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Dynamic lymphoscintigraphy and image fusion of SPECT and pelvic CT-scans allow mapping of aberrant pelvic sentinel lymph nodes in malignant melanoma

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Abstract

To date, there are no reliable criteria to identify those patients with melanoma-infiltrated sentinel lymph nodes (SLNs) of the groin who might benefit from an extended lymphadenectomy, including the pelvic lymph nodes. We hypothesised that there are pelvic lymph nodes that receive lymph directly from the primary tumour, thus being at an increased risk for metastasis. In order to determine the frequency of radioactively labelled pelvic lymph nodes and the kinetics of their appearance, we introduce here a combination of dynamic lymphoscintigraphy, single photon emission computed tomography (SPECT) and image fusion of SPECT and pelvic Computed Tomography (CT)-scans. By dynamic lymphoscintigraphy and intraoperative gamma probe detection, superficially located inguinal SLNs (median 2 nodes) could be identified in all of the 51 patients included in this analysis. The histological search for micrometastases was positive in 16 patients (median Breslow thickness of the primary melanoma 2.5 mm). In 29 patients, SPECT and the image fusion technique were additionally performed. Radioactively labelled pelvic lymph nodes were detected in 20 individuals, 6 of them presenting aberrant pelvic SLNs that, on dynamic lymphoscintigraphy, had appeared simultaneously with the superficial SLN(s). Of the 6 patients in whom radioactive pelvic lymph nodes were excised together with the superficial SLN(s), only one had positive superficial SLNs. In this patient, the aberrant pelvic SLN proved to be tumour-positive. In 9 patients, there was no radiotracer uptake in the pelvic lymph nodes at all. Image fusion of SPECT and pelvic CT-scans is an excellent tool to localise exactly the pelvic tumour-draining nodes. The significance of radioactively labelled pelvic lymph nodes for the probability of pelvic metastases should be analysed further.

Keywords: Melanoma; Inguinal; Pelvic sentinel lymph node; Single photon emission computed tomography; Image fusion

1. Introduction

Presently, in many clinical institutions intraoperative lymphatic mapping and sentinel node biopsy has become a standard procedure for patients with primary cutaneous malignant melanoma and clinically negative regional lymph nodes. The sentinel lymph node (SLN) is defined as the first lymph node draining the primary tumour, i.e. the first lymph node that is at risk from metastatic cells. The histological status of the SLN has been found to be an indicator representative of the whole lymph node basin. Moreover, it has turned out to be the strongest predictor for tumour recurrence and survival [1–4]. The original procedure of intraoperative lymphatic mapping, developed by Morton and colleagues [5], is performed using vital blue dye.

More recently, the addition of intraoperative gamma probe detection to blue dye mapping has been shown to improve the rate of SLN identification compared with the use of blue dye alone (for review see [6]). However, often multiple radioactive nodes are detected by gamma detection probe. It is not always clear whether these

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additional lymph nodes represent true SLNs, or rather second-echelon lymph nodes having collected radiocolloid particles that have passed through the SLN(s). Moreover, it also remains unknown whether radioactively labelled non-SLNs are at an increased risk of metastatic involvement, compared with lymph nodes with no radiotracer uptake.

Until now, the appropriate extent of groin dissection is controversial. A so-called superficial groin dissection consists of *en bloc* removal of all lymph nodes within the femoral triangle, the lymph nodes above the inguinal ligament and the nodes anterior and medial to the common and superficial femoral vessels up to Cloquet's node within the femoral canal. The more extended ilioinguinal dissection additionally includes the deeper lymphatics of the iliac, hypogastric and obturator vessels (also called "deep" or "pelvic" nodes). There are, however, no reliable criteria to determine which patients with positive superficial inguinal SLNs will have additional pelvic metastases and, therefore, might benefit from an extended ilioinguinal lymphadenectomy.

Several surgeons have hypothesised that the histological status of Cloquet's node, situated in the femoral canal, can significantly reflect the tumour status of the pelvic basin [7]. Others have shown that this lymph node is often missing and that its sensitivity to predicting the status of the pelvic lymph nodes is low [8].

Afferent lymphatic channels leading directly to the pelvic nodes have been described (Fig. 1) [9]. So far, no previous study has dealt with details of the pelvic lymphatic drainage in patients with cutaneous malignant melanoma. Performing SLN biopsies using a hand-held gamma probe, we have often found radioactivity underneath the abdominal fascia along the iliac vessel, beyond the Cloquet's node. Moreover, in some cases we have observed blue lymphatic channels draining directly to the deep iliac nodes. Thus, an unknown amount of radioactively labelled non-SLNs or even true SLN should be located in the deeper lymphatics along the iliac, hypogastric and obturator blood vessels. Applying dynamic lymphoscintigraphy, single photon emission computed tomography (SPECT) together with pelvic Computed Tomography (CT)-scans (image fusion technique), the present study aims to determine the frequency of radioactively labelled pelvic lymph nodes as well as the kinetics of their appearance in order to provide the basis for future studies on micrometastasis to the pelvis.

2. Patients and methods

2.1. Patients

At the Georg-August-University of Göttingen from May 1997 to January 2002, 51 patients with primary cutaneous melanoma of the leg or the lower part of the body underwent lymphatic mapping and 50 of them received inguinal SLN biopsy. Patients' data, including clinical characteristics, lymphoscintigraphic findings, and histopathological microstaging, were entered prospectively into an electronic database. By physical examination and staging evaluation these patients showed no evidence of metastatic melanoma in the regional lymph nodes or at distant sites.

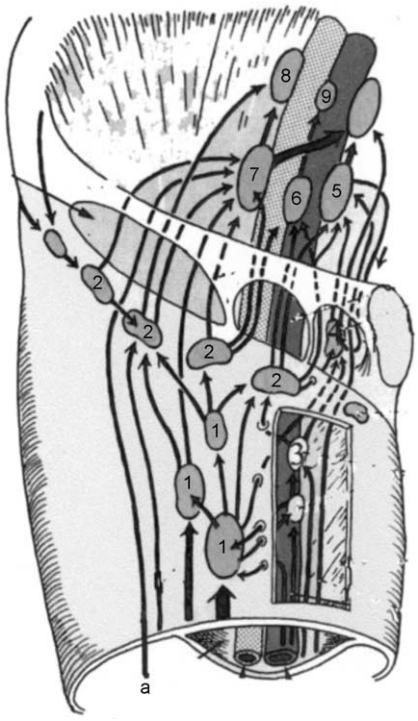

Fig. 1. Lymphatic anatomy of the groin: **a**, afferent lymphatic channel bypassing the inguinal lymph nodes; 1, superficial inguinal lymph nodes, tractus verticalis; 2, superficial inguinal lymph nodes, tractus horizontalis; 3, deep inguinal lymph nodes; 4, Cloquet's lymph node; 5–9, iliac lymph nodes. Reprinted by permission of Urban & Fischer, Munich [9].

2.2. SLN mapping technique

Using PICKER SX 100, a large field of view gamma camera equipped with a low energy high resolution collimator, preoperative dynamic lymphoscintigraphy with dynamic acquisition during the first 30 min and static imaging after 1–2 h was performed on all patients. Approximately 18–24 h before the operation, 37-167 MBq of ^{99m}Tc-human albumin [Nanocoll (Nycomed Amersham Sorin, mean 92.4 MBq, median 102 MBq)] dissolved in a volume of 0.1–0.2 ml were injected into the dermis surrounding the site of the primary melanoma or biopsy scar. This relatively high dose was chosen to better visualise the afferent lymphatics and the deeply situated pelvic nodes. In agreement with Jansen and colleagues [10], we defined the SLN as the node that appeared first on dynamic lymphoscintigraphy.

Additional radioactive lymph nodes were also recorded, but only defined as SLNs if they appeared simultaneously with the first hot node or if they had their own afferent lymphatic vessel. Anterior and lateral static images were taken at 30 min and 2 h after injection. The location of the SLN(s) was marked on the skin.

2.3. SPECT and image fusion technique

Using a dual-headed gamma camera (Picker P 2000, LEHR-collimator), SPECT was performed on 31 patients, starting 30 min after the injection of the radiotracer. For image fusion, three markers (capsules with 0.150 MBq Tc-99m-pertechnetate) were fixed on the skin over the anterior iliac spines and the ventral midline in the same height. Pelvic CT-scans were performed in 31 patients after marking the skin by small lead-bullets. For image fusion, the different skin markers were superimposed. Images of SPECT and pelvic CT-scans could be successfully merged in 29 patients, using a special software package (volume registration, point-match-tool, PICKER).

2.4. Operative procedures

The day after lymphoscintigraphy, immediately before the operative procedure 0.5–1.0 ml patent blue were injected into the dermis around the intact primary tumour or the biopsy site. A small incision was made into the skin over the measured maximum of radioactivity. Lymph nodes that stained blue and had blue afferent lymph channels were generally defined as SLNs. If no blue lymph node could be identified, those radioactive lymph node(s) that had appeared first at dynamic lymphoscintigraphy was (were) defined as SLN(s). All superficial groin nodes displaying more than 10% of the counts of the hottest node were located by a hand-held gamma probe (TECPROBE, STRATEC Biomedical Systems AG) and excised. After SLN biopsy had been performed, we routinely checked the region of the pelvic lymphatics for further radioactivity. The primary tumour or its biopsy site were excised with adequate safety margins. All but 3 patients with positive SLNs underwent inguinal or ilioinguinal block dissection according to established standard techniques.

In 6 patients, radioactively labelled pelvic nodes were extraperitoneally approached using a transverse incision of 5–7 cm through the abdominal fascia exactly over the hot spot. These operations were performed before the superficial SLNs were harvested, in order to avoid disruption of the afferent lymphatics.

2.5. Histological examination

After fixation in formalin, the excised SLN nodes as well as radioactive non-SLNs were cut parallel to the longitudinal axis into 1–2 mm thick slices, which were embedded in paraffin. According to the World Health Organization (WHO)-protocol [1], 10 sections were prepared from each slice. The first and the fifth sections were stained by immunohistochemical methods with anti-protein S-100 serum (Dako, Glostrup, Denmark) and anti-HMB-45 (Enzo, Farmingdale, NY). For all other sections, Haematoxylin and eosin (H&E)-staining was used.

The specimens of the complete lymph node dissections, performed in SLN-positive patients, were examined using routine histology.

2.6. Statistical analysis

Standard statistical techniques as mean, median, percentages and Wilcoxon-signed rank test were used.

3. Results

3.1. Patients' characteristics

The study population consisted of 17 men and 34 women with a median age at diagnosis of 61 years (range 26–84 years). 47 of the patients had leg-located primary tumours, whereas in 4 patients the primary was located at the lower part of the trunk. The mean Breslow thickness was 3 mm (Standard Error (SE) 2.1 mm), the median tumour thickness 2.4 mm (range 0.6–10.8 mm). Twenty of the primary melanomas (39%) showed histological ulceration.

3.2. Lymphoscintigraphic findings

In each patient, at least one superficial inguinal SLN could be identified. The mean number of superficial inguinal SLN identified by dynamic lymphoscintigraphy was 1.7 (SE 0.83), the median number was 2 (range 1–5). On the late images, performed 1–2 h after radiotracer injection, significantly more radioactive lymph nodes had become visible (mean 4.4, SE-2.2, median 4, range 1–9, $P < 0.00001$).

In 32 of the evaluable 44 patients, there was reasonable lymphoscintigraphic evidence that radioactive lymph nodes were situated within the pelvic region. Interestingly, 9 of these patients had true (aberrant) SLNs appearing simultaneously with superficial inguinal SLN(s). The kinetics of pelvic radioactivity are shown in Table 1. Dynamic images of two of the patients with early lymph flow to the pelvic nodes are shown in Figs. 2 and 3. The deep lymphatics, following the major pelvic blood vessels, can be identified on the lymphoscintigraphic images because they show a medial deviation in the anterior images and a dorsal deviation in the lateral images. For confirmation of the deep

Table 1
Kinetics of tumour-draining pelvic lymph nodes as related to the superficial inguinal SLNs[a]

Time interval between the appearance of radioactivity in the superficial inguinal SLN and radioactive pelvic lymph nodes	Patients with dynamic scintigraphy	Patients with image fusion
No delay	9 (20%)	6 (21%)
Less than 2 min	4 (9%)	3 (10%)
2–120 min	19 (43%)	11 (38%)
No pelvic nodes with radiotracer uptake	12 (27%)	9 (31%)
Not evaluable	7	2
Total	51	31

[a] SLN, sentinel lymph node.

location, the gamma probe was used intraoperatively. In another 9 patients, however, the exact anatomical site of the radioactively labelled lymph nodes as related to the inguinal ligament could not be unequivocally established. If the precise location of a radioactive lymph node remained doubtful by the use of conventional lymphoscintigraphic imaging, successful fusion of SPECT and pelvic CT-scans (Fig. 4) was able to clarify the exact anatomical site of the radioactive lymph node(s). Fig. 5 shows an image derived from SPECT demonstrating a radioactive node within the pelvis. As SPECT was performed not earlier than 30 min after radiotracer injection, image fusion alone was not able to

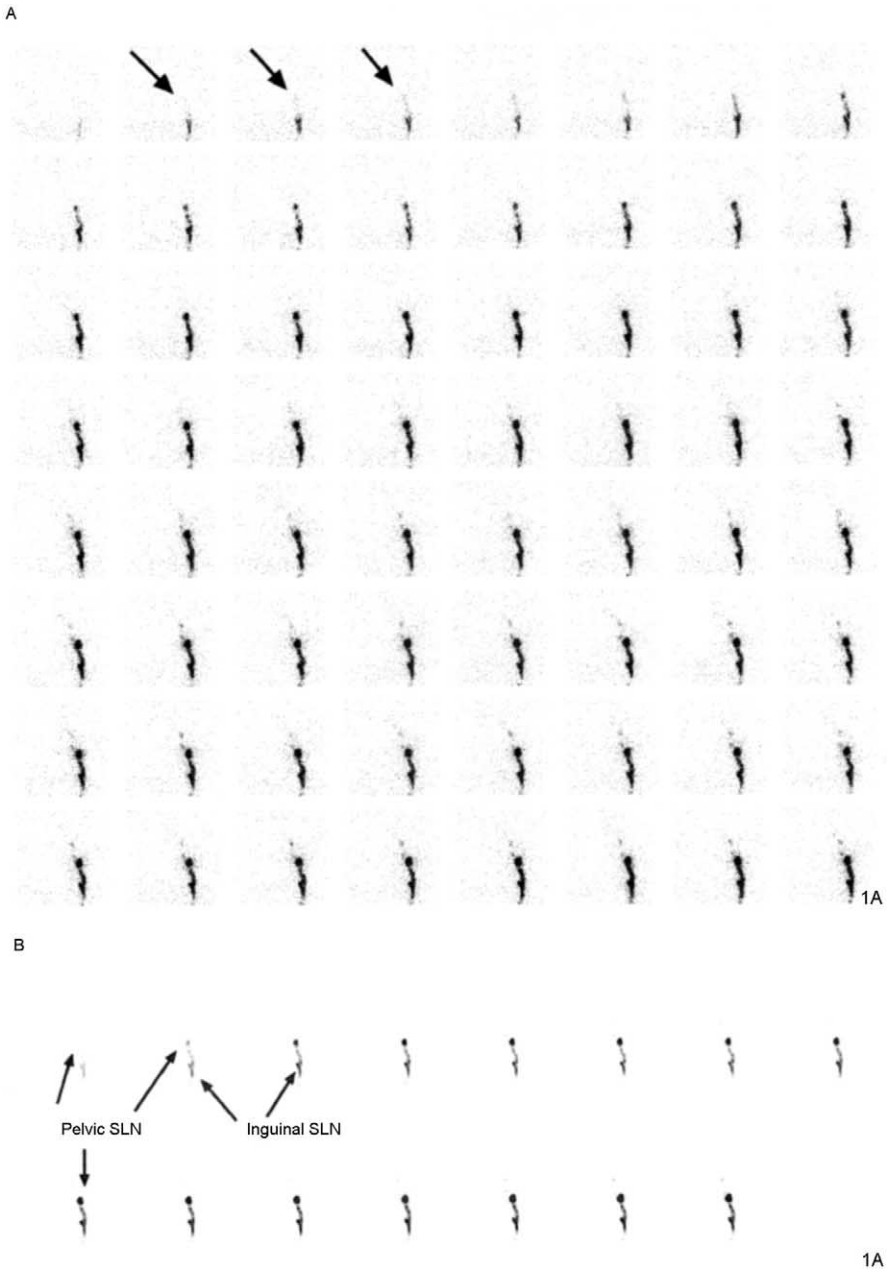

Fig. 2. Dynamic lymphoscintigraphy showing the medial deviation of the lymphatics on their way to the pelvic lymph nodes. The flow off to the pelvic compartment is visible 30 s after radiotracer injection (A, 15 s/frame, B, 1 min/frame).

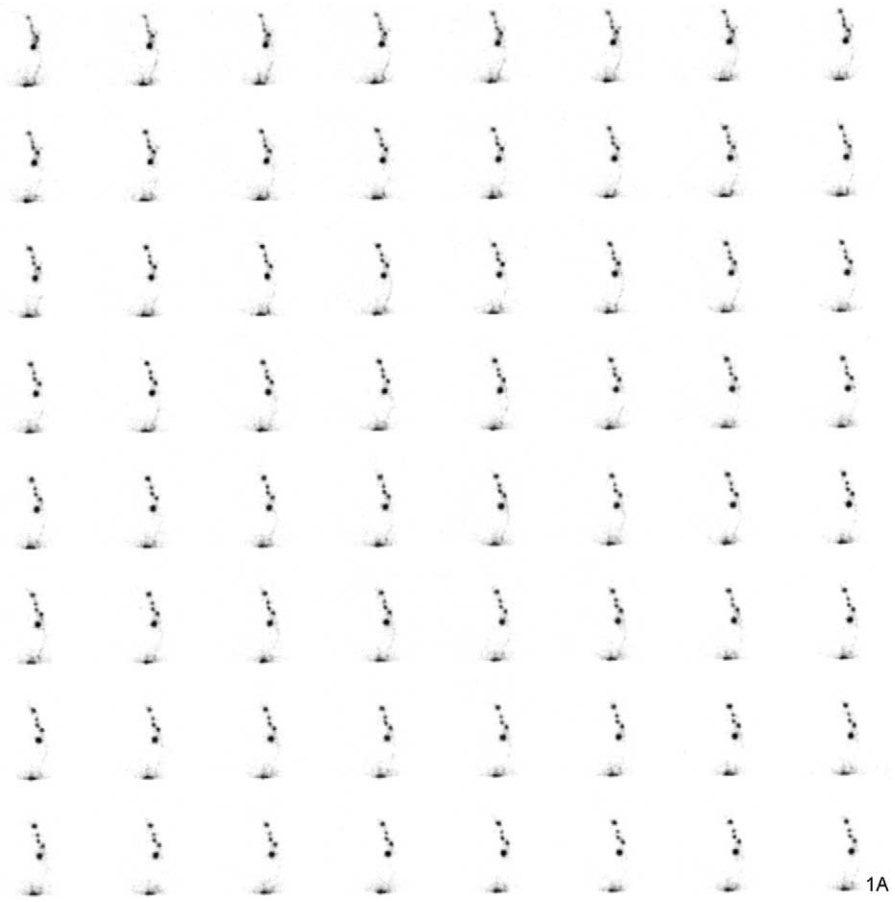

Fig. 3. Dynamic lymphoscintigraphy of a patient with melanoma of the thigh (patient SG, Table 2). Five radioactive nodes appeared simultaneously. At the sentinel-biopsy two blue-stained inguinal and two blue-stained iliac SLNs were harvested.

differentiate between true SLNs and second-echelon pelvic lymph nodes. Of the 29 patients in whom SPECT and image fusion of SPECT and pelvic CT-scans were successfully performed, 20 (69%) had one or two radioactive pelvic lymph nodes. Comparing the fusion images with those of dynamic lymphoscintigraphy, we were able to identify true pelvic SLNs in 6 patients (21% of the patients with image fusion)

3.3. Intraoperative findings

One patient did not receive SLN biopsy because the primary tumour was thin (Breslow thickness 0.6 mm) and as much as 6 SLNs were diagnosed by lymphoscintigraphy. In the remaining 50 patients, at least one superficial SLN was excised (identification rate 100%). The median number of excised superficial lymph nodes was 2 (range 1–5, mean 2.2, SE 1.1), the median number of blue nodes excised was also 2 (range 0–4, mean 1.8, SE 1.0). Overall, 86 blue and 25 non-blue, but radioactive lymph nodes were harvested. All SLNs that had stained blue were also radioactive. In 5 patients, no superficial blue node was found and the SLN was identified by dynamic lymphoscintigraphy and intraoperative gamma probe detection.

Radioactivity underneath the inguinal ligament or the abdominal fascia, as detected intraoperatively by the gamma-probe, was documented in 15 patients. In 6 of these patients, we excised radioactively labelled pelvic lymph nodes together with their superficial inguinal SLNs (Table 2). This did not cause additional morbidity. The anatomical location of these radioactive pelvic lymph nodes was in excellent concordance with the fusion images. In 4 of these patients, the pelvic SLNs had appeared simultaneously with the inguinal SLN(s), whereas in one case a pelvic radioactive lymph node had appeared with a delay of 1.75 min. In these 5 patients, the excised pelvic lymph nodes stained blue and blue lymphatic channels were seen intraoperatively. In the sixth patient, we excised two radioactive pelvic lymph nodes that had appeared 19 min after the inguinal SLN, which had not stained blue. Only 1 of the 6 patients in whom radioactive pelvic lymph nodes had been excised was staged node-positive by histological examination of his superficial inguinal SLNs. In this patient, the additionally excised pelvic SLN also proved to be tumour-infiltrated. Because of various medical problems, we had

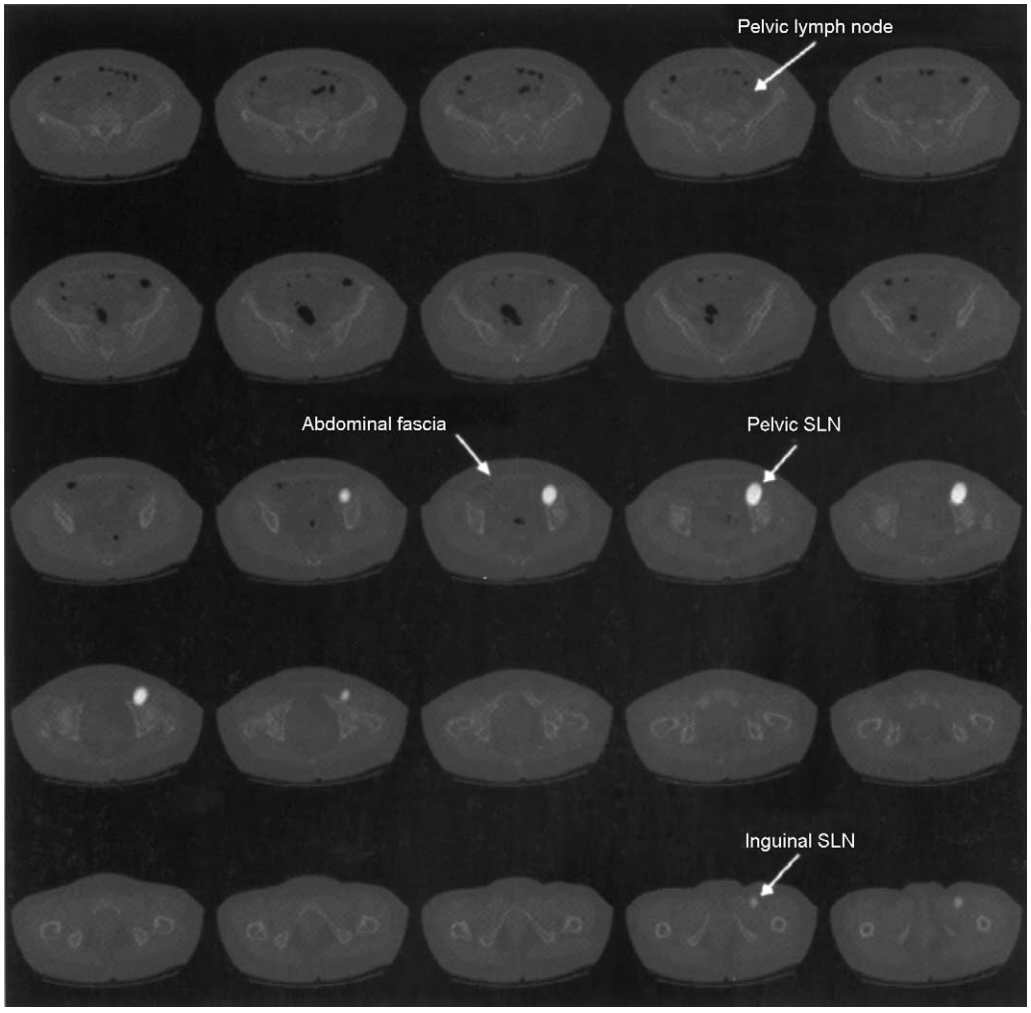

Fig 4. Fusion image of SPECT and pelvic CT-scans demonstrating an inguinal and a pelvic SLN as well as a radioactively labelled pelvic node. The dynamic images of the same patient are shown in Fig. 2.

to perform the complete lymph node dissection six weeks later. Unfortunately, in this case the iliac part of the dissection was significantly impaired by the preceding pelvic SLN biopsy. We did not further explore iliac SLNs as we felt that this might complicate a subsequent complete ilioinguinal dissection.

3.4. Histology of the excised lymph nodes

Of the 50 operatively explored lymph node basins, 16 (32%) were staged positive by histological examination of the superficial SLNs. Only two of the SLN-positive patients had pelvic SLNs. As already mentioned, the

Table 2
Characteristics of 6 patients with surgically excised radioactive pelvic lymph nodes

Patient	Age/ years	Sex	Site	AJCC[a]-primary tumour stage	Time interval between radiotracer injection and appearance of the inguinal SLN/min	Time interval between radiotracer injection and appearance of the pelvic SLN/min	No of blue inguinal SLNs	No of radioactive inguinal nodes not blue	No of blue iliac SLNs	No of iliac nodes not blue
DK	62	♂	Toe	t2b	3	3	3	0	1	0
NM	72	♀	Sole	t3b	0.5	0.5	2	0	1	0
SG	31	♀	Thigh	t3a	1	1	2	1	2	0
SI	44	♀	Sole	t2a	0.25	2	1	1	1	0
SE	49	♀	Sole	t2a	1	20	1	0	0	2
FH	72	♀	Lower leg	t2b	0.25	0.25	3 2 nodes positive	1	1 1 node positive	0

[a] AJCC, American Joint Committee on Cancer.

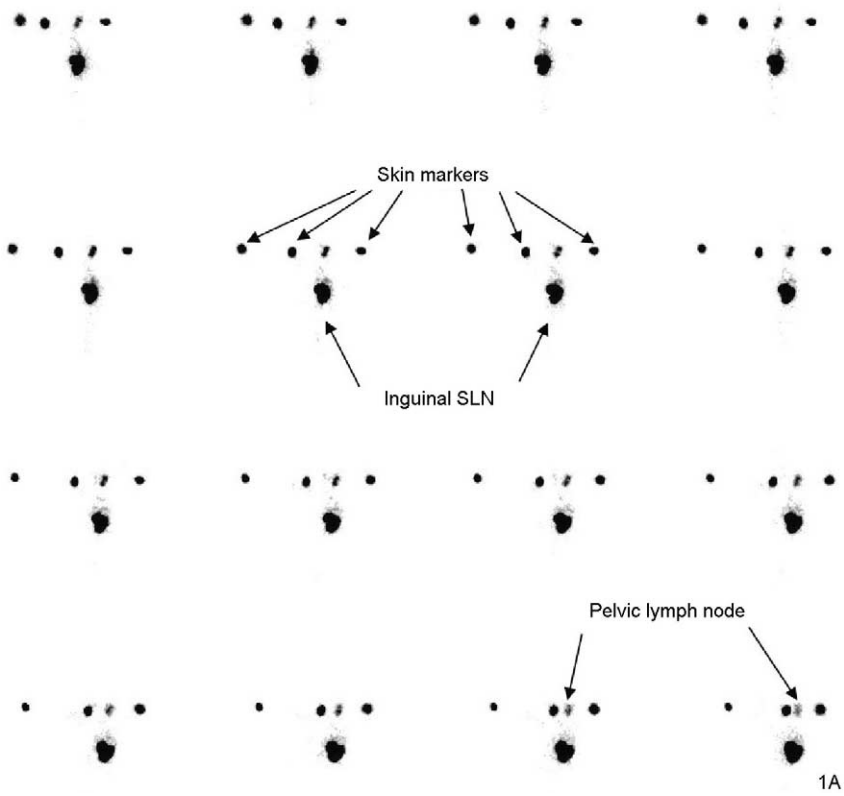

Fig. 5. SPECT images showing a superficial SLN and a radioactive pelvic lymph node in the height of the spinae iliacae anteriores.

only pelvic SLN that was excised in a patient with positive superficial SLNs also proved to be invaded by melanoma.

After positive SLN biopsy, 9 patients underwent ilioinguinal dissection and 4 patients superficial inguinal lymph node dissection. Overall, 185 lymph nodes were harvested at the complete lymphadenectomies. Only two groin dissections revealed micrometastases beyond the SLNs (to superficial inguinal lymph nodes), as detected by routine histology.

4. Discussion

Although presently a complete lymph node dissection is considered to be the correct treatment for patients with proven regional lymph node metastases of malignant melanoma, there is still no general agreement upon the appropriate extent of groin dissection (inguinal versus ilioinguinal dissection). In patients with clinically enlarged groin metastases, the iliac lymph nodes have been found to be positive in approximately 30% of histological specimens [11–13] and, thus, most authors have recommended performing a radical ilioinguinal dissection in this situation. However, the situation for patients with a positive inguinal SLN has still to be clarified. In the present study, the metastatic disease was restricted to only one or two SLNs in 11 of the 13 patients with subsequent groin dissection. Moreover, skip metastases of malignant melanoma to the pelvic nodes have only rarely been observed [12,14]. As a consequence, it is not likely that pelvic metastases are frequent in patients with only microscopically detectable tumour infiltration of the superficial inguinal nodes. These arguments and the fact that radical ilioinguinal dissection can be accompanied by significant morbidity are in favour of a merely superficial dissection in patients with positive SLNs of the groin [15].

On the other hand, in all previous analyses which had focused on melanoma metastases to the iliac/obturator nodes, only routine histology had been applied. Thus, the true percentage of pelvic involvement in patients with micrometastases to the superficial inguinal nodes might have been underestimated and the incidence remains to be established by ilioinguinal dissection and a thorough histological examination of all pelvic nodes. Importantly, in some previous studies including patients with micro- and macrometastases in the groin, the patients with either micrometastases or skip metastases to the pelvic nodes had over-proportionally benefited from ilioinguinal dissection [7,12,14,16,17]. This would imply that the identification of subgroups of patients at high risk for pelvic micrometastases is worthwhile. In order to achieve this goal, identification and precise

mapping of true pelvic SLNs and other tumour-draining pelvic lymph nodes could be helpful. As illustrated in Fig. 1, there are lymphatic channels bypassing the superficial lymph nodes including the Cloquet's node. This anatomical peculiarity might explain the presence of pelvic metastases in some patients with only microscopic nodal disease.

As shown in the present study, dynamic lymphoscintigraphy and lateral imaging are already able to preoperatively detect pelvic tumour draining nodes, including aberrant SLN(s). However, the exact location of radioactive lymph nodes in relation to the abdominal fascia sometimes remains questionable. If radioactive pelvic nodes are situated underneath the inguinal ligament or along the major vessels, their exact location can be confirmed intraoperatively, using a hand-held gamma detection probe. However, deeply situated radioactive lymph nodes, e.g. obturator lymph nodes, can easily be missed using this tool. Here we show for the first time that it is possible to visualise the exact anatomical site of pelvic lymph nodes in relation to the inguinal ligament by means of image fusion of SPECT and CT-scans. However, the question of whether tumour-draining pelvic nodes represent true SLNs can be answered only by taking into consideration the images of dynamic lymphoscintigraphy.

Regarding lymphatic drainage to the pelvis, we identified three groups of patients (Table 1). In the first group (20% of all 44 evaluable patients and 21% of the patients with successful image fusion), besides superficial inguinal SLNs the existence of aberrant true pelvic SLNs could be demonstrated. Four of these pelvic SLNs were surgically explored. The observation that all of these lymph nodes stained blue supports their status as true SLNs. In the second group of our study (52% of all evaluable patients and 48% of the patients with image fusion), radioactive pelvic lymph nodes were registered as appearing with a delay after the superficial inguinal SLNs. Importantly, in the third group (27% of the evaluable patients and 31% of the patients with image fusion), no radiotracer uptake in pelvic nodes could be demonstrated at all.

Our results might have important implications for the surgical strategy after positive sentinel node biopsy. Since we have only found a low percentage of metastases in non-radioactive lymph nodes from the complete groin dissections, we suggest that patients with no radiotracer uptake in pelvic lymph nodes may constitute a sub-group that is at low risk for pelvic metastases. Future studies should clarify whether these patients can be spared the dissection of pelvic nodes. However, patients with tumour-infiltrated superficial inguinal SLN(s) and additional true iliac SLNs should benefit from an ilioinguinal dissection, as the aberrant pelvic SLNs also receive lymph directly from the primary tumour. Interestingly, the only pelvic SLN, that we had excised in a patient with positive superficial SLNs, was indeed tumour-invaded.

In 22 out of 44 patients who could be evaluated, we observed radioactive non-SLNs appearing in the pelvic basin within the first two hours after labelling of the superficial SLN. For optimal staging of a nodal basin, McMasters and colleagues have recommended excising all lymph nodes that measure 10% or more of the radioactive counts of the hottest SLN [18]. However, the excision of radioactively labelled pelvic lymph nodes may cause unnecessary surgical trauma and impair a subsequent iliac dissection. In fact, it would be important to know whether radioactively labelled non-SLNs harbour more micrometastases than non-SLNs with no radiotracer uptake.

It is an important finding of the present study that in general the excision of the superficial inguinal SLN seems to be sufficient for the staging of the inguinal nodal basin. All of our patients had at least one superficial SLN (median 2 nodes). The examination of these exclusively superficial SLNs allowed us to stage 32% of the nodal basins as positive. Although pelvic drainage in general was frequently recorded, the existence of a true pelvic SLN in addition to a tumour infiltrated superficial SLN was a rare event since this constellation could be demonstrated in only two of the 16 SLN-positive patients. Consequently, and in view of increased morbidity of a possible consecutive ilioinguinal dissection, pelvic SLNs should be harvested only if a superficial inguinal SLN is lacking. This is also supported by the findings of Porter and colleagues who have pointed out that the removal of more than two SLNs does not add prognostic information [19].

To date, it remains unclear which patients who need an inguinal dissection following a positive sentinel node biopsy might benefit from an additional pelvic dissection. The question of whether patients with aberrant pelvic SLNs form a sub-group of patients with an increased risk of pelvic metastasis can only be answered by a large multicentre study.

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