Penile Cancer

Lymph Node Metastasis in Intermediate-Risk Penile Squamous Cell Cancer: A Two-Centre Experience

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Abstract

Background: The risk of lymph node (LN) metastasis in G2T1 penile cancer has been previously reported as 0–50% and is classified as “intermediate” in the European Association of Urology (EAU) guidelines. The management of impalpable regional nodes in this cohort of patients remains contentious and varies among treatment centres depending on tumour factors and local resources.

Objectives: To establish the risk of LN metastasis in G2T1 disease.

Design, settings, and participants: We interrogated the databases of two referral centres for penile cancer.

Measurements: Out of 902 patients, 117 (13%) patients were identified with G2T1 cancers. Those with palpable inguinal nodes (cN1) underwent early inguinal LN dissection (iLND). Those with clinically node negative (cN0) inguinal basins were either observed or surgically staged with iLND or by dynamic sentinel LN biopsy (DSLNB). Median follow-up was 44 mo, with minimum follow-up of 6 mo.

Results and limitations: Fifteen of 117 (13%) patients with G2T1 cancer had LN metastasis at initial staging or during follow-up. Six of 12 (50%) cN1 patients had histologically proven LN metastasis on iLND. Those with clinically node negative (cN0) inguinal basins were either observed or surgically staged with iLND or by dynamic sentinel LN biopsy (DSLNB). One hundred five patients were cN0 at presentation. Ten cN0 patients had prophylactic iLND, none of which yielded LN metastasis; 5 of 64 (8%) cN0 patients who had DSLNB had tumour-positive LNs, and 4 of 31 (13%) cN0 patients who were observed developed LN metastasis during follow-up. In cN0 patients, the risk of LN metastasis at initial staging or during surveillance was 9%.

Conclusions: We consider that in cN0 patients with G2T1 penile cancer, the risk of developing metastases during surveillance warrants surgical and potentially curative staging. However, the morbidity of prophylactic bilateral iLND is too great to justify a detection rate of 9%. Less morbid alternatives such as DSLNB are advisable in G2T1 disease.

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1. Introduction

In penile squamous cell carcinoma (SCC), it is well established that the presence and extent of lymph node (LN) metastases are the most important predictors of survival [1]. Patients without regional nodal involvement have an excellent long-term survival (85–90%), but this rate diminishes considerably in the presence of nodal metastases [2].

The risk of LN metastases in G2T1 penile cancer has been reported as low as 0% [3] and as high as 50% [4] and is classified as “intermediate” in the 2004 European Association of Urology (EAU) guidelines [1]. It is recommended that patients with G2T1 disease and palpable inguinal LNs should have fine-needle aspiration cytology (FNAC) of these nodes under ultrasound guidance. If this biopsy is positive for tumour, then an ipsilateral inguinal LN dissection (iLND) should follow, with further surgery and/or radiation therapy dictated by the number of positive nodes and the presence of extranodal disease in the iLND specimen [5].

In patients with G2T1 disease and clinically node-negative (cN0) groins, the management of the inguinal node basins remains contentious and varies among treatment centres. Current imaging modalities are not sufficiently reliable to identify microscopic metastases (<2 mm) [6], so the options are surgical staging or observation. EAU guidelines [1] recommend a modified iLND if the primary tumour histology is unfavourable (ie, lymphovascular invasion [LVI] or infiltrating growth pattern). If the primary tumour shows none of these, then a surveillance programme is mandatory. Dynamic sentinel lymph node biopsy (DSLNB) is suggested as a staging tool in place of predictive factors (level of evidence: 2a). However, the rarity of penile cancer together with the limited availability of DSLNB means that this technique is not widely used.

Our combined prospective database of >900 patients was interrogated to establish the risk of LN metastasis in G2T1 penile cancer and enable recommendations for the management of the regional LNs in cN0 patients.

2. Materials and methods

The recorded data from two supraregional penile cancer treatment centres were combined. The database from St George’s Hospital (SGH) in London contained 370 patients treated from 2000 to September 2007. The database from The Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital (NKI-AVL) contained 532 patients treated between 1956 and September 2005.

Both databases contain detailed information on patient and tumour characteristics, regional LN status, methods of staging, and subsequent follow-up. Only G2T1 patients with a minimum follow-up of 6 mo from diagnosis were included in this study. Tumours were staged according to the 2002 TNM staging system [7] and graded as well, moderately, or poorly differentiated based primarily on cytologic pleomorphism and secondarily on tumour type and pattern of infiltration. Since 2001, histopathology of sentinel node specimens has been standardised, with sectioning of the entire node or nodes and immunohistochemical panels using a combination of low- and high-molecular-weight keratins [8,9].

2.1. Treatment of regional lymph nodes

At both institutions, patients with cN1 groins or pathologically proven tumour-positive nodes underwent an iLND of the affected side. Until the introduction of DSLNB, cN0 patients were managed according to their primary tumour histology. Those with carcinoma in situ, Ta, T1, and G1-2/T2 tumours were observed. Those with higher-staged or graded tumours underwent prophylactic bilateral iLND. DSLNB was introduced at NKI-AVL in 1994 and at SGH in 2004. At SGH, all cN0 patients with at least G2T1 disease underwent DSLNB. This was also the case at NKI-AVL from 2004, although prior to this date, cN0 patients with G2T1 tumours were observed. If a sentinel node was tumour positive, an ipsilateral completion iLND was performed.

2.2. Follow-up

The time of follow-up was defined as the time from diagnosis until the most recent follow-up, discharge, or death. At NKI-AVL, the follow-up consisted of visits every 2 mo for 2 yr after treatment, visits at 3-mo intervals in the third year, and semiannual appointments thereafter. Patients were discharged from follow-up if they were disease free at 10 yr. At SGH, follow-up of patients with G2T1 tumours consisted of visits every 2 mo for the first year, visits every 4 mo for the second year, and semiannual visits thereafter. Those who were disease free after 3 yr were referred to their local urologist for surveillance.

3. Results

A summary of the clinical and pathologic features of the entire cohort of patients is illustrated in Tables 1 and 2. Median follow-up was 44 mo (range: 6–358; interquartile range [IQR]: 53.2), with a minimum follow-up of 6 mo. Overall, 15 of 117 (13%) patients with G2T1 disease had LN metastases at initial staging or during follow-up.

Twelve patients were cN1, and all had iLND. Six of 12 (50%) patients had LN metastases. One hundred five of 117 (90%) patients were cN0 at presentation. Of these, 10 had bilateral prophylactic iLND, 64 had DSLNB, and 31 were...
observed. None of the 10 cN0 patients who had iLND had LN metastases, and there were no recurrences in this cohort.

Five of 64 (8%) cN0 patients who had DSLNB had tumour-positive sentinel nodes, with two patients having bilateral disease. Median follow-up in the DSLNB cohort was 38.5 mo (range: 8–120; IQR: 48.5). One of these five patients developed LN metastasis at 7 mo in a groin previously deemed negative on DSLNB (ie, false negative). Thus, in total, 8 of 128 (6%) groins staged with DSLNB had LN metastases.

Four of 31 (13%) cN0 patients who were observed developed LN metastases, with a median time to recurrence of 18 mo (range: 6–38). Median follow-up in the observation cohort was 30 mo (range: 6–90; IQR: 46.1). Overall, in cN0 patients, the overall risk of LN metastasis at initial staging or during surveillance was 9% (9:105).

| Table 2 – Summary table of the clinical and pathologic features of all G2T1 patients |
|-----------------|-----------------|-----------------|
| No. of patients | 117             |                  |
| Median age, yr (range) | 63 (32–92)   |                  |
| cN status: |                  |                  |
| cN0             | 105             |                  |
| cN1             | 12              |                  |
| Primary tumour surgery: |                  |                  |
| Circumcision     | 18              |                  |
| Circumcision and local excision | 27          |                  |
| Local excision   | 37              |                  |
| Glansectomy      | 16              |                  |
| Partial penectomy | 13            |                  |
| Glans resurfacing | 4              |                  |
| Distal urethrectomy | 1           |                  |
| No surgery       | 1               |                  |
| LVI: |                  |                  |
| Yes             | 11              |                  |
| No              | 77              |                  |
| Unknown         | 29              |                  |
| Regional staging method: |                  |                  |
| iLND            | 22              |                  |
| DSLNB           | 64              |                  |
| Wait and see    | 31              |                  |
| Follow-up period, mo (range) | 44 (6–358) |                  |
| Patient status: |                  |                  |
| Alive          | 95              |                  |
| Died of penile cancer | 3            |                  |
| Died, unrelated | 19              |                  |

cN = clinical node; cN0 = clinically node negative; cN1 = clinically node positive; LVI = lymphovascular invasion; iLND = inguinal lymph node dissection; DSLNB = dynamic sentinel lymph node biopsy.

There were three disease-specific deaths following regional or distant metastatic recurrence during follow-up: one in the cN1pN+ve cohort, and two in the observation group. One of the observed patients died following a penile recurrence and distant metastases, and another died following regional recurrence. Of the three other patients in the observation cohort who developed regional recurrences, two are still alive without disease progression after treatment for the recurrence, and one has died of an unrelated cause.

4. Discussion

The low incidence of penile cancer means that the majority of previously published studies analysing the risk of developing LN metastases in G2T1 disease are based on small series. As such, there is a wide variation between risk estimations in the literature, as illustrated in Table 3.

Most studies describe a low risk of LN metastasis in G2T1 disease, but these data contrast dramatically with Naumann and colleagues’ recently published series [4]. They identified 20 G2T1 patients, of whom 4 had palpable inguinal disease. Three of these four (75%) had LN metastases on iLND. Of the 16 patients who were cN0, 5 were staged with iLND, revealing LN metastasis in 1 of 5 (20%) patients. Eleven cN0 patients were observed rather than surgically staged, and 6 of these 11 (55%) developed LN metastases. Thus, in this series of 20 patients with G2T1 tumours, the risk of LN metastasis was 50% overall and 44% in those who were cN0. This risk is far higher than we noticed in our series: 13% overall and 9% in those who were cN0. The reasons for this discrepancy are unknown, although there may be a difference in the histologic analysis and grading of the primary tumour among pathologists. In our series, the large cohort number, standardised pathologic analysis, and consistent method of staging of regional nodes suggest that the risk assessment we have established is likely to be more reliable.

Traditionally, the difficulty in establishing a reliable risk percentage for LN metastasis from the literature has caused inconsistency in the management of the inguinal basins of G2T1 patients who present with impalpable inguinal nodes. Several studies have shown that although prophylactic iLND offers the best chance of cure, it is unnecessary in approximately 75–80% of patients and 85% of inguinal basins [3,14]. Furthermore, iLND is associated with substantial morbidity, such as lymphoedema (27–100%), seroma (7–25%), wound infection (14–17%), and skin necrosis (50–62%) [5,15,16]. These two factors prompted many to adopt a surveillance policy in cN0 patients, with lymphadenectomy performed only when disease became clinically apparent. Unfortunately, in nonrandomised, retrospective series, patients undergoing salvage iLND for palpable disease had a worse outcome than those undergoing early iLND for microscopic disease (disease-specific survival: 33–35% vs 84%) [10,17,18]. Furthermore, the morbidity associated with prophylactic superficial iLND has been shown to be less than that of therapeutic ilio-inguinal LND [15].
Leijte et al [18] recently reported a regional LN recurrence rate of 2% in patients surgically staged as pN0 compared with a 9% recurrence rate in the watchful waiting group. This correlates with our finding of 1% and 13%, respectively. Further reservations about the observation of cN0 patients include the need for regular hospital visits and surveillance imaging. After surgical staging, pN0 patients can be told with confidence that they have very little chance of developing LN metastases, which could allay patient anxiety and reduces the need for regular surveillance imaging—especially useful in situations where follow-up is difficult. The aforementioned reservations combined with the poor outcome of patients who develop recurrent LN metastases emphasise the advantage of early surgical staging compared with a wait-and-see policy in cN0 patients.

In order to stage patients with cN0 groins accurately yet to avoid the morbidity of prophylactic iLND, some centres have adopted DSLNB. The concept of sentinel LN biopsy relates to the identification and subsequent removal of specific LN centres that predict the nodal status of patients with a malignancy. Its use in penile cancer was first proposed by Cabanas >30 yr ago [19].

In 1994, Horenblas’ group at the NKI-AVL pioneered the use of DSLNB in penile cancer staging. In 2004, their reported false negative rate was 5%, and their complication rate was 6% of groins explored [20]. SGH introduced DSLNB in 2004. In our initial experience of 75 patients with a median follow-up of 11 mo, we had one false negative (5%) and a complication rate of 4% of groins explored [8].

Contemporary analysis of the combined NKI-AVL and SGH database reveals that we have performed DSLNB on >300 patients, with a median follow-up of 17 mo; have a sensitivity of 93%, with three false-negative studies at each institution; and a complication rate of 10% of groins (5% of patients) [21].

Undoubtedly, the best results in DSLNB come from institutions performing many procedures. However, the low incidence of penile cancer, the learning curve associated with the procedure, and the need for multidisciplinary support (nuclear medicine, dedicated uro-pathologists) means that establishing DSLNB is only really practical in supraregional treatment centres or where the infrastructure is already in place, for example, in the treatment of breast cancer and melanoma. Therefore, alternative options recommended in the EAU guidelines include the use of primary tumour histologic factors as predictive prognosticators in establishing a risk for LN metastases and to determine who may benefit from surgical staging. Local extension of the primary tumour and histologic grade form the basis of the EAU guideline stratification, which categorises patients into low-, intermediate-, and high-risk groups. However, strict adherence to these guidelines would have led to unnecessary iLND in 60% of patients considered to be at high risk of nodal metastasis in one large series [21].

In 1996, Lopes et al reported on the significance of vascular and lymphatic embolisation of the primary tumour in predicting LN metastasis in their series of 145 patients with penile SCC [22]. Subsequently, several authors have developed nomograms to establish a risk percentage for LN metastasis based on multiple histologic variables. In Ficarra and colleagues’ nomogram [23], the presence of vascular and/or lymphatic embolisation was a powerful predictor of LN metastasis. Their nomogram showed a good concordance index (0.876) and good calibration. Ornellas and colleagues [24] also found that LVI as well as absent koilocytosis were independent prognostic factors for the risk of LN metastasis, and those patients with koilocytosis and without LVI had a better 5-yr survival.

Criticalisms of nomograms include the lack of external validation and the fact that the outcome of a nomogram is a simply a risk percentage for harbouring nodal metastases: It does not provide a definitive solution. Clinicians still have to decide at what risk percentage patients should be offered an elective iLND.

A limitation of our study is the lack of external review of our pathology. However, both institutions have been referral centres for penile cancer pathology for many years, and each centre has had external audit of its pathologic analysis previously. We do not think that outside review or routine double reporting is justified when we have such a large experience of these tumours. Furthermore, the two main concerns about histology, tumour heterogeneity and sampling error, are unlikely to be resolved by central review.

5. Conclusions

In our large series, the 13% risk of LN metastasis in G2T1 penile cancer is lower than recently reported; but given the large cohort number, it is probably a more reliable figure. This risk and the poor outcome of those who have regional recurrence during surveillance emphasise the importance of surgical and potentially curative staging of clinically node-negative patients. However, the morbidity of prophylactic bilateral lymphadenectomy is arguably too great to justify a detection rate of 9%. Predictive nomograms based on primary tumour factors are useful prognostic tools, but strict adherence to them would still result in unnecessary invasive surgery. Minimally invasive staging of regional LNs using dynamic sentinel node biopsy is recommended as a reliable and oncologically sound procedure in G2T1 disease.

Author contributions: Ben E. Hughes had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hughes, Leijte, Watkin, Horenblas.
Acquisition of data: Hughes, Leijte, Kroon, Shabbir, Swallow, Corbishley, van Boven, Heenan.
Analysis and interpretation of data: Hughes, Leijte.
Drafting of the manuscript: Hughes, Perry, Watkin.
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