Overtreatment of prostate cancer may be prevented by extended pelvic lymphadenectomy

Nessn H. Azawi[1], Katrine Stenfeldt[2] & Tom Christensen[1]

ABSTRACT

OBJECTIVE: Pelvic lymphadenectomy remains the gold standard for providing a diagnosis of lymph node metastasis (N1) in prostate cancer patients who may be candidates for curatively intended radiotherapy (RT). The limited lymphadenectomy technique (L-PLND) provides removal of only a minority of lymph nodes within the expected regions of lymph node drainage of the prostate. We describe our extended lymphadenectomy (e-PLND) and the pathological outcome with a modified template as described by Briganti and compare it with L-PLND.

MATERIAL AND METHODS: This was a retrospective study of 44 patients who underwent e-PLND and 36 patients who underwent L-PLND. The lymph node dissection regions were divided into: (I) the external iliac field, (II) the obturator field and (III) the internal iliac field.

RESULTS: The mean age was 70.2 years for e-PLND and 68.9 years for L-PLND. There was no significant difference in preoperative prostate-specific antigen (PSA), Gleason score or clinical stage between the two cohorts of patients. The mean operative time was 95 min. (range 75–140 min.) for e-PLND and 82 min. (range 30–145 min.) for L-PLND ($p = 0.03$). N1 was found in 18 (41%) and six (17%) in e-PLND versus L-PLND, respectively ($p = 0.03$). Six of the 44 (13.6%) patients who underwent e-PLND had N1 exclusively outside the region related to the limited dissection technique.

CONCLUSION: e-PLND is safe and can prevent overtreatment of at least 13.6% of the prostate cancer patients who may be candidates for RT. Positive needle-core biopsies have a direct impact on N1.

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Pelvic lymphadenectomy remains the gold standard for providing a diagnosis of lymph node metastasis (N1) in prostate cancer patients who may be candidates for curatively intended radiotherapy (RT). A limited lymphadenectomy to the obturator fossa (L-PLND) was the standard technique until a few years ago when it was replaced by extended lymphadenectomy (e-PLND). At best, only a minority of lymph nodes are removed with L-PLND [1]. Many published studies have described the boundaries of e-PLND [2-4]. Anatomical studies have shown that the prostate gland may drain lymphatically through three groups of ducts: the ascending duct from the cranial gland running to the external iliac nodes, the lateral duct running to the hypogastric (internal iliac) nodes and the posterior duct running to the sacral nodes [5]. Dissection technique for these nodes has many complications that render it unattractive for diagnostic purposes [1, 6]. Numerous nomograms have been published in the past few years; Briganti et al for example reported a new nomogram with 87% accuracy to detect positive lymph node metastases, but it could not replace e-PLND [7].

The need for a new template that involves as many lymphatic drainage regions as possible for the prostate gland and has an acceptable diagnostic power and a low complication rate seems evident. We describe our e-PLND and the pathological outcome with a modified template as described by Briganti et al [7]. Furthermore, we compare it with L-PLND and investigate its limitations.

MATERIAL AND METHODS

Between May 2010 and December 2011, a total of 80 patients were evaluated to get RT for localized advanced prostate cancer within intermediate- and high-risk groups; 44 patients underwent e-PLND with a modified template, while 36 patients underwent L-PLND, depending on the surgeon's preferences. An intermediate-risk patient was defined as a patient whose PSA was 10-20 ng/ml, and/or whose Gleason score (GS) was seven, and/or whose clinically estimated T category (cT) was equal to cT2b by rectal exploration. A high-risk patient was defined as a patient whose PSA exceeded 20 ng/ml, and/or whose GS was above seven, and/or whose cT was higher than cT2b by rectal exploration.

Our template divided prostatic lymph node regions into three fields (**Figure 1**): (I) the external iliac field consisting of spermatic vessels laterally, bifurcation of the common iliac artery cranially, inferior epigastric vessels caudally and the external iliac artery medially; (II) the obturator field consisting of the external iliac artery laterally, the obturator nerve inferiorly, the pubic bone caudally, the bifurcation of common iliac artery cranially and the internal iliac artery medially; (III) the internal iliac field consisting of the internal iliac artery laterally, the ureteric cross or one cm from the bifurcation of the common iliac artery cranially, the insertion of medial umbilical ligament to the internal iliac artery caudally, and the ureter laterally.

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1) Department of Urology D, Roskilde Hospital
2) Department of Pathology, Roskilde Hospital

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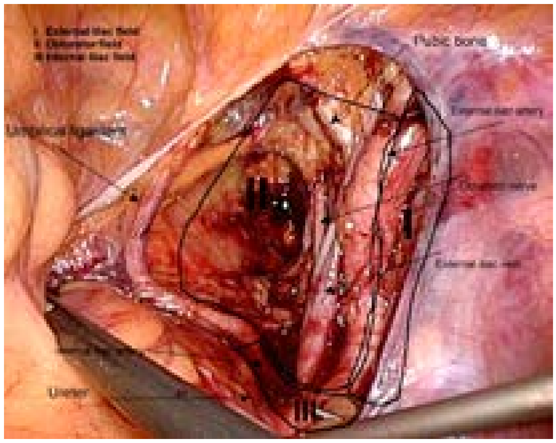
FIGURE 1

Pelvic lymph node regions.



Statistical analysis

The SPSS software statistics programme was used. A comparison of incidences was assessed using Fisher's exact test or χ^2-test. The unpaired t-test and Mann-Whitney U were used to compare the operative techniques. Correlations between preoperative results and metastases were analysed using the point biserial correlation and the receiver-operating characteristic (ROC) curve. Further, a $p < 0.05$ was considered significant.

Trial registration: not relevant.

RESULTS

Table 1 shows the patients' data upon diagnosis. The mean preoperative PSA for patients with metastases (N1) was 17.2 ng/ml (range 3–56) and for patients with no metastases (N0) it was 19.4 (range 3–65) (p = 0.4). The median number of positive needle core biopsies (NPB) with N1 was seven (range 2–10) versus four (range 1–10) in N0 patients (p = 0.006). The mean operative time was 95 min (range 75–140 min) versus 82 min (range 30–145 min) for e-PLND versus L-PLND, respectively (p = 0.03).

The median postoperative hospital stay was one day (range 0-13 days) for e-PLND and one day (range 0-22 days) for L-PLND (p = 0.2). Two patients had major complications with L-PLND – one patient with port bleeding and another with ureter lesion, both requiring re-operation. One patient had a port hernia with e-PLND.

Table 2 shows the distribution of metastases. The number of patients with N1 was 18 (41%) for e-PLND and six (17%) for versus L-PLND (p = 0.03). The mean number of lymph nodes (NLN) removed was 16.9 (range 9-41) for e-PLND and 11.2 (range 1-23) for L-PLND (p = 0.001). N1 ranged between one and five nodes per patient for all patients and 1-2 positive nodes detected outside the limited region per patient. Six of 44 patients (13.6%) had N1 exclusively outside the region related to the limited dissection technique.

N1 was found to be positively correlated with number of lymph nodes removed (p = 0.006) in L-PLND; this finding could not be demonstrated in e-PLND. Sex positive needle core biopsies out of ten biopsies correlated positively with N1 (p = 0.003) (**Figure 2**). There was no correlation between the side of detected cancer by prostate biopsies and the side of pelvic lymph nodes metastases, preoperative PSA and N1, and between cT and N1.

DISCUSSION

Our template achieved the prevention of overtreatment of six patients (13.6%) who had prostate cancer. There were six of 44 patients who had metastases outside the L-PLND region This finding had been confirmed by Yun et al in 2012 [8]. Patients with metastases to the pelvic lymph nodes for prostate cancer were associated with unfavourable prognoses. Computed tomography and magnetic resonance imaging are no longer used to evaluate pelvic lymph nodes because of unacceptable false positive and false negative rates [9]. Positron emission tomography (PET)/CT using fluoromethylcholine trace could not replace L-PLND for prostate cancer

TABLE 1

Patient demographics.

	Extended	Limited
Patients, n	44	36
Age, years, mean (range)	70.2 (61-77)[a]	68.9 (58-77)[a]
Preoperative PSA, ng/ml, mean (range)	19 (3-65)[a]	18.6 (3-54)[a]
Gleason score, n (%)		
6-7	26 (59)[a]	18 (50)[a]
8-10	18 (41)[a]	18 (50)[a]
Intermediate risk, n (%)	11 (25)[a]	6 (16)[a]
High risk, *n (%)*	33 (75)[a]	30 (84)[a]
cT, no. of patients (%)		
cT1	20 (45)[a]	19 (53)[a]
cT2	14 (32)[a]	11 (30)[a]
cT3	10 (23)[a]	6 (17)[a]
No. of positive biopsies, no. of patients (%)		
3-5	23 (52)[a]	25 (66)[a]
6-10	21 (48)[a]	13 (34)[a]
% of positive part of biopsy, no. of patients		
< 50	33[a]	28[a]
> 50	11[a]	8[a]

cT = clinically estimated stage; PSA = prostate-specific antigen.
a) Statistically non-significant.

TABLE 2

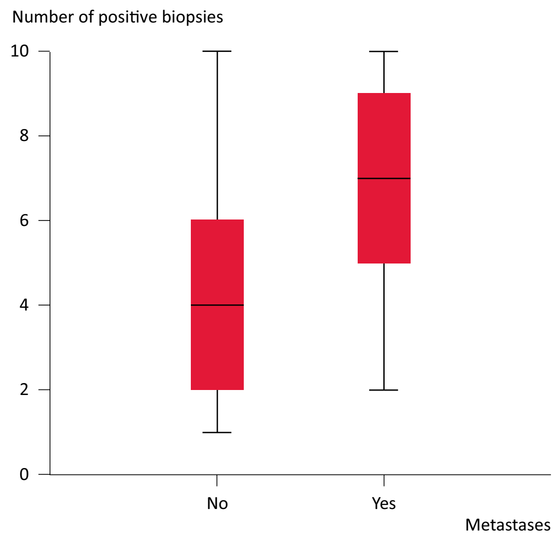
Distribution of metastases.

	Extended	Limited
NLN, mean (range), n	16.9 (9-41), 743*	11.2 (2-23), 406*
N1, n/N (%)	18/44 (41)*	6/36 (17)*
Distribution of N1, n per anatomic region (%)		
External iliac I	3 (11)	(0)
Obturator II	13 (46)	(100)
Internal iliac III	12 (43)	(0)
Distribution of N1, n per one anatomic region exclusively		
External iliac I	2	–
Obturator II	5	–
Internal iliac III	4	–

N1 = metastases; NLN = number of lymph nodes removed.
*) p < 0.05.

FIGURE 2

Correlation between number of positive prostate biopsies and metastases.



lymph node staging because of low sensitivity [10]. Bjerggaard Jensen et al reported that the five-year recurrence-free survival for prostate cancer patients treated with RT after L-PLND was 46% and this could indicate that some of the patients with recurrence actually had N1 that was missed due to the extent of the dissection [11]. According to the anatomical distribution of the lymphatic drainage regions of the prostate described by Mattei et al, our template included 63% of all expected lymph drainage regions of the prostate gland and possibly a little more where we removed the lymph nodes related to the common iliac region distal to the ureter. Among the rest of the lymph nodes, 37% were located around the common iliac vessels to the inferior mesenteric artery and to the per-sacral region. Dissection of these regions is not safe and is associated with a large number of complications and may be without advantages for the patients [1].

The operation time increased 13 min per patient. There was no major complication rate associated with e-PLND. This template can be valid, especially if we take into account the 23% increase in the number of detected N1. The NLN had no correlation with N1 in e-PLND, which indicated that the increase in N1 associated with e-PLND can be related to the quality of dissection and not to the quantity of nodes removed. Increasing the NLN may have a therapeutic effect on the outcome of prostate cancer, but this feature needs more documentation [12]. Our study cannot evaluate this issue.

The impact of pre-PSA and T-stage as an independent predictor of N1 could not be revealed in our study, as was the case in other studies [7, 11]. This can be due to small size sample in this paper. Another limitation to this study is the selection of patients to different type of operation.

CONCLUSION

e-PLND with our template is safe compared with L-PLND; e-PLND can prevent overtreatment of at least 13.6% of the prostate cancer patients who may otherwise be candidates for RT. Extension of the dissection outside the obturator fossa is mandatory. The NPB has a direct impact on N1. More studies are needed to evaluate the therapeutic effect of NLN on outcomes of prostate cancer patients.

CORRESPONDENCE: *Nessn H. Azawi*, Roskilde Hospital, Urologisk Afdeling, Roskilde Sygehus, 4000 Roskilde, Denmark. E-mail: nesa@regionsaelland.dk
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LITERATURE

1. Mattei A, Fuechsel FG, Bhatta DN et al. The template of the primary lymphatic landing sites of the prostate should be revisited: results of a multimodality mapping study. Eur Urol 2008;53:118-25.
2. Merlet B, Ouaki F, Pires C et al. [Pelvic lymph nodes dissection for prostate cancer: Minilap with speculum vs laparoscopy] (in French). Prog Urol 2010;20:279-83.
3. Osmonov DK, Wang C, Hoenle J et al. Extended lymphadenectomy "step by step" in patients undergoing radical prostatectomy. Urology 2011;77:969-74.
4. Arenas LF, Fullhase C, Boemans P et al. Detecting lymph nodes metastasis in prostate cancer through extended vs. standard laparoscopic pelvic lymphadenectomy. Aktuelle Urol 2010; 41 Suppl 1:S10-S14.
5. Gil-Vernet JM. Prostate cancer: anatomical and surgical considerations. Br J Urol 1996;78:161-8.
6. Meinhardt W, Valdes Olmos RA, van der Poel HG et al. Laparoscopic sentinel node dissection for prostate carcinoma: technical and anatomical observations. BJU Int 2008;102:714-7.
7. Briganti A, Larcher A, Abdollah F et al. Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. Eur Urol 2012;61:480-7.
8. Yuh BE, Ruel NH, Mejia R et al. Robotic extended pelvic lymphadenectomy for intermediate- and high-risk prostate cancer. Eur Urol 2012;61:1004-10.
9. Mukamel E, Hannah J, Barbaric Z et al. The value of computerized tomography scan and magnetic resonance imaging in staging prostatic

carcinoma: comparison with the clinical and histological staging. J Urol 1986;136:1231-3.
10. Poulsen MH, Bouchelouche K, Hoilund-Carlsen PF et al. [18F] fluoromethylcholine (FCH) positron emission tomography/computed tomography (PET/CT) for lymph node staging of prostate cancer: a prospective study of 210 patients. BJU Int 2012;110:1666-71.
11. Bjerggaard Jensen J, Johansen JK, Graversen PH. Laparoscopic pelvic lymph-node dissection in prostate cancer before external beam radiotherapy: Risk factors of nodal involvement and relapse following intended curative treatment. Scand J Urol Nephrol 2009;43:19-24.
12. Burkhard FC, Schumacher M, Thalmann GN et al. Is pelvic lymphadenectomy really necessary in patients with a serum prostate-specific antigen level of <10 ng/ml undergoing radical prostatectomy for prostate cancer? BJU Int 2005;95:275-8.