

# Fine-needle aspiration cytology predicts inguinal lymph node metastasis without antibiotic pretreatment in penile carcinoma

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## OBJECTIVE

To evaluate the accuracy of fine-needle aspiration (FNA) cytology of palpable inguinal lymphadenopathy before definitive management of the primary tumour, in predicting inguinal lymph node (LN) metastasis in men with primary squamous cell carcinoma (SCC) of the penis.

## PATIENTS AND METHODS

Sixteen men with primary SCC of the penis and palpable inguinal lymphadenopathy (unilateral or bilateral) were treated by primary resection and bilateral inguinal LN dissection. FNA cytology was analysed for 25

palpable inguinal LNs at the time of penile biopsy. The sensitivity, specificity and accuracy of FNA cytology was compared with the histological findings from surgical LN clearance.

## RESULTS

The 25 FNAs were without complication and without evidence of implantation of metastasis in the needle tracts; 14 FNA samples were positive for metastasis, 10 were negative, and one was inconclusive. From the histological assessment of the surgical inguinal LN specimens, FNA cytology had a sensitivity of 93%, and specificity of 91% in predicting metastatic disease.

## CONCLUSION

FNA cytology of palpable inguinal lymphadenopathy before surgery for the primary tumour has a high sensitivity and specificity for metastatic penile cancer. This procedure permits early inguinal lymphadenectomy where appropriate without need for prolonged initial antibiotic treatment.

## KEYWORDS

carcinoma penis, cytology, inguinal lymphadenopathy, aspiration biopsies, surgery

## INTRODUCTION

Squamous cell carcinoma (SCC) of the penis is uncommon in Western countries, with an incidence of <1 per 100 000 males, but it accounts for 10–20% of all malignancies in men in developing nations [1,2]. Most primary penile SCCs are low-grade, and inguinal lymph nodes (LNs) are usually the site of initial metastasis. The nodal status is the most important prognostic factor, and inguinal LN dissection (LND) may be curative in about half of men with nodal metastases. If untreated, men with inguinal LN metastases seldom survive for >2 years [3]. However, clinical assessment of inguinal LN status is often inaccurate: up to a half of men with palpable inguinal lymphadenopathy are shown on subsequent LND to have reactive inflammatory changes only, rather than metastatic disease [3,4].

Men with penile cancer and palpable lymphadenopathy are usually treated by control of the primary tumour followed by

an extended course of antibiotic therapy and re-evaluation of the inguinal nodal areas after 4–6 weeks, to allow reactive inflammatory changes in these LNs to resolve [3]. However, up to 30% of men with palpable lymphadenopathy after an antibiotic course are ultimately shown, on histological examination, to have reactive rather than metastatic disease [5]. Critical time might be wasted by an antibiotic course in men with penile cancer when early resection of LN metastases is advocated to improve survival [6]. Fine-needle aspiration (FNA) cytology of LNs is a reliable method of diagnosing metastatic nodal malignancy for many primary tumours, including penile cancer [7], and was included in the European Association Urology Guidelines for treatment of penile cancer [1]. FNA cytology has recently gained a role in impalpable nodal disease in penile cancer to help direct sentinel LN biopsy [8].

The role of FNA cytology in primary SCC of the penis before extended antibiotic therapy although proposed [9], has never been

thoroughly investigated by comparison to histological examination of contemporaneous inguinal LNDs. In this study we evaluate our experience with FNA of inguinal LNs in men with palpable lymphadenopathy at the time of treatment of the primary penile malignancy.

## PATIENTS AND METHODS

Twenty-two consecutive patients diagnosed with penile cancer over a 3-year period were recruited. After excluding six men with distant metastatic disease, 16 men with primary penile carcinoma and palpable inguinal lymphadenopathy (unilateral or bilateral) remained. Primary penile lesions were biopsied under local anaesthetic to confirm the diagnosis of SCC with FNA conducted at the same time.

FNAs of palpable LNs were taken by the treating urologist using standard needles (20 G) and a standardised procedure at the

time of penile biopsy. Ultrasonographic guidance was not used. The largest node was measured with a calliper and aspirated five times to obtain the specimen. Needle tracts were noted diagrammatically to ensure complete excision at definitive surgery. If more than one node was palpable, then several nodes were aspirated. Slides were fixed in 95% ethyl alcohol and reported separately from the definitive histological specimens by cytological pathologists. The cytology specimens were diagnosed as positive or negative for metastatic disease. One specimen was regarded by the pathologist as inconclusive, and for this study was regarded as a negative assessment of the presence of metastases.

All men then had partial penectomy and synchronous bilateral inguinal LND without antibiotic treatment as soon as possible. The LND was radical on the involved side(s) with the inguinal ligament, adductor muscle, sartorius muscle and femoral artery and vein as the floor of dissection. On the uninvolved side, a modified radical dissection was undertaken, preserving the saphenous vein with a 2-cm reduction in external and inferior borders from the radical dissection, as previously described [1]. This dissection was extended if positive nodes were found on frozen-section analysis, in accordance with guidelines [1]. Surgical histopathology results were compared with FNA cytology assessments, and the sensitivity, specificity and predictive value of FNA studies were ascertained.

## RESULTS

Sixteen men with 25 palpable regions of inguinal lymphadenopathy (nine bilateral and seven unilateral) were enrolled; their mean age was 52 years, and eight men had a history on presentation of phimosis. The mean (range) diameter of inguinal lymphadenopathy at aspiration was 1.47 (0.5–4.0) cm for individual involved nodes. The primary penile tumour was assessed on histology as T1 in two cases and T2 in 14 cases (1997/2002 TNM classification for penile cancer). No patient with T1 disease ultimately had nodal involvement on histology. Nodal metastases were diagnosed in 14 of 25 FNA studies, including one case where this assessment was a false-positive diagnosis of metastatic spread (Table 1). Eleven FNA studies were negative for

metastases, including one later shown on histological review to be a false-negative. This patient had an inconclusive FNA sample, regarded in this study as a negative assessment for metastatic disease. These results represent a sensitivity of FNA in this setting of 93% and a specificity of 91% for the identification of metastatic disease. The overall accuracy of FNA was 92% (Table 1).

All FNAs were without complication and there was no histological evidence of tumour implantation in the FNA tracts. Overall, the clinical evaluation of LNs had an accuracy of 66% when compared to pathology (Table 1). Having bilateral nodal involvement on clinical assessment reduced accuracy to 50%.

Clinical assessment of the maximal nodal diameter was not an infallible predictor of the FNA cytology result. When nodes were >3 cm in two men with bilateral lymphadenopathy, both cases were positive on FNA cytology. In 13 men, representing 20 LNs, where the maximum nodal size was 1–3 cm, nodal size predicted FNA cytology in only 70% of cases. Finally, in one man with a node of <1 cm there was a positive FNA cytology.

## DISCUSSION

It is well recognised that clinical examination of groin nodes for metastases is inaccurate [10], as in the present study, yet the reported incidence of inguinal LN metastases in penile cancer is 40–50% [4]. The inguinal nodes are the initial drainage point for the lymphatics of the penis, and it is generally accepted that all men with primary SCC of the penis where such nodal metastases are present should be treated by inguinal LND [11]. However, this has a risk of significant morbidity including flap necrosis, lymphoedema, and venous thrombosis [12–14]. Thus, there has been a justifiable reluctance to proceed to inguinal lymphadenectomy before excluding reactive rather than metastatic lymphadenopathy.

Techniques have emerged in an attempt to identify involved nodes, e.g. biopsy of the presumed sentinel inguinal LN at the junction of the long saphenous vein and the superficial epigastric vein [9]. This was initially proposed as the best means of identifying inguinal nodal metastases in penile cancer [15], but its reliability has been extensively questioned [16–18], and biopsy of the most medial inguinal node was proposed as a diagnostic alternative [10]. More recently, dynamic

**TABLE 1** Summary of the cytological, clinical, and histological status of inguinal LNs in all patients.

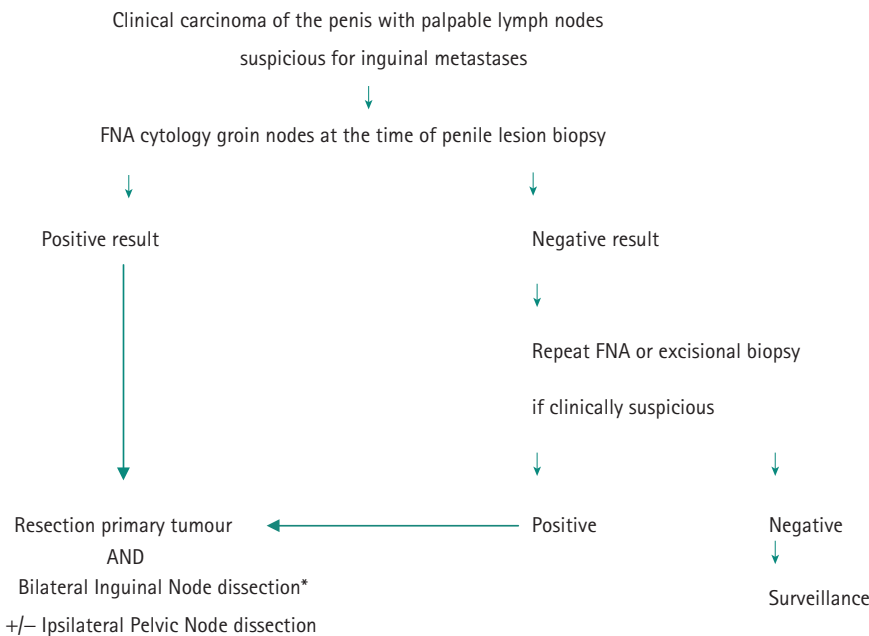
Variable	Positive	Negative	Total
<b>Cytology: palpable nodes</b>			
FNA positive	13	1	14
FNA negative	1	10	11
Total	14	11	25
<b>Clinical evaluation</b>			
Palpable	14	11	25
Impalpable	0	7	7
Total	14	18	32

sentinel LN biopsy has emerged, with better techniques for locating the sentinel node using vital blue dye as well as lymphoscintigraphy and intraoperative gamma probes [8,19–22]. The role of sentinel LN biopsy lies with identifying metastases in impalpable LNs [19]. None of these procedures is widely accepted as mandatory in the management of potentially disseminated penile cancer (those with palpable nodes) and they are still developing, with false-negative results possible [20,23,24].

For clinically palpable nodes, FNA cytology of inguinal LNs was evaluated under different clinical circumstances as a means of determining metastatic involvement from penile cancer. Senthil Kumar *et al.* [10] reported complete sensitivity of FNA cytology for detecting metastatic penile cancer in palpable inguinal lymphadenopathy in a series of 28 patients. The FNA cytology was assessed at the time of inguinal LND and not before antibiotic therapy. Despite the sensitivity, they suggested that men with negative FNA cytology should have medial inguinal LN biopsy to overcome the risk of a false-negative cytological assessment. Accurate sampling by FNA is often cited as an issue when many nodes are enlarged, as is often the case [10]. This has led to other methods of accurately identifying nodes for cytological assessment using lymphangiography and CT, which have been largely discouraging [7,25–27].

The present study shows that FNA of palpable inguinal lymphadenopathy, with local anaesthesia at the time of biopsy of the primary penile carcinoma, is safe and accurate in predicting metastatic disease. The results could have been further improved in our

FIG. 1. An algorithm for managing enlarged groin nodes in men with penile cancer, to be used in conjunction with penile cancer treatment conventional guidelines.



\*Sentinel lymph node biopsy and/or modified inguinal node dissection may have a role at this point depending on the experience at a particular centre

cohort had the FNA been repeated in the patient with an inadequate sample, as suggested by other authors [7,9]. Ultrasonography might also help in improving sample accuracy [9] but sampling of nodes did not appear to be an issue in our series. Clinical nodal size was highly predictive of the FNA cytology result only when >3 cm in the present study.

When the FNA cytology is positive, inguinal LND can be done at the same setting as definitive management of the primary tumour, allowing more expedient treatment of disseminated disease (Fig. 1) [9]. By using this algorithm, 52% of the patients in the present series would have been spared a 6-week period of antibiotic treatment before proceeding to inguinal LND. Thus the present study is the first to support in practice the theory of Horenblas [9], who proposed a similar regimen of early treatment of penile cancer neglecting antibiotics in 2001.

False-positive results for metastatic lymphadenopathy in primary penile cancer have rarely been reported using FNA cytology [8,10,28], but there was one case in the present series. Although some centres, including ours, have advocated routine

inguinal dissection where there is palpable lymphadenopathy, this policy results in some cases where metastatic disease is not identified. Such cases will be reduced but not eliminated using FNA as described. Our institutions have discontinued routine lymphadenectomy since this study, and have adopted FNA cytology for palpable nodes at the time of penile biopsy.

The ideal means of eliminating unnecessary inguinal lymphadenectomy where metastatic disease is not identified on definitive histological review remains to be proven. In palpable disease, treatment algorithms that suggest automatic inguinal lymphadenectomy where nodes remain palpable after a course of antibiotics often still produce histological evidence of inflammation rather than metastatic disease [5,29]. With occult disease in impalpable nodes, the role of sentinel LN biopsy rather than anatomical dissection or observation is yet to be resolved. We do not think that FNA and cytology is applicable where no nodes are palpable without further supportive data.

In conclusion, FNA cytology of palpable inguinal lymphadenopathy, in association with diagnostic biopsy of the primary tumour

in SCC of the penis, has a high sensitivity and specificity for metastatic disease. We think this treatment algorithm may permit early inguinal lymphadenectomy where appropriate, without the need for prolonged initial antibiotic treatment.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **FNA**, fine-needle aspiration; **SCC**, squamous cell carcinoma; **LN(D)**, lymph node (dissection).