

## The role of extended lymphadenectomy for bladder cancer

### The European perspective

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#### 1) Introduction

Pelvic Lymphadenectomy (PLND) combined with radical cystectomy (RC) is considered the standard of care for patients with muscle-invasive bladder cancer (MIBC). The staging role of PLND is unequivocal. The therapeutic value of PLND, however, remains a topic of continuous controversy. [1]. Mapping studies from patients with MIBC have documented the pathways of progression of invasive BC [2, 3]. Sequential dissemination from the lower pelvic to the more proximal lymph nodes in the pelvis and retroperitoneum is the general pattern of spread and the risk of regional lymph node metastases is associated with the depth of invasion of the primary tumor. Because of controversy and heterogeneity in defining the extent of PLND across studies, the extent of PLND was determined as follows (1) limited PLND (L-PLND): PLND confined to the obturator and/or perivesical fossa only; (2) standard PLND (S-PLND): PLND performed up to the common iliac arteries; (3) extended PLND (E-PLND): PLND 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 presacral LNs; and (4) superextended PLND (SE-PLND): PLND performed up to the proximal boundary of the inferior mesenteric artery [1].

#### 2) What we do know about PLND

The available evidence indicates that any kind of PLND is advantageous over no PLND. Similarly, E-PLND appears to be superior to lesser degrees of dissection, while SE-PLND offered no clinical benefits.

E-PLND increases number of nodes identified and N-stage.

PLND improves loco-regional control.

#### 3) What we don't know about E-PLND

The proximal extent of a PLND at the time of RC has always been an issue of controversy. Some reports suggest that a dissection to the common iliac bifurcation or to the ureter crossing over the iliac vessels is adequate whereas others suggest that more proximal dissection to the inferior mesenteric artery may affect survival. Furthermore, removal of the presacral lymph nodes and the deep obturator lymph nodes are not routinely done by all surgeons.

Does E-PLND improve disease-free and overall survival?

Results of comparisons of different types of PLND:

L-PLND versus E-PLND

Five studies addressed this question involving a total of 1 394 patients. The oncologic outcomes comparing L-PLND with E/SE-SE-PLND: Of the five studies available three studies reported improvement of at least one oncologic outcome for E/SE-PLND. One study did not report oncologic outcomes, while one found no statistically significant difference in oncologic outcomes for L-PLND and E-PLND performing univariable analysis [1].

#### S-PLND versus S/E-PLND

Nine studies were identified involving 3 104 patients. The oncologic outcomes of S-PLND compared with E/SE-PLND showed contradicting results. Four studies noted no difference in oncologic outcomes between S-PLND and E-PLND, although only one study reported on data from multivariable analysis. Three studies reported a benefit for E-PLND, and one study reported a benefit for SE-PLND for at least one oncologic outcome [1].

#### 4) Guidelines

To address differences or controversy in regard to E-PLND between Europe and the USA a review of the respective guidelines is helpful:

##### AUA / ASCO / ASTRO / SOU Guideline [4]

##### Pelvic Lymphadenectomy

19. Clinicians must perform a bilateral pelvic lymphadenectomy at the time of any surgery with curative intent. (Strong Recommendation; Evidence Level: Grade B)

20. When performing bilateral pelvic lymphadenectomy, clinicians should remove, at a minimum, the external and internal iliac and obturator lymph nodes S-PLND. (Clinical Principle).

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##### Updated 2016 EAU Guideline on MIBC [5]

In conclusion, extended E- PLND might have a therapeutic benefit compared with less extensive PLND, but due to bias, the overall quality of the data is low and no firm conclusions can be drawn. Further data from ongoing randomised trials on the therapeutic impact of the extent of lymphadenectomy are awaited.

#### 5) RCTs

Currently, two phase 3 RCTs evaluating the impact of different PLND templates on survival-one in Germany and one initiated by SWOG (S1011)-are ongoing. The final results of these studies may provide a more definitive answer to some aspects of this important clinical question. The LEA-study is mature, but has not yet been published. Information is available from the ASCO' 2016 and EAU 2017 presentation.

The LEA AUO AB 257/02 trial: AUO AB 25/02) [6].

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