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# Nodal staging and lymphadenectomy in patients undergoing radical cystectomy

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## Introduction

Pathological stage of the primary bladder tumour and the presence of lymph node metastases are the most important determinants of survival in bladder cancer patients undergoing radical cystectomy (1). Both of these factors are difficult to correctly assess preoperatively. Despite improvements in imaging techniques, overstaging and, especially, understaging are common (2). There has been a continuous search for reliable and robust methods for preoperative assessment of lymph node status. However, today open surgery is still the standard for nodal staging, even if reports indicate that laparoscopic lymphadenectomy gives equivalent efficacy but with a shorter postoperative stay (3).

In the 2002 TNM classification, lymph node-positive patients are stratified according to the number of positive nodes and the size of the metastatic nodes, in stages designated N1, N2 and N3. Some reports have failed to confirm survival differences between the N stages.

Thus, Fleishmann and colleagues (4) found no difference in survival between N1 and N2 patients in an analysis of extracapsular extension of pelvic lymph node metastases, and Herr (5) conducted a retrospective study and did not observe any significant differences in survival between patients in the three N stages. This casts doubt over the reliability of the current TNM classification. However, several studies have confirmed that survival in node-positive patients after radical cystectomy is strongly correlated with the p-stage of the tumour (6-8) and with the extent of the node dissection (9, 10).

Surgical treatment of invasive bladder cancer by cystectomy and regional lymphadenectomy evolved more than seventy years ago (11). In 1950 Leadbetter (12) described a technique for "regional gland dissection" which is still in use today. While pelvic lymphadenectomy has been an integrated part of the cystectomy procedure in most centres in the United States for long time, Europe was slow to follow. The publication by Donald Skinner in 1982 "Management of invasive bladder cancer: a meticulous pelvic node dissection can make a difference" (13) started the current interest in this issue.

In this review we will discuss the optimal extent of the lymph node dissection for accurate staging, the curative potential of the method and the prognosis of lymph node-positive disease after such treatment, issues that are currently matters of debate.

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## How are lymph node dissections classified?

After removing only the bladder; *simple cystectomy*, 16% of bladder cancer patients are identified as having perivesical lymph nodes in the cystectomy specimen (14). Thus, a patient can be classified as being node positive without a formal lymph node dissection. The *limited lymph node dissection* is generally described as an extirpation of the lymphatic tissue in the obturator fossa (i.e., between the obturator nerve and the external iliac vein), which generates at the most 10 nodes for examination (15). Another method of limited dissection usually referred to as a *conventional pelvic dissection* (16) or a *standard dissection* (17) includes the area laterally as far as the genitofemoral nerve and posterior to the internal iliac vessels, and a median of 14 nodes are excised within these boundaries (18). Using this template, the number of nodes removed ranges from 8 to 26 nodes in the literature (17, 19). The approach used by the Berne group (20) also includes the presacral nodes medial to the internal iliac vessels and common iliac nodes as far up as the ureteric crossing. When the lymph node dissection is extended up to the aortic bifurcation, which is in fact the upper limit in the regional gland dissection as described already by Leadbetter (12), or even up to the inferior mesenteric artery (IMA), the technique is generally described as an *extended dissection* (19, 21, 22). Such dissection increases the number of nodes that are harvested. In the literature, the lymph node yield up to the aortic bifurcation varies between 15 (mean) and 39 (median) nodes (7, 9, 17, 18, 23), and the corresponding number of nodes retrieved in series in which the IMA is the upper limit of dissection is 43 (mean) and 56 (median) nodes (19, 22, 24). However, even within the same study and using standardized dissection templates, there is substantial inter-surgeon variability in terms of lymph node retrieval. Thus, Leissner (9) found significant differences in the number of nodes obtained by sixteen surgeons (range 10–21), who used the aortic bifurcation as the upper limit of dissection.

## Current practice of pelvic lymph node dissection in conjunction with radical cystectomy

It is obvious that surgeon's preferences have a great impact on routine clinical care. In a large cohort study

representing 12% of the population of the United States in 1988–1998 it was noticed that 40% of patients who underwent radical cystectomy did not have a pelvic lymph node dissection at all (24), and only 12% of the patients had more than 15 lymph nodes examined. In the Nordic Cystectomy Trial II (25) the obturator and the iliac nodes were to be removed according to the protocol, but 20% of the patients did not have a lymphadenectomy. Other more extensive recommendations for lymphadenectomy have also been given. For example, in a randomized study examining the value of neo-adjuvant chemotherapy in conjunction with radical cystectomy, the midpoint of the common iliac arteries was used as the cranial limit of the lymph node dissection (26). In the large EORTC-30994 study, which was recently launched to ascertain whether adjuvant chemotherapy improves survival after radical cystectomy, it is recommended, but not required, that lymphadenectomy to the aortic bifurcation is performed. However, the EAU guidelines on muscle-invasive and metastatic bladder cancer published in March 2004, advocate a limited lymph node dissection (obturator fossa) only (27). It is obvious that there are widely different views on the value of pelvic lymphadenectomy.

## How should the lymph node specimens be prepared and examined?

The lymph node yield is influenced by whether an en bloc pelvic node package is submitted for pathological investigation, or if nodes from each lymph node basin are submitted as separate specimens. Bochner performed a non-randomized study of 32 patients who underwent a standard or an extended lymphadenectomy (28). Each patient in the study had a fractionated dissection on the left side and an en bloc dissection on the right side. Mean lymph node counts increased from 2 to 9 and from 23 to 37 for standard and extended lymphadenectomies, respectively, when the lymph node specimens were sent fractionated. Equivalent findings have also been described by Skinner's group, who reported that extending the dissection to the inferior mesenteric artery increased the median lymph node count from 30 to 56 nodes (29). It is reasonable to believe, albeit not proven, that such a dramatic increase in lymph node count could improve nodal staging.

Various techniques of fat clearing to increase the yield of lymph nodes have been described, and in cystec-

tomy specimens such a lymph node revealing solution has been evaluated in two small series (10 and 6 patients, respectively) (30, 31). The findings of the cited studies indicated an increase in the lymph node yield and even improved nodal staging when the method was combined with conventional examination of the lymph node specimens.

Two studies on bladder cancer patients have been conducted to determine the power of immunohistochemistry to increase the detection of micrometastases in excised lymph nodes, and thus improve nodal staging, but the results did not indicate that significantly more micrometastases were revealed (32, 33). Wilkinson and Hause (34) used a mathematical model and found that detection of a lymph node metastasis depends on the size of the lymph node, the size of the metastatic lesion, and the method used for sectioning. These authors suggested that the rate of false-negative pathology findings exceeds 30% when studying nodes by conventional methods (i.e., three equally distributed sections per node), and they recommended that extended sectioning be performed to improve the results, especially in larger nodes. However, studying large numbers of lymph nodes with additional methods such as extended sectioning or immunohistochemistry is labour-intensive and costly.

### Does an extended dissection improve nodal staging?

Leissner and co-workers (9) conducted a prospective multicentre study to examine the anatomical distribution of lymph node metastases in patients undergoing extended lymphadenectomies with the IMA as the upper limit. Out of a total of 290 patients, they identified 29 cases with a single-node metastasis, and 10 of those 29 patients (34%) had the metastasis outside the obturator and internal iliac lymph node basins, i.e. in the external iliac, common iliac, or deep obturator space, (the latter referring to the space along the obturator nerve as it continues cephalad up to its origin from the lumbosacral trunk). In the same study, 20/81 (25%) of lymph node-positive patients presented with isolated nodal involvement in the common iliac and/or presacral regions, which strongly suggests that including these areas will optimize nodal staging. The incidence of proximal lymph node metastases (common iliac or above the aortic bifurcation) has been correlated with advanced stage (pT3 and pT4) in a recent lymph node mapping study (23), indicating that using more proximal boun-

daries in patients with advanced tumours might increase the accuracy of the lymph node staging.

Data in the literature are conflicting with regard to whether there is a correlation between the number of lymph nodes excised and lymph node positivity. Two studies could show such a correlation (5, 9), whereas the Mansoura-group could not (8). This discrepancy might be explained by differences in the median number of nodes that were removed (13 and 15 in the first two investigations versus 18 in the study from Mansoura), since it is possible that too few patients with few nodes were investigated in the Mansoura study.

### Can identification of sentinel node improve nodal staging?

The sentinel node (SN) is by definition the first lymph node to receive lymphatic drainage and thus also the first to receive tumour cells. The concept of *ultra-staging*, which has been proposed for colorectal carcinomas, implies that only the intraoperatively identified SN is submitted for extended serial sectioning and immunohistochemistry (35), and thus only a limited amount of lymphatic tissue is subjected to more thorough pathological evaluation. The cited researchers reported that ultrastaging increased the detection of micrometastases (< 2mm) (35). We have applied this concept in a consecutive series of 75 patients undergoing cystectomy with lymphadenectomy to the aortic bifurcation (36). Just before laparotomy, technetium<sup>99</sup> is injected peritumorally through a cystoscope. A handheld gamma probe is used for identifying SN(s) among the lymph nodes, which have been removed in separate packages from the different basins. After lymphadenectomy these basins are checked with the gamma probe. Identified SN(s) are examined using extended serial sectioning and immunohistochemistry. In the study a mean of 40 nodes were removed. 32 patients (43%) were lymph node positive and of these 26 (81%) had a positive SN. In 9 patients (14%) the SN contained micrometastases (less than 2 mm), in 5 of whom the micrometastasis was the only metastatic deposit. We believe that the technique improved nodal staging in these 9 patients and in additional 7 patients in whom an SN was recognized when the nodal basins were assessed with the gamma probe after completion of what was thought to be a complete lymphadenectomy. It should be realized that the false-negative rate was 6 of 32 cases (19%). However, in 5 of these there were macrometastases and/or perivesical metastases, likely to have been diagnosed anyway. This

technique is now an integrated standard part of the cystectomy in our department.

## Does an extended dissection improve survival?

The question of whether an extended lymph node dissection improves survival can be addressed by analysing data on node-negative and node-positive patients separately. Regarding the former group, it is reasonable to assume that some node-negative patients are understaged because micrometastases are missed (34). Leissner and colleagues (9) studied 172 patients with organ-confined lymph node-negative bladder cancer and observed that disease-free survival at 5 years was increased by removal of =16 lymph nodes as compared to fewer nodes (85% vs. 65%). It is thus plausible that the extirpation of undetected micrometastases contributed to the improved survival of their patients. Furthermore, the survival curves presented in their article did not diverge until after 2 years, which suggests that it takes a relatively long time for a limited metastatic deposit to become clinically significant. Herr and co-workers have also observed that extended dissection enhanced survival in node-negative patients. More precisely, these authors investigated 258 lymph node-negative patients and found a 5-year disease free survival of 82% in those with =8 lymph nodes removed as compared to 41% in those with a more limited dissection (10). Likewise, improved survival in node-negative patients who have relatively more lymph nodes excised has been verified in a large population-based bladder cancer registry (National Cancer Institute Surveillance, Epidemiology and End Results [SEER] Program) that included almost 2,000 patients who underwent cystectomy between 1988 and 1998 in 9 areas in the United States (24). In a randomized cooperative group trial investigating neoadjuvant chemotherapy and radical cystectomy in 268 patients, Herr and co-workers found an increased hazard ratio (2.0) for overall survival when ten or more nodes were removed at cystectomy in a multivariate model correcting for confounding factors such as pathological stage, age, node status, and neoadjuvant chemotherapy (37).

In a non-randomized study, Poulsen and colleagues (18) compared 5-year recurrence-free survival in a consecutive cohort of 194 bladder cancer patients. The initial 68 patients underwent limited lymphadenectomy, whereas the following 126 patients were subjected to an extended pelvic lymph node dissection at cystectomy. For the patients in those two groups who had organ-con-

fined node-negative bladder tumours ( $n = 104$ ), the 5-year survival rates were 71% and 90%, respectively. Comparing patients who had been subjected to limited node dissection (obturator fossa) with those who had undergone node dissection to the aortic bifurcation in our department, we found a significantly longer time to recurrence in the latter group (unpublished data).

No randomized studies of node-positive patients subjected to radical cystectomy and varying extents of lymphadenectomy have been published. However, several investigations have provided evidence that lymphadenectomy can be curative in subsets of node-positive patients. Indeed, it has even been observed that 24% of patients with gross adenopathy (i.e., N2 or N3 disease) and subjected to surgical resection without postoperative adjuvant treatment ( $n = 84$ ) survived for 10 years (38). The 5-year disease-free or overall survival in the available studies varies between 4% and 39%. Even if many patients in more recent series have received adjuvant chemotherapy, it is evident that lymphadenectomy in itself can be curative in some lymph node-positive individuals. The role of adjuvant chemotherapy is beyond the scope of this review. However, the highest survival figures (29%-39%) have been seen in series of patients with urothelial carcinomas in which all of the subjects have been treated with radical cystectomy and extended lymphadenectomy, and many have also received adjuvant chemotherapy (6, 16, 39-42).

Herr (43) stratified 637 patients who had undergone radical cystectomy according to the number of lymph nodes that were excised. 148 (23 %) of the patients were node-positive, and the author found a fourfold difference in the local recurrence rate comparing groups in which 0-5 and > 14 nodes had been extirpated (17% and 4%, respectively). Moreover, Leissner and co-workers (9) observed that the risk of local recurrence was increased after removal of = 15 nodes, as compared to > 15 nodes (27% vs. 17%, respectively). The mentioned findings suggest that extending the lymph node dissection can lower the risk of local recurrence.

## Metastatic lymph nodes — pathological features with adverse effects on prognosis

According to the TNM classification, lymph node-positive patients are stratified by number of positive nodes and size of metastatic nodes (stages N1, N2, and N3). In addition, the presence of more than 5 positive

nodes has been verified as an independent prognostic factor in two recent investigations (8, 16). In a study performed by Fleischmann et al. (4), analysing extracapsular extension of pelvic lymph node metastases, no difference in survival between N1 and N2 patients was found. Furthermore, extracapsular extension was the strongest negative predictor of recurrence-free survival in a multivariate analysis, and the authors suggested that this feature should be used to define the N category in the staging system. By comparison, a retrospective study conducted by Herr failed to show significant differences in survival between patients in the three N stages (5). However, this investigator did find that prognostic information could be obtained by calculating the ratio between the number of positive nodes and the total number of nodes; ratio based lymph node staging. Applying this approach, Herr observed that in a cohort of node-positive bladder cancer patients, those with a ratio of = 20% had a significantly better survival compared to those with a ratio = 20%. These results have been confirmed by Stein (7), who used the same concept under a different name (lymph node density) and also with a 20% cut-off, whereas Abdel-Latif and co-workers (8) identified such a relationship in a univariate analysis, but not in a multivariate setting.

### Morbidity caused by extended dissection

It is possible that extending the lymph node dissection will lead to increased morbidity. However, Leissner (9) stratified morbidity into two categories of lymph node counts, = 15 and = 16, but could not detect an increase in lymphoedema or lymphoedema (2% and 1%, respectively). Likewise, Poulsen did not observe any increased morbidity after use of an extended lymph node dissection template compared to a limited template (1.6% and 1.5%, respectively) (18). Also, in a study of patients treated at two different hospitals and using different lymphadenectomy templates, the rates of morbidity (defined as surgical reinterventions) were similar in those who had undergone a limited dissection and those who had been subjected to an extended dissection (11% and 9%, respectively) (44). Nevertheless, long-term complications might however be underreported. In a cohort of 62 patients at our centre who underwent lymphadenectomy extended to the aortic bifurcation, nine patients (15%) developed suprapubic or leg oedema, although this was reversible in most of the cases (unpublished data).

Other aspects of extended lymphadenectomy that should be taken into consideration are time constraints and blood loss. It is difficult to evaluate how these factors affect the surgeon's assessment and application of the procedure but probably they are of importance. Skinner's group (29) believes that cystectomy after an extended lymphadenectomy is an easier and safer approach, because it identifies the pelvic vessels without increasing blood loss. Leissner et al. (22) performed a prospective multi-centre study and found that extending a lymph node dissection from the bifurcation of the iliac arteries to the aortic bifurcation required an extra 60 minutes of operating time.

### Will molecular tools be of clinical use?

The concept of molecular staging is also evolving (not only with regard to lymph nodes), and molecular markers for micrometastases have recently been described in peripheral blood (45) and in bone marrow (46). In a study of 19 bladder cancer patients who had undergone lymphadenectomy during radical cystectomy for bladder cancer, Seraj et al. (47) investigated the largest palpable lymph node by reverse-transcription-PCR (RT-PCR) analysis of the uroplakin II (UPII) gene and routine histology. These researchers found that 4/16 (25%) node-negative patients had positive UPII signals. However, the clinical significance of that finding is not apparent, because the RT-PCR method might also detect contaminating blood carrying circulating cancer cells and benign or apoptotic cells of no importance (48). RT-PCR has also been used to study lymph nodes obtained at cystectomy to detect expression of epithelial mucin 7 (MUC7). This is expressed in carcinoma in situ and in invasive urothelial carcinomas, but not in normal urothelium (49). In the cited investigation, 46/160 (29%) histological normal nodes and all lymph nodes with verified metastasis were positive for MUC7 according to RT-PCR. However, the clinical implications of RT-PCR-detected MUC7 for node-negative patients have not yet been established. Examining the prognostic value of one or several such methods simultaneously in prospective series of patients might add new predictive tools to the morphology-based techniques that are in use today.

### Conclusions

Based on the available literature concerning lymph node preparation and examination, it seems likely that

separating the lymph node specimen into separate packages can significantly increase the lymph node count (28, 29), whereas data are contradictory as to whether an increased lymph node count is equivalent to enhanced detection of positive lymph nodes. Pathoanatomical data from one study (22) suggests that extending the lymph node dissection to the aortic bifurcation can improve nodal staging. This may be beneficial in T3–T4a tumours (23), which more often have lymph node metastases above the iliac bifurcation.

In node-negative patients, disease free survival is probably increased by an extended lymph node dissection due to extirpation of undetected micrometastases. Four investigations in the literature (9, 24, 37, 43) advocate that a minimum number of 8, 10, 10-14, and 16 nodes, respectively, should be excised, and a fifth study suggests the aortic bifurcation as the upper limit of dissection (18).

In node-positive patients, several series have indicated high rates of survival (29%–39%) after extended lymphadenectomy in which a large proportion of the patients have received adjuvant chemotherapy. In addition, it has been found that some node-positive patients can be cured by surgery only, even in cases with gross adenopathy (38). There is no evidence in the literature that extended lymphadenectomy increases the morbidity of surgery (9, 18, 44).

The TNM classification system appears to be inadequate for staging node-positive patients, as indicated by the fact that investigations of several larger series of cystectomy patients have been unable to verify differences in survival between the N groups (4, 5). Alternative methods for staging node-positive patients have been suggested, which consider extracapsular growth (4) and lymph node positivity ratios above or below 20% (5, 7), but these techniques must be confirmed in prospective studies.

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