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Chemoradiation Therapy: The Evolving Role in Head and Neck Cancer and Its Application to Oral Cavity Tumors

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Overview of combined modality therapy

Induction chemotherapy

Early clinical trials demonstrated that treatment-naïve patients with locally advanced head and neck cancer had a high response rate to systemic chemotherapy. In 1982, investigators at Wayne State University were the first to report on the results of a two-drug combination using cisplatin and 5-fluorouracil (FU) [2]. Of 26 evaluable patients, 19% had a complete response and a 70% partial response rate (overall response rate of 89%) after three cycles of induction therapy. Although similar results have been demonstrated by other investigators using other combination regimens, cisplatin and 5-FU became the most commonly used induction regimen for the next two decades.

Because of the high response rates, there was initial enthusiasm about the potential benefit of induction chemotherapy before surgical resection. Unfortunately, the high response rates failed to result in a statistically significant survival. Similarly, adjuvant chemotherapy after surgical resection has failed to demonstrate a survival advantage. Although many adjuvant studies are methodologically flawed, a recent, well-conducted Radiation Therapy Oncology Group (RTOG) trial confirmed the lack of a survival advantage for adjuvant therapy. In this study, patients underwent surgical resection followed by standard radiation or three cycles of cisplatin and 5-FU followed by standard radiation [3]. Results demonstrated no improvement in outcome with the addition of systemic chemotherapy. It must be noted that in a subset of patients with "bulky" disease, patients who received systemic chemotherapy had improved outcome, which must be seen as a hypothesis-generating observation that warrants further investigation.

Induction chemotherapy also has been investigated as a part of combined modality therapy before radiation therapy. These investigations may be divided into three distinct settings: resectable patients who desire organ preservation, patients who have unresectable squamous carcinomas, and patiemts who have locally advanced nasopharynx cancers. In the resectable patient population, a radiation-based organ preservation approach was used most commonly in patients with laryngeal, hypopharyngeal, and base of tongue tumors. In this cohort of patients, surgical resection could lead to significant function loss. Early phase II studies indicated that induction chemotherapy followed by radiation has acceptable toxicity, comparable survival outcome to historical surgical controls, and reasonable rates of organ preservation.

Two sentinel phase III studies have compared induction chemotherapy with radiation to primary surgery with postoperative radiation. The

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Veterans Affairs Laryngeal Cancer Study Group randomized 332 patients with stage III-IV laryngeal cancer to total laryngectomy with postoperative radiation or induction chemotherapy with three cycles of cisplatin and 5-FU followed by definitive irradiation (66–76 Gy). Local recurrences were increased in the induction chemotherapy/radiation arm ($P = 0.0005$), although distant metastases were fewer ($P = 0.016$). The 2-year survival rate was 68% for both treatment arms. The larynx preservation rate was 64% with induction chemotherapy and radiation [4]. An analogous result was shown by the European Organization for Research and Treatment of Cancer in patients with locally advanced hypopharyngeal cancer [5]. Unlike the Veterans Administration trial, however, a complete response was required after two cycles to go on to the third cycle of chemotherapy and definitive radiation. The median survival obtained with induction chemotherapy and radiation was 44 months versus 25 months for immediate surgery (P = ns). At 3 years, 42% of patients who received induction chemotherapy and radiation retained a functional larynx. Treatment failures at local, regional, and second primary sites occurred at the same frequency (12%, 19%, and 16%, respectively, for surgery and 17%, 23%, and 13%, respectively, for induction chemotherapy radiation). These trials have been criticized because they lack a third treatment arm with radiotherapy alone.

Fewer data are available for the role of induction therapy in the unresectable patient population. Paccagnella conducted a randomized trial in which patients were separated into two cohorts: resectable and unresectable [6]. Within each cohort, patients were randomized to no induction or four cycles of cisplatin and 5-FU. Induction therapy did not improve survival in the surgical cohort; however, survival was significantly increased in patients who received induction chemotherapy followed by radiation as opposed to induction therapy alone. These results have been updated and remain statistically significant after 10 years of follow-up. The 5- and 10-year overall survival rates were 21% and 16%, respectively, for chemoradiation and 8% and 6%, respectively, for radiation alone ($P = 0.04$) [7].

As new drugs are being developed they are being incorporated into induction regimens in an attempt to improve the efficacy with hopes of improving survival. Two randomized trials have investigated the use of aggressive three-drug regimens as induction therapy before definitive radiation. Hitt reported the results of a phase III trial of cisplatin and 5-FU compared with cisplatin, 5-FU, and paclitaxel [7]. Patients who received the three-drug regimen had an increase in progression-free (21.7 versus 17.7 months; $P = 0.024$) and overall survival (median survival not reached versus 37.7 months; $P = 0.038$) [7]. Similarly, Vermorken and van Herpen [8] reported the results of a randomized phase III trial of cisplatin and 5-FU versus cisplatin, 5-FU, and docetaxel followed by radiation therapy. The three-drug regimen demonstrated an improved response (67.8% versus 53.6%; $P = 0.007$), progression-free survival (HR 0.72, 95% confidence interval 0.56–0.91; $P = 0.006$), and overall survival (HR 0.73, 95% confidence interval 0.57–0.94; $P = 0.016$). Both studies provide strong support for the further investigation of novel induction regimens in the treatment of locally advanced disease.

Concurrent chemoradiation

An alternative method for combining chemotherapy and radiation therapy is to give them concurrently. There are several postulated mechanisms for radiosensitization: (1) alteration in repair of sublethal cell damage, (2) alteration of cell cycle kinetics, favoring G_2/M arrest, and (3) elimination of clonogens responsible for accelerated repopulation. Preclinical data indicate that several commonly used chemotherapy agents can enhance radiation efficacy, including cisplatin, 5-FU, mitomycin, hydroxyurea (Hydrea), bleomycin, actinomycin D, and doxorubicin (Adriamycin). Numerous phase I/II data demonstrate that these agents can be administered concomitantly with radiation therapy; however, it is at the expense of increased toxicity. Based on promising phase II data, investigators evaluated chemoradiation in comparison to radiation alone in patients with locally advanced squamous carcinoma of the head and neck. The French Head and Neck Oncology and Radiotherapy Group conducted a randomized phase III trial using radiation alone compared with chemoradiation with carboplatin and 5-FU in 226 patients with advanced oropharyngeal cancers [9]. Results showed an improvement in 5-year survival (22% versus 16%; log rank $P = 0.05$), disease-specific survival (27% versus 15%; $P = 0.01$), and local-regional control (48% versus 25%; $P = 0.002$) favoring the combined therapy arm. The results of the intergroup trial comparing radiation alone versus

concurrent radiation plus cisplatin versus a split course concurrent chemoradiation regimen in 295 unresectable patients were similar [10]. The 3-year overall survival for patients enrolled on the concurrent radiation plus cisplatin was superior to radiation alone (37% versus 23%; $P = 0.014$). Several additional phase III trials also support the use of combined chemotherapy with radiation over radiation alone in terms of progression-free, disease-free, relapse-free, and overall survival [3,11–24].

The question arose as to whether induction chemotherapy followed by radiation or concurrent chemoradiation (CCR) provided superior outcomes. For this reason, an intergroup phase III trial was conducted to determine if induction chemotherapy is an essential component of organ preservation. Treatment arms included radiation alone (70 Gy), induction cisplatin and 5-FU followed by radiation, and concomitant cisplatin with radiation [25]. Function preservation rates were 55% versus 65% versus 85%, respectively. Concurrent cisplatin with radiation, although providing no overall survival advantage, showed statistically significant improvement in organ preservation rate and is considered a standard approach [25].

Three meta-analyses—two literature based and one patient based—that evaluated the role of chemotherapy in the primary treatment of squamous cell carcinoma of the head and neck have been reported [26–28]. A reported patient-based meta-analysis with median follow-up of 6 years confirmed these results in 10,717 patients enrolled in 63 trials between 1965 and 1993 [28]. The addition of chemotherapy provided an overall 11% risk reduction, with a 4% absolute survival benefit at 5 years ($P = 0.001$). Adjuvant and neoadjuvant chemotherapy provided a risk reduction of 2% and 5%, respectively (absolute 5-year benefit of 1% and 2%, respectively, $P =$ ns). In a subset of patients who received induction therapy with cisplatin and 5-FU, a significant survival advantage favored induction therapy (HR 0.88, 95% confidence interval 0.79–0.97). Concomitant chemotherapy provided a risk reduction of 19%, with an absolute survival benefit of 8% at 5 years ($P = 0.0001$). It seems that the addition of concomitant chemotherapy confers a modest overall survival advantage to radiation therapy alone which comes at the cost of significantly increased toxicity. The benefit of induction therapy was isolated to patients who received induction therapy with cisplatin and 5-FU.

More recently, the use of CCR has been expanded to use in postoperative patients at high risk for recurrence [29]. Several small trials reported improved survival in patients with locally advanced disease who underwent postoperative CCR when compared with patients who received radiation alone [24,30,31]. Based on these data, two large cooperative group trials, one in Europe [32] and one in the United States [33], were conducted to determine whether CCR improved survival in high-risk postoperative patients. With the exception of eligibility requirements, the studies had a similar design: postoperative patients at high risk for recurrence were randomized to postoperative radiation versus postoperative radiation with concurrent cisplatin 100 mg/m^2 every 3 weeks during radiation therapy. In the European study, local-regional control, progression-free, and overall survival were higher for the combined therapy arm (82%, 47%, and 53%, respectively) when compared with the radiation-only arm (69%, 36%, and 40%, respectively). All values were statistically significant in favor of postoperative CCR. In the US study, which was conducted through the RTOG, CCR resulted in an improvement in local control (82% versus 72%) and disease-specific survival (HR of death 0.78, confidence interval 0.61–0.99; $P = 0.04$). No survival advantage was found (HR of death 0.84, confidence interval 0.65–1.09; $P = 0.19$). The authors note that at the last analysis the survival curves were separating and may eventually demonstrate a survival advantage for combined therapy. Based on the results of these studies, patients at high risk for recurrence who have a good performance status are considered for postoperative chemoradiation.

Future directions

For patients with locally advanced disease who are being treated with a radiation-based regimen, the current standard is to administer chemotherapy concurrently. The role of induction therapy is unclear at this time. It is clear, that CCR has achieved a toxicity ceiling. Further escalation or intensification of regimens using current agents is not feasible due to lack of patient tolerance. In addition, as local disease becomes controlled with CCR, patients are living long enough to develop metastatic disease. This begs the question: in what direction should we take investigative trials? Obviously, one can test new radiation sensitizers that have less toxicity or agents that ameliorate

CCR induced side effects. Bonner et al reported the results of cetuximab, an anti-epidermal growth factor receptor antibody, as a radiation sensitizer in patients with squamous cancer of the head and neck [34]. Patients with stage 3 or 4 squamous cancer of the head and neck were randomized to standard radiation or radiation with cetuximab. Results demonstrated an increase in local-regional control ($P = 0.02$) and overall survival ($P = 0.02$) for patients treated with combined therapy versus patients who were treated with radiation alone. However, we still fail to cure a substantial percentage of patients with locally advanced disease. Thus, an alternative approach, the use of induction chemotherapy followed by CCR has garnered a great of attention over the past several years. The induction chemotherapy would allow systemically effective doses of chemotherapy to decrease metastatic disease, whereas the concomitant chemoradiation would optimize local control.

Several phase II trials have been conducted to investigate various regimens that combine induction and concurrent chemoradiation. These regimens vary in their intensity from highly aggressive regimens that may only be used in good performance status patients to regimens designed to be tolerable for patients with poor performance status, comorbid disease, and suboptimal nutritional status. Based on the intriguing results of phase II studies using induction therapy followed by concurrent chemoradiation, numerous phase III trials are underway to determine whether this approach will enhance outcome and, if so, in which patient populations. The only study reported to date was presented by Hitt and colleagues [7]. They reported on the first 170 patients accrued to a three-arm randomized trial that compared induction therapy with cisplatin and 5-FU versus induction therapy with cisplatin, 5-FU and taxotere, versus no induction therapy. All patients received concurrent cisplatin and radiation. Preliminary results demonstrated a complete response rate of 36% for both induction therapy regimens. The overall complete response rate after completion of treatment was 88% for the two-drug induction regimen, 80% for the three-drug induction regimen, and 47% for chemoradiation alone. Survival data were not available, and accrual continues.

Chemoradiation in oral cavity cancers

Oral cavity tumors comprise approximately 25% of head and neck primaries [1]. They result in between 2.3 and 3.6 deaths per 100,000 in the United States depending on the geographic region [35]. In a recent evaluation of 556 patients diagnosed with oral cavity tumors in Norway, the subsite distribution was 39.9% tongue, 23.9% gingival, 23.4% floor of mouth, and 12.8% other. The stage distribution was 23.2% stage I, 21.2% stage II, 11.2% stage III, 39.7% stage IVA, 4% stage IVb, and 0.7% stage IVC. Survival was similar among subsites, with a 5-year survival rate of 40.6% [36]. Tumors of the oral cavity are heterogeneous with regard to risk factors, genetic abnormalities, and treatment considerations. For example, oropharyngeal cancers have been associated with smoking and alcohol use [37]. The odds ratio varies depending on the site within the oral cavity [38]. Unfortunately, most epidemiologic studies combine all subsites of oral cavity tumors with oropharynx tumors, which makes it difficult to dissect out incidence rates, stage at diagnosis, response to treatment, and survival in patients with various subsites.

Although radiation therapy is effective for treating small tumors at various sites within the oral cavity, most patients are treated with surgery alone for small tumors and surgical resection followed by radiation therapy for locally advanced disease [36]. The combination of chemotherapy and radiation therapy traditionally has been reserved for patients with unresectable disease or patients who refuse surgical resection. The data describing the use of chemoradiation in oral cavity cancers are scant. Few studies or reports have been dedicated solely to patients with oral cavity primaries. The bulk of the data is culled from trials that allow patients from various primary sites to be enrolled. The available data do provide important guidance as to the use of chemoradiation in this setting.

Induction therapy before surgery

Induction therapy before surgery results in downsizing of tumors. There is no proven benefit with regard to local regional control or survival. Licitra and colleagues [39] reported the results of a randomized trial that evaluated the effect of induction chemotherapy on local-regional recurrence and distant relapse. One hundred ninety-five patients with resectable oral cavity tumors were randomized to surgery or three cycles of cisplatin and 5-FU followed by surgery. All high-risk patients subsequently underwent postoperative radiation therapy; 33% of patients had a complete

response and 49% of patients had a partial response, for an overall response rate of 82%. Thirty-three percent of patients in the induction arm versus 46% of patients in the surgery alone arm required postoperative radiation therapy. A mandibular resection was required in 31% versus 52% of patients in the induction and surgery-only arm, respectively. Although there was an improvement in the 5-year event-free survival rate for patients who received induction therapy (57% versus 46%), there was no statistically significant difference in local-regional control or distant relapse. The 5-year survival rate was 55% in both arms. There did seem to be a decrease in second primary tumors. This study was designed to look for an improvement in local-regional control and distant relapse of $\geq$20%, which may have been an overly ambitious goal and the study may have been underpowered. The authors concluded that induction chemotherapy did not improve long-term outcome; however, it may allow less aggressive surgery or spare radiation therapy to the oral cavity in selected patients. They advocated for further evaluation of this approach.

The ability of induction therapy to downstage oral cavity carcinomas was confirmed by Grau and colleagues [40] in a prospective trial of induction chemotherapy for patients with resectable or unresectable stage III or IV oral cavity cancer. The primary outcome measures were response to induction, local control, and survival. Of 1089 patients with oral cavity cancer who were screened, 204 met entry criteria; 66% of patients responded to induction chemotherapy (16% complete response and 50% partial response). Of 46 patients who were considered inoperable, 34 were able to undergo complete resection after induction therapy. Predictors of outcome included initial stage, subsite, response to induction chemotherapy, and adjuvant radiation therapy. Disease-free survival at 5 years was 26% for patients undergoing resection and 22% for patients who received chemoradiation.

Similar response rates were reported by Ruggeri and colleagues [41], who treated 33 patients with stage III or IV oral cavity tumors using one of three different induction regimens. The complete response rate was 48% ($n = 16$) and the pathologic complete response rate was 33% ($n = 9$). The overall 5- and 10-year survival rates were 54.5% and 39.5%, respectively. Patients who achieved a complete response to induction therapy had a clinically significant increase in survival when compared with patients who failed to achieve a complete response ($P = 0.05$).

Concomitant chemoradiation

CCR can be used in patients with resectable and unresectable cancer. In the resectable patient population, substantial data indicate that early stage squamous carcinomas of the oral cavity may be treated effectively with radiation therapy alone. Most patients with oral cavity cancers, regardless of size, are treated with surgical resection to avoid the acute and late effects of radiation to the oral cavity, however (see the section on supportive care issues). Investigators have evaluated the role of CCR as a function preservation approach for oral cavity primaries.

Fuchihata and colleagues [42] reported the results of CCR using bleomycin or peplomycin in patients with resectable squamous cell carcinomas of the lower gingiva. As expected, patients with early stage disease (T1 or T2) had a higher complete response rate (67%, $n = 100$) compared with patients with advanced stage tumors (35%, $n = 62$). Patients who failed to achieve a complete response went on to surgical salvage. Disease-specific 5-year survival rate was 75% for stage I, 87% for stage II, 71% for stage III, and 51% for stage IV. The complete response rate is substantially lower than would be expected at other head and neck primary sites.

Investigators from the University of Michigan undertook a clinical trial in patients with advanced resectable oral cavity tumors using induction chemotherapy as a marker of responsiveness. Patients were scheduled to receive one cycle of cisplatin and 5-FU. Responders were to proceed to definitive CCR with salvage surgery. Patients who failed to respond to one cycle of therapy were to proceed directly to surgical salvage. Eighteen patients were entered on study; 2 patients died after cycle one of therapy before re-evaluation. Nine of 16 patients who were evaluable had a 50% response to therapy and went on to CCR. Of the 9 patients who underwent CCR, 6 had a complete response. The 3-year survival rate was 47%, and the disease-specific survival rate was 68.2%. The investigators concluded that an organ preservation approach was not recommended for patients with locally advanced oral cavity tumors [43].

As with other sites of disease, CCR can result in durable complete response in patients with unresectable oral cavity tumors and should be

considered standard of care for patients with an adequate performance status. The bulk of available data demonstrates a lower response rate and survival for oral cavity tumors when compared with other sites, however. Harrison and colleagues [44] reported the results of a phase II trial of 82 patients with unresectable disease. Three-year survival rate for patients with oral cavity tumors was worse than other sites (0 versus 47%; $P = 0.03$). In an RTOG trial that reported evaluating concurrent chemoradiation with cisplatin in 96 unresectable patients, the complete response rate after therapy was 56% for patients with oral cavity cancers versus 74% for oropharynx, 82% for nasopharynx, 75% of larynx, and 37% for hypopharyngeal lesions [45]. Similarly, in a study by Taylor and colleagues [46], six patients with oral cavity tumors treated with CCR had a worse prognosis (67% failure rate and 0% 8-year survival) compared with other sites.

Two randomized trials have compared postoperative radiation versus postoperative chemoradiation in high-risk patients. Both clinical trials included patients with oral cavity primaries. The RTOG trial stratified based on primary site; thus, there are an equal number of patients with oral cavity primaries in both arms, and oral cavity tumors compose a high percentage of the study population (30% arm one and 20% arm two). Neither study reported the comparative results specifically for oral cavity tumors. Postoperative chemoradiation should be recommended for select patients at high risk for recurrence.

Supportive care issues in patients with oral cavity primaries

A host of supportive care issues must be taken into account when patients are treated with CCR [47]. Unfortunately, space does not permit an exhaustive review of symptom control issues in head and neck cancer. We do, however, mention toxicities most pertinent to patients with oral cavity primaries.

Once patients begin therapy with concurrent chemoradiation, several side effects are encountered. Perhaps the most critical side effect of chemoradiation is mucositis. Radiation induces tissue damage in the mucous membranes and soft tissues within the radiated port. The tissue damage results in the activation of several biologic pathways and is accompanied by an infiltration of inflammatory cells [48]. This damage eventually results in mucosal ulcerations that are painful and usually require high doses of opioids. This tissue damage is also associated with edema, which decreases function of vital structures, such as the tongue and muscles of deglutition. After radiation is completed, tissue damage begins to repair. Unfortunately, scar tissue with lymphedema may develop and result in long-term sequelae. The late effects may include altered speech, swallowing, and nutritional intake [49,50].

A great deal of effort has been expended trying to identify effective preventive and treatment measures. A plethora of traditional treatment for oropharyngeal mucositis has been reported, but rarely have they been substantiated or corroborated by rigorous well-controlled studies. Various mouthwashes have been recommended: hydrogen peroxide [51], chlorhexidine (alone or with nystatin) [52], dilute sodium bicarbonate and salt water [53], and Benzydamine, a nonsteroidal anti-inflammatory agent with antimicrobial and anesthetic properties [54]. Antiulcer medications, such as sucralfate [55] and prostoglandins, have been studied, with mixed results [56,57], and antibiotic lozenges that contain polymyxin, tobramycin, and amphotericin B (PTA-lozenges) have been developed after gram-negative bacteria were shown to play a role in the pathogenesis and exacerbation of radiation mucositis [58]. GM-CSF [59], amifostine [60], and keratinocyte growth factor are newer agents currently undergoing testing in randomized trials [61].

It has long been understood that patients who have head and neck cancer are at risk for malnutrition as a consequence of their tumor or its treatment [62]. Pretreatment patients must be assessed for nutritional status. Although most patients who present with newly diagnosed head and neck cancers are able to maintain adequate oral intake, patients who have malnutrition at presentation are at increased risk for morbidity from treatment [63]. Weight loss also is associated with decrease in quality of life [64]. Unfortunately, radiation-induced mucositis and edema result in poor oral intake and associated weight loss [65,66]. The problem is exacerbated by the use of concurrent chemoradiation, with weight loss averaging 10% over the course of treatment. The placement of a feeding tube does not guarantee adequate intake of calories, nutrients, or water [67]. Metabolic alterations as a result of the tumor and its treatment seem to play a role in the weight loss and deconditioning experienced by patients [68]. Nutritional support during therapy is vital.

Preliminary data indicate that patients' nutritional inadequacies persist long-term [49]; thus, nutritional support should continue through the recovery phase as patients return toward a normal diet. New tools are being developed to allow treating physicians to screen quickly patients who are at risk for nutritional inadequacies [69].

Another important effect of radiation to the oral cavity is xerostomia. Even modest doses of radiation to the salivary gland (25 Gy) begin to result in marked decrease in salivary flow. Saliva has many critical biologic functions, including maintaining a healthy environment for teeth [70,71]. Patients who have severe xerostomia may experience a wide array of symptoms or problems, including rapid dental decay, difficulty swallowing, altered taste, decreased quality of life, and discomfort. Recent studies demonstrate that the prophylactic use of amifostine and the use of intensity modulated radiation therapy can decrease xerostomia [72,73].

Attention to dental status is imperative, and a baseline dental evaluation is imperative, including full mouth radiographs, dental charting, scaling and polishing, oral hygiene and home care instructions. Maxillary and mandibular alginate impressions and neutral pH preparations of fluoride therapy (either sodium or stannous) are mandatory. Preirradiation extractions should be performed on any teeth with questionable ability to tolerate $\geq$50 Gy radiation, and oral mouth guards or changing amalgam filling/crowns to composite material helps reduce radiation scatter to adjacent mucosa and potentially lowers the risk of osteoradionecrosis.

Summary

The use of the combination of chemotherapy and radiation therapy has altered treatment dramatically for head and neck cancers. Oral cavity tumors are unique with regards to response and treatment-related sequelae, however, which makes extrapolation of data from other head and neck sites to cancers of the oral cavity problematic. It is clear that patients who have unresectable disease and high-risk postoperative patients should be considered for concurrent chemoradiation. It must be understood that improved outcome is at the expense of increased toxicity. The treating physician must see patients on a frequent basis during and immediately after therapy. They also must be familiar with support care measures and have access to a team of consultants who can help manage the acute and late effects of therapy.

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