Reliability of Frozen Section Examination of External Iliac, Hypogastric, and Obturator Lymph Nodes During Radical Cystectomy: A Multicenter Study

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OBJECTIVES To evaluate the accuracy of frozen section examination (FSE) for detecting lymph node (LN) metastasis in patients with bladder cancer undergoing radical cystectomy and pelvic LN dissection. To our knowledge, the accuracy of FSE to identify LN metastases in patients with bladder cancer is still undetermined.

METHODS The clinical data of 360 patients who had undergone radical cystectomy with pelvic lymphadenectomy for bladder cancer in six urologic institutions were retrospectively analyzed. The nodal regions included were the external iliac, hypogastric, and obturator LNs. The FSE results of the right and left LN regions were compared with the final histopathologic results of the respective LN regions.

RESULTS The final pathologic examination revealed nodal metastases in 65 patients (18.1%). Of the 720 right and left LN regions in 360 patients, 88 (12.2%) were metastatic at the final pathologic examination. Although the FSE findings were negative, the final pathologic examination revealed LN metastases in 26 patients and in 29 pelvic LN regions. All LN regions with positive FSE findings were positive at the final pathologic examination. When we considered the 720 LN regions, the sensitivity, specificity, and positive and negative predictive values for FSE were 67%, 100%, 100%, and 95.6%, respectively.

CONCLUSIONS Until innovations in imaging methods improve nodal staging in patients with bladder cancer, performing FSE of the external iliac, hypogastric, and obturator LNs seems to be a reliable procedure for the evaluation of the LNs. The information obtained with FSE of the LNs can be used to determine intraoperatively the extent of LN dissection. UROLOGY 69: 83–86, 2007. © 2007 Elsevier Inc.

Radical cystectomy with pelvic lymphadenectomy is routinely performed for invasive bladder carcinoma, and lymph node (LN) involvement is found in 14% to 32% of such cases.[1,2] Lymphadenectomy increases the accuracy of surgical staging and allows for the identification of those patients in greatest need of adjuvant therapy. In addition, it may even be therapeutic in a select subset of patients with micrometastatic disease.[3,4] Although the potential curative role of extended LN dissection and its importance in accurately staging disease has been reported by many investigators, the anatomic extent of LN dissection for accurate staging or to obtain a therapeutic advantage still needs to be defined.[1,5,6]

Anatomic studies have defined the external and internal iliac and obturator sites as the primary lymphatic drainage of the bladder and the common iliac sites as the secondary drainage.[7] Leissner *et al.*[8] reported in a multicenter study that 6.9% of their patients had a single positive node only above the bifurcation of the common iliac artery, suggesting skipped metastases. However, more recent studies evaluating the value of extended LN dissection have revealed that metastases outside the true pelvis were only detected in multinodal disease and that these metastatic deposits were always associated with metastases at the obturator fossa and/or internal iliac region.[7,9] Therefore, these recent studies have concluded that standard lymphadenectomy in bladder cancer should always include all lymphatic tissues in the true pelvis. These studies, and a review by Heidenreich *et al.*,[10] have

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suggested that if frozen section examination (FSE) demonstrated no positive LNs in the true pelvis, LN dissection was not necessary further cranially. If, however, FSE revealed positive LNs, the dissection should be extended cranially up to the inferior mesenteric artery and, under such circumstances, the patients should not be denied any possible additional benefit, even if marginal.[7,9,10] Therefore, FSE seems to be very important to the intraoperative decision of extended LN dissection. However, to our knowledge, no study had been conducted to evaluate the accuracy of FSE in identifying LN metastasis in bladder cancer. In this multicenter retrospective study, we aimed to evaluate the accuracy of FSE for detecting LN metastases by comparing the FSE results with the final pathologic results of external iliac, hypogastric, and obturator LN dissection.

MATERIAL AND METHODS

From July 1993 to July 2005, FSE of the pelvic LNs was performed in 360 patients with bladder cancer who were undergoing radical cystectomy with bilateral pelvic lymphadenectomy. The patients were treated at six urologic institutions. All operations were performed with curative intent on patients with muscle-invasive tumors, high-risk T1 (grade 3 or carcinoma in situ) tumors, or recurrent multifocal superficial disease refractory to repeat transurethral resection with intravesical therapy. Patients who had undergone previous radiotherapy to the pelvis and previous pelvic lymphadenectomy for other reasons and those with missing medical record data were excluded from the study.

The preoperative evaluation included the patient history, routine clinical examination, biochemical and hematologic tests, bimanual examination under anesthesia, transurethral resection of the tumors, abdominal ultrasonography, computed tomography (CT), and chest x-ray. Bone scan and brain CT were used when indicated by signs and symptoms. The histopathologic tumor type and grade and number of LNs dissected were documented from the medical records. The pathologic stage was assigned according to the 2002 TNM classification.[11] The World Health Organization 1998 classification was used for histopathologic type and grade.[12] All 360 patients underwent standard pelvic LN dissection at cystectomy, and FSE of LNs was performed during surgery. The proximal limit of LN dissection was defined by the bifurcation of the common iliac vessels. The nodal regions included were the external iliac, hypogastric, and obturator LNs.

For the pathologic evaluation, all tissue removed from the particular pelvic LN regions was undertaken for intraoperative FSE. The pelvic LNs were received as the left and right side in separate packages. The adipose tissue was palpated and dissected for the LNs. Not only the suspicious LNs, but all the LNs were dissected for FSE. Because the LNs received had generally lipomatous cut surfaces, special effort had been made to dissect only the lymphomatous component of the specimen. Depending on the LN size, they were either bisected or cut into several pieces. The LNs larger than 1 cm and smaller than 1 cm were generally cut into four and two equal pieces, respectively. Afterward, they were frozen for cryostat sectioning at −20°C or −25°C. Depending on the size of the LN, six to eight sections for an LN smaller than 1 cm and two to four sections for an LN larger than 1 cm were obtained. At individual levels, 4 to 5-μm-thick sections were cut from each LN specimen and stained with hematoxylin-eosin. All the tissue from the frozen section preparations, as well as the residual adipose tissue and the LNs that did not undergo FSE, was fixed in 10% formalin for one night and embedded in paraffin. Depending on the LN size or block of the perinodal fat tissue, two to four serial sections were cut and stained with hematoxylin-eosin for definitive histopathologic diagnosis. Immunohistochemistry or any other molecular techniques were not used to find metastasis. No differences were found in the material handling among the six centers. The FSE results of the right and left LN regions were compared with the final histopathologic results of these node regions.

Table 1. Main clinical and pathologic characteristics of 360 patients

Characteristic	Patients (n)
Sex	
Male	324 (90)
Female	36 (10)
Histologic type	
TCC	313 (86.9)
Squamous cell carcinoma	13 (3.6)
Adenocarcinoma	8 (2.2)
Mixed (TCC + squamous)	21 (5.8)
Other (nonepithelial tumors)	5 (1.4)
Tumor grade in TCC cases*	
1	31 (10.5)
2	98 (33.3)
3	165 (56.1)
Pathologic stage of primary tumor	
≤pT1	69 (19.2)
pT2	122 (33.9)
pT3	121 (33.6)
pT4	48 (13.3)
Lymph node	
pN0	295 (81.9)
pN+	65 (18.1)

TCC = transitional cell carcinoma.
Data in parentheses are percentages.
* No grade information available for 19 patients with TCC.

The relationship between the pathologic stage and LN positivity at the final pathologic examination was examined by chi-square test. The Mann-Whitney *U* test was used to determine whether patient age and the number of LNs removed were significant predictors of false-negative FSE findings. Fisher's exact test was used to test whether the histologic cell type was a significant predictor of false-negative FSE findings. To define the independent risk factors for false-negative FSE findings, multiple logistic regression analysis was used, and the adjusted odds ratios were calculated. *P* values less than 0.05 were considered significant. The Statistical Package for Social Sciences, for Windows 11.5 (SPSS, Chicago, Ill), was used for statistical analysis.

RESULTS

The mean patient age was 59 years (range 8 to 83). The clinical and pathologic characteristics of the 360 patients analyzed are summarized in Table 1. Information regarding the number of LNs removed was obtained from the medical records of 266 of the 360 patients; the mean

Table 2. Lymph node involvement ratios according to pathologic stage

Pathologic Stage	Patients (n)	Nodal Involvement at Final Pathologic Examination (n)
≤pT1	69	2 (2.9)
pT2	122	11 (9)
pT3	121	36 (29.8)
pT4	48	16 (33.3)
Total	360	65 (18.1)

Data in parentheses are percentages.

number of LNs removed per patient was 10.4 ± 6. The final pathologic examination revealed nodal metastases in 65 (18.1%) of 360 patients. Of these 65 patients, 23 had bilateral LN metastasis. A total of 720 right and left pelvic LN regions were examined in these 360 patients, and 88 (12.2%) were metastatic at the final pathologic examination. Although the FSE findings were negative, the final pathologic examination revealed LN metastasis in 26 patients and 29 pelvic LN regions. Of the participating centers, the false-negative rates for FSE ranged from 5% to 10%. All false-negative FSE regions had micrometastasis. All LN regions with positive FSE findings were positive on the final pathologic examination. Table 2 shows the pathologic stage in all patients and the ratio of LN metastasis identified at final pathologic examination. The percentage of patients with nodal metastases increased significantly with increasing pT stage of the primary tumor (chi-square test, $P < 0.001$, Table 2). The sensitivity, specificity, and positive and negative predictive values for FSE were 67%, 100%, 100%, and 95.6%, respectively, for the 720 LN regions.

Information regarding the number of LNs removed was available for 22 of the 26 patients with false-negative FSE findings. The mean number of LNs removed per patient in this group was 9.9 ± 5. The mean patient age of these 26 patients was 59 years (range 45 to 76). The patient age and mean number of LNs removed per patient were significant factors for false-negative FSE findings (P = 0.78 for age and P = 0.79 for the mean number of LNs removed). Of the 26 patients with false-negative FSE findings, the histologic cell type was transitional cell carcinoma (TCC) in 18, mixed type in 6, and squamous cell carcinoma in 2. When we stratified patients into two groups according to the histologic cell type (TCC-only versus non-TCC group), the histologic cell type (non-TCC) was a significant factor for false-negative FSE findings (P = 0.012). After adjusting for age and the number of LNs removed, the odds ratio for having false-negative FSE findings was 2.97 (95% confidence interval for odds ratio 1.12 to 7.82, P = 0.028) for non-TCC type compared with the TCC-only type (crude odds ratio 3.36).

COMMENT

Although radical cystectomy with bilateral pelvic LN dissection is widely used for the treatment of invasive bladder cancer, no universally accepted template for pelvic LN dissection at cystectomy currently exists. Extended dissection, as described by Skinner,[13] extending to 2 to 3 cm higher than the aortic bifurcation has been reported to ensure longer survival periods, especially in patients with pelvic node involvement. In a multi-institutional study published by Leissner *et al.*[8] 20 (6.9%) of 290 patients were shown to harbor positive LNs above the bifurcation of the common iliac artery only. Therefore, they recommended extended lymphadenectomy for all patients undergoing radical cystectomy for bladder cancer to completely remove all metastatic tumor deposits. However, a more recent study of 200 patients from a single center revealed no skipped LN metastasis. That study concluded that negative LNs in the endopelvic region (ie, internal iliac and obturator LNs) indicated that more proximal dissection was not necessary.[9] In a series of 176 patients, Vazina *et al.*[7] also showed that all patients, except for one, with LN metastases in the common iliac or aortic bifurcation region had metastases at more distal sites. Previous anatomic studies have also defined the external and internal iliac and obturator sites as the primary lymphatic drainage of the bladder and the common iliac sites as the secondary drainage.[7] According to these studies, Heidenreich *et al.*[10] concluded in a review that if FSE would demonstrate no positive LNs in the true pelvis, LN dissection need not be carried out further cranially. If, however, FSE revealed metastatic deposits along the locoregional areas, extension of the lymphadenectomy, including the aortic bifurcation up to the inferior mesenteric artery, would be worthwhile.[10] Additionally, extended LN dissection lengthens the duration of the operation by nearly 60 minutes[14] and may cause additional morbidity. Therefore, FSE seems to be an important part of the operation to decide whether to perform extended LN dissection. However, to our knowledge, no studies have been reported concerning the accuracy of FSE of the regional LNs during radical cystectomy for bladder cancer. In our study, the sensitivity, specificity, and positive and negative predictive values for FSE were 67%, 100%, 100%, and 95.6%, respectively.

In patients with prostate cancer, the reliability of FSE was studied in the 1980s, with false-negative FSE rates reported as 7% to 18%.[15,16] The number of patients with negative FSE findings and positive final pathologic findings in our study was 26 (7.2%). Of the participating centers, this rate ranged from 5% to 10%. In our study, we considered three main parameters, the histologic cell type, patient age, and the mean number of LNs removed. Of these, only the histologic cell type (non-TCC group) was a significant factor for false-negative FSE findings.

Several criticisms of our study could be made. Although the medical records of patients were carefully examined, the retrospective and multicenter features of this study and the lack of an evaluation of the final pathologic findings by a reference pathologist were disadvantages. However, of the participating centers, the false-positive FSE rate ranged from 5% to 10%, and we believe that this range is not large for such a multicenter study.

As an alternative to intraoperative FSE, clinical locoregional LN involvement can be detected using preoperative imaging methods. For this purpose, abdominopelvic CT is routinely used in invasive bladder cancer staging, although it yields unsatisfactory results with regard to LN involvement.[17,18] The most important limitation of CT is its insufficiency in detecting microscopic or small-volume LN metastasis. Using abdominopelvic CT, Paik *et al.*[18] found a sensitivity of only 14% and specificity of 89% in the detection of LN involvement. In a more recent study, the reported sensitivity, specificity, and positive and negative predictive values of the diagnosis of LN metastasis for CT were 42%, 100%, 100%, and 81%, respectively.[17] When we compared these values with our FSE results, our results with FSE were much better, especially for the sensitivity and negative predictive value.

Promising, but insufficient, data are available for the use of magnetic resonance imaging (MRI) in the clinical staging of bladder cancer. In studies of small cohorts of patients with locally advanced bladder cancer, the overall accuracy of MRI in LN assessment was disappointing, with false-negative rates as great as 40%.[19] Although a recent study with ferumoxtran-10 enhanced MRI revealed a 92% sensitivity rate for nodal staging in patients with bladder cancer, that study had some methodologic weaknesses, because only 43% of the nodes could be matched between the MRI scans and surgical dissection.[20] The results of positron emission tomography in the detection of LN metastases in patients with bladder cancer are still preliminary and have not been very encouraging.[21]

CONCLUSIONS

The currently available imaging techniques cannot identify LN micrometastases and pelvic lymphadenectomy remains part of the radical cystectomy procedure. However, controversy exists as to the exact extent of LN dissection that should be performed for bladder cancer. Several studies have reported that if the obturator and internal iliac LNs are disease free on FSE, more proximal lymphadenectomy is unnecessary. Additionally, extended lymphadenectomy takes longer than standard lymphadenectomy and may cause extra morbidity. Therefore, FSE is important for deciding the extent of LN dissection. However, the correlation of FSE with the final pathologic examination findings of all LN specimens should also be known. In our study, the sensitivity, specificity, and positive and negative predictive values of perioperative FSE in determining LN metastasis were 67%, 100%, 100%, and 95.6%, respectively. Therefore, performing FSE of the obturator and internal iliac LNs seems to be a reliable procedure for the evaluation of these LNs. Until innovations in imaging methods improve nodal staging in patients with bladder cancer, the information obtained with FSE of the LNs can be used to decide intraoperatively on the extent of LN dissection.

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