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Chemotherapy in the Combined Modality Treatment of Penile Carcinoma

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1. Introduction

Penile carcinoma is a rare malignancy accounting for 0.4% to 0.6% of all cancers in men in the United States and Europe (Perksy, 1977). Penile cancers usually originate from the epithelium of the inner prepuce and glans with squamous cell histology accounting for >95% of cancers; melanoma and basal cell carcinoma account for another 3% (Cubilla, 2009). There is a predictable pattern of spread with the first site of metastasis occurring at the regional femoral and iliac nodes (Wood, 2010). The lymphatics of the prepuce connect to the lymphatics from the skin of the shaft, and the lymphatics of the glans and corporal bodies join together in the superficial inguinal nodes. The superficial lymph nodes drain into the deep inguinal nodes, which in turn, drain into the pelvic nodes (internal and external iliac nodes and obturator nodes). This lymphatic system is illustrated in Figure 1. Penile lymphatic drainage occurs bilaterally through crossover drainage at multiple levels. Direct metastasis to the deep inguinal lymph nodes can uncommonly occur, but metastasis directly to the pelvic lymph nodes is rare. Histologic subtypes appear to possess different risks of developing metastatic lymph nodes with sarcomatoid tumors having the highest risk of around 90% (Cubilla, 2009).

Once a diagnosis of penile cancer is determined, treatment is based on stage of disease. The most recent seventh edition of the TNM staging system for penile carcinoma as designated by the American Joint Committee on Cancer is presented in Tables 1 and 2 (Edge et al., 2010).

The Netherlands Cancer Institute evaluated the prognostic value of the TNM staging classification. The current inconsistencies between staging and prognosis include different clinical 5 year disease-specific survival for tumors invading corpus spongiosum and corpora cavernosa and no significant differences in the 5-year disease-specific survival between T2 and T3 tumors or N1 and N2 disease (Leijte et al., 2007). A revision of the current T2 TNM staging system to take this prognostic difference into consideration has been proposed.

2. Treatment overview

2.1 Local disease

Treatment, as with other malignancies, is stratified based on staging. For local control, surgical amputation is the oncologic gold standard for definitive treatment with local recurrence rates ranging from 0-8% (McDougal et al., 1986). Penile tumors with favorable histology with Tis, Ta, grade 1 tumors, and certain grade 2 tumors are at lower risk for metastases. The goal in these patients is for organ-sparing treatment. These treatment

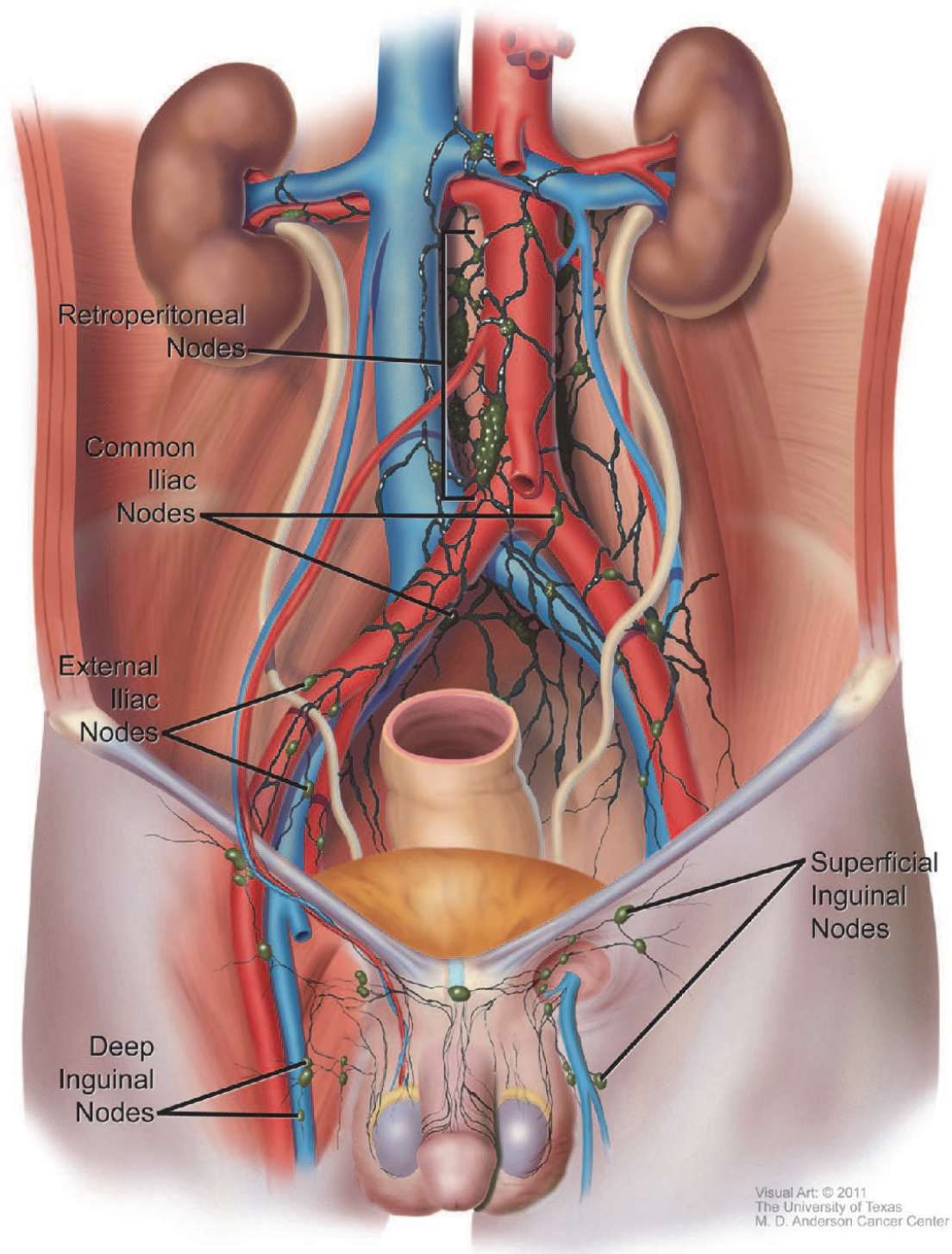


Fig. 1. Lymphatic drainage of the penis (Medical Graphics and Photography, UT M.D. Anderson Cancer Center, 2011).

options include topical therapy, radiotherapy, Mohs surgery, laser ablation, and partial penectomy. Surgery, radiation, and laser therapy have not been compared in a randomized fashion, and in general, the treatment of choice depends on factors such as tumor size,

location, and center experience without noted significant differences in local recurrence rates amongst these options (Pagliaro & Crook, 2009; Pizzocaro et al., 2009). Ablative surgery with partial penectomy does have a lower risk of local recurrence compared to more conservative measures. Proximal tumors or more advanced stages require total penectomy. Appropriate treatment is essential and requires a balance between avoiding overtreatment with ensuring appropriate removal of all cancerous tissues (Leijte et al., 2007).

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Ta	Noninvasive verrucous carcinoma
T1a	Tumor invades subepithelial connective tissue without lymph vascular invasion and is not poorly differentiated (i.e., grade 3-4)
T1b	Tumor invades subepithelial connective tissue and exhibits lymph vascular invasion or is poorly differentiated
T2	Tumor invades corpus spongiosum or cavernosum
T3	Tumor invades urethra
T4	Tumor invades other adjacent structures
Regional Lymph Nodes (N)	
<i>Clinical Stage Definition</i>	
cNX	Regional lymph nodes cannot be assessed
cN0	No palpable or visibly enlarged inguinal lymph nodes
cN1	Palpable mobile unilateral inguinal lymph node
cN2	Palpable mobile multiple or bilateral inguinal lymph nodes
cN3	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral
<i>Pathologic Stage Definition</i>	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in a single inguinal lymph node
pN2	Metastasis in multiple or bilateral inguinal lymph nodes
pN3	Extranodal extension of lymph node metastasis or pelvic lymph nodes(s) unilateral or bilateral
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis*

*Lymph node metastasis outside the true pelvis in addition to visceral or bone sites.

Table 1. Definitions of TNM (AJCC, 2010) Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Stage 0	Tis	N0	M0
	Ta	N0	M0
Stage I	T1a	N0	M0
Stage II	T1b	N0	M0
	T2	N0	M0
	T3	N0	M0
Stage IIIa	T1-3	N1	M0
Stage IIIb	T1-3	N2	M0
Stage IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

Table 2. Stage Grouping for Penile Cancer (AJCC, 2010) Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

2.2 Nodal disease

Metastatic disease in the inguinal region is the most important prognostic factor for survival in penile squamous cell carcinoma. The presence of palpable inguinal lymph nodes is not a definitive indicator of metastatic disease as it may also be secondary to inflammation in as many as 50% of cases at the time of initial diagnosis (Pizzocaro et al., 2009). Likewise, occult metastatic disease can escape detection, and multiple studies have shown an incidence of lymph node metastases in up to 40% of patients who are clinically node negative (Delacroix & Pettaway, 2010). Utilization of imaging with ultrasound, CT, and MRI may identify distortion of lymph node architecture; however, they are also not completely reliable in differentiating between causes (Heyns, 2010b).

Clinical features that suggest advanced regional disease include size of inguinal lymph nodes greater than 4 cm, bilateral and multiple enlarged nodes, overlying skin changes, and enlarged pelvic lymph nodes (Delacroix & Pettaway, 2010). Pathologically, the most important prognostic factors for lymph node spread include tumor grade, lymphovascular invasion, perineural invasion, pathological subtype, tumor depth or thickness, anatomic site, size, and growth pattern, with the first three factors being the most predictive (Cubilla, 2009; Pagliaro, 2011; Pagliaro & Crook, 2009).

The optimal management in patients without inguinal adenopathy consists of a variety of approaches to the lymph nodes including surveillance, fine needle aspiration cytology, dynamic sentinel lymph node biopsy, and different variations of lymphadenectomies (Graafland, 2010; Heyns, 2010a). Lymphadenectomies are divided into early versus delayed, with early lymphadenectomy defined as within 6 weeks after treatment of the primary tumor and delayed defined as therapeutic after the development of palpable nodes during follow-up. Johnson and Lo compared early versus late therapeutic inguinal lymph node dissection and reported a 3-year survival rate of 71% versus 57% and a 5-year survival rate of 50% versus 30% favoring the early group (Johnson & Lo, 1984). This benefit is likely due to the incidence of clinically occult metastatic disease and suggests that surgery with

microscopic disease rather than bulky nodal disease leads to fewer post-operative complications and results in improved overall survival. However, lymphadenectomy does also come with significant morbidities and an associated mortality of 3%, high costs for the approximately 80% of clinically node negative patients who will be free of lymph node involvement (Pagliaro & Crook, 2009; Heyns, 2010a).

The survival in patients with established lymph node metastases after surgical dissection is variable from 20-60%, a range that correlates with the extent of metastatic disease (Heyns, 2010a; Pagliaro, 2011). Metastatic enlargement of the regional nodes can lead to morbidity with skin necrosis and chronic infection; death, which usually occurs within two years if left untreated, can occur from hemorrhage, sepsis, and failure to thrive. However, unlike many other malignancies, regional nodal metastatic disease can be cured with lymphadenectomy alone in appropriately selected patients (Delacroix & Pettaway, 2010).

2.3 Prognostic factors for combined modality consideration

Overall, the pathologic features that are associated with long term survival after attempted curative lymphadenectomy include the following: two or fewer lymph nodes involved, unilateral involvement, no extranodal extension, and absence of pelvic nodal metastases (Pagliaro, 2011). Once bilateral or pelvic lymph nodes are involved (stage N2 or N3 disease), the 5-year overall and disease-free survival rates drop to only 10-20% and are even more dismal with the presence of extranodal extension (Pizzocaro, 1996).

When lymph nodes are initially fixed, chemotherapy is a rational upfront strategy since surgery would be difficult. In the absence of distant metastases, select patients may be candidates for neoadjuvant therapy in the hopes of downstaging to operable disease with curative intent (Leijte, 2007).

3. Combined modality management

3.1 Chemotherapy response rates

Neoadjuvant chemotherapy for solid tumors requires that there be chemotherapeutic drugs or combinations that exceed a certain threshold of efficacy. Historically, the treatments were first found to have high response rates in the setting of advanced metastatic disease, then tested in the adjuvant or neoadjuvant setting. For the treatment of advanced metastatic penile cancer, various combinations were studied and most had only modest response rates. The activity of combination cisplatin and 5-fluorouracil was first reported by Hussain et al in 1990 where 5 advanced penile squamous cell carcinoma patients were treated with sequential cisplatin and 5-fluorouracil, all five achieved partial response, and one even improved to resectable disease (Hussain et al., 1990). Double agent cisplatin and irinotecan was studied in the phase II EORTC 30992 trial that evaluated 26 patients with T3, T4, N1, N2, N3 or M1 disease. Of these 26 patients, 7 were treated in the neoadjuvant setting. They had 8 total responses, 2 CRs and 6 PRs with 3 of the patients receiving neoadjuvant chemotherapy proceeding to lymphadenectomy having pathologically negative lymph nodes. The overall response rate was 30.8% (Theodore et al., 2008).

The most studied triple-drug regimen is cisplatin, methotrexate, and bleomycin. Dexeus et al initially described this regimen with a response in 10 of 14 patients, including 2 CRs (Dexeus et al., 1991). Additional studies by Haas, Hakenberg, Corral, and Leijte found responses, but at the expense of significant hematological and pulmonary toxicities (Protzel

& Hakenberg, 2009). Newer regimens have better toxicity profiles and higher response rates. Bleomycin is no longer recommended for the treatment of penile cancer.

3.2 Neoadjuvant chemotherapy

The literature regarding neoadjuvant chemotherapy for penile cancer is limited with the first prospective series just recently published (Pagliaro et al., 2010). There have been seven retrospective studies assessing the role of neoadjuvant chemotherapy in cases of fixed inguinal lymph nodes (Protzel & Hakenberg, 2009). Pizzocaro et al were able to achieve partial responses with neoadjuvant chemotherapy in 9 of 16 patients (56%) followed by lymphadenectomy with the best results achieved with a cisplatin/5-fluorouracil combination (Pizzocaro et al., 1996). Leijte et al studied 20 patients with initially unresectable penile cancer who received neoadjuvant chemotherapy at the Netherlands Cancer Institute between 1972 and 2005. Several regimens were sequentially used throughout that time period including: single agent bleomycin until 1985, then bleomycin, vincristine, and methotrexate until 1999, then cisplatin and 5-fluorouracil until 2001, and cisplatin, bleomycin, and methotrexate since 2001, with one patient treated with cisplatin and irinotecan in a clinical trial. Twelve patients had a clinical response to chemotherapy (2 complete, 10 partial), and 8 of the 9 patients who went on to resection with curative intent were clinically disease-free at median follow-up time of 20 months (Leijte et al., 2007). There was a significant difference in overall survival in those who responded to chemotherapy (56% overall survival at 5 years) compared to the nonresponders with stable or progressive disease through treatment (0% overall survival at 5 years) due to recurrence after consolidative surgery as shown in Figure 2 (Leijte et al., 2007).

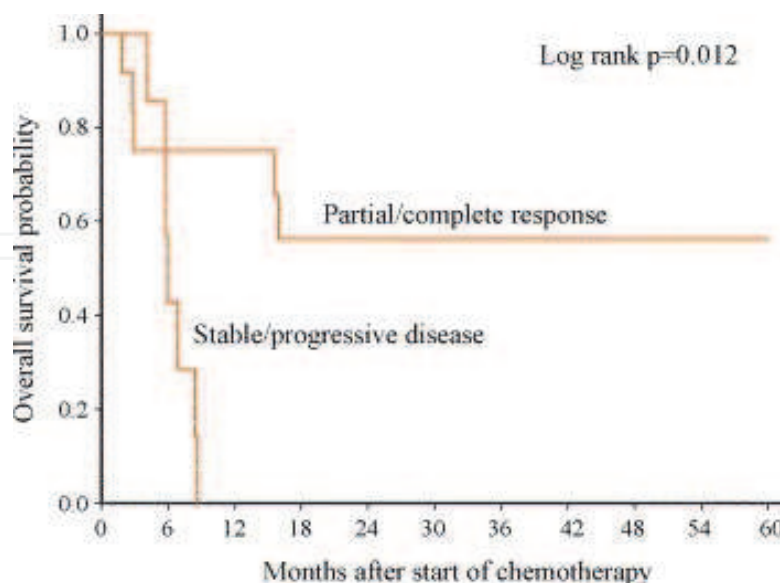


Fig. 2. Overall survival of patients grouped according to response to neoadjuvant chemotherapy (Reproduced from Leijte et al, 2007, with permission).

In another retrospective study, Bermejo et al reviewed 10 patients with advanced penile carcinoma treated from 1985 to 2000 who had received consolidation surgery after having stable, partial, or complete responses on various chemotherapy regimens. After receiving induction regimens consisting of paclitaxel/ifosfamide/cisplatin, bleomycin/methotrexate/cisplatin, and paclitaxel/carboplatin, the authors found that 4 patients achieved CR, 1 achieved PR, and 5 had stable disease after chemotherapy with responses tending to occur quickly during treatment, often after the first or second cycles. After surgical consolidative lymphadenectomy, pathology revealed that 3 patients had no evidence of metastatic disease in the lymph nodes, with all 3 of these patients having had received paclitaxel, ifosfamide, and cisplatin as their neoadjuvant regimen (Bermejo, 2007). Culkin and Beer's literature review of cisplatin-based neoadjuvant chemotherapy found a clinical response in 69% with 23% of patients having no disease in follow-up after surgery. In summary, these authors found that neoadjuvant chemotherapy could render patients disease-free, and in combination with surgical consolidation, could lead to prolonged survival of patients with advanced penile cancer with low toxicity in regards to surgical complications (Culkin & Beer, 2003).

The design of the first prospective study of neoadjuvant chemotherapy for metastatic penile cancer was based on data related to efficacy of paclitaxel, ifosfamide, and cisplatin in head and neck squamous cell carcinoma (Pagliaro et al., 2010). Thirty patients with clinical stage N2 or N3 disease without evidence of distant metastases were enrolled into a phase II trial of which twenty-three (76.7%) completed four courses of neoadjuvant chemotherapy. N2 and N3 disease was defined by the 1987 to 2002 TNM staging system as palpable, mobile, multiple or bilateral inguinal lymph nodes (N2) or fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral (N3). The four cycles were on 21 to 28-day durations depending on count recovery, and paclitaxel was dosed at 175mg/m² over 3 hours on day 1, ifosfamide 1200mg/m² IV over 2 hours on days 1-3, and cisplatin 25mg/m² IV over 2 hours on days 1-3. Twenty-two patients went on to subsequent surgery with bilateral inguinal lymph node dissection and either unilateral or bilateral pelvic lymph node dissection. Three patients (13.6% of those who completed the treatment) had no tumor remaining in the surgical specimen, and 11 patients (36.7% of those enrolled) survived without recurrence, with median follow-up of 34 months at the time of publication (Figure 3A). A total of 3 CRs and 12 PRs were achieved for an overall response rate of 50%.

Figure 3A-B shows an estimated median time to progression of 8.1 months, ranging from 5.4 months to greater than 50 months and an overall survival of 17.1 months, ranging from 10.3 months to greater than 60 months. Univariate analysis showed significantly worse time to tumor progression and overall survival among the patients who did not have an objective response to chemotherapy (Figure 3C-D), had bilateral residual tumor at resection, or had extranodal extension detected after chemotherapy (Pagliaro et al, 2010).

This study determined the outcomes of a specific multimodality approach with neoadjuvant chemotherapy and surgical consolidation; however, it was not randomized and thus was not designed to demonstrate superiority over surgery. However, from the previously published series of penile carcinoma with stage TX, N2-3, M0 disease that document the progression-free and overall survival, as previously mentioned, long-term, disease-free survival was seldom achieved with surgery alone. Based on other series, the estimated

long-term survival for patients with pelvic lymph node metastases and/or extranodal extension was only 10-15% with surgery alone. Importantly, there also were no chemotherapy-related deaths or increased surgical morbidity or mortality following this neoadjuvant regimen as compared to the effective, yet toxic, bleomycin, methotrexate, cisplatin regimen.

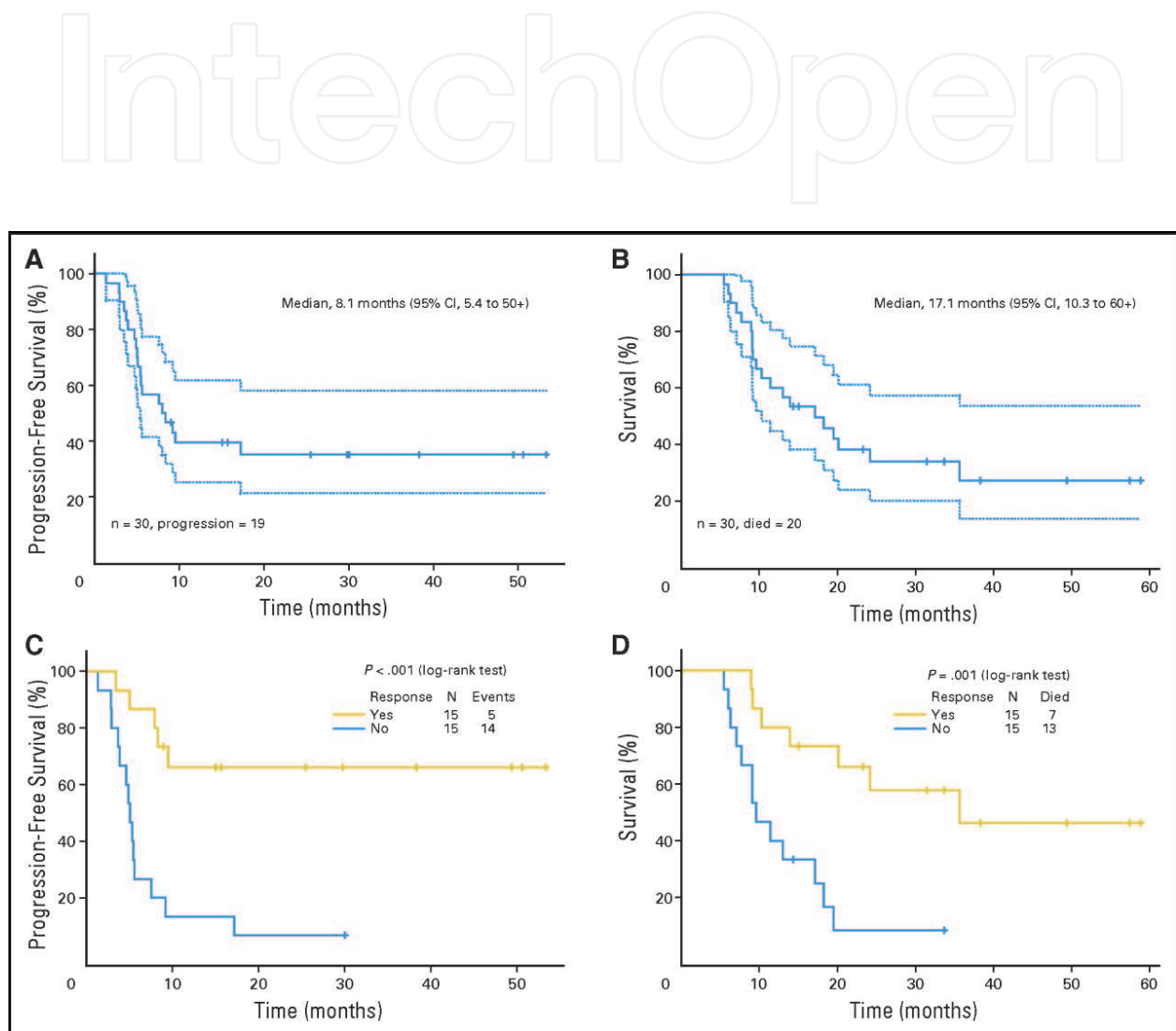


Fig. 3. Overall and progression-free survival for patients treated with neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy (Reproduced from Pagliaro et al, 2010, with permission).

In a special commentary by Pettaway et al, the authors recommend that neoadjuvant chemotherapy should be considered with N1 disease with mobile mass greater than 4 cm, N2-N3 disease, or recurrent regional disease after therapeutic lymph node dissection (Pettaway et al., 2010). This algorithm is demonstrated in Figure 4.

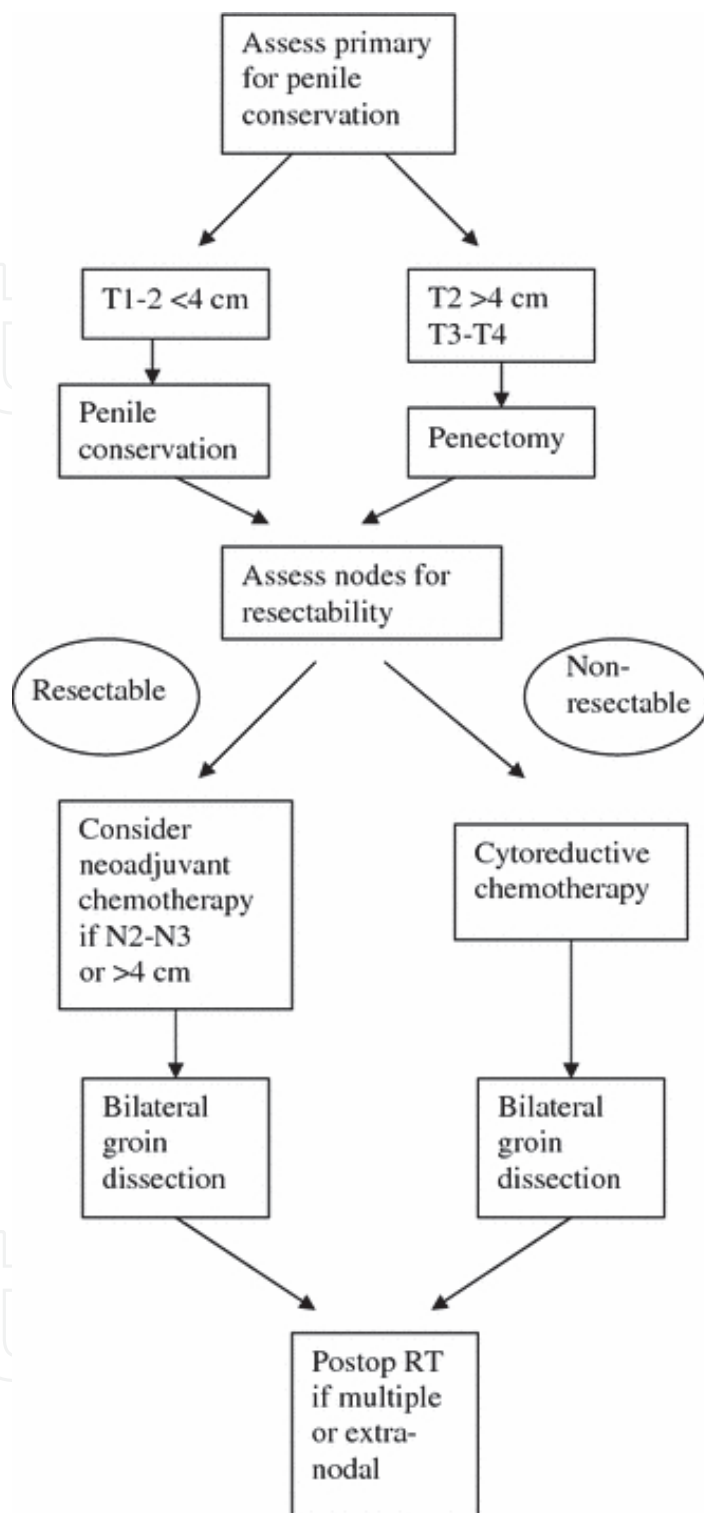


Fig. 4. Algorithm for management of bulky lymph node metastases (Reproduced from Pagliaro and Crook 2009, with permission).

3.3 Post-chemotherapy surgery

Surgical techniques include radical inguinal lymphadenectomy, the gold standard for inguinal metastasis where all lymph nodes in the superficial and deep compartments of the

inguino-femoral region are removed, and pelvic lymphadenectomy when indicated depending on degree of inguinal disease (Pettaway et al., 2010). Chemotherapy has not yet been assessed in a neoadjuvant setting for an aim of organ-sparing surgery. There are also no data in regards to using radiation as consolidation treatment in metastatic penile cancer at this time though it is a promising thought given its utility in other squamous cell carcinomas (NCCN, 2010).

3.4 Adjuvant chemotherapy

Little literature exists regarding adjuvant chemotherapy. In a Pizzocaro et al study of 12 patients who received adjuvant vincristine, bleomycin, and methotrexate, only 1 developed progression with a mean remission time of 42 months (Pizzocaro & Piva, 1988). In another Pizzocaro study, the 5-year survival was 82% after adjuvant chemotherapy compared to only 37% in historical controls without adjuvant treatment (Pizzocaro et al., 1996). In Hakenberg's study, mean duration of remission with adjuvant cisplatin, bleomycin, and methotrexate was only 26 months with 1 treatment-associated death (Hakenberg et al., 2006).

3.5 The role of radiotherapy

Radiation in the neoadjuvant setting has not been studied in detail. A retrospective series in India looked at 77 patients over a 20 year period who had palpable pathological node positive disease at least 4 cm in size. Thirty-four of these patients received 40 Gy/4 weeks of radiation followed by consolidative surgery. The irradiated patients had less extranodal extension (9% versus 33%) with a 70% 5 year disease-free survival. However, there was high morbidity with this approach with local complication rate of 100% with skin necrosis or infection (Ravi et al., 1994).

4. Conclusion

Squamous cell carcinoma of the penis is an uncommon disease, which essentially precludes randomized clinical studies. The prognosis for metastatic penile carcinoma is known to be very poor with either surgery or chemotherapy alone. Evidence from a recent prospective study (Pagliaro et al, 2010) showed promising results with a multimodal approach with the paclitaxel, ifosfamide, and cisplatin chemotherapy regimen before surgery for curative intent in metastatic disease. This disease truly necessitates a multidisciplinary approach in prognostication and management of these patients to improve survival while reducing morbidity or mortality of unnecessary procedures. Not only are members of medical oncology and urology involved, but wound care and plastic surgery specialists have important roles. This now represents a reasonable standard of care for the treatment of regional metastatic disease.

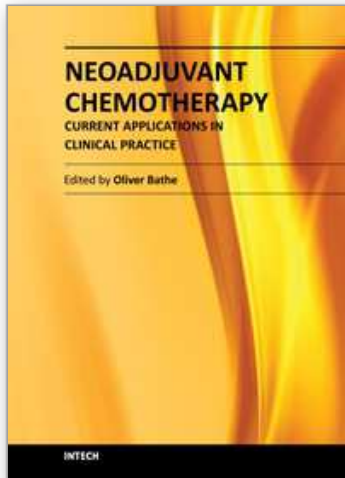
Future directions should include additional studies to promote the further understanding of the utility of neoadjuvant chemotherapy in lower stage disease that may lead to improved organ-sparing, predictive factors for chemotherapy response, possible addition of biologic agents, role of radiation, and measures to decrease the morbidity of surgery. Squamous cell carcinoma of the penis is now becoming a multidisciplinary disease with many exciting opportunities on the horizon.

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Neoadjuvant Chemotherapy - Current Applications in Clinical Practice

Edited by Dr. Oliver Bathe

ISBN 978-953-307-994-3

Hard cover, 268 pages

Publisher InTech

Published online 01, February, 2012

Published in print edition February, 2012

The most significant advances in cancer therapy in recent years have involved the development of systemic therapeutics. With improvements in response rates in solid tumors, opportunities have arisen to enhance the effectiveness of surgery. Administration of systemic therapy prior to surgery - neoadjuvant chemotherapy - represents one approach by which clinicians have successfully reduced the extent of surgery and, in some instances, positively impacted on clinical outcomes. This collection of works by expert clinicians from a variety of disciplines represents an exploration of the current knowledge of the role of neoadjuvant chemotherapy in diverse tumor types.

How to reference

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Jennifer Wang and Lance C. Pagliaro (2012). Chemotherapy in the Combined Modality Treatment of Penile Carcinoma, Neoadjuvant Chemotherapy - Current Applications in Clinical Practice, Dr. Oliver Bathe (Ed.), ISBN: 978-953-307-994-3, InTech, Available from: <http://www.intechopen.com/books/neoadjuvant-chemotherapy-current-applications-in-clinical-practice/chemotherapy-in-the-combined-modality-treatment-of-penile-carcinoma>

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