Review

Lymph Node Metastases and Prognosis in Penile Cancer

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ABSTRACT

Lymph node status is a key prognostic factor in penile squamous cell carcinoma. Recently, growing evidence indicates a multimodality approach consisting of neoadjuvant chemotherapy followed by consolidation surgery improves the outcome of locally advanced penile cancer. Thus, accurate estimation of survival probability in node-positive penile cancer is critical for treatment decision making, counseling of patients and follow-up scheduling. This article reviewed evolving developments in assessing the risk for cancer progression based on lymph node related variables, such as the number of metastatic lymph nodes, bilateral lymph node metastases, the ratio of positive lymph nodes, extracapsular extension of metastatic lymph nodes, pelvic lymph node metastases, metastatic deposit in sentinel lymph nodes and N stage in TNM classification. Controversial issues surrounding the prognostic value of these nodal related predictors were also discussed.

Key words: Lymph node; Metastasis; Penile cancer; Prognosis

Introduction

Penile cancer is a rare disease in urban Shanghai, accounting for less than 1% of all male malignancies[1]. While in certain areas where hygiene and health conditions are poor, it is still a substantial health problem constituting up to 10% of cancers in men[2,3]. Penile squamous cell carcinoma is commonly characterized by regional lymph node spread in a stepwise pattern before distant metastases. Rather than clinicopathological features of the primary disease, the presence and the extent of lymphatic metastases to the ilioinguinal region are the most important prognostic factor for survival[4-6]. A pooled analysis of 217 penile cancer patients showed an average 5-year survival of 77% in those with two or less positive lymph nodes, compared with only 25% when a greater number of nodal involvement was presented[4]. Lymph- adenectomy is the mainstay treatment of node-positive penile cancer and may be curative in patients with limited lymph node metastases (LNM)[7,8]. However, survival advantage of radical surgery seems less likely if there is extensive nodal involvement.

Recently, growing evidence indicates a multi-modality approach consisting of neoadjuvant chemo therapy followed by consolidation surgery improves the outcome of locally advanced penile cancer[9-13]. In a phase II study of neoadjuvant chemotherapy, 9 of 30 eligible patients (30.0%) achieved long-term recurrence- free survival (median follow-up, 34 months; range, 14–59 months), and two patients died of other causes without recurrence[9]. While historical series suggested an expected survival rate of 10% to 15% in the similar population treated with surgery alone[14,15]. The encouraging results of neoadjuvant chemotherapy highlight the need of better patient stratification in those patients with LNM[9]. Besides treatment decision making, both counseling of patients and follow-up scheduling depend on accurate estimation of response to therapy and survival probability based on the assessment of clinical and pathological prognostic factors[16]. The fact that the number of metastatic lymph nodes is an important prognostic factor of penile cancer is well accepted but there is increasing evidence that bilateral involvement, the ratio of positive nodes, extracapsular nodal extension, pelvic LNM and metastatic deposit in sentinel lymph nodes are also of prognostic significance. The goal of this review is to give an overview of the prognostic features of LNM in penile cancer.

Methods

A Medline search was performed for English-language literature (January 1990–September 2010) using

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the MeSH terms "penile neoplasm", "lymph node", and "prognosis". For retrieved articles, full text was obtained and screened by the authors. Manuscripts were excluded because of the following reasons: studies lack of description of prognostic information about LNM, reviews without original data, commentaries, editorials and case reports. Using similar criteria, we also searched and judged abstracts focusing on penile cancer in four international conferences: American Urological Association, European Association of Urology, American Society of Clinical Oncology and Genitourinary Cancers Symposium annual meetings. Sixteen articles and abstracts were identified to be the basis of the review. Exact information (study characteristics, predictors, outcome, statistical results) were extracted from these publications. We also evaluated these prognostic factors in the patient cohort from the authors' institution, Fudan University Shanghai Cancer Center. A total of 60 penile squamous cell carcinoma patients with surgically resected LNM from 1990 to 2008 were analyzed. The level of evidence was low for included studies, as most were retrospective series. Thus we did not attempt to weigh the evidence in this review.

Number of Metastatic Lymph Nodes

The number of metastatic lymph nodes reflects severity of disease and influences survival. The more lymph nodes are involved, the worse the survival is. Ravi from India had reported 201 patients with carcinoma of the penis between 1962 and 1986[14]. The 5-year survival rate was 95% for patients with negative nodes, 76% when only inguinal nodes were positive, and 0% when the pelvic nodes were positive. The 5-year survival rate varied according to the number of positive inguinal lymph nodes. Of 58 patients with 1–3 positive nodes, the 5-year survival rate was 81%. However, the rate decreased to 50% in 10 patients with more than 3 involved lymph nodes. In 2006, Pandey, et al.[15] from the same institution analyzed 102 node positive penile cancer patients between 1987 and 1998. The results showed that the 5-year survival rate for patient with 1 to 3 positive inguinal lymph nodes was 75.6%, while only 8.4% for those with 4–5 metastatic lymph nodes and 0 for those with more than 5 involved lymph nodes. Svatek, et al.[17] had analyzed the number of metastatic lymph nodes in 45 penile cancer patients. They reported only 2 of 24 patients with 2 or less positive lymph nodes died in the last follow-up, while 16 of 21 cases with greater than 2 metastatic lymph nodes succumbed to the disease. Multiple LNM also tend to associate with other important adverse predictors as extracapsular extension and pelvic LNM[18,19].

Although the survival rate decreases when more nodes are involved, the cutoff point of lymph node number between N1 and N2 classification in the current TNM staging system is doubted by many researchers. In two consecutive studies from India, a similar good outcome (5-year survival rate >75%) was observed in patients with 1 to 3 positive nodes[14,15]. We also found there was no significant difference in the survival rates among patients with 1 to 3 positive lymph nodes. Our data showed the 3-year recurrence-free survival rates were 69.8% (n=24), 62.9% (n=14), and 71.4% (n=7) for patients with 1 to 3 metastatic nodes, respectively. The survival rate significantly decreased when there were 4 or more metastatic nodes. In a large cohort of 513 penile cancer patients, Leijte, et al. performed exploratory analysis to find optimal cutoff to better discriminate patients into a good and a poor risk groups[20]. They failed to find a significant survival difference between 1 vs. 2 or greater tumor positive inguinal nodes and 1 or 2 vs. 3 or greater positive inguinal nodes (P=0.629 and 0.209, respectively). A significant difference was observed between 1 to 3 positive inguinal nodes vs. 4 or greater nodes (P=0.029). Taken together, we suggested a cutoff of 3 in number-based risk stratification in node- positive penile cancer. However, other prognostic factors should be incorporated for better prognostication.

Bilateral LNM

Lymphatic mapping study showed that bilateral inguinal drainage was observed in 89% of penile cancer patients[21]. However, bilateral nodal involvement was presented in about 15% to 54% of all node-positive penile cancer patients in large case series[14,15,22-24]. It seems that tumor with bilateral metastases may have an increased capability for migration and therefore have an adverse effect on survival. In Ravi's study, the 5-year survival rates for patients with unilateral and bilateral inguinal LNM were 86% and 60%, respectively[14]. Pandey, et al. found that the 5-year survival rate was 63.1% in unilateral node positive patients and was only 21.2% in those with bilateral disease[15]. In multivariate analysis, bilateral positive node was one of the independent factors affecting survival for node-positive patients (P=0.007, HR=2.669). The laterality of inguinal LNM was introduced into a modification of N stage by Leijte, et al.[20] Survival analysis of the proposed N category demonstrated improved prognostic stratification over number-based stratification.

To analyze whether the existence of bilateral LNM has prognostic significance of its own regardless the number of nodes, we calculated its impact on survival for the group of patients with 2 or more positive nodes. In this subgroup, there was still significant survival difference between unilateral and bilateral LNM on survival (P=0.016). Patients with unilateral and bilateral LNM had a 3-year recurrence-free survival of 59.2% (n=18) and 26.7% (n=18), respectively.

Ratio of Positive Lymph Nodes

Recently, more evidence has confirmed that the ratio

of positive lymph nodes outperforms number- based nodal staging in cancer prognostication[25-27]. Lymph node ratio (LNR) could take into consideration the total number of nodes retrieved by various techniques. Furthermore, LNR may provide an accurate reflection of the disease burden independent of the treatment modalities (with or without neoadjuvant therapy, modified/standard/extended lymphadenec- tomy) and heterogeneous patient characteristics. In a series of 73 penile cancer patients, Zhu, et al. found that pelvic LNM rate correlated with inguinal LNR[19]. LNR of at least 30% had 100% specificity in predicting pelvic nodal disease. Svatek, et al. had reviewed 45 node-positive penile cancer patients from MD Anderson Cancer Center (MDACC)[17]. This study demonstrated that LNR was significantly associated with disease-specific survival when stratified by median value or tertile. The estimated 5-year disease-specific survival in patients with LNR of 6.7% or less was 91.7%, while only 23.3% in those with LNR greater than 6.7%. When included in a model with extracapsular extension (ECE), perioperative chemotherapy, or pN staging criteria, LNR remained statistically significant and the other factors were no longer statistically significant.

To compare the predictive value of LNR to the number of positive lymph nodes for recurrence-free survival, we evaluated the two factors as continuous variables in our group. The concordance index was 0.68 and 0.77 for number- and ratio-based parameter, respectively. Although these preliminary data suggested the promising prognostic value of LNR, there is no clear consensus about the cutoff points that would be required for a staging classification. In Zhu's report, LNR was defined as the number of positive to total nodes per ipsilateral inguinal nodal basin[19]. Ratio-based lymph node staging was evaluated categorically as the ratio of less than to more than 30%. The cutoff was selected because the results of exploratory analysis showed no advantages for quartile ratios of 10%, 20%, or ≥40%. On the contrary, LNR was defined as the number of positive nodes divided by the number of nodes harvested from all sites in the MDACC series[17]. The relationship between LNR and death from disease was analyzed after patient categorization by LNR into 2 and 3 equal percentiles. To identify LNR cut-points with minimization of information loss strongly warranted large patient population study[25].

ECE of Metastatic Lymph Nodes

ECE of metastatic lymph nodes is known as an important prognostic factor in a variety of solid tumors[28-31]. The incidences of ECE in node-positive penile cancer patients varied from 15% to 51%[17, 19, 22]. Graafland, et al. found the presence of ECE was correlated with clinical nodal status (13% cN0 and 66% in cN+ patients)[22]. After retrospective review of 102 patients, Lont, et al. found ECE was an important risk factors of pelvic lymph node involvement[18]. In those patients with 1 or 2 positive inguinal nodes, pelvic nodal involvement was presented in 4 of 22 cases with ECE but absent in 23 without the features. Their observation was further confirmed by another case series that demonstrated the presence of ECE was associated with pelvic nodal disease in univariate analysis[19].

Recently, there was accrued information considering the predictive significance of ECE in survival. In a report from MDACC, 8 of 11 patients with ECE died from disease while only 10 of 34 without the feature succumb to the disease (P=0.002)[17]. Pandey, et al. showed that the 5-year overall survival rate was 8.9% in patients with ECE and was 90.5% in those without ECE. ECE was identified as an independent variable in multivariate model (P<0.001, HR=9.206)[15]. In accordance with the Indian study, Graafland, et al. evaluated ECE as a prognostic factor in a large cohort of 156 node-positive patients[22]. They found the 5-year disease-specific survival for patients without and with ECE was 80% and 42% (P<0.001), respectively. ECE, rather than the laterality of LNM and number of positive lymph nodes, exhibited significant prognostic significance in multivariate analysis (P=0.012, HR=2.37). It should be noted that the higher survival for patients with ECE reported by Graafland, et al. may be due to the fact that postoperative radiotherapy was often given in their patients with ECE[22]. In a recent report of neoadjuvant chemotherapy in penile cancer, ECE in residual tumor was significantly associated with shorter survival (P=0.04)[9]. The median overall survival was 10 months and more than 50 months in patients with and without ECE, respectively.

These evidence suggested that ECE may be one of the most valuable lymph node associated prognostic factor for survival. However, a main drawback of this factor is the lack of insight in the reproducibility of this parameter. Theunissen, et al. had investigated the observer reliability of ECE in early metastatic non-small cell lung cancer[32]. Their data showed only moderate interobserver agreement (kappa=0.50) in initial assessment of ECE in the dissected lymph nodes. The authors proposed strict criteria for ECE: tumor extension was classified as ECE when either tumor penetration of the lymph node capsule was present, or the tissue sample contained fat tissue with tumor infiltration, or when tumor cells were present in the lumen of a vessel that was unequivocally a vein. After the introduction of clear criteria of the growth pattern, the kappa value improved significantly to 0.72 (good agreement).

Pelvic LNM

Pelvic LNM occurred in 19%–48% of all node-positive patients[14,15,18,19,23]. The presence of pelvic nodal

disease, even minimal, is a strong prognostic factor of poor survival. Ravi reported no survivors in 30 patients with positive pelvic nodes[14]. Pandey, et al. recorded similar findings that all of 21 patients with metastases to the pelvic nodes died in a 3-year period[15]. Their data showed pelvic nodal involvement was an independent variable in multivariate analysis (P<0.001, HR=31.68). In Graafland, et al.'s study, the 5-year survival rate was 21% and 72% in those patients with and without metastatic pelvic nodes, respectively (P<0.001)[22]. Pelvic lymph node involvement remained an independent prognostic factor of cancer-specific survival regardless of bilateral involvement, number of positive nodes and ECE (P=0.022, HR=2.2).

In our cohort, we observed only 1 of 8 patients with pelvic metastatic nodes remained disease free 35 months after surgery. Lont, et al. presented consistent findings that 4 of 24 patients with pelvic nodal disease had survived more than 3 years[18]. The best outcome of patients with pelvic LNM was reported by Lopes, et al[33]. In their study, 4 of 13 penile cancer patients with iliac metastatic nodes achieved long-term survival after curative surgery. The previous studies, however, did not find association between pelvic disease burden and long-term outcome[18,33]. Three of the survivors in Lont's report even had strong adverse factors as ECE and more than 1 positive node. Since most patients with pelvic metastatic nodes have significant inguinal nodal disease, the successful management of pelvic nodal disease should comprise not only elimination of spread disease but also good local control. A Gynecologic Oncology Group protocol enrolled 114 patients randomly allocated to postoperative pelvic and groin radiation or to ipsilateral pelvic node resection after radical vulvectomy and inguinal lymphadenectomy[34, 35]. The cancer related death rate was significantly higher for pelvic node resection compared with radiation (51% compared with 29% at the 6th year, P=0.015). The comparison of the recurrence pattern in two treatment arms showed there was no significant difference in the pelvic recurrence rate and distant recurrence rate. However, the groin recurrence rate was 24.1% in the surgery arm and was only 5.3% in the radiation group. Thus, the adverse impact of pelvic LNM on survival may be influenced by the characteristics of inguinal disease.

Metastatic Deposit in Sentinel Lymph Nodes

The sentinel lymph node biopsy is one of the most promising advances in surgical management of early stage penile squamous cell carcinoma. The biopsy of sentinel nodes is typically for pathological ultrastaging to detect micrometastases. The metastatic deposit in sentinel lymph nodes provides useful information for prognosis. In breast cancer, patients with micro- metastases (maximum dimension of the largest lymph- node tumor ≤2.0 mm) have a significantly lower risk of non-sentinel-node involvement compared with patients with macrometastases[36-38]. Those patients with submicrometastases (≤0.2 mm) are classified as N0 and patients are treated as lymph node negative[39]. In vulvar cancer, Oonk, et al. assessed the association between the size of sentinel node metastasis and the risk of metastasis in non-sentinel nodes, and risk of disease-specific survival[40]. They found the risk of additional non-sentinel-node metastases increased with the size of the sentinel-node metastasis. The risk of non-sentinel-node metastases was 4.2% in groin with isolated tumor cells and 62.5% in groin with tumor size >10 mm. Survival was strongly associated with the size of sentinel-node metastases: disease-specific survival for patients with sentinel-node metastases larger than 2 mm was lower than for those with metastases 2 mm or smaller (69.5% vs. 94.4%, P=0.001). A Cox proportional-hazards model showed that disease-specific survival was related to the size of sentinel-node metastases, independent of the number of positive nodes (HR=6.4, P=0.006). According to our search results, there are only two relevant studies discussed the prognostic value of tumor deposit in penile cancer. Kroon, et al. evaluated the association between the size of metastasis in sentinel node and the involvement of additional nodes[41]. On univariate and multivariate analyses, the size of the sentinel node metastasis proved to be the only significant prognostic variable for additional lymph node involvement (each P=0.02). None of the 15 groins with only micro- metastasis (≤2.0 mm) in the sentinel node contained additional involved nodes. On the contrary, Ivaz, et al. found no correlation between the size of nodal metastasis and additional lymph node involvement in their cohort[42]. Furthermore, there was also no relationship between ECE, tumor location within the node or fine needle aspiration result with the finding of further positive inguinal or pelvic lymph nodes. The survival outcome of patients with different tumor deposit, however, is still lacking. Thus, further studies of metastatic deposit in sentinel lymph nodes are warranted to better elucidate the prognostic factor in penile cancer.

N Stage in TNM Classification

The N classification of penile cancer has been revised in the 7th edition of the TNM staging system (Table 1)[39]. The changes are the removal of the anatomic distinction (superficial and deep) in inguinal lymph nodes and including positive node with ECE as N3 disease. The first change is mainly due to the difficulty in distinguishing the two anatomic groups[20,43]. The second change is based on the strong prognostic value of ECE in metastatic nodes. We compared the prognostic value of the old (6th) and new (7th) N staging systems by applying two classifications to our patients. Regarding the 6th N classification, the 3-year recurrence free survival rates were 69.8% (n=24), 48.2% (n=24) and 33.3% (n=12) for the

N1, N2 and N3 categories, respectively. Log rank survival analysis failed to show a statistical difference (P=0.054). For the new 7th N categories, the 3-year recurrence-free survival rates were 87.5% (n=16), 57% (n=22), and 31.8% (n=22) in the corresponding N1 to N3 groups. A better stratification of survival was observed in analysis (P<0.001).

Table 1. Current N staging system and several proposed N categories

Stage	Definition
7th TNM[39]	
N0	No regional lymph node metastasis
N1	Metastasis in a single inguinal lymph node
N2	Metastasis in multiple or bilateral inguinal lymph nodes
N3	Extranodal extension of LNM or pelvic lymph node(s) unilateral or bilateral
Lont, et al.[18]	
N0	No evidence of lymph node metastasis
N1	Metastasis in 1 or 2 inguinal lymph nodes without extracapsular growth
N2	Metastasis in more than 2 lymph nodes metastasis with extracapsular growth
N3	Evidence of involvement of pelvic lymph nodes or bilateral nodes with extgracapsular growth
Leijte, et al.[20]	
N0	No regional lymph node metastasis
N1	Unilateral inguinal metastasis, mobile
N2	Bilateral inguinal metastasis, mobile
N3	Fixed inguinal metastasis or metastasis in pelvic lymph nodes(s)
Zhu and Ye	
N0	No regional lymph node metastasis
N1a	Metastasis in a single inguinal lymph node less than 5 mm
N1b	Metastasis in a single inguinal lymph node 5 mm or greater
N2a	Metastasis in 2 or 3 unilateral inguinal lymph nodes
N2b	Metastasis in more than 4 unilateral or bilateral inguinal lymph nodes
N3	Extranodal extension of LNM or pelvic lymph node(s) unilateral or bilateral

In the new N category, N1 disease is more likely cured by surgery alone and N3 classification is of poor survival. The N2 subgroup which includes patients with multiple or bilateral inguinal nodal disease, however, is heterogeneous. In several reports, there was a significant survival difference between patients with unilateral 2 or 3 positive lymph nodes and those with bilateral multiple nodal disease[15,20]. Since controversy exists regarding N2 disease in the new TNM staging system, some authors also provided proposal of N category for better prognostication (Table 1)[18,20]. The modified N classification by Lont, et al. was validated in an MDACC cohort[17]. The 5-year disease-specific survival in patients with N1, N2 and N3 was 89.5%, 50.6% and 0%, respectively (P<0.001). The new N staging system provided better stratify-cation of survival than the 6th TNM system. Leijte, et al. suggested a proposed clinical N definition which included laterality of metastatic nodes as a distinction of N stage[20]. Although a significant survival difference among all strata was observed in their study[20], an external validation of the system failed to provide similar findings[44].

Hereby, we advocated two improvements in the current N staging system (Table 1). First, the size of a metastatic node should be introduced into the N1 classification. Nowadays, more and more penile cancer patients with clinical negative lymph nodes were subjected to less invasive staging procedures such as sentinel nodal biopsy, and superficial or modified dissection[21,45-49]. Regardless the metastases deposit, extensive dissection is performed if one positive lymph node is found. Preliminary reports had shown that a proportion of "low-risk" patients had confined disease and might spare full dissection[41,50]. Thus, further stratification is needed to divide patients into different risk groups according to the outcome such as residual disease or risk of recurrence. Recently, the size of metastatic nodes is added to the N staging system of vulva cancer with a cutoff of 5 mm[39]. Because this factor is widely used, it warrants further evaluation in penile cancer. Second, more important predictors, such as the number of metastatic lymph nodes and bilateral LNM, should be added in the current N2 group. In our analysis, we found the patients with 2 or 3 unilateral nodal diseases had a better survival compared to those

with more positive nodes or bilateral disease. Thus, N2 classification should be divided into subgroups which indicate varied failure rates after recent treatment. The high-risk subgroup in the N2 classification may be suitable candidates for the multimodality therapy trials.

The optimal management of LNM is of paramount importance in the treatment of penile cancer patients. Identification of high-risk patients not only gives important prognostic information, but also helps determine the need for multimodality treatment in the adjuvant or neoadjuvant setting[9]. Although more evidence has accrued for the prognosis stratification in node-positive patients, most of these studies are from single institution and retrospective. Lack of multicenter studies hinders proper evaluation of these predictive indicators with adequate statistical power. Furthermore, few reports discussed the predictive value of histopathological features (such as *p53* expression and tumor deposit) of metastatic lymph nodes[19,41,51,52]. Patients with sentinel lymph node positive disease are still lack of valuable prognostic factors to stratify long-term outcome. Regionalization of penile cancer care and international collaboration, as adopted by European colleagues[45], will allow investigators to overcome these drawbacks and perform well designed studies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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