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Intraoperative Sentinel Node Detection Improves Nodal Staging in Invasive Bladder Cancer

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Purpose: We evaluated intraoperative SN detection in patients with invasive bladder cancer during radical cystectomy in conjunction with extended lymphadenectomy.

Materials and Methods: A total of 75 patients with invasive bladder cancer underwent radical cystectomy with extended lymphadenectomy. SNs were identified by preoperative lymphoscintigraphy, intraoperative dynamic lymphoscintigraphy and blue dye detection. An isotope (70 MBq ^{99m}Tc-nanocolloid) and Patent Blue® blue dye were injected peritumorally via a cystoscope. Excised lymph nodes were examined ex vivo using a handheld γ probe. Identified SNs were evaluated by extended serial sectioning, hematoxylin and eosin staining, and immunohistochemistry.

Results: At lymphadenectomy an average of 40 nodes (range 8 to 67) were removed. Of 75 patients 32 (43%) were lymph node positive, of whom 13 (41%) had all lymph node metastases located only outside of the obturator spaces. An SN was identified in 65 of 75 patients (87%). In 7 patients an SN was recognized when the nodal basins were assessed with the γ probe after lymphadenectomy and cystectomy. Of the 32 lymph node positive cases 26 (81%) had a positive (metastatic) SN. Thus, the false-negative rate was 6 of 32 cases (19%). Five false-negative cases had macrometastases and/or perivesical metastases. In 9 patients (14%) the SN contained micrometastases (less than 2 mm), in 5 of whom the micrometastasis was the only metastatic deposit.

Conclusions: SN detection is feasible in invasive bladder cancer, although the false-negative rate was 19% in this study. Extended serial sectioning and immunohistochemistry revealed micrometastases in SNs in 9 patients and radio guided surgery after the completion of lymphadenectomy identified SNs in an additional 7. We believe that the technique that we used in this study improved nodal staging in these 16 of 65 patients (25%).

Key Words: bladder, bladder neoplasms, neoplasm invasiveness, cystectomy, lymph nodes

In addition to pathological stage, nodal status represents the most important predictor of the outcome of radical cystectomy for muscle invasive bladder cancer. In the last 2 decades the technique of radical cystectomy has evolved to include fairly extended lymphadenectomy,¹ with published 5-year survival rates of 23% to 35% for node positive disease.^{2,3} Nevertheless, there is still considerable controversy regarding the appropriate extent of lymphadenectomy and the number of nodes that should be dissected. It has been suggested that nodal staging can be improved by removing more than 16 nodes because that strategy would increase the detection of lymph node metastases.⁴ However, a study of Bochner et al did not reveal any staging advantage when lymphadenectomy extended to the aortic bifurcation was compared with standard lymphadenectomy to the iliac bifurcation.⁵

Knowledge of the pathway of the spread of tumor cells is a prerequisite for complete clearance and it is also the basis of the SN concept. According to this view tumor cells metastasizing via the lymphatics enter the SN, that is the first node of the regional lymph node basin, before they disseminate sequentially to other lymph nodes.

The SN is specific in each individual. SN detection allows the identification of a small volume of representative nodal tissue for thorough pathological evaluation. The detection of micrometastases can be improved by ultrastaging, which entails SN analysis by extended serial sectioning combined with IHC techniques.⁶ Radio guided surgery, in which γ emitting substances are injected close to the tumor and a γ detecting probe is used, is done to identify the SN.⁷

A small pilot study was recently performed to evaluate SN detection in patients with invasive bladder cancer in conjunction with limited lymphadenectomy.⁸ We determined whether nodal staging in such cancer cases could be improved by SN detection along with careful examination of the nodes at extended pelvic lymphadenectomy.

MATERIALS AND METHODS

The study was performed from May 2001 to December 2004 in 75 patients, including 59 men and 16 women with a mean age of 65 years (range 46 to 81) who were scheduled for radical cystectomy at the Department of Urology, Lund University Hospital due to locally advanced urothelial carcinoma of the bladder. Two patients had clinical stage T4b disease and received neoadjuvant chemotherapy prior to cystectomy. During the same period 22 additional patients

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FIG. 1. Examination of lymph node tissue ex vivo with handheld γ probe.

underwent radical cystectomy but they were considered unsuitable for the study due to practical or patient related issues (6) advanced tumor stage (7), multifocal tumors or carcinoma in situ (8) and previous full dose radiation for prostate cancer (1).

Preoperative lymphoscintigraphy (first 30 patients).

One to 4 days before cystectomy cystoscopy was performed using local anesthesia. A 3.7Fr Williams cystoscopy needle was used to inject 2 ml ^{99m}Tc -nanocolloid (35 MBq/ml) at 4 locations peritumorally in the detrusor muscle. The bladder was drained with an indwelling catheter and the patient underwent lymphoscintigraphy approximately 1 hour after isotope injection. If no SN was visualized at that time, lymphoscintigraphy was repeated 1 or 2 hours later. Scintigraphy was done in 2 planes with and without a lead shield to decrease uptake from the primary injection site.

Intraoperative SN detection. Immediately preceding surgery 1 ml ^{99m}Tc -nanocolloid (70 MBq/ml) and 1 ml Patent Blue® were injected peritumorally into the detrusor muscle using general anesthesia, as described. Extended lymphadenectomy was subsequently done. Due to possible radioactivity interference from the primary injection site examination of the lymphatic tissue with a handheld γ probe was done ex vivo using a Neoprobe 2000® (fig. 1). Radioactivity was documented in counts per second and nodes that were radioactive were sent in fractions for pathological evaluation as SNs. Intraoperatively blue nodes were identified visually. After the completion of lymphadenectomy and cystectomy the pelvic cavity and nodal basins were investigated with the γ probe. Remaining radioactive tissue and/or nodes in the nodal basins were identified and removed.

Lymphadenectomy. Lymphadenectomy was performed as extended dissection. The anatomical borders were the genitofemoral nerve lateral and the bladder wall medial. The

proximal limit was the aortic bifurcation. The iliac vessels were dissected off of the pelvic side wall to expose the triangle of Marceille, where all lymphatic tissue was extirpated. On each side specimens were fractionated into the obturator fossa, internal iliac, external iliac and common iliac, of which the latter included presacral lymphatic tissue.

Histopathological evaluation. The bladder was fixed in a distended state by instilling formalin via a catheter. The prostate/bladder neck was sectioned by a sagittal whole mount technique and samples of macroscopic tumor manifestations were collected. Bladder wall that appeared normal was sampled in standardized fashion. Macroscopic and microscopic tumor locations were noted. Identified SNs were fixed in formalin. The entire sentinel lymph nodes were paraffin embedded. Nodes larger than 4 mm were divided into 2 to 3 mm slices along the long axis. Each paraffin block was examined at 3 step-section levels separated by 150 μm . Parallel 4 μm sections were stained with hematoxylin and eosin, and by IHC for cytokeratins. The monoclonal antibody MNF 116 (Dakocytomation, Copenhagen, Denmark) was used in 1:200 dilution with protease pretreatment and staining performed on a Ventana™ NexES™ staining machine. Sections from 2 or 3 levels were used to investigate nonSNs. Micrometastasis was defined as a lesion smaller than 2 mm, whereas a conglomerate of isolated tumor cells smaller than 0.2 mm was denoted as a submicrometastasis. All histopathology was performed by 1 pathologist. The study was approved by the Ethics Committee of Lund University.

RESULTS

An average of 40 nodes (range 8 to 67) was extirpated at lymphadenectomy. Of the 75 patients 32 (43%) were lymph node positive. Table 1 lists pathological and nodal stages. In 13 lymph node positive patients metastases were found only outside of the obturator spaces (table 2).

SNs were identified in 65 of the 75 patients (87%). Preoperative lymphoscintigraphy visualized SNs in only 7 of the 30 patients (23%) who were investigated with this method (fig. 2). Furthermore, the scintigraphic picture was difficult to interpret in 1 patient. Due to the low detection rate we subsequently abandoned preoperative lymphoscintigraphy. Intraoperative dye detection identified an SN in 2 patients, whereas intraoperative dynamic lymphoscintigraphy with the handheld γ probe detected SNs in 65 of 75 (87%). In 7 cases SNs were identified when the γ probe was used to assess nodal basins after the completion of extended lymphadenectomy and cystectomy. SNs were located outside of the obturator fossa in 35 of 65 patients (54%). In 2 patients an

TABLE 1. Pathological and nodal stages in 75 patients

Pathological Tumor Stage	No. Pts	No. pN1	No. pN2
pT0	6		
pTa	3		
pTCIS	2	1	
pT1	3		
pT2a	6	1	1
pT2b	13	2	1
pT3a	10	2	1
pT3b	27	10	8
pT4a	5	1	4

Pt Age—Sex	Lymph Node Metastasis Locations
65—M	Common iliac lt
42—F	Int iliac rt, external & common iliac lt
68—F	External iliac rt
60—M	External iliac rt
46—M	Perivesical
48—M	Internal iliac rt
81—M	Perivesical
64—M	External + internal iliac lt
42—M	Perivesical, external + common iliac lt
75—M	Internal iliac rt
67—F	Perivesical, vesicovaginal septum, external + internal iliac lt
56—M	Internal iliac rt
67—M	External iliac lt

Locations	Hematoxylin & Eosin/IHC	Size* (mm)	Only Metastatic Deposit
Obturator fossa rt & external iliac rt	Pos/pos	0.40 & 1.5	Yes
External iliac & pararectal	Pos/	1.80 & 0.40	No
Obturator fossa rt	Neg/pos	0.10	Yes
Obturator fossa lt	Pos/pos	1.00	No
Obturator fossa lt (2 nodes) + internal iliac lt	Pos/pos, internal iliac pos	0.40, 1.10 & 0.10	No
External iliac lt	Pos/pos	0.10	No
Internal iliac lt	Pos/pos	0.30	Yes
External iliac lt	Pos/pos	0.13	Yes
Common iliac lt	Pos/pos	0.30	Yes

* Micrometastasis 0.2 to 2 mm and submicrometastases less than 0.2 mm.

SN was found in the common iliac area, whereas all other SNs were located in the pelvic nodal basins (obturator fossa, external or internal iliac region). An average of 2.4 SNs (range 1 to 8) was identified in the 65 patients.

Of 32 lymph node positive cases 26 (81%) were found to have a positive (metastatic) SN and in 14 of the 32 (44%) the metastatic SN was the only lymph node involved. Thus, the false-negative rate for identified SNs was 19% (6 of 32 cases). Five of the 6 patients with false-negative SNs, ie lymph node metastases in other lymph nodes despite a benign SN, had macroscopically enlarged hard nodes and/or perivesical metastases.

Nine of the 65 patients (14%) with identified SNs had an SN that contained micrometastases (less than 2 mm). In 5 of these cases the micrometastasis was the only metastatic deposit (table 3 and fig. 3).

DISCUSSION

Gould introduced the term SN in 1960 and defined it in relation to a constant anatomical position in tumors of the parotid.⁹ SN detection was first achieved by performing lymphangiography but it was later done using different tracers, which changed the purely anatomical definition to include a functionally identified lymph node with an inconsistent anatomical localization that is unique in each patient. Extended serial sectioning and IHC staining of SNs along with the increased detection of micrometastases (ultrastaging) has led to further development of the concept.⁶

We used 3 methods to detect SNs, of which 2 (preoperative lymphoscintigraphy and intraoperative blue dye detection) showed low sensitivity, which does not agree with

experiences of SN detection in breast carcinoma. Preoperative lymphoscintigraphy is more difficult to use in patients with bladder cancer for certain reasons. 1) Radioactivity from the primary injection site interferes with SN visualization (the shining-through effect). 2) The lymphatic pattern in the pelvis is more complex. 3) It is difficult to transfer preoperatively identified nodes to corresponding anatomical

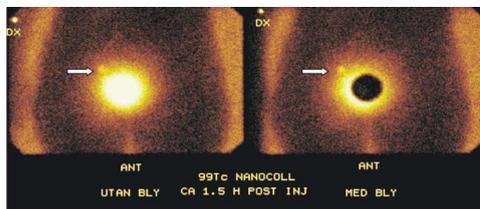


FIG. 2. Preoperative lymphoscintigraphy in anteroposterior plane shows 1 SN in right obturator fossa (arrow).

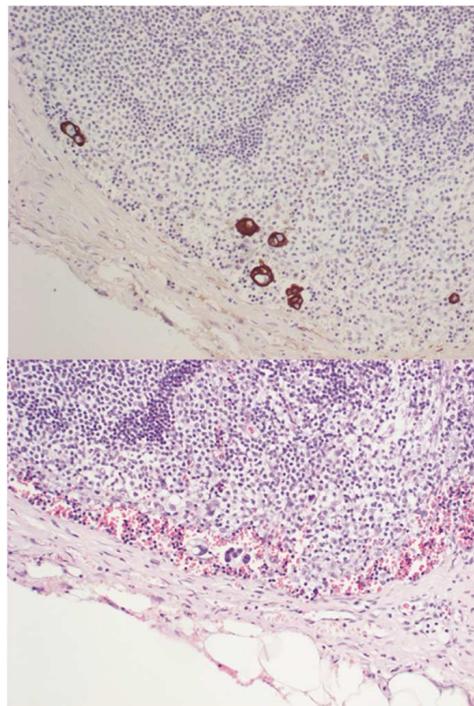


FIG. 3. Submicrometastases in SN detected by IHC (top) and corresponding stained section (bottom). H & E, reduced from $\times 100$.

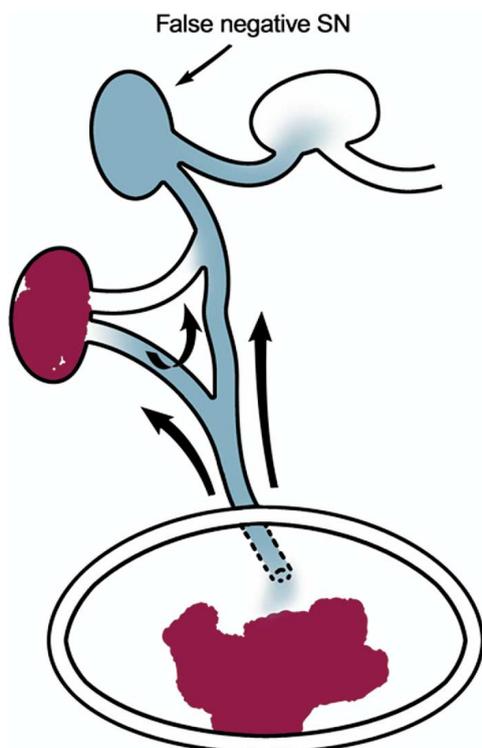


FIG. 4. Lymph nodes with extensive metastasis might obstruct lymph vessels, altering lymph flow and generating false-negative SN.

locations. Dye detection has also been found to be a sensitive method for detecting SNs in patients with breast carcinoma.¹⁰ However, with the methodology that we applied a rather long period elapsed between the transurethral injection of blue dye and the start of nodal examination. Hence, the dye must have passed the regional nodes. The 2 blue SNs that we identified in our material were extensively involved in metastatic disease and it was probably the retention of blue dye that made it possible to detect these nodes.

Considering SN detection, the 19% false-negative rate noted in our study is rather high. There are at least 2 plausible explanations for this finding. Lymph nodes that show extensive metastasis might obstruct the lymph vessels and, thereby, alter the flow of lymph and generate a false-negative SN (fig. 4). Another reason is that we found it difficult to identify perivesical SNs by intraoperative lymphoscintigraphy due to radioactivity interference from the primary injection site. However, we identified a perivesical SN in 3 patients, including 1 with metastasis, whereas metastatic perivesical SNs were missed in 2 other patients. In 5 of the 6 cases with false-negative SNs macrometastases and/or perivesical metastases were present and they were identified by their macroscopic appearance.

Three recent studies of series of patients with bladder cancer indicated an incidence of lymph node metastases of 24%.^{11–13} The proportion of patients with node positive disease was much greater (43%) in our study, which can probably be explained by several factors. 1) The rate of nonorgan confined disease (pT3a or greater) was high (42 of 75 patients or 56%). 2) We observed that 5 of the 75 patients (7%) had isolated micrometastases in SNs, which also increased the number of node positive patients. An average of 40 extirpated nodes is to our knowledge the largest number of nodes reported to be retrieved by clearing the nodal sites to the aortic bifurcation. In a study Bochner et al found that extended dissection to the aortic bifurcation offered no staging advantage over limited dissection to the iliac bifurcation.⁵ Despite that finding it is likely that the high yield of lymph nodes in our series is another factor that might have contributed to the larger proportion of node positive cases. Lymphadenectomy to the level of the aortic bifurcation in our investigation provided a large average lymph node yield (40 nodes). Corresponding yields reported in the literature vary between 15 and 39 nodes,^{5,11} which indicates the need for standardized dissection, fractionation and handling of the specimens by the pathologist.⁵

We found that 13 of the 32 lymph node metastases (41%) and 35 of the 65 SNs (54%) were located only outside of the obturator spaces, which clearly emphasizes that it is not sufficient to limit lymphatic clearance to the obturator fossa. There is probably also a small population of patients who have isolated metastases in the common iliac and presacral areas without the involvement of more distal nodes. That assumption is supported by a prospective multicenter study, in which 6.9% of patients (290) presented with single node metastasis in this region.¹⁴ Moreover, 2 of our patients had SNs in the common iliac area, of whom 1 had a single node metastasis, which lends support to the concept that there might be primary lymph node metastases above the iliac bifurcation.

Considering the high false-negative rate of 19% in our study it is obviously not advisable to omit lymphadenectomy in patients with cystectomy who have a negative SN. The findings of a negative SN in the axilla in patients with breast cancer at many centers today implies that nodal dissection is not done. In bladder cancer more experience is needed to make it feasible to use radio guided surgery to identify the SN in vivo. This might be difficult due to the shining-through effect, even with the appearance of new and better handheld γ probes with improved collimators. Frozen section methodology must also be further developed to minimize the risk that nodes deemed negative on intraoperative investigation of frozen sections prove to be positive when definitive histology is available. Indeed, such a result was described in 0% to 44% of patients with breast cancer undergoing SN detection.¹⁵ This problem can be solved in the axilla by performing a secondary procedure but it would be more complicated to manage in the pelvis. Furthermore, it would probably be even more difficult to examine all endopelvic lymph nodes by intraoperative frozen section as a basis for deciding whether to perform a more proximal lymphadenectomy, as proposed by Abol-Enein et al.¹¹ That conclusion is drawn in the light of the risk for false-negative results connected with frozen sections and the increased amount of labor re-

quired to investigate a large number of nodes intraoperatively.

Traditionally the analysis of lymph node status after radical cystectomy consists of light microscopy evaluation of 1 to 6 hematoxylin and eosin stained sections of each retrieved node, which entails the obvious risk of missing nodal disease. IHC has been used to evaluate bladder cancer¹⁶ to increase the detection of micrometastases (ie a metastasis smaller than 2 mm) in extirpated lymph nodes and, thereby, improve nodal staging. In addition, routine use of fat clearance solutions to increase the number of nodes detected by the pathologist has been tested.^{17,18} However, the results of these methods have been disappointing.

Our finding of micrometastases in SNs in 9 of 65 patients (14%) merits further investigation. These lymph node metastases were detected by extended serial sectioning of identified SNs in conjunction with IHC. Ultrastaging involving radio guided surgery indicated stage migration and the prognostic significance of such a stage shift must be determined in a larger number of patients with longer followup. Notwithstanding, we think that the concept is interesting because many patients have recurrence and adjuvant chemotherapy is an option in node positive patients. Moreover, the handheld γ probe identified SNs in an additional 7 patients after cystectomy when it was assumed that nodal dissection was complete, which indicates that the method provided more optimal node dissection. Thus, based on our observations of micrometastasis in 9 patients and optimized surgery in another 7 we conclude that nodal staging was improved in these 16 of 65 (25%).

CONCLUSIONS

We identified an SN in 65 of 75 patients (87%). In 6 of 32 node positive cases (19%) the SN was false-negative. Investigation with extended serial sections and IHC (ultrastaging) revealed micrometastases in 9 of 65 SNs (14%) and radio guided surgery identified an SN in 7 patients after the completion of extended lymphadenectomy. Inasmuch as we observed micrometastasis in 9 patients and optimized surgery in another 7 we believe that nodal staging was improved in these 16 of 65 patients (25%).

Abbreviations and Acronyms

IHC = immunohistochemistry
SN = sentinel node

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EDITORIAL COMMENT

The concept of sentinel node biopsies has received limited acceptance in urological malignancies. These authors used techniques of intraoperative lymphoscintigraphy as well as blue dye detection combined with immunohistochemistry to identify micrometastases in patients with invasive bladder cancer. Importantly they excluded patients with multifocal tumors or carcinoma in situ. Immunohistochemistry, a procedure not done routinely by pathologists, aided in the iden-

tification of micrometastases (smaller than 2 mm) and submicrometastases (smaller than 0.2 mm) in lymph nodes.

Of concern is the 19% false-negative rate in this study. The further question as to whether the identification of tiny metastatic foci (less than 2 mm or certainly less than 0.2 mm) would alter the prognosis or lead to adjuvant therapy remains unanswered. In this series, the majority of patients with pathological nodal involvement were noted to have pathological stage T3b or T4a, of whom many would receive adjuvant chemotherapy postoperatively based on pathological stage alone. Only 9 of 43 patients who had pathological stage T3a or less would theoretically benefit from sentinel node detection, as advocated by the authors.

This study shows the feasibility of detecting small volume nodal metastases in select patients. Acceptance of this concept into standardized practice will require substantially higher number of patients and ideally proof of therapeutic efficacy in a prospective trial.

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