Urol Res (2000) 28:246–249

ORIGINAL PAPER

Friedhelm Wawroschek · Harry Vogt
Dieter Bachter · Dorothea Weckermann
Michael Hamm · Rolf Harzmann

First experience with gamma probe guided sentinel lymph node surgery in penile cancer

Received: 24 November 1999 / Accepted: 21 April 2000

Abstract Because of the curative approach, the detection of lymph node metastases in squamous cell carcinoma (SCC) of the penis is of significant clinical relevance. Sentinel lymph node (SLN) identification by means of lymphangiography has been proven to be insufficiently safe. However, the high morbidity of inguinal lymphadenectomy and the considerable individual variability regarding the location of lymph node metastases justify the necessity of a technique that enables the identification of SLNs. Since 1998, SLNs have been intraoperatively identified and selectively dissected, after peritumoral injection of technetium-99m nanocolloid and using lymphoscintigraphy, in three patients (one with malignant melanoma and two with SCC). At least one SLN could be detected in each patient. The maximum surgical time was 30 min. There were no severe complications. Lymph node metastases did not occur in any patient. Upon a mean follow-up of 10 months, all patients are currently free of tumor. Owing to the long-term results of sentinel lymphadenectomy in malignant melanoma of other locations and our preliminary results with respect to penile carcinoma, we consider the current method appropriate as the only primary operation for lymph node staging in early stages and, in combination with modified inguinal lymphadenectomy, in locally advanced stages.

Key words Penile neoplasms · Lymph node excision · Radio nuclide imaging

F. Wawroschek (✉) · D. Weckermann · M. Hamm
R. Harzmann
Department of Urology, Zentralklinikum Augsburg,
Stenglinstr. 2, 86156 Augsburg, Germany
Tel.: +49-821-4002848; Fax: +49-821-4004578

H. Vogt
Department of Nuclear Medicine, Zentralklinikum Augsburg,
Augsburg, Germany

D. Bachter
Department of Dermatology, Zentralklinikum Augsburg,
Augsburg, Germany

Introduction

The clinical impact of the sentinel lymph node (SLN) is based on the phenomenon of a primary lymphatic filter level of the tumor beyond which further lymphatic spread into the adjacent lymph nodes takes place. This suggests that a negative SLN excludes lymphatic metastasis.

The term SLN gained clinical popularity toward the end of the 1970s thanks to Cabanas [4]. He was the first to describe the specific regional lymphatic drainage pathways in penile carcinoma. He also postulated the existence of a reproducible SLN, located medial to the saphenofemoral junction, by means of lymphangiography. The lack of reproducibility of the SLN in penile carcinoma with regard to its defined localization was later emphasized by numerous investigations [17, 18]. In these studies, patients with gross lymphatic metastases could be monitored despite negative biopsies of the "Cabanas lymph node".

Histologically, approximately 95% of the penile cancers are squamous cell carcinomas (SCC). In western countries, the incidence is below 1. Malignant melanomas of the penis and urethra are extremely rare. Up to now, less than 100 cases have been published worldwide [2]. Partial or total penectomy with inguinal and optional pelvic lymphadenectomy (LA) are the standard therapies of penile carcinoma. In the case of metastasis, a combined chemotherapy may lead to a remission. However, long-term results are disappointing [21]. This emphasizes the importance of inguinal LA, by which, according to the literature, a high percentage of patients with positive lymph nodes can be cured [8].

The probability of lymph node metastases in SCC of the penis is comparatively high. Up to 50% of cases develop lymph node metastases during the later stages of the disease or lymph node metastases are already present at the time of diagnosis [21]. The frequency depends on the grading (G1: 0–47.5%; G2: 14.5–64.1%; G3: 44.4–85.7%) [11, 22, 23] and the T-stage of the primary

tumor. While lymph node metastases in carcinoma in situ are solely described for single cases [7], they were identified by Pizzocaro et al. [21] already in 16.5% ($n = 121$) of the T1 G1 tumors. There is a continuous increase, up to 100%, of lymph node metastasis [22] in tumors ≥T2 G3. The probability of lymph node metastasis in malignant melanoma is predominantly determined by the tumor thickness. Lymph node metastases in tumors smaller than 0.75 mm are rare. Lymph node-positive stages prevail from a tumor thickness of 4 mm [20].

As the gamma probe guided sentinel lymph nodectomy (SLNE) in malignant melanoma has to be considered sufficiently validated [2, 14, 20, 24], and since initial results of the application of this technique in breast cancer [9] and prostate cancer [25] are very promising, we have performed it, since 1998, in penile carcinoma.

Materials and methods

One day prior to surgery a peritumoral, intracutaneous injection of technetium-99m nanocolloid (Nanocoll, Sorin, Italy) (Fig. 1a) was performed under sterile conditions after application of a local anesthetic gel. The total radioactivity applied was 40–80 MBq in each patient. Planar scintigraphies in posteroanterior projection (Sophy-Camera DSX, LEAP collimator, 100,000 cts/picture or 10 min acquisition time) were performed immediately and a few hours after injection; the injection location was covered (Fig. 3a, b). After having identified the SLN, the skin was marked preoperatively by using the gamma probe.

The local tumor excision controlled by immediate sectioning was performed on patients with SCC by a complete dissection of the glans penis, with the preservation of the cavernous bodies in their full length. The malignant melanoma of the prepuce was locally removed by radical circumcision. Subsequently, it was possible to localize the SLN in the marked area by means of the gamma probe and to remove them (Fig. 1b). The histopathologic examination of the SLN was done immunohistochemically after preparing serial sections. The malignant melanoma was classified according to the International Union Against Cancer (UICC).

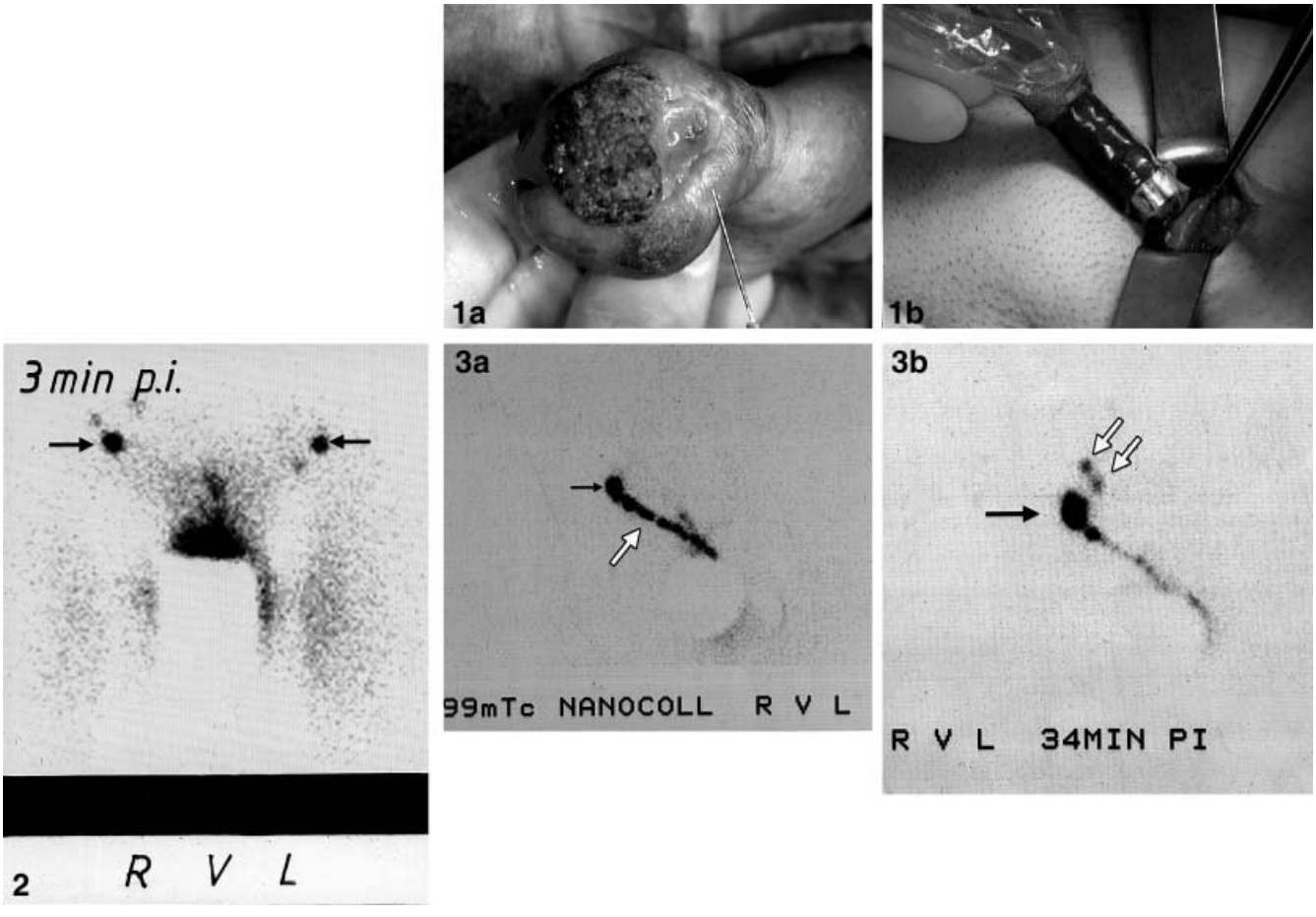
Results

With the two patients with SCC of the glans penis we achieved unilateral proof of one or two SLN (Fig. 3a, b) through the preoperative lymphoscintigraphy. One SLN

Fig. 1 Preoperative peritumoral intracutaneous injection of the colloid (**a**) and intraoperative identification of the sentinel lymph node with a gamma probe (**b**) (patient B.J.)

Fig. 2 Lymphoscintigraphy with early uptake (3 min) and two SLN (*arrows*). The location of the injection is partly shielded (patient M.K.)

Fig. 3 Early (**a**) (10 min) and late uptakes of a lymphoscintigraphy (**b**) with the visualized lymphatic drainage (*white arrow* in **a**) and sentinel lymph nodes (*black arrows* in **a** and **b**). Additional subordinate lymph nodes (*white arrows* in **b**) intraoperatively identified as pelvic lymph nodes



was identified in each groin of the patient with the malignant melanoma (Fig. 2). All lymph nodes that were recognized as SLN preoperatively by using lymphoscintigraphy could be identified intraoperatively using the gamma probe and were dissected. Infiltration beyond microinvasive growth was not found in any of the carcinomas (Table 1). The carcinoma classified as carcinoma in situ by the final histologic evaluation (patient K.V.) was also classified as microinvasive intraoperatively. Thus, in this case, optional SLNE was performed during the same operation.

With regard to the type of operation, the surgical time was rather short (15–30 min). Apart from one superficial wound infection, there were no perioperative complications.

Owing to the relatively superficial localization of the SLN it was not necessary to identify the inguinal blood vessels intraoperatively. Therefore, we could not state the precise localization of the SLN in relation to them.

The postoperative follow-up was 4, 6 and 22 months. During this period none of the patients showed either local tumor relapse or lymphatic or hematogenous metastasis.

Discussion

The literature pertinent to the anatomy of the penile lymphatic drainage is contradictory: Catalona (1980) [5] summarizes that "...the lymphatic drainage of the glans and urethra is believed to go directly to the pelvic nodes, whereas the drainage of the penile shaft and prepuce is believed to go directly to the inguinal nodes and secondarily to the pelvic nodes." Anatomic studies [3, 10] on the lymphatic system of the glans penis, however, demonstrate that we are dealing with a complex plexus of lymphatic drainage primarily being able to go to the lymph nodes of the superomedial, superficial and deep inguinal region, to the external iliac and hypogastric region and which is subject to significant individual variance.

The unilateral lymphatic drainage, in spite of the bilateral injection of the radiotracer as observed in both of our cases of SCC, can be explained anatomically as follows: the initial lymphatics of the efferent network of the glans penis join into either one or several anastomized stems when ascending to the back of the penis, with further lymphatic drainage taking place via the *centrally* located pubic plexus [10], whereas the efferent lymphatics of the prepuce, after running parallel to the superficial dorsal penile vein, bend *on both sides* predominantly into the superficial, superomedial inguinal lymph nodes before reaching the symphysis [10]. We therefore succeeded in the bilateral detection of inguinal SLN in the patient with a malignant melanoma of the prepuce. Another possible explanation for a unilateral lymphatic drainage would be an extensive contralateral lymphatic metastasis, which may lead to a reduction of lymphatic drainage in this region. However, this would lead to the assumption that lymph nodes are suspicious due to their macroscopic aspect or at least due to palpation. In such cases we see a benefit in an additional dissection, even of suspicious lymph nodes, after antibiotic therapy.

The reason for the reservation with respect to the inguinal LA – despite the existing curative approach in the case of metastasis – is to be seen in the comparatively numerous and often severe complications. Skin necrosis and chronic lymphedema of the lower extremities were, for instance, observed in up to 50% of cases of excessive inguinal LA [6], and a perioperative mortality in a maximum of 10% of such cases [15] was reached. Of course, a reduction of frequency and severity of complications could be achieved by reducing the area of LA [6, 16]. From this – and from the data of Solsona et al. [22], who found no lymph node metastases in a relatively small collective of patients with pT1 G1 SCC of the penis ($n = 19$) – recommendations suggesting dispensing with a primary inguinal LA in apparently early stages ($\leq$T1 G1) and in the case of clinically inconspicuous lymph nodes are resulting [27].

To avoid a primary inguinal LA – also in early stages – is, however, problematic for several reasons. The clinical staging of regional lymph nodes in the SCC of the penis is inaccurate. About 20% of patients with clinically inconspicuous lymph nodes have occult micrometastases and ca. 50% of cases with enlarged lymph nodes are free of metastases [6]. Current literature does not allow for any sufficiently secure predictions considering the lymph node status when analyzing, grading and classifying the primary tumor. Moreover, it is considered secure that, in the case of lymph node metastasis,

Table 1 Pre-, intra- and postoperative patient data (*LN* lymph node)

Initials, age (years)	Operation, date of operation	Surgical time SLNE (min)	Diagnoses	Total SLN/ total LN	Location of SLN	Complications
M.K., 50	Circumcision, SLNE, February 1998	30	Acrolentiginous melanoma, depth of infiltration 0.35 mm, Clark-Level II	2/3	Both groins	None
K.V., 78	Resection of glans penis, SLNE, June 1999	20	Carcinoma in situ	1/2	Right groin	Superficial wound infection
B.J., 62	Resection of glans penis, SLNE, August 1999	15	SSC, pT1 G2	2/8	Left groin	None

the delayed inguinal LA leads to a worse prognosis as compared with early LA [12, 13].

Owing to the minimal invasive character of the gamma probe guided SLNE in relation to conventional inguinal LA, we consider it appropriate as the only primary operation for lymph node staging in stages with a relatively low risk of metastasis, which would enable the omitting of the problem-prone inguinal LA. However, we believe that, besides the SLNE, the bilateral inguinal LA is necessary further on, at least in a limited form (e.g., according to Catalona) in patients with locally advanced stages of penile cancer, because, to our knowledge, only seven cases of SLNE in penile carcinoma (including our own three patients) have so far been published or presented [19].

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