



Inguinal Metastasis in Penile Cancer: Diagnosis and Management

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Abstract

We provide an overview of current clinical practice and future developments regarding the diagnosis and management of nodal metastasis in patients with penile carcinoma. The dissemination pattern of penile carcinoma is predominantly lymphogenic. The inguinal regions are the first site of metastasis. Patients with proven inguinal metastasis should undergo an inguinal lymph node dissection. However, the management of clinically node negative patients remains subject of debate. Physical examination and present imaging techniques are not sensitive enough to detect occult nodal metastasis. The current EAU guidelines divide this group of patients into three risk groups (for having nodal metastasis) based on primary tumour characteristics. A wait-and-see policy is advised for patients in the low risk group, while patients in the highest risk group should undergo an elective inguinal lymph node dissection. However, using the guidelines the majority of patients still needlessly undergoes inguinal lymph node dissection, a procedure associated with high morbidity. Dynamic sentinel node biopsy is a minimally-invasive technique to reliably assess the lymph node status of clinically node-negative patients, though its use is currently not widespread. The role of chemo- and radiation therapy is confined to advanced stages of disease. Future developments include the use of new imaging techniques such as nanoparticle enhanced magnetic resonance imaging. Several biomarkers to detect nodal metastasis are under investigation.

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1. Introduction

Penile carcinoma is a rare disease in the western world, with an incidence of <1/100,000 men [1]. More

than 95% of malignant penile neoplasms are squamous cell carcinomas. The pattern of dissemination is predominantly lymphogenic, as is common in squamous cell carcinomas. In penile

carcinoma, the first draining lymph nodes are in the inguinal region. The secondary regional nodes are located in the pelvic region. The treatment of patients with penile carcinoma and proven inguinal metastases is straightforward and consists of treatment of the primary lesion and inguinal lymph node dissection (ILND). However, for clinically node-negative (cN0) patients the management of the inguinal regions has been subject of debate for many years. A routine elective ILND leads to over-treatment in the vast majority of patients because the incidence of occult lymph node metastases is around 20% [1-3]. In contrast, a wait-and-see policy carries the risk of detecting inguinal metastasis in a later stage, negatively influencing oncologic outcome [4]. Conventional imaging modalities like ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) have so far not convincingly improved the detection of occult metastases [5]. In addition, although several primary tumour characteristics are significantly associated with a high risk of nodal involvement, these are still rather unreliable in predicting occult metastases [6,7]. We review current clinical practice and the recent developments in diagnosing and managing lymph node involvement in squamous cell carcinoma of the penis.

2. Lymphatic drainage of the penis

The first draining lymph nodes of the penis are located in inguinal region, and their anatomy has been described by various authors [8-10]. The inguinal nodes can be divided into two groups, superficial and deep. The superficial nodes are located beneath Scarpa's fascia and above the fascia lata covering the muscles of the thigh; typically, 8-25 nodes are present. The deep inguinal lymph nodes, which number three to five, are located around the fossa ovalis, the opening in the fascia lata where the saphenous vein drains into the femoral vein. These deep nodes form the link to the secondary regional nodes, located in the pelvis, and receive their afferent lymphatic fluid from the superficial lymph nodes. The most constant and usually the largest inguinal node is found medial to the femoral vein and just underneath the inguinal ligament, the so-called lymph node of Cloquet. From a clinical perspective, the anatomic distinction between superficial and deep is useless because the superficial nodes cannot be distinguished from the deep nodes by physical examination. Daseler et al divided the inguinal region into

five sections by drawing a horizontal and vertical line through the point where the saphenous vein drains into the femoral vein with one central zone directly overlying the junction [11]. The nodes that are involved in penile carcinoma are typically located in the craniomedial segment, although there is individual variation. The penis drains bilaterally in most patients, as is shown by lymphoscintigraphy studies [12,13]. The pelvic lymph nodes are located around the iliac vessels and in the obturator fossa and usually consist of 12-20 nodes. Skip metastasis, circumventing the inguinal nodes, are very uncommon. Only very late in the natural history does haematogenic spread occur [14-17].

3. Assessing inguinal node status

3.1. Physical examination

Physical examination seems to be of limited value in evaluating inguinal lymph node status. Palpable inguinal lymph nodes are present in approximately 30-60% of patients at presentation [18]. In about half of these cases nodal metastases are found, whereas the rest are caused by an inflammatory reaction [19]. Some have suggested giving antibiotic treatment to patients with an inflammatory component to improve accuracy of physical examination [20]. However, the prolonged period of antibiotic treatment creates a delay that may have a negative effect on oncologic outcome [4].

In contrast, clinically node-negative patients harbour occult metastases in about 20% of cases [3]. These occult metastases are, by definition, not found with physical examination. One study reported specifically on the accuracy of physical examination in assessing nodal status, comparing results with histopathology (pN stage). The sensitivity and specificity of physical examination were 90% and 21%, respectively [5].

3.2. Ultrasound and fine-needle aspiration cytology

Ultrasound in combination combined with fine-needle aspiration cytology (FNAC) has a sensitivity and specificity of 39% and 100%, respectively, in assessing the lymph node status in cN0 patients [21]. FNAC has also been evaluated in the examination of palpable lymph nodes. In a series of 16 patients with palpable inguinal lymph nodes, sensitivity and specificity were 93% and 91%, respectively [22].

3.3. CT scan

The value of CT scanning in staging penile carcinoma is not well known. One report published in 1991 described 14 patients undergoing a CT scan of the abdomen, pelvis, and inguinal regions. In this series, none of the occult metastases in cN0 groins were detected by CT. All positive findings on CT were confirmed by histology, and there were no false-positive cases. Sensitivity and specificity were 36% and 100%, respectively [5]. These figures do, however, reflect an older series. CT technology has developed since and with the use of modern multi-slice CT scanners and their increased spatial resolution, results are probably better.

3.4. MRI

Data on the value of MRI for assessing node status are few. Only one series with seven patients has been described, reporting on the use of nanoparticle-enhanced MRI for staging regional lymph nodes. The reported sensitivity and specificity were 100% and 97%, respectively [23]. However, the smallest metastasis found was 3 mm in size. No additional information on the technique of histopathologic analysis (the gold standard to which MRI results were compared) was reported and it is unclear whether micrometastasis (≤ 2 mm) could have been missed. Therefore, the reported accuracy of MRI might be too optimistic. The spatial resolution of current MRI scanners is limited to 2 mm at best.

3.5. Positron emission tomography

Positron emission tomography (PET) is used for staging a variety of malignancies, but experience with penile carcinoma is limited. Scher et al reported on a series of 13 patients with penile carcinoma. On a nodal-group basis, a sensitivity of 89% was found for the detection of inguinal metastases and 100% for metastases in the deep inguinal and obturator basins [24]. However, the limits of MRI with respect to spatial resolution also hold true for PET.

At our institute, all patients with cN0 groins undergo an ultrasound and FNAC in case of suspicious nodes. In clinically node-positive patients, ultrasound and FNAC are also routinely used to assess the inguinal node status. In case of negative cytology, the FNAC is repeated in these patients. A CT scan of the inguinal and abdominal region is made in all patients with proven nodal metastasis to assess the extent of disease. PET scanning is performed in patients with advanced disease.

4. Primary tumour characteristics to predict node status

Several histopathologic tumour characteristics have been associated with nodal involvement, such as tumour grade, vascular and lymphatic invasion, T category, and infiltration depth [3,6,7]. However, none of these prognosticators seem to be accurate enough to safely use in clinical practice.

In the current European Association of Urology (EAU) guidelines, the management of cN0 patients is based on the probability for nodal metastasis, divided into three risk groups. In the low-risk group (pTis, pTaG1-2, or pT1G1), a surveillance programme is advised, whereas in the intermediate-risk group (T1G2), growth pattern and vascular and lymphatic invasion must be taken into account to determine which patients should be offered ILND. In the high-risk group ($\geq T2$ and G3) an elective ILND is advised [1,25]. Although the advised wait-and-see policy seems a safe approach in the low-risk group, the elective ILND appeared to be unnecessary in 82% of patients in one study prospectively evaluating the guidelines [2]. Clearly, these risk groups need fine-tuning.

Recently, a nomogram was published predicting the risk of inguinal lymph node metastasis in patients with penile carcinoma based on primary tumour characteristics, such as tumour thickness, grade, and growth pattern [26]. Although the nomogram performed well in their own series of patients, it also generated some questions. Intermediately differentiated tumours had a higher risk of metastases than poorly differentiated tumours, which contrasts with results of others [25]. The nomogram also predicts that superficially growing tumours have a greater risk of metastases than vertically growing tumours. This is different from what Cubilla et al, who proposed the classification, found in their series [27]. Evidently, this nomogram needs to be validated before it can be used.

5. Biomarkers predicting lymph node metastasis

Several biomarkers have been investigated for predicting lymph node metastasis in penile carcinoma, such as the transmembrane protein E-cadherin, the matrix metalloproteinases MMP-2 and MMP-9, and expression of p53 and Ki-67. A low E-cadherin immunoreactivity has been associated with lymph node metastases, whereas in the same study MMP-2 and MMP-9 were found to have no prognostic value [28]. Overexpression of p53

in the primary tumour has been significantly associated with lymph node metastasis [29,30]. Another study found a relation between Ki-67 and nodal metastasis and clinical disease progression, although not significantly ($p = 0.07$) [31]. Several other biomarkers that could predict metastasis in squamous cell carcinomas are under investigation [32–34].

All of the mentioned biomarkers, however, have yet to gain a role in clinical practice and more research is needed before they can be used routinely.

6. ILND

ILND has an essential role in the treatment of proven inguinal metastasis and is curative in approximately 80% of patients who present with one or two metastatic lymph nodes [16]. It is, however, a procedure that is associated with significant morbidity, such as severe oedema and wound infections. The reported complication rate varies from 35% to 88% [35–39]. The rate of complications is lower when ILND is performed in a prophylactic or therapeutic setting and is higher in a palliative setting [35,37].

To reduce the high morbidity associated with the standard ILND, efforts have been made to reduce the extent of surgery. Catalonia et al first reported on the modified ILND [40]. In this procedure the extent of nodal tissue removed is limited, and the saphenous vein is spared. The complication rate of the modified ILND is lower, but the oncologic safety of this procedure has been questioned [41].

Mainly because of the morbidity of the procedure, several issues of debate remain on the role and extent of ILND in clinically node-negative groins. First, the timing of ILND is subject of debate. On the one hand, cN0 patients seem to benefit from early dissection compared to late dissection (after a wait-and-see policy) [4]. On the other hand, an elective ILND proves to be unnecessary in up to 82% of patients because of the low incidence of occult metastases in cN0 patients [2].

The second point of discussion is the extent of lymphadenectomy. In general, 20–30% of patients with positive inguinal nodes have positive pelvic nodes, generating the question whether a pelvic lymph node dissection should be performed in all patients with positive inguinal nodes. The likelihood of pelvic node involvement is related to the number of positive nodes in the inguinal region and the tumour grade within these nodes. Patients with two or fewer positive inguinal nodes and no poorly differentiated tumour within these nodes are at low risk of pelvic lymph node involvement [42]. In the

current EAU guidelines, a pelvic lymph node dissection is advised in patients with two or more involved inguinal lymph nodes or extracapsular invasion of the lymph nodes.

The likelihood of metastatic involvement of the contralateral cN0 groin is also related to the number of positive inguinal nodes in the operated groin. With two or more metastases, the probability of occult contralateral involvement is approximately 30% [43]. The EAU guidelines suggest considering a modified ILND in these cases. At our institute we use dynamic sentinel node biopsy (DSNB) to assess the tumour status of cN0 groins.

7. DSNB

The term “sentinel node” was first proposed by Cabañas [44]. Based on lymphoscintigraphic studies of the penis, Cabañas identified the lymph node medial to the superficial epigastric vein as the first draining node or sentinel node of the penis. Sentinel node surgery for penile carcinoma from then on consisted of removal of the lymph node in this predetermined location, not taking into account individual variations in lymphatic drainage patterns. Several false-negative cases were reported, and the technique was largely abandoned [45]. Morton et al revived the concept of the sentinel node, by using blue dye as a tracer of lymphatic drainage. With this technique, individual variations could be mapped and the sentinel node procedure is now used in a variety of malignancies.

DSNB for penile carcinoma was introduced in 1994 [46]. It uses a radioactive tracer (^{99m}Tc nanocolloid) and blue dye to map the pattern of lymphatic drainage of the penis and identify the sentinel nodes. One day before surgery, a lymphoscintigraphy is made after the ^{99m}Tc nanocolloid is injected around the primary tumour. The sentinel node is identified and marked on the skin by a nuclear physician. On the day of surgery, blue dye is injected around the tumour about 10 min before the start of surgery. Intraoperatively, the radioactive sentinel node is located using a γ -ray detection probe and the blue dye. After removal, the sentinel nodes are meticulously analysed for presence of metastasis. In case of a tumour-positive sentinel node, a complementary ILND is performed [47].

The main disadvantage of DSNB is the relatively high false-negative rate of 22% in the initial procedures [48]. Several modifications to the procedure have since been made to improve sensitivity and in a recent analysis of the current DSNB procedure, the false-negative rate was reduced to

4.8% [49,50]. At our institute, DSNB is indicated in all patients with cT1–T3 tumours that are unilaterally or bilaterally cN0. DSNB should only be performed in cN0 groins because it seems to be unreliable in groins with suspicious nodes [51]. Compared to ILND, the morbidity of DSNB is much lower. Complications occur in 7% of cases and tend to be transient and mild [52].

8. Adjuvant and neoadjuvant therapy

8.1. Chemotherapy

The role of chemotherapy as adjuvant or neoadjuvant therapy in the management of inguinal metastasis is not well defined because of the lack of randomised studies in this field. Several chemotherapeutic agents have been reported to have an effect on this type of tumour, both as single agents as in combination chemotherapy. There is some evidence that adjuvant chemotherapy may reduce the number of local recurrences after surgery, although the available evidence is too scarce to recommend its routine use [1,53].

Neoadjuvant chemotherapy seems to be of value in patients presenting with fixed lymph nodes (N3), which are primarily inoperable. In an article combining the published experience of various cisplatin-based regimens used in a neoadjuvant setting in patients with fixed inguinal nodes, a clinical response was found in 24 of 35 patients (68.6%) and 15 patients (42.6%) were able to undergo a lymph node dissection, of whom 8 (22.6%) remained alive without evidence of disease [17]. We found similar results at our own institute [54].

8.2. Radiotherapy

There is no role for radiation therapy as a primary treatment in patients with confirmed lymph node metastasis because the 5-yr survival in this group is only half (25%) that of the group with surgery as primary treatment (50%) [43]. Prophylactic radiotherapy in cN0 groins is not recommended for several reasons: the efficacy has not been proven, the risk of complications is significant, and the associated fibrotic changes hinder reliable follow-up [1]. Too little data are available on the use of preoperative radiotherapy to reliably assess its value [17]. Also the postradiation effects may hamper consecutive surgery.

Adjuvant radiotherapy may be given in case of extracapsular growth of the lymph node or pelvic lymph node involvement.

9. Future developments

Several interesting developments could influence the future of management of inguinal metastasis. Microarray analysis is a technique with which the activity of thousands of genes can be determined in one single experiment. Using this technique in other tumours, genetic expression profiles have been found predicting metastatic potential and prognosis [55,56]. Preliminary results from an analysis of 56 patients with penile carcinoma did, however, fail to identify a reliable expression pattern predicting lymphatic spread (unpublished data).

Video endoscopic inguinal lymphadenectomy (VEIL) is a recently developed minimally invasive approach to perform ILND. Although no results on oncologic safety are available yet, it could significantly reduce the morbidity associated with inguinal lymphadenectomy [57].

Recent studies that have shown that tumours can actively induce lymphangiogenesis enabling lymphatic metastasis. Vascular endothelial growth factors (VEGFs) are a group of signalling proteins involved in angiogenesis. Some subtypes, such as VEGF-C and VEGF-D, have been correlated with lymphangiogenesis and lymph node metastasis in clinical studies, giving rise to possible new diagnostic and therapeutic options [58].

Human papillomavirus (HPV) infection is probably the most common sexually transmitted disease [59]. High-risk HPV has an essential role in the carcinogenesis of cervical cancer [60]. In about 30% of penile carcinomas, high-risk human HPV DNA is found [61]. Recently, the food and drug administration (FDA) approved the first vaccine for prevention of cervical cancer [62], and HPV vaccination programs to prevent cervical cancer are currently being considered. Widespread vaccination against high-risk HPV in women may have a substantial impact on the incidence of penile carcinoma.

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CME questions

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- The majority of penile malignancies are:
 - Melanomas
 - Squamous cell carcinomas
 - Metastases from other primary tumours
 - Adenocarcinomas
- Which percentage of penile carcinoma patients with nonpalpable inguinal nodes at presentation have occult nodal metastases?
 - None
 - 20%
 - 40%
 - 60%
- Which statement regarding lymphatic dissemination of penile tumours is false?
 - Lymphatic drainage of the penis is unilateral in most patients.
 - Skip metastases, circumventing the inguinal nodes, are uncommon.
 - Metastatic lymph nodes are mostly found in the craniomedial segment, according

- to Daseler's division of the inguinal region.
- D. The lymph node of Cloquet is usually the largest inguinal lymph node.
4. Which percentage of palpable inguinal nodes, present at presentation, are caused by an inflammatory reaction?
- A. 20%
 - B. 50%
 - C. 70%
 - D. None
5. Which statement is true about inguinal lymph node dissection?
- A. It is curative in the majority of patients presenting with one or two metastatic lymph nodes.
 - B. The complication rate of inguinal lymph node dissection is up to 88%.
 - C. The complication rate is lower when performed in a prophylactic setting than in a palliative setting.
 - D. All of the above statements are true.
6. Which statement(s) is false about dynamic sentinel node biopsy for penile carcinoma?
- A. Dynamic sentinel node biopsy is reliable in groins that are clinically node-positive.
 - B. The complication rate of the dynamic sentinel node biopsy is lower than the complication rate of an inguinal lymph node dissection.
 - C. This method is suitable for detecting micro-metastasis (≤ 2 mm).
 - D. More than one sentinel node can be identified per groin.