and replicate undergoing clonal expansion within a segment of Barrett's. Hypotheses suggest that as these cells further undergo expansion, these clones develop further genetic abnormalities which can progress to adenocarcinoma [17].

Additionally loss of heterozygosity on chromosome 17p which corresponds to the area coding for the tumor suppression protein p53 allows expansion of abnormal cells. p53 lesions occur frequently in esophageal adenocarcinomas (85–95 %) and almost never in normal tissue from the same patients; their prevalence increases with advancing histologic grade of dysplasia which makes them appropriate candidates for further studies. Reid et al. have evaluated 17p (p53) LOH in a large phase 4 study[48] with prospective observation of 256 patients and esophageal adenocarcinoma as the primary end point. In this study 17p (p53) LOH was a strong and significant predictor of progression to esophageal adenocarcinoma with the relative risk of 16 in patients with this lesion compared to the patients without [17].

Also implicated are DNA content abnormalities (tetraploidy, aneuploidy) [16, 17], sucrose-isomaltase, crypt cell antigen, and cytokeratins 7 and 20 [2]. A murine monoclonal antibody (DAS-1) has been shown to react to an unknown epitope in Barrett's mucosa in 7 cases, and subsequently 6 of these patients developed intestinal metaplasia [2].

Germline mutation of the E-cadherin gene (CDH1) causes familial gastric cancer. Loss of E-cadherin (calcium-dependent cell to cell adhesion molecules, used for cell differentiation, and polarity) expression is associated with many non-familial human cancers, including esophageal

adenocarcinoma. It has been noted that there is a lower expression of E-cadherin in Barrett's esophagitis patients as compared to normal, which proposes that it may have a role as a tumor suppressor in early disease. There is also a suggestion of the role of β-catenin and TNFα and their involvement with the c-Myc gene (oncogene) [17, 25].

COX-2 and derived prostaglandin E2 (PGE2) appear to be implicated in carcinogenesis in some studies, because they prolong the survival of abnormal cells that favors accumulation of genetic changes. They reduce apoptosis and cell adhesion, increase cell proliferation, promote angiogenesis and invasion, and make cancer cells resistant to the host immune response. COX-2 is expressed in the normal esophagus but its expression was found to be significantly increased in Barrett's esophagus and even more in HGD and esophageal adenocarcinoma. Recent studies suggested that COX-2 expression might be of prognostic value in esophageal adenocarcinoma as the COX-2 immunoreactivity study in cancer tissues showed that patients with high COX-2 expression were more likely to develop distant metastases and local recurrence and had significantly reduced survival rates when compared to those with low expression. These data illustrate how chronic inflammation can contribute to the carcinogenesis process in the gastrointestinal tract, but the prognostic value of overexpression of TNFα and COX-2 in Barrett's metaplasia has not been documented in prospective studies [17, 25].

The development of a biomarker panel to aid in the prognosis of Barrett's progression will help with the stratification of risk and hopefully help to tailor surveillance programs to a patient's individual needs.

Diet has been suggested to play a role in the progression of Barrett's to esophageal cancer and a review of the literature by De Ceglie found that consumption of meat and high-fat diets were positively associated with esophageal adenocarcinoma, and while individual studies reported a reduction in cancer rates when diets were high in fruit, vegetables, and antioxidants, this was not consistently shown in the studies. There were a few studies which looked at diet and the development of Barrett's and their findings were inconclusive [18].

A prospective study of 713 patients found that the main risk factors for developing neoplasm on a background of Barrett's were the presence of low-grade dysplasia, duration of Barrett's esophagus for longer than 10 years, longer length of Barrett's, and ongoing esophagitis [19]. Other studies have confirmed that the degree of dysplasia present appears to be the single best indicator for the risk of progression from Barrett's to malignancy, with high-grade dysplasia having a rate up to 10 % per year [4]. It has also been demonstrated that the presence of ongoing esophagitis, indicating ongoing reflux, has been reported to predict a 3.5 times higher risk of developing high-grade dysplasia or esophageal cancer in patients with established Barrett's esophagus compared to those without [1] (Fig. 2.1).

2.2 Prevention

Since the precise mechanisms and risk factors for the development of Barrett's esophagus are not entirely understood, this makes strategies aimed at preventing it difficult to develop. Since the current theory of Barrett's pathogenesis is one of chronic esophageal injury secondary to ongoing gastroesophageal reflux disease, it follows that therapies which reduce the severity of reflux will reduce the likelihood of Barrett's developing. This would include the use of medication such as histamine 2 receptor antagonists (ranitidine), proton pump inhibitors (omeprazole, lansoprazole, esomeprazole), and simple over-the-counter antacid medication. It would also involve the avoidance of medications which increase the incidence of reflux, such as NSAIDs, anticholinergics, calcium channel blockers, nitrates, theophylline, and tricyclic antidepressants.

These therapies will obviously only be indicated when a patient suffers from reflux symptoms. Since 40 % of Barrett's patients have not reported significant reflux symptoms, a large proportion of patients will be missed by only treating symptomatic patients, but given the potential side

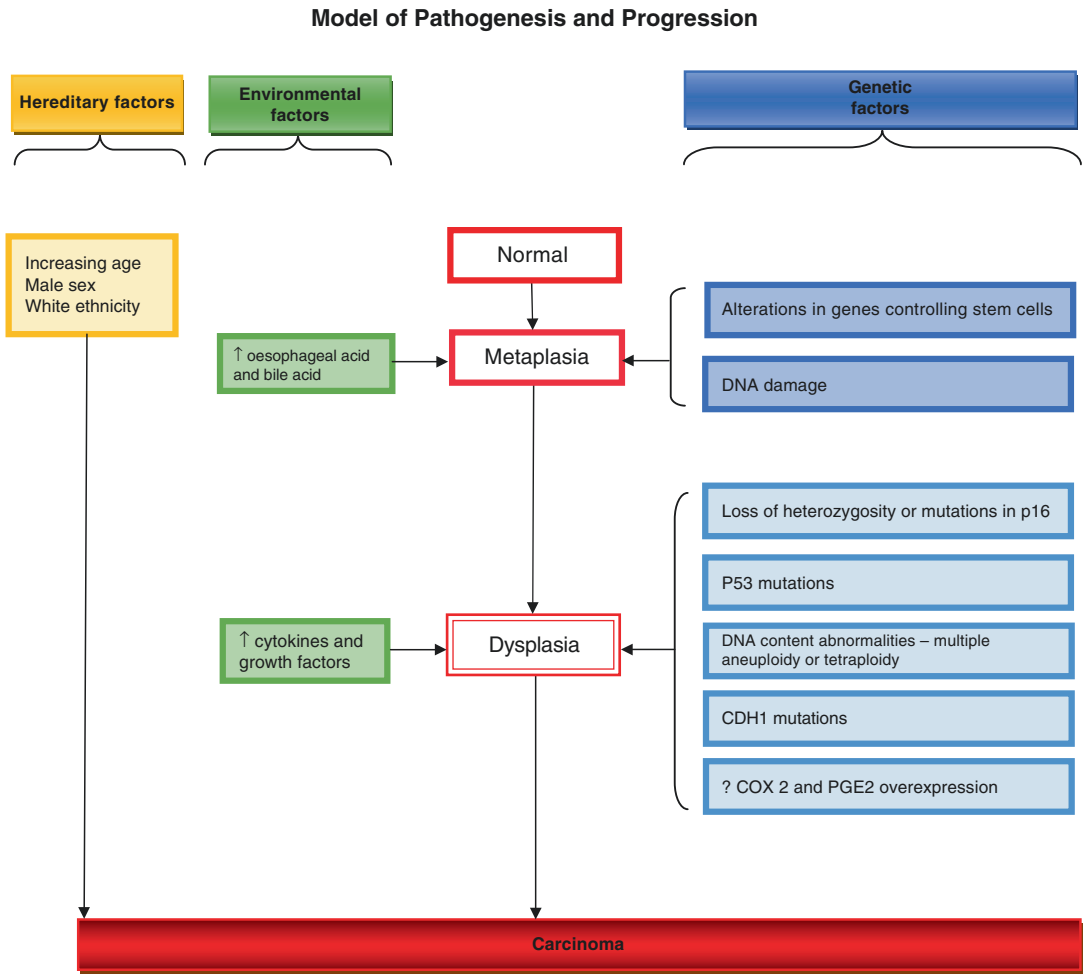

Fig. 2.1 This figure highlights the hereditary, environmental, and genetic factors that are involved in the pathogenesis of Barrett's esophagus (With permission Jankowski et al. [27])

effects of long-term acid suppression medication and the relatively low prevalence of Barrett's in the population, there is no case for a widespread preventative therapy campaign.

Medications which have been proposed to reduce the probability of Barrett's esophagus progressing to high-grade dysplasia and adenocarcinoma include PPIs, statins, NSAIDs, and selective COX-2 inhibitors [4, 20]. PPIs have been shown in a multicenter prospective cohort study to reduce the risk of esophageal cancer and high-grade dysplasia in patients with known Barrett's by 59 %. It also achieved a reduction in the amount of active esophagitis but did not affect the length of Barrett's [21]. Statins have been shown, in a meta-analysis of 5 studies involving Barrett's patients, to give a 41 % reduction in the rate of esophageal cancer, among Barrett's patients [22].

Epidemiological and experimental evidence suggested that chemoprevention with NSAIDs and selective COX-2 inhibitors such as aspirin may help to reduce the risk of cancer progression in Barrett's patients. However, human trials have not shown any reduced risk for cancerous progression [4, 23]. The risk-benefit of aspirin needs careful assessment especially in BE [24, 25]. Currently the ASPECT study (a 2500 randomized multicenter controlled trial of low- or high-dose esomeprazole with or without low-dose

aspirin for 8-year follow-up period) is awaiting final analysis [26].

Surgical management of reflux by anti-reflux surgery has been suggested as a possible method of preventing both the development of Barrett's and the progression from Barrett's through the various degrees of dysplasia to carcinoma. While fundoplication has been shown to effectively control reflux symptoms in most cases, it has not been found to be associated with a decrease in the incidence of esophageal cancer [4].

Better understanding of the molecular changes which cause the metaplastic change from squamous mucosa to columnar mucosa with or without goblet cells is required in order to develop effective therapies for Barrett's esophagus. This would hopefully allow not only the prevention of progression of Barrett's esophagus to low-grade dysplasia, high-grade dysplasia, and adenocarcinoma but also the prevention of Barrett's developing in the first instance. There are now excellent consensus statements especially the Benign Barrett's Cancer Task Force (BoBCAT) which have highlighted key management points for quality management while also indicating new areas of development for the future.

References

1. de Jonge PJ, van Blankenstein M, Grady WM, Kuipers EJ (2014) Barrett's oesophagus: epidemiology, cancer risk and implications for management. Gut 63(1):191–202
2. Oh DS, Demeester SR (2010) Pathophysiology and treatment of Barrett's esophagus. World J Gastroenterol 16(30):3762–3772
3. Jankowski J, Hawk E (2013) Handbook of gastrointestinal cancer. Chapter 2. Esophageal cancer. Wiley-Blackwell, Oxford, UK
4. De Palma GD (2012) Management strategies of Barrett's esophagus. World J Gastroenterol 18(43): 6216–6225
5. Attwood S, Preston S, Harrison LA, Jankowski J (2008) Esophageal adenocarcinoma in mice and men; back to basics. Am J Gastroenterol 103:2367–2372
6. Brito M, Filipe MI, Linehan J, Jankowski J (1995) Association of transforming growth factor α and its precursors with malignant change in Barrett's epithelium: biological and clinical variables. Int J Cancer 60:27–32
7. Jankowski J, Newham P, Hirano S, Takeichi M, Pignatelli M (1994) Differential expression of E-cadherin in metaplastic and dysplastic esophageal mucosa. Int J Oncol 4:441–448
8. Jankowski J, Harrison RF, Perry I, Balkwill F, Tselepis C (2000) Seminar: Barrett's metaplasia. Lancet 356:2079–2085
9. Jankowski J, Wright NA, Meltzer S, Triadafilopoulos G, Geboes K, Casson A, Kerr D, Young LS (1999) Molecular evolution of the metaplasia dysplasia adenocarcinoma sequence in the esophagus (MCS). Am J Pathol 154:965–974
10. Jankowski J, Perry I, Harrison RF (2000) Gastro-oesophageal cancer: death at the junction. Understanding changes at the molecular level could lead to screening opportunities. Br Med J 321:463–464
11. Yang L, Francois F, Pei Z (2012) Molecular pathways: pathogenesis and clinical implications of microbiome alteration in esophagitis and Barrett esophagus. Clin Cancer Res 18(8):2138–2144
12. Lagergren J, Bergström R, Lindgren A, Nyrén O (1999) Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 340(11):825–831
13. Nguyen DM, El-Serag HB, Shub M, Integlia M, Henderson L, Richardson P, Fairly K, Gilger MA (2011) Barrett's esophagus in children and adolescents without neurodevelopmental or tracheoesophageal abnormalities: a prospective study. Gastrointest Endosc 73(5):875–880
14. Romero Y, Slusser JP, de Andrade M, The Barrett's Esophagus Genomic Study Group et al (2006) Evidence from linkage analysis for susceptibility genes in familial Barrett's esophagus and esophageal adenocarcinoma. Gastroenterology 130(4 Suppl 2):A106
15. Su Z, Gay LJ, Strange A, Esophageal Adenocarcinoma Genetics Consortium, Wellcome Trust Case Control Consortium 2 et al (2012) Common variants at the MHC locus and at chromosome 16q24.1 predispose to Barrett's esophagus. Nat Genet 44(10):1131–1136
16. Reid BJ (2010) Early events during neoplastic progression in Barrett's esophagus. Cancer Biomark 9(1–6):307–324
17. Zagorowicz E, Jankowski J (2007) Molecular changes in the progression of Barrett's oesophagus. Postgrad Med J 83(982):529–535
18. De Ceglie A, Fisher DA, Filiberti R, Blanchi S, Conio M (2011) Barrett's esophagus, esophageal and esophagogastric junction adenocarcinomas: the role of diet. Clin Res Hepatol Gastroenterol 35(1):7–16
19. Sikkema M, Looman CW, Steyerberg EW, Kerkhof M, Kastelein F, van Dekken H, van Vuuren AJ, Bode WA, van der Valk H, Ouwendijk RJ, Giard R, Lesterhuis W, Heinhuis R, Klinkenberg EC, Meijer GA, ter Borg F, Arends JW, Kolkman JJ, van Baarlen J, de Vries RA, Mulder AH, van Tilburg AJ, Offerhaus GJ, ten Kate FJ, Kusters JG, Kuipers EJ, Siersema PD (2011) Predictors for neoplastic progression in patients with Barrett's Esophagus: a pro-

spective cohort study. Am J Gastroenterol 106(7):1231–1238
20. Nguyen DM, Richardson P, El-Serag HB (2010) Medications (NSAIDs, statins, proton pump inhibitors) and the risk of esophageal adenocarcinoma in patients with Barrett's esophagus. Gastroenterology 138:2260–2266
21. Kastelein F, Spaander MC, Steyerberg EW, Biermann K, Valkhoff VE, Kuipers EJ, Bruno MJ, ProBar Study Group (2013) Proton pump inhibitors reduce the risk of neoplastic progression in patients with Barrett's esophagus. Clin Gastroenterol Hepatol 11(4): 382–388
22. Singh S, Singh AG, Singh PP, Murad MH, Iyer PG (2013) Statins are associated with reduced risk of esophageal cancer, particularly in patients with Barrett's esophagus: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 11(6):620–629
23. Thiagarajan P, Jankowski JA (2012) Aspirin and NSAIDs; benefits and harms for the gut. Best Pract Res Clin Gastroenterol 26(2):197–206
24. Jankowski J, Moayyadi P (2004) Re: cost-effectiveness of aspirin chemoprevention for Barrett's esophagus. J Natl Cancer Inst 96:885–887
25. Cuzick J, Thorat MA, Bosetti C, Brown PH, Burn J, Cook NR, Ford LG, Jacobs EJ, Jankowski JA, La Vecchia C, Law M, Meyskens F, Rothwell PM, Senn HJ, Umar A (2015) Estimates of benefits and harms of prophylactic use of aspirin in the general population. Ann Oncol 26:47–57
26. Jankowski J et al (2013) Barrett's esophagus: evolutionary insights from genomics. Gastroenterology 144(4):667–9. doi:10.1053/j.gastro.2013.02.014. Epub 2013 Feb 21. (figure 1)
27. Jankowski J et al (2010) Diagnosis and management of Barrett's Oesophagus. BMJ 10(341):c4551. doi:10.1136/bmj.c4551. (figure 2)

Surveillance in Barrett's Esophagus and Dysplasia

3

Luca Faccio and Giovanni Zaninotto

The incidence of esophageal adenocarcinoma is rapidly increasing in Western countries, and, despite advances in surgical and endoscopic treatments, this condition retains a dismal prognosis with an overall 5-year survival rate of 15 % [1]. Barrett's esophagus (BE) is considered a premalignant lesion that can degenerate into esophageal adenocarcinoma (EA), and that is why most gastroenterological and surgical societies recommend regular endoscopic surveillance of BE patients to detect early cancerous lesions when they are still amenable to cure [2, 3]. The real cancer risk associated with BE is not yet entirely clear, however, and even the definition of BE is still a matter of debate. Although Barrett's mucosa is generally recognized as a metaplastic columnar transformation of native squamous esophageal epithelium, the phenotype of the columnar epithelia is described in various ways, and the optimum timing and frequency of endoscopic surveillance have yet to be decided [4].

It is now accepted that BE progresses to EA via a phenotypic sequence involving a condition indefinite for dysplasia (IND), then low-grade dysplasia (LGD), and high-grade dysplasia (HGD). The likelihood of progression from BE to invasive EA increases with the severity of the dysplasia: it is low (less than 0.5 per 100 patient-years) for non-dysplastic BE, but 10 times higher when LGD sets in and 60 times higher when HGD is detected [5, 6].

Observational studies suggest that EA occurring in patients under surveillance for BE is detected at an earlier stage and consequently associated with a better survival and a chance of being treated endoscopically. Unfortunately, no prospective randomized trials have been performed to confirm this hypothesis, and some cohort studies suggest that surveillance has no impact in reducing EA-related mortality [7, 8]. The burden of endoscopic surveillance also continues to generate controversy, given the costs and the resources needed to monitor a condition known to exist in 2 % of the general population, but with a progression rate of around 0.5 % per patient-year [9–11] (Table 3.1). Hence the need to identify patients at higher risk of progression and concentrate our surveillance efforts on them, as supported by the latest guidelines dictated by the Delphi Consensus for Management of Barrett's Esophagus (BOBCAT) [13].

The risk factors for progression to EA in BE patients include several clinical, endoscopic, and

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Table 3.1 Society guidelines on surveillance schedules for Barrett's esophagus [12]

Society	Non-dysplastic BE	LGD BE	HGD BE
American Gastroenterology Association (AGA) [6]	Every 3–5 years	Every 6–12 months	Every 3 months failing eradication therapy
American College of Gastroenterology [7]	Two endoscopies in the first year; if no dysplasia, every 3 years thereafter	Repeat after 6 months, then yearly	Every 3 months Additional intervention needed
American Association for Gastrointestinal Endoscopy (ASGE) [8]	Consider no surveillance; or every 3–5 years	Repeat after 6 months, then yearly; consider ablation	Every 3 months Consider additional intervention
British Society of Gastroenterology (BSG) 2006 [9]	Every 2 years	Repeat after 8–12 weeks (PPI therapy) LGD confirmed every 6 months	Every 6 months if no additional intervention is needed
British Society of Gastroenterology (BSG) 2013 [10]	IM-ve segment <3 cm: no surveillance; IM + ve segment < 3 cm: every 3–5 years; IM + ve segment >3 cm: every 2–3 years	Review by two pathologists Every 6 months	Discuss MDT Therapeutic intervention
French Society of Digestive Endoscopy [11]	Long segment (>6 cm): every 2 years	Repeat after 8 weeks (PPI therapy), then every 6 months, then yearly	Repeat after 4–8 weeks (PPI therapy) Additional intervention needed
American College of Physicians (ACP) [13]	Every 3–5 years	More frequent (no specific recommendation)	No specific recommendation

pathological characteristics such as age and gender, duration, frequency and severity of symptoms, obesity and tobacco smoking, length of the BE segment, and the presence of dysplasia [14, 15]. Much attention and high hopes have been focused on biological markers that might help us to identify BE patients at risk [16], the most promising biomarkers being the presence of aberrant p53 and p16 proteins. Routinely searching for these biomarkers is costly and time consuming, however, and the method has not gained widespread popularity [17, 18]. At the end of the day, there are currently no clinically proven, specific biological markers capable of earmarking BE patients at risk of EA, so stratification should continue to be based on the abovementioned clinical, endoscopic, and pathological features.

3.1 Clinical Features

Gender, age, and duration of symptoms: for men with BE, the risk of developing EA is almost twice as high as for women, and the risk increases for men >60 years old who have had symptoms of GERD (with or without hiatal hernia) for 10 years or more. Some authors recommend endoscopic screening for BE in such patients, but no clear data are available on the efficacy of screening in reducing the death rate due to EA [19].

Central obesity is another accepted risk factor for the progression of BE to EA, since a direct correlation has been shown between abdominal fat and biomarkers of progression (leptin and insulin) [20]. A recent meta-analysis also showed a consistent association between parameters linked to central obesity and esophageal inflammation, metaplasia, and EA [21].

3.2 Endoscopic Features

3.2.1 Length of the BE Segment

The risk of BE progressing from metaplasia to cancer also depends on the length of the segment involved. Initially, a distinction was drawn between two topographical variants of BE, short

and long; the former defined as columnar metaplastic glands extending less than 3 cm (but more than 2 cm) into the distal esophagus, and progression to cancer was associated with the presence of a longer BE segment [22]. This oversimple classification was subsequently challenged, but patients with BE segments longer than 6–7 cm are recognized as being at higher risk of progression [23]. In a recent study by Anaparthy, 44 of 1175 BE patients with a median follow-up of 5.5 years developed HGD or EA. The patients whose disease progressed had a longer BE segment than the others (6.5 cm vs. 3.5 cm, $p < 0.01$), and logistic regression analysis showed a 28 % higher risk for every centimeter of BE beyond the first 2 cm [24]. The results of a multivariate analysis conducted in a multicenter cohort study confirmed that, among other factors, length of BE (relative risk 1.11 per cm increase in length; 95 % confidence interval 1.01–1.2) was a significant predictor of progression to HGD or EA [25].

3.2.2 Nodularity, Ulcers, or Endoscopically Visible Abnormalities

Endoscopic evidence of abnormalities is strongly associated with the presence of dysplastic tissue or cancer, and the areas involved should be carefully biopsied or endoscopically resected. Rather than as a risk factor for progression, such abnormalities should be considered as markers of the presence of more advanced disease [26].

3.3 Pathological Features

While it is well known that BE patients progress to EA via a phenotypic sequence from no dysplasia to low-grade dysplasia, to high-grade dysplasia and adenocarcinoma, these steps follow no preordained schedule, and the process can vary considerably [27]. Dysplasia (or intraepithelial neoplasia) in BE is divided according to the Vienna classification into 4 classes [28]:

- *No dysplasia*: "normal" BE epithelium (goblet columnar epithelium and non-goblet columnar epithelium). Defining BE by means of the morphological identification of mucosal goblet cells alone has proved insufficient, however, as it has been demonstrated that non-goblet columnar epithelium may be an early stage of the process of "intestinalization," showing similar molecular abnormalities to goblet cell epithelium, and carrying some risk of neoplastic progression, albeit lower than that of "goblet cells."
- *Indefinite for dysplasia*: mild cytological changes with nuclear membrane irregularities, increased mitoses in deeper glands, or inflammation, but an otherwise normal architecture of the gland and maturation of the surface.
- *Low-grade dysplasia*: some mild, diffuse cytological abnormalities such as nuclear hyperchromasia and nuclear membrane irregularities with a normal nuclear polarity, a mildly abnormal architecture with glandular crowding but a clearly identifiable basal membrane, and distorted surface maturation with a surface assembling the underlying gland.
- *High-grade dysplasia*: marked cytological changes, nuclear hyperchromasia, irregular nucleoli with loss of nuclear polarity, marked architectural alterations with crowding of cytologically abnormal glands, and lack of surface maturation.

3.4 Risk of Progression in Non-dysplastic Barrett's Esophagus

The risk of progression for patients with non-dysplastic BE (NDBE) is low, ranging between 0.3 and 0.7 per hundred patient-years [29]. The Delphi Consensus recommended performing a repeat esophagogastroduodenoscopy (EGD) 1 year after NDBE has been diagnosed; then, if the NDBE "persists" (i.e., there is no evidence of progression), the interval between endoscopies can be increased to 5 years. This recommendation is based on the observation that, when several endoscopies over a period of years confirm

the persistence of NDBE, there is a lower likelihood of progression to HGD/EA [6].

3.5 Risk of Progression and Management of BE Indefinite for Dysplasia

Cases that are indefinite for dysplasia (IND) form the most difficult group to identify because of the overlap between inflammatory and neoplastic changes. The risk of progression is generally somewhat lower than in cases of LGD, but when IND is multifocal and extends throughout the segment of BE, then the risk may be as high as for LGD. This would suggest that extent might matter more in the early stage of the carcinogenic process than in the more advanced stages, when some cell clones have reached a point of no return [30].

3.6 Risk of Progression in Low-Grade Dysplasia

LGD carries an intermediate risk of progression, higher than in NDBE and lower than in HGD. Gatenby reported an incidence of progression to EA of 2.2 % a year, with a hazard ratio of 2.871 (95%CI: 1.480–5.540; $p<0.002$) by comparison with NDBE [31]. On multivariate analysis, LGD emerged as an independent risk factor for progression to HGD/EA [32]. There are contrasting data in the literature on the incidence of LGD progression to EA, however.

In the EBRA study the presence of LGD was found statistically associated with progression (to HGD or EA): 841 patients with BE were followed up prospectively for 44.4 months (3083 patient-years), performing a median of 3 endoscopies per patient. Patients with incident HGD and/or cancer were excluded. By the end of the study period, 22 patients had progressed, including 7/64 with LGD (3.2 %) and 15/777 with NDBE (0.72 %; p:0.01). LGD remained a risk factor for progression on multivariate analysis too (rr 3.72, CI 1.22–11.43, p:0.02) [33].

The BEST (Barrett's Esophagus Study) challenged this outcome on the grounds of a large database prospectively compiled by 5 high-volume centers. A first report in 2006 concerned 156 LGD patients followed up for a mean of 5 years (range 1–15.5 years), during which time 103 patients (66 %) had NDBE, 32 (20.5 %) had persistent LGD, 16 (10.3 %) developed HGD, and 5 (3.2 %) developed EA. The incidence of cancer was 1 per 156 patient-years of follow-up, or 0.6 % a year, a rate similar to the cancer risk for patients with NDBE. In a second report on the BEST data in 2011, the group of LGD patients had expanded to 210, and the diagnosis of LGD was confirmed by an expert pathologist. The incidence of HGD/EA was 1.83 (95 % CI: 1.23–2.74), and no differences emerged between the cases of prevalent and incident LGD or between cases of focal and diffuse LGD [34].

These differences may have several explanations. For instance, some studies did not distinguish between prevalent and incident LGD, but patients with prevalent LGD are more prone to progression [35]. Another reason might be the instability of the LGD phenotype, which may also regress to NDBE after the use of proton pump inhibitors or surgery [36]. LGD is also a patchy condition and biopsies may miss foci of LGD or remove them completely if they are small. Finally, there is a lack of agreement among pathologists, giving rise to a high inter- and intra-observer variability concerning regenerative or inflammatory tissue that may be misdiagnosed as LGD [35].

The risk of LGD progressing seems to increase considerably when a diagnosis of LGD is confirmed by two or more pathologists. In a study by Curvers et al., two expert pathologists confirmed the presence of LGD in only 15 % of 147 patients initially diagnosed with this condition, and 8 of the 22 patients whose LGD was confirmed progressed to HGD or EA, with a cumulative risk of 85 % [37]. Skacel demonstrated that when three pathologists blindly confirmed a diagnosis of LGD, there was an 80 % risk of progression, i.e., twice the figure (40 %) identified when only two pathologists agreed on

the diagnosis [38]. Given the difficulty of arriving at an "objective" diagnosis of LGD, the British Society of Gastroenterology has extended its double-reporting recommendations to cases of LGD, suggesting that a diagnosis of LGD be corroborated by a second pathologist expert in upper gastrointestinal diseases, as formerly recommended for HGD [39].

Diffuse LGD has also been correlated with a higher risk of progression than focal LGD, though the distinction between diffuse and focal LGD is somewhat controversial. The generally adopted definition of diffuse LGD is based on the involvement of more than 5 crypts [40].

3.7 LGD Management

The above data can be used to construct a flowchart for endoscopic surveillance (Fig. 3.1) [35]. After NDBE has been diagnosed, given the relatively high incidence of a diagnosis of HGD/EA within the first year after the index endoscopy [35] (incident lesion), a follow-up endoscopy should be performed after 1 year. If NDBE is confirmed, then further endoscopies can be scheduled at 5-year intervals [13].

BE biopsies found positive for LGD warrant a change in the timing of surveillance, and a second opinion should be obtained from a pathologist

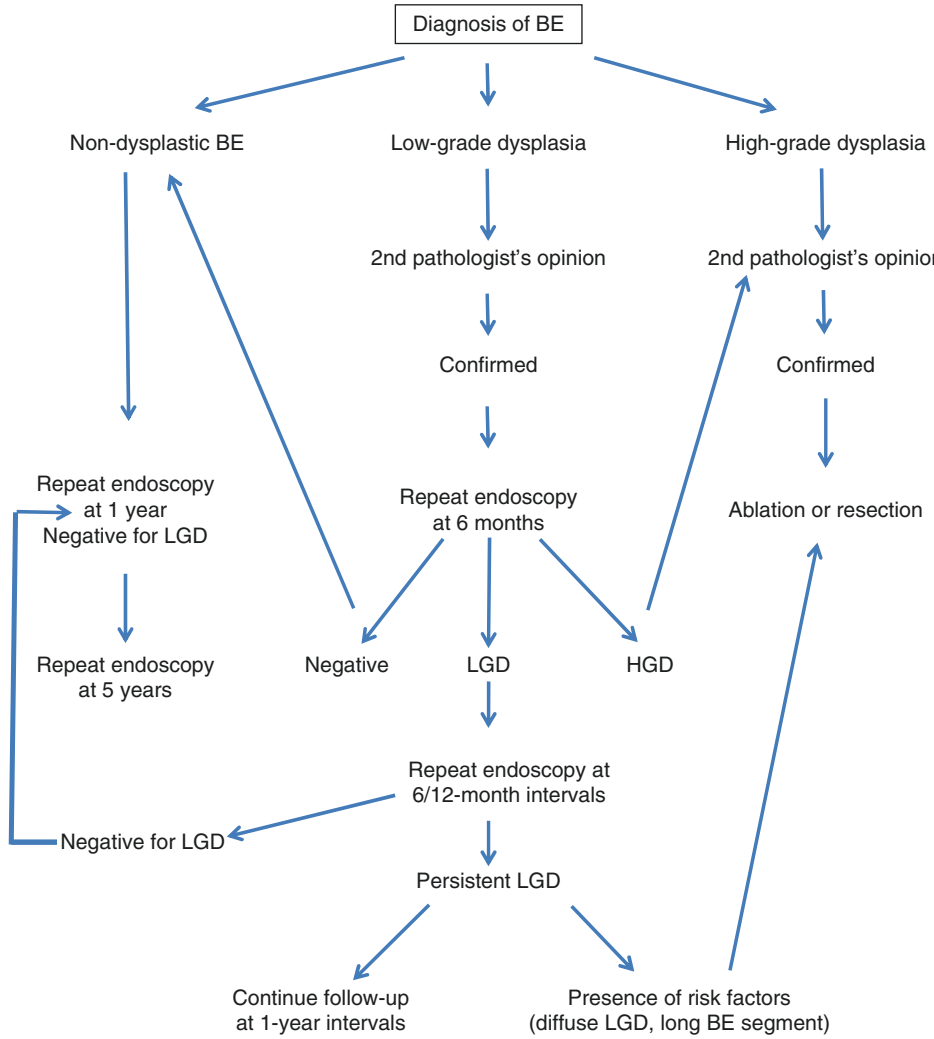

Fig. 3.1 Proposal for surveillance in non-dysplastic and dysplastic BE [35]

expert in upper gastrointestinal diseases. If LGD is confirmed, the patient should undergo repeat endoscopy after 6 months and, in the event of other risk factors (such as a long BE segment, long-standing GERD, or obesity), ablation of the BE segment is recommended [39].

3.8 High-Grade Dysplasia

HGD has been found associated with both a high risk of concomitant carcinoma and a high incidence of progression to invasive carcinoma. A meta-analysis of four studies found that 63/236 HGD patients (30 %) progressed to cancer within 5 years [24]. In recent longitudinal studies on the incidence of EA, HGD was considered an end point "per se," making no difference vis-à-vis invasive adenocarcinoma. A reliable diagnosis of HGD prompts more aggressive therapies with curative intent, such as mucosectomy, esophageal mucosa resection, radiofrequency ablation, or even esophageal resection [41], if the patient is fit for surgery and endoscopic therapies are not feasible.

References

1. Hvid-Jensen F, Pedersen L, Drews AM et al (2011) Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med 365:1375–1383
2. De Jonge PJ, Van Blankenstein M, Grandu WM et al (2014) Barrett's oesophagus: epidemiology, cancer risk and implications for management. Gut 63(1):191–202
3. Wang KK, Sampliner RE et al (2008) Updated Guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. Am J Gastroenterol 103:788–797
4. Rugge M, Pizzi M, Castoro C et al (2014) Definition of Barrett's esophagus dysplasia: are we speaking the same language? World J Surg 39(3):559–565. doi:10.1007/s00268-014-2692-y:10.1007/s00268-014-2692-y
5. Jankowski JA, Harrison RF, Perry I et al (2000) Barrett's metaplasia. Lancet 356(9247):2079–2085
6. Gilbert W, Luna RA, Harrison VL, Hunter JC (2011) Barrett's Esophagus: a review of the literature. J Gastrointest Surg 15(5):708–718
7. Wong T, Tian J, Nagar AB (2010) Barrett's surveillance identifies patients with early esophageal adenocarcinoma. Am J Med 123:426–427
8. Spechler SJ, Sharma P, Souza RF et al (2011) American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterol 140:1084–1091
9. Ronkainen J, Aro P, Storskrubb T et al (2005) Prevalence of Barrett's esophagus in the general population: an endoscopic study. Gastroenterology 129: 1825–1831
10. Inadomi JM, Sampliner R, Lagergren J, Lieberman D, Fendrik M, Vakil N (2003) Screening and surveillance for Barrett's esophagus: a cost utility analysis. Ann Intern Med 138:176–186
11. Coleman HG, Bhat S, Murray LJ et al (2011) Increasing incidence of Barrett's esophagus: a population-based study. Eur J Epidemiol 26:739–745
12. Vaezi MF, Kahrilas PJ (2013) Barrett's esophagus surveillance: time to rethink if one size fits all? Gastroenterology 145(3):503–505. doi:10.1053/j.gastro.2013.07.020, Epub 2013 Jul 25
13. Bennett C, Moayyedi P et al (2015) BOB CAT, a large-scale review and Delphi Consensus for management of Barrett's esophagus with no dysplasia, indefinite for, or low-grade dysplasia. Am J Gastroenterol 110(5):662–682. doi:10.1038/ajg.2015.55
14. Hardikar S, Onstad L, Blount PL et al (2013) Role of tobacco, alcohol, and obesity in neoplastic progression to esophageal adenocarcinoma: a prospective study of Barrett's esophagus. PLoS One 8:e52192
15. Lagergren J, Bergstrom R, Lindgren A et al (1999) Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 340: 825–831
16. Cronin J, McAdam E, Danikas A et al (2011) Epidermal growth factor receptor (EGFR) is overexpressed in high-grade dysplasia and adenocarcinoma of the esophagus and may represent a biomarker of histological progression in Barrett's esophagus (BE). Am J Gastroenerol 106:46–56
17. Rubstein JH (2014) Improving the efficiency of Barrett's esophagus management: do biomarkers hit the mark? Gastrointest Endosc 79:257–259
18. Rubstein JH, Vakil N, Inadomi JM (2005) The cost-effectiveness of biomarkers for predicting the development of esophageal adenocarcinoma. Aliment Pharmacol Ther 22:135–146
19. Rastogi A, Puli S, El Serag HB et al (2008) Incidence of adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia. Gastrointest Endosc 67:394–398
20. Duggan C, Onstad L, Hardikar S et al (2013) Association between markers of obesity and progression from Barrett's to esophageal adenocarcinoma. Clin Gastroenterol Hepatol 11:1399–1412
21. Singh S, Sharma AN, Murad MH et al (2013) Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 11:934–943
22. Fiocca R, Mastracci L, Milione M et al (2011) Microscopic esophagitis and Barrett's esophagus: the histology report. Dig Liver Dis 43(Suppl 4): S319–S330
23. Greenhill C (2013) Barrett oesophagus: using length of Barrett oesophagus to determine risk of progression

to high-grade dysplasia and adenocarcinoma. Nat Rev Gastroenterol Hepatol 10:383
24. Anaparty R, Gaddam S et al (2013) Association between length of Barrett's esophagus and risk of high-grade dysplasia or adenocarcinoma in patients without dysplasia. Clin Gastroenterol Hepatol 11:1430–1436
25. Sikkema M, Looman CV et al (2011) Predictors for neoplastic progression in patients with Barrett's Esophagus: a prospective cohort study. Am J Gastroenterol 106:1231–1238
26. Hillman LC, Chiragakis L et al (2003) Barrett's esophagus: macroscopic markers and the prediction of dysplasia and adenocarcinoma. J Gastroenterol Hepatol 18:426–433
27. Mueller J, Werner M et al (2000) Malignant progression in Barrett's esophagus: pathology and molecular biology. Recent Results Cancer Res 155:29–41
28. Schlemper RJ, Riddell RH, Kato Y et al (2000) The Vienna classification of gastrointestinal epithelial neoplasia. Gut 47:251–255
29. Desai TK, Krishnan K, Samala N et al (2012) The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. Gut 61(7):970–976
30. Thota PN, Lee HJ et al (2015) Risk stratification of patients with Barrett's esophagus and low-grade dysplasia or indefinite for dysplasia. Clin Gastroenterol Hepatol 13(3):459–465
31. Gatenby P, Ramus J et al (2009) Routinely diagnosed low-grade dysplasia in Barrett's oesophagus: a population-based study of natural history. Histopathology 54(7):814–819
32. Sikkema M, Kerkhof M et al (2009) Aneuploidy and overexpression of Ki67 and p53 as markers for neoplastic progression in Barrett's esophagus: a case-control study. Am J Gastroenterol 104(11):2673–2680
33. Rugge M, Zaninotto G et al (2012) Barrett's esophagus and adenocarcinoma risk: the experience of the North-Eastern Italian Registry (EBRA). Ann Surg 256(5):788–794
34. Lao-Sirieix P, Fitzgerald R (2006) Surveillance and screening of Barrett's oesophagus. Br J Hosp Med (Lond) 67(7):355–359, Review
35. Zaninotto G, Bennett C et al (2015) Surveillance for low-grade dysplastic Barrett's oesophagus: one size fits all? World J Surg 39(3):578–585
36. Spechler SJ (2014) Does Barrett's esophagus regress after surgery (or proton pump inhibitors)? Dig Dis 32(1–2):156–163
37. Curvers WL et al (2010) Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. Am J Gastroenterol 105(7):1523–1530
38. Skacel M et al (2000) The diagnosis of low-grade dysplasia in Barrett's esophagus and its implications for disease progression. Am J Gastroenterol 95(12):3383–3387
39. Lim YC, Fitzgerald RC (2013) Diagnosis and treatment of Barrett's oesophagus. Br Med Bull 107:117–132
40. Ishimura N, Amano Y et al (2011) Barrett's esophagus: endoscopic diagnosis. Ann N Y Acad Sci 1232:53–75
41. Rees JR, Lao-Sirieix P, Wong A, Fitzgerald RC (2010) Treatment for Barrett's oesophagus. Cochrane Database Syst Rev 20(1):CD004060

Ablation Techniques for Barrett's Esophagus and Dysplasia

4

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4.1 Introduction

Since the recognition of Barrett's esophagus as a precancerous condition, efforts have focused on its eradication. Aggressive acid suppression with medical or surgical anti-reflux therapy led to inconsistent results in regression of Barrett's epithelium. It has been observed that Barrett's can revert to normal squamous epithelium when it is ablated and maximal acid suppression is maintained. This has led to initial reports of ablation of non-dysplastic Barrett's using endoscopic laser therapy [1]. Subsequent efforts were focused on endoscopic therapy in Barrett's patients with high-grade dysplasia (HGD) who were poor surgical candidates as they are at highest risk of progression to cancer. Since then, ablative therapies have evolved and have become the mainstay of therapy for Barrett's associated neoplasia.

Removal of dysplastic areas only without complete eradication of entire Barrett's segment is associated with high risk of developing metachronous neoplasia [2]. Hence, the current standard of management for Barrett's includes endoscopic mucosal resection (EMR) of visible abnormalities followed by ablation to eradicate remaining Barrett's epithelium with ongoing surveillance. Although endoscopic therapy cannot cure neoplasms that have metastasized to regional lymph nodes, such nodal involvement is present in only 1–2 % of patients with intramucosal adenocarcinoma in Barrett's esophagus and therefore is useful in selected cases of intramucosal cancers. Currently, endoscopic therapy is recommended in patients with HGD and intramucosal cancer and is considered in confirmed cases of low-grade dysplasia (LGD) as there is a higher risk of progression. In addition, there have been recent case series describing the use of endoscopic therapy in early submucosal cancers.

4.2 Ablative Techniques

The various available ablative therapies include radiofrequency ablation (RFA), photodynamic therapy (PDT), cryotherapy, argon plasma coagulation (APC), and multipolar electrocoagulation (MPEC). What are the criteria of an ideal ablation technique in Barrett's esophagus? As described by Bergman et al. [3], firstly it should remove all dysplasia and intestinal metaplasia. Secondly, the neosquamous mucosa that develops after ablation should be free of oncogenetic abnormalities such as those present in the pretreatment metaplastic mucosa, and no residual areas of metaplastic columnar mucosa should remain hidden underneath it ("buried Barrett's").

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Thirdly, it should be very precisely targeted at the mucosa without damaging the deeper layers, thereby minimizing complications and preserving the normal functional characteristics of the esophagus. Finally, it should be quick and easy, removing all Barrett's mucosa, preferentially in one procedure. No such ideal ablation technique exists, but RFA has demonstrated efficacy, durability, and safety in multiple clinical trials making it the preferred technique of ablation.

4.3 Radiofrequency Ablation

The most widely used ablation technique for Barrett's dysplasia is RFA using HALO system first developed in 2000. Well designed, randomized controlled trials and subsequent experience have demonstrated its superior efficacy and safety profile in ablation of dysplastic Barrett's. RFA is performed using the Barrx FLEX system (previously HALO FLEX system), which is comprised of two distinct types of ablation catheters: the circumferential ablation catheter or Barrx 360 for primary ablation and focal ablation catheters which include Barrx 90, Barrx 90 ULTRA, and Barrx 60 and through the scope Channel RFA device. The FLEX generator is used for both circumferential and focal RFA (Fig. 4.1).

4.3.1 Technique

Circumferential ablation: The Barrx 360 ablation catheter consists of a 165-cm-long shaft with a balloon at its distal end that contains a 3-cm-long bipolar electrode. The electrode array encircles the balloon through which radiofrequency energy is applied, ablating the Barrett's mucosa. The ablation catheter is available in five outer diameters (18, 22, 25, 28, and 31 mm once inflated). After careful determination of landmarks and exam for visible abnormalities in the Barrett's segment, the esophagus is cleaned by washing with 1 % acetylcysteine or water. Then, the diameter of esophageal lumen at different levels is assessed by passing a sizing catheter over a guidewire. Based on the size of lumen, a Barrx 360 catheter of appropriate size is selected and advanced over a guidewire. Under endoscopic visualization, the catheter is placed 1 cm above the most proximal extent of the BE and inflated after which radiofrequency energy is applied. Then, the catheter is moved distally and radiofrequency energy is delivered sequentially. Then, the ablation catheter is removed, and the coagulum is scraped off with a cap attached to the tip of the endoscope. Subsequently, a second series of ablation is performed. Recently, a 4-cm-long circumferential 360 Express RFA Balloon catheter is developed which bypasses the need for sizing. Eight to twelve weeks after the first circumferential ablation treatment, patients undergo additional therapy with either Barrx 360 or Barrx 90 depending on the extent of residual Barrett's.

Focal ablation: Barrx 90 consists of 20×13-mm-sized electrode mounted on the tip of endoscope and placed at the 12 o'clock position in the endoscopic video image. Then, the endoscope is passed, and radiofrequency energy (at 12 J/cm^2 in the United States and 15 J/cm^2 in Europe) is applied twice after the endoscope is deflected and electrode is closely applied to the esophageal wall. Then, the coagulated tissue is scraped off with the catheter and ablation is repeated as described before. Simplified regimens without a cleaning phase in between have also been described. Barrx 90 Ultra has a larger surface area and has potential application in patients with dilated and tortuous esophagus when close opposition with Barrx 360 is not feasible. Barrx 60 and Channel catheter can be used in patients with esophageal strictures or tight upper esophageal sphincter.

After ablation, patients are on high-dose twice daily proton pump inhibitor therapy along with liquid sucralfate 4 times a day for 10–14 days. They stay on liquid diet for a day and advance to solid food as tolerated. Then, the procedure is repeated again in 2–3 months.

4.3.2 Efficacy

RFA is highly efficacious in eradication of metaplasia (71–93 %) and dysplasia (91–100 %). The most compelling evidence for the use of RFA

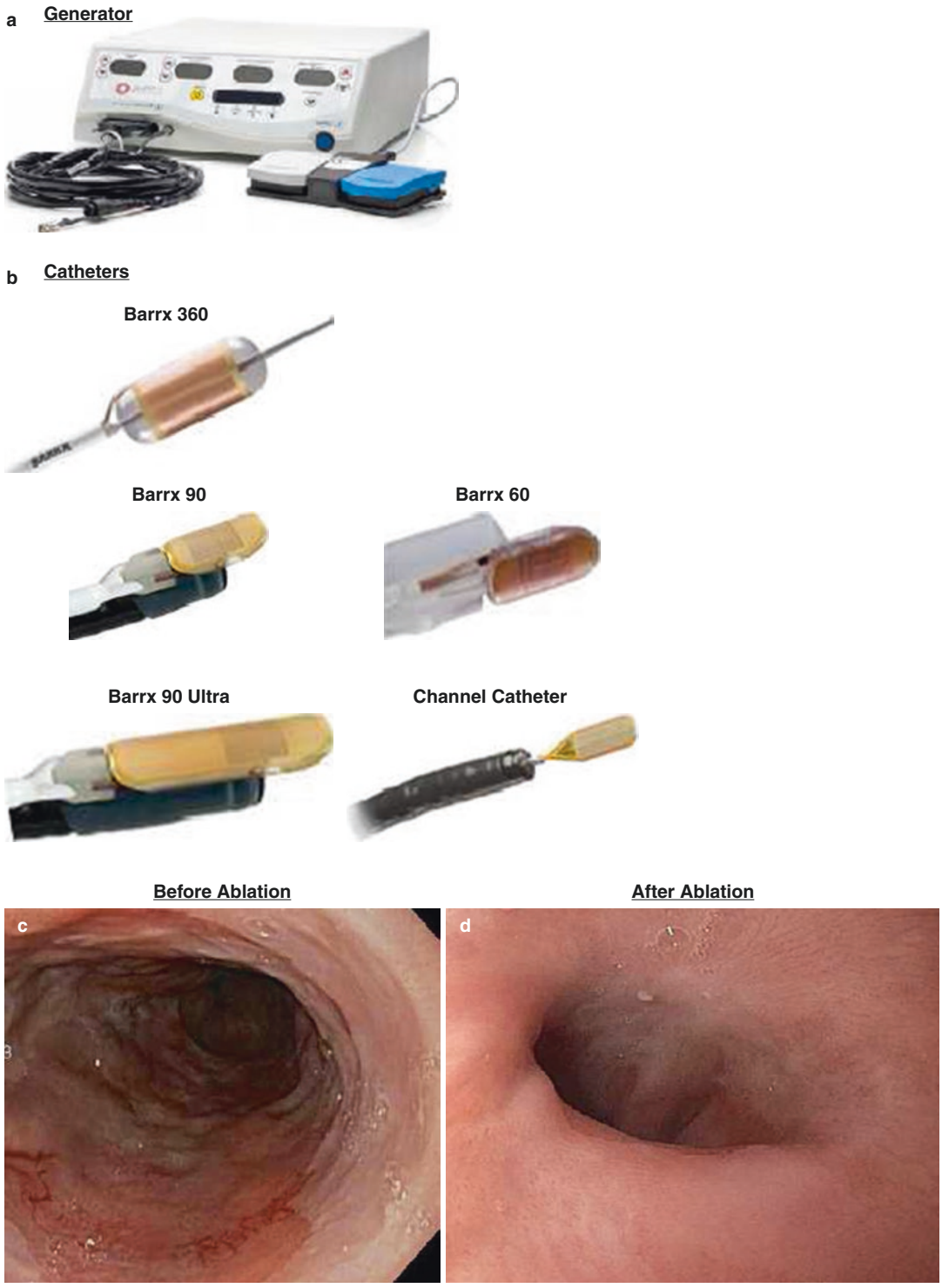

Fig. 4.1 Radiofrequency ablation equipment. (**a**) Generator. (**b**) Catheters. (**c**) Before ablation. (**d**) After ablation

in BE with dysplasia comes from AIM dysplasia trial [4], a US multicenter randomized sham-controlled trial of 127 patients. At 1-year follow-up, 81 % in HGD and 90 % in LGD had eradication of dysplasia. The effect seems to be durable with eradication of dysplasia persisting in more than 85 % of patients at the end of 3 years [5]. Another study demonstrating efficacy of RFA comes from SURF trial, a randomized controlled trial of 136 patients with confirmed LGD. At the end of 2 years, RFA reduced risk of progression to HGD or cancer (1.5 % in RFA group vs. 26.5 %, in surveillance arm $p < 0.001$) [6].

4.3.3 Complications

RFA is a safe procedure with few adverse events. The most commonly reported in order of decreasing frequency are strictures (5 %), chest pain (3 %), and bleeding (1 %).

4.4 Cryotherapy

Cryotherapy is based on the principle of ablating Barrett's tissue by application of a cryogen leading to extremely cold temperatures. Repeated cycles of rapid freezing followed by slow thawing lead to cell membrane rupture. Delayed injury includes tissue anoxia due to the loss of microcirculation and immune-related processes. There are two types of cryotherapy devices commercially available: one is cryospray (CSA Medical) which uses liquid nitrogen delivered at −196 C (Fig. 4.2), and the other is Polar Wand (GI supply) which utilizes carbon dioxide gas cooled to −78 C. A recently developed simplified through the scope focal cryoballoon system (C2 Therapeutics) is being studied for Barrett's ablation. Since cryoablation does not require any contact, it is useful for patients with tortuous esophagus and nodular uneven mucosal surface.

4.4.1 Technique

Cryotherapy is performed by passing the catheter through the accessory channel of an endoscope, and the tip of the catheter is held 5–10 mm away from the target tissue. The foot pedal is depressed, which triggers the release of the cryogen. The cryogen is sprayed onto the target tissue until it turns white, which means that freezing has taken place. This generally occurs after 10–15 s of application. Thawing usually takes place within 10–30 s. The same area is typically subjected to the freezing–thawing cycle 3 or 4 times to achieve ablation. In cryospray system, a decompression tube is used to evacuate the excess gas from the stomach, whereas in Polar Wand system, suction catheter is attached to the tip of the endoscope.

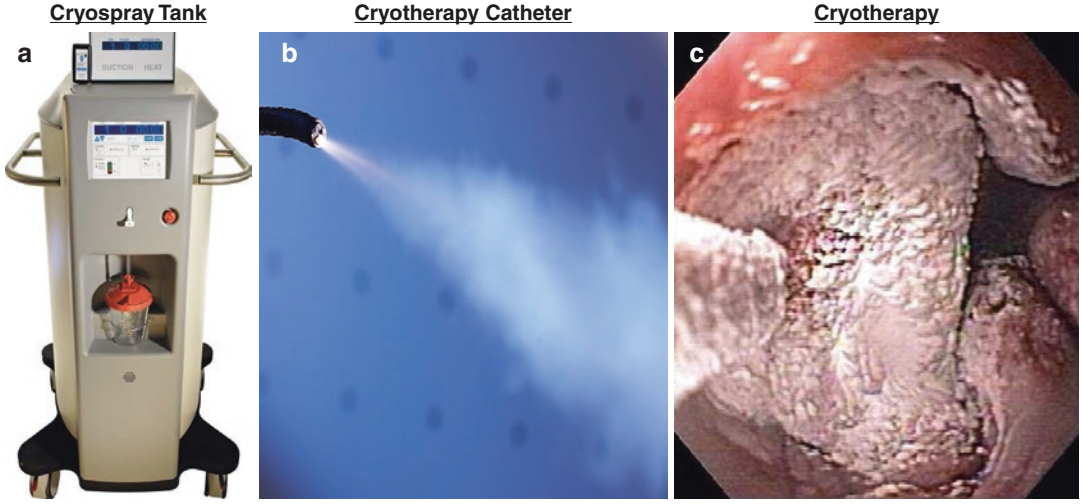

Fig. 4.2 (**a**) Cryospray tank. (**b**) Cryotherapy catheter. (**c**) Cryotherapy

4.4.2 Efficacy

The evidence of efficacy comes from retrospective studies. In a study of 60 Barrett's patients with HGD who underwent cryospray therapy, 87 % had complete eradication of all dysplasia with persistent non-dysplastic intestinal metaplasia, and 57 % had complete eradication of all intestinal metaplasia during a mean follow-up of 10.5 months [7]. The effect seems to be durable as reported by a retrospective study of 32 patients with HGD with a mean follow-up of 37 months where HGD was eradicated in 97 % and eradication of intestinal metaplasia was observed in 81 % [8]. Recurrent HGD was found in 6 (18 %) which was treated by cryotherapy. In another study of 49 patients with esophageal cancer (46 with adenocarcinoma), complete response was seen in 75 % with intramucosal cancer during a mean follow-up of 10.6 months [9]. In a small study of 39 patients published in abstract form, cryotherapy with carbon dioxide was effective in complete eradication of dysplasia in 80.6 % and eradication of metaplasia in 42 % [10].

4.4.3 Complications

Cryotherapy is generally well tolerated, with few side effects and rare complications reported. Common side effects include chest pain (17.6 %), dysphagia (13.3 %), and odynophagia (12.1 %) [11]. One case of gastric perforation occurred in a patient with Marfan syndrome, and another patient developed a lip ulcer, as a result of cold injury from contact with the endoscope, which resolved in 4 days without specific treatment [12]. Esophageal stricture noted in 3–13 % of the patients that responded to balloon dilation therapy [8, 9].

4.5 Photodynamic Therapy (PDT)

PDT was one of the most widely studied ablative therapies used in the treatment of Barrett's esophagus prior to advent of RFA. It was initially used for palliation of advanced esophageal cancer but subsequently found to be useful in management of patients with Barrett's and HGD and early esophageal cancer who are poor surgical candidates.

4.5.1 Technique

Photodynamic therapy is based on the principle of cell destruction induced by photosensitizers when stimulated by light. In the United States, porfimer sodium (Photofrin, Pinnacle Biologics Inc) at a dose of 2 mg/kg of body weight is given as an intravenous bolus over 3–5 min. Two days later, visible red light at approximately 630 nm is transmitted by an optical fiber passed through accessory channel of endoscope or a balloon diffusing fiber. For treatment of Barrett's with HGD, the light dose recommended is 130–200 J/cm fiber. A second endoscopy is performed 2–3 days later to repeat the treatment if necessary. In Europe, other photosensitizers such as 5-aminolevulinic acid (5-ALA) and m-tetrahydroxyphenyl chlorin (mTHPC) are also used. ALA can be administered orally, has shorter duration of skin photosensitivity (24–48 h), and reduced incidence of strictures.

4.5.2 Efficacy

PDT is the first ablation technique proven to be effective and durable in a randomized controlled trial. In this trial of 208 patients with HGD randomized to either porfimer sodium PDT plus omeprazole versus omeprazole alone, complete ablation of HGD was achieved in 77 % of PDT group compared with 39 % in the control group ($p < .0001$) on mean follow-up of 24 months [13]. Complete eradication of metaplasia was seen in 52 % of patients in the PDT group compared with 7 % in the omeprazole group ($p < .0001$). There was also a significant difference in progression to cancer, with 13 % of patients in the PDT group developing cancer compared with 28 % in the omeprazole group. Eradication of HGD at 5-year follow-up was achieved in 77 % of those treated with PDT plus omeprazole and 39 % of those treated with omeprazole alone. Progression to

esophageal cancer at 5-year follow-up was 15 % in the PDT group and 29 % in the omeprazole-only arm [14]. PDT can also be used for eradication of Barrett's after EMR of intramucosal cancer. In a study of 17 patients who underwent PDT following EMR, 94 % remained in remission at 13 months [15]. Comparative retrospective data of patients undergoing PDT vs. surgical esophagectomy for BE HGD at a high-volume expert center demonstrated comparable overall survival over 5 years of median follow-up (83 % in patients treated with EMR only or EMR followed by PDT versus 95 % IN patients who underwent esophagectomy for intramucosal cancer [16]. These data established porfimer sodium PDT as a viable alternative to esophagectomy, particularly among individuals – whether due to advanced age, comorbid illness, or preference against surgical esophagectomy.

4.5.3 Complications

The most common adverse events reported with porfimer sodium use were photosensitivity reactions (69 %), esophageal strictures (36 %), vomiting (32 %), noncardiac chest pain (20 %), pyrexia (20 %), and dysphagia (19 %) [13]. 5-aminolevulinic acid has less frequent side effects but not widely used in the United States.

4.6 Argon Plasma Coagulation (APC)

APC is a noncontact technique wherein ionized argon gas is delivered at energy settings of 40–90 W to ablate Barrett's. It was used for eradication of non-dysplastic Barrett's and LGD but incomplete eradication is common. Buried glands were reported in up to 40 % of patients [17]. APC was also described in ablation of Barrett's with HGD. In a study of 32 patients with HGD, 78 % had eradication of HGD and 69 % had eradication of Barrett's. However, there was 13 % progression to EAC in a mean follow-up period of 34 months [18]. Another potential role is in palliative treatment of advanced cancer causing dysphagia or bleeding [19]. Complications include strictures, fever, bleeding, and, rarely, perforation.

4.7 MPEC

Ablation of Barrett's using multipolar electrocoagulation (MPEC) is a fairly simple technique. A 10 French MPEC probe is passed through a therapeutic endoscope, and thermal energy is applied at 15–20 W setting till a white coagulum appears. Treatment is continued in a circumferential fashion at intervals of few weeks till entire Barrett's is ablated. It has been mainly studied in non-dysplastic Barrett's [20], few cases of LGD [21], and a small case series of intramucosal cancer in combination with laser [22]. Eradication rate is about 78 % with subsquamous intestinal metaplasia (SSIM) observed in about 5–27 % [20, 21]. Since it is time-consuming to treat large areas of Barrett's with this technique, it is best reserved for treating small areas of residual Barrett's after prior ablative therapy with different technique.

4.8 Endoscopic Therapy Versus Esophagectomy

The traditional treatment for Barrett's with HGD and intramucosal cancer had been esophagectomy. The advantage of esophagectomy is that it not only removes the neoplasia but also the at-risk mucosa thereby eliminating the risk of recurrence and also the periesophageal lymph nodes to allow accurate staging. However, it is associated with high rate of morbidity in a range of 30–50 % and a small but definite risk of mortality in even high-volume centers. There are no randomized controlled trials comparing endoscopic therapy to esophagectomy, but a number of studies show comparable long-term outcomes and much fewer complications with added advantage of preserving the esophagus. A recently published meta-analysis of 870 patients with early esophageal neoplasia [23] showed that there was no significant difference between endotherapy and esophagectomy in the neoplasia remission rate (relative risk [RR], 0.96; 95 %

CI, 0.91–1.01). The remission rate varied from 97 to 100 % in patients with esophagectomy and 84 to 97 % in patients with endoscopic treatment. In addition, there was no difference in overall survival rate at 5 years (RR 1.00). The cumulative death rate was 11.4 % in the endotherapy group and 8.7 % in the surgery group during follow-up. Most patients died of baseline comorbidities including cardiovascular disease, pulmonary disease, diabetes, and prior malignancy. The neoplasia-related mortality was 0.2 % in the endotherapy group and 0.3 % in the surgery group. Patients undergoing endotherapy had a higher neoplasia recurrence rate (RR 9.50) and fewer major adverse events (RR 0.38). Most patients (77.8–100 %) with neoplasia recurrence underwent endoscopic retreatment and got neoplasia remission again or had stable disease.

4.9 Postablation Surveillance

There are two issues which need to be taken into consideration after successful eradication of Barrett's which make postablation surveillance mandatory: first is the subsquamous intestinal metaplasia (SSIM or buried Barrett's), and second is the postablation recurrences after successful eradication of Barrett's.

4.10 Subsquamous Intestinal Metaplasia (SSIM)

SSIM or "buried Barrett's" is the presence of intestinal metaplasia in the lamina propria beneath overlying squamous mucosa. This is not visible by endoscopic inspection and is detected either by histological sampling or enhanced imaging techniques. Theoretically, SSIM may have a lower neoplastic potential due to lack of exposure to gastric acid and bile, but there are numerous reports of HGD or cancer developing from SSIM [24]. SSIM is known to exist both prior to and after ablation. The origins are uncertain but thought to be from neosquamous overgrowth over intestinal metaplasia in biopsy sites or as a consequence of ablation. The reported prevalence of SSIM varies from 0 to 28 % [25], but this may not be a true estimate as most of the endoscopic biopsies are not adequate to include subepithelial lamina propria [26]. Studies on SSIM in EMR specimens reported a prevalence of 28–98 % prior to any ablation therapy [27, 28]. The effect of ablation on prevalence of SSIM is not clear but may decrease following RFA. A recent systematic review on SSIM after endoscopic ablation procedures found SSIM in 14.2 % of patients treated with PDT and in 0.9 % of patients after RFA [29]. In view of this uncertainty, patients need to stay in surveillance program even after complete eradication of surface metaplasia.

4.11 Recurrences and Predictors of Recurrence

Recurrences are common and range from 20 to 33 % in up to a 3-year follow-up period. In a multicenter consortium of 448 patients who underwent RFA, 56 % had complete remission of which 33 % had disease recurrence within the next 2 years [29]. Most recurrences were non-dysplastic and endoscopically manageable, but continued surveillance after RFA is essential. Among 5521 patients in the US RFA registry [30], 85 % achieved complete eradication of intestinal metaplasia. In a mean follow-up of 2.4 years after complete eradication, metaplasia recurred 20 % and was non-dysplastic or indefinite for dysplasia in 86 % of patients. In Kaplan–Meier analysis, more advanced pretreatment histology was associated with an increased yearly recurrence rate. Compared with patients without recurrence, patients with recurrence were more likely to be older, have longer BE segments, be non-Caucasian, have dysplastic Barrett's before treatment, and require more treatment sessions. The treatment strategy for recurrent dysplasia is similar to primary dysplasia. EMR is performed for any visible abnormalities for treatment and staging purposes followed by ablative therapy for recurrent flat areas. If resistant to one modality, switching to a different mucosal ablation technique should be considered.

4.12 Follow-Up Intervals

Continued endoscopic surveillance following endotherapy is recommended, with intervals guided by prior grade of dysplasia and response to treatment. Currently, there is no consensus on the frequency of surveillance or biopsy protocol in postablation patients. As per recently published British guidelines [31], in patients treated for HGD, endoscopic follow-up is recommended every 3 months for 1 year and yearly thereafter. This should include biopsies at the cardia and within the previous extent of the Barrett's epithelium. For patients with LGD, annual surveillance is recommended.

4.13 Patient Selection and Technical Considerations

Patients referred for endoscopic therapy should have a detailed white light exam with a high-definition endoscope to identify landmarks and any visible abnormalities. Four quadrant surveillance biopsies should be performed every 1 cm along with endoscopic resection of suspicious areas. Diagnoses of dysplasia need to be confirmed by an expert gastrointestinal pathologist. In cases of HGD and intramucosal cancer with low risk of lymph node metastases such as lesion size less than 2 cm, well-differentiated histology, and absence of lymphovascular invasion, endoscopic therapy is preferred over esophagectomy. After EMR of visible lesions, residual Barrett's needs to be ablated in view of high risk of metachronous neoplasia. In the absence of visible lesions, ablative therapy is the treatment of choice. In view of risk of recurrence, patients need to be on ongoing surveillance with treatment of recurrences endoscopically.

Due to the lack of head-to-head randomized controlled trials comparing different ablative therapies, no one ablation modality suits all patients. A comparison of different ablation techniques is presented in Table 4.1. In patients with long-segment Barrett's where large surface areas need to be treated, RFA is the treatment modality of choice. Other options include PDT and cryotherapy. For small areas of residual Barrett's, APC and MPEC may be cost-effective modalities. For patients with nodular disease where close apposition with RFA is not possible, options are cryotherapy, PDT, and stepwise radical EMR. In patients with persistent areas of Barrett's in spite of repeated ablation, EMR can be used.

Table 4.1 Comparison of different ablative techniques

Ablative technique	Dysplasia eradication (%)	Metaplasia eradication (%)	Strengths	Limitations
RFA	91–100	71–93	RCT available High response rate Low complication rate	High costs
Cryotherapy	87–97	42–81	Good safety profile Useful for nodular areas	Small studies (no RCTs) No long-term follow-up data
PDT	40–77	52	RCT available Treatment of nodular areas	High stricture rate Photosensitivity Buried Barrett's
APC	67–86	69	Widely available Inexpensive	Feasible for short segments only Buried Barrett's
MPEC	–	75–100	Widely available Inexpensive	Feasible for short segments only Buried Barrett's

RCT randomized controlled trial, *RFA* radiofrequency ablation, *PDT* photodynamic therapy, *APC* argon plasma coagulation, *MPEC* multipolar electrocoagulation

References

1. Berenson MM, Johnson TD, Markowitz NR et al (1993) Restoration of squamous mucosa after ablation of Barrett's esophageal epithelium. Gastroenterology 104:1686–1691
2. Pech O, Behrens A, May A et al (2008) Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut 57:1200–1206
3. Bergman JJGHM, Fockens P (2006) Ablating Barrett's metaplastic epithelium: are the techniques ready for clinical use? Gut 55(9):1222–1223
4. Shaheen NJ, Sharma P, Overholt BF et al (2009) Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 360:2277–2288
5. Shaheen NJ, Overholt BF, Sampliner RE et al (2011) Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. Gastroenterology 141:460–468
6. Phoa KN, van Vilsteren FGI, Weusten LAM et al (2014) Radiofrequency ablation vs endoscopic surveillance for patients with Barrett Esophagus and low-grade dysplasia. A randomized clinical trial. JAMA 311(12):1209–1217
7. Shaheen NJ, Greenwald BD, Peery AF et al (2010) Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. Gastrointest Endosc 71:680–685
8. Gosain S, Mercer K, Twaddell WS et al (2013) Liquid nitrogen spray cryotherapy in Barrett's esophagus with high-grade dysplasia: long-term results. Gastrointest Endosc 78(2):260–265
9. Greenwald BD, Dumot JA, Abrams JA et al (2010) Endoscopic spray cryotherapy for esophageal cancer: safety and efficacy. Gastrointest Endosc 71(4):686–693
10. Canto MI, Gorospe EC, Shin EJ et al (2009) Carbon dioxide (CO_2) Cryotherapy is a safe and effective treatment of Barrett's Esophagus (BE) with HGD/Intramucosal Carcinoma. Gastrointest Endosc 69:AB341
11. Greenwald BD, Dumot JA, Horwhat D, Lightdale CJ, Abrams JA (2010) Safety, tolerability, and efficacy of endoscopic low-pressure liquid nitrogen spray cryotherapy in the esophagus. Dis Esophagus 23:13–19
12. Dumot JA, Vargo JJ, Falk GW et al (2009) An open-label, prospective trial of cryospray ablation for Barrett's esophagus high-grade dysplasia and early esophageal cancer in high-risk patients. Gastrointest Endosc 70:635–644
13. Overholt BF, Lightdale CJ, Wang KK et al (2005) Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial. Gastrointest Endosc 62(4):488–498
14. Overholt BF, Wang KK, Burdick JS et al (2007) Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. Gastrointest Endosc 66(3):460–468
15. Pacifico RJ, Wang KK, Wongkeesong LM et al (2003) Combined endoscopic mucosal resection and photodynamic therapy versus esophagectomy for management of early adenocarcinoma in Barrett's esophagus. Clin Gastroenterol Hepatol 1:252–257
16. Prasad GA, Wu TT, Wigle DA et al (2009) Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Barrett's esophagus. Gastroenterology 137:815–823
17. Grade AJ, Shah IA, Medlin SM et al (1999) The efficacy and safety of argon plasma coagulation therapy in Barrett's esophagus. Gastrointest Endosc 50:18–22
18. Lewis CJ, Caplin S, Armstrong G et al (2003) Argon Beam Plasma Coagulation as an ablative therapy for high grade dysplasia in Barrett's Oesophagus. Clin Gastroenterol Hepatol 1(4):258–263
19. Akhtar K, Byrne JP, Bancewicz J et al (2000) Argon Beam Plasma Coagulation in the management of cancers of the esophagus and stomach. Surg Endoscopy 14:1127–1130
20. Sampliner RE, Faigel D, Fennerty MB et al (2001) Effective and safe endoscopic reversal of nondysplastic Barrett's esophagus with thermal electrocoagulation combined with high dose acid suppression: a multicenter study. Gastrointest Endosc 53:554–558
21. Sharma P, Bhattacharyya A, Garewal HS et al (1999) Durability of new squamous epithelium after endoscopic reversal of Barrett's Esophagus. Gastrointest Endosc 50:159–164
22. Sharma P, Jaffe PE, Bhattacharyya A et al (1999) Laser and multipolar electrocoagulation ablation of early Barrett's adenocarcinoma. Gastrointest Endosc 49:442–446
23. Wu J, Pan Y, Wang T et al (2014) Endotherapy versus surgery for early neoplasia in Barrett's esophagus: a meta-analysis. Gastrointest Endosc 79(2):233–241
24. Titi M, Overhiser A, Ulusarac O et al (2012) Development of subsquamous high-grade dysplasia and adenocarcinoma after successful radiofrequency ablation of Barrett's esophagus. Gastroenterology 143:564–566
25. Gray NA, Odze RD, Spechler SJ (2011) Buried metaplasia after endoscopic ablation of Barrett's esophagus: a systematic review. Am J Gastroenterol 106:1899–1908
26. Gupta N, Mathur SC, Dumot JA et al (2012) Adequacy of esophageal squamous mucosa specimens obtained during endoscopy: are standard biopsies sufficient for postablation surveillance in Barrett's esophagus? Gastrointest Endosc 75:11–18
27. Anders M, Lucks Y, El-Masry MA et al (2014) Subsquamous extension of intestinal metaplasia is detected in 98% of cases of neoplastic Barrett's esophagus [published online July 23, 2013]. Clin Gastroenterol Hepatol 12(3):405–410. doi:http://dx.doi.org/10.1016/j.cgh.2013.07.013
28. Chennat J, Ross AS, Konda VJ et al (2009) Advanced pathology under squamous epithelium on initial EMR specimens in patients with Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma: implications for surveillance and endotherapy management. Gastrointest Endosc 70:417–421

29. Gupta M, Iyer PG, Lutzke L et al (2013) Recurrence of esophageal intestinal metaplasia after endoscopic mucosal resection and radiofrequency ablation of Barrett's esophagus: results from a US Multicenter Consortium. Gastroenterology 145:79–86
30. Pasricha S, Bulsiewicz WJ, Hathorn K et al (2014) Durability and predictors of successful radiofrequency ablation for Barrett's Esophagus. Clin Gastroenterol Hepatol 12(11):1840–1847
31. Fitzgerald RC, di Pietro M, Ragunath K et al (2014) British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 63:7–42

Endoscopic Resection for Barrett's Esophagus to Dysplasia

5

Filippo Catalano

5.1 Evidence on Barrett's

Barrett's esophagus (BE) was first described in 1950 as a probable complication of chronic gastroesophageal reflux disease (GERD) in both symptomatic and asymptomatic individuals. In BE squamous cells of the lower organ have changed from normally flat to a rectangular type of epithelial cell called columnar cell (intestinal metaplasia): we are therefore faced with a situation of cellular rehash where these new cells can grow abnormally and the less normal they look, the higher is the grade of dysplasia. In other words precancerous cells can appear in Barrett's tissue. The risk of progression from low-grade dysplasia to either high-grade dysplasia or adenocarcinoma remains controversial, based in large part on the difficulty in distinguishing dysplasia from non-dysplastic Barrett's esophagus and determining with reproducible accuracy the degree of dysplasia. Because dysplasia progresses to cancer in a manner that lacks definitive markers of progression, there are no well-defined cutoff points that separate low-grade from high-grade dysplasia at this time [1]

People with BE are more likely to develop a type of cancer called esophageal adenocarcinoma (BAD, Barrett's adenocarcinoma). The annual incidence of BAD is 0.12–0.50 %. The increase in the incidence of BE has led to a fourfold increase in the incidence of BAD in the West but not in the East. However, in the near future, an increase is also expected in East Asia because of a decrease in *Helicobacter pylori* infection rates and the westernization of the diet, both of which are thought to promote GERD.

BE may be present for many years before cancer develops. The risk of cancer appears to vary with the extent of BE. Patients with long-segment disease may have a higher incidence of BAD than those with shortsegment BE.

Actually the best surveillance for patients is an upper gastrointestinal endoscopy with biopsy monitoring of Barrett's tissue, watching sign of cancer development. Rigorous and systematic biopsy protocol improves detection of dysplasia end early cancer [2]. In Western countries, endoscopic surveillance once every 2 or 3 years is recommended when there is no dysplasia, twice yearly in cases of low dysplasia, and every 3 months in case of high-grade dysplasia. The criterion standard is random endoscopic biopsies from four directions at 2 cm intervals (1 cm intervals if dysplasia is present).

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5.2 Diagnosis

Today it is possible to allow very close examination of this precancerous condition by the high-resolution endoscopic instruments. Chromoendoscopy with indigo carmine at 2 % concentration and acetic acid at 1 % helps a better visualization of entire BE and highlights irregular area. Some endoscopes provide narrow band imaging (NBI), a noninvasive optical technique that uses reflected light to visualize the superficial structure of the organ surface. It is used to visualize morphologic changes in the structure of esophageal lesions because it allows detailed high-resolution and high-contrast imaging of the vascular and mucosal patterns within the BE segment.

Thanks to the advances in endoscopic technologies, in the last years, the incidence of superficial BAD has increased steadily in Western countries.

5.3 Endoscopic Treatment

Surgery is the standard treatment for neoplasms located at the esophagogastric junction, but it is associated with a reported mortality rate ranging between 3.0 and 12.2 % [3] and high postoperative morbidity (20–47 %).

BAD survival rates correlate with the stage. Locally advanced disease show a 5-year survival rate of approximately 20 %, the reason why surveillance and early detection of BAD has become a critical issue.

The morbidity and mortality and low rates of metastases associated with early cancer have led to less invasive therapies as alternatives to esophagectomy.

Early stage of this cancer makes possible a minimally invasive endoscopic treatment.

Studies of esophagectomy specimens show low risk of metastases, from 0.0 to 1.3 % for T1m BAD and 18 to 22 % for T1 sm. Low rates of positive lymph nodes in T1 m has provided a rationale for endoscopic treatment.

Best staging of the disease is done on the acquiring tissue, so endoscopic resection is the best modality against other endoscopic treatments as radiofrequency or argon plasma ablation.

Endoscopic resection (ER) in the form of EMR (endoscopic mucosa resection) and ESD (endoscopic submucosal dissection) has been accepted and widely used as a standard treatment for differentiated gastric adenocarcinoma without ulceration and with a diameter of ≤2 cm (Fig. 5.1).

In East Asia expanded indications were suggested allowing many patients to undergo ESD rather than surgery. Many Japanese and Korean reports have shown excellent results in patients with gastric cancer that fulfilled expanded criteria. Western endoscopists still have not a wide experience and skills in ESD procedures. Lower incidence of early stage do not suggest to use expanded criteria but only in high-volume center in selected study.

In the last decade, many authors have clearly demonstrated in exhaustive way the clear superiority of the ESD regarding the EMR in terms of curability. Excellent en bloc resection rates and curative resection and low rates of major complications (<5 % for bleeding and perforation, respectively) confirm the outstanding role of this procedure for the treatment of EGC. EMR has a too high incidence of locally recurrent EGC. ESD is safe and efficacious for obtaining en bloc resection and for the definitive oncological treatment allowing precise histological staging of EGC patients with higher percentage compared with EMR procedure (Fig. 5.2).

Esophagogastric junction and lower esophagus are difficult locations for ER because of its narrow lumen and sharp angle affecting complete resection and curative resection. Major complications of ESD such as postoperative bleeding and perforation may be influenced by the difficulty of the procedure.

It is important to stress a stricter ESD indication for early esophageal cancer than for gastric one, and such indications adopt if the tumor purely at the cardia has not been fully evaluated.

While ESD indications for superficial esophageal cancer include differentiated mucosal cancer of <20 mm in diameter without lymphovascular, ESD indications for EGJ Early cancer should follow those accepted for EGC.

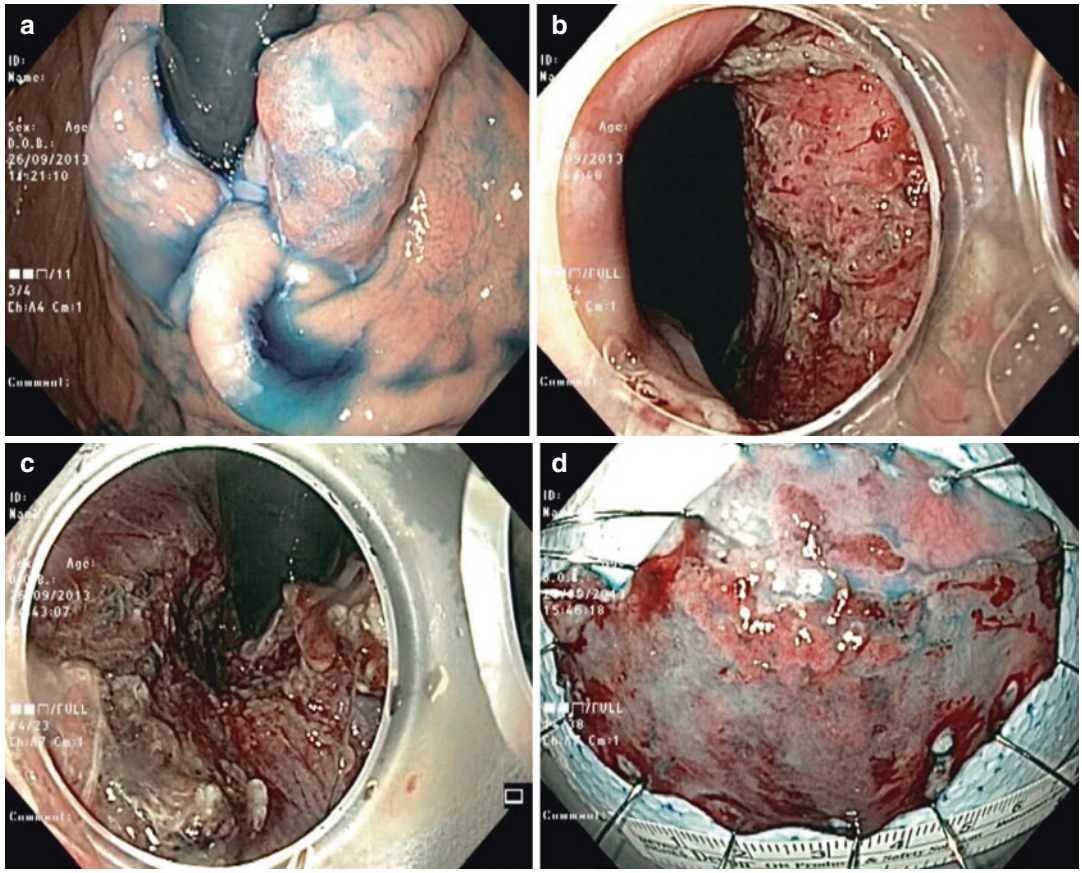

Fig. 5.1 HGD of 23 mm in diameter at the esophagogastric junction highlights by indigo carmine staining (**a**). Patient has been treated with ESD. Early results of the procedure are showed in **b** (anterograde vision) and **c** (retrograde vision). (**d**) Specimen analyzed by expert pathologist confirms a high-grade dysplasia

For early BAD, if submucosal invasion is found, the patients have to undergo surgical resection because of a substantial risk of metastasis. When the lesion invades the muscularis mucosae, a substantial risk of metastasis exits, and additional surgical resection is to be considered based on the patient's condition. If the accurate evaluation of the specimen after complete en bloc resection confirms a tumor confined to the mucosa with negative lateral margins and without lymphovascular invasion, endoscopic resection can be curative because of the very low-risk positive lymph nodes.

Actually few reports exist regarding ESD for superficial BAD [4, 5].

Submucosal dissection is a very difficult and long procedure. The majority of Western endoscopists still prefer EMR for the treatment of the visible dysplastic lesions in Barrett's esophagus. Most times it is necessary to carry out multifragment resection because of several foci of dysplasia. EMR of early neoplasia in BE is associated with recurrence of metachronous neoplasia in remaining Barrett's mucosa in up to 30 % of cases [6]. The more recently introduced technique of multiband mucosectomy (MBM) appears to be even safer, with perforation rates reported in the range of 0–1.2 %. Recently a Dutch meta-analysis [7] compares 16 studies (EMR techniques versus ESD) concluding that MBM technique for EMR appears as effective as ESD when comparing important outcome parameters on the eradication of early Barrett's or EGJ neoplasia.

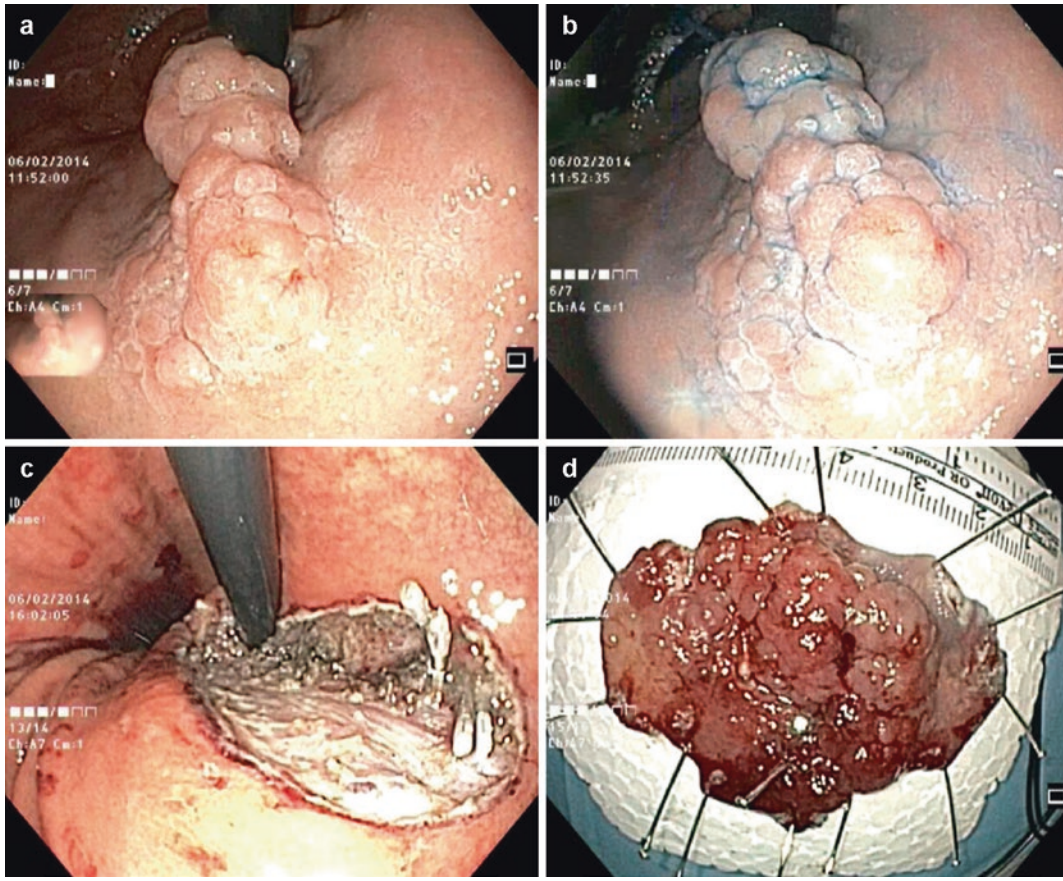

Fig. 5.2 Indigo carmine can help to clarify lateral margin of the lesion before making marking dots (**a**, **b**). Sometimes at the end of the procedure of ESD, on the residual ulcer, it is necessary to apply some clips where the dissection has gone too much in depth (**c**). (**d**) Specimen must be fixed on a support to facilitate histological evaluation

They support the non-inferiority in oncological treatment in the short term, but further studies that comprehend randomized and controlled trials with the MBM technique compared to ESD in early Barrett's or EGJ neoplasia need to be performed to substantiate these results (Fig. 5.3).

Till now endoscopic resection treatment seems a promising technique to treat early BAD and early EGJ cancer. ESD should be preferred over EMR because large lesions can be resected en bloc, allowing for accurate histological assessment. Our experience [8] shows that on 65 gastric lesions, we have witnessed very good long-term results, as the Japanese ones (data not published), but in two cases (one perforation and one procedure abandoned for the difficulty), difficulties were such as to confirm that EGJ is a very dangerous location for a very experienced endoscopist as well. Experiences are still too few, and it will be necessary to understand long-term prognosis after ESD on EGJ early cancer.

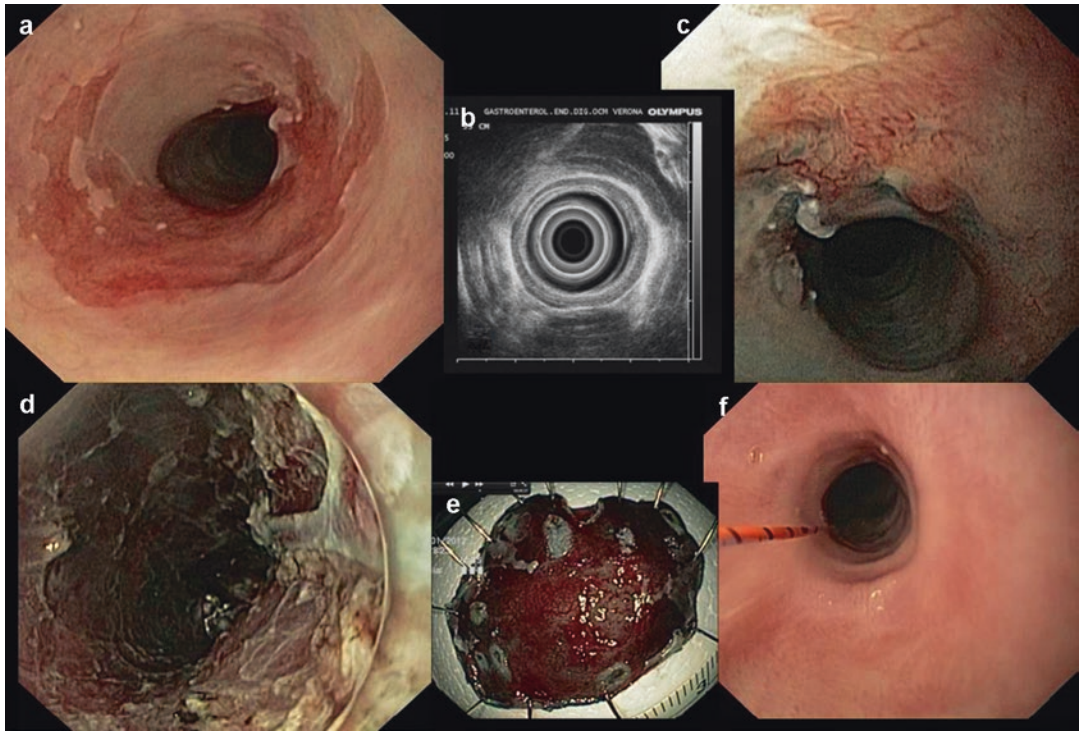

Fig. 5.3 Patient is 41 years old and is HIV+ with a long Barrett's. He had developed an intramucosal adenocarcinoma with unclear margin (**a**, **c**). EUS confirmed a T1 m (**b**). We have performed a nearly circumferential ESD (**d**). Specimen confirms a curative resection with negative lateral margins and without lymphovascular infiltration (**e**). Six months later, patient needs a dilation for severe stenosis of the esophageal lumen. Two sessions of mechanic dilations were enough to resolve any symptom (**f**)

References

1. AGA (2011) American Gastroenterological Association Medical Position Statement on the management of Barrett's esophagus. Gastronetrology 140:1084–1091
2. Abela JE, Going JJ, Mackenzie JF et al (2008) Systematic four quadrant biopsy detects Barrett's dysplasia in more patients than non-systematic biopsy. Am J Gastroenterol 103:850–855
3. Ell C, May A, Pech O et al (2007) Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointest Endosc 65:3–10
4. Ikeda K, Isomoto H, Oda H et al (2009) Endoscopic dissection of a minute intramucosal adenocarcinoma in Barrett's Esophagus. Dig Endosc 21:34–36
5. Hoteya S, Matsui A, Izuka T et al (2013) Comparison of the clinico-pathological characteristics and results of endoscopic submucosal dissection for esophagogastric junction and non junctional cancers. Digestion 87:29–33
6. Buttar NS, Wang KK, Lutzke LS et al (2001) Combined endoscopic mucosal re-section and photodynamic therapy for esophageal neoplasia within Barrett's esophagus. Gastrointest Endosc 54:682–688
7. Komeda Y, Bruno M, Koch A et al (2014) EMR is not inferior to ESD for early Barrett's and EGJ neoplasia: an extensive review on outcome, recurrence and complication rate. Endosc Int Open 02:E58–E64
8. Catalano F, Trecca A, de Manzoni G et al (2009) The modern treatment of early gastric cancer: our experience in an Italian cohort. Surg Endosc 23:1581–1586

7th Edition AJCC/UICC Staging: Esophagus and Esophagogastric Junction

6

Thomas W. Rice

The concept of TNM cancer staging describing the anatomic extent of a cancer was developed by Pierre Denoix at the Cancer Institute Gustave-Roussy between 1943 and 1952. It is based on the principle that as size of an untreated primary cancer (T) increases, regional lymph node metastases (N) and then distant metastases (M) become more prevalent. Although introduced in 1953, it was not until 1968 that the first Cancer Staging Manual was published by the International Union Against Cancer (UICC).

Cancer staging is an evolutionary process. Initially, TNM esophageal cancer staging quickly developed but unfortunately soon stagnated for decades. T classifications for thoracic esophageal cancer were last changed in 1988, N classifications in 1977, and M classifications in 1997. A hindrance to its evolution has been the long held concept that stage groupings of esophageal cancer be based, incorrectly, on a simple, orderly arrangement of increasing anatomic T, then N, then M classifications. This assumption was neither consistent with cancer biology nor survival data. Worldwide collaboration [1] has provided data for a unique, modern machine-learning analysis [2] that has produced data-driven staging for cancer of the esophagus and esophagogastric junction [3]. This new system is the basis for the 7th editions of the AJCC and UICC Cancer Staging Manuals [4, 5]. It is more representative of and consistent with the survival following esophagectomy of patients with esophageal cancer. Changes address problems of empiric stage grouping and prior disharmony with stomach cancer staging. In addition, TNM classifications have been reviewed and revised were data, analysis, and consensus demonstrated a need for change. For the first time, nonanatomic cancer characteristics primary cancer site (location), histologic grade (grade), and histopathologic type (cell type) are incorporated in esophageal cancer staging.

6.1 The Data

At the request of the AJCC, the Worldwide Esophageal Cancer Collaboration (WECC) was inaugurated in 2006. Thirteen institutions from five countries and three continents (Asia, Europe, and North America) submitted deidentified data by July 2007. A database of 4627 esophagectomy patients who had no induction or adjuvant therapy was created [1].

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6.2 The Analysis

Multiple previously proposed revisions of esophageal cancer staging have examined goodness of fit or *P* values to test for a statistically significant effect of stage on survival. Instead, staging for the 7th edition used random forest (RF) analysis, a machine-learning technique that focuses on predictiveness for future patients [2]. RF analysis makes no a priori assumptions about patient survival, is able to identify complex interactions among variables, and accounts for nonlinear effects. It may be viewed as a "backward" analysis which determines the anatomic classifications (TNM) and nonanatomic cancer characteristics which are associated with specific survival groups.

RF analysis first isolated cancer characteristics of interest from other factors influencing survival by generating risk-adjusted survival curves for each patient. Unlike previous approaches that began by placing cancer characteristics into proposed groups, RF analysis produced distinct groups with monotonically decreasing risk-adjusted survival without regard to cancer characteristics. Then, anatomic and nonanatomic cancer characteristics important for stage group composition were identified within these groups. Finally, homogeneity within groups guided both amalgamation and segmentation of cancer characteristics between adjacent groups to arrive at the final stage groups [3–5].

6.3 7th Edition TNM Classifications: Changes and Additions

Primary tumor (T) classification has been changed for Tis and T4 cancers (Fig. 6.1, Table 6.1). Tis is now defined as high-grade dysplasia and includes all noninvasive neoplastic epithelium that was previously called carcinoma

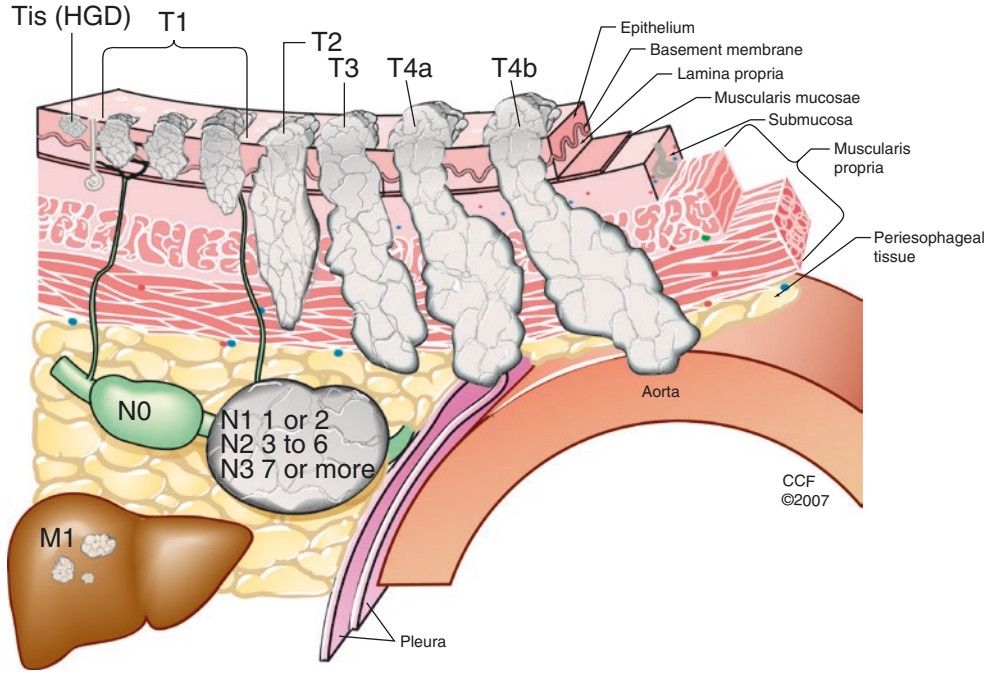

Fig. 6.1 7th edition TNM classifications. T is classified as Tis, high-grade dysplasia; T1, cancer invades lamina propria, muscularis mucosae, or submucosa; T2, cancer invades muscularis propria; T3, cancer invades adventitia; T4a, resectable cancer invades adjacent structures such as pleura, pericardium, or diaphragm; and T4b, unresectable cancer invades other adjacent structures, such as aorta, vertebral body, or trachea. N is classified as N0, no regional lymph node metastasis; N1, regional lymph node metastases involving 1–2 nodes; N2, regional lymph node metastases involving 3–6 nodes; and N3, regional lymph node metastases involving 7 or more nodes. M is classified as M0, no distant metastasis, and M1, distant metastasis

Table 6.1 2010 7th Edition AJCC/UICC TNM classifications

Primary tumor (T)		
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Tis	High-grade dysplasia[a]	
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa	
	T1a	Tumor invades lamina propria or muscularis mucosae
	T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria	
T3	Tumor invades adventitia	
T4	Tumor invades adjacent structures	
	T4a	Resectable tumor invading pleura, pericardium, or diaphragm
	T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.
Regional lymph nodes (N)[b]		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastases involving 1–2 nodes	
N2	Regional lymph node metastases involving 3–6 nodes	
N3	Regional lymph node metastases involving 7 or more nodes	
Distant metastasis (M)		
M0	No distant metastasis	
M1	Distant metastasis	
Histopathologic type		
Squamous cell carcinoma		
Adenocarcinoma		
Histologic grade (G)		
GX	Grade cannot be assessed—stage grouping as G1	
G1	Well differentiated	
G2	Moderately differentiated	
G3	Poorly differentiated	
G4	Undifferentiated—stage grouping as G3 squamous	
Location[c]		
Upper or middle—cancers above lower border of inferior pulmonary vein		
Lower—below inferior pulmonary vein		

Notes
[a]Includes all noninvasive neoplastic epithelium that was previously called carcinoma in situ. Cancers stated to be noninvasive or in situ are classified as Tis
[b]Number must be recorded for total number of regional nodes sampled and total number of reported nodes with metastases
[c]Location (primary cancer site) is defined by position of upper (proximal) edge of tumor in esophagus

in situ. T4, tumors invading local structures, has been subclassified as T4a and T4b; T4a tumors are resectable cancers invading adjacent structures such as pleura, pericardium, or diaphragm. T4b are unresectable cancers invading other adjacent structures, such as aorta, vertebral body, or trachea. Otherwise, T classifications are unchanged (Fig. 6.1, Table 6.1).

A regional lymph node has been redefined to include any paraesophageal lymph node extending from cervical nodes to celiac nodes (Table 6.1). Lymph nodes outside the "bed" of the esophagus are classified as distant metastases. Data analyses support convenient coarse groupings of number of cancer-positive nodes [2–4]. Regional lymph node (N) classification comprises N0 (no cancer-positive nodes), N1 (1 or 2), N2 (3–6), and N3 (7 or more). N classifications for cancers of the esophagus and esophagogastric junction are identical to stomach cancer N classifications.

The subclassifications M1a and M1b have been eliminated, as has MX (Table 6.1). Distant metastases are simply designated M0, no distant metastasis, and M1, distant metastasis.

6.4 7th Edition: Nonanatomic Cancer Characteristics

Nonanatomic classifications identified as important for stage grouping (Table 6.1) are histopathologic cell type, histologic grade, and tumor location (Fig. 6.2). The difference in survival between adenocarcinoma and squamous cell carcinoma is best managed by separate stage groupings for stages I and II. Increasing histologic grade is associated with incrementally decreasing survival for early-stage cancers. For adenocarcinoma, distinguishing G1 and G2 (well and moderately differentiated) from G3 (poorly differentiated) is important for stage I and stage IIA cancers. For squamous cell carcinoma, distinguishing G1 from G2 and G3 is important for stage I and II cancers. Tumor location (upper and middle thoracic versus lower thoracic) is important for grouping T2-3N0M0 squamous cell cancers.

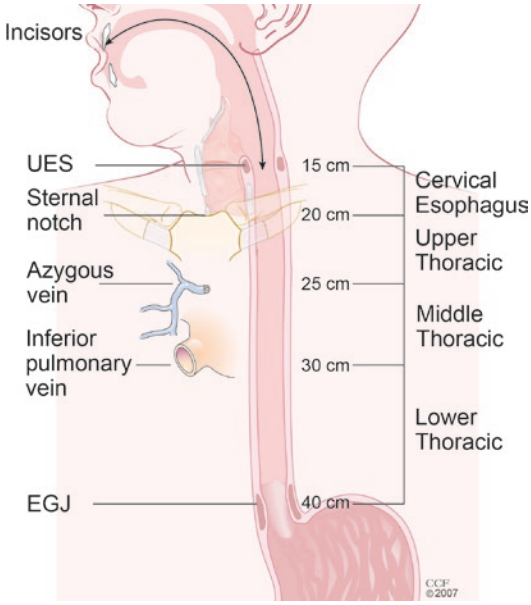

Fig. 6.2 Cancer location. Cervical esophagus, bounded superiorly by the cricopharyngeus and inferiorly by the sternal notch, is typically 15–20 cm from the incisors at esophagoscopy. Upper thoracic esophagus, bounded superiorly by the sternal notch and inferiorly by the azygos arch, is typically >20–25 cm from the incisors at esophagoscopy. Middle thoracic esophagus, bounded superiorly by the azygos arch and inferiorly by the inferior pulmonary vein, is typically >25–30 cm from the incisors at esophagoscopy. Lower thoracic esophagus, bounded superiorly by the inferior pulmonary vein and inferiorly by the lower esophageal sphincter, is typically >30–40 cm from the incisors at esophagoscopy; it includes cancers whose epicenter is within the proximal 5 cm of the stomach that extend into the esophagogastric junction or lower thoracic esophagus

6.5 7th Edition Stage Groupings

Stages 0 and IV are by definition (not data driven) TisN0M0 and T any N any M1, respectively. Stage groupings for M0 adenocarcinoma are shown in Fig. 6.3. For T1N0M0 and T2N0M0 adenocarcinoma, subgrouping is by histologic grade: not G3 (G1 and G2) versus G3.

Stage groupings for M0 squamous cell carcinoma are shown in Fig. 6.4. For T1N0M0 squamous cell carcinoma, subgrouping is by histologic grade: G1 versus not G1 (G2 and G3) (Fig. 6.4a). For T2N0M0 and T3N0M0 squamous cell carcinoma, stage grouping is by histologic grade and location (Fig. 6.4a). The four combinations range from G1 lower thoracic squamous cell carcinoma

Adenocarcinoma

G1-2 / G3	T1	T2	T3	T4 a	T4 b
N0	IA / IB	IB / IIA	IIB	IIIA	IIIC
N1	IIB	IIB	IIIA	IIIC	IIIC
N2	IIIA	IIIA	IIIB	IIIC	IIIC
N3	IIIC	IIIC	IIIC	IIIC	IIIC

Fig. 6.3 Stage groupings for M0 adenocarcinoma by T and N classification and histologic grade (G)

(stage IB), which has the best survival, to G2 to G4 upper and middle thoracic squamous cell carcinomas (stage IIB), which have the worst. G2 to G4 lower thoracic squamous cell carcinomas and G1 upper and middle thoracic squamous cell carcinomas are grouped together (stage IIA), with intermediate survival.

Stage 0, III, and IV adenocarcinoma (Fig. 6.3) and squamous cell carcinoma (Fig. 6.4b) are identically stage grouped. Adenosquamous carcinomas are staged as squamous cell carcinoma.

6.6 Esophagogastric Junction Cancers

Besides being data driven, the 7th edition of the Cancer Staging Manual harmonizes staging of cancer across the esophagogastric junction. Previous staging editions produced different stage groupings for these cancers depending on use of either esophageal or stomach stage groupings. The 7th edition staging is for cancers of the esophagus and esophagogastric junction and includes cancer within the first 5 cm of the stomach that invades the esophagogastric junction.

6.7 The Future: 8th Edition and Beyond

The 7th edition heralded the era of data-driven cancer staging and will serve as the foundation for future staging [6]. However, this edition was

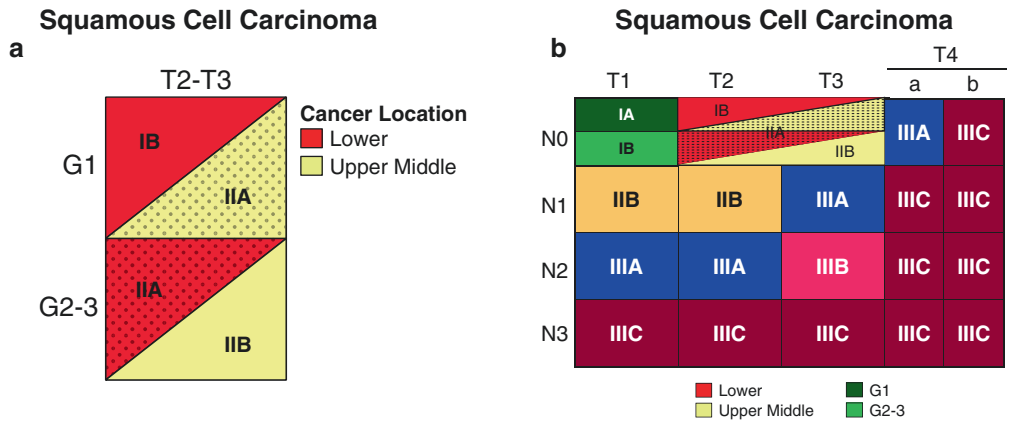

Fig. 6.4 Stage groupings for M0 squamous cell carcinoma. (**a**) Stage groupings for T1N0M0 and T2-3N0M0 squamous cell carcinomas by histologic grade (G) and cancer location. Stage groupings for M0 squamous cell carcinoma. (**b**) Stage groupings for all other M0 squamous cell carcinomas

based on only esophagectomy data, an obvious shortcoming. Improvements in the next iterations of esophageal cancer staging will require:

1. Obtaining better homogeneity of stage 0 and stage IV. This requires abandoning restrictive definitions of these stage groupings and changing composition of adjacent stage IA and stage IIIC (Figs. 6.5 and 6.6).
2. Improving homogeneity of stage IIB adenocarcinoma (Fig. 6.5) and stage IIA and IIB squamous cell cancer (Fig. 6.6). This requires expanding the WECC database of these less common cancers.
3. Adding clinical (cStage), post-induction clinical and post-definitive nonsurgical clinical (ycStage), and post-induction pathologic (ypStage) staging recommendations. This requires expanding the WECC database and analysis.
4. Assessing other nonanatomic tumor characteristics that affect survival. This requires addition of data elements beyond histopathologic cell type, histologic grade, and cancer location.
5. Adding non-esophagectomy survival data, endoscopic treatment in stage 0 and stage IA, and palliative therapy for stage IV. This requires partnering with nonsurgical specialties and professional associations and groups.
6. Adding cancer of the cervical esophagus. This requires partnering and harmonizing with the head and neck task force, mirroring the process used with the gastric cancer task force for the 7th edition.

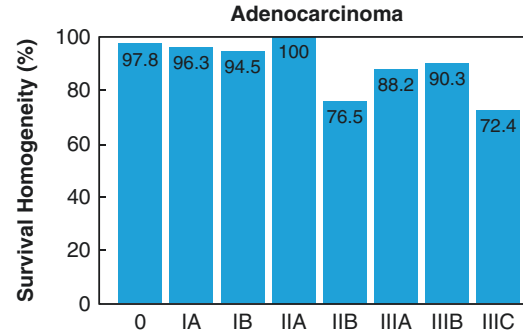

Fig. 6.5 7th edition staging, adenocarcinoma of the esophagus: a measure of homogeneity within stage groupings with respect to survival

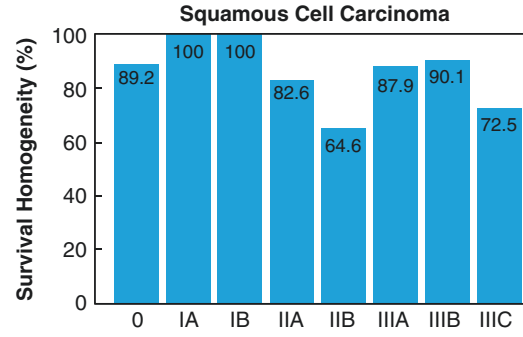

Fig. 6.6 7th edition staging, squamous cell cancer of the esophagus: a measure of homogeneity within stage groupings with respect to survival

Acquisition of multicenter, international data through WECC is key to this effort [1]. Innovative and improved machine-learning techniques will again be used for analysis [2]. Analytic strategies for integration of clinical (cTNM), pathologic (pTNM), and post-induction pathologic staging (ypTNM) are being developed.

6.8 Beyond Anatomic Staging

Differences in the focus and goals of the AJCC and UICC in cancer staging may be obviated by extinction of the printed manual and development of an Internet cancer staging site. This will eliminate the need for a blanket change to all organ systems every 6–7 years, permitting ongoing changes to each organ system when adjustments are indicated and necessary.

The use of patient and treatment factors will be expanded in future analyses that will focus on the individual patient. Patient-specific prognosis requires more than risk adjustment of these factors (used in the 7th edition); it necessitates their addition as variables in the analyses. The analyses will provide two models: a *decision model* based on clinical staging and additional patient factors that will assist in treatment decisions and a *prognostic model* based on pathologic staging, patient factors, and treatment delivered that will facilitate prognostication. Smartphone applications or their equivalent are envisioned for patient and physician use.

Conclusions

The concept of TNM cancer staging describing the anatomic extent of a cancer was developed in the mid-twentieth century. However, it was not uniformly applied to esophageal cancer until 1977. The faithful adherences to the empiric staging process that was based on the stepwise progression of increasing local cancer invasion (T), followed by metastases to regional lymph nodes (N), and finally metastases to distant sites (M) dominated esophageal cancer staging for more than 30 years, through six editions.

The 7th edition staging recommendations for cancer of the esophagus and esophagogastric junction are data driven and harmonized with stomach cancer. This required changes in TNM definitions and addition of nonanatomic cancer characteristics. For cancers of the esophagus and esophagogastric junction, stage 0, III, and IV are identical for both adenocarcinoma and squamous cell carcinoma. However, stage groupings differ for stage I and II cancers based on histopathologic cell type, histologic grade, and cancer location.

Improving cancer staging requires a release from the strict TNM description of anatomic staging. The inclusion of TNM variables with others (to be identified) will allow a more complete definition of the esophageal cancer and aid in treatment decisions and facilitate prognostication.

References

1. Rice TW, Rusch VW, Apperson-Hansen C et al (2009) Worldwide esophageal cancer collaboration. Dis Esoph 22:1–8
2. Ishwaran H, Blackstone EH, Apperson-Hansen C, Rice TW (2009) A novel approach to cancer staging: application to esophageal cancer. Biostatistics 10:603–620
3. Rice TW, Rusch VW, Ishwaran H, Blackstone EH (2010) Cancer of the esophagus and esophagogastric junction: data-driven staging for the 7th edition of the AJCC cancer staging manual. Cancer 116:3763–3773
4. American Joint Committee on Cancer (2010) AJCC cancer staging manual, 7th edn. Springer, New York
5. International Union Against Cancer (2009) TNM classification of malignant tumors, 7th edn. Wiley-Blackwell, Oxford, UK
6. Rusch VW, Rice TW, Crowley J, Blackstone EH, Rami-Porta R, Goldstraw P (2010) The seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Staging Manuals: the new era of data-driven revisions. J Thorac Cardiovasc Surg 139:819–821

7 Siewert Classification of Adenocarcinoma of the Esophagogastric Junction: Still In or Already Out?

Paul M. Schneider and Stefan P. Mönig

The classification and definition of adenocarcinomas of the esophagogastric junction (AEGJ) have not yet been definitively standardized, and the choice of the appropriate surgical procedure is still a subject of controversy. As confusion reigned in the area of the cardia in the 1980s, Siewert and colleagues proposed a classification for these tumors with the intention to put an order into a complex disease and suggest the appropriate surgical strategy [1]. These tumors are nowadays of particular interest, as in contrast to the decreasing frequency of gastric cancer; a number of studies from various Western industrialized nations have reported an increased incidence of adenocarcinomas of the esophagus and cardia in the last 30 years. Studies from population-based cancer registries in the United States, the United Kingdom, and Switzerland have indicated a rapid increase of the incidence of adenocarcinoma of the esophagogastric junction [2–5]. The reasons for this increase remain unclear, and a number of causes are being discussed, such as the malignant potential of Barrett's mucosa and etiologic factors, such as obesity, dietary factors, alcohol, pharmaceutical agents, and tobacco use [2].

Within this chapter, we try to summarize our current understanding of how to classify these tumors in this confusing region of the esophagogastric junction with an attempt to summarize the pros and cons of the most frequently used classification of AEGJ, the so-called Siewert classification.

7.1 The Esophagogastric Junction

7.1.1 Definition

Because of the lack of a clear definition and classification, cancer of the esophagogastric junction has been considered and treated sometimes as distal esophageal cancer, sometimes as proximal gastric cancer, and sometimes as an entity separate from both esophageal and gastric cancers [1]. The confusion may be in part due to the imprecise definition of the gastric cardia. It is so called, as it is that part of the stomach close to the heart which is called "kardia" in the old Greek language [6].

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Even though anatomists describe the cardia as that zone of the stomach adjacent to the orifice of the tubular esophagus, the orifice can also be defined as the esophagogastric junction (EGJ), and the primary problem lies in the precise identification of this very junction. The EGJ is localized at the level of the angle of His that is the point at which the tubular esophagus joins to the saccular stomach, which is not clinically applicable in the preoperative setting. The EGJ is defined differently by anatomists, physiologists, endoscopists, and pathologists. Physiologists define the EGJ as the distal border of the lower esophageal sphincter as determined by manometry. Endoscopically, the EGJ is defined as the proximal margin of the longitudinal gastric mucosal folds [7]. For the distal margin of the cardia, there is no anatomical landmark. The squamocolumnar junction (Z-line) is the endoscopically visible line formed by the juxtaposition of squamous and columnar epithelia, which has been reported to be located 3–10 mm proximal of the anatomically defined EGJ [8–10]. Chandrasoma and coworkers define the esophagogastric junction histologically as the proximal limit of the oxyntic (gastric fundus) mucosa [11]. The maximal length of the cardiac mucosa and oxyntocardiac mucosa, where the cardiac glands are distributed, is reported to average 3–15 mm [9, 12, 13], and the maximal length of the squamous epithelium under which the cardiac glands are distributed has been described to average 1–5 mm [9, 12]. The use of the end of the tubular esophagus or proximal limit of the rugal gastric folds to define the esophagogastric junction places it at a point that can be more than 2 cm proximal to the true esophagogastric junction [14]. Therefore, DeMeester and coworkers describe adenocarcinomas of the distal esophagus and "gastric cardia" predominantly as esophageal carcinomas [11].

7.1.2 Different Classification Systems

Most population-based studies of carcinomas of the esophagus and stomach are based on data collected by cancer registries, which currently use the ICD-O subsite classification [15]. ICD-O classifies carcinomas of the esophagogastric junction as esophageal, subsite "lower third," if the majority of the lesion is in the esophagus, and as gastric, subsite "cardia" if the lesion is centered on or just distal to the esophagogastric junction. The fact that the distal extent of the cardia is not defined and the lack of an accurate definition of the cardia itself has resulted in the misclassification of up to 15 % of these cancers [16]. The TNM classification of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) differentiated only between esophageal and stomach cancer up to the sixth edition and did not separately classify adenocarcinoma of the EG junction [17, 18]. This has changed in the actual seventh editions. From this new esophageal classification for AEGJ, cancers whose epicenter is in the esophagogastric junction (EGJ) or within 5 cm of the stomach that extend into the EGJ or esophagus are considered as esophageal cancer, and all other cancers with epicenter in the stomach that is greater than 5 cm distal to the EGJ or within 5 cm of the EGJ but not extending into the cardia are considered as gastric cancer [19].

The definition of the cardia commonly employed in Japan is the area within 2 cm above and below the EGJ [9, 20], and tumors whose center is in this area are considered to be cancer of the cardia; such tumors are distinguished from upper gastric cancers.

The Liverpool classification of the esophagogastric junction was proposed in 1999 based on the clinico-epidemiological features of over 15,000 carcinomas of the esophagus and stomach [16]. In this classification, the site of the esophagogastric junction is represented by the proximal extent of the gastric rugae [21], and carcinomas involving the EG junction are classified as esophageal carcinomas, subsite esophagogastric junction. Carcinomas located exclusively in the esophagus and not involving the junction are classified as esophageal, subsite lower third. Carcinomas in the region of the stomach close to the esophagus and not involving the junction are classified as stomach, subsite proximal. Carcinomas which involve the proximal and distal subsites of the stomach

are classified as overlapping, even if they extend to the junction.

A topographical classification of these carcinomas was proposed by Ellis and coworkers [22–24]. Carcinomas of the cardia in this classification system are defined as a tumor arising in the upper third of the stomach and involving the esophagogastric junction and the lower esophagus. Adenocarcinomas in Barrett's esophagus are not included even though they may involve the EG junction.

To the present day, none of these different classification systems are internationally accepted.

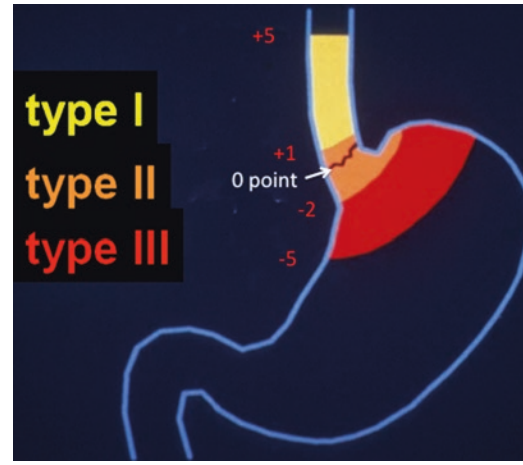

Fig. 7.1 Siewert classification of adenocarcinomas of the esophagogastric junction. *Type I*: tumor center 1 cm above to 5 cm above the cardia (zero point). *Type II*: tumor center 1 cm above to 2 cm below the cardia (zero point). *Type III*: tumor center 5 cm below to 2 cm below the cardia (zero point)

7.2 The Siewert Classification of Adenocarcinoma of the EGJ

In order to clarify the definition of cancer of the esophagogastric junction and design the therapeutic strategy, Siewert and colleagues published a topographic-anatomic subclassification of adenocarcinomas of the EGJ in 1987 [25]. This classification was approved at the consensus meetings of the International Society of Diseases of the Esophagus in 1995 and the International Gastric Cancer Association in 1997 [26].

7.2.1 Definition and Topographical Classification

The Siewert classification is purely based on the anatomic localization of the tumor center, which can be defined by endoscopy using the proximal end of the longitudinal gastric mucosa folds as a pragmatic reference for the endoscopic cardia (zero point). The AEGJ includes all tumors 5 cm proximal (+5 cm) and distal (−5 cm) of the endoscopic cardia (point zero). Adenocarcinomas of the distal esophagus and subcardial gastric carcinomas are only included if they infiltrate the anatomical cardia. Based on this definition, carcinomas of the esophagogastric junction can be classified as three different types according to their location (Fig. 7.1).

Type I tumor (Fig. 7.2)
An adenocarcinoma of the distal esophagus (center >1 cm to +5 cm), which usually arises from an area of specialized intestinal metaplasia (Barrett's esophagus) is classified as a type I cancer.

Type II tumor (Fig. 7.3)
A true carcinoma of the cardia is a type II cancer (center +1 cm to −−2 cm) that develops immediately at the esophagogastric junction. It can arise from the cardiac mucosa or from short segments with intestinal metaplasia at the esophagogastric junction.

Type III tumor (Fig. 7.4)
A type III cancer (center −2 cm to −5 cm) is a subcardial gastric carcinoma that infiltrates the esophagogastric junction or the distal esophagus from below. The difference to a "pure" proximal gastric cancer is the infiltration of the cardia ± distal esophagus.

7.2.2 Diagnosis

Since the assignment of these tumors to the three different types is morphological, based on the anatomic localization of the tumor center, the

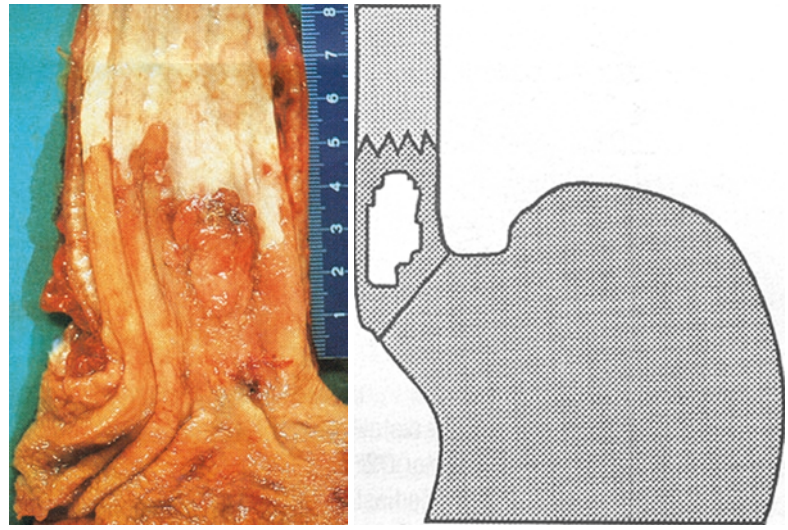

Fig. 7.2 Macroscopic appearance of type I adenocarcinoma of the esophagogastric junction

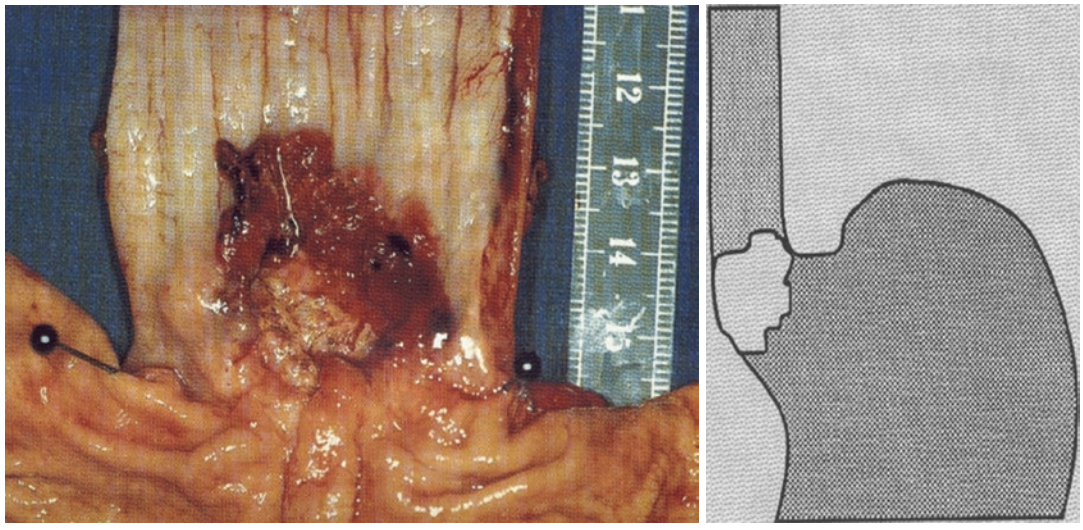

Fig. 7.3 Macroscopic appearance of type II adenocarcinoma of the esophagogastric junction

best way to assign adenocarcinomas of the EG junction to one of these three types is based on a combination of endoscopical and radiological examinations. Esophagogastroscopy must be performed in the prograde as well as retrograde view to localize the major part of the tumor. Modern CT scans can also be helpful for the assignment of the tumor type, whereas contrast radiography as also suggested by the authors is nowadays practically not performed to answer this question [26, 27]. The stringent classification of AEGJ poses some problems. Particularly locally advanced tumors obliterate the EGJ, making it difficult to tell whether they originated above or below the junction. For these cases, Siewert suggests to use the location of the major tumor mass. After all, the final assignment to one of the three types must be reconfirmed intraoperatively and on the resected specimen, and if necessary, the preoperative assignment has to be revised.

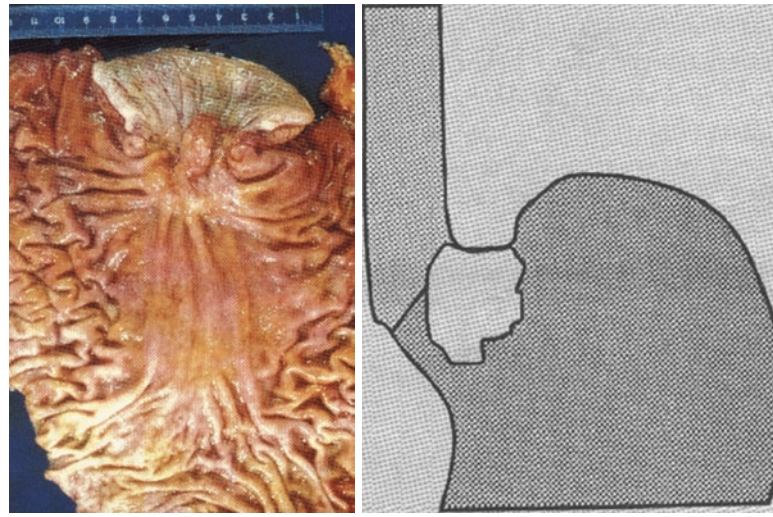

Fig. 7.4 Macroscopic appearance of type III adenocarcinoma of the esophagogastric junction

7.2.3 Epidemiological, Morphological, and Biological Differences

Although all AEGJ share a number of common epidemiological and morphological features, a series of observations in the literature following the introduction of the Siewert classification may provide arguments for a biological justification a posteriori [26].

Epidemiological data from surgical studies using Siewert's classification show marked differences in sex distribution, presence of intestinal metaplasia (Barrett's mucosa), Laurén's type, and degree of differentiation (WHO grading) between types I–III [28].

In a series of 1346 patients with AEGJ, a preponderance of male patients with type I tumors compared to type II or III carcinomas was detected [29, 30]. The presence of intestinal metaplasia (Barrett's epithelium) adjacent to the tumor could be demonstrated in 77 % of type I tumors but only in 10 % of type II and 2 % of type III tumors. More than 80 % of type I carcinomas showed a so-called intestinal growth pattern according to the Laurén classification, whereas more than 60 % of type III cancers had a diffuse growth pattern, and more than 70 % of these type III tumors were also undifferentiated G3/G4 types [28].

The proportion of HER2/neu positivity in type II tumors has recently been shown to be higher than in type I or III tumors [31].

7.2.4 Lymphatic Drainage and Metastases

One major aspect of the current discussion concerning the choice of the surgical procedure in patients with AEGJ is the adequate extent of lymphadenectomy. Lymph node dissection should be based on the knowledge of the lymphatic system draining these regions, the actual incidence of lymph node metastases, and the effect on survival.

In a microscopic analysis of AEGJ, Siewert et al. reported that invasion of lymph nodes by type I tumors was less frequent than in type II and III tumors and was associated with prognosis [28, 32]. This difference in lymph vessel involvement between type I and type II/III carcinomas led to the hypothesis that a chronic inflammatory process in type I tumors leads to a degeneration/obliteration of lymphatic vessels over time, and therefore lymphatic spread is reduced or delayed in type I compared to type II/III tumors. However, these comparisons have not been shown for the different T categories but only for the type I compared to type II/III entities.

Akiyama et al. showed that in squamous cell esophageal cancer, the distribution of lymph node metastases is widespread in the area between the superior mediastinum and the celiac region and therefore proposed lymph node dissection of the whole length of the posterior mediastinum, superior gastric region, and celiac region [33]. Aikou et al., however, reported a low frequency of 6.6 % in lymph node metastases above the tracheal bifurcation in type I and 0 % in type II tumors [34]. Griffin et al. found a low incidence of cervical recurrence after radical esophagectomy with two-field lymphadenectomy in patients with adenocarcinoma of the esophagus [35].

These results are challenged by two groups applying extensive 3-field lymphadenectomy of the abdominal, mediastinal, and cervical nodes. Altorki found metastases in the cervical lymph nodes in 27 % of patients with adenocarcinoma of the lower esophagus after three-field lymphadenectomy [36]. Lerut et al. reported lymphatic spread to cervical nodes in 26 % of patients with adenocarcinoma of the lower esophagus and 18 % of patients with adenocarcinoma of the esophagogastric junction (Siewert type I and II) after three-field lymphadenectomy [37, 38]. These results indicate that tumor cells of type I and II tumors can spread to the mediastinal and even cervical lymph nodes as well as toward the abdominal stations. Contrary to type I carcinomas, type II and type III carcinomas showed lower rates of lymphatic spread to the mediastinum and higher rates to abdominal compartments I and II [39]. Lymphoscintigraphic studies are in favor of the latter study [40]. Tachimori et al. found lymph node involvement in the lower mediastinum in 19 % of patients with adenocarcinoma of the cardia involving the esophagus (type II), and Wang et al. reported lymph node metastases of the inferior paraesophageal region in 18 % of patients with cardia carcinoma [41, 42]. In our Cologne series [43], the incidence of lower mediastinal lymph node metastases in type II and III carcinomas was 11 %, respectively, 13 % and similar to the 10 % reported by Aikou and Shimazu [34]. In summary, type I cancer appears to display more frequent lymph node involvement at the area of the tracheal bifurcation and in the upper mediastinum compared to types II and III. On the other hand, in type II and III carcinomas, lymph node metastases are more frequently found in the lower mediastinum and in the area of the celiac trunk. Thus, there appear to be differences in the distribution pattern of lymph node metastases between type I and type II/III tumors, whereas this is similar in types II and III.

7.2.5 Differences in Prognosis

Long-term survival analysis (Fig. 7.5) showed a markedly better prognosis for patients with type I carcinoma than patients with type II and III carcinomas, with type III showing the worst prognosis [28]. Siewert explains the particular poor prognosis for type III tumors with the high prevalence of diffuse type according to Laurén and poor differentiation (G3/G4) and the frequent presence of lymphatic spread in type III

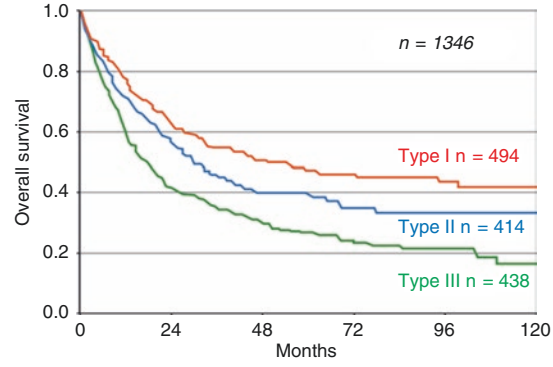

Fig. 7.5 Survival rates for AEGJ I–III (modified from Siewert et al. [44])

cancers. In contrast, Yuasa et al. from Japan described higher rate of lymph node metastases, an increased risk of hepatic recurrence, and a lower 5-year survival in type II compared with type III tumors [45]. These comparisons were, however, not performed between T categories but only between the tumor entities. The group from the Seoul National University reviewed 497 AEGJ Siewert type II/III and 4027 gastric cancers (GC) treated from 2003–2009 and demonstrated that the prognosis of AEGJ was similar to that of GC. There was no difference in clinicopathologic features between AEGJ II and III. Even though AEJ extending into the EGJ (AEJe) showed more advanced pathologic features than AEJ not extending into the EGJ (AEJg), the prognosis of AEJe and AEJg was not significantly different when stratified by T stage. Compared with the classification of gastric cancer applied for AEGJ, esophageal classification for AEGJ from the seventh AJCC TNM classification showed a loss of distinctiveness at each TNM stage. The authors conclude that AEGJ II and III tumors should be considered a part of gastric cancer staging in the future irrespective of EGJ involvement [46].

7.2.6 Therapeutic Consequences of Siewert's Classification

The Siewert classification of AEGJ was introduced as a "therapeutically relevant classification." This topic will be also dealt within in chap. 14 about treatment options and indications. The aim of the surgical therapy of AEGJ is the complete resection (R0-resection) of the primary tumor and an adequate lymphadenectomy. A type I adenocarcinoma clearly represents a distal esophageal cancer and is consequently best treated by an abdomino-thoracic en bloc esophagectomy with 2-field lymphadenectomy. A randomized controlled Dutch trial has demonstrated that transthoracic esophagectomy leads to better overall survival than the transhiatal approach for type I tumors. This survival difference is significant, if ≤ 8 lymph node metastases are present [47, 48]. In a subgroup analysis based on the Siewert classification, the advantage in 5-year overall survival with the transthoracic approach versus the transhiatal approach was as large as 14 % for type I patients ($n = 90$) and 4 % for type II patients ($n = 115$) [48]. Due to an inadequate sample size, this study could not show any statistically significant differences, but the results strongly suggest that thorough mediastinal dissection via a right thoracotomy is necessary for Siewert type I but not for type II tumors. However, significant debate is still ongoing about the best surgical approach for type II.

A randomized trial from the Japan Clinical Oncology Group showed that there was no survival benefit for the left thoracoabdominal approach (LTA) for type II/III carcinomas compared to the transhiatal extended gastrectomy (TH) approach. Subgroup analysis showed no survival benefit for Siewert type II patients with the transthoracic approach. The transhiatal approach, however, was associated with a better survival than the transthoracic approach for type III tumors. This trial was closed after the first interim analysis, and the authors concluded that LTA does not improve survival compared to TH and leads to increased morbidity in patients with cancer of the cardia or subcardia. Therefore, LTA cannot be justified to treat these tumors [49, 50]. Yamashita et al. [50] retrospectively analyzed the optimal extent of lymph node dissection in 225 Siewert type II cancers. Their data suggest that extensive mediastinal lymph node dissection via thoracotomy offers no survival benefit over periesophageal node clearance alone by the transhiatal approach. In addition, nodal recurrence was most frequently observed in the para-aortic nodes and less frequent in the mediastinal nodes in their series. This is in line with the anatomical location of type II and III tumors since there are associated retroperitoneal lymphatics, which drain to the supra- and infrapancreatic nodes and nodes at the left renal vein [51]. Furthermore, type II EGJ carcinomas show a different biological behavior from gastric carcinomas and are strongly associated with microscopic hematogenous dissemination of the tumor [50].

Similar results were obtained in a multicenter trial in France [52] showing that for type II carci-

noma, extended total gastrectomy was superior to esophagectomy.

All current evidence suggests that type III tumors are best treated by transhiatal extended gastrectomy with distal esophageal resection [51] and should be staged as gastric cancers [46]. The transhiatal approach can sometimes lead to difficulties in obtaining sufficient margins if the tumor has invaded the distal esophagus 3 cm or more beyond the EGJ [53]. This situation is aggravated if a diffuse-type tumor is present and for those rare cases esophagogastrectomy is the procedure of choice.

7.2.7 Criticism

Despite the recommendation of this classification by the International Society for Diseases of the Esophagus in 1995 and International Gastric Cancer Association in 1997, there is an ongoing scientific debate. Some of this recurring criticism must be taken seriously. The "zero reference point" somehow changed over time as the end of the longitudinal gastric folds as a pragmatic reference point to define the cardia (zero point) was not mentioned in the 1987 inaugural publication [25] but was later added in 1998 [26]. One of the serious issues with respect to this classification is the lack of a formal validation process which cannot be replaced by expert consensus commissions. Grotenhuis et al. [54] have demonstrated that the overall accuracy in predicting tumor location according to the Siewert classification was 70 % for endoscopy/endoscopic ultrasound (EUS) and 72 % for CT. Preoperative data could not be compared with the pathologic assessment in 22 %, as large tumors obscured the landmark of the gastric folds. The authors conclude that given the frequent discrepancy between the endoscopic and pathologic location of the EGJ and the common problem of advanced tumors obscuring the landmarks used in the assessment of the Siewert classification, its usefulness is limited.

This is further aggravated as there are no prospective validation studies available with respect to the stability of the classification system before and after neoadjuvant chemotherapy or chemoradiation therapy which is meanwhile standard of care for locally advanced tumors. Furthermore, as Siewert and colleagues pointed out, the preoperative classification has to be reevaluated and confirmed intraoperatively and finally by histopathology. With the increasing use of hybrid and completely minimally invasive procedures, the surgical treatment strategy has to be defined before and not intraoperatively as in open surgery where a change from a transhiatal approach to an abdomino-thoracic approach is possible. Furthermore, the "biological justification" a posteriori of this pragmatic surgical classification is somehow arbitrary, and differences as claimed by Siewert and colleagues have been challenged. In a recent Korean study, there were no clinical or histopathologic differences between AEGJ Siewert types II and III observed, and after stratification for the T-category, no survival differences were present [46].

Conclusions

In summary, the Siewert classification of adenocarcinoma of the EG junction originally proposed in 1987 is still the most frequently used classification system both in the Western and Eastern hemispheres. Whereas the suggested types I and III are generally accepted with respect to their different biology and therapeutic approach, the type II is a matter of ongoing debate. Despite serious and justified criticism, the Siewert classification enormously stimulated the scientific discussion in our common goal for the best therapeutic approach in AEGJ and will surely be around until replaced by a better classification system which is yet to be defined.

References

1. Schneider PM (2010) Preface. The Siewert Lesson for Adenocarcinomas of the esophagogastric junction: a plea for an order in a complex disease. Recent Results Cancer Res 182:vii–viii
2. Bollschweiler E, Wolfgarten E, Gutschow C, Hölscher AH (2001) Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. Cancer 92:549–555
3. Bollschweiler E, Wolfgarten E, Nowroth T, Rosendahl U, Mönig SP, Hölscher AH (2002) Vitamin intake and

risk of subtypes of esophageal cancer in Germany. J Cancer Res Clin Oncol 128:575–580
4. Devesa SS, Blot WJ, Fraumeni JF Jr (1998) Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 83: 2049–2053
5. Sharma R, Samantaray S, Shukla NK, Ralhan R (2003) Transcriptional gene expression profile of human esophageal squamous cell carcinoma. Genomics 81:481–488
6. Marsman WA, Tytgat GN, ten Kate FJ, van Lanschot JJ (2005) Differences and similarities of adenocarcinomas of the esophagus and esophagogastric junction. J Surg Oncol 92:160–168
7. Ectors N, Driessen A, de Hertog G, Lerut T, Geboes K (2005) Is adenocarcinoma of the esophagogastric junction or cardia different from Barrett adenocarcinoma? Arch Pathol Lab Med 128:183–185
8. Bombeck CT, Dillard DH, Nyhus LM (1966) Muscular anatomy of the gastroesophageal junction and role of phrenoesophageal ligament: autopsy study of sphincter mechanism. Ann Surg 164:643–654
9. Misumi A, Murakami A, Harada K, Baba K, Akagi M (1989) Definition of carcinoma of the gastric cardia. Langenbecks Arch Chir 374:221–226
10. Takubo K, Sawabe M, Esaki Y (1995) Pathology of the esophagogastric junction. Dig Endosc 7:479–488
11. Chandrasoma P, Wickramasinghe K, Ma Y, DeMeester T (2007) Adenocarcinomas of the distal esophagus and "gastric cardia" are predominantly esophageal carcinomas. Am J Surg Pathol 31:569–575
12. Ogawa M, Inui T, Shimoda T et al (2001) Pathology of the gastroesophageal junction in Japanese. Stomach Intestine 36:625–633
13. Sarbia M, Donner A, Gabbert HE (2002) Histopathology of the gastroesophageal junction: a study on 36 operation specimens. Am J Surg Pathol 26:1207–1212
14. Chandrasoma P, Makarewicz K, Wickramasinghe K, Ma Y, Demeester T (2006) A proposal for a new validated histological definition of the gastroesophageal junction. Hum Pathol 37:40–47
15. Percy C, Holten VV, Muir C (1990) ICD-O, 2nd edn. WHO, Geneva
16. Dolan K, Sutton R, Walker SJ, Morris AL, Campbell F, Williams EMI (1999) New classification of oesophageal and gastric carcinomas derived from changing patterns in epidemiology. Br J Cancer 80:834–842
17. American Joint Committee on Cancer (2002) Cancer staging manual. 6th ed. AJCC, Springer Verlag, Berlin, Heidelberg, New York.
18. Sobin LH, Wittekind C (eds) (2002) International Union against cancer. TNM classification of malignant tumors. Wiley-Blackwell, New York
19. Sobin LH, Gospodarowicz MK, Wittekind CH (ed) (2009) TNM classification of malignant tumours, 7th ed. Wiley-Blackwell, Oxford
20. Nishi M, Kajisa T, Aiko T, Kaneko Y, Kawaji T et al (1973) The proposal of carcinoma of gastric cardia. Gekarinshou 15:1328–1338
21. McClave SA, Boyce HW Jr, Gottfried MR (1987) Early diagnosis of columnar-lined esophagus: a new endoscopic diagnostic criterion. Gastrointest Endosc 33:413–416
22. Ellis FH (1980) Esophagogastrectomy for carcinoma technical considerations based on anatomic location of the lesion. Surg Clin North Am 60:265–279
23. Ellis FH, Maggs PR (1981) Surgery for carcinoma of the lower esophagus and cardia. World J Surg 5:527–533
24. Ellis FH, Gibb SP, Watkins E (1988) Limited esophagogastrectomy for carcinoma of the cardia: indications, technique and results. Ann Surg 208:354–360
25. Siewert JR, Hölscher AH, Becker K, Gössner W (1987) Kardiakarzinom: Versuch einer therapeutisch relevanten Klassifikation. Chirurg 58:25–32
26. Siewert JR, Stein HJ (1998) Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg 85:1457–1459
27. Cordin J, Lehmann K, Schneider PM (2010) Clinical staging of adenocarcinoma of the esophagogastric junction. Recent Results Cancer Res 182:73–83
28. Siewert JR, Feith M, Stein HJ (2005) Biologic and clinical variations of adenocarcinoma at the esophagogastric junction. relevance of a topographic-anatomic subclassification. J Surg Oncol 13:139–146
29. Nakamura T, Ide H, Eguchi R, Ota M, Shimizu S, Isono K (2002) Adenocarcinoma of the esophagogastric junction: a summary of responses to a questionnaire on adenocarcinoma of the esophagus and the esophagogastric junction in Japan. Dis Esophagus 15:219–225
30. Siewert JR, Feith M, Werner M, Stein HJ (2000) Adenocarcinoma of the esophagogastric junction. Ann Surg 232:353–361
31. Schoppmann SF, Jesch B, Friedrich J, Wrba F, Schultheis A, Pluschnig U, Maresch J, Zacherl J, Hejna M, Birner P (2010) Expression of Her-2 in carcinomas of the esophagus. Am J Surg Pathol 34(12): 1868–1873
32. von Rahden BH, Stein HJ, Feith M, Becker K, Siewert JR (2005) Lymphatic vessel invasion as a prognostic factor in patients with primary resected adenocarcinomas of the esophagogastric junction. J Clin Oncol 23:874–879
33. Akiyama H, Tsurumaru M, Kawamura T, Ono Y (1981) Principles of surgical treatment for carcinoma of the esophagus: analysis of lymph node involvement. Ann Surg 194:438–446
34. Aikou T, Shimazu H (1989) Difference in main lymphatic pathways from the lower esophagus and gastric cardia. Jpn J Surg 19:290–295
35. Griffin SM, Chung SC, Woods SD, Li AK (1990) Adenocarcinoma of the cardia: treatment by thoracoabdominal R3 radical gastrectomy. Br J Surg 77:937–939
36. Altorki K, Skinner DB (1997) Occult cervical nodal metastasis in esophageal cancer: preliminary results of three field lymphadenectomy. J Thorac Cardiovasc Surg 113:540–544
37. Lerut T (1998) Esophageal surgery at the end of the millennium. J Thorac Cardiovasc Surg 116:1–20
38. Lerut T, Nafteux P, Moons J, Coosemans W, Decker G, de Leyn P, van Raemdonck D, Ectors N (2004)

Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome. Ann Surg 240:962–974
39. Dresner SM, Lamb PJ, Bennett MK, Hayes N, Griffin SM (2001) The pattern of metastatic lymph node dissemination from adenocarcinoma of the esophagogastric junction. Surgery 129:103–109
40. Cense HA, Sloof GW, Jlaase JM, Bergman JJ, van Hemert FJ, Fockens P, van Lanschot JJ (2004) Lymphatic drainage routes of the gastric cardia visualized by lymphoscintigraphy. J Nucl Med 45:247–252
41. Tachimori Y, Kato H, Watanabe H, Sasako M, Kinoshita T, Maruyama K (1996) Difference between carcinoma of the lower esophagus and the cardia. World J Surg 20:507–510
42. Wang LS, Wu CW, Hsieh MJ, Fahn HJ, Huang MH, Chien KY (1993) Lymph node metastasis in patients with adenocarcinoma of gastric cardia. Cancer 71:1948–1953
43. Mönig SP, Baldus SE, Zirbes TK, Collet PH, Schröder W, Schneider PM, Dienes HP, Hölscher AH (2002) Topographical distribution of lymph node metastasis in adenocarcinoma of the gastroesophageal junction. Hepatogastroenterology 49:419–422
44. Siewert JR, Feith M (2007) Adenocarcinoma of the esophagogastric junction: competition between Barrett and gastric cancer. J Am Coll Surg 205(4 Suppl):49–53
45. Yuasa N, Miyake H, Yamada T, Ebata T, Nimura Y, Hattori T (2006) Clinicopathologic comparison of Siewert type II and III adenocarcinomas of the gastroesophageal junction. World J Surg 30: 364–371
46. Suh YS, Han DS, Kong SH, Lee HJ, Kim YT, Kim WH, Lee KU, Yang HK (2012) Should adenocarcinoma of the esophagogastric junction be classified as esophageal cancer? A comparative analysis according to the seventh AJCC TNM classification. Ann Surg 255(5):908–915
47. Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, Stalmeier PF, ten Kate FJ, van Dekken H, Obertop H, Tilanus HW, van Lanschot JJ (2002) Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 347:1662–1669
48. Omloo JM, Lagarde SM, Hulscher JB, Reitsma JB, Fockens P, van Dekken H, Ten Kate FJ, Obertop H, Tilanus HW, van Lanschot JJ (2007) Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg 246:992–1000
49. Sasako M, Sano T, Yamamoto S, Sairenji M, Arai K, Kinoshita T, Nashimoto A, Hiratsuka M, Japan Clinical Oncology Group (JCOG9502) (2006) Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. Lancet Oncol 7:644–651
50. Yamashita H, Katai H, Morita S, Saka M, Taniguchi H, Fukagawa T (2011) Optimal extent of lymph node dissection for Siewert type II esophagogastric junction carcinoma. Ann Surg 254(2):274–280
51. Schiesser M, Schneider PM (2010) Surgical strategies for adenocarcinoma of the esophagogastric junction. Recent Results Cancer Res 182:93–106
52. Sauvanet A, Mariette C, Thomas P et al (2005) Mortality and morbidity after resection for adenocarcinoma of the gastroesophageal junction: predictive factors. J Am Coll Surg 201:253–262
53. Kurokawa Y, Sasako M, Doki Y (2013) Treatment approaches to esophagogastric junction tumors. Dig Surg 30(2):169–173
54. Grotenhuis BA, Wijnhoven BP, Poley JW, Hermans JJ, Biermann K, Spaander MC, Bruno MJ, Tilanus HW, van Lanschot JJ (2013) Preoperative assessment of tumor location and station-specific lymph node status in patients with adenocarcinoma of the gastroesophageal junction. World J Surg 37(1):147–155

8 Preoperative Work-Up: Conventional Radiology, CT Scan, Ultrasonography, and MRI

Angela M. Riddell

8.1 Conventional Radiology

Barium Swallow

The initial investigation of choice for patients with dysphagia or suspected gastroesophageal reflux disease is upper gastrointestinal endoscopy as it offers an opportunity for biopsy and a definitive diagnosis at the time of investigation, either by demonstrating the presence of esophagitis or providing specific pathologic identification of the obstructive lesion. Fluoroscopy in the form of a barium swallow is still frequently performed as part of the initial investigation for patients with upper gastrointestinal (GI) symptoms of dysphagia, dyspepsia, and heartburn. The investigation identifies most anatomic causes of dysphagia and some motor disorders and is better than endoscopy at identifying extrinsic esophageal compression and intramural lesions not involving the esophageal mucosa. The demonstration of a stricture within the esophagus should trigger further investigation with endoscopy for both diagnostic and therapeutic purposes. Malignant strictures tend to be longer and irregular in contour with "shouldering" at the superior and inferior margins (Fig. 8.1). Smooth tapering strictures at the distal end of the esophagus are characteristic of achalasia. More subtle changes such as mucosal irregularity or nodularity are somewhat nonspecific but may be associated with Barrett's esophagus or superficial spreading tumors. Complications related to locally advanced tumors such as tracheoesophageal fistula can be readily demonstrated on a barium study.

Technique: The optimum technique is the double-contrast technique where the esophagus is coated with barium and then distended to demonstrate regions of luminal narrowing. The volume of barium solution given varies but is generally 100–300 ml. This is given in combination with an effervescent agent. A smooth muscle relaxant such as scopolamine butylbromide (20 mg, via intramuscular injection) can also be administered to help maintain gastric distension. This however affects gastric motility and may hamper diagnosis of motility disorders so should not be used routinely.

8.2 Multi-detector Computed Tomography (MDCT)

Multi-detector computed tomography (MDCT) is the cornerstone for the initial staging of esophageal cancer. It enables assessment of the extent of local disease and detects the presence of regional lymph nodes and metastatic disease. Thus, it offers a robust method for stratifying patients into those who are potentially suitable

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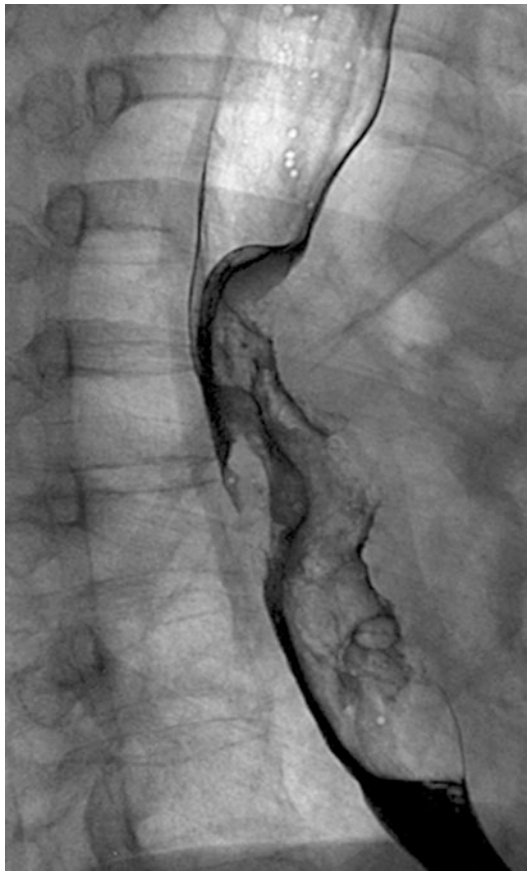

Fig. 8.1 This image from a double-contrast barium swallow shows an irregular malignant appearing stricture within the lower esophagus

for radical therapy with curative intent or those who have advanced disease and are appropriate for palliative therapy.

Technique: With multi-detector scanning technology, it is possible to achieve high spatial resolution. This generates isotropic voxels enabling post-processing in multiple planes. As a consequence, the relationship of the tumor to surrounding structures within the posterior mediastinum can be fully evaluated. A standard protocol for staging will position the patient supine and include imaging from the lower cervical region (including the supraclavicular lymph nodes) to the iliac crests. CT of the pelvis is often included in a staging protocol, but research has shown that it does not alter tumor staging [1]. Imaging is performed following the administration of intravenous iodinated contrast medium with the scan acquisition timed to obtain imaging of the liver during the portal venous phase to optimize the identification of liver metastases. Water as a negative oral contrast is also used to help distend the stomach, aiding visualization of the gastroesophageal junction.

A standard MDCT protocol should generate reconstructions of the source data with a slice thickness of 3–5 mm in multiple planes. The craniocaudal extent of tumor can be best appreciated and measured on a sagittal reformat, and coronal imaging is often useful for evaluation of tumors at the gastroesophageal junction, demonstrating the extent of the disease located above and below the diaphragmatic hiatus.

T Staging

The value of computed tomography (CT) lies mainly in the exclusion of metastatic disease and the detection of locally advanced cancer, determined by the extent of infiltration of tumor beyond the esophageal wall (T3 disease) or invasion of surrounding structures (T4 disease). Due to the lack of inherent soft tissue contrast, tumor confined to the esophageal wall cannot be distinguished from surrounding normal tissue, preventing accurate staging of early disease. T staging is determined by surrogate measures, namely, the thickness of the wall of the distended esophagus, the appearance of the outer margin of the wall, and the extent of any contact between the wall of the diseased esophagus and surrounding structures. The thickness of the normal esophageal wall when the esophagus is mildly distended should not exceed 3 mm. The T staging according to wall thickness and appearance of the outer wall is given in Table 8.1.

Some studies have shown that the addition of dual phase CT scanning, both in the arterial

Table 8.1 MDCT T staging stratified by the thickness and appearance of the esophageal wall

T stage	Wall thickness	Wall contour
T1/T2	>3 mm, <5 mm	Smooth
T3	5–15 mm	Irregular
T4	>15 mm	Contact with adjacent structure

and portal venous phase, enables identification of early tumors confined to the inner layers of the esophageal wall. The tumor appears as a region of increased contrast enhancement on the arterial phase series [2]. This technique may help to differentiate T1 from T2 tumors. However, if a standard single portal venous phase study is used, it is not possible to reliably differentiate between these early disease stages. For tumors confined within the muscularis propria layer (up to T2 disease), the outer margin of the esophageal wall will remain smooth (Fig. 8.2). Any irregularity of the outer margin indicates that the tumor has spread beyond the muscularis propria into the periesophageal fat, indicating T3 disease (Fig. 8.3). The fat planes with surrounding structures should be preserved, but the extent of periesophageal fat varies between patients, depending upon body habitus.

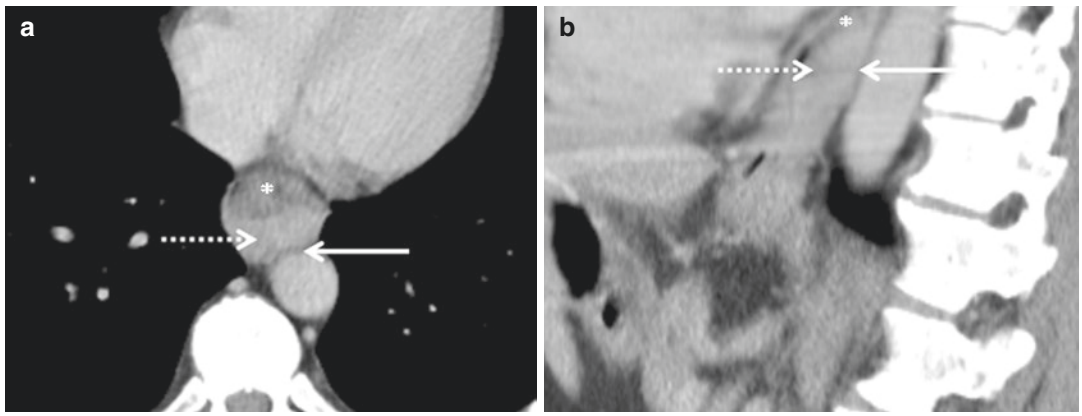

Fig. 8.2 (**a**) Axial and (**b**) sagittal CT image of a pT2N0 tumor. The polypoidal tumor mass (*dashed arrows*) arises from the posterior wall of the esophagus. The outer margin of the wall is smooth with no evidence of extension beyond the muscularis propria on axial or sagittal imaging (*solid arrows*). Fluid is located within the esophageal lumen superior to the tumor (*)

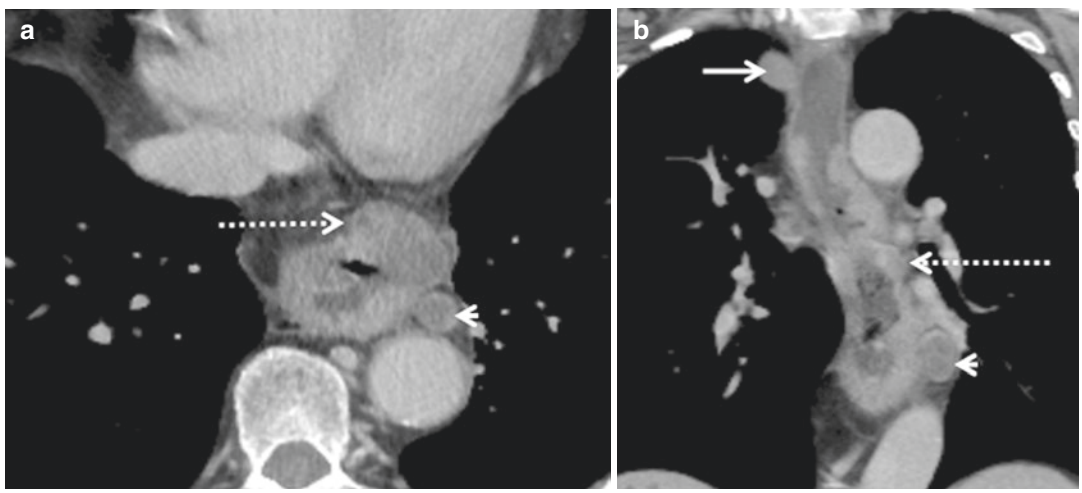

Fig. 8.3 (**a**) Axial and (**b**) coronal CT images showing a T3 tumor with tumor extending beyond the esophageal wall into the periesophageal tissues (*dashed arrows*). There is an involved (>10 mm) periesophageal lymph node demonstrated on both the axial and coronal images (*arrowhead*). A further involved lymph node is demonstrated on the coronal image in the superior mediastinum (*Solid arrow*)

On MDCT, it remains challenging to differentiate tumor abutting an adjacent structure (T3 disease) and direct invasion (T4 disease). Positioning the patient prone or in the decubitus position can result in displacement of the lower esophagus away from the diaphragmatic crura or aorta helping differentiate simple contact between these structures, which can occur when the patient is lying supine, from direct invasion. There are established criteria which predict for invasion into surrounding structures:

- An arc of contact of greater than 90° of the circumference of the descending thoracic aorta is considered to represent invasion of the aortic adventitia (Fig. 8.4) [3].
- Loss of the triangular fat plane between the esophagus, aorta, and spine also indicates aortic invasion [4].
- Tumor contact resulting in inward distortion/displacement of the posterior wall of the left main bronchus or trachea is also considered to represent T4 disease [5].

The identification of soft tissue extending into the tracheal lumen is strong evidence of direct invasion, as is the presence of a tracheoesophageal fistula. Pericardial invasion is suspected if there is focal thickening of the pericardium or a pericardial effusion.

Using these criteria, the sensitivity and specificity for detecting T4 disease has been shown to be between 88–100 % and 85–100 % respectively [3, 6]. Overall, despite the multiplanar capability of MDCT to improve the delineation of extramural disease spread, particularly at the gastroesophageal junction, the lack of inherent soft tissue contrast prevents confident differentiation of tumor from normal surrounding soft tissue. Therefore, in spite of the advances in CT technology, the primary function of CT remains the exclusion of metastatic disease.

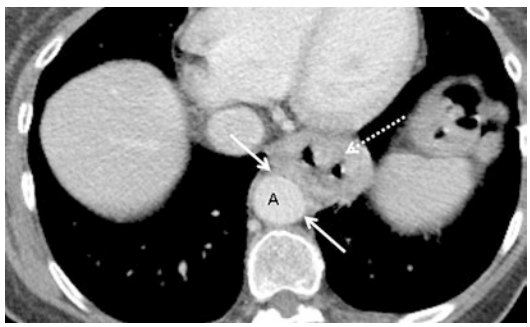

Fig. 8.4 Axial CT image of a bulky, circumferential lower esophageal tumor (*dashed arrow*). The arc of contact with the thoracic aorta (*A*) is almost 180° (*solid arrows*), indicating T4 disease

N Staging

The criteria for nodal involvement on CT are based on size. The majority of published literature uses a short axis diameter of 10 mm as the upper limit for a normal lymph node within the mediastinum (5 mm for the supraclavicular region) (Fig. 8.3). Although many studies use the same cutoff for subdiaphragmatic lymph nodes, other studies use a cutoff of 6–8 mm in the perigastric territories. Using the threshold of 10 mm, CT has a high specificity (60–80 %) but low sensitivity, as micrometastases can be present within lymph nodes below this size. Reactive lymph nodes can also become enlarged to greater than 10 mm. The overall accuracy for nodal staging using CT is 68 % [7].

M Staging

It is crucial that metastatic disease is identified at the earliest opportunity, to prevent patients being inappropriately referred for radical treatment, such as surgery, in the presence of disseminated disease. Distant metastases are present at the time of initial presentation in 20–30 % of patients [8]. MDCT has a high sensitivity and specificity for detecting both liver and pulmonary metastases [9]. The identification of peritoneal disease on CT is more variable. In the presence of ascites, the sensitivity and specificity is 51 % and 97 % respectively [9]. In the absence of ascites, the sensitivity falls to just 30 % [10]. Laparoscopy is still advocated for all patients with tumor extending below the diaphragm who are being considered for radical therapy, as a consequence of this variability in detection of peritoneal disease on CT.

8.3 Ultrasound

Both conventional ultrasound and endoscopic ultrasound (EUS) are used in the evaluation of patients with esophageal cancer. Conventional ultrasound is used for targeted problem-solving and for biopsy or needle puncture of equivocal lesions identified on other imaging modalities. EUS plays an important part in refining the local staging for patients considered potentially operable by MDCT.

8.3.1 Conventional Ultrasound

Linear probes 9–16 MHz can be used for the assessment of cervical lymph nodes. Involved nodes are round rather than elliptical and lose their internal echogenic fatty hilum. These are amenable to fine needle aspiration (FNA) sampling under ultrasound guidance. Studies have shown that with FNA, the test is highly sensitive and specific (100 % and 96 % respectively) [11]. In centers not routinely using PET-CT for primary staging, the addition of cervical ultrasound has been shown to be a cost-effective addition to MDCT for primary staging [12]. Even if PET-CT is performed, ultrasound and FNA sampling under ultrasound guidance has been shown to improve staging by identifying false-positive or -negative PET-CT findings [13, 14].

Ultrasound can also be used in the targeted characterization of focal liver lesions identified on MDCT. However, liver MRI is more sensitive and specific both in terms of lesion detection and characterization and is generally the preferred modality for this purpose.

8.3.2 Endoscopic Ultrasound

This technique offers the optimum method for staging tumors confined within the wall of the esophagus. Using this technique, three to five layers of the esophageal wall can be identified which represent interfaces of ultrasound reflectivity [15].

Technique: A side-viewing endoscope is used with a sonographic transducer at its tip. The ultrasound frequencies range from 7.5 to 12 MHz, giving a maximum depth of view of 7 and 3 cm respectively. The probes provide a 240–360° field of view orthogonal to the plane of the endoscope. It is possible using specific ultrasound probes (curved linear array) to obtain fine needle aspiration (FNA) samples from suspicious lymph nodes, which helps improve the accuracy of nodal staging. In addition, higher-frequency mini-probes are available, which can be used for the evaluation of stenotic tumors, otherwise impossible to pass with a conventional echoendoscope. The mini-probes consist of a cable with a mechanical transducer at its end. The majority of mini-probes use a radial transducer with a frequency range of between 12 and 30 MHz (2.9–1 cm depth of view).

T Staging

The extent of the tumor identified on EUS is classified according to the TNM classification system, dependent upon the depth of tumor invasion into the layers of the esophageal wall (Fig. 8.5). The most recent evaluation of T staging using EUS showed an accuracy of 60 % using the miniprobe [16]. The figures quoted in the literature range from 60 to 91 % for echoendoscopes [7, 17]. The accuracy is acknowledged to fall below these levels following neoadjuvant chemotherapy as it is not possible to differentiate post-treatment fibrosis from residual tumor [18].

N Staging

The morphology of lymph nodes is used for N stage classification. Hyperechoic, heterogeneous, flat, or oval lymph nodes are considered benign; malignant lymph nodes are round, hypoechoic, homogeneous, masses which are more clearly defined than benign nodes [19]. Using specific endoscopic ultrasound probes (curved linear array), it is possible to obtain fine needle aspiration (FNA) samples from suspicious lymph nodes. The procedure however is time-consuming, and the ultrasound probe used is regarded as being less suited to staging than

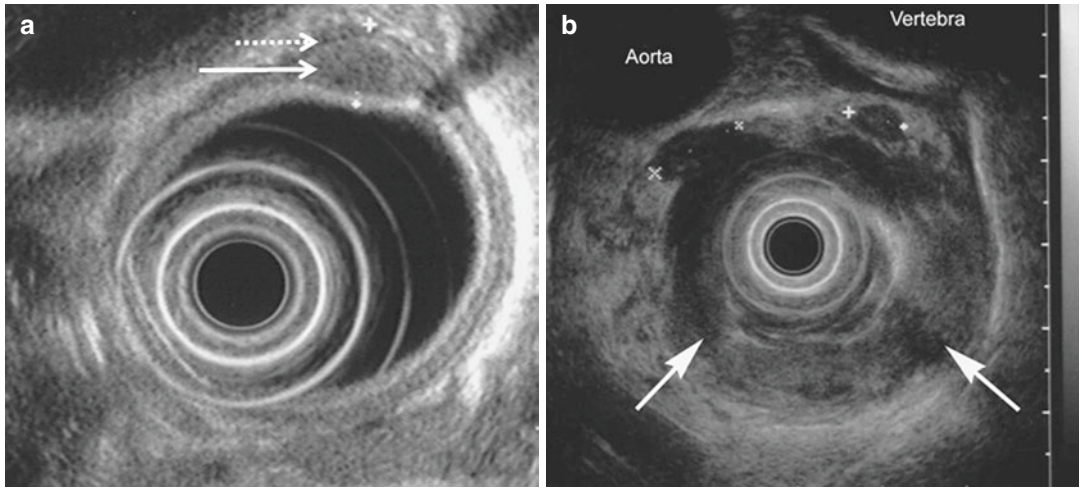

Fig. 8.5 (**a**) EUS image of a T1 tumor (*solid arrow*) confined to the submucosa; the muscularis propria layer (*dotted arrow*) is intact over the outer margin of the tumor. (**b**) A T3 tumor extending through all layers of the esophageal wall, mainly on the anterior and right lateral side (*solid arrows*); note two small reactive lymph nodes marked with calipers

the conventional echoendoscopes with radial ultrasound probes. Therefore patients require an initial staging EUS with a radial probe and a repeat EUS using a linear array probe for the FNA, adding time and complexity to the procedure. This technique is also limited to nodes more distant from the primary tumor, to prevent sample contamination if the needle passes through the primary tumor prior to needle puncture of the lymph node. The accuracy for N staging varies in the literature but is in the order of 74 % [16].

M Staging

EUS has limited value in the assessment of distant metastases. The left lateral segment of the liver and part of the upper retroperitoneum may be evaluated, but the value of the technique lies in its capability for local staging.

8.4 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) currently has a limited role in the staging of esophageal cancer, namely, in the characterization of focal liver lesions identified on MDCT and considered suspicious for metastatic disease. There is an emerging role in the local staging of esophageal cancer.

Technique: A standard protocol is applied for the characterization of liver lesions, including unenhanced T1- and T2-weighted sequences together with diffusion-weighted imaging (DWI). These are supplemented with dynamic and delayed imaging following the administration of intravenous contrast (Fig. 8.6).

For local staging, an external surface coil is used, and high-resolution (thin slice, small field of view) T2-weighted images are acquired which, with the superior soft tissue contrast of MRI, enables demonstration of the individual layers of the esophageal wall. Tumor returns intermediate signal intensity, and the extent of invasion through and beyond the wall can be demonstrated using this technique (Fig. 8.7) [20, 21]. A sagittal sequence through the esophagus is performed to plan axial images, which are acquired perpendicular to the plane of the esophagus. These oblique axial images enable accurate evaluation of the extent of infiltration of tumor through the wall and also the relationship of extramural disease to surrounding structures within the posterior mediastinum.

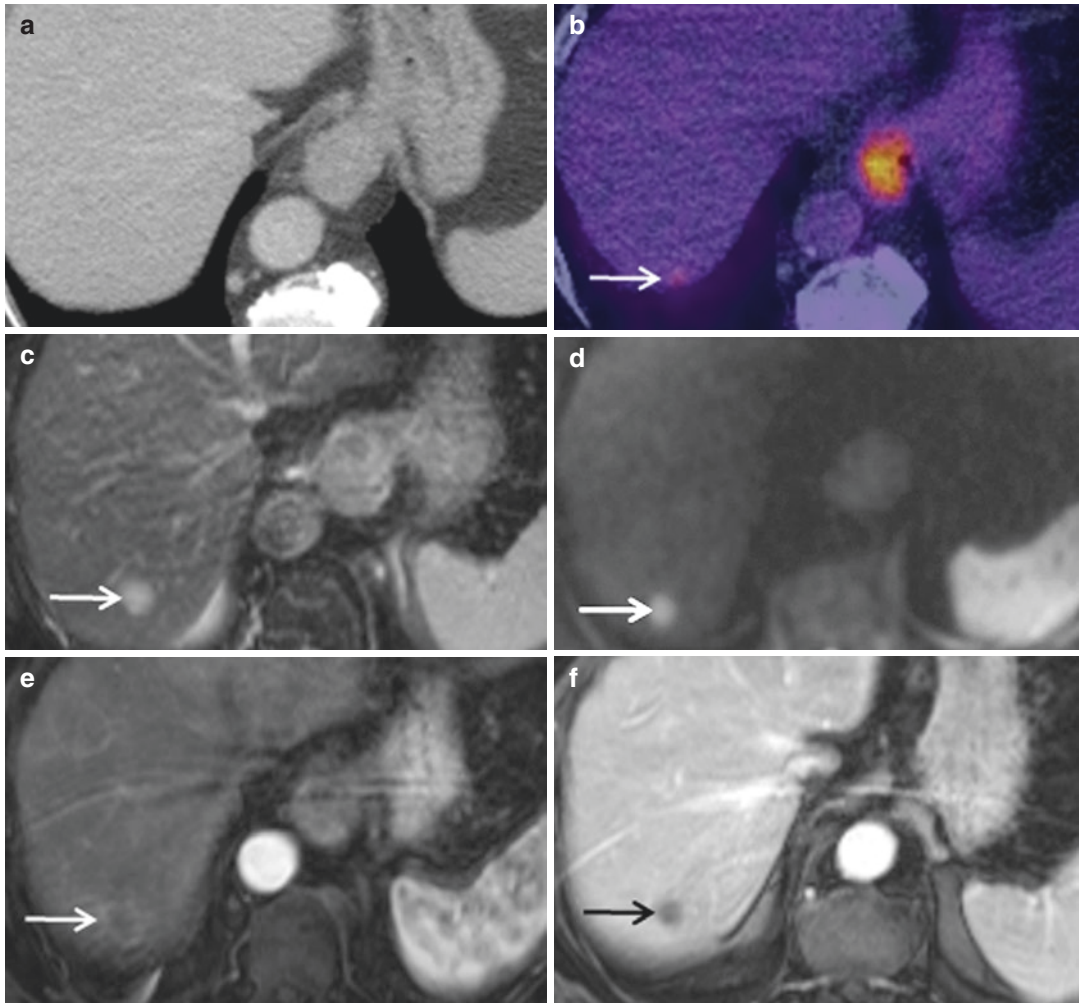

Fig. 8.6 The staging CT (**a**) did not show any focal liver lesions. The PET-CT (**b**) showed a possible lesion in segment VII of the liver (*arrow*). The T2-weighted MRI (**c**) confirmed a focal lesion at this position (*arrow*), which demonstrated restricted diffusion on the b500 sequence (**d**). Post-gadolinium, the lesion showed arterial rim enhancement (*arrow*). (**e**) and low signal on the portal venous phase (*arrow*) (**f**) consistent with a metastasis

Current research protocols include diffusion-weighted imaging. This sequence has been shown to delineate the tumors, and in early studies, the calculated apparent diffusion coefficient (ADC) has been shown to be of value for assessing response to neoadjuvant chemotherapy [22]. The soft tissue contrast provides information regarding the morphology of the tumor. As imaging technology advances, this technique is likely to become more established for both primary staging and in assessment of treatment response.

MRI has also been used for functional evaluation of esophageal motility disorders. Patients undergo MRI during swallowing of clear liquid. The MRI techniques employed use very short acquisition times and a good signal-to-noise ratio (SNR), with strong signal from fluid-filled structures. Studies have shown that using these techniques enables the diagnosis of conditions such as achalasia with a similar accuracy to that of manometry [23, 24].

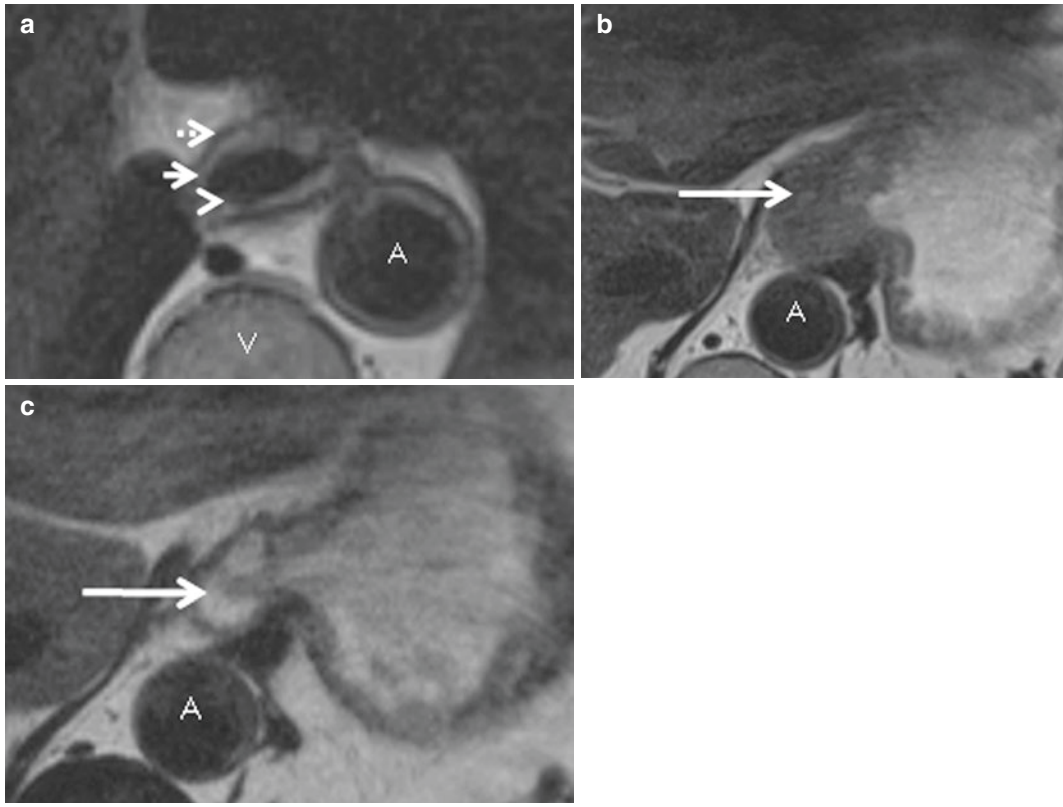

Fig. 8.7 MRI of the normal esophageal wall (**a**) shows the low-signal mucosa (*arrowhead*), high-signal submucosa (*short arrow*), low-signal muscularis propria (*short dashed arrow*). The thoracic aorta (*A*) and vertebral body (*V*) are marked. (**b**) T3 tumor invading all layers of the esophageal wall (*arrow*) (**c**) shows a good response to neoadjuvant chemotherapy; the tumor has reduced in size and now returns high signal, indicating the presence of necrotic tumor or mucin

References

1. Gollub MJ et al (2005) Pelvic CT in patients with esophageal cancer. AJR Am J Roentgenol 184(2):487–490
2. Umeoka S et al (2006) Esophageal cancer: evaluation with triple-phase dynamic CT – initial experience. Radiology 239(3):777–783
3. Picus D et al (1983) Computed tomography in the staging of esophageal carcinoma. Radiology 146(2):433–438
4. Takashima S et al (1991) Carcinoma of the esophagus: CT vs MR imaging in determining resectability. AJR Am J Roentgenol 156(2):297–302
5. Halvorsen RA Jr et al (1986) Esophageal cancer staging by CT: long-term follow-up study. Radiology 161(1):147–151
6. Daffner RH et al (1979) CT of the esophagus. II. Carcinoma. AJR Am J Roentgenol 133(6): 1051–1055
7. Davies AR et al (2006) The multidisciplinary team meeting improves staging accuracy and treatment selection for gastro-esophageal cancer. Dis Esophagus 19(6):496–503
8. Quint LE et al (1995) Incidence and distribution of distant metastases from newly diagnosed esophageal carcinoma. Cancer 76(7):1120–1125
9. Yajima K et al (2006) Clinical and diagnostic significance of preoperative computed tomography findings of ascites in patients with advanced gastric cancer. Am J Surg 192(2):185–190
10. D'Elia F et al (2000) Hydro-dynamic CT preoperative staging of gastric cancer: correlation with pathological findings. A prospective study of 107 cases. Eur Radiol 10(12):1877–1885
11. Cwik G et al (2011) The value of ultrasound in the assessment of cervical and abdominal lymph node metastases and selecting surgical strategy in patients with squamous cell carcinoma of the thoracic esophagus treated with neoadjuvant therapy. Adv Med Sci 56(2):291–298

12. van Vliet EP et al (2007) Detection of distant metastases in patients with oesophageal or gastric cardia cancer: a diagnostic decision analysis. Br J Cancer 97(7):868–876
13. Blom RL et al (2012) External ultrasonography of the neck does not add diagnostic value to integrated positron emission tomography-computed tomography (PET-CT) scanning in the diagnosis of cervical lymph node metastases in patients with esophageal carcinoma. Dis Esophagus 25(6):555–559
14. Omloo JM et al (2009) Additional value of external ultrasonography of the neck after CT and PET scanning in the preoperative assessment of patients with esophageal cancer. Dig Surg 26(1):43–49
15. Botet JF, Lightdale C (1991) Endoscopic sonography of the upper gastrointestinal tract. AJR Am J Roentgenol 156(1):63–68
16. Meister T et al (2013) Miniprobe endoscopic ultrasound accurately stages esophageal cancer and guides therapeutic decisions in the era of neoadjuvant therapy: results of a multicenter cohort analysis. Surg Endosc 27(8):2813–2819
17. Lee WC et al (2015) Staging accuracy of endoscopic ultrasound performed by nonexpert endosonographers in patients with resectable esophageal squamous cell carcinoma: is it possible? Dis Esophagus 28(6):574–578
18. Sun F et al (2015) Staging accuracy of endoscopic ultrasound for esophageal cancer after neoadjuvant chemotherapy: a meta-analysis and systematic review. Dis Esophagus 28(8):757–771
19. Richards DG, Brown TH, Manson JM (2000) Endoscopic ultrasound in the staging of tumours of the oesophagus and gastro-oesophageal junction. Ann R Coll Surg Engl 82(5):311–317
20. Riddell AM et al (2007) The appearances of oesophageal carcinoma demonstrated on high-resolution, T2-weighted MRI, with histopathological correlation. Eur Radiol 17(2):391–399
21. Riddell AM et al (2006) The development and optimization of high spatial resolution MRI for imaging the oesophagus using an external surface coil. Br J Radiol 79(947):873–879
22. De Cobelli F et al (2013) Apparent diffusion coefficient modifications in assessing gastro-oesophageal cancer response to neoadjuvant treatment: comparison with tumour regression grade at histology. Eur Radiol 23(8):2165–2174
23. Panebianco V et al (2006) Initial experience with magnetic resonance fluoroscopy in the evaluation of oesophageal motility disorders. Comparison with manometry and barium fluoroscopy. Eur Radiol 16(9):1926–1933
24. Miyazaki Y et al (2014) Magnetic resonance imaging for simultaneous morphological and functional evaluation of esophageal motility disorders. Surg Today 44(4):668–676

9 Role of PET/CT and MRI in the Prediction of Response to Neoadjuvant Treatment

Daniela Cenzi, Lisa Zantedeschi, Michele Zuffante, Endrit Strazimiri, and Stefania Montemezzi

9.1 Introduction

Carcinoma of the esophagogastric junction (EGJ) is an extremely aggressive malignancy and patients often face a poor prognosis [1, 2].

Even if surgery is still considered the main treatment in patients with EGJ cancer, neoadjuvant chemotherapy or chemoradiation has become an accepted choice for reducing the incidence of local recurrence and improving overall survival rate [3].

However, currently there is no definite standardized imaging method to determine tumor response to chemoradiation. The ideal imaging modality would be able to detect the presence of cancer with high sensitivity and specificity and assess the effect of chemoradiation on tumor burden. It would serve to facilitate the "real-time" evaluation of therapeutic effectiveness with serial scanning, potentially eliminate the need for surgery in complete responders, improve the quality of palliation by stopping chemoradiation in those who progress with therapy, improve prognostication based in tumor response, facilitate the evaluation of new therapies, and enhance the quality of clinical trials [4].

As a matter of fact, for patients who do not respond, the prognosis after neoadjuvant chemotherapy or chemoradiation might be worse than that of a primarily surgical approach. Additionally, inefficient neoadjuvant treatment leads to adverse events, allows tumor progression during therapy, costs time, and increases health expenses. The poor response of tumors (in terms of pathological response and survival) to chemotherapy or chemoradiation suggests the need to predict or identify responders to neoadjuvant therapy at an early stage [5, 6].

Today's stage-dependent treatment relies on modern diagnostic tools such as multidetector helical computed tomography (CT), high-frequency endoscopic ultrasound (EUS), positron emission tomography (PET), image fusion techniques, and magnetic resonance imaging (MRI). Specialists cooperate on multidisciplinary tumor boards that follow transparent decision trees based on the newest evidence [7]. While EUS and CT are of relatively limited value, fluorodeoxyglucose (FDG)-PET (CT) and MRI have demonstrated a potential role in assessing tumor response.

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9.2 PET/CT

Since several years fluorodeoxyglucose (FDG)-PET has become part of the standard of care in staging and restaging of a variety of malignant diseases, focusing on the detection of malignant lesions at early stages and early detection of recurrence and metastatic spread [2, 8].

Metabolic changes measured by PET have been shown to be more sensitive in detecting response early in the course of chemotherapy or chemoradiation as compared with both conventional imaging techniques (EUS and CT) and endoscopy [6].

PET images' metabolic activity, via the distribution of positron emitting tracers that are incorporated into metabolic processes, offers the potential to determine response to treatment for EGJ at an early stage, after only two weeks of induction therapy, because metabolic changes often precede structural changes associated with any given disease (Fig. 9.1) [1, 6].

PET/CT has some limits to determinate the T staging, although tumor invasion into adjacent organs (T4) can sometimes be detected. Another limit of PET, with or without CT, is to recognize locoregional lymph node status: FDG uptake within periesophageal nodes close to the primary tumor is difficult to differentiate from uptake within the esophageal tumor itself due to the limited spatial resolution of PET. Further limiting the interpretation of nodes is the observation that FDG uptake can occur in benign disease such as granulomatous inflammation (e.g., sarcoidosis), aspiration pneumonitis, or other inflammatory/infectious conditions.

A meta-analysis of 12 publications reported a pooled sensitivity and specificity for FDG-PET in determination of N classification of 59 % and 81 %, respectively [9, 10].

However, PET has emerged as an important, increasingly common staging tool, particularly for the detection of distant metastases (Figs. 9.2 and 9.3) [10].

As PET/CT is a whole body imaging technique, we also should keep in mind that it could allow the recognition of other pathological hypermetabolism captation, correlated to the presence of another neoplasm, synchronous or metachronous with EGJ (Fig. 9.4). This could change the choice of treatment for the patient.

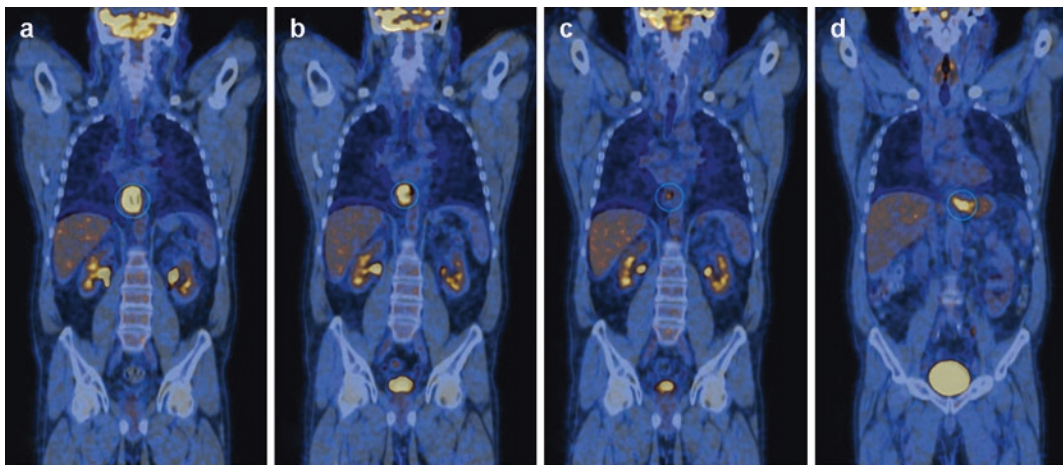


Fig. 9.1 PET/CT staging and re-staging during and after CRT. Case of complete response to CRT in EGJ cancer. (**a**) Staging before treatment. EGJ cancer is well demonstrated with SUVmax 18. No pathologic lymph nodes nor distant metastases are highlighted. (**b**) PET/CT performed the first day after first cycle of induction chemotherapy shows a significant decrease in SUVmax 11.5 (-36%). (**c**) After 3 weeks of chemotherapy an almost complete response to treatment is observed with SUVmax 5,2 (-71%). (**d**) Re-staging 6 week after the end of CRT demonstrates a diffuse increase in metabolic processes due to inflammatory reaction, with SUV max 7.5

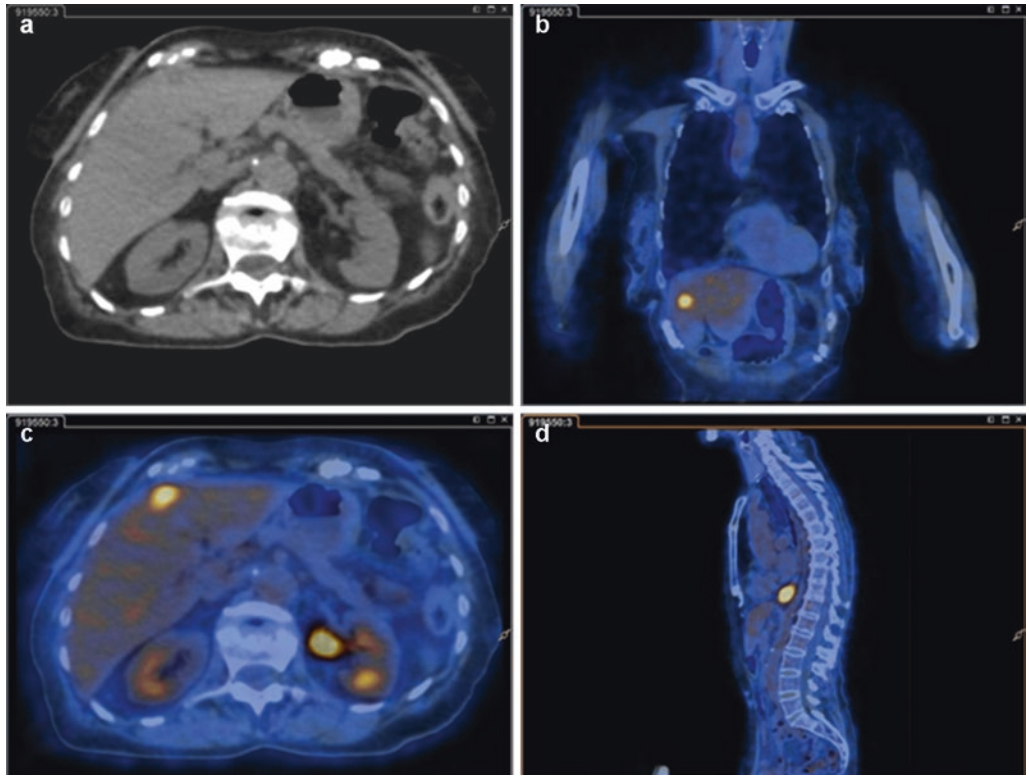


Fig. 9.2 EGJ cancer with metastatic disease. Evidence of metastatic liver disease at initial staging. At CT scan (**a**) a small hypodensity is seen on liver's IV segment. PET/CT images in different planes (**b**, **c**) show an increase metabolism inside the lesion which stands for a metastatic lesion

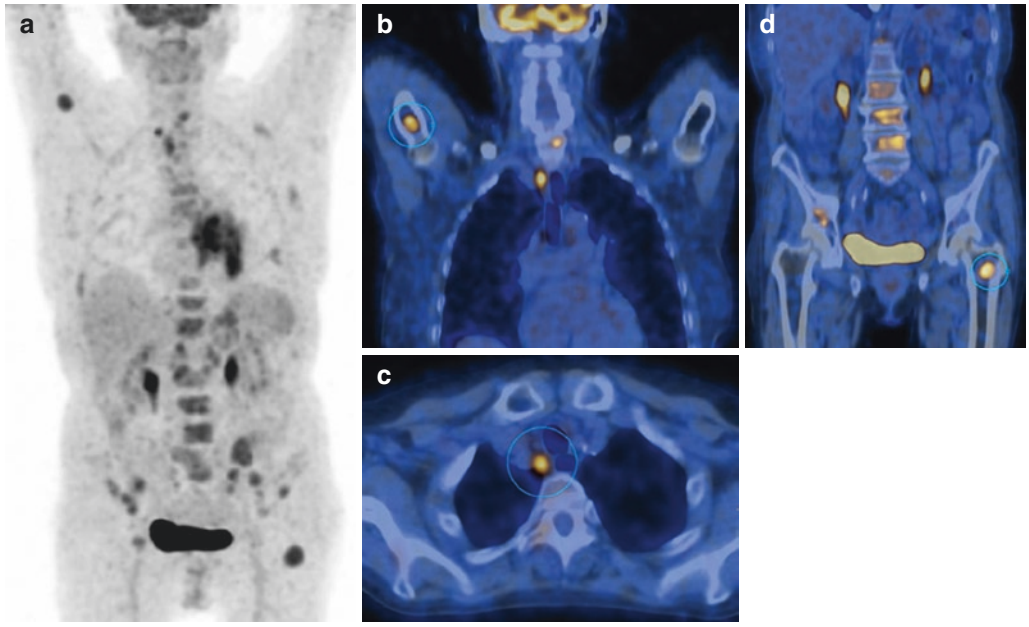


Fig. 9.3 Advanced EGJ cancer with multiple bone metastases. Different multiple bone metastatic lesions are demonstrated at PET images: on right proximal homerus, cervical and lumbar vertebra, right iliac bone and left hip. Lesion become visible only evaluating the increase of SUV, as no lytic lesion is still evident on CT images. In the same patient it is also highlighted a pathological node on right para-esophageal space in the upper mediastinum (**a**–**c**)

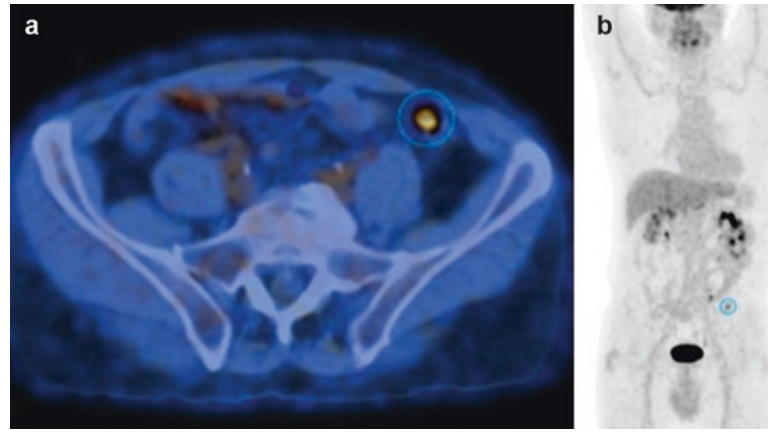


Fig. 9.4 Early EGJ cancer with incidentally demonstration of a focal area of increased methabolism at sigmoid tract. While the EGJ cancer is not demonstrated at PET/CT (**b**), probably as a consequence of the small volume of the tumor, the lesion located at the sigmoid tract is well demonstrated (**a**) and it was proven to by a polipoid cancer at colonoscopy

Furthermore, many studies show that PET/CT is useful for planning radiotherapy (RT) treatment. As a matter of fact, Drudi et al. (2002) found that the lengths of esophageal carcinoma measured by CT scan and esophagogram corresponded to the lengths of surgical specimens in only 32 % and 59 % of cases, respectively [11]. The union of the metabolic information to RT treatment plan allows a more accurate delineation of tumor volume, by reducing the toxicity to tissues and contiguous geographic missing and permitting to include in the field of radiation possible hypermetabolic lymph nodes not evident on CT. Ki Ho Seol and Jeong Eun Lee (2014) confirm that PET/CT during chemotherapy or chemoradiation can provide additional information on radiotherapy planning in esophageal cancer due to its greater sensitivity, specificity, and accuracy than CT [12]. In a prospective trial of PET for radiotherapy planning in esophageal cancer, Leong et al. (2006) demonstrated that PET has a significant impact on gross tumor volume (GTV) and often helps avoid geographic misses by identifying unsuspected lymph node involvement [13]. Moureau-Zabotto et al. (2005) focused on the additional role of PET/CT for RT planning and highlighted as it altered GTV values in 19 of 34 patients (56 %); GTV was reduced in 12 and increased in 7 (21 %) patients [14]. In another study, Muijs et al. (2009) reported that the additional use of PET led to the modification of CT-based RT planning in 57 % of esophageal cancer patients [15].

9.2.1 Evaluation During Neoadjuvant Therapy for Prognostication

The early detection of response to neoadjuvant chemotherapy or chemoradiation is the main point to change the therapeutic strategy, that is, either to continue treatment or to proceed with surgery. Early response evaluation is defined as the assessment of response during treatment, whereas late evaluation is performed after the completion of induction therapy. So only responding patients would complete treatment, while nonresponding patients would avoid potentially harmful treatments (Fig. 9.1) [16].

Various studies have demonstrated that 18FDG-PET, measuring early changes in tumor glucose uptake after only two weeks of induction therapy, is a promising tool in the prediction of clinical and histopathologic response as well as prognosis to neoadjuvant treatment in adenocarcinomas of the EGJ type I and II [1, 10, 17].

Available evidence suggests that metabolic response might be a useful predictive marker for the early identification of nonresponding patients (Fig. 9.5).

The MUNICON-I trial prospectively showed that early metabolic assessment with therapy stratification after only 2 weeks helps to select

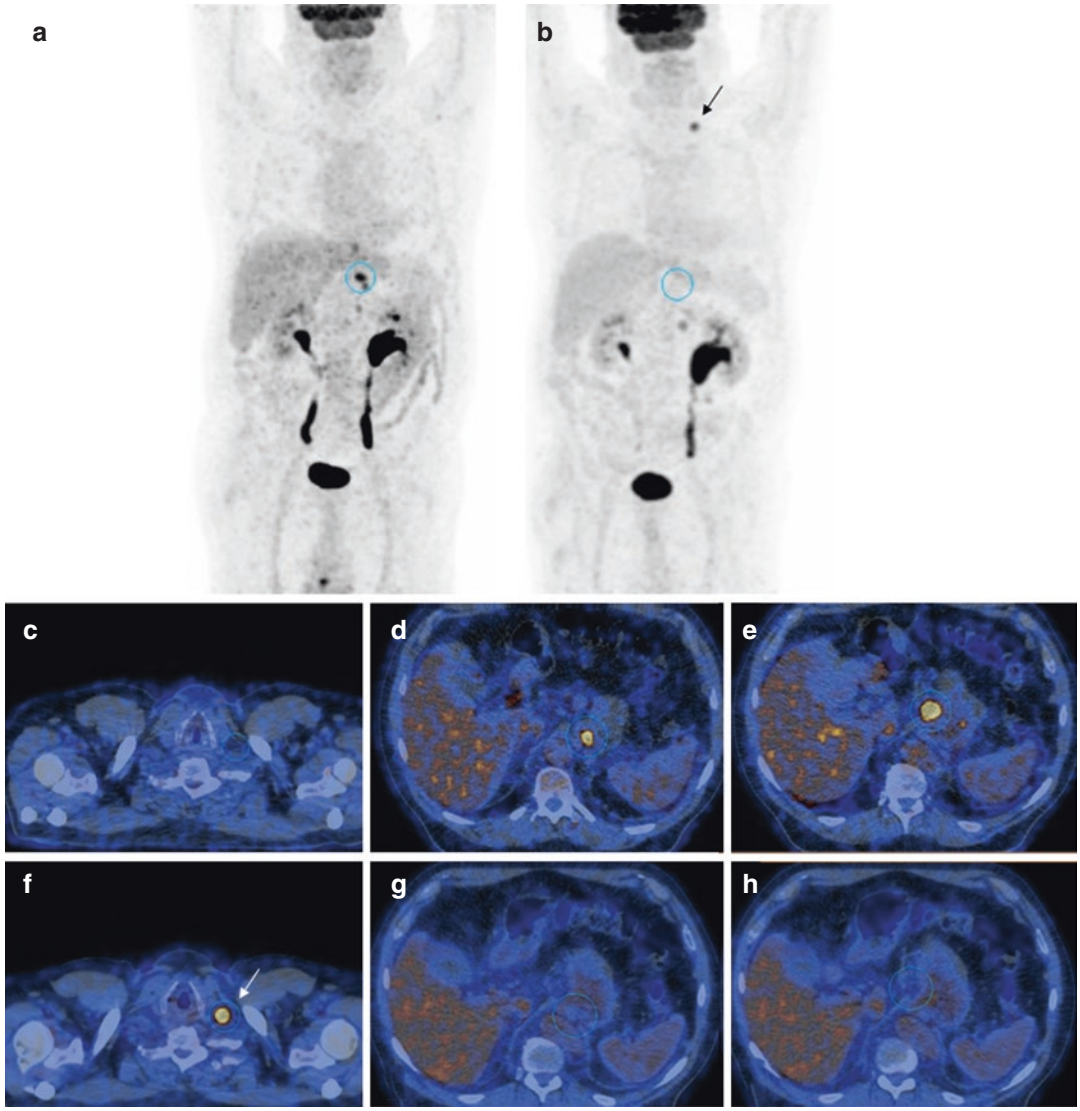


Fig. 9.5 EGJ cancer before (**a**, **c**–**e**) and after CRT (**b**, **f**–**h**). MIP whole-body PET (**a**–**b**) as well as PET/CT images (**c**–**h**) before and after CRT demonstrate a complete response to treatment in perigastric lymph nodes and EGJ cancer. Anyway, at the end of CRT a left supraclavear node becomes evident (*arrow* in f) with significant increase in SUV: that stands for lymph node progression of disease

nonresponding patients with EGJ I and II, who are not benefiting from neoadjuvant chemotherapy and can therefore avoid ineffective and toxic therapy [6, 18]. In this trial, a PET scan was performed in 119 patients before the start and after 2 weeks of platinum and fluorouracil-based induction chemotherapy. Patients with a predefined decrease in standardized uptake value (SUV) of ≥35 %, compared with baseline FDG-PET/CT, were defined as metabolic responders. Responders continued to receive neoadjuvant chemotherapy for 12 weeks (15–100 days) and then proceeded to surgery [8]. In metabolic PET-nonresponders, chemotherapy was discontinued after the two-week evaluation period, and these patients proceeded to chemoradiation, as recommended by the HICON trial [6], with surgical resection 28–42 days after the end of the chemoradiation [17].

9.2.2 Evaluation After Neoadjuvant Therapy for Restaging

Only 40–50 % of the patients respond to neoadjuvant chemotherapy or chemoradiation. Quality of life and survival must be balanced against the toxicity of the neoadjuvant treatment as well as the surgical mortality and morbidity [5, 19].

The same staging modalities used for clinical staging are available for restaging. However, effective therapy reduces clinical restaging accuracy and makes response (downstaging) prediction difficult [9].

Many studies have found various measures, including change in maximal standardized uptake value, metabolic cancer length, metabolic cancer volume, and total lesion glycolysis, to be useful in assessing response to therapy [9, 20, 21]. On the other hand, it should be taken in mind that a negative PET/CT cannot distinguish small-volume residual disease from complete response to treatment [22, 23]. A possible limit of the PET/CT for the evaluation of the tumor at the end of RT is given by the radiation-induced inflammatory alterations that may cause an increased uptake tissue not distinguishable from a possible persistence of the disease. This increased uptake post-actinic is poorly predictable, depends in part on the type of treatment, and can last several months.

The main role of FDG-PET in restaging following neoadjuvant chemotherapy or chemoradiation remains the identification of distant metastases before performing surgery (interval metastases) (Fig. 9.5), as shown in the recent study of Schollaert et al. (2014) [19].

However, PET shouldn't be used routinely to assess the response after chemotherapy or chemoradiation for guiding subsequent therapy [10].

9.2.3 Evaluation After Neoadjuvant Therapy for Prognostication

Only pathological staging of a surgical specimen seems to be a good predictor of survival.

Recent studies suggested that the quantitative decrease in FDG uptake seen after neoadjuvant chemotherapy or chemoradiation correlates with pathologic response to therapy and patient survival [5, 9, 24].

The study of Lordick et al. (2006) confirms that early metabolic response measured by PET identifies patients with EGJ type 1 and EGJ type 2 who have a high chance of achieving major histological responses after neoadjuvant treatment and, therefore, have a favorable prognosis. PET helps select patients who are benefiting from chemotherapy. Additionally, PET-response-guided treatment helped avoid the administration of inefficient chemotherapy to patients with no metabolic response [24].

The study of Ott et al. (2006) found that a decrease of tumor metabolic activity by more than 35 % after 2 weeks of therapy predicts a high histopathologic response rate (53 %) and is associated with a favorable prognosis (median survival, >50 months) [25].

Both trials demonstrated that patients who respond to neoadjuvant chemotherapy who are identified by early metabolic imaging have a favorable prognosis, and this is especially true for metabolic responders who also achieve a major histopathological response. However, patients who do not achieve a histological response, despite previous metabolic response, prognosis remains dismal. Therefore, histological response remains an important prognosticator that seems to be stronger and more robust than early metabolic response (Figs. 9.1 and 9.6). The important effect of metabolic imaging in this context is that PET can predict histological response earlier and with higher accuracy than any other clinical assessment [24, 26, 27].

9.3 MRI

The role of MRI in the diagnosis and staging of EGJ has not been thoroughly evaluated, so that evidence of a distinct advantage over traditional imaging modalities has not been yet established [28, 29]. However, recent advances in MRI technology have improved the achievable signal-to-noise ratio, thus improving performance in terms of spatial and temporal resolution. This has opened new possibilities in the local staging of EGJ. It is well known that MRI, like CT, can suc-

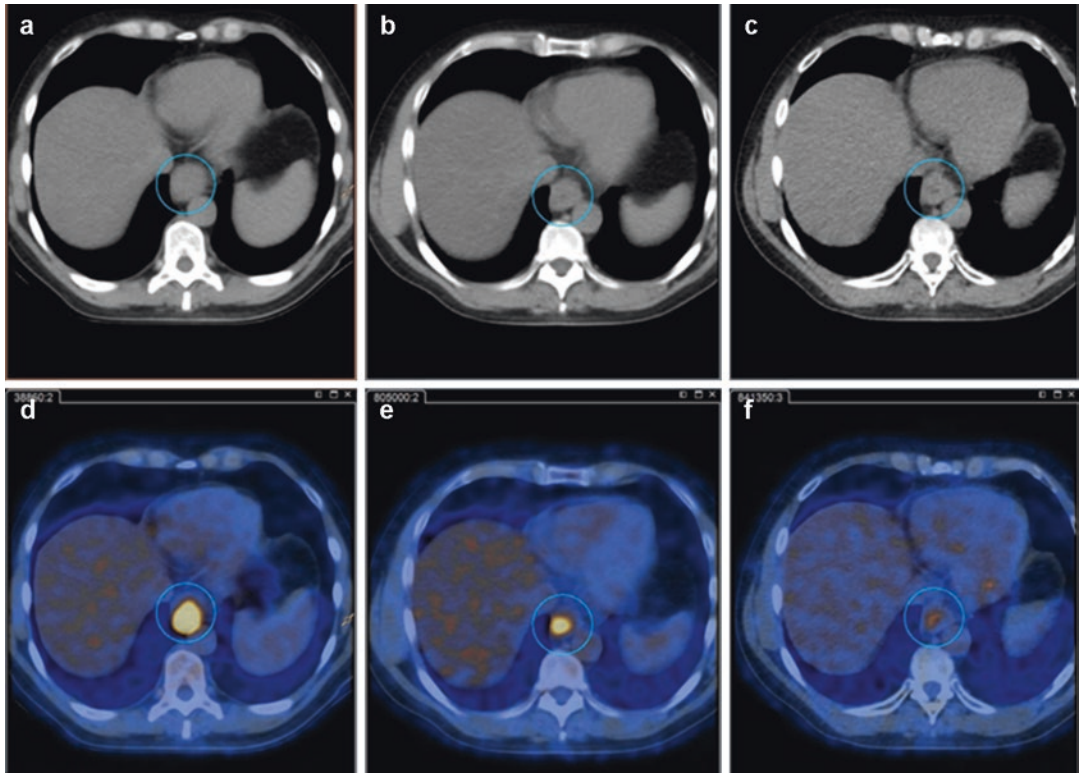


Fig. 9.6 Complete response to CRT. CT and PET/CT images before (**a**, **d**), during (**b**, **e**) and after (**c**, **f**) treatment. At pre-treatment images EGJ cancer is a large lesion with initial SUVmax 14 (**a**, **d**). After inductive chemotherapy (**b**, **e**) there is only a small decrease in volume, but a significant reduction in SUV max 7.2 (–49%). At the end of CRT SUV max is 4.2 (–70%), suggestive of a complete methabolic response, which was proven at definite histology after surgery

cessfully be used in the evaluation of mediastinal involvement, adjacent lymphadenopathy, and distant spread, with contrast resolution higher than CT, while it offers a better contrast resolution than CT, permitting the exact evaluation of the different layers of the wall that results in a potential better definition of T stage [30, 31]. MRI is feasible in patients with esophageal cancer, and the application of an ECG-trigger reduces pulsation artifact and allows the assessment of kinetic parameters in tumors near the aorta and the beating heart [32].

Recent studies have developed imaging criteria for the local staging of EGJ using high-resolution T2-weighted imaging and have shown diffusion-weighted magnetic resonance imaging (DWI) may be an attractive alternative to 18FDG-PET (Fig. 9.7); MRI-reported advantages are no need to fast before the examination, no radiation used, no exogenous contrast material, and a shortened acquisition time [33, 34].

Another possible advantage of MRI over PET/CT might be the capability to demonstrate small-volume residual disease from complete response to chemoradiation by combining T2-weighted morphological imaging with functional technique, such as DWI and perfusion (DCE) (Fig. 9.8). Multiparametric MRI has been tested in other different types of neoplasms, such as rectal, breast, or prostatic cancers, and preliminary results are extremely promising.

DWI is based on the degree of mobility of water protons, quantifiable by the apparent diffusion coefficient (ADC). The ADC measures the degree of free diffusion of water molecules within tissues, which is mainly influenced by the

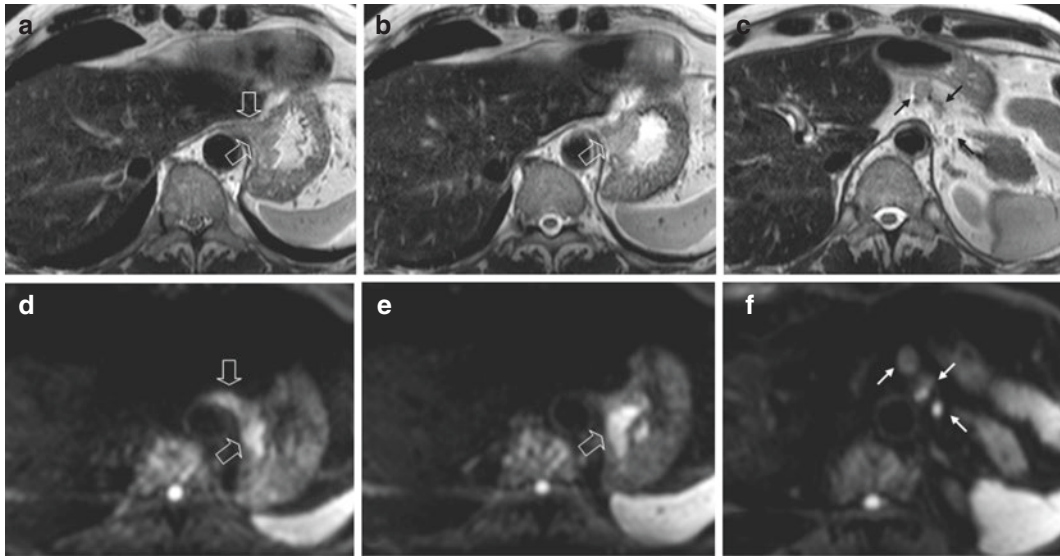
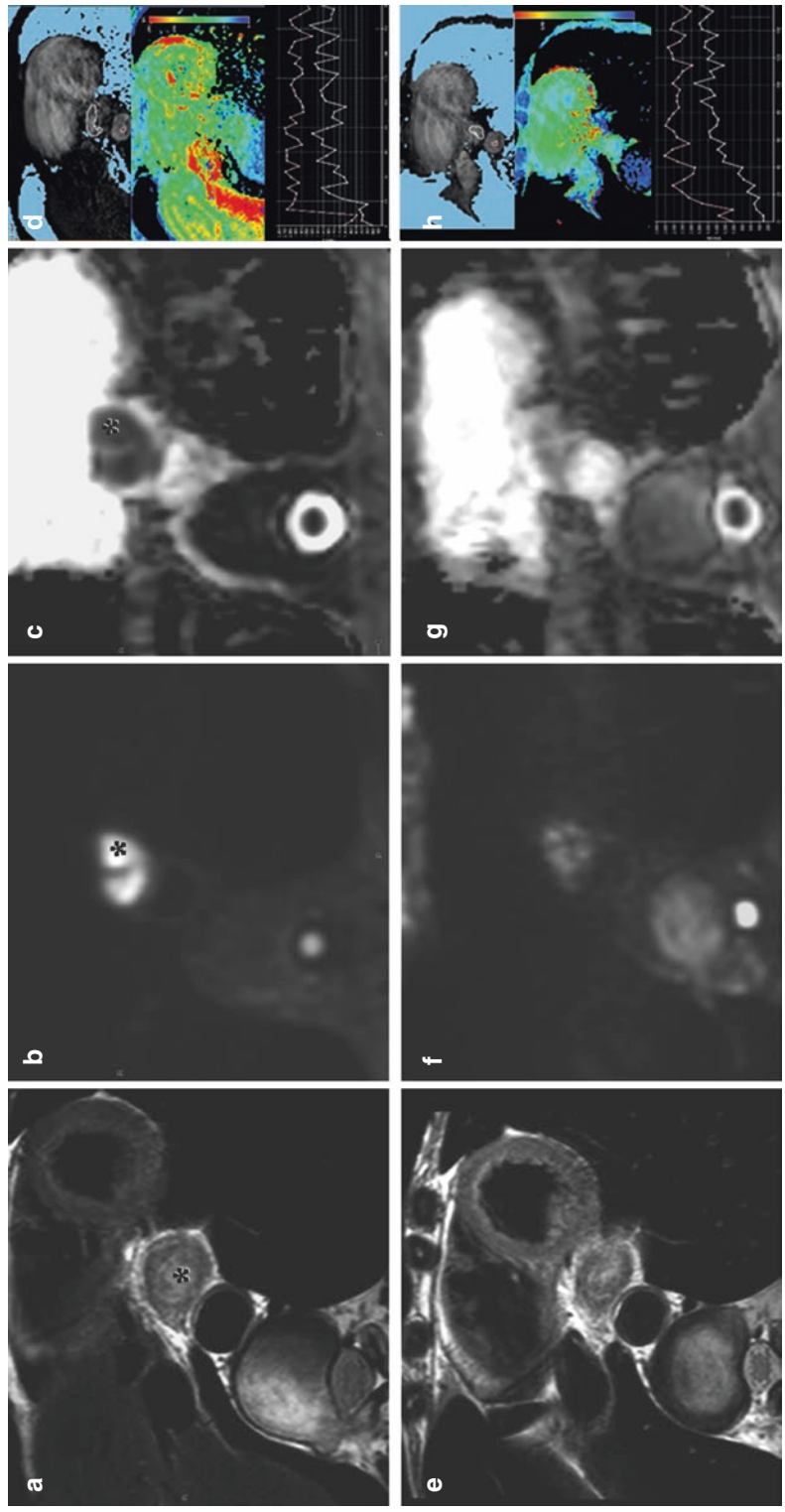


Fig. 9.7 EGJ cancer T3N2: pre-treatment local staging. On T2 weighted images (**a**–**b**) a large neoplastic lesion envolves EGJ site (*open arrow*); the lesion is slightly hyperintense and envolves all the wall's layers, with irregular margins and small dictations into the perigastric fat. Enlarged lymph nodes (*arrows*) at the origin of celiac trunk are demonstrated, with a round shape, suggestive for metastatic nodes (**c**). At DWI images at b 1000 (d-f) the EGJ cancer is highly hyperintense, as well as the pathological nodes

cell organization, size, and density. Cell death leads to a loss of cell membrane integrity and density, which determines an increase in ADC values. This explains why the ADC has recently emerged as a potential biomarker of the response to cancer therapy (Fig. 9.9) [35]. Although the application of DWI to predict and monitor treatment response has been investigated in different types of neoplasms, few data in the literature have reported the correlation between ADC modifications and objective histological parameters of treatment response. Furthermore, to date there are no established protocols for performing DWI in EGJ: improvements to MRI scanner hardware could change the resolution of MRI images, which may further improve reproducibility of tumor ADC value measurements.

Also dynamic contrast-enhancement MRI (DCE-MRI) provides functional information and may be used for the detection and characterization of primary malignant tumors on the basis of their altered vascular integrity, which may result from pathologic angiogenesis and metastases [4, 36]. In DCE-MRI altered vascularity

Fig. 9.8 Multiparametric MRI approach in the evaluation of EGJ cancer before (**a**–**d**) and after CRT (**e**–**h**). A huge EGJ cancer (star) is demonstrated at T2 weighted image (**a**) before treatment, responsible of substenosis of esophago-gastric junction. The lesion envolves ¾ of the circumference of the esophagus and causes almost obstruction of the lumen. The tumour is hyperintense on DWI image at b 1000 (**b**) and shows low ADC values, with a significant hypointensity on ADC's map image (**c**). At DCE (d) a representative region of interest (ROI) is placed over the tumor and signal intensity time curve (white curve) is obtained compared to the arterial input function (pink curve). In the EGJ cancer we observe a rapid initial signal intensity increase, followed by a plateau and a gradual decrease. After neoadjuvant treatment (**e**–**h**), a moderate decrease in volume and signal of neoplastic tissue is seen at T2 weighted image (**e**), while there is the evidence of significant loss of intensity on DWI (f) and an increase on ADC values. At ADC's map only a slight hypointensity is demonstrated (**g**). Furthermore, at DCE signal intensity time curve (**h**) is changed with a slow progressive signal intensity increase, as well as a decrease in the mean signal intensity. All these results are related to a complete response to CRT, which was confirmed at hystopathological exam after surgery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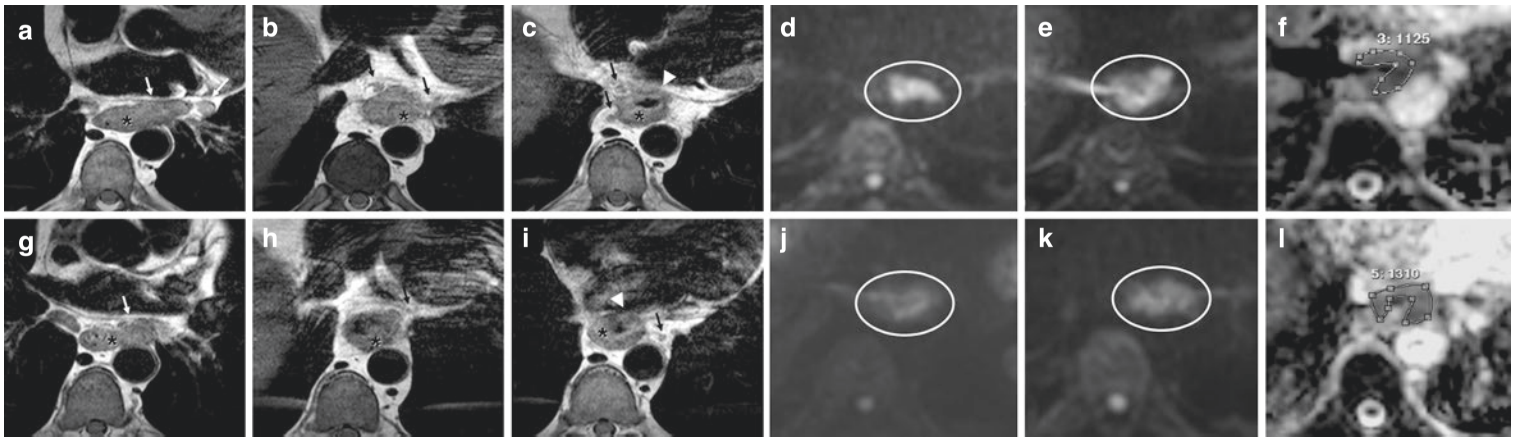


Fig. 9.9 EGJ cancer T4N3 before (**a**–**f**) and during CRT, after 3 week from the start of neoadjuvant therapy (**g**–**l**): evidence of progression of disease. At pre-treatment staging, T2 weighted images (**a**–**c**) demonstrate a large lesion (star) which envolves all the margins and widespreads into the periesophageal fat tissues. It infiltrates pericardium (*arrowhead*) too. Several enlarged pathologic lymph nodes are detected (arrows). At DWI images at b 1000 (**d**, **e**) both the EGJ lesion and lymph nodes are hyperintense and on ADC's map there is the real evidence of low ADC mean value (1125) inside the lesion (**f**). During CRT, there is a progression of disease. At T2 images, despite the reduction in volume and intensity of some periesophageal nodes (**h**, **i**) there is the evidence of enlargement of subcarenal pathological nodes (**g**). Furthermore, there is only a small decrease in tumor volume and a focal infiltration of left atrium becomes evident (*arrowhead* in i). Both on DWI images (**j**, **k**) and ADC map (**l**) there are only few changes in signal intensity, which is reflected into an insignificant increase in ADC mean value (1310)

and/or vascular permeability of malignancies are detected by measurement of subsequent changes in signal intensity during contrast agent passage [31]. The analysis K^{trans} is a pseudo first-order rate constant measuring the circulation rate between intravascular space and the interstitial one in the tissue of interest. Preliminary experiences found a decrease in contrast agent exchange across the vascular wall after chemotherapy or chemoradiation [4, 32].

9.3.1 Evaluation of Treatment Response for Restaging

The identification after chemotherapy or chemoradiation of patients who had a good response and thus may benefit from surgery is an important objective, with a strong impact on treatment choices.

In the early response, a short time after the start of treatment, tumor responsiveness is evaluated and nonresponding patients are identified (Fig. 9.9). In the late response, several weeks after the completion of induction therapy, the extent of downstaging of the primary tumor is determined (Figs. 9.10 and 9.11).

As diffusion within tumors is impeded by the presence of cellular membranes and macromolecular structures, treatment with chemotherapy and radiation therapy can result in the loss of cell membrane integrity, which can be detected as an increase in mean tumor ADC [32].

To date, there are only few published studies investigating the clinical value of DWI-MRI in evaluating esophageal cancer [31]. An initial study by Sakurada et al. in 24 patients showed that DWI only has a limited role in detecting esophageal cancer and nodal staging. However, results were obtained without combining DWI with cardiac triggering: it might increase detection of small lesions although the expense of elongation of acquisition time [36]. Aoyagi et al. (2011) showed that tumors with lower ADC values had more stromal collagen and higher

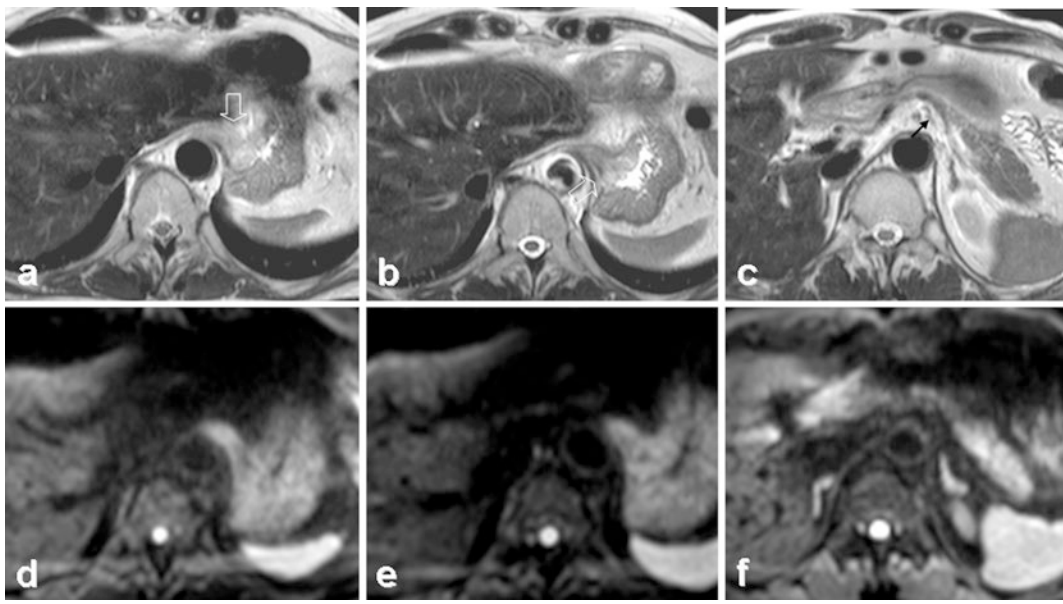
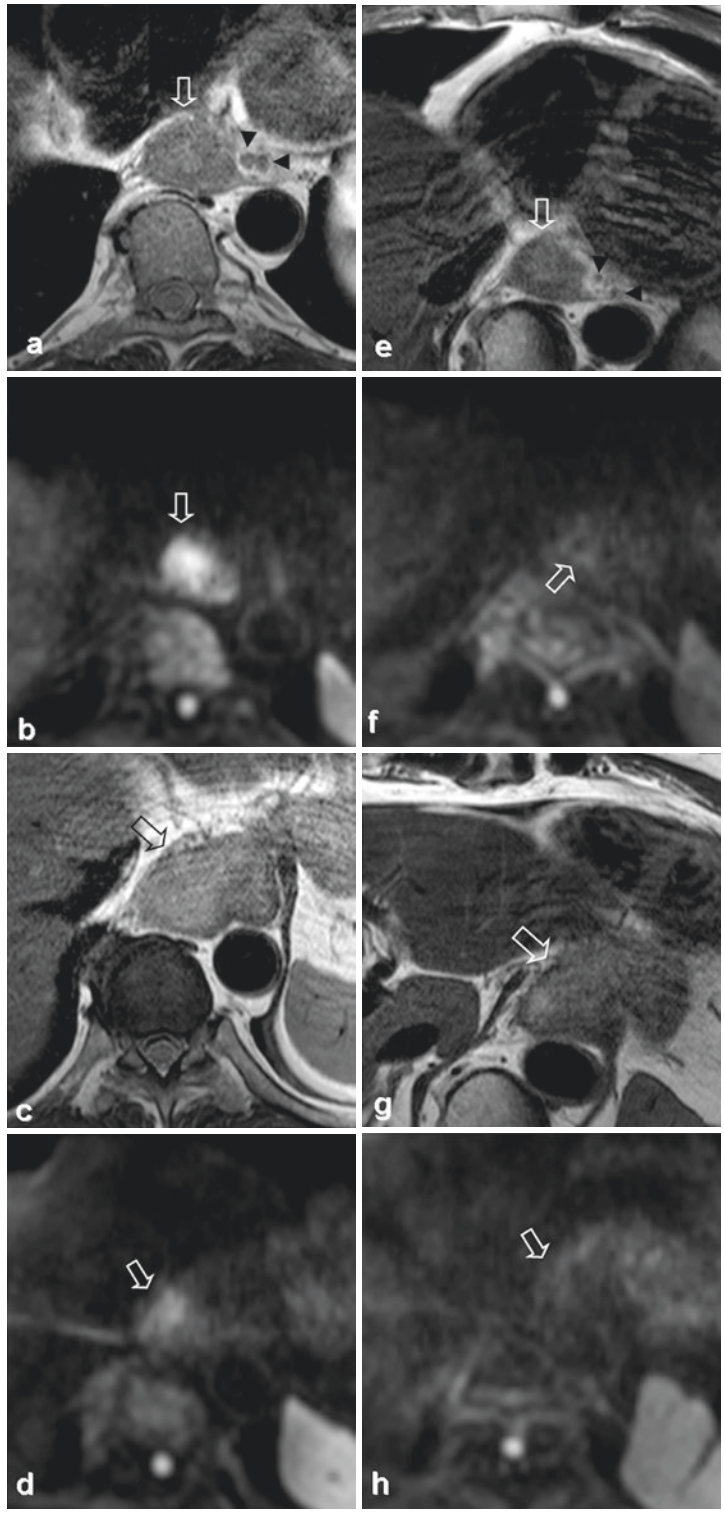


Fig. 9.10 EGJ cancer: re-staging after CRT (same patient of figure 7). On T2 weighted images (**a**, **b**) there is the evidence of a focal thickness of walls of EGJ site (*open arrow*), with a slight hyperintensity related the inflammatory edema. We observe the complete disappearance of previously enlarged lymph nodes at the origin of celiac trunk: nowadays, there is only the evidence of small hypointense nodes with a decrease in signal intensity, which stands for complete response (**c**). At DWI images at b 1000 (**d**–**f**) there is no evidence of significant hyperintensity both in the EGJ lesion, as well as no demonstration of lymph nodes. The images are suggestive of complete response to neoadjuvant therapy, as demonstrated at hystopathological exam after surgery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amount of vascular endothelial growth receptor expression (a marker for tumor neoangiogenesis) [37]. In another study in 123 patients with esophageal cancer, the same research group highlighted that ADC values of primary tumors were lower as clinical T and N stages were more advanced [38].

The study of Weber et al (2013) in 15 patients investigated the correlation of ADC and SUV changes with histological regression under neoadjuvant treatment. Concordance of ADC increase and PET response was observed in 73.3 % of all patients, with a reported significantly higher increase in ADC tumor in PET responders than in PET nonresponders [17]. Also De Cobelli et al. (2013) in 32 patients evaluated changes in volume and ADC before and after treatment and correlated those with histological tumor regression: while no differences in tumor volume values and changes were found between responders and nonresponders, significant differences were observed evaluating ADC, with a significant increase after treatment in responder group [35]. On the other hand, in the study of Kwee et al. (2014) in 11 patients with esophageal cancer, no significant difference was seen in mean tumor ADC increase after chemotherapy or chemoradiation between responders and nonresponders, suggesting that ADC changes do not correlate to tumor response. Further studies should be encouraged in a larger population investigating DWI as a tool for response evaluation [33].

Also DCE-MRI, particularly changes in K^{trans}, might be promising in gauging response to treatment, providing useful information that would be clinically helpful before esophagectomy. Oberholzer et al. (2008) reported a significant decrease of the contrast agent exchange rate and a moderate increase of the amplitude in 12 patients with carcinoma before and after treatment [32]. Chang et al. (2008) demonstrated that motion-corrected region of interest (ROI) data of K^{trans} is greater in esophageal cancer than in the normal tissue [4]. Anyway further studies are necessary to correlate kinetic parameters prior and after neoadjuvant treatment with histopathological response and to better investigate the prediction of response.

9.3.2 Evaluation of Treatment Response for Prognostication

Accurate preoperative staging is mandatory for appropriate patient management. It has been reported that nonresponsiveness to neoadjuvant therapy is associated to a worse prognosis [39], so that accurate staging after the end of chemotherapy or chemoradiation may prove to be of clinical value for individual prognostication. In particular, preoperative determination of nodal status is important, since the presence and number of lymph node metastases are significant independent predictors for the likelihood of developing systemic disease and long-term survival, and the presence of lymph node metastases may require neoadjuvant chemotherapy or chemoradiotherapy [37, 40]. DWI may be used for the detection and characterization of primary malignant tumors and nodal metastases (Figs. 9.9 and 9.11) [33, 41]. Normal lymph nodes have a relatively restricted diffusion because of their high cellular density, while metastatic lymph nodes may have an even more restricted diffusion because of increased cellular density, and this may allow discrimination between both groups using DWI [36]. Many

Fig. 9.11 EGJ cancer T3 N2 before (**a**–**d**) and after-CRT (**e**–**h**): local re-staging at MRI. At initial MRI staging a large mass, slightly hyperintense on T2 weighted TSE images (**a**, **c**), is demonstrated at the esophagogastric junction (*open arrow*) which envolves all the esophagogastric wall's layers and widespreads into the peri-esophageal fat tissue. Some small pathologic lymph nodes on the left side of AEG cancer (*arrowheads*) are demonstrated (**a**). DWI images at b 1000 (**b**, **d**) the EGJ cancer before CRT is highly hyperintense, as a consequence of restricted diffusion inside the neoplastic lesion (*open arrow*). After CRT, a decrease in tumor volume is demonstrated and the lesion appears less hyperintense on T2 weighted images (*open arrow*), as a consequence of tumor regression and fibrotic changes. At DWI images (**f**, **h**) there is no significant hyperintensity, which stands for complete response to neoadjuvant therapy

studies report an insufficient detection of locoregional lymph node metastases by PET and MRI [17, 31, 42]; in particular, micrometastases may not be detected. Additionally, the continuation of either chemotherapy or even radio-chemotherapy strongly influences the post-therapeutic lymph node involvement. Responders are known to have a significantly lower rate of lymph node metastases [43] and the addition of radiotherapy might increase the histopathological response of initially metabolically nonresponding patients. Of note, endosonography is the method of choice for T and local N staging, but in 30–50 % of all esophageal cancers the tumor stenosis cannot be passed by the endoscope, which makes MRI and PET/CT in these cases very important to give precise information on both T and N stage (Fig. 9.10) [17, 44]. The study of Weber et al. (2013) reported a concordance of PET/CT and MRI in 100 % cases, but only in 60 % of cases, there was concordance between the sincere classification of local lymph node metastases by imaging and histopathology, so that neither ADC changes nor PET response was correlated to the clinical prognosis [17]. Sun et al. (2011) assessed tumor ADC values before and after radiotherapy in 12 patients and demonstrated a longer overall survival in those patients with a higher increase in ADC values [45]. In another study, Aoyagi et al. (2011) in 80 patients with esophageal carcinoma, who were treated with chemotherapy or chemoradiation, demonstrated that higher mean pretreatment tumor ADC values were associated with a longer overall survival [37]. Anyway, it is worth noticing that De Cobelli et al. (2013) stated apparent opposite results: they observed a significant lower pretreatment ADC value among responder than nonresponders, suggesting that patients with lower pretreatment ADC value have a greater chance to respond to neoadjuvant treatment. Anyway, pretreatment ADC value alone is a poor predictor of response in single patient [35].

Also in our experience among 35 patients with EGJ cancer, we observed a longer overall survival in those patients with a higher increase in ADC values after chemotherapy or chemoradiation; anyway we did not observed any significant correlation between pretreatment ADC value and prediction of response to neoadjuvant treatment.

So despite MRI appear promising in assessing tumor regression, according to our experience, as well as the results reported in literature, we think that we need prospective larger trials, to exactly define its role in the prediction of response to neoadjuvant treatment.

9.4 Tumor Recurrence

Long-term survival after cancer of the esophagus or the EGJ remains poor despite significant improvements in surgical techniques and postoperative management. Even after curative surgery, recurrence is the main cause of death within two years after surgery [46].

In detection of tumor recurrence, imaging modalities are important in many regards. First of all, the imaging modality must be suitable, cost-effective, and able to detect the pathology in early stage. After esophagectomy and gastric excision, the anatomy of the posterior mediastinum is markedly changed. This makes the assessments of the possible local tumor recurrence difficult; for example, CT-scanning is often inconclusive in the search for local recurrence disease. Wall thickening or adjacent mass and suspicious lymph nodes are highly predictive for recurrent disease [46].

The role of FDG-PET in restaging is still being defined. It may not differentiate anastomosis recurrence from stricture. However, it is valuable in detecting regional and distant recurrences [9].

Siersema et al. (2007) demonstrated that metabolic response was the only factor predicting recurrence in patients after resection [47]. Roedl et al. (2008) showed that the reduction of tumor length, as demonstrated by PET-CT before and after treatment, was a better prediction of time to recurrence than the decrease in SUV. PET-CT has a sensitivity of 91 % and a specificity of 81 % in identifying sites of tumor recurrence [48]. For the identification of metastasis, many studies have

shown that the combination of CT and FDG-PET would be superior to each test considered singularly [4, 9].

Evaluation for direct invasion by EGJ into adjacent vital structures by MRI is based on two criteria: mass effect and loss of fat planes. MRI is accurate in detecting masses following esophageal surgery but is not tissue specific. However an enhanced mass with Gd-DTPA should be suspected for tumor recurrence when there is the evidence of a thickened wall at least after one year postoperative or radiation therapy. Before one year, inflammatory changes are very similar to neoplastic recurrence at morphological imaging. So early postoperative cases with possible inflammatory reaction or early postradiation fibrosis especially must be interpreted with caution.

Moreover, MRI is useful in the detection of abdominal lymph node enlargement, intraluminal mass, liver metastasis, and pleural and pericardial effusion [29, 49].

Conclusions

The current literature on treatment and response prediction of EGJ cancer is still quite limited. A potential role of PET/CT in early evaluation of response would avoid unnecessary chemotherapy or chemoradiation and a delay in surgery. However, RT may induce inflammatory alterations, difficult to differentiate from persistent disease.

Furthermore, there is some evidence that PET/CT might provide valuable information for diagnosis of recurrent disease.

Also MRI has a great potential to impact the treatment of EGJ adenocarcinoma. It may improve the clinician's ability to stage patients and to determine the most appropriate treatment. In patients who undergo chemotherapy or chemoradiation, it may provide a tool to gauge therapeutic response, a function that no other modality has been able to demonstrate, through a multiparametric approach that combine morphological and functional information about the cancer. Thus, cross-sectional imaging and its further optimization for this issue are mandatory.

References

1. Smith JW et al (2009) The influence of (18)fluorodeoxyglucose positron emission tomography on the management of gastroesophageal junction carcinoma. Am J Surg 197(3):308–312
2. Shenfine J, Barbour AP, Wong D, Thomas J, Martin I, Gotley DC, Smithers BM (2009) Prognostic value of maximum standardized uptake values from preoperative positron emission tomography in resectable adenocarcinoma of the esophagus treated by surgery alone. Dis Esophagus 22:668–675
3. Boige V et al (2007) Final results of a randomized trial comparing preoperative 5-fluorouracil (F)/cisplatin (P) to surgery alone in adenocarcinoma of stomach and lower esophagus (ASLE): FNLCC ACCORD07-FFCD 9703 trial. J Clin Oncol 25(18S):4510
4. Chang EY et al (2008) The evaluation of esophageal adenocarcinoma using dynamic contrast-enhanced magnetic resonance imaging. J Gastrointest Surg 12(1):166–175
5. Suttie SA, Welch AE, Park KG (2009) Positron emission tomography for monitoring response to neoadjuvant therapy in patients with oesophageal and gastro-oesophageal junction carcinoma. Eur J Surg Oncol 35(10):1019–1029
6. Lorenzen S et al (2011) Sequential FDG-PET and induction chemotherapy in locally advanced adenocarcinoma of the oesophago-gastric junction (AEG): the Heidelberg imaging program in cancer of the oesophago-gastric junction during neoadjuvant treatment: HICON trial. BMC Cancer 11:266
7. Zacherl J (2014) The current evidence in support of multimodal treatment of locally advanced, potentially resectable esophageal cancer. Dig Dis 32(1–2):171–175
8. de Geus-Oei LF et al (2012) FDG-PET/CT based response-adapted treatment. Cancer Imaging 12:324–335
9. Li Z, Rice TW (2012) Diagnosis and staging of cancer of the esophagus and esophagogastric junction. Surg Clin North Am 92(5):1105–1126
10. Yoon HH et al (2009) The role of FDG-PET and staging laparoscopy in the management of patients with cancer of the esophagus or gastroesophageal junction. Gastroenterol Clin North Am 38(1):105–120, ix
11. Drudi FM et al (2002) Esophagogram and CT vs endoscopic and surgical specimens in the diagnosis of esophageal carcinoma. Radiol Med 103(4): 344–352
12. Seol KH, Lee JE (2014) PET/CT planning during chemoradiotherapy for esophageal cancer. Radiat Oncol J 32(1):31–42
13. Leong T et al (2006) A prospective study to evaluate the impact of FDG-PET on CT-based radiotherapy treatment planning for oesophageal cancer. Radiother Oncol 78(3):254–261
14. Moureau-Zabotto L et al (2005) Impact of CT and 18F-deoxyglucose positron emission tomography image fusion for conformal radiotherapy in esophageal carcinoma. Int J Radiat Oncol Biol Phys 63(2):340–345

15. Muijs CT et al (2009) Consequences of additional use of PET information for target volume delineation and radiotherapy dose distribution for esophageal cancer. Radiother Oncol 93(3):447–453
16. Taketa T et al (2012) Outcome of trimodality-eligible esophagogastric cancer patients who declined surgery after preoperative chemoradiation. Oncology 83(5):300–304
17. Weber MA et al (2013) Assessment of diffusion-weighted MRI and 18F-fluoro-deoxyglucose PET/CT in monitoring early response to neoadjuvant chemotherapy in adenocarcinoma of the esophagogastric junction. J Gastrointestin Liver Dis 22(1):45–52
18. Lorenzen S et al (2011) Association of the VEGF 936C>T polymorphism with FDG uptake, clinical, histopathological, and metabolic response in patients with adenocarcinomas of the esophagogastric junction. Mol Imaging Biol 13(1):178–186
19. Schollaert P et al (2014) A systematic review of the predictive value of 18FDG-PET in esophageal and esophagogastric junction cancer after neoadjuvant chemoradiation on the survival outcome stratification. J Gastrointest Surg 18:894–905
20. Kwee R (2010) Prediction of tumor response to neoadjuvant therapy in patients with esophageal cancer with use of 18FDG PET: a systematic review. Radiology 254:707–717
21. Chen Y et al (2011) 18F-fluorodeoxyglucose positron emission tomography predict responses to neoadjuvant therapy in oesophageal cancer patients? a meta-analysis. Nucl Med Commun 32:1005–1010
22. Kato H et al (2002) Usefulness of positron emission tomography for assessing the response of neoadjuvant chemoradiotherapy in patients with esophageal cancer. Am J Surg 184(3):279–283
23. Arslan N et al (2002) Evaluation of response to neoadjuvant therapy by quantitative 2-deoxy-2-[18F] fluoro-D-glucose with positron emission tomography in patients with esophageal cancer. Mol Imaging Biol 4(4):301–310
24. Lordick F et al (2007) PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol 8(9):797–805
25. Ott K (2006) Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. J Clin Oncol 24(29): 4692–4698
26. Ott K et al (2008) The new credo: induction chemotherapy in locally advanced gastric cancer: consequences for surgical strategies. Gastric Cancer 11(1):1–9
27. Wieder HA et al (2007) Prediction of tumor response by FDG-PET: comparison of the accuracy of single and sequential studies in patients with adenocarcinomas of the esophagogastric junction. Eur J Nucl Med Mol Imaging 34(12):1925–1932
28. Wu LF et al (2003) Preoperative TN staging of esophageal cancer: comparison of miniprobe ultrasonography, spiral CT and MRI. World J Gastroenterol 9(2):219–224
29. Jamil LH, Gill KR, Wallace MB (2008) Staging and restaging of advanced esophageal cancer. Curr Opin Gastroenterol 24(4):530–534
30. Jang KM et al (2002) The spectrum of benign esophageal lesions: imaging findings. Korean J Radiol 3(3):199–210
31. van Rossum PS et al (2013) Imaging strategies in the management of oesophageal cancer: what's the role of MRI? Eur Radiol 23(7):1753–1765
32. Oberholzer K et al (2008) Assessment of tumor microcirculation with dynamic contrast-enhanced MRI in patients with esophageal cancer: initial experience. J Magn Reson Imaging 27(6): 1296–1301
33. Kwee RM et al (2014) Interobserver reproducibility of diffusion-weighted MRI in monitoring tumor response to neoadjuvant therapy in esophageal cancer. PLoS One 9(4):e92211
34. Riddell AM et al (2006) Potential of surface-coil MRI for staging of esophageal cancer. AJR Am J Roentgenol 187(5):1280–1287
35. De Cobelli F et al (2013) Apparent diffusion coefficient modifications in assessing gastro-oesophageal cancer response to neoadjuvant treatment: comparison with tumour regression grade at histology. Eur Radiol 23(8):2165–2174
36. Sakurada A et al (2009) Diagnostic performance of diffusion-weighted magnetic resonance imaging in esophageal cancer. Eur Radiol 19(6):1461–1469
37. Aoyagi T et al (2011) Apparent diffusion coefficient values measured by diffusion-weighted imaging predict chemoradiotherapeutic effect for advanced esophageal cancer. Dig Surg 28(4):252–257
38. Aoyagi T et al (2012) Apparent diffusion coefficient correlation with oesophageal tumour stroma and angiogenesis. Eur Radiol 22(6):1172–1177
39. Law S et al (1997) Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus: a prospective randomized trial. J Thorac Cardiovasc Surg 114(2):210–217
40. Krupski-Berdien G (2007) MRI of esophagus. N staging and more…. Radiologe 47(2):119–122
41. Pultrum BB et al (2009) Detection of lymph node metastases with ultrasmall superparamagnetic iron oxide (USPIO)-enhanced magnetic resonance imaging in oesophageal cancer: a feasibility study. Cancer Imaging 9:19–28
42. Becker K et al (2003) Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. Cancer 98(7):1521–1530
43. Becker K et al (2012) Proposal for a multifactorial prognostic score that accurately classifies 3 groups of gastric carcinoma patients with different outcomes after neoadjuvant chemotherapy and surgery. Ann Surg 256(6):1002–1007
44. zum Buschenfelde CM et al (2011) (18)F-FDG PET-guided salvage neoadjuvant radiochemotherapy of adenocarcinoma of the esophagogastric junction: the MUNICON II trial. J Nucl Med 52(8):1189–1196

45. Sun YS et al (2011) Early evaluation of cancer response by a new functional biomarker: apparent diffusion coefficient. AJR Am J Roentgenol 197(1):W23–W29
46. Kantarci M et al (2004) Comparison of CT and MRI for the diagnosis recurrent esophageal carcinoma after operation. Dis Esophagus 17(1):32–37
47. Siersema PD (2007) Pathogenesis, diagnosis and therapeutic possibilities of esophageal cancer. Curr Opin Gastroenterol 23(4):456–461
48. Roedl JB et al (2008) Assessment of treatment response and recurrence in esophageal carcinoma based on tumor length and standardized uptake value on positron emission tomography-computed tomography. Ann Thorac Surg 86(4):1131–1138
49. Alper F et al (2011) Effectiveness of the STIR turbo spin-echo sequence MR imaging in evaluation of lymphadenopathy in esophageal cancer. Eur J Radiol 80(3):625–628

10 Molecular Markers in the Prediction of Response to Neoadjuvant Treatments in Esophagogastric Junction Adenocarcinoma

Davide Melisi, Melissa Frizziero, Geny Piro, and Giampaolo Tortora

Despite the global incidence of upper gastrointestinal tract cancers which has significantly declined over the past three decades, the incidence of adenocarcinoma of the esophagogastric junction (EGJ) is continuously and rapidly rising in the Western countries, representing a major health problem [1, 2].

The adenocarcinoma of the EGJ, defined as the cancer arising within 5-cm proximal or distal to the point of transition from esophageal squamous epithelium to gastric mucosa, has been widely recognized as a distinct clinic-pathological entity from either squamous cell esophageal cancer or "non-cardia" adenocarcinoma of the stomach for its different epidemiology, biological behavior, and sensitivity to treatments [3]. Given the modest improvements in patient outcomes achieved by recent therapeutic progresses, the prognosis of this disease remains dismal with 5-year survival rates rarely exceeding 30–40 % [1, 4].

While very early-stage (T1N0) tumors can be cured by surgery alone, even submucosal involvement greatly increases the risk of margin-positive resection, locoregional relapse, and

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distant recurrence [5], requiring the integration of surgery with systemic strategies. Thus, the multimodal approach, consisting of either preoperative combined chemoradiotherapy followed by surgery [6] or perioperative chemotherapy [7], has become the standard of care for resectable locally advanced (T2 or greater; nodal involvement) esophageal and EGJ cancers as a whole [8].

Many evidences indicate that the histopathological response to preoperative chemotherapy or chemoradiotherapy is considerably variable among adenocarcinomas of the EGJ, with only approximately 20 % of patients neoadjuvant treated achieving a complete response (CR) [9] and another 20 % of cases defined as "extremely resistant," corresponding to the presence of more than 50 % of residual cancer in the surgical specimen [10]. Moreover, the histopathological response to neoadjuvant treatments identifies patients who are more likely to derive a survival benefit, as it is positively correlated with overall survival (OS) duration, with responder patients having statistically significant superior OS rates than nonresponders (3-ys OS 70 % vs 35 %) ([9, 11, 12]. In this regard, a very recent retrospective analysis involving 400 patients with resectable adenocarcinoma of the esophagus and EGJ who received preoperative chemotherapy demonstrated that local downstaging after preoperative chemotherapy was the strongest independent predictor of survival in this clinical setting and that tumor stage after preoperative chemotherapy was more relevant for prognosis than initial stage at diagnosis [13].

These clinical evidences provide a strong argument for the urgent development of molecular biomarkers able to predict primary resistance to preoperative chemoradiotherapy in esophageal and esophagogastric junction adenocarcinoma, in order to avoid this preoperative treatment in those patients unlikely to benefit.

A number of molecular pathways and genetic mutations likely to be involved in the carcinogenesis of adenocarcinoma of the EGJ have been investigated either as putative markers of resistance to standard treatments and novel biologic agents or as potential therapeutic targets. The most relevant included growth factor receptors, tumor suppressor genes, apoptosis-related and chemotherapy metabolism-related genes, and genomic signatures [4, 14, 15].

10.1 Growth Factor Receptors

10.1.1 Epidermal Growth Factor Receptor

The expression of the epidermal growth factor receptor (EGFR) and the *EGFR* gene amplification have been reported in, respectively, 30–60 % and 8–31 % of adenocarcinomas of the EGJ and distal esophagus [16–18]. Whereas an association between EGFR overexpression or *EGFR* gene amplification and worse prognosis has been demonstrated in primarily resected patients [16, 19], the correlation of these aberrations with histopathological response and survival in patients receiving neadjuvant treatments has not been defined yet.

Pretreatment tumor specimens from 54 patients with locally advanced esophageal cancers receiving neoadjuvant chemotherapy with 5-flurouracil plus cisplatin and concurrent radiotherapy were assessed for a panel of putative predictive biomarkers, including EGFR protein expression, by immunohistochemistry [20]. The vast majority of patients in this series had an adenocarcinoma of distal esophagus or EGJ. The distinction between high and low EGFR expression levels was based on an immunoreactive score (IRS) ranging between 0 and 12, which takes into account both the intensity of staining and the percentage of positive cells. Interestingly, EGFR overexpression (IRS > 9) was found to significantly correlate with poorer OS [$p = 0.009$], and at the multivariate analysis, EGFR overexpression resulted in an independent predictor for OS. However, whether EGFR overexpression had a predictive rather than a prognostic role was not addressed.

Recently, two cohorts of patients with locally advanced esophageal adenocarcinomas either treated with preoperative cisplatin-based chemotherapy followed by surgery or with surgical resection alone were evaluated for EGFR protein

expression and gene copy number [21]. A strong positive correlation between EGFR expression and gene copy number [$p<0.01$] was found in both cohorts. The group of patients receiving neoadjuvant treatment was stratified into responder and nonresponder patients. Among responders, EGFR expression levels significantly correlated with disease-free survival (DFS) and OS, with those patients with low expression levels surviving significantly longer than those with high expression levels [DFS, $p=0.0015$; OS, $p=0.0032$]. However, no correlations between EGFR expression and survival outcomes were observed among nonresponder patients. In the multivariate Cox regression analysis, EGFR overexpression resulted in an independent adverse predictor for both DFS and OS in patients who respond to neoadjuvant chemotherapy and in patients who were primarily resected, suggesting a negative prognostic role for EGFR. Moreover, in the case that either EGFR expression levels or gene copy number was low, patients responding to chemotherapy had a significantly longer DFS [low EGFR expression levels, $p=0.0152$; low EGFR gene copy number, $p=0.005$] and OS [low EGFR expression levels, $p=0.0036$; low EGFR gene copy number, $p=0.0032$] than nonresponders. Conversely, when either EGFR expression levels or gene copy number was high, there were no differences in survival duration according to the response to neoadjuvant chemotherapy. These findings suggested that EGFR could have a negative prognostic value; however, they do not provide enough evidence for sustaining its predictive potential.

10.1.2 Human Epidermal Growth Factor Receptor–2

The human epidermal growth factor receptor (HER)-2 is a key driver in the tumorigenesis of a portion of esophageal and gastric adenocarcinomas, with HER-2 overexpression or gene amplification being reported in up to 30 % of cases [22–25]. The prognostic significance of HER-2 upregulation in the adenocarcinoma of the esophagus and EGJ is still unclear, since data in this regard are conflicting [26–28], likely because of the heterogeneity of the studies and of HER-2 scoring methods. HER-2 status can be determined in pathological samples using immunohistochemistry (IHC) and in situ hybridization, either by fluorescence (FISH) or by colorimetry (CISH). HER-2 positivity is commonly defined as 3+ in IHC or 2+ in IHC with amplification in ISH [22].

In locally advanced unresectable/metastatic adenocarcinomas of the stomach and of the EGJ, HER-2 positivity is a well-validated predictor of response to anti-HER-2 systemic therapies. In the phase III ToGA trial, HER-2-positive patients derived a statistically significant DFS and OS advantage when the anti-HER-2 monoclonal antibody trastuzumab was added to standard fluoropyrimidines/cisplatin-based chemotherapy [29]. Basing on the results in the advanced/metastatic setting, the predictive potential of HER-2 has been explored also in the resectable stage disease.

A biomarker analysis was performed on pretreatment and surgical resection specimens of gastric and EGJ adenocarcinomas from 415 out of 503 patients (82.5 %) enrolled in the phase III MAGIC trial comparing perioperative epirubicin/5-fluorouracil/cisplatin chemotherapy with surgery alone [26]. In this series the overall HER-2 positivity rate was 10 % in both arms. Among HER-2-positive patients, there was not a statistically significant trend toward improved OS in favor of those treated with preoperative chemotherapy compared to those treated with surgery alone [HR 0.74 (95 % CI 0.14–3.77)]. The lack of statistical significance was likely due to the small number of this subgroup of patients. A statistically significant OS advantage was observed in favor of preoperative chemotherapy in the HER-2-negative subgroup [HR 0.58 (95 % CI 0.41–0.82)]. However, there was no differential effect between treatment arms according to HER-2 status (heterogeneity $p=0.7$). Moreover, no differences were observed in terms of OS between HER-2-positive and HER-2-negative patients neither among patients receiving preoperative chemotherapy or primarily resected patients.

In a retrospective series of 228 patients with esophageal and gastric adenocarcinomas treated either with neoadjuvant chemotherapy followed by surgery or surgery alone, HER-2 status was assessed in both pretreatment biopsies and surgical specimens and correlated with clinical outcomes [30]. HER-2-positive tumors were significantly more frequently proximal [$p=0.02$], intestinal type according to Lauren's classification [$p=0.002$], and well differentiated [$p<0.0001$] compared with HER-2-negative tumors. Among patients treated with neoadjuvant chemotherapy, an increase in the relative rate of HER-2 positivity of 23.5 % was seen among surgical specimens of those achieving histopathological response compared with the corresponding pretreatment biopsies [p not reported]. Moreover, eight patients receiving neoadjuvant chemotherapy presented discordant results between surgical specimen and pretreatment biopsy, with four positive and four negative shifts. Among the four tumors that showed negative shifts, three of them presented major histological response, and one presented minor histological response. The four positive shifts were all detected in patients with no histological response. These findings as a whole suggest a lack of predictive as well as prognostic significance for HER-2 in patients with resectable adenocarcinoma of the stomach and EGJ.

10.2 Chemotherapy Metabolism-Related Biomarkers

Disregulations in the activity of the enzymes involved in the metabolism of fluoropyrimidines and platinum derivates have been correlated with response to neoadjuvant treatments in resectable esophageal and EGJ cancers [14]. In a series of 38 pretreatment bioptic specimens from patients affected by locally advanced esophageal adenocarcinoma treated with neoadjuvant fluorouracil/cisplatin chemotherapy with or without paclitaxel followed by surgery, mRNA expression levels of a panel of fluoropyrimidine metabolism-related enzymes were determined and correlated with clinical outcomes [31]. Tumors from patients responding to neoadjuvant chemotherapy had significantly higher mRNA expression levels of methylenetetrahydrofolate reductase (MTHFR) [$p=0.012$], caldesmon [$p=0.016$], and multidrug resistance gene 1 (MRP1) [$p=0.007$]. Moreover, higher mRNA expression levels of MTHFR and MRP1 correlated with longer survival after surgery [$p=0.013$ and $p=0.015$, respectively].

In another small series of 21 patients with locally advanced esophageal adenocarcinoma receiving a preoperative fluorouracil/cisplatin-based chemotherapy regimen and subsequent surgery, both pretreatment biopsies and surgical tumor specimens were investigated for mRNA expression levels of several genes associated with chemotherapy metabolism [32]. This study demonstrated a significant posttreatment decrease in mRNA expression levels of MRP1 [$p=0.006$] and thymidine phosphorylase (TP) [$p=0.028$]. More interestingly, downregulation of posttreatment mRNA expression of MRP1 and thymidylate synthase (TYMS) significantly correlated with response to neoadjuvant chemotherapy [$p=0.041$ and $p=0.028$, respectively].

TYMS protein expression (total, free, bound) was quantified in both pre- and posttreatment tumor specimens from 22 patients with locally advanced gastric and EGJ adenocarcinoma treated with neoadjuvant fluorouracil-based chemotherapy followed by surgery within a phase II prospective trial, and it was correlated with response to preoperative treatments [33]. Pretreatment total TYMS expression levels resulted significantly higher in nonresponder patients than in responders. Moreover, after exposure to chemotherapy, levels of free TYMS were significantly lower, and those of bound TYMS were significantly higher in responder patients than in nonresponders. These preliminary findings suggest that response to neoadjuvant fluorouracil-based chemotherapy might be associated with lower levels of total TYMS in pretreatment specimens and with decreased free TYMS levels in posttreatment surgical specimens.

In a cohort of 99 patients with locally advanced esophageal cancers treated with concurrent cisplatin/fluorouracil-based chemotherapy plus

radiotherapy and subsequent surgery, pretreatment biopsies were analyzed to determine mRNA expression levels of chemotherapy metabolism-associated biomarkers [34]. The most of patients had an adenocarcinoma histotype. Interestingly, an inverse correlation was observed between mRNA expression levels of TYMS and response to preoperative treatments [$p < 0.001$]. Moreover, at multivariate analysis, higher RMN expression levels of TYMS, excision cross-complementing gene 1 (ERCC1), and glutathione S-transferase (GSTP1) were statistically significant predictors of decreased OS.

10.3 Apoptosis-Related Biomarkers

10.3.1 p53

Abnormalities of the oncosuppressor protein p53 are the most frequently detected in human malignancies, as they considerably contribute to carcinogenesis through the impairment of DNA damage sensing, cell cycle arrest, and apoptosis [35, 36]. However, studies on the correlation between p53 mutation and either survival outcomes or response to systemic treatments in esophagogastric cancers have provided inconsistent results [37, 38].

A retrospective analysis on pretreatment tumor specimens from 54 locally advanced distal esophageal adenocarcinomas treated with neoadjuvant chemoradiation followed by surgery showed a significant correlation between p53 positivity and better OS, although with borderline statistical significance [$p = 0.051$] [20]. On the contrary, in another series including both squamous cell and adenocarcinoma histotypes, the presence of p53 mutation in pretreatment specimens was associated with significantly worse DFS [14.1 vs 38 months; $p = 0.0004$] and OS [21.6 vs 40 months; $p = 0.0038$] after neoadjuvant chemoradiation and surgical resection [39].

In a series of 48 patients with either adenocarcinoma or squamous cell carcinoma of the esophagus preoperatively treated with concurrent chemoradiation, p53-positive patients resulted more likely to not achieve pathological complete response (pCR) after chemoradiation than those p53-negative patients [40]. In a further study on 30 pretreatment bioptic specimens from patients with locally advanced esophageal adenocarcinomas receiving neoadjuvant chemoradiation followed by surgery, no correlation was found between p53 expression assessed by IHC and response to neoadjuvant treatments. However, the shift from p53 positivity in pretreatment bioptic specimens to p53 negativity in the surgical specimens correlated with better response to preoperative therapies and longer survival [$p = 0.036$] [41].

10.3.2 Nuclear Factor Kappa B (NF-kB)

The nuclear factor kappa B (NF-kB) is a transcription factor with critical biologic functions in the regulation of cell survival, proliferation, and migration. Aberrant NF-kB activation has been widely associated to inflammatory disorders and cancers [42].

The expression of NF-kB protein was analyzed by IHC on pre- and posttreatment tumor specimens from 43 patients with locally advanced esophageal cancers who received preoperative chemoradiation within a clinical prospective trial [43]. The 98 % of the whole population have adenocarcinomas, and the 23 % have arisen from the EGJ. NF-kB positivity significantly correlated with lack of response to preoperative treatments [$p < 0.001$], and it was associated with more aggressive biologic features and worse prognosis, with a higher proportion of patients who died at the date cutoff [48 % vs 5 %, $p = 0.0013$]. Moreover, in the multivariate analysis, NF-kB resulted in an independent predictor of DFS [$p = 0.01$] and OS [$p = 0.015$].

In a different study [44], patients with locally advanced esophageal NF-kB-positive tumors displayed a lack of pCR after neoadjuvant chemoradiation [$p = 0.006$], and NF-kB expression resulted in an only independent adverse predictor of DFS [$p = 0.01$] and OS [$p = 0.007$] in the multivariate analysis. Interestingly, in this series almost half of patients had a cancer of the EGJ, and the vast majority had adenocarcinoma.

10.3.3 Baculoviral Inhibitor of Apoptosis Repeat-Containing 3 Gene

Baculoviral inhibitor of apoptosis (IAP) repeat-containing (BIRC)3 gene encodes for the cellular IAP (cIAP)-2 protein [45], a member of the IAP family that inhibits apoptosis by directly inhibiting caspase cascade [46, 47]. A sequence analysis of the BIRC3 promoter revealed two critical nuclear factor kB (NF-kB) and two potential activator protein-1 (AP-1)-binding sites [48]. Transforming growth factor (TGF)-β-activated kinase 1 (TAK1, also called MAP3K7) is a serine/threonine kinase with a critical role in the inflammatory responses and cell survival control by integrating signals from various cytokines – including interleukin-1 (IL-1), TGF-β, and TNFα – and controlling, in turn, the activation of different transcription factors, including AP-1 and NF-kB [49]. Our group demonstrated that suppressing the expression of BIRC3 through the genetic silencing or the pharmacological inhibition of TAK1 dramatically reverted the intrinsic chemoresistance of pancreatic cancer [50]. More recently, we hypothesized that the TAK1-regulated expression of BIRC3 might be responsible for the resistance of distal esophageal and esophagogastric junction carcinoma to the pro-apoptotic effect of chemoradiotherapeutic treatments [51]. We demonstrated that the suppression of the expression of the antiapoptotic gene BIRC3 regulated by TAK1 significantly increases the sensitivity of esophageal adenocarcinoma cells to the chemotherapy and radiotherapy-induced cell death. More importantly, we measured the expression levels of BIRC3 mRNA in pretreatment biopsies from 32 patients with adenocarcinoma and 33 patients with squamous cell carcinoma treated with a preoperative schedule including weekly docetaxel and cisplatin, continuous infusion of 5-fluorouracil, and concomitant radiotherapy. Initially, we demonstrated a significantly lower expression of BIRC3 in the more sensitive population of patients affected by squamous cell carcinoma than in those affected by adenocarcinoma. Next, we performed ROC analyses to validate the potential usefulness of BIRC3 tumor expression as a biomarker to predict response to preoperative chemoradiotherapy. Whereas tumor expression levels of BIRC3 could not distinguish between sensitive or resistant esophageal squamous cell carcinoma, it significantly discriminated patients with sensitive or resistant adenocarcinoma, with AUC values of 0.7773 or 0.8074 by using the SPR or TRG classifications, respectively. Taken together, these results candidate BIRC3 as a useful predictive marker for discriminating patients with esophageal and esophagogastric junction adenocarcinoma who will most likely benefit from preoperative chemoradiotherapy.

10.4 Leptin

Leptin is an adipose tissue-secreted hormone, also referred to as adipocytokine, which plays a key role in the control of food intake and energy expenditure by regulating appetite at hypothalamic appetite centers [52, 53]. A strong relationship between overweight and increased risk of development of esophageal and EGJ cancers has been extensively demonstrated, and it has been corroborated by the emerging evidence on the carcinogenic properties of adipocytokines [54, 55]. Moreover, there are preclinical evidences supporting the role of leptin in stimulating cell proliferation and inhibiting cell death in gastric and EGJ carcinoma cell lines [56], and leptin receptors were found overexpressed in gastric cancer epithelia [57].

In a recent study investigating novel potential predictive biomarkers of response to chemotherapy in esophagogastric cancers [58], gene expression profiling was performed in an exploratory cohort of pretreatment tumor biopsies from 14 patients with stage I–IV esophagogastric adenocarcinoma receiving cisplatin-based chemotherapy, in order to identify those genes that were differentially expressed between radiological responder and nonresponder patients. They found 520 genes with statistically significant differential expression according to response to chemotherapy [$p < 0.02$]. Subsequent gene enrichment analysis indicated six signal-

ing pathways, including adipocytokine pathway, as the most likely to be involved in chemoresistance. Thereafter, they investigated the correlation between IHC expression of leptin protein and the histopathological response to preoperative chemotherapy and survival outcomes in an independent series of 154 patients with esophagogastric adenocarcinomas treated either with surgery alone ($n=90$) or with neoadjuvant cisplatin-based chemotherapy followed by surgery ($n=64$). Interestingly, among neoadjuvantly treated patients high expression levels of leptin protein were found to significantly correlate with lack of histopathological response [$p=0.007$], whereas there was no correlation between expression levels of leptin protein and survival. On the contrary, among primarily resected patients high expression levels of leptin protein were significantly associated with better survival [$p=0.021$]. Stratifying patients according to IHC expression levels of leptin protein, they found that in the subgroup with high leptin expression there were no differences in survival outcomes between those primarily resected and those receiving neoadjuvant chemotherapy, whereas in the subgroup with low leptin expression, those receiving neoadjuvant chemotherapy had significantly better survival [p for interaction $=0.038$], consistently with the previous evidence supporting the role of leptin in mediating chemoresistance.

These findings as a whole suggest that leptin might be a negative predictor of response to neoadjuvant chemotherapy and a treatment-independent favorable prognostic factor.

10.5 Aldehyde Dehydrogenase

Aldehyde dehydrogenase (ALDH)-1 is a marker of cancer stem cells (CSCs), which are a population of chemoresistant cells with self-renewal properties. ALDH-1 has been found highly expressed in various cancers, including those arising from the gastrointestinal tract, and it has been correlated with worse prognosis and lack of response to chemotherapy in many preclinical tumor models [59, 60].

In a series of 167 potentially resectable esophageal and EGJ adenocarcinomas treated with chemoradiation and subsequent surgery, pretreatment tumor specimens were investigated for ALDH-1 expression by IHC [61]. Consistently with data from previous studies [9, 10], the 24 % of patients had a pathological complete response (CR), and the 16 % had a "extremely resistant" cancer. Interestingly, a significant association was found between pathological CR and lower ALDH-1 expression levels [odds ratio 0.432, $p<0.001$] and between extremely resistant to chemoradiation and higher ALDH-1 expression levels [odds ratio 3.782, $p<0.001$]. Moreover, assays performed on human esophageal adenocarcinoma cell lines confirmed the correlation between ALDH-1 overexpression and both resistance to chemotherapy and aggressiveness of phenotypes and showed upregulation of ALDH-1 in those cell lines with acquired chemoresistance. The results of this study indicate a role for ALDH-1 as a negative predictor of response to neoadjuvant systemic therapy and, thus, as a biomarker of chemoresistance.

10.6 Genomic Signatures

Genomic processing has become a promising and widely applied instrument for the study of molecular mechanisms driving the response to cytotoxic treatments in many diseases, including locally advanced esophagogastric adenocarcinomas [62, 63].

Pretreatment endoscopic specimens from 19 patients with localized esophageal cancers who had received preoperative chemoradiation were investigated by performing gene expression profiling, in order to identify the key molecular pathways involved in the mediation of response to neoadjuvant treatments [64]. The most of the patients had an adenocarcinoma of distal esophagus or of the EGJ (14/19). Unsupervised hierarchical cluster analysis identified two distinct molecular subtypes, each consisting of nine and ten cancer patients, respectively. Approximately 400 genes were found differentially expressed between these two subtypes. Seven out of nine patients in the molecular sub-

type I were adenocarcinomas, while only one adenocarcinoma was included in the subtype II. Moreover, five out of six patients achieving pathological complete response (pCR) clustered into subtype I, whereas the most of patients who displayed less than pCR clustered into subtype II. Interestingly, the molecular subtype II portended shorter DFS [22.42 vs 28.55 months, p not reported] and OS [23 vs 27.3 months, p not reported] than the subtype I and displayed more downregulation of the genes associated with apoptosis, calcium homeostasis, stress response, and proliferation. Moreover, among genes with lower expression in the subtype II compared to the subtype I, those encoding the TP53 effector related to peripheral myelin protein 22 (PERP); the calcium-binding protein S100A2 and the small proline-rich protein (SPRR)3 were able to discriminate between pCR and less than pCR with high sensitivity and specificity [86 % and 85 %, respectively]. This genomic dichotomization could become a useful tool for patient selection, avoiding unnecessary toxic treatments to those not expected to respond to neoadjuvant chemoradiation.

Conclusions

The discovery of predictive biomarkers of response to neoadjuvant chemotherapy and radiotherapy for locally advanced resectable adenocarcinoma of the distal esophagus and the EGJ has become an urgent need, as current therapeutic options still provide only modest improvements in survival outcomes and, thus, required to be optimized through a better selection of patients most likely to benefit, as well as through the development of novel tailored approaches able to overcome chemo- and radioresistance.

A number of studies have indicated molecular and genetic markers as potential predictors of response to preoperative cytotoxic treatments and survival; however, none of them has been validated to date for use in clinical practice. This is likely because data come from retrospective and small series and frequently do not allow a clear discrimination between the predictive and prognostic significance of the biomarker investigated. In addition, these studies are extremely heterogeneous in terms of histotypes (adenocarcinoma vs squamous cell carcinoma), sites of origin (the stomach vs esophagus vs EGJ), and treatment arms (neoadjuvant chemotherapy vs chemoradiotherapy), not allowing to draw uniform conclusions.

The most promising insights come from studies evaluating the predictive potential of EGFR, TAK1/BIRC3, leptin, and ALDH-1. However, their results need to be confirmed in larger and prospective series in which patients will be stratified according to the value of the biomarker investigated and randomized to receive or not preoperative treatments.

Genomic signatures represent another potentially useful tool for discriminating patients expected to benefit from preoperative chemotherapy and/or radiotherapy; however, they are still at an early phase of investigation.

References

1. Siegel R et al (2014) Cancer statistics, 2014. CA Cancer J Clin 64(1):9–29
2. Edgren G et al (2013) A global assessment of the oesophageal adenocarcinoma epidemic. Gut 62(10): 1406–1414
3. Siewert JR et al (2001) Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more than 1,000 consecutive resections at a single center in the Western world. Ann Surg 234(3):360–367, discussion 368–9
4. Bain GH, Petty RD (2010) Predicting response to treatment in gastroesophageal junction adenocarcinomas: combining clinical, imaging, and molecular biomarkers. Oncologist 15(3):270–284
5. Oppedijk V et al (2014) Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol 32(5):385–391
6. van Hagen P et al (2012) Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 366(22):2074–2084
7. Cunningham D et al (2006) Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 355(1):11–20
8. Burtness B, Ilson D, Iqbal S (2014) New directions in perioperative management of locally advanced esophagogastric cancer. Am Soc Clin Oncol Educ Book e172–e178.
9. Brucher BL et al (2009) Response to preoperative therapy in upper gastrointestinal cancers. Ann Surg Oncol 16(4):878–886

10. Chirieac LR et al (2005) Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. Cancer 103(7):1347–1355
11. Berger AC et al (2005) Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. J Clin Oncol 23(19):4330–4337
12. Brucher BL et al (2006) The clinical impact of histopathologic response assessment by residual tumor cell quantification in esophageal squamous cell carcinomas. Cancer 106(10):2119–2127
13. Davies AR et al (2014) Tumor stage after neoadjuvant chemotherapy determines survival after surgery for adenocarcinoma of the esophagus and esophagogastric junction. J Clin Oncol 32(27):2983–2990
14. Fareed KR et al (2009) Biomarkers of response to therapy in oesophago-gastric cancer. Gut 58(1):127–143
15. Popa EC, Shah MA (2013) Met, IGF1R, and other new targets in upper GI malignancies. Curr Treat Options Oncol 14(3):321–336
16. Wang KL et al (2007) Expression of epidermal growth factor receptor in esophageal and esophagogastric junction adenocarcinomas: association with poor outcome. Cancer 109(4):658–667
17. Yacoub L, Goldman H, Odze RD (1997) Transforming growth factor-alpha, epidermal growth factor receptor, and MiB-1 expression in Barrett's-associated neoplasia: correlation with prognosis. Mod Pathol 10(2):105–112
18. Miller CT et al (2003) Gene amplification in esophageal adenocarcinomas and Barrett's with high-grade dysplasia. Clin Cancer Res 9(13):4819–4825
19. Marx AH et al (2010) Homogeneous EGFR amplification defines a subset of aggressive Barrett's adenocarcinomas with poor prognosis. Histopathology 57(3):418–426
20. Gibson MK et al (2003) Epidermal growth factor receptor, p53 mutation, and pathological response predict survival in patients with locally advanced esophageal cancer treated with preoperative chemoradiotherapy. Clin Cancer Res 9(17):6461–6468
21. Aichler M et al (2014) Epidermal growth factor receptor (EGFR) is an independent adverse prognostic factor in esophageal adenocarcinoma patients treated with cisplatin-based neoadjuvant chemotherapy. Oncotarget 5(16):6620–6632
22. Hofmann M et al (2008) Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology 52(7):797–805
23. Gravalos C, Jimeno A (2008) HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol 19(9):1523–1529
24. Tanner M et al (2005) Amplification of HER-2 in gastric carcinoma: association with Topoisomerase IIalpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. Ann Oncol 16(2):273–278
25. Hechtman JF, Polydorides AD (2012) HER2/neu gene amplification and protein overexpression in gastric and gastroesophageal junction adenocarcinoma: a review of histopathology, diagnostic testing, and clinical implications. Arch Pathol Lab Med 136(6):691–697
26. Okines AF et al (2013) Effect of HER2 on prognosis and benefit from peri-operative chemotherapy in early oesophago-gastric adenocarcinoma in the MAGIC trial. Ann Oncol 24(5):1253–1261
27. Janjigian YY et al (2012) Prognosis of metastatic gastric and gastroesophageal junction cancer by HER2 status: a European and USA International collaborative analysis. Ann Oncol 23(10):2656–2662
28. Shitara K et al (2012) Reporting patient characteristics and stratification factors in randomized trials of systemic chemotherapy for advanced gastric cancer. Gastric Cancer 15(2):137–143
29. Bang YJ et al (2010) Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 376(9742):687–697
30. Watson S et al (2013) Combined HER2 analysis of biopsies and surgical specimens to optimize detection of trastuzumab-eligible patients in eso-gastric adenocarcinoma: a GERCOR study. Ann Oncol 24(12):3035–3039
31. Langer R et al (2005) Association of pretherapeutic expression of chemotherapy-related genes with response to neoadjuvant chemotherapy in Barrett carcinoma. Clin Cancer Res 11(20):7462–7469
32. Langer R et al (2007) Comparison of pretherapeutic and posttherapeutic expression levels of chemotherapy-associated genes in adenocarcinomas of the esophagus treated by 5-fluorouracil- and cisplatin-based neoadjuvant chemotherapy. Am J Clin Pathol 128(2):191–197
33. Alexander HR et al (1995) Thymidylate synthase protein expression: association with response to neoadjuvant chemotherapy and resection for locally advanced gastric and gastroesophageal adenocarcinoma. Cancer J Sci Am 1(1):49–54
34. Joshi MB et al (2005) High gene expression of TS1, GSTP1, and ERCC1 are risk factors for survival in patients treated with trimodality therapy for esophageal cancer. Clin Cancer Res 11(6):2215–2221
35. Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100(1):57–70
36. Muller PA, Vousden KH (2014) Mutant p53 in cancer: new functions and therapeutic opportunities. Cancer Cell 25(3):304–317
37. Johnstone RW, Ruefli AA, Lowe SW (2002) Apoptosis: a link between cancer genetics and chemotherapy. Cell 108(2):153–164
38. Dumont P et al (2003) The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. Nat Genet 33(3):357–365
39. Ribeiro U Jr et al (1998) p53 sequence analysis predicts treatment response and outcome of patients with esophageal carcinoma. Cancer 83(1):7–18
40. Beardsmore DM et al (2003) Apoptotic and proliferative indexes in esophageal cancer: predictors of

response to neoadjuvant therapy [corrected]. J Gastrointest Surg 7(1):77–86, discussion 86–7
41. Heeren PA et al (2004) Predictive effect of p53 and p21 alteration on chemotherapy response and survival in locally advanced adenocarcinoma of the esophagus. Anticancer Res 24(4):2579–2583
42. Melisi D, Chiao PJ (2007) NF-kappa B as a target for cancer therapy. Expert Opin Ther Targets 11(2): 133–144
43. Izzo JG et al (2006) Association of activated transcription factor nuclear factor kappab with chemoradiation resistance and poor outcome in esophageal carcinoma. J Clin Oncol 24(5):748–754
44. Izzo JG et al (2006) Pretherapy nuclear factor-kappaB status, chemoradiation resistance, and metastatic progression in esophageal carcinoma. Mol Cancer Ther 5(11):2844–2850
45. Srinivasula SM, Ashwell JD (2008) IAPs: what's in a name? Mol Cell 30(2):123–135
46. Wang CY et al (1998) NF-kappaB antiapoptosis: induction of TRAF1 and TRAF2 and c-IAP1 and c-IAP2 to suppress caspase-8 activation. Science 281(5383):1680–1683
47. Park SM, Yoon JB, Lee TH (2004) Receptor interacting protein is ubiquitinated by cellular inhibitor of apoptosis proteins (c-IAP1 and c-IAP2) in vitro. FEBS Lett 566(1–3):151–156
48. Hong SY et al (2000) Involvement of two NF-kappa B binding elements in tumor necrosis factor alpha -, CD40-, and epstein-barr virus latent membrane protein 1-mediated induction of the cellular inhibitor of apoptosis protein 2 gene. J Biol Chem 275(24): 18022–18028
49. Sakurai H (2012) Targeting of TAK1 in inflammatory disorders and cancer. Trends Pharmacol Sci 33(10): 522–530
50. Melisi D et al (2011) Modulation of pancreatic cancer chemoresistance by inhibition of TAK1. J Natl Cancer Inst 103(15):1190–1204
51. Piro G et al (2015) TAK1-regulated expression of BIRC3 predicts resistance to preoperative chemoradiotherapy in oesophageal adenocarcinoma patients. Br J Cancer 113(6):878–885. doi: 10.1038/bjc.2015.283
52. Munzberg H, Morrison CD (2015) Structure, production and signaling of leptin. Metabolism 64(1):13–23
53. Park HK, Ahima RS (2015) Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. Metabolism 64(1):24–34
54. Housa D et al (2006) Adipocytokines and cancer. Physiol Res 55(3):233–244
55. Garofalo C, Surmacz E (2006) Leptin and cancer. J Cell Physiol 207(1):12–22
56. Pai R et al (2005) Leptin activates STAT and ERK2 pathways and induces gastric cancer cell proliferation. Biochem Biophys Res Commun 331(4): 984–992
57. Howard JM et al (2010) Associations between leptin and adiponectin receptor upregulation, visceral obesity and tumour stage in oesophageal and junctional adenocarcinoma. Br J Surg 97(7):1020–1027
58. Bain GH et al (2014) Tumour expression of leptin is associated with chemotherapy resistance and therapy-independent prognosis in gastro-oesophageal adenocarcinomas. Br J Cancer 110(6):1525–1534
59. Jiang F et al (2009) Aldehyde dehydrogenase 1 is a tumor stem cell-associated marker in lung cancer. Mol Cancer Res 7(3):330–338
60. Zhang G et al (2012) Esophageal cancer tumorspheres involve cancer stem-like populations with elevated aldehyde dehydrogenase enzymatic activity. Mol Med Rep 6(3):519–524
61. Ajani JA et al (2014) ALDH-1 expression levels predict response or resistance to preoperative chemoradiation in resectable esophageal cancer patients. Mol Oncol 8(1):142–149
62. Brabender J et al (2004) A multigene expression panel for the molecular diagnosis of Barrett's esophagus and Barrett's adenocarcinoma of the esophagus. Oncogene 23(27):4780–4788
63. Dahlberg PS et al (2004) Gene expression profiles in esophageal adenocarcinoma. Ann Thorac Surg 77(3):1008–1015
64. Luthra R et al (2006) Gene expression profiling of localized esophageal carcinomas: association with pathologic response to preoperative chemoradiation. J Clin Oncol 24(2):259–267

11 Pathological Response to Neoadjuvant Treatment: More Questions Than Answers

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11.1 Introduction

Multimodal therapy (As described in Chap. 14) is currently the standard of care for EGJ cancer. In particular, induction chemoradiation is widely accepted as the standard in Siewert I and II cancers, while perioperative or induction chemotherapy is the preferred approach in Siewert III. Patients' survival is strictly related to the grade of response to preoperative therapy; indeed, it is well known that patients with pathological complete response show a higher survival rate compared to nonresponders.

Anyway, between these two extremes, there is a group of patients who respond to neoadjuvant therapy but who still have residual disease; the prognosis of this group of patients is more difficult to predict. A staging system able to stratify patients after preoperative therapy according to long-term prognosis is needed. In this chapter, we are going to discuss in detail this topic.

11.2 TNM Staging System

As described in Chap. 6, last TNM has introduced many changes in the classification of EGJ tumors; it, also, has identified specific rules to define them as esophageal or gastric tumors. The TNM staging system after neoadjuvant therapy reflects the same rules of TNM as regards depth of invasion, nodal involvement, and metastatic disease. The addition of "yp" prefix underlines that it's the post-induction TNM stage. The ypTNM classification is easily applicable and very confident for pathologists and clinicians. The main merit of the 7th TNM version is the data-driven processing [1]. The group of patient used for statistical analysis had surgery alone with no added chemotherapy or radiotherapy; the elaboration of TNM, therefore, had not taken into account the relationship between stage and survival in patients receiving neoadjuvant chemo or chemoradiation. The application of the prefix "yp" is only supported by the simplicity of use and not by data. Mehta [2] and coworkers compared 6th and 7th TNM in a cohort of patients treated with chemotherapy followed by surgery: no significant survival difference between T categories in both staging systems was reported

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except for ypT4 compared with ypT3. More effective was N stratification but only comparing ypN2 with ypN3. In multivariate analysis using the TNM 7th edition, only ypN was an independent prognostic predictor of survival.

Some conflicting results were reported more recently; indeed, Schmidt et al. [3] reported the ypT and the ypN stages to be independent prognostic factors in the multivariable analysis. Anyway, based on the available data, the prognostic role of the ypTNM staging system is questionable.

Furthermore, there are some main limits of ypTNM classification; these could, at least partially, explain its low prognostic accuracy.

First, ypTNM stage grouping is not applicable to some patients because some new groups created by multimodal therapy such as ypT0N1–ypT0N3 are not considered in the pTNM.

Moreover it cannot give any information about the rate of response to the therapy that is a well know independent prognostic factor: the ypTNM may classify as identical, two malignancies, one arising from a downstaging and the other by a progression of the disease.

In conclusion, TNM, probably, cannot provide reliable informations on the level of response to therapy, the long-term survival, or risk of relapse; it is only a snapshot of the disease in the particular case.

11.3 Histopathological Response in Siewert I and II

Mandard [4] and coworkers in the 1990s noticed that TNM was unsuccessful to describe prognosis after induction treatments and thus were the first to propose a classification of response to chemoradiotherapy for esophageal carcinoma, which was published in 1994. In their classification, they created five classes of response on primary site, named tumor regression grades (TRG): TRG1, no residual cancer; TRG2, rare residual cancer cells; TRG3, an increased number of residual cells, with fibrosis outgrowing residual cancer; TRG4, residual cancer outgrowing fibrosis; and TRG5, absence of regression. Authors could detect that in multivariate analysis, tumor regression (TRG1-3 versus TRG4-5) was the only significant predictor of survival ($P<0.001$) and suggested to consider tumor regression grade when evaluating treatment results.

Although the creation of this classification was an invaluable intuition, it has a number of drawbacks. First, TRG is a qualitative evaluation, which can be affected by pathologist's expertise and training. Moreover, while it is pretty easy to define TRG1 cases, which do not show residual cancer, and TRG4-5, where absent or nearly absent response to treatment is present, the definition of partial responders is by no means objective, and, in a preliminary survey proposed to our pathologists, agreement in differentiating TRG2 and TRG3 was poor.

Secondly, TRG has been reported to provide good prognostic definition irrespective of node (N) category, but the role of nodal metastases on prognosis of EGJ cancer is renowned. We previously used Mandard classification on a cohort of our patients [5] and demonstrated that when N category was considered, the impact of TRG on survival was impaired: although TRG retained its prognostic significance in N0 patients, survival in N+ patients was poor, irrespective of Mandard grade.

After Mandard classification was published, other authors created their own classification of response to induction treatments for esophageal and, with lesser extent, gastric cancer. So far, many classifications have been proposed, but none is currently widely accepted.

In contrast to Mandard, who considered only response on T, other authors [6–8] correctly considered response both on T and N. However, some authors [7, 8] coupled patients without residual cancer both on primary site and nodal level (ypT0N0), with patients with up to 10 % of residual cancer cells. Although probably survival differences are difficult to detect when residual cancer is marginal, we strongly believe that coupling patients without residual cancer and patients with residual cancer is deeply incorrect from a theoretical point of view.

All studies, despite differences in definition of classes, demonstrated that response to treatment

is a key prognostic determinant and that patients with better response show significant survival advantage [6–8].

We also previously created a classification of response for esophageal and EGJ cancer [5] and demonstrated that pathological complete responders (pCR) have the best prognosis, while ypN+ patients the worse. In our classification, named size-based pathological response (SPR) classification, tumor regression was divided into four classes: SPR1, pathological complete response (pCR) (ypT0N0); SPR2, minimal residual disease (MRD) (residual foci ≤1 cm, ypN0); SPR3, nonresponse (residual foci >1 cm, ypN0); and SPR4, node-positive cases (ypN+). SPR3 had low survival, similar to ypN+, while SPR2 showed an intermediate prognosis between SPR1 and SPR3–SPR4 (Fig. 11.1). The fact of considering nodal involvement and the possibility to objectively measure residual cancer, improving agreement among pathologists, are the main advantages of this classification. Furthermore, the class of partial responders (SPR2) seems to have prognostic differences compared with all the other classes of response and deserves recognition.

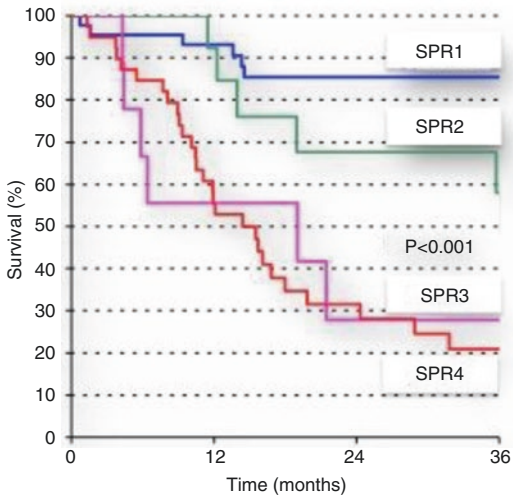

Fig. 11.1 Three-year disease-related survival curves for patients staged with SPR (size-based pathological response) classification of response ($p<0.001$) (Reproduced with permission from Verlato et al. [5])

The best possible result of induction treatments is then pathological complete response: we previously reported a 94 % 5-year disease-related survival for adenocarcinoma Siewert I and II pCR patients [9]. Hence every effort should be made to increase the number of pCR patients, which in our experience can exceed 40 % of cases.

If primary tumor can downstage and even disappear, the same might happen to lymph nodes. Hence we can take a little step forward and consider tumor regression on lymph nodes. We postulated that natural N0 patients, those who were both cN0 and ypN0, might have a better survival than those who downstaged to ypN0 after induction treatments and that however the latter group might have a better survival than ypN+. In our results after induction CRT (manuscript under revision), we found that 5-year disease-related survival was almost 80 % in natural N0 and around 40 % in downstaged N0, while no ypN+ patient was alive at 5 years ($P<0.05$). Hence, although the best prognosis can actually be found in natural N0 patients, in case of nodal downstaging survival significantly improves compared with ypN+ patient.

All these results have clinical implications: while response on T is a prognostic determinant and hence all locally advanced cancers deserve multimodal treatments, also nodal downstaging gives a significant survival advantage, and multimodal treatments, especially induction CRT in Siewert I and II cancers, should be offered to all cN+ patients. Thus, a pathological classification after neoadjuvant treatment should evaluate the regression grade of both the primary tumor and the lymph nodes in order to correctly predict the prognosis of patients treated with multimodal therapy.

11.4 Histopathological Response in Siewert III

Siewert III cancers are normally considered gastric cancers and are staged accordingly. There are no dedicated studies specifically on response to treatment in Siewert III, hence they are considered together with gastric cancers.

In 2003, Becker [10] and coworkers published a study on histopathological changes of gastric

cancer after neoadjuvant chemotherapy. The authors described three grades of response to chemotherapy in the primary tumor bed: grade 1a, complete tumor regression (0 % residual tumor) and grade 1b, subtotal tumor regression (<10 % residual tumor per tumor bed); grade 2, partial tumor regression (10–50 % residual tumor per tumor bed); and grade 3, minimal or no tumor regression (>50 % residual tumor per tumor bed). In 2011 [11], the authors validated their classification in a series of about 500 patients ($p < 0.001$), and they noted a strong correlation between tumor regression and pathological ypTNM; however, there were no differences in survival between patients with complete pathological response (ypT0N0) and patients with subtotal tumor regression probably because only 3.3 % of patients had a complete tumor regression. The multivariable analysis revealed that tumor regression and ypN were independent prognostic factors for survival. A similar classification was proposed by the Japanese Gastric Cancer Association [12]: in the 3rd english edition of Japanese classification of gastric carcinoma, they subdivided response to neoadjuvant therapy in four grades: grade 0, no evidence of effect; grade 1, divided in two subgroups (grade 1a, very slight effect with viable tumor cells occupying more than 2/3 of the tumorous area (>67 % residual tumor per tumor bed) and grade 1b, slight effect with viable tumor cells occupying more than 1/3 but less than 2/3 of the tumorous area (33–67 % residual tumor per tumor bed); grade 2, considerable effect (<30 % of tumor per tumor bed); and grade 3, complete response (confirmed on additional sectioning). Both classification systems are based on the same principle: the relationship between fibrosis and neoplastic cells, but assuming different cutoff. The classification proposed by Becker is more commonly used in the West as the Japanese classification is most prevalent in Eastern countries, making it difficult to compare different case studies. Recently Nakamura and coworkers [13] considered the percentage of residual tumor as a continuous variable, in an attempt to identify which definition of the cutoff is the most accurate for predicting survival: they define 10 % cutoff the best in terms of the hazard ratio of overall survival. In subgroup analysis, the other cutoffs (33 %, 50 %, and 67 %) predict survival well except for linitis plastica probably because the percentage of residual tumor may not be as accurate as in not linitis tumors. They suggested using the 10 % cutoff as the global standard cutoff except for Bormann type 4 tumors.

Although the use of this rule can solve some controversies, it has a number of disadvantages. First, only less than 5 % of gastric cancer has a pathological complete response, and only 20–25 % [9, 13] shows a subtotal tumor regression (<10 % of residual tumor) after neoadjuvant chemotherapy; therefore only for less than 1/4 of cases, it is possible to predict the survival. Secondly, ypN parameter is not considered and near 70 % of patient are N+ after therapy [14]. Starting from the impact that ypN has on prognosis, Becker [15] has developed a multifactorial prognostic score (PRSC) to stratify gastric cancer patients with different outcomes after chemotherapy; this score takes in consideration in addition to ypN also ypT and the degree of regression of the neoplasm. Interestingly PRSC showed a significant value for the prediction on survival especially in proximal gastric cancer; probably, it can be a useful tool in Siewert III cancer but it must be validated on multicentric series.

In conclusion, in the era of multimodal treatment, we need a classification of response to treatment that can be more descriptive than TNM and that can provide clear prognostic information. A key feature of the "perfect" classification will be to consider regression both on primary tumor and at nodal level.

References

1. Ishwaran H, Blackstone EH, Apperson-Hansen C, Rice TW (2009) A novel approach to cancer staging: application to esophageal cancer. Biostatistics 10(4): 603–620
2. Mehta SP, Jose P, Mirza A et al (2013) Comparison of the prognostic value of the 6th and 7th editions of the Union for International Cancer Control TNM staging system in patients with lower esophageal cancer undergoing neoadjuvant chemotherapy followed by surgery. Dis Esophagus 26(2):182–188

3. Schmidt T, Sicic L, Blank S et al (2013) Prognostic value of histopathological regression in 850 neoadjuvantly treated oesophagogastric adenocarcinomas. Br J Cancer 2014:1–9
4. Mandard AM, Dalibard F, Mandard JC, Marnay J et al (1994) Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer 73:2680–2686
5. Verlato G, Zanoni A, Tomezzoli A et al (2010) Response to induction therapy in oesophageal and cardia carcinoma using Mandard tumor regression grade or size of residual foci. Br J Surg 97(5): 719–725
6. Swisher SG, Hofstetter W, Wu TT et al (2005) Proposed revision of the esophageal cancer staging system to accommodate pathologic response (pP) following preoperative chemoradiation (CRT). Ann Surg 241(5):810–817; discussion 817–820
7. Schneider PM, Baldus SE, Metzger R et al (2005) Histomorphologic tumor regression and lymph node metastases determine prognosis following neoadjuvant radiochemotherapy for esophageal cancer: implications for response classification. Ann Surg 242(5):684–692
8. Hölscher AH, Drebber U, Schmidt H et al (2014) Prognostic classification of histopathologic response to neoadjuvant therapy in esophageal adenocarcinoma. Ann Surg 260(5):779–785
9. Zanoni A, Verlato G, Giacopuzzi S et al (2012) Neoadjuvant concurrent chemoradiotherapy for locally advanced esophageal cancer in a single high-volume center. Ann Surg Oncol 20(6):1993–1999
10. Becker K, Mueller JD, Schulmacher C et al (2003) Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. Cancer 98(7):1521–1530
11. Becker K, Langer R, Reim D et al (2011) Significance of histopathological tumor regression after neoadjuvant chemotherapy in gastric adenocarcinomas: a summary of 480 cases. Ann Surg 253(5):934–939
12. Sano T, Kodera Y (2011) Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 14(2):101–112
13. Nakamura K, Kuwata T, Shimoda T et al (2015) Determination of the optimal cutoff percentage of residual tumors to define the pathological response rate for gastric cancer treated with preoperative therapy (JCOG1004-A). Gastric Cancer 18(3):597–604
14. Cunningham D, Allum WH, Stenning SP et al (2005) Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. World Health 355(1):877–889
15. Becker K, Reim D, Novotny A et al (2012) Proposal for a multifactorial prognostic score that accurately classifies 3 groups of gastric carcinoma patients with different outcomes after neoadjuvant chemotherapy and surgery. Ann Surg 256(6):1002–1007

Hospital Volume and Centralization in EGJ Cancer

12

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Cancer of the esophagus has a dismal prognosis [1]. Surgical resection, either primarily or after neoadjuvant treatment, is considered in case of local disease. However, the mortality rate for this intervention is high notwithstanding the significant progresses made in perioperative care and surgical technique [2]; postoperative and in-hospital mortality rate after this operation remain among the highest of all cancer resections [3, 4], and tumor prognosis remains poor with a cumulative 5-year survival in the range of 20–30 % [2, 5].

Among factors considered to have an impact on postoperative mortality rate and on late survival after surgical treatment of cancer of the esophagus, hospital and surgeon volume seem to be important parameters.

In 1979 Luft et al. [6] described that for selected procedures, a hospital volume–outcome relationship was evident and this was the first report supporting this evidence. Since then, there have been many papers in the medical literature suggesting that procedural volume is an important determinant of outcome in cancer surgery: this relationship is especially evident for high-risk procedures, such as esophagectomy and pancreatectomy [7–9].

Studies examining the volume–outcome relationship for esophagectomy suggest that high-volume institutions with a larger caseload and appropriate infrastructure are better prepared to deliver high-quality care at all individual levels [9–11]; therefore, some authors believe that high-risk procedures such as esophagectomy should be performed only in high-volume centers in order to improve clinical outcome [10].

Two recent systematic reviews and meta-analyses of the literature on the relation between procedural volume and outcome further confirmed that there is a strong evidence for hospital volume as an important outcome determinant in esophageal cancer surgery [8, 9]. In Makar's review [9], the overall in-hospital mortality was 8.48 % in the low-volume group compared with 2.82 % in the high-volume group. Furthermore, pooled analysis of the selected trials revealed a significantly increased incidence of in-hospital mortality associated with surgery in the low-volume group (pooled odds ratio = 0.29; 95 % C.I. = 0.16–0.53; $P < 0.0001$). Hospital volume also has a strong inverse relation with late mortality, and patients operated on in high-volume centers have better survival.

Another recent meta-analysis [12] addressed the relation between hospital and single-surgeon

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volume to long-term survival after esophagectomy: the study demonstrated an improved long-term survival when the esophagectomy is conducted at high-volume hospitals by high-volume surgeons, since individual surgeon volume influences the risk of tumor recurrence.

The results of the existing literature thus support the centralization of esophageal resections in high-volume centers, with operations performed by high-volume surgeons [13–15] in order to obtain better results in terms of low postoperative mortality and longer survival rates.

We recently published our analysis regarding the impact of hospital volume on postoperative mortality after esophageal resections in Lombardy during the period 2005–2011 [16]: 43 % of resections were made in low-volume hospitals (<7 procedures/year), with only 32.6 % or resections being performed in four high-volume hospitals (>21 procedures/year). In our study we could confirm the inverse relation between hospital volume and postoperative 30-day mortality rate. A significant reduction of mortality rate after resections was found when comparing high-volume with intermediate- and low-volume centers: the 30-day mortality rate was 5.7 %, 2.6 %, and 1.7 % in low-, intermediate-, and high-volume hospitals, respectively. The odds ratio of 30-day mortality (corrected in a logistic model for age, sex, and comorbidity index) was 0.47 (95 % CI 0.28–0.78) for intermediate-volume hospitals and 0.36 (95 % CI 0.20–0.53) for high-volume hospitals ($p < 0.0001$).

In our analysis, the median postoperative length of stay was 20 days in high-volume hospitals as compared to more than 25 days in low- and intermediate-volume hospitals, even if patients cured at high-volume centers had more comorbidities, suggesting a significantly more efficient process of care in these centers.

However, there are some aspects of the relationship hospital volume/mortality which are unclear: among them the cutoff values to define high- and low-volume centers are variously defined, with criteria that are not objective [17]; moreover, a high-volume center for esophagectomy in the West would be considered a low-volume center in the East where the general number of esophagectomies is definitely higher (Table 12.1).

Moreover, as far as the surgeon–outcome relationship is concerned, it has been demonstrated that among high-volume surgeons for esophagectomy, there are significant differences in terms of parameters such as blood loss and major complications, making some authors questioning the effect of the previous relationship [23] and returning to the old concept of craftsmanship based on surgical attitude and ability of the single operators. In fact, there are studies that have failed to demonstrate an improvement in clinical outcome associated with surgery in high-volume centers [24, 25]: in 2009 Wright analyzed more than 2300 esophagectomies from the database of the Society of Thoracic Surgeons and identified several predictors of major morbidity and mortality for this operation without finding a significant volume–outcome relationship.

One solid data consists of the lower postoperative mortality observed in high-volume versus low-volume centers, with a comparable early morbidity. This evidence suggests that the main determinant for a low in-hospital mortality is the timely recognition and effective management of postoperative complications after major cancer

Table 12.1 Classification of low- and high-volume hospitals for a number of esophagectomy/year

Author	Country	Publ. year	Low volume	High volume
Begg [18]	USA	1998	<5	>11
Birkmeyer [19]	USA	2002	<2	>19
Lin [20]	Taiwan	2006	<78	>346
Wouters [15]	Netherlands	2009	<9	>9
Fujita [21]	Japan	2010	<4	>80
Munasinghe [22]	USA	2014		>26.4

surgery [26], thus underlining the importance of the hospital context in which this high-risk operation is performed. High-volume hospitals can offer trained multidisciplinary teams, effective diagnostics, treatment, and care, beyond surgeons' experience and expertise. The postoperative mortality rate may thus be reduced, thanks to the presence of various professional experts aiming at the same goal: the patient outcome. The concomitance of experienced anesthetists (including ICU staff), nursing and surgical teams, physiotherapists, and nutritionists, the availability of expert endoscopists who are very active in endoscopic management of anastomotic complications, and the presence of specific perioperative care pathways can all contribute to improve the results in high-volume hospitals. The outcome of these very complex surgical procedures such as esophagectomy thus directly depends on the "supporting cast" of the hospital [27, 28] and not only on surgeon and case volume.

Notwithstanding some conflicting results, it still appears that the concentration of these procedures in high-volume centers could lead to better short-term results and decreased mortality [9, 10], and basing on the differences in outcomes that have been reported [19, 29] between high-volume and low-volume providers, some European countries have started programs of regionalization of upper gastrointestinal surgery [10, 30–32].

In the UK, in 2001, the NHS started a process of centralizing cancer of the foregut in services with a target of at least 40 esophagectomies and 60 gastrectomies each year [30]. By 2008 and 2009, 82 % of esophageal cancer resections were done in the 41 designated centers, with 63 % of esophagectomies being performed in high-volume centers (at least 50 resections per year) [33]. The centralization of esophageal resections in England has led to a consistent improvement in perioperative mortality [31, 34]. In other recent experiences, the process of regionalization of major thoracic surgery [35] proved feasible but uneffective in reducing the mortality rate for esophagectomy.

In 2006 the Netherlands started a program of centralization of esophageal surgery with a minimum annual volume of ten per year [36]; this volume was increased to 20 per year in 2011.

In Denmark the majority of esophagectomies are performed in hospitals with a volume of over 40 per year.

In a recent publication, the results of esophagectomy in England after the centralization process had been introduced and were compared with the results of the same operation in the United States with no centralization of care [22]. The data from the United States were collected from the National Inpatient Sample (NIS); they were representative of 20 % of all the US hospitals. The results of this retrospective analysis, considering esophagectomies performed between 2005 and 2010, showed that being operated in the United States compared with England was an independent predictor of mortality. However, if the centers performing esophagectomy were divided into high- and low-volume centers using as a cutoff value of the upper quartile threshold of case volume for English hospitals (26.4 resections per year), the unadjusted in-hospital mortality rate among the high-volume hospitals was higher in England than in the United States (3.5 % vs 2.1 %, $P=0.02$). With this analysis being operated in England was identified as significant predictors of mortality, therefore again suggesting the existence of the hospital volume/mortality inverse relationship. Among the high-volume centers in the United States, there was also a significant reduction in length of stay from 12 to 10 days ($P<0.001$), which may be a surrogate for the potential cost efficiencies that may be achieved within high-volume centers.

It appears then that a policy of centralization of care for upper gastrointestinal surgery on a regional level in dedicated surgical units of high-volume referral hospitals might be beneficial for care of these patients, even if procedural volume should not be the only quality criteria. Beyond that it must be considered that the process of regionalization of major surgical procedures carries also some potential problems such as the travel costs for patients living at distance from high-volume centers and for their family.

References

1. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R, EUROCARE Working Group. EUROCARE-4 (2009) Survival of cancer patients diagnosed in 1995–1999. Results and commentary. Eur J Cancer 45:931–991
2. Jamieson GG, Mathew G, Ludemann R, Wayman J, Myers JC, Devitt PG (2004) Postoperative mortality following oesophagectomy and problems in reporting its rate. Br J Surg 91:943–947
3. Finks JF, Osborne NH, Birkmeyer JD (2011) Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med 364:2128–2137
4. Damhuis RA, Wijnhoven BP, Plaisier PW, Kirkels WJ, Kranse R, van Lanschot JJ (2012) Comparison of 30-day, 90-day and in-hospital postoperative mortality for eight different cancer types. Br J Surg 99:1149–1154
5. Kohn GP, Galanko JA, Meyers MO, Feins RH, Farrell TM (2009) National trends in esophageal surgery: are outcomes as good as we believe? J Gastrointest Surg 13:1900–1910; discussion 1910–1912
6. Luft HS, Bunker JP, Enthoven AC (1979) Should operations be regionalized? The empirical relation between surgical volume and mortality. N Engl J Med 301(25):1364–1369
7. Dikken JL, Dassen AE, Lemmens VEP, Putter H, Krijnen P, van der Geest L, Bosscha K, Verheij M, van de Velde CJH, Wouters MWJM (2012) Effect of hospital volume on postoperative mortality and survival after oesophageal and gastric cancer surgery in the Netherlands between 1989 and 2009. Eur J Cancer 48:1004–1013
8. Wouters MWJM, Gooiker GA, van Sandick JW, Tollenaar RAEM (2012) The volume-outcome relation in the surgical treatment of esophageal cancer: a systematic review and meta-analysis. Cancer 118: 1754–1763
9. Markar SR, Karthikesalingam A, Thrumurthy S, Low DE (2012) Volume-outcome relationship in surgery for esophageal malignancy: systematic review and meta-analysis 2000–2011. J Gastrointest Surg 16: 1055–1063
10. Anderson O, Ni Z, Møller H, Coupland VH, Davies EA, Allum WH, Hanna GB (2011) Hospital volume and survival in oesophagectomy and gastrectomy for cancer. Eur J Cancer 47:2408–2414
11. Birkmeyer JD, Sun Y, Wong SL, Stukel TA (2007) Hospital volume and late survival after cancer surgery. Ann Surg 245:777–783
12. Brusselaers N, Mattsson F, Lagergren J (2014) Hospital and surgeon volume in relation to long-term survival after oesophagectomy: systematic review and meta-analysis. Gut 63:1393–1400
13. Chang KH, McAnena OJ, Smith MJ, Salman RR, Khan MF, Lowe D (2010) Surgery for oesophageal cancer at Galway University Hospital 1993–2008. Ir J Med Sci 179:521–527
14. Forshaw MJ, Gossage JA, Stephens J, Strauss D, Botha AJ, Atkinson S, Mason RC (2006) Centralisation of oesophagogastric cancer services: can specialist units deliver? Ann R Coll Surg Engl 88:566–570
15. Wouters MW, Karim-Kos HE, le Cessie S, Wijnhoven BP, Stassen LP, Steup WH, Tilanus HW, Tollenaar RA (2009) Centralization of esophageal cancer surgery: does it improve clinical outcome? Ann Surg Oncol 16:1789–1798
16. Fumagalli U, Bersani M, Russo A, Melis A, de Pascale S, Rosati R (2013) Volume and outcomes after esophageal cancer surgery: the experience of the region of Lombardy-Italy. Updates Surg 65(4):271–275
17. Varghese TK, Wood DE, Farjah F, Oelschlager BK, Symons RG, MacLeod KE, Flum R, Pellegrini CA (2011) Variation in esophagectomy outcomes in hospitals meeting leapfrog volume outcome standards. Ann Thorac Surg 91:1003–1010
18. Begg CB1, Cramer LD, Hoskins WJ, Brennan MF (1998) Impact of hospital volume on operative mortality for major cancer surgery. JAMA 280: 1747–1751
19. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, Welch HG, Wennberg DE (2002) Hospital volume and surgical mortality in the United States. N Engl J Med 346:1128–1137
20. Lin HC, Xirasagar S, Lee HC, Chai CY (2006) Hospital volume and inpatient mortality after cancer-related gastrointestinal resections: the experience of an Asian country. Ann Surg Oncol 13:1182–1188
21. Fujita H, Ozawa S, Kuwano H, Ueda Y, Hattori S, Yanagawa T, Committee for Scientific Affairs, Japanese Association for Thoracic Surgery (2010) Esophagectomy for cancer: clinical concerns support centralizing operations within the larger hospitals. Dis Esoph 23:145–152
22. Munasinghe A, Markar SR, Mamidanna R, Darzi AW, Faiz OD, Hanna GB, Low DE (2015) Is it time to centralize high-risk cancer care in the United States? Comparison of outcomes of esophagectomy between England and the United States. Ann Surg 262:79–85
23. Rutegård M, Lagergren J, Rouvelas I, Lagergren P (2009) Surgeon volume is a poor proxy for skill in esophageal cancer surgery. Ann Surg 249:256–261
24. Gillison EW, Powell J, McConkey CC, Spychal RT (2002) Surgical workload and outcome after resection for carcinoma of the oesophagus and cardia. Br J Surg 89:344–348
25. Wright CD, Kucharczuk JC, O'Brien SM, Grab JD, Allen MS, Society of Thoracic Surgeons General Thoracic Surgery Database (2009) Predictors of major morbidity and mortality after esophagectomy for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk adjustment model. J Thorac Cardiovasc Surg 137:587–595; discussion 596

26. Wong SL, Revels SL, Yin H, Stewart AK, McVeigh A, Banerjee M, Birkmeyer JD (2015) Variation in hospital mortality rates with inpatient cancer surgery. Ann Surg 261:632–636
27. Ghafer AA, Birkmeyer JD, Dimick JB (2009) Variation in hospital mortality associated with inpatient surgery. N Engl J Med 361:1368–1375
28. Louie BE (2010) Is esophagectomy the paradigm for volume–outcome relationships? J Gastrointest Surg 14(Suppl 1):S115–S120
29. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL (2003) Surgeon volume and operative mortality in the United States. N Engl J Med 349:2117–2127
30. NHS Executive Guidance on Commissioning Cancer Services (2001) Improving outcomes in upper gastrointestinal cancers, the manual. Department of Health, London
31. Palser TR, Cromwell DA, Hardwick RH, Riley SA, Greenaway K, Allum W, van der Meulen JH (2009) Re-organisation of oesophago-gastric cancer care in England: progress, remaining challenges. BMC Health Serv Res 9:204
32. Dikken JL, van Sandick JW, Allum WH, Johansson J, Jensen LS, Putter H, Coupland VH, Wouters MWJM, Lemmens VEP, van de Velde CJH (2013) Differences in outcomes of oesophageal and gastric cancer surgery across Europe. Br J Surg 100:83–94
33. National Cancer Intelligence Network (NCIN) Improving outcomes: a strategy for cancer – NCIN information supplement. http://www.ncin.org.uk. Accessed 5 Oct 2012
34. Coupland VH, Lagergren J, Lüchtenborg M, Jack RH, Allum W, Holmberg L, Hanna GB, Pearce N, Møller H (2013) Hospital volume, proportion resected and mortality from oesophageal and gastric cancer: a population-based study in England, 2004–2008. Gut 62:961–967
35. Sundaresan S, McLeod R, Irish J, Burns J, Hunter A, Meertens E, Langer B, Stern H, Sherar M (2013) Early results after regionalization of thoracic surgical practice in a single-payer system. Ann Thorac Surg 95:472–479
36. van Lanschot JJ, Hulscher JB, Buskens CJ, Tilanus HW, ten Kate FJ, Obertop H (2001) Hospital volume and hospital mortality for esophagectomy. Cancer 91:1574–1578

Patient Selection and Tailored Treatment Principles

13

Francesco Casella, Andrea Zanoni, Simone Giacopuzzi, Andrea Sansonetti, and Giovanni de Manzoni

13.1 Introduction

The curative treatment of esophagogastric junction (EGJ) cancers requires major surgical procedures often along with multimodal treatments. Surgery is always very demanding also for otherwise healthy patients, and issues increase when adding chemo- and radiotherapy. The best chance of cure is obtained using all the weapons we have, such as the combination of different treatments, as described in Chaps. 14 and 19. Unfortunately, chance of cure decreases with increasing comorbidities, which limit the possibilities to benefit from the best treatment options. Indeed, despite technical advances and improvements in perioperative care, the procedure is complex and physiologically demanding and requires careful perioperative management for optimal results.

Moreover, in this era of tailoring treatment, the best approach is not only based on cancer stage but also on patients' characteristics.

Therefore, it is important to select the best tailored treatment for each patient to provide the best chance of cure and prolonged survival.

13.2 Predictors of Morbidity and Mortality

Modern management of EGJ cancers requires a multidisciplinary approach. To ensure favorable outcomes, proper patient selection, by means of accurate staging and preoperative risk assessment, must be undertaken [1, 2].

Consequently, there has been considerable interest in identifying specific factors that contribute to complications or death after surgical resection for esophagogastric cancer.

An accurate and individualized operative risk stratification can help physicians to choose the proper extent of surgery and to identify high-risk patients, who should be referred to a high-volume center.

Nomograms based on preoperative data can facilitate the design of treatment strategies, but require a large volume of data, from multiple centers, to be created.

One of the first predictive models was the Charlson comorbidity index (CCI), developed in 1987 to predict 10-year mortality for any type of

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major surgery [3]. Later, Copeland et al. [4] designed the Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) algorithm to predict the risk of morbidity and mortality for any surgical procedure. This initial algorithm often overpredicted mortality risk for a given procedure, which led to the development of a second-generation algorithm, the Portsmouth modification (P-POSSUM). This P-POSSUM algorithm was designed primarily to assess risk of perioperative mortality rather than for complications or morbidity, including physiological parameters (age, cardiac and respiratory signs, blood pressure, pulse rate, GCS, Hb and WBC levels, electrocardiography, urea, potassium and sodium levels) and operative parameters (operative severity, multiple procedures, total blood loss, peritoneal soiling, cancer, and mode of surgery).

Since the development of the P-POSSUM algorithm, several specialty-specific models have been developed, with the esophagogastric model (O-POSSUM) designed for gastric and esophageal surgery [5]. The initial study of 538 patients undergoing either a gastric or an esophageal resection highlighted that multiple risk factors contributed to mortality [6]. Urgency of surgery, preoperative stage, type of surgery, and preoperative POSSUM score were the factors used to calculate risk. The O-POSSUM provided an accurate risk-adjusted prediction of death from esophageal and gastric surgery for individual patients, and this model may be used in practice for perioperative counseling of patients and their care.

Bosch et al. [7] recently compared five risk-prediction models (P-POSSUM, O-POSSUM modification, Charlson comorbidity index, Charlson age-adjusted score, and American Society of Anesthesiologists) for esophagectomy-related morbidity and mortality. O-POSSUM was the most accurate in predicting perioperative risk for EGJ cancer.

Using a less complex approach, Dhungel et al. [2] used the National Surgical Quality Improvement Program database of the American College of Surgeons (ACS-NSQIP) to assess perioperative risk factors to predict postoperative complications. These values were subdivided based on each specific complication: the highest risks for morbidity and mortality were related to diabetes mellitus, advanced age, preoperative weight loss, and pulmonary disease.

Recently, Takeuchi et al. [8] reported the first risk stratification esophagectomy study based on a Japanese nationwide web-based database. Postoperative mortality in this study population was 3.4 %, relatively lower than that of previous reports. Authors concluded that these scoring systems seem suitable for patients undergoing esophagectomy, but further studies are needed for creation of a novel scoring system.

These nomograms have been proposed to score the risk of morbidity and mortality for both major surgical procedures and for EGJ cancers in particular, but their use in clinical practice is still limited. Anyway, these studies highlighted the most important features related to complications to surgery, in particular advanced age, poor preoperative performance, pulmonary conditions, cardiovascular status, and nutritional status.

13.3 Patients' Characteristics

The abovementioned studies focused on risk factors for complications after esophagogastrectomy, in order to construct reliable predictive models. These models identified advanced age, poor preoperative performance, pulmonary conditions, cardiovascular status, nutritional status, and neoadjuvant chemotherapy/radiotherapy as potential risk factors for poor outcome [1, 2, 9].

However, few studies have examined the effect of specific patient factors on postoperative morbidity and mortality. We will here try to describe these main features separately, in order to determine their role in predicting complications.

13.3.1 Body Mass Index

It has been well demonstrated that obesity is associated with several medical comorbidities, such as diabetes, hypertension, and coronary artery disease. Likewise, obesity is a recognized

risk factor for adenocarcinoma of the distal esophagus and esophagogastric junction, due to its association with gastroesophageal reflux and Barrett's esophagus [10–12]. In the USA there is a strong association between esophageal adenocarcinoma and obesity, whereas this association occurs less frequently in Europe.

Furthermore, overweight affects surgery and perioperative outcomes, because of excessive adipose tissue (gastric, omental and perigastric fat) and comorbidities. The most relevant issue in overweight patients is the amount of adipose tissue, which could result in longer operation time, increased intraoperative blood loss, caused by technical difficulties accessing and dissecting lymph nodes deeply embedded in fatty tissues around major abdominal vessels, and more frequent postoperative complications [13].

Extensive lymph node dissections on overweight patients have often been reported as unsuccessful with number of retrieved lymph nodes (an indicator of adequacy of lymphadenectomy) significantly smaller for obese patients than for normal-weight patients [14].

The presence of excessive subcutaneous fat predisposes the obese to impaired wound healing and thus wound infections [15]. Another factor linked to higher postoperative complication rates is the increased presence of comorbidities in obese patients, such as hypertension, diabetes mellitus, coronary heart disease, and respiratory dysfunction [13]. Interestingly, trans-hiatal esophagectomy is performed more frequently in obese patients theoretically in order to reduce pulmonary complications.

Zhang et al. [16] analyzed the prognostic value of BMI on short- and long-term outcomes in patients who had undergone resection for esophageal cancer. Obese patients more frequently experienced severe complications, and the rate of anastomotic leaks and cardiovascular diseases was double than that seen in normal-weight and underweight patients. However, overall morbidity, mortality, and reoperation rates did not differ among normal-weight, underweight, and obese patients. Hence, although with increased risk, obese patients eligible for esophagogastrectomy should not be denied surgery just on the basis of their BMI. Similar findings were reported by other authors [17–19].

Interestingly, in their population-based study, Sundelof et al. [20] reported better prognosis for obese patients (BMI ≥30) compared to patients with a normal weight (BMI 22–24.9), and so did a Canadian surgical series [21]. These findings were confirmed also by other studies [22–25].

Indeed, some surgical series [17–19, 23] and a meta-analysis [26] found that obesity (preoperative BMI ≥30) did not independently influence survival for esophageal adenocarcinoma.

Although obese patients often suffer from more comorbidities than normal-weight patients and surgeons are scared by more difficult and awkward surgical procedures, BMI itself seems not independently related to worst outcome, and probably the reported better outcomes from some studies might be related to both early diagnosis in patients with known gastroesophageal reflux and to the reduced weight loss that these patients suffer. More dedicated studies are needed in order to draw more reliable conclusions, but obese patients without significant comorbidities should not be denied the best treatment options just in consideration of their BMI.

13.3.2 Age

Population aging makes it inevitable that more elderly patients will present with EGJ malignancies. It is increasingly important to assess the effect of age on treatment decisions and outcomes.

Greater medical comorbidities may result in denial of best surgical approach or multimodal treatments in some elderly patients with resectable EGJ tumors.

The effect of age on short- and long-term outcomes of esophagogastrectomy has been examined, often setting a cutoff of 70 years of age, but cutoff can widely vary from 70 to 85 years. In our experience patients with age ≥70 years undergoing surgery represent about a quarter of all cases (24 %), while the octogenarians are about 5 %; hence almost one-third of all our patients is older than 70.

Individual studies have suggested that elderly patients encounter more complications and experience a poorer short- and long-term outcomes following esophagectomy [27, 28]. Adverse outcomes following esophagectomy in patients over 70 have been reported with an increased operative and in-hospital mortality as well as decreased 5-year overall survival [29, 30]. In addition, a previous research has demonstrated that patients over 80 have an increased risk of perioperative and postoperative mortality, independent of comorbidities [31].

In the majority of the studies, elderly patients had an increased incidence of preoperative cardiac, respiratory, and renal comorbidities. Several risk scores have identified the importance of preexisting cardiac and respiratory diseases in predicting adverse outcome following esophagectomy. Thus, the increased cardiac and pulmonary complications and in-hospital mortality seen in the elderly may be due to these preexisting medical comorbidities [32–34].

Furthermore, risk associated with surgery in the elderly is also caused by frailty and cognitive impairment.

A recent review [35] found that elderly patients undergoing surgical resections for esophagogastric malignancies present with more medical comorbidities, undergo less neoadjuvant therapy, and have increased incidence of cardiac and pulmonary complications, in-hospital mortality, and reduced 5-year overall survival.

On the contrary, some studies have demonstrated that elderly patients with less or well-controlled medical comorbidities can tolerate neoadjuvant chemoradiotherapy and have outcomes comparable to younger patients [36–38].

Moreover, some other studies have demonstrated that esophagectomy can be performed safely in octogenarians, who have good underlying cardiac and lung function [27]. Further reports have concluded that patients aged over 70 must not be presumed unsuitable for major cancer operations, including esophagectomy, if medical comorbidities can be identified and well controlled during the perioperative period [39].

All these studies are burdened with significant bias. First, age cutoff values are widely different, and results may be difficult to compare. Second, many patients aged less than 75–80 have good performance status; consequently a cutoff value of 70 years is no more applicable in our daily practice. Third, it is easily comprehensible that long-term overall survival is shorter in the elderly, but this should not imply that only palliation should be proposed. Hence, heterogeneity in age classification, comorbidities, and physiological fitness of elderly patients among studies may have significantly impaired the possibility of correct comparisons.

We think that, although more studies are needed to better define the role of age in EGJ cancer, old age itself should not preclude correct oncological indications, and comorbidities should be taken into account more than age itself.

Multimodal treatments in elderly patients are often feasible, and outcomes are similar to younger patients.

Surgical resection should be offered routinely as the standard treatment for EGJ adenocarcinoma in elderly patients with good performance status and low comorbidities, as it is in younger patients [28, 40].

We suggest, as we do in our current practice, to offer multimodal treatments to all fit patients aged 75 or less, while upfront surgery should be proposed for older patients with potentially curable disease and good performance status.

13.3.3 Pulmonary Condition

Pulmonary complications are the most common cause of postoperative morbidity and mortality after esophagogastrectomy.

These complications can range from atelectasis to pneumonia to respiratory insufficiency requiring prolonged ventilatory support. Preoperative status can significantly affect postoperative recovery, and preoperative pulmonary function tests are recommended for any patient undergoing esophagogastrectomy with thorax opening [41, 42].

Pulmonary dysfunction was classified into two major categories based on the results of preoperative spirometry. Restrictive pulmonary

dysfunction was defined as a predicted vital capacity (VC) of less than 80 %, and chronic obstructive pulmonary disease (COPD) was defined as an FEV1/FVC (forced expiratory volume in 1 s/forced vital capacity) ratio, also called Tiffeneau-Pinelli index, of less than 70 %.

FEV1 is an easy and available measure of pulmonary function. Indeed, it has been demonstrated that a decrease in FEV1 independently predicts postoperative complications after esophagectomy [2, 34]. An FEV1 value of <60 % is considered the threshold at which overall and pulmonary complication rates increase insomuch as surgery should be avoided [1, 2].

Preoperative impaired pulmonary function has also been associated with prolonged mechanical ventilation and prolonged hospital stay [41].

The American College of Physicians guidelines [43] recommend obtaining pulmonary function tests at least in high-risk patients: patients older than 60 years, patients with history of tobacco smoking, or patients with signs/symptoms of pulmonary disease.

Those with FEV1 between 60 and 70 % could benefit from intense pulmonary rehabilitation to strengthen respiratory muscles before surgery. This rehabilitation may reduce risks of postoperative pulmonary complications [44, 45].

Smoking history presents a significant challenge in the perioperative management of patients undergoing esophagogastrectomy. In addition to chronically reduced pulmonary function, these patients have significant issues with bronchorrhea, sputum retention, atelectasis, and pneumonia. Smokers should be counseled regarding smoking cessation at the time of diagnosis.

In an American study [2], most patients who were current smokers at the time of surgery developed pulmonary complications that required prolonged mechanical ventilatory support.

Respiratory comorbidities are particularly relevant in elderly patients. Cijs et al. [30] and Elsayed et al. [46] reported that COPD is an independent predictor of postoperative mortality in patients older than 70 years. In patients with severe respiratory comorbidities, the use of induction CT or CRT should be carefully weighed due to the potentially adverse effect of chemotherapy and particularly radiotherapy on the lungs.

Thorax opening predisposes to pulmonary complications. A trans-hiatal approach, rather than a trans-thoracic approach, should be considered in high-risk patients with important respiratory comorbidities, because it seems to reduce the risk of such complications. Theoretically, minimally invasive surgery (MIS) could reduce the impact of associated pulmonary comorbidity, though no clear benefit has been demonstrated to date. According to Decker et al. [47], MIS is feasible for EGJ cancer patients with mild or moderate COPD, and their results were similar to patients with COPD treated with an open procedure and to those with normal pulmonary function undergoing MIS. However, these results should be considered with caution and need further evaluation.

In summary, the risk of morbi-mortality due to pulmonary complications is so high in patients with FEV1 < 60 % that these patients are poor surgical candidates, especially if a trans-thoracic approach is considered. Patients with FEV1 > 70 % are good candidates for multimodal treatments and radical surgery. For patients with reduced FEV1 (between 60 and 70 %), the best therapeutic approach should not be denied, but careful preventative measures should be taken to reduce risks of respiratory complications: perioperative respiratory physiotherapy, smoking cessation, and probably a minimally invasive approach.

13.3.4 Cardiovascular Status

The presence of cardiovascular comorbidities did not seem to significantly influence postoperative mortality rates [2, 23, 34]. The reported incidence of myocardial infarction after esophagectomy is low (1–2 %), while atrial fibrillation, the most common postoperative cardiac complication in patients with EGJ cancer, occurs in about 20 % of the cases [48, 49].

However, these data should be considered with caution, since patients with severe cardiovascular comorbidities may have been excluded

from surgical resection and neoadjuvant treatments in some studies.

According to the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines [50], an adequate preoperative cardiac workup is warranted if risk factors are present, such as family history of cardiac problems, smoking history, hypertension, diabetes, angina symptoms, symptoms of congestive heart failure, significant arrhythmia, severe valvular disease, and history of myocardial infarction.

There is no clear evidence for routine stress testing before surgery for patients undergoing esophagogastrectomy if no risk factors or symptoms are present. Forshaw and colleagues [51] evaluated the usefulness of routine preoperative cardiopulmonary exercise testing in 78 consecutive patients before esophagectomy. Routine cardiopulmonary exercise testing was a poor predictor of postoperative morbidity. More research is needed to discover if preoperative cardiac tests are useful in daily practice for non-high-risk patients and to evaluate the optimal method of cardiac stress testing in patients undergoing esophagogastrectomy.

There is currently no clear benefit for routine use of perioperative beta-blockers for prevention of cardiovascular outcomes in patients undergoing non-cardiac surgery. The benefits of perioperative beta-blockers depend primarily on magnitude of the operation, medical comorbidities, and patient's current use of beta-blockers [50]. Esophagectomy is considered at intermediate risk for cardiac complications. Hence, while beta-blockers should not be stopped in current users, beta-blockers introduction should be considered only for patients who are also at intermediate risk for medical comorbidities, such as diabetes, prior myocardial infarction, compensated heart failure, and renal insufficiency [50].

Statins have been shown to decrease mortality after non-cardiac surgery, probably secondary to their anti-inflammatory and plaque-stabilizing effects. A recent meta-analysis evaluating the benefits of perioperative statin use included patients undergoing cardiac and non-cardiac surgery. Analysis of the pooled results showed that perioperative statin use decreased the risk of myocardial infarction also in non-cardiac surgery [52]. Although no study evaluated specifically patients undergoing esophagogastrectomy, it can be extrapolated from these results that statins may be beneficial and should be restarted soon after esophagogastrectomy in current users.

It has been demonstrated [50] that aspirin suspension before surgery is contraindicated, since the risk of ischemia far outweighs the risk of bleeding due to aspirin assumption.

Regarding neoadjuvant treatments, radiotherapy as well as some chemotherapeutic agents, such as 5-FU, may induce short- and long-term complications involving the cardiovascular system. The most common symptom associated with 5-FU cardiotoxicity is angina-like chest pain. Myocardial infarction, arrhythmias, heart failure, cardiogenic shock, and sudden death have also been reported. The incidence of cardiotoxicity associated with 5-FU varies in the current literature, ranging from 1 to 68 %. Risk factors have not been firmly established, but high doses (800 mg/m^2) and continuous infusions, history of preexisting cardiovascular disease, prior mediastinal radiation, and concurrent use of other chemotherapeutics have been linked to higher cardiotoxicity rates. Patients with history of cardiac comorbidities deserve careful evaluation before the beginning of chemotherapy.

No advantage has been reported for a transhiatal approach in patients with cardiovascular comorbidities, and thus a trans-thoracic approach should not be precluded to these patients [53].

In conclusion, patients without cardiovascular risk do not need cardiovascular tests before surgery or chemo-/chemoradiation, while those with cardiovascular comorbidities certainly require preoperative investigations. Surgical approach, anyway, should not be modified based on cardiovascular state.

13.3.5 Hepatic Dysfunction

In patients undergoing major surgical procedures, liver cirrhosis increases significantly the risk of

postoperative complications. This is especially true for esophagogastrectomy, where technically demanding surgery couples with high surgical stress.

Specific studies for esophagogastrectomy in cirrhotic patients are scanty. The most important and recent review [54] reported a morbidity rate of 83–87 % and a mortality rate of 17–30 %. The main postoperative complications (pulmonary complications and anastomotic leaks) are equally frequent in cirrhotic and non-cirrhotic patients, but their impact on survival is even stronger.

The most common specific complication is ascitic effusion, related to interruption of the peri-cardia vascular collaterals and extensive lymphadenectomy, and this condition is responsible for about one-third of postoperative deaths. Moreover, bleeding occurs with a higher frequency in cirrhotic patients and is an important cause of morbidity and mortality. Finally, acute liver failure, portal thrombosis, and hepatorenal syndrome are other fatal specific complications. For all these reasons, accurate hemostasis, nutritional support, water and sodium restriction, the use of albumin, and fresh frozen plasma infusions are deemed essential in the perioperative period.

Risk of complications is related to the degree of hepatic decompensation. The most commonly used classification in clinical practice is Child-Pugh score. However, if portal hypertension is present, the risk of perioperative morbidity is increased, even in patients with Child class A cirrhosis [55]. For instance, in a Taiwanese trial on esophagectomy [56], surgical mortality was 10 % for patients with Child A cirrhosis, 50 % in those with Child B, and 100 % for Child C patients. These results are consistent with other reports in the current literature [54, 55, 57].

However, in terms of survival, prognosis of cirrhotic patients after the perioperative period is similar to that of non-cirrhotic patients. Indeed, if well managed, these patients have a comparable long-term survival [54, 57].

Child A patients without portal hypertension are the “ideal” candidates for upfront surgery, although perioperative risks are increased and chemotherapy usually not possible. Patients with Child A and portal hypertension have instead a higher probability of venous flow congestion in the gastric tube and a consequently increased risk of anastomotic leak. Preoperative use of transjugular intrahepatic portosystemic shunt (TIPSS), as a bridge to esophagectomy, can reduce hypertension and has shown promising results, allowing patients to more safely undergo surgery [56, 58].

Several experiences on abdominal surgery with colectomy and cholecystectomy demonstrated that morbi-mortality is unacceptably high in Child B and C patients [59, 60].

Since the extremely high risk of fatal complications in Child B and C cases, surgery is contraindicated for these patients, and palliative therapies, such as radiotherapy, are standardly proposed. The role of chemotherapy in patients with liver disease is debated, and in most cases chemotherapy is not indicated. Conversely, endoscopic resection can be a valid hypothesis for patients with early cancer and Child B and C, but risk of bleeding is still relevant [61].

Early or compensated cirrhotic liver disease may escape preoperative detection and be discovered at the time of surgery. Intraoperative liver biopsy may help determine the degree of fibrosis and guide the surgeon in the decision whether to proceed with resection.

In summary, cirrhotic patients requiring esophagogastrectomy must be carefully selected, and more intense attention in perioperative period is always deemed essential to achieve a good survival probability in these fragile patients.

Upfront surgery is the mainstay of treatment in Child A cases, since chemotherapy is rarely possible in patients with liver disease. The procedure is feasible and should be carried out, since long-term survival after radical surgery is similar to that of non-cirrhotic patients treated with upfront surgery. If portal hypertension is present in Child A patients, preoperative use of TIPSS, about one month before esophagogastrectomy, can reduce hypertension, thus allowing the surgical procedure.

Conversely, surgery is not appropriate in Child B and C patients.

13.4 Tailored Treatment Principles

Tailoring treatment means creating a custom-made therapy that perfectly fits each patient. So far, patients were included in closed groups based on stage, and the only discriminating factor was the presence of comorbidities that precluded the best treatment choice.

In the near future, this will be no longer accepted, since different multimodal treatments can provide alternative approaches with acceptable results that, although not perfectly identical in greater groups of cases, may be effective on a particular patient. This all means that it will no longer be the patient who fits a treatment, but the treatment that fits the patient. It may seem only speculation, but it is a turning point in oncological therapy. A patient can be young or old and can have comorbidities, and his/her cancer has a site, a stage, and a histology. Moreover when induction treatments are used, the patient can show a good or a bad response to treatment. The need for an operation and subsequent treatments is still based on a pretreatment strategy, but when a tailored treatment is created, strategy may change based on evolution of the disease and on response to treatment. Surgery on demand, as we previously postulated [62], is part of this concept. We believe that multimodal treatments should be proposed to all patients, whose comorbidities allow their use. In patients with excellent response to treatment and low risk of recurrence, follow-up without surgery might be considered. We previously demonstrated that Siewert types I and II with pathological complete response have excellent prognosis and rarely develop relapse, which was always systemic in our study. Along with these data, we discovered that patients without nodal involvement at clinical staging have better survival than those who downstaged from cN+ to ypN0 after induction chemoradiation and that however the latter have better survival than ypN+. Combining these results, we may speculate that a patient with Siewert I or II with cN0 and a good response to induction CRT might be a good candidate to avoid surgery. On the contrary, a patient with cN+, even after good response to treatment, should undergo surgery to improve survival. These are only two simple examples of different approaches to patients that are presently treated with a standard strategy. Unfortunately preoperative diagnostic tools are still not enough sophisticated, and more studies are needed to better discriminate patients who will be candidates to surgery on demand. However, we believe that nomograms comprising comorbidities assessment, clinical stage, type of multimodal treatment, surgical approach, and response to treatment will in a near future allow us to tailor a custom-made therapy for each patient, offering the best chance of cancer cure.

References

1. Hashimi S, Smith M (2012) Medical evaluation of patients preparing for an esophagectomy. Surg Clin North Am 92:1127–1133
2. Dhungel B, Diggs BS, Hunter JG (2010) Patient and peri-operative predictors of morbidity and mortality after esophagectomy: American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP), 2005–2008. J Gastrointest Surg 14:1492–1501
3. Charlson ME, Pompei P, Ales KL et al (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40(5):373–383
4. Copeland GP, Jones D, Walters M (1991) POSSUM: a scoring system for surgical audit. Br J Surg 78(3):355–360
5. Dutta S, Horgan PG, McMillan DC (2010) POSSUM and its related models as predictors of postoperative mortality and morbidity in patients undergoing surgery for gastro-oesophageal cancer: a systematic review. World J Surg 34:2076–2082
6. Tekkis PP, McCulloch P, Poloniecki JD et al (2004) Risk-adjusted prediction of operative mortality in oesophagogastric surgery with O-POSSUM. Br J Surg 91(3):288–295
7. Bosch DJ, Pultrum BB, de Bock GH et al (2011) Comparison of different risk-adjustment models in assessing short-term surgical outcome after transthoracic esophagectomy in patients with esophageal cancer. Am J Surg 202(3):303–309
8. Takeuchi H, Miyata H, Gotoh M et al (2014) A risk model for esophagectomy using data of 5354 patients included in a Japanese nationwide web-based database. Ann Surg 260(2):259–266
9. Sauvanet A, Mariette C, Thomas P et al (2005) Mortality and morbidity after resection for adenocarcinoma of gastroesophageal junction: predictive factors. J Am Coll Surg 201:253–262
10. Hoyo C, Cook MB, Kamangar F et al (2012) Body mass index in relation to oesophageal and oesophagogastric

junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. Int J Epidemiol 41(6):1706–1718
11. Smith M, Zhou M, Whitlock G et al (2008) Esophageal cancer and body mass index: results from a prospective study of 220 000 men in China and a meta-analysis of published studies. Int J Cancer 122:1604–1610
12. Turati F, Tramacere I, La Vecchia C et al (2012) A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. Ann Oncol 24:609–917
13. Oh CA, Kim DH, Oh SJ et al (2012) Impact of body mass index on surgical outcomes in radical total gastrectomy. Hepatogastroenterology 59:934–937
14. Ojima T, Iwahashi M, Nakamori M et al (2009) Influence of overweight on patients with gastric cancer after undergoing curative gastrectomy: an analysis of 689 consecutive cases managed by a single center. Arch Surg 144:351–358
15. Mullen JT, Davenport DL, Hutter MM et al (2008) Impact of body mass index on perioperative outcomes in patients undergoing major intra-abdominal cancer surgery. Ann Surg Oncol 15:2164–2172
16. Zhang SS, Yang H, Luo KJ et al (2013) The impact of body mass index on complication and survival in resected oesophageal cancer: a clinical-based cohort and meta-analysis. Br J Cancer 109(11):2894–2903
17. Healy LA, Ryan AM, Gopinath B (2007) Impact of obesity on outcomes in the management of localized adenocarcinoma of the esophagus and esophagogastric junction. J Thorac Cardiovasc Surg 134:1284–1291
18. Scipione CN, Chang AC, Pickens A et al (2007) Transhiatal esophagectomy in the profoundly obese: implications and experience. Ann Thorac Surg 84:376–382
19. Grotenhuis BA, Wijnhoven BP, Hötte GJ et al (2010) Prognostic value of body mass index on short-term and long-term outcome after resection of esophageal cancer. World J Surg 34(11):2621–2627
20. Sundelof M, Lagergren J, Ye W (2008) Patient demographics and lifestyle factors influencing long-term survival of oesophageal cancer and gastric cardia cancer in a nationwide study in Sweden. Eur J Cancer 44:1566–157112
21. Madani K, Zhao R, Lim HJ et al (2010) Obesity is not associated with adverse outcome following surgical resection of oesophageal adenocarcinoma. Eur J Cardiothorac Surg 38:604–608
22. Hayashi Y, Correa AM, Hofstetter WL et al (2010) The influence of high body mass index on the prognosis of patients with esophageal cancer after surgery as primary therapy. Cancer 116:5619–5627
23. Melis M, Weber JM, McLoughlin JM et al (2011) An elevated body mass index does not reduce survival after esophagectomy for cancer. Ann Surg Oncol 18:824–831
24. Scarpa M, Cagol M, Bettini S et al (2012) Overweight patients operated on for cancer of the esophagus survive longer than normal-weight patients. J Gastrointest Surg 17:218–227
25. Thrift AP, Nagle CM, Fahey PP et al (2012) Predictors of survival among patients diagnosed with adenocarcinoma of the esophagus and gastroesophageal junction. Cancer Causes Control 23(4):555–564
26. Li L, Li X, Chu S et al (2014) Does overweight affect outcomes in patients undergoing gastrectomy for cancer? A meta-analysis of 25 cohort studies. Jpn J Clin Oncol 44(5):408–415
27. Zehetner J, Lipham JC, Ayazi S et al (2010) Esophagectomy for cancer in octogenarians. Dis Esophagus 23:666–669
28. Yoon HY, Kim CB (2011) Gastroesophageal junction adenocarcinoma of young patients who underwent curative surgery: a comparative analysis with older group. Surg Today 41:203–209
29. Yang HX, Ling L, Zhang X et al (2010) Outcome of elderly patients with oesophageal squamous cell carcinoma after surgery. Br J Surg 97:862–867
30. Cijs TM, Verhoef C, Steyerberg EW et al (2010) Outcome of esophagectomy for cancer in elderly patients. Ann Thorac Surg 90:900–907
31. Moskovitz AH, Rizk NP, Venkatraman E et al (2006) Mortality increases for octogenarians undergoing esophagogastrectomy for esophageal cancer. Ann Thorac Surg 82:2031–2036
32. Braiteh F, Correa AM, Hofstetter WL et al (2009) Association of age and survival in patients with gastroesophageal cancer undergoing surgery with or without preoperative therapy. Cancer 115(19):4450–4458
33. Bosh DJ, Pultrum BB, de Bock GH et al (2011) Comparison of different risk-adjustment models in assessing short-term surgical outcome after transthoracic esophagectomy in patients with esophageal cancer. Am J Surg 202:303–309
34. Wright CD, Kucharczuk JC, O'Brien SM et al (2009) Predictors of major morbidity and mortality after esophagectomy for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk adjustment model. J Thorac Cardiovasc Surg 137:587–595
35. Markar SR, Karthikesalingam A, Thrumurthy S et al (2013) Systematic review and pooled analysis assessing the association between elderly age and outcome following surgical resection of esophageal malignancy. Dis Esophagus 26(3):250–262
36. Fogh SE, Yu A, Kubicek GJ et al (2011) Do elderly patients experience increased perioperative or postoperative morbidity or mortality when given neoadjuvant chemoradiation before esophagectomy? Int J Radiat Oncol Biol Phys 80:1372–1376
37. Rice DC, Correa AM, Vaporciyan AA et al (2005) Preoperative chemoradiotherapy prior to esophagectomy in elderly patients is not associated with increased morbidity. Ann Thorac Surg 79:391–397
38. McLoughlin JM, Lewis JM, Meredith KL (2013) The impact of age on morbidity and mortality following esophagectomy for esophageal cancer. Cancer Control 20(2):144–150
39. Ruol A, Portale G, Zaninotto G et al (2007) Results of esophagectomy for esophageal cancer in elderly

patients: age has little influence on outcome and survival. J Thorac Cardiovasc Surg 133:1186–1192
40. Camerlo A, D'Journo XB, Ouattara M et al (2012) Adenocarcinoma of the esophagus and esophagogastric junction in patients older than 70 years: results of neoadjuvant radiochemotherapy followed by transthoracic esophagectomy. J Visc Surg 149(3):e203–10
41. Law S, Wong KH, Kwon KF et al (2004) Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. Ann Surg 240:791–800
42. Inokuchi M, Kojima K, Kato K et al (2014) Risk factors for post-operative pulmonary complications after gastrectomy for gastric cancer. Surg Infect 15(3):314–321
43. Qaseem A, Wilt TJ, Weinberger SE et al (2011) Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med 155(3):179–191
44. Nakamura M, Iwahashi M, Nakamoni M et al (2008) An analysis of the factors contributing to a reduction in the incidence of pulmonary complications following an esophagectomy for esophageal cancer. Langenbecks Arch Surg 393:127–133
45. Zingg U, Smithers BM, Gotley DC et al (2011) Factors associated with postoperative pulmonary morbidity after esophagectomy for cancer. Ann Surg Oncol 18:1460–1468
46. Elsayed H, Whittle I, McShane J et al (2010) The influence of age on mortality and survival in patients undergoing esophagogastrectomies. A seven years experience in a tertiary center. Interact Cardiovasc Thorac Surg 11:65–69
47. Decker G, Coosemans W, De Leyn P et al (2009) Minimally invasive esophagectomy for cancer. Eur J Cardiothorac Surg 35:13–20
48. Whooley BP, Law S, Murthy SC et al (2001) Analysis of reduced death and complication rates after esophageal resection. Ann Surg 233:338–344
49. Murthy SC, Law S, Whooley BP et al (2003) Atrial fibrillation after esophagectomy is a marker for postoperative morbidity and mortality. J Thorac Cardiovasc Surg 126:1162–1167
50. Fleisher LA, Fleischmann KE, Auerbach AD et al (2014) ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 64(22):e77–e137
51. Forshaw MJ, Strauss DC, Davies AR et al (2008) Is cardiopulmonary exercise testing a useful test before esophagectomy? Ann Thorac Surg 85:294–299
52. Chopra V, Wesorick DH, Sussman JB et al (2012) Effect of perioperative statins on death, myocardial infarction, atrial fibrillation and length of stay. Archaeology 147:181–189
53. Wei MT, Zhang YC, Deng XB et al (2014) Transthoracic vs transhiatal surgery for cancer of the esophagogastric junction: a meta-analysis. World J Gastroenterol 20(29):10183–10192
54. Mariette C (2008) Is there a place for esogastric cancer surgery in cirrhotic patients? Ann Surg Oncol 15:680–682
55. Friedman LS (2010) Surgery in the patient with liver disease. Trans Am Clin Climatol Assoc 121:192–204
56. Lu MS, Liu YH, Wu YC et al (2005) Is it safe to perform esophagectomy in esophageal cancer patients combined with liver cirrhosis? Interact Cardiovasc Thorac Surg 4:423–425
57. Hwang SH, do Park J, Jee YS et al (2009) Risk factors for operative complications in elderly patients during laparoscopy-assisted gastrectomy. J Am Coll Surg 208:186–192
58. Kim JJ, Dasika NL, Yu E et al (2009) Cirrhotic patients with a transjugular intrahepatic portosystemic shunt undergoing major extrahepatic surgery. J Clin Gastroenterol 43:574–579
59. Gervaz P, Pak-art R, Nivatvongs S et al (2003) Colorectal adenocarcinoma in cirrhotic patients. J Am Coll Surg 196(6):874–879
60. Currò G, Iapichino G, Melita G et al (2005) Laparoscopic cholecystectomy in Child-Pugh class C cirrhotic patients. JSLS 9(3):311–315
61. Kato M, Nishida T, Hamasaki T et al (2014) Outcomes of ESD for patients with early gastric cancer and comorbid liver cirrhosis: a propensity score analysis. Surg Endosc 29(6):1560–1566
62. Zanoni A, Verlato G, Giacopuzzi S et al (2013) Neoadjuvant concurrent chemoradiotherapy for locally advanced esophageal cancer in a single high-volume center. Ann Surg Oncol 20(6):1993–1999

14 How to Treat EGJ Cancer: Indications and Treatment Strategy

Andrea Zanoni, Simone Giacopuzzi, Silvia Laiti, Alberto Di Leo, and Giovanni de Manzoni

14.1 Introduction

Esophagogastric junction (EGJ) adenocarcinoma has been differently classified over time. In 1996, Siewert and coworkers introduced a classification (AEG classification or Siewert classification) for this cancer, which has been adopted by the ISDE Congress in 1997, and it was used without modifications ever since. It is undoubtedly the most used classification for EGJ cancer worldwide and it is described thoroughly in Chap. 7.

Surgery with lymphadenectomy has always been considered the standard approach to EGJ cancer, with some differences due to Siewert type. Aims of surgery are reaching a curative R0 resection and good survival. If this is possible for superficial cancers, especially for T1m, where also endoscopic resections are now widespread, the high risk of non-curative resections and the low survival achieved with surgery alone in locally advanced and N+ cases prompted the search for multimodal treatments to both increase the rate of R0 and to improve long-term outcomes. The initial multimodal approaches and comparative studies are now dated and many meta-analyses [1, 2] of the randomized trials and a recent Cochrane review [3] clearly reported a survival advantage, together with an increased rate of curative resections, after multimodal approaches compared to surgery alone.

These results have clinical implications, with consensus conferences [4] and international guidelines [5–7] recommending multimodal approaches in all fit patients with locally advanced cancers and/or nodal involvement.

Whether to prefer perioperative chemotherapy (CT) or induction chemoradiotherapy (CRT) is still a matter of debate. Radiotherapy alone is not supported as a viable treatment choice, for no trial demonstrated any advantage in rate of curative resections and survival [1, 2]. Also adjuvant CT is to proscribe, because it failed to demonstrate any survival benefit and moreover it is difficult to apply to patients already treated with prostrating surgery [8].

The type of multimodal treatment is related to Siewert type. For Siewert type I cancers, the most used approach consists in induction chemoradiotherapy. According to the recent CROSS trial [9],

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induction CRT showed significantly improved survival as compared with surgery alone. Only two studies compared induction CT and CRT. Their results and a subsequent meta-analyses reported best results with CRT [1, 10, 11]. Hence, the preferred approach for Siewert I is induction CRT, according to consensus conferences [4], national guidelines [5], and the experience of many high-volume dedicated centers like ours. The use of perioperative CT might be considered a valid alternative according to German and UK guidelines [6, 7], but evidence for type I is weaker than for CRT, and thus CRT remains the recommended approach for Siewert I.

Siewert type II can be defined differently: if it is considered as an esophageal cancer, then its treatment is assimilated to Siewert I, while if it is considered more similar to a gastric cancer, then perioperative CT is preferred. While many centers prefer CRT, UK guidelines, which are based on MAGIC trial [12], suggest perioperative CT for all esophageal and gastric cancers. Indeed, some type II cancers tend to invade mainly downward into the stomach and, although categorized as type II, resemble more a type III cancer: thus, perioperative CT might be taken into account. Nevertheless, many reasons prompts the use of induction CRT for most Siewert II patients: the good response rate to CRT reported for Siewert II; the improved survival after CRT; and the high risk of non-completion of postoperative cycles in case of perioperative CT, as reported in MAGIC trial.

The ongoing ICORG 10–14 trial is a phase III randomized clinical trial of perioperative chemotherapy (modified MAGIC regimen) versus neoadjuvant chemoradiation (CROSS protocol) for adenocarcinoma of the esophagus and esophagogastric junction (cT2-3, N0-3, M0 Siewert types I, II, and III). This study might give us important information about the best approach. We think that if supposedly CRT is better for type I and, as discussed below, CT is indicated for type III, information provided by this trial will shade light especially on Siewert II.

Siewert III cancers do not have a homogenous treatment, have very few dedicated studies, and are often excluded from study protocols. Nonetheless, it represents around 40 % of EGJ cancer and is the one with worst prognosis [13–15]. Siewert type III is considered a gastric cancer invading the esophagus. The consensus conference of St. Gallen and NCCN guidelines [4, 5] clearly state that Siewert III is a gastric cancer and should be treated as such. As in gastric cancer, then, the role of radiotherapy is uncertain and it is not proposed in the setting of induction and perioperative treatments. As abovementioned, there are no dedicated studies for Siewert III, and it is either explicitly excluded from trials on gastric or esophageal cancers or included in trials like MAGIC, which include all esophagogastric cancers together. The type of multimodal protocol then might be a perioperative CT or an induction CT. Perioperative is more frequently used, after MAGIC triplet has become the standard of care for gastric cancer in many Western countries. Nonetheless, postoperative cycles are completed in less than 50 % of the cases, leading to a suboptimal only preoperative CT. Siewert III patients undergo even more complicated procedures than patients with distal gastric cancer, with anastomosis in the mediastinum, mediastinal nodal dissection, and sometimes thorax opening. We believe that an induction CT protocol, without postoperative cycles, would better fit Siewert III patients, but no study has been published yet, and data are scanty. Anyway, a multimodal approach, with CT and surgery, is now considered the standard of care also for locally advanced Siewert III patients.

Surgical approach principles remain valid also after induction treatments. The decision about the type of surgery is taken at diagnosis; hence, it will not change even in case of excellent clinical response to chemotherapy or chemoradiation. Although it is renown that in particular cancers, like upper cervical esophageal cancer or rectal cancer, many centers modify the surgical strategy based on the response to induction treatment to spare organs and improve quality of life, this is not the case of EGJ cancer, where larger resections do not imply sacrifice of organs that will impact on the quality of life, and no changes of surgical strategy are required based on response to treatment.

Surgical choices are based on neoplastic diffusion, which differs based on cancer site. Mucosal cancers, anyway, are similar for all Siewert types and will be considered together in the next paragraph.

14.2 T1m

Endoscopic resections are gaining interest in the treatment of upper G. I. malignancies, since they are safe, effective, and significantly less invasive than esophagectomy and can be performed with limited hospital stay, sometimes even on outpatient basis. The main technical drawbacks are the risk of incomplete resections and the incorrect staging in case of piecemeal dissections, together with the risks of bleeding and perforation.

Mucosal and submucosal dissections are technically feasible and deserve implementation. But, while technically feasible, the question is if they are also oncologically correct. Endoscopic dissections can remove cancers located in mucosa and submucosa, but of course lymphadenectomy is not possible. Endoscopic resections are adequate only if the risk of nodal metastases is absent or at least lower than the risk of mortality due to surgery. The risk of nodal involvement is pretty high in case of submucosal involvement, and all patients with T1sm cancers need surgery and lymphadenectomy.

For mucosal cancer, instead, the risk of nodal involvement is reasonably low and endoscopic dissections should be considered, bearing in mind that upfront surgery still remains the standard curative approach. Lymphadenectomy, although not mandatory, is normally performed during surgery and guarantees correct staging.

The type of endoscopic dissection is beyond the scopes of this chapter (see Chap. 5), but the preferred technique is the one that offers the best chance of complete one-piece resection, allowing correct staging and reducing the risk of local recurrence. With endoscopic submucosal dissection (ESD), the chance of a one-piece resection is higher than with endoscopic mucosal resection (EMR) [16].

We strongly believe that the standard criteria for endoscopic resection in gastric cancer, i.e., mucosal cancers up to 2 cm, well differentiated (G1) and not ulcerated, should be applied also to EGJ adenocarcinoma.

In the Eastern experience on esophageal carcinoma [17], mucosa is further divided into three layers: m1 indicates the involvement of the epithelium, m2 the invasion of the lamina propria, and m3 the invasion of muscularis mucosae (Fig. 14.1). These layers can be defined precisely only at pathological examination, but they can be suspected with endosonography. Data on the risk of nodal involvement in mucosal adenocarcinoma are limited in the current literature, and little is known about specific risk of nodal involvement of m3 cancers, which seems at higher risk. A recent meta-analysis [18] on type I cancers reported that 5 % of m3 patients are N+, although in 90 % of the cases only one node is involved. This percentage is not negligible, and in case of other risk factors, surgery and lymphadenectomy might be considered also in m3 cases. According to another recent review on Siewert I [19], features at risk of nodal involvement in T1m are moderately or poorly differentiated cancers (G2-3) and lymphovascular invasion.

Lymphovascular invasion seems to correlate with the risk of nodal involvement [16]; hence,

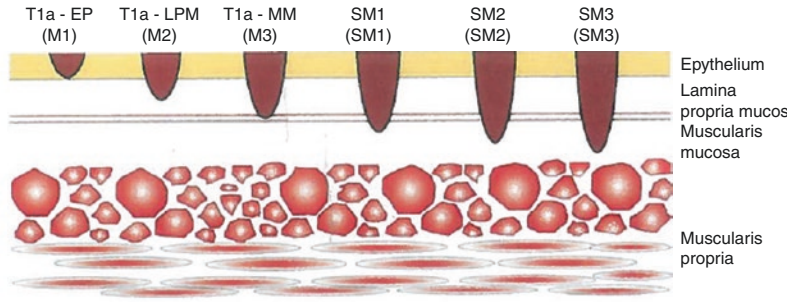

Fig. 14.1 Layers of tumor invasion in superficial cancers (Reproduced with permission from [17])

probably those patients with lymphovascular invasion should be considered for surgery and lymphadenectomy.

Siewert type I is the EGJ cancer with more extensive data, since surveillance of Barrett's esophagus leads to early detection and diagnosis. In this regard, together with the treatment of the visible lesion, also treatment of Barrett's esophagus should be accomplished (for a complete dissertation on this topic, please see Chaps. 4–5).

According to studies comparing endoscopic resection and surgery [20–22], endoscopic resection is appropriate for all Siewert type I T1m cancers whenever possible.

Data on Siewert II are really scanty. Most studies are either about cancer on Barrett's esophagus, i.e., Siewert I, or on gastric cancer. Most Siewert II cancers might be considered together with type I, and indications are similar [16, 23, 24].

Data on Siewert III are even more rare. Siewert III cancers resemble strictly gastric cancers of the upper third, but they are difficult to discover. First, superficial type III cancers are rarely diagnosed, since they tend to manifest only in advanced stage. Second, by Siewert's definition, a type III cancer must have its epicenter at least 2 cm below the "Z line" and must infiltrate the esophagus. According to this definition, there is no way to have a small cancer defined as type III. Hence, those early cancers are defined either as type II or gastric cancers. If this might seem mere speculation, it accounts for the virtual impossibility to have data about early Siewert III. Anyway, endoscopic rules are the same.

In summary, endoscopic resection is indicated for T1m cancers of all three Siewert types in expert and dedicated centers, where a one-piece radical dissection can be carried out. Indications are dimension of the lesion up to 2 cm, well differentiated (G1) and not ulcerated. If there is absolute consensus about the indication for endoscopy in m1, m2, and m3 without lymphovascular invasion, doubts persist on m3 cases with lymphovascular invasion. In these patients, a surgical resection with lymphadenectomy could be considered. Anyway, if a dedicated endoscopic center is not available, surgery remains the standard curative approach to all T1m patients.

14.3 ≥T1sm

T1sm cancers, although superficial, are not candidates to endoscopic resection, due to the high risk of nodal involvement, and all patients with T1sm cancers need surgery and lymphadenectomy. Upfront surgery is generally indicated in all T1sm cancers, independent of nodal staging. Although this topic is still debated, in case of high suspicion of nodal involvement at clinical staging, induction treatments might be offered also to T1sm patients.

Advanced cases (T2-T4) are now considered candidates to multimodal treatments, whenever possible.

Surgery, both if upfront and after chemotherapy or chemoradiation, aims at achieving a curative resection. Curative R0 surgery is defined as resection of the primary tumor without any residual disease; otherwise, the resection is non-curative: R1 or R2, respectively, for microscopic or macroscopic residual cancer. To achieve this aim, surgery is guided by neoplastic diffusion both on primary site and on lymph nodes. In this regard, the key factors are resection margins and lymphadenectomy.

14.3.1 Resection Margins

14.3.1.1 Longitudinal Margins

Outcome after non-curative resections is reportedly poor in the current literature [25], and achieving an R0 surgery is the mainstay of cancer treatment. The effect of positive margins on locoregional recurrences and survival is hence highly detrimental, mining the results of an otherwise correct surgical procedure and lymphadenectomy. Avoiding positive margins is a key step also in the treatment of EGJ cancer.

Margins that can be involved are both longitudinal (proximal and distal) and circumferential.

The tendency of esophageal cancer to spread intramurally is renown, but few reports specific on adenocarcinoma of the EGJ exist. Intramural metastases are those lesions that form cancer nests beneath the regular epithelium separate from the primary tumor, while subepithelial

extension is the direct extension of a primary neoplasm. While direct extension does not exceed 2–2.5 cm, intramural metastases can be found at greater distance.

In 1980, Papachristou et al. [26] reported that to achieve a safe proximal margin in gastric and EGJ cancer, a resection of at least 12 cm of esophagus was necessary. If theoretically this can be accepted, the need of such extended esophageal resections was hardly applicable in current practice, especially for more distal EGJ cancers. Hence, some authors tried to demonstrate that reduced margins were sufficiently safe and compatible with clinical practice. Gao et al. [27] reported that 24 % of a cohort of Siewert II and III patients without induction treatments had positive proximal margin, although a 5 cm proximal clear in vivo margin was achieved. Interestingly, 56 % of the R+ patients had infiltration of the submucosa without infiltration of the mucosa. Szanto and colleagues [28], considering all three Siewert types, reported that intramural metastases were present in 4 % of their patients. Although the case series was really small, all lesions were located between 2 and 5 cm above the proximal edge of cancer in vivo, and 50 % of the lesions were roofed by intact mucosa. These data seem to indicate that also in EGJ cancer intramural metastases are present and an adequate longitudinal resection margin is important.

The definition of longitudinal margins and mainly proximal margin is complicated by the shrinkage of the specimen after resection. Hence, it is mandatory to know what is the in vivo or in situ length of margin, which is more applicable in clinical practice during surgery than ex vivo margin after resection. Some authors [29–31] reported that shrinkage of esophageal specimen ranges from 10 to 45 % of the in vivo length. Shrinkage begins immediately after resection, but this phenomenon can be reduced if the specimen is measured fresh, stretched, and pinned onto a corkboard. In a recent interesting although with very small sample size study, Khoshnevis et al. [32] reported that after immersion in 10 % buffered formalin, shrinkage continues through at least 72 h. Main shrinkage occurs after 24 h and is around 27 % but reaches 33 % and 38 % after 48 and 72 h, respectively. Hence, a reduction of around one third of in vivo length has to be acknowledged in formalin-fixated specimens.

The main issue in longitudinal margins is the risk of involvement conducting to a non-curative resection. Most studies focused then on defining correct proximal and distal margins to theoretically avoid R+, but with the least destructive surgical procedure.

Considering proximal margin, Barbour et al. [33] reported that resection margins greater than 3.8 cm ex vivo in the esophagus (corresponding to around 5 cm in vivo) are associated with improved outcome for patients with Siewert types I, II, and III cancer. Mariette and colleagues [34] claimed that, in their series of type I and II patients, there were no positive proximal margins beyond 7 cm, and thus an 8 cm in vivo proximal margin could be considered the safest. All measurements used in this study were taken from fresh contracted gross specimen, because it was not always possible to measure the in vivo length before dividing the esophagus. To obviate the problem of shrinkage, authors multiplied by two all measurements of length of proximal resection margin used in the study. This probably overestimated shrinkage, which is less than 50 %, and then probably a less long margin of around 5–6 cm would be adequate. Considering types II and III, Ito et al. [35] did not find positive proximal margins with a 6 cm wide resection, defining lengths of resection margins as the distance from the gross tumor to the edge of the freshly resected specimen measured before fixation. More recently, Mine et al. [36] reported that a gross proximal margin (measured on resected specimen stretched maximally on a board) of more than 20 mm (approximately corresponding to at least 28 mm in vivo) was an independent prognostic factor for patients with Siewert types II and III. R+ was recorded in 1.4 % of the patients and only in those with less than 20 mm gross proximal margin. Greater margins did not show statistically significant impact on survival. Shen and coworkers [37] reported an 11 % R+ on proximal margin in Siewert III patients with a 5 cm in vivo margin, but this study was not focused on

length of proximal margins and errors in measuring the margin might have occurred.

A 5 cm wide in vivo proximal margin is then probably adequate in all Siewert types and compatible with clinical practice.

A distal in vivo margin of 4–6 cm is reported as safe for all Siewert types by several authors [35, 38, 39].

In summary, 5 cm in vivo margins both proximally and distally seem appropriate for all Siewert types. In Siewert I cancers and probably in type II, a wider proximal margin is advisable and normally easy achievable. In Siewert III cancers, a wider proximal margin is probably unnecessary, and thus, if a 5 cm proximal margin can be obtained from the abdomen, a thoracic approach would not be required.

14.3.1.2 CRM

The concept of circumferential resection margin (CRM) comes from rectal cancer surgery. A CRM < 1 mm is related to high local recurrence rate and dismal survival [40]. The same concept has been proposed for esophageal cancer, and two main different classifications have been described [41]. The Royal College of Pathologists (RCP) considers the CRM as positive if cancer is found within 1 mm of the surgical margin, whereas the College of American Pathologists (CAP) considers the CRM as positive only if cancer involves the margin.

CRM that is directly involved indicates clearly an R+ resection. According to RCP classification anyway, also patients without infiltration of the CRM but with cancer found within 1 mm of the margin are considered R+. Considerable debate exists on which classification is better.

It must be highlighted that CRM must be considered only for pT3 cancers [40, 42, 43], because a circumferential positive margin in pT1 and pT2 cancers implies inadequate surgery, with esophageal wall involved by cancer left in situ (corresponding to an R2 resection), and CRM is always involved in pT4 cancers.

Circumferential margins are studied for adenocarcinoma of the EGJ only for Siewert types I and II, since this margin is of no use in gastric cancer, and circumferential margin is considered only in the portion of esophagus of the specimen. However, in type III we could consider serosal infiltration and positive peritoneal cytology as a sort of circumferential resection margin. Indeed, positive peritoneal cytology and serosal infiltration are indicative of poor prognosis [44], and in TNM 7th edition positive peritoneal cytology is considered a metastatic disease [45].

A number of studies have been carried out about circumferential resection margin and allowed the execution of two recently published meta-analyses [46, 47]. The first [46] considered 14 trials, eight of which compared RCP and CAP criteria. Interestingly, CAP was considered more informative on prognosis in four studies and RCP in the other four studies, not allowing drawing definitive conclusions. Altogether R+ was 15 % with CAP criteria and 36 % with RCP criteria. In both groups survival was worse in case of CRM positivity, but hazard ratio of mortality was higher for CRM+ patients according to CAP criteria. Although methodologically incorrect, in some studies all patients and not only T3 patients were considered. However, comparable results were achieved when only T3 patients were contemplated. Interestingly, when comparing cancer within 1 mm (0.1–1 mm) from CRM and > 1 mm, survival was lower for the former after upfront surgery but not after induction chemoradiotherapy. After chemoradiation indeed all studies showed that CAP criteria worked better. Authors concluded that CRM+ patients had worse prognosis than CRM- patients with both CAP and RCP criteria. Despite these results that clearly do not allow drawing definitive conclusions, authors stated that RCP was more informative than CAP.

The second meta-analysis [47] considered 19 trials, nine of which compared RCP and CAP criteria. Results were comparable to the other meta-analysis, with R+ in 17 % of the patients using CAP criteria and 40 % using RCP criteria. According to these authors, CRM positivity maintains its significance after neoadjuvant treatments, although they did not separate chemotherapy and chemoradiotherapy. Interestingly, even though prognosis was worse for CRM+ patients compared with CRM- patients with both CAP and RCP criteria, authors considered CAP as more informative.

From the opposite conclusions drawn by two different groups obtaining similar results, we can deduce that we are far from consensus about what classification is to be used.

CRM positivity in CAP describes patients at higher risk of death due to infiltrated margin, although excludes patients with probably reduced survival (CRM 0.1–1 mm). On the contrary, CRM positivity in RCP considers together patients of two classes of probably different prognosis, i.e., patients with clearly involved CRM and patients with free margin but cancer within 1 mm of the CRM.

We believe that more studies are needed to discover what classification is better, and we think that a subdivision into three classes (CRM involved, cancer 0.1–1 mm from CRM, and cancer > 1 mm form CRM) would probably be useful to avoid defining as R+ patients without infiltration of the margin but with probably worse prognosis than patients with wider CRM.

Probably, CAP criteria are more useful after chemoradiation, since the effect of induction therapy could mitigate the significance of uninvolved but close CRM (0.1–1 mm).

Only few studies considered CRM and nodal status; hence, definitive data regarding CRM as independent factor are still pending.

While waiting for definitive conclusions, we strongly recommend to describe CRM in all patients with both surgery alone and after induction treatments, using both classifications and reporting exactly the distance from the margin. Moreover, and this is especially true for upfront surgery, where no modifications of esophageal anatomy might have occurred, it is important to highlight that CRM has to be considered only in pT3 patients.

14.3.2 Type of Lymphadenectomy

14.3.2.1 General Issues on Lymphadenectomy

Number of Positive Nodes. The importance of the number of positive nodes has been studied extensively. Some studies have also tried to determine the efficacy of lymph node ratio (LNR) in estimating prognosis. LNR is defined as the ratio between involved and total resected nodes.

The main issues in the research for cutoffs for both number of positive nodes and LNR consist in the nonhomogeneous characteristics of the published trials. First, often SCC and adenocarcinoma are considered together; second, type of lymphadenectomy may vary from 3-field lymphadenectomy to trans-hiatal esophagectomy without formal lymphadenectomy; third, the study populations can be as small as less than 100 patients or as big as more than 1000; and finally, neoadjuvant treatments can be included or explicitly excluded. This all makes definitions hard to create. Anyway, all studies described significantly decreased survival and/or a higher risk of death when number of involved nodes or LNR increased [48–50]. The cutoff for the number of metastatic nodes varied between three and eight positive nodes, and LNR cutoff was 20 % in almost all trials. According to Peyre et al. [48], the involvement of eight or more nodes means almost 100 % probability of systemic disease, thus making radical surgery not indicated. This is in line with other trials [51, 52], where no survival benefit from surgery was detected when > 8 lymph nodes were involved.

The number of involved nodes and LRN seem to retain their role also after neoadjuvant treatments [49, 53]. By subdividing patients in adequately staged (≥ 15 nodes harvested) and inadequately staged (< 15 nodes analyzed), Mariette and coworkers [49] found that, in patients with adequately staged disease, the number of involved nodes better correlated with survival, whereas in inadequately staged disease the ratio was more important. According to the German study [53], ypN2 and ypN3 had similar prognosis, and thus probably after neoadjuvant treatments, the main prognostic difference is between patients with limited nodal involvement and patients with more than two metastatic nodes.

While the number of involved nodes is pretty objective and comprehensible as a prognostic factor, LNR might be confounding. LNR is a quotient measuring nodal metastasis potential and lymphadenectomy competence, thus mixing cancer biology with surgical technique. As

reported by Rice and Blackstone [54], the problem with quotients is that larger denominators produce smaller fractions. This means that a similar LNR of 25 % can result from 1 positive node of 4 resected, 4 of 16, or 10 of 40. If the LNR is the same, it is pretty obvious that those patients will have different prognosis. Hence, the risk of using LNR is to compare surgical adequacy and not to compare metastatic potential, with an intrinsic methodological error. Hence LNR should be used with caution.

Total Number of Resected Nodes Total number of resected nodes is a good marker of lymphadenectomy adequacy. While the number of involved nodes depends on cancer biology, the total number of harvested nodes depends on the surgeon. The ability of the surgeon to remove lymph nodes is, together with the ability to reach an R0 resection, what makes surgery the mainstay of treatment of esophageal cancer.

Besides, more nodes harvested mean more precise staging. Reducing stage migration, thus obtaining a real picture of a particular cancer in a particular patient, will give the most accurate survival information. Indeed, when a sufficient number of nodes are resected, patients will be located in the correct stages, allowing almost perfect survival analyses. However, extended lymphadenectomy would not be justified if the only advantage were to obtain better staging. Conversely, if increasing the number of resected nodes correlated to better survival, extended lymphadenectomy would be instead justified. Many trials investigated the topic [55–58]. Most of these studies had very large study populations for both SCC and adenocarcinoma, most comprising more than 1000 patients. A 5-year overall survival advantage and/or a reduced hazard of death were found in all these studies when more nodes were removed. The cutoff of number of harvested nodes leading to a survival advantage ranged from ≥6 to ≥30. Rizk et al. [55] proposed to resect at least 10, 20, and 30 nodes, respectively, for T1, T2, and T3. Stiles and associates [59] claimed that these recommendations should be applied also following neoadjuvant treatment and particularly with patients without downstaging and those with persistent nodal metastases. Altorki et al. [56] claimed that 16 nodes are enough for staging and to obtain a survival benefit for N+ patients, while for N0 patients some advantage is obtained when more than 40 nodes are resected. Groth et al. [57] affirmed that maximum survival advantage is obtained with 30 or more harvested nodes, but the probability of finding a positive node does not increase when more than 15 nodes are removed; hence, the accuracy of nodal staging probably is not increased by more extensive lymphadenectomy.

As abovementioned, the use of neoadjuvant treatments does not cancel the need of a correct lymphadenectomy [57, 59, 60]. Probably after neoadjuvant treatments and especially chemoradiation, the size of metastatic nodes reduces, making harvesting by the pathologist harder. Although nodes are harder to detect, according to a German trial [61], their number seems not influenced by the treatment.

The reason why increasing the number of resected nodes reflects on survival is not fully understood. However, a possible explanation is the elimination of micrometastases. The main point is that the presence of micrometastases in supposed node-negative patients could explain the improved survival after extended lymphadenectomy in pathological N0 patients. Actually, in an Irish meta-analysis on micrometastases [62], the hazard ratio for disease relapse in patients with micrometastases was threefold higher compared with negative patients. Hence, the probability to eliminate micrometastases could explain the survival advantage with extended lymphadenectomy.

Conclusions In summary, the number of involved nodes is a main prognostic determinant, and probably prognosis decreases progressively with the increasing of this number, to such an extent that with more than eight involved nodes, prognosis is no more influenced by surgical treatment. In inadequately staged patients, hence in patients with few nodes removed, LNR might be used, even if with caution, to differentiate between N+ patients.

Extended lymphadenectomy increases the number of total nodes removed and this corre-

lates with improved survival. The correct cutoff number of nodes to remove remains controversial, but probably at least 15 nodes need to be resected, and the number required seems to increase with increasing T stage. Hence, we believe that 30 nodes removed are the target to define a fully satisfactory lymphadenectomy. The daily increase in the use of multimodal treatments does not reduce nor modify the indication to perform a correct lymphadenectomy with adequate number of nodes removed.

14.3.2.2 Nodal Involvement by T

Although nodal spread is strictly dependent on site of cancer (Siewert type), the incidence of nodal metastasis is related to the depth of tumor invasion (pT). Nodal involvement indeed varies markedly going from superficial to advanced cancers. As shown in Table 14.1 [23, 63–70], the median incidence of nodal metastases in T1sm cancers is around 20 % but peaks up to 78 % in some reports. In advanced cancers, the incidence of N+ progressively increases from T2 to T4, with medians of nodal involvement of 61, 83, and 90 % for T2, T3, and T4, respectively.

14.3.2.3 Nodal Spread by Site

Siewert I

Lymphatic flow in Siewert type I cancer is mainly toward the abdomen. Indeed virtually all patients with node metastases have abdominal nodes involved. Data from important recent studies of nodal diffusion are reported in Table 14.2 [66, 68, 71–73]. Although normally accompanying abdominal involvement, mediastinal nodes are extremely frequently affected, accounting for around 45 % (17–77 %) of cases. In all these studies, a transthoracic esophagectomy with at least standard mediastinal lymphadenectomy was carried out.

Most trials considering the pattern of lymphatic diffusion name nodal stations according to the Japanese Gastric Cancer Association (JGCA) [17]. Paracardial (stations 1 and 2), lesser curvature (station 3), and left gastric artery nodes (station 7) were the most frequently involved abdominal stations, while mid- and lower mediastinal (stations 108 and 110, respectively) were the main thoracic stations. Celiac trunk and splenic artery nodes (stations 9 and 11) can be also involved; thus, they should be removed when performing lymphadenectomy. Some authors proposed a three-field lymphadenectomy even for EGJ adenocarcinoma. Both Lerut et al. [74] and Altorki et al. [75], although with relatively small sample sizes of patients with adenocarcinoma treated with three-field dissection, reported a relevant prevalence of cervical nodal involvement in EGJ cancer. Lerut described the presence of cervical metastatic nodes in 26 % of Siewert type I cancers, while Altorki reported a 37 % involvement of cervicothoracic nodes (cervical and recurrent nerve nodes). Although possible, anyway, the

Table 14.1 Incidence of nodal metastasis according to the depth of tumor invasion (pT)

	Gertler et al. [63]	Barbour et al. [64]	Westerterp et al. [23]	Bollschweiler et al. [65]	Pedrazzani et al. [66]	Zhang et al. [67]	Meier et al. [68]	Feith et al. [69]	Leers et al. [70]
T 1 sm	18	20	66	78	–	22	17	22	3
T 2	–	–	–	–	61	33	78	77	21
T 3	–	–	–	–	88	74	86	83	50
T 4	–	–	–	–	100	86	90	96	87

Table 14.2 Sites of nodal diffusion in Siewert I

	Pedrazzani et al. [66]	Dresner et al. [71]	Monig et al. [72]	Kakeji et al. [73]	Meier et al. [68]
Abdomen and chest	46 %	77 %	24 %	17 %	55 %
Only abdomen	54 %	15 %	76 %	83 %	45 %
Only chest	–	8 %	–	–	–

interest of cervical nodes is not common or at least not commonly studied in Siewert type I cancer.

In summary, Siewert type I cancers diffuse mainly to abdominal and thoracic nodes in the vicinity of the primary tumor at both sides of the diaphragm. Abdominal stations (stations 1, 2, 3, 7) are virtually always involved, but almost half of the patients with N+ have also mid-lower thoracic nodes affected.

Siewert II

Nodal spread in Siewert type II is mainly toward the abdomen. Table 14.3 shows the different diffusion in abdomen and chest [66, 68, 71–73, 76, 77]. Mediastinal nodes are never affected alone, while abdominal stations are the only metastatic sites in 64–95 % of the patients. A simultaneous interest of both mediastinal and abdominal nodal stations is reported in 5–30 % of the patients.

The mainly interested nodal stations are paracardial (stations 1 and 2), lesser curvature (station 3), and left gastric artery nodes (station 7) in the abdomen and mid- and lower mediastinal (stations 108 and 110, respectively) in mediastinum. Celiac trunk and splenic artery nodes (stations 9 and 11) are also frequently involved. Lerut et al. [74] and Kakeji et al. [73] performed a three-field lymphadenectomy also for some 30 and 60 patients, respectively, with type II cancer. Lerut reported an impressive 18 % involvement of cervical nodes and Kakeji a 2 %. Studies about three-field dissection in Siewert type II are scanty and prevent from drawing any conclusion.

Also splenic hilar nodes and para-aortic nodes are frequently involved and this raises the problem of splenectomy and para-aortic dissection. For instance, Mine et al. [78] reported a 17 % involvement of para-aortic nodes around the left renal vein (station 16A2lat) in locally advanced Siewert II patients.

In a previous experience in Siewert II patients in our department (data not published), patients with greater invasion of the esophagus had increased involvement of mid-lower mediastinal nodes and decreased involvement of para-aortic nodes compared with cases with main gastric invasion. This is in line with the current literature. Kakeji and associates [73] reported an increased incidence of mediastinal N+ when invasion of the esophagus was more than 1 cm. Hosokawa et al. [79] and Nunobe et al. [80] reported a markedly increased risk of inferior mediastinal nodal metastases in case of esophageal invasion ≥2 cm. Meier and colleagues [68] referred that mediastinal nodal disease was 16 % if esophageal invasion was <15 mm, compared with 47 % if tumor invaded beyond 15 mm of the esophagus. Furthermore, Kurokawa et al. [81] reported that upper and middle mediastinal nodes were significantly more probably affected when esophageal invasion was >3 cm, and inferior mediastinal nodes were significantly more probably affected when esophageal invasion was >2 cm.

In summary, virtually all patients with N+ have abdominal nodal stations involved; hence, the lymphatic spread is mainly toward the abdomen with also a non-negligible interest of splenic hilar nodes and para-aortic nodes. Mid-lower mediastinal stations are frequently involved and the risk increases with the increase of esophageal invasion.

Siewert III

Diffusion of Siewert type III is mainly toward the abdomen. As shown in Table 14.4 [66, 68, 72, 73, 76, 77], abdominal stations are involved in practically all N+ patients, with around 10 % of them having mediastinal nodes involved simultaneously. While only lower mediastinal nodes are

Table 14.3 Sites of nodal diffusion in Siewert II

	Pedrazzani et al. [66]	Dresner et al. [71]	Monig et al. [72]	Nakamura et al. [76]	Kakeji et al. [73]	Meier et al. [68]	Yuasa et al. [77]
Abdomen and chest	30 %	6 %	11 %	10 %	5 %	18 %	13 %
Only abdomen	70 %	64 %	89 %	90 %	95 %	82 %	87 %
Only chest	–	–	–	–	–	–	–

Table 14.4 Sites of nodal diffusion in Siewert III

	Pedrazzani et al. [66]	Monig et al. [72]	Nakamura et al. [76]	Kakeji et al. [73]	Meier et al. [68]	Yuasa et al. [77]
Abdomen and chest	7 %	13 %	10 %	2 %	18 %	2 %
Only abdomen	91 %	87 %	90 %	88 %	82 %	98 %
Only chest	2 %	–	–	–	–	–

reported as metastatic sites in the mediastinum (station 110), paracardial (stations 1 and 2), lesser curvature (station 3), and left gastric artery nodes (station 7) are the most frequently affected abdominal stations in N+ patients. Celiac trunk, common hepatic artery, splenic artery, and infrapyloric nodes (stations 9, 8a, 11, and 6) are also frequently involved. Noteworthy, non-first-tier nodes are involved in around half of all locally advanced patients; hence, abdominal diffusion is similar to gastric cancer patients. Para-aortic nodes are reported in around 30 % of locally advanced patients in a previous study of our group [66]. Normally, the para-aortic nodes removed are those around the left renal vein (station 16A2lat). Both Hasegawa et al. [82] and Nunobe et al. [80] reported a 20 % involvement of station 16A2lat in type III cancers. In Japan it is still very popular the use of an index of estimated benefit from lymph node dissection (IEBLD), proposed by Sasako in 1995 [83], to compute the usefulness and priority of dissection of nodal stations. This IEBLD is calculated as the frequency of metastasis in the node station x 5-year survival rate of metastatic cases/100. With this index, both authors reported a survival benefit from dissection of para-aortic nodes similar to that obtained from second-tier nodes like celiac trunk station (station 9). According to the IEBLD, both authors considered also lower mediastinal nodes (station 110) as a high priority station. Moreover, Hosokawa et al. [79] reported for locally advanced cancers an increased risk of inferior mediastinal nodal metastases by 21 times in case of esophageal invasion ≥2 cm.

Splenic hilum nodes are involved in 15–20 % of cases [80, 82, 84].

In summary, Siewert type III diffuses toward abdominal nodal stations in all N+ patients. The frequent interest of distant nodal stations like para-aortic and splenic hilar nodes raises the issue of extent of lymphadenectomy. Lower mediastinal node metastases are not negligible and should be taken into account when performing lymphadenectomy.

14.3.2.4 Extent of Lymphadenectomy

The role of lymphadenectomy in EGJ cancer is now widely accepted and considered part of a standard approach to this disease. The reasons to perform lymphadenectomy are multiple. First, survival increases with increasing the number of resected nodes; second, patients with limited number of nodes involved treated with transthoracic lymphadenectomy demonstrated a survival advantage compared with patients treated with limited lymphadenectomy with a trans-hiatal approach [52]; third, the high incidence of nodal involvement since T1sm cancers would limit the role of any treatment, if we decide that no treatment can be useful in case of N+, and this is not in line with the recent improvement in prognosis of patients with EGJ cancer.

At the 1995 Consensus Conference of the International Society for Diseases of the Esophagus (ISDE), the terms and types of lymphadenectomy for esophageal and esophagogastric junction cancer were defined [85] and are still in use. Lymphadenectomy area was divided into three fields: the abdomen (field I), thorax (field II), and neck (field III) (Fig. 14.2). Japanese guidelines for abdominal lymphadenectomy [17] were used for abdominal nodal dissection; while, nodal dissections for the chest were subdivided into three classes: "standard" lymphadenectomy included mid- and lower mediastinal nodal dissection; "extended," comprised also the upper mediastinum on the right side; and "complete" or "total," encompassed bilateral upper mediastinal dissection. Two-field lymphadenectomy include

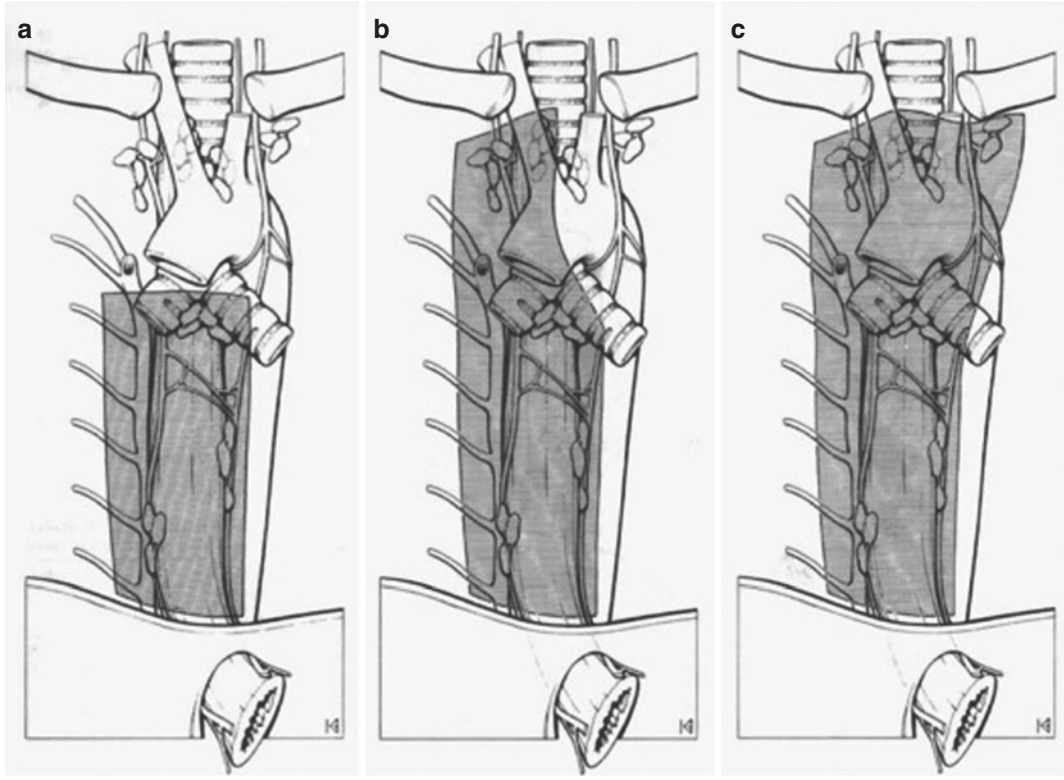

Fig. 14.2 Extent of lymphadenectomy according to the ISDE classification (1995) [85]: standard (**a**), extended (**b**), and complete (**c**) mediastinal lymphadenectomy (Reproduced with permission from [85])

an abdominal and a thoracic dissection, while in three-field lymphadenectomy also neck nodes are dissected.

The concept of en bloc resection was proposed by Logan and later reintroduced by Skinner, especially for adenocarcinoma of the esophagogastric junction in the 1960s. The aim is to maximize local tumor control by removing the esophagus together with an envelope of surrounding tissue. In particular, the tumor-bearing esophagus is resected with both pleural surfaces laterally, pericardium anteriorly, and all tissues between the esophagus and aorta or vertebral bodies, i.e., thoracic duct, azygos vein, and segments of intercostal arteries and veins. In minor modifications, intercostal vessels and trunk of the azygos vein or thoracic duct can be spared. If necessary, a cuff of diaphragm is dissected with the esophagus. Even if two-field lymphadenectomy and en bloc resection are not synonymous, normally, in en bloc esophagectomy, a standard mediastinal node dissection along with an abdominal dissection is carried out. A possible role of en bloc esophagectomy is in the better determination of circumferential margins. Whether en bloc esophagectomy has any use after induction chemoradiation (CRT) remains a matter of debate. However, CRT offers good local control, which may reduce the utility of this demanding technique. Thus, two-field lymphadenectomy without en bloc resection seems a valid alternative, especially after CRT.

Three-field lymphadenectomy, developed by Japanese surgeons in the 1980s for SCC, has been proposed by some authors also for adenocarcinoma Siewert type I and II, in which cervical nodal involvement, even if rare, is sometimes reported. Actually, the "third field" consists not only of the cervical nodes but also a continuous, anatomically inseparable chain of nodes from the superior mediastinum (recurrent nerve nodes) to

the lower neck. These nodes can be referred to as the cervicothoracic nodes [75]. Three-field dissection would be justified only if it had a prognostic impact. If its role in SCC is debated, in adenocarcinoma there is general consensus that its risks far outweigh the benefits, and three-field dissection is generally not performed.

The use of multimodal treatments does not preclude the necessity of correct nodal dissection.

The extent of lymphadenectomy in Siewert type I depends on the nodal stations potentially involved and on the risk of nodal involvement. The risk of nodal involvement for T1sm is relevant. At least one of four patients has nodal metastases, but some reports indicate that nodal involvement might be more. Hence, lymphadenectomy is important for T1sm. The incidence of nodal metastases is so high in advanced cancers (T2-4) that lymphadenectomy is mandatory.

The fields to dissect are those with frequent involvement. Abdominal paracardial nodes (stations 1 and 2), together with lesser curvature (station 3) and left gastric artery nodes (station 7), should always be included in the field of dissection, followed by celiac trunk nodes (stations 9). Hence, a D1+ abdominal dissection is indicated.

Mid- and lower mediastinal nodes (stations 108 and 110, respectively) are frequently involved; therefore, a standard mediastinal dissection is indicated. These indications are in line with recent reviews and consensus conferences [4, 86].

The risk of nodal metastases in Siewert type II is similar to type I. Abdominal paracardial nodes (stations 1 and 2), together with lesser curvature (station 3), left gastric artery nodes (station 7), celiac trunk (station 9), and splenic artery nodes (station 11) should always be included in the field of dissection. Hence, a D2 abdominal dissection is recommended.

Mid- and lower mediastinal nodes (stations 108 and 110, respectively) are frequently involved; therefore, a standard mediastinal dissection is in our opinion indicated.

The incidence of para-aortic nodes metastases is not negligible in Siewert II, mainly in those with principal gastric involvement, and according to Japanese authors [78, 80], the estimate benefits of the dissection of para-aortic nodes are similar to second-tier nodes, like celiac nodes. Nevertheless, in western countries dissection of para-aortic nodes is hardly performed even in gastric cancer; hence, a D3 abdominal dissection is not recommended, but it could be considered in advanced cases.

Another hot topic is the need of splenectomy to carry on a complete D2 dissection. Actually, data from both eastern and western centers [86, 87] do not recommend splenectomy to carry out a D2 dissection but indicate the value of splenectomy to obtain an R0 in case of infiltration.

The diffusion of Siewert type III is mainly toward the abdomen. As abovementioned, abdominal stations are involved in practically all N+ patients, with around 10 % of them having mediastinal nodes involved simultaneously.

Only inferior mediastinal nodes are reported as metastatic sites in the chest (station 110), and the risk of nodal involvement increases with increasing the esophageal invasion [79, 80]. There is general consensus that inferior mediastinal nodal dissection should be performed along with abdominal lymphadenectomy.

Paracardial (stations 1 and 2), lesser curvature (station 3), left gastric artery nodes (station 7), celiac trunk, common hepatic artery, splenic artery, and infrapyloric nodes (stations 9, 8a, 11, and 6) are frequently involved. Noteworthy, non-first-tier nodes are involved in around half of all advanced patients, similarly to gastric cancer patients, while the incidence of non-first-tier nodes seems lower for T1sm, but data are scanty to draw conclusions. Anyway a D2 abdominal lymphadenectomy is recommended for all Siewert type III patients.

Para-aortic nodes are reported in around 20–30 % of advanced patients in both Western and Eastern center experiences. Like for type II, a D3 lymphadenectomy might be proposed for advanced cases.

Like in Siewert II, splenic hilar nodes might be involved, but no survival advantage is reported adding splenectomy to carry out a D2 lymphadenectomy. Hence, reviews and consensus conferences [4, 86] are concordant to propose splenectomy only to achieve an R0 resection.

14.3.3 Treatment Strategy

14.3.3.1 Siewert I

Siewert I cancers are esophageal cancers and two surgical approaches have been proposed: transthoracic esophagectomy (TTE) and trans-hiatal esophagectomy (THE). Both approaches can obtain the requested 5 cm clear proximal margins and for this purpose are equally effective. Nonetheless, THE does not allow a complete removal of surrounding tissues, increasing the risk of CRM involvement [88], and moreover lymphadenectomy in the mediastinum is limited and suboptimal at most. The topic is so hot that since the late 1990s various authors tried to determine if TTE was superior to THE in terms of morbi-mortality, extent of lymphadenectomy and survival. A recent meta-analysis [89] considered 52 comparative studies for a total of almost 6000 patients for both squamous cell carcinoma and adenocarcinoma of all Siewert types together. As reported by the authors, most studies were pretty old and burdened with low methodological and surgical quality. THE showed reduced pulmonary complications and postoperative mortality, but TTE had fewer anastomotic leaks and fewer vocal cord palsies. Although survival did not differ, THE was significantly more frequently used in earlier stage cancers and lymphadenectomy was seldom reported. When reported, lymph node retrieval was significantly higher with TTE. The results of this meta-analysis are particularly interesting, since they underline the fact that even with evident selection bias, such as higher rate of advanced cancers treated with TTE and suboptimal lymphadenectomy, TTE and THE had comparable survival. So, we might speculate that with really comparable groups, TTE might be superior to THE.

In another meta-analysis [90], authors considered only EGJ cancer. Results were similar to those reported by the abovementioned meta-analysis.

In a very recent cohort study on Siewert I and II, Davies and coworkers [91] reported that with TTE more nodes were retrieved, CRM was less frequently involved in T3 cancers, and R0 resection was significantly more frequent.

One of the most cited randomized trials was carried out by Omloo et al. [52] on Siewert I and II patients. Authors reported that more nodes were retrieved with TTE and that survival was better with a transthoracic approach when up to eight nodes were involved. In subgroup analysis, TTE for type I showed a trend toward better survival.

We believe that all these studies, although interpretation is debated among researchers, indicate that a transthoracic approach provides better lymphadenectomy and reduced risk of CRM involvement, with probable impact on survival. We strongly believe that a transthoracic approach with mediastinal nodal dissection is paramount in the treatment of Siewert I cancer.

Hence, for T1sm and more advanced cancers, a transthoracic approach is indicated with 5 cm of clear proximal margin and a two-field nodal dissection with D1+ abdominal and standard mediastinal lymphadenectomy. Clear 5 cm distal margins can be obtained sparing great part of the stomach, which can be used, entire or tubularized, for reconstruction.

A curative resection (R0) can be easily obtained in T1sm cases and this is the reason for upfront surgery as the standard treatment. Although R0 and complete lymphadenectomy can be easily obtained with upfront surgery, nodal involvement is non-negligible in T1sm patients. Since prognosis is strictly related to nodal involvement, also cT1smN+ patients should be considered for multimodal treatments.

Similarly, it is debated if induction treatments are needed in cT2N0 patients. If preoperative stage is correct, good survival might be achieved with surgery and lymphadenectomy alone. Unfortunately the risk of nodal involvement in T2 patients is pretty high and, as reported by Stiles et al. [92] for esophageal and EGJ cancer, 55 % of the patients defined as cT2N0 were actually pN+ and showed reduced survival. We then believe that cT2 patients should undergo some kind of multimodal treatment, in accordance also with some national guidelines [5].

Induction CT or better CRT is then indicated in all locally advanced and node-positive Siewert I patients and surgical principles remain unaltered.

A particular case is that of T4 cancers, those invading surrounding adjacent organs: T4a are those invading resectable organs (pleura, pericardium, diaphragm), while T4b are those infiltrating unresectable organs (aorta, vertebral bodies, and trachea). T4a cancers deserve induction treatments and surgery similarly to all other advanced cancers. Instead, for T4b cancers often only palliative CT or CRT is proposed. Nonetheless, we think that multimodal treatments should be offered to all fit patients, and an attempt to achieve a radical resection should be made in case of good response to treatment.

14.3.3.2 Siewert II

Siewert type II cancer has a borderline position, being considered variably as either an esophageal or a gastric cancer by researchers. TNM 7th edition considers Siewert II as an esophageal cancer, partially solving the problem. Preoperative definition of Siewert type is not always easy, and actually some type II cancers resemble more esophageal cancers, while others are more similar to type III. To increase the difficulty, there is always the East vs. West different perspective. In Eastern countries, where Barrett's esophagus and Siewert I are rare and Siewert III very common, Siewert II resembles Siewert III, and probably the origin is the same [93, 94]. In the USA, where obesity and reflux are more common, Siewert II shares the pathological pattern with Siewert I. In Europe, probably both pathological patterns exist, with some Siewert II originating from an ultrashort Barrett's esophagus, and some presenting a strong association with H. pylori infection like type III [95].

However, Siewert II cancers often show significant esophageal invasion, so long longitudinal margins are needed. For this reason, also for Siewert II, both transthoracic esophagectomy (TTE) and trans-hiatal esophagectomy (THE) have been proposed. Both approaches can obtain the requested 5 cm clear proximal margins and for this purpose are equally effective. Although TTE allows better lymphadenectomy and reduced risk of CRM involvement, no study so far could show an increased survival in Siewert II patients treated with a transthoracic approach. Also a total gastrectomy with distal esophagectomy via a solo abdominal approach is considered possible in the current literature [4, 86]. Siewert et al. [96] in 2005 reported better survival for Siewert II with gastrectomy, but authors stressed the importance of clear proximal margins and stated also that an adequate lymphadenectomy can be achieved even without total gastrectomy, admitting the use of a transthoracic esophagectomy without total gastrectomy in these patients. Indeed, in Siewert II patients, the incidence of nodal involvement on stations along the greater curve is marginal [66, 82].

Recently, Parry and coworkers [97] focused their trial on Siewert II and reported a trend to better survival with esophagectomy, with reduced risk of CRM involvement and more complete mediastinal nodal dissection, but equal morbi-mortality and disease recurrence compared with gastrectomy.

Moreover, most Siewert II cancers show huge similarities with type I in many regards, such as nodal diffusion and response to CRT.

However, some type II cancers have limited esophageal invasion. When esophageal invasion is limited, as reported in the paragraph on nodal spread in Siewert type II, the risk of mediastinal-positive nodes is reduced at both middle and inferior mediastinal stations. Indeed, when the esophagus is infiltrated for 2 cm or less, a solo abdominal approach may provide both adequate margins and correct lymphadenectomy in inferior mediastinal and abdominal nodes. In these cases, lymphadenectomy should focus on abdominal nodes, and, although not mandatory, a total gastrectomy might provide a more extensive nodal dissection. This is in line with a previous Japanese randomized study [98], which did not show any survival advantage with left thoraco-abdominal (LTA) approach compared with a trans-hiatal approach, which consisted of total gastrectomy via laparotomy and lower esophagectomy accessed trans-hiatally, in Siewert II and III patients, when esophageal invasion was limited (3 cm or less). This was also confirmed by the results of the 10-year follow-up study by the same group [99].

Since in case of esophageal infiltration of more than 2 cm the risk of mediastinal nodal involvement

is relevant and a solo abdominal approach would be detrimental, we must be reasonably sure of the degree of infiltration before planning the surgical strategy. Gastroscopy and endoscopic ultrasonography (EUS) can determine with good sensitivity and specificity if esophageal infiltration is less than 2 cm [100]. This can help plan the correct approach to Siewert II cancers.

The clear proximal margin required is 5 cm. In patients with significant esophageal invasion, a transthoracic approach provides adequate margins, both proximal and circumferential, and allows a two-field nodal dissection, with D2 abdominal and standard mediastinal lymphadenectomy. Clear 5 cm distal margins can be obtained sparing great part of the stomach, which can be used, entire or tubularized, for reconstruction. When esophageal invasion is ≤2 cm, total gastrectomy and distal esophagectomy via a solo abdominal approach is the preferred approach, and reconstruction of the digestive tract can be accomplished with a Roux-en-y esophagojejunal anastomosis.

Indications for multimodal treatments are the same as for Siewert I: induction CT or CRT are indicated in all locally advanced and node-positive Siewert II patients, and surgical principles remain unaltered after induction treatment. T4a cancers merit induction treatments and surgery like all other advanced cancers. Instead, for T4b cancers, like for Siewert I, we think that multimodal treatments should be offered to all fit patients, and an attempt to achieve a radical resection should be made in case of good response to treatment.

14.3.3.3 Siewert III

Siewert type III cancer was defined by TNM 7th edition as an esophageal cancer. If the statistical model seems to fit this type of cancer, clinicians do not seem to adapt to that model. Consensus conferences [4] and American guidelines [5] are pretty categorical in defining Siewert III as a gastric cancer. Certainly some characteristics must be taken into account: biology of cancer is different from type I and probably from type II, nodal diffusion is mainly toward the abdomen, and response to CRT is really poor.

The typical surgical approach consists of total gastrectomy and distal esophagectomy with, if necessary, resection of nearby organs to achieve an R0 resection.

According to a meta-analysis comparing transthoracic and trans-hiatal approach to EGJ cancer [90], there was a potential trend toward better survival with trans-hiatal approach in Siewert III. In Japanese experience, a left thoraco-abdominal (LTA) approach for Siewert II and III with esophageal infiltration limited to 3 cm did not show any survival advantage compared to total gastrectomy and distal esophagectomy from a solo abdominal approach, both at the initial randomized trial [98] and after a 10-year follow-up [99].

For T1sm and more advanced cancers, the correct approach requires 5 cm of clear proximal margin. A solo abdominal approach is possible only if the invasion of the esophagus is not superior to 2 cm. In case of esophageal invasion >2 cm, adequate margins cannot be achieved via a solo abdominal approach, and the risk of inferior mediastinal nodal metastases increases markedly, as previously reported [79, 80]. Thus, a transthoracic approach becomes necessary.

Clear 5 cm distal margins are required and so a total gastrectomy is needed. Furthermore, a total gastrectomy is necessary to obtain a complete abdominal lymphadenectomy. Splenectomy is recommended only to obtain an R0 resection and not to carry out lymphadenectomy.

Hence, a total gastrectomy and distal esophagectomy, with 5 cm of clear proximal margin and a D2 abdominal and inferior mediastinal lymphadenectomy, is indicated. D3 lymphadenectomy might be considered in advanced cases, like reported on paragraph about extent of lymphadenectomy. Reconstruction of the digestive tract can be achieved with a Roux-en-y esophagojejunal anastomosis, which can be performed via a solo abdominal approach if esophageal invasion is inferior to 2 cm or otherwise with a transthoracic approach.

Multimodal treatments are indicated in all locally advanced and node-positive Siewert III patients, and surgical principles remain unaltered after multimodal treatments.

A particular case is that of T4b cancers, those invading surrounding adjacent organs. Although

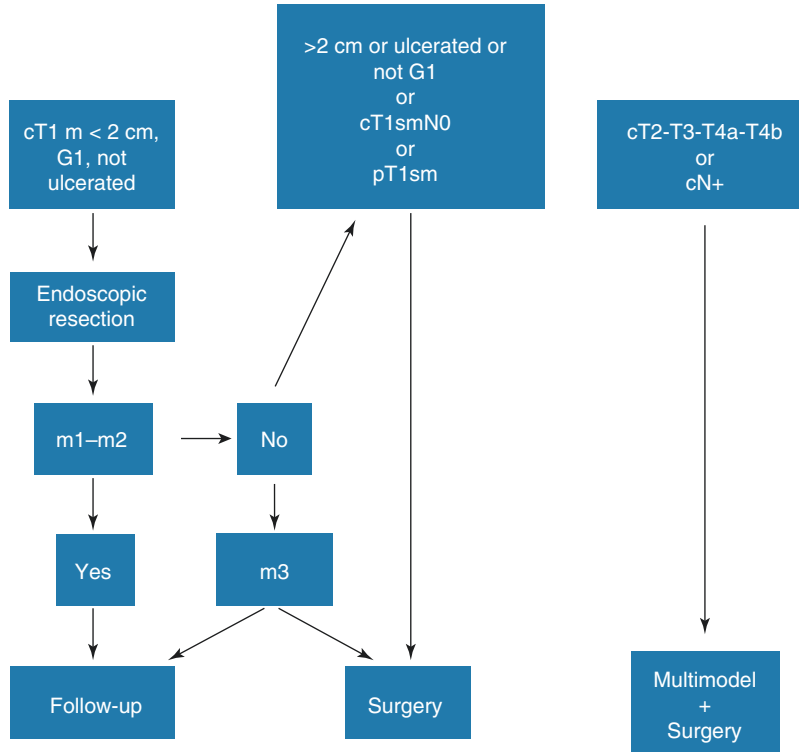

Fig. 14.3 Flowchart of the suggested approach to EGJ cancers

often only palliative CT or CRT is proposed, we think that surgical resection of the infiltrated organ should be attempted in order to obtain an R0 resection. Multimodal treatments should be offered to all fit patients, since they might increase the probability of a curative resection.

Conclusions

In conclusion, we can draw a flowchart of the suggested approach to EGJ cancers (Fig. 14.3): T1m cancers should be treated with endoscopic resection. If the involvement of cancer is limited to the mucosa (m1-m3), follow-up is sufficient, but cases at higher risk of nodal involvement, like m3 cases with lymphovascular invasion, might be considered for surgery or stricter follow-up. In all patients where T1sm is suspected clinically or diagnosed after endoscopic resection, upfront surgery with lymphadenectomy is mandatory. Multimodal treatments should be considered in case of clinical N+. For T2, T3, T4a, and T4b, multimodal treatments are indicated in all fit patients. For Siewert type I and most cases of type II, induction chemoradiation is indicated, while for type III and type II cases with limited esophageal invasion, perioperative or induction chemotherapy is preferred.

For Siewert I and II T4b cancers, CRT is the preferred option, with possible surgical resection considered in cases with good response to treatment, while for Siewert III T4b cancers, resection of nearby organs is indicated to obtain an R0 resection, possibly after chemotherapy.

References

1. Sjoquist KM, Burmeister BH, Smithers BM et al (2011) Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 12(7):681–692

2. Lv J, Cao XF, Zhu B et al (2009) Effect of neoadjuvant chemoradiotherapy on prognosis and surgery for esophageal carcinoma. World J Gastroenterol 15(39):4962–4968
3. Ronellenfitsch U, Schwarzbach M, Hofheinz R et al (2013) Perioperative chemo(radio)therapy versus primary surgery for resectable adenocarcinoma of the stomach, gastroesophageal junction, and lower esophagus. Cochrane Database Syst Rev 5(5): CD008107
4. Lutz MP, Zalcberg JR, Ducreux M et al (2012) Highlights of the EORTC St. Gallen international expert consensus on the primary therapy of gastric, gastroesophageal and oesophageal cancer – differential treatment strategies for subtypes of early gastroesophageal cancer. Eur J Cancer 48(16):2941–2953
5. National Comprehensive Cancer Network. Esophageal and esophagogastric junction cancers NCCN Guidelines. Version 3.2015
6. Moehler M, Baltin CT, Ebert M et al (2015) International comparison of the German evidence-based S3-guidelines on the diagnosis and multimodal treatment of early and locally advanced gastric cancer, including adenocarcinoma of the lower esophagus. Gastric Cancer 18(3):550–563
7. Allum WH, Blazeby JM, Griffin SM et al (2011) Guidelines for the management of oesophageal and gastric cancer. Gut 60(11):1449–1472
8. Malthaner R, Wong RKS, Spithoff K (2010) Preoperative or postoperative therapy for resectable oesophageal cancer: an updated practice guideline. Clin Oncol 22(4):250–256
9. Van Hagen P, Hulshof MCCM, van Lanschot JJB et al (2012) Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 366(22):2074–2084
10. Stahl M, Walz MK, Stuschke M et al (2009) Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol 27(6):851–856
11. Burmeister BH, Thomas JM, Burmeister E et al (2011) Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. Eur J Cancer 47(3):354–360
12. Cunningham D, Allum WH, Stenning SP et al (2006) Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 355:11–20
13. Curtis NJ, Noble F, Bailey IS et al (2014) The relevance of the Siewert classification in the era of multimodal therapy for adenocarcinoma of the gastro-oesophageal junction. J Surg Oncol 109(3): 202–207
14. Hasegawa S, Yoshikawa T (2010) Adenocarcinoma of the esophagogastric junction: Incidence, characteristics, and treatment strategies. Gastric Cancer 13(2):63–73
15. Reynolds JV, Ravi N, Muldoon C et al (2010) Differential pathologic variables and outcomes across the spectrum of adenocarcinoma of the esophagogastric junction. World J Surg 34(12): 2821–2829
16. Sgourakis G, Gockel I, Lang H (2013) Endoscopic and surgical resection of T1a/T1b esophageal neoplasms: a systematic review. World J Gastroenterol 19(9):1424–1437
17. Japanese Esophageal Society (2008) Japanese classification of esophageal cancer, 10th edn. Kaneara & Co., Tokyo. 6(1):1–25
18. Dunbar KB, Spechler SJ (2012) The risk of lymph node metastases in patients with high grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. Am J Gastroenterol 107(6):850–863
19. Luna RA, Gilbert E, Hunter JG (2012) High-grade dysplasia and intramucosal adenocarcinoma in Barrett's esophagus: the role of esophagectomy in the era of endoscopic eradication therapy. Curr Opin Gastroenterol 28(4):362–369
20. Prasad GA, Wu TT, Wigle D et al (2009) Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Barrett's esophagus. Gastroenterology 137(3):815–823
21. Zehetner J, Demeester SR, Hagen J et al (2011) Endoscopic resection and ablation versus esophagectomy for high-grade dysplasia and intramucosal adenocarcinoma. J Thorac Cardiovasc Surg 141(1):39–47
22. Ngamruengphong S, Wolfsen HC, Wallace MB (2013) Survival of patients with superficial esophageal adenocarcinoma following endoscopic treatment vs surgery. Clin Gastroenterol Hepatol 11(11):1424–e81
23. Westerterp M, Koppert LB, Buskens CJ et al (2005) Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch 446(5):497–504
24. Oh DS, Hagen J, Chandrasoma PT et al (2006) Clinical biology and surgical therapy of intramucosal adenocarcinoma of the esophagus. J Am Coll Surg 203(2):152–161
25. Raziee HR, Cardoso R, Seevaratnam R et al (2012) Systematic review of the predictors of positive margins in gastric cancer surgery and the effect on survival. Gastric Cancer 15:116–124
26. Papachristou DN, Agnanti N, D'Agostino H et al (1980) Histologically positive esophageal margin in the surgical treatment of gastric cancer. Am J Surg 139(5):711–713
27. Gao F, Chen J, Wang T et al (2014) Incidence of microscopically positive proximal margins in adenocarcinoma of the gastroesophageal junction. PLoS One 9(2):e88010
28. Szántó I, Vörös A, Nagy P et al (2002) Esophageal intramural metastasis from adenocarcinoma of the gastroesophageal junction. Endoscopy 34(5): 418–420

29. Lam KY, Ma LT, Wong J (1996) Measurement of extent of spread of oesophageal squamous carcinoma by serial sectioning. J Clin Pathol 49(2): 124–129
30. Tsutsui S, Kuwano H, Watanabe M et al (1995) Resection margin for squamous cell carcinoma of the esophagus. Ann Surg 222(2):193–202
31. Law S, Arcilla C, Chu KM et al (1998) The significance of histologically infiltrated resection margin after esophagectomy for esophageal cancer. Am J Surg 176(3):286–290
32. Khoshnevis J, Moradi A, Azargashb E et al (2013) A study of contractility of proximal surgical margin in esophageal cancer. Iran J Cancer Prev 6(1):25–27
33. Barbour AP, Rizk NP, Gonen M et al (2007) Adenocarcinoma of the gastroesophageal junction: influence of esophageal resection margin and operative approach on outcome. Ann Surg 246(1):1–8
34. Mariette C, Castel B, Balon JM et al (2003) Extent of oesophageal resection for adenocarcinoma of the oesophagogastric junction. Eur J Surg Oncol 29(7):588–593
35. Ito H, Clancy TE, Osteen RT et al (2004) Adenocarcinoma of the gastric cardia: what is the optimal surgical approach? J Am Coll Surg 199(6):880–886
36. Mine S, Sano T, Hiki N et al (2013) Proximal margin length with transhiatal gastrectomy for Siewert type II and III adenocarcinomas of the oesophagogastric junction. Br J Surg 100(8):1050–1054
37. Shen KR, Cassivi SD, Deschamps C et al (2006) Surgical treatment of tumors of the proximal stomach with involvement of the distal esophagus: a 26-year experience with Siewert type III tumors. J Thorac Cardiovasc Surg 132(4):755–762
38. Casson AG, Darnton SJ, Subramanian S et al (2000) What is the optimal distal resection margin for esophageal carcinoma? Ann Thorac Surg 69(1): 205–209
39. DiMusto PD, Orringer MB (2007) Transhiatal esophagectomy for distal and cardia cancers: implications of a positive gastric margin. Ann Thorac Surg 83(6):1993–1999
40. Chao YK, Yeh CJ, Chang HK et al (2011) Impact of circumferential resection margin distance on locoregional recurrence and survival after chemoradiotherapy in esophageal squamous cell carcinoma. Ann Surg Oncol 18(2):529–534
41. Deeter M, Dorer R, Kuppusamy MK et al (2009) Assessment of criteria and clinical significance of circumferential resection margins in esophageal cancer. Arch Surg 144(7):618–624
42. Scheepers JJG, Van Der Peet DL, Veenhof A et al (2009) Influence of circumferential resection margin on prognosis in distal esophageal and gastroesophageal cancer approached through the transhiatal route. Dis Esophagus 22(1):42–48
43. Sujendran V, Wheeler J, Baron R et al (2008) Effect of neoadjuvant chemotherapy on circumferential margin positivity and its impact on prognosis in patients with resectable oesophageal cancer. Br J Surg 95(2):191–194
44. De Manzoni G, Verlato G, Di Leo A et al (2006) Peritoneal cytology does not increase the prognostic information provided by TNM in gastric cancer. World J Surg 30(4):579–584
45. Rice TW, Blackstone EH, Rusch VW (2010) 7th edition of the AJCC cancer staging manual: esophagus and esophagogastric junction. Ann Surg Oncol 17(7):1721–1724
46. Chan DSY, Reid TD, Howell I et al (2013) Systematic review and meta-analysis of the influence of circumferential resection margin involvement on survival in patients with operable oesophageal cancer. Br J Surg 100(4):456–464
47. Wu J, Chen QX, Teng LS et al (2014) Prognostic significance of positive circumferential resection margin in esophageal cancer: a systematic review and meta-analysis. Ann Thorac Surg 97(2): 446–453
48. Peyre CG, Hagen JA, DeMeester SR et al (2008) Predicting systemic disease in patients with esophageal cancer after esophagectomy: a multinational study on the significance of the number of involved lymph nodes. Ann Surg 248(6):979–985
49. Mariette C, Piessen G, Briez N et al (2008) The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. Ann Surg 247(2):365–371
50. Smit JK, Pultrum BB, Van Dullemen HM et al (2010) Prognostic factors and patterns of recurrence in esophageal cancer assert arguments for extended two-field transthoracic esophagectomy. Am J Surg 200(4):446–453
51. Johansson J, DeMeester TR, Hagen JA et al (2004) En bloc vs transhiatal esophagectomy for stage T3 N1 adenocarcinoma of the distal esophagus. Arch Surg 139(6):627–631
52. Omloo JMT, Lagarde SM, Hulscher JBF et al (2007) Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg 246(6):992–1000
53. Hölscher AH, Drebber U, Schmidt H et al (2014) Prognostic classification of histopathologic response to neoadjuvant therapy in esophageal adenocarcinoma. Ann Surg 260(5):779–785
54. Rice TW, Blackstone EH (2013) Lymph node ratio: a confounded quotient. Ann Thorac Surg 96(2):744
55. Rizk NP, Ishwaran H, Rice TW et al (2010) Optimum lymphadenectomy for esophageal cancer. Ann Surg 251(1):46–50
56. Altorki NK, Zhou XK, Stiles B et al (2008) Total number of resected lymph nodes predicts survival in esophageal cancer. Ann Surg 248(2):221–226
57. Groth SS, Virnig BA, Whitson BA et al (2010) Determination of the minimum number of lymph

nodes to examine to maximize survival in patients with esophageal carcinoma: data from the Surveillance Epidemiology and End Results database. J Thorac Cardiovasc Surg 139(3):612–620
58. Peyre CG, Hagen JA, DeMeester SR et al (2008) The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg 248(4):549–556
59. Stiles BM, Nasar A, Mirza FA et al (2012) Worldwide oesophageal cancer collaboration guidelines for lymphadenectomy predict survival following neoadjuvant therapy. Eur J Cardiothorac Surg 42(4): 659–664
60. Lerut T (2012) Cancer of the oesophagus and gastrooesophageal junction: neoadjuvant therapy should not be a surrogate for suboptimal lymphadenectomy. Eur J Cardiothorac Surg 42(4):664–666
61. Bollschweiler E, Besch S, Drebber U et al (2010) Influence of neoadjuvant chemoradiation on the number and size of analyzed lymph nodes in esophageal cancer. Ann Surg Oncol 17(12):3187–3194
62. McGuill MJ, Byrne P, Ravi N et al (2008) The prognostic impact of occult lymph node metastasis in cancer of the esophagus or esophago-gastric junction: systematic review and meta-analysis. Dis Esophagus 21(3):236–240
63. Gertler R, Stein HJ, Schuster T et al (2014) Prevalence and topography of lymph node metastases in early esophageal and gastric cancer. Ann Surg 259(1):96–101
64. Barbour AP, Jones M, Brown I et al (2010) Risk stratification for early esophageal adenocarcinoma: analysis of lymphatic spread and prognostic factors. Ann Surg Oncol 17(9):2494–2502
65. Bollschweiler E, Baldus SE, Schröder W et al (2006) High rate of lymph-node metastasis in submucosal esophageal squamous-cell carcinomas and adenocarcinomas. Endoscopy 38(2):149–156
66. Pedrazzani C, de Manzoni G, Marrelli D et al (2007) Lymph node involvement in advanced gastroesophageal junction adenocarcinoma. J Thorac Cardiovasc Surg 134(2):378–385
67. Zhang X, DI Watson JG (2007) Lymph node metastases of adenocarcinoma of the esophagus and esophagogastric junction. Chin Med J 120(24): 2268–2270
68. Meier I, Merkel S, Papadopoulos T et al (2008) Adenocarcinoma of the esophagogastric junction: the pattern of metastatic lymph node dissemination as a rationale for elective lymphatic target volume definition. Int J Radiat Oncol Biol Phys 70(5): 1408–1417
69. Feith M, Stein HJ, Siewert JR (2003) Pattern of lymphatic spread of Barrett's cancer. World J Surg 27(9):1052–1057
70. Leers JM, DeMeester SR, Chan N et al (2009) Clinical characteristics, biologic behavior, and survival after esophagectomy are similar for adenocarcinoma of the gastroesophageal junction and the distal esophagus. J Thorac Cardiovasc Surg 138(3):594–602
71. Dresner SM, Lamb PJ, Bennett MK et al (2001) The pattern of metastatic lymph node dissemination from adenocarcinoma of the esophagogastric junction. Surgery 129(1):103–109
72. Mönig SP, Baldus SE, Zirbes TK et al (2002) Topographical distribution of lymph node metastasis in adenocarcinoma of the gastroesophageal junction. Hepatogastroenterology 49(44):419–422
73. Kakeji Y, Yamamoto M, Ito S et al (2012) Lymph node metastasis from cancer of the esophagogastric junction, and determination of the appropriate nodal dissection. Surg Today 42(4):351–358
74. Lerut T, Nafteux P, Moons J et al (2004) Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. Ann Surg 240(6):962–972
75. Altorki N, Kent M, Ferrara C et al (2002) Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Ann Surg 236(2): 177–183
76. Nakamura M, Iwahashi M, Nakamori M et al (2012) Lower mediastinal lymph node metastasis is an independent survival factor of siewert type II and III adenocarcinomas in the gastroesophageal junction. Am Surg 78(5):567–573
77. Yuasa N, Miyake H, Yamada T et al (2006) Clinicopathologic comparison of Siewert type II and III adenocarcinomas of the gastroesophageal junction. World J Surg 30(3):364–371
78. Mine S, Sano T, Hiki N et al (2013) Lymphadenectomy around the left renal vein in Siewert type II adenocarcinoma of the oesophagogastric junction. Br J Surg 100(2):261–266
79. Hosokawa Y, Kinoshita T, Konishi M et al (2012) Clinicopathological features and prognostic factors of adenocarcinoma of the esophagogastric junction according to Siewert classification: experiences at a single institution in Japan. Ann Surg Oncol 19(2):677–683
80. Nunobe S, Ohyama S, Sonoo H et al (2008) Benefit of mediastinal and para-aortic lymph-node dissection for advanced gastric cancer with esophageal invasion. J Surg Oncol 97(5):392–395
81. Kurokawa Y, Hiki N, Yoshikawa T et al (2015) Mediastinal lymph node metastasis and recurrence in adenocarcinoma of the esophagogastric junction. Surgery 157(3):551–555
82. Hasegawa S, Yoshikawa T, Rino Y et al (2013) Priority of lymph node dissection for Siewert type II/III adenocarcinoma of the esophagogastric junction. Ann Surg Oncol 20:4252–4259
83. Sasako M, McCulloch P, Kinoshita T (1995) New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. Br J Surg 82(3):346–351

84. De Manzoni G, Morgagni P, Roviello F et al (1998) Nodal abdominal spread in adenocarcinoma of the cardia. Results of a multicenter prospective study. Gastric Cancer 1(2):146–151
85. Fumagalli U, Akiyama H, DeMeester T (1996) Resective surgery for cancer of the thoracic esophagus: results of a consensus conference held at the VIth World Congress of the International Society for Diseases of the Esophagus. Dis Esophagus 9:30–38
86. Mariette C, Piessen G, Briez N et al (2011) Oesophagogastric junction adenocarcinoma: which therapeutic approach? Lancet Oncol 12(3):296–305
87. Goto H, Tokunaga M, Sugisawa N et al (2013) Value of splenectomy in patients with Siewert type II adenocarcinoma of the esophagogastric junction. Gastric Cancer 16(4):590–595
88. Suttie SA, Nanthakumaran S, Mofidi R et al (2012) The impact of operative approach for oesophageal cancer on outcome: the transhiatal approach may influence circumferential margin involvement. Eur J Surg Oncol 38(2):157–165
89. Boshier PR, Anderson O, Hanna GB (2011) Transthoracic versus transhiatal esophagectomy for the treatment of esophagogastric cancer. Ann Surg 254(6):894–906
90. Wei MT, Zhang YC, Deng XB et al (2014) Transthoracic vs transhiatal surgery for cancer of the esophagogastric junction: a meta-analysis. World J Gastroenterol 20(29):10183–10192
91. Davies AR, Sandhu H, Pillai A et al (2014) Surgical resection strategy and the influence of radicality on outcomes in oesophageal cancer. Br J Surg 101(5):511–517
92. Stiles BM, Mirza F, Coppolino A et al (2011) Clinical T2-T3N0M0 esophageal cancer: the risk of node positive disease. Ann Thorac Surg 92(2):491–498
93. Hasegawa S, Yoshikawa T, Cho H et al (2009) Is adenocarcinoma of the esophagogastric junction different between Japan and western countries? The incidence and clinicopathological features at a Japanese high-volume cancer center. World J Surg 33(1):95–103
94. Suh YS, Han DS, Kong SH et al (2012) Should adenocarcinoma of the esophagogastric junction be classified as esophageal cancer? A comparative analysis according to the seventh AJCC TNM classification. Ann Surg 255(5):908–915
95. Pedrazzani C (2015) Should adenocarcinoma of the esophagogastric junction be classified as gastric or esophageal cancer, or else as a distinct clinical entity? Ann Surg 261(4):e107–e108
96. Siewert JR, Feith M, Stein HJ (2005) Biologic and clinical variations of adenocarcinoma at the esophago-gastric junction: Relevance of a topographic-anatomic subclassification. J Surg Oncol 90(3): 139–146
97. Parry K, Haverkamp L, Bruijnen RCG et al (2014) Surgical treatment of adenocarcinomas of the gastro-esophageal junction. Ann Surg Oncol 22(2): 597–603
98. Sasako M, Sano T, Yamamoto S et al (2006) Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. Lancet Oncol 7(8):644–651
99. Kurokawa Y, Sasako M, Sano T et al (2015) Ten-year follow-up results of a randomized clinical trial comparing left thoracoabdominal and abdominal transhiatal approaches to total gastrectomy for adenocarcinoma of the oesophagogastric junction or gastric cardia. Br J Surg 102(4):341–348
100. Pedrazzani C, Bernini M, Giacopuzzi S et al (2005) Evaluation of Siewert classification in gastro-esophageal junction adenocarcinoma: what is the role of endoscopic ultrasonography? J Surg Oncol 91(4): 226–231

15 Chemotherapy in Oesophagogastric Junctional Cancer

Paul M. Wilkerson, Stephen T. Hornby, and William H. Allum

15.1 Introduction

The role of chemotherapy in the management of oesophagogastric junctional (EGJ) cancers has evolved rapidly over the last three decades. From single-agent therapies in the palliative setting with response rates (RR) of 10–25 % [1], a range of multi-agent regimens is now used in neoadjuvant, perioperative and palliative settings as well as in combination with radiotherapy. More recently in the era of targeted medicine, novel agents targeting specific pathways have been introduced in EGJ cancer.

In this chapter we will discuss the roles of chemotherapy in EGJ cancer and present the data that has established these roles. We will show the evidence behind the current gold standard regimens and describe likely future developments

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15.2 Neoadjuvant Chemotherapy

In the UK the recommended treatment for T2 and T3 oesophageal cancer with or without nodal involvement is neoadjuvant chemotherapy followed by surgical resection [2]. This practice is informed by the OE02 study. Overseen by the Medical Research Council Oesophageal Cancer Working Group, OE02 was a large multicentre randomized trial that compared neoadjuvant chemotherapy to surgery alone. 802 patients were randomized to either a course of 2 × 4 day cycles of cisplatin 80 mg/m^2 over 4 h, plus 5-fluorouracil 1000 mg/m^2 (5-FU) daily for 4 days followed by surgery ($n=400$), or surgical resection alone ($n=402$).

The initial results showed a survival advantage for the patients who had undergone chemotherapy (hazard ratio 0.79, 95 % CI, 0.67–0.93, $p=0.004$). The chemotherapy group had an increase in median survival of 107 days and an increase in 2-year survival of 9 % (43 vs 34 %). There was no increased risk of postoperative complications in the chemotherapy arm, and the majority ($n=350$) of patients were able to tolerate both cycles of neoadjuvant treatment [3].

The long-term results of this study were published in 2009. There was a continued survival benefit for the chemotherapy group, but this was more modest (23 vs 17 %) (Fig. 15.1).

The study highlighted the importance of complete resection of the surgical specimen with very

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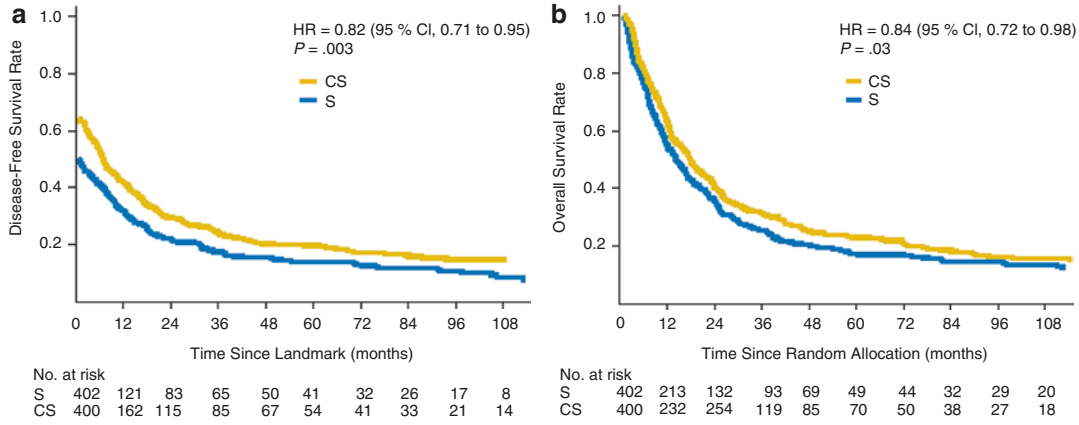

Fig. 15.1 (**a**) Disease-free survival (DFS) by allocated treatment. OEO2 Trial was calculated from a landmark time of 6 months from random assignment to allow for the difference in timing of surgery between the two groups. (**b**) Overall survival by S surgery alone and CS chemotherapy and surgery

poor survival observed in both groups when macroscopic tumour tissue was left behind or no resection had been performed. There was, however, the observation that unresectability was significantly more common in the patients who had progressed straight to surgery than in the neoadjuvant arm. This suggests that the chemotherapy exerts an early influence locally to enable resection [4].

In contrast the US Intergroup-0113 trial showed no difference in overall survival with the addition of preoperative chemotherapy [5]. In this study 467 patients with oesophageal and EGJ cancers were randomized to surgery alone or to three cycles of cisplatin and 5-FU. The responders also received the same combination for three cycles postoperatively. There are differences between OE02 and Intergroup-0113 in that there was greater treatment toxicity and a longer delay in timing of definitive surgery, which have been implicated in the Intergroup trial outcomes.

In 2007 the Australian Gastrointestinal Trials Group published a meta-analysis of eight randomized trials with a pooled analysis of 1600 patients, which favoured survival in the chemotherapy patients (HR 0.90, 95 % CI, 0.81–1.00) [6]. This meta-analysis is heavily influenced by the OE02 trial, which contributed over half of the patients to the pooled results. The group then updated the analysis in 2011 adding two further trials and 400 more patients. The effect of chemotherapy on overall survival remained similar (HR 0.87, 95 % CI, 0.79–0.96) (Fig. 15.2). In a subgroup analysis, the effect on survival was not observed in squamous cell carcinoma of the oesophagus as it was in adenocarcinoma [7].

The successor trial to OE02 is the OE05 trial [8] which has randomized 842 patients with operable oesophageal adenocarcinoma to receive either the OE02 regimen of chemotherapy followed by surgery or a course of epirubicin, cisplatin and capecitabine (ECX) and then surgery. It should be noted that this study was designed after the MAGIC era [9], in which ECF became the reference regimen, and after the REAL-2 study [10], which demonstrated that oral capecitabine was not inferior to infusional 5-FU. The aim of OE05 was to determine a survival benefit with the modified regime, with secondary endpoints including any decreased toxicity from treatment and improvements in patient quality of life. The results of OEO5 have been presented in abstract form and showed no difference in survival between the treatment groups despite an apparent benefit in progression free and disease free survival for ECX [11].

15.3 Perioperative Chemotherapy

Although the 5-FU/cisplatin doublet has been the reference regimen in many trials of oesophageal and EGJ cancer since the 1980s, key trials in the late

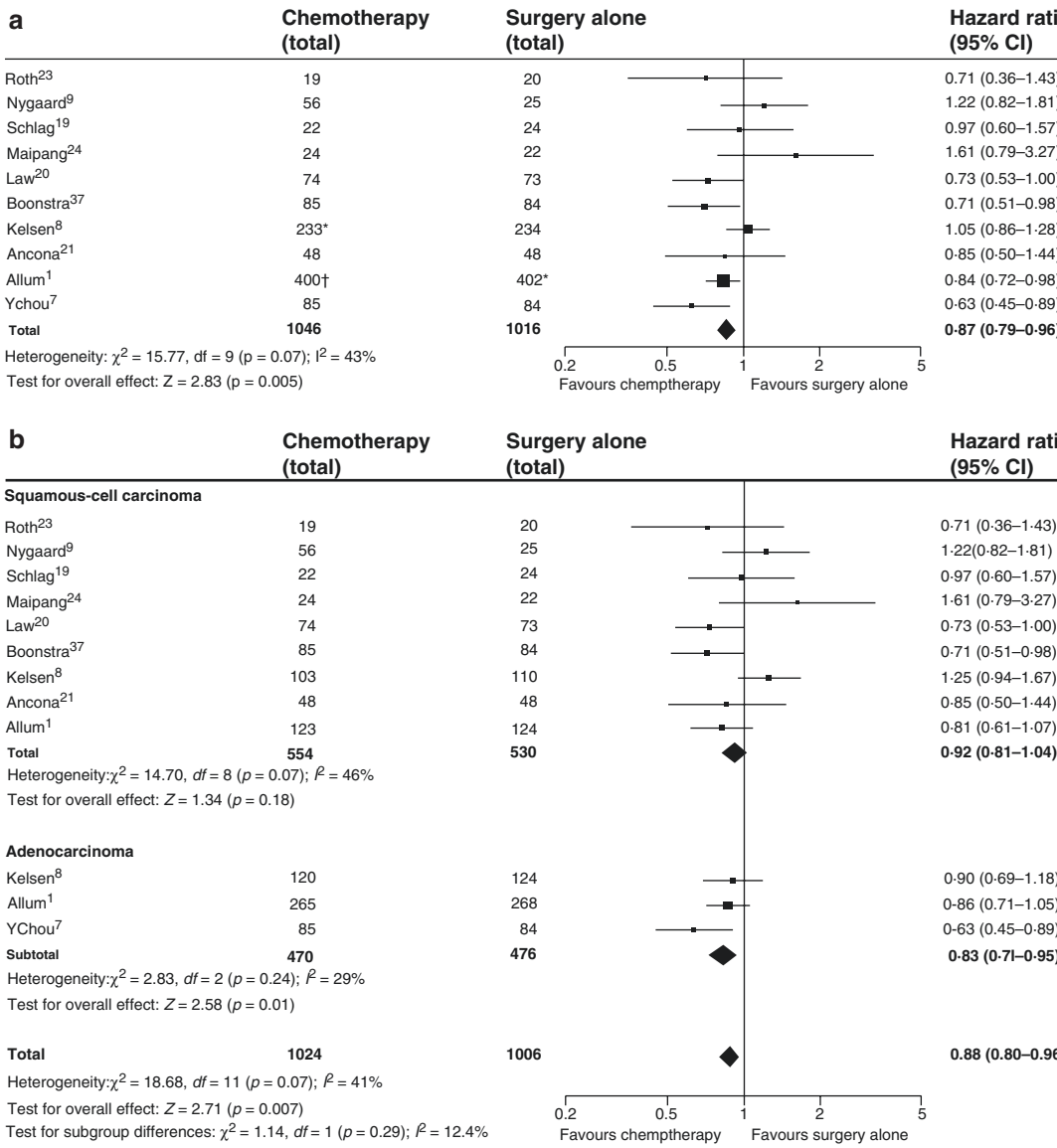

Fig. 15.2 Effects of chemotherapy compared with surgery alone on survival in patients with oesophageal cancer (**a**) and in subgroups of patients with oesophageal carcinoma (squamous-cell carcinoma or adenocarcinoma histology (**b**))

1990s changed this paradigm. The inclusion of the anthracycline epirubicin in the ECF regimen together with a lower dose of cisplatin and 5-FU than the CF regimen with prolonged infusion of 5-FU as opposed to bolus resulted in a prolonged disease-free interval in advanced disease [12]. In comparison with a triplet incorporating 5-FU/doxorubicin/methotrexate (FAMTX) [13], the response rates (RRs) in the ECF arm were higher (45 vs 21 %) coupled with a significant increase in overall survival (OS) (8.9 vs 5.7 months). An improvement in quality of life at 24 weeks was also noted, and as a result ECF became the reference regimen in the UK.

In 2006, the seminal MAGIC trial was published, which has set the standard of care for perioperative chemotherapy in gastric and EGJ cancers throughout the UK and most of Europe [9]. This study randomized 503 patients from four continents with gastric or EGJ cancer (75/25 % split) to receive either perioperative

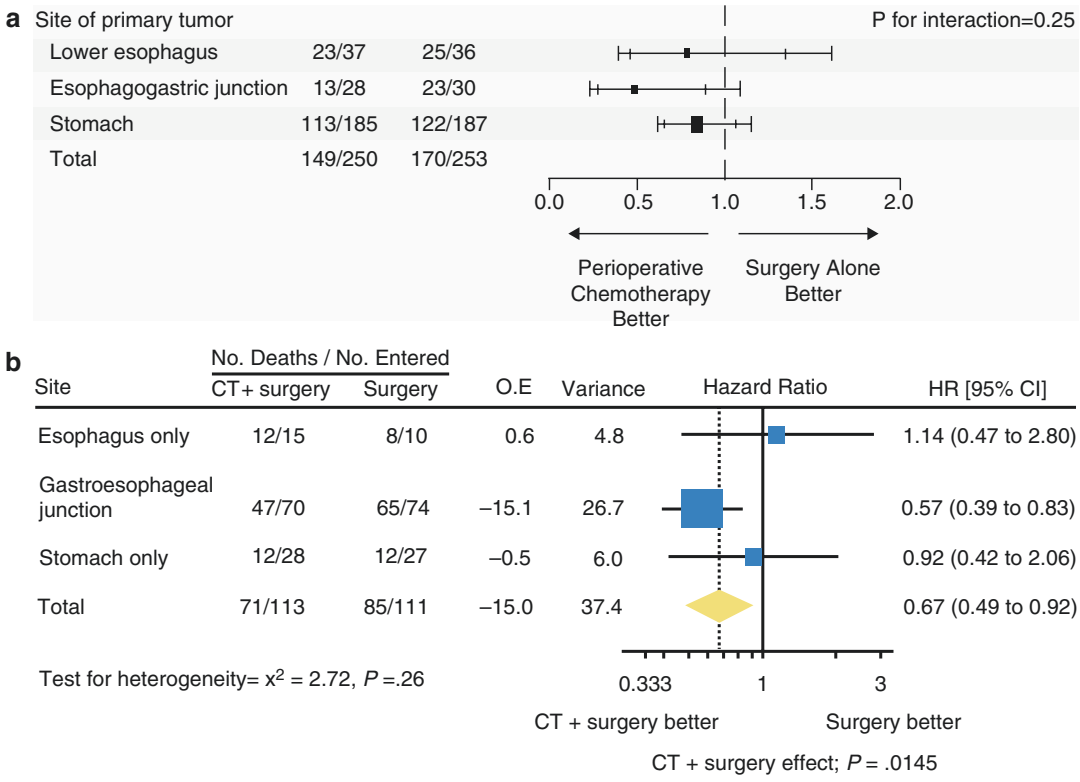

Fig. 15.3 Hazard ratio of death according to tumour site (*CT* chemotherapy, *O-E* observed to expected) (**a**) MAGIC. (**b**) FFCD trials

ECF (3 cycles before and after surgery) or surgery alone. The primary endpoint for this phase III RCT was OS, with secondary endpoints of progression-free survival (PFS) and evidence of downstaging (tumour size and TNM stage). This regimen was found to be associated with a significant improvement in 5-year OS (36 vs 23 %). In a subgroup analysis the greatest effect on survival was seen in the EGJ cancers although the numbers were small (Fig. 15.3).

In 2011, the French FFCD group published the similar ACCORD trial [14]. In this trial, 224 patients from 28 French centres were randomized to receive perioperative CF (2 or 3 before and 3 or 4 cycles after surgery) or surgery alone. The study population included a higher proportion of EGJ to gastric cancers (75/25 % split). This regimen found a similar improvement in 5-year OS (38 vs 24 %). A similar finding to MAGIC was noted in this trial with the largest effect in the EGJ subgroup (Fig. 15.3).

While they have together highlighted the benefit of chemotherapy for EGJ cancer, these trials have both been criticized over various aspects of the trial methodology. Cited concerns include issues with patient selection, changes in protocol, homogeneity of subjects and surgical quality. For example, in both trials, the protocol was amended during the trial to expand the inclusion criteria. While in the case of the MAGIC trial, the authors explained that the inclusion of EGJ cancers was to reflect changes in the patterns of disease; no explanation was provided by the FFCD group. The result of this inclusion was that patient cohorts in each trial were heterogeneous particularly since the prognosis of oesophageal, EGJ and gastric cancers is not identical [15, 16]. The study populations in each study were approximately 60 years of age, which does not reflect the average age of patients with distal oesophageal and gastric cancers [17]. There were also concerns with regard to quality control

(QC) of the surgical aspects of treatment, with only 42.5% of the chemotherapy arm of the MAGIC trial receiving a standard D2 lymphadenectomy (compared with 40.4% of the surgery arm), partly reflecting the trial including patients treated by 129 surgeons on 4 continents. Finally, in the MAGIC and ACCORD trials, only 41.6 and 50% of patients completed the protocol planned postoperative chemotherapy.

It is appropriate to include in this discussion the smaller EORTC 40954 trial [18] which compared neoadjuvant treatment with two cycles of cisplatin, 5-FU infusion and leucovorin, to surgery alone in gastric cancer. This study did not identify a significant increase in 5-year OS with neoadjuvant chemotherapy, but the survival in both groups was above average at 48% (median survival 36 months). This may have reflected a more consistent approach to surgery with reported D2 lymphadenectomy rates of >90%. There was however a significant increase in resectability (81.9 vs 66.7%) in the chemotherapy group. This suggests that the more radical surgery may have not only contributed to the improved survival but also blunted the trial's power to detect a smaller difference in survival related of the trial with chemotherapy in this context [19]. Unfortunately this study halted early due to poor recruitment.

Recently a meta-analysis of 5-FU-based neoadjuvant regimens in locally advanced gastric and EGJ cancers has confirmed improved overall survival (HR 1.40, 95% CI, 1.11–1.76) as well as downstaging and an increase in R0 resection with chemotherapy [20].

Although perioperative chemotherapy trials have reported improved OS, the benefits of this strategy include treatment of micrometastases as well as local downstaging facilitating surgically complete resection – the EORTC trial [18] reported dramatic increases in R0 resection rate from 67 to 87% [21, 22].

In a recent retrospective cohort study of 584 patients treated at two UK centres [23], 400 patients who received either neoadjuvant CF or ECF were stratified according to their response to chemotherapy by comparing their pretreatment radiological stage with their pathological postoperative stage. As part of a validation of the staging process, 185 patients who were treated with primary surgery also had their pre- and postoperative stage compared, showing a staging accuracy of 78% – only 6% were over-staged, making this an unlikely confounding factor. When comparing the responders with nonresponders, the R0 rate was higher (74 vs 40%) and incidence of isolated locoregional recurrence was lower (6 vs 13%). However, there was also a significant reduction in systemic relapse rates, either alone (19 vs 29%) or in combination with locoregional recurrence (30 vs 48%). This tumour downstaging effect on survival was still significant in a multivariable adjusted Cox regression analysis (HR 0.49, CI 0.35–0.68). In fact, patients with cT3/4 N+ tumours with response to chemotherapy had survival rates equivalent to stage matched early cancers (Fig. 15.4). This study highlights the importance of selecting patients for treatment in a more tailored way, though there are currently no predictive biomarkers for response to chemotherapy. Furthermore, conventional investigations are poor at determining response accurately, though diffusion-weighted MRI (DW-MRI) and PET-CT are gaining favour in this field [24].

Interestingly, in both this observational cohort and in the MAGIC and ACCORD trials, systemic relapse even in treated patients still occurred at rates approaching 30%. Even patients achieving pathological complete response (pCR) following chemoradiotherapy (CRT) demonstrate a significant rate of systemic relapse. In the CROSS trial, 29% of patients receiving CRT had systemic relapse [25]. This becomes important when one considers the effect of chemotherapy on systemic control, beyond the local downstaging effect [22]. Proponents of CRT cite higher rates of pCR and R0 resection [26, 27]. However, when used as radiosensitizing agents, to reduce toxicities, chemotherapy dose is reduced, and it is not clear if equivalent systemic control can be achieved with these regimens. Therefore, there is still an urgent need for robust biomarkers for prediction of response to neoadjuvant chemotherapy and a consideration

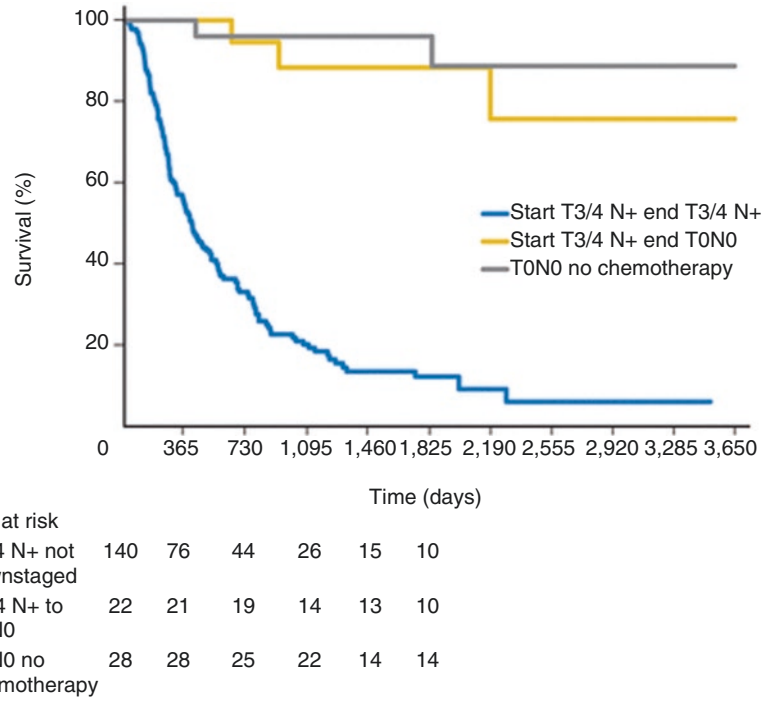

Fig. 15.4 Comparison of surgically treated patients with oesophageal adenocarcinoma, downstaged from cT3/4 N+ to ypT0NO. Control groups are represented by cT3/4 N+ to ypT3/4 N+ (not downstaged and T0N0 no chemotherapy)

of the role of radiotherapy in the setting of patients at high risk of systemic relapse.

15.4 Inoperable and Metastatic EGJ Cancer

Although there is limited evidence for chemotherapy in inoperable locally advanced or metastatic EGJ cancer alone, many studies have included EGJ cancer with gastric cancer. There is a clear benefit for chemotherapy over best supportive care, and the selection of patients is largely dependent on their performance status. A Cochrane review of 35 trials and 5726 patients favoured chemotherapy over best supportive care with a hazard ratio (HR) of 0.37 and 95 % confidence intervals (CI) 0.24–0.55 (184 participants). This pooled analysis also found in favour of combination therapies over single regimes (HR 0.82, 95 % CI, 0.74–0.90, 1914 participants) [28].

Current regimens include fluoropyrimidines, platinums, taxanes, topoisomerase inhibitors and anthracyclines in combinations designed for best efficacy and minimal toxicity. The standard of ECF has been developed with an alternative platinum, oxaliplatin and an oral fluoropyrimidine capecitabine. The REAL-2 trial [10] confirmed non-inferiority when capecitabine substituted for 5-FU. Substituting cisplatin with oxaliplatin resulted in a longer median survival. In addition capecitabine has been shown in a meta-analysis to be superior to infusional 5-FU when included in doublet and triplet combinations [29].

Taxanes have been included in regimens because of concern about the cardiotoxicity of anthracyclines. The combination of docetaxel, cisplatin and 5-FU has shown increased activity but have increased rates of neutropaenia. The current German studies combining docetaxel with 5-FU, leucovorin and oxaliplatin (FLOT) are promising with downstaging disease to enable resection [30]. There is also potential for second-line therapies in those with good performance status. Docetaxel has also been shown to be of some benefit as a second-line treatment to platinum refractory cancer in a phase III COUGAR-02 randomized controlled trial [31].

15.5 Targeted Agents

Targeted agents have been developed in attempts to personalize treatment strategies. The identification of molecular targets specific for EGJ cancer has evaluated a variety of extra- and intracellular pathways and mechanisms. These have identified targets for a spectrum of monoclonal antibodies, which have undergone clinical evaluation. In many cases this has not been only in EGJ cancer but has included proximal gastric cancer.

15.5.1 HER2-Targeting Agents

While HER2 amplification appears to be an early event in gastric and EGJ cancers, intra-tumour heterogeneity and differences in staining patterns on immunohistochemistry have created problems in defining a standardized scoring method for HER2, which has impacted on the consistency of published data [32].

Initial preclinical studies and early clinical evaluations demonstrated a benefit in advanced disease with the addition of trastuzumab to cisplatin monotherapy [33]. The phase III open-label ToGA trial [34] randomized 585 patients with HER2+ve inoperable, recurrent or metastatic gastric or EGJ tumours to receive CF (or capecitabine instead of 5-FU) with or without trastuzumab. In an intention to treat analysis, the trastuzumab arm had a significantly higher median survival (13.8 vs 11.1 months, HR 0.74, CI 0.6–0.91). Those with the strongest HER2 expression pattern had the most impressive effect, with median survival of 17.9 months. Although it might be considered that the CF doublet was not the most effective basis for trastuzumab, this was a pragmatic decision, given the predicted increased cardiotoxicity of combining trastuzumab with an epirubicin-containing regimen [35]. A number of trials are currently investigating the combination of trastuzumab with other chemotherapy doublets, e.g. taxanes and oxaliplatin [32].

There are other novel HER2-targeting agents available, though these are not yet in widespread use in gastric and EGJ cancer. Pertuzumab is a monoclonal antibody targeting domain II of HER2 which inhibits dimerization with HER3 (the most mitogenic dimerization partner for HER2). A phase II study investigating the addition of pertuzumab to capecitabine/cisplatin/trastuzumab is underway in advanced gastric cancer.

Lapatinib, an orally active small molecule inhibitor of the HER2 tyrosine kinase, has shown limited efficacy as monotherapy [36, 37]. There are however a number of ongoing studies assessing the effectiveness of lapatinib with combination chemotherapy, both in the inoperable disease setting (e.g. LOGIC trial, testing CAPOX ± lapatinib) and the inoperable disease setting (as in the amended ST03 trial) [32]. Although HER2 is amplified in only 15–25 % of patients with gastric or EGJ cancers, it is hoped that the efforts to develop targeted agents for this molecular aberration will form a template for future drug development as other novel molecular features are detected in EGJ cancers.

15.5.2 Anti-angiogenesis Agents

Recognition that vascular endothelial growth factor (VEGF) receptors are pro-angiogenic and expressed in malignant cells in gastrointestinal cancers is well established with associated poor prognosis in EGJ cancers [38].

Bevacizumab is a monoclonal antibody targeting VEGF-A, preventing binding to VEGF receptors 1 and 2, whose activity has been established in several clinical settings. A series of phase II studies in advanced gastric and EGJ cancers has demonstrated an acceptable safety profile with modest responses (RRs ~65 % with median OS 10.8–16.8 months [39–42]). Two phase III trials (AVAGAST [43] and AVATAR [44] trials) did not show a statistically significant survival advantage when bevacizumab was given in combination with capecitabine and cisplatin although there was at trend for prolonged progression-free survival. The addition of bevacizumab to ECX in the perioperative setting has been evaluated in the UK ST03 trial. The results which have recently been presented show that the addition of bevacizumab did not improve survival [45].

Ramucirumab is a monoclonal antibody targeting the VEGF receptor 2 extracellular domain. Following promising data from two phase II trials, the global phase III REGARD trial [46] randomized 355 chemoresistant gastric cancer patients to ramucirumab or placebo. This led to a significant improvement in OS (5.2 vs 3.8 months, HR 0.776). These data were recently corroborated by the RAINBOW trial [47] investigating the addition of ramucirumab to paclitaxel. While these trials were promising in the refractory setting, trials investigating ramucirumab in the first-line setting have been less convincing [38]. Based on the positive results of the REGARD trial, ramucirumab has achieved FDA approval as a second-line treatment for inoperable gastric and EGJ cancers.

Conclusions

Chemotherapy is now considered one of the standard approaches to EGJ cancer and the preferred one in UK and other countries. The most important benefit of chemotherapy is systemic control. We will also see an expansion in the repertoire of available targeted agents either alone or in combination with cytotoxic agents. There is an urgent need for validated predictive biomarkers for response to chemotherapy as well as the available targeted agents, including strategies to deal with resistance to therapy.

References

1. Ku GY, Ilson DH (2013) Chemotherapeutic options for gastroesophageal junction tumors. Semin Radiat Oncol 23(1):24–30
2. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R et al (2011) Guidelines for the management of oesophageal and gastric cancer. Gut 60(11):1449–1472
3. Working Party MRC (2002) Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 359 (9319):1727–1733
4. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE (2009) Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 27(30):5062–5067
5. Kelsen DP, Ginsberg R, Pajak TF et al (1998) Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 339:1979–1984
6. Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J et al (2007) Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol 8(3):226–234
7. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A et al (2011) Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 12(7):681–692
8. Cunningham D, Alderson D, Nankivell MG, Stenning SP, Blazeby JM, Griffin M et al (2014) Toxicity, surgical complications, and short-term mortality in a randomized trial of neoadjuvant cisplatin/5FU versus epirubicin/cisplatin and capecitabine prior to resection of lower esophageal/gastroesophageal junction (GOJ) adenocarcinoma (MRC OEO5, ISRCTN01852072, CRUK 02/010). J Clin Oncol 32:5s
9. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M et al (2006) Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 355(1):11–20
10. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F et al (2008) Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 358(1):36–46
11. Alderson D, Langley RE, Nankivell MG et al (2015) Neoadjuvant chemotherapy for resectable oesophageal and junctional adenocarcinoma: Results from the UK Medical Research Council randomised OEO5 trial (ISRCTN 01852072). J Clin Oncol 33(15):Suppl. 4002
12. Waters JS, Norman A, Cunningham D et al (1999) Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. Br J Cancer 80:269–272
13. Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK et al (1997) Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 15(1):261–267
14. Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G et al (2011) Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 29(13): 1715–1721
15. Wittekind C (2010) 2010 TNM system: on the 7th edition of TNM classification of malignant tumors. Pathologe 31(5):331–332
16. Rice TW, Rusch VW, Ishwaran H, Blackstone EH, Worldwide Esophageal Cancer C (2010) Cancer of

the esophagus and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals. Cancer 116(16):3763–3773
17. Bauer K, Porzsolt F, Henne-Bruns D (2014) Can perioperative chemotherapy for advanced gastric cancer be recommended on the basis of current research? A critical analysis. J Gastric Cancer 14(1):39–46
18. Schuhmacher C, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF et al (2010) Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 28(35):5210–5218
19. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ (2010) Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 11(5): 439–449
20. Ge L, Wang H-J, Yin D, Lei C et al (2012) Effectiveness of 5-fluorouracil-based neoadjuvant chemotherapy in locally advanced gastric/gastroesophageal cancer: a meta-analysis. Worl J Gastroenterol 18:7384–7393
21. Sujendran V, Wheeler J, Baron R, Warren BF, Maynard N (2008) Effect of neoadjuvant chemotherapy on circumferential margin positivity and its impact on prognosis in patients with resectable oesophageal cancer. Br J Surg 95(2):191–194
22. Matsuyama J, Doki Y, Yasuda T, Miyata H, Fujiwara Y, Takiguchi S et al (2007) The effect of neoadjuvant chemotherapy on lymph node micrometastases in squamous cell carcinomas of the thoracic esophagus. Surgery 141(5):570–580
23. Davies AR, Gossage JA, Zylstra J, Mattsson F, Lagergren J, Maisey N et al (2014) Tumor stage after neoadjuvant chemotherapy determines survival after surgery for adenocarcinoma of the esophagus and esophagogastric junction. J Clin Oncol 32(27):2983–2990
24. Wang L, Han C, Zhu S, Shi G, Wang Q, Tian H et al (2014) Investigation of using diffusion-weighted magnetic resonance imaging to evaluate the therapeutic effect of esophageal carcinoma treatment. Oncol Res Treat 37(3):112–116
25. Oppedijk V, van der Gaast A, van Lanschot JJ, van Hagen P, van Os R, van Rij CM et al (2014) Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol 32(5):385–391
26. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP et al (2012) Preoperative chemoradiotherapy for esophageal or junctional cancer. N Eng J Med 366(22):2074–2084
27. Stahl M, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J et al (2009) Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol 27(6):851–856
28. Wagner AD, Grothe W, Haertling J et al (2006) Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 24:2903–2909
29. Okines AF, Norman AE, McCloud P et al (2008) Meta-analysis of the REAL-2 and ML 17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann Oncol 19:1450–1457
30. Lorenzen S, Pauligk C, Homann H et al (2013) Feasibility of perioperative chemotherapy with infusional 5-FU, leucovorin and oxaliplatin with (FLOT) or without (FLO) docetaxel in elderly patients with locally advanced oesophagogastric cancer. Br J Cancer 108(3):519–526
31. Ford H, Marshall A, Bridgewater J et al (2014) Docetaxel versus active symptom control for refractory oesophago-gastric adenocarcinoma (COUGAR-02): an open-label, phase III randomised controlled trial. Lancet Oncol 15:78–86
32. Okines AF, Cunningham D (2012) Trastuzumab: a novel standard option for patients with HER-2-positive advanced gastric or gastro-oesophageal junction cancer. Therap Adv Gastroenterol 5(5):301–318
33. Gravalos C, Gomez-Martin C, Rivera F, Ales I, Queralt B, Marquez A et al (2011) Phase II study of trastuzumab and cisplatin as first-line therapy in patients with HER2-positive advanced gastric or gastroesophageal junction cancer. Clin Transl Oncol Off Pub Fed Spanish Oncol Soc National Cancer Inst Mexico 13(3):179–184
34. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A et al (2010) Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 376(9742):687–697
35. Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M et al (2002) Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 20(5):1215–1221
36. Hecht JR, Urba SG, Koehler M, Ellis C, Gagnon R, Kemner A (2008) Lapatinib monotherapy in recurrent upper gastrointestinal malignancy: phase II efficacy and biomarker analyses. Proceedings of the Gastrointestinal Cancers Symposium, Chicago
37. Iqbal S, Goldman B, Fenoglio-Preiser CM, Lenz HJ, Zhang W, Danenberg KD et al (2011) Southwest Oncology Group study S0413: a phase II trial of lapatinib (GW572016) as first-line therapy in patients with advanced or metastatic gastric cancer. Ann Oncol Off J Eur Soc Med Oncology ESMO 22(12): 2610–2615
38. Fontana E, Sclafani F, Cunningham D (2014) Anti-angiogenic therapies for advanced esophago-gastric

cancer. In J Med Paediatric Oncol Off J In Soc Med Paediatric Oncol 35(4):253–262
39. Shah MA, Ramanathan RK, Ilson DH, Levnor A, D'Adamo D, O'Reilly E et al (2006) Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol 24(33):5201–5206
40. Shah MA, Jhawer M, Ilson DH, Lefkowitz RA, Robinson E, Capanu M et al (2011) Phase II study of modified docetaxel, cisplatin, and fluorouracil with bevacizumab in patients with metastatic gastroesophageal adenocarcinoma. J Clin Oncol 29(7):868–874
41. El-Rayes BF, Zalupski M, Bekai-Saab T, Heilbrun LK, Hammad N, Patel B et al (2010) A phase II study of bevacizumab, oxaliplatin, and docetaxel in locally advanced and metastatic gastric and gastroesophageal junction cancers. Ann Oncol 21(10):1999–2004
42. Uronis HE, Bendell JC, Altomare I, Blobe GC, Hsu SD, Morse MA et al (2013) A phase II study of capecitabine, oxaliplatin, and bevacizumab in the treatment of metastatic esophagogastric adenocarcinomas. Oncologist 18(3):271–272
43. Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR et al (2011) Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 29(30):3968–3976
44. Shen L, Li J, Xu J, Pan H, Dai G, Qin S et al (2015) Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: randomized, double-blind, phase III study (AVATAR study). Gastric Cancer 18(1):168–176
45. Cunningham D, Smyth E, Stenning S, Stevenson L, Robb C, Allum W et al (2015) Peri-operative chemotherapy +/- bevacizumab for resectable gastro-oesophageal adenocarcinoma: Results from the UK Medical Research Council randomised STO3 trial (ISRCTN 46020948) Eur J Cancer 51(Suppl 3):S400 abstract 2201
46. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C et al (2014) Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 383(9911):31–39
47. Wilke H, Van Cutsem E, Cheul Oh S, Bodoky G, Shimada Y, Hironaka S (2014) RAINBOW: a global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy. J Clin Oncol 32(Suppl 3, abstr LBA7)

16 Chemoradiation in Esophagogastric Junction Cancer

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16.1 Introduction

For decades, primary surgery and radiotherapy (RT) alone were two treatment options for potentially curable esophageal cancer. Outcomes were poor, with most patients developing recurrent disease with associated morbidity and mortality. Both treatment options evolved over time as a result of better staging [1–3] and improved surgical [4–6] and radiation techniques [7, 8]. Furthermore, the addition of chemotherapy (CT) to RT and the combination of surgical and non-surgical approaches were important developments in the treatment of esophageal cancer. However, due to a lack of high-quality evidence, treatment of choice for esophageal cancer still remains controversial. Institutional preferences and clinical opinions still dominate the applied treatments. In this chapter, we give an overview of the role of chemoradiotherapy (CRT) in the treatment of adenocarcinomas (AC) of the distal esophagus and esophagogastric junction (EGJ).

16.1.1 Classification of Junctional Tumors

In 1997, the Siewert classification was introduced for the classification of ACs of the esophagus and EGJ (see Chap. 7). Using the Siewert classification, three different tumor entities (esophageal, cardiac, and subcardiac) are distinguished, based on specific anatomical landmarks [9]. Because advanced tumors often obscure these landmarks and frequent discrepancy is encountered between endoscopic, radiologic, peroperative, and pathologic localization, its usefulness and applicability were shown to be limited [10]. Some studies on neoadjuvant therapies selected patients based on histology type (AC or squamous cell carcinoma (SCC)) irrespective of location; others classified patients according to the location of the tumor (e.g., lower/upper esophagus, EGJ) irrespective of histology. Most studies included all patients with esophageal or junctional tumors, regardless of the histology type. As a consequence, the majority of studies on esophageal cancer are only to a limited extent applicable for patients with ACs of the EGJ. In this chapter, we focus on studies in patients with ACs originating in a Barrett segment or with cardiac carcinomas substantially invading the distal esophagus.

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16.1.2 Rationale for Combination of Chemotherapy and Radiotherapy

Studies have tested the safety and efficacy of combining CT and RT. Theoretically, both modalities may be active against different tumor cell populations (additive effect). CT may be effective against distant micrometastases while radiation acts locoregionally (spatial cooperation). Furthermore, CT increases the effect of radiation by inhibiting the repair of sublethal radiation damage, may synchronize cells to a specific cell-cycle phase that has increased sensitivity to RT, may decrease repopulation after RT, and, by shrinking the tumor, may enhance reoxygenation, which is advantageous for RT (synergistic effect) [11–13].

16.2 Definitive Chemoradiotherapy

16.2.1 Definitive Chemoradiotherapy Versus Definitive Radiotherapy Alone

Earliest references to the treatment of esophageal cancer with RT alone date back to the beginning of the twentieth century. Outcomes were generally very disappointing with 5-year overall survival rates ranging from 0 to 5 % [14]. With the advent of more potent chemotherapeutic agents, combined CRT became a more effective treatment option. Due to the observed synergistic effect of the combination of CT and RT, definitive CRT in patients with potentially curable esophageal cancer was further explored.

Addition of CT to RT in patients with esophageal cancer was studied in a stratified phase III trial performed by the Radiation Therapy Oncology Group (RTOG 85-01 trial) [15]. Patients ($n = 121$) with potentially curable ACs or SCCs of the esophagus were randomized between RT alone (64 Gy in 32 fractions) and CRT (two courses of 5-fluoruracil (5-FU) and cisplatin combined with 50 Gy RT, followed by two courses 5-FU and cisplatin). Interim analysis showed a significant difference in median survival between the RT (8.9 months) and combined therapy group (12.5 months, $p < 0.001$). This led to an early closure of the trial. Of all analyzed patients, only 15 (12 %) had ACs and 37 (31 %) had a primary tumor located in the lower esophagus. The remaining patients had SCC, mainly located in the mid-esophagus. No subgroup analysis based on histology or location was presented [15]. Therefore, it remains unclear to what extent these results are applicable to ACs of the EGJ. Interestingly, long-term results did not show any survival difference related to histology in patients treated with CRT, but separate results based on tumor location were still not presented. In line with the medium-term results, 5-year overall survival was improved in the combined modality group, as compared to patients treated with RT alone: 26 % (95 % confidence interval (CI) 15–37 %) versus 0 %, respectively [16].

16.2.2 Dose of Radiotherapy in Definitive Chemoradiotherapy

Although the combination of CT and RT improved results compared to RT alone, the incidence of locoregional residual or recurrent disease remained high (e.g., 47 % in the RTOG 85-01 trial) [16]. In an attempt to improve locoregional control and overall survival, the subsequent RTOG 94-05 (intergroup 0123) phase III trial intensified RT dose [17]. This trial compared the same CRT regimen as was used in the RTOG 85-01 trial (50 Gy) with a higher dose of RT (64.8) combined with the standard CT dose. After interim analysis, the RTOG 94-05 trial was closed prematurely because of a high number of treatment-related deaths in the high-dose radiotherapy group, albeit that some of these deaths occurred before the end of study treatment. There was no significant difference in locoregional control or long-term survival between the two arms. This study included 31 (14 %) patients with ACs. Patients whose tumors

extended to within 2.0 cm of the EGJ were excluded because of the concern that the stomach could not tolerate 64.8 Gy. No subgroup analyses were performed [17]. Hence, these results cannot be translated directly to EGJ tumors but suggest that higher radiation dose is not favorable. However, recent improvements in RT techniques using conformal multiple field techniques or intensity-modulated radiotherapy will reduce doses to the normal tissues (especially the heart, anterior mediastinum, and lung) and might lead to improved tolerability of increased radiation dose in an attempt to improve locoregional control.

16.2.3 Sequential Versus Concurrent Chemoradiotherapy

The effects of sequential versus concurrent CRT were studied in a Cochrane meta-analysis by Wong et al. Eight studies including 857 patients on sequential CRT were analyzed. No clinical benefit in terms of mortality (hazard ratio (HR) 0.87, 95 % CI 0.74–1.02) and local control was found, as compared to the RT alone group. Moreover, patients in the sequential CRT group experienced significant toxicities. Concurrent CRT was shown to improve overall survival significantly, compared to RT alone (HR 0.73, 95 % CI 0.64–0.84). This analysis on concurrent CRT was based on eleven studies including 998 patients (Table 16.1). In these meta-analyses, patients with AC and SCC were pooled and no subgroup analysis on tumor location was presented [18].

Due to the superior effects of concurrent CRT over a sequential regimen, subsequent studies mainly focused on concurrent CRT. Taken together, these studies suggest that concurrent CRT should be recommended over RT alone or sequential CRT as a nonsurgical therapy for potentially curable ACs of the distal esophagus and EGJ. A high dose of RT (64 vs. 50 Gy) combined with CT increases toxicity rates with no difference in survival, but more sophisticated radiation techniques might change this viewpoint in the future.

16.2.4 Salvage Surgery

Although organ preservation is a notable advantage of the nonoperative strategy of CRT, this approach is associated with a high rate (up to 40 %) of recurrent or persistent locoregional disease [16]. Selective surgical resection is a treatment option in patients after failed definitive CRT with curative intent. This so-called salvage surgery is more demanding than primary esophagectomy. Due to improvements in patient selection, perioperative management, surgical technique, and centralization of care, perioperative morbidity and mortality are nowadays substantially lower [19]. Furthermore, the increased use of neoadjuvant CRT in addition to surgery for esophageal cancer familiarized surgeons with the resection of an irradiated esophagus.

Results of surgical salvage after failed definitive CRT were presented in a non-randomized phase II trial [20]. Forty-three patients, of whom 41 were eligible for analysis, were treated with definitive CRT. This consisted of induction CT (5-FU, cisplatin, and paclitaxel) followed by concurrent CRT (50.4 Gy with 5-FU and cisplatin). Esophagogastroscopy with biopsies, endoscopic ultrasound (EUS), CT scans of the chest and abdomen, and positron emission tomography (PET, optional but encouraged) were performed after completion of CRT and serially thereafter. Seventeen patients with residual or recurrent disease, but without distant metastases, underwent salvage esophagectomy. During follow-up, esophageal resection was performed in three additional patients because of clinical suspicion of recurrent disease. Tumor cells were found in all these resected specimens. One-year overall survival rate was 71 % (95 % CI 54–82 %). However, since the intended predefined 1-year survival rate of 77.5 % was not achieved, a subsequent phase III trial was not initiated. It should be noted that the preset 1-year survival rate of 77.5 % is deducted from the RTOG database, which consists mainly of SCC patients, whereas the proportion of patients with ACs in this trial was 73 %. Moreover, a total of three CRT-related deaths were reported. As suggested by the authors, elimination of induction CT from the

Table 16.1 Randomized controlled trials: definitive concurrent CRT versus definitive RT

First author	Year	Period	*N*	Tumor	CRT/RT	Survival, HR (95 % CI) (RT vs CRT)
Andersen et al. [55]	1984	1977–1981	82	SCC	CRT: Ble + 55 Gy RT: 63 Gy	0.94 (0.59–1.50)
Araujo et al. [56]	1991	1982–1985	59	SCC	CRT: 5-FU, Ble, Mit + 50 Gy RT: 50 Gy	0.64 (0.36–1.14)
Cooper et al. [16]	1999	1985–1990	123	SCC/AC	CRT: 5-FU + 50 Gy RT: 64 Gy	0.59 (0.45–0.77)
Earle et al. [57]	1980	N/A	77	SCC	CRT: Ble + 50–60 Gy RT: 50–60 Gy	1.43 (0.81–2.54)
Gao et al. [58]	2002	N/A	81	SCC	CRT: Cis + 60 Gy RT: 60 Gy	0.79 (0.46–1.37)
Kaneta et al. [59]	1997	1994–1996	24	SCC	CRT: Cis + 70–72 Gy RT: 70–72 Gy	0.75 (0.23–2.40)
Li et al. [60]	2000	N/A	96	SCC/AC	CRT: Cis, 5-FU + 50–60 Gy RT: 60–70 Gy	0.65 (0.43–1.00)
Roussel et al. [61]	1994	N/A	221	SCC	CRT: Cis + 40 Gy RT: 40 Gy	0.82 (0.62–1.09)
Slabber et al. [62]	1998	1991–1995	70	SCC	CRT: Cis, 5-FU + 40 Gy RT: 40 Gy	0.83 (0.50–1.40)
Zhang et al. [63]	1984	N/A	99	N/A	CRT: Ble + 39-73 Gy RT: 39–73 Gy	0.63 (0.39–1.01)
Zhu et al. [64]	2000	N/A	66	SCC	CRT: Car + 60 Gy RT: 60 Gy	0.62 (0.36–1.06)

Reprinted with permission and adapted from Wong et al. [18]
5-FU 5-fluorouracil, *AC* adenocarcinoma, *Ble* bleomycin, *Car* carboplatin, *CI* confidence interval, *Cis* cisplatin, *CRT* chemoradiotherapy, *Gy* gray (J/kg), *HR* hazard ratio, *Mit* mitomycin, *N/A* not available, *N* number of patients, *RT* radiotherapy, *SCC* squamous cell carcinoma

regimen might lead to less treatment-related toxicity and perhaps achievement of the target 1-year survival rate [20].

Also in this study, patients with AC were not analyzed separately. Given the high proportion of patients with ACs in the study population and the possibly more positive effect of surgical salvage that might be feasible than was achieved by the authors of the study, salvage surgery in addition to definitive CRT in patients with ACs of the distal esophagus and EGJ is an interesting topic, which remains to be investigated more extensively.

16.2.5 Definitive Chemoradiotherapy Versus Surgery Alone

Historically, primary surgical resection was considered as the only curative treatment for esophageal cancer [21]. With more effective and less toxic chemotherapeutic agents and more sophisticated radiotherapeutic techniques, curative treatment of esophageal cancer with definitive CRT is now also potentially feasible. But is definitive CRT preferred over surgery alone? High-quality evidence on this subject is absent.

Two randomized trials comparing definitive CRT with curative intent to primary esophagectomy have been conducted. Results of the CURE (Chinese University Research Group for Esophageal Cancer) trial were reported by Chiu et al. in 2005 [22]. The CRT regimen consisted of 5-FU and cisplatin CT, combined with concurrent 50–60 Gy RT. In case of incomplete clinical response or recurrence without systemic disease, salvage surgery was performed. No significant difference in 2-year overall survival between the CRT group ($n=36$) and the surgery group ($n=45$) was found (relative risk 0.89, 95 % CI 0.37–2.17,

$p=0.45$) [22]. Given the higher incidence of SCC in the East, this study only included SCC patients; thus, results are not necessarily applicable to patients with EGJ cancer. In 2007, results of a the second trial comparing definitive CRT (64 Gy and three courses of cisplatin and 5-FU) to surgery alone were published as abstract by Carstens et al. Patients ($n=91$) with both AC (50 %) and SCC (50 %) were included. There was no significant difference in survival between the two treatment arms. Unfortunately, detailed information about study design and results is not available, because so far the trial has not been published as a full paper [23].

16.3 Neoadjuvant Chemo- and/or Radiotherapy Plus Surgery

16.3.1 Neoadjuvant Radiotherapy Plus Surgery

The earliest reports on neoadjuvant RT plus surgery date back to the early 1970s [24]. These reports all consist of uncontrolled case series, often from single institutions. In those days, the majority of esophageal cancers were SCC and treatment consisted of either surgery or RT, depending on patient and tumor characteristics and individual and institutional preferences. Due to disappointing long-term locoregional control after primary surgery, interest developed in the addition of preoperative RT to surgery as a possible means of downstaging the primary tumor. The rationale was that tumor downstaging might increase the radical resectability rate, thereby reducing locoregional recurrence rate and – possibly – improving long-term survival.

A Cochrane meta-analysis from 2005 by Arnott et al. reviewed the effects of the addition of preoperative RT to surgery as compared to surgery alone [25]. This review was based on five randomized controlled trials, published between 1981 and 1992, totaling 1147 patients (Table 16.2) [26–30]. The majority of patients were men (78 %), younger than 65 years (80 %) with SCCs (89 %). The planned total dose of RT ranged from 20 to 40 Gy given in 10–20 fractions over a period of 1–4 weeks, with the delay from end of RT to surgery ranging from 1 to 4 weeks. Median follow-up time was 9 years. In patients that received neoadjuvant RT, the risk of death was reduced by 11 %, HR of 0.89 (95 % CI 0.78–1.01), and absolute survival at 2 and 5 years improved (nonsignificantly) from 30 to 34 % and 15 to 18 %, respectively. Radical resectability rates were reported as not significantly different between the groups. A subgroup analysis did not show a difference in benefit from preoperative RT for patients with tumors located at the upper/middle esophagus compared to patients with a tumor of the lower esophagus. Due to the high number of patients with SCC, the authors considered analysis by histology as uninformative.

The authors of this meta-analysis concluded that, based on the existing randomized data, there is no clear evidence that preoperative RT alone improves the survival of patients with potentially resectable esophageal cancer.

16.3.2 Neoadjuvant Chemotherapy Plus Surgery

With the advent of more effective and less toxic chemotherapeutic regimens, similar interest

Table 16.2 Randomized controlled trials: neoadjuvant RT plus surgery versus surgery alone

First author	Year	Period	*N*	Tumor	RT	Survival (RT + S vs S alone)
Launois et al. [26]	1981	1973–1976	107	SCC	40 Gy/8–12d	1.01 (0.67–1.53)
Gignoux et al. [27]	1988	1976–1982	229	SCC	33 Gy/10 frc/28d	1.02 (0.78–1.33)
Wang et al. [28]	1989	1977–1988	418	SCC	40 Gy/10 frc/12d	0.81 (0.65–1.01)
Arnott et al. [29]	1992	1979–1983	176	SCC/AC	20 Gy/10 frc/14d	1.19 (0.87–1.62)
Nygaard et al. [30]	1992	1983–1988	108	SCC	35 Gy/20 frc/28d	0.60 (0.40–0.91)

Reprinted with permission and adapted from Arnott et al. [25]
AC adenocarcinoma, *d days, frc* fractions, *Gy* gray (J/kg), *N* number of patients, *RT* radiotherapy, *S* surgery, *SCC* squamous cell carcinoma

developed in the addition of neoadjuvant CT to surgery as a means of reducing locoregional tumor burden, thereby potentially increasing locoregional resectability. Moreover, systemic therapy might be able to eradicate distant micrometastatic disease. It is often concluded that compared to historical controls, the outcome improves after treatment with preoperative CT [31]. In summary, results of the individual trials and a recent update of an earlier published meta-analysis indicate that preoperative CT plus surgery offers a slight survival advantage (HR for all-cause mortality 0.87, 95 % CI 0.79–0.96, $p=0.005$) as compared to surgery alone for resectable thoracic esophageal cancer of any histological type [32]. For detailed information on neoadjuvant CT combined with surgery, we refer to Chap. 18.

16.3.3 Neoadjuvant Chemoradiotherapy Plus Surgery

In their meta-analysis, Sjoquist et al. [32] identified 13 randomized trials comparing neoadjuvant CRT plus surgery to surgery alone [30, 33–44], published between 1992 and 2012, totaling 1932 patients (Table 16.3). Two trials, by Mariette et al. and Van der Gaast et al., were only available as abstracts at the time of this meta-analysis but have now been completed and fully reported [45, 46]. The largest of these trials, the CROSS trial [45], will be discussed separately in more detail below.

Sample sizes of included trials ranged from 56 to 364 patients. Seven trials included only SCCs [30, 33–35, 37, 39, 42], five trials included both SCC and ACs [38, 40, 41, 45, 47], and one trial included ACs only [36]. Various CT and RT regimens were used. The pooled HR for all-cause mortality in these included trials, when comparing neoadjuvant CRT plus surgery with surgery alone, was 0.78 (95 % CI 0.70–0.88, $p<0.0001$). This corresponds to an absolute survival benefit of 8.7 % at 2 years. The survival benefit for neoadjuvant CRT was similar for AC and SCC. In AC, the HR was 0.75 (95 % CI 0.59–0.95, $p=0.02$) and in SCC the HR was 0.80 (95 % CI 0.68–0.93, $p=0.004$). Assessment of the effects of neoadjuvant CRT on survival by tumor site was not possible, because this information was not provided in most included trials.

The conclusion of this meta-analysis was that there is a significant survival benefit for preoperative CRT in patients with AC or SCC of the esophagus.

16.3.4 CROSS Trial

The recently completed CROSS trial was a multicenter, randomized phase III trial [45]. The study included and analyzed 366 patients during a 5-year period. It included patients from five academic and two nonacademic high-volume teaching hospitals in the Netherlands. Most patients (75 %) had an AC and most tumors were located at the EGJ (24 %) or in the distal esophagus (58 %). The study compared neoadjuvant CRT followed by surgery with surgery alone in patients with potentially curable esophageal cancer (cT2-3N0-1M0 and cT1N1M0), with a planned inclusion of 175 patients per arm. The neoadjuvant regimen consisted of carboplatin ($AUC=2$) and paclitaxel (50 mg/m^2) given by intravenous infusion on days 1, 8, 15, 22, and 29, combined with concurrent radiation therapy using a multiple field technique. A total dose of 41.4 Gy was given in 23 fractions of 1.8 Gy, 5 fractions per week, starting on the first day of the first cycle of CT. The aim of this trial was to compare overall survival between patients treated with neoadjuvant CRT followed by surgery and patients treated with surgery alone for potentially curable, esophageal AC or SCC.

Neoadjuvant treatment was well tolerated, with >90 % of all patients receiving full treatment. The most common toxic effects in the CRT followed by surgery group were leukopenia (6 %), anorexia (5 %), fatigue (3 %), and neutropenia (2 %). One patient died of major bleeding while awaiting surgery, probably due to an esophago-aortic fistula. Median overall survival of patients who received neoadjuvant CRT plus surgery was 49 months, compared to 24 months

Table 16.3 Randomized controlled trials: neoadjuvant CRT plus surgery versus surgery alone

First author	Year	Period	*N*	Tumor	CRT (days)		pCR	Survival, HR (95 % CI) (CRT + S vs S)
Walsh et al. [35]	1990	N/A	61	SCC	CT: Cis, 5-FU RT: 40 Gy/ 15 frc/21	Con		0.74 (0.46–1.18)
Nygaard et al. [30]	1992	1983–1988	106	SCC	CT: Cis, Ble RT: 35 Gy/20 frc/28	Seq		0.76 (0.45–1.28)
Apinop et al. [33]	1994	1986–1992	69	SCC	CT: Cis, 5-FU RT: 40 Gy/20 frc/28	Con		0.80 (0.48–1.34)
Le Prise et al. [34]	1994	1988–1991	86	SCC	CT: Cis, 5-FU RT: 20 Gy/10 frc/10	Seq	9.8 %	0.85 (0.50–1.46)
Walsh et al. [36]	1996	1990–1995	113	AC	CT: Cis, 5-FU RT: 40 Gy/ 15 frc/21	Con	25 %	0.58 (0.38–0.88)
Bosset et al. [37]	1997	1989–1995	293	SCC	CT: Cis RT: 37 Gy/10 frc/14	Seq	21 %	0.96 (0.73–1.27)
Urba et al. [38]	2001	1989–1994	100	SCC/AC	CT: Cis, 5-FU, Vinb RT: 45 Gy/30 frc/21	Con	28 %	0.74 (048–1.12)
Lee et al. [39]	2004	1999–2002	101	SCC/AC	CT: Cis, 5-FU RT: 45.6 Gy/38 frc/28	Con	43 %	0.88 (0.48–1.62)
Burmeister et al. [40]	2005	1994–2000	256	SCC/AC	CT: Cis, 5-FU RT: 35 Gy/15 frc/21	Con	16 %	0.94 (0.70–1.26)
Tepper et al. [41]	2008	1997–2000	56	SCC	CT: Cis, 5-FU RT: 50.4 Gy/28 frc/35	Con	40 %	0.40 (0.18–0.87)
Lv et al. [42]	2010	2000–2009	160	SCC	CT: Cis, Pac RT: 40 Gy/20 frc/28	Con		0.55 (0.36–0.84)
Van Hagen et al. [45]	2012	2004–2008	366	SCC/AC	CT: Cis, Pac RT: 41.4 Gy/23 frc/35	Con	29 %	0.66 (0.50–0.87)
Mariette et al. [46]	2014	2000–2009	195	SCC/AC	CT: Cis, 5-FU RT: 45 Gy/25 frc/35	Con	33.3 %	0.92 (0.63–1.34)

Reprinted with permission and adapted from Sjoquist et al. [32]
5-FU 5-fluorouracil, *AC* adenocarcinoma, *Ble* bleomycin, *CI* confidence interval, *Cis* cisplatin, *Con* concurrent, *CRT* chemoradiotherapy, *CT* chemotherapy, *frc* fractions, *Gy* gray (J/kg), *HR* hazard ratio, *N* number of patients, *Pac* paclitaxel, *S* surgery, *pCR* pathologically complete response, *RT* radiotherapy, *SCC* squamous cell carcinoma, *seq* sequential, *Vinb* vinblastine

for those who underwent surgery alone. With a median follow-up of 32 months, 70 patients had died in the neoadjuvant CRT group versus 97 in the surgery alone group. Three-year overall survival was superior in the neoadjuvant CRT arm (HR 0.66, 95 % CI 0.50–0.87, $p = 0.003$). Patients with an AC had a significant survival advantage ($p = 0.049$). No subgroup analysis based on location of the tumor was provided.

In conclusion, results from the CROSS trial show that the addition of neoadjuvant CRT (carboplatin, paclitaxel, and 41.4 Gy of concurrent RT) to surgery significantly increases survival as compared to surgery alone in patients with potentially curable AC and SCC of the esophagus or EGJ. Therefore, neoadjuvant CRT plus surgery is now considered the therapy of first choice in the Netherlands and several other countries for potentially curable esophageal cancer (cT2-3N0-1M0 and cT1N1M0) in patients fit to undergo this treatment.

The improvement of survival after neoadjuvant CRT as found in the CROSS trial was not demonstrated in the recent FFCD9901 study by Mariette et al. This group randomized 195 patients with stage I or II (cT1-2N0-1M0 and T3N0M0) esophageal cancer between neoadjuvant CRT (45 Gy with concurrent 5-FU and cisplatin) and surgery alone. Of all included patients only 29 % had an AC. Tumor location was separated in above (9 %) or below the carina. The difference in outcome as compared

to the CROSS trial might be explained by a more toxic CT regimen and a lower tumor stage in the French trial. A majority of patients in the French trial had middle-third SCC, whereas the CROSS trial consisted of mostly lower-third ACs. Since SCCs tend to be more radiosensitive than ACs, the absence of improvement of survival after neoadjuvant CRT in this study is surprising. Furthermore, a postoperative mortality rate of 11.1 % in the multimodality group was reported, versus 3.4 % in the surgery only group. The CROSS study reported an inhospital mortality of 4 % in both groups. In the French trial, 86 % of the neoadjuvant CRT patients underwent surgery compared to 92 % in the CROSS study, which could be the result of the more toxic chemotherapy regimen and is expected to have a negative influence on survival. Another important point is that the 195 included patients were recruited from 30 centers during a period of 9 years, corresponding with less than one inclusion per center per year. It is well known that high volume is associated with improved survival [48]. Despite this limitation, state-of-the-art results were achieved in the surgery alone group. Finally, increased radiation dose as compared to the CROSS trial (45 Gy vs. 41.4 Gy, respectively), or differences in radiation technique (conventional APPA-technique vs. more sophisticated conformal four-field radiation), might be responsible for the relatively high mortality rate.

16.3.5 Neoadjuvant Chemotherapy Versus Neoadjuvant Chemoradiotherapy

Although results on neoadjuvant RT or neoadjuvant CT did not show convincing improvement of survival, the additive effect of both modalities led to studies on neoadjuvant CRT. The addition of RT to neoadjuvant CT was compared to neoadjuvant CT alone by Stahl et al. and Burmeister et al. [49, 50]. The first group included 126 patients with locally advanced (T3-4NxM0) EGJ ACs (Siewert type 1–3), of whom 119 eligible patients were randomized in their POET (preoperative chemotherapy or radiochemotherapy in esophagogastric adenocarcinoma trial). The neoadjuvant CT regimen consisted of cisplatin, 5-FU, and leucovorin followed by esophagectomy. Patients in the CRT group received the same induction CT, followed by concurrent CRT (cisplatin and etoposide combined with 30Gy). The trial was closed prematurely due to poor accrual. Although not significantly, preoperative CRT improved 3-year survival with 20 % (47.4 % compared to 27.7 % in the neoadjuvant CT group, $p=0.07$). Furthermore, patients in the CRT arm had a significantly higher probability of showing tumor-free lymph nodes (64.4 % vs. 36.7 %, $p=0.01$) and pathologically complete response (15.6 % vs. 2.0 %, $p=0.03$) at resection. A few comments can be made. First, postoperative mortality in the CRT group was more than doubled (10.2 % vs. 3.8 %). Given the low total radiation dose applied, it seems likely that other factors than radiation therapy were responsible for this relatively high mortality rate. If these deaths could have been prevented, significantly improved 3-year survival might have been achieved. For comparison, in the CROSS trial, postoperative mortality in the neoadjuvant CRT group was 3.8 % [45]. Second, the low radiation dose might have contributed to a relatively low pathologically complete response (pCR) rate (15.6 % vs. 23 % in the CROSS trial) but still significantly higher than after CT (2 %, $p=0.03$). Increased radiation dose, as used in the CROSS study, might have led to increased pCR rates, which are known to be associated with increased survival. Third, the trial closed prematurely and was consequently underpowered. Significant results might have been achieved if more patients were included. Taken together, these considerations suggest a more positive conclusion than was made by the authors of the trial and seem to point to superiority of neoadjuvant CRT over neoadjuvant CT [49].

In 2011, Burmeister et al. published the results of a phase II trial that randomized patients with ACs of the esophagus and EGJ to preoperative CT or preoperative CRT. The regimen consisted of cisplatin and 5-FU with or without concurrent

radiation therapy (35Gy). Seventy-five patients were included, of whom 66 proceeded to resection. Median overall survival did not differ significantly between the neoadjuvant CT group and the neoadjuvant CRT group (29 months and 32 months, respectively, $p=0.83$). Nevertheless, R0 resection rate (100 % in the neoadjuvant CRT group, 86 % in the neoadjuvant CT group) and histopathological response rate (<10 % viable cells, 31 % in neoadjuvant CRT group, and 8 % in the neoadjuvant CT group, $p=0.01$) favored those receiving neoadjuvant CRT. Toxicity and surgical morbidity were not increased by the addition of RT to neoadjuvant CT. An explanation for the absence of improved survival in the neoadjuvant CRT group, despite improvement of two well-known prognostic indicators, might be the restricted size of the cohort. Furthermore, increased dose of RT might have led to further improvement of survival rates. This study only included patients with ACs but did not distinguish between patients based on location of the tumor [47].

A significant advantage of both neoadjuvant CRT and neoadjuvant CT was found in the meta-analysis by Sjoquist et al. To quantify the relative survival benefits of neoadjuvant CRT compared to neoadjuvant CT, treatment arms of different trials were compared. This indirect comparison showed a trend in favor of neoadjuvant CRT (HR for all-cause mortality for neoadjuvant CRT vs. neoadjuvant CT 0.88, 95 % CI 0.76–1.01, $p=0.07$) [32]. A recent meta-analysis of perioperative mortality and postoperative morbidity in 23 studies on neoadjuvant CT and neoadjuvant CRT in esophageal carcinoma did not find a difference in mortality or morbidity between both modalities. Furthermore, no increase in mortality or morbidity attributable to neoadjuvant therapy as compared to surgery alone was found. Subgroup analysis of neoadjuvant CRT in patients with SCC suggested an increased risk of treatment-related mortality compared with surgery alone (RR 1.95, 95 % CI 1.06–3.60, $p=0.032$) [51], which is in line with the increased postoperative mortality rate as reported in the FFCD9901 study [46].

16.4 Definitive Chemoradiotherapy Versus Neoadjuvant Chemoradiotherapy Plus Surgery

In recent years, two randomized trials were reported in literature comparing definitive CRT to neoadjuvant CRT plus surgery for esophageal cancer. Results of both studies were mainly based on patients with SCC.

The first study, by Stahl et al., included 172 patients from 11 centers [52]. In this trial, definitive CRT (without salvage surgery) was compared with neoadjuvant CRT plus surgery for "locally advanced" (T3-4N0-1M0) SCCs of the upper and mid-third of the esophagus. The design of the study is debatable in some points, but this is beyond the scope of this chapter. In summary, no difference in overall survival was found. However, locoregional failure was less common, and treatment-related death was more common in the neoadjuvant CRT plus surgery group.

In 2007, Bedenne et al. reported the second randomized trial (FFCD 9102) comparing definitive CRT with neoadjuvant CRT plus surgery [53]. Patients with resectable T3N0-1M0 AC or SCC of the esophagus (SCC >90 %) were included. All patients were treated with neoadjuvant CT (5-FU and cisplatin) combined with 30 Gy RT in two split courses or 46 Gy RT given continuously. Subsequently, clinical response was evaluated by abdominal ultrasonography, chest X-ray, esophagography, and when possible endoscopic ultrasonography. Of all included patients, 259 (58.3 %) showed an objective clinical response after neoadjuvant CRT. These patients were randomized between surgery and definitive CRT (15 Gy or 20 Gy in the split course regimen or the continuous regimen, respectively). Both concurrent and sequential CRT were used in the neoadjuvant CRT and definitive CRT treatment strategies. The authors considered both treatment modalities as equivalent if there would be a difference in 2-year survival rate of less than 10 % between the two treatment arms. Two-year survival rates for the definitive CRT arm and neoadjuvant CRT plus surgery arm were 39.8 % and

33.6 %, respectively, leading to the conclusion that both treatment modalities are equivalent ($p = 0.03$, representing the chance that the actual difference is > 10 %). Conclusions of this trial are limited by a few remarkable results. For example, survival rates are substantially lower as compared to survival rates as reported in other trials [45]. Furthermore, locoregional progression differed significantly between definitive CRT and neoadjuvant CRT plus surgery (64.3 % and 40.7 %, respectively, $p = 0.003$), but this was not translated in different survival rates. Most importantly, the study included mainly patients with SCCs, and therefore, applicability for patients with EGJ tumors is questionable [53].

In conclusion, the role for definitive CRT in patients with ACs of the EGJ remains unclear. However, these studies have addressed an important topic, which is relevant in patients with EGJ cancer. Specifically, whether definitive CRT can replace neoadjuvant CRT plus surgery in patients with a clinically complete response on CRT. Larger studies comparing definitive CRT versus neoadjuvant CRT plus surgery in this group of patients are needed.

16.5 Future Perspectives

16.5.1 Classification by Location and Histology

Currently, most tumors of the esophagus, regardless of location and histology, are staged and treated similarly. However, these different tumor types differ in etiology, biology, and radiosensitivity. Therefore, when adopting an evidence-based approach for optimal management, it is important to consider the proportions of tumors for anatomical subsite and histological type enrolled in a study. The absence of proper subgroup analyses often complicates applicability of results to specific groups of patients. Consequently, current and future trials should focus more on tumor location and histological subtype. Given the strong association between geographic location and histology – in the West the majority of the patients have AC, while in the East most esophageal cancers are SCC – a current three-arm phase III trial in Japan compares two neoadjuvant CT regimens with neoadjuvant CRT in patients with SCC specifically [54]. In parallel with this Japanese study, the Irish NeoAEGIS (NEOadjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric Junction International Study) study investigates the effect of neoadjuvant CRT versus neoadjuvant plus adjuvant CT in patients with AC only. These studies will hopefully lead to a more biology-directed treatment strategy.

16.5.2 Dose Escalation in Definitive Chemoradiotherapy

Definitive concurrent CRT is the treatment of choice for esophageal cancer when a nonsurgical approach is preferred. Driven by the high rates of recurrent or persistent locoregional disease, current studies in the field of definitive CRT focus on improvement of locoregional control. Although previous studies showed increased treatment-related toxicity and no benefit in terms of locoregional control, recent developments in radiation techniques led to the present Dutch ART DECO (A Randomized Trial of Dose Escalation in definitive Chemoradiotherapy for patients with Oesophageal cancer) study. This study aims to improve locoregional control after definitive CRT for patients with potentially curable esophageal cancer (T1-4N0-3M0AC or SCC) using a conformal multiple field radiation technique. Patients are randomized between standard definitive CRT (carboplatin and paclitaxel plus concurrent 50.4 Gy) and an escalated radiation dose. Patients in the escalated radiation dose arm receive a daily concomitant boost to the primary tumor leading to a total tumor dose of 61.6 Gy. Overall, treatment time and chemotherapy are similar in both arms. Primary endpoints in this study are local recurrence rate, survival, and treatment-related toxicity.

16.5.3 Surgery as Needed Approach

By the addition of CT and salvage surgery to definitive RT and the use of neoadjuvant CRT in

addition to primary surgery, nonoperative and operative treatment modalities have moved closer toward each other. However, the benefits of adding salvage surgery to definitive CRT have never been proven. The high pCR rate in the CROSS study led to the imperative to reconsider the necessity of standard esophagectomy in all patients after neoadjuvant CRT. Therefore, we propose a "surgery as needed" approach after completion of neoadjuvant CRT for patients with potentially curable esophageal cancer. In this approach, patients will undergo close surveillance after completion of neoadjuvant CRT according to CROSS. Surgical resection will be offered only to patients in whom a locoregional recurrence is highly suspected or proven, without signs of distant metastases. Such an organ-preserving strategy would have great advantages but only if long-term survival would be comparable to that of the neoadjuvant chemoradiotherapy followed by standard surgery approach. As a first step toward an organ-preserving strategy, we are currently performing the multicenter feasibility preSANO (surgery as needed approach in oesophageal cancer) study to determine the accuracy by which residual disease after neoadjuvant chemoradiotherapy can be detected. After the completion of neoadjuvant CRT, patients will undergo two clinical response evaluations (CRE). The first CRE (CRE-I) consists of endoscopy with (random) conventional mucosal biopsies of the primary tumor site and of any other suspected lesions in the esophagus and radial endoultrasonography (EUS) for measurement of tumor thickness and area. Patients who are found to be clinically complete responders (i.e., those patients in whom no locoregional or disseminated disease can be proven by histology) will be offered a postponed surgical resection, which will be scheduled approximately 6 weeks after CRE-I (i.e., approximately 12–14 weeks after completion of neoadjuvant CRT). In the 2 weeks preceding the postponed surgical resection, a second clinical response evaluation (CRE-II) will be planned, which will include a whole body PET-CT, plus the investigations as performed at CRE-I. If this preSANO study shows that residual tumor can be predicted reliably, a trial (SANO trial) comparing neoadjuvant chemoradiotherapy plus standard surgery with neoadjuvant chemoradiotherapy plus "surgery as needed" will be conducted.

References

1. Lightdale CJ (1992) Endoscopic ultrasonography in the diagnosis, staging and follow-up of esophageal and gastric cancer. Endoscopy 24(Suppl 1):297–303
2. Block MI et al (1997) Improvement in staging of esophageal cancer with the addition of positron emission tomography. Ann Thorac Surg 64(3):770–776; discussion 776–777
3. Hulscher JB et al (2000) Laparoscopy and laparoscopic ultrasonography in staging carcinoma of the gastric cardia. Eur J Surg 166(11):862–865
4. Skinner DB et al (1986) Selection of operation for esophageal cancer based on staging. Ann Surg 204(4):391–401
5. Van Lanschot JJ et al (1999) Randomized comparison of prevertebral and retrosternal gastric tube reconstruction after resection of oesophageal carcinoma. Br J Surg 86(1):102–108
6. Hulscher JBF et al (2002) Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 347(21):1662–1669
7. Gaspar LE et al (1997) A phase I/II study of external beam radiation, brachytherapy and concurrent chemotherapy in localized cancer of the esophagus (RTOG 92-07): preliminary toxicity report. Int J Radiat Oncol Biol Phys 37(3):593–599
8. Toita T et al (2001) Concurrent chemoradiotherapy for squamous cell carcinoma of thoracic esophagus: feasibility and outcome of large regional field and high-dose external beam boost irradiation. Jpn J Clin Oncol 31(8):375–381
9. Siewert JR, Stein HJ (1998) Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg 85(11):1457–1459
10. Grotenhuis BA et al (2013) Preoperative assessment of tumor location and station-specific lymph node status in patients with adenocarcinoma of the gastroesophageal junction. World J Surg 37(1):147–155
11. Tannock IF (1996) Treatment of cancer with radiation and drugs. J Clin Oncol 14(12):3156–3174
12. Hennequin C, Favaudon V (2002) Biological basis for chemo-radiotherapy interactions. Eur J Cancer 38(2):223–230
13. Seiwert TY, Salama JK, Vokes EE (2007) The concurrent chemoradiation paradigm--general principles. Nat Clin Pract Oncol 4(2):86–100
14. Earlam R, Cunha-Melo JR (1980) Oesophogeal squamous cell carcinoma: II. A critical view of radiotherapy. Br J Surg 67(7):457–461

15. Herskovic A et al (1992) Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 326(24):1593–1598
16. Cooper JS et al (1999) Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA. 281(17):1623–7
17. Minsky BD et al (2002) INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 20(5):1167–1174
18. Wong R, Malthaner R (2006) Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus. Cochrane Database Syst Rev 1, CD002092
19. Markar SR et al (2014) Evolution of standardized clinical pathways: refining multidisciplinary care and process to improve outcomes of the surgical treatment of esophageal cancer. J Gastrointest Surg 18(7):1238–1246
20. Swisher SG et al (2012) A Phase II study of a paclitaxel-based chemoradiation regimen with selective surgical salvage for resectable locoregionally advanced esophageal cancer: initial reporting of RTOG 0246. Int J Radiat Oncol Biol Phys 82(5):1967–1972
21. Earlam R, Cunha-Melo JR (1980) Oesophageal squamous cell carcinoma: I. A critical review of surgery. Br J Surg 67(6):381–390
22. Chiu PW et al (2005) Multicenter prospective randomized trial comparing standard esophagectomy with chemoradiotherapy for treatment of squamous esophageal cancer: early results from the Chinese University Research Group for Esophageal Cancer (CURE). J Gastrointest Surg 9(6):794–802
23. Carstens H et al (2007) A randomized trial of chemoradiotherapy versus surgery alone in patients with resectable esophageal cancer. J Clin Oncol (Meeting Abstracts) 25(18S Suppl):4530.
24. Gignoux M et al (1987) The value of preoperative radiotherapy in esophageal cancer: results of a study of the E.O.R.T.C. World J Surg 11(4):426–432
25. Arnott SJ et al (2005) Preoperative radiotherapy for esophageal carcinoma. Cochrane Database Syst Rev 4, CD001799
26. Launois B et al (1981) Preoperative radiotherapy for carcinoma of the esophagus. Surg Gynecol Obstet 153(5):690–692
27. Gignoux M et al (1988) The value of preoperative radiotherapy in esophageal cancer: results of a study by the EORTC. Recent Results Cancer Res 110:1–13
28. Wang M et al (1989) Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of esophageal carcinoma: report on 206 patients. Int J Radiat Oncol Biol Phys 16(2):325–327
29. Arnott SJ et al (1992) Low dose preoperative radiotherapy for carcinoma of the oesophagus: results of a randomized clinical trial. Radiother Oncol 24(2):108–113
30. Nygaard K et al (1992) Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second scandinavian trial in esophageal cancer. World J Surg 16(6):1104–1109
31. Hilgenberg AD et al (1988) Preoperative chemotherapy, surgical resection, and selective postoperative therapy for squamous cell carcinoma of the esophagus. Ann Thorac Surg 45(4):357–363
32. Sjoquist KM et al (2011) Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 12(7):681–692
33. Apinop C, Puttisak P, Preecha N (1994) A prospective study of combined therapy in esophageal cancer. Hepatogastroenterol 41(4):391–393
34. Prise EL et al (1994) A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. Cancer 73(7):1779–1784
35. Walsh TN (1995) The role of multimodality therapy in improving survival: a prospective randomised trial. In: Predicting, defining and improving outcomes for oesophageal carcinoma, Trinity College. University of Dublin, Dublin. As cited by: Sjoquist KM et al (2011) Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 12(7):681–692.
36. Walsh TN et al (1996) A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 335(7):462–467
37. Bosset JF et al (1997) Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 337(3):161–167
38. Urba SG et al (2001) Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 19(2):305–313
39. Lee JL et al (2004) A single institutional phase III trial of preoperative chemotherapy with hyperfractionation radiotherapy plus surgery versus surgery alone for resectable esophageal squamous cell carcinoma. Ann Oncol 15(6):947–954
40. Burmeister BH et al (2005) Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol 6(9):659–668
41. Tepper J et al (2008) Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 26(7):1086–1092
42. Lv J et al (2010) Long-term efficacy of perioperative chemoradiotherapy on esophageal squamous cell carcinoma. World J Gastroenterol 16(13):1649–1654

43. Mariette C et al (2010) Impact of neoadjuvant chemoradiation in localised oesophageal cancer: results of a randomised controlled phase III trial FFCD 9901. Ann Oncol 21:250
44. Van der Gaast AV, van Hagen P et al (2010) Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: results from a multicenter randomized phase III study. J Clin Oncol 28:15s, (suppl; abstr 4004).
45. van Hagen P et al (2012) Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 366(22):2074–2084
46. Mariette C et al (2014) Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol 32(23):2416–2422
47. Robb WB et al (2012) Surgery alone vs chemoradiotherapy followed by surgery for stage I and II oesophageal cancer: final analysis of a randomised controlled phase III trial FFCD 9901. Gut 61:A37–A38
48. Verhoef C et al (2007) Better survival in patients with esophageal cancer after surgical treatment in university hospitals: a plea for performance by surgical oncologists. Ann Surg Oncol 14(5):1678–1687
49. Stahl M et al (2009) Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol 27(6):851–856
50. Burmeister BH et al (2011) Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. Eur J Cancer 47(3):354–360
51. Kumagai K et al (2014) Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers. Br J Surg 101(4):321–338
52. Stahl M et al (2005) Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 23(10):2310–2317
53. Bedenne L et al (2007) Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 25(10):1160–1168
54. Nakamura K et al (2013) Three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU (DCF) versus radiotherapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer (JCOG1109, NExT study). Jpn J Clin Oncol 43(7):752–755
55. Andersen AP, Berdal P, Edsmyr F, Hagen S, Hatlevoll R, Nygaard K et al (1984) Irradiation, chemotherapy and surgery in esophageal cancer: a randomized clinical study. The first Scandinavian trial in esophageal cancer. Radiother and Oncol 2:179–188
56. Araujo CM, Souhami L, Gil RA, Carvalho R, Garcia JA, Froimtchuk MJ et al (1991) A randomized trial comparing radiation therapy versus concomitant radiation therapy and chemotherapy in carcinoma of the thoracic esophagus. Cancer 67:2258–2261
57. Earle JD, Gelber RD, Moertel CG, Hahn RG (1980) A controlled evaluation of combined radiation and bleomycin therapy for squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys 6:821–826
58. Gao XS, Qiao XY, Yang XR, Asaumi J, Zhou ZG, Wang YD et al (2002) Late course accelerated hyperfractionationradiotherapy concomitant with cisplatin in patients with esophageal carcinoma. Oncol Reports 9(4):767–772
59. Kaneta T, Takai Y, Nemoto K, Kakuto Y, Ogawa Y, Ariga H et al (1997) Effect of combination chemotherapy with daily lowdose CDDP for esophageal cancer: results of a randomized trial. Jpn J Can Chemother 24:2099–2104
60. Li AE, Shu BA, Lin YZ, Hu YH (2000) 48 Patients with advanced esophageal cancer treated with DDP-5-FU combined radiotherapy. Chin J Clin Oncol and Rehabilit 7(6):79–80
61. Roussel A, Haegele P, Paillot B, Gignoux M, Marinus A, Sahmoud T et al (1994) Results of the EORTC-GTCCT Phase III trial of irradiation vs irradiation and CDDP in inoperable esophageal cancer [abstract]. Proceedings, Annual Meeting of the American Society of Clin Oncol 13:199
62. Slabber CF, Nel JS, Schoeman L, Burger W, Falkson G, Falkson Cl (1998) A randomized study of radiotherapy alone versus radiotherapy plus 5-Fluorouracil and platinum in patients with inoperable, locally advanced squamous cancer of the esophagus. Amer J Clin Oncol 21:462–465
63. Zhang A (1984) Radiation combined with bleomycin for esophageal carcinoma - a randomized study of 99 patients. Chung Hua Chung Liu Tsa Chih 6(5):372–374
64. Zhu S, Wan J, Zhou D et al (2000) Combination of external beam and intracavitary radiation and carboplatin chemotherapy in the treatment of esophageal carcinoma. Chin J Clin Oncol 27(1):5–8

Signet Ring Carcinoma in EGJ: What Is It?

17

Riccardo Piagnerelli, Daniele Marrelli, and Franco Roviello

17.1 Epidemiology

ADC of EGJ and the distal esophagus represent a disease that has demonstrated a fourfold increase in incidence in the past three decades [1]. The SRCc is a histological subtype of that tumor. The incidence of this variant ranges from 0.1 % in the Japanese population [2] to 8–15 % in the western countries [3, 4].

17.2 Pathology

Patients with this disease histologically demonstrate signet ring cells (SRCs), characterized by the presence of abundant cytoplasmic mucin vacuoles that displace the nucleus to the periphery.

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SRC variants of ADC are, also, found in other poorly differentiated neoplasms located throughout the gastrointestinal tract, including the stomach and colon.

The World Health Organization (WHO) defines SRCc those tumors where more than 50 % of the cells have SRC morphology [5] without distinguishing the sole presence of SRC from the presence of SRCs and extracellular mucin. This, sometime, generated a lack of uniformity in data colleting (Table 17.1).

It was observed that SRC is associated with female gender, gastric localization, and advanced ypT and R1/2 categories.

Several studies recently described gastric SRC characteristics in comparison with to non-SRCs. Such characteristics include their highly infiltrative nature, high affinity for both lymphatic and peritoneal spread, and evidence of chemoresistance. All these factors lead to a dismal prognosis and hence demand the development of a dedicated oncological and surgical strategy for this histological subtype [6–8].

Many efforts were spent to understand the molecular mechanism behind the SRC [9].

One of the recent hypotheses behind the formation of signet ring cell is stressed in a recent work of Yasuhisa Fukui [10]. He observed that in highly differentiated ADCs, the ErbB2/ErbB3 complex is activated, which is followed by phosphatidylinositol 3-kinase (PI3K) activation. p38 MAP kinase is activated downstream of PI3K,

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Table 17.1 Differences between the most relevant series describing and treatments and their outcomes of SRC carcinoma

Authors	Years	Histological type	Site	CH–RT	Patients (n)	DFS	OS
Patel VR [28]	2014	SRC vs non-SRC	Esophageal + EGJ	Yes	85 vs 638	16 vs 35 (months)	22 vs 48 (months)
Heger U [26]	2014	SRC vs non-SRC	Esophageal or gastric	Yes	235 vs 488		26.3 vs 46.6 (months)
Nafteaux PR [34]	2014	ADC vs SRC < 50 vs SRC > 50 %	Esophageal + EGJ (no Siewert III)	Missing	806 vs 82 vs 32	59.3 vs 24.49 vs 16.82 (months)	Missing
Piessen G. [15]	2014	Esophageal SRC (including Siewert I and II) vs gastric SRC (including Siewert III)	Esophageal or gastric	Yes	136 vs 363	Missing	17.9 vs 19.9
Gronnier C. [35]	2013	Early GC SRC vs early GC non-SRC	Gastric	No	104 vs 317	5-year DFS: 92 % vs 90 %; $p = .403$	5-year OS: 85 % vs 76 %; $p = .035$
Enlow JM [36]	2013	SRC vs non-SRC	Esophageal + EGJ	Yes	23 vs 128	Missing	3-year OS: 34.8 % vs 65.6 %; $p = .006$
Kim BM [37]	2013	Early GC SRC vs early GC other subtype	Gastric	No	345 vs 1740	No difference	Missing
Taghavi S. [38]	2012	SRC vs non-SRC	Gastric	Missing	2666 vs 7580	14.0 vs 13.0 months $p = .073$	Missing
Chirieac LR [3]	2005	SRC + MC vs non-MC and non-SRC	Esophageal + EGJ	Missing	*Surgery alone*: 40 vs 179 *Preoperative CRT*: 33 vs 160	Missing	*Surgery alone*: 17.5 vs 22.9; $p = .05$ *Preoperative CRT:* 42.3 vs 31.6; $p = .06$

and adherence junctions are disrupted via Rac1 activation. This loss of adherence junctions leads to the disappearance of tight junctions, which results in a loss of intercellular interactions. Secretion of mucin is enhanced by activation of PI3K. One of the mucins (Muc4) can activate ErbB2. In a physiological setting, Muc4 and ErbB2 are separated by tight junctions, but in signet ring cells, they are able to interact, since these junctions have been lost. Moreover, a loop interaction, consisting of ERbB2/ErbB3–Muc4–ErbB2/ErbB3, is formed. As a result, the ErbB2/ErbB3 signaling pathway becomes constitutively activated, cell–cell interactions are lost, and signet ring carcinomas are formed. As a result of constitutive activation of the ErbB2/ErbB3 complex, cell growth is continuously enhanced.

In this study, the author found that some SRCcs carried mutations in the E-cadherin gene as well.

In a recent original work, in order to understand the molecular features of gastric and EGJ SRC ADC, Konno-Shimizu M and colleagues found that cathepsin E (CTSE), a non-lysosomal intracellular protease, is expressed in SRC-type, sometimes in poorly differentiated-type, and rarely in tubular-type gastric cancer (GC) cell lines in resected specimens obtained both endoscopically and with a surgical approach.

In healthy tissues, CTSE is expressed in normal fundic, pyloric, and cardiac glands of the stomach, but rarely in part of the digestive tract. Analyzing dysplastic intestinal metaplasia of the stomach, CTSE is observed in mixed gastric-and-intestinal type but not in pure intestinal type.

Due to the submucosal infiltrative and non-mass-forming behavior of SRC ADC [11] and the need of a correct preoperative histological disease assessment, they suggest the use of immunostaining of CTSE to detect isolated GC cells nests [12] and to understand the tumor's future behavior.

17.3 Clinical Behavior and Preoperative Workup

The scientific community did not reach a consensus about which diagnostic workup is the most reliable in esophagogastric tumors [13]. A study conducted by Nafteux et al. has raised an important issue about the dismal ability of the pretreatment biopsies in identifying the presence of SRC > 50 %, advocating the need to develop combined methods to identify percentage of SRCs and to guide the treatment since patients with an advanced-stage disease (i.e., SRC < 50 % with R0 resection) seem to have a similar behavior and survival rate as similar stage ADC [14].

Several studies recently described gastric SRC characteristics in comparison with non-SRCs.

A recent study conducted among 924 western patients demonstrates the specific role of SRC location and its impact on prognosis [15]. The results of the abovementioned study lead the authors to consider esophagus SRC different from the gastric one.

Despite similar pre-therapeutic clinical stage and preoperative treatment, gastric tumors were more advanced with a tendency for more peritoneal disease both at the time of surgical exploration and recurrence. This could suggest a specific developing pathway of the linitis plastica form and may be due to the microenviroment of the surrounding stroma [16]. Laparoscopic exploration of the abdominal cavity seems suggested during the pretreatment assessment of the disease.

They concluded that esophageal location was independently predictive of poor prognosis. This could be due to the infiltrative nature of the SRC and the later onset of symptoms in comparison with a non-SRC esophagogastric tumor.

Multislice CT (MSCT) scan besides other methods (i.e., DWI-MRI, endoscopic – US, PET, PET–MSCT) is one of the mainstays of the diagnostic workup. MSCT is mandatory in staging the disease and may be useful to assess nodes status and to select patients in which para-aortic nodal dissection (PAND) or lymph node sampling could be omitted as well. In the diffuse histotype of the upper third of the stomach, Marrelli et al. described how lymph node sized less than 8 mm can be the site of para-aortic metastases [17]. Those results matched with Lee's, suggesting that different bidimensional cutoff values may be established according to Lauren histotype [18].

Considering the dismal response of SRC ADC of EGJ to the neoadjuvant treatments, an emerging important aspect is the possibility to test in vivo the chemosensitivity of the primary tumor. This might influence the administration and the regimens applied postoperatively or consider the employ of an early salvage therapy in nonresponder patients, as the MUNICON II trial showed with non-SRC of EGJ. In this trial early was investigated whether PET nonresponders can benefit from a preoperative salvage neoadjuvant radiochemotherapy. Investigators stated that salvage neoadjuvant radiochemotherapy in metabolic nonresponders leads to local remissions in a considerable number of patients but was not able to change the clinical course in general [19].

As underlined before in this chapter, SRC histology shows unique features in contrast with other GCs; one of them is the reduced glucose uptake.

Chemotherapy decreases the tumor glucose uptake, and positron emission tomography (PET) with 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) has been widely used for detecting primary tumors, staging, planning treatment, assessing response to induction chemotherapy and after treatment follow-up.

FDG is transported into the intracellular space by glucose transporter (GLUT-1) and then phosphorylated to FDG-6-phosphate. Since FDG-6-phosphate is not a substrate of the Krebs cycle, it accumulates within cell. In some tumors, cells exhibit increased FDG uptake mediated by elevated levels of GLUT and hexokinase. An important SRC feature is the non-avid behavior toward glucose intake due to the low expression of GLUT-1 on cellular membrane [20]. Thus, FDG-PET failed to find and predict the response to neoadjuvant therapy in SRC.

In order to assess the response to induction therapy in non-avid tumors like SRC of EGJ, it has been proposed to employ 3′-deoxy-3′-18F-fluorothymidine (FLT) PET [21, 22]. This seems to be a promising tool but needs further studies to be validated.

Weber et al. proposed the employ of MRI-DWI besides the PET scan to asses local and lymphatic response to adjuvant chemotherapy in the ADC of EGJ especially in those tumors where endoscopic ultrasonography is not feasible due to stenosis [23].

17.4 Neoadjuvant Therapy and Surgical Treatment

Several therapeutical strategies were considered in the neoadjuvant treatment during last decades, and several regimens of chemotherapy were employed besides huge heterogeneity of histological type; those are the bias to keep in mind when a retrospective work on this issue is analyzed.

While locally advanced esophagogastric and esophagus ADC could be treated with an induction of chemotherapy–radiotherapy (CHT–RT) followed by surgery according to several randomized controlled trials [24, 25], a different behavior after chemotherapy is shown by SRC of the EGJ, both on clinical feature and on prognosis.

In a retrospective study, Heger et al. [26] analyzed clinical outcomes of a large series of EGJ ADC (723 patients, of which 235 with SRC). Along with other studies, SRCs were significantly associated with female gender ($p<0001$), gastric localization ($p<0001$), advanced ypT ($p<0072$) and R1/2 categories ($p<0001$), and lower risk of surgical complications and anastomotic leakage after resection ($p<0001$). SRC, after neoadjuvant treatment, had a significantly worse survival than all other WHO histopathological classifications with 26.3 months of median survival. Both clinical and complete histopathological responses are rare but, if present, are associated with significantly improved prognosis.

General exclusion of SRC from the only neoadjuvant chemotherapy with both platinum or platinum–docetaxel regimens [27] as hypothesized by some authors [7, 28] seems unjustified, at the moment, because a small subgroup seems to profit, and no randomized study showing a general survival benefit for SRC after primary resection only exists so far.

Better results in terms of overall survival and recurrence rate come from combining CHT–RT in a neoadjuvant setting as proved by Bekkar et al.[29].

They studied a subpopulation of 135 patients affected by a stage III SRC ADC of the EGJ, of whom 23 underwent preoperative CHT–RT and 74 underwent primary surgical resections.

CT scan and upper gastrointestinal endoscopy with biopsy and endoscopic ultrasonography were employed in pretreatment assessment.

The overall survival was significantly better in the CHT–RT group then in the surgery group (51 % vs 21 % $p<0002$). The only independent favorable prognostic factor in multivariable analysis was administration of neoadjuvant CHT–RT ($p<0.02$), underlying the ability of the sole radiotherapy in controlling local and metastatic spreading of the disease.

Surgical approach has been widely discussed. In T1–2 N0 tumors, esophagectomy with lymphadenectomy is the recommended treatment for type I EGJ ADC and gastrectomy with lymphadenectomy for type III EGJ ADC. For type II EGJ ADC, superior polar esogastrectomy or total esogastrectomy is used in order to reach an R0 resection. In node-positive lesion, perioperative chemotherapy could be a wise approach for type I or II EGJ ADC; neoadjuvant CHT–RT should be considered in those locally advanced tumors developed on the esophageal side. For type III EGJ ADC, perioperative chemotherapy or postoperative CHT–RT is a valid strategy.

Due to the infiltrative nature of SRC, intraoperative frozen sections of the surgical margins could be considered.

Some advantages would come from resection of the surroundings organs especially in locally advanced cancers.

Although, according to some authors, PAND seems to carry an increase of postoperative complications without carrying real oncological benefits [30], nevertheless, according to some authors, the N.16 station node harvesting could increase a better pathological staging, especially in the diffuse type of gastric and EGJ cancer [31].

17.5 Adjuvant Treatment

Some encouraging data comes from the use of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) in adjuvant setting. According to Sugarbaker et al., a significant improvement in overall survival was associated with HIPEC alone or combined with early postoperative intraperitoneal chemotherapy [32].

Actually, in order to define the best postoperative treatment for SRC of EGJ, postoperative CHT–RT compared with surgery alone has been evaluated in the intergroup 0116 phase III trial in patients after gastric and EGJ tumor resection. The 10-year follow-up of this study, of a population in which 20 % of tumors were EGJ ADC, showed that, in contrast to non-SRC ADC, SRC tumors do not benefit from postoperative CHT–RT [33]. This leads the authors to underline the weight of chemoradiation induction therapy in neoadjuvant setting.

Conclusions

SRCc of the EGJ is an uncommon histological subset of gastric diffuse tumor. Its rising incidence in the last decades could be partially due to a better preoperative workup and to a better knowledge of its complex biology.

MSCT, MRI-DWI, FDG-PET, and EUS with multiple deep FNA biopsies nowadays remain the mainstay of diagnostic workup. FLT-PET seems to have promising capabilities to forecast SRC responsivity to CHT–neoadjuvant therapy as well as the in vitro chemosensitivity testing.

Due to the tumor infiltrative nature and tendency of peritoneal and nodal seeding, staging laparoscopy should be integrated in the preoperative workup.

Chemoradiation seems to be the best choice in neoadjuvant setting.

Surgery should include station N.16 node harvesting and resection of the nearby organs in order to improve staging and to reach circumferential free margins.

Intraoperative frozen section could be considered to assess resection margins.

HIPEC could be employed in those cases with positive intraperitoneal lavage without macroscopic peritoneal seeding.

Further efforts should be made to deeply understand tumor biology in order to set up a tailored approach to this histotype.

References

1. Pera M, Manterola C, Vidal O et al (2005) Epidemiology of esophageal adenocarcinoma. J Surg Oncol 92(3):151–159
2. Terada T (2013) A clinicopathologic study of esophageal 860 benign and malignant lesions in 910 cases of consecutive esophageal biopsies. Int J Clin Exp Pathol 6(2):191
3. Chirieac LR, Swisher SG, Correa AM et al (2005) Signet-ring cell or mucinous histology after preoperative chemoradiation and survival in patients with esophageal or esophagogastric junction adenocarcinoma. Clin Cancer Res 11(6):2229–2236
4. Rice MD, Thomas W, Zuccaro MD Jr et al (1998) Esophageal carcinoma: depth of tumor invasion is predictive of regional lymph node status. Ann Thorac Surg 65(3):787–792
5. Watanabe H, Jass JR, Sobin LH (1990) Histological typing of esophageal and gastric tumors. WHO international histo-logical classification of tumors, 2nd edn. Springer, Berlin
6. Piessen G, Messager M, Leteurtre E et al (2009) Signet ring cell histology is an independent predictor of poor prognosis in gastric adenocarcinoma regardless of tumoral clinical presentation. Ann Surg 250(6):878–887
7. Messager M, Lefevre JH, Pichot-Delahaye V et al (2011) The impact of perioperative chemotherapy on survival in patients with gastric signet ring cell adenocarcinoma: a multicenter comparative study. Ann Surg 254(5):684–693
8. Lorenzen S, Blank S, Lordick F et al (2012) Prediction of response and prognosis by a score including only pretherapeutic parameters in 410 neoadjuvant treated gastric cancer patients. Ann Surg Oncol 19(7):2119–2127
9. Yue G, Sun X, Gimenez-Capitan A et al (2014) TAZ Is Highly Expressed in Gastric Signet Ring Cell Carcinoma. Biomed Res Int 2014:393064
10. Fukui Y (2014) Mechanisms behind signet ring cell carcinoma formation. Biochem Biophys Res Commun 450(4):1231–1233
11. Lauren P (1965) The Two Histological Main Types of Gastric Carcinoma: Diffuse and So-Called Intestinal-Type Carcinoma. An Attempt at a Histo-Clinical Classification. Acta Pathol Microbiol Scand 64:31–49
12. Konno-Shimizu M, Yamamichi N, Inada KI et al (2013) Cathepsin E is a marker of gastric differentiation and signet-ring cell carcinoma of stomach: a novel suggestion on gastric tumorigenesis. PLoS One 8(2):e56766
13. Moehler M, Baltin CT, Ebert M, et al (2015) International comparison of the German evidence-based S3-guidelines on the diagnosis and multimodal treatment of early and locally advanced gastric cancer, including adenocarcinoma of the lower esophagus. Gastric Cancer 18(3):550–563
14. Nafteux PR, Lerut TE, Villeneuve PJ, et al (2014) Signet ring cells in esophageal and gastroesophageal junction carcinomas have a more aggressive biological behavior. Ann Surg 1–7
15. Piessen G, Messager M, Lefevre JH et al (2014) Signet ring cell adenocarcinomas: different clinical–pathological characteristics of oesophageal and gastric locations. Eur J Surg Oncol 40(12): 1746–1755
16. Ikeda Y, Mori M, Kamakura T et al (1995) Immunohistochemical expression of sialyl Tn and sialyl Lewis^a antigens in stromal tissue correlates with peritoneal dissemination in stage IV human gastric cancer. Eur J Surg Oncol 21(2):168–175
17. Marrelli D, Mazzei MA, Pedrazzani C et al (2011) High accuracy of multislices computed tomography (MSCT) for para-aortic lymph node metastases from gastric cancer: a prospective single-center study. Ann Surg Oncol 18(8):2265–2272
18. Lee JH, Paik YH, Lee JS et al (2006) Candidates for curative resection in advanced gastric cancer patients who had equivocal para-aortic lymph node metastasis on computed tomographic scan. Ann Surg Oncol 13(9):1163–1167
19. zum Büschenfelde CM, Herrmann K, Schuster T et al (2011) 18F-FDG PET–guided salvage neoadjuvant radiochemotherapy of adenocarcinoma of the esophagogastric junction: the MUNICON II trial. J Nucl Med 52(8):1189–1196
20. Choi BH, Song HS, An YS et al (2011) Relation between fluorodeoxyglucose uptake and glucose transporter-1 expression in gastric signet ring cell carcinoma. Nucl Med Mol Imaging 45(1):30–35
21. Francis DL, Freeman A, Visvikis D et al (2003) In vivo imaging of cellular proliferation in colorectal cancer using positron emission tomography. Gut 52(11):1602–1606
22. Wieder HA, Geinitz H, Rosenberg R et al (2007) PET imaging with [(18)F]39-deoxy- 39-fluorothymidine for prediction of response to neoadjuvant treatment in patients with rectal cancer. Eur J Nucl Med Mol Imaging 34:878–883
23. Weber MA, Bender K, von Gall CC et al (2013) Assessment of diffusion-weighted MRI and 18F-fluoro-deoxyglucose PET/CT in monitoring early response to neoadjuvant chemotherapy in adenocarcinoma of the esophagogastric junction. J Gastrointestin Liver Dis 22:45–52
24. Cunningham D, Allum WH, Stenning SP et al (2006) Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 355(1):11–20

25. Boige V, Pignon J, Saint-Aubert B et al (2007) Final results of a randomized trial comparing preoperative 5-fluorouracil (F)/cisplatin (P) to surgery alone in adenocarcinoma of stomach and lower esophagus (ASLE): FNLCC ACCORD07-FFCD 9703 trial. J Clin Oncol 25(18S):4510
26. Heger U, Blank S, Wiecha C et al (2014) Is preoperative chemotherapy followed by surgery the appropriate treatment for signet ring cell containing adenocarcinomas of the esophagogastric junction and stomach? Ann Surg Oncol 21(5):1739–1748
27. Chen L, Shi Y, Yuan J et al (2014) Evaluation of docetaxel-and oxaliplatin-based adjuvant chemotherapy in postgastrectomy gastric cancer patients reveals obvious survival benefits in docetaxel-treated mixed signet ring cell carcinoma patients. Med Oncol 31(9):1–11
28. Patel VR, Hofstetter WL, Correa AM et al (2014) Signet ring cells in esophageal adenocarcinoma predict poor response to preoperative chemoradiation. Ann Thorac Surg 98(3):1064–1071
29. Bekkar S, Gronnier C, Messager M et al (2014) The impact of preoperative radiochemotherapy on survival in advanced esophagogastric junction signet ring cell adenocarcinoma. Ann Thorac Surg 97(1):303–310
30. Mariette C, Piessen G, Briez N et al (2011) Oesophagogastric junction adenocarcinoma: which therapeutic approach? Lancet Oncol 12(3):296–305
31. de Manzoni G, Di Leo A, Roviello F et al (2011) Tumor site and perigastric nodal status are the most important predictors of para-aortic nodal involvement in advanced gastric cancer. Ann Surg Oncol 18(8):2273–2280
32. Yan TD, Black D, Sugarbaker PH et al (2007) A systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. Ann Surg Oncol 14(10):2702–2713
33. Smalley SR, Benedetti JK, Haller DG et al (2012) Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol 30(19):2327–2333
34. Nafteux PR, Lerut TE, Villeneuve PJ et al (2014) Signet ring cells in esophageal and gastroesophageal junction carcinomas have a more aggressive biological behavior. Ann Surg 260(6):1023–1029
35. Gronnier C, Messager M, Robb WB et al (2013) Is the negative prognostic impact of signet ring cell histology maintained in early gastric adenocarcinoma? Surgery 154(5):1093–1099
36. Enlow JM, Denlinger CE, Stroud MR et al (2013) Adenocarcinoma of the esophagus with signet ring cell features portends a poor prognosis. Ann Thorac Surg 96(6):1927–1932
37. Kim BS, Oh ST, Yook JH et al (2014) Signet ring cell type and other histologic types: differing clinical course and prognosis in T1 gastric cancer. Surgery 155(6):1030–1035
38. Taghavi S, Jayarajan SN, Davey A et al (2012) Prognostic significance of signet ring gastric cancer. J Clin Oncol 30(28):3493–3498

Morbid-Mortality and Treatment of Complications

18

Jacopo Weindelmayer, Simone Giacopuzzi, Andrea Zanoni, and Giovanni de Manzoni

18.1 Introduction

Despite the growing importance of chemotherapy and radiotherapy, surgery is still the preferred curative treatment for esophageal adenocarcinoma (EAC). Depending on the esophageal and gastric involvement of this tumor, a gastrectomy (with an exclusive abdominal approach) or an esophagectomy is required. The latter needs an abdomino-thoracic approach or a gastric pull-up, resulting in an increased morbidity and mortality.

Even if EAC is classified as an esophageal cancer together with squamous cell carcinoma (SCC), patients that suffer from these two cancers are very different. SCC patients are often smokers, heavy drinkers, and malnourished, resulting in significantly impaired pulmonary and hepatic functions. Conversely EAC patients often present a better general status, with half of patients suffering from obesity. This good preoperative performance status of EAC patients compared to the SCC leads to a smaller percentage of postoperative complications.

In studies with large cohort of patients receiving esophagectomy, mortality ranged between 2.7 % and 9.8 % with a morbidity of 17.9–57 %. This high variability was due to two main factors: (1) these large studies are mainly conducted on patient data collected from national databases, where both high and low volume centers are included without any weighting in the analysis for volume or type of operations; (2) there is a large variability in the definition of the postoperative complications making impossible to compare the different clinical trials.

Morbidity can be mainly divided in medical and surgical, with respiratory complications being the most frequent medical complications, occurring in 21–27 % of patients, and anastomotic leaks representing the main surgical complication, with percentages that stand between 3.7 % and 14 %. Other notable complications are atrial arrhythmias, chylothorax, and necrosis of the gastric conduit.

Complications seem to have an impact also in long-term patient prognosis, with a significantly higher risk of cancer recurrence in patients with complications after esophagectomy than in those where the operation was uneventful [1, 2]. The explanation for this phenomenon remains uncertain, but it seems to be correlated to the systemic inflammatory response with release of chemokines that guide the spreading of microscopic residual cancer using the same pathways as leukocytes during inflammation [3].

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In recent years many studies have demonstrated a reduction up to four times in postoperative mortality in high volume centers, as discussed at length in Chap. 12. However, morbidity remains significant even in these centers, with percentages that range between 40 and 60 %[4, 5]. These results highlight how complications are bound to occur due to the technical complexity of this operation. Therefore, better "know-how" in managing postoperative complications can lead to a higher percentage of resolutions, significantly reducing postoperative mortality.

Until now there is no widely accepted classification system for postoperative morbidity in esophageal surgery. As a consequence, it is difficult to compare morbidity-related outcomes between different studies. The heterogeneity of classifications relates to both the definition and the severity ranking of complications. Blencowe published in 2012 a systematic review on this topic, evidencing how most of the published papers lack in definitions and descriptions of complications and how many different definitions of the complications have been proposed [6]. This is apparent even for the main complications in esophageal surgery: anastomotic leak and pneumonia. As a consequence, the reported incidence in literature for anastomotic leak ranges between 0 % and 35 % and for pneumonia ranges between 1.5 % and 38.9 %.

Clavien-Dindo and Accordion classifications are used worldwide to classify complications on the basis of resource utilization [7, 8]. They have been validated in esophageal surgery, but they are nonspecific with regard to the different types of complication.

Recently Low established the esophagectomy complications consensus group (ECCG) among 21 high volume centers worldwide. The group is studying a system for defining and recording perioperative complications after esophagectomy. This could result in a standardization of international data collection on morbidity, to facilitate the interpretation and the comparison of data in the literature [9].

18.2 Patient Selection

EAC surgery is a major operation, highly demanding for the patient that is often already strained by the disease and by neoadjuvant treatments. Consequently the clinical status has to be analyzed when electing a patient for surgical resection, trying to identify patients at high risk before surgery in order to perform targeted perioperative treatments or to redirect them to other nonsurgical treatments.

Large cohort studies have been conducted to analyze the factors associated with morbidity and mortality after esophagectomy; in Table 18.1 data from seven large population studies are reported highlighting only the factors significant in multivariable analysis [10–16].

As evidenced from the table, age is a significant factor in all the studies considered, with a cutoff mostly set at 75 years old. A review conducted by Markar and colleagues confirmed a higher risk of morbid-mortality in elderly people [17]. However,

Table 18.1 Factors associated with morbidity and mortality at multivariable analysis in large cohort studies

Author	Associated with morbidity	Associated with mortality
Dhungel B et al. [13]	Age DM Smoking/alcohol status Transfusion	Wound infection DM Dyspnea
Bailey SH et al. [12]	Age Dyspnea DM Smoking CRT	Age DM Dyspnea Liver function CRT
Atkins et al. [16]	Age Pneumonia	Age Pneumonia
Ott K et al. [11]	n.r.	Age
Sauvanet A [10]	ASA Age Male gender	ASA
Wright CD et al. [15]	Age Cardiopathy DM Smoking	Age Cardiopathy DM Smoking
Zingg U et al. [14]	n.r.	Smoking Comorbidities

DM diabetes mellitus, *CRT* neoadjuvant chemoradiotherapy, *n.r.* not reported

two recent studies in high volume centers on octogenarians demonstrated that with a careful selection (even with a higher incidence of overall complications) mortality is not increased [18, 19]. It is probably not the age that defines an increase in the complications rate, rather the fact that elderly patients present more comorbidities that in turn determine a higher fragility. Surgery should therefore not be denied to the elderly on the basis of their age alone; they should instead be redirected to a high volume center for assessment.

When an esophagectomy has to be performed, pulmonary morbidities are the main complications occurring in up to 30 % of the patients. Preoperative impaired pulmonary function is associated with higher morbidity. A careful functional study of the lung has to be done to properly decide if it is possible to perform a thoracotomy or if it is necessary to perform a transhiatal (THE) or thoracoscopic (MIE) approach. Bartels identified an increased mortality risk for patients with a vital capacity <90 % and a preoperative PaO2 < 70 mmHg [20]. Perioperative cares to optimize pulmonary function are described in the "pulmonary complication" section of this chapter.

Neoadjuvant treatments seem not to increase postoperative morbidity. Only a few studies evidenced a significant relation of these treatments with morbidity and mortality. Neither in the CROSS trial nor in a recent paper from the FREGAT group was there evidence of differences in postoperative complications between no-CRT and CRT group [21, 22]. Probably, even if neoadjuvant treatment is heavily demanding for the patient due to its side effects, it shrinks the cancer, thus improving patient's ability to eat and therefore their nutritional and general status.

Some studies have tried to develop a reliable scoring system to rank patients for morbid-mortality risk. The most notable work came from the Siewert group and was subsequently validated by Schröder et al. in 2006 [20, 23]. They identified four factors associated with mortality (Karnofsky index, aminopyrine breath test, pulmonary vital capacity, and PaO2) and produced a composite risk score, based on these factors, to predict postoperative mortality. Nevertheless the results of this study are limited and widely accepted scoring system has not yet been made.

Admittedly, scoring systems could be useful tools to identify patients that are most likely to develop postoperative complications; however strict adherence to these rankings for decision-making should be avoided, and every case should be evaluated on its own merit.

18.3 Medical Complications

The main medical complications are pulmonary and cardiac. These are more frequent in esophagectomy than gastrectomy due to the stress on the lungs and heart caused by the direct violation of the thorax and the mediastinum during a transthoracic or transhiatal approach.

18.3.1 Cardiac Complications

During the mediastinal dissection of the esophagus, the heart is directly manipulated and pressed by the retractors, while vagal dissection above the azygos is associated with the disruption of the vagal cardiac nerves, both resulting in possible rhythm alterations. Cardiac complications post-esophagectomy have been classified by Low et al. as follows [9]:

- Cardiac arrest
- Myocardial infarction
- Dysrhythmia atrial requiring treatment
- Dysrhythmia ventricular requiring treatment
- Congestive heart failure requiring treatment
- Pericarditis requiring treatment

The most frequent cardiac complication is atrial fibrillation (AF), which is described in 15–25 % of patients and occurs mostly during the second and third postoperative day [24]. Two studies found an association between AF and an increased postoperative mortality of up to four times [25, 26]. Mortality was not directly related to AF; instead there were often more severe underlying complications which triggered a series of other complications including AF.

A recent study by Cormack et al. on 473 SCC and EAC found that new onset AF occurred in 20 % of the patients and was associated with older age, preoperative cardiovascular disease, DM, and, interestingly, neoadjuvant treatment. AF was associated with other complications in more than 80 % of these patients, mainly pulmonary complications. Interestingly mortality of FA patients was not increased. The author explained the low mortality in FA patients by a close observation and early treatment of the underlying complication [26].

Strategies to prevent AF are still limited and come from studies conducted in cardiothoracic surgery. Proposed strategies include intraoperative fluid restriction, balancing of electrolytes, and cardiac nerves sparing. Many drugs have been studied including amiodarone, digoxin, b-blockers, calcium antagonist, and magnesium sulfate, with limited results and no indications for prophylactic use at present [24, 27, 28].

Concluding, care must be exercised when a patient has postoperative AF. Although the complication is not difficult to treat properly (even at ward level), it may be an indirect sign of other underlying complications that have to be promptly diagnosed and treated in order to not increase the postoperative mortality.

18.3.2 Pulmonary Complications

Esophagectomy is a stressful operation for the lungs because of supra-mesocolic surgery, thoracotomy, and lung manipulation, which require an increase of the perioperative ventilatory demand. When the request exceeds the patient's ventilatory capacity, there can be a ventilatory pump failure, resulting in an alveolar hypoventilation that can lead to pneumonia and respiratory failure.

Pulmonary complications are the most frequent cause of morbidity after esophagectomy, ranging from 2.5 to 27 % in the different studies [10–16]. High variability of the results is due to a wide range of definitions for documenting or stratifying these complications, making it difficult to compare results from different papers.

A physiopathology of pulmonary complications has been recently published by Boshier et al., a group from London. The paper describes different stress mechanisms that act during and after esophagectomy, briefly consisting of ischemia-reperfusion lung injury, high fraction of inspired oxygen of the ventilating lung, ventilator-induced lung injury, and pulmonary capillary stress failure of the ventilating lung [29].

Reported pulmonary complications are many, ranging from pleural effusion with atelectasis to pneumonia, to ALI and ARDS with possible respiratory failure requiring prolonged mechanical ventilation [30]. Low et al. classified pulmonary complications as follows [9]:

- Pneumonia (definition of the American Thoracic Society and Infectious Diseases Society of America [31, 32])
- Pleural effusion requiring drainage
- Pneumothorax requiring treatment
- Atelectasis mucous plugging requiring bronchoscopy
- Respiratory failure requiring intubation
- Acute respiratory distress syndrome (ARDS)
- Acute aspiration
- Tracheobronchial injury
- Chest tube maintenance for air leak for > 10 days postoperatively

Of these complications pneumonia is the most frequent, and it has a significant impact on patient's prognosis raising the mortality rate from 3 % up to 20 % [33]. Less frequent than pneumonia but more severe is ARDS that has an incidence of up to 10–15 % and a mortality rate of about 50 %.

This data highlights the importance for pulmonary complications of correct preoperative prevention and intraoperative and postoperative care.

Objectives of preoperative prevention include optimization of nutritional status and smoking cessation. The correction of malnutrition and cachexia leads to an optimization of respiratory muscle function and efficacy of immune system. To stop smoking is of primary importance, and the patient has to be informed of the increased

morbidity risk due to an active perioperative tobacco consuming. It is still debated on how long before the operation consumption has to be stopped in order to have the best results, but a period of four weeks seems to guarantee significantly better outcomes [34]. In a recent study on gastrectomy, the authors evidenced statistically significant improvements even for a quitting period of two weeks or more [35]. Shorter periods, even if not harmful, do not seem to influence postoperative morbidity [36].

Patients should be assessed and treated by a physiatrist in order to optimize the preoperative lung function. In the literature there are limited studies describing the use of intensive respiratory training in small cohort esophagectomy patients. Positive results have been obtained with the use of IMT (inspiratory muscle training) in two recent studies, which found a significative reduction in pulmonary complications in the IMT group [37, 38]. An ongoing multicenter RCT from the Netherlands is studying the incidence of pneumonia after esophagectomy in patients treated with IMT is expected to provide further evidence on this argument in the coming years [39].

It has to be noted that many EAC patients are overweight. Even if obesity is not an absolute contraindication for esophageal surgery, a BMI >30 mg kg-2 seems to be associated with a higher risk of pulmonary complications [40, 41]. In these patients an effort should be made to optimize the preoperatory respiratory function and to reduce the pulmonary injury during the operation (MIE, THE) [42].

Intra- and postoperatory management require fluid restriction, protective ventilation with reduced tidal volume and the introduction of positive end-expiratory pressure (PEEP) during one lung ventilation, early extubation and mobilization, an aggressive management of secretions with intense physiotherapy and toilet bronchoscopies, and an adequate analgesia [43]. All these strategies are part of ERAS (enhanced recovery after surgery) protocols that are fully described in Chap. 21.

The use of a transhiatal approach, without a direct access in the thoracic cavity, has been proposed to reduce respiratory complications, at the cost of an incomplete mediastinal lymph node dissection. Results of two recent meta-analyses seem to confirm this benefit; both Boshier and Wei evidenced a statistically significant reduction of pulmonary complications in the pooled analysis [44, 45]. THE has to be reserved to high risk pulmonary patients, where even a thoracoscopy should be avoided, because in THE the impossibility of performing a correct mediastinal lymph nodal harvesting and a higher percentage of positive circumferential margin may affect the oncological outcome of the operation.

18.4 Surgical Complications

Esophagectomy and total gastrectomy are challenging operations that require a great amount of surgical experience in the operating room and expertise in the postoperative treatment in order to reduce intraoperative and postoperative morbidity.

Anastomotic leak is the most frequent surgical complication for both esophagectomy and gastrectomy, while necrosis of the gastric conduit, chylothorax, and tracheobronchial fistulization belong exclusively to the esophagectomy.

18.4.1 Anastomotic Leak

There is still no consensus on the definition of anastomotic leak, and consequently the incidence of this complication in the literature is variable (from 0 % to 35 %). Leak definitions range from a radiological contrast swallow finding in the absence of symptoms up to discharge of gastrointestinal content through a drain. Many groups have proposed different leak classifications. Urschel et al. published a classification based on location and symptoms, while Schuchert et al. used a classification based on direct endoscopic vision of the defect and the degree of intervention required [46, 47]. However, these classifications are not widely accepted, and, at present, Low et al. are working on an international consensus on standardization of complication definitions for

esophagectomy [9]. Low et al.'s definition of anastomotic leak is a full thickness gastrointestinal defect involving esophagus, anastomosis, or staple line irrespective of presentation or method of identification.

Different factors contribute to the high incidence of anastomotic leakage, at both systemic and local level. Systemic factors include severe malnutrition, impaired cardiovascular and pulmonary function, and advanced tumor stage. Local factors are the absence of an outer serosa layer and longitudinal orientation of esophageal muscle fibers that seem to make esophageal anastomosis disadvantaged compared to other visceral anastomosis; impaired vascularization of the graft end due to an insufficient arterial supply or venous drainage; and an excessive mechanical tension on the anastomosis. It is still under investigation if the positioning of the esophago-gastro anastomosis in the neck (TTE) is associated with a higher incidence of anastomotic leak due to the necessity of performing a longer conduit, with consequently a microvascular insufficiency of the apex and a higher mechanical tension on the anastomosis. In a recent meta-analysis conducted by Markar and Al on RCT and retrospective studies, neck and thoracic anastomosis resulted in the same leakage rate (neck 8.8 % vs thoracic 7.8 %). However, if only RCT were considered, there was a statistically significant higher percentage of leak in neck anastomosis compared to thoracic anastomosis (13,64 % vs 2,96 %) [48]. Thoracic anastomosis should therefore be preferred in all patients fit for a thoracotomy, reserving cervical anastomosis to the patients with low pulmonary function in order to perform a THE or a thoracoscopic approach.

Cervical anastomosis can be performed either hand sewn or mechanically, depending on the surgeon's preference, as the incidence of anastomotic leak has been found comparable in our experience and in two recent meta-analyses [48–50].

With reference to intrathoracic anastomosis, nowadays it is performed almost always mechanically. This raises questions on the possibility of performing safely an intrathoracic anastomosis with a minimally invasive technique.

18.4.2 Diagnosis and Treatment

An anastomotic leak has different clinical presentations according to the anastomosis location (neck or mediastinum) and to the entity of the defect. Based on this, anastomotic leak can range from an asymptomatic radiologic finding to a necrotizing infection accompanied by sepsis.

Timing in diagnosis and severity assessment with early proper treatment is crucial to obtain healing using the least invasive efforts in a frail patient.

There is no agreement at present on the necessity of performing a postoperative upper GI study to assess anastomotic integrity. Many centers still perform a routine contrast swallow within ten days of the esophagectomy, before allowing the patient any oral intake, but the sensibility of this test is low (and with high variability, probably depending on operator experience) ranging between 20 % and 87 %, thus accounting for a large number of false-negative patients [51–53]. On the other hand, contrast swallow has a high specificity (94–100 %), so that a positive test represents almost always a leak. In our opinion routine use of contrast esophagogram is not recommended and has to be reserved to clinically suspicious patients due to its high specificity [54].

Recent studies demonstrated the safety of early postoperative endoscopy, pointing the attention to its high sensibility and specificity (close to 100 %) for anastomotic leak, and the fact that the exam also gives information about the condition of the gastric conduit [51, 55]. This tool is of great clinical interest, but it is still an invasive procedure and should be performed mainly on the basis of a clinical suspect.

At present no guidelines exist on this argument, the evidences are low, and literature is still at an "expert opinion" level. Below are described our recommendations on the diagnosis and treatment of the anastomotic leaks based on anastomotic site and patient symptoms (as proposed by Urschel et al.[46]):

1. Clinically silent cervical and thoracic leaks: They are detected using a contrast swallow imaging or endoscopy in asymptomatic

patients with no laboratory signs of infection. These leaks are usually small and are limited by surrounding tissues. In this case conservative management with avoidance of oral intake, nasogastric tube decompression, nutritional parenteral or, preferably, enteral support (via a feeding jejunostomy placed during the operation or a fine-bore nasojejunal tube), broad spectrum antibiotics, and antifungal therapy provide a high success rate. Patient must be carefully monitored for signs of sepsis or leak progression in order to perform a more aggressive treatment (percutaneous drainage, endoscopic procedure) where necessary. In our clinical practice, we do not perform a routine contrast swallow anymore, and consequently we cannot discover clinically silent leaks before resuming oral intake. Despite this change, we did not experience an increase of clinical leaks. Hence, we have come to conclude that clinically silent leaks heal without any specific treatment in the majority of cases.

2. Clinically evident leaks:
   (a) Clinical cervical leaks are usually clinically detectable within ten days from the operation by neck erythema, with a palpable cavity with fluid and subcutaneous crepitus. Fever and laboratory sepsis exams reveal an ongoing infection. The main treatment consists in opening the wound to drain the leak. When the cavity is cleaned, the positioning of a compressive medication can help the healing process, together with fasting, nasogastric tube decompression, nutritional support, and antibiotic therapy. In some cases low esophago-gastro cervical anastomosis can drop down in the upper thorax; in these cases the anastomotic leak has to be managed as a thoracic leak.
   (b) Clinical thoracic leaks usually appear at the 7th–10th postoperative day with fever, leucocytosis, high CRP levels, and a quick deterioration of the patient conditions toward a mediastinitis. If mediastinal drainage is in place, an increased drain volume, odor, and turbidity appear. A water-soluble contrast swallow can confirm the diagnosis, but a CT scan is mandatory to assess the entity of the thoraco-mediastinal fluid collections. Endoscopy allows to have a direct visualization of the dehiscence and to perform endoluminal treatments, but it has to be done by an expert GI endoscopist to avoid further damage to the anastomosis.

In stable patients a conservative treatment can be attempted through an adequate drainage of the infected fluid collections (under CT scan or ultrasonographic guidance). Systemic measures are the same described in the cervical leak paragraph.

Endoscopic techniques for anastomotic leak treatment include clip placement, stent placement, and vacuum therapy. We consider clip placement to close leaks smaller than 30 %. During a preliminary endoscopy, an accurate analysis of the defect has to be performed: the absence of ischemia and vital wound margins are necessary to try the clip placement. Normal clips (through-the-scope clips) can be used for small anastomotic defects, while the newly developed over-the-scope clip (OVESCO™) has been proposed to close larger dehiscence with a reported success rate of 70 %[56, 57].

Stent placement is proposed for a >30 % degree dehiscence of the anastomosis [58]. An extractible stent is placed along the anastomosis in order to cover the defect and isolate the mediastinal space, promoting the healing of the leak and allowing the patient to resume oral intake earlier. Success rate is 70–80 % with 30–70 % of stent-related complications, including migration, bleeding, perforation, and ingrowth [59–61]. Stent migration is the commonest complication occurring in up to 30 % of cases. It is probably caused by the absence of a stenosis that can help the stent to hold the position and by the different diameters of the esophageal remnant and the conduit. This hypothesis of lumen discrepancy is supported by recent data that evidenced a lower incidence of stent migration in esophago-jejunal anastomosis with respect to esophago-gastro anastomosis, probably due to the closer diameter

of the two conduits [61]. Partially covered self-expanding metal stent seems to have the better results than the other types of stent with a migration of 12 %[62].

Vacuum therapy has the advantage of keeping clean the perianastomotic cavity, continuing to remove the wound secretion and to improve the tissue microcirculation, thus facilitating anastomotic healing. Limited studies have been published on the topic, with a high closure rate (which is 83–100 %) and no significant complications [59, 63]. These data have to be carefully generalized because they come from studies that used small populations. At the moment, endoscopic treatments should only be considered in experienced centers, as an option in patients with limited mediastinal or pleural contamination.

Surgery is indicated in case of unstable septic patient or after failure of conservative treatments. For complete anastomotic disruption or leak with an associated conduit necrosis, a takedown of the gastric conduit has to be done. Main steps are a thoracotomy with a toilet of the pleural and mediastinal cavity with the placement of a drainage, the takedown of the gastric conduit, a laparotomy with jejunostomy, and a cervicotomy with proximal esophageal diversion.

Direct repair of the defect is possible only for early leaks (within 48 h after the operation). As discussed later, early leaks are caused by a technical problem during the primary operation and have to be operated as soon as they are discovered in order to fix the defect or redo the anastomosis.

In case of late leaks (>48 h) a direct repair is no more effective. If the leak is limited and there are no signs of ischemia, a combined endoscopic and surgical approach can be attempted. During the reoperation, after the toilet of the thorax, the endoscopist places a stent to cover the defect, while the surgeon fixes the stent on the esophageal wall with slow-reabsorbable stitches in order to reduce the possibility of stent migration. With this treatment the anastomosis is covered and will heal by secondary intention. We performed this treatment on three patients with septic shock due to a thoracic leak with a defect of 80 %. In all cases the leak healed, and the stent was removed easily by the endoscopist, cutting the stitches before taking out the stent.

3. Early clinical anastomotic leaks (within 48 h): They are considered a technical error, usually treated with a reoperation and, if technically feasible, a redo of the anastomosis. If a diffuse conduit necrosis is also associated, a takedown of the conduit has to be performed with a proximal and a distal diversion.

Figure 18.1 illustrates a flowchart for the treatment of anastomotic leak after transthoracic esophagectomy.

18.4.3 Conduit Necrosis

Conduit necrosis is a vascular suffering of the gastric/jejunal substitute due to an insufficient arterial blood supply or an inadequate venous outflow. It can be caused by systemic or local problems such as hypotension, the use of vasopressor agents, conduit distension, vascular pedicle torsion, or strangulation. Its incidence ranges between 0 and 3 % in the different studies on the subject [64]. Historically, conduit necrosis was diagnosed only in case of extensive and symptomatic necrosis. Today, with the increasing use of postoperative endoscopy, now considered safe even in the early postoperatory phase [55], a more detailed description of the conduit vascular suffering has been achieved. It has been hypothesized that an early identification of a limited conduit ischemia can predict the occurrence of an anastomotic leakage; therefore it makes possible to perform preventive measures to stop the leakage development. However, it has to be specified that early postoperative endoscopy is still used only in controlled studies because its clinical utility is under investigation. CT scan has been proposed for the diagnosis of the conduit necrosis because it is less invasive than endoscopy, but it has demonstrated low accuracy [65].

Conduit necrosis is classified, on endoscopic and treatment basis, as follows:

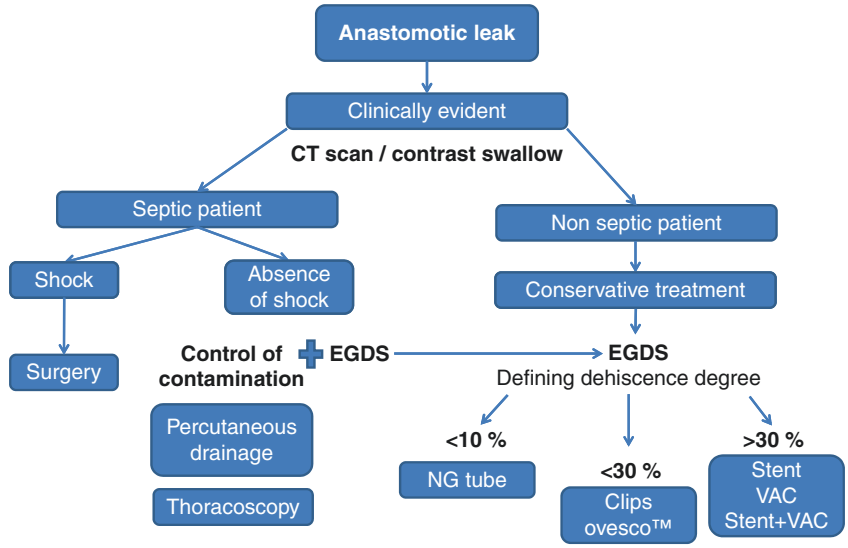

Fig. 18.1 Proposed flowchart for the treatment of anastomotic leak in transthoracic esophagectomy. *CT scan* computed tomography scan, *EGDS* esophagogastroduodenoscopy, *NG tube* nasogastric tube, *VAC* vacuum-assisted closure

1. Asymptomatic focal necrosis identified endoscopically and requiring nonsurgical therapy
2. Focal necrosis not associated with an extensive anastomotic or conduit leak, requiring surgical therapy not involving esophageal diversion
3. Extensive conduit necrosis requiring resection with esophageal diversion [9]

Treatment of asymptomatic limited necrosis without involvement of the anastomosis is the cessation of oral intake with nasoenteric decompression and nutritional support. A careful monitoring of patient conditions and a short-term endoscopic reevaluation are needed to assess the viability of the conduit.

If a focal necrosis of the conduit close to the anastomosis is discovered, the treatment depends on the clinical conditions of the patient. These patients have to be treated according to the anastomotic leak section.

Extensive conduit necrosis generally presents within 48 h with sepsis and often purulent anastomotic drainage. On clinical suspicion an early endoscopic diagnosis and reoperation are mandatory. Re-exploration with resection of the necrotic conduit, cervicostomy, and jejunostomy are often necessary to secure the survival of the patient.

An increased incidence of conduit necrosis has been evidenced after minimally invasive esophagectomy, reaching 3–10 %; this has been related to technical factors [66, 67]. The main ones are the impossibility in intracorporeal gastric tubulization of stretching the organ during stapling, consequently making a shorter conduit, and an insufficient Kocher maneuver. To overcome this problem, alternative techniques have been proposed, such as ischemic conditioning and the extracorporeal preparation of the gastric conduit [68, 69]. Ischemic conditioning of the conduit is not widely used as it has not demonstrated significant advantage in reducing conduit necrosis and at present is not used. Extracorporeal preparation of the conduit requires a small laparotomy but has the theoretical advantage of performing an adequate stretching of the stomach during stapling obtaining therefore a longer conduit.

18.5 Chylothorax

Chylothorax is an important complication after esophagectomy with an incidence of 0.5–4 % according to different reports. Historically, mortality was at 50 %; nowadays, in high volume

centers with an early recognition and an aggressive treatment, it has been decreased to <10 %[70, 71]. Chylothorax is defined as the presence of chyle in the pleural cavity and is caused by a damage to the thoracic duct or to one of its tributaries that lay close to the esophagus, between the aorta and the azygos vein. The duct has a wide anatomical variability that can be partially responsible for the possible occurrence of this complication, despite the surgeon's experience. Chyle loss becomes generally clinically apparent after 2–7 days after surgery, when oral or enteral intake is resumed. It presents with a huge pleural fluid collection that compresses the lung and can cause a hemodynamic impairment, or, if a drainage is within the thorax, with an increased drainage output usually with a milky aspect. The diagnosis is confirmed by the presence of a high concentration of chylomicrons, triglyceride, and leukocyte in the fluid.

Consequences of chylothorax are respiratory, immunological, and nutritional. Pulmonary impairment is directly consequent to the pleural effusion that causes the development of atelectasis. A prolonged depletion of chyle causes a reduction in lymphocytes and immunoglobulins with consequent immunodepression. Moreover, the loss of chyle leads to electrolyte disturbance and, in the long term, depletion of fatty acids and proteins, causing a severe malnutrition state [72].

Optimal treatment for chylothorax is still controversial, and literature is limited to small studies in high volume centers. The two main options are conservative treatment and surgical ligation of the thoracic duct. It is generally accepted that a conservative attempt has to be done before considering surgery, but a precise indication on how to decide whether to continue or abandon this treatment still does not exist.

Conservative treatment consists of the elimination of oral or enteral nutrition in order to reduce the output of the fistula, with the setup of an adequate total parenteral nutrition to rebalance the chylous loss (electrolyte and fluid balance). Prophylactic antibiotic therapy is not indicated, but these patients have to be carefully monitored because they are at high risk of infection. Limited data exists on the use of octreotide, a somatostatin analogues, in the reduction of the chyle output, but its use can be considered [72, 73]. An effective drainage of the pleural cavity has to be completed. If a thoracic drainage is not present, this has to be placed and aspiration has to be avoided in order not to sustain the fistula. A precise daily monitoring of the loss from the drainage is the main predictor of success in the conservative approach.

An output of less than 10 ml/kg/24 h after five days of conservative treatment is considered a predictor of success, and, on this basis, different flowcharts have been proposed [70–72, 74]. We consider it appropriate to try with a conservative approach for five days, with careful monitoring of the patient condition and reserve surgery if either the condition decays or if chyle output does not improve significantly or if after five days output is still >1000 ml/24 h.

Conservative management of chyle leaks has a success rate of 70–80 % within four weeks [5]. A prolonged treatment with persistent high chyle output can put the patient at high risk of severe infectious and metabolic complications. Therefore, we suggest to not prolong the treatment over a two-week period if the chyle output does not considerably reduce [75, 76].

The aim of surgical management is the closure of the thoracic duct. Even if some studies suggest the possibility of closing the thoracic duct with an abdominal approach, we suggest the thoracic approach because of the wide variability of the abdominal lymphatic tree. Surgery can be performed either via right thoracotomy or thoracoscopy [77, 78]. We treated three cases with a thoracoscopic approach successfully ligating the duct in patients with a three-field esophagectomy, after five days of conservative treatment, without encountering many adhesions, possibly because of the continued "washing" of the chyle in the thoracic cavity.

One hour before the operation, a high fat liquid (such as butter or cream) is administered enterally to the patient in order to stimulate chylous production and facilitate the visualization of the leak during the operation.

The thoracic duct should be visualized and ligated just above the diaphragm. If the duct is

not visible, some surgeons suggest a "mass ligation" of the prevertebral tissues between the azygos and the aorta, in which the duct and its collateral should be located [72].

Lymphangiography with endovascular closure of the thoracic duct has been proposed as an alternative to surgery in different studies with variable success rates, but this method is complex and should be considered only as a second choice and in experienced centers [4, 79].

Concluding, surgery for EAC has a high morbidity and mortality because of patient general status and technical difficulties. Therefore, it requires experienced centers with dedicated staff that can optimize the perioperative patient conditions (nutritionist, physiatrist, physiotherapist, and psychologist) and adequately diagnose and treat the postoperative complications (anesthesiologist, surgeon, and radiologist).

References

1. Lerut T, Moons J, Coosemans W et al (2009) Postoperative complications after transthoracic esophagectomy for cancer of the esophagus and gastroesophageal junction are correlated with early cancer recurrence: role of systematic grading of complications using the modified clavien classification. Ann Surg 250:798–807. doi:10.1097/SLA.0b013e3181bdd5a8
2. Luc G, Durand M, Chiche L, Collet D (2014) Major post-operative complications predict long-term survival after esophagectomy in patients with adenocarcinoma of the esophagus. World J Surg 39:216–222. doi:10.1007/s00268-014-2754-1
3. Balkwill F, Mantovani A (2001) Inflammation and cancer: back to Virchow? Lancet 357:539–545. doi:10.1016/S0140-6736(00)04046-0
4. Low DE, Bodnar A (2013) Update on clinical impact, documentation, and management of complications associated with esophagectomy. Thorac Surg Clin 23:535–550. doi:10.1016/j.thorsurg.2013.07.003
5. Paul S, Altorki N (2014) Outcomes in the management of esophageal cancer. J Surg Oncol 110:599–610. doi:10.1002/jso.23759
6. Blencowe NS, Strong S, McNair AGK et al (2012) Reporting of short-term clinical outcomes after esophagectomy. Ann Surg 255:658–666. doi:10.1097/SLA.0b013e3182480a6a
7. Strasberg SM, Linehan DC, Hawkins WG (2009) The accordion severity grading system of surgical complications. Ann Surg 250:177–186. doi:10.1097/SLA.0b013e3181afde41
8. Dindo D, Demartines N, Clavien P-A (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213. doi:10.1097/01.sla.0000133083.54934.ae
9. Low DE, Alderson D, Cecconello I et al (2015) International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy. Ann Surg 00:1. doi:10.1097/SLA.0000000000001098
10. Sauvanet A, Mariette C, Thomas P et al (2005) Mortality and morbidity after resection for adenocarcinoma of the gastroesophageal junction: predictive factors. J Am Coll Surg 201:253–262. doi:10.1016/j.jamcollsurg.2005.02.002
11. Ott K, Bader FG, Lordick F et al (2009) Surgical factors influence the outcome after Ivor-Lewis esophagectomy with intrathoracic anastomosis for adenocarcinoma of the esophagogastric junction: a consecutive series of 240 patients at an experienced center. Ann Surg Oncol 16:1017–1025. doi:10.1245/s10434-009-0336-5
12. Bailey SH, Bull DA, Harpole DH et al (2003) Outcomes after esophagectomy: a ten-year prospective cohort. Ann Thorac Surg 75:217–222. doi:10.1016/S0003-4975(02)04368-0
13. Dhungel B, Diggs BS, Hunter JG et al (2010) Patient and peri-operative predictors of morbidity and mortality after esophagectomy: American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP), 2005–2008. J Gastrointest Surg 14:1492–1501. doi:10.1007/s11605-010-1328-2
14. Zingg U, Smithers BM, Gotley DC et al (2011) Factors associated with postoperative pulmonary morbidity after esophagectomy for cancer. Ann Surg Oncol 18:1460–1468. doi:10.1245/s10434-010-1474-5
15. Wright CD, Kucharczuk JC, O'Brien SM et al (2009) Predictors of major morbidity and mortality after esophagectomy for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk adjustment model. J Thorac Cardiovasc Surg 137:587–596. doi:10.1016/j.jtcvs.2008.11.042
16. Atkins BZ, Shah AS, Hutcheson KA et al (2004) Reducing hospital morbidity and mortality following esophagectomy. Ann Thorac Surg 78:1170–1176. doi:10.1016/j.athoracsur.2004.02.034
17. Markar SR, Karthikesalingam A, Thrumurthy S et al (2013) Systematic review and pooled analysis assessing the association between elderly age and outcome following surgical resection of esophageal malignancy. Dis Esophagus 26:250–262. doi:10.1111/j.1442-2050.2012.01353.x
18. Markar SR, Low DE (2013) Physiology, not chronology, dictates outcomes after esophagectomy for esophageal cancer: outcomes in patients 80 years and older. Ann Surg Oncol 20:1020–1026. doi:10.1245/s10434-012-2703-x
19. Morita M, Egashira A, Yoshida R et al (2008) Esophagectomy in patients 80 years of age and older with

carcinoma of the thoracic esophagus. J Gastroenterol 43:345–351. doi:10.1007/s00535-008-2171-z
20. Bartels H, Stein HJ, Siewert JR (1998) Preoperative risk analysis and postoperative mortality of oesophagectomy for resectable oesophageal cancer. Br J Surg 85:840–844. doi:10.1046/j.1365-2168.1998.00663.x
21. Gronnier C, Tréchot B, Duhamel A et al (2014) Impact of neoadjuvant chemoradiotherapy on postoperative outcomes after esophageal cancer resection. Ann Surg 260:764–771. doi:10.1097/SLA.0000000000000955
22. Van Hagen P, Hulshof MCCM, van Lanschot JJB et al (2012) Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 366:2074–2084. doi:10.1056/NEJMoa1112088
23. Schröder W, Bollschweiler E, Kossow C, Hölscher AH (2006) Preoperative risk analysis - a reliable predictor of postoperative outcome after transthoracic esophagectomy? Langenbecks Arch Surg 391:455–460. doi:10.1007/s00423-006-0067-z
24. Force S (2004) The "innocent bystander" complications following esophagectomy: atrial fibrillation, recurrent laryngeal nerve injury, chylothorax, and pulmonary complications. Semin Thorac Cardiovasc Surg 16:117–123. doi:10.1053/j.semtcvs.2004.03.009
25. Murthy SC, Law S, Whooley BP et al (2003) Atrial fibrillation after esophagectomy is a marker for postoperative morbidity and mortality. J Thorac Cardiovasc Surg 126:1162–1167. doi:10.1016/S0022-5223(03)00974-7
26. Mc Cormack O, Zaborowski A, King S et al (2014) New-onset atrial fibrillation post-surgery for esophageal and junctional cancer. Ann Surg 260:772–778. doi:10.1097/SLA.0000000000000960
27. De Decker K, Jorens PG, Van Schil P (2003) Cardiac complications after noncardiac thoracic surgery: an evidence-based current review. Ann Thorac Surg 75:1340–1348. doi:10.1016/S0003-4975(02)04824-5
28. Tisdale JE, Wroblewski HA, Wall DS et al (2010) A randomized, controlled study of amiodarone for prevention of atrial fibrillation after transthoracic esophagectomy. J Thorac Cardiovasc Surg 140:45–51. doi:10.1016/j.jtcvs.2010.01.026
29. Boshier PR, Marczin N, Hanna GB (2015) Pathophysiology of acute lung injury following esophagectomy. Dis Esophagus 28(8):797–804. doi: 10.1111/dote.12295. Review. PubMed PMID: 25327623
30. Tandon S, Batchelor A, Bullock R et al (2001) Perioperative risk factors for acute lung injury after elective oesophagectomy. Br J Anaesth 86:633–638
31. Cunha A (2014) Nosocomial and healthcare-associated pneumonia. Medscape. http://emedicine.medscape.com/article/234753-overview. December 2
32. American Thoracic, Society H (2005) Guidelines for the management of adults with hospital-acquired. Am J Respir Crit Care Med 171:388. doi:10.1164/rccm.200405-644ST
33. Atkins BZ, D'Amico TA (2006) Respiratory complications after esophagectomy. Thorac Surg Clin 16:35–48. doi:10.1016/j.thorsurg.2006.01.007
34. Wong J, Lam DP, Abrishami A et al (2012) Short-term preoperative smoking cessation and postoperative complications: a systematic review and meta-analysis. Can J Anaesth 59:268–279. doi:10.1007/s12630-011-9652-x
35. Jung KH, Kim SM, Choi MG et al (2014) Preoperative smoking cessation can reduce postoperative complications in gastric cancer surgery. Gastric Cancer. doi:10.1007/s10120-014-0415-6
36. Myers K, Hajek P, Hinds C, McRobbie H (2011) Stopping smoking shortly before surgery and postoperative complications: a systematic review and meta-analysis. Arch Intern Med 171:983–989. doi:10.1001/archinternmed.2011.97
37. Van Adrichem EJ, Meulenbroek RL, Plukker JTM et al (2014) Comparison of Two preoperative inspiratory muscle training programs to prevent pulmonary complications in patients undergoing esophagectomy: a randomized controlled pilot study. Ann Surg Oncol 21(7):2353–2360. doi:10.1245/s10434-014-3612-y
38. Inoue J, Ono R, Makiura D et al (2013) Prevention of postoperative pulmonary complications through intensive preoperative respiratory rehabilitation in patients with esophageal cancer. Dis Esophagus 26:68–74. doi:10.1111/j.1442-2050.2012.01336.x
39. Valkenet K, Trappenburg JC, Gosselink R et al (2014) Preoperative inspiratory muscle training to prevent postoperative pulmonary complications in patients undergoing esophageal resection (PREPARE study): study protocol for a randomized controlled trial. Trials 15:144. doi:10.1186/1745-6215-15-144
40. Madani K, Zhao R, Lim HJ et al (2010) Obesity is not associated with adverse outcome following surgical resection of oesophageal adenocarcinoma. Eur J Cardiothorac Surg 38:604–608. doi:10.1016/j.ejcts.2010.03.054
41. Healy LA, Ryan AM, Gopinath B et al (2007) Impact of obesity on outcomes in the management of localized adenocarcinoma of the esophagus and esophagogastric junction. J Thorac Cardiovasc Surg 134:1284–1291. doi:10.1016/j.jtcvs.2007.06.037
42. Kilic A, Schuchert MJ, Pennathur A et al (2009) Impact of obesity on perioperative outcomes of minimally invasive esophagectomy. Ann Thorac Surg 87:412–415. doi:10.1016/j.athoracsur.2008.10.072
43. Michelet P, D'Journo XB, Roch A et al (2006) Protective ventilation influences systemic inflammation after esophagectomy: a randomized controlled study. Anesthesiology 105:911–919. doi:10.1097/00000542-200611000-00011
44. Boshier PR, Anderson O, Hanna GB (2011) Transthoracic versus transhiatal esophagectomy for the treatment of esophagogastric cancer. Ann Surg 254:894–906. doi:10.1097/SLA.0b013e3182263781
45. Wei MT, Zhang YC, Deng XB et al (2014) Transthoracic vs transhiatal surgery for cancer of the esophagogastric junction: a meta-analysis. World J Gastroenterol 20:10183–10192. doi:10.3748/wjg.v20.i29.10183

46. Urschel JD (1995) Esophagogastrostomy anastomotic leaks complicating esophagectomy: a review. Am J Surg 169(6):634–640. Review. PubMed PMID: 7771633
47. Schuchert MJ, Abbas G, Nason KS et al (2010) Impact of anastomotic leak on outcomes after transhiatal esophagectomy. Surgery 148:831–840. doi:10.1016/j.surg.2010.07.034
48. Markar SR, Arya S, Karthikesalingam A, Hanna GB (2013) Technical factors that affect anastomotic integrity following esophagectomy: systematic review and meta-analysis. Ann Surg Oncol 20:4274–4281. doi:10.1245/s10434-013-3189-x
49. Laterza E, De' Manzoni G, Veraldi GF et al (1999) Manual compared with mechanical cervical oesophagogastric anastomosis: a randomised trial. Eur J Surg 165:1051–1054. doi:10.1080/110241599750007883
50. Markar SR, Karthikesalingam A, Vyas S et al (2011) Hand-sewn versus stapled oesophago-gastric anastomosis: systematic review and meta-analysis. J Gastrointest Surg 15:876–884. doi:10.1007/s11605-011-1426-9
51. Schaible A, Sauer P, Hartwig W et al (2014) Radiologic versus endoscopic evaluation of the conduit after esophageal resection: a prospective, blinded, intraindividually controlled diagnostic study. Surg Endosc 28:2078–2085. doi:10.1007/s00464-014-3435-8
52. Strauss C, Mal F, Perniceni T et al (2010) Computed tomography versus water-soluble contrast swallow in the detection of intrathoracic anastomotic leak complicating esophagogastrectomy (Ivor Lewis): a prospective study in 97 patients. Ann Surg 251:647–651. doi:10.1097/SLA.0b013e3181c1aeb8
53. Jones CM, Heah R, Clarke B, Griffiths EA (2015) Should routine radiological assessment of anastomotic integrity be performed after oesophagectomy with cervical anastomosis? Best evidence topic (BET). Int J Surg 15:90–94. doi:10.1016/j.ijsu.2015.01.034
54. Cools-Lartigue J, Andalib A, Abo-Alsaud A et al (2014) Routine contrast esophagram has minimal impact on the postoperative management of patients undergoing esophagectomy for esophageal cancer. Ann Surg Oncol 21:2573–2579. doi:10.1245/s10434-014-3654-1
55. Page RD, Asmat A, McShane J et al (2013) Routine endoscopy to detect anastomotic leakage after esophagectomy. Ann Thorac Surg 95:292–298. doi:10.1016/j.athoracsur.2012.09.048
56. Mönkemüller K, Peter S, Toshniwal J et al (2014) Multipurpose use of the "bear claw" (over-the-scope-clip system) to treat endoluminal gastrointestinal disorders. Dig Endosc 26:350–357. doi:10.1111/den.12145
57. Mennigen R, Colombo-Benkmann M, Senninger N, Laukoetter M (2013) Endoscopic closure of postoperative gastrointestinal leakages and fistulas with the Over-the-Scope Clip (OTSC). J Gastrointest Surg 17:1058–1065. doi:10.1007/s11605-013-2156-y
58. Girard E, Messager M, Sauvanet A et al (2014) Anastomotic leakage after gastrointestinal surgery: diagnosis and management. J Visc Surg 151:441–450. doi:10.1016/j.jviscsurg.2014.10.004
59. Schaheen L, Blackmon SH, Nason KS (2014) Optimal approach to the management of intrathoracic esophageal leak following esophagectomy: a systematic review. Am J Surg 208:536–543. doi:10.1016/j.amjsurg.2014.05.011
60. Dasari BVM, Neely D, Kennedy A et al (2014) The role of esophageal stents in the management of esophageal anastomotic leaks and benign esophageal perforations. Ann Surg 259:852–860. doi:10.1097/SLA.0000000000000564
61. Hoeppner J, Kulemann B, Seifert G et al (2014) Covered self-expanding stent treatment for anastomotic leakage: outcomes in esophagogastric and esophagojejunal anastomoses. Surg Endosc 28:1703–1711. doi:10.1007/s00464-013-3379-4
62. Van Boeckel PG, Sijbring A, Vleggaar FP, Siersema PD (2011) Systematic review: Temporary stent placement for benign rupture or anastomotic leak of the oesophagus. Aliment Pharmacol Ther 33:1292–1301. doi:10.1111/j.1365-2036.2011.04663.x
63. Bludau M, Hölscher AH, Herbold T et al (2014) Management of upper intestinal leaks using an endoscopic vacuum-assisted closure system (E-VAC). Surg Endosc 28:896–901. doi:10.1007/s00464-013-3244-5
64. Meyerson SL, Mehta CK (2014) Managing complications II: conduit failure and conduit airway fistulas. J Thorac Dis 6:364–371. doi:10.3978/j.issn.2072-1439.2014.03.32
65. Oezcelik A, Banki F, Ayazi S et al (2010) Detection of gastric conduit ischemia or anastomotic breakdown after cervical esophagogastrostomy: the use of computed tomography scan versus early endoscopy. Surg Endosc 24:1948–1951. doi:10.1007/s00464-010-0884-6
66. Safranek PM, Cubitt J, Booth MI, Dehn TCB (2010) Review of open and minimal access approaches to oesophagectomy for cancer. Br J Surg 97:1845–1853. doi:10.1002/bjs.7231
67. Veeramootoo D, Parameswaran R, Krishnadas R et al (2009) Classification and early recognition of gastric conduit failure after minimally invasive esophagectomy. Surg Endosc 23:2110–2116. doi:10.1007/s00464-008-0233-1
68. Berrisford RG, Veeramootoo D, Parameswaran R et al (2009) Laparoscopic ischaemic conditioning of the stomach may reduce gastric-conduit morbidity following total minimally invasive oesophagectomy. Eur J Cardiothoracic Surg 36:888–893. doi:10.1016/j.ejcts.2009.01.055
69. Palanivelu C, Prakash A, Senthilkumar R et al (2006) Minimally invasive esophagectomy: thoracoscopic mobilization of the esophagus and mediastinal lymphadenectomy in prone position-experience of 130 patients. J Am Coll Surg 203:7–16. doi:10.1016/j.jamcollsurg.2006.03.016
70. Lagarde SM, Omloo JMT, De Jong K et al (2005) Incidence and management of chyle leakage after

esophagectomy. Ann Thorac Surg 80:449–454. doi:10.1016/j.athoracsur.2005.02.076
71. Kranzfelder M, Gertler R, Hapfelmeier A et al (2013) Chylothorax after esophagectomy for cancer: impact of the surgical approach and neoadjuvant treatment: systematic review and institutional analysis. Surg Endosc 27:3530–3538. doi:10.1007/s00464-013-2991-7
72. Smati B, Sadok Boudaya M, Marghli A et al (2006) Management of postoperative chylothorax. Rev Mal Respir 23:152–156. doi:10.1016/j.jviscsurg.2011.09.006
73. Fujita T, Daiko H (2014) Efficacy and predictor of octreotide treatment for postoperative chylothorax after thoracic esophagectomy. World J Surg 38:2039–2045. doi:10.1007/s00268-014-2501-7
74. Dugue L, Sauvanet A, Farges O et al (1998) Output of chyle as an indicator of treatment for chylothorax complicating oesophagectomy. Br J Surg 85:1147–1149. doi:10.1046/j.1365-2168.1998.00819.x
75. Li W, Dan G, Jiang J et al (2013) A 2-wk conservative treatment regimen preceding thoracic duct ligation is effective and safe for treating post-esophagectomy chylothorax. J Surg Res 185:784–789. doi:10.1016/j.jss.2013.07.012
76. Wemyss-Holden SA, Launois B, Maddern GJ (2001) Management of thoracic duct injuries after oesophagectomy. Br J Surg 88:1442–1448. doi:10.1046/j.0007-1323.2001.01896.x
77. Mishra PK, Saluja SS, Ramaswamy D et al (2013) Thoracic duct injury following esophagectomy in carcinoma of the esophagus: ligation by the abdominal approach. World J Surg 37:141–146. doi:10.1007/s00268-012-1811-x
78. Schumacher G, Weidemann H, Langrehr JM et al (2007) Transabdominal ligation of the thoracic duct as treatment of choice for postoperative chylothorax after esophagectomy. Dis Esophagus 20:19–23. doi:10.1111/j.1442-2050.2007.00636.x
79. Marthaller KJ, Johnson SP, Pride RM et al (2015) Percutaneous embolization of thoracic duct injury post-esophagectomy should be considered initial treatment for chylothorax before proceeding with open re-exploration. Am J Surg 209:235–239. doi:10.1016/j.amjsurg.2014.05.031

19 Long-Term Results with Surgery Alone and Multimodal Treatments

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19.1 Introduction

Esophagogastric junction (EGJ) adenocarcinoma survival improved recently, thanks to the use of multimodal treatments. Survival with surgery alone is instead still poor in all locally advanced and node-positive patients. Recurrence is still the main cause of death, and it is particularly high within 24 months. In this chapter we will discuss the long-term results with surgery alone and multimodal treatments in EGJ cancer patients and then the characteristics and types of recurrence.

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19.2 Long Term with Surgery Alone

Survival with surgery alone is still poor in all locally advanced and node-positive patients of the three Siewert types. Siewert III shows the worst prognosis and Siewert I the best, with type II patients showing intermediate survival. In comparative studies survival ranges 35–40 % in Siewert I, 25–35 % in Siewert II, and 20–25 % in Siewert III [1, 2].

The need of radical resections is paramount, with R+ patients showing dismal prognosis, ranging from 0 to 13 % [1]. Mariette et al. [3] reported that non-curative resections (R1 or R2) are associated with high morbidity and mortality and have no therapeutic benefit compared with palliative treatments. Indeed, authors state that 5-year overall survival for patients with R0 resection ranges from 43 to 49 %, compared with 0–11 % for microscopically incomplete resections (R1) and 0–4 % for macroscopically incomplete resections (R2).

Provided that an R0 resection is obtained, nodal status is undoubtedly the main prognostic determinant; actually, in all studies, N+ patients have a disappointing 5-year survival, reaching less than 40 % at best, compared to an overall survival of at least 50 % in node-negative patients [4–8].

Survival depends also on depth of tumor invasion. Patients with T1m cancers show excellent

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survival after either surgery or endoscopic resections, reaching an 80–100 % 5-year survival [9, 10]**.** T1sm patients show decreased but still good survival (around 70 %) [6, 8], while survival decreases markedly for pT2, pT3, and pT4 patients (Table 19.1 [4–8]).

Survival difference is particularly marked in T1sm and T2 patients, where survival is good in case of pN0 after upfront surgery, but absolutely disappointing in pN+ patients [11], making the debate on the best approach of these patients really hot.

19.3 Long Term with Multimodal Treatments

Multimodal treatments have been introduced to improve survival in locally advanced patients, and actually improvements have been obtained, and this was demonstrated by the results of meta-analyses comparing multimodal approaches and surgery alone in the current literature. Although the treatment to choose and the best protocols are still matter of debate, many dedicated centers and the most important international guidelines now consider multimodal treatments as the standard of care for locally advanced patients.

In the University of Verona, induction chemoradiation (CRT) followed by surgery is the standard treatment for locally advanced and N+ Siewert I and II patients, while induction or perioperative chemotherapy (CT) with a triplet of drugs followed by surgery is our preferred approach to Siewert type III. Due to the difficulty to complete the postoperative chemotherapy cycles, we believe that induction CT better fits Siewert III patients.

Our CRT protocol consists of 5-fluorouracil (5-FU) administered by protracted intravenous infusion (PVI) with weekly administration of i.v. cisplatin and docetaxel [12]. The first part of the treatment consists of induction chemotherapy alone followed by 50 Gy of concurrent chemoradiotherapy. Surgery is planned after 6–8 weeks after completion of the treatment.

Pathological modifications on primary cancer in esophageal and gastric walls and on lymph nodes caused by preoperative CT and CRT make restaging difficult. If the problem

Table 19.1 5-year overall survival with surgery alone

	Mariette et al. [4]	Talsma et al. [5]	Gertler et al. [6]	de Manzoni et al. [7]	Barbour et al. [8]
pT1	74 %	69 %	pT1a 83 %	55 %	pT1a 97 %
			pT1b 69 %		pT1b 65 %
pT2	37 %	51 %	37 %	20 %	–
pT3	50 %	23 %	19 %	20 %	–
pT4	–	–	pT4a 10 %	0 %	–
			pT4b 0 %		–
pN0	68 %	66 %	63 %	50 %	82 %
pN1	–	28 %	33 %	25 %	38 %
pN2	–	17 %	20 %	0 %	–
pN3	–	3 %	8 %	0 %	–
pN+	27 %	–	–	–	–
Stage I a	–	88 %	78 %	–	–
Stage I b	–	73 %	53 %	–	–
Stage II a	–	55 %	42 %	–	–
Stage II b	–	40 %	52 %	–	–
Stage III a	–	24 %	25 %	–	–
Stage III b	–	12 %	20 %	–	–
Stage III c	–	3 %	11 %	–	–
Stage IV	–	0	6 %	–	–

with clinical restaging is considerable, the main issue is pathological staging. After upfront surgery pathology represents the exact reality and TNM classification perfectly fits, and this is particularly true with 7th edition for Siewert types I and II, although significant debate exists for Siewert III. Anyway, if TNM correctly discriminates patients' survival according to stage after upfront surgery, it is not as much appropriate after induction treatments. Indeed, many centers tried to overcome the problem proposing different classifications of pathological response that more correctly describe survival after induction treatments. For a complete dissertation on the topic, please see Chap. 11. Briefly, patients with significant response to treatment show increased survival compared with patients without cancer modifications. Patients with partial response show instead an intermediate prognosis. The best possible response to treatment is the complete disappearance of cancer both on primary site and at nodal level. These patients are named pathological complete responders (pCR) and correspond to ypT0N0. We previously created a classification of response to treatment, named size-based pathological response (SPR) classification, where pCR corresponded to SPR1 and showed the best prognosis with an 85 % 3-year disease-related survival [13] (Fig. 19.1).

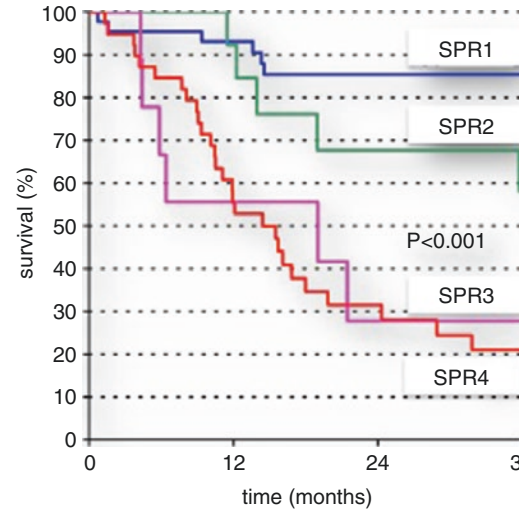

Fig. 19.1 Three-year disease-related survival curves for patients staged with SPR (size-based pathological response) classification of response ($p<0.001$) (Reproduced with permission from Verlato et al. [13])

Nonresponders (SPR3) were those patients without tumor regression on T but N0. Their survival was low and comparable to that of patients with nodal metastases (SPR4), which had the worst prognosis. Partial responders had intermediate survival. In our classification, we defined minimal residual disease (MRD) as the presence of residual tumor ≤10 mm at the primary site and no nodal metastases (SPR2). These SPR2 patients had almost 60 % 3-year disease-related survival, and so we think that this class of patients deserves consideration and deep inspection.

We believe this classification correctly addresses two key issues: first, it considers nodal involvement together with tumor regression on primary site; second, it defines pCR as only those patients without any residual cancer. Although, in her initial experience, Mandard et al. [14] considered only response on T, jeopardizing the accuracy of this classification, other authors [15–19] correctly considered both T and N status. Nevertheless, some of these authors [16, 17, 19] coupled pCR with patients with up to 10 % of residual cancer. If a certain degree of stage migration might happen when defining pCR, possibly accidentally including patients with minimal residual cancer into pCR class, and probably survival differences are difficult to detect when residual cancer is marginal, we strongly believe that considering patients without residual cancer together with patients with the presence of cancer cells is deeply incorrect from a theoretical point of view.

Bearing in mind that there is no consensus in the definition of response and often also squamous cell carcinoma is included in some studies, we tried to summarize some trials about response in Table 19.2 [13, 15–18, 20]. To make Table 19.2 more comprehensible and to harmonize the data, results are expressed in terms of response: complete, partial, or no response. Tumor regression and nodal involvement are differently defined in the literature; hence data are difficult to compare. This table aims at stressing that, although differ-

Table 19.2 5-year survival after induction treatment and surgery according to pathologic response

	Verlato et al.[a] [13]	Holscher et al. [17]	Meredith et al. [18]	Swischer et al.[a] [15]	Schneider et al. [16]	Reim et al. [20]
pCR	85 %	64 %[b]	52 %	69 %	92 %[b]	79 %[b]
pPR	58 %	42 %	36 %	45 %	65 %	–
pNR	28 %	18 %	22 %	18 %	20 %	45 %

pCR: pathological complete response; *pPR:* pathological partial response; *pNR:* pathological non-response
[a]:3-year survival

[b]:pCR and nearly complete response with less than 10 % vital residual tumor cells

ently expressed, response to treatment plays a relevant prognostic role.

Nonresponders demonstrated the worst prognosis, while in all reported studies, partial response, although differently defined, showed to have an intermediate prognosis between that of complete responders and nonresponders.

Since multimodal treatments are now standard of care for locally advanced cases, the need of definition of response to treatment has become vital.

Nodal status is a main prognostic determinant even after induction treatments and N+ patients show the worst prognosis. Nevertheless, we think that being N0 since the beginning or becoming N0 after downstaging is not equivalent.

In an ongoing trial of our group, presented as an abstract at 14th ISDE Congress held in Vancouver in 2014, we hypothesized that natural ypN0 patients (N0 since the beginning) had better prognosis than ypN0 after nodal downstaging. We demonstrated that survival was indeed significantly better for natural ypN0 compared with downstaged ypN0 and that the latter had better survival than ypN+ patients. This is in line with other reports in the literature for esophageal cancer [21, 22].

The best theoretical classification of pathological response to induction treatments would then consider nodal status along with response on primary site and should in particular discriminate between patients without nodal involvement since the beginning and patients with tumor regression on lymph nodes. Further studies are needed in order to create a better and more suitable classification of response.

19.4 Recurrence

Recurrence may appear either with clinical symptoms or during follow-up in asymptomatic patients. Diagnosis is made with imaging and/or gastroscopy. CT scans of chest and abdomen are able to detect most recurrences. In case of peculiar symptoms leading to suspect brain injury, a cerebral CT scan is mandatory to rule out metastases. Ultrasound is the best tool to detect suspected nodes in the neck area. In case of diagnostic doubt, second-line imaging, such as PET-CT, might be considered, but no data are available in the literature about the standard use of PET-CT to confirm relapse in esophagogastric junction cancer.

Follow-up timing is debated; nevertheless, since its value is the early detection of recurrence, when treatment is still possible, it should be acceptably frequent. Most recurrences manifest within 2–3 years after surgery. Hence, in the first two years, frequent follow-up controls are suggested. According to Abate et al. [23], >90 % of recurrences occur by 3 years after surgery alone and by 2 years following neoadjuvant therapy.

Since late recurrences are anyway present within 5 years, we recommend follow-up controls every 6 months for the first 5 years.

A recent Japanese trial [24] compared pattern of recurrence of 127 patients with EGJ carcinoma treated with surgery alone. All patients reached an R0 resection and none received neoadjuvant nor adjuvant treatments. All Siewert types were represented, although only 5 % were Siewert type I, consistently with all Eastern literature. Recurrence was reported in 44 % of the patients and most recurred within 24 months. There was no difference in

recurrence rate among Siewert types, yet pattern of recurrence differed: lymphatic recurrence was most common in type I, hematogenous in type II, and peritoneal in type III. Siewert II patients, who represented the great majority of this study population, had mainly hematogenous and lymphatic recurrences and, in this trial, resembled more a type I than a type III, more similarly to what was experienced in many European realities like ours. Indeed, mediastinal recurrences were as frequent as in type I, and thus authors claimed that, because of the pattern of recurrence, Siewert type II should be treated with subtotal esophagectomy and mediastinal lymphadenectomy like Siewert I. Moreover, para-aortic recurrences were the most common sites of lymphatic recurrence in Siewert types II and III, and authors hypothesized that there might be a direct lymphatic flow from left paracardial nodes (station 2) to para-aortic nodes (station 16) and this would be more important in EGJ cancer than in gastric cancer. Hence, although para-aortic prophylactic lymphadenectomy was denied by Sasako et al. for gastric cancer [25], these authors suggest to reconsider it for EGJ adenocarcinoma.

Previously, we published a trial on pattern of recurrence after surgery alone in EGJ adenocarcinoma [26]. In our study, Siewert I patients represented 24 % of the cases, much more frequent than what was reported in Eastern experiences. Recurrence occurred in 60 % of the patients and 80 % of those recurrences developed within 24 months. Time to recurrence did not differ among Siewert types. Hematogenous recurrences were the most frequent, representing more than 50 % of the cases, but locoregional recurrences were pretty frequent as well, since they developed in 30 % of the patients. Peritoneal recurrence was most common for Siewert III, and no Siewert I patients showed peritoneal diffusion. Liver and lung represented the most common sites of hematogenous recurrence, accounting for more than 80 % of the cases, followed by bone and distant nodes. Our results, although differences between West and East must be acknowledged, are in line with the abovementioned Japanese trial.

Similar results were also reported by an English study on Siewert types I and II [27]. Peritoneal recurrences were twofold more common in type II, and the most common sites of recurrence were liver and bone, followed by brain, lung, skin, and adrenal glands.

An interesting Dutch trial [28] focused on early adenocarcinoma. Authors reported a 15 % recurrence rate with a mean time to recurrence of 16 months, with liver, lung, and bone as the main involved sites. It is noteworthy that when patients were subdivided according to mucosal and submucosal invasion, recurrence was 4 % in T1m and never in case of m1 (i.e., only involvement of the epithelium), and it was 24 % for T1sm with only one patient with sm1 (i.e., involvement of the first 500 μm of esophageal wall) showing recurrence.

Recurrence in surgery alone gives information not only about cancer biology and behavior but also about the ability of surgery to control and treat the disease. If distant recurrence is probably not dependent on the ability of surgeon or surgical technique, it is undoubtedly more probable that surgery influences the risk of locoregional relapse. When we consider induction treatments, the modifications induced by the treatment itself should somehow modify the pattern of recurrence. Theoretically both distant and locoregional ones should be reduced, for the sterilization of circulating tumor cells caused by chemotherapy and the effect of radiation on locoregional target.

Pattern of recurrence of patients included in the two arms of the randomized CROSS trial has been recently published [29]. In chemoradiation group, also patients previously involved in the preliminary phase II trial with CROSS protocol were included. The final analysis compared 213 vs 161 patients, mainly adenocarcinoma. Recurrence was more common after surgery alone: 57 % compared with 35 % after chemoradiation and surgery. All types of recurrence were less frequent after CRT, also peritoneal ones, but the main difference was noted in locoregional relapse, which was 20 % after surgery alone and 7 % after CRT ($p < .001$). Moreover, recurrence was only 5 % within radiation field, confirming the hypothesis that CRT reduces locoregional recurrences.

Seventeen percent of pathological complete responders in this trial developed recurrence, but only one had locoregional recurrence. This is in line with what was previously reported by our group in a phase II trial on induction CRT in both squamous cell carcinoma and adenocarcinoma [30]**.** We reported a 17 % recurrence rate for pCR in the entire population, but a lower 11 % when considering only adenocarcinoma, and recurrence was always systemic.

Meguid et al. [31] compared pattern of recurrence after neoadjuvant chemoradiation and surgery for esophageal cancer. They found that pCR had 22 % recurrence vs 35 % of patients with partial or no response (p = .055). There was no difference in pattern of recurrence according to response to treatment, and most patients had distant recurrences regardless of pathological response. Median time to recurrence was longer for pCR.

Again, Shiozaki et al.[32] reported a 40 % recurrence rate after CRT and surgery, which was mainly systemic. Most recurrences developed within 2 years and almost all within 3 years. The most involved sites were lung, distant nodes, liver, peritoneum, bone, and brain.

To summarize, recurrence is still the main cause of death after treatment for EGJ cancer and hence remains the greatest concern when dealing with this neoplasm. Distant metastases are the most common type of recurrence both after surgery and multimodal treatments; however multimodal treatments seem to sterilize both hematogenous and peritoneal circulating cells, reducing the risk of developing recurrence. Radiation has a significant role in reducing locoregional relapse; of course it should be coupled with radical surgical resection, with clear margins and correct lymphadenectomy.

All studies report a 35 % recurrence rate at best, and most are detected within 2 or 3 years after surgery. This pushes the need of strict follow-up in these very first years; however, follow-up should be continued at least for 5 years, since some patients might recur later and early recognition of relapse is of utmost importance to try curative treatments.

In conclusion, studying pattern of recurrence is mandatory to discover how to treat EGJ cancer, and every effort should be made to improve both local and systemic control of disease. Multimodal treatments seem to provide advantages on both these issues and should be implemented and offered to all fit patients.

References

1. Siewert RJ, Feith M, Werner M et al (2000) Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. Ann Surg 232(3):353–61
2. Reynolds JV, Ravi N, Muldoon C et al (2010) Differential pathologic variables and outcomes across the spectrum of adenocarcinoma of the esophagogastric junction. World J Surg 34(12):2821–9
3. Mariette C, Piessen G, Briez N et al (2011) Oesophagogastric junction adenocarcinoma: which therapeutic approach? Lancet Oncol 12(3):296–305
4. Mariette C, Piessen G, Balon JM et al (2004) Surgery alone in the curative treatment of localised oesophageal carcinoma. Eur J Surg Oncol 30(8):869–76
5. Talsma K, Hagen P, Grotenhuis B et al (2012) Comparison of the 6th and 7th editions of the UICC-AJCC TNM classification for esophageal cancer. Ann Surg Oncol 19(7):2142–8
6. Gertler R, Stein HJ, Langer R et al (2011) Long-term outcome of 2920 patients with cancers of the esophagus and esophagogastric junction: evaluation of the New Union Internationale Contre le Cancer/American Joint Cancer Committee staging system. Ann Surg 253(4):689–98
7. De Manzoni G, Pedrazzani C, Pasini F et al (2002) Results of surgical treatment of adenocarcinoma of the gastric cardia. Ann Thorac Surg 73(4):1035–40
8. Barbour AP, Jones M, Brown I et al (2010) Risk stratification for early esophageal adenocarcinoma: analysis of lymphatic spread and prognostic factors. Ann Surg Oncol 17(9):2494–502
9. Prasad GA, Wu TT, Wigle DA et al (2009) Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Barrett's esophagus. Gastroenterology 137(3):815–23
10. Zehetner J, Demeester SR, Hagen J et al (2011) Endoscopic resection and ablation versus esophagectomy for high-grade dysplasia and intramucosal adenocarcinoma. J Thorac Cardiovasc Surg 141(1):39–47
11. Crabtree TD, Yacoub WN, Puri V et al (2011) Endoscopic ultrasound for early stage esophageal adenocarcinoma: implications for staging and survival. Ann Thorac Surg 91(5):1509–16
12. Pasini F, de Manzoni G, Pedrazzani C et al (2005) High pathological response rate in locally advanced esophageal cancer after neoadjuvant combined modality therapy: dose finding of a weekly chemotherapy schedule with protracted venous infusion of 5-fluorouracil and dose escalation of cisplatin, docetaxel. Ann Oncol 16(7):1133–9

13. Verlato G, Zanoni A, Tomezzoli A et al (2010) Response to induction therapy in oesophageal and cardia carcinoma using Mandard tumour regression grade or size of residual foci. Br J Surg 97(5):719–25
14. Mandard AM, Dalibard F, Mandard JC et al (1994) Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer 73(11):2680–6
15. Swisher SG, Hofstetter W, Wu TT et al (2005) Proposed revision of the esophageal cancer staging system to accommodate pathologic response (pP) following preoperative chemoradiation (CRT). Ann Surg 241(5):810–7
16. Schneider PM, Baldus SE, Metzger R et al (2005) Histomorphologic tumor regression and lymph node metastases determine prognosis following neoadjuvant radiochemotherapy for esophageal cancer: implications for response classification. Ann Surg 242(5):684–92
17. Hölscher AH, Drebber U, Schmidt H et al (2014) Prognostic classification of histopathologic response to neoadjuvant therapy in esophageal adenocarcinoma. Ann Surg 260(5):779–85
18. Meredith KL, Weber JM, Turaga KK et al (2010) Pathologic response after neoadjuvant therapy is the major determinant of survival in patients with esophageal cancer. Ann Surg Oncol 17(4):1159–67
19. Becker K, Langer R, Reim D et al (2011) Significance of histopathological tumor regression after neoadjuvant chemotherapy in gastric adenocarcinomas: a summary of 480 cases. Ann Surg 253(5):934–9
20. Reim D, Gertler R, Novotny A et al (2012) Adenocarcinomas of the esophagogastric junction are more likely to respond to preoperative chemotherapy than distal gastric cancer. Ann Surg Oncol 19(7):2108–18
21. Leers JM, DeMeester SR, Chan N et al (2009) Clinical characteristics, biologic behavior, and survival after esophagectomy are similar for adenocarcinoma of the gastroesophageal junction and the distal esophagus. J Thorac Cardiovasc Surg 138(3):594–602
22. Rice TW, Blackstone EH, Adelstein DJ et al (2001) N1 esophageal carcinoma: the importance of staging and downstaging. J Thorac Cardiovasc Surg 121(3):454–64
23. Abate E, DeMeester SR, Zehetner J et al (2010) Recurrence after esophagectomy for adenocarcinoma: defining optimal follow-up intervals and testing. J Am Coll Surg 210(4):428–35
24. Hosokawa Y, Kinoshita T, Konishi M et al (2014) Recurrence patterns of esophagogastric junction adenocarcinoma according to siewert's classification after radical resection. Anticancer Res 34(8):4391–7
25. Sasako M, Sano T, Yamamoto S et al (2008) D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med 359(5):453–62
26. de Manzoni G, Pedrazzani C, Pasini F et al (2003) Pattern of recurrence after surgery in adenocarcinoma of the gastro-oesophageal junction. Eur J Surg Oncol 29(6):506–10
27. Wayman J, Bennett MK, Raimes S et al (2002) The pattern of recurrence of adenocarcinoma of the oesophago-gastric junction. Br J Cancer 86(8):1223–9
28. Westerterp M, Koppert LB, Buskens CJ et al (2005) Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch 446(5):497–504
29. Oppedijk V, Van Der Gaast A, Van Lanschot JJB et al (2014) Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol 32(5):385–91
30. Zanoni A, Verlato G, Giacopuzzi S et al (2013) Neoadjuvant concurrent chemoradiotherapy for locally advanced esophageal cancer in a single high-volume center. Ann Surg Oncol 20(6):1993–9
31. Meguid R, Hooker CM, Taylor JT et al (2009) Recurrence after neoadjuvant chemoradiation and surgery for esophageal cancer: does the pattern of recurrence differ for patients with complete response and those with partial or no response? J Thorac Cardiovasc Surg 138(6):1309–17
32. Shiozaki H, Sudo K, Xiao L et al (2014) Distribution and timing of distant metastasis after local therapy in a large cohort of patients with esophageal and esophagogastric junction cancer. Oncology 86(5–6):336–9

20 Open or Minimally Invasive? Comparison of Early and Late Results

William B. Robb and Christophe Mariette

20.1 Introduction

Esophageal cancer's global incidence continues to increase rapidly. In Western society this is reflected by an increasing incidence of esophageal adenocarcinomas, with the epidemiological shift felt to be related to increased obesity, gastroesophageal reflux disease, and Barrett's esophagus – the dominant risk factors for the development of this tumor. Surgical resection with radical lymphadenectomy, usually after the administration of neoadjuvant chemotherapy or chemoradiotherapy, remains the key component in the multimodality treatment of esophageal cancer. Esophagectomy is a complex surgical procedure for which the mortality rates have historically been significant [1]. In modern practice, in high-volume centers with appropriate multidisciplinary teams, the mortality rate after esophageal resection has been reduced significantly [2]. Despite this, it remains an operation associated with substantial rates of morbidity. During the previous three decades, minimally invasive surgery has been championed as providing a means of reducing postoperative morbidity for a variety of oncological gastrointestinal resections. With regard to esophageal resection, it has been hoped that the application of minimally invasive surgery may similarly reduce postoperative morbidity and mortality. By the early 1990s, some surgeons had developed and used protocols for thoracoscopic esophagectomy, initially restricting its use to T1 and T2 esophageal cancer without neoadjuvant chemoradiation [3, 4]. With time indications for minimally invasive esophageal resection have been expanded to include more advanced disease, irrespective of whether patients have received neoadjuvant treatments.

The techniques which have been described as minimally invasive approaches to esophageal resection vary widely. Many authors have described completely minimally invasive approaches, while others describe hybrid procedures where one stage of the operation is performed either by thoracoscopy or laparoscopy and the other by conventional open surgery. Unlike other minimally invasive procedures, minimally invasive esophagectomy (MIE) has

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not been broadly adopted. No matter what approach is used, MIE remains a very complex operation with many questions remaining unanswered as to the real advantages of applying a minimally invasive technique for resection of a disease which is often advanced at the time of surgery. Mortality, morbidity, oncological radicality, reproducibility of a minimally invasive approach, and the cost of the procedure are some of the topics under debate. Recent reviews [5–7] focusing on the role of MIE have emphasized that the benefits of this approach are controversial. Many comparative nonrandomized and retrospective studies have been conducted between MIE and open esophagectomy, but uncertainty remains about the advantages of any one technique compared to another. In the absence of meta-analyses of randomized controlled studies, this chapter appraises the available literature with regard to the short-term perioperative outcomes and longer-term oncological outcomes for patients undergoing minimally invasive resection for esophageal cancer.

20.2 MIE Techniques

As there has never been a consensus regarding the superiority of any of the various open esophagectomy techniques, it is unsurprising that there is no agreement on what constitutes the best minimally invasive approach.

Completely minimally invasive approaches to esophageal resection attempt to replicate established open procedures. A minimally invasive transhiatal technique utilizes laparoscopic abdominal dissection and preparation of the gastric conduit followed by a cervical anastomosis created via a traditional open approach in the neck. Mediastinal dissection of periesophageal lymph nodes, including those in the subcarinal station, can be assessed through the hiatus using the lighting and magnification afforded by the laparoscopic camera. The esophageal specimen can be removed through the neck incision. Some surgeons prefer to combine the laparoscopic transhiatal approach with a minilaparotomy to facilitate gastric tube creation as well as to remove the specimen. Finally, the esophagus can also be removed from the mediastinum via an inversion technique with or without division of the vagus nerve. As with open surgery, many surgeons prefer a thoracoscopic approach, typically performed through the right chest, with patients positioned in lateral decubitus or prone positions [8, 9]. Thoracoscopy can be used as a part of a three-stage MIE, where the procedure begins in the chest and ends with laparoscopy and a cervical anastomosis, or as part of the two-stage Ivor-Lewis esophagectomy where the esophagogastric anastomosis resides in the chest. In this procedure the specimen is removed through a mini-thoracotomy, and the anastomosis is created at the apex of the chest.

Combinations of open and minimally invasive techniques (hybrid techniques) are perhaps more widely utilized, such as laparoscopy with thoracotomy or thoracoscopy with laparotomy. These hybrid techniques are applied for a variety of reasons and may be necessitated by oncological considerations, prior surgery in either cavity, surgeon experience, and surgeon preference.

Although the goal of MIE is to perform an equivalent operation to the open procedure without omitting any critical steps, some aspects considered as routine for open esophagectomy have fallen out of favor with many surgeons, such as performance of a pyloroplasty and jejunostomy placement.

20.3 Early Results (Tables 20.1 and 20.2)

The primary goal of MIE is to decrease surgical morbidity associated with the open approach. In the setting of a randomized controlled trial, only a single direct comparison of open and minimally invasive approaches has been published [31] with the final results of the French MIRO (oesophagectoMIe pour cancer paR voie conventionnelle ou coeliO-assistée) trial awaited [32]. At present, the majority of data derives from retrospective nonrandomized series and suggests that mortality rates appear equivalent with some suggestion of benefit in terms of overall morbidity favoring a

Table 20.1 Mortality and overall morbidity of minimally invasive and open esophagectomy

Authors (year)	*n*	Approaches	Mortality *n* (%)	Overall morbidity *n* (%)
Law et al. (1997) [10]	22	MIE (TSO)	0	18 (81.8)
	63	Open	0	63 (100)
Nguyen et al. (2000) [11]	18	MIE (TLSO)	0	7 (38.9)
	36	Open	0	19 (52.8)
Osugi et al. (2003) [12]	77	MIE (VATS)	0	31 (40.3)
	72	Open	0	32 (44.4)
Kunisaki et al. (2004) [13]	15	MIE (VATS + HALS)	0	NS
	30	Open	0	NS
Van den Broek et al. (2004) [14]	25	MIE (THO)	0	14 (70)
	20	Open	0	18 (72)
Bresadola et al. (2006) [15]	14	MIE (THO and TLSO)	0	8 (57.1)
	14	Open	0	6 (42.9)
Bernabe et al. (2005) [16]	17	MIE (THO)	0	NS
	14	Open	0	NS
Shiraishi et al. (2006) [17]	116	MIE (TLSO)	3 (2.6)	NS
	37	Open	3 (8.1)	NS
Braghetto et al. (2006) [18]	47	MIE (VATS/LSO)	3 (6.3)	18 (38.2)
	119	Open	13 (10.9)	72 (60.5)
Smithers et al. (2007) [19]	332	MIE (TLSO)	7 (2.1)	207 (62.3)
	114	Open	3 (2.6)	76 (66.7)
Fabian et al. (2008) [9]	22	MIE (TLSE)	1 (4.5)	15 (68.2)
	43	Open	4 (9.8)	31 (72.1)
Zingg et al. (2009) [20]	56	MIE (TLSO)	2 (3.6)	19 (34.5)
	98	Open	6 (6.1)	20 (23.5)
Perry et al. (2009) [21]	21	MIE (LIO)	0	13 (62)
	21	Open	1 (5)	17 (81)
Parameswaran et al. (2009) [22]	50	MIE (TLSO)	1 (2)	24 (48)
	30	Open	1 (3)	15 (50)
Pham et al. (2010) [23]	44	MIE (TLSO)	3 (6.8)	NS
	46	Open	2 (4.3)	NS
Schoppman et al. (2010) [24]	31	MIE (TLSO)	0	11 (35.5)
	31	Open	0	23 (74.2)
Singh et al. (2010) [25]	33	MIE (TLSO)	Values NS	Values NS
	31	Open	$p = 0.34$	$P = 0.06$
Mamidanna et al. (2012) [26]	1155	MIE (TLSO,HMIO)	46 (4.0)	NS
	6347	Open	274 (4.3)	NS
Ben-David et al. (2012) [27]	100	MIE (TLSO)	1 (1)	NS
	32	Open	2 (5)	NS
Briez et al. (2012) [28]	140	MIE (HMIO)	2.1	35.7
	140	Open	12.9	59.3
Xie et al. (2014) [29]	106	MIE (TLSO)	2 (1.9)	28 (26.4)
	163	Open	4 (2.5)	56 (34.4)
Hsu et al. (2014) [30]	66	MIE (TLSO)	5 (7.6)	NS
	63	Open	5 (7.9)	NS

MIE minimally invasive esophagectomy, *VATS* video-assisted thoracoscopic surgery esophagectomy, *HMIO* hybrid MIO, *HALS* hand-assisted laparoscopic oesophagectomy, *TSE* thoracoscopic-assisted esophagectomy, *TLSE* thoraco-laparoscopic surgery esophagectomy, *LIE* laparoscopic inversion esophagectomy, *LSE* laparoscopic esophagectomy, *NS* not stated

Table 20.2 Comparison of rates of morbidities for MIE and open esophagectomy

Authors (year)	*n*	Approaches	Pneumonia *n* (%)	Cardiac arrhythmia *n* (%)	Anastomotic leak *n* (%)	Gastric conduit ischemia n (%)	Chylothorax *n* (%)	Length of stay (days)	Operative blood loss (mls)	Operative time (minutes)
Law et al. (1997) [10]	22	MIE (TSO)	3 (13.6)	3 (13.6)	0	NS	NS	NS	450 (200–800)	240 (160–350)
	63	Open	11 (17.5)	14 (22.2)	2 (3.2)	NS	NS	NS	700 (300–2500)	250 (190–420)
Nguyen et al. (2000) [11]	18	MIE (TLSO)	2 (11.1)	NS	2 (11.1)	0	0	11.3 ± 14.2	297 ± 233	364 ± 73
	36	Open	6 (16.7)	NS	4 (11.1)	1 (2.8)	1 (2.8)	22.8 ± 18.0	1108 ± 790	411 ± 93
Osugi et al. (2003) [12]	77	MIE (VATS)	12 (15.6)	1 (1.3)	1 (1.3)	0	3 (3.9)	NS	284 (330)	227 (90)
	72	Open	14 (19.4)	3 (4.2)	2 (2.8)	0	0	NS	310 (170)	186 (35)
Kunisaki et al. (2004) [13]	15	MIE (VATS + HALS)	0	NS	2 (13.3)	NS	NS	29.6 ± 12.9	447.9 (±214.8)	544.4 (±64.5)
	30	Open	1 (3.3)	NS	1 (3.3)	NS	NS	32.7 ± 14.0	674.7 (±445.6)	487.8 (±97.8)
Van den Broek et al. (2004) [14]	25	MIE (THO)	2 (8)	NS	2 (8)	0	2 (8)	16	NS	NS
	20	Open	2 (10)	NS	3 (15)	0	0	16	NS	NS
Bresadola et al. (2006) [15]	14	MIE (THO and TLSO)	1 (7.1)	NS	1 (7.1)	NS	0	16.4 (±8.4)	NS	469.0 (±42.6)
	14	Open	2 (14.2)	NS	2 (14.2)	NS	0	22.3 (±10.6)	NS	370.8 (±16.7)
Bernabe et al. (2005) [16]	17	MIE (THO)	NS	NS	NS	NS	NS	9.1 (±3.2)	331 (±220)	336 (±53)
	14	Open	NS	NS	NS	NS	NS	11.6 (±2.9)	542 (±212)	388 (±102)
Shiraishi et al. (2006) [17]	116	MIE (TLSO)	25 (21.6)	3 (2.6)	13 (11.2)	NS	NS	NS	670.2 (±561.1)	426.0 (±87.1)
	37	Open	12 (32.4)	4 (10.8)	9 (24.3)	NS	NS	NS	487.4 (±110.5)	487.4 (±110.5)
Braghetto et al. (2006) [18]	47	MIE (VATS/LSO)	7 (14.8)	NS	3 (6.4)	0	1 (2.1)	NS	NS	NS
	119	Open	22 (18.5)	NS	17 (14.3)	1 (0.8)	0	NS	NS	NS

Smithers et al. (2007) [19]	332	MIE (TLSO)	87 (26.2)	55 (16.6)	18 (5.4)	5 (1.5)	17 (5.1)	11 (7–49)	300 (15–1000)	330 (270–540)
	114	Open	35 (27.8)	21 (18.4)	10 (8.7)	2 (1.7)	7 (6.1)	14 (8–44)	600 (0–3000)	300 (150–480)
Fabian et al. (2008) [9]	22	MIE (TLSE)	1 (4.5)	4 (18.2)	3 (13.6)	1 (4.5)	0	9.5	178 (±96)	333 (±72)
	43	Open	10 (23.3)	8 (18.6)	3 (7.0)	0	2 (4.7)	11	356 (±136)	270 (±87)
Zingg et al. (2009) [20]	56	MIE (TLSO)	17 (30.9)	NS	NS	NS	NS	19.7 (±2.0)	320 (±49)	250 (±7.2)
	98	Open	33 (38.8)	NS	NS	NS	NS	21.9 (±2.0)	857 (±82)	209 (±7.8)
Perry et al. (2009) [21]	21	MIE (LIO)	1 (5)	4 (19)	4 (19)	NS	NS	10 (8–14)	168 (149)	399 (86)
	21	Open	2 (10)	7 (33)	6 (29)	NS	NS	14 (10–19)	526 (289)	408 (127)
Parameswaran et al. (2009) [22]	50	MIE (TLSO)	4 (8)	NS	4 (8)	5 (16)	3 (6)	12 (8–86)	NS	442 (305–580)
	30	Open	2 (7)	NS	1 (3)	2 (10)	1 (3)	10 (6–56)	NS	266 (219–390)
Pham et al. (2010) [23]	44	MIE (TLSO)	11 (25)	NS	4 (9)	1 (2)	NS	15 (12–20)	407 (±267)	543 (72.6)
	46	Open	7 (15)	NS	5 (11)	1 (2)	NS	14 (11–23)	780 (±610)	437 (97.0)
Schoppman et al. (2010) [24]	31	MIE (TLSO)	2 (6.2)	NS	1 (3.2)	0	2 (6.4)	NS	NS	411 (270–600)
	31	Open	11 (35.5)	NS	8 (25.8)	1 (3.2)	1 (3.2)	NS	NS	400 (240–550)
Singh et al. (2010) [25]	33	MIE (TLSO)	NS	NS	NS	NS	NS	No difference ($p=0.17$)	Reduced after MIE ($p<.01$)	Longer for MIE ($p<0.01$)
	31	Open	NS	NS	NS	NS	NS			
Mamidanna et al. (2012) [26]	1155	MIE (TLSO, HMIO)	230 (19.9)	102 (8.8)	NS	NS	NS	15 (12–23)	NS	NS
	6347	Open	1181 (18.6)	611 (9.6)	NS	NS	NS	15 (12–22)	NS	NS
Ben-David et al. (2012) [27]	100	MIE (TLSO)	9 (9)	8 (8)	5 (5)	NS	3 (3)	7.5 (6–49)	125 (100–300)	330 (270–480)
	32	Open	5 (15.6)	NS	4 (12.5)	NS	NS	14 (10–98)	NS	NS

(continued)

Table 20.2 (continued)

Authors (year)	*n*	Approaches	Pneumonia *n* (%)	Cardiac arrhythmia *n* (%)	Anastomotic leak *n* (%)	Gastric conduit ischemia n (%)	Chylothorax *n* (%)	Length of stay (days)	Operative blood loss (mls)	Operative time (minutes)
Briez et al. (2012) [28]	140	MIE (HMIO)	15.7	NS	5.7	0.7	NS	12 (8–80)	NS	NS
	140	Open	42.9	NS	4.3	0.0	NS	16 (8–180)	NS	NS
Xie et al. (2014) [29]	106	MIE (TLSO)	2 (1.9)	NS	5 (4.7)	NS	4 (3.8)	11.8 (±6.7)	187.2 (±37.8)	249.6 (±41.7)
	163	Open	8 (4.9)	NS	6 (3.7)	NS	5 (3.1)	13.9 (±7.3)	198.5 (±46.5)	256.3 (±41.7)
Hsu et al. (2014) [30]	66	MIE (TLSO)	7 (10.6)	NS	18 (27.3)	NS	4 (6.1)	NS	462.4 (±467.8)	510.9 (±121.3)
	63	Open	16 (25.4)	NS	19 (30.2)	NS	3 (4.8)	NS	615.5 (±591.6)	460.5 (±92.4)

MIE minimally invasive esophagectomy, *VATS* video-assisted thoracoscopic surgery esophagectomy, *HMIO* hybrid MIE, *HALS* hand-assisted laparoscopic oesophagectomy, *TSE* thoracoscopic-assisted esophagectomy, *TLSE* thoracolaparoscopic surgery esophagectomy, *LIE* laparoscopic inversion esophagectomy, *LSE* laparoscopic esophagectomy, *NS* not stated

minimally invasive approach (Tables 20.1 and 20.2). It is likely that the benefits of MIE may be overshadowed by the persistent rate of significant morbidity which continues to occur independent of surgical approach. It seems conceivable that, in the absence of such complications, patients with a minimal access approach enjoy quicker recovery, quicker return to normal activities, and decreased long-term pain when compared to patients with similarly uncomplicated open procedures. This, however, has yet to be proven.

Results coming from three published meta-analyses, based on nonrandomized comparative data, are contradictory. Two did not find significant differences between the MIE and the open approaches [33, 34]. The third suggests that patients undergoing MIE had better operative and postoperative outcomes with no compromise in oncological outcomes (as assessed by lymph node retrieval) [7]. Patients undergoing MIE had significantly lower blood loss and shorter postoperative ICU and hospital stay. There was a 50 % decrease in total morbidity in the MIE group. Subgroup analysis of comorbidities demonstrated significantly lower incidence of respiratory complications after MIE; however, other postoperative outcomes such as anastomotic leak, anastomotic stricture, gastric conduit ischemia, chyle leak, vocal cord palsy, and 30-day mortality were comparable between the two techniques. The benefit of at least one endoscopic stage in hybrid techniques (thoracoscopy with laparotomy or laparoscopy with thoracotomy) was noted. Even with only one phase being minimally invasive, blood loss and respiratory complications were still found to be lower, consistent with open versus totally MIE analysis, and highlight the purported advantages of applying a minimally invasive approach to esophagectomy.

20.4 Long-Term Results (Table 20.3)

If MIE is to become the approach of choice, then it must be demonstrated not to compromise oncological outcomes. Improved lighting and visibility, along with the magnification afforded by minimally invasive equipment, may prove superior for meticulous dissection and lymph node harvest. However, until large series report long-term survival by stage or results of large randomized trials are published, the true oncologic value of MIE will remain controversial. Table 20.3 reflects the fact that no study to date has shown conclusive evidence of improved overall survival favoring a minimally invasive resection. While several studies have suggested a benefit in terms of lymph node harvest, many have failed to meet the broadly accepted recommendations of the number of lymph nodes which should be retrieved for optimum staging and prognosis (Table 20.3). This puts into some question the quality of resection in several studies and makes oncological comparisons difficult. More data is simply required in this regard from future randomized controlled trials.

20.5 Randomized Controlled Trials

To date, only one multicenter randomized controlled trial (TIME) has been published comparing the results of minimally invasive and open esophagectomy [31]. This trial randomly assigned 56 patients to open esophagectomy and 59 to a minimally invasive operation with all patients receiving equivalent neoadjuvant chemotherapy or chemoradiotherapy regimes. Both minimally invasive and open surgical groups had a mixture of two-stage and three-stage operations with the majority of patients having a cervical anastomosis. The primary outcome measure chosen was pulmonary infection within 2 weeks of surgery defined by clinical manifestation of pneumonia confirmed by radiological imaging and a positive sputum sample. Sixteen (29 %) patients in the open surgical group and 5 (9 %) patients in the minimally invasive group ($p=0.005$) developed pneumonia in the first two postoperative weeks. Prima facie this appears to suggest a significant benefit in terms of respiratory complications in favor of the minimally invasive approach. Several observations and qualifications do however need

Table 20.3 Long-term oncological outcomes for MIE and open esophagectomy

Authors (year)	*N*	Approaches	Number of lymph nodes retrieved (median)	RO resection rate n (%)	3-year survival
Law et al. (1997) [10]	22	MIE (TSO)	7 [2–13]	10	62 % (2 years)
	63	Open	13 [5–34]	NS	63 % (2 years)
Nguyen et al. (2000) [11]	18	MIE (TLSO)	10.8 ± 8.4	18	NS
	36	Open	6.6 ± 5.8	NS	NS
Osugi et al. (2003) [12]	77	MIE (VATS)	33.9 ± 12	NS	70 %
	72	Open	32.8 ± 14	NS	60 %
Kunisaki et al. (2004) [13]	15	MIE (VATS + HALS)	24.5 ± 10	NS	NS
	30	Open	26.6 ± 10.4	NS	NS
Van den Broek et al. (2004) [14]	25	MIE (THO)	7 ± 4.9	21 (84)	60 % (f/u 17 ± 11 months)
	20	Open	6.5 ± 4.9	18 (90)	50 % (f/u 54 ± 16 months)
Bresadola et al. (2005) [15]	14	MIE (THO/TLSO)	22.2 ± 12	NS	NS
	14	Open	18.6 ± 13.4	NS	NS
Bernabe et al. (2005) [16]	17	MIE (THO)	9.8 (NS)	NS	NS
	14	Open	8.7 (NS)	NS	NS
Shiraishi et al. (2006) [17]	116	MIE (TLSO)	31.8 (NS)	NS	NS
	37	Open	30.1 (NS)	NS	NS
Braghetto et al. (2006) [18]	47	MIE (VATS/LSO)	NS	NS	45.5 %
	119	Open	NS	NS	32.5 %
Smithers et al. (2007) [19]	332	MIE (TLSO)	17 [9–33]	263	42 %
	114	Open	16 [1–44]	90	30 %
Fabian et al. (2008) [9]	22	MIE (TLSE)	15 ± 6	22 (100)	NS
	43	Open	8 ± 7	NS	NS
Zingg et al. (2009) [20]	56	MIE (TLSO)	5.7 ± 0.4	NS	Median survival – 35 months MIE, 29 months open
	98	Open	6.7 ± 0.5	NS	
Perry et al. (2009) [21]	21	MIE (LIO)	10 [4–12]	NS	NS
	21	Open	3 [0–7]	NS	NS
Parameswaran et al. (2009) [22]	50	MIE (TLSO)	23 [7–49]	NS	74 % (2-year survival)
	30	Open	10 [2–23]	NS	58 % (2-year survival)
Pham et al. (2010) [23]	44	MIE (TLSO)	13 [9–15]	NS	NS
	46	Open	8 [3–14]	NS	NS
Schoppman et al. (2010) [24]	31	MIE (TLSO)	17.9 ± 7.7	29 (93.5)	64 %
	31	Open	20.5 ± 12.6	30 (96.8)	46 %
Singh et al. (2010) [25]	33	MIE (TLSO)	14 (6–16)	30	55 % (2-year survival)
	31	Open	8 (3–14)	30	32 % (2-year survival)
Mamidanna et al. (2012) [26]	1155	MIE (TLSO/HMIO)	NS	NS	NS
	6347	Open	NS	NS	NS
Ben-David et al. (2012) [27]	100	MIE (TLSO)	NS	99 (99)	NS
	32	Open	NS	32 (100)	NS

Table 20.3 (continued)

Authors (year)	*N*	Approaches	Number of lymph nodes retrieved (median)	RO resection rate n (%)	3-year survival
Briez et al. (2012) [28]	140	MIE (HMIO)	22 [8–53]	85.7	58 % (2-year survival)
	140	Open	22 [6–56]	87.9	57 % (2-year survival)
Xie et al. (2014) [29]	106	MIE (TLSO)	30.4 (±5.4)	NS	NS
	163	Open	30.2 (±5.0)	NS	NS
Hsu et al. (2014) [30]	66	MIE (TLSO)	28.3 (±16.6)	64 (97.0)	70.9 %
	63	Open	25.9 (±15.3)	61 (96.8)	47.6 %

MIE minimally invasive esophagectomy, *VATS* video-assisted thoracoscopic surgery esophagectomy, *HMIO* hybrid MIO, *HALS* hand-assisted laparoscopic oesophagectomy; *TSE* thoracoscopic-assisted esophagectomy, *TLSE* thoraco-laparoscopic surgery esophagectomy, *LIE* laparoscopic inversion esophagectomy, *LSE* laparoscopic esophagectomy, *NS* not stated

to be made. Intraoperative single-lung ventilation was practiced only for the open surgical group, and the open group had a very high level of recurrent laryngeal nerve palsy (14 %) compared to the minimally invasive group (2 %). Both of these factors clearly put the patients having an open operation at higher risk of postoperative respiratory complications. Further many non-studied variables – malnutrition, previous and current smoking, pulmonary comorbidities, functional status, and clinical TNM (tumor, node, metastases) stage – have all been shown to strongly influence the primary end point of this trial. More data is therefore required.

There are two other multicenter randomized controlled trials of interest. The French multicenter phase III MIRO trial [32] has randomized patients to either hybrid esophagectomy (laparoscopic gastric mobilization and open right thoracotomy) or open esophagectomy. The MIRO trial tests the impact of laparoscopic gastric conduit creation with open thoracotomy (hybrid procedure) on major 30-day postoperative morbidity, especially on pulmonary complications. It hypothesizes that hybrid MIE may decrease major postoperative morbidity without compromising oncological outcomes through an easily reproducible surgical procedure. Secondary objectives are to assess the overall 30-day morbidity, 30-day mortality, disease-free and overall survival, quality of life, and medico-economic analysis. The short-term results have been recently presented [35]. The trial randomly assigned 104 patients to open esophagectomy and 103 to a hybrid approach group. Sixty-seven (64.4 %) patients in the open group had major postoperative morbidity compared to 37 (35.9 %) in the hybrid group (OR 0·31, 95 % CI 0·18-0·55; $p=0·0001$). Thirty-one (30.1 %) patients after an open operation had major pulmonary complications compared to 18 (17.7 %) after a hybrid approach ($p=0·037$), whereas 30-day mortality was 5 (4.9 %) versus 5 (4.9 %), respectively. The MIRO results provide further evidence that a minimally invasive approach may reduce the short-term insult of esophagectomy. The longer-term oncological results are awaited with interest. In the United Kingdom, patients are currently being recruited into a phase II trial [36] comparing a totally minimally invasive operation, hybrid approach (laparoscopic gastric mobilization and open chest) and open esophagectomy. Results for phase II of this study are not yet accumulated and recruitment to the planned phase III trial not yet commenced.

Conclusions

MIE has been gaining in popularity, but, as with open surgery, no consensus has been reached regarding the superiority of any particular MIE adaptation. Even if some large comparative studies suggest a significantly

better postoperative course following MIE, without compromise of oncological outcomes, more data is needed from randomized trials. Randomized trials are, however, difficult due to the wide variety of techniques available, the heterogeneity in surgeons' preferences, the relative low number of procedures performed, the complexity of such surgery, and the variety and definition of postoperative complications after esophagectomy. Certainly the positive results of the TIME trial and the soon to be published MIRO trial add credence to what many surgeons find intuitive – that a less invasive approach can reduce morbidity after esophagectomy. Rates of postoperative mortality have fallen in specialist centers; focus must turn to minimizing the traditionally high level of morbidity associated with this operation.

To date, data coming from nonrandomized studies do suggest MIE is safe and at least comparable to open resection for both surgical and oncological outcomes. Data from meta-analyses suggest that MIE may have advantages in terms of less blood loss, less time in intensive care, fewer pulmonary complications, and shorter hospital stay. However, the effect of MIE on quality of life and return to normal activity has not been assessed nor have medico-economic analyses been performed. More large randomized controlled trials are required. Results from the MIRO trial will soon be published and will offer a higher level of evidence for this highly debated procedure.

Conflicts of Interest The authors declare that they have no competing interests.

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References

1. Birkmeyer JD, Siewers AE, Finlayson EV et al (2002) Hospital volume and surgical mortality in the United States. N Engl J Med 346:1128–1137
2. Low DE, Kunz S, Schembre D et al (2007) Esophagectomy–it's not just about mortality anymore: standardized perioperative clinical pathways improve outcomes in patients with esophageal cancer. J Gastrointest Surg 11:1395–1402
3. Akaishi T, Kaneda I, Higuchi N et al (1996) Thoracoscopic en bloc total esophagectomy with radical mediastinal lymphadenectomy. J Thorac Cardiovasc Surg 112:1533–1540
4. Gossot D, Fourquier P, Celerier M (1993) Thoracoscopic esophagectomy: technique and initial results. Ann Thorac Surg 56:667–670
5. Gemmill EH, McCulloch P (2007) Systematic review of minimally invasive resection for gastro-oesophageal cancer. Br J Surg 94:1461–1467
6. Mariette C, Robb WB (2012) Open or minimally invasive resection for oesophageal cancer? Recent Results Cancer Res 196:155–167
7. Nagpal K, Ahmed K, Vats A et al (2010) Is minimally invasive surgery beneficial in the management of esophageal cancer? A meta-analysis. Surg Endosc 24:1621–1629
8. Dapri G, Himpens J, Cadiere GB (2008) Minimally invasive esophagectomy for cancer: laparoscopic transhiatal procedure or thoracoscopy in prone position followed by laparoscopy? Surg Endosc 22:1060–1069
9. Fabian T, Martin JT, McKelvey AA et al (2008) Minimally invasive esophagectomy: a teaching hospital's first year experience. Dis Esophagus 21: 220–225
10. Law S, Fok M, Chu KM et al (1997) Thoracoscopic esophagectomy for esophageal cancer. Surgery 122:8–14
11. Nguyen NT, Follette DM, Wolfe BM et al (2000) Comparison of minimally invasive esophagectomy with transthoracic and transhiatal esophagectomy. Arch Surg 135:920–925
12. Osugi H, Takemura M, Higashino M et al (2003) A comparison of video-assisted thoracoscopic oesophagectomy and radical lymph node dissection for squamous cell cancer of the oesophagus with open operation. Br J Surg 90:108–113
13. Kunisaki C, Hatori S, Imada T et al (2004) Video-assisted thoracoscopic esophagectomy with a voice-controlled robot: the AESOP system. Surg Laparosc Endosc Percutan Tech 14:323–327
14. Van den Broek WT, Makay O, Berends FJ et al (2004) Laparoscopically assisted transhiatal resection for malignancies of the distal esophagus. Surg Endosc 18:812–817
15. Bresadola V, Terrosu G, Cojutti A et al (2006) Laparoscopic versus open gastroplasty in esophagectomy for esophageal cancer: a comparative study. Surg Laparosc Endosc Percutan Tech 16:63–67
16. Bernabe KQ, Bolton JS, Richardson WS (2005) Laparoscopic hand-assisted versus open transhiatal esophagectomy: a case-control study. Surg Endosc 19:334–337

17. Shiraishi T, Kawahara K, Shirakusa T et al (2006) Risk analysis in resection of thoracic esophageal cancer in the era of endoscopic surgery. Ann Thorac Surg 81:1083–1089
18. Braghetto I, Csendes A, Cardemil G et al (2006) Open transthoracic or transhiatal esophagectomy versus minimally invasive esophagectomy in terms of morbidity, mortality and survival. Surg Endosc 20:1681–1686
19. Smithers BM, Gotley DC, Martin I et al (2007) Comparison of the outcomes between open and minimally invasive esophagectomy. Ann Surg 245:232–240
20. Zingg U, McQuinn A, DiValentino D et al (2009) Minimally invasive versus open esophagectomy for patients with esophageal cancer. Ann Thorac Surg 87:911–919
21. Perry KA, Enestvedt CK, Pham T et al (2009) Comparison of laparoscopic inversion esophagectomy and open transhiatal esophagectomy for high-grade dysplasia and stage I esophageal adenocarcinoma. Arch Surg 144:679–684
22. Parameswaran R, Veeramootoo D, Krishnadas R et al (2009) Comparative experience of open and minimally invasive esophagogastric resection. World J Surg 33:1868–1875
23. Pham TH, Perry KA, Dolan JP et al (2010) Comparison of perioperative outcomes after combined thoracoscopic-laparoscopic esophagectomy and open Ivor-Lewis esophagectomy. Am J Surg 199:594–598
24. Schoppmann SF, Prager G, Langer FB et al (2010) Open versus minimally invasive esophagectomy: a single-center case controlled study. Surg Endosc 24:3044–3053
25. Singh RK, Pham TH, Diggs BS et al (2010) Minimally invasive esophagectomy provides equivalent oncologic outcomes to open esophagectomy for locally advanced (stage II or III) esophageal carcinoma. Arch Surg 146:711–714
26. Mamidanna R, Bottle A, Aylin P et al (2012) Short-term outcomes following open versus minimally invasive esophagectomy for cancer in England: a population-based national study. Ann Surg 255:197–203
27. Ben-David K, Sarosi GA, Cendan JC et al (2012) Decreasing morbidity and mortality in 100 consecutive minimally invasive esophagectomies. Surg Endosc 26:162–167
28. Briez N, Piessen G, Torres F et al (2012) Effects of hybrid minimally invasive oesophagectomy on major postoperative pulmonary complications. Br J Surg 99:1547–1553
29. Xie MR, Liu CQ, Guo MF et al (2014) Short-term outcomes of minimally invasive Ivor-Lewis esophagectomy for esophageal cancer. Ann Thorac Surg 97:1721–1727
30. Hsu PK, Huang CS, Wu YC et al (2014) Open versus thoracoscopic esophagectomy in patients with esophageal squamous cell carcinoma. World J Surg 38:402–409
31. Biere SS, van Berge Henegouwen MI, Maas KW et al (2012) Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. Lancet 379:1887–1892
32. Briez N, Piessen G, Bonnetain F et al (2011) Open versus laparoscopically-assisted oesophagectomy for cancer: a multicentre randomised controlled phase III trial – the MIRO trial. BMC Cancer 11:310
33. Biere SS, Cuesta MA, van der Peet DL (2009) Minimally invasive versus open esophagectomy for cancer: a systematic review and meta-analysis. Minerva Chir 64:121–133
34. Sgourakis G, Gockel I, Radtke A et al (2010) Minimally invasive versus open esophagectomy: meta-analysis of outcomes. Dig Dis Sci 55:3031–3040
35. Mariette C, Meunier B, Pezet D et al (2014) Hybrid minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised phase III controlled trial, the MIRO trial. Paper presented at the American society of clinical oncology gastrointestinal cancers symposium, San Francisco, 15–17 Jan 2015
36. Avery KN, Metcalfe C, Berrisford R et al (2014) The feasibility of a randomized controlled trial of esophagectomy for esophageal cancer–the ROMIO (Randomized Oesophagectomy: Minimally Invasive or Open) study: protocol for a randomized controlled trial. Trials 15:200

Enhanced Recovery After Surgery (ERAS) and Nutritional Aspects

21

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21.1 Introduction

Enhanced recovery after surgery (ERAS) is a multimodal, perioperative care pathway designed to facilitate the recovery of patients undergoing major surgery. The principles are directed at reducing surgical stress and supporting basic bodily functions with the aim of improving outcomes, shortening inpatient stay, and reducing the costs associated with major surgery. The ERAS principles have resulted in the reevaluation of traditional practice and highlighted multiple areas, which, if targeted by evidence-based best practice, can lead to improved outcomes throughout the entire patient journey.

Until recently the majority of the publications on ERAS in gastrointestinal surgery came from work in colorectal surgery. An increasing number of esophageal cancer centers are now using ERAS principles in reproducible, evidence-based, management protocols for all patients undergoing esophageal resection. The aim is to optimize the overall outcome of surgery, while minimizing associated morbidity and mortality. Defined steps in management are sequenced by time, or achievement of goals, with interventions dependent on specific targets or outcomes. The exact components of each center's protocol may vary depending on local priorities and circumstances as evidenced by those published to date [1–11].

A successful ERAS pathway involves all members of the wider multidisciplinary team who must support the core ERAS objectives outlined in Fig. 21.1. These include appropriate patient selection and preparation for surgery combined with optimized decision-making throughout the perioperative period to minimize pain and the stress response to surgery. The anesthetist has a key role in ensuring appropriate and effective analgesia and fluid replacement therapy. The wide variety of allied health professionals within the upper gastrointestinal multidisciplinary team (upper GI MDT) also has a major impact upon patient recovery. Physiotherapists facilitate early mobilization and reduce respiratory complications; dietitians assess nutritional status and optimize nutritional delivery; nurses, as the most regular contact with the patient, provide ward-based care and work with occupational

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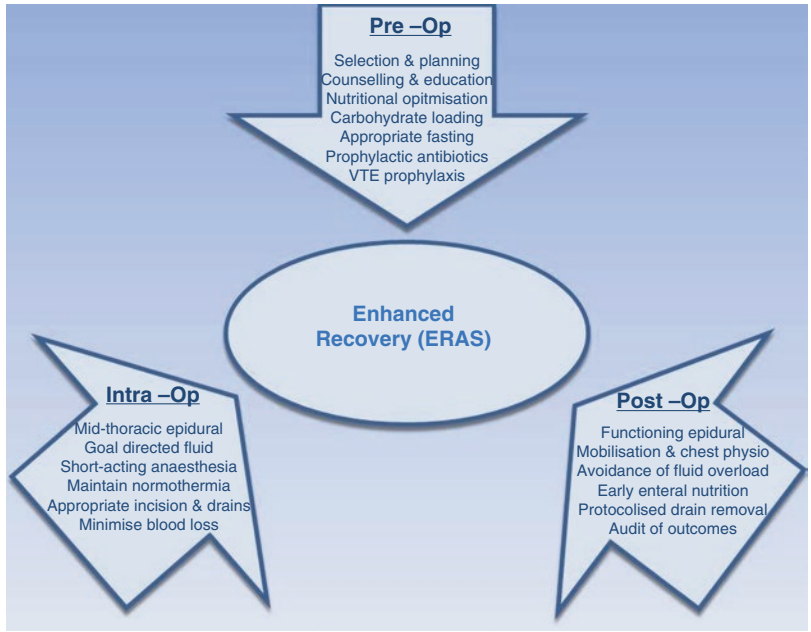

Fig. 21.1 A schematic summary of the pre-, intra-, and postoperative aspects of a successful ERAS pathway. Enhanced recovery is a multimodal process requiring inputs from all members of the wider upper GI multidisciplinary team if the process is to be a success. While the difference made by each individual component is difficult to prove statistically, these combine synergistically to deliver a definite improvement in outcomes [12, 13]

therapists to minimize avoidable delays in discharge. In UK practice, liaison between the involved professionals and both patient and family is optimized by the active involvement of a dedicated clinical nurse specialist (CNS).

21.2 Evolution of ERAS After Esophagectomy

The origin of ERAS is indelibly associated with the seminal work performed by Professor Henrik Kehlet in the early 1990s [14]. The concept of a standardized clinical pathway has however been around even longer. In the mid 1980s Karen Zander and Kathleen Bower, working at the New England Medical Center, Boston, USA, translated the principles of standard operating procedures from industry into case management plans and later clinical pathways [15, 16]. These principles were first applied to esophageal resection by the thoracic surgery team at The Johns Hopkins Hospital Baltimore in 1994 [1]. This pathway included many of the principles which would now be regarded as elements of an ERAS system (Fig. 21.1), such as early removal of lines, drains, and urinary catheter along with early enteral feeding. The implementation of this pathway resulted in a significant reduction in length of stay (LOS) and cost [1]. In 2003 [17] and 2004 [2], two further teams from the USA reported the beneficial impact of clinical pathways on recovery following esophagectomy. The first from Virginia Mason in Seattle published a case series (1999–2000) where standardized multimodal management and intraoperative fluid restriction had been implemented [17]. The second from University of Alabama published a 4-year case series on "Fast Tracking After Ivor Lewis Esophagogastrectomy" utilizing an algorithm to guide postoperative care [2]. Review of both pathways again demonstrated them to revolve around what are now regarded as ERAS principles.

The steady reduction in the mortality and improved survivorship associated with esophageal resection encouraged the belief that clinical pathways and ERAS principles could be

applied to such major surgery. The subsequent publication by the team from Virginia Mason in 2007 "It's Not Just About Mortality Anymore: Standardized Perioperative Clinical Pathways Improve Outcomes in Patients with Esophageal Cancer" [3] reported a series of 340 consecutive patients from 1991 to 2006 with a 30-day mortality of 0.3 % and a mean stay of 11.5 days. This appears to have triggered an explosion of interest in the potential clinical benefit of standardized pathways and ERAS in esophagectomy with nine full papers published between 2009 and 2014. The papers were almost exclusively comparative and case-controlled studies, with a single small randomized controlled trial from a Chinese center [11]. The relevant data have been assessed in detail in two recent systematic reviews [12, 13]. The Findlay paper [12] assessed the evidence base for both the overall process and its constituent parts and issued clinical guidelines where possible. The Markar systematic review [13] demonstrated the benefits afforded by ERAS pathways in terms of fewer leaks, pulmonary complications, and a shorter hospital stay, with no significant difference in terms of mortality or readmission [13]. These reviews are supportive of the process, but there is a lack of randomized trials on ERAS pathways and esophageal resection. The series from Virginia Mason has recently been updated [18] and reported the results of 595 patients over 4 sequential time periods between 1991 and 2012. The overall in-hospital mortality rate remained at 0.3 %, with the median LOS in the most recent 6-year time period being 8 (range 5–115) days. A summary of the papers on ERAS pathways selected for the Markar et al. [13] and/or Findlay et al. [12] reviews is summarized in Table 21.1.

21.3 The Core Components of ERAS After Esophagectomy

The published post-esophagectomy ERAS pathways share core components in the pre-, intra-, and postoperative periods (Fig. 21.1).

21.3.1 Preoperative

21.3.1.1 Focussed Counseling and Psychological Preparation

Focussed preoperative patient counseling has been shown to be an independent predictor of a successful ERAS pathway in colorectal surgery [20, 21]. Most surgeons use the outpatient clinic as the forum to outline the management plan and procedure proposed. This may be supplemented by anesthetic assessment and further discussion with the CNS. The provision of supplementary written information outlining the daily goals should also be offered as both reference and reinforcement. A good relationship with family members should be fostered and they should be encouraged to attend. The early engagement of relatives to support patients in achieving daily targets and to plan for their role within the primary support structure following discharge is essential. Discharge planning should therefore be considered at this point and discussed with both patient and family. A preoperative home visit by an occupational therapist may be required, and in units where a feeding jejunostomy is placed at time of resection, pump training can be initiated preoperatively to reduce postoperative delays. Some patients find it helpful to be partnered with a "buddy" who has already experienced the surgery or to attend a support group. A hospital visit to the theater complex, ITU, and ward may also benefit.

21.3.1.2 Physical Preparation for Esophagectomy

Fitter patients and those with less comorbidity are better placed to cope with the stresses placed on them by major surgery. Most patients however have significant comorbid conditions that may impact upon surgery. All patients due to undergo esophageal resection should be assessed preoperatively by a consultant anesthetist with an interest in esophageal surgery and a discussion of analgesic options and their associated potential complications conducted. The traditional methods for evaluating preoperative fitness for major surgery may be supplemented by risk stratification tools such as P-POSSUM [22] and O-POSSUM

Table 21.1 A summary of the original literature published on ERAS after esophagectomy

Author	Year	Design	Total *n* number (ERAS group)	Primary outcomes Conventional vs ERAS groups
Zehr [1]	1998	Retrospective case control	152 (96)	Complications: not reported Mortality reduced: 3.6–0 % Length of stay reduced: 13.6–9.5 days Readmissions: not reported Costs reduced: $22,000–$18,000
Cerfolio [2]	2004	Retrospective observational	90	Complications: 17.7 % (major only) Mortality: 4.4 % Length of stay: 7 days Readmissions: 4.4 % Compliance with protocol: 76 %
Low [3]	2007	Retrospective observational	340	Complications: 45 % Mortality: 0.3 % Length of stay: 12 days Readmissions: not reported
Jiang [4]	2009	Retrospective observational	114	Complications: 29.8 % Mortality: 2.6 % Length of stay: 7 days Readmissions: 4 %
Munitiz [5]	2010	Retrospective case control	148 (74)	Complications reduced: 38–31 % Mortality reduced: 5–1 % Length of stay reduced: 13–9 days Readmissions reduced: 1.4–0 % Compliance with protocol: 69 %
Tomaszek [19]	2010	Retrospective case control	386 (110)	Complications: 42.8 % (all patients) Mortality: 3.6 % (all patients) Length of stay reduced: 9–7 days Readmissions reduced: 27–25 %
Li [6]	2012	Retrospective case control	106 (59)	Complications unchanged: 32 % (major only) Mortality increased: 0–2 % Length of stay reduced: 10–8 days Readmissions reduced: 6–5 %
Preston [7]	2012	Retrospective case control	36 (12)	Complications reduced: 75–33 % (12 pts) Mortality unchanged: 0 % Length of stay reduced: 17–7 days Readmissions: not reported

Table 21.1 (continued)

Author	Year	Design	Total *n* number (ERAS group)	Primary outcomes Conventional vs ERAS groups
Blom [8]	2013	Retrospective case control	181 (103)	Complications increased: 68–71 % Mortality increased: 1–4 % Length of stay reduced: 15–14 days Readmissions reduced: 10.3–9.7 %
Cao [9]	2013	Retrospective case control	112 (55)	Complications reduced: 47–29 % Mortality reduced: 5.3–1.8 % Length of stay reduced: 14.8–7.7 days Readmissions reduced: 5.3–2.6 %
Tang [10]	2013	Retrospective case control	63 (36)	Complications reduced: 25.9–16.7 % Mortality increased: 3.7–5.6 % Length of stay reduced: 14.5–11 days Readmissions increased: 14.8–19.4 %
Zhao [11]	2014	Randomized controlled trial	68 (34)	Complications reduced: 11.7–5.9 % Mortality unchanged: 0 % Length of stay reduced: 12.5–7.2 days Readmissions increased: 0–2.9 % Costs reduced 40,000–32,000 renminbi

These papers were of sufficient methodological quality to meet the inclusion criteria for the two recently published systematic reviews on ERAS after esophagectomy [12, 13]. Only one RCT has been performed, but when the findings were combined in the systematic reviews, significant benefits were demonstrated. Some series had no control group (observational); others compared results following introduction of an ERAS pathway to an earlier pre-ERAS group, almost always at the same institution (case control). The numbers in parentheses in column 4 are for the ERAS group. All outcome data in the final column are for the ERAS group in the observational studies and both groups (where published) in the case-control studies

scoring [23] or by objective assessment utilizing cardiopulmonary exercise testing [24, 25]. All patients are likely to benefit from taking exercise in the run up to surgery, but a subset may be selected for formal preoperative inspiratory muscle training (IMT). High-intensity IMT improves respiratory muscle function and may reduce postoperative pulmonary complications following esophageal surgery [26] and is currently undergoing further evaluation as a multicenter randomized controlled trial (PREPARE Study) [27].

Anemia should be corrected prior to esophagectomy as it is associated with an increased risk of transfusion, morbidity, and mortality. The time interval required for the staging and neoadjuvant treatment commonly involved with esophageal surgery means that oral iron or iron transfusion is suitable agent in iron deficiency anemia. Nutritional assessment and support from a specialist dietitian should also be performed with optimization of nutritional status by oral or enteral supplementation when required.

21.3.2 Intraoperative

21.3.2.1 Surgical Management

The majority of surgical decision-making is made preoperatively based upon the staging of the disease but is also influenced by patient-specific factors such as physiology, body mass index, previous surgery, and conduit availability. These all impact on the choices made with respect to the procedure, incision, and anticipated reconstruction. The preoperative plan should aim to minimize the surgical stress response, while still giving the patient the best possible chance of long-term cure. Intraoperative technique may however influence blood loss which should be minimized. The number of drains inserted is often dictated by the procedure performed but should be kept to a minimum. Local practice varies regarding use of nasogastric drainage tubes and performing a gastric drainage procedure, with the literature remaining too heterogeneous to give exact recommendations [12].

There remains ongoing interest in minimally invasive esophagectomy (MIO). This is technically demanding and time consuming and has a marginal impact on length of stay [28]. Many centers have tried fully minimally invasive and hybrid techniques in an attempt to minimize the surgical stress response. These techniques are fully consistent with the principles of ERAS and oncological outcomes appear comparable [29]. The one RCT published to date [30] of open versus minimally invasive techniques showed benefit in terms of reduced complications, length of stay, and blood loss, with no significant difference in terms of oncological outcome [30].

21.3.2.2 Anesthetic Management

Whenever possible the patient should be safely extubated immediately following esophagectomy. This requires a functioning mode of analgesia (usually mid-thoracic epidural) adequate warming and fluid resuscitation. With long, complex procedures such as esophagectomy, this process may be facilitated by ensuring a prompt start (and end) to surgery. All of these measures facilitate the ability to commence the patient recovery on the day of surgery. While the surgeon's focus is on delivering the best possible oncological procedure while minimizing associated blood loss, the anesthetist has to address the majority of the other intraoperative aspects shown in Fig. 21.1. The analgesic plan is of primary importance to the patient. A well-placed and functioning thoracic epidural can have a significant impact on patient pain, ability to mobilize, and respiratory complications [31]. It may be possible to deliver the same level of analgesia using paravertebral blocks and/or wound catheters, but it is the degree of analgesia rather than the manner it is achieved which is the key to minimizing respiratory complications and promoting early postoperative mobilization. Fluid therapy is an evolving science. Too much or too little fluid both have deleterious effects. Judicious fluid resuscitation, rather than a liberal approach is favored, with 1500–2500 milliliters (ml) during surgery usually considered an appropriate target. Goal-directed fluid resuscitation at time of surgery may be beneficial, with the aim of achieving neutral fluid balance thereafter. As long as the patient is not dehydrated, judicious use of vasopressors rather than excessive fluid resuscitation benefits, rather than risks, the conduit and anastomosis. The mean arterial pressure should be no lower than 70 mmHg. Whether goal-directed fluid therapy is better than more simple methods of keeping the patient's fluid balance neutral remains unproven, and, once again, practice varies between centers. The other aims of maintaining temperature, administration of prophylactic antibiotics, and minimizing the thromboembolic risk are not contentious. There is good evidence for combined mechanical and pharmacological thrombo-prophylaxis, and fractionated heparin should be continued for 30 days from day of surgery [32].

21.3.3 Postoperative

Most esophagectomy patients will be managed in the immediate postoperative period in a critical care or step-down care environment. Here the professions allied to medicine take on a

leading role, and all members of the wider upper GI MDT must support the process if it is to succeed. The physiotherapy and nursing teams are key. The central tenet of the postoperative aspect of an ERAS pathway is early mobilization. The use of a profiling bed ensures that the patient's position can be controlled from the time they first arrive on the high dependency unit. Sitting patients up on the day of surgery and maintaining a head-up position at all times facilitate sitting up and out of bed, then walking the day after (or sometimes on the day of) surgery. The frequency and distance walked increase progressively each day. Pumps and drains should be on a single drip stand to aid mobility. Optimum analgesia and regular chest physiotherapy help minimize respiratory complications. The current literature demonstrates that the implementation of the ERAS principles results in a significant reduction in respiratory complications (Fig. 21.2) [13].

Practice varies between centers and the literature too heterogeneous to give exact recommendations on drainage tube output and when they can safely be removed. In general terms, the ERAS principle of removal as early as is safe holds true. At the author's center, the nasogastric tube is removed on the second post-op day if the output is less than 300 ml over the previous 24 h. Basal chest drains are removed from third postoperative day provided the output is less than 250 ml. The apical chest drain, which lies adjacent to the anastomosis, is removed once the patient has progressed to a pureed diet.

Many units use a feeding jejunostomy to meet nutritional requirements. At discharge, ERAS patients will frequently be taking only liquids and pureed diet, and the majority will struggle to meet their nutritional requirements without supplementary feeding.

Medication should be optimized for each patient. Patients' exact requirements will vary with their comorbidities, but all will require regular analgesia. In addition to the epidural, the author's center uses regular paracetamol from time of surgery with rectal diclofenac started on the third postoperative day, provided that there are no concerns regarding renal function.

Fig. 21.2 A patient mobilizing on the first postoperative day after an open two-phase esophagogastrectomy with radical two-field lymph node dissection. To mobilize on the evening of surgery or the first postoperative day, the patient needs to have adequate analgesia, normally provided by a functioning mid-thoracic epidural. The profiling bed is used to keep the patient head up while sleeping and in a chair position when awake, to maintain baroceptor function. All drains and pumps need to be placed on a single drip stand, and the patient should wear nonslip socks. Assistance is provided by physiotherapy and nursing staff and tailored to patient needs

A proton-pump inhibitor or H_2-receptor antagonist is usually utilized to reduce the risk of stress ulceration and bleeding.

The 2013 UK National Oesophago-Gastric Cancer Audit shows that overall median LOS is 13 days for an esophagectomy [28]. In the papers used in the systematic reviews, introduction of an ERAS pathway reduced LOS from a median of 17–13 days. In Virginia Mason, the median stay in their most recent 6-year block is 8 (range, 5–115) days [18]. There are obvious clinical benefits for the patient and potential cost savings for treating hospital.

21.3.4 Nutrition

Patients undergoing esophagectomy are a high-risk group from a nutritional point of view with the incidence of malnutrition estimated at 79 % [33]. The nature of the disease means that patients frequently present after weeks or months of a combination of progressive dysphagia, odynophagia, obstructive regurgitation, and epigastric or retrosternal pain. The resultant poor intake and associated weight loss may also be affected by the side effects of neoadjuvant treatment. Traditionally, this was further compounded by the surgical practice of limited preoperative nutritional support, prolonged preoperative fasting, and delays recommencing nutrition. ERAS has brought a renewed emphasis on the importance of nutrition as centers strive to further improve outcomes. The assessment of nutritional status and rigorous correction of nutritional deficiencies is an integral component of an effective enhanced recovery pathway.

21.3.4.1 Preoperative Assessment and Optimization

The first step in optimizing nutrition involves the completion of a comprehensive nutritional assessment. This should be performed by a specialist upper GI dietitian as a core member of the MDT. Once the nutritional risk has been evaluated, preoperative goals should be set to provide caloric and nitrogenous support. The aim is to meet the patient's specific nutritional requirements, avoid excessive loss of lean body mass, attenuate the hypermetabolic response to surgery, and provide micro- and macronutrients to optimize healing and recovery. Perioperative maintenance of normoglycemia improves surgical outcomes and may be the single most important factor in the prevention of surgical site infection. Symptoms associated with esophageal cancer may increase the difficulty in achieving this.

Techniques to optimize oral intake include texture modification, food fortification, and oral nutritional supplements (sip feeds). While oral intake may be improved by insertion of self-expanding metal stents (SEMS), their role in the preoperative setting remains controversial. Several trials have shown that if oral supplementation remains insufficient, patients with dysphagia or severe anorexia may benefit from preoperative enteral nutrition support via a naso-jejunal feeding tube or a feeding jejunostomy. European guidelines recommend that patients with severe nutritional risk receive nutritional support, preferably using the enteral route for 10–14 days prior to major surgery, even if surgery has to be delayed [34]. Many centers now place a feeding jejunostomy during the staging laparoscopy that can then be used for nutrition supplementation during neoadjuvant treatment, in the lead up to and after esophagectomy [35]. This has the advantage of enabling the patient to work toward nutritional goals during neoadjuvant treatment, ensures that patients are nutritionally optimized before resection, and removes a further step from the post-resection discharge process.

Preoperative vitamin and mineral requirements remain understudied and relatively controversial. Little data exist on preoperative supplementation. Local practice is to encourage a varied diet, where possible including a wide range of fruit and vegetables. Nutritionally complete sip feeds can be used to support those with obstructive dysphagia with an associated restricted intake.

21.3.4.2 Perioperative Nutritional Care

Historically, oral nutrition is withheld from midnight on the night before surgery in an effort to minimize the aspiration risk during anesthesia. Fasting promotes insulin resistance, hyperglycemia, and muscle breakdown. Patients should be starved for no longer than 6 h for solids and 2 h for clear fluids prior to surgery [36]. Carbohydrate loading has been studied extensively in the development of enhanced recovery pathways, particularly in colorectal surgery. Its administration in the preoperative period aims to minimize the catabolic influence and insulin resistance associated with postoperative stress [37], although the most recent meta-analysis showed no reduction in in-hospital complication rates [38]. There are no specific data on carbohydrate loading in esophagectomy patients nor in patients with diabetes.

Aspects of Perioperative Feeding

Parenteral nutrition was traditionally the chosen route for the perioperative period following esophagectomy. It is now accepted that enteral nutritional support is safer and more efficacious whenever possible, with data including several studies of early enteral nutrition (jejunostomy) following major upper GI resection [39, 40]. Jejunostomy tubes are now routinely placed at the time of esophagectomy at most UK centers. They are associated with a low, but not insignificant, level of morbidity [41], and meticulous surgical technique is important to minimize this. An appropriate feeding device designed for jejunal placement should be used. Local practice is to place a percutaneous nine French Freka feeding tubes into the jejunum either at staging laparoscopy (in those predicted to require preoperative feeding) or at time of esophagectomy.

Feeding regimens can be commenced safely from the first postoperative day. Whole protein, low fiber, 1 kcal/ml feeds are most commonly used. These are usually delivered at a low rate through a pump with the feeding rate increasing gradually over several days. Caloric delivery is not the prime objective with early postoperative feeding, rather the maintenance of the gut mucosal barrier and stimulation of gut function. When enteral nutrition tolerance is established and oral intake commenced, patients can be transitioned to supplementary nocturnal feeding cycles.

Immuno-nutrition

Immune-modulating nutrition products are hydrolyzed peptide-based high-protein formulas that include a combination of fish oils, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), arginine, nucleic acids, and antioxidants. Studies in non-esophageal patients have shown that immuno-nutrition reduces infections and wound complications, but randomized controlled trials in esophageal and stomach cancer patients did not reproduce these results [42–44]. There is currently insufficient evidence to support routine administration in esophageal cancer surgery.

Reintroduction of Oral Intake

Dietary reintroduction programs differ widely. Patients tend to move from sips of water through clear and then free fluids before building up to soft diet with a small but frequent meal pattern. Esophagectomy requires a significant change to long-established dietary habits and behaviors, and postoperative nutrition-related complaints are common. In a recent study from Sweden, patients frequently reported early satiety, postprandial dumping, inhibited passage due to high viscosity, reflux of food and/or fluids, and absence of hunger [45]. One study demonstrated an insufficient oral intake at time of hospital discharge following esophagectomy in 60 % of patients [46].

21.3.4.3 Postoperative Nutrition Support

Malnutrition continues to be a concern following surgery with 64 % of patients losing 10 % of their body weight in the first 6 months following surgery [47]. Hypermetabolism can last for weeks or months after major surgery, entailing significant protein losses of lean body mass. Most patients will benefit from continued enteral nutrition support via a jejunostomy after discharge. This ensures success in the majority of patients rather than allowing a significant proportion to fail to achieve adequate nutritional input and potentially require readmission. As oral intake improves, patients can decrease their reliance on tube feeding. It is prudent to leave the feeding jejunostomy in situ until the completion of any planned adjuvant treatment. The optimal time to remove a feeding tube will vary between patients with removal being a joint decision between the surgical and dietetic team.

21.3.5 Discussion

The use of ERAS pathways after esophagectomy appears to offer significant benefit with very little associated risk. The series from the Virginia Mason Medical Center [18] are among the best in the world, and the principles and processes appear to be transferable to other centers and across dif-

fering health-care systems [7]. Establishing a post-esophagectomy, ERAS pathway requires a significant investment of time but only requires resources and services that already exist in almost all cancer centers. The greatest challenge lies in achieving a change in mind-set and practice beliefs. The lack of randomized controlled trials is noted; however, it would be difficult to randomize patients to non-ERAS care in an institution where the mind-set and practice change have already occurred. It may also prove difficult to obtain ethical approval to randomize patients to a "traditional management" arm in a cancer center offering enhanced recovery to others.

The use of protocols and pathways frequently meets resistance for fear that protocols undermine the skill required for medical decision making in patient management. However, as William Edwards Deming, Professor of statistics at New York and Colombia University graduate schools of business, stated "uncontrolled variation is the enemy of quality." The ERAS principles combined with standardized clinical pathways are a means of applying evidence-based practice in a structured, reproducible manner and thereby improvements in quality. Desire to adhere to a protocol or pathway should not stop clinical evaluation and reactive management but should provide a scaffold around which the individual's recovery is built.

21.4 Summary

The use of standardized clinical pathways and ERAS principles in esophagectomy results in reduced LOS and complication rates along with associated cost savings [1, 11, 48] with no increase in mortality or readmission [13]. Nutrition is a core part of any pathway and specialist upper GI dietetic input is essential in assessment, delivery, and post-discharge monitoring. It is likely that the principles and processes outlined above will spread across the upper GI cancer community and act as a base for future improvements in care.

References

1. Zehr KJ, Dawson PB, Yang SC, Heitmiller RF (1998) Standardized clinical care pathways for major thoracic cases reduce hospital costs. Ann Thorac Surg 66(3):914–919. Epub 1998/10/13
2. Cerfolio RJ, Bryant AS, Bass CS, Alexander JR, Bartolucci AA (2004) Fast tracking after Ivor Lewis esophagogastrectomy. Chest 126(4):1187–1194. Epub 2004/10/16
3. Low DE, Kunz S, Schembre D, Otero H, Malpass T, Hsi A et al (2007) Esophagectomy – it's not just about mortality anymore: standardized perioperative clinical pathways improve outcomes in patients with esophageal cancer. J Gastrointest Surg 11(11):1395–1402; discussion 402. Epub 2007/09/04
4. Jiang K, Cheng L, Wang JJ, Li JS, Nie J (2009) Fast track clinical pathway implications in esophagogastrectomy. World J Gastroenterol WJG 15(4):496–501. Epub 2009/01/20
5. Munitiz V, Martinez-de-Haro LF, Ortiz A, Ruiz-de-Angulo D, Pastor P, Parrilla P (2010) Effectiveness of a written clinical pathway for enhanced recovery after transthoracic (Ivor Lewis) oesophagectomy. Br J Surg 97(5):714–718. Epub 2010/02/27
6. Li C, Ferri LE, Mulder DS, Ncuti A, Neville A, Lee L et al (2012) An enhanced recovery pathway decreases duration of stay after esophagectomy. Surgery 152(4):606–614; discussion 14–6. Epub 2012/09/05
7. Preston SR, Markar SR, Baker CR, Soon Y, Singh S, Low DE (2013) Impact of a multidisciplinary standardized clinical pathway on perioperative outcomes in patients with oesophageal cancer. Br J Surg 100(1):105–112. Epub 2012/11/20
8. Blom RL, van Heijl M, Bemelman WA, Hollmann MW, Klinkenbijl JH, Busch OR et al (2013) Initial experiences of an enhanced recovery protocol in esophageal surgery. World J Surg 37(10):2372–2378. Epub 2013/06/29
9. Cao S, Zhao G, Cui J, Dong Q, Qi S, Xin Y et al (2013) Fast-track rehabilitation program and conventional care after esophagectomy: a retrospective controlled cohort study. Suppor Care Cancer Off J Multinational Assoc Support Care Cancer 21(3):707–714. Epub 2012/08/31
10. Tang J, Humes DJ, Gemmil E, Welch NT, Parsons SL, Catton JA (2013) Reduction in length of stay for patients undergoing oesophageal and gastric resections with implementation of enhanced recovery packages. Ann R Coll Surg Engl 95(5):323–328. Epub 2013/07/11
11. Zhao G, Cao S, Cui J (2014) Fast-track surgery improves postoperative clinical recovery and reduces postoperative insulin resistance after esophagectomy for esophageal cancer. Suppor Care Cancer Off J Multinational Assoc Support Care Cancer 22(2):351–358. Epub 2013/09/27

12. Findlay JM, Gillies RS, Millo J, Sgromo B, Marshall RE, Maynard ND (2014) Enhanced recovery for esophagectomy: a systematic review and evidence-based guidelines. Ann Surg 259(3):413–431. Epub 2013/11/21
13. Markar SR, Karthikesalingam A, Low DE (2015) Enhanced recovery pathways lead to an improvement in postoperative outcomes following esophagectomy: systematic review and pooled analysis. Dis Esophagus Off J Int Soc Dis Esophagus ISDE 28(5):468–475. Epub 2014/04/05
14. Kehlet H (1997) Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth 78(5):606–617. Epub 1997/05/01
15. Zander K (1985) Second generation primary nursing. A new agenda. J Nurs Adm 15(3):18–24. Epub 1985/03/01
16. Zander K (1985) Revising the production process: when "more" is not the solution. Health Care Superv 3(3):44–54. Epub 1985/03/11
17. Neal JM, Wilcox RT, Allen HW, Low DE (2003) Near-total esophagectomy: the influence of standardized multimodal management and intraoperative fluid restriction. Reg Anesth Pain Med 28(4):328–334. Epub 2003/08/29
18. Markar SR, Schmidt H, Kunz S, Bodnar A, Hubka M, Low DE (2014) Evolution of standardized clinical pathways: refining multidisciplinary care and process to improve outcomes of the surgical treatment of esophageal cancer. J Gastrointest Surg 18(7):1238–1246. Epub 2014/04/30
19. Tomaszek SC, Cassivi SD, Allen MS, Shen KR, Nichols FC 3rd, Deschamps C et al (2010) An alternative postoperative pathway reduces length of hospitalisation following oesophagectomy. Eur J Cardiothorac Surg Off J Eur Assoc Cardiothorac Surg 37(4):807–813. Epub 2009/11/11
20. Aarts MA, Okrainec A, Glicksman A, Pearsall E, Victor JC, McLeod RS (2012) Adoption of enhanced recovery after surgery (ERAS) strategies for colorectal surgery at academic teaching hospitals and impact on total length of hospital stay. Surg Endosc 26(2):442–450. Epub 2011/10/21
21. Younis J, Salerno G, Fanto D, Hadjipavlou M, Chellar D, Trickett JP (2012) Focused preoperative patient stoma education, prior to ileostomy formation after anterior resection, contributes to a reduction in delayed discharge within the enhanced recovery programme. Int J Colorectal Dis 27(1):43–47. Epub 2011/06/11
22. Whiteley MS, Prytherch DR, Higgins B, Weaver PC, Prout WG (1996) An evaluation of the POSSUM surgical scoring system. Br J Surg 83(6):812–815. Epub 1996/06/01
23. Tekkis PP, McCulloch P, Poloniecki JD, Prytherch DR, Kessaris N, Steger AC (2004) Risk-adjusted prediction of operative mortality in oesophagogastric surgery with O-POSSUM. Br J Surg 91(3):288–295. Epub 2004/03/03
24. Nagamatsu Y, Shima I, Yamana H, Fujita H, Shirouzu K, Ishitake T (2001) Preoperative evaluation of cardiopulmonary reserve with the use of expired gas analysis during exercise testing in patients with squamous cell carcinoma of the thoracic esophagus. J Thorac Cardiovasc Surg 121(6):1064–1068. Epub 2001/06/01
25. Forshaw MJ, Strauss DC, Davies AR, Wilson D, Lams B, Pearce A et al (2008) Is cardiopulmonary exercise testing a useful test before esophagectomy? Ann Thorac Surg 85(1):294–299. Epub 2007/12/25
26. van Adrichem EJ, Meulenbroek RL, Plukker JT, Groen H, van Weert E (2014) Comparison of two preoperative inspiratory muscle training programs to prevent pulmonary complications in patients undergoing esophagectomy: a randomized controlled pilot study. Ann Surg Oncol 21(7):2353–2360. Epub 2014/03/08
27. Valkenet K, Trappenburg JC, Gosselink R, Sosef MN, Willms J, Rosman C et al (2014) Preoperative inspiratory muscle training to prevent postoperative pulmonary complications in patients undergoing esophageal resection (PREPARE study): study protocol for a randomized controlled trial. Trials 15:144. Epub 2014/04/29
28. National Oesophago-Gastric Cancer Audit (NOGCA) 2013. http://www.hscic.gov.uk/catalogue/PUB11093/clin-audi-supp-prog-oeso-gast-2013-rep.pdf
29. Luketich JD, Pennathur A, Awais O, Levy RM, Keeley S, Shende M et al (2012) Outcomes after minimally invasive esophagectomy: review of over 1000 patients. Ann Surg 256(1):95–103. Epub 2012/06/07
30. Biere SS, van Berge Henegouwen MI, Maas KW, Bonavina L, Rosman C, Garcia JR et al (2012) Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. Lancet 379(9829):1887–1892. Epub 2012/05/04
31. Ong CK, Lirk P, Seymour RA, Jenkins BJ (2005) The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg 100(3):757–773. Epub 2005/02/25
32. Rasmussen MS, Jorgensen LN, Wille-Jorgensen P (2009) Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. The Cochrane Database Syst Rev (1):CD004318. Epub 2009/01/23
33. Baker A, Wooten LA, Malloy M (2011) Nutritional considerations after gastrectomy and esophagectomy for malignancy. Curr Treat Options Oncol 12(1):85–95. Epub 2011/01/26
34. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P et al (2006) ESPEN guidelines on enteral nutrition: surgery including organ transplantation. Clin Nutr 25(2):224–244. Epub 2006/05/16
35. Ben-David K, Kim T, Caban AM, Rossidis G, Rodriguez SS, Hochwald SN (2013) Pre-therapy laparoscopic feeding jejunostomy is safe and effective in patients undergoing minimally invasive esophagectomy for cancer. J Gastrointest Surg 17(8):1352–1358. Epub 2013/05/28

36. Brady M, Kinn S, Stuart P (2003) Preoperative fasting for adults to prevent perioperative complications. Cochrane Database Syst Rev (4):CD004423. Epub 2003/10/30
37. Li L, Wang Z, Ying X, Tian J, Sun T, Yi K et al (2012) Preoperative carbohydrate loading for elective surgery: a systematic review and meta-analysis. Surg Today 42(7):613–624. Epub 2012/05/15
38. Awad S, Varadhan KK, Ljungqvist O, Lobo DN (2013) A meta-analysis of randomised controlled trials on preoperative oral carbohydrate treatment in elective surgery. Clin Nutr 32(1):34–44. Epub 2012/12/04
39. Lewis SJ, Egger M, Sylvester PA, Thomas S (2001) Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. BMJ 323(7316):773–776. Epub 2001/10/06
40. Barlow R, Price P, Reid TD, Hunt S, Clark GW, Havard TJ et al (2011) Prospective multicentre randomised controlled trial of early enteral nutrition for patients undergoing major upper gastrointestinal surgical resection. Clin Nutr 30(5):560–566. Epub 2011/05/24
41. Fenton JR, Bergeron EJ, Coello M, Welsh RJ, Chmielewski GW (2011) Feeding jejunostomy tubes placed during esophagectomy: are they necessary? Ann Thorac Surg 92(2):504–511; discussion 11–2. Epub 2011/06/28
42. Lobo DN, Williams RN, Welch NT, Aloysius MM, Nunes QM, Padmanabhan J et al (2006) Early postoperative jejunostomy feeding with an immune modulating diet in patients undergoing resectional surgery for upper gastrointestinal cancer: a prospective, randomized, controlled, double-blind study. Clin Nutr 25(5):716–726. Epub 2006/06/17
43. Sultan J, Griffin SM, Di Franco F, Kirby JA, Shenton BK, Seal CJ et al (2012) Randomized clinical trial of omega-3 fatty acid-supplemented enteral nutrition versus standard enteral nutrition in patients undergoing oesophagogastric cancer surgery. Br J Surg 99(3):346–355. Epub 2012/01/13
44. Zhang Y, Gu Y, Guo T, Li Y, Cai H (2012) Perioperative immunonutrition for gastrointestinal cancer: a systematic review of randomized controlled trials. Surg Oncol 21(2):e87–e95. Epub 2012/02/10
45. Haverkort EB, Binnekade JM, Busch OR, van Berge Henegouwen MI, de Haan RJ, Gouma DJ (2010) Presence and persistence of nutrition-related symptoms during the first year following esophagectomy with gastric tube reconstruction in clinically disease-free patients. World J Surg 34(12):2844–2852. Epub 2010/09/16
46. Ryan AM, Rowley SP, Healy LA, Flood PM, Ravi N, Reynolds JV (2006) Post-oesophagectomy early enteral nutrition via a needle catheter jejunostomy: 8-year experience at a specialist unit. Clin Nutr 25(3):386–393. Epub 2006/05/16
47. Martin L, Lagergren J, Lindblad M, Rouvelas I, Lagergren P (2007) Malnutrition after oesophageal cancer surgery in Sweden. Br J Surg 94(12):1496–1500. Epub 2007/08/03
48. Lee L, Li C, Robert N, Latimer E, Carli F, Mulder DS et al (2013) Economic impact of an enhanced recovery pathway for oesophagectomy. Br J Surg 100(10):1326–1334. Epub 2013/08/14

Unresectable and Metastatic Cancer

22

Felice Pasini, Anna Paola Fraccon, and Yasmina Modena

22.1 Chemotherapy for Metastatic/Unresectable Cancer

The principal guidelines uniformly agree on the importance of decision-making process by multidisciplinary teams, in locally advanced unresectable gastroesophageal junction adenocarcinoma (GEJ AD).

NCCN guidelines version 3.2015, for unresectable, medically fit GEJ AD patients, indicate that concomitant chemoradiation, radiotherapy, or chemotherapy are all possible treatment options; however, it does not detail the criteria for selecting the most appropriate one. ESMO 2013 guidelines did not even take into account the subset of unresectable tumors.

In metastatic disease, chemotherapy has been accepted for long as the keystone treatment.

In the past decades, survival improvement was overall modest, due to the lack of effective chemotherapy agents. 5-FU- and cisplatin are the backbone traditional chemotherapy, resulting in a 25–35 % response rate (RR).

Taxanes (paclitaxel, docetaxel), new fluoropyrimidines (S1 in Asian patients, capecitabine), and oxaliplatin have been variously combined and tested in numerous phase II and III trials. RR was reported to be about 40 % (range 26–57 %), but median OS remained in the magnitude of 9 months (range 6.4–18). In adenocarcinoma (AD) patients with a good general condition, triplet regimen, such as ECF, ECX (epirubicin/cisplatin/5-FU/capecitabine), EOF, EOX (epirubicin/oxaliplatin/5-FU/capecitabine), or DCF/DCX (docetaxel/cisplatin/5-FU/capecitabine), were more effective in terms of response rate at a price, however, of an increased toxicity.

Furthermore, the peak age of esophageal cancer patients is 65–70 years, an age correlated with the presence of clinical comorbidities [1].

Presently, phase III randomized trials devoted to GEJ AD are lacking, and historically, GEJ AD have been included in gastric cancer trials; however, these studies were not statistically powered to examine separately the two entities. GEJ AD represented the 13–29 % of the study population, and the 2-year survival rate did not exceed the 20 % [2].

Recently, a German database reported the data of GEJ AD and gastric cancer over the years 2006–2009; consistently with other reports, median age was 67 years with male preponderance

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(64 %). Older or less fit patients were treated preferably with monotherapy or doublets, while in younger patients, the use of triplets was twice as frequent (21 % vs. 40 %). This interesting analysis reflects the transfer of study data into clinical practice, but, because the database lacks of outcome data, the actual impact on survival cannot be stated [3].

Given the disappointing survival after conventional treatments, a large effort has been made over the last decade to test innovative approaches.

22.2 Targeted Therapies Anti Epidermal Growth Factor Family

The epidermal growth factor receptor (*EGFR*) is a member of the ErbB family receptors, which is composed of four closely related receptor tyrosine kinases (TK): EGFR (EGFR/ErbB-1), Her 2 (HER2/c-neu, ErbB-2), Her 3 (ErbB-3), and Her 4 (ErbB-4). Epidermal growth factor receptors are receptor TK proteins located in the cell membrane; physiological function is to transduce signals promoting cell proliferation and survival. Growth factor receptors (GFR) signaling can be deregulated in cancer by various mechanisms including aberrantly increased receptor expression, autocrine or paracrine ligand secretion, and somatic mutations.

Some pharmacologic strategies have been developed to target GFR in gastrointestinal cancers:

(i) Monoclonal antibodies (moAbs) which bind epitopes of the extracellular domain of EGFR
(ii) Small molecules that interfere with the intracellular enzymatic function of receptor TK or intracellular signaling molecules to inhibit aberrant signal transduction

22.2.1 moAbs Binding Epitopes of the Extracellular Domain of EGFR

EGFR is approximately expressed by immunohistochemistry (IHC) in 30–70 % of esophageal AD and may correlate with a dismal survival [4]. EGFR inhibition was attempted using moAbs cetuximab, panitumumab and matuzumab and results were reported in several phase I–II studies [5–11].

In metastatic first line after cetuximab or matuzumab and chemotherapy, RR was 31–62 %, PFS 5–9 months, OS 7.6–12 months. In second line, RR was about 3 % and median OS 3–4 months with cetuximab alone. GEJ AD represented the 18–60 % of the patients. Therefore, cetuximab and matuzumab provided modest, if any, survival benefit, either as a single agent or in association to standard therapy.

Cetuximab and panitumumab were also evaluated in two large phase III randomized trials: panitumumab in the REAL-3 study [12] and cetuximab in the EXPAND trial [13]. Both trials failed to meet their primary end point (Table 22.1).

The panitumumab arm was even detrimental in terms of OS; however, in an exploratory analysis, the development of rash due to panitumumab was significantly associated with improved OS (10.3 vs. 4.3 months) and PFS (6.8 vs. 3.7 months).

The Her 2 receptor is another member of the EGFR family; activation plays a key role in cell proliferation and survival. Her 2 overexpression in esophagogastric tumors is distinct from that in breast tumors; it is therefore important to utilize new disease-specific criteria for interpreting Her 2 expression by immunohistochemistry (HIC). It is generally agreed that GEJ AD patients showing strong Her 2 expression (IHC 3+), or weak-moderate Her 2 expression (IHC 2+) with gene amplification as measured by fluorescence in situ hybridization (FISH), are candidates for therapy including the moAb trastuzumab.

The clinical role of Her 2 overexpression has been evaluated in the ToGA international phase III trial [14]. The study compared cisplatin/fluoropyrimidine chemotherapy alone or with trastuzumab with OS as the primary end point. All patients had immunohistochemical overexpression of Her 2 or gene amplification by FISH. Among the screened tumors, Her 2 overexpression was positive in 21 % of gastric carcinomas and in 33 % of GEJ AD. The cohort receiving trastuzumab had a significant improvement in OS, PFS, and response rate. An explorative analysis showed that patients with

Table 22.1 Phase III studies with anti-EGFR moAbs

Study and year	Patients	Setting	Primary end point	Population	Therapy	Outcome
REAL-3 (2013) [12]	553	Metastatic first line	OS	Gastric and GEJ AD (34 %)	Panitumumab + mEOX vs. standard EOX	RR = 42 vs. 46 % mPFS = 6 vs. 7.4 months $p = 0.068$ mOS = 8.8 vs. 11 months $p = 0.01$
EXPAND (2010) [13]	904	Metastatic first line	PFS	Gastric and GEJ AD (16 %)	Cetuximab ± capecitabine/cisplatin	RR = 30 vs. 29 % mPFS = 4.4 vs. 5.9 months mOS = 9.4 vs. 10.7 months

mOS median overall survival, *mPFS* median progression-free survival, *GEJ* gastroesophageal junction, *AD* adenocarcinoma, *RR* response rare, *mEOX* modified Epirubicin, Oxaliplatin, Capecitabine

Table 22.2 Phase III randomized trials targeting HER2

Study and year	Patients	Setting	Primary end point	Population	Therapy	Outcome
ToGA (2010) [14]	594	Metastatic first line	OS	Gastric and GEJ AD (18 %)	Trastuzumab ± fluoropyrimidine/cisplatin	RR = 47 vs. 35 % mPFS = 6.7 vs. 5.5 months mOS = 13.8 vs. 11.1 months
LOGIC (2013) [15]	545	Metastatic first line	OS	Gastric and GEJ AD (9 %)	Lapatinib ± capecitabine/oxaliplatin	RR = 53 vs. 40 % mPFS = 6 vs. 5.4 months mOS = 12.2 vs. 10.5 months

strongly Her 2-positive tumors derived the greatest OS benefit with the addition of trastuzumab (16.0 vs. 11.8 months). Based on these data, trastuzumab was approved, in combination with cisplatin and a fluoropyrimidine, for first-line treatment of metastatic Her 2-overexpressing gastric or GEJ adenocarcinoma (Table 22.2).

Lapatinib ditosylate is a dual anti-EGFR and anti-Her 2 TK. This oral drug was investigated in the LOGIC phase III randomized trial [15]. The primary efficacy population (PEP) comprised subjects with centrally confirmed FISH amplification. Patients were randomized to chemotherapy with or without lapatinib. The study failed to meet its primary end point (i.e., OS of PEP).

Pre-specified subgroup analyses showed significant improvements in OS in the Asian patients and those under 60 years. There was no association between IHC and OS. Toxicity profile shows that lapatinib increased diarrhea and skin toxicity.

Given these negative results, lapatinib is not recommended outside clinical trials.

22.2.2 Small Molecules: Tyrosine Kinase Inhibitors

Erlotinib and gefitinib, tyrosine kinase inhibitors (TKI), were also tested as single agent or in combination with chemotherapy [16–20].

Response rate and stable disease were in the magnitude of 10 %; PFS and OS were in the range of few months only. One trial suggested

that GEJ AD were more likely to respond to erlotinib than gastric cancers [19].

A possible explanation is that KRAS and EGFR mutations are uncommon and thus not predictive of response to TKI in esophageal cancer. In conclusion in the metastatic setting, results were very modest at best for these agents.

22.3 Targeted Therapies Antiangiogenesis

Aberrant tumor angiogenesis has been considered a potential target in cancer therapy.

Strategies have been developed to modulate angiogenic signaling:

(i) Depletion of proangiogenic factors with MoAbs (i.e., by the anti-VEGF MoAb bevacizumab)
(ii) Targeting angiogenic receptors with MoAbs (i.e., by the moAb ramucirumab)
(iii) Targeting angiogenic receptors with TKI (i.e., sunitinib, sorafenib).

22.3.1 Targeting Proangiogenic Factors with moAbs

Bevacizumab is a anti-VEGF-A moAb, a protein playing a significant role in angiogenesis. The antitumor role of the drug was tested in the AVAGAST phase III trial [21] that enrolled 774 patients (14 % GEJ AD) and compared the combination of cisplatin capecitabine (or fluorouracil) with and without bevacizumab in first-line treatment. The trial failed to meet the primary end point (OS); subgroup analysis for GEJ AD was also consistent with the overall result of the study.

Median OS was 10.1 and 12.1 months in the control and bevacizumab arms, respectively; on the other hand, there was a significant improvement in PFS (5.3 vs. 6.7 months) and ORR (37 % vs. 46 %). Bevacizumab safety profile was as expected, with increased rates of hypertension (6.2 % vs. 0.5 %) and gastrointestinal perforation (2.3 % vs. 0.3 %).

22.3.2 Targeting Angiogenic Receptors with moAbs

Ramucirumab is an anti-VEGF receptor-2 moAb. The REGARD [22] and RAINBOW [23] randomized phase III clinical trials tested the efficacy of ramucirumab in advanced/metastatic pretreated gastric or GEJ AD patients with ECOG PS≤1. The primary end point (OS) was met in both studies.

In the REGARD trial, 355 pretreated patients (25 % GEJ AD) were randomized (2:1) to receive ramucirumab or placebo.

In the ramucirumab arm, mOS was 5.2 vs. 3.8 months ($p=0.047$), mPFS was 2.1 vs. 1.3 months ($p<0.0001$), and disease control rate was 49 % vs. 23 % ($p<0.0001$).

In the subgroup analysis for GEJ AD, significance was maintained only for PFS (HR 0.39) and not for OS.

Hypertension, an adverse event associated with most antiangiogenic treatments was doubled in the ramucirumab arm (16 % vs. 8 %).

Ramucirumab has been approved by FDA as a single agent for the treatment of patients with advanced or metastatic gastric, or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

In the RAINBOW study, 665 patients were randomized (1:1) to paclitaxel with or without ramucirumab. In the ramucirumab arm, mOS was 9.6 vs. 7.4 months ($p=0.017$), mPFS was 4.4 vs. 2.9 months ($p<0.0001$), and ORR 28 % vs. 16 % ($p=0.0001$) (Table 22.3).

22.3.3 Targeting Angiogenic Receptors with TKI

Sorafenib and sunitinib are multitargeted TKI that inhibit angiogenesis by targeting different signaling pathways. Phase II studies have been conducted mostly in second line, but, at present, only was shown modest activity and further development is unlike. OS was about 7 months and PFS in the range of 1.3–3.6 months [24–28].

Table 22.3 Phase III randomized trials targeting angiogenesis

Study and year	Patients	Setting	Primary end point	Population	Therapy	Outcome
AVAGAST (2011) [21]	774	Metastatic first line	OS	Gastric and GEJ AD (14 %)	Fluoropyrimidine/cisplatin ± bevacizumab	RR = 37 vs. 46 % mPFS = 5.3 vs. 6.7 months mOS = 10.1 vs. 12.1 months
RAINBOW (2014) [22]	665	Metastatic pretreated	OS	Gastric and GEJ AD	Paclitaxel ± ramucirumab	RR = 28 vs. 16 % mPFS = 4.4 vs. 2.9 months mOS = 9.6 vs. 7.4 months
REGARD (2014) [23]	355	Metastatic pretreated	OS	Gastric and GEJ AD (25 %)	Ramucirumab vs. placebo	RR = 49 vs. 23 % mPFS = 2.1 vs. 1.3 months mOS = 5.2 vs. 3.8 months

22.4 Targeted Therapies Anti-MET (Hepatocyte Growth Factor Receptor)

The overexpression and amplification of MET pathway induces proliferation and antiapoptotic signals. Approximately 10 % of gastric cancers exhibit MET amplification and 20–30 % MET overexpression; both amplification and overexpression have been associated with poor prognosis. However, quantification of MET overexpression is flawed by the different evaluation criteria used by individual authors; pathologist training and inter-laboratory quality control are needed for standardization of the results [29].

A phase II randomized study evaluated anti-HGF moAb rilotumumab with or without chemotherapy in 121 non-MET selected naïve patients. Rilotumumab improved OS (11.1 vs. 5.7 months, $p = 0.01$) in MET-high tumors [30].

Onartuzumab and rilotumumab are presently under evaluation in phase III trials. The TKi crizotinib, tivantinib, and foretinib failed to demonstrate significant antitumor activity.

22.5 Targeted Therapies: The Mammalian Target of Rapamycin (mTOR) Complex

mTOR is an intracellular serine/threonine kinase that acts in two protein complexes, TORC1 and TORC2, the mammalian target of rapamycin complex. mTOR is involved in multiple pathways regulating cell survival, motility, metabolism, and protein synthesis, frequently deregulated in cancer. Everolimus is an oral drug inhibiting mTOR pathway.

A phase II study in chemotherapy-pretreated patients reported a disease control rate of 56 % after everolimus; mOS was 10 months and mPFS 2.7 months. Mild pneumonitis (G1-2) related to everolimus was observed in 15 % of the patients [31].

Based on these data, everolimus was evaluated in the GRANITE-1, a placebo-controlled phase III trial. mPFS and mOS were 1.7 and 5.4 months, respectively, in the intervention arm, and disease control rate was 43 %; the primary end point (i.e., OS) was not met. Pneumonitis occurred in 3 % of the patients [32].

The ability of everolimus to enhance the activity of second-line treatment with paclitaxel is currently investigated in another randomized phase III trial.

Conclusions

In unresectable and metastatic GEJ AD, chemotherapy has produced a modest impact on overall survival.

The availability of new drugs, such as targeted agents, gives new hope to the patients; to date, however, the survival improvement has been overall unsatisfactory.

Nevertheless, the various targeted drugs tested in clinical trials appear promising and shine new light on the difficult steep path of cure of this aggressive tumor.

Two other major points has to be taken into account: clinical results must be balanced against the high cost of these treatments, and treatment options should primarily take into account the quality of life and quality-adjusted survival of patients.

References

1. Wiedmann MW, Mössner J (2013) New and emerging combination therapies for esophageal cancer. Cancer Manag Res 5:133–146
2. Pasini F, Fraccon AP, de Manzoni G (2011) The role of chemotherapy in metastatic gastric cancer. Anticancer Res 31(10):3543–3554
3. Hofheinz RD, Al-Batran SE, Ridwelski K et al (2010) Population-based patterns of care in the first-line treatment of patients with advanced esophagogastric adenocarcinoma in Germany. Onkologie 33(10):512–518
4. Wang KL, Wu TT, Choi IS et al (2007) Expression of epidermal growth factor receptor in esophageal and esophagogastric junction adenocarcinomas: association with poor outcome. Cancer 109(4):658–667
5. Pinto C, Di Fabio F, Barone C et al (2009) Phase II study of cetuximab in combination with cisplatin and docetaxel in patients with untreated advanced gastric or gastro-oesophageal junction adenocarcinoma (DOCETUX study). Br J Cancer 101:1261–1268

6. Lordick F, Luber B, Lorenzen S et al (2010) Cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric cancer: a phase II study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Br J Cancer 102:500–505
7. Moehler M, Mueller A, Trarbach T et al (2011) Cetuximab with irinotecan, folinic acid and 5-fluorouracil as first-line treatment in advanced gastroesophageal cancer: a prospective multi-center biomarker-oriented phase II study. Ann Oncol 22:1358–1366
8. Rao S, Starling N, Cunningham D et al (2010) Matuzumab plus epirubicin, cisplatin and capecitabine (ECX) compared with epirubicin, cisplatin and capecitabine alone as first-line treatment in patients with advanced oesophago-gastric cancer: a randomised, multicentre open-label phase II study. Ann Oncol 21:2213–2219
9. Gold PJ, Goldman B, Iqbal S et al (2010) Cetuximab as second-line therapy in patients with metastatic esophageal adenocarcinoma: a phase II Southwest Oncology Group Study (S0415). J Thorac Oncol 5(9):1472–1476
10. Trarbach T, Przyborek M, Schleucher N et al (2013) Phase I study of matuzumab in combination with 5-fluorouracil, leucovorin and cisplatin (PLF) in patients with advanced gastric and esophagogastric adenocarcinomas. Invest New Drugs 31:642–652
11. Okines AF, Ashley SE, Cunningham D et al (2010) Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for advanced esophagogastric cancer: dose-finding study for the prospective multicenter, randomized, phase II/III REAL-3 trial. J Clin Oncol 28(25):3945–3950
12. Waddell T, Chau I, Cunningham D et al (2013) Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol 14:481–489
13. Lordick F, Kang YK, Chung HC et al (2013) Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol 14:490–499
14. Bang YJ, Van Cutsem E, Feyereislova A et al (2010) Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial. Lancet 376:687–697
15. Hecht JR, Bang YJ, Qin S et al (2013) Lapatinib in combination with capecitabine plus oxaliplatin (CapeOx) in HER2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma (AC): the TRIO-013/LOGiC Trial. J Clin Oncol 31(Suppl LBA 4001)
16. Ferry DR, Anderson M, Beddard K et al (2007) A phase II study of gefitinib monotherapy in advanced esophageal adenocarcinoma: evidence of gene expression, cellular, and clinical response. Clin Cancer Res 13:5869–5875
17. Adelstein DJ, Rodriguez CP, Rybicki LA et al (2012) A phase II trial of gefitinib for recurrent or metastatic cancer of the esophagus or gastroesophageal junction. Invest New Drugs 30(4):1684–1689
18. Wainberg ZA, Lin LS, Di Carlo B et al (2011) Phase II trial of modified FOLFOX6 and erlotinib in patients with metastatic or advanced adenocarcinoma of the oesophagus and gastro-oesophageal junction. Br J Cancer 105(6):760–765
19. Dragovich T, McCoy S, Fenoglio-Preiser CM et al (2006) Phase II trial of erlotinib in gastroesophageal junction and gastric adenocarcinomas: SWOG 0127. J Clin Oncol 24(30):4922–4927
20. Ilson DH, Kelsen D, Shah M et al (2011) A phase 2 trial of erlotinib in patients with previously treated squamous cell and adenocarcinoma of the esophagus. Cancer 117(7):1409–1414
21. Ohtsu A, Shah MA, Van Cutsem E et al (2011) Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 29:3968–3976
22. Fuchs CS, Tomasek J, Yong CJ et al (2014) Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 383(9911):31–39
23. Wilke H, Van Cutsem E, Oh SC et al (2014) RAINBOW: a global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy rainbow IMCL CP12-0922 (I4T-IEJVBE). J Clin Oncol 32(Suppl 3 abstr LBA7)
24. Martin-Richard M, Gallego R, Pericay C et al (2013) Multicenter phase II study of oxaliplatin and sorafenib in advanced gastric adenocarcinoma after failure of cisplatin and fluoropyrimidine treatment. A GEMCAD study. Invest New Drugs 31:1573–1579
25. Sun W, Powell M, O'Dwyer PJ et al (2010) Phase II study of sorafenib in combination with docetaxel and cisplatin in the treatment of metastatic or advanced gastric and gastroesophageal junction adenocarcinoma: ECOG 5203. J Clin Oncol 28:2947–2951
26. Moehler MH, Thuss-Patience PC, Schmoll HJ et al (2013) FOLFIRI plus sunitinib versus FOLFIRI alone in advanced chemorefractory esophagogastric cancer patients: a randomized placebo-controlled multicentric AIO phase II trial. J Clin Oncol 31(Suppl abstr 4086)
27. Bang YJ, Kang YK, Kang WK et al (2011) Phase II study of sunitinib as second-line treatment for advanced gastric cancer. Invest New Drugs 29:1449–1458
28. Moehler M, Mueller A, Hartmann JT et al (2011) An open-label, multicentre biomarker-oriented AIO phase II trial of sunitinib for patients with chemorefractory advanced gastric cancer. Eur J Cancer 47:1511–1520

29. Morishita A, Gong J, Masaki T (2014) Targeting receptor tyrosine kinases in gastric cancer. World J Gastroenterol 20(16):4536–4545
30. Oliner KS, Tang R, Anderson A et al (2012) Evaluation of MET pathway biomarkers in a phase II study of rilotumumab (R, AMG 102) or placebo (P) in combination with epirubicin, cisplatin, and capecitabine (ECX) in patients (pts) with locally advanced or metastatic gastric (G) or esophagogastric junction (EGJ) cancer. J Clin Oncol 30(Suppl abstr 4005)
31. Doi T, Muro K, Boku N et al (2010) Multicenter phase II study of everolimus in patients with previously treated metastatic gastric cancer. J Clin Oncol 28(11):1904–1910
32. Ohtsu A, Ajani JA, Bai YX et al (2013) Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. J Clin Oncol 31(31):3935–3943

Recurrence: Treatment or Just Palliation?

23

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23.1 Timing and Patterns of Recurrence

Gastroesophageal adenocarcinoma has a poor prognosis despite aggressive treatment. Recurrent cancer is one of the main causes of death in patients undergoing surgery. The pattern of recurrence is determined by the complex anatomic features of this region. In fact the direct tumor extension could explain local recurrence, and the spread through the rich submucosal lymphatic or vascular structures could justify lymph-nodal failure and recurrence at distant sites; finally transcoelomic spread could lead to peritoneal recurrence. Only few reports have analyzed time and site of recurrence in gastroesophageal cancer patients. Furthermore, the data available in literature are often not comparable for radicality of resection, tumor location according to the Siewert classification, histology, and preoperative chemoradiotherapy (Table 23.1).

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Blomjous et al. in a study published in the early 1990s investigated the rate and site of recurrence in 93 patients that underwent resective surgery for adenocarcinoma of gastric cardia (12 patients had positive resection margin) [1]. At a mean follow-up of 24 months, 57 % of these patients had a recurrence of disease with cumulative recurrence rate of 69 % at 5 years. Positive resection margin was significantly related to locoregional failure. The 5-year rates for locoregional and distant recurrence were 36 % and 64 %, respectively. Distant metastases occurred more frequently in the liver, peritoneum, and lungs. Similar results were reported by Mattioli et al. in a retrospective analysis of 126 patients surgically treated for adenocarcinoma of the cardia [2]. At a median follow-up of 33 months, they reported a recurrence rate of 48.28 %. Some 15 patients (26 %) had local recurrence, while 44 patients (74 %) had distant recurrence. The median disease-free survival for local failure and distant recurrence was 26 and 19 months, respectively. Another interesting analysis of recurrence after resection for adenocarcinoma of gastric cardia was performed by Stassen with a retrospective, single institution 10-year study [3]. The author identified 184 patients operated on for gastric cardia cancer with 102 recurrences of disease (55.43 %) at a mean follow-up of 26 months. Metastatic lymph nodes were significantly related to recurrence at multivariate analysis. Wayman and colleagues compared the

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Table 23.1 Patterns of recurrence of gastroesophageal cancer

Authors	Year	Resection margin	Cohort size	Percentage of recurrence	Median follow-up (months)	Tumor location	Pattern of relapse
Blomjous [1]	1991	R0 + R1	53/93	57	24	Cardia	*Distant* (HE + peritoneal) 64 % *LR* 36 %
Mattioli [2]	2000	R0 + R1	59/116	48.28	33	Cardia	*Distant* (HE + supraclavicular lymph nodes) 74 % *LR* 26 %
Stassen [3]	2000	R0 + R1 + R2	102/184	55.43	26	Cardia	Unknown
Waymann [4]	2002	R0 + R1	103/169	60.95	75.3	Siewert I Siewert II	Similar between type I and type II *HE* 54.5 % vs 54.2 % *L* 32.7 % vs 29.2 % *LN* 18.2 % vs 25 % *PE* 7.3 % vs 14.6 %
De Manzoni [6]	2003	R0	55/92	55.78	58.5	Siewert I Siewert II Siewert III	Different patterns of recurrence between type I vs II vs III *LR* 27.3 % vs 36.8 % vs 32 % *HE* 45.5 % vs 47.4 % vs 32 % *HE* + *L* 27.3 % vs 5.3 % vs 4 % *PE* 0 % vs 10.5 % vs 32 %
Wang [5]	2013	R0	147/299	49.16	25	GEJ	*PE* 35.4 % *HE* 32.7 % *LR* 28.6 % *Extra-abdominal* 3.4 %
Hosakawa [7]	2014	R0	56/127	44.1	48.9	Siewert I Siewert II Siewert III	Different patterns of recurrence between type I vs II vs III *HE* 0 % vs 50 % vs 31.3 % *LN* 50 % vs 33.3 % vs 25 % *PE* + *PL* 25 % vs 30.6 % vs 43.8 % *L* 25 % vs 5.6 % vs 0 %

pattern of dissemination and recurrence in patients with Siewert I and Siewert II adenocarcinomas of esophagogastric junction [4]. The median follow-up of patients was 75.3 months. Of the 169 patients that underwent surgery, 103 patients (60.95 %) developed recurrent disease (58.51 % among Siewert I and 64 % among Siewert II type). Type I and type II cancers showed similar time to recurrence (23.3 and 20.5 months, respectively). The patterns of recurrence were similar; the most common type of recurrence was hematogenous, followed by local and lymph-nodal failure, and finally peritoneal dissemination. The median time to relapse for hematogenous, lymphatic, local, and peritoneal recurrence was 12, 18.2, 12, and 5 months, respectively. In a multivariate analysis, lymph node status and histological evidence of lymphatic invasion were correlated with disease-free survival. In a recent report, enrolling 147 patients with evidence of recurrent disease, Wang et al. tried to identify the risk factors associated with early relapse (within 1 year) [5]. The median follow-up was 25 months. At multivariate analysis, the degree of differentiation and vascular tumor thrombi resulted in independent risk factors for early recurrence. The mean time to recurrence was 16.3 months, and the recurrence rate within 1 year was 48.3 %.

Only two studies have investigated the pattern and the timing of recurrence according to the Siewert classification, in R0 surgery and in patients not receiving neoadjuvant therapy [6, 7]. Interestingly, different types of cancer showed different patterns of recurrence. Type III tumors showed a pattern of peritoneal dissemination comparable to that of gastric cancer, while peritoneal recurrence was less common in subtype II and rare in subtype I. The most frequent pattern of spreading in Siewert I and Siewert II adenocarcinomas was hematogenous spread. In both studies, the median time to relapse was not different for different Siewert subtypes. As reported in published papers by other authors, the only risk factor for recurrence was the number of metastatic lymph nodes [1, 3].

In a series of 326 consecutive patients with Siewert type II and III carcinomas from the Italian Research Group for Gastric Cancer (GIRCG) database, the 10-year cumulative risk of recurrence (± standard error, SE) was 64 ± 3 % (Fig. 23.1). Most recurrences (84 %) occurred in the first 2 years after surgery. Figure 23.2 reports the cumulative risk of recurrence in the GIRCG series, according to the pattern of recurrence (local vs. distant). The cumulative 10-year risk of recurrence was higher for distant recurrences (42 ± 4 %) than locoregional failures (28 ± 4 %), and the median time to recurrence was slightly shorter (median 11 vs. 12 months after surgery). Survival after recurrence was also evaluated in the GIRCG database (Fig. 23.3). The median survival was higher in locoregional than distant recurrence (6 vs. 3 months). However, it is of note that no survival probability at 30 months was observed after diagnosis of recurrence in both groups. As such, these data indicate that treatment of recurrence of esophagogastric junction cancer should be considered within palliation perspectives.

Which is the influence of neoadjuvant chemotherapy and/or radiotherapy on the patterns of recurrence? Even if different randomized trials have shown contrasting results about the overall survival, the role of neoadjuvant therapy in local control is clear [8–14]. Patterns of failure analyses in these trials strongly suggest a significant decrease of locoregional recurrence. Smit et al. in a nonrandomized study showed a marked improvement of locoregional control in the chemoradiotherapy + surgery (CRS) arm primarily due to a significant decrease in nodal recurrences of the paraesophageal basin [15]. No differences were found in distant recurrence rates. However, a subgroup analysis revealed a statistically significant difference in skeletal recurrences, occurring in 12 % of surgery-alone group vs 1 % in the CRS group ($P = 0.009$).

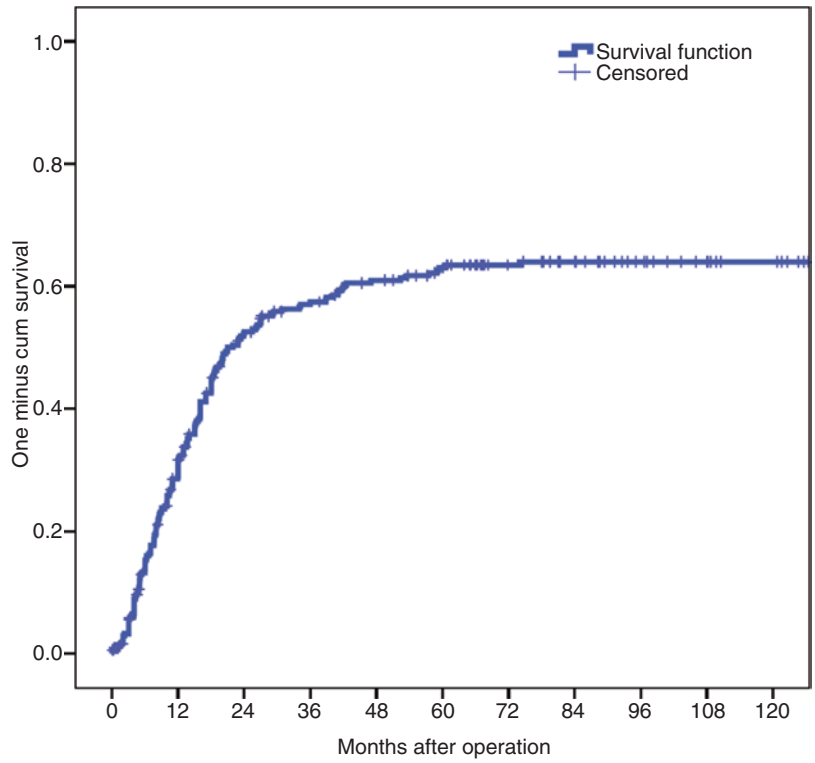

Fig. 23.1 Cumulative risk of recurrence in 326 consecutive patients with Siewert type II and III carcinomas from the Italian Research Group for Gastric Cancer (GIRCG) database

The CROSS trial reported that the majority of locoregional recurrences occur within 2 years of follow-up [15]. Interestingly, in this study, the CRS group of patients had a lower rate of recurrences either at the anastomosis and mediastinal lymph nodes or on the peritoneal surface and distant sites as well. No differences between both arms were reported in the recurrence rates at the supraclavicular and paraortic lymph nodes and at celiac axis. Only 5 % of recurrences occurred into irradiated field volume.

Fields et al. investigated recurrences after pathologic complete response (pCR) to preoperative therapy followed by surgery in gastric or gastroesophageal (Siewert II–Siewert III) adenocarcinoma patients [16]. They showed that patients who achieved a pCR after preoperative therapy (chemoterapy ± radiotherapy) maintained a significant risk of recurrence. The 5-year probability of recurrence in non-pCR patients and pCR patients was 51 % and 27 %, respectively. The distribution of local/regional vs distant recurrence in the pCR and non-pCR arms was similar. However, there is a significantly higher incidence of symptomatic central nervous system first recurrences in pCR patients.

23.2 Treatment or Just Palliation?

Local failures of gastroesophageal cancers without distant metastasis occur in about 3–5 % of patients with relapsing disease. Treatment options of this condition are limited, and the common management strategy usually includes palliative methods to alleviate dysphagia. Different palliative treatment modalities have been reported in the literature with the aim to relieve symptoms, ensure nutrition, and improve patient's quality of life. The palliation in terms of lumen obstruction may be achieved with different strategies: surgical bypass, stent placement, external radiation, brachytherapy, chemotherapy, intratumoral injection of absolute alcohol, balloon dilation, laser ablation (thermal Nd: YAG or photodynamic), or percutaneous endoscopic gastrostomy.

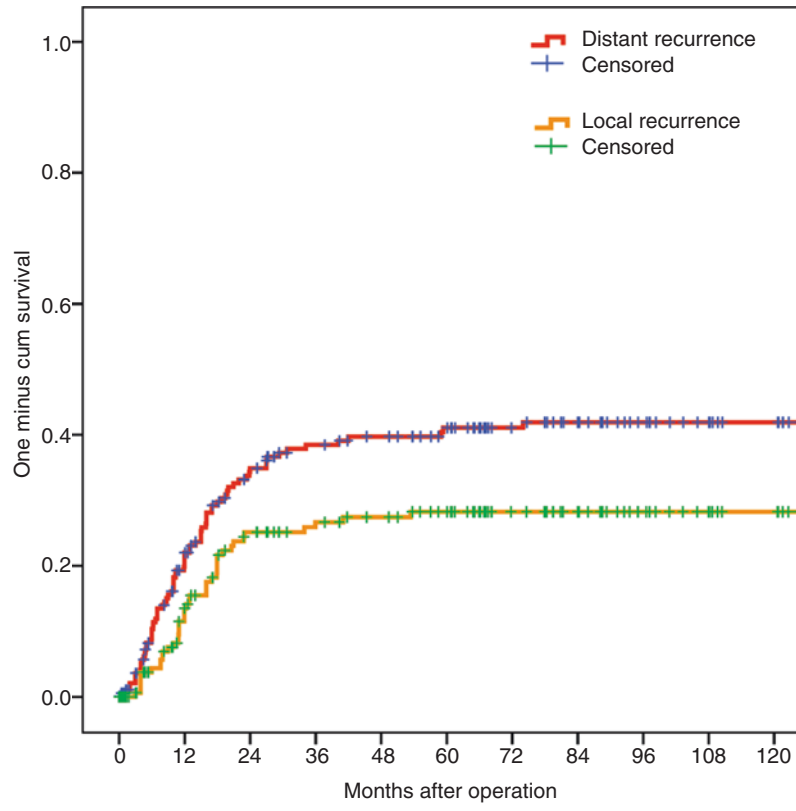

Fig. 23.2 Cumulative risk according to the pattern of recurrence (locoregional vs. distant) in Siewert type II and III carcinomas (Data from GIRCG database)

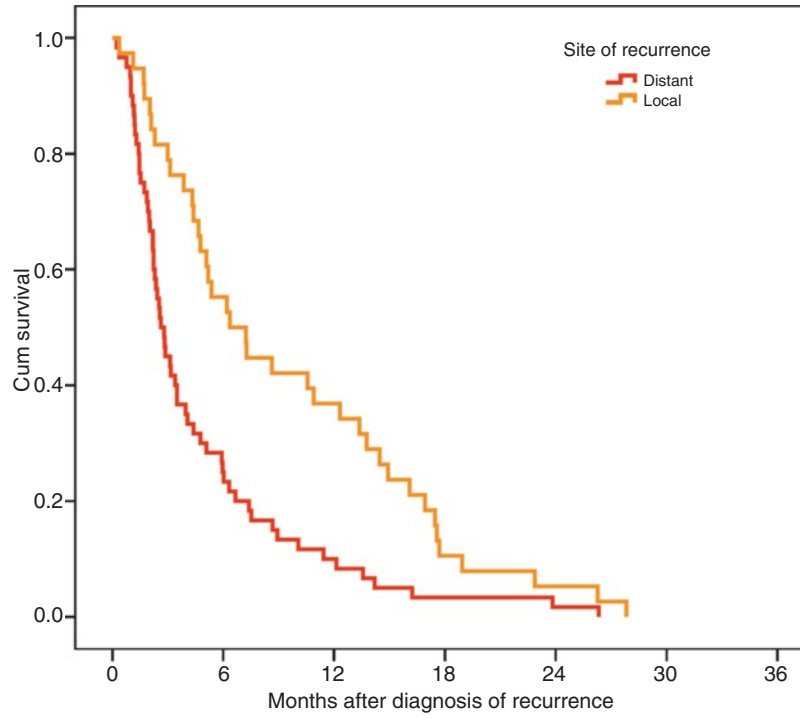

Fig. 23.3 Survival after diagnosis of recurrence according to the site of failure (locoregional vs. distant) in Siewert type II and III carcinomas (Data from GIRCG database)

23.2.1 Surgery

Only patients with local failure (surgical anastomosis, esophageal or gastric remnants) are possible candidates for tumor re-resection, and a possible survival improvement for these patients has been supposed. The literature is rather sparse on this subject; indeed, only few reports exist with small numbers of patients or case reports. Another important limitation of these studies is the lack of informations about the site of primary cancer according to Siewert classification. Also, the inclusion criteria of patients are anecdotal because the cohorts analyzed in such studies include either patients with primary esophageal cancer (squamous cell carcinoma or adenocarcinoma) or patients with primary gastroesophageal junction cancer or gastric cancer.

Schipper et al. published the largest series of patients submitted to re-resection for recurrent esophageal carcinoma. It's a retrospective, single institutional study based on a 30-year period [17]. They identified 27 patients with recurrent esophageal or gastroesophageal cancers (24 adenocarcinomas with 16 gastroesophageal junction tumors); 19 cases underwent a re-resection (15 R0, 4 R1), while 8 received a biopsy only for intraoperative evidence of unresectable disease. One-, three-, and five-year survival for R0 patients was 62 %, 44 %, and 35 %, respectively. Survival for incomplete resection was 27 % at 1 year, 18 % at 2 years, and null at 3 years. The authors reported that these surgical procedures were associated with significant morbidity that occurred in 16 patients (59 %); reoperation to treat a complication was necessary in 10 patients (37 %).

Another interesting study by Badgwell et al. reported 60 consecutive patients who underwent attempted resection for recurrent gastric or gastroesophageal adenocarcinoma [18]. Only 29 patients, including 10 primary cancers of the gastroesophageal junction, underwent a complete re-resection (23 with isolated local recurrence), while 31 patients (52 %) were classified as unresectable at exploratory laparotomy. One-, three-, and five-year OS rates were 72 %, 38 %, and 28 %, respectively, for patients who underwent re-resection, and 36 %, 6 %, and 0, respectively, for patients who had unresectable disease. The morbidity of second respective surgery was high, with 52 % of patients presenting complications (Fig. 23.4).

In conclusion, re-resection should be considered in highly selected patients with no evidence of disseminate disease. The significant morbidity and mortality procedure related may be justified by prolonged survival.

23.2.2 Stents

To date, endoscopic self-expanded stent is the most frequently adopted method worldwide to relief dysphagia because it is a minimally invasive and technically easy approach (Figs. 23.5 and 23.6).

Prior to 1990, the lumen obstruction was treated by rigid plastic devices. These stents were characterized by fixed diameter and were difficult to place. Furthermore, they were associated with unacceptable high complication rates. With the introduction of self-expanding metal stents (SEMSs), rigid stents have disappeared. The main advantages of SEMS, developed in early 1990s, are the easy placement, due to stent flexibility, and the rapid improvement of dysphagia. However, there are some disadvantages like high cost, chest pain, risk of stent migration, visceral perforation, hemorrhage, and intractable reflux in distal stents that lay across the gastroesophageal junction.

Newer stents that include an antireflux mechanism should theoretically reduce this complication. However, according to a recent meta-analysis, conventional self-expanding stents and antireflux stents are equally effective for the relief of reflux [19].

The recurrence of dysphagia varies between 6.4 and 52 % [20, 21] and may occur as a consequence of tumor ingrowth, tissue overgrowth, stent migration, impacted food, or spontaneous

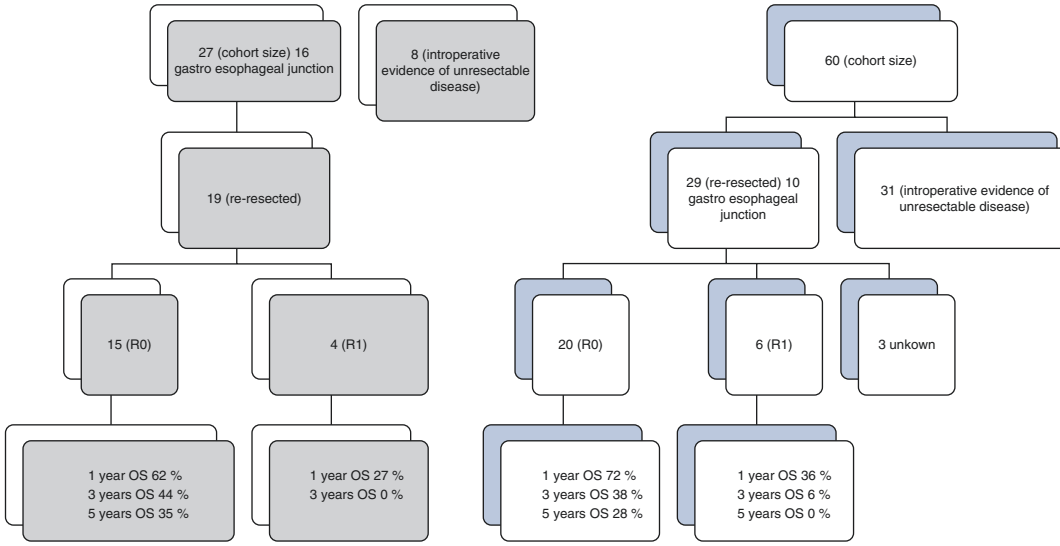

Fig. 23.4 Results of surgical resection after recurrence of gastroesophageal cancer [17, 18]

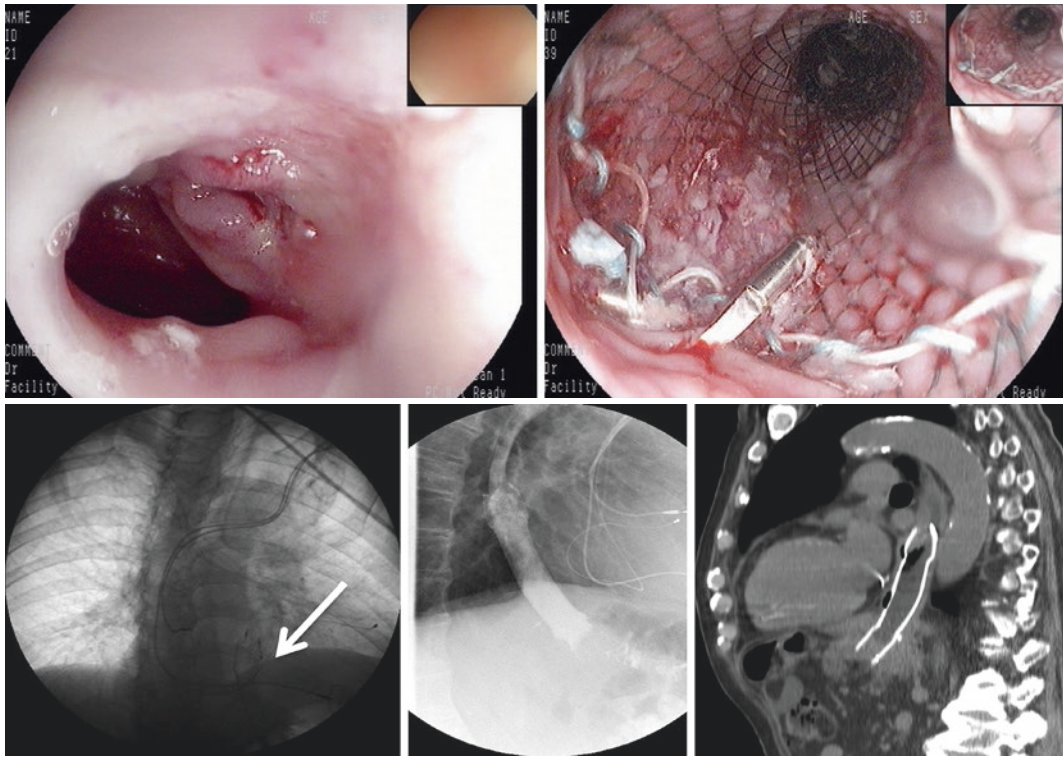

Fig. 23.5 Locoregional failure after total gastrectomy for Siewert III cancer. Palliation with a self-expanding metallic stent the radiograph indicates successful placement of stent (*white arrow*)

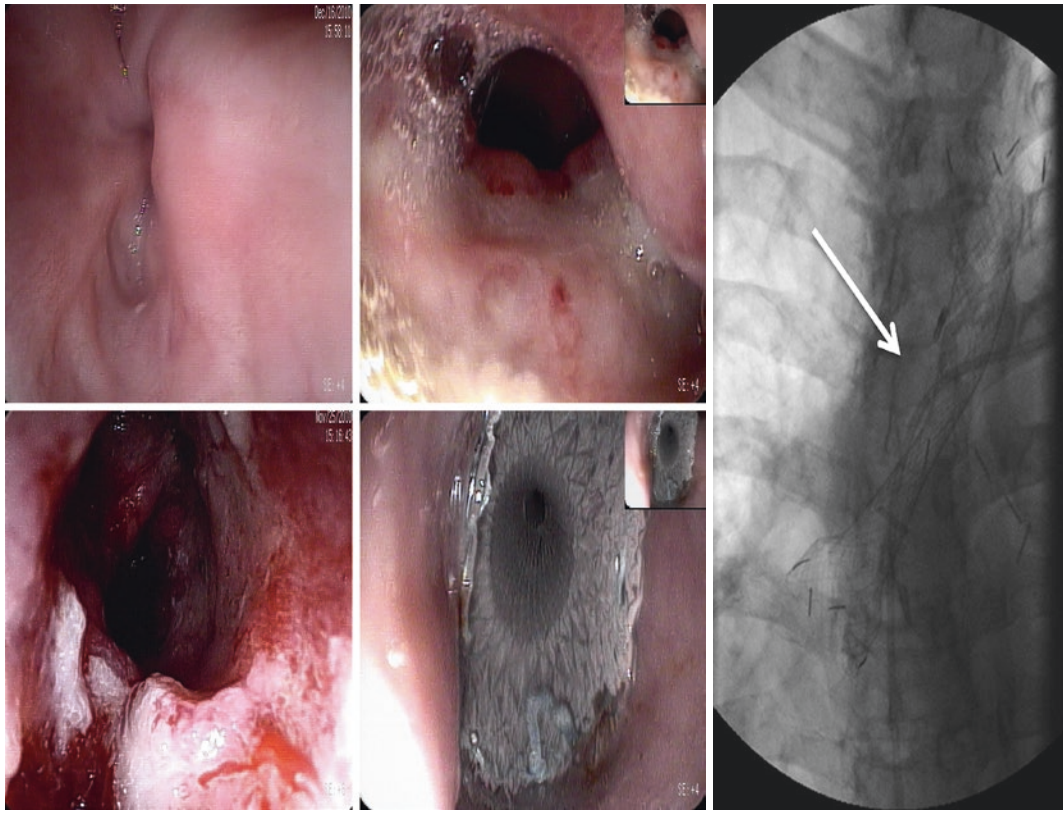

Fig. 23.6 Local failure after distal esophagectomy and proximal gastrectomy for Siewert I cancer. Self-expanding stent in place the radiograph indicates successful placement of stent (*white arrow*)

stent fracture with collapse. To solve the problem of tumor ingrowth, several companies covered the stents with plastic membrane. SEMS can be partially or fully covered with semipermeable membranes; tissue overgrowth at the uncovered ends allows better anchoring but renders difficult their removal. Fully covered stents can be removed, but the reverse procedure is associated with higher risk of migration [22]. The most recent stents are self-expanding plastic stents (SEPSs). SEPS are larger and less flexible than SEMS; therefore, insertion is technically more difficult. Verschuur et al. [23] reported high risk of failure of stent placement (17 %). Furthmore, Conio et al. [21], in a randomized study, revealed significantly higher rates of complications and recurrent dysphagia.

To date, there are no differences between different stents in terms of efficacy and safety for the palliative treatment of malignant obstruction. Each type of the stents has its own merit and demerit relatively.

23.2.3 Photodynamic Therapy

Photodynamic therapy (PDT) is a non-thermal tumor ablative treatment. The rationale for the use of PDT in oncology is based on the toxic effect on malignant cells of photosensitizing agents after light stimulation. A hematoporphyrin derivative is generally used in clinical practice. After intravenous injection, the photosensitizing agent preferentially accumulates in malignant tissues and adsorbs photons emitted by the light source. This results in the conversion into an excited electronic state with transferral of energy to the surrounding oxygen and production of reactive oxygen species. The reactive oxygen species determine microvasculature damage and subsequent ischemia of the

tumor. This reaction results in an endoluminal superficial tumor necrosis [24].

One PDT course is defined as an injection of the photosensitizing agent followed by two sessions of laser exposure. After 24–48-h from the injection, patients undergo to endoscopic application of monochromatic laser light (red dye laser wavelength 630 nm). A second session, to administer additional laser therapy, can be repeated 24–48 h later.

PDT is a technically easy procedure to relief malignant dysphagia in the palliative treatment of esophageal cancer. According to Litle et al., significant dysphagia relief was achieved in up to 85 % of the patients with a mean dysphagia-free interval of 9 weeks [25]. Lightdale, in a randomized multicenter trial involving 236 patients, compared PDT to Nd-YAG laser ablation. PDT and Nd-YAG laser therapy had similar overall efficacy in terms of dysphagia relief. Perforations occurred in 7 % of the Nd-YAG patients but in only 1 % of the patients treated by PDT [26].

Yano et al. report their experience of esophageal cancer patients treated with salvage PDT for local failure after completion of definitive CRT [27]. The study included uT1 or uT2 cancers without evidence of pathological lymph nodes or distant metastases. A complete response was achieved in 62 % of the patients. The main disadvantages of this procedure included chest pain, posttreatment esophagitis, and skin photosensitivity persisting for 4–6 weeks after treatment. In summary salvage PDT represents a potentially new and promising treatment option.

23.2.4 Nd-YAG Laser

Another endoscopic approach to relieve malignant dysphagia is the neodymium yttrium aluminium garnet (Nd-YAG) laser, which causes heating and vaporization of tumor tissue through the delivery of an intense beam of laser light. This causes a burn deep enough to reconstitute the patency of the esophageal lumen, with a rapid improvement of patient's ability to swallow. This laser therapy can coagulate up to 6 mm in depth and can obliterate vessels up to 4 mm in diameter. Endoscopic Nd-YAG laser therapy is suitable for patients with exophytic tumors, while infiltrating tumors should not be treated by this approach for increasing risk of perforation.

23.2.5 Radiation Therapy and Brachytherapy

The feasibility and effectiveness of radiotherapy (RT) for postoperative recurrent gastroesophageal cancer are still unknown. In literature, few data exist about the effectiveness of RT for symptom palliation in recurrent esophageal cancers. Furthermore, the majority of these studies involve patients with proved primary squamous cell carcinoma.

Fakhrian et al., in a recent retrospective report, analyzed 54 patients (37 squamous cell carcinomas and 17 adenocarcinomas) with recurrent local or locoregional esophageal cancer.

They reported a poor survival with only 19 % of patients surviving beyond 3 years; a symptom improvement was present in 67 % of patients with acceptable procedure-related acute and late toxicities [28].

In 2009, Baxi et al. retrospectively assessed 14 patients treated with salvage chemoradiotherapy after primary surgery. Ten patients had esophageal adenocarcinoma and four esophageal squamous cell carcinoma. The median overall survival for these patients was 16 months with only one patient alive after 2 years. The authors reported a toxicity of salvage therapy acceptable [29].

Some authors suggest, for patients with a life expectancy of more than 3 months, the combination of RT and esophageal stent placement as a multimodal approach to relief dysphagia [30]. Brachytherapy is another therapeutic option to alleviate dysphagia. The improvement of dysphagia ranges between 26.5 and 73 %, while recurrent dysphagia occurs frequently (7–43 %) [31, 32]. In the literature, there are some randomized trials comparing brachytherapy with metal stent placement for the palliation of dysphagia [33, 34]. The SIREC trial involved 209 patients with a mean age 69 years old, recruited in 9 hospitals in the Netherlands. According to this study, dysphagia improves more rapidly

after stent placement than after single-dose brachytherapy, but long-term relief of dysphagia is better after brachytherapy. Complications occurred more frequently in the stent placement arm. They concluded that stent placement was not preferable to single-dose brachytherapy as palliation treatment for inoperable esophageal cancer patients with dysphagia.

23.2.6 Chemotherapy

A phase II trial investigated the feasibility and safety of gefitinib in patients with recurrent or metastatic cancer of the esophagus or gastro-esophageal junction [*ClinicalTrials.gov Identifier*: NCT00268346]. The primary outcome was the response rate in a cohort of 58 patients, while the secondary end point was the drug-related toxicity. The authors reported a response rate of 6.9 %. Serious adverse events occurred in 8/58 patients (13.8 %) with a difference between patients that have not received previous systemic therapy and patients who previously received systemic treatments (22.2 % vs. 10 %).

23.3 Conclusions

Recurrence of esophagogastric junction cancer is a frequent event even after potentially curative R0 resection. Most recurrences occur in the first 2 years from surgery. Treatment approach to recurrent esophagogastric junction carcinoma offers very low probability of cure and should be considered within palliative perspectives. Strategies to prevent recurrence should be implemented in clinical practice.

References

1. Blomjous JG, Hop WC, Langenhorst BL et al (1992) Adenocarcinoma of the gastric cardia. Recurrence and survival after resection. Cancer 70(3):569–574
2. Mattioli S, Di Simone MP, Ferruzzi L et al (2001) Surgical therapy for adenocarcinoma of the cardia: modalities of recurrence and extension of resection. Dis Esophagus 14(2):104–109
3. Stassen LP, Bosman FT, Siersema PD et al (2000) Recurrence and survival after resection of adenocarcinoma of the gastric cardia. Dis Esophagus 13(1):32–38
4. Wayman J, Bennett MK, Raimes SA et al (2002) The pattern of recurrence of adenocarcinoma of the oesophago-gastric junction. Br J Cancer 86(8):1223–1229
5. Wang G, Wu A, Cheng X et al (2013) Risk factors associated with early recurrence of adenocarcinoma of gastroesophageal junction after curative resection. Chin J Cancer Res 25(3):334
6. de Manzoni G, Pedrazzani C, Pasini F et al (2003) Pattern of recurrence after surgery in adenocarcinoma of the gastro-oesophageal junction. Eur J Surg Oncol 29(6):506–510
7. Hosokawa Y, Kinoshita T, Konishi M et al (2014) Recurrence patterns of esophagogastric junction adenocarcinoma according to Siewert's classification after radical resection. Anticancer Res 34(8):4391–4397
8. Urba SG, Orringer MB, Turrisi A et al (2001) Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 19(2):305–313
9. Walsh TN, Noonan N, Hollywood D et al (1996) A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 335(7):462–467
10. Burmeister BH, Smithers BM, Gebski V et al (2005) Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol 6(9):659–668
11. Tepper J, Krasna MJ, Niedzwiecki D et al (2008) Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 26(7):1086–1092
12. van Hagen P, Hulshof MC, van Lanschot JJ et al (2012) Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 366(22):2074–2084
13. Mariette C, Dahan L, Mornex F et al (2014) Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol 32(23):2416–2422
14. Smit JK, Güler S, Beukema JC et al (2013) Different recurrence pattern after neoadjuvant chemoradiotherapy compared to surgery alone in esophageal cancer patients. Ann Surg Oncol 20(12):4008–4015
15. Oppedijk V, van der Gaast A, van Lanschot JJ et al (2014) Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol 32(5):385–391
16. Fields RC, Strong VE, Gonen M et al (2011) Recurrence and survival after pathologic complete response to preoperative therapy followed by surgery for gastric or gastrooesophageal adenocarcinoma. Br J Cancer 104(12):1840–1847
17. Schipper PH, Cassivi SD, Deschamps C et al (2005) Locally recurrent esophageal carcinoma: when is re-resection indicated? Ann Thorac Surg 80(3):1001–1006

18. Badgwell B, Cormier JN, Xing Y et al (2009) Attempted salvage resection for recurrent gastric or gastroesophageal cancer. Ann Surg Oncol 16(1):42–50
19. Sgourakis G, Gockel I, Radtke A et al (2010) The use of self-expanding stents in esophageal and gastroesophageal junction cancer palliation: a meta-analysis and meta-regression analysis of outcomes. Dig Dis Sci 55(11):3018–3030
20. Siersema PD, Hop WC, van Blankenstein M et al (2001) A comparison of 3 types of covered metal stents for the palliation of patients with dysphagia caused by esophagogastric carcinoma: a prospective, randomized study. Gastrointest Endosc 54(2):145–153
21. Conio M, Repici A, Battaglia G et al (2007) A randomized prospective comparison of self-expandable plastic stents and partially covered self-expandable metal stents in the palliation of malignant esophageal dysphagia. Am J Gastroenterol 102(12):2667–2677
22. Uitdehaag MJ, van Hooft JE, Verschuur EM et al (2009) A fully-covered stent (Alimaxx-E) for the palliation of malignant dysphagia: a prospective follow-up study. Gastrointest Endosc 70(6):1082–1089
23. Verschuur EM, Repici A, Kuipers EJ et al (2008) New design esophageal stents for the palliation of dysphagia from esophageal or gastric cardia cancer: a randomized trial. Am J Gastroenterol 103(2):304–312
24. Hayata Y, Kato H, Okitsu H et al (1985) Photodynamic therapy with hematoporphyrin derivative in cancer of the upper gastrointestinal tract. Semin Surg Oncol 1(1):1–11
25. Litle VR, Luketich JD, Christie NA et al (2003) Photodynamic therapy as palliation for esophageal cancer: experience in 215 patients. Ann Thorac Surg 76(5):1687–1692
26. Lightdale CJ, Heier SK, Marcon NE et al (1995) Photodynamic therapy with porfimer sodium versus thermal ablation therapy with Nd:YAG laser for palliation of esophageal cancer: a multicenter randomized trial. Gastrointest Endosc 42(6):507–512
27. Yano T, Muto M, Minashi K et al (2005) Photodynamic therapy as salvage treatment for local failures after definitive chemoradiotherapy for esophageal cancer. Gastrointest Endosc 62(1):31–36
28. Fakhrian K, Gamisch N, Schuster T et al (2012) Salvage radiotherapy in patients with recurrent esophageal carcinoma. Strahlenther Onkol 188(2):136–142
29. Baxi SH, Burmeister B, Harvey JA et al (2008) Salvage definitive chemo-radiotherapy for locally recurrent oesophageal carcinoma after primary surgery: retrospective review. J Med Imaging Radiat Oncol 52(6):583–587
30. Rueth NM, Shaw D, D'Cunha J et al (2012) Esophageal stenting and radiotherapy: a multimodal approach for the palliation of symptomatic malignant dysphagia. Ann Surg Oncol 19(13):4223–4228
31. Bhatt L, Tirmazy S, Sothi S (2013) Intraluminal high-dose-rate brachytherapy for palliation of dysphagia in cancer of the esophagus: initial experience at a single UK center. Dis Esophagus 26(1):57–60
32. Sharma V, Mahantshetty U, Dinshaw KA et al (2002) Palliation of advanced/recurrent esophageal carcinoma with high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 52(2):310–315
33. Homs MYV, Steyerberg EW, Eijenboom WMH et al (2004) Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: a multicentre randomised trial. Lancet 364(9444):1497–1504
34. Bergquist H, Wenger U, Johnsson E et al (2005) Stent insertion or endoluminal brachytherapy as palliation of patients with advanced cancer of the esophagus and gastroesophageal junction. Results of a randomized, controlled clinical trial. Dis Esophagus 18(3):131–139

Follow-Up and Quality of Life

24

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24.1 Follow-Up for Upper Gastrointestinal Cancers

One of the main debated points in the clinical path of patients with gastric and esophagus–gastric junction (EGJ) cancer concerns the practice of follow-up after radical surgery. At present, there is no incontrovertible evidence about the role of routine controls, and albeit many retrospective series, both from the Eastern [1–3] and Western centers [4–6] and a systematic review [7], have clearly demonstrated that diagnosis of tumor recurrence in the asymptomatic phase has not resulted in an improvement in survival compared to late diagnosis which is generally consequent to the appearance of symptoms, the clinical practice guidelines in many high-volume centers imply that patients are submitted to scheduled clinical and instrumental checks, with the aim to minimize the nutritional sequelae of gastrectomy and to timely diagnose tumor recurrence.

On one hand, a number of considerations adverse to follow-up have been raised. Finding recurrence in the asymptomatic phase is unable to improve survival and, in certain instances, worsens the patients' quality of life from the psychological point of view, by anticipating by some months the diagnosis of death. Some authors pointed out, comparing patients with symptomatic and asymptomatic recurrence, that symptomatic cases are inherently aggressive and are characterized by a lower overall survival, from which the identification of such patients in the asymptomatic phase cannot lead to a better prognosis, though it may be relevant to the therapeutic decision [5]. Others authors, while acknowledging that a diagnosis of recurrence in the asymptomatic phase prolongs survival after diagnosis of recurrence, clarify that the delayed diagnosis in the group with symptomatic relapse makes no difference in overall survival [2]. Finally, the cost of follow-up programs is clear. An assessment made by the Tokyo Cancer Center estimates that a surgical department with a medium volume of gastric cancer surgery – about 50 radical resections for gastric cancer a year – must bear the weight of 150 patients in follow-up every year in the fifth year and 200 in the tenth year; these figures are even higher in Eastern centers with high volume and high percentage of early gastric cancers [7].

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On the other hand, in the absence of scientific data providing evidence-based indications on this topic, it may prove to be worthwhile to come back to surgeons' personal feeling and experience; thus, it may be useful to note how do centers with high volume of gastric cancer activity and high-quality care behave. According to a recent national survey in Korea [8] and to the official position of the Italian Research Group for Gastric Cancer [9], there are some merely theoretical remarks according to which patients need to be regularly followed after gastrectomy: first of all, the hope that biomedical research will offer in the future therapeutic weapons for the metastatic and/or relapsed patients, with results similar to those currently available for patients with colorectal cancer [10]. Moreover, the process of improving the standard of quality in surgical oncology cannot be separated from a daily evaluation of the results of therapies, by comparing these results between different surgical schools and different patterns of complementary therapies, and this evaluation is made possible only by reliable data on recurrence and survival. Finally, it has been demonstrated (and we have the distinct feeling) that being subjected to seriated scheduled checks does not represent a source of stress for most patients but this has rather the potential of reassuring them [11].

Thus, it is certainly needed that follow-up schedules are based on a more solid evidence, by identifying tests and examinations with the best reliability and sensitivity and by limiting them to a period of time when recurrence is likely and concentrating clinical efforts and expenses on those recurrences whose diagnosis shows a notable impact on survival and quality of life [12]. Randomized controlled trials (RCTs) are considered as the most rigorous tool for determining whether a cause–effect relationship exists between one intervention and its outcome; nevertheless, RCTs are unlikely to be rewarding in this peculiar field, since excessively large sample sizes and huge amount of money and time would be needed to clearly demonstrate the efficacy of follow-up. Another means of dealing with conflicting or scarce scientific evidence relies in consensus methods. The focus of consensus lays where unanimity of opinion does not exist owing to a lack of scientific evidence or when there is contradictory evidence on an issue. Consensus methods overcome some of the disadvantages normally found with decision-making in groups or committees, which are commonly dominated by one individual or by coalitions [13].

In January 2012, more than 1 year before the 10th International Gastric Cancer Congress, a Web table entitled "Rationale and limits of oncological follow-up after gastrectomy for cancer" was launched [14]; at first, five questions have been proposed (Fig. 24.1), and a further "open

Fig. 24.1 Preliminary questions of the Web round table "Rationale and limits of oncological follow-up after gastrectomy for cancer"

discussion" tool was made available for the participants. Authors having specific expertise have been invited commenting their previous publications, and an open debate has been developed in the Web. During a 3-month discussion, 32 authors from 12 countries participated; overall, 107 comments were posted and 2299 people visited the dedicated Web page until January 2013 (they became 4732 on 24 October 2013). Substantial differences emerged between the participants: authors from Japan, Korea, Italy, Brazil, Germany, and France are currently engaged in the instrumental follow-up, while authors from Eastern Europe, Peru, and India never do; British and American surgeons instead practice it in a rather limited manner (e.g., only with the clinical evaluation) or in the context of experimental studies. Although all the authors recognize that contrast-enhanced CT scan is the method of choice to detect recurrence, many limit follow-up to clinical and biochemical examinations; endoscopy is considered by most authors still useful [14].

In the following months, owing to the great success of this Web round table, the more ambitious project of an International Consensus Conference was launched [15], whose process of construction started in December 2012 by establishing a restricted working group (RWG): the RWG reviewed the literature, formulated seven unresolved issues (Fig. 24.2), shared a proposal statement for each of them, and submitted to the Scientific Committee of 10th IGCC a list of international experts including surgeons, oncologists, radiation oncologists, gastroenterologists, statisticians, and methodologists with a geographical distribution reflecting different health cultures worldwide, therefore from "emerging" and highly developed countries. Forty-eight of these experts have agreed to participate in an enlarged working group (EWG) which – according to the dictates of the Delphi method – worked blindly to create an online preliminary consensus on the seven statements. On 22 June 2013, in Verona (Italy), during the 10th International Gastric Cancer Congress (IGCC) of the International Gastric Cancer Association (IGCA) organized by the Italian Research Group for Gastric Cancer, a consensus meeting entitled "Rationale of oncological follow-up after gastrectomy for cancer" was held, with the ultimate purpose to produce a charter. The aim of this Charter Scaligero was to lay the foundations for articulating a common universal vision, implementing global standards of effectiveness and efficiency in the struggle against the effects of gastric cancer, with the ultimate scope of ameliorating the quality of life of people affected by the disease. In this context, the topic of follow-up was chosen as the main and only clinical point of the charter, with the goal of presenting an ideal prototype of follow-up after gastrectomy for cancer, based on shared experiences, and also taking into account the need to rationalize the diagnostic course and not to lose the chance to catch a recurrence at its earliest stage. Other factors taken into account were the need of reliable data on surgical outcome, the patients' desire not to be abandoned, the psychological stress induced by unuseful controls, the cost–benefit ratio of instrumental examinations, the side effects of invasive diagnostic procedures, and the possibility of causing a premature "diagnosis of death." Therefore, one out of 15 articles of the Charter Scaligero on Gastric Cancer has been devoted to "Rationale and Limits of

Table 1 Questions to be answered

1. Should patients be clinically abandoned after curative surgery (and adjuvant chemotherapy)?
2. Should follow-up be exclusively managed by GP instead of surgeon, oncologist, gastroenterologist?
3. Should follow-up be differentiated on the basis of recurrence risk?
4. Should only clinical checks be performed during follow-up?
5. Should advanced imaging techniques be regularly prescribed during follow-up?
6. Should upper GI endoscopy be regularly prescribed during follow-up?
7. After how many years follow-up should be stopped?

Fig. 24.2 Questions to be answered at the beginning of the International Web-based Consensus Conference "Rationale of oncological follow-up after gastrectomy for cancer"

Oncological Follow-up after Gastrectomy for Cancer" and reads as follows:

Art. 13 – The role of the "follow up" in the management of Gastric Cancer

> The appropriate management of the disease is fundamental not only for improving the patients' quality of life but also in order to decrease unnecessary costs for the health systems. A panel of experts who participated in the 10th IGCC have elaborated a vision and reached a consensus on a number of statements that are intended as a guide of principles that would be of help to better manage the follow up of the disease after surgery. The Institutions and Professionals who endorsed this Charter and the "statements on the follow up" commit themselves to implement methodologies that will be reviewed, on the bases of evidence, in future congresses with the scope to come in the future to common approaches. The statements are attached to this charter and available to all the scientific community.

The approved and signed statements were published in the Annex 1 of the Charter Scaligero on Gastric Cancer:

> *Statement #1*
> There is no evidence that routine follow-up after curative treatment of gastric cancer (R0 resection with or without adjuvant therapy) is associated with improved long-term survival. However, routine follow-up should be offered to all patients for the following reasons: oncological (detection and management of cancer recurrence), gastroenterological (endoscopic surveillance and management of postgastrectomy symptoms), research (collection of data on treatment toxicity, time to and site of recurrence, survival, and cost–benefit analyses), and pastoral (psychological and emotional support). Follow-up should include lifetime monitoring of the nutritional sequelae of gastrectomy, including, but not limited to, adequate vitamin B12, iron, and calcium replacement.
>
> *Statement #2*
> Follow-up should be offered by members of the multidisciplinary team who managed the initial diagnosis, staging, and treatment, including the gastroenterologist, the surgeon, the medical and radiation oncologists, and the general practitioner.
>
> *Statement #3*
> Follow-up of patients following curative treatment of gastric cancer should be tailored to the individual patient, to the stage of their disease, and to the treatment options available in the event that recurrence is detected.
>
> *Statement #4*
> Physical examination rarely detects asymptomatic recurrence of gastric cancer. A follow-up program intended to detect asymptomatic recurrence should be based on cross-sectional imaging. There is no evidence that intensive cross-sectional imaging surveillance of gastric patients is associated with improved long-term survival. However, as a matter of clinical care following curative treatment of gastric cancer, it is reasonable to prescribe periodic imaging at a frequency consistent with recurrence risk. The incremental value of screening for elevated biochemical markers in addition to cross-sectional imaging remains undefined.
>
> *Statement #5*
> Upper GI endoscopy may be used to detect local recurrence or metachronous primary gastric cancer in patients that have undergone a subtotal gastrectomy. True local recurrence is uncommon but if present may be considered for resection with curative intent, especially in patients who initially presented with early stage disease. The cost–benefit ratio of endoscopic surveillance of the anastomosis and/or gastric remnant remains undefined.
>
> *Statement #6*
> Routine screening for asymptomatic recurrence of gastric cancer may be discontinued after 5 years, as recurrence beyond that interval is very rare.

The board of experts recognized that follow-up is good clinical practice and should be offered to all patients for the reasons already mentioned. Follow-up should be individualized and appropriate to the patient and the health-care setting. The GIRCG proposed a tailored follow-up based upon a validated prognostic score [9] (Fig. 24.3). High-risk patients will probably recur within few months after surgery, and these patients should be strictly followed up in this period, although we could not expect any significant survival benefit. Follow-up should be mild in low-risk patients, but it should be prolonged (late recurrences are more frequently locoregional) and also considering the risk of second primaries (particularly in EGC). In the intermediate group, we believe that a further selection of patients and follow-up schedule according to nonconventional factors (biological?) may be necessary. It may be not a case that most of the few curatively treated patients belonged to this group. Instead, it appears very difficult to establish what diagnostic tools are better characterized by a favorable cost–benefit ratio. Guidelines actually provide only "complete

MILD

Months	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
Tumor markers*		X		X		X		X		X		X	X	X	X	X
Abdominal Ultrasound		X		X		X		X		X		X	X	X	X	X
Chest X-ray				X				X				X				
Thoraco-abdominal CT scan																
Endoscopy				X				X				X				X

* CEA, CA 19-9, CA 72-4
CT scan: increase of tumor marker levels, clinical or radiological suspicion of recurrence

MODERATE

Months	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
Tumor markers*	X	X	X	X	X	X	X	X		X		X	X	X	X	X
Abdominal Ultrasound		X				X				X			X		X	X
Chest X-ray																
Thoraco-abdominal CT scan				X				X				X		X		
Endoscopy				X				X				X				X

* CEA, CA 19-9, CA 72-4

INTENSIVE

Months	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
Tumor markers*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Abdominal Ultrasound													X		X	
Chest X-ray																
Thoraco-abdominal CT scan		X		X		X		X		X		X		X		X
Endoscopy				X				X				X				X

* CEA, CA 19-9, CA 72-4

Fig. 24.3 Follow-up protocols proposed by the IRGGC, on the basis of recurrence risk and patients' compliance with follow-up. The model to calculate the IRGGC prognostic score can be downloaded from the website: www.gircg.it (Reproduced with permission from Marrelli et al. [9])

history and physical examination (investigations are recommended as clinically Indicated by symptoms)" (NCCN) and "symptom-driven visits (directed investigations only in patients who are candidates for further treatment)" (ESMO) [16]; at the other end, in the current clinical practice of many centers around the world, patterns of follow-up are very complex. According to the results of the Charter Scaligero suggestions, follow-up should consist of clinical review and cross-sectional imaging ± upper GI endoscopy and should be discontinued after 5 years. But the most important point of discussion is the fate of patients to whom asymptomatic recurrence of GC is diagnosed. Indeed, very few papers demonstrate that recurrence is still subject to some kind of treatment. Kodera reported a series in which the diagnosis of recurrence at an earlier stage allowed a greater proportion of patients to be treated with chemotherapy; a possible explanation is related to the fact that the performance status was higher in this subgroup of patients [2]. In addition, a recent small series was published by Villarreal Garza, in which the percentage of curative redo-resections and chemotherapy was significantly higher in patients whose recurrence was detected in asymptomatic phase than in patients who were not submitted to regular follow-up (14.3 % versus 1.3 % and 70.5 % versus 42.9 %, respectively). However, the actual numbers in this series are really very low [17]. We should also mention another brief series of 26 patients who underwent exploratory laparotomy for suspected recurrence and a radical resection was possible in 50 % of the cases [18] and the series of 11 liver resections for metachronous liver metastasis presented by the GIRCG in 2009 [19].

24.2 Quality of Life

While routine follow-up may be unable to prolong survival, it may certainly improve the health-related quality of life (HRQL) after

demolitive surgery. On this point, the vast majority of participants to the abovementioned Web round table and consensus meeting unanimously stated that one of the most important reasons to follow over time patients undergoing surgery for upper GI cancer is precisely to diagnose and correct any nutritional deficiency. The effects of resection surgery are both predictable (i.e., weight loss) and unpredictable (i.e., dumping). It is therefore useful that patients are seen regularly after surgery to provide support and advice, particularly regarding nutrition. The first months after the intervention need a close monitoring of diet; the oral intake is often slow and requires a change of patient habits. The same is in the medium term: in a Swedish series of 87 patients having undergone esophagectomy for cancer, those alive at 3 years reported significantly poorer role and social function and significantly more problems with fatigue, diarrhea, appetite loss, nausea, and vomiting, than in the reference population [20].

In general, careful evaluation of weight and, later, of hemoglobin, iron, and electrolytes is useful; in some cases, nutritional supplements such as vitamin B12, iron, and folates should be given. Clearly, there is a difference between patients according to age, total gastrectomy versus esophagectomy, and method of reconstruction; total gastrectomy in elderly patients is the most risky clinical scenario for nutritional deficits. Pancreatic enzymes could theoretically help patients who have lived for over 6 months after surgery, feel hunger, and can eat a relatively large amount yet do not begin to gain weight. Finally, new and adequate habits of oral intake after gastrectomy could best be taught by nutricians and other co-medicals rather than by surgeons. While stoma therapists seem to have a lot of roles at the outpatient clinic after colorectal operations, unfortunately no health professionals seem to help upper GI surgeons. Indeed, nutritional status of resected patients would not improve simply by regular visits to the hospital unless interventions such as enteral or parenteral feeding are conducted.

The first step toward an effective treatment of postoperative complaints is the search for a diagnostic tool for HRQL evaluation, having specific interest to impaired nutritional status. Recognizing a worsened quality of food intake and absorption may be quite difficult in the context of postoperative checks, when physicians usually focus the attention most specifically on the oncological features and patients themselves don't clearly report most symptoms. The European Organization for Research and Treatment of Cancer developed and validated the EORTC QLQ-C30 questionnaire designed to assess the quality of life of cancer patients [21]. Disease-specific aspects of the questionnaire provide detailed information about the patients' perception of their health. EORTC questionnaires were combined for assessing HRQL for esophageal (QLQ-OES18) and stomach cancer (QLQ-STO22), into a single questionnaire for tumors of the esophagus, esophagogastric junction, or stomach, named QLQ-OG25. QLQ-OG25 has six scales: dysphagia, eating restrictions, reflux, odynophagia, pain, and anxiety. The QLQ-OG25 is recommended to supplement the EORTC QLQ-C30 when assessing HRQL in patients with esophageal, junctional, or gastric cancer.

The next step should be the identification of patients mostly at risk for postoperative worsened HRQL, which is the object of a number of papers. In a Swedish nationwide population-based study, collected prospectively between 2001 and 2005 and including 355 patients undergoing esophagectomy, age, sex, and BMI showed no associations with HRQL 6 months after surgery, but patients with comorbidity, a more advanced tumor stage (III to IV), or a tumor located in the middle or upper esophagus had an increased risk of poor HRQL. Patients with adenocarcinoma had a lower risk of poor HRQL than patients with squamous cell carcinoma [22]. Another relevant study on prognostic factors for HRQL was published by McKernan and Coll, including 152 Scottish patients who received either potentially curative surgery or palliative treatment between 1997 and 2002; in this study, tumor site was not associated with major differences in EORTC QLQ-C30, while there were

major differences in quality of life and symptom scores with increasing stage of disease. In particular, social functioning, fatigue, appetite loss, and global quality of life were all impaired with increasing tumor stage [23]. Surprisingly, the hospital volume was investigated by another paper, having as object the abovementioned Swedish series and reporting no HRQL advantages of being treated at high-volume hospitals or by high-volume surgeons [24].

Once patients at risk are identified, surgeons should be aware of the impact of their technical choices on HRQL. A recent study published by Barbour and Coll. compared the functional results of transthoracic esophagectomy (TTO) and abdominal-only total gastrectomy (TG) in a series of 63 consecutive cases. Patients were similar with respect to disease stage, treatment-related mortality, and survival, but those selected for TTO were younger and with less comorbidity than those undergoing TG. So, baseline HRQL scores were better in patients selected for TTO. Six months after surgery, however, HRQL showed a greater deterioration after TTO than after TG in terms of role and social function, global quality of life, and fatigue. Symptom scores for pain and diarrhea increased in both groups [25]. However, these results are not confirmed by the abovementioned population-based Swedish network of esophageal cancer surgery, in which extensive surgery (transthoracic approach, more extensive lymphadenectomy, wider resection margins, and a longer duration of operation) was not associated with worse HRQL measures than less extensive operations [26]. Other factors influencing postoperative HRQL after upper GI cancer resection have been sparsely studied. In the series by Rutegard, for instance, dysphagia was similar in patients who had hand-sewn and stapled anastomoses, and surgical complications had significant deleterious effects on several aspects of HRQL. The occurrence of surgery-related complications was the main predictor of reduced global quality of life 6 months after surgery (p for trend = 0.03) even in the series published by Viklund and Coll [27]. In another study, focusing on a series of patients treated by proximal gastrectomy for Siewert type II and III cardia cancer, patients with gastric tube reconstruction had better quality of life than patients undergoing traditional direct anastomosis (anastomosis between gastric remnant and esophagus) with respect to global health status, emotional function, cognitive function, nausea and vomiting, reflux, and anxiety scales at 1-year post-surgery [28]. It is actually unclear if minimally invasive surgery improves medium-term and long-term HRQL; a recent, uncontrolled series of 56 cases in which EORTC QLQ-C30 and QLQ-OES18 were administered before surgery and at 6 weeks, 3, 6, and 12 months after surgery demonstrated a postoperative (6 weeks) deterioration in functional aspects of HRQL and more symptoms than at baseline but a rapid restoration (most patients improved by 3 months and had returned to baseline levels by 6 months, and after 1 year, 85 % of patients recovered in more than 50% of the HRQL domains). Unfortunately, this study has not a control arm of open surgery [29]. A more recent comparative series of 175 patients undergoing minimally invasive esophagectomy (MIE) versus open esophagectomy (OE) for early esophageal and gastroesophageal junction carcinoma revealed that gastrointestinal complications ($p = 0.005$), particularly gastroparesis ($p = 0.004$), were more frequent in MIE, while at 3 months, postoperative fatigue, pain (general), and gastrointestinal pain were less in MIE ($p = 0.09$, 0.05, and 0.01, respectively) [30].

All the efforts should be made for improving HRQL results. Indeed, in a study of 121 patients undergoing surgery for esophageal and gastric cancer, preoperative HRQL scores were not associated with major morbidity but were significantly related to survival status at 6 months after adjusting for known clinical risk factors [31]. Measures of self-reported health predict also long-term survival, as it was shown in the study by McKernan, in which on multivariate survival analysis, tumor stage ($P < 0.0001$), treatment ($P < 0.001$), and appetite loss ($P < 0.0001$) were significant independent predictors of cancer-specific survival. This was confirmed by many studies investigating gastroesophageal cancers.

References

1. Eom BW, Ryu KW, Lee JH et al (2009) Oncologic effectiveness of regular follow-up to detect recurrence after curative resection of gastric cancer. Ann Surg Oncol 18:358–364
2. Kodera Y, Ito S, Yamamura Y, Mochizuki Y et al (2003) Follow-up surveillance for recurrence after curative gastric cancer surgery lacks survival benefit. Ann Surg Oncol 10:898–902
3. Tan IT, So BY (2007) Value of intensive follow-up of patients after curative surgery for gastric carcinoma. J Surg Oncol 96:503–506
4. Bohner H, Zimmer T, Hopfenmller W et al (2000) Detection and prognosis of recurrent gastric cancer; is routine follow-up after gastrectomy worthwhile? Hepatogastroenterology 47:1489–1494
5. Bennett JJ, Gonen M, D'Angelica M, Jaques DP, Brennan MF, Coit DG et al (2005) Is detection of asymptomatic recurrence after curative resection associated with improved survival in patients with gastric cancer? J Am Coll Surg 201:503–510
6. Baiocchi GL, Tiberio G, Minicozzi A et al (2010) A multicentric western analysis of prognostic factors in advanced, node-negative gastric cancer patients. Ann Surg 252:70–73
7. Whiting J, Sano T, Saka M, Fukagawa T, Katai H, Sasako M et al (2006) Follow-up of gastric cancer: a review. Gastric Cancer 9:74–81
8. Hur H, Song KY, Park CH, Jeon HM et al (2010) Follow-up strategy after curative resection of gastric cancer: a nationwide survey in Korea. Ann Surg Oncol 17:54–64
9. Marrelli D, Caruso S, Roviello F (2012) Follow-up and treatment of recurrence. In: de Manzoni G, Roviello F, Siquini W (eds) Surgery in the multimodal management of gastric cancer. Springer-Verlag Italia, Milan
10. Bang YJ, Cutsem EV, Feyereislova A et al (2010) Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 376:687–697
11. Allum WH, Griffin SM, Watson A et al (2002) Guidelines for the management of oesophageal and gastric cancer. Gut 50:v1–v23
12. Baiocchi GL, Marrelli D, Verlato G et al (2014) Follow-up after gastrectomy for cancer: an appraisal of the Italian research group for gastric cancer. Ann Surg Oncol 21:2005–2011
13. Jones J, Hunter D (1995) Consensus methods for medical and health services research. BMJ 311:376–380
14. Baiocchi GL, Kodera Y, Marrelli D et al (2014) Follow-up after gastrectomy for cancer: results of an international web round table. World J Gastroenterol 20:11966–11971
15. D'Ugo D, Baiocchi GL (2013) Rationale of oncological follow-up after gastrectomy for cancer—the consensus conference. Transl Gastrointest Cancer 2:233–234
16. Jackson C, Cunningham D, Oliveira J, On behalf of the ESMO Guidelines Working Group (2009) Gastric cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 20:iv34–iv36
17. Villarreal-Garza C, Rojas-Flores M, Castro-SÃ¡nchez A et al (2011) Improved outcome in asymptomatic recurrence following curative surgery for gastric cancer. Med Oncol 28:973–980
18. Ozer I, Bostanci EB, Ozogul Y et al (2009) Laparotomy with a curative intent in patients with suspected locally recurrent gastric cancer. Tumori 95:438–441
19. Tiberio GA, Coniglio A, Marchet A et al (2009) Metachronous hepatic metastases from gastric carcinoma: a multicentric survey. Eur J Surg Oncol 35:486–491
20. Djärv T, Lagergren J, Blazeby JM (2008) Long-term health-related quality of life following surgery for oesophageal cancer. Br J Surg 95:1121–1126
21. Aaronson NK, Ahmedzai S, Bergman B et al (1993) The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365–376, for the European Organization for Research and Treatment of Cancer Study Group on Quality of Life
22. Djärv T, Blazeby JM, Lagergren P (2009) Predictors of postoperative quality of life after esophagectomy for cancer. J Clin Oncol 27:1963–1968
23. McKernan M, McMillan DC, Anderson JR (2008) The relationship between quality of life (EORTC QLQ-C30) and survival in patients with gastro-oesophageal cancer. Br J Cancer 98:888–893
24. Rutegård M, Lagergren P (2008) No influence of surgical volume on patients' health-related quality of life after esophageal cancer resection. Ann Surg Oncol 15:2380–2387
25. Barbour AP, Lagergren P, Hughes R, Alderson D, Barham CP, Blazeby JM et al (2008) Health-related quality of life among patients with adenocarcinoma of the gastro-oesophageal junction treated by gastrectomy or oesophagectomy. Br J Surg 95:80–84
26. Rutegård M, Lagergren J, Rouvelas I et al (2008) Population-based study of surgical factors in relation to health-related quality of life after oesophageal cancer resection. Br J Surg 95:592–601
27. Viklund P, Lindblad M, Lagergren J (2005) Influence of surgery-related factors on quality of life after esophageal or cardia cancer resection. World J Surg 29:841–848
28. Shen C, Yang H, Zhang B et al (2013) Improved quality of life in patients with adenocarcinoma of esophagogastric junction after gastric tube reconstruction. Hepatogastroenterology 60:1985–1989
29. Parameswaran R, Blazeby JM, Hughes R et al (2010) Health-related quality of life after minimally invasive oesophagectomy. Br J Surg 97:525–531
30. Nafteux P, Moons J, Coosemans W et al (2011) Minimally invasive oesophagectomy: a valuable alternative to open oesophagectomy for the treatment of early oesophageal and gastro-oesophageal junction carcinoma. Eur J Cardiothorac Surg 40:1455–1463
31. Blazeby JM, Metcalfe C, Nicklin J et al (2005) Association between quality of life scores and short-term outcome after surgery for cancer of the oesophagus or gastric cardia. Br J Surg 92:1502–1507

25 Surgical Anatomy of the Esophagus and Esophagogastric Junction

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25.1 General Anatomy

25.1.1 Esophagus

The adult human esophagus is a flattened muscular tube that connects the pharynx to the stomach. Depending on the height of the individual, its length is 25–30 cm, ranging from 19 to 25 cm (median 22 cm) in men and 18–22 cm (median 21 cm) in women. It begins in the neck, at the pharyngoesophageal junction, which is normally located at the inferior border of the cricoid cartilage (interspace between the fifth and the sixth cervical vertebra), and descends anteriorly to the vertebral column through the superior and posterior mediastinum. After passing the diaphragm at the diaphragmatic hiatus at the level of the tenth thoracic vertebra, the esophagus ends at the cardia orifice of the stomach (11th-12th thoracic vertebral level). Although essentially a midline structure, the esophagus deviates slightly to the left in the neck at the first thoracic vertebral level and to the right in the thorax at the sixth thoracic vertebral level. It then curves to the left again as it passes through the hiatus in the diaphragm at the level of the tenth thoracic vertebral body (Fig. 25.1). It also presents an anteroposterior flexure, corresponding to the curvature of the cervical and thoracic portions of the spine [1–3].

The tube remains under permanent tension and is proximally secured by the upper esophageal sphincter (UES) and distally by the lower esophageal sphincter (LES), which create two high-pressure zones. The UES closure prevents esophageal air insufflation during negative intrathoracic pressure events (inspiration) and prevents esophagopharyngeal/laryngeal reflux during esophageal peristalsis. The LES function is to create a barrier against reflux of gastric juice into the esophagus. The presence of a submucosal venous plexus optimizes the closure function of these two sphincters [1, 4, 5].

The esophagus has three areas of normal narrowing of its lumen: the cricopharyngeal (pharyngoesophageal) constriction at the cricoid cartilage, the bronchoaortic constriction, and the diaphragmatic constriction at the diaphragmatic hiatus. The bronchoaortic constriction is anatomically constituted by the aortic and the left main bronchial constrictions, at the level of the fourth and the fifth thoracic vertebras [1, 6].

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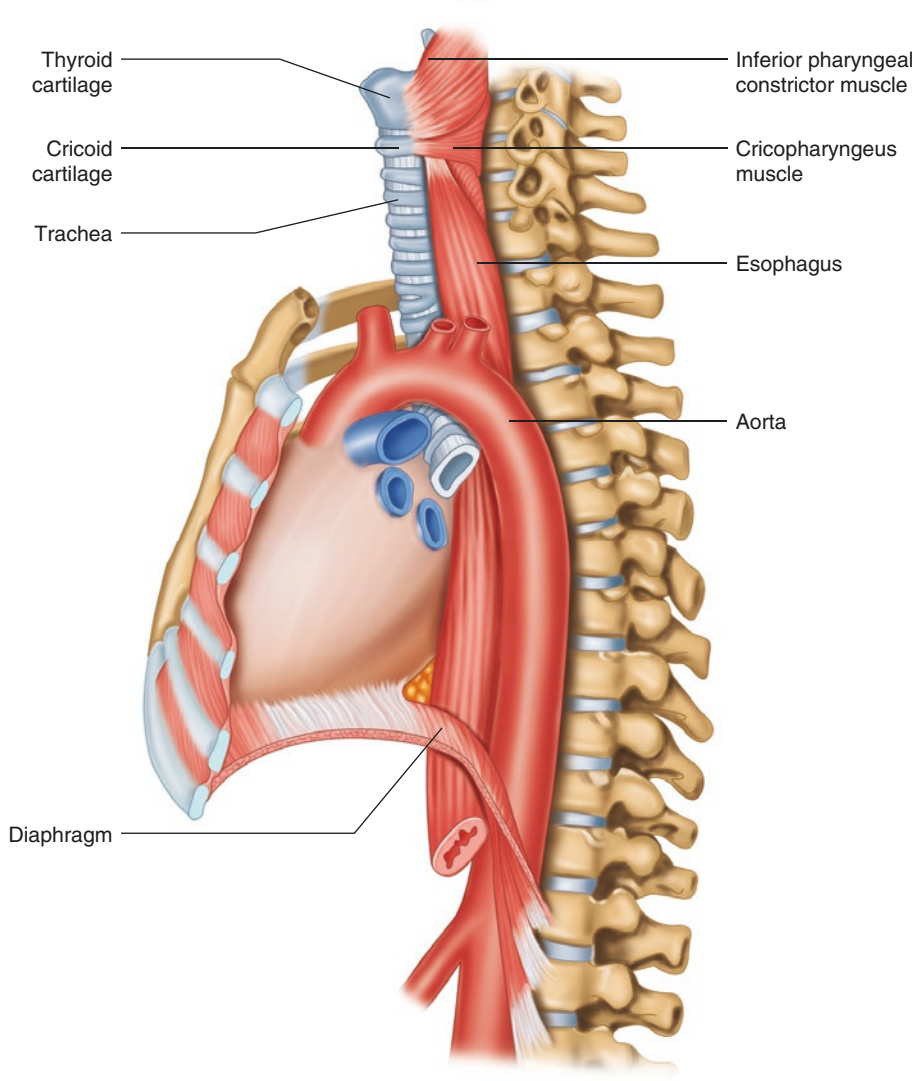

Fig. 25.1 The esophagus is a muscular tube which extends from the sixth cervical to the 11th thoracic vertebra, across three anatomic regions

25.1.2 Esophagogastric Junction

The esophagus joins the stomach at the esophagogastric junction (EGJ), which lies in the abdomen just below the diaphragm. Therefore, the term "esophagogastric junction" implies a transition from the esophagus to the stomach (Fig. 25.2). Although this term is understandable, controversy continues today about the precise location of the EGJ. Indeed, EGJ is a complex of structures, which may be defined differently by the surgeon, the anatomist, the radiologist, and the endoscopist [1].

The surgeon identifies the EGJ just below the diaphragm at the upper border of the peritoneal reflection from the stomach to the distal esophagus.

The gross anatomist considers EGJ the termination of the tubular esophagus and the saccular stomach. The criteria used by microscopic anatomist to define EGJ are the distal extent of the esophageal squamous epithelium, the proximal

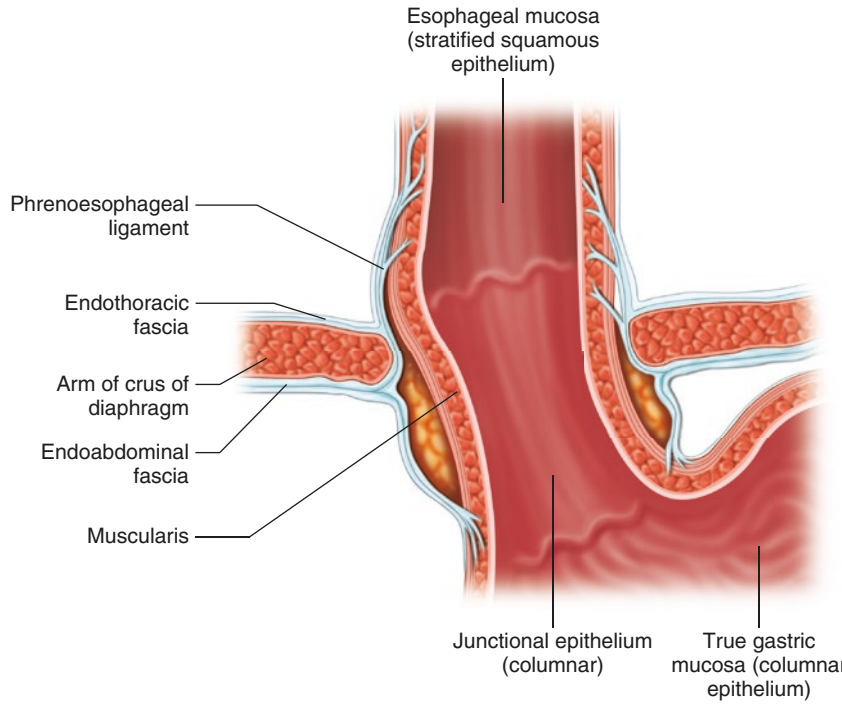

Fig. 25.2 The esophagogastric junction (Copyright ©2006 by the McGraw-Hill Companies, Inc. All rights reserved)

extent of gastric oxyntic mucosa, the point beyond which no submucosal esophageal glands are found, and the change in the muscularis propria from a circular and longitudinal layer in the esophagus to a less defined muscularis propria of the stomach with a third oblique layer.

The EGJ of the radiologist is the imaginary line of the gastric sling from the acute angle of His to the middle of the junctional mucosa at the lesser curvature, where longitudinal mucosal folds of the esophagus change to transverse folds of the stomach.

The endoscopist defines the EGJ as the junction of the pale pink esophageal mucosa with the bright red gastric mucosa (Z line), but also considers the distal end of esophageal longitudinal mucosal veins (palisade vessels) and the proximal end of gastric longitudinal mucosal folds [7]. Moreover, the muscular structure of the EGJ, forming the LES, can be evaluated by physiologic manometric methods, and EGJ can be defined as the manometric distal end of the LES [8].

Therefore, several criteria are used to define the EGJ. Some are anatomic or histologic criteria, some endoscopic, some physiologic, and some surgical, but as all these approaches are rarely available simultaneously, their correlation remains ambiguous. The external EGJ can be described as the point at which the esophageal tube becomes the gastric pouch and lies in the abdomen at the level of the 11th or 12th thoracic vertebra. Internally, the junction is marked by an irregular boundary between stratified squamous esophageal epithelium and columnar gastric epithelium, but this boundary may lie as far as 1–2 cm above the external junction. The columnar epithelium below the internal junction contains mucus-secreting glands (the cardiac glands of the histologists), and lacks the chief and parietal cells that characterize the true gastric glands of the body of the stomach. The term "junctional epithelium" was proposed for this area by Hayward [9]. The external and internal junctions do not coincide. In addition, the loose submucosal connective tissue permits considerable sliding of the mucosa on the muscularis propria, changing the relation between them as the

stomach fills with food. Furthermore, with damage to the distal esophagus from gastroesophageal reflux and development of a hiatal hernia, the landmarks and relationships of structures around the junction become altered, and the identification of the precise EGJ becomes even more difficult [10].

25.1.3 Structure of the Esophageal Wall

The esophageal wall contains four layers: mucosa, submucosa, muscularis propria, and tunica adventitia. Unlike other areas of the gastrointestinal tract, it does not have a serosal layer [1, 2, 4].

The *mucosa membrane* is made up of three sublayers: epithelium, lamina propria, and muscularis mucosae. The epithelium is stratified, nonkeratinized squamous epithelium, bordered inferiorly by the basement membrane. It covers the entire inner surface of the esophagus, except for the esophagogastric junction, where both squamous and columnar epithelium coexist in a sharp transition called Z line. The epithelium overlies the lamina propria, a thin layer of connective tissue, and the muscularis mucosae, containing a small layer of mainly longitudinal smooth muscle fibers, which separates the mucosa from the submucosa.

The *submucosa* is a thick, loose fibrous layer connecting the mucosa to the muscularis propria. This is the strongest layer of the esophageal wall, since it contains elastic and fibrous tissue. It contains mucous and tubular glands and arterial, venous, and lymphatic vessels. The esophageal veins run longitudinally in the submucosa, where they have a truncal structure, consisting of a few large columns. At the EGJ, the veins penetrate the muscularis mucosae and become superficial, forming the longitudinal palisade vessels, which are absent in the stomach. Histologically, in esophageal transverse sections, the palisade vessels are large veins exceeding 100 μm in diameter observed in the lamina propria, which are also visible endoscopically. Mucosa and submucosa together form long longitudinal folds, which disappear upon distention. These folds explain why a cross section of the esophagus is star-shaped [10].

The *muscularis propria* is composed of an inner circular and an outer longitudinal layer of fibers. Both muscle layers are wound around and along the tube, but the inner one has a very tight spiral, so that the windings are virtually circular, whereas the outer one has a so slowly unwinding spiral that is virtually longitudinal. In the upper esophageal third, musculature consists of skeletal (striated) muscle. In the middle third, the skeletal muscle dominates, but smooth muscle fibers are blended. In the lower third, esophageal musculature consists of smooth muscle alone. The UES is composed of the cricopharyngeus muscle along with fibers from the esophageal wall and the inferior constrictors of the pharynx. The LES is not a distinct anatomic structure but is a physiologic region of intrinsic high pressure identifiable using manometry [8].

The *tunica adventitia* is the outermost layer of the esophageal wall and is composed of loose fibrous tissue that connects the esophagus with neighboring structures. It contains small vessels, lymphatic channel, and nerve fibers.

25.1.4 Upper Esophageal Sphincter (UES)

The UES is a high-pressure zone, which is located between the pharynx and the cervical esophagus, and has a vertical length of 2–4 cm. The UES is a musculocartilaginous structure composed of the posterior surface of the thyroid and cricoid cartilage, the hyoid bone, and three muscles: thyropharyngeus, cricopharyngeus, and musculature of the cervical esophagus. These three muscles spread from anteriorly to posteriorly, where they insert into the esophageal submucosa after crossing the muscle bundles of the opposite side (Fig. 25.1).

The *thyropharyngeus* (cranially) and the *cricopharyngeus* (caudally) are the two parts of the inferior pharyngeal constrictor muscle; the fibers of the thyropharyngeus are obliquely oriented (pars obliques), whereas the cricopharyngeus

muscle is transversely oriented (pars profundus) to form the UES. Between these two muscles, there is a V-shape area, with its apex directed superiorly in the midline, of sparse musculature, the "Killian's triangle or dehiscence," from which Zenker's diverticulum might emerge. The thyropharyngeus muscle arises from an oblique line on the thyroid ala and a fibrous arch between the thyroid and cricoid cartilages. Its upper fibers overlap the superior and middle constrictors, and the lower fibers lie edge to edge with the cricopharyngeus muscle. It is the thickest of the three UES muscles and contains a thick external layer of predominantly fast-twitch fibers and a thin inner layer of predominantly slow-twitch fibers which most likely contribute to the tonic contractions of the UES. The cricopharyngeus muscle is a striated muscle attached to the cricoid cartilage and is 1 cm in width. It originates from the cricoid cartilage, loops around the pharynx in a "C-shape" or "horseshoe shape" manner, and is inserted back into the cricoid cartilage (unique muscle in the entire body that has origin and insertion into the same structure). This muscular band produces maximum tension in the anteroposterior direction and less tension in lateral direction. Structurally, it is different from the surrounding pharyngeal and esophageal muscles; indeed it is composed of a mixture of fast-twitch and slow-twitch fibers, with the slow fibers being predominant. Therefore, the cricopharyngeus can maintain constant basal tone but also have a rapid response during swallowing, belching, and vomiting. The cricopharyngeus is suspended between the cricoid processes, surrounds the narrowest part of pharynx, and extends caudally where it blends with the circular muscle of the cervical esophagus.

The *cervical esophagus* contains predominantly striated muscle fibers, but occasionally smooth fibers are found in the center of the muscle. As it contains predominantly slow-twitch fibers, it is similar to the cricopharyngeus. The muscle fibers are arranged in an outer layer containing longitudinal fibers and an inner layer containing circular or transversely arranged fibers. The former blends superiorly with the cricopharyngeus muscle. The outer layer, however, diverges at the upper end, forming two bands that swing laterally and anteriorly around the esophagus to attach to a common tendon behind the cricoid cartilage. The posterior esophageal wall between these divergent bands is therefore covered with a single layer of circular fibers, which forms a second potentially weak V-shape area, with its apex directed inferiorly in the midline, known as "Laimer's triangle" or "Laimer-Haeckermann area." A third triangle of weakness, known as "Killian-Jamieson triangle," is located inferiorly to the cricopharyngeus on both sides of this muscle's insertion into the cricoid cartilage, in the anterolateral wall of the proximal cervical esophagus. This muscle gap is the weak region just inferior to the adhesion area of the cricopharyngeus with cricoid cartilage and is lateral to the esophagus suspensor ligament, which is attached to the posterior aspect of the cricoid cartilage and is also a part of the fascial sheath that is common to the hyoid, thyroid, and cricoid. It was initially described by Killian as the site where the recurrent laryngeal nerve inserts into the pharynx. Jamieson confirmed such finding, and thus this area was named Killian-Jamieson triangle. Both Laimer's and Killian-Jamieson triangles may rarely become the site of acquired pulsion diverticula. Moreover, the Killian's and the Laimer's triangles may be the site of possible perforation by an endoscope [1–5, 11–13].

25.1.5 Lower Esophageal Sphincter (LES)

The LES is a high-pressure zone located in the distal esophagus at the level of the esophagogastric junction, which plays an important role in protecting the esophagus against reflux of acid. This sphincter is a functional unit composed of an *intrinsic* and an *extrinsic* component.

The intrinsic component of the LES consists of 2–4 cm long tonically contracted segment, with a resting pressure of 15–25 mmHg above intragastric pressure. In normal individuals, the terminal esophagus passes the diaphragmatic hiatus, and therefore the LES has both a 1–2 cm long thoracic and a 1–2 cm abdominal part. The total length,

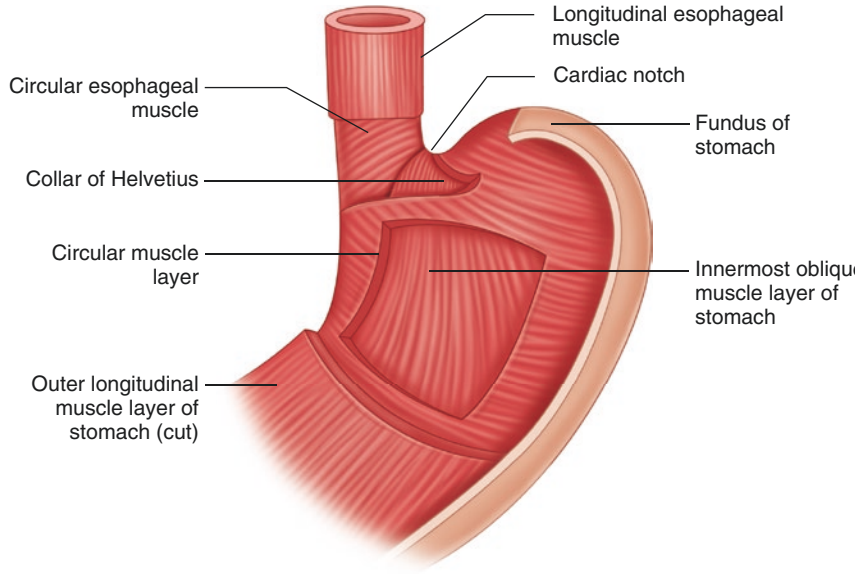

Fig. 25.3 The muscle layers of the esophagogastric junction

abdominal length, and resting pressure of the LES work together to create a barrier against retrograde flow of gastric contents into the negative pressure environment of the thoracic esophagus. The intrinsic component is composed of inner circular muscular layer of the esophagus, which is thicker than adjacent esophagus, and spread out onto the gastric cardia. In the cardiac region, the inner muscular layer of the esophagus changes into clasp-like semicircular smooth muscle fibers on the right side, along the lesser curvature, and into sling-like oblique gastric muscle fibers on the left side, along the greater curvature and the angle of His (Fig. 25.3). Three-dimensional manometric assessment of the LES shows a marked radial and longitudinal asymmetry of the pressure profiles, with the highest pressure in the left posterior direction. This high-pressure zone seems to coincide with asymmetric thickening of the muscular layer at the esophagogastric junction, which corresponds to the gastric sling-like and to the semicircular clasp-like fibers.

The extrinsic component of the LES consists of the left and the right crus of diaphragm. The right and the left diaphragm crura are composed of muscular fibers which arise as tendinous bands from the anterolateral surface of the first-fourth lumbar vertebras. The two crura together constitute a tether for muscular contraction, the crural diaphragm, which forms the esophageal hiatus and represents a channel through which the esophagus enters into the abdomen. The esophageal hiatus is formed normally by the right crus, but there are anatomic variations, and in approximately 20 % of cases, the left crus also contributes partially to its formation. The fibers of the crus are oriented in the craniocaudal direction. The esophageal hiatus is a two-staged canal; the upper part is fully muscular and measures 2.5 cm in length, but the lower part forms a gutter that is open anteriorly and surrounded by the muscles of the right crus on the posterior and lateral aspects. The central fibers have a relatively circular arrangement, but the peripheral fibers are oriented in a craniocaudal direction. The unique arrangement of its muscle fibers results in two different types of actions on the esophagus when it contracts: a vertical or craniocaudal motion and a circumferential squeeze. The crural diaphragm encircles the proximal 2–4 cm of the LES and determines inspiratory increases in LES pressure. During quiet inspiration, the LES pressure increases by 10–20 mmHg, but it can rise as much as 100–150 mmHg with maximal diaphragmatic contraction. The end-expiratory

LES pressure is due to tonic contraction of the intrinsic component of the LES [1–5, 8, 14].

25.2 Topographical Anatomy

The esophagus passes through three anatomical regions: neck, chest, and abdomen. Therefore, it is divided into cervical, thoracic, and abdominal esophagus.

25.2.1 Cervical Esophagus

The cervical portion of the esophagus is about 5–6 cm long and extends from the cricopharyngeus (sixth cervical vertebra) to the thoracic inlet at the level of suprasternal notch (interspace between the first and the second thoracic vertebras). The carotid tubercle (Chassaignac tubercle), which is the palpable anterior tuberosity of the transverse process of sixth cervical vertebra, is a useful landmark for the upper limit of the esophagus. The cervical esophagus is prevertebral, between the deep and the middle cervical fascia, and its course deviates slightly to the left. It is bordered anteriorly by the larynx and trachea, posteriorly by the longissimus cervicis muscle under prevertebral fascia, and anterolaterally on each side, from the periphery inward, by carotid sheaths, inferior thyroid arteries, and thyroid gland. The trachea (membranous part) is connected to the esophagus by a loose connective tissue, and in a groove between the two organs, recurrent nerves ascend on each side to the larynx. Posteriorly, cervical esophagus is related to the visceral layer (buccopharyngeal fascia) of the middle cervical fascia, which encloses pharynx, trachea, esophagus, and thyroid. This thin fibrous layer extends inferiorly onto the posterior wall of the esophagus and laterally to the carotid sheaths and forms the anterior border of the retroesophageal (retropharyngeal) and the paraesophageal (parapharyngeal) spaces. Bounded posteriorly by the alar fascia (the anterior lamina of the deep cervical fascia), the *retroesophageal space* extends superiorly to the base of the skull and inferiorly to the mediastinum at the level of the tracheal bifurcation. Between the alar fascia and the prevertebral fascia (the posterior lamina of the deep cervical fascia), in close proximity to the retroesophageal space, there is the so-called *danger space*, which extends down the mediastinum to the level of the diaphragm. The two potential spaces (retroesophageal and danger space) may be important for infection spread to the mediastinum, leading to potentially fatal mediastinitis. Bilaterally, the carotid sheath contains common carotid arteries, internal jugular veins, and vagal nerves. The lower poles of the lateral lobes of the thyroid gland are located between the esophagus and the carotid arteries on both sides. Also related to the distal cervical esophagus is the thoracic duct, which ascends for a short distance along the left side of the esophagus before arriving to the left confluence of subclavian and internal jugular veins [1–5, 15].

25.2.2 Thoracic Esophagus

The thoracic segment of the esophagus is about 20 cm long and extends from the level of the first-second to the tenth-eleventh thoracic vertebras (Fig. 25.4). Thoracic esophagus is located in the superior and posterior mediastinum. It lies between the trachea and vertebral column in the superior mediastinum, where it is attached to the left main bronchus, and then it descends behind the aortic arch and turns slightly to the right to enter the posterior mediastinum at the level of the interspace between the fourth and the fifth thoracic vertebras. The thoracic aorta gives rise to branches which directly supply blood to the thoracic portion of the esophagus. Anteriorly, from the thoracic inlet to the tracheal bifurcation, the esophagus is related to the trachea (membranous part) and the left main bronchus. Afterwards, it descends and is related to subcarinal lymph nodes, right pulmonary artery, pericardium of the adjacent left atrium, and diaphragm hiatus. Below tracheal bifurcation (interspace between the fourth and the fifth thoracic vertebras), the esophageal wall is surrounded by a vagal plexus, which gives rise to an anterior and a posterior vagal trunk at the

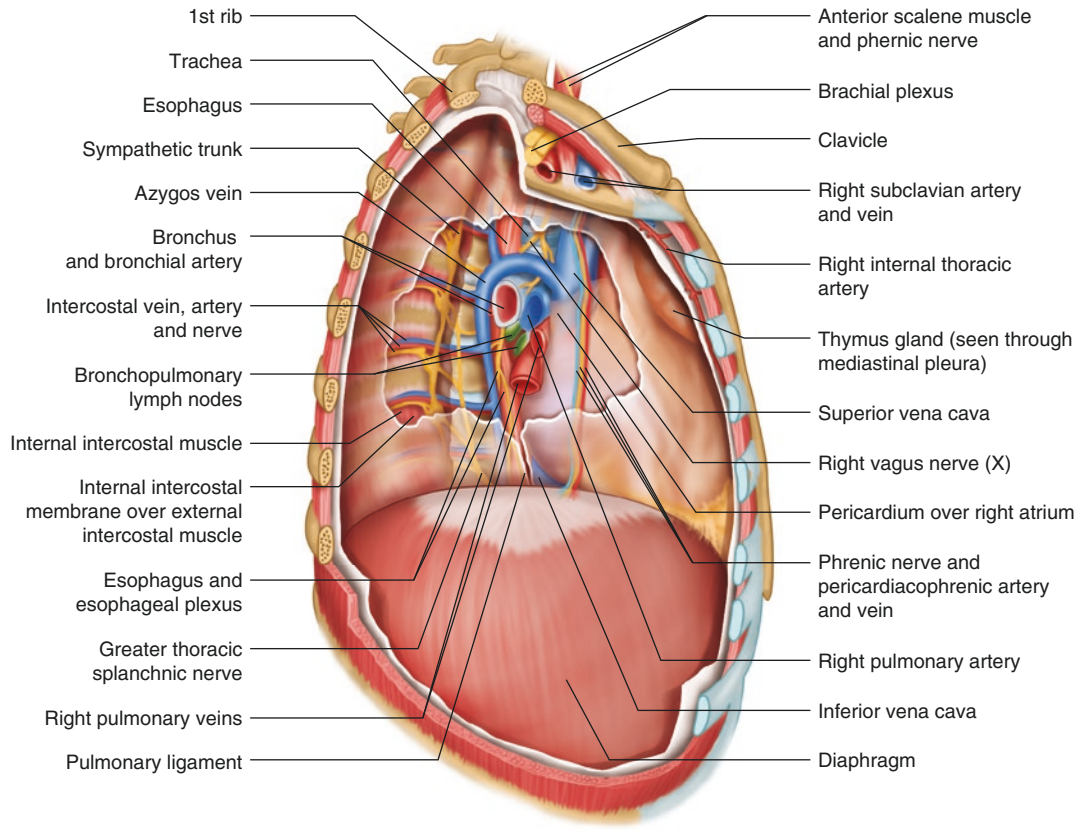

Fig. 25.4 Thoracic esophagus; right lateral view

level of the diaphragm hiatus. Posteriorly, the thoracic esophagus remains in contact with the vertebral column, and it is related to right posterior intercostal arteries and the thoracic duct until the eighth thoracic vertebra. At this level, the thoracic aorta crosses behind the esophagus and enters through the aortic hiatus into the abdomen. On the right, the lateral surface of the thoracic part of the esophagus is covered by the right mediastinal pleura. At the level of the right main bronchus, the azygos vein ascends from a paravertebral right position anteriorly to the superior mediastinum to drain into the superior vena cava, crossing over the esophagus on its way. The sympathetic chain and ganglia run vertically, parallel and lateral to the azygos vein, crossing over the intercostal vessels. Below the inferior pulmonary vein, the esophagus lies between the heart and descending aorta that is behind and on the left of the esophagus. The right pleura is in contact with the lower one-third of the esophagus, almost up to the diaphragmatic hiatus. This proximity of the right pleura to the hiatus introduces the risk of pneumothorax during abdominal operations on the hiatus. On the left side, in the superior mediastinum, the lateral surface of thoracic esophagus is covered proximally by the last part of the aortic arch with the left subclavian artery and by the left mediastinal pleura. Further to the left, there is the thoracic duct, which passes superiorly and to the left, at the level of the fifth thoracic vertebra, behind the esophagus, and then it ascends on the left side of the esophagus into the superior mediastinum. Caudally, in the posterior mediastinum, left side of the esophagus is covered by the descending thoracic aorta until the level of the eight thoracic vertebra and then only by the left mediastinal pleura. Hence, there are two triangles within which the esophagus, covered by the mediastinal pleura, can be encountered from the left side. In the superior

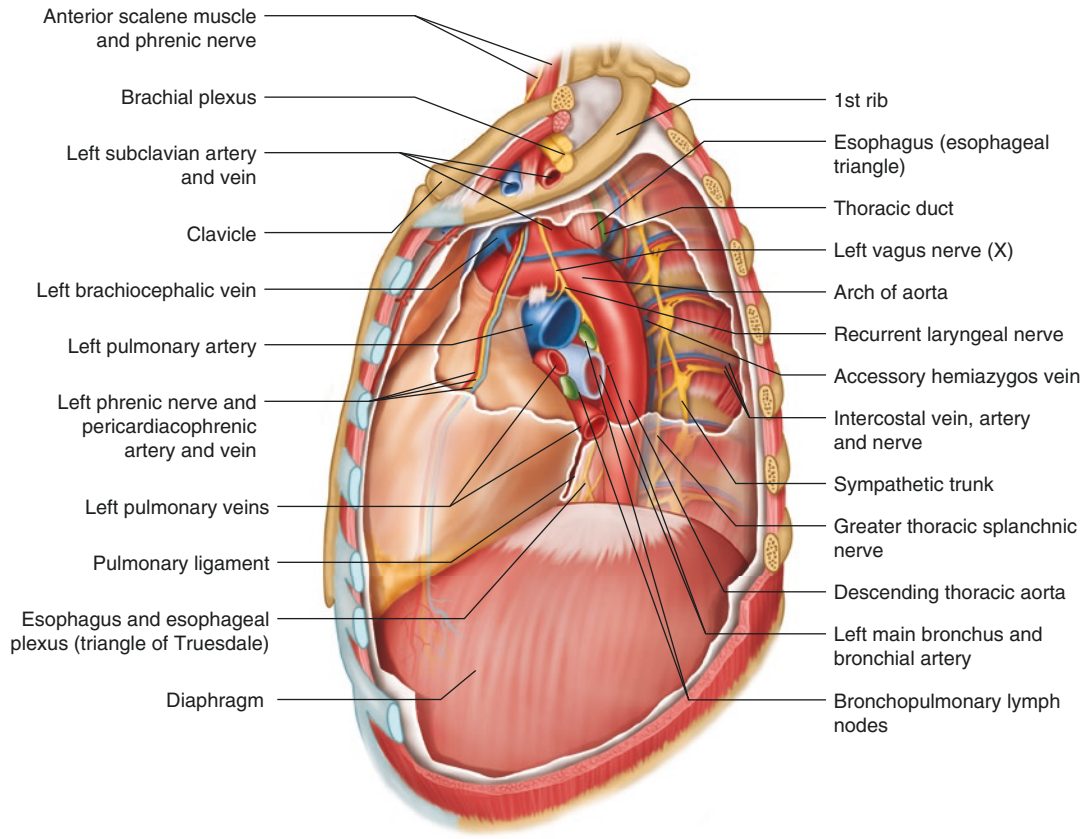

Fig. 25.5 Thoracic esophagus; left lateral view

mediastinum, the *esophageal triangle* is formed by the descending aorta, the subclavian artery, and the vertebral column. In the posterior mediastinum, the *Truesdale's triangle* is bounded inferiorly by the diaphragm, anteriorly by the pericardium, and posteriorly by the descending aorta (Fig. 25.5). Behind and lateral to the aorta, hemiazygos vein runs the anterolateral aspect of the vertebral bodies, receiving the left intercostal veins. It crosses behind the thoracic esophagus to join the azygos vein on the right at the level of the eight thoracic vertebra. The anatomy of the sympathetic chain on the left is similar to that on the right. The tubular thoracic esophagus progresses inferiorly, bounded in the lower thorax by pericardium anteriorly, aorta posteriorly, and pleurae laterally. Two to three centimeters above the hiatus of the diaphragm, it is anchored at its lower end by the insertion of a tough, skirtlike prolongation of the endoabdominal fascia from the undersurface of the diaphragm, the ascending leaf of the *phrenoesophageal ligament*. This inserts into the esophagus and is attached to the submucosa and intermuscular septa of the esophageal wall by fascicles of fibroelastic tissue. The posterior approximation of the right and the left mediastinal pleurae between the thoracic esophagus and the descending aorta forms the so-called meso-esophagus [1–6, 15].

25.2.3 Abdominal Esophagus and Esophagogastric Junction

The length of abdominal esophagus ranges from 0.5 to 4 cm, but occasionally it is as long as 7 cm. It begins once the tube transits the diaphragm hiatus (tenth thoracic vertebra level) and ends at the cardia of the stomach along the high lesser curvature (11th–12th thoracic vertebral level). This portion of the esophagus is partially covered by peritoneum in front and on its

left side. The anterior vagal trunk runs on the anterior surface of the esophagus, partially embedded in the musculature, while the posterior vagal trunk is placed on the posterior surface. Its bifurcation is usually hidden in the gastroesophageal fat pad. About 12 % of patients exhibit variations of typical anatomy, usually consisting of extension of esophageal plexus into the abdomen or early bifurcation of the two trunks above the diaphragm. Anteriorly, the abdominal esophagus is in close contact with the left lobe of the liver that forms an esophageal groove. Its right border continues evenly into the lesser curvature, whereas the left border is separated from the fundus of the stomach by the angle of His. Posteriorly, the esophagus is related to the right or both crura of the diaphragm, left inferior phrenic artery, and abdominal aorta. Abdominal aorta lies anterior to the vertebral bodies and directly posterior to the esophageal hiatus. The hiatus and the abdominal esophagus are covered by the *phrenoesophageal membrane of Laimer-Bertelli*, which arises primarily from the endoabdominal (transversalis, subdiaphragmatic) fascia. At the lower margin of the esophageal hiatus, it decussates into an upper and a lower leaf or ligament. The upper leaf extends through the hiatus into the thorax to insert into the esophagus 2–3 cm above it. The lower leaf, which exists as a loosely defined collection of fibroelastic fibers, descends to insert into the abdominal esophagus, blending into the adventitial coat, and may also insert onto the gastric fundus. The upper leaf, consisting of pleura and the subpleural fascia, has the character of a strong, well-defined membrane rather than a ligament, despite its name. The two leaves of the membrane are separated by loose alveolar tissue, which allow for greater mobility of the distal esophagus through the hiatus. Five ligaments are related to abdominal esophagus and esophagogastric junction: *left triangular ligament*, left portion of the posterior layer of *coronary ligament*, *hepatogastric* (*gastrohepatic*) *ligament*, *gastrosplenic* (*gastrolienal*) *ligament*, and *gastrophrenic ligament*. A section of the left triangular ligament and left portion of the posterior layer of the coronary ligament is necessary to approach the abdominal esophagus and the gastroesophageal junction. The abdominal esophagus lies between the two layers of the hepatogastric ligament, which extends from the porta hepatis to the lesser curvature of the stomach, and separates the lesser sac from the rest of the peritoneal cavity. This ligament contains the left gastric vessels, hepatic division of the left vagus nerve, and lymph nodes and may also contain the left hepatic artery, when it arises from the left gastric artery. On the right, the hepatogastric ligament divides to enclose the stomach, and its peritoneal leaves rejoin on the left to form the gastrosplenic ligament. At the level of the abdominal esophagus, as the posterior leaf does not reach the gastroesophageal junction, the hepatogastric ligament is formed only by its anterior leaf. Therefore, a small bare area is left on the posterior wall of the stomach, which lies over the left crus of the diaphragm. The gastrosplenic ligament contains short gastric vessels, and lymph nodes into its upper portion, left gastroepiploic vessels, lymph nodes, and terminal branches of the splenic artery into its lower portion. Gastrophrenic ligament arises from the greater curvature, at the level of the gastric fundus, and extends upward to the diaphragm. Its upper part is avascular and continuous with the posterior layer of the coronary ligament on the left, whereas its lower part contains some short gastric vessels and lymph nodes and is continuous with the gastrosplenic ligament [1–6, 15–18].

25.3 Vessels and Nerves

25.3.1 Arterial Blood Supply

UES and cervical esophagus are supplied by branches of the right and left inferior thyroid arteries, which arise from the thyrocervical trunk of the subclavian artery. Inferior thyroid arteries give off branches 2–3 cm long called tracheoesophageal arteries. These travel caudal and medial on each side toward the tracheoesophageal groove. Vessels

of both sides are joined by anastomotic twigs along the trachea and divide into three to four tracheal branches with two to three branches to the esophagus. These, in turn, subdivide within the periesophageal tissue into vessels of less than 0.5 mm luminal diameter before they enter the esophageal wall. Rare variants, such as direct esophageal branches from subclavian artery, superior thyroid artery, thyroidea ima artery, and common carotid artery, are rather insignificant [4, 5, 15, 19, 20].

Proximal thoracic portion is supplied by 1–4 unpaired tracheobronchial arteries, originating from the concavity of the arch and upper descending aorta, and bronchoesophageal artery. Tracheobronchial arteries give off several small branches to the esophagus which subdivide within the periesophageal tissue into vessels of less than 0.5 mm in diameter. Frequently, one bronchoesophageal artery originates 1–3 cm caudal to the vascular bundle from the anterolateral aspect of descending aorta. In this area, which relates to the tracheal bifurcation, all vessels are straight and short (<1.5 cm) and form a firm connection between aorta, trachea, and esophagus. Variants, if any, such as branches from intercostal arteries, seem to be insignificant for the blood supply of the human esophagus. Caudally, 1–2 unpaired proper esophageal arteries rise directly from the anterior aspect of thoracic aorta. When present, these vessels descend obliquely toward the esophagus within the mediastinum to divide into recurrent ascending and descending branches. Both subdivide into several periesophageal vessels of less than 0.5 mm in diameter before entering esophageal wall [4, 5, 15, 19–23].

Abdominal esophagus and EGJ are supplied by branches of left gastric, left phrenic, and splenic arteries. The left gastric artery mainly supplies the anterior and right lateral aspects of the esophageal wall with its ascending branches, which run on the lateral side of the EGJ following the longitudinal axis of the esophagus. The dorsal wall of abdominal esophagus is supplied by branches of left inferior phrenic and splenic arteries. The splenic artery primarily supports the posterior and left lateral aspects (cardiac notch) by either one or two direct branches or by vessels of the gastric fundus, including connections with short gastric arteries. Branches from both stem vessels give rise to minute branches which surround the circumference to communicate with the opposite side. Moreover, they extend straight upward 4–6 cm within periesophageal tissue across the diaphragmatic hiatus forming a longitudinal network. At variable distances small tributaries of less than 0.5 mm internal diameter emerge before the main vessels pierce the esophageal wall [4, 5, 15, 19–23].

Arterial branches supplying cervical, thoracic, and abdominal esophagus are connected altogether. Indeed, except 1–2 proper esophageal arteries of direct aortic origin, the vascular pattern derives from the larger stem vessels needed for the supply of different organs. Hence, the arterial blood supply of the esophagus depends on a shared vasculature. Before entering into the esophageal wall, repetitive branching of the already small esophageal vessels gives rise to very small vessels in the periesophageal tissue, which can undergo contractile hemostasis when torn. Moreover, having penetrated muscular wall, arteries supplying the esophagus end in an extensive, dense network and form the *submucosal plexus*. In the submucosa, most of the fine vessels run parallel each other in longitudinal orientation, and the others form circumferential vessels. This submucosal network connects all the extramural vessels. Therefore, the esophagus has no poorly supplied or avascular zone. This copious blood supply permits the placement of anastomoses at any level and may explain the rarity of the esophageal infarction [5, 21, 24].

25.3.2 Venous Drainage

Within the lamina propria, the *subepithelial plexus* receives venous blood from the adjacent capillaries and drains into the *submucosal plexus*. From this extensive plexus, venous blood drains into the *periesophageal plexus*, which is longitudinally oriented. Esophageal veins arise from this plexus and drain in a segmental way

similar to the arterial supply. In the neck, veins from cervical esophagus drain into inferior thyroid veins, which finally drain into brachiocephalic veins. In the thorax, veins from thoracic esophagus drain into azygos, hemiazygos, intercostal, and bronchial veins. Caudally, periesophageal venous plexus of the abdominal esophagus drains into left gastric and left phrenic veins. Hence, as the left gastric vein is a tributary of the portal system, the submucosal plexus of the lowest portion of the esophagus connects the caval and the portal venous systems [4, 5, 15].

25.3.3 Lymphatic Drainage

Lymph capillaries originate as a network of endothelial channels or as blind endothelial sacculations in the space between the lower border of mucosa and submucosa. Within the submucosa, abundant lymphatics form a dense submucosal plexus, where lymph runs longitudinally. In the upper two-thirds of the esophagus, the lymph flows mainly cranially and caudally in the lower third. Efferent vessels from the cervical part drain into the paraesophageal and the retropharyngeal lymph nodes. The former lymph nodes are located laterally to the esophagus and the retropharyngeal lymph nodes behind the pharynx on the prevertebral fascia. From these lymph nodes, lymph flows into the internal jugular, supraclavicular, and upper paratracheal nodes. Lymphatic vessels from the thoracic esophagus drain into the posterior mediastinal nodes. Lymph from the upper thoracic third flows into the superior paraesophageal lymph nodes, laterally attached to the esophagus, and caudally into the prevertebral lymph nodes. Lymphatic drainage from the middle thoracic third goes into the medial paraesophageal lymph nodes and into the paratracheal, tracheobronchial, and bronchopulmonary lymph nodes. Nevertheless, some lymphatic vessels may pass directly to the thoracic duct and to the lymph nodes of the cranial or caudal compartment. Lymphatic flow from the lower thoracic third drains into the inferior paraesophageal, prevertebral, and superior diaphragmatic lymph nodes. Lymphatic flow from the abdominal esophagus and esophagogastric junction empties into the perigastric lymph nodes, along the lesser and the greater curvature, and into the left gastric and celiac lymph nodes [3–5, 15].

The thoracic duct arises from the cisterna chyli, which lies in the abdomen to the right of the aorta at the level of the first-second lumbar vertebra. The duct passes from the abdomen into the thorax through the aortic hiatus and travels in the posterior mediastinum to the right of the midline between the esophagus and azygos vein. In this region, behind the duct, there are the vertebral column, the right intercostal arteries, and the hemiazygos veins as they cross the midline to open into the azygos vein; diaphragm, esophagus, and pericardium lie in front of the duct, which is separated from pericardium by a recess of the right pleural cavity. Although often a single channel, in the thorax, about 30–40 % of people have multiple (two or more) thoracic ducts. At the level of the fifth or sixth thoracic vertebra, it crosses behind the esophagus to the left and enters the superior mediastinal cavity. Here it ascends behind the aortic arch and the thoracic part of the left subclavian artery, between the left side of the esophagus and left pleura, to the base of the neck. There it ascends 2–3 cm above the left clavicle before curving to the right and caudad to drain into the lymphovenous junction. In two-thirds of people, the duct passes posterior to internal jugular vein and common carotid artery. As it arches to descend, the thoracic duct passes anterior to subclavian artery, vertebral artery and vein, and thyrocervical trunk or its branches. It also passes in front of the phrenic nerve and the medial border of the scalenus anterior, but is separated from these two structures by prevertebral fascia. Left common carotid artery, vagus nerve, and internal jugular vein are in front of it. The duct commonly drains in the left internal jugular vein within 2 cm of the jugulovenous angle; less frequently it drains into the junction of the left subclavian vein with the left internal jugular vein (jugulovenous angle) or into the left subclavian vein. The thoracic duct terminates into the venous system either as a single channel or as multiple channels; in nearly three-quarters of cases, it ends as a single channel, even if the duct may initially divide into two or

more channels, up to 5 cm from the lymphovenous junction, before merging back into a single duct [5, 25].

25.3.4 Innervation

The nerve supply of the esophagus has two sources, which exert mutually antagonistic actions (*extrinsic innervation*): sympathetic (vasoconstriction, contraction of sphincters, and relaxation of the muscular wall) and parasympathetic (increase of glandular and peristaltic activity). Similar to the other gastrointestinal tracts, within the esophageal wall, there are two nervous plexuses (*intrinsic innervation*), which have different actions: the Meissner's plexus in the submucosa regulates mucosal secretion and contraction of the muscularis mucosae, and the Auerbach's plexus between the longitudinal and circular muscle layers regulates the peristaltic contraction of the muscularis propria [3–5].

The sympathetic supply of pharynx, larynx, and proximal esophagus comes from both right and left branches of the superior and inferior cervical ganglia and from the upper thoracic ganglia. The sympathetic nerves supply the distal esophagus and the esophagogastric junction through branches from the greater and sometimes the lesser splanchnic nerves and through branches from the plexuses on the left gastric and inferior phrenic vessels, which come from the celiac plexus. Commonly, the sympathetic branches run with the arterial vessels and are interlaced with fibers of the parasympathetic cervical and thoracic plexuses [3–5, 26].

The parasympathetic supply comes from laryngeal nerves and esophageal plexus arising from the vagal nerves (tenth pair of cranial nerves). The vagal trunks run along either side of the neck until they reach the thoracic esophagus, where they form an extensive plexus. At the level of tracheal bifurcation, behind the lung hilum, the vagal nerves form the pulmonary and esophageal plexus. The left vagus contributes primarily to the anterior and the right vagus to the posterior esophageal plexus (LARP = left anterior, right posterior). Above the diaphragm they coalesce once more into two trunks. The left trunk courses more anterior and the right trunk posterior as they pass through the esophageal hiatus. Then, the anterior trunk divides into the hepatic branch and the anterior nerve of Latarjet, while the posterior trunk divides into the celiac branch and the posterior nerve of Latarjet. This latter branch runs in the gastrohepatic ligament about 1 cm from the lesser curvature of the stomach, parallel but deeper than the anterior nerve of Latarjet. The innervation of the musculature and mucosa of pharynx, larynx, UES, and upper half of the esophagus is formed by the bilateral superior laryngeal nerves and/or inferior laryngeal (recurrent) nerves. Close to the nodose ganglion, the superior laryngeal nerve arises from the vagal trunk. It runs down in the neck adjacent to the pharynx, medial to the carotid sheath, and divides into the internal and external branches approximately 2–3 cm above the superior pole of the thyroid. The external branch is motor and supplies the cricothyroid muscle and the cricopharyngeus portion of the inferior pharyngeal constrictor (UES). The internal laryngeal nerve, containing parasympathetic and sensory fibers, supplies the laryngeal mucosa above the vocal folds and the region of the piriform fossae. The inferior laryngeal nerve originates on the right side from the vagus nerve, at the level of T1–T2 or more inferiorly, in front of the subclavian artery, turns backward around the artery, and ascends obliquely to the right lateral aspect of the trachea, slightly anterior to the tracheoesophageal groove, before coursing between the trachea and the thyroid. On the left, the inferior laryngeal nerve arises from the left vagus nerve in the thorax, in front of the aortic arch. It travels inferior and, after looping around the aortic arch, posterior to the arch behind the ligamentum arteriosum and ascends obliquely to the left of the trachea. It travels cranially into the neck to the left side of the trachea, slightly anterior to the tracheoesophageal groove, but closer to it than the right. An aberrant nonrecurrent pathway for the inferior laryngeal nerve is rare (<1 %) on the right side and exceptional (<0.1 %) on the left. Three conditions are usually required for this anomaly to exist: the right aortic arch, the retroesophageal left subclavian artery, and the right arterial ligament on the right side. Although the

triple anomaly is very rare, an aberrant nonrecurrent pathway for the inferior laryngeal nerve represents a major surgical risk. Along their course, both inferior laryngeal nerves give an equal number of nerve fibers to the trachea and esophagus (from 8 to 14 branches). Reaching the pharyngoesophageal junction, they gain close proximity to the esophagus, the left side usually closer than the right. Near the lower pole of the thyroid gland, both nerves are always intimately related to the gland and often pass between branches of the inferior thyroid vessels. The ends of both inferior laryngeal nerves pass superiorly, deep to the inferior border of the inferior pharyngeal constrictor muscle, just posterior to the cricothyroid joint to supply the interarytenoid, posterior cricoarytenoid, and lateral cricoarytenoid muscles. Occasionally the major terminal branch communicates with the superior laryngeal nerve. As the inferior and superior laryngeal nerves supply the same laryngeal muscles and mucosa, this double innervation may compensate for some sequelae of inferior laryngeal nerve injury [27–32].

References

1. Oezcelik A, DeMeester SR (2011) General anatomy of the esophagus. Thorac Surg Clin 21:289–297
2. Long JD, Orlando RC (2002) Anatomy, histology, embryology, and developmental abnormalities of the esophagus. In: Feldman M, Fieldman LS, Sleisenger MH (eds) Gastrointestinal and liver diseases. WB Saunders, Philadelphia, pp 551–560
3. Gavaghan M (1999) Anatomy and physiology of the esophagus. AORN J 69:372–386
4. Broering DC, Walter J, Halata Z (2009) Surgical anatomy of the esophagus. In: Izbicki JR, Broering DC, Yekebas EF, Kutup A, Chernousov AF, Gallinger YI, Bogopolski PM, Söehendra N (eds) Surgery of the esophagus. Textbook and atlas of surgical practice. Springer, Berlin/Heidelberg, pp 3–10
5. Patti MG, Gantert W, Way LW (1997) Surgery of the esophagus. Anatomy and physiology. Surg Clin North Am 77:959–970
6. Riddell AM, Davies DC, Allum WH, Wotherspoon AC, Richardson C, Brown G (2007) High-resolution MRI in evaluation of the surgical anatomy of the esophagus and posterior mediastinum. AJR Am J Roentgenol 188:W37–W43
7. Huang Q (2011) Definition of the esophagogastric junction: a critical mini review. Arch Pathol Lab Med 135:384–3898
8. Mittal RK, Balaban DH (1997) The esophagogastric junction. N Engl J Med 336:924–932
9. Hayward J (1961) The lower end of the esophagus. Thorax 16:36–41
10. Takubo K, Aida J, Sawabe M, Arai T, Kato H, Pech O, Arima M (2008) The normal anatomy around the esophagogastric junction: a histopathologic view and correlation with endoscopy. Best Pract Res Clin Gastroenterol 22:569–5483
11. Kumoi K, Ohtsuki N, Teramoto Y (2001) Pharyngoesophageal diverticulum arising from Laimer's triangle. Eur Arch Otorhinolaryngol 258:184–187
12. Rubesin SE, Levine MS (2001) Killian-Jamieson diverticula: radiographic findings in 16 patients. AJR Am J Roentgenol 177:85–89
13. Sivarao DV, Goyal RK (2000) Functional anatomy and physiology of the upper esophageal sphincter. Am J Med 108(Suppl 4a):27S–37S
14. Preiksaitis HG, Diamant NE (1997) Regional differences in cholinergic activity of muscle fibers from the human gastroesophageal junction. Am J Physiol 272(6 Pt 1):G1321–G1327
15. Skandalakis JE, Ellis H (2000) Embryologic and anatomic basis of esophageal surgery. Surg Clin North Am 80:85–155
16. Bombeck CT, Dillard DH, Nyhus LM (1966) Muscular anatomy of the gastroesophageal junction and role of phrenoesophageal ligament; autopsy study of sphincter mechanism. Ann Surg 164:643–654
17. Eliska O (1973) Phrenoesophageal membrane and its role in the development of hiatal hernia. Acta Anat (Basel) 86:137–150
18. Friedland GW (1978) Progress in radiology: historical review of the changing concepts of lower esophageal anatomy: 430 B.C.--1977. Am J Roentgenol 131:373–378
19. Miura T, Grillo HC (1966) The contribution of the inferior thyroid artery to the blood supply of the human trachea. Surg Gynecol Obstet 123:99–102
20. Williams DB, Payne WS (1982) Observations on esophageal blood supply. Mayo Clin Proc 57:448–453
21. Liebermann-Meffert D, Siewert JR (1992) Arterial anatomy of the esophagus. A review of literature with brief comments on clinical aspects. Gullet 2:3–10
22. Yan Y, Chen C, Chen Y, Wu Y, Shi Z (1998) Arterial patterns in the thoracic and abdominal segments of the esophagus: anatomy and clinical significance. Surg Radiol Anat 20:399–402
23. Liebermann-Meffert D, Lüscher U, Neff U, Rüedi TP, Allgöwer M (1987) Esophagectomy without thoracotomy: is there a risk of intramediastinal bleeding? A study on blood supply of the esophagus. Ann Surg 206:184–192

24. Orringer MB, Orringer JS (1983) Esophagectomy without thoracotomy: a dangerous operation? J Thorac Cardiovasc Surg 85:72–80
25. Phang K, Bowman M, Phillips A, Windsor J (2014) Review of thoracic duct anatomical variations and clinical implications. Clin Anat 27:637–644
26. Cunningham ET, Sawcenko PE (1990) Central neural control of esophageal motility: a review. Dysphagia 5:35–51
27. Cernea CR, Ferraz AR, Nishio S, Dutra A Jr, Hojaij FC, dos Santos LR (1992) Surgical anatomy of the external branch of the superior laryngeal nerve. Head Neck 14:380–383
28. Haller JM, Iwanik M, Shen FH (2012) Clinically relevant anatomy of recurrent laryngeal nerve. Spine (Phila Pa 1976) 37:97–100
29. Skandalakis JE, Droulias C, Harlaftis N, Tzinas S, Gray SW, Akin JT (1976) The recurrent laryngeal nerve. Am Surg 42:629–634
30. Liebermann-Meffert D, Walbrun B, Hiebert CA, Siewert JR (1999) Recurrent and superior laryngeal nerves: a new look with implications for the esophageal surgeon. Ann Thorac Surg 67:217–223
31. Henry JF, Audiffret J, Denizot A, Plan M (1988) The nonrecurrent inferior laryngeal nerve: review of 33 cases, including two on the left side. Surgery 104:977–984
32. Galletta G, Cesario A, Margaritora S, Granone P (2008) Anomalous intrathoracic left vagus and recurrent laryngeal nerve course. Ann Thorac Surg 86:654–655

Surgical Technique: Open Procedures

26

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26.1 Introduction

The choice of surgical excision in adenocarcinoma of the cardia and the type of reconstruction depend directly on the oncological principles, especially in terms of the extent of visceral resection (stomach and esophagus) and in terms of the choice of lymphadenectomy (see Chap. 14).

The classification of Siewert, as previously described, helps in the surgical choice. It should also be considered, for a correct definition of the surgical planning, that the morbidity and postoperative mortality are influenced both by the choice of the organ and by the position of the anastomosis.

We can simply assert that Siewert I requires a subtotal esophagectomy with reconstruction of the digestive route through the use of a gastric conduit. The choice to reconstruct using transthoracic approach is widely shared by many authors, but the choice of a transhiatal esophagectomy remains an option, as published in recent international case studies. In cases of type III of Siewert, the choice falls on total gastrectomy with distal esophagectomy and reconstruction through intramediastinal esophagojejunal anastomosis.

The Siewert II requires a decision: esophagectomy with esophagogastric anastomosis (as in Siewert I), gastrectomy and distal esophagectomy with intramediastinal esophagojejunal anastomosis or subtotal esophagectomy with total gastrectomy, and reconstruction by esophagojejunal anastomosis. On the basis of what previously described in Siewert type II tumors, we choose an esophagectomy in the case of tumor which extend in the esophagus for more than 2 cm; otherwise, we do a total gastrectomy with distal esophagectomy and intramediastinal anastomosis.

The location and type of anastomosis are parts of the surgical choice. We do not believe that it is a valid systematic resort to cervical anastomosis, there being neither advantage in terms of control of the tumor nor of postoperative morbidity; we reserve the choice of cervical anastomosis only for patients who can not receive a thoracotomy. The type of anastomosis is considerably controversial; literature is unable to have sufficient evidence to determine the best option (Chap. 20). We favor the use of mechanical anastomosis for the greater degree of standardization that this guarantees.

We describe the surgical techniques most frequently used, according to our personal practice based on the clinical experience, analysis of personal results, and comparison with literature.

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26.2 Transthoracic Esophagectomy

26.2.1 Abdominal Stage

26.2.1.1 Positioning

The patient is positioned on the operating table in the supine position with legs closed and with a dorsal rolled sheet to improve access to the cardia. The arms are adducted to the median axis along the sides of the patient. The surgeon stands on the patient's right side, opposite to the first assistant. The second assistant stands on the surgeon's left side.

26.2.1.2 Incision

The common approach to the abdominal cavity is the median xifo-umbilical laparotomy; sometimes it is necessary to extend the incision below the umbilicus, especially in obese patients.

Superiorly you can extend the incision to the left of the xiphoid process to make more evident the esophageal hiatus. After the peritoneal cavity has been opened, retractors with lateral traction and costal self-retaining retractors are positioned to better approach the subcostal region.

26.2.1.3 Exploration

The first exploration phase provides visualization and palpation of the liver surface and the inspection of the parietal peritoneum, the greater omentum, and the diaphragmatic peritoneum in order to exclude metastases and peritoneal implants.

The exploratory stage provides the peritoneal lavage cytology; about 200 ml of saline is introduced into the peritoneal cavity for about 2 min, taking a sample of at least 50 ml for assessment of circulating cancer cells. It is important to perform this procedure at the beginning, before the gastric mobilization in order to avoid a nondiagnostic cytology for the excessive amount of red blood cells. It may be indicated, if the disease involves the posterior gastric wall, the dissection of the lesser omentum to perform a peritoneal lavage in the lesser sac. The exploration of the area of the diaphragmatic crura, to confirm the extent of the disease, requires the separation of the left triangular ligament of the liver; the operator with the right hand pulls down the left lateral segment of the liver facilitating the section of the ligament with the electric scalpel.

The section must be performed in a lateromedial direction until the falciform ligament, obtaining a complete mobilization of the left hepatic lobe, which can be partially dislocated to the right, completely exposing the anterior surface of the cardia.

26.2.1.4 Mobilization of the Stomach

The greater omentum is separated from the stomach from right to left about 5 cm from the pylorus to facilitate the visualization of the gastroepiploic arch. The assistant pulls the colon caudally while the operator with the left hand raises the greater omentum and pulls it cranially. This maneuver makes more evident the avascular plane of dissection between the leaflets of the greater omentum, the colic surface, and the upper surface of the transverse mesocolon. Detachment of the greater omentum from the tranverse colon provides access to the lesser sac. To facilitate the completion of this time, the lesser omentum can be opened and the gastric body suspended on tape (Fig. 26.1) that will be drawn by an assistant. The dissection continues to the left, up to the lower pole of the spleen. It is important to pay attention to cut spleo-omental adhesions, in order to avoid, during the traction on the omentum, the tearing of the splenic capsule. The operator pulls to the right the grater curvature of the stomach, while the assistant moves the colon caudally stretching the left gastroepiploic vessels, which are divided at the origin to preserve any vascular supply to the conduit. The mobilization of the fundus of the stomach continues ligating and dividing selectively short gastric vessels and gastrosplenic ligament, until the identification of the left diaphragmatic crura.

Coloepiploic detachment is completed to the right, in the direction of the duodenum. To facilitate this step can be useful the mobilization of the hepatic flexure, thereby exposing the surface of the

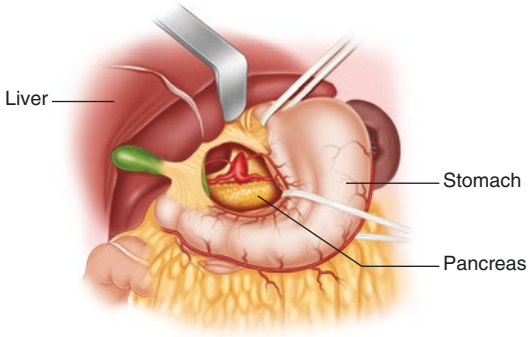

Fig. 26.1 Opening of the lesser omentum and the traction of the gastric body on tape

duodenum; at this point it will be easier to identify the position of the right gastroepiploic vein, following the middle colic vein along its route that joins, in about half the cases, the right gastroepiploic vein to form the venous trunk of Henle. The right gastroepiploic vein will be partially freed from the surrounding structures to make the stomach more movable, taking care not to damage the vein.

The assistant pulls the stomach caudally, stretching above the pylorus the fold, corresponding to the right gastric artery. The artery must be ligated and divided near the origin of the proper hepatic artery. The identification and the section of the pyloric vein allow the complete liberation of the superior antropyloric region, and suprapyloric lymph node dissection will be completed (lymph nodes # 5).

The completion of the section of the lesser omentum occurs caudal-cranial to the diaphragmatic crura near the lower edge of the liver. The operator is preparing the opening of the Laimer-Bertelli membrane and the esophagus is freed with a digital maneuver.

The first assistant moves medially and upward the stomach to release the posterior wall by loose adhesions of gastropancreatic ligament. At this point the two tapes, gastric and esophageal, are pulled to the left, making evident the gastropancreatic fold and then the left gastric vessels inside. The first assistant is positioned with the right hand on the lesser curve, raising with two fingers the gastropancreatic fold; with his left hand, he pushes through a gauze the pancreatic body toward the spine. In this way it becomes evident the left gastric vein that must be ligated and divided at the origin. The next step is to identify the left gastric artery that is ligated and divided close to the celiac trunk, taking care to remove all the lymph nodes along the artery and around the celiac trunk (lymph nodes # 7 and 9). Lymphadenectomy should be completed on the suprapancreatic region and along the anterior hepatoduodenal ligament (D2 lymphadenectomy).

The stomach is now released from the vascular axis (with the exception of the left gastroepiploic vessels) and from the peritoneal ligaments. To make the stomach more mobile, Kocher's maneuver can be performed.

26.2.1.5 Tubulization

By a linear stapler, the esophagus is divided from the stomach. If the lesion extends below the cardia, it will be crucial to dissect at the gastric level, starting from the greater curvature of the stomach in the direction of the lesser curvature, about 5 cm from the margin of the lesion. The stomach, completely mobilized, is rotated caudally taking care not to stretch the vascular axis. The omentum is dissected at about 3 cm from the gastroepiploic arcade which is vital to maintain its integrity. An Allis clamp is placed at the cranial extreme of the greater curve, which corresponds to the apex of the conduit that we're going to model. From this point, the surgeon performs a section parallel to the greater curve, by means of a linear stapler, at a distance of about 3–4 cm (diameter of the gastric tube) for a length of about 5–6 cm. The section is then performed in the direction of the lesser curve. Starting from the lesser curve, 2 cm above the pylorus, the stomach is sectioned parallel to the greater curve up to approximately 4–5 cm from the previous suture line. This results in an access pouch that will be used during thoracic stage for entry of the circular stapler (Fig. 26.2). The suture lines are fully covered by means of a running suture with 4–0 absorbable monofilament.

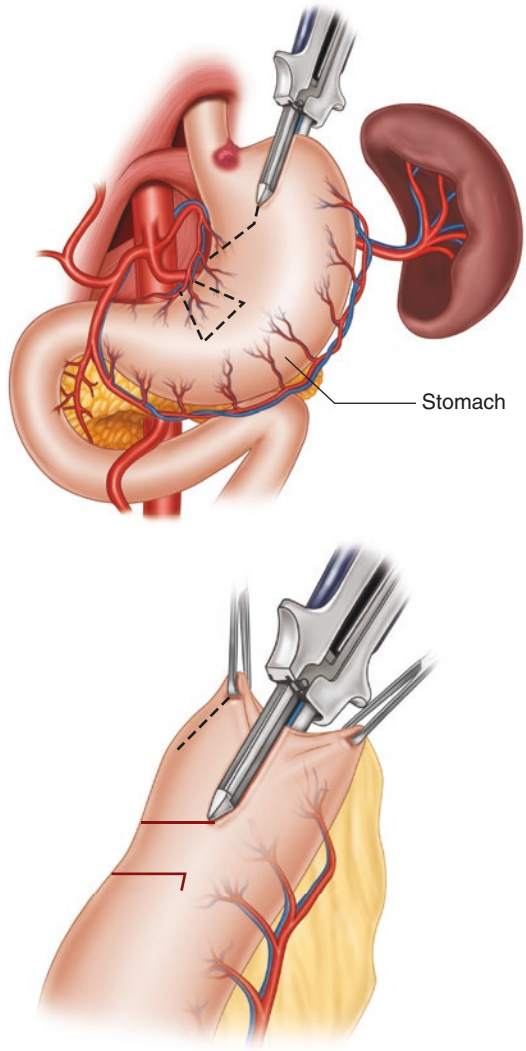

Fig. 26.2 Gastric conduit preparation: an access pouch is created to facilitate entry of the circular stapler

26.2.1.6 Abdominal and Mediastinal Dissection of the Esophagus

The esophageal stump is pulled caudally to expose the diaphragmatic hiatus. With digital maneuver, the pericardium is dissected by the diaphragm, and the surgeon performs an anterior phrenotomy of about 2 cm to access more easily to the lower mediastinum. Placing a retractor to the diaphragmatic crura, the operator dissects upward the mediastinal esophagus. The use of ultrasonic or radio frequency scalpel makes these steps easier. Normally the dissection started posteriorly, sliding on the surface of the aorta, and then continues on both sides making sure to fully remove the periesophageal tissue which are contained in the lower periesophageal and diaphragmatic lymph nodes. (lymph nodes # 110–111) (Fig. 26.3).

The accidental opening of the left pleura does not need necessarily thoracic drainage but will be monitored in the postoperative period, the possible appearance and growth of pneumothorax and pleural collections. The opening of the right pleura will facilitate proper dissection of the esophagus.

Attention should be paid to the anterior dissection that we recommend performing only by blunt maneuvers. Completed the esophageal liberation, the conduit is anchored with two sutures to the stump of the esophagus. The abdominal stage is now completed.

26.2.2 Thoracic Stage

26.2.2.1 Positioning and Thoracotomy

The patient is positioned on the surgical table in the left lateral decubitus with the right arm raised and fixed to an arm board. The left leg is flexed. A chest roll is positioned at the apex of the left scapula to expand the intercostal space.

Access to the chest is carried out through a right anterolateral thoracotomy in correspondence of the fifth intercostal space. The skin incision along the body of the sixth rib usually does not exceed 15 cm in length from the anterior border of the latissimus dorsi muscle to the lateral margin of the pectoralis major muscle.

Later the latissimus dorsi muscle is separated from the surface of the serratus. The fibers of the latter are separated and opened out to expose the costal plane. It is then accessed through the intercostal space to the thoracic cavity, extending the section of the intercostal muscles, posteriorly below the posterior muscles of the chest.

26.2.2.2 Esophagectomy

After exploring the pleural cavity, the mediastinal pleura is divided at the level of the upper and lower margins of the azygos vein. The vein is surrounded with Finocchietto forceps, being careful not to

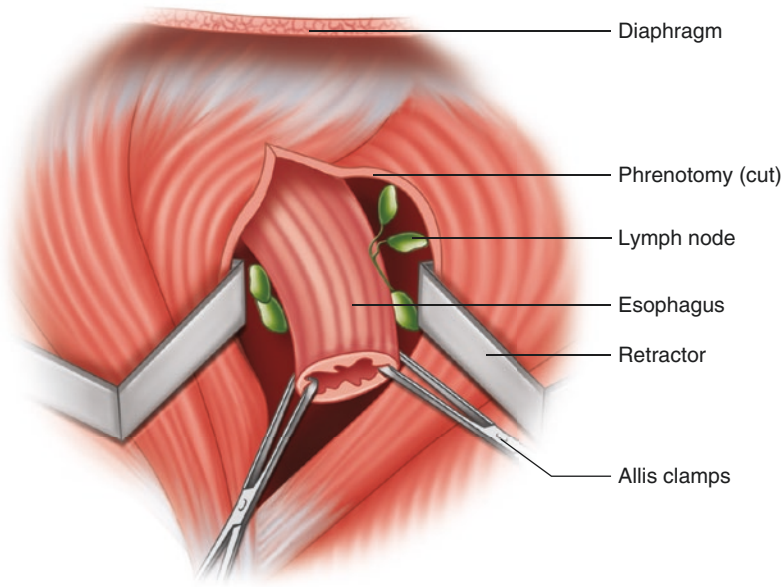

Fig. 26.3 After an anterior phrenotomy of about 2 cm, the operator dissects upward mediastinal esophagus placing a retractor to the diaphragmatic crura

damage the right bronchial artery, which possibly may be cut. The azygos vein is ligated and divided. The mediastinal pleura is then sectioned from the top downward in correspondence with the anterior edge of the esophagus and posteriorly along the course of the azygous vein. Esophageal dissection begins below the carina, clipping or coagulating the esophageal vessels. The esophagus is surrounded with a Penrose drain and draws upward by the first assistant. The surgeon can thus complete the dissection of the esophagus along its entire length, taking care to remove en bloc the middle and lower periesophageal lymph nodes and lower mediastinal lymph nodes (# 108–110–112). Cranially, care must be taken to remove the esophagus from the membranous part of the trachea by blunt dissection. The anastomosis is performed above the azygos vein, but if necessary, we can extend the resection to the apex of the chest. The tubularized stomach is then pulled into the chest.

26.2.2.3 Preparation of the Anastomosis and Lymphadenectomy

There are different anastomoses that can be performed to restore the esophagogastric continuity. Our choice falls on end-to-end mechanical anastomoses by a 25 circular stapler, for the standardization that this allows and for the relative ease of execution; freed the esophageal stump above the tracheal carina, the operator places a purse forceps, about 2 cm above the azygos vein to run a purse string. The esophagus is dissected above the forceps with a curve scissor and the clamp is removed. The integrity of the purse sting should be evaluated paying attention that the mucosa is involved in the suture. Using two Allis clamps, the operator inserts the anvil of the circular stapler within the stump and closes the purse string. The mediastinum is now completely free and is easy to remove the lymph nodes of the carina (# 107), for dissection should start at the lower edge of the right bronchus; in this position the right vagus nerve can be identified with its bronchial and cardiac branches that must be respected, interrupting selectively esophageal branches. If previously preserved, the bronchial artery can be identified and is raised on vascular tape during maneuvers of lymph node dissection, to avoid damage. The dissection is done through bipolar dissector, first in caudal-cranial direction at the margin of the right bronchus and then in cranio-caudal direction along the left bronchus.

26.2.2.4 Anastomosis

To complete the gastric conduit for the esophagogastric anastomosis, the apex of the conduit is dissected with a linear stapler beginning from the previous sutured line toward the greater curve (Fig. 26.4).

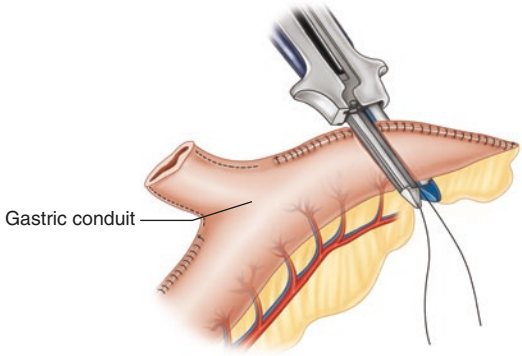

Fig. 26.4 Completion of gastric conduit

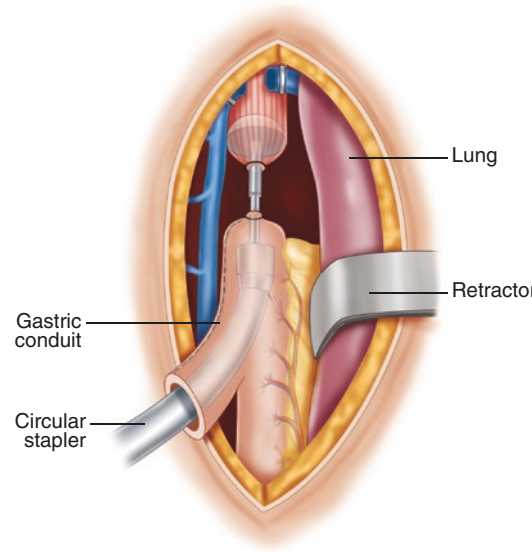

Fig. 26.5 Introduction of the circular stapler through the gastrostomy on the access pouch

The achievement of an adequate vascularization and a tension-free anastomosis should be considered in choosing the section level of the conduit.

The conduit should be not too long, because a long conduit cannot be entirely placed in the posterior mediastinum, but it would be running in the free-thoracic cavity, suffering a greater pressure gradient between the abdomen and the thorax, with a delayed conduit emptying and an increased reflux.

Then, the access pouch is pulled up by using two Ellis clamps and it is laterally opened. The circular stapler is introduced through the gastrostomy and then advanced throughout the gastric conduit. The spike of the stapler holes the conduit close to the suture line (Fig. 26.5). Thus, the anvil of the stapler is positioned in the esophagus and the cartridge in the gastric conduit. Therefore, the stapler is closed, and checking that the stomach and the esophagus are aligned properly, the stapler is fired. It is important that there is just a cross corner between the clips of the linear suture and the circular stapler as to limit the weak point of the anastomosis. The access pouch is closed by a TA 60 suture stapler (Fig. 26.6). Then, the stapled lines are oversewn with a running suture.

Considerations on technical aspects:

1. Conduit width: gastric conduit diameter should be not greater than 4 cm; in this way, the conduit is less influenced by the pressure gradient between abdomen and thorax, because just a small portion of the antrum remains under the diaphragm and also because the whole conduit can be placed in the posterior mediastinum. Moreover a smaller diameter ensures a better vascularization of the organ.

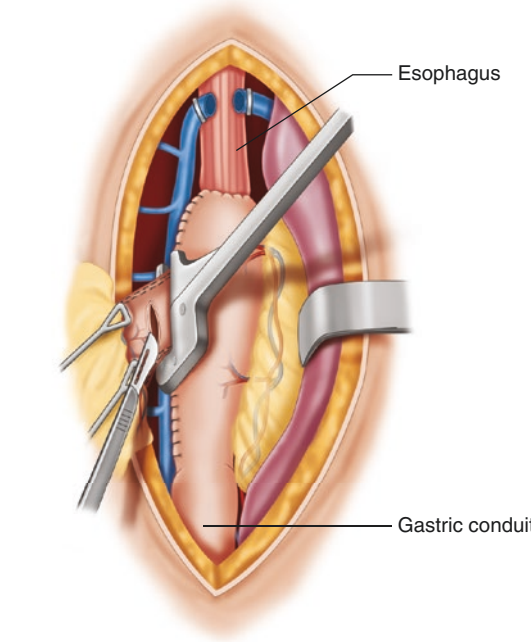

Fig. 26.6 The access pouch is closed by a TA 60 suture stapler

2. Pyloroplasty: pyloromyotomy is not necessary; we have just completed a trial dealing with patients treated by this technique, and the results do not show significant differences about the solid and liquid discharges and the reflux (data not published).
3. End-to-end anastomosis: our technique provides an end-to-end anastomosis with the advantage of a proper vascularization that surrounds the anastomosis, without ischemic areas.

26.2.3 Transhiatal Esophagectomy Without Thoracotomy (Orringer Procedure)

26.2.3.1 Positioning

The patient is positioned on the operating table in the supine position with arms adducted and head hyperextended and turned on the right. A small rolled sheet is placed under the shoulder blades, just to extend the head and expose the neck.

26.2.3.2 Abdominal Step

The beginning of this step is similar to the explorative phase and to the gastric mobilization time described in the transthoracic esophagectomy. We prefer to divide the stomach before starting with the dissection maneuvers of the mediastinic and thoracic esophagus. It is not necessary to perform an introducing pocket to the circular stapler. Starting from the top at the angle of His, the stomach is divided for the entire length parallel to the greater curvature, using multiple serial firings of a linear stapler. The stapled line stops 2 cm proximally to the pylorus, on the lesser curvature, decreasing the antrum size. The stapled line of the gastric conduit is oversewn with running absorbable monofilament suture.

26.2.3.3 Cervical Step

This stage can be performed by a second surgical team at the same time of the previous step.

The incision is made along the anterior edge of the left sternocleidomastoid muscle, for about 6–7 cm length. If it is necessary, the incision can be extended 2 cm above the jugulum.

After the dissection of the platysma muscle, the sternal edge of the sternocleidomastoid muscle is identified, retracted, and gently dissected laterally, after section of the superficial cervical fascia. The omohyoid muscle is dissected by electrocautery at the level of the medial tendon, and the medium cervical fascia is opened to expose the main vessels of the neck. Usually, we prefer dissecting some sternohyoid muscle fibers to the distal side of the incision, just to increase the surgical field.

The first assistant, placed on the right of the patient, dislocates gently the left lobe of the thyroid to the right with two fingers. The inferior thyroid artery, such as the thyroid veins, often crosses the surgical field and it has to be ligated and transected. The dissection continues toward the prevertebral fascia. By a blunt finger dissection, along the preverterbral fascia, it is possible to release posteriorly the esophagus in its cervical tract, continuing distally in its superior mediastinic tract. The soft tissue between the esophagus and the trachea is dissected by bunt dissection.

The cervical esophagus is partially surrounded by a finger, retracted laterally with a right-angled clamp and suspended with a cotton umbilical tape. With digital maneuver, it is possible to release totally the esophagus in its mediastinic tract up to the tracheal carina.

26.2.3.4 Mediastinic Step

At the same time of the cervical dissection, it is possible to perform the dissection at the inferior mediastinic level. The esophagus edge is retracted by the operator that dissects the pericardium from the diaphragm with blunt finger dissection. It is useful to perform an anterior phrenotomy for about 2 cm. The dissection of the esophagus continues to the top under vision until it is possible, retracting the diaphragmatic pillars. Then, blindfold, the dissection keeps on introducing the right hand into the diaphragmatic hiatus, posteriorly to the esophagus in traction. In this way the esophagus is separated from the prevertebral fascia.

At the same time, from the neck, the same maneuver is performed with a surgical swab on a forester clamp. When the esophagus is entirely released on the back, it is possible to continue with the front paying attention to the medium mediastinal structures. The fixity ele-

ments of the esophagus (arteries or the esophageal branches form the vagus) can be surrounded with a right-angled clamp and then dissected through a radio-frequency scalpel. When the entire thoracic esophagus is mobilized, the gastric conduit is ligated to the lower esophagus that it is pulled up and removed from the cervical incision. The gastric conduit is then transposed to the neck.

26.2.3.5 Cervical Anastomosis

We have different options for the cervical anastomosis and the choice depends on the size of the esophagus and the length of the gastric conduit. We prefer to reserve the manual anastomosis just to the cervicothoracic squamous carcinomas to ensure a proper dissection margin; in the case of adenocarcinoma, the choice is a mechanical anastomosis.

End-to side stapled anastomosis with the 21 circular stapler anvil placed in the esophageal stump: a gastrostomy is performed to the apex of the conduit from which the circular stapler is introduced. Stapler is advanced throughout the gastric conduit for 4–5 cm and the tip comes out from the posterior wall of gastric tube. The anastomosis is created, taking care not to include the omentum in the suture line. The gastrostomy is closed using a linear stapler. All the suture lines are oversewn (Fig. 26.7).

Side-to-side stapled anastomosis: posterior wall of the esophagus and posterior wall of gastric conduit are joined with a seromuscular running suture, for a length of 5 cm, at their side margins. After creating two small symmetrical holes in both organs, linear stapler is inserted and fired. Common entry hole is closed using a linear stapler. All the suture lines are oversewn (Fig. 26.8).

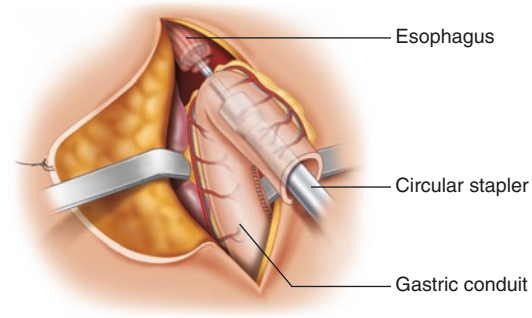

Fig. 26.7 End-to side stapled anastomosis with the 21 circular

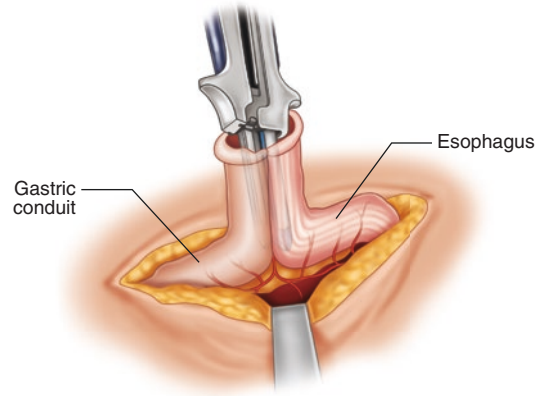

Fig. 26.8 Side-to-side stapled anastomosis

26.3 Total Gastrectomy

26.3.1 Gastrectomy

The first target of the procedure is to achieve a correct exposition of the cardio-fundal region. The left lateral segment of the liver is mobilized dividing the left triangular ligament. Then, it is necessary to disconnect the greater omentum from the transverse colon, where it is easier to reach an avascular dissection plane. The omentum has to be released on the right and then on the left, with the dissection of the peritoneum overlying the cephalad portion of the transverse mesocolon, continuing on the pancreatic head and the pancreatic body (bursectomy). After the complete release of the omentum, surgery goes on with the mobilization of the right colic flexure by transecting the phreno-colic and the hepato-colic ligaments and on the left colic flexure, by transecting the spleno-colic and the phreno-colic ligaments. After opening the lesser omentum, a cotton umbilical tape is placed around the gastric body. The first assistant puts on traction the right flexure of the colon and the transverse colon,

while the second assistant pulls on the stomach with an umbilical tape. Once the omentum and the right colic flexure are mobilized, the right gastroepiploic vessels and the infrapyloric lymph nodes are identified. After mobilization of the inferior pancreatic edge, the right gastroepiploic vein is identified and ligated at its origin at the level of superior anterior pancreaticoduodenal vein; the right gastroepiploic artery is ligated and divided at its origin from the gastroduodenal artery; the surrounding infrapyloric lymph nodes are dissected. Thus, the right short gastric vessels are isolated and ligated as the right gastric artery at the origin from the hepatic artery. Therefore, the suprapyloric lymph nodes are removed (#5). At this point, it is possible to achieve the whole mobilization of the antrum and the first portion of the duodenum that it is transected with a stapling device just 1–2 cm distal to the pylorus. The staple line is oversewn with a row of running adsorbable monofilament suture. The release of the stomach is completed with the transection of the lesser omentum close to inferior edge of the liver. An aberrant or accessory left hepatic artery may originate from the left gastric artery and reside in the lesser omentum. Usually, this artery is isolated and ligated without a hepatic function loss. Therefore, the gastropancreatic ligament, the short gastric vessels at the origin of the splenic hilum, and the gastroepiploic vessels are transected. The stomach is pulled on, so left gastric vessels are exposed, isolated and sectioned to the origin of the celiac trunk, paying attention to the dissection of the surrounding fatty tissue with lymph nodes (station #7). The Laimer-Bertelli membrane is dissected and the cardia and abdominal esophagus are released en bloc with right and left cardial lymph node station (#1,2). The stomach is stretched cranially and the esophagus is encircled with the forefinger removing the connective tissue adherent to the posterior wall of the esophagus. A bilateral troncular vagotomy is necessary to allow the esophagus to be more stretched caudally. The next step involves sectioning of the diaphragmatic fiber, in vertical direction from the hiatus for 2–3 cm. In this way, the diaphragm can be released from the pericardium by blunt dissection and the abdominal and mediastinic esophagus is released for 5–6 cm.

The diaphragm is retracted with special retractors and the esophagus is divided 4–5 cm proximal to the cardiac after preparing a purse string.

The distal esophagus, the stomach, the omentum, and the perivisceral fatty tissue are removed en bloc, with all the perigastric lymph node stations.

26.3.2 Reconstruction

Our choice fell on a Roux-en-Y reconstruction. It is necessary to check the first jejunal loops from the angle of Treitz and their vascularization. The first and the second jejunal arteries should not be used for the transposition of the loop due to the individual anatomical varieties. Usually, the mesentery and the jejunal loop are sectioned between the second and the third vascular arcade, at the origin of the jejunal artery. The jejunal loop may be brought up through a mesocolic opening, to ensure the adequate length of the jejunal interposition. The first step of the reconstruction is the jejunojejunostomy that may be manual or mechanical.

In manual anastomosis, the reconstruction is achieved with two layers of interrupted synthetic absorbable 4/0 monofilament suture. In the mechanical one, a circular stapler (usually 21 mm) is introduced through the proximal jejunal section edge and moved into the loop for 30–40 cm. Here, the spike is pushed out.

Through a purse forceps, a purse string is set up on the jejunal loop at the base of the Roux-en-Y loop and the anvil is inserted. After the connection of the stapler with the anvil, a side-to-end anastomosis is realized, taking care of disposing the mesentery on the same horizontal level. The anastomosis is completed with a running synthetic absorbable monofilament suture. Then, the esophagus-jejunal end-to-side anastomosis is performed, resecting 5–6 cm of the jejunal and saving the mesentery, so as to realize a well-vascularized and tension-free anastomosis. On the esophageal stump, a purse string is performed with a purse forceps or manually, and the anvil of circular stapler (usually

n°25) is introduced. The anastomosis is realized introducing the stapler through the proximal edge of the interposed loop. The jejunal edge is transected with a linear stapler and the stapled line is oversewn with a running absorbable 4/0 monofilament suture. To conclude, the mechanical esophagus jejunostomy is oversewn with running suture.

Suggested Reading

1. Battocchia A, Laterza E (2002) Le malattie dell'esofago. Piccin Nuova Libreria, Padua, pp 443–456, 497–516
2. Cordiano C, de Manzoni G (1991) Staging and treatment of gastric cancer. Piccin Editore, Padua, pp 243–278.
3. Cordiano C, de Manzoni G, Guglielmi A (1996) Il trattamento del carcinoma gastrico. Collana monografica della società italiana di chirurgia. Società italiana di Chirurgia, Roma, pp 245–250
4. Cordiano C, Stipa V, Tendella E (1982) Chirurgia dell'esofago e dell'ipofaringe, Trattato di tecnica chirurgica, vol. V/2. Piccin Editore, Padua, pp 700–800
5. de Manzoni G (2012) Treatment of esophageal and hypopharyngeal squamous cell carcinoma. Springer, Milan, pp 241–256
6. Orringer MB (2005) Transhiatal esophagectomy without thoracotomy. Oper Tech Thorac Cardiovasc Surg 10(1):63–83. doi:10.1053/j.optechstcvs.2005.03.001

Surgical Technique: Minimally Invasive Procedures

27

Simone Giacopuzzi, Andrea Zanoni,
Maria Bencivenga, and Giovanni de Manzoni

27.1 Laparoscopic Subtotal Esophagectomy

The patient is in the supine position with arms and legs abducted. We use the five-port technique. The camera port is inserted at the umbilicus; the other four ports are placed in a V-shaped line: one 5 mm port at the right hypochondriac region and one 10 mm port in the middle of a slightly curved line between the two ports. The other two are positioned specularly with the lateral of 10 mm and medial of 5 mm (Fig. 27.1). The surgeon stands at the right side of the patient, camera operator between the patient's legs, and the assistant at the left side.

After the 12-mmHg pneumoperitoneum is created, we insert a Penrose drain to lift the left lobe of the liver: three sutures are attached to the drainage, approximately 5 cm from each other. We create a small hole between the diaphragm and the liver, in the triangular ligament, close to the falciform. Through the hole, we pass the suture placed in the center of the Penrose (from below to above the liver) that is pulled out from the abdomen with an Endo CloseTM (Covidien, Mansfield, MA, USA) near the xiphoid process. Second suture is pull out from the abdomen at the right side of the triangular ligament and the third at the left of the xiphoid process. The three sutures are pulled at the same time to lift the liver.

The dissection starts at the gastrocolic ligament, 3 cm from the gastroepiploic arcade. The vascular arcade must be carefully preserved to ensure the vascularization of gastric conduit. The assistant raises the body of the stomach with his right hand (not on grater curve to not injure it) while his left hand pulls the greater omentum caudally and to the left side. The surgeon with his left hand pulls the greater omentum caudally to the right, thereby creating a triangle (which must be maintained at all stages of omental dissection) that makes evident the dissection area of the omentum. Usually we use the ultrasonic scalpel for the section of the omentum. Left gastroepiploic vessels are identified and divided. The short gastric vessels and gastrophrenic ligament are divided up to the esophageal hiatus. The most delicate step is the section of the right side of the omentum where it can disguise the origin of the right gastroepiploic vein; especially in obese patient, the vein can be damaged, if you do not put adequate attention. In these cases, for better orientation, it may be useful to identify and follow the middle colic vessels. The lesser omentum is dissected. The assistant elevates the

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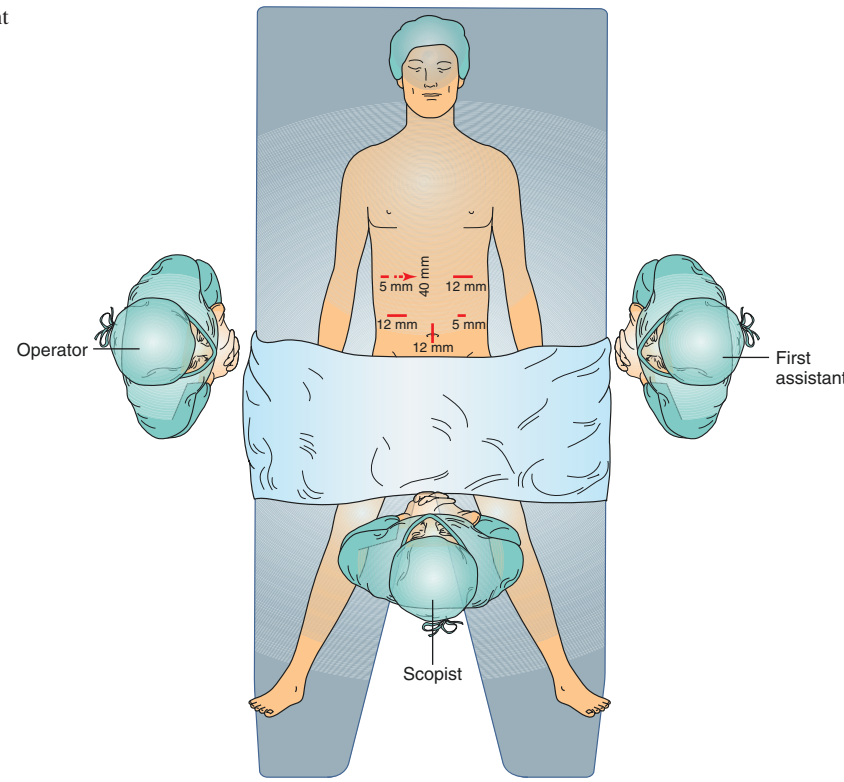

Fig. 27.1 Port placement and operators' position

gastropancreatic fold with the right surgical forceps, and the left lowers and rotates with gauze the pancreas. The roots of the left gastric vein and artery are easily detectable. Vein is then ligated with clips and divided. Common hepatic artery's lymph nodes (#8a) are lift up, and the dissection plan over the nerves around the artery is easily detectable. Taking this plan, the lymph node dissection continues toward the left gastric artery. Soft tissue on the left and right sides of the artery can be separate and dissection is complete imagining "U" shape line on the right side and the "V" shape line on the left side. In this way common hepatic, celiac, and proximal splenic arteries (#8, 9 and 11p) are dissected and left gastric artery can be divided (Fig. 27.2). The completion of lymphadenectomy occurs with lymph node dissection of the common hepatic and distal splenic artery. The right diaphragm crus is freed. By pulling the stomach down, the *phrenoesophageal membrane of Laimer-Bertelli* is open and the esophagus is freed and surrounded by a Penrose drain. With an Endo-GIA entered by the left side port, stomach is dissected below the cardia. We usually perform a small section of the diaphragm crura on the left side. The assistant pulls caudally the esophagus and the surgeon continues mediastinal esophageal dissection for 4–5 cm.

The stomach is pulled out from the peritoneal cavity through a transverse incision in line with the projection of the pylorus on the abdominal wall. The gastric conduit is created as in the open procedure. Reinserted in the abdomen, the conduit is connected with two stitches to the esophageal stump. The patient is placed in the left lateral decubitus position and thoracic stage continues as described above for open surgery. We do not think there is an indication to perform an intrathoracic anastomosis in minimally invasive surgery for the high technical difficulty and the risk of dehiscence. We reserve totally minimally invasive surgery in three-field esophagectomy in cases of squamous cell carcinoma.

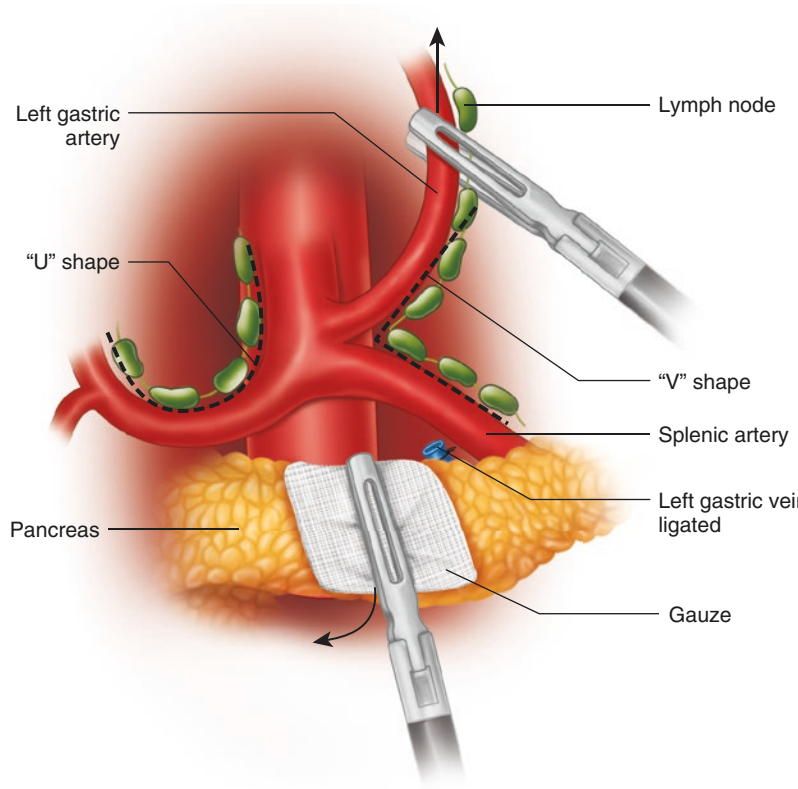

Fig. 27.2 Suprapancreatic lymph node dissection following a "U" shape line on the right side and the "V" shape line on the left side

27.2 Laparoscopic Total Gastrectomy (LTG)

In our technique, the operator's position is on the right side and the first assistant's position is on the left side.

For LTG, we usually use five trocars. The trocar placement follows a V-shaped line having its apex on the umbilicus: we first insert the umbilical trocar through an open approach, and then we insert two right side trocars and two left side trocars under the scope vision. On the right, the upper trocar is just 1 cm below the end of the last cost and the lower trocar is halfway between the upper one and the umbilicus. On the left, the position of the trocar is almost the same but the upper one is at about 3 cm from the costal arch.

The umbilical and the right lower ones are 12 mm trocars, and all the others are 5 mm trocars. An additional 5 mm trocar in the epigastric region can be added for liver retraction.

Considering that currently we adopt the laparoscopic approach only in case of early gastric cancers, a partial omentectomy is our usual first step in case of LTG.

In this step, while the assistant lifts up the anterior wall of the stomach with his right hand and pulls down the colon side of the greater omentum with his left hand, the operator starts dissecting the greater omentum about 4–5 cm from the greater curvature of the stomach and enters the bursa. Then, the dissection continues to the left side up to the left gastroepiploic vein and artery, dividing the latter distal to the feeding artery to the lower pole of the spleen. To ease this part of the procedure, the patient should be positioned in the Trendelenburg position tilted to the right. At this step, lymph nodes of stations No. 4sb and 4d are removed.

Next, we dissect the short gastric vessels and detach the greater curvature of the stomach from the spleen up to the left side of cardia region.

Then, we continue the partial omentectomy to the right side dissecting the fusion plane between the transverse mesocolon and the omentum from the head of the pancreas to the descending part of the duodenum. In this step, the assistant is lifting upward and to the left side the posterior wall of gastric antrum and is pushing downward and medially the transverse mesocolon.

While carefully dissecting this fusion plane, the root of the right gastroepiploic vein and artery will be exposed, and then both of them are ligated and divided at level of pancreatic head border. All the soft tissue of this area cranially to the anterior-superior pancreaticoduodenal vein should be removed for a proper dissection of the nodes at station No. 6.

Next step is the dissection between the medial wall of the proximal duodenum and the pancreatic head exposing the gastroduodenal artery. Then we continue dissection along the cranial border of the pancreas, carefully developing the plane between the pancreas and the common hepatic artery and exposing the right gastric artery. At this point, we flip to work from the anterior side of the stomach.

While the assistant's left hand pushes downward the anterior wall of the stomach and the assistant right hand lifts up the lesser omentum, the operator carefully follows the cranial margin of the duodenum and distal stomach to enter the previously dissected space, making sure not to injure the right gastric artery that is isolated and dissected with the removal of suprapyloric (No.5) lymph nodes. At this point, the duodenum is transected and then the stomach is lifted upward and to the left side.

Next, we continue with the suprapancreatic dissection by carefully lifting the lymphatic tissue and dividing along the natural plane, medially and dorsally bordered by the proper hepatic artery and portal vein, caudally by common hepatic artery, and laterally by the celiac trunk. During this dissection, the coronary vein will be exposed, usually cranial or caudal to the common hepatic artery, to the right of the celiac trunk, and then we divide it and continue the dissection, releasing the lymphatic tissue from its adhesions along the aorta and the proximal celiac trunk to the right crus. We further continue dissection along the cranial border of the pancreas, taking all the lymphatic tissue along the splenic artery and vein and the left adrenal gland toward the splenic hilum. At this point by dissecting the left side of the celiac trunk, we visualize the root of the left gastric artery which is isolated and divided. During the suprapancreatic dissection, nodes at stations No. 8a, 9, 11p, and 7 are sequentially removed.

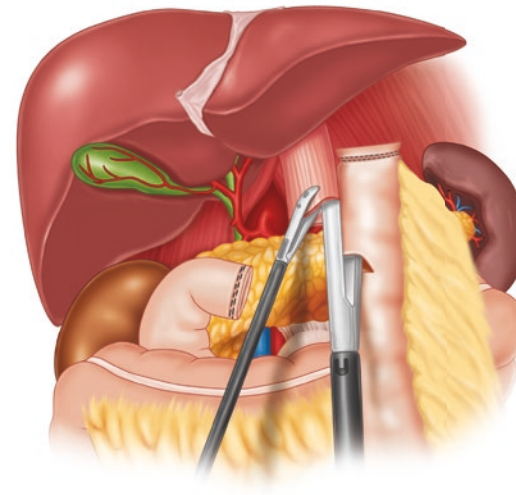

Fig. 27.3 Side-to-side intracorporeal esophagojejunostomy

At this point, we start the clearance of the lesser curvature starting from the right side of the cardiac region (lymph nodes at station No. 1 and 3), and then we isolate the esophagus dividing the anterior and posterior vagal nerves.

At this point, if we want to perform a hand-assisted anastomosis, we make a 5–6 cm midline laparotomy and proceed making a Roux-en-Y anastomosis like in the open total gastrectomy.

If we want to perform an intracorporeal anastomosis, we usually use a linear stapler. After cutting the esophagus with a linear stapler, we proceed to the extraction of the specimen through the umbilical port site slightly widening the incision. Then, through this same incision, we can prepare the jejunal limb and perform the side-to-side jejuno-jejunal anastomosis. At this point, we make an insertion hole in both the left distal esophagus and the jejunal limb through which we insert the linear stapler and complete the anastomosis between the lateral wall of the esophagus and the jejunum. The insertion hole is closed by and hand-sewn suture (Fig. 27.3).

Suggested Reading

1. de Manzoni G (2012) Treatment of esophageal and hypopharyngeal squamous cell carcinoma. Springer, Milan, pp 257–270
2. Inaba K, Satoh S, Ishida I et al (2010) Overlap method: novel intracorporeal esophagojejunostomy after laparoscopic total gastrectomy. J Am Coll Surg 211(6): e25–e29. doi:10.1016/j.jamcollsurg.2010.09.005
3. Kitaino S, Yang HK (2012) Laparoscopic gastrectomy for cancer: standard techniques and clinical evidences. Springer, Tokyo/London
4. Shinohara T, Kanaya S, Yoshimura F et al (2011) A protective technique for retraction of the liver during laparoscopic gastrectomy for gastric adenocarcinoma: using a Penrose drain. J Gastrointest Surg 15: 1043–1048. doi:10.1007/s11605-010-1301-0

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