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Lymph Node Staging in Clinically Negative Groin Nodes

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Abstract

Introduction: Nodal involvement is the most important prognostic factor in patients with squamous cell carcinoma of the penis (SCCp). However, optimal staging of regional lymph node remains controversial.

Methods: The literature was reviewed to examine current management of regional lymph nodes in SCCp patients with clinically nonpalpable inguinal lymph nodes (cNO).

Results: Radiological staging and selective risk-profile nomograms are unreliable in the detection of occult micrometastases in cNO patients. Prophylactic inguinal lymph node dissection (ILND) is associated with significant morbidity and a high rate of postoperative complications. Dynamic sentinel lymph node biopsy (DSNB) is a reliable minimally invasive surgical staging technique for cNO patients. Ipsilateral ILND is indicated only in inguinal basins with positive DSNB.

Conclusions: DSNB has excellent performance characteristics in staging cNO patients, with high sensitivity and a low morbidity rate.

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1. Introduction

The presence and extent of nodal metastasis are the most important prognostic factors for survival in patients with squamous cell carcinoma of the penis (SCCp) [1,2]. In a recent study, 5-yr cancer-specific survival of 98.4% was reported for patients without regional lymph node involvement [3]. However, this rate diminishes considerably if nodal metastases are present.

Lymphatic spread in patients with SCCp typically follows a stepwise manner via a well-characterised anatomic route. Superficial inguinal lymph nodes (located beneath Camper's fascia and above the fascia lata) and deep inguinal lymph nodes (located deep to the fascia lata

and medial to the femoral vein) are the first groups of regional lymph nodes reached by metastatic lymphatic spread from penile cancer. Metastasis to ipsilateral pelvic lymph nodes follows. This process can be unilateral or bilateral. Crossover lymphatic drainage of inguinal or pelvic lymph nodes to contralateral regional lymph nodes has not been demonstrated in lymphoscintigraphy studies [4]. SCCp metastasis via circumvention of inguinal lymph nodes and direct spreading to pelvic nodes has not been identified in similar studies [4,5].

Fewer than 5% of patients have distant metastasis on initial presentation. However, these patients almost always have clinically evident regional lymph node involvement [6]. Haematogenous dissemination occurs only in advanced

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stages of the disease [7], although it has been reported that primary haematogenous spread occurs rarely (<1%) in SCCp of the sarcomatoid subtype [8].

It has been shown that early resection of regional metastatic lymph nodes in patients with SCCp improves survival [9]. Historically, inguinal lymph node dissection (ILND) has been the standard procedure offered to patients with regional lymph nodes metastasis, or in those with high-risk primary disease. However, ILND is associated with a high morbidity rate of 30–50% [10,11]. Therefore, accurate nodal status assessment should be performed to determine which patients require radical nodal treatment and which could be spared from unnecessary ILND. This article discusses the assessment and staging of regional lymph node in patients with SCCp.

2. Patients with clinically impalpable inguinal lymph nodes (cN0)

The nodal management of cN0 patients remains controversial. Historically, there was debate regarding whether cN0 patients should be kept under surveillance or offered prophylactic ILND. While the latter offers a good chance of cure, it is associated with substantial morbidities. These include lymphoedema (27–100%), seroma (7–25%), wound infection (14–17%), and skin necrosis (50–62%). However, only 20% of cN0 patients harbour occult metastasis [12]. Therefore, prophylactic ILND is unnecessary in 80% of cN0 patients.

2.1. Active surveillance

The high morbidity rate associated with prophylactic ILND prompted many to adopt a close surveillance approach in patients with cN0 inguinal basins. This involves regular examinations and proceeds to radical ILND when lymph node metastasis becomes clinically evident. Although surveillance avoids overtreatment and potential complications from ILND, it has several disadvantages. First, it has been reported that inoperable lymph node metastasis developed in >20% of patients under surveillance [14]. The opportunity for cure was therefore missed. Second, a nonrandomised study showed a survival benefit in patients undergoing prophylactic ILND when compared with patients who underwent therapeutic ILND [9]. Surveillance should only be reserved for selected SCCp cN0 patients with a low risk of occult metastasis after appropriate counselling. It is also important that they are compliant with their follow-up arrangements.

2.2. Risk-adapted approach and nomograms

The probability of nodal metastasis is related to the histopathological features of the primary tumor and. This allows a risk-adapted approach to identify cN0 patients at high risk of occult inguinal nodal metastasis and patients who are at low risk and eligible for close surveillance. This approach was previously recommended in the European Association of Urology (EAU) guidelines in 2004 [15].

Three risk groups were identified (Table 1). Low-risk tumours have favourable primary tumour characteristics and very low risk of occult nodal metastasis (0–2%). They can be safely observed under a surveillance program. For patients in the intermediate and high risk categories, prophylactic ILND was recommended (Table 2). However, a recent study showed that strict adherence to these EAU guidelines would have led to negative bilateral ILND in 77% of the high-risk patients [16]. Therefore, a large number of patients would undergo ILND unnecessarily with this approach.

Various nomograms have been developed to improve accuracy in identifying patients at high risk of lymph node metastasis. They involve the use of various primary tumour histopathological variables to predict inguinal lymph node metastasis. Grade, stage, lymphovascular invasion (LVI), and p53 expression have been used in a nomogram developed by Zhu et al [17]. A high concordance index of 0.79 was reported, but external validation is lacking. Ficarra et al [18] used tumour thickness, microscopic growth pattern, grade, LVI, corpora cavernosa, corpus spongiosum, or urethra infiltration, and cN status as parameters in their nomogram. This model showed a good concordance index of 0.876. However, some variables used in this nomogram are contradictory to findings from other studies. It also included patients with cN+ disease.

2.3. Radiological staging

The use of an ultrasound scan (USS) to detect cN0 nodal metastasis has previously been investigated. USS relies on the detection of abnormal changes in lymph node architecture, such as size, shape, absence of an echogenic hilum, abnormal hypoechogenicity, and vascularity. Fine-needle aspiration cytology (FNAC) is performed if suspicious lymph node morphological changes are detected. Although noninvasive, it is associated with a high false-negative rate [19]. Therefore, USS on its own in staging cN0 SCCp is unreliable and not recommended.

The detection of lymph node involvement via cross-sectional imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), rely primarily on changes in size. Inflammatory lymph node changes lead to a high false-positive rate. It has been reported that staging of cN0 inguinal basins via CT or MRI is unreliable and inaccurate.

Previous reports described higher uptake of the glucose analogue ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) in patients with

Table 1 – Risk stratification of regional nodal metastasis according to the European Association of Urology 2014 guidelines

Low risk	PeIN, G1/2Ta, G1T1, without any evidence of lymphovascular invasion
Intermediate risk	pT1G2 without lymphovascular invasion
High risk	pT1G3 or pT2/3G1–3, or lymphovascular invasion in primary tumour
PeIN = penile intraepithelial neoplasia.	

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