

Review

Lymph Node Metastases and Prognosis in Penile Cancer

Yao Zhu^{1,2}, Ding-wei Ye^{1,2*}¹Department of Urology, Fudan University Shanghai Cancer Center, Shanghai 200032, China²Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China

DOI: 10.1007/s11670-012-0090-2

©Chinese Anti-Cancer Association and Springer-Verlag Berlin Heidelberg 2012

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 multimodality 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

Received 2011–04–20; Accepted 2011–08–02

*Corresponding author.

E-mail: dwye@shca.org.cn

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