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Penile Cancer

Diagnosis and Treatment

Second Edition

Humana Press

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Preface

This second edition of our book *Penile Cancer: Diagnosis and Treatment* as part of the book series *Current Clinical Urology* by the Springer® Publishing Group expands on the topics mentioned in our first edition and successfully integrates some meaningful advances that have been made across these areas. In an attempt to broaden the scope of knowledge on the diverse clinical facets of penile cancer management, we have added some additional chapters to areas where there is very little in terms of reference material but similarly holds great clinical value such as the management of pelvic lymph nodes for which there has been meaningful recent peer-reviewed literature guiding patient management and what is the specific role of radiotherapy in penile cancer written by leading world expert on the subject Dr. Juanita Crook.

There is no question that the implementation of national treatment guidelines by the National Comprehensive Cancer Network® (NCCN) has greatly enhanced the consistency and standardization of the diagnostic and stage-specific approach to penile cancer. These guidelines however only provide a framework as to how such patients should be cared for but developing a reference textbook which embodies the knowledge and clinical experience of world experts on the subject is far more empowering in providing the healthcare provider with not only appreciating how best a patient should be treated but similarly what is the underlying tumor biology at play and appreciate why a given approach may be best suited in a given clinical scenario. Clearly, this work embodies the cumulative clinical experience and knowledge of some of the world leaders on these given topics such that patient outcomes can be guided by the best currently available data and treatment standards. We owe it to our patients and similarly to ourselves to push the envelope and integrate the most contemporary diagnostic and therapeutic discoveries within our armamentarium. Failure to do so is violating the values and principles that our medical mentors created and imparted upon us. Lastly, I would like to dedicate this work to all of our unfortunate patients who have been abruptly faced with such a life-altering and potentially lethal diagnosis, not only accepting the cruel reality of what they presently face but actively pursuing therapeutic choices with nothing short of heroism. You truly are the source of inspiration we continually look up to as the benchmark of the boundless potential of humanity.

Tampa, FL — Philippe E. Spiess

Contents

Abbreviations

5-FU	5-Fluorouracil
BMP	Bleomycin, methotrexate, and cisplatin
BXO	Balanitis xerotica obliterans
CIS	Carcinoma in situ
cN+	Clinically node positive
cN0	Clinically node negative
CO_2	Carbon dioxide
COX-2	Cyclooxygenase-2
CR	Complete response
CRP	C-reactive protein
CRUK	Cancer Research UK
CSS	Cancer-specific survival
CTV	Clinical target volume
DFS	Disease-free survival
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSNB	Dynamic sentinel node biopsy
DSS	Disease-specific survival
DUS	Doppler ultrasound
DVT/PE	Deep vein thrombosis/pulmonary embolism
EAU	European Association of Urology
EGFR	Epidermal growth factor receptor
ENE	Extranodal extension
EORTC	European Organization for Research and Treatment of Cancer
FDG	Fluorodeoxyglucose
FNAC	Fine needle aspiration cytology
GFR	Glomerular filtration rate
GHQ	General Health Questionnaire
GOG	Gynecologic Oncology Group
HADS	Hospital Anxiety and Depression Score
HPV	Human papilloma virus
HR	Hazard ratio
ICG	Indocyanine green
ILND	Inguinal lymph node dissection
InPACT	International Penile Advanced Cancer Trial

IQ	Imiquimod
IQR	Interquartile range
IRCI	International Rare Cancers Initiative
LCR	Long control region
LDR	Low-dose rate
LN	Lymph node
LND	Lymph node dissection
LVI	Lymphovascular invasion
MMP	Matrix metalloproteinase
MMS	Mohs micrographic surgery
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-MATCH	NCI-Molecular Analysis for Therapy Choice
Nd:YAG	Neodymium:yttrium aluminum garnet
NIRF	Near-infrared fluorescence
OR	Odds ratio
OS	Overall survival
PCNA	Proliferating cell nuclear antigen
pCR	Pathologic complete response
PEIN	Penile intraepithelial neoplasia
PET	Positron emission tomography
PET-CT	Positron emission tomography-computed tomography
PGE2	Prostaglandin E2
PGR	Partial glans resurfacing
PLND	Pelvic lymph node dissection
PR	Partial response
pRB	Retinoblastoma protein
PSS	Penile-sparing surgery
QOL	Quality of life
RR	Relative risk
SCC	Squamous cell carcinoma
SCC-Ag	SCC antigen
SEER	Surveillance, Epidemiology, and End Results
SLN	Sentinel lymph nodes
SPECT	Single photon emission computed tomography
SWOG	Southwest Oncology Group
TGR	Total glans resurfacing
TIP	Paclitaxel (Taxol®), ifosfamide, cisplatin
TNM	Tumor node metastasis
TPF	Docetaxel, cisplatin, and 5-fluorouracil
TTP	Time to progression
VBM	Vincristine, bleomycin, and methotrexate

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Understanding the Pathophysiology of Penile Cancer and Its Preneoplastic Lesions

1

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Epidemiology of Penile Cancer

Penile carcinoma is typically a disease of older men, arising predominantly in men over 50 years of age with a peak incidence in men over 70 years old [1]. Penile cancer is a relatively rare malignancy in the United States and in developed countries, representing 0.24 % of all cancer diagnoses [2]. The incidence can be much higher in undeveloped countries, specifically regions of South America and Africa where socioeconomic status and religious practices are likely to account for this variation [3–5]. In lower resource countries such as Uganda and Brazil, the incidence reaches

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2.8 in 100,000 and up to 3.7 in 100,000, respectively, whereas in populations abiding by religious practices that mandate neonatal circumcision, such as Israeli Jews, the incidence plummets to 0.1 in 100,000 [6]. The incidence of penile cancer is also higher in more impoverished regions of the United States compared to regions of the United States with greater proportions living above poverty [7].

Primary tumors of the penis are typically squamous cell carcinoma (SCC) and most commonly originate from the glans, followed by the prepuce and are most commonly of squamous cell histology in origin [4, 8]. Subtypes include basaloid, warty, warty-basaloid, papillary, verrucous, sarcomatoid, and adenosquamous [8].

Risk Factors for Penile Carcinoma

Several well-known risk factors for penile carcinoma have been identified; the most commonly documented risk factors include circumcision status, phimosis, human papillomavirus (HPV) infection, lichen sclerosus, cigarette smoking, and exposure to psoralen with ultraviolet light [9, 10].

Circumcision status, specifically an intact prepuce, has been associated with an increased risk of developing penile cancer [11]. Circumcision in childhood has been shown to be preventative for invasive penile cancer; however circumcision after puberty does not alter one's risk of developing penile cancer [12]. Phimosis has also been associated with an increased risk of developing the disease and is likely associated with inflammatory processes occurring under the prepuce and is associated with lichen sclerosus [13–15]. Historically, it was believed that smegma was the carcinogenic factor involved; however, more recent studies have shown that smegma is in fact not carcinogenic [16]. Circumcision is often implemented as early surgical intervention for penile lesions of the prepuce [17].

HPV infection with high-risk types has been highly associated with the development of SCC of the penis with several mechanisms of pathogenesis have been described [18]. These will be discussed later in this chapter. Similarly, sexual activity at an early age, number of sexual partners, and marital status have also been identified as risk factors, likely due to an increased risk of inoculation with high risk HPV serotypes [19, 20].

Cigarette smoking and tobacco use have also been associated with an increased risk of developing penile cancer. Although variations exist among the degree of exposure of cigarette smoking and the associated risk, several studies have shown clear correlations between increasing risk of developing penile cancer with increasing tobacco exposure [21–23].

Pathophysiology

Two carcinogenic pathways, HPV-mediated and an HPV-independent pathway, exist for the development of penile cancer. HPV DNA has been found in up to 60–80% of penile carcinoma, primarily basaloid and warty histologies [24]. Because of its strong association with SCC of the penis, it will be discussed in detail.

Human Papillomavirus

The HPV viruses represent a distinct group of double-stranded viruses with particular propensity in human disease. The genome consists of a circular double-stranded DNA with 800 nucleotide base pairs [25]. DNA sequencing techniques have been used to classify the family of papillomaviruses into genera and species. This is based on sequence homology and corresponds to their pathogenesis.

Among women and men a large diversity of HPV types are detected in the anogenital epithelia. From an evolutionary standpoint, the alpha genus is of particular interest to benign and malignant anogenital lesions [26]. The alpha genus itself encompasses both carcinogenic high types, as well as types associated with condyloma, considered low risk types for cancer.

Although there are numerous HPV types, the virus maintains a high degree of homology from a genomic and molecular standpoint. Structurally, the virus is composed of an icosahedral capsid surrounding a nucleohistone core [27]. There are approximately eight genes coded by the genome. These consist of "early genes" E1–E7. Additionally, there is a noncoding region referred to as the long control region. The final region contains the L1 and L2 capsid proteins [28]. The E6 and E7 genes are believed to be the most highly conserved of all the HPV subtypes and have been implicated in the majority of cancer-associated types. The influence of these genes on the molecular pathways of cancer development is of particular importance in penile cancer [29].

HPV-Mediated Pathway

The ability of HPV to infect healthy cells and potentially progress to carcinogenesis is a complex process. This is reliant on numerous host and viral.

HPV infection begins with epithelial trauma, which permits for infection of an epithelial basal cell with the virus [30]. Next, the viral DNA is taken up in an endosomal fashion to be followed by transfer to the host nucleus. The viral genome is established in the host cell as a stable episome in cells of the basal layer [31]. The viral genome replicates during the S phase of cell division. It is during this portion that the E2 protein of the HPV genome has particular importance due to its anchoring of the viral episome to the host mitotic chromosomes [32]. The time between infection and the appearance of lesions varies. This appears to be highly dependent on initial viral load, the specific HPV type involved, and whether the virus is integrated into the host genome [33].

Cell proliferation is primarily mediated by the E6 and E7 viral oncogenes. Under normal circumstances, the retinoblastoma protein (pRb) is involved with cell cycle progression (Fig. 1.1). In noncycling cells, the pRb associates with the E2F transcription factors [31]. Under normal situations, activation of the cyclin/CDK complexes leads to the phosphorylation of pRb and E2F release with subsequent protein expression. However, these pathways are typically altered in HPV infection.

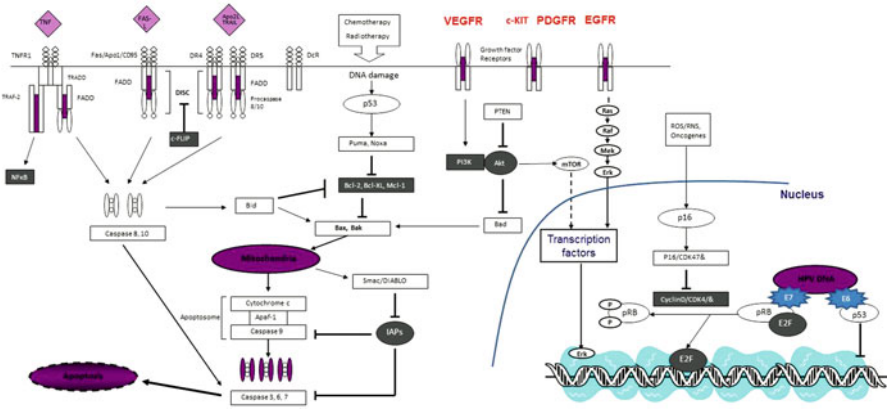

Fig. 1.1 Schematic diagram illustrating molecular pathways implicated in HPV- and non-HPV-associated penile cancer. Reprinted with permission from [57]

In these situations, the E7 protein instead complexes with pRb which leads to unregulated dissociation of E2F and protein expression. Normal regulatory mechanisms in place involve an increase in p53 expression as a response to increased proliferation, which ultimately increases cell degradation. However, in the HPV proliferation cycle, particularly high risk HPV types such as HPV 16, E6 instead forms an ubiquitin ligase which leads to p53 degradation and prevention of subsequent cell degradation [31]. An additional consideration between low risk and high risk HPV types is the expression of p21 and p27 kinase inhibitors. If present in sufficient quantity, they will bind with E7 and other cyclin proteins, rendering them inactive [34]. In high risk forms, this is believed to be overcome by the high levels of E7 protein present in the viral genome [31]. An additional mechanism of cell proliferation in high-risk HPV types involves E6 independent mediated proliferation via its terminal PDZ binding domain. E6 is believed to mediate cell proliferation and may be important in the metastatic potential of some HPV-related neoplasms [35].

The progression to malignancy requires a complex interplay between continued viral genome expression, packaging, and release to promote infection. Some theories suggest that the progression to malignancy occurs after uncontrolled cell proliferation, which ultimately leads to continued point mutations and ultimately carcinogenesis. However, this remains an area of debate and continued research.

HPV-Independent Pathway

While non-HPV-related penile cancers may be managed in similar manners as their HPV counterparts, they indeed represent a separate entity in regard to pathophysiologic mechanisms. While the understanding of HPV-mediated penile cancers is more robust, HPV-negative carcinogenesis is less understood.

Lichen sclerosus and leukoplakia are two commonly noted HPV-negative precursor lesions associated with SCC development. Lichen sclerosus is typically

associated with chronic infection, trauma, or inflammation and is also noted to have an association with urethral stricture disease [36]. Progression to SCC is noted to occur between 5 and 10 % of patients, and yearly surveillance is recommended [3]. Conversely, while leukoplakia is also associated with chronic inflammation, the rate of progression to malignancy is higher, affecting approximately 15–20 % of patients [2].

From a molecular standpoint, HPV-negative penile cancers are typically associated with p53 mutations, and this itself has been identified as being a negative prognostic factor [37]. Via p53-induced mechanisms, cell cycle inhibitors including cyclin p21 and D1 are normally induced to delay or terminate replication. However, mutational effects on p53 itself ultimately lead to uninhibited cell proliferation and malignant transformation. However, despite the involvement of these cyclins as well as other identified proteins including Ki67 (a nuclear matrix protein involved in the cell cycle), they have not yet proven to yield prognostic value similar to that of p53 [38].

Ongoing research continues to evaluate other possible HPV-negative etiologies on a molecular level. These include evaluation of the mTOR-mediated cell cycling pathways as well as those involving the human epidermal growth factor family. An additional area of focus is on the involvement of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) in penile carcinogenesis, related to their role in the inflammatory process. In fact, mouse studies have identified increased amounts of these molecules in tissue samples representing invasive SCC as well as lymph node metastases [39].

Penile Cancer Precursor Lesions

The following section will focus on the pathophysiology of penile cancer and its preneoplastic lesions. Several penile SCC precursor lesions, often referred to as penile intraepithelial neoplasia (PeIN), can be classified as either HPV related or non-HPV related (Fig. 1.2).

Condyloma Acuminatum

Condyloma acuminatum refers to nontender wart like or papillary frondular lesions that are better known as genital warts. These lesions are typically caused by HPV types 6 and 11 and are acquired by direct skin-to-skin contact. They can occur anywhere on the external genitalia but are most common on the glans and penile shaft [40]. Condyloma acuminatum has a very low risk of conversion to invasive penile carcinoma; although in a cohort of 200 cases, Cubilla et al. detected solely low-risk HPV types in 6 % of tumors [41]. Routine biopsy is not recommended for condyloma acuminatum unless lesions are atypical, pigmented, indurated, fixed, or ulcerated. Although there is a small chance of cancer progression with low-risk HPV types, the likelihood of progression is low and Condyloma acuminatum should be treated as a benign lesion.

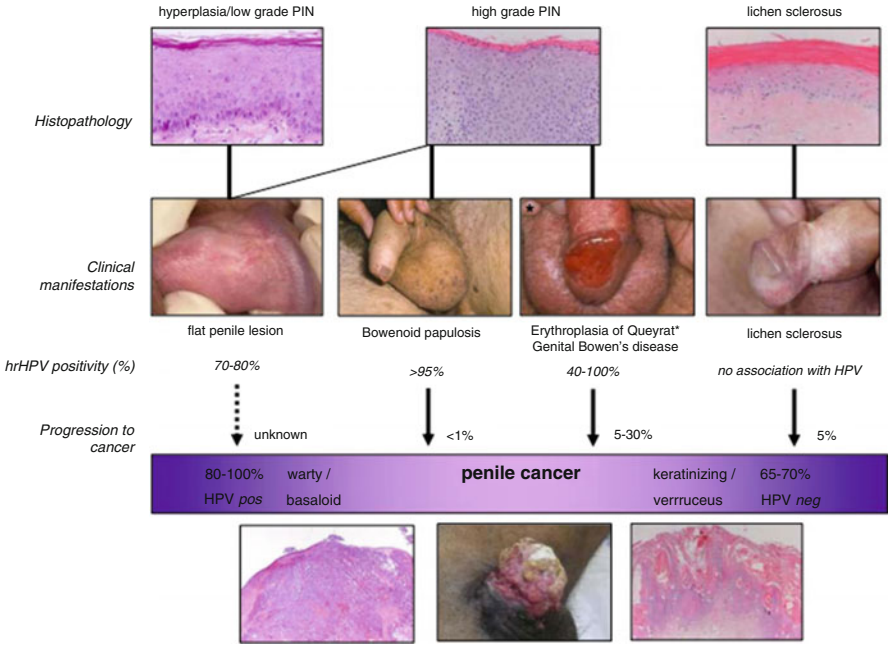

Fig. 1.2 Relationship between histology, HPV presence, clinical manifestation, and putative transformation of penile precursor lesions into penile cancer. Reprinted with permission from [58]

Giant Condyloma Acuminatum (Buschke-Lowenstein Tumor)

First described in 1925 by Buschke and Löwenstein, the giant condyloma acuminatum or Buschke-Lowenstein tumor is a rare manifestation of condyloma acuminatum. It is characterized by the development and slow-progression of exophytic, cauliflower-like masses in the genital or anorectal region that infiltrate adjacent tissues [42]. These verrucous carcinomas are usually attributed to HPV types 6 and 11. Biologically, giant condyloma acuminatum is characterized by a low incidence of metastases but does have a high rate of recurrence [43]. Radical excision is recommended for complete histological examination. Other less invasive treatment options include radiotherapy, laser therapy, and topical therapy [44].

Bowenoid Papulosis

Bowenoid papulosis is characterized by red-brown pigmented popular lesions on the glans or shaft of the penis. It is typically seen in circumcised men and is diagnosed in younger patients, on average between 20 and 30 years of age. HPV 16 is most intimately associated with Bowenoid papulosis; however, multiple other HPV types have been implicated [45]. Histologically, Bowenoid papulosis is characterized by full thickness cytological atypia, which make it very difficult to distinguish from SCC in situ [25]. Bowenoid papulosis is generally considered benign; however, as it is

associated with high-risk HPV types, there have been reports of it progressing to invasive cancer, especially seen in immunocompromised patients [46]. Treatment options include surveillance, topical therapy (5-florouracil), and ablation.

Lichen Sclerosus (Balanitis Xerotica Obliterans)

Lichen sclerosis, also known as Balanitis xerotica obliterans or BXO, is characterized by flat white patches on the prepuce, glans, urethral meatus, or fossa navicularis. Its mechanism of disease is unknown, but it is thought to be caused by chronic infection, trauma, or inflammation. Lichen sclerosus is often asymptomatic, however and can be associated with phimosis, meatal stenosis, and urethral stricture as the disease progresses [47]. Infrequently (4–8 %) lichen sclerosis will progress into SCC of the penis [47, 48]. Diagnosis is made by skin biopsy and should be considered in specific cases to exclude subclinical *carcinoma* in situ or invasive penile cancer [49]. Asymptomatic lichen sclerosus requires no treatment, while symptomatic lichen sclerosus can be treated with topical/intralesional steroids. Phimosis can be treated with circumcision, and meatal or urethral strictures should be treated accordingly. Excision of lichen sclerosus is not recommended, as recurrence rates are typically high.

Carcinoma In Situ (Erythroplasia of Queyrat and Bowen's Disease)

Erythroplasia of Queyrat and Bowen's disease both refer to forms of squamous intraepithelial neoplasia with a high rate of progression to invasive SCC. Progression rates to penile cancer are cited as high as 10–33 % [3], with Erythroplasia of Queyrat tending to have a slightly higher chance of progression [50]. The main difference between the two lies in the location of the lesion; Erythroplasia of Queyrat refers to *carcinoma* in situ (CIS) of the glans or prepuce, while Bowen's disease signifies CIS of the penile shaft or of the remainder external genitalia. Erythroplasia of Queyrat is typically described as well-marginated plaques with a red, velvety appearance, while Bowen's disease is characterized by sharply defined plaques of scaly erythema. Both are generally asymptomatic. Like most SCCs of the penis, HPV types 16 and 18 play an important role in the pathophysiology of CIS of the penis. Prior to treatment, adequate biopsies must be performed to rule out invasion. When CIS is confirmed, treatment modalities include wide local excision if isolated to a discrete site, topical therapies (5-fluorouracil or 5 % imiquimod), and laser ablation (although typically less successful).

Histologic Subtypes

As previously noted, penile cancer can manifest histopathologically as several different subtypes: basaloid, warty, papillary, verrucous, sarcomatoid, adenosquamous, and mixed [8]. Verrucous subtype is a low-grade, slow-growing non-HPV-related subtype

that represents 3–8% of penile SCC [41, 51–54]. These tumors have varying gross features but often have a cobblestone or filiform morphology and histologically show variations of squamous differentiation [55]. Papillary subtype is a low-grade, non-HPV-related group encompassing verruciform histology not otherwise specified that represents 5–15% of penile SCC [41, 51–54]. Morphologically, these tumors are large, exophytic lesions with hyperkeratosis and papillomatosis with fibrovascular cores on histology [55]. Papillary subtype is often associated with lichen sclerosus and differentiated PeIN [56]. Warty subtype represents 7–10% of penile carcinoma and is typically associated with the HPV-related pathway [41, 51–54]. Morphologically, they produce exophytic white or gray tumors. These tumors are typically slow-growing and low grade. Histologically the tumor invades stroma in a jagged irregular fashion [55]. Basaloid subtype represents 4–10% of penile SCC and is also related to the HPV-related pathway [41, 51–54]. It typically arises in the glans and follows an aggressive course [41]. These typically present as tan ulcerated lesions and have nests of basaloid cells histologically [55]. Sarcomatoid subtype is a less common, aggressive subtype found in 1–3% of penile SCC with high associated mortality and recurrence [41, 51–54]. Morphologically, these tumors are bulky, polypoid masses with characteristic spindle cell histology [55].

Conclusions

SCC of the penis is a rare disease. Specific risk factors have been identified, and HPV has been proven to play a pivotal role in a significant subset of cases. Precursor lesions demonstrate variable risk to progression to invasive cancer depending upon the lesion itself, with CIS lesions carrying the highest risk of progression.

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Diagnostic Tools in the Evaluation and Management of Penile Cancer

2

Pranav Sharma, Mariela R. Pow-Sang, and Julio M. Pow-Sang

Introduction

Penile cancer is rare in the industrialized countries of North America and Europe, representing only 0.4–0.6 % of all malignancies in men [1]. In the third-world nations of South America, Africa, and Asia, however, poor hygiene, low socioeconomic status, low circumcision rates, and high sexual promiscuity result in a much higher incidence of 1–2 % [2, 3].

Squamous cell carcinoma (SCC) represents the far majority of cases with verrucous, warty, and papillary subtypes having a more favorable prognosis and basaloid, sarcomatoid, and adenosquamous histologies having a less favorable prognosis with early metastatic spread [4].

The presence of human papillomavirus (HPV) DNA has also been detected in approximately 60–80 % of penile cancer tumors [5]. The most common subtypes of HPV are HPV-16 and -18 with the development of cancer mediated through oncogenes E6 and E7 and their downstream effects on tumor suppresser genes such as

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p53 and Rb1 [3]. The prognostic role of HPV in penile cancer is not clearly known with some studies showing favorable prognosis in HPV-positive penile tumors, while others reporting no appreciable effect on cancer outcomes in the presence of HPV infection [6, 7]. Expression of HPV, however, may predict not only disease prognosis but also treatment response to surgery, radiation, and systemic therapy, which has been shown to be the case in other SCC tumor phenotypes particularly of the head and neck [8].

Penile carcinoma can be effectively cured in up to 80% of patients if treated appropriately at an early stage with aggressive management of the inguinal region in high-risk cases even in the absence of clinical disease [9]. Pathologic stage and grade of the primary penile tumor drives survival in addition to the extent of subsequent loco-regional lymph node (LN) spread [10].

Treatment paradigms have shifted to emphasize the increase utilization of penile sparing approaches for treatment of the primary tumor while identifying patients who will most likely benefit from inguinal and/or pelvic lymphadenectomy as well as the use of neoadjuvant chemotherapy in bulky nodal disease [11]. Novel diagnostic tools to more effectively identify these patients are essential to better customize treatment options for penile cancer and minimize its associated morbidity.

Novel Image-Based Diagnostic Tools

Evaluation and Management of the Primary Penile Lesion

Surgical resection of the primary penile tumor should result in complete removal of the cancerous lesion with negative surgical margins to minimize the risk of recurrence [12]. Treatment of the primary penile tumor can be curative, but it can also be devastating to a patient's quality of life (QOL) and mental well-being. Partial or complete penile amputation is associated with significant psychological morbidity, voiding, and sexual dysfunction [13].

Primary treatment of the penile tumor has historically involved radical or partial penectomy with a 2-cm margin for oncologic efficacy, but the 2-cm margin is a historical value with little scientific evidence to support it [14]. A recent literature review on penile-sparing surgery (PSS) showed that cancer-specific survival (CSS) is similar for penile sparing and ablative techniques for low-stage disease while providing better functional and cosmetic outcomes [15]. There are no randomized controlled studies comparing primary tumor treatments, and thus the level of evidence is based on retrospective analyses and small cohorts. Despite lack of level one evidence, however, penile sparing strategies should be employed for low-stage distal penile tumors whenever possible in order to preserve anatomical and sexual function [16].

Magnetic resonance imaging (MRI) may be useful in deciphering which patients may be appropriate for PSS [17]. This imaging modality may accurately predict corpora cavernosa or corpora spongiosum invasion as well as proximal extent of tumor involvement on the penile shaft or glans (Fig. 2.1) [18]. MRI has also been

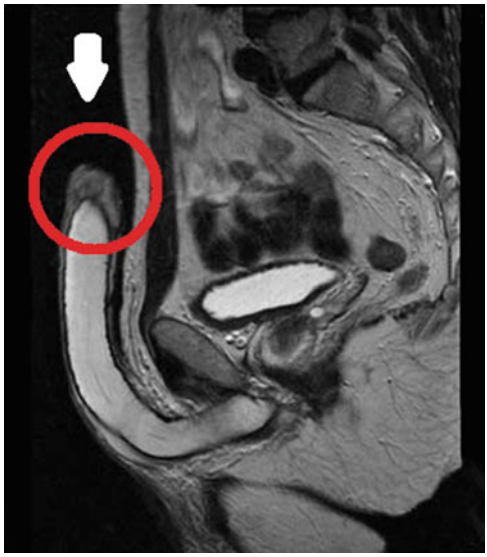

Fig. 2.1 Magnetic resonance imaging of a penile carcinoma of the glans with the proximal extent of tumor seen on the penile shaft

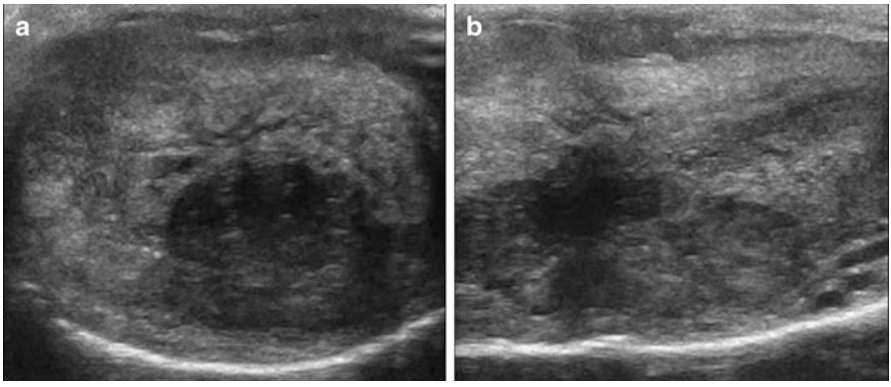

Fig. 2.2 Heterogeneous penile tumor visualized transversely (**a**) and longitudinally (**b**) on penile Doppler ultrasound

shown to be highly accurate in the local staging of penile cancer with stage-specific sensitivities and specificities of 85 and 83 % (pT1), 75 and 89 % (pT2), and 88 and 98 % (pT3) [19]. MRI, therefore, can accurately predict corpora cavernosa invasion in all cases of pathologically proven disease in order to maximize penile preservation when appropriate [20].

There is recent evidence to suggest that penile Doppler ultrasound (US) may be equivalent to MRI in the preoperative diagnostic evaluation of patients with penile SCC (Fig. 2.2) [21, 22]. In a prospective study of 200 patients presenting with a clinical diagnosis of penile SCC, penile Doppler US versus MRI accuracy in predicting primary tumor stage after surgery was 96.5 % versus 90.5 %, precision was

92.6 % versus 96 %, sensitivity was 96.9 % versus 73.8 %, and specificity was 96.2 % versus 98.5 %, respectively [23]. The authors concluded, therefore, that penile Doppler US had a statistically similar outcome in detecting tumor infiltration of the corpora cavernosa compared to MRI, and it could be used as a less expensive tool to drive surgical strategy in patient with a diagnosis of penile SCC.

Evaluation and Management of Loco-Regional Metastatic Lymphatic Spread

Multiple different imaging modalities have been explored to more accurately predict metastatic lymphatic spread for high-risk penile tumors. The value of 18F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) has recently come into the spotlight in the clinical staging of penile cancer due to its increased utilization and value in other aspects of oncology [24]. Scher et al. [25] initially demonstrated the diagnostic value of 18F-FDG PET-CT in 13 patients with suspected penile cancer or suspected recurrent disease and correlated this with histopathological findings obtained at the time of biopsy or during surgery. The sensitivity and specificity for PET-CT imaging to detect malignancy in the primary penile lesion was 75 % and 75 %, respectively, but it was 80 % and 100 % for the detection of malignancy in the LNs (sensitivity: 89 % for superficial inguinal LNs, 100 % for deep and pelvic LNs) (Fig. 2.3).

Leijte et al. [26] subsequently evaluated 18F-FDG PET-CT to detect occult inguinal metastasis in patients with clinically node negative (cN0) penile carcinoma. Only one of the five tumor-positive cN0 groins was correctly predicted by PET-CT although 34 of 37 negative groins were appropriately ruled out by preoperative imaging (specificity, 92 %). This same group also evaluated the diagnostic accuracy of 18F-FDG PET-CT to detect pelvic nodal involvement in 18 patients with unilateral or bilateral tumor-positive inguinal nodes on cytological assessment. Ten of 11 tumor-positive pelvic nodal basins were correctly predicted by PET-CT scan (sensitivity 91 %) as were all 17 tumor-negative pelvic nodal basins (specificity

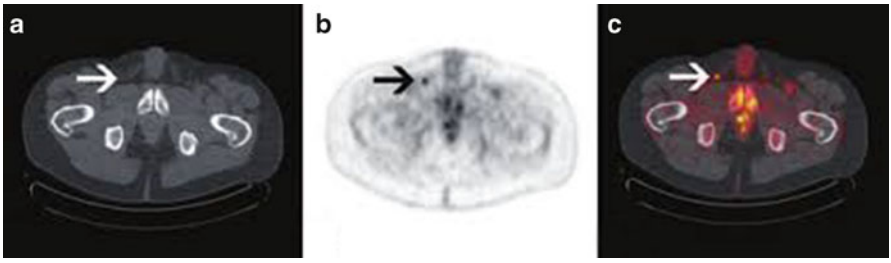

Fig. 2.3 Suspicious inguinal node detected on 18F-fluorodeoxyglucose positron emission tomography-computed tomography in a high-risk cancer. (**a**) CT image; (**b, c**) Contrast image

100 %). Four of five patients with positive distant metastasis on PET-CT had pathologically confirmed M1 disease (sensitivity 75 %). The authors, therefore, concluded that PET-CT may be useful in the routine clinical staging for inguinal node positive patients to detect further disease progression [27].

More recently, Souillac et al. [28] evaluated 22 patients with invasive SCC of the penis and negative groins (cN0) with 18F-FDG PET-CT to assess inguinal LN status. Eight patients with clinically node positive (cN+) groins were also assessed separately. Of 44 cN0 groins, PET-CT had a 75 % sensitivity and 87.5 % specificity, but it had 100 % sensitivity and 100 % specificity in cN+ groins. Schlenker et al. [29] also showed an 88.2 % sensitivity rate and a 98.1 % specificity rate for PET-CT in 70 inguinal groins (35 patients) with invasive penile carcinoma staged with this modality. All missed groin metastasis in both of the above studies were less than 1 cm in size. These results demonstrate that PET-CT may be useful in confirming inguinal LN invasion as well as detecting subclinical inguinal LN invasion in a large majority of cases although its ability to detect micro-metastasis has come into question due to higher false negative rates reported by some centers [30]. Close follow-up in these patients, therefore, is still recommended and is imperative to avoid subpar oncological outcomes.

A comprehensive systematic review and meta-analysis of the literature showed a pooled sensitivity and specificity of 80.9 % and 92.4 %, respectively, for 18F-FDG PET-CT in the accuracy of inguinal LN staging for penile SCC [31]. The pooled sensitivity was 96.4 % for cN+ patients and 56.5 % for cN0 patients. The authors, therefore, concluded that routine use of PET-CT is not justified, but patients with clinically palpable LNs may benefit due to the higher sensitivity of this technology in this subgroup of patients. Future clinical trials, however, comparing PET-CT to standard clinical assessment (i.e. physical examination) are necessary to truly elucidate the benefits that this additional imaging can provide in terms of early detection of occult metastatic disease in the groin or pelvis, minimizing patient morbidity from unnecessary treatments, and possibly improving survival-related outcomes.

Magnetic resonance imaging (MRI) and MRI-PET are additional imaging techniques that may be useful in both local and LN staging for penile cancer (Fig. 2.4). Novel magnetic resonance (MR) imaging techniques such as lymphotropic nanoparticle-enhanced MR imaging may help identify metastatic LN disease [32]. Currently, a clinical trial is being conducted and is recruiting patients in the United Kingdom to establish the effectiveness of MRI-PET compared to dynamic sentinel node biopsy (DSNB) and ultrasound-guided biopsy in detecting the presence of metastatic disease in the LNs of patients with penile cancer. If MRI-PET is effective in detecting LN involvement in patients with locally advanced penile cancer, it could potentially replace these more invasive procedures.

Additionally, while DSNB has traditionally been performed with radiotracer ^{99m}Tc-nanocolloid, new literature suggests the possible use of a fluorescent dye called indocyanine green (ICG) with similar effectiveness. Markuszewski et al. [33] recently reported on a small prospective study of 14 patients who underwent

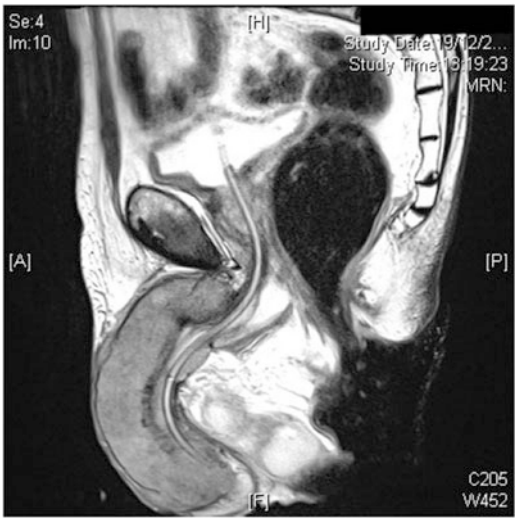

Fig. 2.4 Locally advanced penile carcinoma seen on magnetic resonance imaging

injection of both ^{99m}Tc-nanocolloid and ICG at the primary penile tumor site just before DSNB. Sentinel LNs (SLNs) were localized intraoperatively using the gamma-ray detection probe for radiocolloid and near-infrared fluorescence (NIRF) camera for ICG. Percutaneously, LNs were identified in all 14 patients using the gamma probe and in 10 patients using the NIRF camera. After skin incision, fluorescent nodes were observed using the NIRF camera in the remaining four patients. The intraoperative examination led to the identification of 32 total SLNs using technetium and ICG and additionally three more nodes visible only using ICG. Of the 35 SLNs, 30 were negative and 4 were positive for metastasis. Brouwer et al. [34] also reported on a hybrid radioactive and fluorescent tracer for DSNB in penile cancer as a potential replacement for blue dye (Fig. 2.5). Sixty-five patients with penile SCC underwent peritumor injection of a combination ICG-(99m) Tc-nanocolloid tracer prior to surgery followed by patent blue dye and/or NIRF imaging. Fluorescence imaging enabled visualization of 96.8 % of SLNs, while only 55.7 % were stained by blue dye ($P < 0.01$), suggesting a hybrid radioactive and fluorescent ICG-(99m)Tc-nanocolloid tracer can improve optical SLN detection compared with blue dye.

Other future directions for novel imaging strategies in penile cancer include molecular imaging with ferrous nanoparticles or alternative nontoxic drug delivery systems. These agents can potential identify and label penile cancer cells and enhance MRI visualization of micro-metastatic disease not visible with traditional imaging [35]. Various applications using targeted iron oxide nanoparticles have been evaluated in vitro and in animal experiments for the labeling of mesenchymal stem cells and dendritic cells [36]. Future studies, however, will be needed to determine their utility in vivo in penile cancer patients.

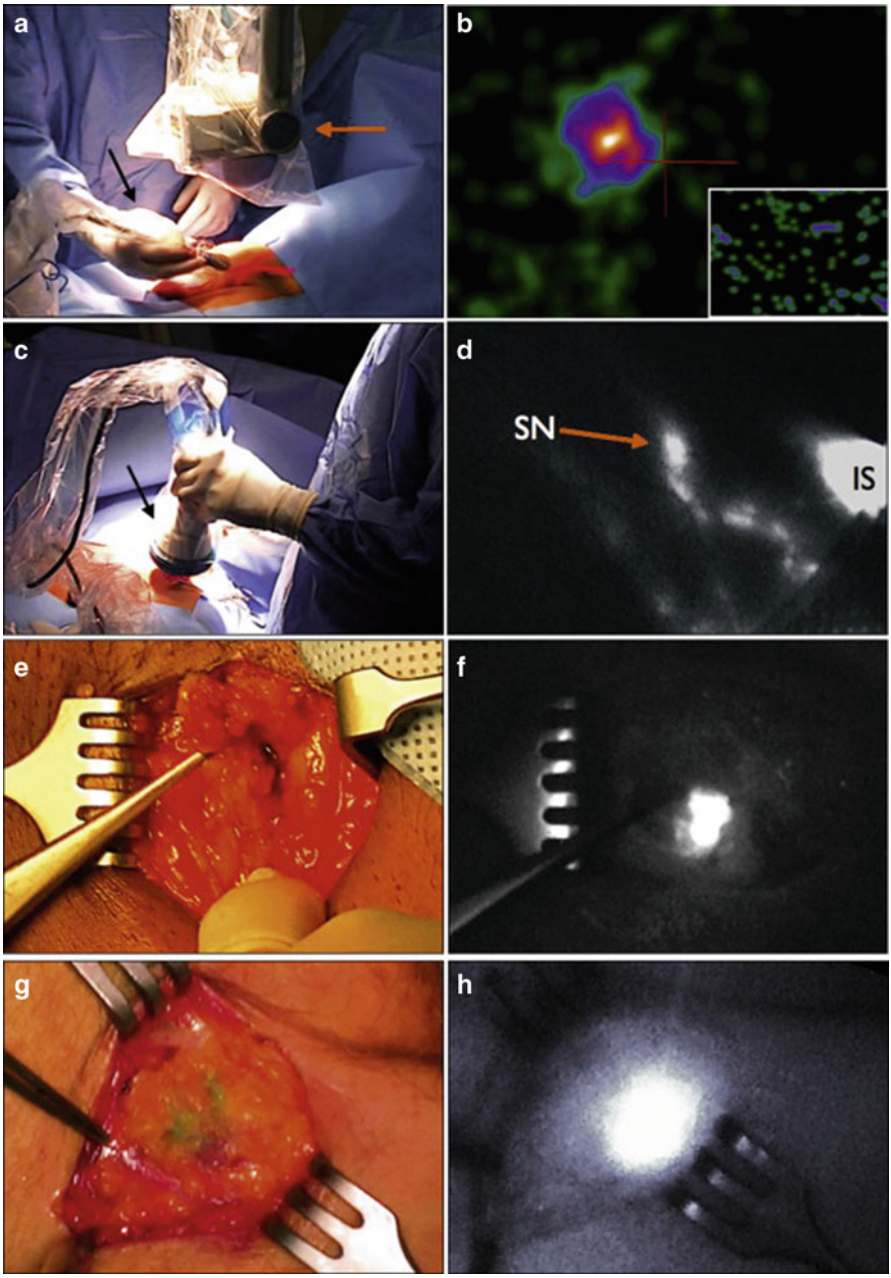

Fig. 2.5 A hybrid radioactive and fluorescent tracer technique using indocyanine green for dynamic sentinel node biopsy in penile cancer as a potential replacement for blue dye. (**a, c, e,** and **g**) Probe position at lymph node area. (**b, d, f** and **h**) Images showing sentinel node

Penile Cancer Biomarkers

Advancement in the techniques for molecular genomics has made biomarkers an increasingly important aspect of a clinician's diagnostic and predictive tools with regard to penile tumor metastasis and disease recurrence. A list of several biomarkers studied in penile carcinoma is summarized in Table 2.1.

Despite initial promising results, the evidence supporting the routine use of biomarkers in the diagnosis and management of penile cancer is still not well established enough to consider their inclusion in cancer guidelines [37]. Data are still controversial regarding the ability of biomarkers to predict the presence of occult LN metastasis. There is a need for large prospective studies to ascertain the clinical utility of biomarkers, but several candidates have been shown to be potential candidates for future investigation.

p53

Tumor protein p53 is a tumor suppressor gene that plays a role in apoptosis, genomic stability, and inhibition of angiogenesis. It can activate DNA repair proteins when DNA has sustained damage and can arrest growth by holding the cell cycle at the G1/S regulation point on DNA damage recognition. The International Cancer Genome Consortium has established that the p53 gene is the most frequently mutated gene (>50 %) in human cancer, indicating that the p53 gene plays a crucial role in preventing cancer formation [38].

Expression of p53 has been evaluated in several studies with regard to prognosis in penile carcinoma. Lopes et al. initially studied 82 patients with penile carcinoma who underwent amputation and bilateral lymphadenectomy to evaluate the prognostic value of immunohistochemical p53 staining in the primary penile tumor [39]. Immunoreactivity of p53 was studied with other clinical and pathological variables, including patient age, stage, histological grade, tumor thickness, lymphatic and venous embolization, corpora cavernosa, corpus spongiosum and urethral infiltration, and HPV status. The association of p53 with LN metastasis, survival, and risk of death was determined as the primary endpoints.

Nuclear accumulation of p53 was detected in 34 of 82 samples in the study (41.5 %) [39]. Clinical nodal stage ($P=0.045$), lymphatic ($P<0.001$) and venous ($P=0.04$) embolization by neoplastic cells, p53 positivity ($P=0.012$), and p53 grade ($P=0.004$) were all significantly associated with LN metastasis. Multivariate analysis revealed that only lymphatic embolization (relative risk [RR], 9.4; 95 % CI, 2.8–31.6) and p53 positivity (RR, 4.8; 95 % CI, 1.6–14.9) were independent factors for LN metastasis. Patients with negative p53 had significantly better 5- and 10-year overall survival (OS) than those in whom tumors stained positive for p53 (64.5 % and 54.6 % vs. 30.2 % and 26.4 %, respectively; $P=0.009$). When tumors were p53 positive and HPV DNA positive, OS was worse. Multivariate analysis, however, revealed that only age (RR, 2.9; 95 % CI, 1.6–5.1) and LN metastasis (RR, 3.2; 95 % CI, 1.8–5.8) were independent risk factors for death. The authors concluded,

Table 2.1 Biomarkers in penile cancer

Biomarkers	Number of studies	Function	Prognosis
p53	6	Tumor suppressor gene	Expression indicated higher risk of LN metastasis, disease progression, and worse DSS
$p16^{INK4a}$	5	Surrogate marker for high-risk HPV infection	Positivity was associated with less tumor invasion, lower risk of disease recurrence, and possibly better survival
Ki-67	4	Marker for tumor cell proliferation in the cell cycle	Labeling correlated with higher tumor grade, advanced local tumor stage, a greater risk of nodal metastasis, and clinical disease progression
PCNA	2	Marker of cell proliferation essential for replication	Expression was associated with presence of nodal metastasis
CRP	3	Pro-inflammatory marker	Elevated plasma levels found more often in patients with advanced tumor stage, positive nodal disease, and worse DSS
Cyclin D1	2	Regulates progression of cells through G1-phase of the cell cycle	No clear prognostic value; implicated in tumor differentiation
E-cadherin	1	Maintains cellular adhesion and signal transduction	Immunoreactivity was associated with a greater risk of LN metastasis
MMP-2 and MMP-9	1	Degrades the basement membrane of a cell	Immunoreactivity was associated with a greater risk of disease recurrence
Fox-P3	1	Oversees the development and function of regulatory T cells	Increased levels correlated to a lower inflammatory infiltrate worse OS
ARID1A	1	Involved in chromatin remodeling	Higher expression was associated with a higher histologic grade

therefore, that immunoreactivity of p53 was an independent risk factor for LN metastasis, and the association of positive p53 with positive HPV DNA was related to a worse prognosis.

Martins et al. [40] reported that p53 staining exhibited correlation with penile tumor pT stage ($P=0.0005$), grade ($P=0.02$), lymphatic spread ($P=0.02$), and CSS ($P=0.003$) in 50 patients with penile SCC [40]. Multivariate analysis showed that p53 immunoreactivity was the only risk factor with prognostic significance for disease progression and CSS. Since p53 overexpression was associated with tumor

progression and CSS, the authors argued that it should be evaluated in staging and therapeutic planning for patients with SCC of the penis.

Gunia et al. [41] showed p53 was an independently significant prognostic factor for CSS in penile cancer patients (hazard ratio [HR], 3.20; $P=0.041$) indicating worse prognosis. Zargar-Shoshtari et al. [42] reported that positive p53 status on immunohistochemistry was associated with pN+ disease (odds ratio [OR], 4.4; 95 % CI, 1.04–18.6) [42]. Liu et al. [43] also studied risk factors for the presence of pelvic LN metastasis in penile SCC patients undergoing inguinal lymph node dissection (ILND). Primary tumor strong p53 expression was a significant predictor of pelvic LN metastasis and OS (OR, 5.997; 95 % CI, 1.62–22.3). Finally, Zhu et al. [44] reported that the expression of p53 was an independent predictor of CSS in Chinese patients with penile cancer, and in stage T1 tumors, high expression of p53 was significantly associated with metastasis and poor survival.

$p16^{INK4a}$

Up to 50 % of penile SCC develops in the context of high-risk HPV infection [45]. Most of these tumors have been reported to show basaloid differentiation, and overexpression of the tumor suppressor protein $p16^{INK4a}$ is seen [46]. Whether HPV-triggered carcinogenesis in penile SCC has an impact on tumor aggressiveness, however, is still subject to debate with $p16^{INK4a}$ overexpression often used as a surrogate marker for high-risk HPV infection [8].

Steinestel et al. [47] analyzed tissue specimens from 58 patients with surgically treated penile SCC and performed $p16^{INK4a}$ immunohistochemistry and DNA extraction followed by HPV subtyping using a PCR-based approach. The sensitivity and specificity of $p16^{INK4a}$ staining to predict the presence of high-risk HPV DNA were 100 % and 57 %, respectively, and by focusing on samples with intense nuclear staining patterns for $p16^{INK4a}$, specificity could be improved to 83 %. Both expression of $p16^{INK4a}$ and presence of high-risk HPV DNA, but not histologic grade, were inversely associated with penile SCC tumor invasion ($P=0.01$, $P=0.03$, and $P=0.71$). However, none of these correlated with nodal involvement or distant metastasis. In contrast to pathological tumor stage, the high-risk HPV status, histologic grade, and $p16^{INK4a}$ positivity failed to predict CSS. These results confirmed that intense nuclear positivity for $p16^{INK4a}$, rather than histologic subtype, was a good predictor for the presence of high-risk HPV DNA in penile tumors. High-risk HPV/$p16^{INK4a}$ positivity, independent of histological tumor grade, indicated a less aggressive local behavior, but its value as an independent prognostic indicator remains to be determined.

Bezerra et al. [48] also showed a significant association of $p16^{INK4a}$ overexpression and high-risk HPV status with histologic subtype ($P=0.017$ and $P=0.01$, respectively) and lymphovascular invasion (LVI) ($P=0.015$ and $P=0.015$, respectively). Regarding survival outcome analyses, neither HPV infection nor $p16^{INK4a}$ overexpression significantly predicted OS or CSS using Cox proportional hazards regression model.

Ferrándiz-Pulido et al. also showed that strong $p16^{INK4a}$ immunostaining correlated with high-risk HPV infection [49]. Both high-risk HPV-positive and $p16^{INK4a}$-positive tumors showed a better OS without reaching statistical significance. The authors argued that routine use of $p16^{INK4a}$ staining should be incorporated in histologic evaluation of penile SCC.

Tang et al. [50] evaluated $p16^{INK4a}$ overexpression by immunohistochemistry for 119 consecutive patients with penile SCC[50]. $P16^{INK4a}$ overexpression was detected in 49.5 % (59 of 119) of samples. There was no significant difference between $p16^{INK4a}$ negative and $p16^{INK4a}$ positive tumors in terms of stage ($P=0.518$), histological grade ($P=0.225$), LVI ($P=0.388$), OS ($P=0.156$) or LN metastasis ($P=0.748$). $P16^{INK4a}$ negative tumors were more likely to recur overall ($P=0.04$), especially if patients had positive LNs at diagnosis ($P=0.002$). These data suggest that $p16^{INK4a}$/high-risk HPV status is associated with recurrence, especially in patients with positive LNs at diagnosis. Thus, patients with $p16^{INK4a}$ negative penile cancer, particularly those with LN metastases, may warrant closer observation after surgery.

Finally, Zargar-Shoshtari et al. [42] reported that in 57 cases of invasive penile SCC, estimated OS was insignificantly longer in $p16^{INK4a}$-positive patients (median OS, 75 vs. 27 months; $P=0.27$) and median CSS was not reached ($P=0.16$). In a multivariable Cox proportional hazard model, when controlling for pathological nodal status and adjuvant chemotherapy, $p16^{INK4a}$ status was a significant predictor for improved CSS (HR, 0.36 [95 % CI, 0.13–0.99]). Only one study has shown alterations in the tumor suppressor gene $p16^{INK4a}$ that are associated with aggressive behavior of penile carcinomas [51].

Ki-67

Ki-67 is a nuclear matrix protein expressed in the cell cycle phases that is a marker for tumor cell proliferation [52]. Its expression can be detected by immunohistochemistry. Its prognostic value in penile carcinoma is still considered controversial.

In a retrospective study of 44 patients in whom primary SCC of the penis was treated with amputation and bilateral lymphadenectomy (pT1 in 24, pT2 in 20, pN+ in 10; G1 in 12, G2 in 28, and G3 in 4), there was a tendency for high Ki-67 expression to be associated with advanced local tumor stage, nodal metastasis, and clinical disease progression, but these correlations were not statistically significant ($P=0.07$, 0.07, and 0.06, respectively) [53]. The authors concluded, therefore, that Ki-67 labeling may correlate with tumor grade in penile cancer and indicate a greater risk of nodal involvement.

The prognostic significant of Ki-67 was further supported by a small study from 73 Chinese patients who had penile amputation and regional lymphadenectomy [44]. LN metastasis was significantly correlated with tumor stage, histological grade, presence of LVI, and the expression of Ki-67. On multivariate analysis, presence of LVI and the expression of p53 were independent predictors of metastasis. Survival analysis showed that the expression of p53 was an independent prognostic

factor for CSS. In stage T1 tumors, high expression of p53 was also significantly associated with metastasis and poor survival.

Another study found a similar association between Ki-67 and tumor grade with Ki-67 expression notably increased with advanced tumor grade ($P<0.01$), but no association was found with tumor stage ($P=0.22$), presence of nodal metastasis ($P=0.74$), CSS (HR, 1.00; 95 %, CI, 0.99–1.02; $P=0.54$), or OS (HR, 1.00 95 %, CI, 0.99–1.02; $P=0.45$) [54]. High tumor stage, LN status, high tumor grade, and age at diagnosis were all independent prognostic factors for CSS and OS in this study.

May et al. [55] evaluated 158 consecutive patients with surgically treated penile SCC. Ki-67 displayed a significant positive correlation with histological tumor grade, LVI, and nodal status. On multivariable analysis, however, only pathologic tumor stage (HR, 1.67; $P=0.003$) and nodal stage (HR, 2.62; $P=0.015$) as well as tumor grade (HR, 1.89; $P=0.036$) and LVI (HR, 2.66; $P=0.028$) were identified as independent prognostic parameters for CSS. The authors concluded, therefore, that Ki-67 adds little to conventional histopathological criteria as powerful predictors of CSS in surgically treated penile carcinoma. It may just represent a marker of more aggressive behavior in this disease.

Finally, Guimaraes et al. [56] found an inverse relationship between Ki-67 and LN metastasis with low expression correlating with LN involvement. Ki-67 immunohistochemical expression also did not have an association with survival and death risk.

Proliferating Cell Nuclear Antigen

Proliferating cell nuclear antigen (PCNA) is another marker of cell proliferation found in the nucleus that is essential for cell replication. Martins et al. [40] found that PCNA expression was significantly associated with nodal disease ($P=0.04$) on univariate analysis, but it had no prognostic significance for nodal metastases, disease progression, or cause-specific death on multivariate analysis.

Guimaraes et al. [56] retrospectively evaluated 125 patients with penile SCC and found PCNA was an independent prognostic factor for LN metastasis but not CSS. Since there is no standardization in the execution and interpretation of PCNA, making comparison of results is challenging.

C-Reactive Protein

C-reactive protein (CRP) is produced by the liver in response to an inflammatory stimulus involving increased cytokine expression. It is elevated during malignancy by various mechanisms including inflammation caused by tumor growth, immune response, to tumor antigen, or the chronic inflammation itself, which can be the source for carcinogenesis. High plasma CRP has been linked to poor prognosis in other genitourinary malignancies including renal cell carcinoma and urothelial carcinoma, and dynamic changes in CRP concentrations over time could predict tumor aggressiveness and potential treatment efficacy [57].

Several studies have evaluated serum CRP levels as a prognostic marker in penile cancer. Steffens et al. [58] retrospectively analyzed 79 patients with information about their serum CRP value prior to surgery who underwent either radical or partial penectomy. A significantly elevated CRP blood level (>15 vs. ≤15 mg/L) was found more often in patients with an advanced tumor stage (≥pT2) (38.9 % vs. 11.6 %; $P=0.007$) and in those with nodal disease at diagnosis (50.0 vs. 14.6 %; $P=0.007$). High CRP levels, however, were not associated with tumor grade ($P=0.53$). The 5-year CSS rate was 38.9 % for patients with preoperative CRP levels above 15 mg/L and 84.3 % for those with lower CRP levels ($P=0.001$). Applying multivariate analysis and focusing on the subgroup of patients without metastasis at the time of penile surgery, both advanced local tumor stage (≥pT2; HR 8.8; $P=0.041$) and an elevated CRP value (>15 mg/L; HR 3.3, $P=0.043$) were identified as independent predictors of poor clinical outcomes in patients with penile cancer. A high preoperative serum CRP level, therefore, was associated with poor survival in patients with penile cancer.

Al Ghazal et al. [59] studied 51 penile cancer patients and found that high presurgical CRP levels were significantly associated with the diagnosis of nodal involvement ($P=0.04$) [59]. The optimal CRP cut-off value to predict LN metastasis was set at 20 mg/L based on ROC analysis. Since a high preoperative serum CRP level was closely correlated with nodal disease, it could be used as an additional marker to help identify patients with penile cancer who may benefit from ILND.

Finally, Li et al. [60] evaluated the association between pretreatment levels of CRP and SCC antigen (SCC-Ag) on 124 Chinese penile SCC patients treated between November 2007 and October 2014. Levels of CRP ≥4.5 mg/L and SCC-Ag ≥1.4 ng/mL were both significantly associated with LN metastasis laterality ($P=0.041$), extranodal extension (ENE) ($P<0.001$), pelvic LN metastases ($P=0.024$), pathologic tumor status ($P=0.002$), pathologic nodal status ($P<0.001$), and disease-specific survival (DSS) ($P<0.001$). Moreover, the influence of CRP and SCC-Ag levels on CSS ($P=0.033$; HR, 3.390; 95 % CI 1.104–10.411) remained after adjusting for smoking history, phimosis, tumor status, tumor cell differentiation, and nodal status. The combined measurement of preoperative CRP and SCC-Ag levels may serve as an independent biomarker for LN metastasis, advanced tumor stage, and DSS in penile SCC patients.

Cyclin D1

Cyclin D1 plays an important role as a cell cycle activator in regulating the progression of cells through the G1-phase of the cell cycle. Cyclin D1 overexpression may be used as a prognostic factor of poor outcome in penile carcinoma.

Papadopoulos et al. [61] evaluated 21 penile SCC patients and a tendency for an association between cyclin D1 expression and tumor differentiation ($P=0.07$), but not the level of tumor invasion ($P=0.50$) was found. Gunia et al. also analyzed the role of p53, p21, and cyclin D1 expression in patients with penile cancer [41]. Specimens and clinical data from 110 men treated surgically for primary penile

cancer were collected. Multivariable analysis showed p53 (HR, 3.20; $P=0.041$) and pT-stage (HR, 4.29; $P<0.001$) as independent significant prognostic factors for CSS. Cyclin D1 and p21 expression were not correlated with survival. However, incorporating p21 into a multivariable Cox model did contribute to improved model quality for predicting CSS.

Other Biomarkers

Other biomarkers in penile cancer have been sparsely studied. In a study by Campos et al. [62], 125 penile cancer patients who had undergone primary penile tumor excision and bilateral lymphadenectomy had their tissues stained for the presence of E-cadherin, matrix metalloproteinase (MMP)-2, and MMP-9 [62]. E-cadherin is a protein responsible for maintaining cellular adhesion and signal transduction, while MMPs help degrade the basement membrane of a cell resulting in tumor metastasis. The authors reported that low E-cadherin immunoreactivity was associated with a greater risk of LN metastases on univariate analysis ($P=0.03$), and high levels of MMP-9 immunoreactivity were independently associated with a greater risk for disease recurrence on multivariate analysis ($P=0.02$).

Since there is growing evidence that immune cells may trigger various mechanisms that enhance tumor growth and metastasis, this same group also evaluated the immunohistomorphology of peritumoral inflammation in penile cancer and correlated it with clinical and pathological parameters [63]. Fox-P3 is a master transcription factor protein that oversees the development and function of regulatory T cells, which generally turns the immune response down. As such, an increase in Fox-P3 expression can result in excess regulatory T-cell activity and prevents the immune system from destroying cancer cells. In the study mentioned above, Vassallo et al. [63] correlated increased levels of Fox-P3-positive lymphocytes with a lower inflammatory infiltrate and subsequently more unfavorable 5-year OS in penile cancer patients.

Finally, ARID1A, a member of the chromatin remodeling genes family, has been suggested as a novel tumor suppressor gene in gynecologic malignancies, but its role in penile cancer is largely unknown. Faraj et al. assessed the immunohistochemical staining of ARID1A in 112 cases of penile SCC from Paraguay and found ARID1A expression in 90% or more of tumor cells in over 85% of cases [64]. There was also a significant correlation between higher ARID1A expression and higher histologic grade, but there was no association with HPV status or the risk of LN metastasis.

Conclusions

Novel diagnostic tools in the evaluation and management of penile cancer continue to be developed to enhance patient selection for both PSS and lymphadenectomy in order to minimize treatment-related morbidity and improve overall QOL.

Future studies will further enhance these imaging-based modalities or tissue-based biomarkers to provide further information of a patient's clinical status and create a more patient-centered approach to treatment.

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Penile-Sparing Surgical Approaches in the Management of Primary Penile Tumours

3

Arunan Sujenthiran, Paul K. Hegarty, and Nicholas A. Watkin

Introduction

The incidence of penile cancer is increasing and contemporary treatment approaches continue to advance. Radical surgery traditionally formed the mainstay of treatment due to excellent long-term oncological control, but the emasculating consequences of radical surgery were often associated with significant psychological and sexual morbidity. To overcome this, there has been an increased uptake in the use of penile-sparing approaches with the aim of achieving good oncological control with minimal anatomical and functional disruption [1].

Basis for Penile-Preserving Surgery

The surgical management of penile cancer is largely governed by the grade and stage of disease. Stage T4, high-grade stage T3, or advanced stage T2 still remain best managed by conventional radical surgery. However, the requirement for radical surgery in less advanced, lower grade disease has been challenged which has resulted in a paradigm shift in practice.

Historically, it was widely perceived that adequate clearance following surgery required at least a 2 cm tumour-free margin. However, a number of studies had challenged the need for such an extensive margin. Agrawal and co-workers reviewed 64 partial and total penectomy specimens to determine the

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microscopic spread of the primary tumour beyond the macroscopic tumour margin. They concluded that 81 % did not extend beyond the visible tumour margin and of those that did; only 25 % extended more than 5 mm from the margin [2]. Hoffman et al. examined surgical specimens from 14 patients undergoing conventional surgery for penile cancer. At 33 months of follow-up none of these patients had developed local recurrence, including seven patients with tumour resection margins less than 10 mm [3]. In a similar study, Minhas et al. reported on 51 cases who underwent penile-sparing surgery. They concluded that despite 90 % of patients having a margin less that 20 mm (48 % of which were less than 10 mm), only three (6 %) patients had positive margins and only two (4 %) developed local recurrence within an average follow-up of 26 months [4]. By assessing the effect of reducing the surgical clearance margin on the incidence of local tumour recurrence, these studies paved the way for a transition to penile-sparing surgery. It is also important to note that most recurrences after penile-sparing surgery are surgically salvageable and local failure does not seem to compromise long-term survival [5].

The selection of the most appropriate penile-preserving technique depends primarily on the stage and location of the disease. Treatment is tailored to the individual, taking into account the lesion, the effect of surgery on penile length and associated co-morbidities. Here, we discuss the different treatment modalities available and their role in the management of penile cancer.

Topical Therapies

Suitable for Stage Tis Disease Only

5 % 5-Fluorouracil (5-FU)

The non-invasive nature of carcinoma in situ (Tis) makes it amenable to curative treatment with preservation of the penis. Topical application of chemotherapeutic agent 5 % 5-Fluorouracil (5-FU) is the most commonly used first line treatment. It is usually applied on alternate days for 4 weeks and has few side effects due to minimal systemic absorption. It is best suited to immunocompetent patients with small (1–2 cm), mucosal and superficial lesions. It should be avoided, due to poor efficacy, in immunosuppressed or those with widespread “field changes” [6]. The largest study to date reported an overall response rate with 5-FU of 50 % at 3 years [7].

Imiquimod

Non- or partial responders to 5-FU are usually treated with immunotherapy using 5 % imiquimod (IQ) cream as second-line treatment for a similar length of time as 5-FU [8]. The exact mechanism of this novel immunomodulatory therapy is not fully understood. It is known to utilize the toll-like receptor 7 to activate immune cells, to secrete cytokines including interferon-α, tumour necrosis factor, and various interleukins [9]. Other cells believed to be activated are natural killer cells, macrophages, and B lymphocytes [10]. While success has been reported in number of case reports and small case series,

no large-scale, long-term efficacy data are available [6, 8]. The overall complete response rate to topical agents has been reported to be approximately 57 % at 3 years [7].

Laser Therapy

For Stage Tis, But Has Been Used Up to Stage T2 Lesions

Laser therapy exists in two main forms:

1. Neodymium: yttrium aluminium garnet (Nd:YAG) lasers which have a tissue penetration of 4–6 mm allowing treatment of more invasive lesions but can cause tissue coagulation preventing histological analysis, thereby leading to a risk of tumour understaging.
2. Carbon dioxide (CO_2) lasers have a tissue penetration of 2–2.5 mm, and direct focussing of the beam allows it to function as a scalpel and excise tissue for histological analysis.

Treatment with either of these forms of laser therapy is usually well tolerated and results in good functional and cosmetic outcomes. However, there are concerns related to a high re-treatment and progression rate. In a study of 19 patients with Tis treated with laser therapy, 26 % of patients required re-treatment for a histologically confirmed Tis recurrence over a follow-up period of 32 months, with one patient progressing to invasive disease [11]. Larger studies have also shown high recurrence rates (19–48 %) and nodal progression rates (5–23 %), with poorest outcomes for higher stage tumours [12, 13]. As a result, this modality is more commonly used for low stage tumours.

Penile-Sparing Surgical Techniques

Circumcision

For Lesions Confined to the Prepuce

Circumcision is the most common operation in the surgical management of penile carcinoma and has a multifaceted role in its management. From a therapeutic standpoint, circumcision is suitable for lesions involving solely the prepuce. It also has a preventative role in cases of glanular Tis where excision of the prepuce removes a human papilloma virus (HPV) favourable microenvironment suited to chronic inflammation and progression to invasive disease. Circumcision aids the follow-up of men with Tis by facilitating clinical examination and allowing easier application and retention of topical therapies.

Achieving adequate clear margin and excluding co-existing glanular disease are important factors when performing a circumcision. If the lesion is more extensive, the excision can be extended on to the shaft skin or coronal sulcus [14]. Acetic acid may be applied to guide excision margins however concerns about low sensitivity and false positive staining persist, particularly with regard to HPV detection [14–17].

Total Glans Resurfacing

For Glanular Tis/Ta and Up to Stage T1a Disease

Total glans resurfacing (TGR) was first described by Bracka for the treatment of Balanitis Xerotica Obliterans (BXO) but has since been adapted to also treat glandular lesions up to stage T1a disease [18, 19] (Figures 3.1 & 3.2). TGR is now the gold-standard surgical management for glandular lesions up to T1a and is recommended in men with recurrent disease, those who have failed conservative therapies, those unlikely to adhere to a surveillance programme, and those with extensive field change.

The procedure is performed under general anaesthesia with pre-operative antibiotics and the use of a penile tourniquet for haemostasis. All epithelium and subepithelium of the glans are marked leaving only a perimeatal and circumcoronal margin. This is undertaken in quadrants starting from the meatus to the coronal

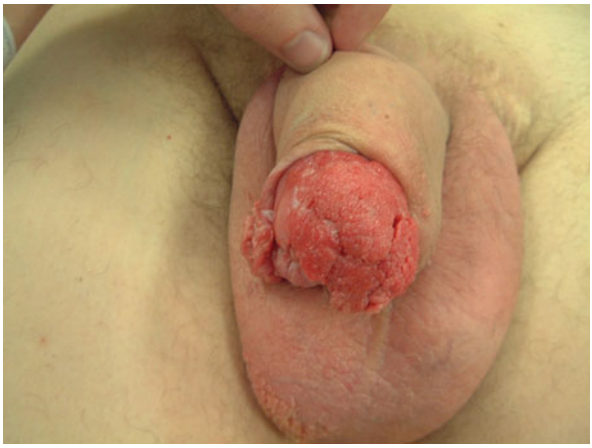

Fig. 3.1 Superficial SCC suitable for total glans resurfacing

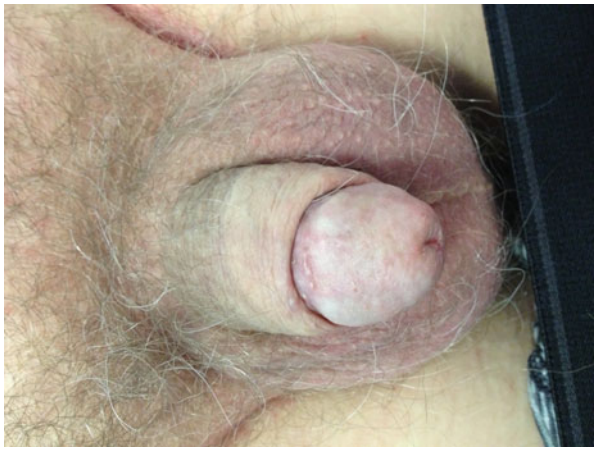

Fig. 3.2 Three months post total glans resurfacing

Table 3.1 Oncological outcomes following glans resurfacing

Study	Treatment	Patients (T stage)	Patients	Reported outcomes	Mean follow-up (months)
Hadway et al. [19]	TGR	Tis	10	No recurrence/progression	30
Shabbir et al. [20]	TGR/PGR	Tis	25	Recurrence 4 %, no progression	29
Ayres et al. [21]	TGR	T1a	36	Early revision rate 8 %	21
				Local recurrence rate 6 %	
Shabbir et al. [20]	TGR (5)	T1a	7	No recurrence or progression	29
	PGR (2)				

sulcus for each quadrant. Deep biopsies from the corpus spongiosum are taken for separate frozen section analysis to exclude invasive disease and confirm complete excision. A split-thickness graft is harvested from the thigh with an air dermatome and should be between 0.008 and 0.016 in. in thickness. The graft is sutured and quilted to the denuded glans with 5-0 interrupted vicryl sutures and dressed with soft paraffin gauze followed by foam dressing to help protect and immobilize the graft. A catheter (14 French silicone) should be placed to keep the wound clean and dry, and the patient is placed on 48-h strict bed rest. The dressing and catheter should be removed on the fifth day post-operatively when the patient is discharged.

An advantage of this surgical approach is its combined diagnostic and therapeutic ability. As well as completely removing the diseased epithelium, TGR also allows more accurate histopathological staging compared to incisional biopsies which are used alongside previously described non-surgical therapies. Shabbir et al. reported that 10 of 25 patients (40 %) who underwent either total or partial glans resurfacing (PGR) had evidence of invasive carcinoma on the final pathological specimens despite all 25 patients having pre-operative incisional biopsies showing Tis only [20]. This finding raises concerns as the majority of patients diagnosed with glanular Tis are primarily treated based on pathology from incisional biopsies and therefore may be under-treated by topical chemotherapy or laser therapy. This is a possible explanation for the higher recurrence rate with laser therapy (26 %) compared to surgical excision/resection (0–4 %) [12, 19–21] (Table 3.1).

TGR allows optimal preservation of penile length, form, and function, and a number of studies have reported good functional and cosmetic outcome results. Shabbir et al. reported 96 % total graft uptake in a study of 25 patients and another series of 10 patients experienced a 100 % graft uptake [19, 20]. Neither authors reported any postoperative complications nor were there any cases of recurrence following TGR. In another series of ten patients treated with TGR for recurrent, refractory, or extensive disease, there was no evidence of disease recurrence after a mean follow-up of 30 months and over 80 % were sexually active within 3 months of surgery [10].

Partial Glans Resurfacing

For Isolated Foci of Tis/Ta Affecting < 50 % of Glans

PGR is an alternative to TGR in the absence of multifocal tumour, if glanular involvement is below 50 % and only for tumours up to Ta (Figures 3.3 & 3.4). PGR applies the same principles as TGR but has the inherent benefit of conserving normal glans skin which offers increased preservation of sensation and better cosmesis. PGR is associated with a high risk of positive surgical margins, and a sub-analysis of one study found a 67 % positive margin rate in this cohort. Forty percent of men in the PGR cohort required further surgical intervention, but there were still no cases of recurrence or progression over a mean follow-up of 29 months [20]. Another study with 36 patients similarly cited a low

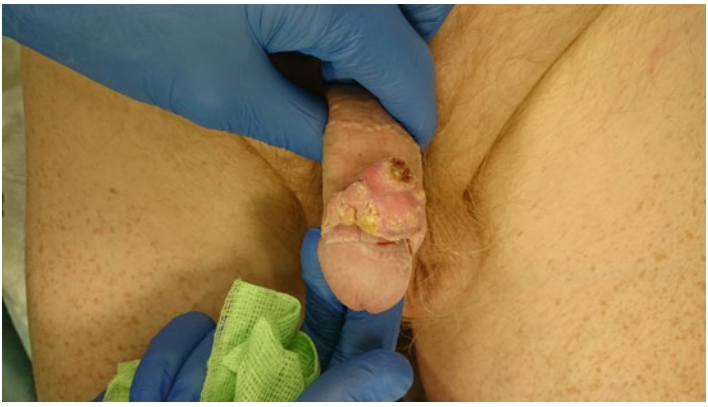

Fig. 3.3 Superficial inner prepuce tumour with differentiated penile intraepithelial neoplasia (PeIN) extending onto the glans, suitable for partials glans resurfacing

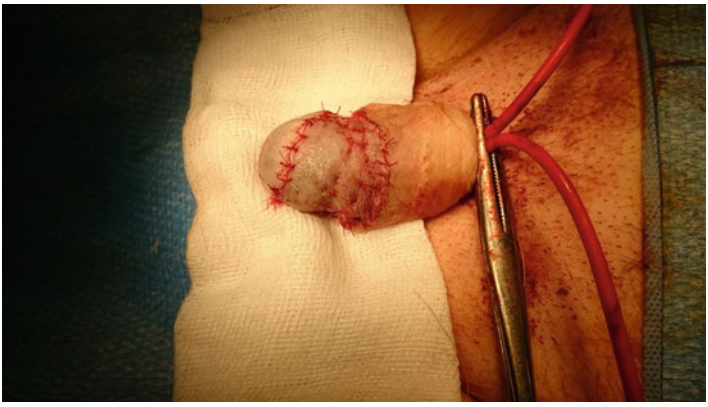

Fig. 3.4 Intra-operative: after partial glans resurfacing and circumcision

recurrence rate of 6 % [21]. Evidence suggests that, where possible, PGR may be a more attractive option for young, sexually active men although all should be counselled that further surgical intervention may be required, which may be in the form of TGR or glansectomy.

Moh's Micrographic Surgery

For Stage T1a, But Has Been Used Up to Stage T3

Moh's Micrographic surgery (MMS) is a form of microscopically controlled chemotherapy which can be performed under local anaesthetic. This technique involves removing the entire abnormal lesion in thin sections, with concurrent histological examination using frozen sections to ensure clear margins microscopically [22]. MMS allows maximal preservation of normal penile tissue but is limited by being time-consuming, technically challenging, requiring both a surgeon and pathologist trained in the technique and high recurrence rates. These limitations have meant MMS is used infrequently in centres managing penile cancer. A study by Shindel et al. found a local recurrence rate of 32 %, and Moh himself acknowledging that distal tumours had better cure rates compared to just 57 % in cancers with penile shaft involvement [22, 23]. Due to the above limitations, MMS still remains an infrequently used intervention.

Wide Local Excision/Partial Glansectomy

For Small, Discrete Lesions on the Glans Up to Stage T1a

In the majority of patients, if the defect is small, primary closure results only in minimal glans deformity. In those with larger lesions, or those in close proximity to the urethral meatus, a split skin graft or shaft skin advancement may be required to achieve a good cosmetic and functional outcome.

Partial glansectomy and TGR are best suited to patients with 'low risk' T1a disease (G1/G2 disease, with no evidence of lymphovascular invasion). It is vital that patients are compliant and adhere to a close surveillance programme following surgery to ensure early detection of recurrences. Local recurrence or positive surgical margins should be treated by total glansectomy. Early detection with subsequent 'salvage' surgery has a high success rate, with no adverse impact on disease survival [24, 25].

Glansectomy and Reconstruction

For Stage T1b/T2 Tumours Confined to the Glans

Glansectomy offers the best surgical approach for T2 or high grade T1 disease (Figures 3.5 & 3.6). This procedure utilizes knowledge of the anatomical planes between the corpora cavernosa and corpus spongiosum initially described by Austoni and colleagues [26]. In this procedure the glans is separated from the corpora cavernosa with subsequent formation of a new urethral meatus at the tip of the shaft.

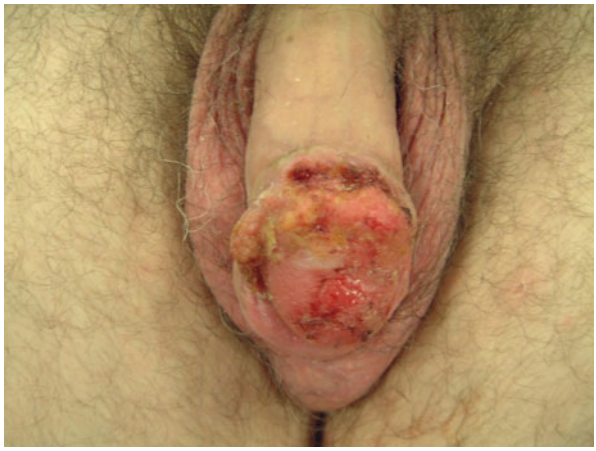

Fig. 3.5 T2a SCC of glans spongiosum, suitable for glansectomy

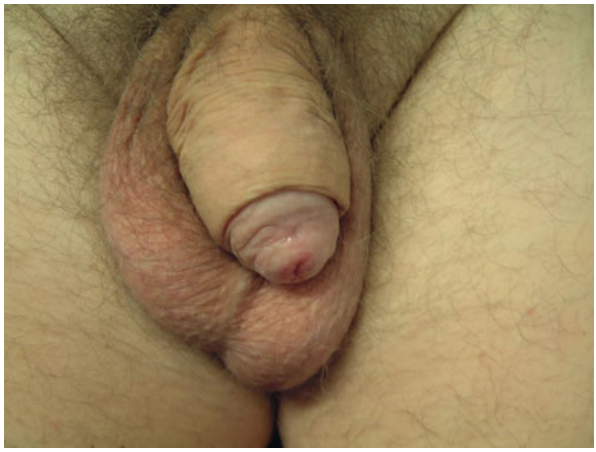

Fig. 3.6 Post-operative appearance at 3 months' post glansectomy

A circumferential incision is made in the distal shaft skin (approximately 1 cm below the corona) down to Buck's fascia. Depending on the location and extension of the penile lesion, a plane of dissection is created to separate the glans from the underlying corporal heads. The urethra is transected and frozen-sections from the corpora and distal urethra can be taken if there are concerns about positive margins. If a positive margin is identified on frozen section, the 'shaving' of the corporal heads should be performed prior to mobilization of the urethra or reconstruction.

In situations when the urethra is too ventrally positioned, spatulation and mobilization of the urethra may be required. Shaft skin is advanced to 2–3 cm distal to the tip of the penis and the neoglans created using a split thickness skin graft. Similar to technique for TGR, the graft is harvested from the thigh with an air dermatome and should be between 0.008 and 0.016 in. in thickness. It is sutured and

quilted with 5-0 interrupted vicryl sutures and dressed with soft paraffin gauze and a foam dressing. A catheter is placed to keep the graft-site clean and dry. Following 48 h of bed-rest, the dressings and catheter are removed on the fifth post-operative day prior to discharge.

Complications following this procedure include graft failure, graft stenosis, and urethral stenosis but have a relatively low incidence (8 % in a study of 25 patients) [27]. Patients also often have high risk invasive cancer therefore positive margins are not uncommon. Despite this, Veeratterpillay et al. cited only a 13 % positive margin rate and a 4 % recurrence rate in their cohort of 46 patients [28]. Morelli et al. reported their experience with glansectomy and reconstruction in 15 patients with tumours confined to the glans. At a mean follow-up of 36 months, all patients were disease-free, with no cases of local recurrence. All patients were sexually active 2–6 months post-operatively, but all reported reduced glans sensitivity [29]. In the largest series to date of 72 patients who underwent glansectomy and reconstruction, only three local recurrences (4 %) were reported (Table 3.2).

Distal Corporectomy/Partial Penectomy and Reconstruction

For Stage T2b/Distal T3 Disease

For tumours extending into the corporal bodies or urethra, partial penectomy offers low recurrence rates, and if used in conjunction with reconstructive or lengthening techniques, may offer an acceptable functional and cosmetic outcome.

Table 3.2 Oncological outcomes following glansectomy (partial/total)

Study	Procedure	Tumour stage	Patients (number)	Local recurrence rate (%)	Mean follow-up (months)
Pietrzak et al. [33]	Partial/total glansectomy	Ta-T3	39	2.5	16
Brown et al. [34]	Partial/total glansectomy	T1-T2	5	0	12
Gulino et al. [35]	Partial/total glansectomy	Ta-T3	14	0	13
Smith et al. [36]	Partial/total glansectomy	T1-T2	72	4	27
Palminteri et al. [37]	Partial/total glansectomy	T1-T2	12	0	32
Morelli et al. [29]	Partial/total glansectomy	Ta-T3	15	0	36
O'Kane et al. [27]	Total glansectomy	T1-T3	25	4	28
Hakansson et al. [38]	Total glansectomy	T0-T3	15	0	10

A circumferential incision 1–2 cm proximal to the lesion is made to deglove the penis and expose the underlying corpora. The corpora and urethra should then be transected proximal to the lesion. This should result in a 'fish mouth' appearance to the corpora which allows for midline vertical closure. Care should be taken to ensure the urethra is at least 1 cm longer than the corpora to allow for spatulation and reconstruction. Successive frozen section biopsies should be sent from the remaining corpora to confirm adequate clear margins before the corpora is closed with 2-0 PDS suture. The urethra is spatulated dorsally and then sutured circumferentially to the tip of the penis. The penile shaft skin is then advanced and sutured 2–3 cm from the tip of the penis using 4-0 interrupted vicryl sutures. To cover the exposed corpora, a neoglans should be created using a split thickness skin graft (0.008–0.016 in. in thickness) harvested from the thigh. It should be sutured and quilted with 5-0 interrupted vicryl sutures and dressed with soft paraffin gauze followed by a foam dressing. A catheter should be placed to keep the wound clean and dry, and the patient is then placed on 48 h strict bed rest. The dressing and catheter should be removed on the fifth day prior to discharge, with a plan for wound review after 1 week.

For patients with either multiple co-morbidities or for whom cosmetic and sexual function is less of a priority, a skin graft may not be required. Instead, shaft skin can be advanced over the corpora and sutured circumferentially around the urethra. Following partial penectomy, the length of the resultant phallus is a common concern due to its implications on potency and urinary function. In some cases, lengthening procedures may be required involving division of the penile suspensory ligament beneath the penile arch and reattachment to the inferior pubic bone. Alternatively, a scrotoplasty may relieve tethering and traction. Men with large suprapubic fat pads may benefit from liposuction or fat pad excision. Penile prostheses also remain an option for some men.

A multi-faceted approach is required to measuring outcomes following penile-sparing surgery and particularly partial penectomy. These include urinary symptoms, complication burden, erectile function, patient-reported satisfaction, and oncological outcomes. A study on 25 patients who underwent partial penectomy and pseudoglans reconstruction with an inverted distal urethral flap reported 72 % were confident of their post-operative potency and 64 % were able to achieve an orgasm [30]. Despite this, all patients reported less frequent sex and embarrassment in the size of their penis. A study by Kieffer et al. compared patient reported outcomes of men undergoing partial penectomy with those undergoing less aggressive penile-preserving surgery and found that urinary function, concerns related to appearance and orgasm were all less of a concern in the latter category [31]. However, oncological outcomes are favourable following partial penectomy with Rempelakos et al. reporting no recurrences in their cohort of 227 patients after 120 months of follow-up [32]. Similar oncological outcomes from other studies following partial penectomy have been reported (Table 3.3).

Table 3.3 Oncological outcomes following glansectomy (partial/total)

Study	Patients (number)	Tumour stage	Local recurrence rate (%)	Mean follow-up (months)
Bañón Pérez et al. [39]	42	T1	7.1	67
Ficarra et al. [40]	30	NR	0	69
Rempelakos et al. [32]	227	T1-3; N1-3	0	>120
Chen et al. [41]	34	Ta-T4	5.8	37
Korets et al. [42]	32	Tis-T3; N1-3	3.2	34
Leitje et al. [43]	214	Tis-T3	5.3	60.6
Ornellas et al. [44]	522	Ta-T3	4	11

Conclusions

With close follow-up and self-examination, penile preserving surgery offers an excellent oncological and functional outcome for use in distal penile malignancy. For more novel techniques, outcome reporting using validated questionnaires is limited; however it is clear that they offer significantly less psychological and physical morbidity than traditional techniques.

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Dynamic Sentinel Node Biopsy and FDG-PET/CT for Lymph Node Staging in Penile Cancer

4

Niels M. Graafland, Sarah R. Ottenhof, Renato A. Valdés Olmos, and Erik Vegt

Introduction

The presence and extent of inguinal lymph node metastases are important determinants in the staging and prognosis of patients with penile squamous cell carcinoma [1–8]. Penile cancer typically shows a stepwise lymphogenic dissemination pattern. The first draining lymph nodes are always the inguinal nodes. Spread to the inguinal lymph nodes can be unilateral or bilateral [9]. The second draining regional lymph nodes are the pelvic lymph nodes. Pelvic nodal involvement in the absence of inguinal lymph node metastasis or cross-over of metastases from one inguinal nodal side to the contralateral pelvic nodal region has never been reported [10].

The optimal management of clinically node-negative (cN0) patients is controversial [11, 12]. Approximately 20 % of these cN0 patients have occult metastases. An inguinal nodal dissection can be curative in those patients with metastatic spread confined to the inguinal lymph nodes: 5-year survival is over 90 % if occult inguinal metastatic disease is treated early by lymphadenectomy but decreases significantly if lymphadenectomy is postponed until lymphadenopathy becomes clinically

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evident [13]. On the other hand, lymphadenectomy is associated with significant morbidity: up to 35–70 % of patients have short- or long-term complications [14–17]. This morbidity is justified in the 20 % of cN0 patients with lymph node metastases, but not in the other 80 % [18, 19]. Conventional imaging techniques, such as ultrasonography, CT, or MRI, are unable to detect small lymph node metastases. Because of the prognostic importance of inguinal nodal staging, more sensitive techniques need to be applied.

Risk-Adapted Approach

The optimal treatment of cN0 patients depends on their actual risk of metastases. Therefore, a risk-adapted approach has been proposed [10]: patients with pTis, pTa, and low grade (G1) pT1 tumors have a low risk of inguinal micrometastases (0–6 %) and are suitable for close surveillance. In patients with higher chances of micrometastases (i.e., ≥pT1G2), close surveillance may lead to unnecessary delay in treatment and increased mortality. Therefore, in these intermediate to high risk patients, a (minimally) invasive staging procedure should be performed.

Currently, two minimally invasive staging procedures are considered evidence-based: dynamic sentinel node biopsy and modified inguinal lymphadenectomy. As mentioned above, a prophylactic radical inguinal lymph node dissection is considered overtreatment in the majority of cN0 patients.

Dynamic Sentinel Node Biopsy

The principle of sentinel node biopsy is the identification, excision, and pathological analysis of only the lymph nodes receiving direct lymphatic drainage from the tumor [20, 21]. It is based on the theory that these so-called sentinel nodes are always the first to become colonized by metastases, and that other nodes are very unlikely to be affected if the sentinel nodes are tumor-negative. Initially, it was thought that the sentinel nodes from penile tumors were invariably located anteromedially to the superficial epigastric vein in the groins [22]. However, using lymphoscintigraphy, Horenblas et al. demonstrated that the distribution of sentinel nodes from penile cancer in the groins varied [20]: 73 % of sentinel nodes were located in the superior medial zone, 9 % in the superior lateral zone, and 18 % in the central zone, according to Daseler's inguinal zones [23]. Exceptionally, a prepubic sentinel node has been reported [24].

The procedure of dynamic sentinel node biopsy entails the injection of a radiolabeled colloid, such as ^{99m}Tc-nanocolloid, in three or four deposits in the skin around the tumor, followed by dynamic and static lymphoscintigraphy directly and approximately 10 min and 2 h after injection (Fig. 4.1a). The location of the radioactive sentinel nodes can be marked on the skin. Three-dimensional multimodality imaging with SPECT/CT (Fig. 4.1c, d) can have added value to pinpoint the exact location of the sentinel nodes and can differentiate between the true inguinal sentinel

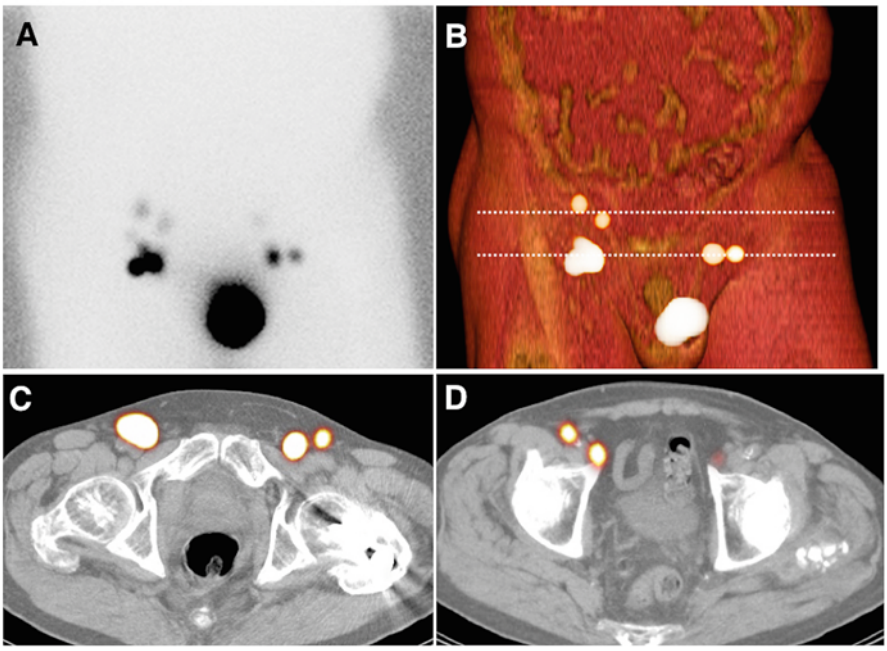

Fig. 4.1 Lymphatic drainage in penile cancer. Anterior planar lymphoscintigraphy (**a**) shows drainage from the central injection site to both groins. On SPECT/CT (volume rendered, **b** and transversal slices **c**, **d**), inguinal sentinel nodes (*lower dotted line*) are clearly differentiated from second echelon iliac lymph nodes (*upper dotted line*)

nodes and possible higher echelon nodes in the pelvis. If no sentinel nodes are visualized in one or both groins, tracer reinjection is performed. In case of persistent nonvisualization, close surveillance or an inguinal lymphadenectomy can be considered on the side of nonvisualization.

Surgery can be performed on the same or the next day. The markings on the skin are used to guide the incision, and a gamma probe is used to guide the surgeon to the sentinel node(s). The radio-guided procedure may be combined with the intraoperative use of blue dye, which is injected around the tumor for visual assistance a few minutes before the skin incision in the groin. Recently, as an alternative to blue dye, the use of a hybrid fluorescent and radioactive tracer (indocyanine green-^{99m}Tc-nanocolloid) has been studied, which combines acoustic gamma probe detection with live optical sentinel node visualization using a near-infrared camera [25].

If the sentinel node is tumor-positive after definitive histopathological examination, completion ipsilateral radical lymphadenectomy is done. Groins without tumor-positive sentinel nodes are managed with close surveillance, avoiding the lymphadenectomy-associated morbidity.

It is important to emphasize that a sentinel node procedure always needs to be preceded by a groin ultrasonography with fine needle aspiration cytology (FNAC) of suspicious nodes. Ultrasonography with FNAC can identify macroscopically

tumor-positive nodes, which may be bypassed by the radioactive tracer due to obstruction of lymph flow by macroscopic metastases. In such cases, another lymph node which might be tumor-negative will falsely be identified as the sentinel node, potentially leading to a false negative procedure. Furthermore, when preoperative ultrasonography with FNAC identifies tumor-positive nodes, this obviates the need for DSNB on the affected side, and a radical inguinal lymph node dissection can be done directly [26, 27].

The accuracy of sentinel node biopsies depends on the experience of the team of surgeons and nuclear medicine physicians. In a pooled meta-analysis of 18 studies, the pooled sensitivity of sentinel node biopsy procedures was 88 % (false negative rate 12 %), but in experienced groups, sensitivities of 90–95 % are reported (false negative rate 5–10 %) [28]. It is important to realize that a modified inguinal lymph node dissection is also associated with false negatives, with a false-negative rate that is comparable to DSNB [29]. Complications of sentinel node biopsy occur in less than 5 % of explored groins, and almost all are transient and can be managed conservatively [21].

FDG-PET/CT

Over the past decades, positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) has proven to be useful for the staging and follow-up of many types of cancer. FDG-PET is a functional imaging modality that can detect tumors and metastases based on increased uptake of glucose and FDG, resulting from their increased glycolytic activity. Modern PET scanners are combined with a CT (or MRI) scanner in one machine (PET/CT). The combination of functional PET data and anatomical information from CT has led to a higher accuracy and diagnostic confidence than separate PET and CT.

Penile cancers generally exhibit a high uptake of FDG, which makes FDG-PET/CT a potentially useful tool for staging of penile tumors (Fig. 4.2). Unlike palpation and anatomical imaging with CT, MRI, or ultrasound, FDG-PET/CT does not use lymph node size as the main criterion for malignancy. However, because of its limited spatial resolution, the sensitivity of PET drops progressively for metastases smaller than 8–10 mm, and lesions smaller than 4–5 mm are rarely detectable. False positive results can occur due to high uptake of FDG in inflammation, including reactive lymph nodes.

The main characteristics of available studies about the accuracy of PET/CT for nodal staging of penile cancer are summarized in Table 4.1. The first study of FDG-PET/CT in 13 penile cancer patients reported a promising sensitivity of 80 % and specificity of 100 % for inguinal and obturator node metastases on a per-patient basis [30]. These results were confirmed in a larger study by Schlenker et al. ($n = 35$), who found a sensitivity of 88 % and specificity of 98 % for inguinal nodal metastases [31]. Souillac et al. studied 22 cN0 patients with PET/CT. They found a sensitivity of 75 % and specificity of 88 % [32]. However, in a study of 24 patients (42 cN0 groins) by our group, PET/CT detected only one out of five inguinal node

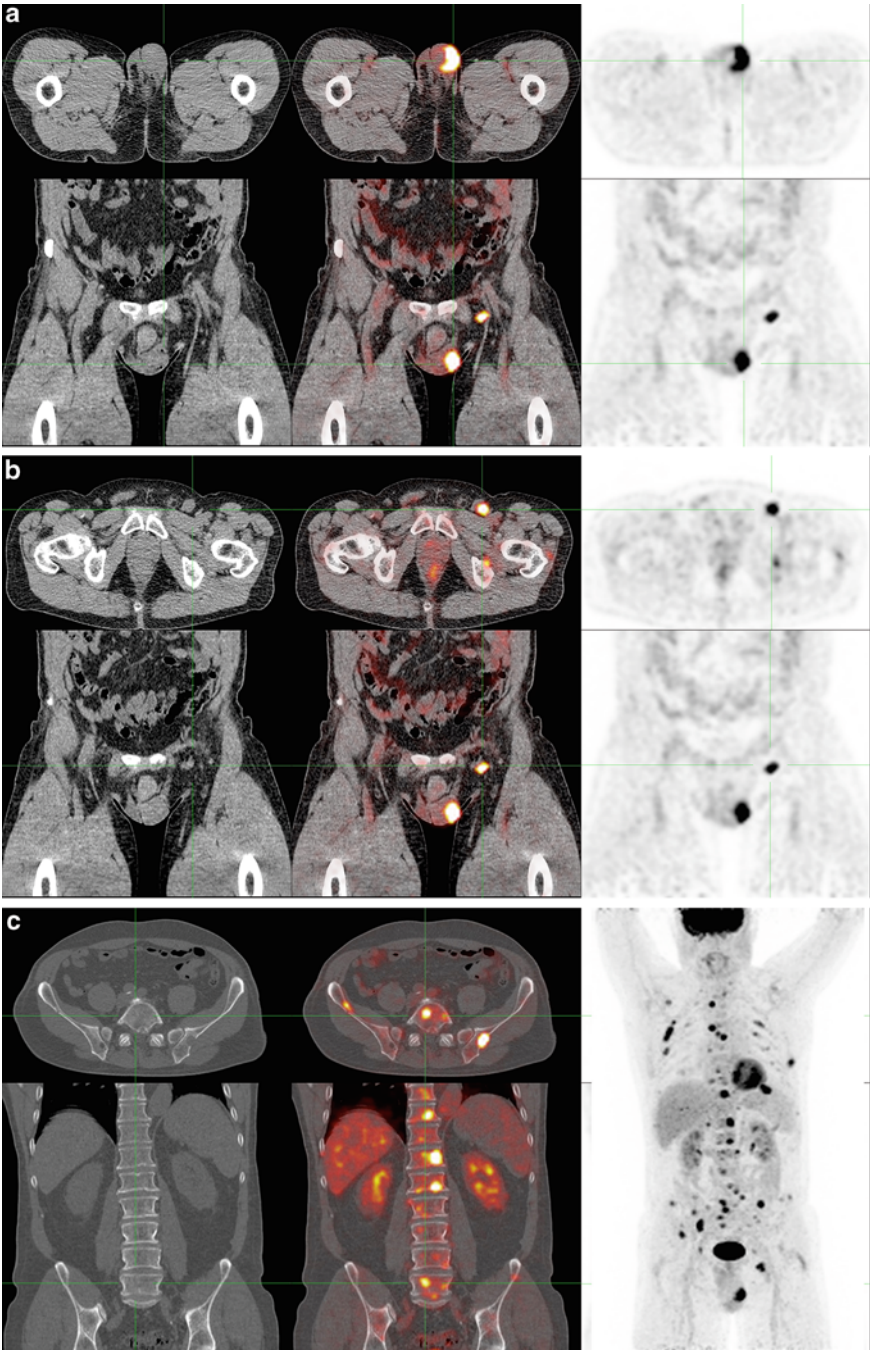

Fig. 4.2 FDG-PET/CT scan of a patient with penile cancer. The penile tumor exhibits high uptake of FDG (**a**). In the left groin, a prominent lymph node with high uptake of FDG is visualized (**b**), which is highly suspicious for metastasis. In addition, multiple bone metastases can be seen in the rest of the body (**c**)

Table 4.1 Characteristics of studies on accuracy of FDG-PET/CT for inguinal and pelvic staging of penile cancer

First author	Year	Initial risk stratification	*n*	cN-stage	*n*	Reference standard	Sensitivity	Specificity
Inguinal staging								
Scher [30]	2005	Susp. penile cancer	10	N/A		ILND/6 mo FU/None[a]	80 %	100 %
		Susp. local recurrence	2	N/A				
		Susp. ing. recurrence	1	N+				
Leijte [33]	2009	T1-T2		N0	19	US-FNAC and DSNB	20 %	92 %
				N+ unilat.	5			
Schlenker [31]	2012	Low-intermed.	13	N0	22	ILND/24 mo FU	88 %	98 %
		High	22	N+	13			
Souillac [32]	2012	pT1b	12	N0	22	mILND/rILND	75 %	88 %
		pT2	13	N+	8		100 %	100 %
		pT3	5					
Pelvic staging								
Graafland [34]	2009	N/A		N+	18	PLND/12 mo FU	91 %	100 %

[a]Three patients had no penile cancer, so were not followed-up

n number of patients, *Susp.* suspected, *Ing.* inguinal, *N/A* data not available, *Mo* month, *FU* follow-up, *Unilat.* unilateral, *US-FNAC* ultrasound with fine needle aspiration cytology, *DSNB* dynamic sentinel node biopsy, *(m/r)ILND* (modified/radical) inguinal lymph node dissection, *PLND* pelvic lymph node dissection

metastases (sensitivity 20 %). Three false-positive results were found (specificity 92 %) [33]. The difference between these studies may be explained by differences in reference standard and initial risk stratification; some studies also included clinically node-positive patients.

A meta-analysis of FDG-PET/CT for inguinal staging of penile cancer from 2012 found a pooled sensitivity in clinically negative groins of 57 %. In cN+ groins, the calculated sensitivity was 96 %. Overall, the pooled sensitivity and specificity were 81 and 92 %, respectively. However, in this meta-analysis about *inguinal* nodal staging, the data from Graafland et al. about *pelvic* nodal staging [34] were also included, as were the data from another paper about monitoring response to chemotherapy. Therefore, the calculated pooled sensitivities and specificities for overall and cN+ patients are probably flawed [35].

Only one paper studied the use of FDG-PET/CT for pelvic and distant staging of penile cancer, in eighteen inguinal node-positive patients. In this group, sensitivity for pelvic nodal metastases was 91 % and specificity 100 %. Five patients had evidence of distant metastases on PET, of which two were confirmed by pathology and two by CT [34].

In summary, the sensitivity of FDG-PET/CT for staging of inguinal nodes remains suboptimal, probably due to its limited spatial resolution. PET/CT is therefore not suitable to replace staging by inguinal node dissection or dynamic sentinel node biopsy. However, PET/CT is a promising modality for pelvic and distant staging in inguinal node-positive patients.

Conclusion

Accurate nodal staging of penile cancer is of the utmost importance, since a radical inguinal lymphadenectomy can cure many patients with (occult) inguinal lymph node metastases, but is also associated with significant morbidity. The majority of cN0 patients with intermediate to high risk penile cancer do not have lymph node involvement (approximately 80 %). Current noninvasive staging tools (including FDG-PET/CT) are not accurate enough to identify occult metastases. Sentinel node biopsy can quite reliably identify nodal involvement in cN0 patients and is associated with low morbidity. A downside is the false negative rate of 5–10 %. The risks of false negative results and their implications on prognosis should be discussed with the patient before deciding on which method to use (i.e., dynamic sentinel node biopsy or direct inguinal lymphadenectomy).

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5 Surgical Decision-Making, Technical Considerations, and Clinical Pearls in Therapeutic Inguinal Node Dissection for Penile Cancer

Curtis Pettaway and Ahmed Sarhan

Surgical Decision-Making in Patients with CN +ve Penile Cancer

Thirty to sixty percent of patients with penile cancer have palpable lymph nodes at presentation [1]. This cohort of patients represents a challenging problem in treatment. The mainstay for successful management in this setting depends on identifying patients who are highly curable with lymphadenectomy alone versus patients who need additional therapy.

More than two histopathologically proven unilateral metastatic inguinal nodes, extranodal extension of cancer, bilateral inguinal nodal metastasis, and pelvic lymph node metastasis have been identified as pathological risk factors for poor outcome [2, 3]. Five-year cancer-specific survival was 33, 42, 51, and 22 % for patients with these pathological risk factors. On the other hand patients with two or less histopathologically proven unilateral metastatic inguinal nodes, No extranodal extension, unilateral inguinal nodal metastasis and No pelvic lymph node metastasis showed 5 years cancer-specific survival 74, 68, 80, and 72 %, respectively. Adjuvant radiation therapy has been utilized in small single center reports among patients with adverse risk factors after surgery. There is a suggestion of some benefit among those patients with extranodal extension, but this remains to be proven in larger prospective trials [4, 5].

Selected patients with advanced metastatic disease might benefit from neoadjuvant chemotherapy followed by aggressive consolidation surgery [6]. To date adjuvant chemotherapy has been sparsely studied in this disease but may have a role among patients with pelvic lymph node metastasis [7, 8].

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Given that neoadjuvant chemotherapy has shown some efficacy, preoperative identification of patients who are more likely to have these pathological risk factors at surgery would be beneficial. Such patients may be candidates for systemic therapy before definitive treatment (i.e., induction or neoadjuvant treatment).

Graafland and associates identified radiological predictors for adverse pathological risk factors through reevaluating CT scans for 30 patients with clinically palpable inguinal lymph nodes and positive FNAC who underwent inguinal lymphadenectomy for penile cancer. Among multiple radiological features studied, central nodal necrosis and/or irregular nodal border of the regional lymph nodes on the preoperative CT identified the high-risk subgroup with a sensitivity of 95 % (21 of 22) and a specificity of 82 % (31 of 38). Of note the authors reported low sensitivity (20 %) of CT in diagnosing pelvic nodal metastasis based on short-axis diameter 11 mm or greater and/or central nodal necrosis. These results support previous studies, which showed the low sensitivity (37.5 %) in spite of high specificity (100 %) of CT scan in detecting abnormal pelvic lymph nodes. However in this study the prevalence of nodal involvement was higher than in a general patient population with penile cancer and diagnostic accuracies of CT imaging in detecting pathological nodal involvement might be overestimated [9].

FNAC was also investigated as a diagnostic tool for bilateral palpable inguinal adenopathy. Older studies reported 100 % sensitivity, but the procedure was performed at the time of lymphadenectomy not before antibiotic therapy [10]. More recent studies have reported a 93 % sensitivity and a 91 % specificity of FNAC with US guidance at the time of penectomy in patients who did not receive antibiotic therapy [11]. CT-guided biopsy for abnormal pelvic lymph nodes on CT scan can be used to confirm metastasis in this setting.

Pet/CT scan using 18F-FDG-PET/CT showed promising results in detecting pelvic lymph node metastasis in patients with clinically positive inguinal lymphadenopathy with a sensitivity of 91 % and specificity of 100 %. Sensitivity was particularly dependent on tumor burden and increased significantly with the size of the nodal lesion [12].

In summary patients with clinically palpable inguinal lymph nodes are at increased risk to harbor adverse features for cure with surgery alone and should be carefully evaluated with imaging to identify patients who may benefit from neoadjuvant chemotherapy prior to consolidative surgical resection [5, 9, 11, 13].

Unresectable Inguinal Lymphadenopathy

High-volume inguinal nodal disease represents another challenging group of patients who require a multimodal approach for optimal outcomes. Palliative resection alone is feasible from a technical standpoint with minimal perioperative morbidity; however, 1 year overall survival was less 10.3 % (4 out of 39 patients) [14]. This result highlights the role of systemic therapy in high-volume node disease before surgical resection.

Role of Systemic Therapy in High-Volume Lymph Node Metastasis

In a prospective Phase II trial evaluating the efficacy of neoadjuvant chemotherapy (paclitaxel, ifosfamide, and cisplatin) for 30 patients with N2-N3 disease in terms of overall survival and time to progression. Objective response rate was 50 %. Among 22 patients who subsequently underwent surgery three patients had no remaining tumor on histopathology. Statistically significant improvement in time to progression (5 vs. >50 months, $P = 0.002$) and overall survival (10 vs. 36 months, $P = 0.017$) was observed among patients who experienced an objective response versus those who did not [13]. (Nine patients (30.0 %) remained alive and free of recurrence median follow-up, 34 months.) Because it was not a randomized trial, the study did not compare the results of neoadjuvant chemotherapy to a control group (i.e., with surgery alone).

Zou et al. exclusively evaluated patients with N3 penile cancer, who received BMP (bleomycin, methotrexate, and cisplatin) neoadjuvant chemotherapy. The response rate was 62.5 %. It should be noted that response in this study was defined as reduced size of metastatic lymph nodes, or metastatic lymph nodes became mobile after treatment. Responders received consolidative surgery followed by adjuvant chemotherapy while nonresponders received salvage radiation therapy because their lymph nodes were deemed fixed and not amenable for resection. One, two, and five years overall survival rates between responders and nonresponders were 86.7 vs. 44.4 %, 73.3 vs. 11.1 %, 73.3 vs. 0 %, $P = 0.001$ [15]. It should be noted that The International Consultation on Urologic Disease for Penile Cancer subcommittee on the treatment of Stage IV penile cancer stated that the use of bleomycin was associated with an unacceptable level of toxicity and should be discouraged as first-line therapy (level of evidence 3, grade of recommendation B) [16].

In another study from Netherland overall response to five different neoadjuvant chemotherapy regimens (1) single agent bleomycin; (2) bleomycin, vincristine, and methotrexate; (3) cisplatin and 5-flurouracil; (4) bleomycin, cisplatin, and methotrexate; (5) cisplatin and irinotecan was 63 % (12 patients). Nine of twelve responders underwent consolidative lymphadenectomy, and eight patients were free of disease at median follow-up of 20.4 months. On the other hand three of eight nonresponders underwent lymphadenectomy for palliative intent, and all three died within 4–8 months of cancer [17]. The results highlight the positive impact of neoadjuvant chemotherapy on survival, but toxicity was a major concern as three deaths were directly related to bleomycin toxicity. Also the small sample size in each treatment group made it difficult to compare different regimens in terms of efficacy and toxicity.

In the largest single center study evaluating the role of perioperative chemotherapy and surgical resection 61 patients were treated with five different chemotherapy regimens including (1) TIP, (2) carboplatin/paclitaxel, (3) 5-fluorouracil/cisplatin, or (4) methotrexate/bleomycin/ cisplatin. Most of those patients were treated with TIP including 30 patients previously reported by Pagliaro et al. [13]. Objective responses were noted in 65 % of patients, and one-third of patients were alive at 3 years after chemotherapy and surgical resection. Five-year survival was

significantly different in responders versus stable versus disease progression (50 % vs. 25 % vs. 7.7 %, $P = 0.045$–0.001). In univariate analysis response to chemotherapy and postchemotherapy pathological staging were significant predictors of overall and disease-specific survival. Multivariate analysis was not conducted due to relatively small number of cases (61 patients) [18].

Failure of systemic therapy in the setting of advanced nodal disease is associated with poor prognosis regardless of second line salvage therapy. In a recent study by Wang and associates median overall survival was <6 months after failure of first-line chemotherapy [19]. Progression-free survival in patients who underwent salvage lymphadenectomy was less than 2 months. Moreover there was no difference in Median overall survival between who received second line cisplatin-based treatment versus those who did not (5.6 vs. 4.3, $P = 0.4$).

Technical Considerations Among Patients Undergoing Lymphadenectomy for Clinically Positive Nodes

Initial Resection of Clinically Mobile Nodes Less Than 4 cm with No Overlying Skin Fixation

Perioperative Care

Taking in consideration the morbidity of the procedure, perioperative preparation should be carefully planned focusing on thromboembolism (DVT/PE) prophylaxis and antibiotic administration.

DVT/PE prophylaxis is of significant importance for many reasons. This cohort of patients often exhibits the classic risk factors of Virchow's triad for DVT/PE including (1) slow down of blood flow during intraoperative and postoperative periods and (2) endothelial injury during vascular dissection and hypercoagulable status induced by malignancy. Moreover, the frequent use of myocutaneous flaps to cover skeletonized femoral vessels might delay postoperative ambulation and increase the risk for DVT/PE.

Our recommendation is to keep patients on heparin or low-molecular-weight heparin while on bed rest. For patients with a remote history (more than 6 months) of DVT/PE perioperative low-dose low-molecular-weight heparin is recommended until postoperative day 28 [20]. Patients with recent history of DVT should be restarted on therapeutic dose LMWH once risk of postoperative bleeding is minimal then conversion to oral warfarin as indicated [21]. Other measures to reduce the risk of DVT include early ambulation (especially for patients not requiring myocutaneous flaps), antiembolic stockings, and sequential compression devices throughout the perioperative period until ambulation.

The moist nature of inguinal region and microorganisms that colonize this region pose increased risk of wound infection following ILND [21]. Rates of wound infection vary from 10 to 16 % with no improvement when comparing old to contemporary series [21–23]. Specific measures to reduce risk of wound infection in the

perioperative period include prophylactic antibiotics to cover groin species: staphylococcus species, diptheroids, and peptostreptococcus. Cellulitis and Infected inguinal lymph nodes should be treated preoperatively by culture-guided antibiotic therapy.

Patient Position

Patient should be in the supine position for most cases. Lithotomy might be indicated if a simultaneous total penectomy is to be performed. The thigh on ipsilateral side is abducted and externally rotated. A pillow is placed under the knee for support and the feet are secured in place at the foot of the bed. Elastic stockings are used in conjunction with sequential compression devices and are placed prior to induction of anesthesia. The surgical prep and draping are performed to expose from the Xiphoid process down to the knees bilaterally as well as both anterior superior iliac spin landmarks laterally (Fig. 5.1).

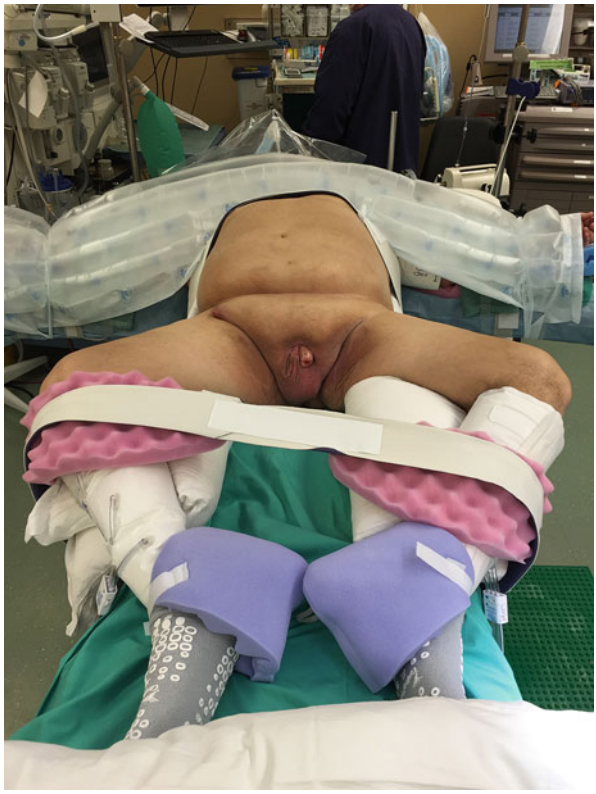

Fig. 5.1 Patient positioning for inguinal lymph node dissection in the setting of clinically positive nodes. Exposure provided for inguinal and pelvic fields of dissection in addition to harvesting myocutaneous flaps if required

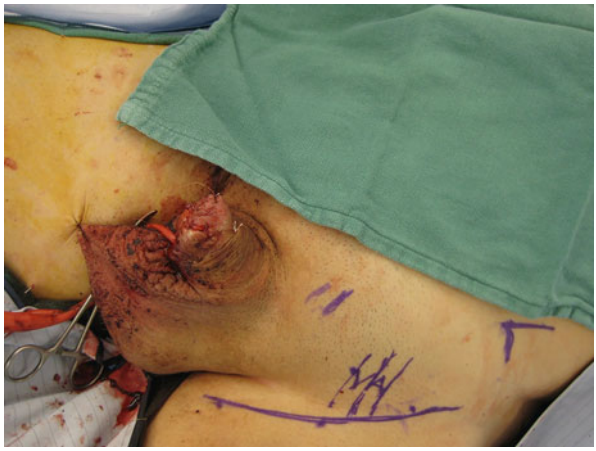

Fig. 5.2 Skin marked for incision prior to inguinal lymphadenectomy

Skin Incision

A Horizontal incision extending medially and laterally two fingerbreadths lateral to and below the pubic tubercle is created for inguinal dissections where the mass does not tent the skin up and there is no ulceration (Fig. 5.2). Alternatively a straight incision extending from the anterior superior iliac spin to pubic tubercle running parallel and 2 cm above the inguinal ligament allows adequate exposure and has been shown to minimize the risk of wound dehiscence and skin necrosis (8 %) [24]. Previously used S and T incisions were associated with higher rates of wound dehiscence and skin necrosis (72 and 82 %, respectively) [25]. If a biopsy was previously obtained, a strip of skin should be excised to include that site. Similarly if the skin is tented up by the mass or skin ulceration is present, the overlying skin should also be excised. Skin flaps should be developed below scarp's fascia and extended to above the level of the spermatic cord and to the level of the apex of the femoral triangle. Meticulous control of subcutaneous lymphatics is essential to reducing the risk of postoperative lymphocele. The edges of skin flaps should be handled gently.

Surgical Boundaries

Clinically Node Positive Inguinal Field

The surgical boundaries of lymphadenectomy field are the lateral border of adductor longus medially, lateral border of Sartorius muscles laterally, spermatic cord superomedially reaching to 2–3 cm above inguinal ligament with inferior border being apex of femoral triangle with complete removal of muscular fascia, skeletonization of the femoral vessels. The saphenous vein may be spared as this has shown to significantly decrease postoperative edema in similar procedures [26, 27] unless there is bulky disease (Fig. 5.3). In this case of minimal palpable disease resection of the muscular fascia was recently omitted in one series with oncologic control maintained and decreased complications rate [28]. During lymphadenectomy dissection lateral to and below the plane of the femoral artery should be avoided in

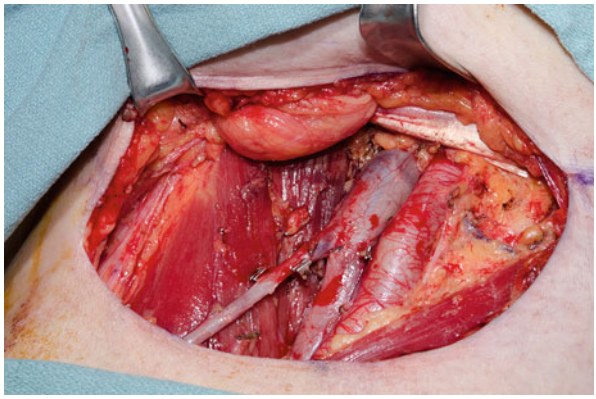

Fig. 5.3 Completed superficial and deep inguinal lymphadenectomy

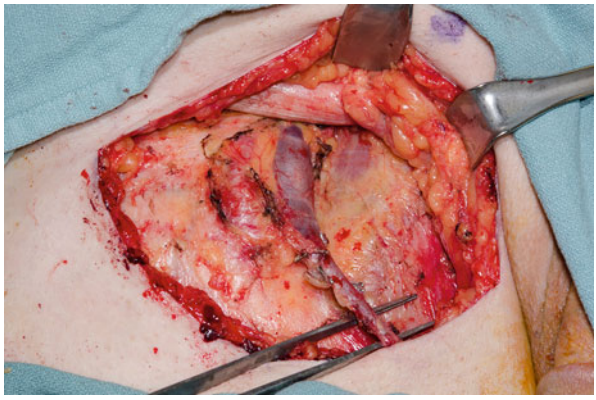

Fig. 5.4 Completed superficial inguinal lymphadenectomy with preservation of the muscular fascia and saphenous vein

order to avoid the motor branches of femoral nerve. Superficial branches of femoral artery supplying traveling through the lymphatic packets to supply the overlying subcutaneous tissue are carefully ligated and divided. After completing lymphadenectomy 1-2 closed suction drain are placed to avoid seroma formation. Recently we have covered drain entry sites with patches impregnated with chlorhexidine in order to prevent drain tract infections [29].

Contralateral Clinically Node Negative Inguinal Field

A superficial inguinal dissection as described by Bevan-Thomas is performed [25]. Lymphatic tissue above the fascia lata of the thigh is removed between the midpoint of the Sartorius and the adductor longus muscles and 2–3 cm above the inguinal ligament superiorly and inferiorly to 2–3 cm above the apex of the femoral triangle. The saphenous vein was dissected from the nodal packet and preserved (Fig. 5.4). Frozen section analysis of lymph nodes is performed and, if metastases are absent,

the procedure is concluded. If metastasis is detected, a complete inguinal dissection is performed. An alternative strategy to stage the clinically negative inguinal field is to perform a dynamic sentinel node biopsy [30] through intradermal, peritumoral injection of a 99mtechnetium-labeled nanocolloid followed by immediate dynamic and static imaging was at 30 min, 90 min, and 2 h. The sentinel node was defined as a node on a direct lymphatic drainage pathway from the primary tumor, and its location(s) were marked on the skin.

Indications for Pelvic Lymph Node Dissection

Pelvic lymphadenectomy is usually preserved for cases with clinically positive pelvic nodes or high-risk pathologically positive inguinal nodes. Given that patients with clinically positive inguinal nodes are at risk to exhibit high-risk pathologic features [9], it is reasonable to perform simultaneous pelvic lymphadenectomy on the ipsilateral side in patients with proven metastases who present with clinically palpable lymph nodes. Lymphadenectomy is usually performed on the ipsilateral side(s) of inguinal nodal metastasis through midline suprapubic incision. In the setting of bilateral inguinal lymph node metastases one recent retrospective study showed that patients with four or more total inguinal nodes were at increased risk for bilateral pelvic metastases and should undergo a bilateral procedure [31]. Given the risk level, we would typically perform a bilateral pelvic dissection among those patients with bilateral inguinal metastases for surgical consolidation as many of these patients would have received neoadjuvant chemotherapy prior to surgery. The boundaries of pelvic lymphadenectomy are the bladder wall medially, genitofemoral nerve laterally, bifurcation of common iliac artery superiorly, and lymph node of Cloquet distally.

Special Consideration for Postchemotherapy Resection of Inguinal Metastases

Surgical Approach and Boundaries

The ultimate goal of neoadjuvant chemotherapy is to improve survival by achieving cytoreduction of metastatic deposits prior to consolidative surgery. Patients who achieve an objective response to systemic therapy are ideal candidates for consolidative surgery. An elliptical skin incision with resection of the area of skin overlying bulky lymph nodes, tumor deposits fixed to the overlying skin, or ulcerated tumors is recommended to ensure complete removal of grossly palpable or visible residual disease with negative surgical margins (Fig. 5.5). Intraoperative frozen sections should be utilized to achieve thus goal. In the setting of bulky disease the saphenous vein and fascia lata are usually resected. Additional procedures occasionally used to ensure local control of advanced disease include excision of the inguinal ligament, spermatic cord and testicle, anterior abdominal wall or femoral vessels with subsequent vein patch or a bypass graft if these structures are grossly invaded by tumor [6].

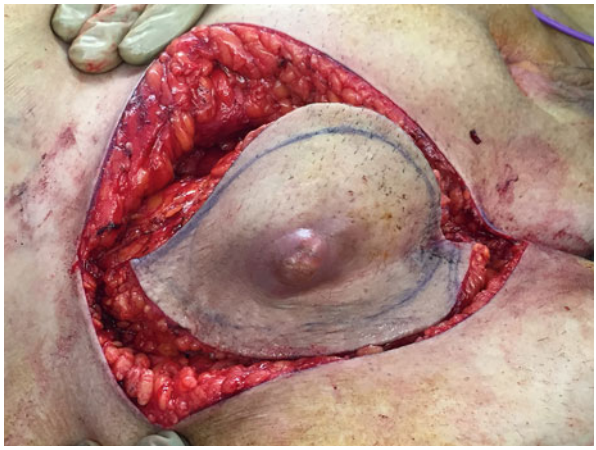

Fig. 5.5 Elliptical incision around mass with initial enbloc resection of skin superficial and deep inguinal nodes subsequent to chemotherapy

Myocutaneous Flap and Skin Graft

Providing coverage to the skeletonized femoral vessels with vascularized muscle flaps along with bridging skin defects without tension are important steps to decrease postoperative morbidity following ILND by providing for rapid wound healing. A Sartorius muscle flap can be used by dividing the Sartorius muscle from anterior superior iliac spine and transposing it to cover femoral vessels. Other options include the vertical rectus abdominis muscle via raising a flap of muscle with or without the overlying ellipse of skin depending on size of skin defect (Fig. 5.6a, b). The anterolateral thigh musculocutaneus flap is another popular alternative for inguinal reconstruction that may be less morbid than the vertical rectus flap.

The above surgical considerations highlight the importance of preoperative planning when considering surgical consolidation among patients with advanced inguinal metastases. Multidisciplinary input from urologic, plastic, and vascular surgical teams helps insure optimal care for these patients.

Postoperative Care

Postoperative care for patients who undergo ILND for penile cancer is of specific importance to maximize quality of life and functional return. Patients with no limitations on activity based on the type of procedure performed should be encouraged to ambulate as early as possible. Support hose and sequential compression devices are utilized as standard along with low-molecular-weight heparin. Based upon the need for rotational muscular flaps certain positions may need to be avoided such as prolonged periods with the hips flexed at 90°. Drains are typically kept until drainage is less than 30–50 cm^3 per 24 h for 2 days after ambulation, and antibiotics are discontinued once all drains are removed. The same principle applies for pelvic drains in the setting of pelvic lymphadenectomy. A physical therapy consult once all

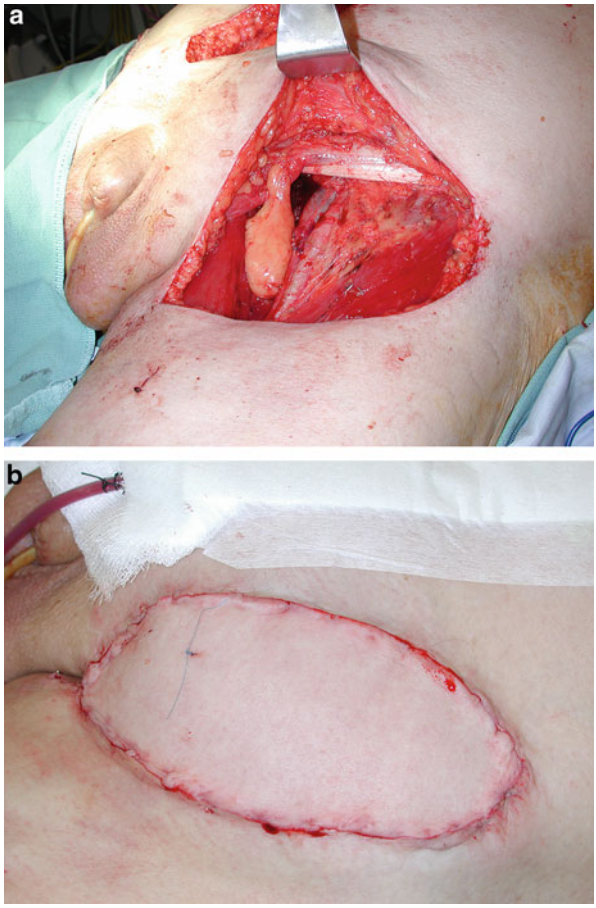

Fig. 5.6 (**a**) Inguinal tissue defect subsequent to postchemotherapy inguinal lymph node dissection. (**b**) Vertical rectus myocutaneous flap reconstruction

drains are removed is helpful to evaluate patients and prescribe specific strategies to prevent lymphedema. Typically patients are measured for fitted stockings and taught massage techniques to reduce the volume of fluid in the extremities. Early prophylactic intervention is preferred to waiting for lymphedema to develop and then subsequent treatment.

Postoperative Complications

Early postoperative complications were reported to be as high as 55.4 % in a recent study which analyzed data from four tertiary referral centers in United States and Europe [32]. However 65.7 % of these complications were deemed minor according to the Clavien-Dindo system. Wound infection (34.8 %) seroma (26.5 %), lymphocele (10.4 %) (requiring no intervention and wound dehiscence (7.2) were the most

frequent minor complications while wound infection (requiring iv antibiotic) (22.1 %), skin flap necrosis (12.7 %), lymphocele (requiring intervention) (3.3), and no-healing wound (2.2 %) were the most frequent major complications. In multivariate analysis number of lymph nodes removed was an independent predictor of experiencing any complication, while the median number of lymph nodes removed was an independent predictor of major complications. The American Joint Committee on Cancer stage was an independent predictor of all wound infections. While the patient's age, ILND with Sartorius flap transposition, and surgery performed before the year 2008 were independent predictors of major wound infections.

Early and late postoperative complications for patients who received chemotherapy and underwent subsequent lymphadenectomy were previously reported [13]. It shows that the procedure was well tolerated among patients who underwent protocol-driven surgery. In another study Major and minor complications were both significantly lower in prophylactic/therapeutic lymphadenectomy versus palliative lymphadenectomy [24]. Spiess et al. reviewed several series and recommended several strategies to minimize postoperative complications [21].

Conclusions

The likelihood of cure among patients with palpable inguinal lymph node metastasis with surgery alone is low. This is due to the higher risk for adverse pathologic findings at surgery. Therefore careful risk stratification utilizing physical examination and imaging should be performed to identify patients who might benefit from neoadjuvant chemotherapy versus those patients who should proceed straight to surgery. The optimal integration of multimodal therapeutic strategies awaits accrual to and analysis of the International Penile Advanced Cancer Trial (InPACT). This unique study will provide objective evidence for the role Neo adjuvant therapy versus surgery alone for patients with clinically positive inguinal nodes in addition to providing clarity on the role of pelvic lymphadenectomy among patients with adverse inguinal node findings at surgery [33]. Experience has shown that there is no substitute for thoughtful preoperative planning, maintenance of oncologic principles during surgery, and attentive postoperative care in the optimal management of patients that present with clinically positive inguinal adenopathy.

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Minimally Invasive Surgical Approaches to Inguinal Nodes in the Absence of Palpable Adenopathy

6

Amar P. Patel and Viraj Master

Introduction

Malignancies of the genitals, skin of the trunk, and lower extremities can metastasize to lymph nodes in the groin. In many of these malignancies, groin lymphadenectomy is believed to be diagnostic as well as therapeutic mainly due to a prolonged loco-regional phase of disease [1, 2]. Groin lymphadenectomy is indicated in penile cancer for palpable lymphadenopathy as well as for non-palpable lymph nodes in patients with high-risk features of localized disease (≥pT2, vascular invasion, poorly differentiated histology). The major dilemma in penile cancer is that significant lymphatic spread is mostly diagnosed when there is palpable disease. Nonetheless, there is still potential for lymphatic spread and micrometastases.

Several studies have shown high morbidity rates with traditional surgical approaches. The complication rate of open groin lymphadenectomy has been reported from 50 to 100 % [3, 4]. Higher complication rates make the open approach a challenge to the surgeon managing the patient and may also discourage both patients and physicians from undergoing a vital part of their treatment. However, the use of minimally invasive endoscopic techniques may represent a favorable approach to treat patients with penile cancer and decrease post-surgical morbidity. In this chapter, we will review both imaging and minimally invasive surgical approaches to diagnosing and treating patients with penile cancer in the absence of inguinal lymphadenopathy.

Bishoff et al. originally reported the attempted use of endoscopy in groin dissection, but had to convert to open, in one patient after confirmation of feasibility in a cadaver model in 2003. Further endoscopic approaches were not described in the literature until 2006 by Tobias-Machado et al. [5] and Sotelo et al. [6] from South America.

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Surgical Technique

Mimicking open surgery, the dissection of superficial and deep inguinal node groups is undertaken. The femoral triangle encompassing the anatomic boundaries that define the extension are the Sartorius muscle (lateral border), the adductor longus muscle (medial border), and the inguinal ligament and spermatic cord (superior border) (Fig. 6.1).

Video Endoscopic Inguinal Lymphadenectomy

Patient Preparation and Position

The risks and benefits of groin dissection, particularly the risks of lymphocele, prolonged lymphorrhea, blood clot, permanent leg swelling, neuromuscular damage, bleeding, and the potential inability to remove all inguinal lymph nodes should be discussed with all patients in detail. Given the relative novelty of this procedure, some of the risks may not be clearly anticipated.

Routine perioperative antibiotics should be administered. The patient is then positioned in a frog-leg fashion on a regular table, with the knee supported with small towels. Pay attention to the knee supports to ensure they are not obstructing port placement, especially medially. Later patients are positioned on a split-leg table (Fig. 6.2). Before prepping and draping, the boundaries of the femoral triangle are drawn. This is an inverted triangle, where the base is a line that is drawn from the anterior superior iliac spine to the pubic tubercle, tracing the course of the inguinal ligament. The lateral boundary is the sartorius muscle angling toward the apex. The medial boundary is the adductor longus muscle,

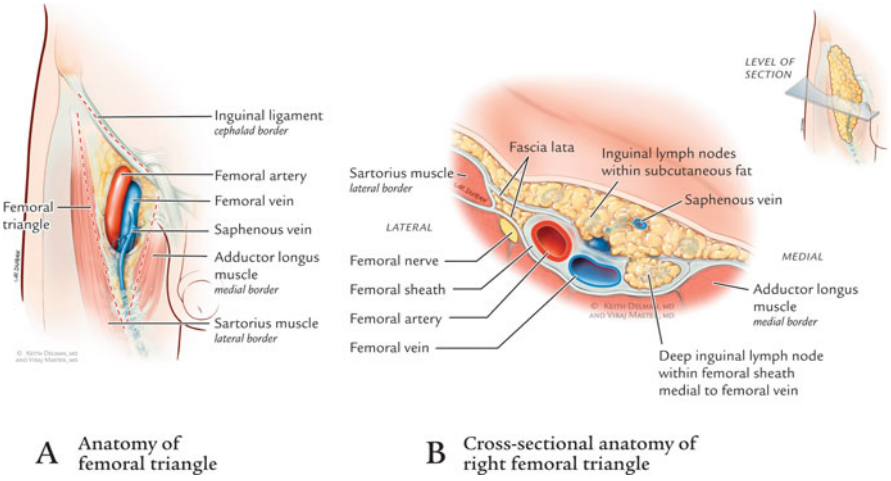


Fig. 6.1 The femoral triangle. (**a**) Anatomy of femoral triangle. (**b**) Cross-sectional anatomy of right femoral triangle

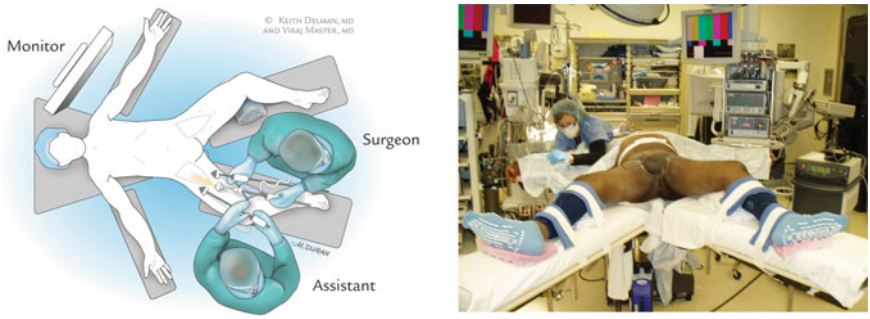


Fig. 6.2 Positioning. (**a**) Surgeon positioning in operating room. (**b**) Patient positioning with split-leg table

again extending toward the apex. These marks both aid in the correct placement of trocars as well as in determining the extent of dissection. Prepping was via standard techniques, including preparation of the suprapubic skin so that the development of crepitus could be monitored.

Room Setup

On a split-leg table, the surgical assistant should stand on the lateral side of the leg and the surgeon medially in between the patient's legs. There is no difference in setup between left and right dissections. Monitors are placed at the shoulders on either side of the patient. Bilateral procedures can be done simultaneously by two teams [7].

Trocar Placement

The first incision is made 3 cm inferior to the apex of the femoral triangle. A 12-mm incision is made through skin, Camper's fascia, and, importantly, above Scarpa's fascia. In many patients, the classic teaching of a 5-mm thickness is unreliable and, instead, the presence of a white layer is the identifying landmark for Scarpa's fascia. At this point, a finger is used to develop the potential space ideally above Scarpa's fascia in the plane traditionally utilized to develop flaps in an open procedure. This is carried out to the extent of at least 5 cm on either side of the initial skin incision. The initial finger dissection is a critical maneuver as it allowed one to rapidly and safely establish a working space with minimal blood loss. It is important to note that, with experience, the avascular plane is easily located and palpably different, reassuring the surgeon that he or she is in the appropriate space.

Once complete, the 12-mm Origin balloon port trocar (Origin Medsystems Inc, Menlo Park, CA, USA) is inserted and patient pressure is set at 25 mmHg for 10 min. The high pressure aids in rapidly establishing a working space. A zero-degree 10-mm laparoscope is then inserted. Next, two 10-mm Ethicon Endopath Bladeless trocars are placed, separated about a hands' breadth from the visualizing port (Fig. 6.3).

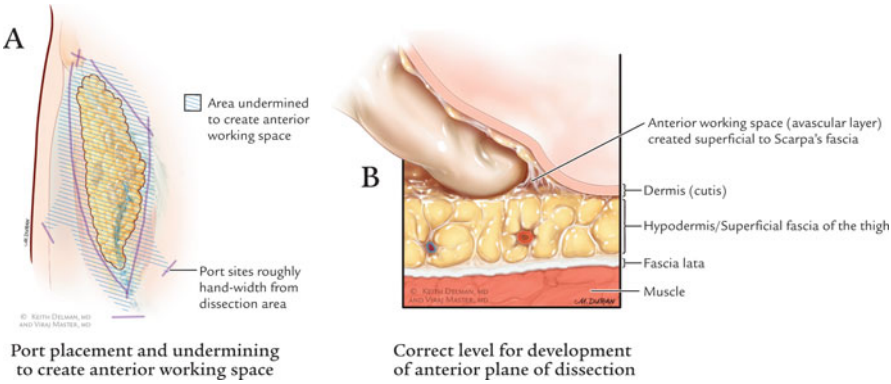


Fig. 6.3 (**a**) Port placement and undermining to create anterior working space. (**b**) Correct level for development of anterior plane of dissection

Insuring dissection in the correct plane is the single most crucial aspect of the procedure. In addition to the digital manipulation described above, endoscopic visual cues such as the anterior clear glistening layer of Scarpa's fascia being part of the dissection aids in the identification of the correct plane of dissection. If one is too thin on the dermis, the delicate tracery of blood vessels easily appreciated through the illumination of the scope, will vanish, and potentially result in skin necrosis. Dissection is initiated using the harmonic scalpel (Ethicon Endosurgery, Cincinnati, OH, USA) or Ligasure Device (Medtronic, Minneapolis, MN, USA). The assistant operates the camera.

Anterior Working Space

Initially, every effort is made to completely develop the anterior working space to the inguinal ligament. The inguinal ligament is usually identified at the end of this dissection as being a transverse structure with white fibers. An Endo-Kittner (Ethicon Endosurgery, Cincinnati, OH, USA) is helpful in verifying identification of the extent of dissection by gently palpating against the firm inguinal ligament.

Medial and Lateral Boundaries

Identification of the adductor longus and sartorius muscles is done by identifying the fascia of the respective muscles and correlating the transillumination to the prior skin markings. Once the dissection is started and the fascia lata is incised, so as to make it easy to 'roll' the packet. Inadvertent dissection deep to the fascia lata is apparent when reddish muscular fibers appear. With blunt dissection, the node packet can be rolled inward bilaterally. This maneuver is continued superiorly and inferiorly as much as possible to define the posterior tail of the node packet. Small perforating vessels are observed, more frequently on the lateral (sartorius) side than the medial (adductor) side, and are controlled with the harmonic scalpel. Lymph vessels are also sealed with the harmonic scalpel (Fig. 6.4).

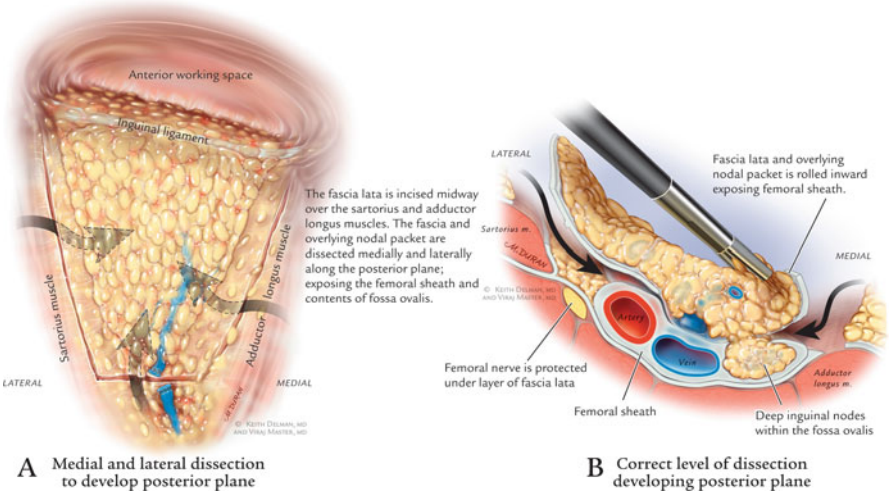


Fig. 6.4 (**a**) Medial and lateral dissection to develop posterior plane. (**b**) Correct level of dissection developing posterior plane

Posterior Packet Division and Saphenous Vein Division

Many times, the saphenous vein can be visualized at the apex of the femoral triangle. In cases where it is not visible, the entire posterior packet is dissected from where one could visualize the sartorius and adductor muscles coming together. We routinely divided the saphenous vein with an endovascular stapler (EndoGIA 35-mm stapler, 2.5-mm staples) (Fig. 6.5) and then the harmonic scalpel was used to complete the dissection at the apex of the femoral triangle. It is also technically feasible to dissect and spare this saphenous vein. The packet is then bluntly dissected off the muscles with a rolled gauze sponge. This dissection continues to the fossa ovalis (Fig. 6.6).

Fossa Ovalis

Once the fossa ovalis is encountered, the packet is dissected away at its superolateral and superomedial limits, thereby narrowing the packet and pulling it away from the inguinal ligament. At this point, every effort is made to sight characteristic palpations of the femoral artery by means of visualization and palpation with the Hunter grasper as well as blunt dissection with the Endo-Kittner. Laparoscopic ultrasound may be used when the vessels are very scarred, for example, after invasive cardiology procedures. Dissection is carried out deep to the fascia lata overlying the femoral vessels. Dissection further lateral to the femoral artery risks injury to the femoral nerve, and, given the location of the nodal tissue in the groin, is not indicated.

Saphenofemoral Vein Dissection and Transection

After the anterior surface of the artery is cleaned off, the use of blunt dissection and small incision with the Harmonic scalpel or Ligasure is made until the inferior edge of the saphenous vein is identified as it entered into the femoral vein (i.e., the

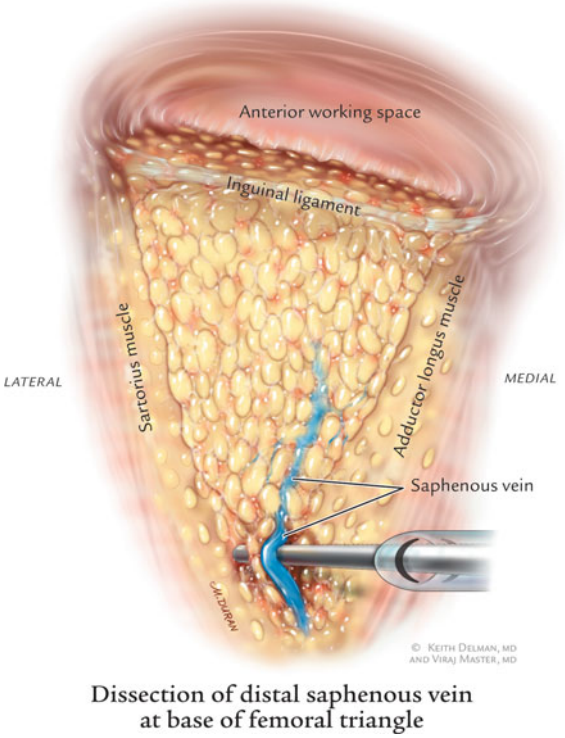


Fig. 6.5 Dissection of distal saphenous vein at the base of femoral triangle

saphenofemoral junction). A right-angle dissector and Hunter grasper are used to dissect out the entire saphenofemoral junction. An endovascular stapler is used to transect at this junction. It is important to remember that this insertion is often longer than anticipated and that dissection should proceed meticulously until this is clearly visualized. During the exposure of the saphenofemoral junction, inferomedial dissection around the femoral vein will enable resection of the deep inguinal nodes [8]. This should be continued to the level of the femoral canal and until the pectineus muscle is seen to insure complete nodal retrieval (Fig. 6.7).

Dissection Along the Inguinal Ligament

At this point, some fascial attachments to the inguinal ligament may remain, depending on the initial extent of the anterior dissection. To completely separate the nodal packet requires manipulation of the tissue inferiorly or medially and laterally. This maneuver provides visualization to achieve either a blunt dissection of the tissue off the fascia or, in some cases, dissection of the tissue from the inguinal ligament using the harmonic scalpel or ligasure.

Removal of the Packet and Drain Placement

After the packet is freed, it is placed into an Endocatch bag and withdrawn from the visualizing port. Many times the packet is quite large, and the extraction site needs

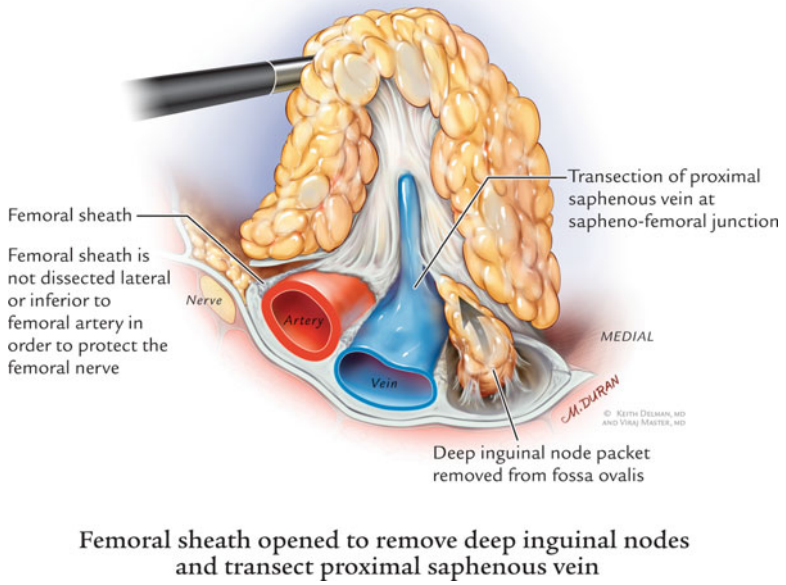


Fig. 6.6 Femoral sheath opened to remove deep inguinal nodes and transect proximal saphenous vein

to be extended, but usually only by a few millimeters (Fig. 6.8). Finally, the procedure is concluded with placement of a 19-French full-fluted drain, placed through the most lateral port and skin closure (Fig. 6.9). The patient is allowed to ambulate the day of surgery and start a regular diet. Discharge of the patient takes place the day after surgery, unless concomitant pelvic node dissection is performed. The drain stays in place until output is <50/mL per 24-h period. Patients were given elastic compression stockings to be worn for several weeks. Antibiotics are not administered after the patient is discharged.

Robot-Assisted Video Endoscopic Inguinal Lymphadenectomy

The concept and surgical technique associated with R-VEIL is similar to that described above. Robotic technologies allow for three-dimensional optics, enhanced magnification, and a more ergonomic platform. It also allows for greater precision, dexterity, and degrees of freedom than that attainable using standard laparoscopic instruments, but the surgeon does lose the ability to check on the presence of blood vessels in the skin to ascertain appropriate thickness of the flap. Since 2007 there have been several cases reported of EIL assisted by robot [9–12]. The results of a phase I prospective study on patients with cancer of the penis T1-3N0 have recently

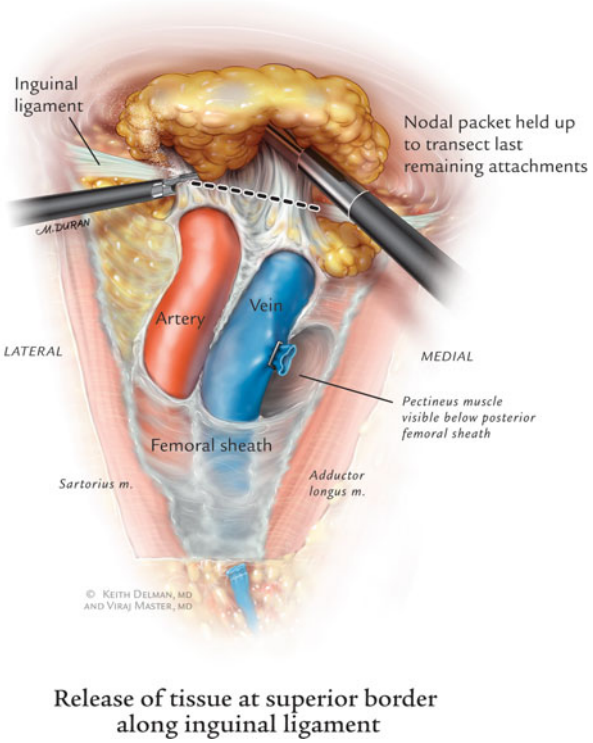


Fig. 6.7 Release of tissue at superior border along inguinal ligament

been published, concluding that robotic inguinal dissection is acceptable and should continue with the next phase to formally determine the incidence and types of complications, as well as the long-term oncological effectiveness [11].

Single-Site Video Endoscopic Inguinal Lymphadenectomy

Laparo-endoscopic single-site (LESS) surgery is the result of natural evolution of standard laparoscopy. Instead of multiple incision, LESS aims to achieve similar surgical outcomes with a single incision while reducing post-operative complications and pain with better cosmetic results.

This was first described in a case report by Tobias-Machado [13]. Recently, Yuan and colleagues [14] prospectively evaluate a total of 12 patients with squamous cell carcinoma of the penis who underwent penectomy. All 12 patients underwent bilateral inguinal lymphadenectomy (LESS inguinal lymphadenectomy in one limb and conventional endoscopic inguinal lymphadenectomy in the other) with preservation of the saphenous vein. All lymphatic tissue in the boundaries of the adductor longus muscle (medially), the sartorius muscle (laterally), 2 cm above the inguinal ligament (superiorly), the Scarpa fascia (superficially),

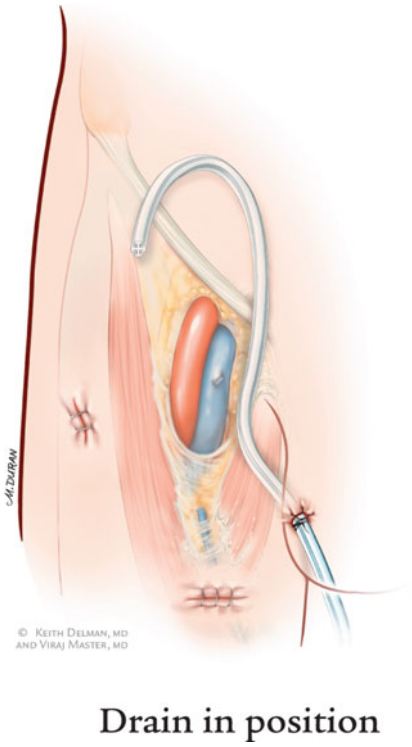
Fig. 6.8 Nodal packet is placed in endoscopic specimen retrieval bag and removed en bloc through the 12-mm apical port site

and femoral vessels (deeply) were removed in both surgical techniques. Intraoperative data and post-operative outcomes (operating time, complications, number of nodes, etc.) were similar between both groups.

Saphenous Vein Sparing

In 1988, Catalona first described the modified inguinal lymphadenectomy for penile cancer with the preservation of the saphenous vein [15], and a smaller template of dissection. Since then several studies have evaluated the outcomes of sparing the saphenous vein in patients undergoing inguinal lymphadenectomy. A retrospective study analyzed the outcomes of a 139 dissections in 83 patients where the saphenous vein was preserved in 62 and ligated in 77 patients. Cellulitis occurred in 39 % of the patients who underwent vein ligation compared with 18 % of the patients who underwent a vein-sparing procedure ($P = 0.006$). Short-term (<6 months) lower extremity lymphedema occurred in 70 % of the vein-ligated group compared with 32 % of the vein-spared group ($P < 0.001$). Chronic edema (>2 years) was present in only 3 % of the patients who underwent saphenous vein preservation compared

Fig. 6.9 Drain in position



with 32 % of those who underwent vein ligation ($P = 0.003$). Overall, individuals with preservation of the saphenous vein were less likely to develop complications (56 % vs. 23 %; $P < 0.001$). There was no difference in the rate of incidence of recurrent disease between the two groups [16]. A recent meta-analysis also showed significant reduction in lymphedema (odds ratio 0.24, 95 % CI 0.11–0.53) and other complications of inguinal node dissection when the saphenous vein was spared [17]. Overall, it appears that many contemporary series attempt to spare the saphenous vein when able during inguinal node dissections.

Complications and Morbidity

Current results in the literature suggest that the minimally invasive VEIL techniques have a great potential in decreasing post-operative morbidity previously seen with the open approach. The most common complications reported from open lymphadenectomy are skin infections, deep venous thrombosis, seroma, edema, and lymphoceles [18]. In several studies, cutaneous and overall morbidity is less frequent in patients undergoing VEIL than open procedure. Other added benefits of VEIL include earlier discharge from the hospital, faster return to daily activities, and better cosmesis.

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7 Pelvic Lymph Node Dissection for Penile Cancer: Answering the Conundrum of When and How It Should Be Conducted

Pranav Sharma, Kamran Zargar-Shoshtari, Homayoun Zargar, and Philippe E. Spiess

Introduction

The survival of high-risk patients with penile carcinoma is highly dependent on the extent of loco-regional metastatic lymphatic nodal spread [1]. The progression of metastatic lymphatic spread follows a typical pattern that is easily predictable based on clinical, imaging, and histopathological criteria [2, 3].

From the primary penile lesion, lymphatic nodal spread can be unilateral or bilateral to the inguinal LNs in the groin [3]. After inguinal metastasis, lymphatic spread proceeds to the pelvic LNs (obturator, external iliac, and internal iliac nodal packets) prior to further systemic disease progression [2]. Skip lesions in penile carcinoma have never been reported to date. Both direct metastatic spread from the primary penile tumor to the pelvic LNs as well as from the groin to the contralateral pelvic nodal packet have never been described in the literature. Additionally, crossover nodal metastasis from the right to left pelvis or left to right pelvis has never been demonstrated. Positive pelvic nodal disease, therefore, typically only seems to occur in the presence of ipsilateral inguinal metastatic spread [4].

It has been estimated that 20–30 % of patients with inguinal nodal disease will also have metastatic lymphatic spread to the pelvic LNs [5]. Patients with pelvic

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node-positive metastasis have a generally poor survival, especially when compared to patients with disease only in the inguinal LNs, with an average 5-year overall survival (OS) of 10 % [6].

Lughezzani et al. reported that the prevalence of positive pelvic LNs was found to be less than 5 % in patients who had only one positive inguinal metastatic site, 23 % in patients with two positive inguinal metastatic sites, and 56 % in patients with three positive inguinal metastatic sites or extranodal extension (ENE) in at least one inguinal LN [7]. The authors reported that there were three significant variables independently predictive of pelvic nodal disease including: inguinal ENE, ≥3 inguinal sites of metastatic disease, and an inguinal nodal diameter ≥3 cm [7]. The cancer-specific survival (CSS) rate of patients with pelvic nodal disease at 5 years was 33 % versus 71 % in patients without pelvic nodal disease.

Pelvic lymph node dissection (PLND), therefore, is recommended for penile carcinoma patients with ≥2 positive inguinal LNs or in the setting of inguinal ENE (pN3) due to a higher risk of pelvic nodal involvement [7, 8]. Early PLND in patients with micro-metastatic pelvic nodal disease may result in some sustained, long-term recurrence-free survival outcomes in a small percentage of patients (16–20 %) [9].

PLND can be done during the same operative setting (with use of intraoperative frozen section) as inguinal lymphadenectomy or in a delayed fashion through an open midline, infraumbilical, extraperitoneal approach [10]. Since no crossover from inguinal to pelvic LNs has been described, the utilization of unilateral versus bilateral PLND is still considered controversial. There is increasing evidence, however, that bilateral PLND may be appropriate for certain high-risk penile cancer patients with a large volume of inguinal metastatic disease, and that bilateral PLND may improve survival-related outcomes in this setting [11, 12].

For penile cancer patients with clinically enlarged pelvic LNs on cross-sectional imaging with CT, MRI, or PET-CT (cN3), neoadjuvant systemic chemotherapy is recommended due to the high risk of systemic micro-metastatic disease. Post-chemotherapy inguinal and pelvic lymph node dissection (LND) may be considered for surgical consolidation in appropriately selected patients who were clinical responders to systemic therapy [13].

Indications

PLND should ideally be offered to penile cancer patients at high risk for pelvic nodal disease. Recent advances in imaging have also improved the ability to clinically detect micro-metastatic disease in the pelvic LNs. Leijte et al. evaluated the diagnostic accuracy of 18F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) to identify micro-metastatic involvement of the pelvic LNs in 18 patients with unilateral or bilateral inguinal LN positive disease on cytological assessment [14]. Ten of 11 tumor-positive pelvic nodal packets were correctly predicted by PET-CT scan (sensitivity 91 %) as were all 17 tumor-negative

Table 7.1 Studies evaluating survival of pelvic node positive penile cancer patients

Study	*N*	OS	CSS	Follow-up (months)
Lont et al. [6]	25	5-year: 10 %	–	85
Liu et al. [5]	33	3-year: 12.1 %	–	42
Lughezzani et al. [7]	45	–	5-year: 33.2 %	51
Djajadiningrat et al. [9]	19	–	5-year: 17 %	59
Sharma et al. [26]	84	Median: 13.9 months	–	12.1
Zargar-Shoshtari et al. [12]	51	Median: 14.0 months	–	13.3

pelvic nodal packets (specificity 100 %). Four of five patients with positive distant metastasis on PET-CT had pathologically confirmed M1 disease (sensitivity 75 %). The study, therefore, suggested that 18F-FDG PET-CT could be beneficial in the routine clinical staging for inguinal node positive penile cancer patients to detect further disease progression systemically as well as in the pelvis.

Several studies have also studied criteria in penile squamous cell carcinoma (SCC) predictive of the presence of pelvic nodal disease and its associated survival (Table 7.1). Liu et al. evaluated 146 patients with SCC of the penis who underwent bilateral ILND with or without PLND between January 1998 and April 2011 [5]. Seventy patients had inguinal LN metastasis and 33 (47.1 %) had pelvic LN metastasis. Factors associated with pelvic nodal disease included: high p53 immunoreactivity in the primary penile tumor, the presence of lymphovascular invasion (LVI) on histology, ≥2 positive inguinal metastatic sites, and a positive nodal density ≥30 % for disease. Variables associated with worse OS in this study population included: high p53 expression in the primary penile tumor (odds ratio [OR]: 6.0, 95 % confidence interval [CI]: 1.6–22.3), ENE (OR: 2.2, 95 % CI: 1.2–4.2), ≥2 positive inguinal LNs (OR: 2.5, 95 % CI: 1.1–5.7), and presence of pelvic metastatic nodal spread (OR: 18.2, 95 % CI: 6.8–48.7).

Lughezzani et al. similarly analyzed risk factors for the presence of pelvic nodal disease in high-risk penile SCC patients [7]. The authors retrospectively evaluated 142 high-risk penile cancer patients treated at their center with 188 groins that were inguinal LN positive. Patients with ≥3 inguinal LN metastases as well as those with a positive inguinal nodal diameter ≥3 cm were at 4.8- and 2.5-fold increased risk, respectively, of having pelvic nodal metastatic spread ($p < 0.05$). The presence of pelvic LN metastases increased from 0 % in patients with none of the above risk factors to 57 % when all three risk factors were present ($p < 0.05$).

Currently, the National Comprehensive Cancer Network (NCCN)© and European Association of Urology (EAU)© have published guidelines recommending pelvic lymphadenectomy in patients with ≥2 positive inguinal LNs, inguinal ENE, or in the clinical context of high-grade cancer within the inguinal LN pathologic specimen (Fig. 7.1) [15, 16].

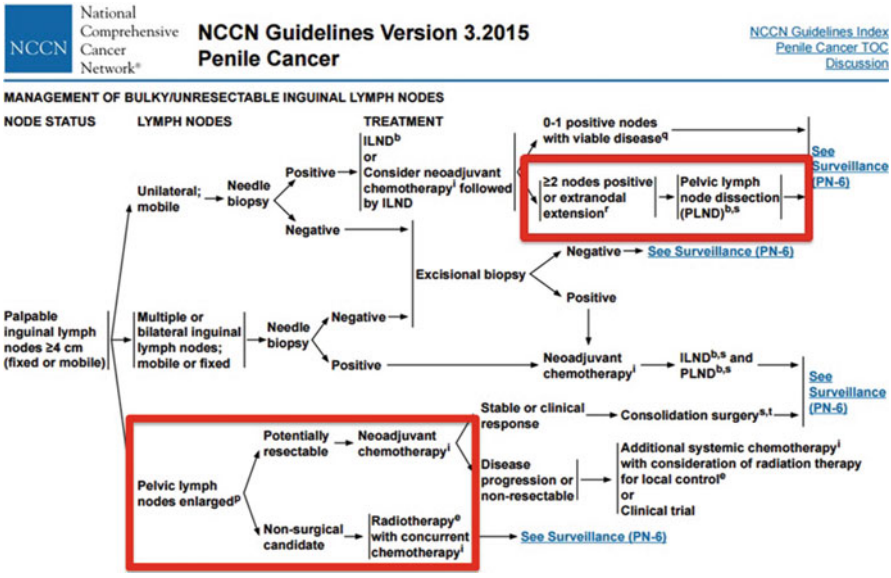

Fig. 7.1 NCCN© penile cancer guidelines for the management of advanced loco-regional nodal disease including pelvic LNs [Reprinted from Clark et al. [36], copyright (2013), with permission from NCCN©]

Surgical Technique

PLND is typically performed through a midline, suprapubic, infraumbilical extraperitoneal incision [17]. Laparoscopic approaches may also be utilized for PLND in order to minimize surgically related morbidity and reduce postoperative complications. The rapid adoption of minimally invasive robotic-assisted surgery can additionally allow for greater accuracy and wrist-motion than traditional laparoscopic instruments due to the magnification and three-dimensional visualization of Da Vinci© technology.

The boundaries of PLND include: superior—common iliac artery and vein bifurcation; lateral—ilioinguinal nerve; and medial—obturator nerve (Fig. 7.2) [9, 12]. During PLND, all nodal tissue is removed from the obturator, internal iliac, and external iliac packets, and any enlarged LNs in the pelvis should also be excised. Meticulous hemostasis during PLND must be achieved to prevent excess venous bleeding and development of a pelvic hematoma [10]. Additionally, ligation or clipping of lymphatic channels is of the utmost importance during PLND to prevent the occurrence of a pelvic lymphocele during the postoperative period.

PLND can be done at the same time as inguinal lymph node dissection (ILND) or in a delayed fashion since there is very little evidence to suggest that the timing of PLND in relation to ILND affects clinical outcomes. Currently, PLND is typically performed in a unilateral fashion since no crossover effect

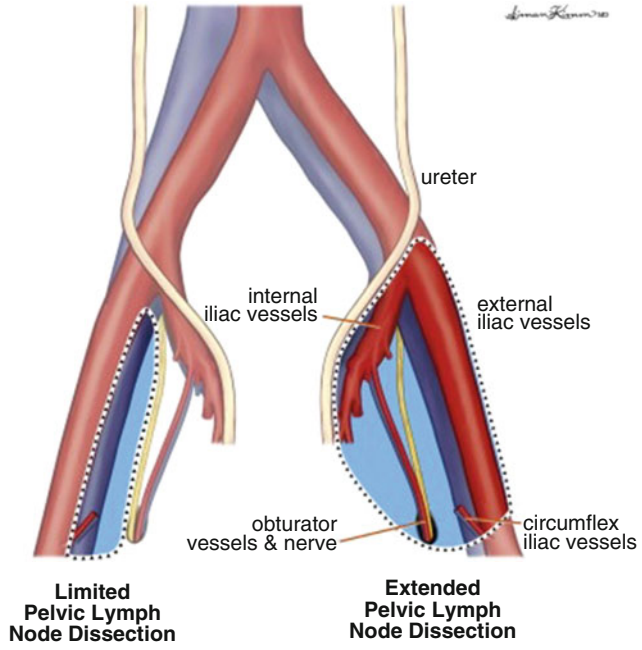

Fig. 7.2 Template for boundaries of dissection during PLND for high-risk penile cancer [Reprinted from Yuh et al. [37], copyright (2014), with permission from Elsevier]

has been reported in penile cancer from the inguinal to pelvic LNs, but bilateral PLND may be indicated for bilateral inguinal metastatic disease.

Unilateral Versus Bilateral PLND

Most current recommendations would suggest unilateral PLND in patients with unilateral inguinal LN metastasis. Although bilateral pelvic lymphatic metastatic spread is theoretically possible, it is extremely rare and associated with very poor survival-related outcomes.

One area of controversy is whether the PLND should be performed ipsilaterally or bilaterally in patients with unilateral positive inguinal metastatic disease. Since crossover (right to left or left to right) of inguinal to pelvic nodes has not been well studied, unilateral or bilateral PLND are both feasible approaches and left at the discretion of the surgeon based on case-specific characteristics.

Zargar-Shoshtari et al. retrospectively analyzed 51 men with penile SCC and unilateral inguinal node-positive disease with pelvic LN metastatic disease after ILND and PLND across four international centers of excellence [12]. Thirty-eight men (75 %) in the study population had a unilateral pelvic lymphadenectomy, and 13 (25 %) had bilateral pelvic lymphadenectomy. Patients who underwent unilateral versus bilateral PLND were similar with respect to clinicodemographic criteria,

disease-specific characteristics, and utilization of multimodal therapy. Penile cancer patients who underwent bilateral PLND had a statistically significant better estimated median OS compared to those who underwent unilateral PLND (21.7 vs. 13.1, $p=0.05$). On multivariate analysis, bilateral PLND [HR: 0.25, (95 % CI: 0.10–0.64)], multiple positive pelvic nodes [HR: 2.12 (95 % CI: 1.02–4.43)], use of neoadjuvant chemotherapy [HR: 0.01, (95 % CI: 0.02–0.44)], and use of adjuvant systemic therapy and/or radiation therapy (compared to surveillance) [HR: 0.16, (95 % CI: 0.06–0.45)] were independently associated with better OS. These findings suggest that men with pelvic node positive penile carcinoma may have improved long-term outcomes from a bilateral PLND.

Zargar-Shostari et al. also evaluated risk factors for bilateral pelvic metastatic lymphatic disease in penile cancer patients with positive inguinal LNs [11]. Sixty-four patients with pelvic node positive disease who underwent bilateral pelvic lymphadenectomy and had positive bilateral inguinal LNs were included for analysis. Bilateral pelvic node positive disease was found in 16 patients (25 %). The detection of four or more positive inguinal LNs had a 95 % sensitivity to predict bilateral pelvic nodal metastasis on final pathology (area under receiver operating characteristic [ROC] curve of 0.76; $p<0.05$). Additionally, on multivariate analysis, ≥4 positive inguinal LNs was the only statistically significant predictor of bilateral pelvic LN metastasis (OR: 14.0, 95 % CI: 1.7–115). Variables independently associated with OS included ≥4 positive inguinal LNs, use of adjuvant chemotherapy, inguinal ENE, and a bilateral pelvic lymphadenectomy. These findings were used to establish criteria for bilateral PLND in patients with high-volume inguinal metastatic lymphatic spread (Fig. 7.3). The authors concluded that for patients with bilateral inguinal metastatic lymphatic spread and ≥4 positive inguinal LNs, bilateral PLND should be considered due to a higher risk of bilateral pelvic node positive disease and improved survival.

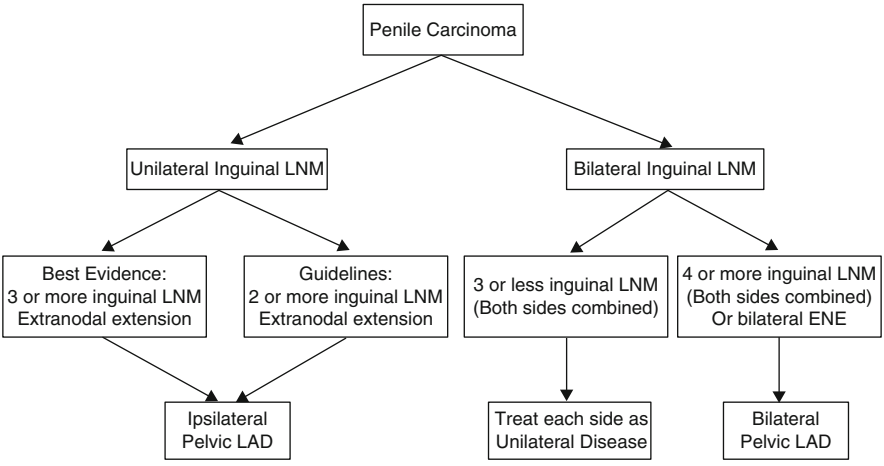

Fig. 7.3 Proposed algorithm to manage high-volume inguinal metastatic nodal disease with unilateral versus bilateral PLND [Reprinted from Zargar-Shoshtari et al. [11], copyright (2015), with permission from Elsevier]

Systemic Therapy for Pelvic Nodal Disease

Although surgery alone may cure a small percentage of high-risk penile cancer patients with micro-metastatic pelvic LN disease (16–20 %), recurrence is very common, and patients may have an overall poor prognosis with a low 5-year OS rate. Patient with pelvic node positive disease, therefore, may benefit from additional systemic chemotherapy due to the high risk of microscopic systemic spread [1, 18].

Adjuvant chemotherapy is recommended by the NCCN© and EAU© for pN2 and pN3 penile SCC based on evidence from well-designed case–control and cohort studies as well as evidence from descriptive and qualitative studies (Table 7.2) [19–22]. Pizzocaro et al. reported that 12 weekly cycles of adjuvant vinblastine, bleomycin, and methotrexate in 25 inguinal node positive patients resulted in a better overall disease-free survival (DFS) rate compared to 38 inguinal node positive patients that did not receive any chemotherapy (84 % vs. 39 %, $p < 0.05$) [23]. The authors also showed that treatment of 19 inguinal node positive penile cancer patients with three to four cycles of adjuvant docetaxel, cisplatin, and 5-fluorouracil resulted in a 52.6 % DFS rate at a median follow-up of 42 months [15]. Noronha et al. used an alternative regimen of four cycles of adjuvant cisplatin and paclitaxel at 21-day intervals in 19 patients with penile SCC and pN2/N3 disease, and they reported a sustained increase in DFS compared to the control arm of pN2/N3 patients who were just monitored with surveillance (23.1 vs. 2.2 months, $p < 0.05$) [24].

Houédé et al. analyzed response rates after induction chemotherapy with six cycles of gemcitabine and cisplatin in 25 penile cancer patients with locally advanced, unresectable lymphadenopathy in the pelvis and groin and/or systemic metastatic disease [25]. In this non-randomized, phase II trial, the primary endpoint included the objective response rate with second endpoints of time to progression (TTP), OS, and side effects related to this treatment regimen. Only 6 of 25 patients (24 %) were able to complete the full induction course of chemotherapy. Treatment was stopped in six patients (24 %) because of a severe (grade 3 or 4) toxicity profile with intolerable adverse effects. The overall objective partial or complete response rate was 8 % ($n = 2$). Thirteen patients (56.5 %) had stable disease after intention-to-treat analysis on follow-up imaging, and eight patients (34.8 %) had progression of their penile SCC. With regards to secondary endpoints, the estimated median TTP was 5.5 months, estimated median OS was 15 months, and estimated 2-year OS in the study population was 39 %.

Table 7.2 Adjuvant chemotherapy studies in node-positive penile cancer

Study	Regimen (cycles)	*N*	Follow-up (months)
Maiche et al. [20]	Bleomycin	19	–
Pizzocaro et al. [23]	VBM × 12	12	42
Hakenberg et al. [19]	CMB × 2–6	8	54
Noronha et al. [24]	CP × 4	15	15.3
Giannatempo et al. [13]	TPF × 3–4	19	42

Finally, Sharma et al. retrospectively evaluated the potential benefit of adjuvant chemotherapy in penile SCC patients with metastatic pelvic lymphatic spread after inguinal and pelvic lymphadenectomy [26]. Eight-four chemo-naïve penile cancer patients were identified from four centers of excellence across the world that underwent ILND and PLND from 1978 to 2013 and had positive pelvic nodal disease on final pathology. The median number of positive pelvic nodes in the study population was 2 (interquartile range [IQR]: 4–7), and 10 % of patients had bilateral positive pelvic LNs while 55 % had extracapsular extension (i.e. ENE) in their affected pelvic nodal packets. Adjuvant chemotherapy within 3 months of surgery was used to treat 36 (43 %) patients in the study population although it is unclear how many patients were untreated due to a decline in functional status after surgery.

Patients who were treated with adjuvant chemotherapy were, in general, of younger age, had a less advanced primary penile tumor stage, were less likely to receive postoperative radiation therapy, had a reduced occurrence of bilateral positive inguinal lymphatic metastatic spread, and were at increased risk of having inguinal ENE on histopathological LN examination ($p < 0.05$). Median follow-up in this study was 12.1 months, and estimated median OS in pelvic node positive penile cancer patients was improved in the adjuvant chemotherapy group compared to those who received no additional treatment (21.7 months [IQR: 11.8–104] vs. 10.1 months [IQR: 5.6–48.1]; $p < 0.05$). On multivariate Cox regression survival analysis, use of adjuvant chemotherapy was an independent predictor of better OS in the study population (HR: 0.40; 95 % CI: 0.19–0.87; $p < 0.05$). Adjuvant chemotherapy, therefore, may be beneficial in patients with penile SCC and positive pelvic LNs after inguinal and pelvic lymph node dissection (LND). Larger, prospective, randomized studies, however, are necessary to demonstrate causality in this unique patient cohort.

Neoadjuvant chemotherapy for pelvic node positive patients with penile cancer has been increasingly advocated and utilized due to a higher risk of micrometastatic systemic disease in this setting as well as the overall poor prognosis in clinical non-responders. This recommendation stems from results extrapolated from patients with locally advanced, fixed, unresectable, bulky inguinal nodal disease [27, 28]. Pagliaro et al. conducted a phase II trial of neoadjuvant paclitaxel, ifosfamide, and cisplatin and treated 30 penile SCC patients with pN2/N3 disease [29]. The authors reported an objective partial or complete response rate in 15 (50 %) patients with 9 (30 %) patients who were recurrence-free at a median follow-up of 34 months. Similarly, Dickstein et al. published an objective response rate of 50 % to neoadjuvant chemotherapy in patients with penile carcinoma [30]. The disease-free survival rate was 33 % at a median follow-up of 67 months, and over 40 % were alive at the end of the study. Clinical response to chemotherapy was the strongest predictor of long-term 5-year OS in both of the above studies, suggesting that non-responders should not undergo any further aggressive surgical therapy due to a poor prognosis. Guideline statements regarding neoadjuvant chemotherapy for patients with positive pelvic nodal metastatic spread still cannot be made since high-level evidence with regards to this study question is still not available.

Radiation Therapy for Pelvic Nodal Disease

Utilization of radiation for penile SCC patients with positive pelvic LNs varies across institutions and often follows traditional practice patterns instead of recommendations based on clinical evidence. Literature regarding the role or therapeutic value of radiation therapy in the multimodal management of high-risk penile cancer with loco-regional nodal spread is limited. Regardless, many centers utilize targeted radiation therapy frequently for both treatment of the primary penile tumor as well as for inguinal and pelvic LN metastases.

There are little data that either neoadjuvant or adjuvant radiotherapy can improve survival-related outcomes in inguinal or pelvic node positive penile SCC [31]. To our knowledge, the only prospective trial comparing radiation therapy of the groins with ILND showed better survival with surgery compared to radiation therapy or surveillance alone (5-years OS: 74 % vs. 66 % vs. 63 %, respectively; $p < 0.05$) [32]. Franks et al. also reported poor oncological outcomes in penile cancer patients treated with adjuvant inguinal and/or pelvic radiation therapy after lymphadenectomy [33]. The authors suggested, however, that radiation may have some clinical utility after LND in patients with ENE, in whom historically survival rates have been poor.

Adjuvant radiation therapy after ILND in penile SCC patients with node positive metastatic lymphatic spread has been demonstrated to be far inferior to adjuvant chemotherapy based on institutional cohort studies [34]. By utilizing a large set of clinical data maintained by the National Cancer Institute called Surveillance, Epidemiology, and End Results (SEER) Program database, 2458 patients with penile carcinoma treated with surgery along or surgery in combination with radiotherapy were evaluated in terms of oncological and long-term CSS outcomes [35]. Multivariate analysis showed that the impact of adjuvant radiation therapy on these endpoints was negligible with neither a positive nor negative effect on CSS.

Due to lack of high-level evidence and expert consensus with regards to (1) treatment criteria, (2) standardization of treatment patterns, and (3) appropriate follow-up, radiation therapy for pelvic node positive penile cancer is typically not recommended. Adjuvant inguinal radiotherapy could be useful for local control in selected patients with inguinal or pelvic extracapsular nodal spread or as palliation for fixed, bulky, surgically unresectable LN disease.

Conclusions

PLND is an important component of the management of penile cancer with locally advanced metastatic nodal disease and clinically suspicious pelvic LNs. Although associated with surgical morbidity, it may improve disease-specific survival for select patients in combination with systemic chemotherapy and/or radiation therapy. The timing and extent of PLND is still controversial in penile cancer patients, but future large-scale, prospective, multi-institutional randomized studies such as the International Penile Advanced Cancer Trial (InPACT) may better define the appropriate indications and role of PLND in the multimodal management of this disease (Fig. 7.4).

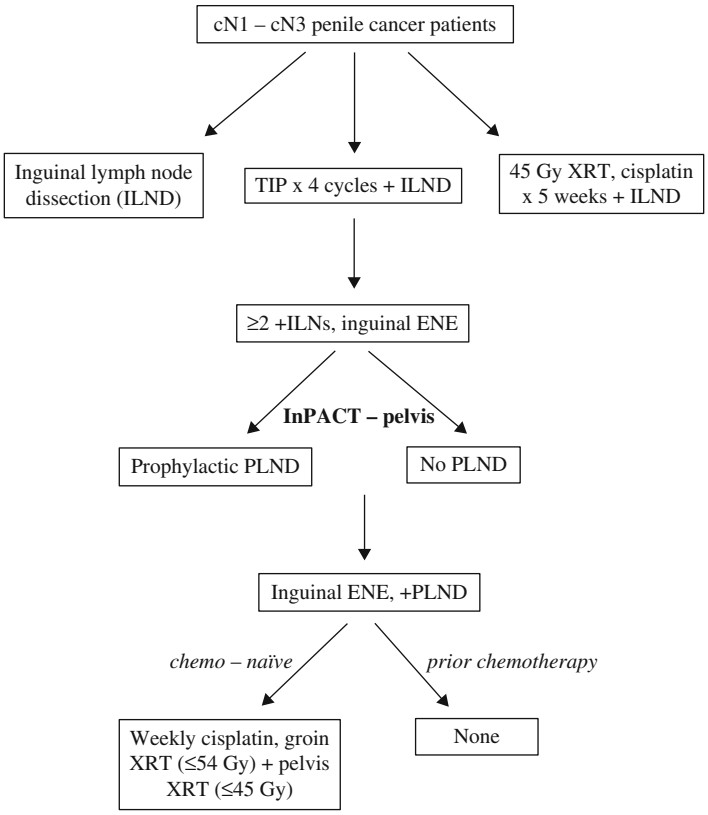

Fig. 7.4 Flow diagram of InPACT (currently in patient recruitment)

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Multimodal Approach to Locally Advanced and Metastatic Penile Cancer

8

Praful Ravi and Lance C. Pagliaro

Introduction

Penile cancer is an extremely rare cancer in the United States, with an estimated 1820 cases and 310 deaths in 2015 [1]. While the majority of cases are diagnosed at a localized stage and carry a good prognosis, up to 40 % of patients present with locally advanced or metastatic disease and outcomes for such patients have historically been poor [2, 3]. Squamous cell carcinoma of the penis classically spreads in an organized loco-regional manner, first to the draining inguinal lymph nodes and then to pelvic nodes, which makes it a candidate for multimodal therapy. Moreover, combined modality therapy in other squamous cell carcinomas, such as head and neck [4], anus [5], or vulva [6], has been proven to be efficacious, prompting further study of the approach in this disease.

However, the rarity of this cancer in the United States and Western Europe has hampered clinical study into the management of locally advanced or metastatic disease, and indeed, there have been no randomized clinical trials in this setting. The majority of data are in the form of either small single- or multi-center retrospective series [7–9], although the past decade has seen emergence of evidence from larger, phase II prospective studies [10–12]. Additionally, it is hoped that global collaboration in the form of the International Rare Cancers Initiative will help accrue sufficient numbers of patients in clinical studies that will provide robust evidence on the multimodal approach to managing this disease.

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Locally Advanced and Regionally Metastatic Penile Cancer

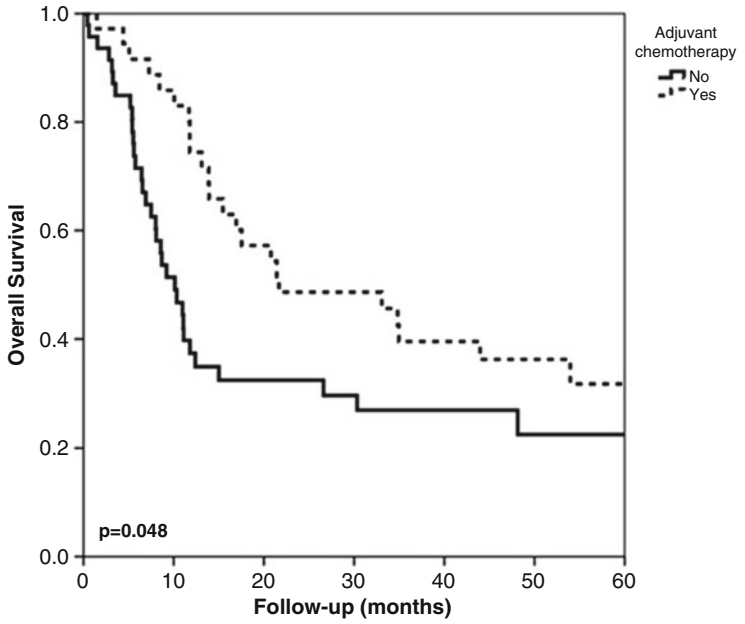
At the time of first presentation, 28–64 % of men with penile cancer will have clinically palpable inguinal lymph nodes, with metastatic disease being the cause in only 47–85 % of such individuals (the remainder are due to inflammatory nodal reaction), and the likelihood of pelvic nodal metastases is 22–56 % if inguinal lymph nodes are involved [13–15]. The presence of inguinal lymph node metastases is the single-most important prognostic factor in penile cancer, with additional prognostic information provided by the number of positive lymph nodes, whether inguinal nodal disease is uni- or bilateral, the presence of pelvic nodal involvement, and if there is extranodal metastatic extension [16]. Even in the absence of clinically palpable inguinal lymph nodes, micrometastatic disease will be present in about 25 % of cases, with tumor stage, grade, and lymphovascular invasion being predictive factors [17].

Role of Adjuvant Chemotherapy in Node-Positive Disease

A multimodal approach may be employed in managing patients who are found to be node-positive after undergoing radical inguinal lymphadenectomy. There is evidence to support the use of adjuvant chemotherapy in men with pN2 or pN3 disease, although the data are all from single- or multi-center retrospective studies and rely on small numbers of patients.

Some of the earliest data to support the role of adjuvant chemotherapy in pathologic node-positive penile cancer came from a pilot study in Milan, Italy, published in the late 1980s [18]. Pizzocaro and Piva reported the outcomes for adjuvant vincristine, bleomycin, and methotrexate (VBM) administered on a weekly basis for 12 weeks, for 12 men who had undergone either uni- or bilateral lymphadenectomy for penile cancer, with 5 also having pelvic nodal disease. After a median follow-up of 42 months, 11 of the 12 men (92 %) were alive and disease-free, with the treatment being largely well tolerated (two cases of bleomycin-induced lung injury). However, more recent data from the same institution evaluating adjuvant cisplatin and 5-fluorouracil in combination with a taxane (either paclitaxel or docetaxel) in 19 men with pN2 or pN3 disease showed less impressive outcomes, with a 2-year disease-free survival of 36.8 % [19]. There was greater toxicity, principally hematologic, with six cases of grade 3 or 4 anemia, neutropenia, or thrombocytopenia. Similar outcomes were also seen in a small retrospective review from Dresden, Germany, which reported on outcomes of adjuvant bleomycin, methotrexate, and cisplatin (BMP) in men with pN1-3 disease [8]. At a mean follow-up of 4.5 years, three of eight men (38 %) were alive and disease-free but there was a treatment-related death arising from bleomycin-induced pulmonary toxicity.

Interestingly, improved outcomes were reported in a retrospective single-center report from Mumbai, India, where adjuvant doublet chemotherapy (either carboplatin or cisplatin in combination with paclitaxel) was administered in 19 men with



Number at risk						
No adj. chemo (n=48)	26	18	17	16	15	15
Yes adj. chemo (n=36)	31	21	18	15	14	13

Fig. 8.1 Overall survival stratified by receipt of adjuvant chemotherapy in chemotherapy-naïve men with pelvic node-positive penile cancer. (Reproduced, with permission from Sharma et al. [21])

"high-risk" locally advanced disease (defined as perinodal extension, bilateral nodal involvement, pelvic node disease, and those with incomplete resections) [20]. Noronha et al. reported a 2-year overall survival of 68 %, after a median of four cycles of chemotherapy, with six men (32 %) suffering a loco-regional relapse at a median follow-up of 15 months, and three deaths, including one treatment-related death due to diarrhea and febrile neutropenia.

The largest series reporting outcomes of adjuvant chemotherapy for penile cancer was published in 2015, and combined data from four tertiary centers in the US, the Netherlands, Italy, and China (the Italian data were from the same Milan center whose data are discussed above) [21]. They reviewed the results of adjuvant chemotherapy in 36 men with positive pelvic lymph nodes (i.e., pN3), the majority (78 %) of whom received platinum-based regimens (most commonly docetaxel, cisplatin, and 5-fluorouracil [TPF]). At a median follow-up of just over 1 year, the median overall survival in men who had been given adjuvant chemotherapy was significantly greater than that observed in 48 men who had not received adjuvant treatment (21.7 months vs. 10.1 months, $p=0.048$; Fig. 8.1). In a multivariate analysis

adjusting for age, pathologic stage, bilaterality of nodal disease, and delayed pelvic surgery, receipt of adjuvant chemotherapy was the only independent predictor of overall survival (hazard ratio [HR] = 0.40, $p = 0.021$). However, it must be noted that these data are limited by potential selection bias and were not adequately powered for a multivariate analysis. Moreover, the authors excluded men who had received salvage chemotherapy after disease recurrence, which may have introduced a systematic bias. This is due to the likely enrichment of the adjuvant chemotherapy-treated group with men who had recovered quickly after surgery and never recurred; in contrast, the group who had not received adjuvant chemotherapy likely included men who were candidates for adjuvant treatment but had been unable to receive it due to rapid disease recurrence post-surgery or poor postoperative recovery, precluding the delivery of adjuvant chemotherapy.

The summary of evidence on adjuvant chemotherapy in node-positive penile cancer is shown in Table 8.1. Taken together, there does appear to be a role for adjuvant platinum-based therapy for chemotherapy-naïve patients with pN3 penile cancer. There are no randomized prospective data, however, and reported follow-up is short, raising questions on whether a durable disease-free survival can be achieved. Additionally, the optimum regimen (platinum-based triplet or doublet) has not been defined, and all of the tested regimens appear to carry at least moderate toxicity. The lack of unequivocal evidence is reflected in the discordance between the current European Association of Urology (EAU) and National Comprehensive Cancer Network [NCCN] guidelines [22, 23], with the former advocating upfront surgery and the use of adjuvant chemotherapy in pN2-3 disease, and the latter recommending neoadjuvant chemotherapy based on clinical staging.

Role of Postoperative Radiotherapy in Node-Positive Disease

There is a paucity of data on the role of adjuvant radiotherapy for men with resectable nodal disease who undergo inguinal lymphadenectomy. Yet, despite this, adjuvant radiation is widely used in several European countries to manage regionally metastatic disease, whereas population-based data have shown that it is much less commonly utilized in the US, with less than one in six men who undergo a lymph node dissection receiving adjuvant radiation [24].

Chen and colleagues from Taiwan reported an 11 % regional recurrence rate with adjuvant radiotherapy for men with pathologic inguinal lymph node metastasis, compared to 60 % for men who did not receive any radiotherapy; however, the overall number of patients was very small ($n = 14$) and no details were reported on the pathologic node characteristics (e.g., extranodal extension) [25]. A similar experience from Leeds, United Kingdom, showed a rate of regional relapse in 6 of 14 men (43 %) treated with adjuvant radiation, including 3 of 4 patients with extranodal extension (pN3) [26]. The authors commented that the 3-year overall survival of 32 % observed in their cohort with pN3 disease was favorable in comparison to a corresponding figure of 18 % that was reported in a surgical series from India [27]. The evidence from these very small series is inconclusive.

Table 8.1 Summary of studies on adjuvant chemotherapy in node-positive penile cancer

Citation	Patient cohort	*N*	Regimen(s)	Median (mean) follow-up, months	Survival outcomes	Toxicity
Pizzocaro and Piva [18]	Involved inguinal and/or pelvic nodes	12	VBM	42	11 alive and disease-free	Bleomycin-induced lung damage ($n=2$)
					1 died of disease	
Hakenberg et al. [8]	pTx pN1-3 M0	8	BMP	(54)	3 alive and disease-free	Treatment-related death ($n=1$)
					4 died of disease	Any grade 3 or 4 ($n=24/45$)
Noronha et al. [20]	High-risk nodal disease	19	TP	15	6 loco-regional relapses	Treatment-related death ($n=1$)
					2 died of disease	Any grade 3 or 4 ($n=6$)
Nicolai et al. [19]	≥pN2 M0	19	TPF ($n=16$)	n/a	10 alive and disease-free	Any grade 3 or 4 ($n=10$)
					8 died of disease	
					1 died of other cause	
			Paclitaxel-PF ($n=3$)		2-year DFS of 37%	
Sharma et al. [21]	pN3 M0	36	TPF ($n=18$)	12	mOS = 21.7 months (versus 10.1 months in 48 men who did not receive adjuvant chemotherapy, $p=0.048$)	n/a
			PF ($n=8$)			
			VBM ($n=8$)			
			TIP ($n=1$)			
			BMP ($n=1$)			

VBM vincristine, bleomycin, methotrexate; *BMP* bleomycin, methotrexate, cisplatin; *TP* paclitaxel, cis/carboplatin; *TPF* docetaxel, cisplatin, 5-fluorouracil; *PF* cisplatin, 5-fluorouracil; *TIP* paclitaxel, ifosfamide, cisplatin; *DFS* disease-free survival; *(m)OS* (median) overall survival

Adding to this uncertainty are data from an analysis utilizing the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Medicare-linked database, which abstracts data from approximately 28 % of the US population. In this study, Burt and colleagues analyzed stage at presentation and treatment outcomes in 2458 patients with squamous cell cancer of the penis, and noted that adjuvant radiation was not associated with cause-specific survival on a multivariate analysis adjusting for tumor stage, grade, and receipt of lymphadenectomy (HR = 1.09 [0.74–1.61], $p = 0.65$) [24].

In summary, there is limited evidence in favor of postoperative radiotherapy for prophylaxis in node-positive penile cancer, and its use is controversial. While a few case series have postulated a survival benefit, particularly in pN3 disease, the data are from extremely small numbers of patients. Larger series or prospective studies are needed before its use can receive an evidence-based recommendation.

Multimodal Approach to Bulky, Fixed, or Unresectable Nodal Disease

There is good-quality evidence suggesting that surgery alone is not a curative option in men with advanced inguinal or pelvic nodal disease; bilateral, numerous and bulky inguinal involvement, extranodal extension, and the presence of pelvic nodal metastases are well-known prognostic factors in penile cancer, and the use of a multimodal approach in these patients is desirable [3, 27, 28].

The earliest significant study attempting to evaluate initial chemotherapy for metastatic disease was the Southwest Oncology Group (SWOG) phase II evaluation of bleomycin, methotrexate, and cisplatin (BMP) in 45 men with locally advanced or metastatic penile cancer. Although a response was seen in almost one in three evaluable patients, this did not translate into a durable survival benefit, with a median overall survival of only 28 weeks. More importantly, there was a significant toxicity burden, with five treatment-related deaths (due to infection or pulmonary complications) and nearly one in three men suffering grade 4 toxicity of any kind [29].

Although these early results were disappointing, they have instigated further study on optimizing a multimodal approach to treating locally advanced disease. Similarities between squamous cell carcinomas of the penis and head and neck have led investigators to study other neoadjuvant chemotherapy regimens. Leijte and colleagues from the Netherlands reported the outcomes for 20 patients who received neoadjuvant chemotherapy for M0 penile cancer between 1972 and 2005 [7]. The regimens were heterogeneous, including VBM and BMP, in addition to single-agent bleomycin or irinotecan, and an objective response (either complete or partial response) was seen in 12 of 19 evaluable patients (63 %). Notably, nine responders went on to undergo lymphadenectomy (with two found to be in pathologic complete response (pCR) on postoperative histology), and eight of these men had durable long-term survival with no evidence of disease at a median follow-up of 20 months. Response to neoadjuvant therapy was also prognostic, with a 5-year overall survival of 56 % in those who responded, while all non-responders had died within 9 months of treatment. As seen with the SWOG and adjuvant chemotherapy studies, there was notable toxicity, with three treatment-related deaths (two men who received BMP and one who received VBM).

Italian investigators from Milan have also reported retrospective data on their experience, the overall results of which appear to be slightly poorer compared to the Dutch data. A median of four cycles of a taxane (paclitaxel or docetaxel) in combination with cisplatin and 5-fluorouracil was given in the neoadjuvant setting to 28 men with clinical N3 disease, producing an overall response rate of 43 % [19]. Seven of the 22 men (32 %) who went on to undergo surgery were alive and disease-free at a median follow-up of more than 12 months, including two of the four who achieved a pCR. Overall, 12 of the 28 men relapsed, with nine dying of disease, and another dying of treatment-related cardiac toxicity. Although response to treatment was not associated with survival in this dataset, the study was underpowered for this, and overall, these retrospective European data serve to confirm that a multimodal approach involving neoadjuvant platinum-based chemotherapy is feasible and has the potential to achieve long-term remissions.

Four prospective studies have bolstered the evidence base on neoadjuvant chemotherapy for locally advanced disease, although the small numbers of patients involved make it difficult to generate robust conclusions. A phase II study of irinotecan in combination with cisplatin was performed by the European Organization for Research and Treatment of Cancer (EORTC) and reported in 2008 [11]. Seven men in that study had T3 and/or N1/N2 disease and were treated in the neoadjuvant setting, with two (29 %) achieving a partial or complete response, and three (43 %) achieving a pCR at lymphadenectomy. This report did not provide any survival data, but again adds to the body of evidence on the feasibility of a multimodal approach to locally advanced penile cancer.

The largest prospective study on neoadjuvant chemotherapy for locally advanced disease was a phase II trial conducted at the University of Texas MD Anderson Cancer Center [10]. Thirty men with clinical stage Tx N2-3 M0 disease were given four cycles of paclitaxel, ifosfamide, and cisplatin (TIP) prior to undergoing planned bilateral inguinal and uni- or bilateral pelvic lymph node dissection. Most of the patients (70 %) had clinical N3 disease at baseline, and the majority completed all four cycles with minimal toxicity (grade 3 infection was the most commonly observed adverse event, occurring on five occasions), with 15 of 30 men (50 %) achieving an objective response. All but four individuals went on to undergo lymphadenectomy, including 22 of the 23 men who completed all four cycles of chemotherapy, with 3 of these 22 men (13.6 %) being found to have a pCR. Survival data were comparable to that observed in previous retrospective studies [7, 19], with nine men (30 %) remaining alive and without evidence of disease at a median follow-up of 34 months; median overall survival in the entire cohort was 17 months. Importantly, response to neoadjuvant TIP was significantly associated with a longer overall survival and time to disease progression (Fig. 8.2), while postoperative complications were comparable to those seen in contemporary lymphadenectomy series [30].

A follow-up report from the same group expanded on this phase II trial by retrospectively reviewing results from an additional 31 men with Tx N1-3 M0 disease who underwent neoadjuvant chemotherapy, to produce an overall cohort of 61 patients, 21 of whom had undergone a prior inguinal procedure and were being treated for disease recurrence or persistence [31]. The majority of this 61-man

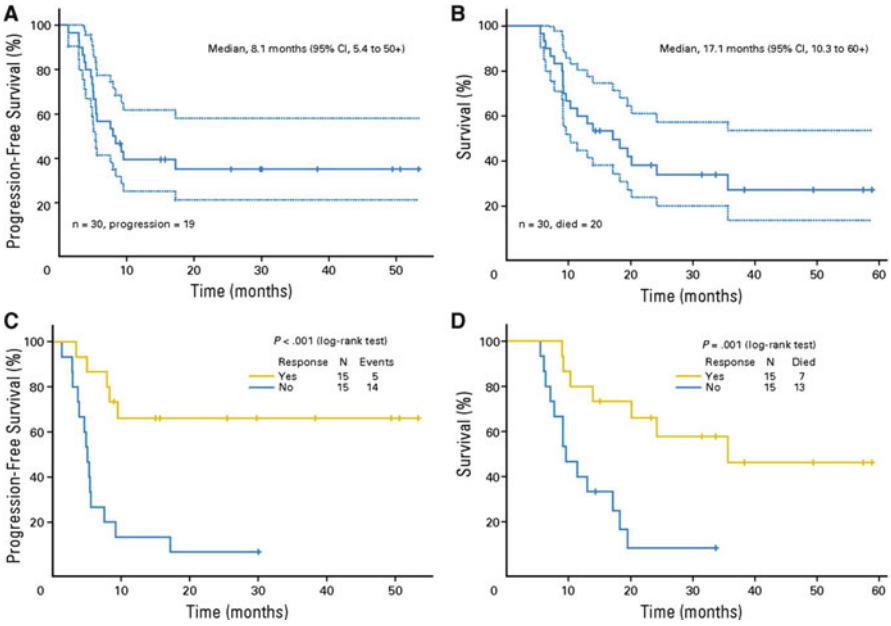


Fig. 8.2 Kaplan–Meier curves showing (**a**) time to disease progression and (**b**) overall survival in men receiving neoadjuvant TIP, and (**c**, **d**) time to progression and overall survival stratified by response to neoadjuvant chemotherapy respectively. The 95 % CI are shown (**a**, **b**) with *dashed lines* above and below. (Reproduced, with permission from Pagliaro et al. [10])

cohort received TIP and an impressive overall response rate of 65 % (39 of 61 patients) was observed. Fifty-two patients (85 %) went on to undergo surgery, with ten (19 % of those operated) achieving a pCR. Twenty men (33 %) were alive and disease-free at a median follow-up of more than 5 years, including seven of the ten who achieved a pCR, and overall, 50 % of men who responded to neoadjuvant therapy were alive at 5 years.

Prospective studies of other platinum-based regimens in the treatment of metastatic penile cancer were not as successful as the MD Anderson experience with TIP [10]. Nicholson et al. administered a median of three cycles of TPF to 21 men with Tx N1-3 M0 disease, including 15 (71 %) with N3 disease, as part of a phase II clinical trial in the UK [32]. They aimed to assess response clinically and via RECIST after the planned three cycles of chemotherapy, and determine how many patients were subsequently operable. An overall response was seen in 7 of 19 evaluable patients (37 %) in this neoadjuvant group, and of the 20 patients deemed inoperable at trial entry, 5 were sufficiently downstaged to be operable, although one was considered too frail to undergo surgery. Notably, more than two in three patients suffered any grade 3 or 4 toxicity, which was substantially greater than that observed with neoadjuvant TIP [10].

The latest prospective data to examine the role of neoadjuvant chemotherapy come from a recent report from The Netherlands Cancer Institute [12]. This group reported the outcomes of 26 men with T4 and/or N3 disease who were treated with neoadjuvant TPF as part of a nonrandomized institutional study, with the dose of cisplatin used being higher than that in the aforementioned UK TPF trial [32]. As with the previous study, they aimed to achieve sufficient downstaging to permit surgical resection with curative intent. Almost half of the cohort completed all of the planned four cycles of therapy, with 11 of the 25 evaluable patients (44 %) achieving at least a partial radiographic response. Fourteen men underwent surgery, and a pCR was seen in one (7 %), similar to the pCR rate in the MD Anderson study of neoadjuvant TIP [10]; however, only four men (15 % of the entire cohort) were alive and disease-free at a median follow-up of 30 months. The median overall survival was 10 months, which was disappointingly lower than the 17 months seen with neoadjuvant TIP, although it must be noted that the Dutch cohort was heterogeneous, with almost half being treated for recurrent disease, which may have selected for more aggressive disease biology. Additionally, six men discontinued therapy owing to toxicity, while all enrolled men experienced some grade of chemotherapy-related toxicity.

A synthesis of published evidence of the use of neoadjuvant chemotherapy for locally advanced penile cancer is shown in Table 8.2. It is apparent that adopting a multimodal approach to treat locally advanced disease is feasible, and response rates to neoadjuvant chemotherapy of between 29 and 65 % have been seen with retrospective and prospective data. Platinum-based therapy has emerged as the standard of care, with TIP offering the highest response rates. While all studies generally demonstrate a reasonable response rate, the difference in durable survival benefit is less clear. Current EAU [22] and NCCN [23] guidelines do recommend neoadjuvant chemotherapy followed by consolidation surgery in responders for nodal disease that is initially bulky or unresectable, with a triplet regimen, containing cisplatin and a taxane, preferred wherever feasible.

Chemoradiotherapy for Locally Advanced Disease

Concurrent chemoradiation has been shown to produce superior outcomes to either modality alone for locally advanced squamous cell cancers of the vulva and anus, two uncommon perineal cancers which share anatomic and biologic disease characteristics with penile cancer [5, 6, 33]. This has naturally raised the question of whether chemoradiotherapy may be a feasible option for locally advanced and regionally metastatic penile cancer, particularly since neoadjuvant radiotherapy has also been shown to reduce inguinal recurrence rates in men with bulky nodal disease [34].

Isolated case reports have shown successful outcomes with the use of neoadjuvant TIP in combination with radiotherapy to the involved disease sites [35], as well as multimodal therapy comprising cisplatin and 5-fluorouracil followed by radiotherapy to the primary lesion in clinically node-negative disease [36]. The only multi-center report examining chemoradiation collated data between 2000 and 2012 from five

Table 8.2 Summary of studies on neoadjuvant chemotherapy for unresectable nodal disease

Citation	Patient cohort	*N*	Regimen(s)	Median follow-up, months	Response rate, %	Underwent surgery (%)	pCR at surgery (% of those operated)	Survival outcomes
Leijte et al. [7]	Tx N0-3 M0	20	BMP ($n=10$)	23	63	9 (45)	2 (22)	5-years OS = 32 %,
			VBM ($n=5$)					8 of 9 undergoing surgery alive and disease-free at median follow-up of 20 months
			Bleomycin ($n=3$)					
			PF ($n=1$)					
			Cisplatin-irinotecan ($n=1$)					
Theodore et al. [11]	T3 N1-2 M0	7	Cisplatin-irinotecan	n/a	29	3 (43)	3 (100)	n/a
Pagliaro et al. [10]	Tx N2-3 M0	30	TIP	34	50	22 (73)	3 (14)	9 alive and disease-free, median OS = 17 months
Dickstein et al. [31][a]	Tx N1-3 M0	61	TIP ($n=53$)	n/a	65	52 (85)	10 (19)	20 alive and disease-free at 5 years; 32 died of disease at 5 years
			TP, PF, BMP ($n=7$)					
Nicolai et al. [19]	Tx N3 M0 (5 with relapsed disease)	28	TPF ($n=23$)	n/a	43	22 (79)	4 (18)	2-year DFS = 7 %
			Paclitaxel-PF ($n=5$)					
Djajadiningrat et al. [12]	T4 and/or N3 (incl. 12 with relapsed disease)	26	TPF	30	44	14 (54)	n/a	13 died of disease
								Median OS = 10 months
								1-year OS = 46 %
								2-year OS = 27 %

[a]This study included patients from Pagliaro et al. [10]

VBM vincristine, bleomycin, methotrexate; *BMP* bleomycin, methotrexate, cisplatin; *TP* paclitaxel, cis/carboplatin; *TPF* docetaxel, cisplatin, 5-fluorouracil; *PF* cisplatin, 5-fluorouracil; *TIP* paclitaxel, ifosfamide, cisplatin; *mPFS* median progression-free survival; *(m)OS* (median) overall survival; *DFS* disease-free survival

tertiary centers across the US, Canada, and Italy [9]. Of the 26-man cohort, 5 had M1 disease and 16 had clinical stage IV disease; the majority (92 %) received a cisplatin-based radiosensitizing regimen along with a median dose of 4900 cGy to involved disease areas. Clinical outcomes were disappointing, with a 1-year overall survival of 37 % in patients with M0 disease, which is lower than that reported with neoadjuvant chemotherapy alone followed by surgical consolidation. It must be noted that the majority of patients had stage IV disease at outset and some had relapsed disease.

The paucity of data as well as some uncertainty about the efficacy of chemoradiotherapy, therefore, makes this modality an investigational approach requiring further evaluation within clinical trials, a conclusion that is reflected in consensus guidelines [22].

Future Directions

The future of multimodal therapy for penile cancer is likely to involve greater stratification of patients according to risk profiles and targeting of specific pathogenic molecular pathways. The rarity of the disease has meant that, as other solid tumors embark on an era of genomic classification and targeted therapy, much of the study on penile cancer has focused on optimizing cytotoxic therapy and outlining an initial multimodal approach to treatment. However, there are emerging data on two aspects, which will likely be incorporated into future therapeutic strategies.

HPV and Penile Cancer

Human papillomavirus (HPV) infection has been identified in the pathobiology of head and neck, cervical and anal cancers, and there is increasing evidence of a link to penile cancer. HPV DNA is detected in approximately 50 % of squamous cell cancers of the penis, with HPV16 being the most prevalent serotype [37]. Its pathophysiologic role in carcinogenesis is thought to be mediated by its E6 and E7 oncoproteins, which downregulate p53 and pRb respectively, thereby promoting uncontrolled cell division and growth [38]. The presence of HPV may affect cancer biology and disease prognosis, but current evidence on this issue is mixed, with some data suggesting it an independent prognosticator of survival and other series finding no association between HPV status and outcome [39, 40]. It is clear that further research into the role of HPV in penile carcinogenesis is needed, and this may ultimately lead to improved risk-stratification of patients and identification of patient cohorts who may benefit from specific treatment strategies.

Targeted Therapy for Penile Cancer

The past decade has seen greater focus on outlining the molecular biology underlying penile cancer and various attempts to develop therapies that target these molecular events. As with other solid tumors, the aim is to add to the therapeutic arsenal as

well as finding therapies that may produce durable responses. One of the principal targets is the epidermal growth factor receptor (EGFR), with the largest pathologic series suggesting that the majority of penile cancers have high EGFR expression [41]. Although there are limited prospective data on the use of EGFR inhibitors in penile cancer, a few case reports and case series have reported encouraging outcomes. A proof-of-concept case report showed significant clinical response of metastatic disease to single-agent panitumumab, with a response being seen as early as 2 weeks after treatment initiation [42]. Another case series of three patients demonstrated clinical response in two men to EGFR-directed therapy, with one of the individuals, who had received cetuximab followed by radiotherapy, being disease-free 42 months after the treatment [43].

The largest series examining targeted therapy in penile cancer to date evaluated 24 men who received one or more EGFR-targeted therapies between 2004 and 2009 at MD Anderson, with the majority receiving cetuximab [44]. Four of seventeen men (24 %) treated with cetuximab alone or in combination with cisplatin achieved a partial response, including two men whose tumors had been refractory to TIP, suggesting that targeted therapy may act synergistically with cytotoxic therapy. Targeted therapy was also well tolerated, with the most common adverse effect being grade 1 or 2 skin rash, which was observed in more than 70 % of patients. Similarly, preliminary data on the use of sofarenib or sunitinib in men with advanced disease have also shown some degree of promise, with a partial response seen in one of six patients treated [45].

These data do suggest a place for targeted therapy within the armamentarium against penile cancer, possibly given neoadjuvantly to enhance the effect of cytotoxic therapy, or in relapsed or metastatic disease. Larger prospective trials are required before these approaches acquire a sufficient evidence base to merit widespread adoption.

An International Clinical Trial

The rarity of penile cancer necessitates multi-center collaboration to enable sufficient numbers of patients to be enrolled in clinical trials such that they produce clinically meaningful results. Several of the phase II studies discussed earlier in this chapter took several years to complete enrolment, and even the largest such study enrolled fewer than 50 men. To address this issue, a partnership between the UK National Institute for Health Research Cancer Research Network, Cancer Research UK, the US National Cancer Institute, and the EORTC was formed in 2011, comprising the International Rare Cancers Initiative (IRCI). The IRCI aims to facilitate the development of international clinical trials for patients with rare cancers, including penile cancer [46].

The first planned IRCI trial for penile cancer is the International Penile Advanced Cancer Trial (InPACT; NCT02305654, Fig. 8.3) [47]. It plans to recruit 400 men with locally advanced penile cancer (i.e., with nodal metastases) and will randomize them to upfront surgery (inguinal lymphadenectomy),

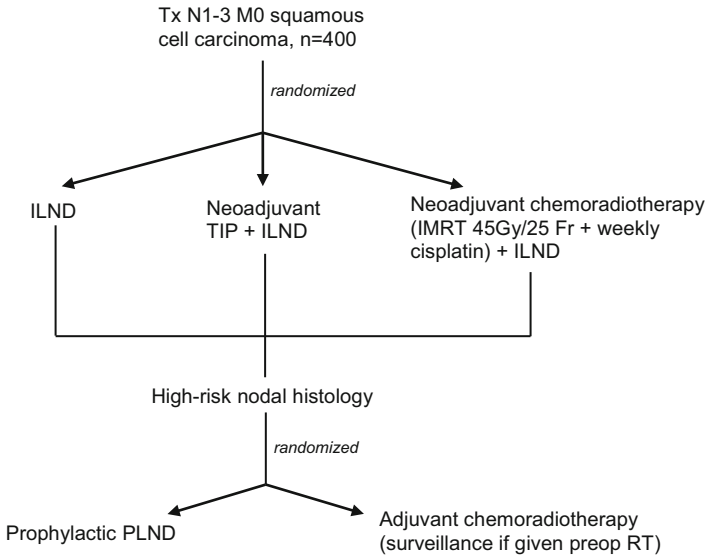


Fig. 8.3 InPACT trial design. *ILND* inguinal lymph node dissection, *PLND* pelvic lymph node dissection, *TIP* paclitaxel, ifosfamide, cisplatin, *IMRT* intensity-modulated radiotherapy

neoadjuvant chemotherapy (with TIP) followed by surgery, or neoadjuvant chemoradiotherapy (with cisplatin) followed by surgery. A secondary randomization process will apply for men deemed at high risk of recurrence after inguinal lymphadenectomy, who will be randomized to either receive prophylactic pelvic lymph node dissection or no further surgery. The primary outcome for this trial is overall survival, with secondary outcomes measures including disease-specific survival, pathologic complete remission rates, quality of life, and surgical complication rates. This trial, if successful, will represent a landmark event in the penile cancer field and will likely open the door to further multi-institutional collaborations that will ultimately provide a robust evidence base to the treatment of men with penile cancer.

Conclusion

The past two decades have seen significant progress made in establishing an evidence base to support a multimodal approach to regionally metastatic penile cancer (Fig. 8.4), in much the same way as multimodal therapy is used to treat squamous cell carcinoma of the head and neck and other anogenital sites. Several prospective trials, albeit limited by small patient numbers, have shown that neoadjuvant chemotherapy (with TIP seeming to be the most active regimen) followed by surgical consolidation can lead to durable and long-term survival in men with bulky or initially unresectable lymph node metastases. There is also evidence that adjuvant

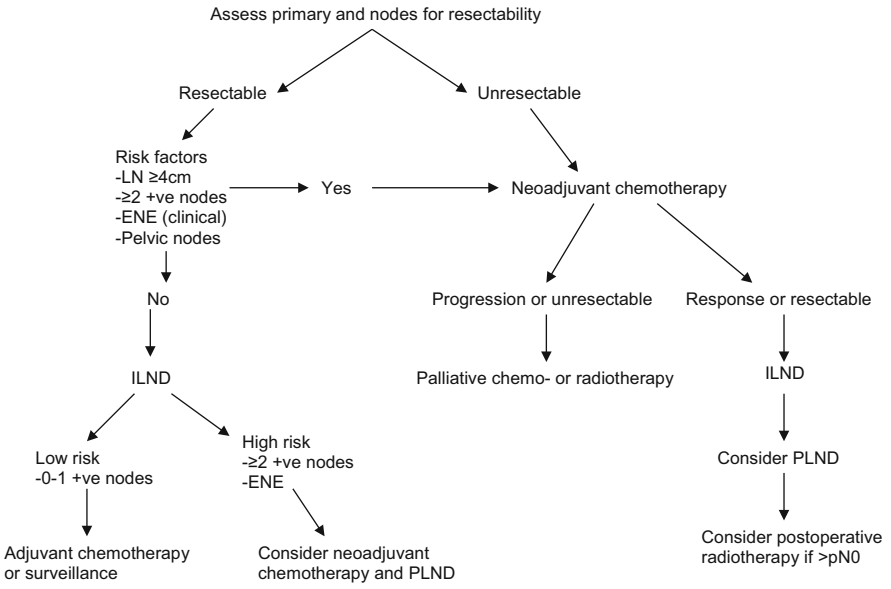


Fig. 8.4 Algorithm of current approach to multimodal therapy in men with loco-regionally advanced squamous cell penile cancer. *ENE* extranodal extension, *ILND* inguinal lymph node dissection, *PLND* pelvic lymph node dissection

chemotherapy can improve outcomes for men who have undergone lymphadenectomy for resectable disease and who are chemotherapy-naïve.

In the next two decades, it is hoped that international collaboration will provide the first randomized data in the setting of locally advanced or metastatic penile cancer, and will guide further multimodal approaches to treatment, including determining if there is a role for concurrent chemoradiotherapy. Further work on patient stratification by molecular status and HPV positivity is also needed, which may ultimately lead to defining the optimal use of targeted therapies, as an adjunct or combination with other cytotoxic chemotherapy, radiotherapy and surgery, in this disease.

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The Role of Radiotherapy in the Management of Penile Cancer

9

Juanita Crook

Introduction

The vast majority of penile cancers are squamous cell carcinoma (SCC), a radiosensitive and radiocurable malignancy. There is consistent evidence across other SCC sites, including head and neck, cervix, vulva, and anal canal, that both radiotherapy and the combination of sensitizing chemotherapy and radiotherapy are effective treatment. Furthermore, all these sites share a common etiologic pathway in that HPV exposure plays a role in a significant percentage of cases, from nearly all cervical cancers to one-third to one-half of penile cancers, especially the warty and basaloid types. HPV positivity is associated with a better outcome and higher response rates to chemo-radiation, and in penile cancer has been associated with improved 5-year survival [1, 2].

Largely due to the relative rarity of penile cancer in western societies, there is a paucity of Level One evidence to guide treatment. The incidence of approximately 1 per 100,000 in North America and the developed countries of western Europe does not lend itself to completion of randomized studies such as are needed to compare surgery to radiotherapy or radiation to chemo-radiation [3].

The traditional surgical approach to penile cancer has been partial or total penectomy. There are obvious quality of life advantages to organ preservation such as can be provided by minimally invasive or non-surgical alternatives. The impact of penectomy or partial penectomy on sexual function has been well documented, and incidents of suicide or attempted suicide have been reported [4, 5].

Recent advances in surgery toward maximizing penile preservation, such as glansectomy and glans resurfacing, attempt to address these issues but are not widely adopted [6, 7].

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In localized disease, various forms of radiotherapy including external beam, interstitial brachytherapy, and surface mold brachytherapy offer a high chance of cure with organ preservation, reserving surgery for local recurrence. In those patients with apparently localized disease but who have an elevated risk of regional node involvement by virtue of their stage or grade, management of the primary tumor with radiation can be combined with surgical staging of the nodes. The indications for postoperative adjuvant radiation to regional lymphatics following nodal staging are well established from other anogenital SCC sites and include multiplicity of node involvement, extracapsular extension, or positive margins. For those men presenting with locally and/or regionally advanced disease, chemo-radiotherapy may render the disease resectable or can be continued to a definitive therapeutic radiation dose.

Radiotherapy for the Primary Tumor

Penile preserving therapeutic options should be considered for the primary tumor whenever possible. Although not always feasible, especially in more locally advanced T3-T4 disease, the quality of life advantages are well established with maintenance of normal voiding, erectile and sexual function and a preserved sense of manliness. Delaunay et al. have published results of a self-reported questionnaire administered to 21 French men treated with brachytherapy an average of 80 months previously [8]. The response rate was 90 %. Of 18 men who had erections prior to brachytherapy, 17 reported maintenance of erections after treatment and 10 were still in an active sexual relationship, age and health of the partner being the main determining factors. Although the capacity for erection and ejaculation can be maintained after partial penectomy, the small size of the penis and lack of a glans are cited as reasons for lack of continuation of sexual activity [9]. Emotional and mood disorders, anxiety, depression [10, 11], and even suicide or attempted suicide are reported [5]. In a small study reported by Opjordsmoen et al., patients undergoing radiation therapy had better global sexual scores than those undergoing partial penectomy or local excision [12]. Maddineni et al. analyzed 128 patients from six studies of surgical management of penile carcinoma. Five contained retrospective data while one study collected prospective data on erectile function [10]. Two studies using the General Health Questionnaire (GHQ) showed impaired well-being in up to 40 %, with the patients who underwent more mutilating treatments more likely to have impairment. Two used the Hospital Anxiety and Depression Score (HADS) and demonstrated pathological anxiety in 31 % [10]. One study used the Diagnostic and Statistical Manual of Mental Disorders of psychiatric illness (DSM III-R) and found 53 % of patients exhibiting mental illness, 25 % avoidance behavior and 40 % impaired well-being. The authors concluded that surgical treatment of penile cancer negatively effects well-being in up to 40 % of patients with psychiatric symptoms in approximately 50 %. Additionally, up to 75 % of patients report a reduction in sexual function after surgery.

Carcinoma In Situ (Tis)

Penile squamous cell carcinoma in situ is also known as erythroplasia of Queyrat when occurring on the glans or prepuce of uncircumcised men, or Bowen's disease when it occurs elsewhere on the penile shaft. A penile-sparing approach is preferred. Preputial lesions are adequately treated with circumcision. Topical therapies such as 5-FU cream or Imiquoid provide excellent cosmetic results but careful follow-up is mandatory as recurrence is not uncommon.

Studies with long-term follow-up on laser ablation have reported up to 50 % local recurrence with carbon dioxide laser largely due to the shallow depth of tissue penetration (~1 mm) whereas Nd-YAG lasers which penetrate up to 6 mm have shown good local tumor control (only 7 % local recurrence at 4 years) and highly satisfactory function and cosmesis with 75 % of men resuming sexual activity [13, 14]. Mohs micrographic surgery has been described as a less-deforming alternative to partial amputation but may not offer any benefit over surgical excision when frozen sections are used for intra-operative margin verification. Most require immediate tissue flap reconstruction and up to one-third of patients develop local recurrence and require repeat surgery [15, 16]. External beam radiation therapy may be used to eradicate these lesions with one report of 100 % local control rate for in situ disease [17].

Invasive Cancer

Curative radiotherapy of the primary tumor can be delivered either through external beam radiation, interstitial brachytherapy or surface mold plesiotherapy. For external beam radiotherapy, 5-year local control and penile preservation rates are about 60 %. For low-dose rate interstitial brachytherapy, local control and penile preservation are about 85 % at 5 years and 70 % at 10 years. Two series reporting long-term results cite penile preservation in 67 % and 72 % at 10 years [18, 19]. As surgery is highly successful for salvage of local failures, late local recurrence does not effect disease-specific mortality. Each of these modalities will be considered in turn.

External Beam Radiotherapy

Although widely available, external beam radiotherapy is not generally considered the treatment of choice for early stage localized T1-T2 SCC of the penis. There are challenges of supporting and isolating the organ from adjacent normal structures while positioning it for treatment, and supplying a full bolus effect to eliminate the skin-sparing capacity of modern megavoltage beams. The most common approach is to position the patient supine, and support the penis vertically in a bi-valved tissue-equivalent block with a central chamber that will house the penis without any air gap (Fig. 9.1). Initially wax blocks were used for this purpose but being opaque, do not allow verification of position of the penis within the block prior to each treatment. However, an advantage of wax is that it is easily modified to accommodate penile swelling during the course of treatment. Alternatively, a Plexiglas or Lucite

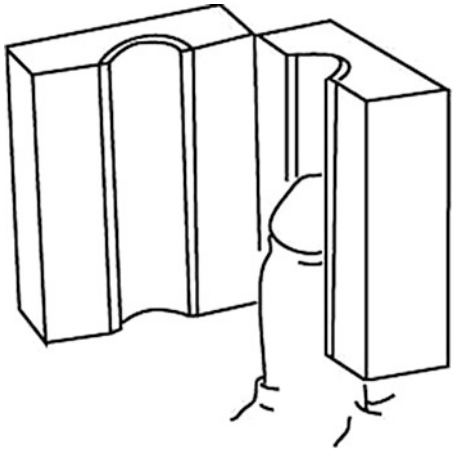

Fig. 9.1 Bi-valved block made of tissue-equivalent material with a central chamber to encase the penis during external beam radiotherapy

chamber can be used. These have the advantage of being sterilizable and thus re-usable, and penile position at set-up can be visually checked daily. They should be available in the department in a range of diameters of the central chamber so that a larger size can be substituted if necessary to accommodate penile swelling or tumor response over the course of treatment. With either type of block, it is important to place a plug or "cork" of the same material in the open end to supply full electron build-up to the distal end of the glans. Erythema, desquamation, and edema are expected during treatment and take 2–4 weeks to heal subsequently.

The clinical target volume (CTV) is the visible/palpable disease with a 1 cm margin. The planning target volume should add another cm to be 2 cm beyond visible/palpable disease to allow for minor set-up variation (larger margin advisable if an opaque block is used) and beam penumbra. Depth of invasion is not a concern as the treated volume includes the full thickness of the penis.

Dose and fractionation have varied over the decades but the currently accepted prescription would be 66–70 Gy over 6.5–7 weeks. Fraction sizes <2 Gy, treatment courses longer than 45 days, and total dose <60 Gy are associated with an increase in local failure [4, 20]. Five-year local control ranges from 41 to 70 % [4, 17, 21–24] with a weighted average of about 61 %.

Penile preservation is approximately the same since most local failures are salvaged surgically with either partial or total penectomy. Results from selected series are presented in Table 9.1.

External beam radiotherapy is most frequently considered in very elderly or debilitated patients or those presenting with loco-regionally advanced disease where the primary would be treated in contiguity with the nodal regions, including both groins and the pelvis. This will be addressed further under *Regional Radiotherapy.*

Interstitial Low Dose Rate (LDR) Brachytherapy

The penis lends itself well to the application of interstitial brachytherapy and has been successfully treated with LDR brachytherapy for decades with reports from Europe, India, and Canada. Interstitial brachytherapy can deliver the required dose

Table 9.1 Published results for external beam radiotherapy

Author		*n*	Fup(m)	Dose Gray	CSS	DFS	LC	compln	Penile preservn
Neave et al. [23]	1993	20	36+	50–55/20–22	58 %	–	70 %	10 % sten	–
McLean et al. [17]	1993	26	116	35/10–60/25	69 %	15/26	62 %	27 % unspec	100 %
Ravi et al. [64]	1994	128	83	50–60	–	84 %	65 %	6 % nec	–
								24 % sten	
Sarin et al. [4]	1997	59	62	50–60	66 %	–	35/59	3 % nec	55 %
								14 % sten	
Gotsadze et al. [24]	2000	155	40	40–60	88 %		65 %	1 % nec	65 %
								7 % sten	
Zouhair et al. [20]	2001	23	70	45–074 @ 1.8–2 Gy	–		57 %	10 % sten	36 %
Ozsahin et al. [65]	2006	33	62	52	53 % 10y	-	44 %	10 % sten	52 %
Azrif et al. [21]	2006	41	54	50–52/16	96 %	51 %	62 %	8 % nec	62 %
								29 % sten	
Mistry et al. [22]	2007	18	62	50/20–55/16	85 %	63 %	63 %	2 nec	66 %
								1 sten	

n number of patients, *Fup* follow-up (months), *Dose* Gray/number of fractions, *CSS* cause-specific survival, *DFS* disease-free survival, *LC* local control, *compln* complications, *Penile preservn* penile preservation, *Nec* necrosis, *Sten* stenosis of the meatus

precisely and accurately to the target without excessive treatment of the penile shaft or concerns about daily set-up. Furthermore, for well lateralized lesions it is not necessary to treat the full thickness of the penis and some sparing of the contralateral glans is possible [25]. Technique and dose prescription have been more consistent over time with LDR brachytherapy than in the external beam literature.

LDR interstitial brachytherapy is performed with sterile technique in a dedicated brachytherapy procedure room or operating room under general anesthesia or penile block. The procedure generally takes 45 min to 1 h with the patient admitted afterward for the duration of the brachytherapy (4–6 days). After skin cleansing and creation of a sterile field, the penis is examined carefully and the visible/palpable lesion is delineated with sterile pen and the appropriate margins chosen. The patient is catheterized and an in-dwelling Foley catheter is left in situ until completion of treatment and removal of the brachytherapy needles. The position and spacing of the interstitial needles is chosen so as to avoid the urethra, and to have the superficial needles within 3 mm of the treated surface. If they are too deep, the surface will be underdosed, while if they are too shallow, skin ulceration and scarring will result. A minimum of a two-plane implant is required (Fig. 9.2). The needle direction can be either antero-posterior for a lateral lesion, or right–left for a thicker infiltrating lesion. If the anatomy does not allow both avoidance of the urethra and optimal depth under the surface, then a plesiotherapy plane can be added externally on the side of the cancer with the air gap filled with appropriate bolus material such as "superflab", available from several radiotherapy supply companies (Fig. 9.3).

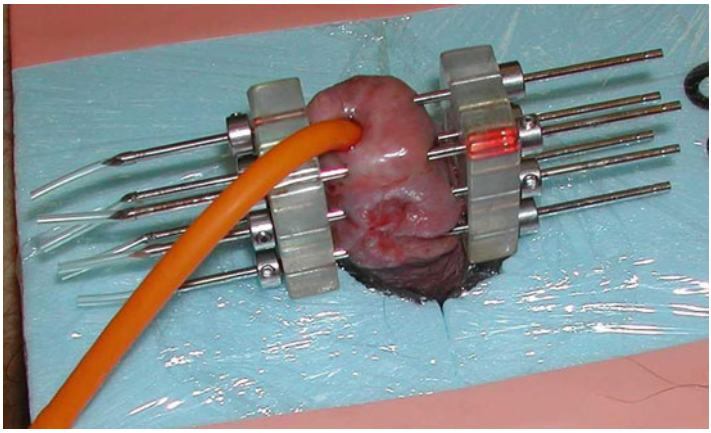

Fig. 9.2 Two-plane implant showing Foley catheter and styrofoam plaque to support penis and distance the treated area from the normal tissues

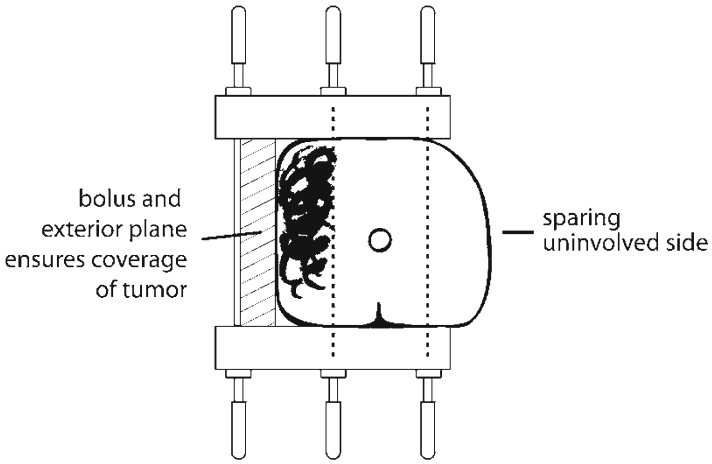

Fig. 9.3 Schematic of a three-plane implant showing a lateral plane of needles exterior to the penis to supply plesiotherapy, with a layer of tissue-equivalent bolus filling the gap. The depth of needles on the uninvolved side allows some sparing of the skin surface on that side. (*Reproduced with permission from* [25])

Guide templates are required to ensure parallelism and equal spacing. Both the needles and planes should be equidistant in an LDR implant. Ideal spacing is 12–18 mm with 15 mm most commonly used. Pairs of templates should be available, predrilled with an appropriate range of needle spacing but a "universal template" with holes drilled every 3 mm allows more flexibility once the first couple of needles have been placed (Fig. 9.4). Once positioned, the needles are fixed in place with washers against the template with a single set-screw in each to tighten against the shaft of the needle. Since the implant geometry is totally stable throughout

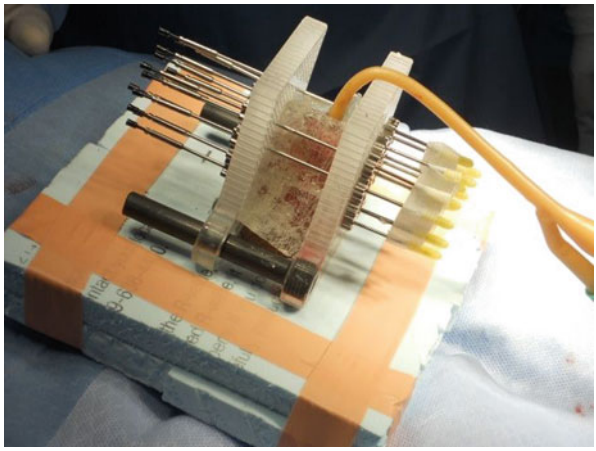

Fig. 9.4 "Universal" template with holes drilled every 3 mm, so spacing can be selected as suitable at 9, 12, 15 mm, etc. Nine to twelve millimeter would be suitable for an HDR implant while 15 mm is the preferred spacing for LDR brachytherapy. A layer of superflab bolus can be seen

the duration of the treatment, dosimetry can be calculated based on measurements of spacing and treated lengths but more commonly a CT scan is performed and the needles reconstructed from the scan.

The basic rules of geometry of the Paris System of Dosimetry should be appreciated in order to place the needles optimally [26]. When using classic LDR treatment with Iridium wire, it is essential to be aware that the length of your treated volume along the axis of the needles is 0.75 of the active length of the wire sources and to allow for the consequent in-drawing of the isodoses between the ends of the wires. Similarly, the spacing between the needles determines the lateral margin treated beyond the sources (0.27 × spacing; i.e.: 4 mm for 15 mm spacing; Fig. 9.5). If a stepping source is used from an automated afterloader, such as in Pulse Dose Rate Brachytherapy, then dose optimization is possible. Nonetheless, the prescribing rules of the Paris System give guidance as to desirable homogeneity, such that dose rate minima between the sources are 115 % of the prescription isodose, and the sum of the high dose sleeve around each source (V200) is <10 % of the treated volume.

Classic continuous LDR brachytherapy aims for a dose rate of 50–60 cGy per hour. Pulse dose rate brachytherapy (Fig. 9.6) is radiobiologically equivalent if hourly fractions of 0.5–0.6 Gy are delivered, 24 h per day [27–29]. Most PDR results are mixed with classic LDR in single institution reports but Kamsu-Kom et al. from Institut Gustav Roussy recently reported on 27 patients treated from 2008 to 2013 exclusively with PDR brachytherapy to a dose of 60–70 Gy with 0.4–0.5 Gy per hour, with results indistinguishable from those reported with classic LDR [30]. The total dose recommended is generally 60–65 Gy over 5 days. Minimal analgesia is required during the duration of the implant and the patient can even mobilize within the hospital room, disconnected from the afterloader between fractions for PDR cases. If the patient is less mobile, then anti-embolic stockings and low molecular weight heparin are advised as anti-thrombotic measures. Needle removal can occur at the bedside after premedication with a narcotic analgesic such as Demerol or morphine. Bleeding is usually minimal and the patient can be discharged the same day.

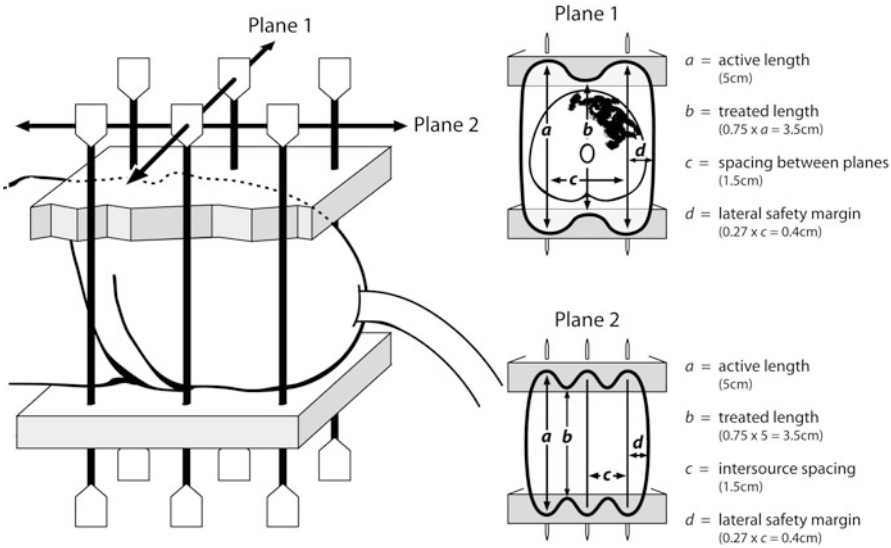

Fig. 9.5 Schematic of a two-plane interstitial implant typical of LDR brachytherapy and adhering to the Paris Rules of Dosimetry for geometry and needle spacing. In-drawing of the prescription isodose between the ends of the sources is represented by "*b*" and the lateral margin around the prescription isodose is shown as "*d*". (*Reproduced with permission from reference* [25])

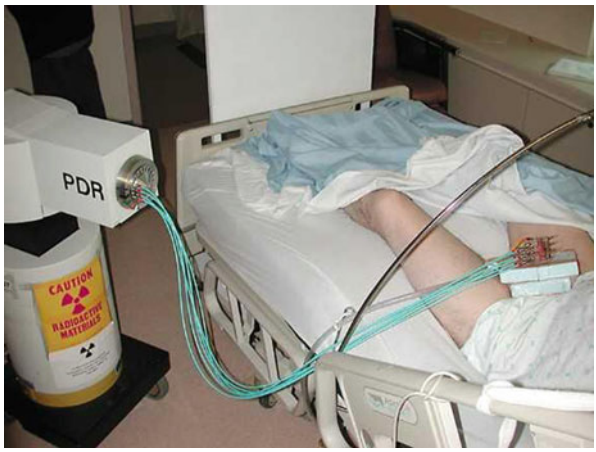

Fig. 9.6 Patient connected to Pulse Dose Rate afterloader with a transfer tube attached to each interstitial needle

Selected results from the literature for interstitial brachytherapy are shown in Table 9.2. Five-year local control ranges from 70 to 96 % and 10-year from 70 to 80 %, with penile preservation at 10 years being 70 %. Local failures can be salvaged surgically and, as they can occur late, up to 8–10 years after treatment, continued surveillance and patient-awareness are essential. Crook et al. found that although five of eight local recurrences occurred in the first 2 years, the remaining three occurred at 4.5, 7, and 8 years after brachytherapy [18]. Similarly, Mazeron et al. [31] reported that 18 % of local recurrences occurred between 5 and 8 years and DeCrevoisier et al. found that with longer follow-up, 20 % were diagnosed beyond 8 years [19].

Table 9.2 Published results for brachytherapy

Author	Year	HDR LDR	*n*	Fup(m) (range)	Dose Gray	CSS	DFS	LC	compln	Penile preservn
Mazeron et al. [31]	1984	LDR	50	36–96	60–70	79 %	63 %	78 %	3 % nec 16 % sten	74 %
Delannes et al. [46]	1992	LDR	51	65 (12–144)	50–65	85 %	–	86 %	23 % nec 45 % sten	75 %
Rozan et al. [40]	1995	LDR	184	139	59	88 % 5y 88 %10y	78 % 5y 67 %10y	85 %	21 % nec 45 % sten	76 %
Soria et al. [5]	1997	LDR	102	111	61–70	72 % 5y 66 %10y	56 % 5y 42 %10y	89 %	1 nec 1 sten	68 %
Chaudhary et al. [47]	1999	LDR	23	24 (4–117)	50 (40–60)	–	–	70 %	0 nec 2/23 sten	70 %
Kiltie et al. [39]	2000	LDR	31	61.5	63.5	85 %	85 %	81 %	8 % nec 44 % sten	75 %
de Crevoisier et al. [19]	2009	LDR	144	68 (6–348)	65	92 %10y	78 %10y	80 %10y	26 % nec 29 % sten	72 %10y
Crook et al. [18]	2009	LDR	67	48 (44–194)	60	84 %	71 %5y	87 %5y 72 %10y	12 % nec 9 % sten	88 %5y 67 %10y
Pimenta et al. [66]	2015	LDR	25	110 (0–228)	60–65Gy	91 %	92 %5y crude	1 LF @ 4 months	8 % nec 43 %sten	86 %(5y)
Petera et al. [33]	2011	HDR	10	20	3 Gy bid = 42–45	100 %	NS	100 %	0 nec 0 sten	100 %
Sharma et al. [32]	2014	HDR	14	22 (6–40)	3 Gy bid = 51 Gy	83 % 3y	NS	12/14	0 nec 0 sten	93 %
Rouscoff et al. [36]	2014	HDR	12	27 (5–83)	36/9–39/9 bid	100 %	83 %	11/12	1/12 nc 1/12 sten	11/12
Kellas-Sleczka et al. [34]	2015	HDR	55	55 (8–154)	3–3.5 bid = 30–54	NS	NS	73 %	0 nec 0 sten	80 %

n number of patients, *Fup* follow-up (months), *Dose* expressed as range and/or median, *CSS* cause-specific survival, *DFS* Disease-free survival, *LC* local control, *compln* complications, *Penile preservn* penile preservation, *Nec* necrosis, *Sten* stenosis of the meatus

High-Dose Rate Interstitial Brachytherapy

The use of manually afterloaded sources such as Iridium 192 wires is no longer available in most departments due to reasons of staff exposure, logistics of source disposal after use, and risks of contamination from having to cut brittle wire to the correct length. On the contrary, HDR afterloaders are available in most radiotherapy centers for use in more common malignancies such as breast and prostate, and as an essential component of curative treatment of cervical cancer. Recently, there has been renewed interest in brachytherapy for penile cancer using HDR. The technique is very similar to that described above for LDR but with a few notable exceptions.

1. Needle spacing should be closer than for LDR since HDR is less forgiving of "high dose sleeves" around sources. Ideal spacing is 9–12 mm.
2. Needle spacing does not have to be equidistant as variations in spacing are easily compensated for with the stepping source.
3. A "universal template" with holes every 3 mm is ideal since the spacing around the urethra can be 12 mm and elsewhere reduced to 9 mm.
4. Attention to homogeneity is very important. The desired parameters are still being established.

Recent publications indicate that 3 Gy bid, 6 h apart is safe and effective for a total dose of 45–51 Gy delivered over 7.5–8.5 days [32, 33]. Penile preservation rates are reported between 80 and 100 %. Kellas-Slezka et al. report the largest series of 55 patients with median follow-up of 4.5 years [34]. A freehand flexible catheter technique was used to place 2–7 catheters to create either a single plane implant ($n=31$) or two-plane ($n=24$). Fraction size was 3.0–3.5 Gy with a median total dose of 49 Gy after biopsy (range 30–54 Gy) or 36 Gy (range 30–45.5) after previous total gross excision. Median duration of implant was 11 days and median follow-up was 59 months (8–152 months). Persistent tumors were seen in four patients and seven had a subsequent local recurrence. Regional failures were seen in 22 % and distant metastases in 5 %. Penile preservation was achieved in 80 % [34]. Although this is a large series with mature follow-up, at the time of writing, HDR brachytherapy for penile cancer must still be considered to be in evolution, as optimal fractionation and homogeneity parameters are yet to be established.

Crook et al. have reported their learning experience in switching from a long experience with LDR penile brachytherapy to HDR. All six patients, with a minimum follow-up of 3 years are NED but one required salvage partial penectomy and groin dissection for local and regional recurrence. Symptomatic necrosis was seen in five of six patients (including the patient with local recurrence) before needle spacing was decreased from a median of 17 mm to 9 mm. Fraction size ranged from 3.12 to 3.75 Gy bid for total doses of 38.4/12 to 53/17. Homogeneity is very important with limitation of the V125 to ~40 %, V200 < 5 % and limiting the volume of confluent 125 % on the skin surface. Greater experience and longer follow-up is required to verify these recommendations [35]. Rouscoff et al. reported experience with 12 patients treated from 2006 to 2013 with 36 Gy/9 fractions over 5 days (6 Gy day 1 and then 4 Gy bid) [36]. There was an average of three planes and nine needles. V150 was 40 % and V200 15 % and the urethra maximum dose was limited

to 115 % (UV115 % < 1 %). Follow-up is only at a median of 27 months; there has been one local recurrence and one regional recurrence. Although significantly "hotter" than the experience reported by Crook et al., there was only one necrosis requiring hyperbaric oxygen, and mild telangiectasia in 33 %. The median V150 in Crook et al.'s experience was 42 % but ranged up to 89 % whereas the maximum V150 in Rouscoff et al.'s series was 57 % [35, 36].

Surface Mold Plesiotherapy

Surface mold plesiotherapy was originally reported by Neave in the LDR era involving an appliance containing Iridium-192 wire sources arranged circumferentially in a cylindrical Perspex template around the long axis of the penis [23]. Since the patient had to wear the appliance for several hours each day, mold plesiotherapy did not catch on as it was too labor-intensive and inconvenient. Neave et al. reported results for 24 patients who wore the molds for a total of 84 h to deliver 55.6 Gy to the penile surface and 46.3 Gy at the center [23]. There was a 79 % complete response rate, 13 % urethral strictures, but nine patients required subsequent salvage surgery. The dose may have been too low as 55.6 Gy at a dose rate of 0.6 Gy per hour over 7 days is less than that typically prescribed with LDR interstitial brachytherapy. Furthermore, mold plesiotherapy does not have the benefit of the inherent inhomogeneity of interstitial brachytherapy which delivers 150–200 % of the dose to significant intratumoral volumes.

Nonetheless, recently there is renewed interest in mold plesiotherapy using HDR afterloading with 2 fractions per day, especially for patients whose tumor has recurred after laser surgery or topical therapy. Matys et al. and Helou et al. have reported techniques involving custom molds produced with 3D printing [37, 38]. The typical dose is 40 Gy given over 5 days with twice daily fractions of 4 Gy each. With the sources embedded in the mold or applicator at a depth of 5 mm from the skin surface, it is possible to limit the skin dose to ~120 % of the prescription dose and achieve 100 % at a 5–10 mm depth tailored to the clinical presentation, with 90 % of the dose at a further depth of 5 mm (Fig. 9.7). A clear Lucite applicator allows verification of penile position for each fraction. There is minimal swelling or dermatitis at the completion of treatment; the reaction peaks at about 3 weeks and takes 6–10 weeks to heal (Fig. 9.8a–c). As there are no long term results reported yet, this technique is investigational at present but if determined to be effective and well tolerated, it may quickly become widely accepted because of availability of the equipment and ease of application.

Patient Selection

For either interstitial or plesio brachytherapy to tumors involving the glans, the patient should be circumcised prior to treatment to allow full exposure of the lesion and to prevent subsequent painful necrosis of the sensitive prepuce, and ultimately phimosis and fibrosis. This procedure will often remove a substantial portion of the tumor burden as frequently both the glans and foreskin are involved.

For interstitial brachytherapy, ideally tumors should be confined to the glans and 4 cm or less in maximal diameter [19, 31, 39]. Extension to the coronal sulcus is common but adequate coverage should be obtained with a proximal

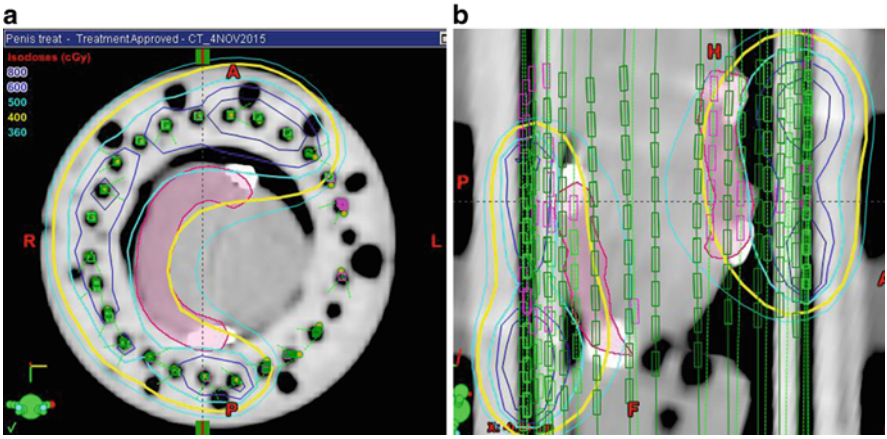

Fig. 9.7 HDR mold plesiotherapy. (**a**) Transverse view of dosimetry through the mold. Fraction size is 400 cGy, given bid with 6 h between. The 100 % isodose is *yellow*, the surface dose is limited to 120 %, and the centre receives 90 % of prescription. The CTV is shown in *pink*. (**b**) Longitudinal view of the same

plane of needles either at, or just proximal to, the sulcus. Of note, these recommendations are based on quite a limited experience and small numbers of patients in each size category. This means that tumor size recommendations are only a guideline for consideration and not an absolute. Kiltie et al. reported three failures in five patients (60 %) with a tumor diameter >4 cm as compared to 3 of 21 (14 %) < 4 cm ($p = 0.05$) [39]. Similarly, Mazeron et al. observed a LF rate of 50 % (2/4) for >4 cm as compared to 11 % (2/19) for <2 cm and 26 % (7/27) for 2–4 cm [31]. A larger multi-institution French experience [40, 41] of 184 patients reported a LF rate of only 20 % for tumor diameter >3 cm versus 14 % ≤ 3 cm ($p = 0.05$) [40]. Crook et al. [42] also reported success with larger tumors in a series of 49 patients; although there were 19 tumors >3 cm, size was not a predictive factor for LF ($p = 0.43$) [43]. This supports the philosophy that although LF may be of greater risk with larger tumors, a strict size limit may not be appropriate. Larger tumors do require a higher volume implant and the risks of both local recurrence and complications such as soft tissue ulceration or necrosis are more common. Thus, these selection guidelines should not be used to exclude patients from brachytherapy, especially if the alternative will be penectomy, but to give them realistic expectations concerning success of treatment and adverse effects.

Grade of the lesion does not impact local control with brachytherapy. In the 74 cases reported by Crook et al., half were well differentiated and half moderately or poorly differentiated. Six of eight local recurrences occurred in well differentiated cases while only two were in moderately or poorly differentiated tumors [18]. However, high-grade lesions are associated with a higher rate of metastatic and regional failure; the status of the regional nodes must be addressed with both imaging and either sentinel lymph node biopsy or groin dissection.

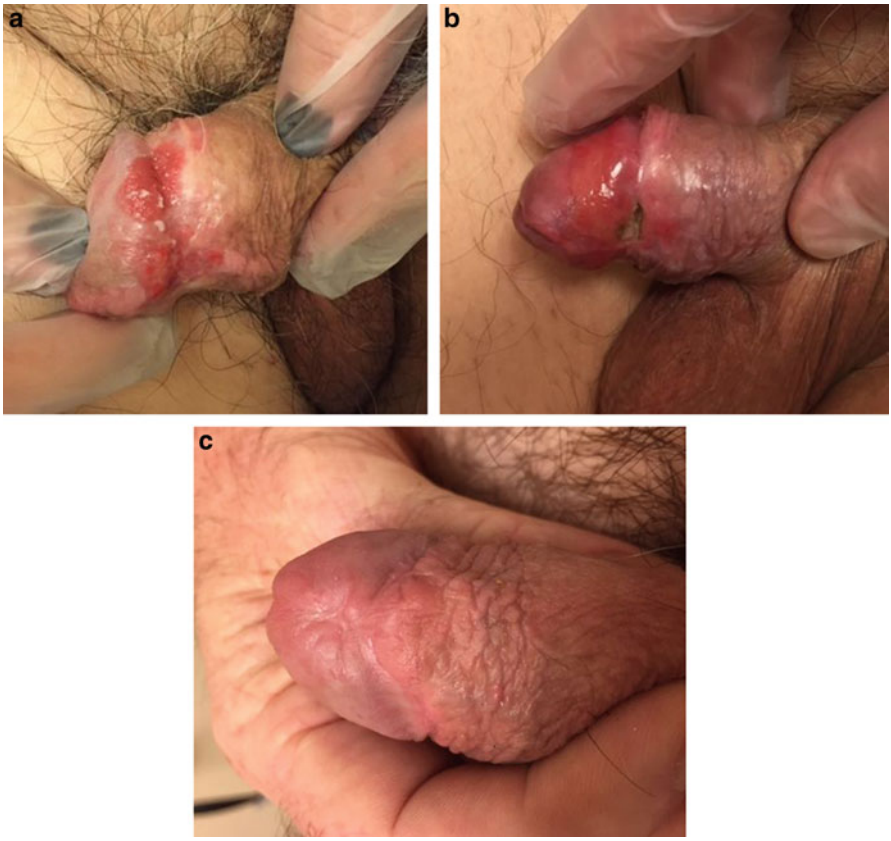

Fig. 9.8 Clinical photos at baseline (6a), and at 6 weeks (6b) post treatment and 3 months post treatment. 4000 cGy in 10 fractions was delivered over 5 days, 2 fractions of 400 cGy bid 6 h apart. (**a**) Tumor at baseline appears suitably superficial. Biopsies showed well differentiated SCC 0.8 mm thick with only superficial invasion of lamina propria and no LVI, clinical stage T1a. (**b**) Six weeks post treatment the ulcer on the ventral glans suggests that deeper invasion was present at that site, but with the prescription dose at 5 mm depth, this was adequately covered. (**c**) Healing at 3 months post treatment

In the 7th edition TNM, tumor stage is determined by the presence of lymphovascular invasion (T1a: no LVI; T1b LVI present) and invasion of the deeper structures of the penis (T2 demonstrates invasion of corpus spongiosum/cavernosum) or T3 (invasion of the urethra) [44]. In Rozan et al.'s experience with 184 patients local failure was seen in 15 % of T1, 16 % of T2, and 23 % of T3 tumors (6/26) [40]. This is similar to Mazeron et al. where local failures were seen in 11 % of T1 (1/9), 22 % of T2 (6/27), and 29 % of T3 (4/14) tumors [31]. Both these reports were published during the 4th edition of the TNM but the definition of T1, T2, and T3 was very similar [45].

Plesio brachytherapy, on the other hand, should be limited to superficial tumors (Tis, T1a or b) and should not be used for those invading the corpus spongiosum or thicker than 5 mm. The same requirement for circumcision prior to treatment holds.

Aftercare

Both interstitial and plesio brachytherapy will cause moist desquamation throughout the treated volume which peaks at about 3 weeks and heals in 6–10 weeks for plesiotherapy but may take 2–3 months after interstitial brachytherapy (Fig. 9.8b). Tumor resolution will result in tissue ulceration, the depth of which corresponds to the depth of invasion of the tumor (Fig. 9.8c). Healing is much slower in diabetics. Local hygiene is important and patients are advised to soak the penis 3–4 times per day in warm water with the addition of baking soda or salt. This is most easily achieved using a coffee mug. A non-stick sterile bandage should be applied using telfa, applied in a tubular fashion and taped to the healthy skin of the shaft and left open at the distal end. Polysporin or Flamazine can be applied after each soak. Antibiotics, either oral or topical, are not usually necessary. Any meatal adhesions, presenting as a restricted or deviated urinary stream, should be gently separated using either the tip of a Foley catheter inserted a 4 cm into the distal penis, or a meatal dilator. Patients can be given their own dilator after their first visit with instructions on how and when to use it.

Late Toxicity

The most common late sequellae are meatal stenosis and soft tissue ulceration. Skin changes are usually very acceptable showing minor telangiectasia, hypo- or hyperpigmentation (Fig. 9.9). Meatal stenosis is reported in 9–45 % [18, 19, 31, 39, 40, 46] of patients but increases with doses over 60 Gy (LDR interstitial) and with proximity of the needles to the meatus [40].

Stenoses tend to occur relatively late but usually before 3 years. Many are low grade and can be managed with self-dilatation once or twice a week, or as necessary, which will avoid more severe stenosis. Meatal stenosis can be largely prevented if adhesions are managed as outlined above. In a series of 50 patients Mazeron et al. reported eight patients with meatal stenosis, three of whom required meatoplasty or reconstructive surgery but used a brachytherapy dose up to 70 Gy [31].

Soft tissue ulceration is reported in 0–26 % of patients after LDR interstitial brachytherapy [18, 19, 31, 40, 46, 47] with the higher rates being seen with larger volume implants (≥3 planes), larger and more deeply invasive tumors [31], and doses >60 Gy [40]. Most will gradually heal over 3–6 months with careful attention to local hygiene, and topical antibiotics. Hydrogen peroxide, topical Vitamin E and topical steroid can also be beneficial. Deeper lesions will respond to a course of hyperbaric oxygen, requiring 30–40 “dives” at 2–2.5 atmospheres breathing 100 % oxygen for 90 min [48] (Fig. 9.10a, b).

Regional Radiotherapy

Prophylactic radiation of the inguinal regions for patients at high risk of node involvement due to moderate or poor differentiation, the presence of lymphovascular invasion, or stageT2 or greater [41, 49] is not generally recommended. Surgical staging of the groins is the preferred approach. Lymph node status is the most

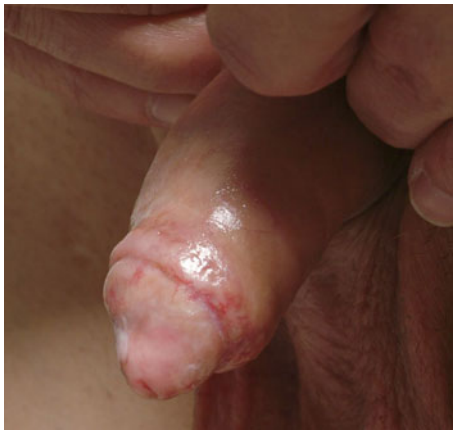

Fig. 9.9 Seven years following LDR interstitial brachytherapy for a T2N2 SCC penis treated with brachytherapy and bilateral inguinal lymph node dissection. A hypo-pigmented scar is seen in the tumor bed and mild telangiectasia. Patient remains potent

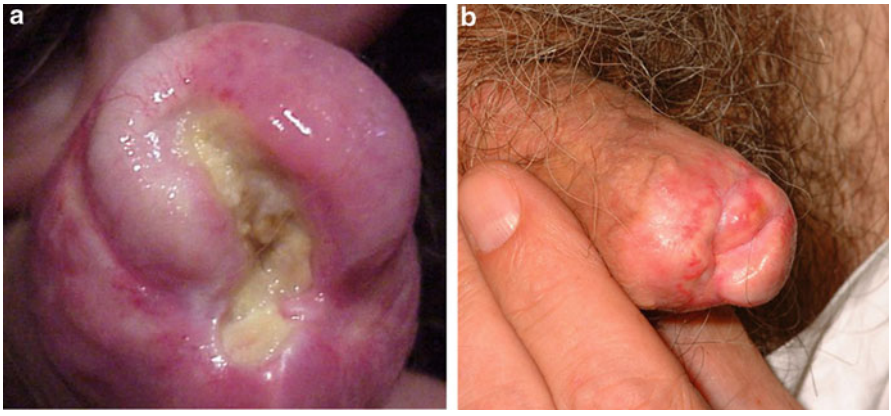

Fig. 9.10 (**a**) Deep tissue necrosis 8 months after LDR interstitial brachytherapy in a 47-year-old with a T3 SCC (invasion of ventral urethra), subsequently healed after hyperbaric oxygen. (**b**) Result 5 years later. Patient remains potent. (*Reproduced with permission from reference* [48])

important prognostic factor for survival, and groin node status determines subsequent pelvic management [50]. Therapeutic node dissection performed for nodal failure is much less efficacious than prophylactic/diagnostic dissection.

Following inguinal node dissection, the same guidelines for postoperative radiotherapy are generally followed as for SCC of the vulva: multiple node involvement or extracapsular extension. If the pelvic nodes are known to be clear pathologically, the radiotherapy can be limited to the inguinal region but for a high risk groin with unknown pelvic node status, the pelvis should be included. If the nodes are negative on imaging the dose does not need to exceed 45 Gy in 25 fractions over 5 weeks. The dose to the groin depends on the completion of the dissection and the presence of positive margins or extracapsular disease in which case a boost to 54–63 Gy should be considered.

Combined Chemo-radiotherapy

Review of the Evidence on the Efficacy of Chemo-radiotherapy from Other SCC Sites

Head and Neck Cancer

In 2013, Forastière et al. reported on the RTOG (Radiotherapy Oncology Group) 91-11 randomized trial of 520 men with Stage III and IV glottic or supraglottic SCC randomized to receive either induction chemotherapy using platinum and 5 flouro-uracil followed by radiotherapy, concomitant platinum and radiotherapy, or radiotherapy alone [51]. There was a significant improvement at 10 years in loco-regional control (65 % vs. 47–49 %; $p=0.003$) and larynx preservation (82 % vs. 64–68 %; $p=0.005$) with concomitant platinum and radiotherapy.

They also found that early salvage laryngectomy was important for long-term survival.

Anal Canal SCC

The EORTC treated 110 patients with locally advanced SCC of the anal cancer (T3-4N0-3/T1-2/N1-3) with external radiotherapy to an initial dose of 45 Gy in 25 fractions followed by a further 15–20 Gy for those with a partial or complete response. Surgery was reserved for non-responders or those with residual disease after completion of treatment, and was offered to this subset when disease was considered resectable. Randomization was between the above-described radiotherapy alone, or combined with concomitant infusion of 5 fluorouracil at 750 mg/m^2 days 1–5 and days 29–33 plus mitomycin C 15 mg/m^2 on day 1. The addition of chemotherapy to radiotherapy increased the complete response rate from 54 to 80 % (85 to 96 % if patients salvaged by surgery are included). The improvement in loco-regional control was 18 % at 5 years ($p=0.02$) and in colostomy-free survival was 32 % ($p=0.002$). Forty-six percent of the studied population was over age 60 [52].

Cervical Cancer

In 2007, Stehman et al. reported an update on the Gynecologic Oncology Group (GOG) trial #123 which randomized 374 women with bulky cervical cancer (>80 % SCC) to either radiotherapy alone or combined with weekly cisplatin at a dose of 40 mg/m^2 [53]. Age range was 21–81 years. Forty percent of the tumors were >6 cm in diameter. The relative risk for progression for women receiving concomitant platinum and radiotherapy was 0.61 (0.43–0.85) compared to radiotherapy alone and at 72 months 71 % of patients treated with concomitant platinum and radiotherapy were alive and disease-free compared to 60 % for those receiving radiotherapy alone. Weekly cisplatin and radiotherapy is considered to be the standard for SCC of the cervix against which all other regimens should be compared.

Vulvar Cancer

Vulvar cancer is the site most commonly compared to penile cancer because of the similarities in histopathology, lymph node drainage, age groups, and HPV etiology. In 1986,

Homesley et al. reported a survival advantage for post-operative groin-plus-pelvic radiotherapy after a positive inguinal lymph node dissection [54]. One hundred and fourteen women who had undergone radical vulvectomy plus inguinal lymph node dissection were randomized in this phase III GOG study to either pelvic lymph node dissection ($n=55$) or groin-plus-pelvic radiotherapy ($n=59$). A simple parallel-opposed beam arrangement was used to deliver 45–50 Gy in 4.5–6 weeks. Those women receiving pelvic plus groin radiotherapy showed a 14% increase in 2-year survival, from 54 to 68% ($p=0.02$) compared to those undergoing pelvic node dissection. If two or more lymph nodes were involved then the improvement was from 37 to 63%. The addition of post-operative radiotherapy reduced groin failures from 13/55 to 3/59. Surgery, however, was better at controlling pelvic disease. There were 15/55 patients with positive pelvic nodes in the surgical arm but only one subsequent pelvic failure as compared to four pelvic failures in the radiotherapy arm. Mild lymphedema was not significantly different between the two groups (19% vs. 11%).

A phase II trial, GOG 101, went on to explore the concept of pre-operative combined chemo-radiotherapy for advanced vulvar cancer. In 2000, Montana et al. reported the results for 52 women with N2-3 SCC of the vulva [55]. Although 52 were registered, 6 were found to be ineligible, 4 did not complete treatment, and 2 died of other causes. Treatment consisted of 4760 cGy in a split course with cisplatin 50 mg/m^2 and 5FU for 4 days at the start of each radiotherapy course. In 38/40 patients, the nodes became resectable and a complete histologic response was seen in 15 patients. There was only one groin recurrence; two patients died of treatment complications. At a median follow-up of 78 months, 20 women were alive without evidence of disease.

Given the success with this regimen, the next GOG trial investigating management of advanced vulvar cancer involved a continuous course of radiotherapy rather than a split course, and the chemotherapy was chosen to follow the successful example from cervical cancer. The 5FU infusion was dropped as it was considered to add unnecessary toxicity. In 2012, this Phase 2 trial of radiotherapy plus weekly cisplatin for locally advanced T3-T4 N0-3, SCC vulva (GOG 205) was reported by Moore et al. [56]. Fifty-eight women with disease that was not surgically resectable received radiotherapy to 57.6 Gy plus weekly platinum at a dose of 40 mg/m^2.

Complete response was documented in 64%, and pathologically confirmed by biopsy. Forty-seven percent of the women were over 60 years and 24% over 70. A maximum of seven weekly cycles of platinum was allowed; 69% completed at least five cycles. There was one death from treatment-related complications. The radiotherapy in this protocol was mandated as a simple parallel opposed pair of beams. Intensity-modulated radiotherapy was specifically not allowed as there were felt to be potential quality assurance issues with this new and technologically complex advance in radiation delivery and planning.

Beriwal et al. have subsequently reported on the use of IMRT for stage II–IVa vulvar cancer, with combined chemotherapy and has described excellent tolerance with no grade 3 or higher toxicity in 18 patients [57].

From this series of sequential clinical trials on vulvar cancer, current management of loco-regionally advanced disease has been defined as employing a continuous course of radiotherapy in 1.8 Gy daily fractions to a dose of 57.6 Gy, combined with

weekly cisplatin at 40 mg/m^2. Intensity-modulated radiotherapy is recommended to decrease toxicity and spare normal organs. The American College of Radiology (ACR) Appropriateness Criteria for the management of loco-regionally advanced SCC of the vulva specifically recommend either neoadjuvant chemo-radiotherapy or definitive chemo-radiation [58]. Only in countries where radiation therapy is not available would neoadjuvant chemotherapy alone be considered as a potential option.

The weight of evidence from other SCC sites would suggest that a similar approach for penile cancer would be a rational choice. Currently, the International Rare Cancers Initiative, Cancer Research UK (CRUK), the Institute of Cancer Research (ICR), and the National Cancer Institute (NCI) are collaborating in InPACT, the International Penile Advanced Cancer Trial, hoping to define the role of neoadjuvant therapy in node-positive penile cancer. Using a Bayesian design, 400 patients from Europe and the United States will be accrued over a 5-year period. For patients presenting with clinically involved groin nodes, surgery will be compared to neoadjuvant chemotherapy and neoadjuvant chemo-radiotherapy. For those men with a high risk of pelvic node involvement due to high-risk groin pathology, prophylactic pelvic lymph node dissection followed when indicated by chemo-radiation will be compared to chemo-radiation alone, without surgery to the pelvis [59]. If successful, this trial will provide much needed evidence to define the role of adjuvant and neoadjuvant treatments in penile cancer.

Following the evidence from other SCC sites including vulvar SCC and cervical cancer, the combination of weekly cisplatin at a dose of 40 mg/m^2 plus radiotherapy is well tolerated and effective even in elderly patients provided they have adequate renal function [53, 60]. This approach is recommended for loco-regionally advanced presentations not considered operable. If response to treatment renders the disease resectable, this can be planned after a dose of 45 Gy, the alternative being to continue to a definitive dose for the bulk of disease, bearing in mind that lower radiation doses will be effective when combined with weekly cisplatinum.

The following case illustrates the application of this approach. A 76-year-old solitary ranch hand presented with a 6.5×4.5×4.3 moderately differentiated SCC involving the entire penis from the meatus to the penile-scrotal junction, deeply infiltrating the corpora, with positive margins following total penectomy. Clinical bilateral inguinal adenopathy (10×6 cm on the left) extended on CT to the distal paraaortic region (Fig. 9.11a–c). Figure 9.11e shows his radiation fields and Fig. 9.11b–d document the response on CT 5 months after treatment. He had no evidence of disease on repeat CT scan 2 years after treatment and declined further follow-up due to advancing age and travel difficulties. He later died of pulmonary metastases at 3.5 years with no evidence of local or regional failure.

The International Penile Advanced Cancer Trial (InPACT), sponsored by the International Rare Cancers Initiative, the Institute of Cancer Research (ICR), Cancer Research UK (CRUK), and the National Cancer Institute (NCI) will test this approach in the neoadjuvant scenario against surgery alone or neoadjuvant chemotherapy (TIP regimen: paclitaxel, ifosfamide, and platinum) [61] for men with pathologically involved inguinal nodes, and for those men with high risk groin pathology in an adjuvant postoperative setting or in place of pelvic node surgery.

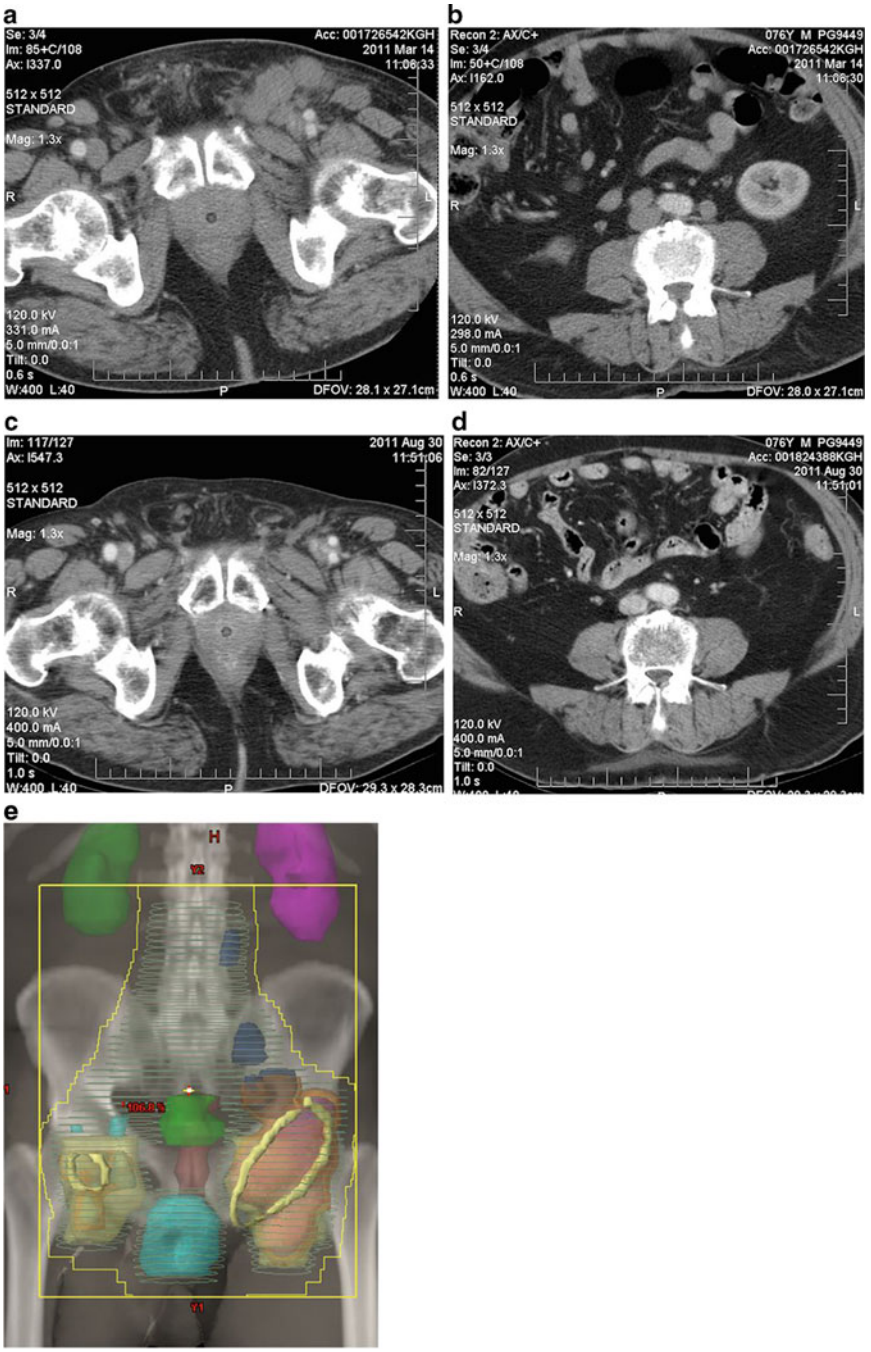

Fig. 9.11 CT scan showing baseline staging and response at 5 months for 76-year-old with locoregionally advanced penile SCC treated with external beam radiotherapy and concurrent weekly cisplatinum. (**a**) Bilateral inguinal adenopathy (**b**) Adenopathy at level of L4. (**c**) Resolution of inguinal adenopathy 3 months after completion of treatment. (**d**) Resolution of lower para aortic adenopathy 3 months after completion of treatment. (**e**) Treatment fields with adenopathy contoured on CT and outlined with wire in the inguinal regions. 4500 cGy was delivered in 25 fractions over 5 weeks to the entire volume, followed by a boost to the right groin to 5500 cGy and to the left groin to 6500 cGy

Palliative Treatment

Standard short course radiotherapy of a single, 5 or 10 fractions, may palliate metastatic disease but is not that effective for bulky groin adenopathy. Although these patients may be elderly and frail, consideration should be given to combined platinum and radiotherapy provided kidney function is adequate with a GFR > 50 mL/min.

Conclusions

Radiotherapy has a clear role to play in the curative management of SCC of the penis, both in management of the primary tumor and in control of the high-risk groin or pelvis following surgical nodal staging. Acceptance of the latter is growing and the success of InPACT will provide much needed Level One evidence in this regard. In management of the primary tumor, penile preservation is recognized as an important goal. Penile cancer is relatively uncommon and much of it is managed in the community where urologic surgeons may not be experienced in the surgical alternatives to partial or total penectomy. Access to radiotherapy, on the other hand, in the developed world is generally readily available, and provides effective penile sparing alternatives to surgery. A recent meta-analysis by Hasan et al. looked at the outcome of surgery compared to brachytherapy for 2178 men, 1505 treated by penectomy and 673 by brachytherapy [62]. Organ preservation for brachytherapy was 74 %. Limiting the analysis to Stage I or II disease, 5-year overall survival was 80 % for surgery ($n = 659$) and 79 % for brachytherapy ($n = 209$) and local control was 86 % versus 84 %, respectively (n.s.). Despite these excellent results, urologists are not always aware that radiotherapy maybe a very well suited option not compromising oncological outcomes in appropriately selected patients, and some radiation oncology departments, presumably through lack of expertise and familiarity, have literally abandoned radiotherapy of the primary tumor as a viable treatment option they offer [63]. This is regrettable and is being addressed in some jurisdictions by national specialty societies.

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New Systemic Approaches and Clinical Trials in Penile Cancer

10

Mayer Fishman

Introduction

In a more ideal future, one may imagine a chapter about clinical trials for penile cancer with completed, "level 1" evidence from phase III randomized trials, comparative efficacy and toxicity evaluations, and perhaps a discussion of for which subset a particular treatment had appeared more efficacious, and confirmatory or exploratory plans. However, at this point in 2016, there are no results and only limited plans of phase III trials. This is an intrinsic, and not unique, limitation for the situation of a rare cancer. While potentially discouraging from the standpoint of sketching a diagram a couple of arrows indicating recommended treatment approaches, we must not be deterred, neither from working toward a treatment plan for a patient, nor from developing earlier-phase clinical trial efforts. In the chapter are surveyed some of the systemic approaches (not altogether new) and what one will hope will be an evolving clinical trials survey. These are presented organized by the dominant modality: Classical cytotoxic chemotherapy; radiation therapy; immunotherapy; and targeted therapies. As addressed below, the coordinated use of radiation and surgery may be the key to getting the most out of the chemotherapy impact on penile cancer. While it is convenient for clinical trials to describe the treatment series as separate phases, for an individual patient, strategic combination of these pieces—not generically or exactly described in the literature or a pathway flowchart—could be the individual's path to a better outcome.

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Table 10.1 Selected drug categories of interest for development in penile cancer therapy

General class	Mechanism	Examples
Conventional cytotoxic drugs	Platinating DNA damaging agents	Cisplatin
		Cyclophosphamide
		Bleomycin
	Microtubule agents	Vinblastine
		Paclitaxel
	Antimetabolites	Gemcitabine
		5-fluorouracil
Targeted drugs	Cell surface and intracytoplasmic tyrosine kinase enzymatic inhibition	Pazopanib (VEGFR)
		Afatinib (EGFR)
	DNA repair enzyme inhibition	Olaparib (PARP)
	NCI-MATCH trial	Various (over 30)
Immunotherapy	General immune	Nivolumab, pembrolizumab, atezolizumab
	Modulation: Checkpoint inhibitors (PD-1, PD-L1, CTLA-4, others)	Ipilumimab
	Specific to HPV	E6 HPV vaccine
		CAR-T cells

Chemotherapy: A Sparse History

Cisplatin

The sensitivity of squamous cancer to platinum drugs, that is to the say the potential for significant, major regressions, has been observed for decades. Cisplatin-based therapy, mostly in combinations with medications for which synergistic efficacy had been already demonstrated in cancers with higher incidences than for penile cancer, is the subject of several single-arm series. The mechanism of action for cisplatin and many other conventional cytotoxic drugs depends on introducing single-strand, or for others double-strand breaks and other lesions in DNA, and then thus initiating apoptosis. Other conventional type cytotoxic drugs can include those that affect nucleic acids at the point of, or before the point of incorporation, such as 5-fluoruracil or methotrexate. The taxanes and vinca alkaloids are class of medication that bind tubulin, and so affect microtubules; defects of mitotic spindle function then do also favor an apoptotic process. None of these mechanisms would be considered unique to squamous cancer.

The history of the application of cisplatin use in squamous cancer is as early as 1979, when Sklaroff and Yagoda published a penile cancer series, with one complete response (CR) and two partial responses (PR; duration 2 and 7 months) among eight patients [1]. While not all patients have a practical organ reserve for this medication, these series serve as basis for treatment planning for many patients. The

factors that can be prohibitive for cisplatin use—and this would not be represented in these series—can include performance status and comorbid burden, renal function, neuropathy, and marrow reserve.

The next series using a monotherapy of cisplatin, with a schedule of 50 mg/m^2/dose on days 1 and 8 of a 28-day schedule, was organized through the Southwest Oncology Group (SWOG) [2]. Only 4 of 26 patients had partial response (PR), and with duration of only up to 3 months. The practical issue for cisplatin therapy has evolved considerably since that era with innovations including understanding the importance of careful pre- and post-hydration with each dose, a depth of experience with dosing regimen and combinations, neutrophil growth factors, and anti-emetic regimens incorporating 5-HT3 antiemetics (such as ondasetron, granisetron, or palonosetron) as well as NK1 (neurokinin1) antiemetics (such as aprepitant or fosaprepitant; or rolapitant).

Earlier Cisplatin Combinations

The earliest published report is a 1990 report by Hussein and colleagues who described combination therapy, adding 5-fluorouracil (5-FU) to cisplatin, in a series of six patients (apparently earlier stage than the prior series), and finding of one complete response (CR) and five PRs, including patients then resected or treated with radiation therapy to no evidence of disease [3]. The cisplatin was dosed at 100 mg/m^2 on day 1, and the 5-FU was then over 96 h starting on the second day. A report with a similar schedule, from Europe in 1992 [4] also described responders, with PR in two of eight. A more contemporary retrospective review about 25 patients was presented by Di Lorenzo and colleagues in 2012. In this series, encompassing four institutions and a decade, none had CR; eight had PR; additional ten were designated as stable [5].

A different combination approach, for which three responses were seen among 14 patients, some of whom had tumor ulceration, was described by Dexeus and colleagues from MD Anderson in 1991, with cisplatin and bleomycin intravenously (11) or intra-arterially (3) and addition of intravenous methotrexate [6]. In 1993 Kattan and colleagues also described 3 responders, among 13 patients with penile cancer in France, who had had combination treatments all of which included cisplatin; of still contemporary interest, this was 12 years' experience, reflecting the practical difficulty for making conventional prospective, fixed-regimen format trial for studying this diagnosis [7]. A single-arm cooperative group study (cisplatin 75 mg/m^2/dose, every 21 days and methotrexate and bleomycin on days 1 and 8) from SWOG was reported by Haas et al. in 1999 and described that among 45 penile squamous cancer patients, of whom 40 were evaluable had been observed five CR and eight PR, but also five treatment relate deaths, and additional six patients with at least one life-threatening toxicity event [8]. Thus, while the experience with the triplet did reproducing anticancer responses (32.5 %) seen in the prior smaller series, the key limitation of escalated intensity, a key factor in personalized care, was brought to the fore.

Taxanes

Already a decade after the routine use in non-small cell lung cancer, breast cancer and other settings, paclitaxel activity in the post-cisplatin setting was described with 3 of 12 partial responses in a monotherapy prospective trial, by Di Lorenzo et al. [9]. Taxane combinations have been developed further for penile cancer therapy, notably in the TIP (paclitaxel [Taxol®] ifosfamide cisplatin) and the TPF (docetaxel [Taxotere®] cisplatin 5-fluorouracil) combinations; the paclitaxel cisplatin-5-FU combination also may be termed TPF. With reference to cancers that are the subjects for more formal prospective studies, the former has resemblance to some germ cell cancer regimens; the latter to a treatments used in head and neck and esophageal cancers.

Bermejo and colleagues described that in a retrospective review of 59 patients treated at MD Anderson, among those receiving neoadjuvant intravenous chemotherapy ten had then been treated with subsequent surgical resection. Median survival of those with three or fewer positive lymph nodes was 48 months [10]. The same group addressed use neoadjuvant cisplatin (25 mg/m^2/dose x3) ifosfamide (1200 mg/m^2/dose x3) paclitaxel (175 mg/m^2 x1) TIP chemotherapy in 30 patients. Fifteen of the 30 had major response; 22 went on to definitive-intent surgery; among these patients 11 were long-term disease-specific survivors (two died of other causes). Favorable predictive features observed included chemotherapy response, no bilateral residual cancer, no extranodal extension, and no skin involvement [11].

Nicholson and colleagues reported in 2013 on a multicenter 29 patient phase II study of TPF from the UK. Although 10 of 26 evaluable patients (38 %, 95 % CI: 20.2–59.4) had objective response, including two with locally advanced disease having CR, this did not meet the pre-specified target of >14 PR, and two-thirds of the patients had at least one toxicity of at least grade 3 [12]. Another slightly larger prospective study from China is reported by Zhang and colleagues, and described a similar response rate, 15 of 39 patients (38 %, 95 % CI 23–55 %), but still median PFS only 3 months, and median OS 7 months [13].

Irinotecan and Gemcitabine

Among combinations with relatively newer conventional cytotoxic drugs is and irinotecan. Irinotecan is a topoisomerase I inhibitor. A combination series from the EORTC was reported by Theodore and colleagues in 2008, consolidating reports for patients on neoadjuvant treatment (four cycles) or advanced disease treatment (up to eight cycles). They observed two CR and six PR among 26 evaluable patients; this ORR of 31 %, 80 % confidence interval 19–45 %, which failed to exclude the study hypothesis to exclude a response rate below 30 % [14].

Gemcitabine with cisplatin is a dominant consideration for therapy of urothelial cancers, also extends to intra-arterial treatments. Again, the largest base of experience is outside the genitourinary system, in non-small cell lung cancers. Power and colleagues described in 2009, two patients with good palliative impact for intravenous gemcitabine-cisplatin treatment [15]. An intermediate report on a phase II trial

presented by Houédé and colleagues gives results for 25 patients treated between 2004 and 2010, with two PR and ten SD responses, and 5.5 months median time to progression—a response rate deemed not high enough to recommend an emphasis for further development [16].

Intravenous or Intra-arterial Therapy

This intra-arterial approach was a part of the 1991 report of Dexeus et al. [6], and is the subject of later series as well. The anatomy of the perineum, particularly being distal to the renal and most of enteric circulation, does allow for potential use of intra-arterial cisplatin or other conventional chemotherapy in a way that bypasses renal arterial first-pass exposure. Roth and colleagues describe the position as a femoral artery approach, with the tip beyond the inferior mesenteric artery, above the aortic bifurcation [17]. Roth and colleagues described the treatment of eight penile cancer patients (as well as eight anal cancer patients, by the same approach), using a five-part combination (cisplatin; 5-FU; methotrexate; mitomycin C; and bleomycin), with three each of penile and anal cancer having CR; and additional partial responses.

Clearly, for most medical oncology contexts, a reliance on intra-arterial therapy does involve coordination of the infusion process with interventional radiologist, for the placement of the intra-arterial catheter, and the administration of the chemotherapy which may be in a setting very different from a typical infusion center. Myelotoxicity or nausea risks would be expected to not be different.

An additional five patients treated in Japan with intra-arterial chemotherapy (same five drugs, one patient had carboplatin instead) were reported by Chen and colleagues. Among these neoadjuvant patients who had refused up-front surgery, were observed one CR and four PR [18]. Overall, however, the experience with this route of administration remains quite limited. Huang et al. reported one CR and two PR among three patients receiving monthly intra-arterial cisplatin methotrexate and bleomycin, reported in 1999 [19].

A Chinese series describing outcomes for 12 subjects with intra-arterial gemcitabine and cisplatin treatment of locally advanced penile cancer, over a period of 12 years, was reported by Liu and colleagues in [20]. Ten had major response, and three were long-term survivors. Overall, despite the long term of the experience, the base of intra-arterial treatments and the logistics remain limiting, although the rationale and particularly the potential for organ preservation do present a key appeal. Further formal study and standardization of protocols to accommodate prospective testing are lacking.

Timing Considerations

While there are few data to guide which chemotherapy to use, notwithstanding the above experiences of a couple hundred patients over a few decades, there are even less data to guide a uniform recommendation on treatment before, during, or after other

modalities. A treatment for advanced disease that is metastatic and not potentially surgically resectable to potential cure is the most straightforward medical context; recurrent metastatic disease after surgery is a similar context, although it is logical to define a distinction between small-volume, longer-latency cancers as compared to widely metastatic, rapid early regrowth. Similarly to those patients with a demonstrable metastatic pattern, a penile cancer that at presentation technically unresectable but only apparently locally spread presents a situation for which initial medical therapy (the neoadjuvant schedule) is a relatively rational recommended consideration for initial treatment.

On the other hand, the period time immediately after potentially or apparently definitive resection of the primary cancer is one for which treatment decisions are further less well-defined. Clearly there will be some patients for whom the recurrence risk defined by the [residual] cancer in the resected specimen appears minimal—small volume, single superficial node area, for example. And at the other end of the risk spectrum will be patients (still technically resected to no evident disease) with features such as were identified as adverse by Pagliaro and colleagues [11]: Large volume of nodal disease, bilateral pattern, extranodal pattern, and skin-extension pattern. For the latter group, the balance of risk would be to favor immediate action to escalate treatment intensity, to try to tip the balance to prevent recurrence.

Thus is framed the question of how much disease risk should be present before a recommendation of adjuvant treatment, whether regional radiotherapy, radiotherapy with concurrent chemotherapy, or single- or multi-agent chemotherapy systemic treatment. In a small series (cisplatin/bleomycin/methotrexate) that includes some adjuvant patients, Hakenberg et al. describe the risk of treatment-related death in plain terms [21]. Adjuvant use of cytotoxic chemotherapy in most other cancer has been approached cautiously, recognizing that the incident population represents an uncertain ratio of patients who could not benefit and those who might benefit. (The former include a proportion who would have been cured anyway, or whose disease was absolutely insensitive to the treatment planned, or died first of other causes before the disease in question, or died from treatment-related toxicity; the latter are those for whom the disease is sensitive, and eventual progression is substantially delayed or actually prevented.) The situation for penile cancer therapy is that there are no generalized trial results to interpret. This risk:benefit ratio is left for the judgment of the treating physician and the patient's own interpretive perspective. The NCCN guidelines identifies a key tipping point for greater than pathological N1 (that is pN2 or pN3; or cN3 [pelvic LN]; or pM1) for adjuvant chemotherapy, or for lymph node dimension over 4 cm for neoadjuvant chemotherapy [22].

Overall, any regimen known to show activity in advanced disease could reasonably be discussed in this adjuvant context; however this adjuvant timing for chemotherapy, as well as the choice of medications, are ones that are not amenable for description as a standardized intervention. Nicolai and colleagues present what is probably the largest specific neoadjuvant and adjuvant experience, using a taxane (paclitaxel or docetaxel), cisplatin and 5-FU for 28 neoadjuvant patients and 19 adjuvant patients with N2M0 or N3M0 pattern of regional spread. Over the 8 years in which this non-randomized series accrued (2004–2012), they describe a practice pattern shift toward neoadjuvant treatment. Among the neoadjuvant treatment patients

were recorded 43 % "clinical responses" and 14 % complete pathologic remissions. Response was not associated with survival; however, associations of worse outcomes for N3 disease, and for p53 status, and for bilateral disease were observed [23].

Practically speaking the key decision for pursuing a neoadjuvant approach will be based on the clinical assessment of the extent to which the disease could be completely resected. Conversely, the key decision point on adjuvant therapy, whether as chemotherapy alone or concurrent with radiation therapy, will be on the clinical and pathologic assessment of the extent of remaining or metastatic disease.

Radiation Therapy

Radiation therapy is not per se a systemic treatment, but there are few points that can be mentioned in the interface of radiation treatment and systemic therapies. The first relates to timing in relation to other modalities of treatment. Extrapolating from the experience of other cancer diagnoses, an *induction* multiagent chemotherapy treatment could be used prior to a definitive-intent radiation therapy approach. While certainly rationale in favor or opposed to this for a given penile cancer, patient could be developed along lines exactly parallel to those for neoadjuvant chemotherapy before surgery; the data for this diagnosis quite limited. Extrapolating from experiences, for example, in head and neck cancer, a phase III trial adding TPF induction before definitive radiotherapy did not improve outcomes [24], although a prior meta-analysis did show better outcomes [25].

The two key interactions of radiation therapy with systemic treatments relate to concurrent use of radiosensitizing chemotherapy, and to the role of local tissue destruction as a potential priming event of an immune response [26, 27]. The former is not the subject of any series particularly devoted to penile cancer, but approaches extrapolated from experiences for therapy of other squamous cancers, such as weekly cisplatin (squamous cervical cancer, e.g. [28]; head and neck cancer, e.g. [29]) or mitomycin and 5-FU (squamous anal cancer, e.g. [30]; muscle invasive urothelial bladder cancer, e.g. [31]).

The latter concept, to leverage tumor and stromal changes from radiotherapy to cause a better anticancer immune response is among many in development in conjunction with checkpoint inhibitor treatments. Some of the latter may ultimately include penile cancer patients not as a separate cohort, but rather as part of a multi-diagnosis immunotherapy development process, particularly in early-phase clinical trials.

Immunotherapy

The potential for anticancer immunotherapy, manifested in contemporary trials for many malignancies, with checkpoint inhibitors and other new technologies, was presaged by penile cancer immunotherapy treatment with interferon and by use of imiquimod on genital warts, an HPV-associated lesion that may be precursor of some penile cancers. Work from Greece, described by Mitrolopous et al. introduced

a biologic, immunotherapy partner for cisplatin. Thirteen patients with nonmetastatic cancers had cisplatin treatment (fractionated as 20 mg/m^2/daily for five consecutive days) in combination with interferon α treatment. There were nine responders, four of which were CR, and patients were then able to have less extensive, but definitive-intent surgery [32]. Once again cisplatin-based therapy was understood as a part of a strategic multidisciplinary approach. The use of imiquimod is supported through conventional randomized trials leading to an on-label medical therapy of squamous penile lesions, although not actually for penile cancer [33].

In contrast, for the current era, new trials have immunotherapy as the central mechanism of action. Future emphases that can be considered for development for the application to penile cancer immunotherapy can be organized into three general categories: Checkpoint inhibition, specific HPV-directed immunization, and autologous cell therapies.

General immune modulation such as checkpoint inhibitors are in wide development and with practical on-market access to nivolumab and pembrolizumab (PD-1) and atezolizumab (PDL-1), and ipilumimab (CTLA-4) and hundreds of translational and clinical projects including those and other inhibitors of similar pathways, such as darvelumab, avelumab (PD-1); tremilumab (CTLA-4); lirilumab (KIR); can be expected to continue with the rapid progress in transforming cancer care. Considering a couple examples focused on squamous cancers from other anatomic sites: lung squamous cancer [34], HPV positive head and neck cancer [35], and (nonmelanoma) skin cancer [36]. It would seem unlikely that penile squamous cancers do not have some potential for a major therapeutic response. Mechanistic evaluation of resistance to these includes not only features of the tumor cells (such as tumor cell PDL-1), but also phenotypic polarization of the infiltrating leukocytes, such as lymphocytes, dendritic cells, and macrophages, and intratumoral tertiary lymphoid structures [37–39]. Checkpoint inhibition therapy is not a category that would be expected to be restricted for its efficacy to only HPV-associated penile cancers.

While the driving neoplastic events for penile cancers are no doubt heterogeneous, at least with regard to a divergence between those that are HPV-related and those that are apparently independent of an antecedent viral infections, those that are HPV-related can be extrapolated to have epidemiologic mechanistic similarity to HPV-associated cervical cancers. Vaccination directed at proteins specific for HPV-associated cancers, such as E6/E7, or with virus like particles specific to high-risk HPV serotypes are under active development dominantly in the cervical cancer and the head and neck cancer fields. Looking in the longer term, global efforts for HPV vaccination both of girls and of boys should be anticipated to impact the extent to which high-risk serotypes are prevalent, and thus, directly the eventual decrease of penile cancers. While primary impact on HPV epidemiology can be a long-term target to then attenuate the incidence on early stages of HPV-associated penile cancer, the same biology derives opportunities for intervention on advanced cancers.

Some vaccine approaches, including both murine models with established HPV positive cancers (e.g. [40, 41]) and localized CIN3 cervical cancer (e.g. [42]), are promising; migration to use of these to be testable for treatment of penile cancer would seem straightforward.

T-cell receptor gene transfer, again using the same antigenic target is an evolving technology. The autologous leukocytes are modified so as to have TCR specific for HPV, expanded and re-infused [43]. The leading application of the chimeric antigen receptor (CAR-T) technology has been in the setting of lymphoid cancers (e.g. [44]). The further logistic development of these and similar modified autologous lymphocyte applications could be an exciting step forward for solid tumor therapies. In the initial cervical cancer treatment series, three of nine patients had major response [45].

Targeted Pathways

The targeted drugs, covering both small molecule kinase inhibitors [46], many other pathways such as PI3K, p53, PARP, and many more, and antibodies to proteins that are mechanistically associated with driving the malignant phenotype have been developed widely across oncology, with new indications and new drugs appearing monthly. Can targeted drugs be relevant for a particular case of penile cancer, or generally active? The rarity of the population, the high number of candidate drugs, and the absence of a clear, specific driver pathway of penile cancer for the whole population appear prohibitive of a single-diagnosis, single-trial conventional clinical trial approval approach. Fortunately, this issue of different kinase or cell surface protein heterogeneity across the population of patients with the diagnosis is not an issue unique to penile cancer. As with other rare cancers, subsets of cancers with more common sites of origin and histology may also be in this situation.

The process of matching a particular individual's tumor with a candidate-targeted drug has been addressed by commercially available products for molecular testing of the tumor. While testing with a panel of probes to look for actionable mutations, a couple examples include diagnostic products such as FoundationOne (www.foundationmedicine.com) or Guardant360 (www.guardanthealth.com). These may identify a seemingly culprit mutation, and that mutation may be associated with a particularly, technically available medicine; there are still issues to be addressed for practical application. First, there may be no medicines suggested, or one that is suggested may be not yet on the market. Second, there may be multiple medicines suggested, with no practical way for them to be ranked as far as chance of response. Third while the molecular matching concept is intellectually appealing, it does represent a departure from the way a medical recommendation would be conventionally presented to the patient. To estimate the risk/benefit ratio, the benefit needs to be estimated. Risks, on the one hand may be an empirically derived base side effect profiles derived from registrational trials or other broader post-marketing experiences. Although the specialized, individualized test suggests a chance of response, benefit chances really are unknown. This is not a new issue, because the same situation of no base of response experiences is there for an individual participating in an early phase clinical trial. As much as the appeal, and the real, but still isolated, successes, there is still a potential disconnect between an elaborate, elegant, and accurate mechanistic development and a worthwhile, durable response for any particular individual. The patient must face this unambiguously.

Contemporary Trials

This short section is meant as a survey—trial options could change rapidly. These several trials are all on an exploratory scale, with a single arm and a limited number of projected subjects. Just because a trial is open does not prove that the intervention under study will be a therapeutic success. Practically speaking the trial search may include these several trials, that can be found on Clinicaltrials.gov (with a search term of *penile cancer*), or also open-diagnosis trials, which may be open to unspecified diagnosis, a category that may be *solid tumor*, *adult*.

In Europe, is the Spanish trial, PAZOPEN-SOGUG (NCT # NCT02279576), which addresses use of VEGFR-TKI pazopanib and microtubule-chemotherapy, paclitaxel. Pazopanib has an indication for therapy of renal cancer and of soft tissue sarcoma. The microtubule-directed vinca alkaloid vinflunine, which has an indication for bladder cancer treatment in Europe, but not in the US, is the subject of the VinCAP (NCT# NCT02057913) open in the UK.

In the US, the University of Alabama (Birmingham, Alabama) has open an EGFR-targeted drug monotherapy, with afatinib (NCT # NCT02541903). The FDA indication for afatinib is for non-small cell lung cancer (which include squamous cancer) for patients whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R). In a multi-arm trial (NCT# NCT02721732), at MDACC (Houston, Texas) there is a squamous penile cancer arm using PD-1 checkpoint inhibitor immunotherapy, pembrolizumab, which has US FDA indications for therapy of non-small cell lung cancer and for metastatic melanoma. In Baylor (Waco, Texas), the HESTIA trial (NCT02379520) is a treatment with autologous dendritic cells that have been stimulated ex vivo with HPV proteins E6 and E7, also have been transduced with a mutant TGF-beta receptor, to decrease the potential for downregulation by TGF-beta.

An open diagnosis trial, the NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) Trial (NCT02465060), is one for which penile cancer patients could be eligible. In the testing phase is a comprehensive analysis of known target proteins, and then in the treatment phase a patient would be then assigned to a marker- and drug-specific cohort, independent of the anatomic site-of-origin of the cancer. It is acknowledged that no such target may be particularly evident for most patients, and the question of the clinical activity for that target:drug pairing is the issue being tested: Just because a match is observed, clinical activity is still the question.

The planned cooperative group trial InPACT (International Penile Advanced Cancer Trial ECOG-EA8134) (Fig. 10.1) will address the two fundamental timing questions, these are neoadjuvant and adjuvant treatment with cisplatin-based treatment, with a prospective single diagnosis, multicenter, randomized allocation format. The proposed schema is illustrated here. For patients with inguinal adenopathy, there is an initial randomized allocation to upfront surgery (inguinal lymph node dissection), or neoadjuvant chemotherapy then surgery, or neoadjuvant chemoradiotherapy, and then surgery. Following surgery, the pathologic response will be evaluated, to define further treatment. Those with low-risk features would continue on observation, and then those without prior radiotherapy are to be randomly allocated to either chemoradiation therapy, or pelvic lymph node dissection surgery then chemoradiation

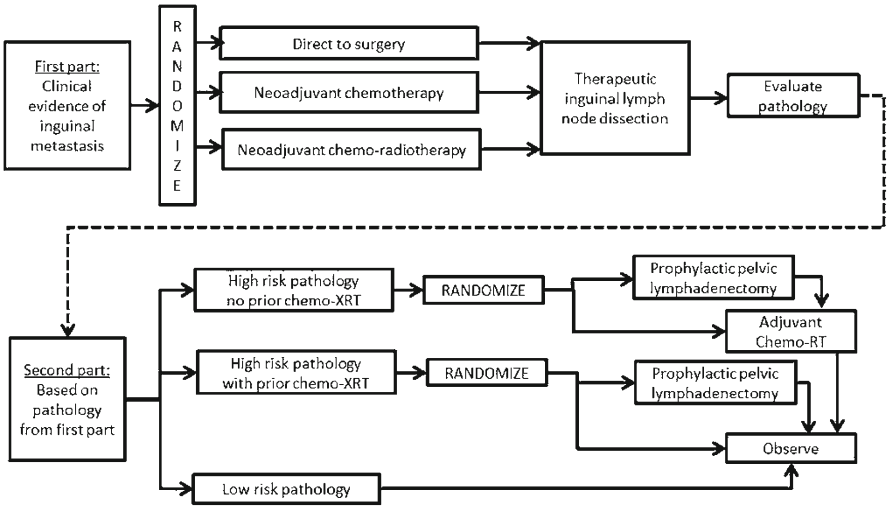

Fig. 10.1 Schema of InPACT trial

therapy; for those with high-risk features and prior radiation therapy, are to be randomly allocated to either surveillance or to the pelvic lymph node dissection surgery.

Conclusions

Progress in medical therapy for penile squamous cancer has been limited by issues that are common to the study of many rare tumors: Lower numbers of patients for clinical trials, heterogeneity of the underlying oncogenic mechanism, and heterogeneity of stage and extent of spread are intrinsic to penile cancer. Progress in treatment strategies, centered on the studies discussed above has been significant, in that there is no doubt that outcomes of some patients have been impacted, in some cases critically, effecting a complete response in the setting of multimodality treatments. Large-scale comparative trials require a functional high level of cooperation, and represent one dimension to standardization of systemic treatments. The process of the personalized definition of the culprit mutations, and the class-related (particularly HPV) potential target antigens is one that is in wide development, outside of just the penile cancer field.

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