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The impact of the extent of lymphadenectomy on oncological outcomes in patients undergoing radical cystectomy for bladder cancer:

A systematic review

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ABSTRACT

Context:

Controversy exists regarding the therapeutic value of lymphadenectomy (LND) in patients undergoing radical cystectomy (RC) for muscle-invasive bladder cancer (MIBC).

Objective:

To systematically review relevant literature assessing the impact of LND on oncological and peri-operative outcomes in patients undergoing RC for MIBC.

Evidence acquisition:

MEDLINE, MEDLINE-in-Process, Embase, the Cochrane Central Register of Controlled Trials and LILACS were searched up to December 2013. Comparative studies reporting on no, limited, standard, extended, and super-extended LND, and oncological and peri-operative outcomes were included. Risk of bias and confounding assessments were performed.

Evidence synthesis:

23 studies reporting on 19,793 patients were included. All but one study were retrospective. Planned meta-analyses were not possible due to study heterogeneity therefore data were synthesized narratively. There were high risks of bias and confounding across most studies, and extreme heterogeneity in the definition of the anatomic boundaries of LND templates. All seven studies comparing LND with no LND favored LND in terms of better oncological outcomes. Seven of 14 studies comparing (super-)extended with limited or standard LND reported a beneficial outcome for (super-)extended LND in at least a subset of patients. No difference in outcome was reported in two studies comparing extended and super-extended LND. The comparative harms of different extents of LND remain unclear.

Conclusions:

Although the quality of the data was poor, the available evidence indicates that any kind of LND is advantageous over no LND. Similarly, extended LND appears to be superior to lesser degrees of dissection, while super-extended LND offered no additional

benefits. Data from ongoing randomised clinical trials will hopefully clarify remaining uncertainties.

Patient summary:

The current literature suggests that removal of lymph nodes in bladder cancer surgery is beneficial and might result in better outcomes in terms of prolonging survival. However, the quality of the available studies is poor and high quality studies are needed.

1. INTRODUCTION

Lymphadenectomy (LND) combined with radical cystectomy (RC) is considered the standard of care for patients with muscle-invasive bladder cancer (MIBC). Up to 25% of patients harbour lymph node (LN) metastases at the time of RC and the staging role of LND is unequivocal. In 1982, Skinner [1] was the first to report long term survival in LN positive patients undergoing RC and LND without systemic treatment. The therapeutic value of LND, however, remains a topic of continuous debate. Whilst the results of two ongoing randomised clinical trials (RCTs) evaluating the impact of different LND templates on survival are awaited, the current evidence base remains uncertain with regard to the true benefits and harms of LND. In this study we systematically reviewed the available literature to evaluate the impact of the extent of LND on survival and peri-operative outcomes in patients undergoing RC for MIBC.

2. EVIDENCE ACQUISITION

2.1 Search strategy

The review was performed in accordance with the PRISMA statement and principles outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. [2,3] Highly sensitive electronic searches were conducted to identify all reports of RCTs or non-randomised comparative studies (NRCS) assessing LND in patients undergoing RC for MIBC. The searches were not limited by language or publication date. The databases searched were MEDLINE (1946 to December 2013), MEDLINE In-Process (December 20th 2013), Embase (1974 to December 2013), Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 8, 2013) and Latin American and Caribbean Center on Health Sciences Information (LILACS; December 2013). The database search was complemented by additional sources, including the reference lists of included studies which were hand searched, and additional reports identified by an expert panel (European Association of Urology (EAU) Working Group on MIBC). Ongoing trials were identified on clinicaltrials.gov. The full search strategy is presented in Appendix 1.

Two reviewers independently screened titles and abstracts of all citations identified by the search strategies. Full text copies of all potentially relevant reports were obtained and independently assessed by the reviewers to determine whether they met the pre-defined inclusion criteria. Any disagreements were resolved by consensus or arbitration by a third person. A data extraction form was developed specifically for the purpose of

this assessment to collect information on study design, characteristics of participants, characteristics of interventions, and outcome measures.

2.2 Inclusion and exclusion criteria

The inclusion criterion was comparative studies only, and these included RCTs, prospective NRCS, prospective observational studies with a comparator arm, and retrospective comparative studies. Registry or database studies were also eligible, if the analysis was clearly structured as a comparison between control and intervention groups. Studies with no comparator group (e.g. single-arm case series), non-effectiveness studies (e.g. nomogram studies), reviews, or studies with fewer than 10 patients in each arm, were excluded. The study population was limited to patients with localized muscle-invasive urothelial or squamous cell carcinoma of the bladder (cT2-4 N0M0). Studies including predominantly patients with variant histology other than squamous cell carcinoma were excluded because of its low incidence and the potentially different biological behavior of these cancers. Clinical staging was preferred, but if this was not reported, staging based on RC specimen was accepted. Studies with mixed populations (e.g. cTa, cTis, cT1) were retained for consideration for inclusion if there were no studies which included patients with MIBC exclusively. Studies including patients who underwent neo-adjuvant or adjuvant treatment were also retained. The types of interventions included LND undertaken during RC for bladder cancer. Due to the expected heterogeneity in defining the extent of LND across studies, the extent of LND was determined *a priori* based on discussion in an expert panel (EAU Working Group on MIBC) and were categorised as follows: (a) limited LND (or L-LND): LND confined to the obturator and/or peri-vesical fossa only; (b) standard LND (or S-LND): LND performed up to the common iliac arteries; (c) extended LND (or E-LND): LND performed up to the proximal boundary of the crossing of the common iliac vessels with the ureters or the aortic bifurcation, with or without the pre-sacral lymph nodes; and (d) super-extended LND (or SE-LND): LND performed up to the proximal boundary of the inferior mesenteric artery. The primary outcome was overall survival (OS); secondary outcomes included recurrence-free survival (RFS), disease-free survival (DFS), progression-free survival (PFS), cancer-specific survival (CSS) and peri-operative outcomes (e.g. operative time, blood loss, lymphocele).

2.3 Assessment of risks of bias

Two reviewers independently assessed the risk of bias (RoB) of individual studies. Any disagreement was resolved by discussion or reference to a third reviewer. The standard Cochrane Collaboration RoB tool [4] was used to assess the RoB in RCTs, whilst for NRCS, the RoB tool recommended by the Cochrane Non-Randomised Studies Methods Group was used. [5,6] In addition, for NRCS, the main confounders were identified *a priori* based on a study by Palmer et al. [7] In this study, a survey among bladder cancer experts was performed to identify and rank potential confounding variables and defining thresholds for imbalance for these variables. The main confounders identified are summarized in Table 1. Each confounder was assessed according to whether it had been considered by the authors, whether the confounder was balanced across the groups, and the degree to which adjustment had been made for the confounder. [7] The risk of confounding bias was considered to be high if the confounder was not described/considered, imbalanced between the groups or was not adjusted for in the statistical analysis. Review Manager 5.2 was used to present these results (Table 1). [8]

2.4 Data analysis

A narrative synthesis was performed. [9] Descriptive statistics were used to summarize baseline characteristics data. For continuous outcomes, data were summarized using mean (+/- standard deviation if available) and median (+/- interquartile range if available); for categorical outcomes, data were summarized using proportions. For summarizing outcome data, categorical outcomes were presented as proportions at 5 and 10 year time points following surgery based on crude point estimates as reported by authors, with level of significance set at 5%. Outcomes at other time points were narratively described. For time-to-event data reported by authors using univariable or multivariable Cox regression analysis, data were summarized as hazard ratios (HRs) and 95% confidence intervals (CIs).

3. EVIDENCE SYNTHESIS

3.1 Quantity of evidence identified and characteristics of included studies

One thousand eight hundred and ninety-seven abstracts were identified by the search (Figure 1). Of these, 38 were selected for full text screening. One additional study was identified through reference searching. After full text screening, a total of 23 studies met the inclusion criteria. [10-32] Seven studies were reported only in the form of

conference meeting abstracts, while 16 studies were reported in full-text papers. With one exception, all studies were retrospective comparative studies. Sixteen studies were single-centre studies, of which eight studies used a historical cohort as control group, and seven studies were multicentre studies.

3.2 Risk of bias and confounding assessment of included studies

Risk of bias (RoB) and confounding assessment for each of the individual studies were performed and the results are presented in Table 1. Due to the retrospective design in 22 of 23 studies, there was high or unclear RoB across all domains. The issue of confounding was also poorly addressed by the majority of studies, as it was unclear in most studies if any of the confounding factors had been considered, either prospectively, or retrospectively through statistical adjustment.

3.3 Results of comparisons of interventions

3.3.1 No LND vs LND

3.3.1.1 Baseline characteristics

A total of seven studies comparing LND with no LND were identified, including a total of 13,833 patients (Table 2a). [10-16] The intervention differed between the studies and included any LND [10,14,15], L-LND [13], S-LND [11,12,16], E-LND [16] or SE-LND [16].

3.3.1.2 Oncological outcomes

Table 2b summarizes the oncological outcomes comparing no LND vs any LND. All studies reported a benefit for LND in at least one oncological outcome. Liu et al. [10] did not report any numerical data but stated that LND was associated with improved OS and DFS in pT1 patients only compared with no LND.

3.3.1.3 Peri-operative outcomes

No studies reported on these outcomes.

3.3.2 Limited LND vs standard LND

No studies were identified for this comparison.

3.3.3 Limited LND vs (super-)extended LND

3.3.3.1 Baseline characteristics

Five studies addressed this question involving a total of 1,394 patients (Table 3a). [17-21] Brossner et al. [21] focused on peri-operative outcomes. Bostrom et al. [19] compared L-LND with E-LND, however, an unknown number of patients in the E-LND group underwent SE-LND and over 50% of patients in the L-LND group did not undergo LND at all.

3.3.3.2 Oncological outcomes

Table 3b summarizes the oncological outcomes comparing L-LND with E/SE-LND. Of the five studies inluded, three studies reported improvement of at least one oncological outcome for E/SE-LND. [18-20] Brossner et al. [21] did not report oncological outcomes, while Hori et al. [17] found no statistically significant difference in oncological outcomes for L-LND and E-LND performing univariable analysis.

3.3.3.3 Peri-operative outcomes

Jensen et al. [20] reported no prolonged operative time for E-LND compared with L-LND (mean 306 vs 302 minutes, $p = 0.92$). Brossner et al. [21], however, reported prolonged operative time for SE-LND compared with L-LND (median 330 vs 277 minutes, $p < 0.01$). No differences in number of blood units transfused (1.15 vs 0.38 respectively, $p = 0.37$), lymphoceles (none in both groups), 30-day complication rate (11% vs 9% respectively, $p=0.28$), and 30-day mortality (3 vs 1 event respectively, $p = 0.57$) were reported in this study. [21]

3.3.4 Standard LND vs (super-)extended LND

3.3.4.1 Baseline characteristics

Nine studies were identified involving 3,104 patients (Table 4a). [22-30] Four studies used data from the Cleveland Clinic. [22, 23, 25,28] Abd El Latif [23] differed from their previous study [22] by extending the study period by 2 years (2004-2010 vs 2006-2010). One study specifically looked at the outcomes of laparoscopic LND. [25]

3.3.4.2 Oncological outcomes

Table 4b summarizes the oncological outcomes comparing S-LND with E/SE-LND and contradicting results were reported. Four studies noted no difference in oncological

outcomes between S-LND and E-LND [22-24,30], although only one study on data from multivariable analysis. [22] Three studies reported a benefit for E-LND and one study reported a benefit for SE-LND for at least one oncological outcome. Subgroup analysis in these studies revealed no consistent subgroup that benefited most from E-LND. For example, Poulsen et al. [26] reported a RFS benefit for E-LND in patients with organ-confined disease, while Dhar et al. [28] only found a RFS benefit for patients with >pT2 disease.

3.3.4.3 Peri-operative outcomes

Poulsen et al. [26] reported a lymphocele rate of 1.6% for E-LND and 1.5% for S-LND. One patient (0.8%) in the E-LND group died peri-operatively from complications unrelated to LND. Finelli et al. [25], performing laparoscopic LND, reported an estimated increase in operative time from 30-45 minutes for S-LND to 90 minutes for E-LND (no p-value reported).

3.3.5 Extended LND vs super-extended LND

3.3.5.1 Baseline characteristics

Two multi-institutional studies, involving 1,462 patients were included. (Table 5a) [31,32]

3.3.5.2 Oncological outcomes

Table 5b summarizes the oncological outcomes comparing E-LND with SE-LND. Both studies reported no statistically significant difference in survival outcomes between E-LND and SE-LND, irrespective of tumor stage or nodal status.

3.3.5.3 Peri-operative outcomes

No studies reporting on these outcomes were identified.

3.4 Discussion

3.4.1 Principal findings

To the best of our knowledge, this study represents the most robust literature review focusing on the impact of the anatomical extent of LND on post-RC oncological and peri-operative outcomes. The findings of this study suggest that any extent of LND is better than no LND for patients undergoing RC for MIBC, in terms of oncological

outcomes. Additionally, E-LND might improve oncological outcomes compared with lesser degrees of dissection, although extending the dissection beyond E-LND is unlikely to yield any further benefits. With respect to peri-operative outcomes, a secondary outcome of this study, SE-LND resulted in increased operative time compared with less extended LND templates, but does not appear to substantially increase post-operative morbidity.

3.4.2 Clinical implications of our study findings

The data in this study support the routine performance of LND in patients undergoing RC. Whether the reported beneficial oncological outcomes are a result of stage migration (the so-called Will-Rogers Phenomenon), a true therapeutic benefit of LND, or a combination of both, remains uncertain. There is, however, a clear staging role of LND as supported by LN mapping studies [33, 34]. Thus, in spite of the lack of RCTs, the current evidence base is sufficiently convincing to recommend LND for patients undergoing RC for MIBC. While limited LND may contribute to disease staging, performing LND outside the true pelvis (i.e. ≥S-LND) should be considered a potential therapeutic intervention as skip nodal lesions are rare, therefore unlikely contributing to disease staging [33,34]. To date, however, questions remain about the potential therapeutic value of LND and what extent of LND is the most efficacious. Based on the current data, consisting of retrospective studies with a significant risk of bias and confounding, the evidence base is not strong enough to provide firm recommendations regarding the most optimal extent of LND. Conversely, these studies are currently the best available evidence and fairly consistently report an oncological benefit for E-LND compared with less extended LND templates. In addition, E-LND appears not to increase peri-operative morbidity. Collectively, there is accumulating evidence that E-LND may be beneficial for patients undergoing RC for MIBC and is therefore recommended in patients undergoing RC for MIBC.

3.4.3 How does this systematic review compare with other recent reviews?

To our knowledge, two systematic reviews on the importance of LND in bladder cancer have been published. [35,36] Fan et al. [36] performed a systematic review and meta-analysis of studies comparing E-LND and non-extended LND and its impact on RFS. The authors concluded that E-LND was associated with improved RFS compared with non-extended LND. Subgroup analysis revealed that patients with ≥pT3 bladder cancer,

independently of LN status, benefit from E-LND. Tilki et al. [35] performed a systematic review only and concluded that the extent of LND may influence DFS after RC, independently of LN status and pT stage.

The outcomes of our present study are in line with these reviews. However, there are important methodological differences which deserve discussion. Tilki et al. [35] included studies using the LN count as a surrogate for the extent of LND. Although an association between LN count, the extent of LND or even post-RC outcomes have been suggested [37-39], using the LN count as a surrogate for the extent of LND has limitations as acknowledged by the authors. Differences in surgical technique, sample processing and pathologic assessment greatly influence the LN count and consequently affect reproducibility. [37,40,41] Furthermore, the LN count cannot adequately be determined intra-operatively whereas surgeons can adhere to anatomic templates, making studies comparing LND templates more clinically relevant. For these reasons, only studies describing anatomic templates for the extent of LND were included in our review. In addition, although Tilki et al. [35] described some studies comparing LND templates (references 26,28,29,32), an additional 19 studies were included in this study providing a more comprehensive overview of studies comparing different LND templates.

The attempt by Fan et al. [36] to perform a meta-analysis is noteworthy. Yet, the results of this study should be interpreted with caution. Aside from the low quality studies included in the analysis with its associated bias, differences in the definition of the extent of LND were not adjusted for in this study. Reflecting the lack of consensus on what constitutes a limited, standard, and extended or super-extended LND, there was significant heterogeneity in the definition regarding the extent of LND across studies. To illustrate, Abol-Enein et al. [29] and Dhar et al. [28] were both classified as E-LND studies while the proximal boundaries were the inferior mesenteric artery and crossing of the ureter with the common iliac vessels, respectively. For this reason, we chose to define the LND templates *a priori* and, if necessary, re-classify accordingly if sufficiently large numbers of studies did not match our chosen definitions. Although the definitions chosen for each of the LND templates may not be universally accepted by all clinicians, it at least allows for a certain degree of standardisation, which enables a comparison of outcomes among different LND templates.

3.4.4 Strengths and limitations of the review

The strength of the current study is the comprehensive literature review evaluating the impact of the extent of LND on post-RC outcomes using a robust and transparent methodological approach based on Cochrane review principles, incorporating the assessment of RoB and confounding which are essential in any review involving non-randomised studies. The search strategy was complemented by additional sources for potentially important articles, which included an expert panel (EAU Working Group on MIBC). The review was limited to comparative studies, in order to maintain at least moderate levels of evidence. Throughout the entire review process, peer review was obtained from the expert panel, which represents a reference group of international experts. This approach ensured a comprehensive review of the literature, whilst maintaining methodological rigour, and enabled the authors to put into clinical context the relevance and implication of the review findings.

The major limitation of the review is the quality of included studies; except for one prospective study, all studies were retrospective, non-standardized comparative studies with high risks of bias and confounding. **In particular selection bias may have affected clinical outcomes, for example, cases with apparent nodal disease intra-operatively where no LND was performed or less extended LND than anticipated.** This review highlights the lack of high quality and reliable evidence concerning the benefits and harms of LND during RC in terms of oncological and peri-operative outcomes. The results, on the other hand, are supported by the fact that these studies are fairly consistent in reporting an oncological benefit. Currently, two phase III RCTs, one in Germany and one initiated by the Southwest Oncology Group (SWOG S1011), evaluating the impact of different LND templates on survival are ongoing. The final results of these studies, which will take several years (personal communication), may provide a more definitive answer to some aspects of this important clinical question. Standardization of the LND templates and surgeon expertise, however, are of critical importance for the success of these trials.

4. CONCLUSION

This systematic review set out to determine the evidence base in regard with the comparative effectiveness of LND in patients undergoing RC for MIBC, in terms of oncological benefits and peri-operative outcomes. The findings reveal a lack of randomised studies, and an evidence base derived mainly from retrospective studies

with significant risks of bias and confounding. Nevertheless, the data indicate that any form of LND produces more favorable oncological outcomes compared with no LND. There was no evidence that LND results in increased perioperative adverse events than no LND. In terms of how different extents of LND influence outcomes, the findings indicate that E-LND might be superior to lesser degrees of dissection from an oncological perspective; however, extending the dissection beyond this (e.g. SE-LND) is not beneficial. The results of ongoing RCTs will hopefully clarify the remaining uncertainties regarding the role of LND during RC for MIBC.

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Take Home Message

Current evidence suggests that extended LND might be superior to lesser degrees of dissection in terms of oncological outcomes with comparable peri-operative morbidity. However, high quality data from randomised clinical trials are needed to draw a firm conclusion.