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European Association of Urology

Platinum Priority – Bladder Cancer

Editorial by Harry W. Herr on pp. 212–213 of this issue

A New Multimodality Technique Accurately Maps the Primary Lymphatic Landing Sites of the Bladder

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Article info

Article history:
Accepted October 14, 2009
Published online ahead of print on October 23, 2009

Keywords:
Bladder cancer
Location of lymph nodes
Lymph node dissection
Sentinel nodes of the bladder

Abstract

Background: Pathoanatomic studies have failed to map accurately the primary lymphatic landing sites of the urinary bladder.
Objective: To use single-photon emission computed tomography (SPECT) combined with computed tomography (CT) plus intraoperative gamma probe verification to map the primary lymphatic landing sites of the bladder.
Design, setting, and participants: Clinical trial of 60 consecutive cystectomy patients at a single centre.
Intervention: Flexible cystoscopy-guided injection of technetium nanocolloid into one of six non-tumour-bearing sites of the bladder for preoperative detection of radioactive lymph nodes (LNs) with SPECT/CT followed by intraoperative verification with a gamma probe. Backup extended pelvic LN dissection (PLND) for ex vivo detection of missed LNs.
Measurements: Three-dimensional projection of each LN site.
Results and limitations: A median of 4 (range: 1–14) radioactive LNs were detected per site and patient. Ninety-two percent of all LNs were found distal and caudal to where the ureter crosses the common iliac arteries. Eight percent were found proximal to the uretero-iliac crossing, none without simultaneous detection of additional radioactive LNs within the endopelvic region. Extended PLND resected 92% of all primary lymphatic landing sites; limited PLND resected only 52%. A few LNs may have been missed despite preoperative SPECT/CT, intraoperative gamma probe verification, and extended backup PLND.
Conclusions: Multimodality SPECT/CT plus intraoperative gamma probe show the template of the bladder's primary lymphatic landing sites to be larger than is often thought. PLND limited to the ventral portion of the external iliac vessels and obturator fossa removes only about 50% of all primary lymphatic landing sites, whereas extended PLND along the major pelvic vessels, including the internal iliac, external iliac, obturator, and common iliac region up to the uretero-iliac crossing, removes about 90%.
Trial registration: ClinicalTrials.gov, ISRCTN39379749.

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0302-2838/$ – see back matter doi:10.1016/j.eururo.2009.10.026

1. Introduction

Histologic examination of the pelvic lymph nodes (LNs) provides the most accurate staging of pelvic LN status in patients with urinary bladder cancer. Although the optimal field of lymphadenectomy is still debated, evidence is growing that extended pelvic LN dissection (PLND) improves survival in patients with both node-positive and node-negative bladder cancer [1–6]. The lymphatic drainage pattern of a cancer determines the extent of LN dissection. A less extended lymphatic drainage pattern should require less extensive LN dissection and thus reduce morbidity. Visualisation of lymphatic drainage via lymphoscintigraphy has lowered morbidity in breast and penile cancer as well as in melanoma [7–9]; it is also employed in prostate, vulvar, and endometrial cancer [10–12]. However, preoperative planar lymphoscintigraphy allows only limited detection of positive LNs with potential underestimation [13–15] compared with intraoperative gamma probe. But the gamma probe detects only LNs that it touches, entailing its own risk of incomplete dissection. Detection of radioactive LNs is also hampered by obstruction of lymph vessels by lymphatic metastases, altering lymph flow, thus generating a high rate of false-negative sentinel LNs [10,13].

Several sentinel LN mapping studies have been conducted on urinary bladder cancer patients [13,14]. Liedberg et al. [13] successfully detected sentinel LNs, but the false-negative rate was high (19%), and preoperative planar lymphoscintigraphy was abandoned due to a low detection rate of only 23%. In a small series of only six patients, Sherif et al achieved a better detection rate by combining lymphoscintigraphy and computed tomography (CT) preoperatively [14].

LN mapping studies may help to define the pattern of lymphatic tumour spread [16–18]. Leissner et al. [16] examined LNs at 12 different anatomic sites in 290 patients who underwent radical cystectomy and extended PLND. Sixteen percent of LN metastases were found above the aortic bifurcation, but only in patients with two or more LN metastases. Interestingly, none of the 29 single LN metastases was located cephalad to the aortic bifurcation. Vazina et al. [17] evaluated 176 patients undergoing radical cystectomy and PLND. Of those with T3 or T4, 16% had LN metastases along the common iliac artery and at or above the aortic bifurcation but always combined with other LN metastases in the small pelvis. In a prospective mapping study of 200 patients, Ghoneim's group [18] again found no skipped lesions outside the small pelvis.

Still, comparison between the different studies is difficult due to some overlap between the various areas of LN dissection. Furthermore, a LN at the bifurcation of the common iliac artery can be attributed to either the external iliac, internal iliac, obturator fossa, or even common iliac region. Because LN regions are defined by the surgeon, striking differences exist in reported average number of LNs removed from the various anatomic sites [16], the exact location and number of regional LNs of the bladder remain unknown.

Thus we injected technetium Tc 99m nanocolloid into non-tumour-bearing sites of the bladder to map the primary lymphatic landing sites precisely using preoperative single-photon emission CT (SPECT)/CT plus intraoperative gamma probe and verification by backup extended PLND.

2. Patients and methods

2.1. Patients

Drainage patterns in 60 consecutive patients (43 men, 17 women; median age: 68 yr; range: 35–87 yr) with bladder cancer T1 to T3 and no metastatic disease (cN0, cM0) based on CT or magnetic resonance imaging (MRI) were evaluated between April 2007 and December 2008. Exclusion criteria were LNs >1 cm in diameter, previous radiotherapy to the pelvis, neoadjuvant chemotherapy, a history of pelvic surgery, and coincident prostate cancer. The study was approved by the local ethics committee. All patients gave their informed consent.

2.2. Injection of the radiopharmaceutical

One day prior to surgery, flexible guided cystoscopy was performed with local anaesthesia. A 3.7-F cystoscopy needle (Cook Urological, Spencer, IN, USA) was used to inject 100 MBq (subdivided into four aliquots of 25 MBq each) transurethrally in 1 ml of technetium Tc 99m nanocolloid (Nanocoll; GE Healthcare, Amersham Health, Braunschweig, Germany) into the detrusor muscle of one of the six defined non-tumour-bearing bladder sites (Fig. 1) opposite the bladder tumour. All injections (10 per site per patient) were performed by the same urologist (BR).

2.3. Single-photon emission computed tomography/computed tomography

All patients underwent SPECT and CT 3 and 6 h after injection of the radiopharmaceutical with the bladder-flushing catheter in place.

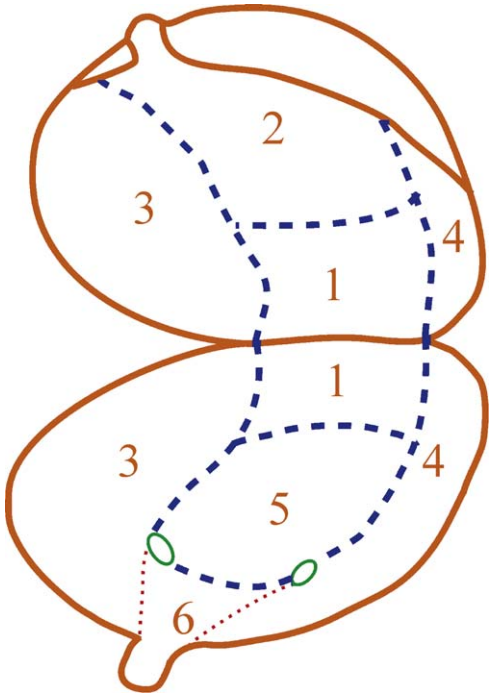

Fig. 1 – Non-tumour-bearing injection sites of the bladder: (1) dome, (2) anterior wall, (3) right lateral wall, (4) left lateral wall, (5) posterior wall, (6) bladder neck/trigone.

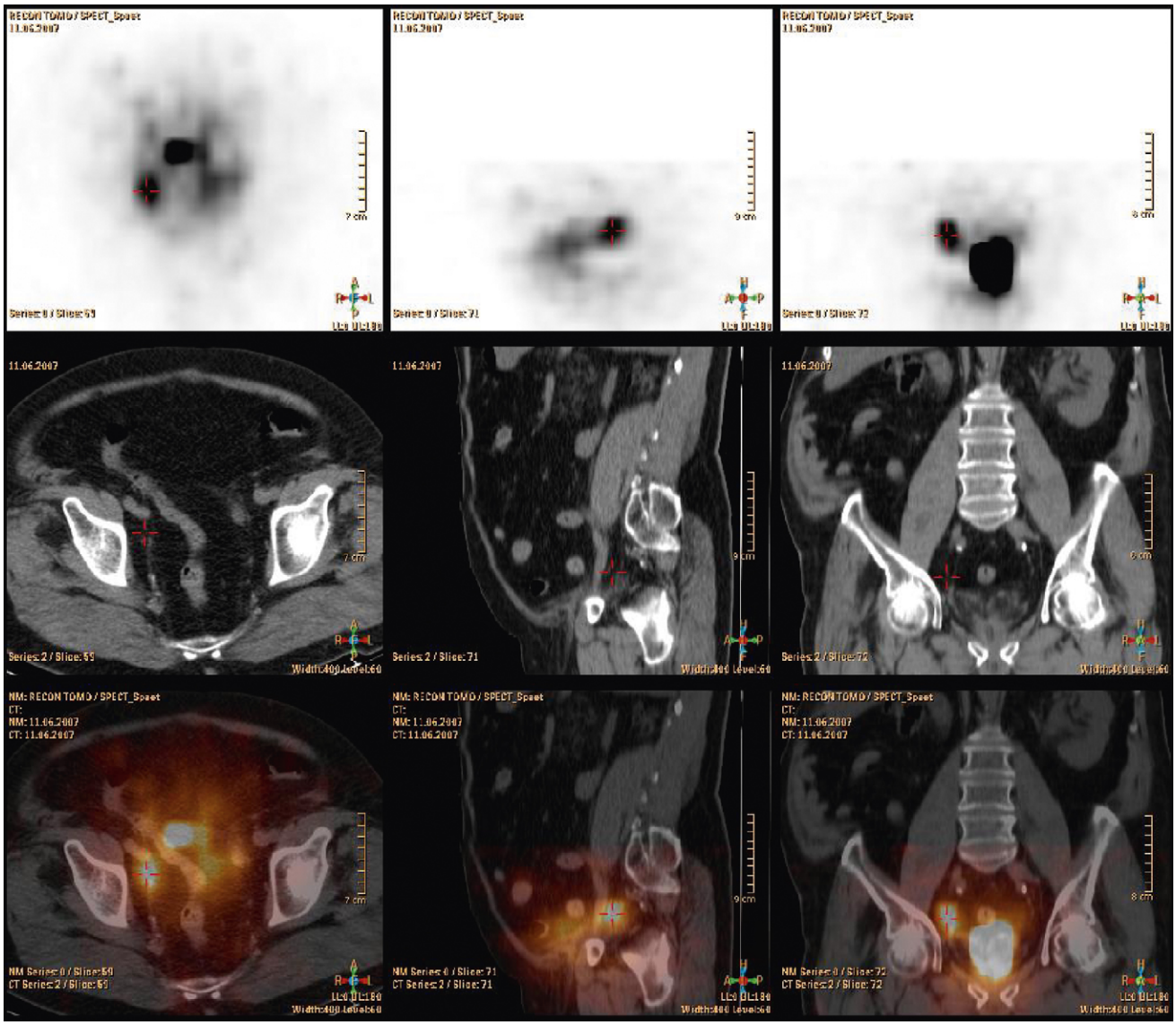

Fig. 2 – Single-photon emission computed tomography: transverse, sagittal, and coronal fused image showing a radioactive node of the right external iliac region.

In the first 26 patients, the 5-mm CT slices were manually overlaid with the SPECT (IRIX; Philips Medical Systems, Cleveland, OH, USA) as described elsewhere [11]. The data of the next 34 patients were acquired on a dedicated SPECT/CT system (Precedence 6; Philips Medical Systems, Cleveland, OH, USA) with automatic reconstruction and image overlay.

All LNs were identified and localised on displays providing transverse, sagittal, and coronal views (Fig. 2). Images were read by two experienced physicians, and the location of each LN was transferred to a projection model of the pelvis.

2.4. *Intraoperative lymph node detection*

The day after imaging studies, all patients underwent PLND prior to cystectomy. After midline incision and mobilisation of the colon, bladder lymphatic drainage areas were systematically explored for radioactive LNs using a standard handheld gamma probe (C-Track; Care Wise Medical Products, AEA Technology, Morgan Hill, CA, USA) wrapped in a sterile polyvinylchloride sheath. The bladder was shielded with a malleable sterilised lead plate to decrease radioactivity spillover and improve the signal-to-noise ratio. The gamma probe was kept close to vascular structures at different angulations. All radioactive LNs were resected prior to backup PLND and sent to histologic workup. LNs identified in para-aortic and paracaval locations where resection would require enlargement of the operation field entailing a risk disproportionate to the potential gain were counted as identified LNs without resection.

Gamma probe–guided LN dissection was always followed by bilateral extended PLND along major pelvic vessels including the internal iliac, external iliac, obturator, and common iliac regions. The proximal anatomic border was set at the junction of the retracted and medialised ureters with the common iliac vessels on both sides. To detect any radioactive LNs missed by the gamma probe, the removed lymphatic tissue was screened ex vivo for radioactivity with a gamma camera without collimators to increase sensitivity.

Each LN location was transferred to a projection model of the pelvis so as to depict it in relation to anatomic structures.

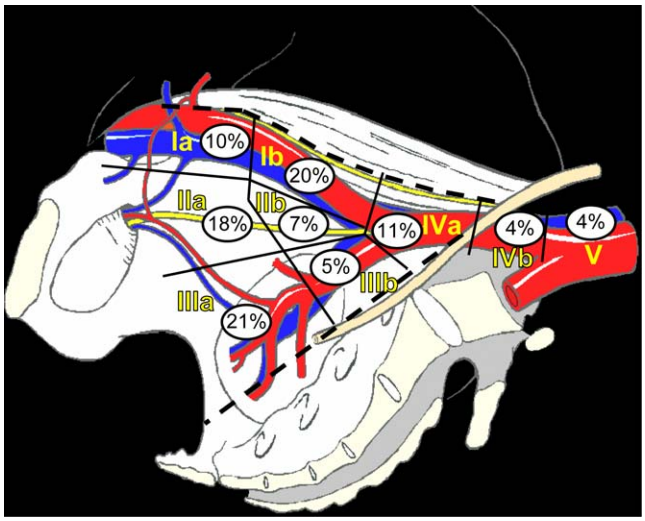

Fig. 3 – Boundaries of pelvic lymph node dissection subdivided into different regions and distribution of the corresponding technetium Tc 99m–positive lymph nodes: external iliac (Ia) distal and (Ib) proximal, obturator fossa (IIa) distal and (IIb) proximal, internal iliac (IIIa) distal and (IIIb) proximal, common iliac (IVa) distal and (IVb) proximal, (V) para-aortic/caval.

3. Results

Two hundred and eighty-one Tc 99 m–positive LNs (median: 4 LNs per patient and site; range: 1–14) were identified preoperatively and confirmed at surgery. Of these, four were not removed because of difficult and/or risky surgical access. Postoperative ex vivo imaging by a noncollimated gamma camera revealed three additional radioactive LNs, which were removed in the internal iliac ($n = 2$) and obturator ($n = 1$) regions.

The overall 284 Tc 99m–positive LNs were distributed as follows: external iliac, $n = 86$ (30%), of which 10 (12%) were situated in the fossa of Marcille; obturator fossa, $n = 70$ (25%); internal iliac, $n = 74$ (26%); common iliac, $n = 42$ (15%); para-aortic/paracaval, $n = 11$ (4%) (Fig. 3). Thirty-one of the 74 internal iliac Tc 99m–positive LNs (42%) were located medially to the internal iliac artery. Only 22 of 284 (8%) radioactive LNs were cephalad to the uretero-iliac junction; all patients with such LNs had additional radioactive LNs in the external iliac, internal iliac, or obturator fossa regions. The distribution of radioactive LNs is shown in Figs. 4 and 5.

Bilateral backup extended PLND along the internal iliac, external iliac, common iliac, and obturator regions removed another 1710 nonradioactive LNs. Thus histologic examination revealed a total of 1990 LNs in 60 patients (median per patient: 33; range: 13–72). Sixteen patients (27%) had LN metastases. Histologic examination revealed micrometastases in 20 of 280 (7%) resected radioactive LNs.

4. Discussion

Discovery of LN metastases during radical cystectomy and PLND indicates poor prognosis in bladder cancer patients. Today, pretreatment assessment of LN status is usually done with CT and MRI, both liable to discrepancies between clinical and pathologic staging [19]. The present results confirm this major shortcoming: 27% of patients with positive LNs were preoperatively staged N0. This accords with other studies showing LN metastases in approximately one of four patients [1,2,6,17,20,21]. Some patients with LN involvement are cured by PLND [1–6]. Dhar et al. [5] found significantly higher recurrence rates in patients with muscle-invasive bladder cancer undergoing radical cystectomy with limited PLND versus those undergoing more

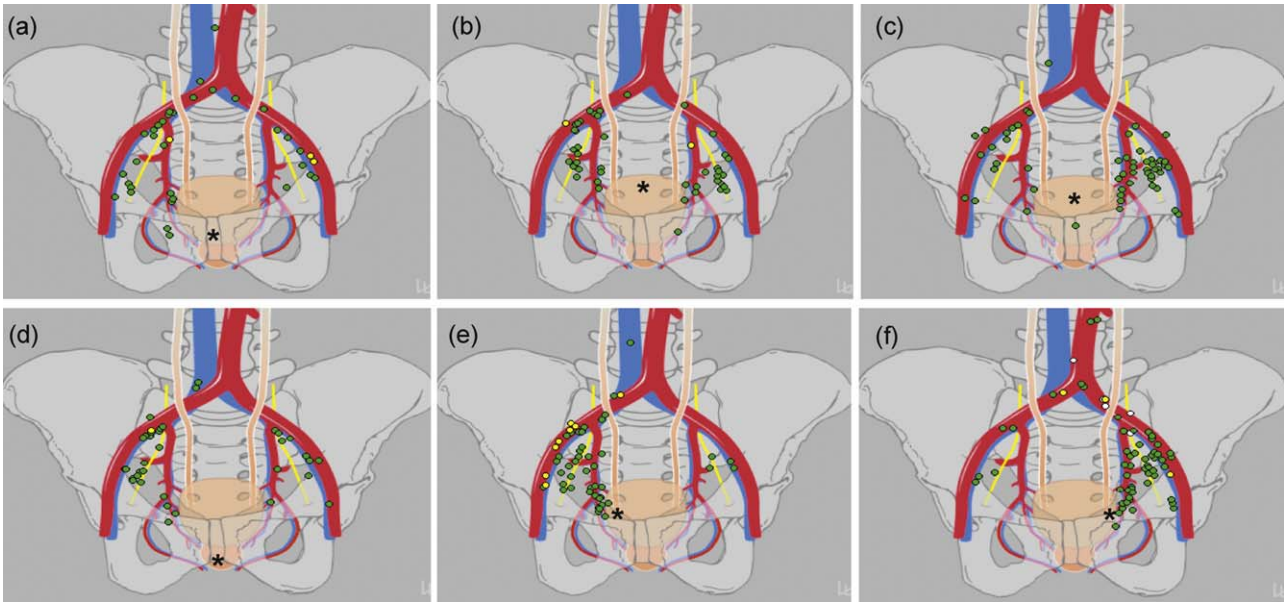

Fig. 4 – Primary lymphatic landing sites according to the different injection sites: (a) posterior wall ($n = 36$), (b) dome ($n = 44$), (c) anterior wall ($n = 54$), (d) trigone/bladder neck ($n = 35$), (e) right lateral wall ($n = 52$), (f) left lateral wall ($n = 63$).

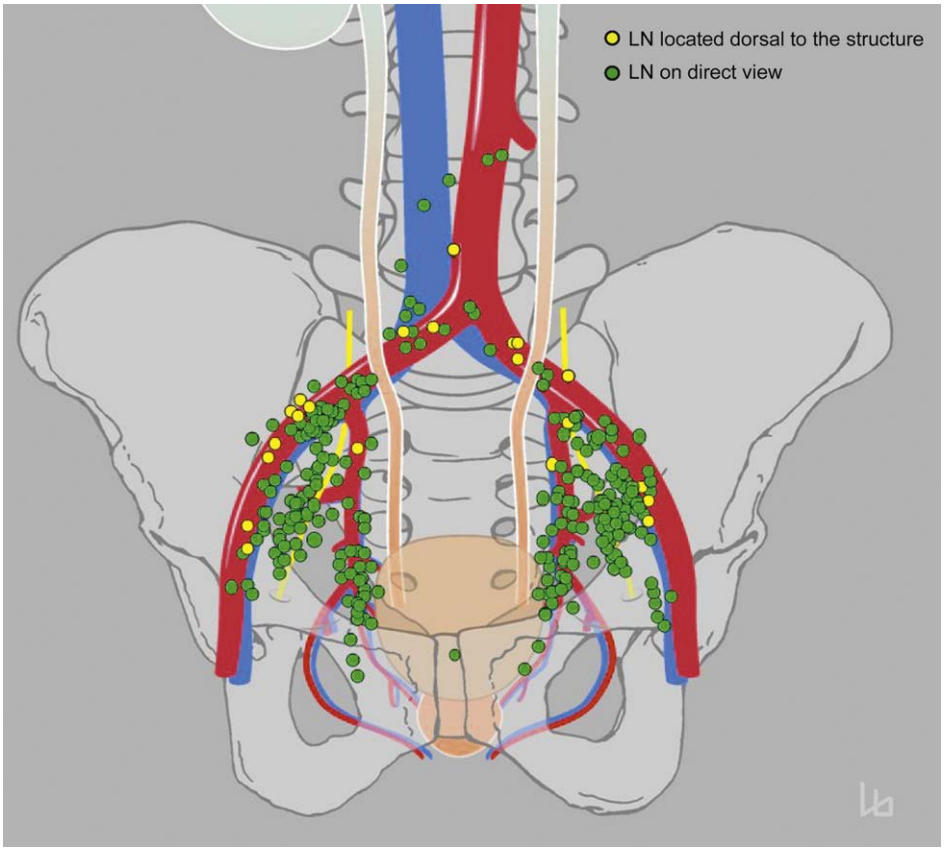

Fig. 5 – Fusion image of the primary lymphatic landing sites (*n* = 284 of 60 bladder sites) transferred from three-dimensional (3D) data sets and superimposed into an idealised anterior-posterior projection of the pelvis. All lymph nodes (LNs) depicted 3D reconstruction of single-photon emission computed tomography/computed tomography data sets and confirmed by surgery were subsequently transferred into a template projection of the pelvis. LNs are colour coded in relation to the vascular structures and ureters.

extended PLND. Yet the optimal field for lymphadenectomy is still debated.

To elucidate the pattern of lymphatic spread, we applied SPECT/CT preoperatively to obtain a fused three-dimensional image and verified it intraoperatively using a gamma probe and backup extended PLND. This multimodality technique enabled us to map every single LN accurately. Previous pathoanatomic studies [16–18] could only enumerate positive LNs without precise node-by-node identification. Moreover, pathoanatomic studies remove all LNs of the small pelvis whether they are bladder-draining nodes or not, whereas our multimodality technique identifies the true lymphatic draining sites of the bladder. Unlike other studies [13,14], we did not inject peritumourally so as to avoid false-negative results due to altered lymph flow in patients with lymph vessels obstructed by cancer cells.

This study produced several interesting findings regarding lymphatic drainage of the urinary bladder. First, because a median of four primary lymphatic landing sites were found per one of the six non-tumour-bearing bladder sites, the median number of primary lymphatic landing sites per bladder is 24. It is impossible to remove only bladder-specific pelvic LNs, so more LNs should be resected. Thus, although Leissner et al. [6] reported a significantly better outcome in patients with a PLND of $\geq$16 LNs, they appear to have underestimated the number of LNs that should be removed. Second, the large range of 1–14 radioactive LNs per site and patient confirms a more complex lymphatic pattern in bladder cancer than in, for example, breast cancer, a finding that others have demonstrated [13,16,22]. The number of bladder-draining LNs varies from patient to patient. Due to this individual variability it is difficult to judge the quality of PLND from patient to patient by comparing the number of LNs removed. Most important is the extent of the PLND template. Third, all six bladder sites have lymphatic drainage to the different areas of the pelvis: to the internal, external, and common iliac, and to the obturator fossa. Fifteen percent of all LNs are found along the common iliac vessels. Interestingly, almost three times as many common iliac LNs are located distal to the uretero-iliac junction than proximal (11% vs 4%). Only 4% of LNs are situated along the aorta and vena cava as high as the origin of the inferior mesenteric artery (IMA). Thus only 8% of Tc 99m–positive LNs were found cephalad to the uretero-iliac junction. All patients with these so-called extrapelvic radioactive LNs had at least one additional radioactive LN in the external iliac, internal iliac, or obturator fossa region. This agrees with the findings of Leissner et al. [16] and Abol-Enein et al. [18], who encountered no metastatic LNs

exclusively above the aortic bifurcation. Whether para-aortic/paracaval LNs represent primary landing sites or juxtaregional LNs is debatable. However, their appearance in the SPECT/CT simultaneously with intrapelvic LNs 3 h postinjection suggests a direct lymphatic flow.

The clinical implications of this study are significant. It is the first reported series documenting the primary lymphatic landing sites of the bladder. It demonstrates that limited PLND resects only approximately 50% of LNs. The percentage of LNs left in situ can be significantly reduced (to 8%) with the extended PLND we employed (Fig. 3). This accords with the findings of Dhar et al. [5] showing improved survival with extended PLND (median: 22 LNs resected) versus limited PLND (median: 12 LNs resected).

Is it worthwhile to resect the remaining 8–10% of possible primary lymphatic landing sites between the uretero-iliac junctions and the IMA? A cure is possible only in patients with a few metastases to normal-sized nodes, which rarely occurs only outside the small pelvis [1]. The potential additional benefit of extending PLND up to the IMA can be calculated as follows: The prevalence of histologically positive LNs in patients with clinically normal-sized LNs (cN0) is approximately 25% [1,2,6,17,20,21]; of patients with positive LNs, 35% [1] will survive (8% of 100 cystectomy patients). Because at most 8–10% of patients may have a few positive LNs above the uretero-iliac junction, only about 1 in 100 cystectomy patients may benefit from "superextended" PLND up to the IMA. Clearly, overtreatment in 99% of cystectomy patients is not justifiable. Thus the present mapping study provides an objective basis for setting the upper limit for meticulous LN dissection at the level where the retracted ureters cross the common iliac vessels. Higher resection would be too demanding in both time and extent of surgical field, increasing the risk of complications and injury to the autonomic sympathetic nerves, threatening both continence and sexual function [4,23]. Conversely, we found 4% of all Tc 99m–positive LNs—or 12% of all Tc 99m–positive LNs along the external iliac vessels—in the fossa of Marcille, that is, dorsolateral to the proximal external iliac vessels and dorsal to the junction of the ureters with the common iliac vessels. In view of their easy access, we recommend including LNs of the fossa of Marcille instead of para-aortic/paracaval LNs in the PLND template.

We found 26% of all Tc 99m–positive LNs in the internal iliac region, most (80%) distally to the origin of the superior vesical artery. Notably, 42% of all internal iliac LNs are located medial to the vessel, by some authors also called the presacral LNs. This requires meticulous dissection of the internal iliac vessels and their branches on both the lateral and medial sides of the internal vesical artery.

A potential limitation of this study is the difficult intraoperative gamma probe detection of LNs outside the fields of comprehensive search, with its potential for inadvertent overlooking of radioactive LNs. However, the preoperative imaging studies mapped the exact location of Tc 99m–positive nodes, facilitating their gamma probe detection in regions of the pelvis outside the area of routine search.

5. Conclusions

Our multimodality technique accurately located the primary lymphatic landing sites of the bladder, showing their template to be larger than is often appreciated. Limited PLND removes only about 50% of all primary lymphatic landing sites. To remove 90%, PLND should be extended to include LNs lateral and medial to the internal iliac vessels and the common iliac region up to the uretero-iliac crossing. Resection cephalad to the retracted ureters appears unwarranted for reasons of both time and the unfavourable risk–benefit ratio (only 1–2% of patients may benefit).

Author contributions: Urs E. Studer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

Study concept and design: Roth, Studer.
Acquisition of data: Roth, Birkhäuser, Zehnder, Wissmeyer.
Analysis and interpretation of data: Roth, Studer.
Drafting of the manuscript: Roth.
Critical revision of the manuscript for important intellectual content: Studer, Thalmann, Wissmeyer, Krause.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Studer.
Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

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