LYMPH NODE METASTASIS IN BLADDER CANCER

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ABSTRACT

Objective: We reviewed the literature on nodal staging in bladder cancer patients treated with radical cystectomy and lymphadenectomy.

Results: Fractionating the lymph node specimen significantly increases the node count, whereas results are contradictory as to whether that increase improves detection of positive nodes. Pathoanatomical data indicate that extending lymph node dissection to the aortic bifurcation improves nodal staging. That approach might be beneficial, especially in cases of T3/T4a tumours, which more often have lymph node metastases above the iliac bifurcation as compared to less advanced tumours. In node-negative patients, extended lymph node dissection probably removes undetected micrometastases and thereby increases disease-free survival. Four studies suggested that a minimum of 8, 10, 10–14, and 16 nodes must be removed, to improve survival, and in another investigation aortic bifurcation was proposed as the upper limit for dissection. Some node-positive patients can be cured by surgery alone, even in cases with gross adenopathy.There is no evidence that extended lymphadenectomy increases surgery-related morbidity. The TNM classification is apparently insufficient for stratifying node-positive patients, since several larger cystectomy series could not verify differences in survival between N groups.

Conclusions: Fractionating the lymphadenectomy specimen increases the lymph node count. In node-negative patients, more meticulous and extended lymph node dissection (8–16 nodes or to the aortic bifurcation) probably improves disease-free survival by removing undetected micrometastases. Lymph-node positive patients should also be offered radical cystectomy.

INTRODUCTION

The 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). There has been a continuous search for reliable and robust methods for preoperative assessment of lymph node status. Lymphangiography with fine needle aspiration has been evaluated in several studies, but it is not reliable due to a high false-negative rate (2). Only a few investigations have appraised positron emission tomography (PET) and its capacity to detect lymph node metastases in bladder cancer, and the results have been largely disappointing (3). Also, with computed tomography (CT) a high (21%) false-negative rate has been observed (4). However some investigators (5) have recently claimed that new ferumoxtran-enhanced MRI imaging for nodal staging offers 91% sensitivity and a 98% negative predictive rate. Nonetheless, open surgery is still the standard for nodal staging, although one report has indicated that limited laparoscopic lymphadenectomy offers equivalent efficacy and a shorter postoperative stay (6).

In the 2002 TNM classification, lymph node-positive patients are stratified into three stages (N1, N2 and N3) based on the number of positive nodes and the size of the metastatic nodes. However, Fleishmann and colleagues (7) found no difference in survival between N1 and N2 patients in an analysis of extracapsular extension of pelvic lymph node metastases. Similarly, in a retrospective study Herr (8) found no significant variation in survival among patients in the three N stages.

Surgical treatment of invasive bladder cancer by cystectomy and regional lymphadenectomy evolved more than seventy years ago (9). In 1950, Kerr (10) reported long-term survival of two patients who had node-positive disease and underwent cystectomy, and that investigator also observed that the local recurrence rate decreased after pelvic lymphadenectomy. Based on those results, Kerr advocated that such dissection be added to the procedure. More than a decade later, Whitmore and Marshall (11) noted that radical cystectomy and pelvic lymph node dissection led to 5-year survival in 16% (2/13) of node-positive patients.

In 1950, Leadbetter (12) described a technique for "regional gland dissection" that is still in use today. 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 are matters of debate that are discussed in this review.

Classification of lymph node dissections

Perivesical lymph nodes are identified in cystectomy specimens from 16% of bladder cancer patients who have not undergone pelvic lymphadenectomy (13). Thus, a patient can be classified as 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 provides a maximum of 10 nodes for examination (14). Another method of limited dissection usually referred to as a *conventional pelvic dissection* (15) or a *standard dissection* (16) includes the area stretching laterally as far as the genitofemoral nerve and posteriorly to the internal iliac vessels. A median of 14 nodes are excised within these boundaries (17), and reports indicate that surgeons using this template have removed from 8 to 26 nodes (16, 18). Thalmann et al. (19) have employed an approach that also includes presacral nodes medial to the internal iliac

vessels and common iliac nodes, as far up as the ureteral junction. In a technique that is commonly called *an extended dissection* (18, 20, 21), the lymphadenectomy is expanded to the aortic bifurcation, as in the regional gland dissection described by Leadbetter (12) (see Fig. 1), or even up to the inferior mesenteric artery (IMA). Extending the dissection to the aortic bifurcation increases the number of nodes that are harvested, and yields reported in the literature vary between 15 (mean) and 39 (median) nodes (16, 17, 22-24). Corresponding results in series using the IMA as the upper limit of dissection are 43 (mean) and 56 (median) nodes (18, 21, 25). However, even within the same study and using standardized dissection templates, there is substantial inter-surgeon variability in terms of lymph node retrieval. Leissner et al. (22) found significant variation in the number of nodes obtained (range 10–21) by sixteen surgeons who used the aortic bifurcation as the upper limit of dissection.

Current practices in pelvic lymph node dissection performed in conjunction with radical cystectomy

In a large study representing 12% of the population of the United States in 1988–1998, it was found that pelvic lymph nodes were not retrieved in 40% of patients who underwent radical cystectomy (25), and only 12% of such patients had more than 15 lymph nodes examined. By comparison, in the Nordic Cystectomy Trials 1 (26) and 2 (27), obturator and iliac nodes were exposed, but 20% of the patients in the latter investigation did not have a lymphadenectomy. Other recommendations for more extensive 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 common iliac arteries was used as the cranial limit of the lymph node dissection (28). Also, in the large EORTC-study that was recently launched to ascertain whether adjuvant chemotherapy improves survival after radical cystectomy, it is recommended, but not required, that lymphadenectomy

be extended to the aortic bifurcation. However, the EAU guidelines published in March 2004 (29) advocate only a limited lymph node dissection (obturator fossa).

Preparation and examination of lymph node specimens

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 et al. (30) performed a non-randomized study comprising 32 patients who underwent standard or extended lymphadenectomy. Each of the patients in the study had a fractionated dissection on the left side and an en bloc dissection on the right side, and it was found that submitting separate specimens increased the mean lymph node counts from 2 to 9 and from 23 to 37 for standard and extended lymphadenectomies, respectively. Similarly, Skinner and co-workers (31) observed that fractionating specimens from a dissection extended to the IMA increased the median count from 30 to 56 nodes. It is reasonable to assume, albeit not proven, that such a dramatic increase in the lymph node count will improve nodal staging.

Various techniques have been described for clearing fat to increase the yield of lymph nodes, and a method using a lymph node-revealing solution has been evaluated in two small series of cystectomy specimens (from 10 and 6 patients, respectively) (32) (33). The findings of the cited studies indicated that the fat-clearing solution increased the lymph node yield, and it also improved nodal staging when used in combination with conventional examination of the lymph node specimens.

Studies of two series of bladder cancer patients (34) (35) have been conducted to determine whether immunohistochemistry can enhance the detection of micrometastases in excised

lymph nodes and thereby improve nodal staging, but the results do not indicate any significant increase in the number of micrometastases revealed. Wilkinson and Hause (36) used a mathematical model and found, not surprisingly, that detection of a lymph node metastasis depends on the size of the node, the size of the metastatic lesion, and the method used for sectioning. These authors suggested that the rate of false-negative pathology findings is greater than 30% when studying nodes by conventional methods (i.e., three equally distributed sections per node), thus they recommended that extended sectioning, especially in larger nodes. However, investigation of many lymph nodes by additional techniques such as extended sectioning and immunohistochemistry is a labour-intensive task.

By definition, the sentinel node (SN) is the first lymph node to receive lymphatic drainage and therefore also the first to be affected by metastasis. According to the concept of ultrastaging, which has been proposed for colorectal carcinomas, only the intraoperatively identified SN is submitted for extended serial sectioning and immunohistochemistry (37), hence only a limited amount of lymphatic tissue is subjected to more thorough pathological evaluation. Mulsow and colleagues (37) reported that ultrastaging increases the detection of micrometastases (< 2 mm), and we have found that applying that strategy at cystectomy in bladder cancer patients improved the rate of detection of micrometastases by 14% (38).

Extended dissection and nodal staging

In a prospective multicentre study, Leissner and co-workers (21) examined the anatomical distribution of lymph node metastases in relation to extended lymphadenectomy with the IMA as the upper limit. Of a total of 290 patients, 29 were identified as having a single-node metastasis, and 10 of those 29 patients (34%) had the metastasis outside the obturator and internal iliac lymph node basins, that is, the external iliac, common iliac, or deep obturator

spaces, (deep referring to the space dorsal to the obturator nerve continued cephalad up to its origin from the lumbosacral trunk). In the same study, 20 of 81 (25%) of lymph node-positive patients had isolated nodal involvement in the common iliac and/or presacral regions, which strongly suggests that including these areas will optimize nodal staging. A recent study involving lymph node mapping (24) revealed a correlation between the incidence of more proximal lymph node metastases (common iliac or above the aortic bifurcation) and advanced stage (pT3 and pT4), which indicates that proximal extension of the boundaries in patients with advanced tumours might increase the accuracy of 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 (8) (22) demonstrated a significant connection between the mentioned factors, whereas Abdel-Latif and co-workers in the Mansoura-group found no such association (39). This discrepancy might be explained by differences in the median number of nodes that were removed (13 and 15 in the first two investigations and 18 in the Mansoura study), since it is possible that Abdel-Latif et al. investigated comparatively few patients with few nodes.

Number of nodes detected—possible impact on survival

The question of whether detection of a larger number of lymph nodes improves survival can be addressed by separate analysis of data on node-negative and node-positive patients. It is reasonable to assume that some node-negative patients are understaged because all micrometastases are not found (36). Leissner and colleagues (22) studied 172 patients with organ-confined, lymph node-negative bladder cancer and observed that the rate of 5-year disease-free survival in that group was increased by removal of ≥16 lymph nodes as compared to fewer nodes (85% and 65%, respectively). However, it should be remembered that if N0

patients only are considered, a selection bias is introduced that favours extended dissection, because such dissection increases the sensitivity of detecting nodal metastases. Other factors such as more radical surgery with wider margins can also partly explain the results reported by Leissner and co-workers, but it is still plausible that extirpation of undetected micrometastases contributed to the improved survival of their patients. The survival curves published by Leissner et al. did not diverge until 2 years after surgery, which suggests that it takes a relatively long time for a limited metastatic deposit to become clinically significant. Herr et al. (40) have also observed that examining a larger number of nodes enhanced survival in N0 patients. The mentioned authors investigated 258 lymph node-negative patients and found a 5-year disease-free survival rate of 82% in those with ≥8 lymph nodes removed compared to 41% in those with a more limited dissection (40). Likewise, improved survival in N0 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 nine areas in the United States (25). Herr and co-workers (41) conducted a randomized cooperative group trial to investigate neoadjuvant chemotherapy and radical cystectomy in 268 patients. Those researchers used a multivariate model correcting for confounding factors such as pathological stage, age, node status, and whether neoadjuvant treatment was given, and the results showed an increased hazard ratio (2.0) for overall survival when ten or more nodes were removed at cystectomy.

In another study by Herr (42), 637 patients who had undergone radical cystectomy were stratified by the number of lymph nodes that were excised. It was found that 148 (23 %) of the patients were node positive, and there was a fourfold difference in local recurrence rate between the groups in which 0–5 nodes and > 14 nodes had been extirpated (17% and 4%,

respectively). Similarly, Leissner and co-workers (22) observed that the risk of local recurrence was increased after removal of ≤ 15 nodes, as compared to > 15 nodes (27% and 17%, respectively). The mentioned findings suggest that examining a larger number of lymph nodes can lower the risk of local recurrence.

Extended dissection and survival

In a non-randomized study, Poulsen and colleagues (17) compared 5-year recurrence-free survival in a consecutive cohort of 194 bladder cancer patients. The initial 68 patients underwent conventional lymphadenectomy, whereas the following 126 patients had an extended pelvic lymph node dissection during cystectomy. For the patients with organ-confined node-negative bladder tumours (n = 104), the 5-year survival rates in the two treatment groups were 71% and 90%, respectively.

We found no publications describing randomized studies that were conducted to compare simple cystectomy with radical cystectomy and varying degrees of lymphadenectomy in node-positive patients. Nevertheless, several investigations have provided evidence that lymphadenectomy can be curative in subsets of node-positive patients (see Table 1). Indeed, in one study (43), 24% (20/84) of patients with gross adenopathy (i.e., N2 or N3 disease) and subjected to surgical resection without postoperative adjuvant treatment survived for 10 years. The rates of 5-year disease-free or overall survival found in the literature vary between 4% and 39%. Even if many patients in more recent series have received adjuvant chemotherapy, it is evident that lymphadenectomy per se can be remedial in lymph node-positive individuals. The role of adjuvant chemotherapy is beyond the scope of this review. However, as shown in Table 1, the highest rates of survival (29%–39%) have been seen in series of urothelial carcinomas in which the patients have been treated with radical cystectomy and extended

lymphadenectomy, and many have also received adjuvant chemotherapy (44) (45) (46) (47) (48) (15).

Metastatic lymph nodes—pathological features with adverse effects on prognosis

In the TNM classification system, lymph node-positive patients are stratified by number of positive nodes and size of metastasis (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 (15) (39). Fleischmann et al. (7) found no difference in survival between N1 and N2 patients. In multivariate analysis they showed that extracapsular extension was the strongest negative predictor of recurrence-free survival, and Fleischmann and associates suggested that this feature should be used to define the N category in the staging system. Also Herr (8) failed to show significant differences in survival between patients in the three N stages in a retrospective study. 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 dissected. Thus, in a cohort of node-positive bladder cancer patients survival was significantly higher in subjects with a ratio of ≤ 20% than in those with a ratio > 20%. These results have been confirmed by Stein (23), who used the same concept under a different name (lymph node density) and also a 20% cut-off. Abdel-Latif and co-workers (39) identified such a relationship in a univariate analysis but not in a multivariate setting.

Morbidity caused by extended dissection

It is possible that extending lymph node dissection will lead to increased morbidity. However, Leissner (22) stratified morbidity into two categories of lymph node counts, ≤ 15 and ≥ 16, but could not detect an increase in lymphoceles 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) (17). Also, in a study of patients treated at two different hospitals and using different lymphadenectomy templates, the rates of morbidity (defined as surgical reinterventions within 30 days of cystectomy) were similar after limited and extended dissection (11% and 9%, respectively) (49). Nevertheless, long-term complications such as leg oedema might be underreported.

Other important aspects of extended lymphadenectomy are time constraints and blood loss, but it is difficult to evaluate how these factors affect the surgeon's assessment and application of the procedure. Sanderson et al. (31) believe that cystectomy after an extended lymphadenectomy is an easier and safer approach, because it identifies the pelvic vessels. Leissner et al. (21) 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 increased the operating time by 60 minutes.

Future prospects

Use of the sentinel node concept in the treatment of bladder cancer is being investigated at our centre, and our results thus far show that this technique has improved nodal staging in one out of four cases. More precisely, the improvement has been achieved by detection of micrometastases in 14% of patients (ultrastaging), and detection of sentinel node in another 10% after completion of an extended lymphadenectomy (radioguided surgery) (38). However, the clinical significance of micrometastases is still unclear.

The concept of molecular staging is also evolving (not only in regard to lymph nodes), and molecular markers for micrometastases have recently been described in peripheral blood (50)

and bone marrow (51). In a study of 19 bladder cancer patients who had undergone lymphadenectomy during radical cystectomy for bladder cancer, Seraj et al. (52) investigated the largest palpable lymph node by reverse-transcription-PCR (RT-PCR) analysis of the uroplakin II (UPII) gene and routine histology. Those researchers found that 4/16 (25%) node-negative patients had positive UPII signals, although the clinical usefulness of that finding is not apparent, because the RT-PCR method might also detect contaminating blood carrying circulating cancer cells or insignificant benign or apoptotic cells (53). RT-PCR has also been used to study expression of epithelial mucin 7 (MUC7) in lymph nodes obtained at cystectomy; MUC7 is expressed in carcinoma in situ and in invasive urothelial carcinomas, but not in normal urothelium (54). In the cited investigation, 46/160 (29%) histologically 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 literature concerning preparation and examination of lymph nodes, it seems likely that dividing the lymph node package into separate specimens can significantly increase the lymph node count (30) (31). However, the findings are contradictory as to whether an increased lymph node count is equivalent to enhanced detection of positive lymph nodes. Pathoanatomical data obtained in one study (21) suggest that extending the lymph node dissection to the aortic bifurcation can improve nodal staging. This may be beneficial in T3–

T4a tumours (24), which more often comprise lymph node metastases above the iliac bifurcation as compared to less advanced tumours.

In node-negative patients, extended lymph node dissection probably increases disease-free survival by removing undetected micrometastases. Four investigations in the literature (42) (25) (22) (41) recommended that a minimum number of 8, 10, 10-14, and 16 nodes should be excised, and a fifth study suggested aortic bifurcation as the upper limit of dissection (17).

High rates of survival (29%–39%) have been observed in series of node-positive urothelial carcinomas in which the subjects had undergone extended lymphadenectomy and a large proportion had received adjuvant chemotherapy. In addition, it has been found that some node-positive patients can be cured by surgery alone, even in cases with gross adenopathy (43). There is no evidence in the literature that extended lymphadenectomy increases the morbidity of surgery (22) (17) (49).

The TNM classification system appears to be inadequate for stratifying 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 (7) (8). Alternative methods for staging node-positive patients have been suggested, which are based on extracapsular growth (7) and lymph node positivity ratios above or below 20% (8) (23), but the usefulness of those techniques must be confirmed in prospective studies.

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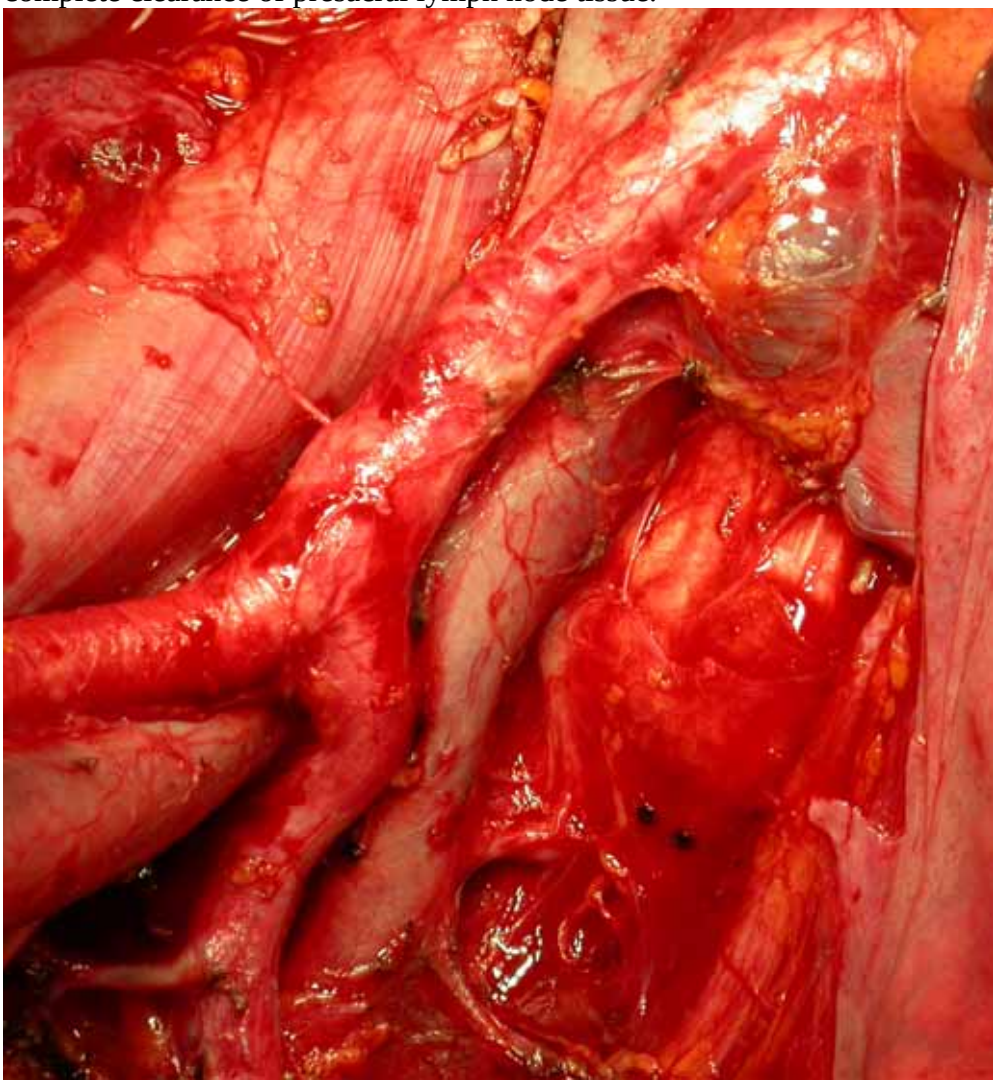
Figure 1. An extended lymphadenectomy with the upper limit at the aortic bifurcation. Note complete clearance of presacral lymph node tissue.



Year	No. of patients	Reference	5-year survival	N1	N2	Comments
1962	55	Whitmore (11)	16% d s			
1973	35	Dretler (55)	17% d s			
1976	24	Reid (56)	18% d s			Preoperative radiation
1980	26	Bredael (57)	4% d s			
1981	134	Smith (58)	7% d s			
1982	36	Skinner (59)	35% o s			
1985	57	Zincke (60)	10% o s			
1988	41	Zungri (61)	2% at 4 years			
1991		Pagano (62)	4% o s			
1991	42	Roehrborn(63)	Not reported	23%	18%	
1993	132	Lerner (42)	29% d s			Prospectively collected. Extended lymphadenectomy, 74/132 adjuvant chemotherapy
1996	40	Bretheau (64)	14% d s	22%	8%	
1997	188	Ghoneim (65)	23% o s			
1998	51	Poulsen (17)	24 vs. 7% d s			Extended vs. conventional dissection
1999	193	Vieweg (43)	31% d s			110 adjuvant chemo-therapy, 119 preop radiation, 32 surgery only
1999	78	Bassi (66)	14.5% d s			
2001	83	Mills (44)	29% d s			29/83 adjuvant chemo-therapy
2001	84	Herr (41)	24% 10 year d s			Grossly node positive patients.
2002	17	Gaitonde (67)	12% d s	13%	0%	
2003	244	Stein (45)	35% d s			52% adjuvant chemo-therapy
2003	124	Madersbacher (46)	33% d s			35% adjuvant chemo-therapy
2003	154	Frank (16)	39% d s	47%	34%	28 % adjuvant chemo-therapy
2003	24	Knap (14)	0%			Limited pelvic lymph node dissection (2/3 only unilaterally)
2004	163	Nishiyama (68)	35% d s			26 % cT1 tumours. Extent of lymph node dissection not stated
2004	110	Abdel-Latif (38)	38% 3 year d s			

Table 1: 5-year survival, overall (o s) or disease specific (d s) in small series of N+ patients without adjuvant chemotherapy and large series in which some patients received such treatment.