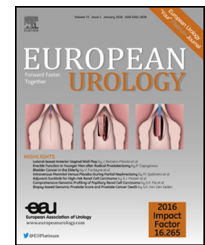


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Platinum Priority – Bladder Cancer
Editorial by XXX on pp. x–y of this issue

Extended Versus Limited Lymph Node Dissection in Bladder Cancer Patients Undergoing Radical Cystectomy: Survival Results from a Prospective, Randomized Trial

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Abstract

Background: The extent of lymph node dissection (LND) in bladder cancer (BCa) patients at the time of radical cystectomy may affect oncologic outcome.

Objective: To evaluate whether extended versus limited LND prolongs recurrence-free survival (RFS).

Design, setting, and participants: Prospective, multicenter, phase-III trial patients with locally resectable T1G3 or muscle-invasive urothelial BCa (T2–T4aM0).

Intervention: Randomization to limited (obturator, and internal and external iliac nodes) versus extended LND (in addition, deep obturator, common iliac, presacral, paracaval, interaortocaval, and para-aortal nodes up to the inferior mesenteric artery).

Outcome measurements and statistical analysis: The primary endpoint was RFS. Secondary endpoints included cancer-specific survival (CSS), overall survival (OS), and complications. The trial was designed to show 15% advantage of 5-yr RFS by extended LND.

Results and limitations: In total, 401 patients were randomized from February 2006 to August 2010 (203 limited, 198 extended). The median number of dissected nodes was 19 in the limited and 31 in the extended arm. Extended LND failed to show superiority over limited LND with regard to RFS (5-yr RFS 65% vs 59%; hazard ratio [HR] = 0.84 [95% confidence interval 0.58–1.22]; $p = 0.36$), CSS (5-yr CSS 76% vs 65%; HR = 0.70; $p = 0.10$), and OS (5-yr OS 59% vs 50%; HR = 0.78; $p = 0.12$). Clavien grade ≥ 3 lymphoceles were more frequently reported in the extended LND group within 90 d after surgery. Inclusion of T1G3 tumors may have contributed to the negative study result.

Conclusions: Extended LND failed to show a significant advantage over limited LND in RFS, CSS, and OS. A larger trial is required to determine whether extended compared with limited LND leads to a small, but clinically relevant, survival difference (ClinicalTrials.gov NCT01215071).

Patient summary: In this study, we investigated the outcome in bladder cancer patients undergoing cystectomy based on the anatomic extent of lymph node resection. We found that extended removal of lymph nodes did not reduce the rate of tumor recurrence in the expected range.

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1. Introduction

Radical cystectomy (RC) with lymph node dissection (LND) is the standard of care in patients with muscle-invasive bladder cancer (BCa). LND is crucial as a staging procedure and provides important prognostic information. Lymph node (LN) metastases are detected in 20–25% of patients at the time of RC, which is the main risk factor for poor oncologic outcome besides pathologic tumor stage [1,2]. Thus, LND triggers adjuvant cisplatin-based chemotherapy, which is indicated in patients with LN metastases or locally advanced BCa [3,4].

Although the diagnostic role of LND at the time of RC in BCa patients is generally accepted, the therapeutic value of LND is under ongoing debate. In the early 20th century, Colston and Leadbetter [3] were the first to challenge the initial belief that advanced BCa with LN metastases was a uniformly fatal disease, which is not curable by surgery. They performed an autopsy study on 98 cases of BCa in 1936 and identified 25% with metastatic disease limited to the pelvic LNs. As a conclusion, they postulated that surgical resection could cure early metastatic BCa. In 1982, Skinner [4] was the first who demonstrated long-term survival in LN-positive patients undergoing RC with concomitant LND. Contemporary cystectomy series report a 10-yr recurrence-free survival (RFS) rate of 15–35% in node-positive patients after RC and LND without systemic treatment [1,2].

To date, controversy exists with regard to the optimal anatomic extent of LND and the corresponding therapeutic benefit in BCa patients undergoing RC. From a diagnostic point of view, it seems sufficient to perform a limited LND including the obturator, and external and internal iliac region. Mapping studies have revealed that it is uncommon to find metastatic LNs above the common iliac bifurcation if the limited LND field is free of tumor [5–8]. However, the lymphatic landing sites of early metastatic BCa have been described up to the level of the inferior mesenteric artery (IMA) [6,7,9]. Up to now, consensus has not been achieved regarding whether extension of LND outside the limited field improves oncologic outcome [10–12]. The discussion arises from a lack of prospective randomized studies. As a consequence, we undertook a prospective, randomized, multicenter phase-III trial with the aim of assessing whether an extended LND up to the level of IMA improves RFS compared with a limited LND in patients with urothelial BCa undergoing RC.

2. Patients and methods

2.1. Study design

The Association for Urologic Oncology (AUO) of the German Cancer Society conducted this prospective, randomized phase-III study at 16 centers in Germany to investigate the therapeutic efficacy of a limited versus an extended LND at the time of RC (LEA AUO AB 25/02). Eligibility of participating sites included sufficient surgical experience of >30 RCs per surgeon and >15 RCs per site per year. The review boards of all participating institutions approved the study, which was conducted according to the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization.

2.2. Patients

Inclusion criteria were locally resectable, histologically confirmed T1G3 or muscle-invasive urothelial BCa (T2–T4a). Patients were excluded if they had radiologic evidence of a T4b tumor with infiltration of the pelvis or other organ systems, enlarged LNs (>1 cm) above the aortic bifurcation, and bone or visceral metastases. Additional exclusion criteria were neoadjuvant chemotherapy for BCa, a history of pelvic radiotherapy or pelvic LND, or coexisting malignant disease. It was mandatory to assess local tumor extension and exclude distant metastatic disease by preoperative staging with computed tomography. All patients provided written informed consent to participate in the study.

2.3. Randomization and treatment

Patients were randomly assigned in a 1:1 ratio to receive either a limited or an extended LND at the time of RC. Block-wise randomization was used with a block size of 8. Further details of the randomization process are described in the Supplementary material.

LND was performed according to a template that defined six fields (bilateral obturator, and internal and external iliac nodes) in the limited LND arm and 14 fields (in addition, bilateral deep obturator fossa and common iliac nodes as well as presacral, paracaval, interaortocaval, and para-aortal nodes up to the inferior mesenteric artery) in the extended LND arm (Fig. 1). Each field was submitted separately for histopathologic examination. In the limited LND group, removal of at least four out of six

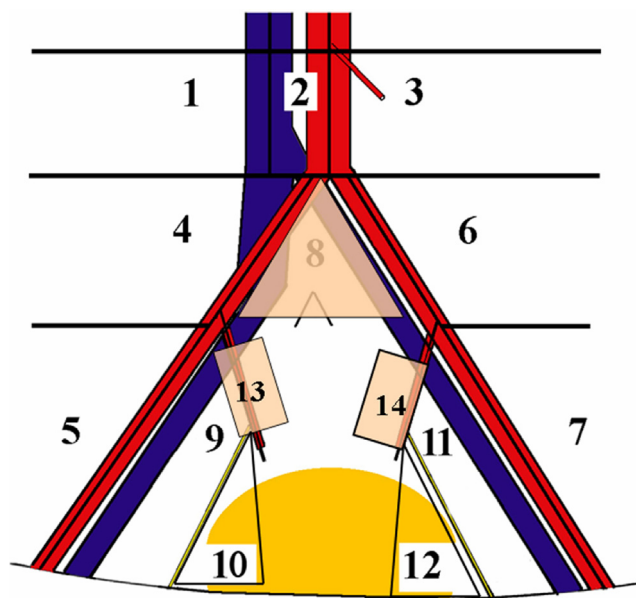


Fig. 1 – Anatomic template for lymph node dissection. Limited lymph node dissection (LND) included obturator (9, 11), and internal (13, 14) and external iliac (5, 7) nodes. The limited field was defined proximally by the bifurcation of internal and external iliac artery, distally by the pelvic floor, laterally by the genitofemoral nerve, and dorsally by the obturator nerve. Extended LND additionally included deep obturator (10, 12), presacral (8), common iliac (4, 6), paracaval (1), interaortocaval (2), and para-aortal (3) nodes up to inferior mesenteric artery. The extended field was defined proximally by the inferior mesenteric artery, distally by the pelvic floor, laterally by the genitofemoral nerve, and dorsally by pelvis and rectum. **Note.** Nomenclature for LND templates was adopted from the original study protocol. Meanwhile, the nomenclature has undergone several changes in international guidelines in order to homogenize different template definitions used in the literature. The definition of a limited LND in this study currently is referred to as standard LND, and the definition of an extended LND in this study currently is referred to as extended or superextended LND [10–12].

LND fields as well as resection of four or more LNs was demanded. In the extended LND group, removal of at least 10 out of 14 LND fields and resection of 12 or more LNs were mandatory.

2.4. Adjuvant treatment and follow-up

Postoperative adjuvant chemotherapy was optional and given at the discretion of the treating physician in patients with histologically confirmed locally advanced disease (pT3/4) or regional LN metastases (pN+) best within 12 wk after surgery. The advised adjuvant treatment regimen included chemotherapy with gemcitabine and cisplatin every 3 wk (gemcitabine 1200 mg/m² on days 1 and 8, and cisplatin 70 mg/m² on day 2) or every 4 wk (gemcitabine 1000 mg/m² on days 1, 8, and 15, and cisplatin 70 mg/m² on day 2) for four courses.

Follow-up examinations including computed tomography were performed every 3 mo in the 1st year and then every 6 mo up to 5 yr postoperatively.

2.5. Outcomes

The primary endpoint was RFS defined as the time from RC to tumor recurrence or death from bladder cancer. The prespecified secondary endpoints included cancer-specific survival (CSS), overall survival (OS), complication rate, influence of adjuvant chemotherapy, influence on histopathologic N stage, and localization of tumor recurrence (local recurrence within the pelvis vs metastatic recurrence outside of the pelvis). Clavien-Dindo grades were used to classify 30- and 90-d complication rates [13].

2.6. Statistical analysis

The sample size was estimated based on a retrospective analysis [14], assuming a 5-yr RFS rate of 65% for the extended LND group and 50% for the limited LND group. The planned sample size of 400 patients

(200 patients in each group) was calculated according to the method described by Dupont and Plummer [15] and provided 80% power, with a two-sided significance level (alpha) of 0.05 and a dropout rate of 5%.

Time-to-event variables and associated 95% confidence intervals (CIs) were calculated with the use of the Kaplan-Meier method. The log-rank test was used as the primary analysis for comparison of treatment groups. Analyses were performed by intention to treat in all randomly assigned patients. Additional per-protocol analyses are provided in the Supplementary material. There were no stratification factors.

Reporting of results was performed under consideration of the CONSORT guidelines for randomized trials.

Data analysis was performed using SPSS (version 24.0). The trial registration number at ClinicalTrials.gov is NCT01215071.

3. Results

3.1. Patients and treatment

Patients were enrolled from February 2006 to August 2010. Overall, 401 patients met the eligibility criteria and were randomly assigned to receive a limited LND (203 patients) or an extended LND (198 patients; Fig. 2). LND was performed according to study protocol in 190 of 203 (94%) patients in the limited LND group and 173 of 198 (87%) patients in the extended LND group.

Information on baseline patient characteristics, final histopathology, and application of adjuvant chemotherapy is provided in Table 1 (information on the per-protocol cohort is presented in Supplementary Table 1). Final histopathology showed locally confined disease (\leq pT2 pN0) in 196 (49%) and LN metastases (pN+) in 100 (25%) patients. The median number of dissected LNs was 19 in the limited and 31 in the extended LND group ($p < 0.001$). Adjuvant chemotherapy

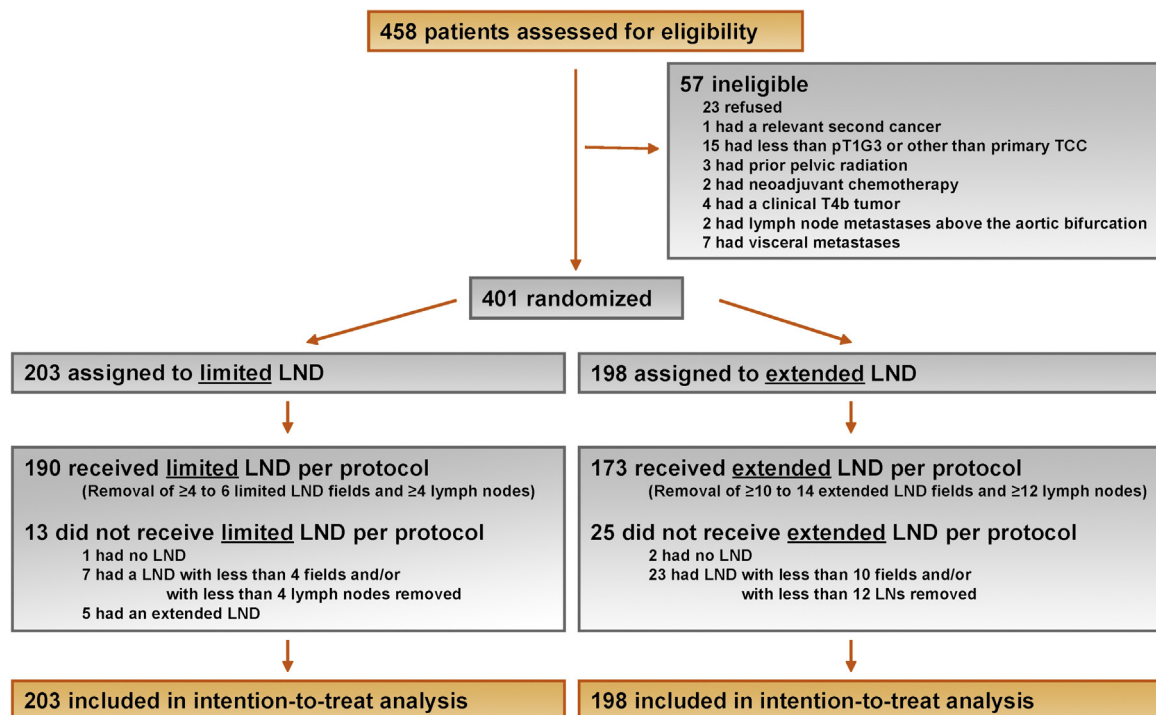


Fig. 2 – Study flow chart. LND was not performed in one patient of the limited group due to intraoperative cardiopulmonary decompensation and in two patients of the extended group—due to intraoperative diagnosis of peritoneal carcinomatosis in one patient and due to severe adhesions from prior surgery with an extra-anatomic crossover bypass in the second patient. LND = lymph node dissection; TCC = transitional cell carcinoma.

Table 1 – Baseline patient characteristics, final histopathology, and adjuvant chemotherapy

Characteristic	Limited LND (n = 203)	Extended LND (n = 198)
Gender, number of patients (%)		
Male	163 (80)	151 (76)
Age (yr)		
Median	68	67
Interquartile range	61–73	59–74
Removed lymph nodes, number		
Median	19	31
Interquartile range	12–26	22–47
pN status, number of patients (%)		
pNx	0	2 (1.0)
pN0	147 (72)	152 (77)
pN+	56 (28)	44 (22)
pN1	15 (7.4)	14 (7.1)
pN2	41 (20)	29 (15)
pN3	0	1 (0.5)
pT status, number of patients (%)		
pT1	24 (12)	31 (16)
pT2	81 (40)	88 (44)
pT3	68 (34)	63 (32)
pT4	30 (15)	16 (8.1)
R status, number of patients (%)		
R0	181 (89)	179 (90)
R+	18 (8.9)	17 (8.6)
Rx	4 (2.0)	2 (1.0)
Adjuvant chemotherapy, number of patients (%)	30 (15)	28 (14)
LND = lymph node dissection.		

was administered in 30 (15%) patients of the limited and 28 (14%) patients of the extended LND group.

3.2. Clinical outcome

Median follow-up of patients being alive without disease recurrence was 43.0 mo. At the time of analysis, tumor recurrence was observed in 115 (29%) patients (63 [31%] in the limited vs 52 [26%] in the extended LND group). Detailed information on the localization of tumor recurrence is provided in Supplementary Table 2. A total of 158 (39%) patients deceased (89 [44%] in the limited vs 69 [35%] in the extended LND group), including 87 (22%) patients who died of BCa (51 [25%] in the limited vs 36 [18%] in the extended LND group).

Extended LND failed to meet the primary endpoint RFS. The 5-yr RFS estimate showed an advantage in the extended LND group reaching 64.6% compared with 59.2% in the limited LND group, but this difference (5.45% [95% CI–6.43% to 17.33%]) did not reach statistical significance (hazard ratio 0.84 [95% CI 0.58–1.22]; $p = 0.36$). Median RFS was not reached in both study arms (Fig. 3A).

The secondary endpoints CSS and OS also showed a reduced risk in the extended LND group but did not meet conventional levels of significance. The 5-yr CSS rate was 64.5% in the limited compared with 75.9% in the extended LND group (hazard ratio 0.70 [95% CI 0.46–1.07]; $p = 0.10$). Median CSS was not reached in both study arms (Fig. 3B). The 5-yr OS rate was 49.7% in the limited compared with 58.9% in the extended LND group (hazard ratio 0.78 [95% CI

0.57–1.07]; $p = 0.12$). Median OS was 52.2 mo in the limited and 70.6 mo in the extended arm (Fig. 3C).

The per-protocol analysis did not reveal further significances (Supplementary Fig. 1A–C).

3.3. Complication rates

Overall, 30- and 90-d mortality rates in the intention-to-treat population were 2.2% ($n = 9$) and 3.7% ($n = 15$), respectively, and were not related to LND (Table 2). Mortality (Clavien grade 5) and overall major complications (Clavien grade ≥ 3) after 30 and 90 d did not differ between the limited and extended LND groups. Solely, lymphoceles requiring intervention within 90 d postoperatively were more frequent in the extended compared with the limited LND group (3.4% [$n = 7$] in the limited vs 8.6% [$n = 17$] in the extended LND group; $p = 0.04$). These results were similar in the per-protocol analysis (Supplementary Table 3). Detailed information on complications classified by organ system and Clavien grade in both study arms is reported in Supplementary Tables 4 and 5.

3.4. Adjuvant chemotherapy

Application of adjuvant chemotherapy in 58 of 205 (28%) patients with pT3/4 and/or pN+ BCa improved RFS significantly (hazard ratio 0.56 [95% CI 0.38–0.83]; $p = 0.004$). Median RFS was 11.5 mo without versus 35.4 mo with adjuvant chemotherapy (Fig. 4). Similar results were present in the per-protocol analysis (Supplementary Fig. 2).

3.5. Histopathologic N stage

Of 198 patients in the extended LND group, 17 (8.6%) had LN metastases in the limited as well as in the extended LND field and four (2.0%) had LN metastases exclusively in the extended outside of the limited LND field. Thus, a limited LND would have left behind LN metastases in 21 (11%) patients, including four (2.0%) patients who would have falsely been classified to have pN0 (Supplementary Fig. 3).

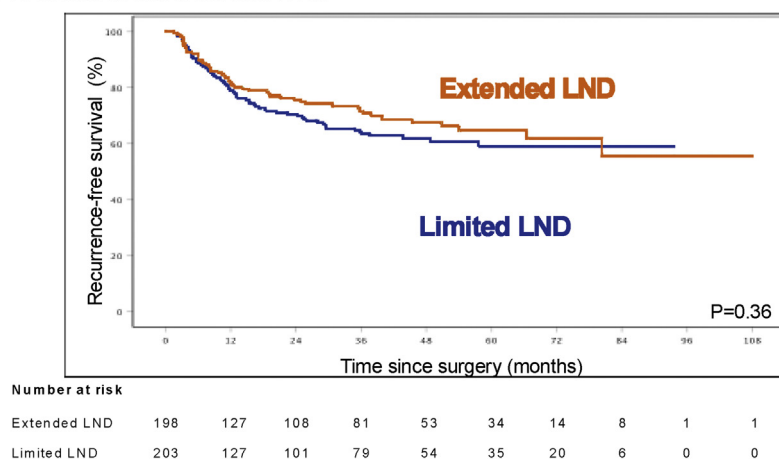
4. Discussion

This is the first randomized surgical phase-III trial investigating the therapeutic role of an extended versus a limited LND in urothelial BCa patients undergoing RC. In this trial, extended LND failed to show a statistically significant advantage over limited LND in the primary endpoint RFS and the secondary endpoints CSS and OS.

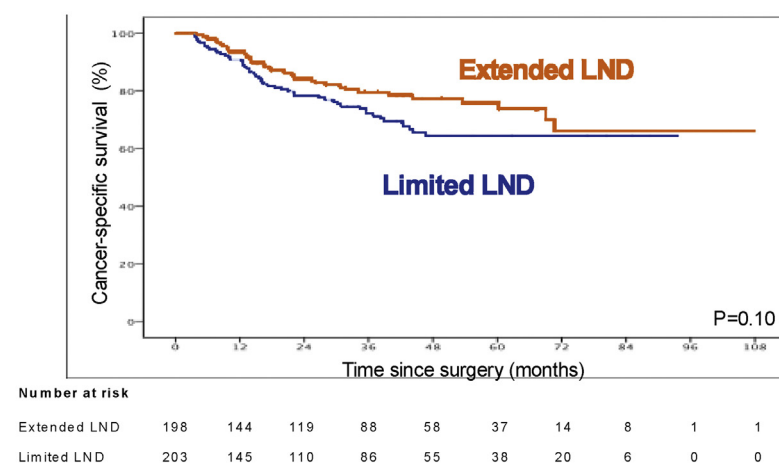
Our study was designed to show an absolute improvement of 15% in 5-yr RFS by extended LND based on retrospective data [14]. However, the observed difference between the limited and extended LND groups was smaller than expected, and the predefined primary endpoint RFS and the secondary endpoints CSS and OS were not met.

The study results may have been affected by the high number of resected LNs in both groups, with a median of 19 LNs in the limited and 31 LNs in the extended LND arm. The

A Recurrence-free survival



B Cancer-specific survival



C Overall survival

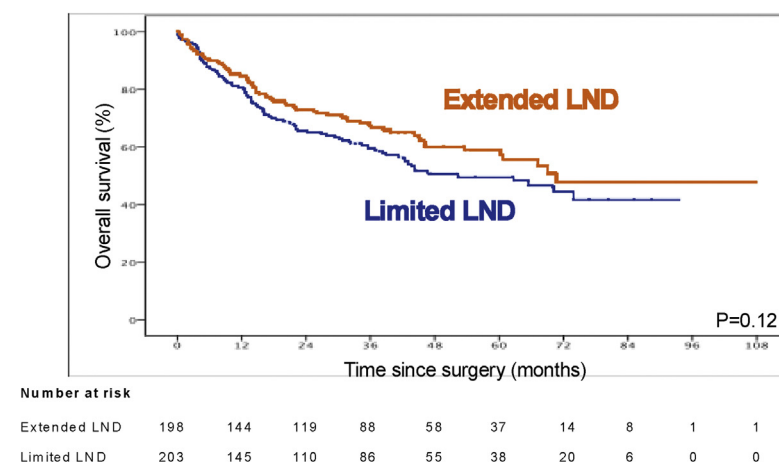


Fig. 3 – Kaplan-Meier estimates of (A) recurrence-free, (B) cancer-specific, and (C) overall survival in the intention-to-treat cohort. LND = lymph node dissection.

Table 2 – Complications following radical cystectomy and limited or extended pelvic lymph node dissection

Complications	Limited LND (n = 203)	Extended LND (n = 198)	p value
30 d, number patients (%)			
Lymphocele requiring drainage (Clavien ≥ 3)	7 (3.4)	15 (7.6)	0.08
Major complication (Clavien ≥ 3)	52 (26)	53 (27)	0.8
Mortality (Clavien 5) ^a	5 (2.5)	4 (2.0)	1
90 d, number patients (%)			
Lymphocele requiring drainage (Clavien ≥ 3)	7 (3.4)	17 (8.6)	0.04
Major complication (Clavien ≥ 3)	53 (26)	58 (29)	0.5
Mortality (Clavien 5) ^b	7 (3.4)	8 (4.0)	0.8

LND = lymph node dissection.

^a Reasons for postoperative mortality within 30 d in the limited group were cardiopulmonary in four patients and sepsis in one patient, and in the extended group the reasons were cardiopulmonary in two patients, rectal perforation in one patient, as well as anastomotic bowel leak in one patient.

^b Reasons for postoperative mortality between 31 and 90 d in the limited group were cardiopulmonary in one patient and sepsis following colon perforation in one patient; in the extended group, reasons for mortality were cardiopulmonary in one patient, acute spleen bleeding following anastomotic bowel leak in one patient, secondary malignancy unknown prior to randomization in one patient, and complications following fascial dehiscence in one patient.

LN count at LND has been identified as a strong prognostic factor in BCa patients undergoing RC. Statistical considerations in our study were based on a retrospective study by Leissner et al. [14], which showed that a more extensive LND with the removal of ≥ 16 LNs was associated with longer RFS compared with the removal of <16 LNs. Several studies have confirmed the prognostic impact of LN count, whereas the recommended number of dissected LNs varied between 9 and 16 [14,16–19]. In favor of the surgical performance of the participating centers in our study, LN counts in both study groups exceeded these thresholds by far. This may have contributed to a smaller difference in RFS than expected between both study arms. Notably, the LN count may vary depending on a number of factors, including interindividual variability as well as pathologic diligence. Therefore, the LN count is less important than the anatomical LND template, provided that the dissection is meticulous.

In addition, inclusion of patients with T1G3 disease may have contributed to the negative result since the node-positive rate in these patients is low.

Although the primary and secondary endpoints did not meet conventional levels of statistical significance, the longer RFS, CSS, and OS support an accumulating evidence

of a potential therapeutic benefit from a thorough extended LND. A recent systematic review summarized the results of 22 retrospective and one prospective, nonrandomized study including a total of $>19\,000$ BCa patients treated with RC [20]. It was concluded that any kind of LND was advantageous over no LND and that a more extended LND including at least the common iliac region might be superior to lesser degrees of dissection, although extending the dissection beyond the aortic bifurcation was unlikely to yield any further benefit [20]. Limited by an evidence mainly based on retrospective studies, the authors stated that the underlying data were of poor quality with significant risks of bias and confounding. In the only prospective, nonrandomized study, Abol-Enein et al. [21] compared limited with extended LND in 400 BCa patients undergoing RC. The anatomic boundaries of LND fields were the same as that in our trial. The authors reported a significant absolute improvement of 11.9% (from 54.7% to 66.6%) in 5-yr disease-free survival in the extended LND group ($p = 0.04$). However, direct comparison with our study is intricate because Abol-Enein et al. [21] included nonurothelial BCa in approximately half of the patients. Moreover, there is a risk of selection bias without

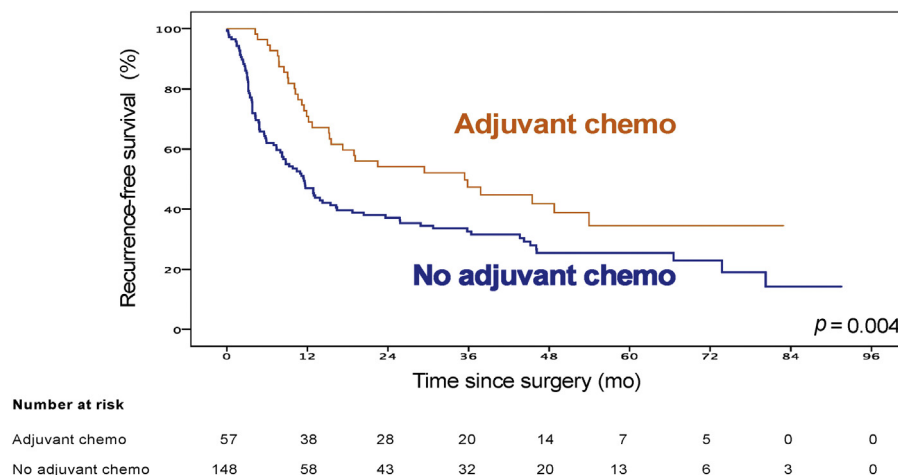


Fig. 4 – Impact of adjuvant chemotherapy on recurrence-free survival in patients with locally advanced (pT3/4) and/or node-positive (pN+) bladder cancer.

randomization in their trial. The Southwest Oncology Group (SWOG) initiated another prospective, randomized phase-III trial evaluating limited versus extended LND in BCa patients treated with RC, which has recently completed study accrual but is still ongoing (SWOG S1011; ClinicalTrials.gov number, NCT01224665). The SWOG study results may further elucidate the therapeutic role of extended LND.

With regard to morbidity, the rate of lymphoceles requiring intervention within 90 d after surgery was higher in the extended (8.6%) compared with that in the limited LND group (3.4%; $p = 0.04$). However, the major complication rates (Clavien grade ≥ 3) after 30 and 90 d did not differ between the limited and extended LND groups. Thus, extended LND did not lead to relevant added morbidity.

As a limitation of this study, neoadjuvant chemotherapy was excluded and application of adjuvant chemotherapy was only optional. Neoadjuvant chemotherapy was no standard of care in Germany at the time the trial was designed and started. Therefore, we excluded neoadjuvant chemotherapy in this study to avoid imbalances. Adjuvant chemotherapy was optional in patients with pT3/4 or pN+ BCa, and was equally applied in both study arms. However, the overall application rate was rather low, and only 28% of patients with locally advanced or node-positive BCa received adjuvant chemotherapy. This might be attributable to a lack of evidence in support of adjuvant chemotherapy at the time this study was performed. In 2005, a meta-analysis evaluating adjuvant chemotherapy was conducted but had limited power to fully support its use [22]. In 2014 and 2015, two new meta-analyses updated the available literature of randomized, controlled trials, and demonstrated a significant 34% reduction in the risk of tumor recurrence and a significant 23% reduction in mortality by application of adjuvant chemotherapy [4,23].

The benefit of adjuvant chemotherapy was also reflected in our cohort. However, our trial was not designed to determine efficacy of adjuvant chemotherapy, and as this result is based on a nonrandomized comparison, there is a potential risk of selection bias in the observed effect size.

With approximately one-fourth of patients being node positive, our data underline the diagnostic role of a proper LND in general as a trigger of adjuvant treatment. An extended LND had the advantage of additionally detecting LN metastases in 11% of patients, including 2% of patients who would have falsely been classified to have pN0 by limited LND. In support of our findings and the diagnostic importance of an extended LND, Roth et al. [24] demonstrated in a radio-guided LN mapping study that 8% of the primary lymphatic landing sites of the bladder were located above the ureteroiliac junction.

5. Conclusions

This trial assessing the therapeutic benefit of extended versus limited LND at the time of RC for urothelial BCa failed to show a significant improvement in the primary endpoint RFS and the secondary endpoints CSS and OS. There were survival differences between groups, but these did not reach

conventional levels of statistical significance. A larger trial would be required to determine whether extended compared with limited LND leads to a small, but clinically relevant, survival difference.

Author contributions: Juergen E. Gschwend 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: Gschwend, Leißner.

Acquisition of data: Gschwend, Rübben, Albers, Wolff, Frohneberg, de Geeter, Heidenreich, Kälble, Stöckle, Schnöller, Stenzl, Müller, Truss, Roth, Liehr, Leißner, Retz.

Analysis and interpretation of data: Gschwend, Heck, Lehmann, Bregenzer.

Drafting of the manuscript: Heck, Gschwend, Retz, Lehmann.

Critical revision of the manuscript for important intellectual content: Rübben, Albers, Wolff, Frohneberg, de Geeter, Heidenreich, Kälble, Stöckle, Schnöller, Stenzl, Müller, Truss, Roth, Liehr, Leißner.

Statistical analysis: Lehmann, Bregenzer.

Obtaining funding: Gschwend.

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Supervision: Gschwend.

Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.eururo.2018.09.047>.

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