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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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- 1 ABSTRACT
- 2

## 3 Context:

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

7

# 8 **Objective:**

9 To systematically review relevant literature assessing the impact of LND on oncological10 and peri-operative outcomes in patients undergoing RC for MIBC.

11

# 12 **Evidence acquisition:**

13 MEDLINE, MEDLINE-in-Process, Embase, the Cochrane Central Register of 14 Controlled Trials and LILACS were searched up to December 2013. Comparative 15 studies reporting on no, limited, standard, extended, and super-extended LND, and 16 oncological and peri-operative outcomes were included. Risk of bias and confounding 17 assessments were performed.

18

## 19 Evidence synthesis:

20 23 studies reporting on 19,793 patients were included. All but one study were 21 retrospective. Planned meta-analyses were not possible due to study heterogeneity 22 therefore data were synthesized narratively. There were high risks of bias and 23 confounding across most studies, and extreme heterogeneity in the definition of the 24 anatomic boundaries of LND templates. All seven studies comparing LND with no 25 LND favored LND in terms of better oncological outcomes. Seven of 14 studies 26 comparing (super-)extended with limited or standard LND reported a beneficial 27 outcome for (super-)extended LND in at least a subset of patients. No difference in 28 outcome was reported in two studies comparing extended and super-extended LND. 29 The comparative harms of different extents of LND remain unclear.

30

## 31 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 remaininguncertainties.

# **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.

#### 46 **1. INTRODUCTION**

47 Lymphadenectomy (LND) combined with radical cystectomy (RC) is considered the 48 standard of care for patients with muscle-invasive bladder cancer (MIBC). Up to 25% of 49 patients harbour lymph node (LN) metastases at the time of RC and the staging role of 50 LND is unequivocal. In 1982, Skinner [1] was the first to report long term survival in 51 LN positive patients undergoing RC and LND without systemic treatment. The 52 therapeutic value of LND, however, remains a topic of continuous debate. Whilst the 53 results of two ongoing randomised clinical trials (RCTs) evaluating the impact of 54 different LND templates on survival are awaited, the current evidence base remains 55 uncertain with regard to the true benefits and harms of LND. In this study we 56 systematically reviewed the available literature to evaluate the impact of the extent of 57 LND on survival and peri-operative outcomes in patients undergoing RC for MIBC.

58

## 59 2. EVIDENCE ACQUISITION

#### 60 2.1 Search strategy

61 The review was performed in accordance with the PRISMA statement and principles 62 outlined in the Cochrane Handbook for Systematic Reviews of Interventions. [2,3] 63 Highly sensitive electronic searches were conducted to identify all reports of RCTs or 64 non-randomised comparative studies (NRCS) assessing LND in patients undergoing RC 65 for MIBC. The searches were not limited by language or publication date. The 66 databases searched were MEDLINE (1946 to December 2013), MEDLINE In-Process 67 (December 20th 2013), Embase (1974 to December 2013), Cochrane Central Register 68 of Controlled Trials (The Cochrane Library, Issue 8, 2013) and Latin American and 69 Caribbean Center on Health Sciences Information (LILACS; December 2013). The 70 database search was complemented by additional sources, including the reference lists 71 of included studies which were hand searched, and additional reports identified by an 72 expert panel (European Association of Urology (EAU) Working Group on MIBC). 73 Ongoing trials were identified on clinicaltrials.gov. The full search strategy is presented 74 in Appendix 1. 75 Two reviewers independently screened titles and abstracts of all citations identified by 76 the search strategies. Full text copies of all potentially relevant reports were obtained 77 and independently assessed by the reviewers to determine whether they met the pre-78 defined inclusion criteria. Any disagreements were resolved by consensus or arbitration 79 by a third person. A data extraction form was developed specifically for the purpose of

- 80 this assessment to collect information on study design, characteristics of participants,
- 81 characteristics of interventions, and outcome measures.
- 82

#### 83 2.2 Inclusion and exclusion criteria

84 The inclusion criterion was comparative studies only, and these included RCTs, 85 prospective NRCS, prospective observational studies with a comparator arm, and 86 retrospective comparative studies. Registry or database studies were also eligible, if the 87 analysis was clearly structured as a comparison between control and intervention 88 groups. Studies with no comparator group (e.g. single-arm case series), non-89 effectiveness studies (e.g. nomogram studies), reviews, or studies with fewer than 10 90 patients in each arm, were excluded. The study population was limited to patients with 91 localized muscle-invasive urothelial or squamous cell carcinoma of the bladder (cT2-4 92 N0M0). Studies including predominantly patients with variant histology other than 93 squamous cell carcinoma were excluded because of its low incidence and the potentially 94 different biological behavior of these cancers. Clinical staging was preferred, but if this 95 was not reported, staging based on RC specimen was accepted. Studies with mixed 96 populations (e.g. cTa, cTis, cT1) were retained for consideration for inclusion if there 97 were no studies which included patients with MIBC exclusively. Studies including 98 patients who underwent neo-adjuvant or adjuvant treatment were also retained. The 99 types of interventions included LND undertaken during RC for bladder cancer. Due to 100 the expected heterogeneity in defining the extent of LND across studies, the extent of 101 LND was determined *a priori* based on discussion in an expert panel (EAU Working 102 Group on MIBC) and were categorised as follows: (a) limited LND (or L-LND): LND 103 confined to the obturator and/or peri-vesical fossa only; (b) standard LND (or S-LND): 104 LND performed up to the common iliac arteries; (c) extended LND (or E-LND): LND 105 performed up to the proximal boundary of the crossing of the common iliac vessels with 106 the ureters or the aortic bifurcation, with or without the pre-sacral lymph nodes; and (d) 107 super-extended LND (or SE-LND): LND performed up to the proximal boundary of the 108 inferior mesenteric artery. The primary outcome was overall survival (OS); secondary 109 outcomes included recurrence-free survival (RFS), disease-free survival (DFS), 110 progression-free survival (PFS), cancer-specific survival (CSS) and peri-operative 111 outcomes (e.g. operative time, blood loss, lymphocele).

- 112
- 113

#### 114 2.3 Assessment of risks of bias

115 Two reviewers independently assessed the risk of bias (RoB) of individual studies. Any 116 disagreement was resolved by discussion or reference to a third reviewer. The standard 117 Cochrane Collaboration RoB tool [4] was used to assess the RoB in RCTs, whilst for 118 NRCS, the RoB tool recommended by the Cochrane Non-Randomised Studies Methods 119 Group was used. [5,6] In addition, for NRCS, the main confounders were identified a 120 priori based on a study by Palmer et al. [7] In this study, a survey among bladder cancer 121 experts was performed to identify and rank potential confounding variables and defining 122 thresholds for imbalance for these variables. The main confounders identified are 123 summarized in Table 1. Each confounder was assessed according to whether it had been 124 considered by the authors, whether the confounder was balanced across the groups, and 125 the degree to which adjustment had been made for the confounder. [7] The risk of 126 confounding bias was considered to be high if the confounder was not 127 described/considered, imbalanced between the groups or was not adjusted for in the 128 statistical analysis. Review Manager 5.2 was used to present these results (Table 1). [8]

129

#### 130 2.4 Data analysis

131 A narrative synthesis was performed. [9] Descriptive statistics were used to summarize 132 baseline characteristics data. For continuous outcomes, data were summarized using 133 mean (+/- standard deviation if available) and median (+/- interquartile range if 134 available); for categorical outcomes, data were summarized using proportions. For 135 summarizing outcome data, categorical outcomes were presented as proportions at 5 and 136 10 year time points following surgery based on crude point estimates as reported by 137 authors, with level of significance set at 5%. Outcomes at other time points were 138 narratively described. For time-to-event data reported by authors using univariable or 139 multivariable Cox regression analysis, data were summarized as hazard ratios (HRs) and 140 95% confidence intervals (CIs).

141

#### 142 **3. EVIDENCE SYNTHESIS**

#### 143 **3.1** Quantity of evidence identified and characteristics of included studies

144 One thousand eight hundred and ninety-seven abstracts were identified by the search

145 (Figure 1). Of these, 38 were selected for full text screening. One additional study was

146 identified through reference searching. After full text screening, a total of 23 studies met

147 the inclusion criteria. [10-32] Seven studies were reported only in the form of

- 148 conference meeting abstracts, while 16 studies were reported in full-text papers. With
- 149 one exception, all studies were retrospective comparative studies. Sixteen studies were
- 150 single-centre studies, of which eight studies used a historical cohort as control group,
- 151 and seven studies were multicentre studies.
- 152

# 153 3.2 Risk of bias and confounding assessment of included studies

- 154 Risk of bias (RoB) and confounding assessment for each of the individual studies were
- 155 performed and the results are presented in Table 1. Due to the retrospective design in 22
- 156 of 23 studies, there was high or unclear RoB across all domains. The issue of
- 157 confounding was also poorly addressed by the majority of studies, as it was unclear in
- 158 most studies if any of the confounding factors had been considered, either
- 159 prospectively, or retrospectively through statistical adjustment.
- 160
- 161 **3.3 Results of comparisons of interventions**
- 162
- 163 3.3.1 No LND vs LND
- 164 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
- 167 included any LND [10,14,15], L-LND [13], S-LND [11,12,16], E-LND [16] or SE-
- 168 LND [16].
- 169

# 170 3.3.1.2 Oncological outcomes

- 171 Table 2b summarizes the oncological outcomes comparing no LND vs any LND. All
- 172 studies reported a benefit for LND in at least one oncological outcome. Liu et al. [10]
- 173 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.
- 175
- 176 3.3.1.3 Peri-operative outcomes
- 177 No studies reported on these outcomes.
- 178
- 179 3.3.2 Limited LND vs standard LND
- 180 No studies were identified for this comparison.
- 181

#### 182 3.3.3 Limited LND vs (super-)extended LND

## 183 3.3.3.1 Baseline characteristics

- 184 Five studies addressed this question involving a total of 1,394 patients (Table 3a). [17-
- 185 21] Brossner et al. [21] focused on peri-operative outcomes. Bostrom et al. [19]
- 186 compared L-LND with E-LND, however, an unknown number of patients in the E-LND
- 187 group underwent SE-LND and over 50% of patients in the L-LND group did not
- 188 undergo LND at all.
- 189

## 190 3.3.3.2 Oncological outcomes

- 191 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
- 193 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
- 195 oncological outcomes for L-LND and E-LND performing univariable analysis.
- 196

## 197 3.3.3.3 Peri-operative outcomes

- 198 Jensen et al. [20] reported no prolonged operative time for E-LND compared with L-
- 199 LND (mean 306 vs 302 minutes, p = 0.92). Brossner et al. [21], however, reported
- 200 prolonged operative time for SE-LND compared with L-LND (median 330 vs 277
- 201 minutes, p < 0.01). No differences in number of blood units transfused (1.15 vs 0.38
- 202 respectively, p = 0.37), lymphoceles (none in both groups), 30-day complication rate
- 203 (11% vs 9% respectively, p=0.28), and 30-day mortality (3 vs 1 event respectively, p =
- 204 0.57) were reported in this study. [21]
- 205

## 206 3.3.4 Standard LND vs (super-)extended LND

## 207 3.3.4.1 Baseline characteristics

- 208 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-
- 211 2010). One study specifically looked at the outcomes of laparoscopic LND. [25]
- 212

### 213 3.3.4.2 Oncological outcomes

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

- 216 outcomes between S-LND and E-LND [22-24,30], although only one study on data
- 217 from multivariable analysis. [22] Three studies reported a benefit for E-LND and one
- 218 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
- 222 patients with >pT2 disease.
- 223

# 224 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).

230

# 231 3.3.5 Extended LND vs super-extended LND

232 3.3.5.1 Baseline characteristics

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

235

## 236 3.3.5.2 Oncological outcomes

237 Table 5b summarizes the oncological outcomes comparing E-LND with SE-LND. Both

238 studies reported no statistically significant difference in survival outcomes between E-

239 LND and SE-LND, irrespective of tumor stage or nodal status.

240

# 241 3.3.5.3 Peri-operative outcomes

- 242 No studies reporting on these outcomes were identified.
- 243
- 244 3.4 Discussion

# 245 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 250 outcomes. Additionally, E-LND might improve oncological outcomes compared with 251 lesser degrees of dissection, although extending the dissection beyond E-LND is 252 unlikely to yield any further benefits. With respect to peri-operative outcomes, a 253 secondary outcome of this study, SE-LND resulted in increased operative time 254 compared with less extended LND templates, but does not appear to substantially 255 increase post-operative morbidity.

256

#### 257 3.4.2 Clinical implications of our study findings

258 The data in this study support the routine performance of LND in patients undergoing 259 RC. Whether the reported beneficial oncological outcomes are a result of stage 260 migration (the so-called Will-Rogers Phenomenon), a true therapeutic benefit of LND, 261 or a combination of both, remains uncertain. There is, however, a clear staging role of 262 LND as supported by LN mapping studies [33, 34]. Thus, in spite of the lack of RCTs, 263 the current evidence base is sufficiently convincing to recommend LND for patients 264 undergoing RC for MIBC. While limited LND may contribute to disease staging, 265 performing LND outside the true pelvis (i.e. *S*-LND) should be considered a potential 266 therapeutic intervention as skip nodal lesions are rare, therefore unlikely contributing to 267 disease staging [33,34]. To date, however, questions remain about the potential 268 therapeutic value of LND and what extent of LND is the most efficacious. Based on the 269 current data, consisting of retrospective studies with a significant risk of bias and 270 confounding, the evidence base is not strong enough to provide firm recommendations 271 regarding the most optimal extent of LND. Conversely, these studies are currently the 272 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 273 274 increase peri-operative morbidity. Collectively, there is accumulating evidence that E-275 LND may be beneficial for patients undergoing RC for MIBC and is therefore 276

- recommended in patients undergoing RC for MIBC.
- 277

#### 278 3.4.3 How does this systematic review compare with other recent reviews?

279 To our knowledge, two systematic reviews on the importance of LND in bladder cancer 280 have been published. [35,36] Fan et al. [36] performed a systematic review and meta-281 analysis of studies comparing E-LND and non-extended LND and its impact on RFS. 282 The authors concluded that E-LND was associated with improved RFS compared with 283 non-extended LND. Subgroup analysis revealed that patients with  $\geq$ 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.

287 The outcomes of our present study are in line with these reviews. However, there are 288 important methodological differences which deserve discussion. Tilki et al. [35] 289 included studies using the LN count as a surrogate for the extent of LND. Although an 290 association between LN count, the extent of LND or even post-RC outcomes have been 291 suggested [37-39], using the LN count as a surrogate for the extent of LND has 292 limitations as acknowledged by the authors. Differences in surgical technique, sample 293 processing and pathologic assessment greatly influence the LN count and consequently 294 affect reproducibility. [37,40,41] Furthermore, the LN count cannot adequately be 295 determined intra-operatively whereas surgeons can adhere to anatomic templates, 296 making studies comparing LND templates more clinically relevant. For these reasons, 297 only studies describing anatomic templates for the extent of LND were included in our 298 review. In addition, although Tilki et al. [35] described some studies comparing LND 299 templates (references 26,28,29,32), an additional 19 studies were included in this study 300 providing a more comprehensive overview of studies comparing different LND 301 templates.

302 The attempt by Fan et al. [36] to perform a meta-analysis is noteworthy. Yet, the results 303 of this study should be interpreted with caution. Aside from the low quality studies 304 included in the analysis with its associated bias, differences in the definition of the 305 extent of LND were not adjusted for in this study. Reflecting the lack of consensus on 306 what constitutes a limited, standard, and extended or super-extended LND, there was 307 significant heterogeneity in the definition regarding the extent of LND across studies. 308 To illustrate, Abol-Enein et al. [29] and Dhar et al. [28] were both classified as E-LND 309 studies while the proximal boundaries were the inferior mesenteric artery and crossing 310 of the ureter with the common iliac vessels, respectively. For this reason, we chose to 311 define the LND templates a priori and, if necessary, re-classify accordingly if 312 sufficiently large numbers of studies did not match our chosen definitions. Although the 313 definitions chosen for each of the LND templates may not be universally accepted by all 314 clinicians, it at least allows for a certain degree of standardisation, which enables a 315 comparison of outcomes among different LND templates.

316

#### 317 3.4.4 Strengths and limitations of the review

318 The strength of the current study is the comprehensive literature review evaluating the 319 impact of the extent of LND on post-RC outcomes using a robust and transparent 320 methodological approach based on Cochrane review principles, incorporating the 321 assessment of RoB and confounding which are essential in any review involving non-322 randomised studies. The search strategy was complemented by additional sources for 323 potentially important articles, which included an expert panel (EAU Working Group on 324 MIBC). The review was limited to comparative studies, in order to maintain at least 325 moderate levels of evidence. Throughout the entire review process, peer review was 326 obtained from the expert panel, which represents a reference group of international 327 experts. This approach ensured a comprehensive review of the literature, whilst 328 maintaining methodological rigour, and enabled the authors to put into clinical context 329 the relevance and implication of the review findings.

330

331 The major limitation of the review is the quality of included studies; except for one 332 prospective study, all studies were retrospective, non-standardized comparative studies 333 with high risks of bias and confounding. In particular selection bias may have 334 affected clinical outcomes, for example, cases with apparent nodal disease intra-335 operatively where no LND was performed or less extended LND than anticipated. 336 This review highlights the lack of high quality and reliable evidence concerning the 337 benefits and harms of LND during RC in terms of oncological and peri-operative 338 outcomes. The results, on the other hand, are supported by the fact that these studies are 339 fairly consistent in reporting an oncological benefit. Currently, two phase III RCTs, one 340 in Germany and one initiated by the Southwest Oncology Group (SWOG S1011), 341 evaluating the impact of different LND templates on survival are ongoing. The final 342 results of these studies, which will take several years (personal communication), may 343 provide a more definitive answer to some aspects of this important clinical question. 344 Standardization of the LND templates and surgeon expertise, however, are of critical 345 importance for the success of these trials.

346

## 347 **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

352 with significant risks of bias and confounding. Nevertheless, the data indicate that any 353 form of LND produces more favorable oncological outcomes compared with no LND. 354 There was no evidence that LND results in increased perioperative adverse events than 355 no LND. In terms of how different extents of LND influence outcomes, the findings 356 indicate that E-LND might be superior to lesser degrees of dissection from an 357 oncological perspective; however, extending the dissection beyond this (e.g. SE-LND) 358 is not beneficial. The results of ongoing RCTs will hopefully clarify the remaining uncertainties regarding the role of LND during RC for MIBC. 359

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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.