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ORIGINAL PAPER

The impact of extended lymph node dissection versus neoadjuvant therapy with limited lymph node dissection on biochemical recurrence in high-risk prostate cancer patients treated with radical prostatectomy: a multi-institutional analysis

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Abstract The optimal treatment for high-risk prostate cancer (Pca) remains to be established. The current guidelines recommend extended pelvic lymph node dissection (e-PLND) for selected intermediate- and high-risk patients treated with RP. However, the indications, optimal extent, and therapeutic benefits of e-PLND remain unclear. The aim of this study was to assess whether e-PLND confers an oncological benefit for high-risk Pca compared to neoadjuvant luteinizing hormone-releasing hormone and estramustine (LHRH + EMP). The Michinoku Urological Cancer Study Group database contained the data of 2403 consecutive Pca patients treated with RP at four institutes between March 2000 and December 2014. In the e-PLND group, we identified 238 high-risk Pca patients who underwent RP and e-PLND, with lymphatic tissue removal around the obturator and the external iliac regions, and hypogastric lymph node dissection. The neoadjuvant therapy with limited PLND (l-PLND) group included 280 high-risk Pca patients who underwent RP and removal of the obturator node chain between September 2005 and June 2014 at Hirosaki University. The outcome measure was BRFS. The 5-year biochemical recurrence-free survival rates for the neoadjuvant therapy with l-PLND group and e-PLND group were 84.9 and 54.7%, respectively ($P < 0.0001$). The operative time was significantly longer in the e-PLND group compared to that of the neoadjuvant therapy with l-PLND group. Grade 3/4 surgery-related complications were not identified in both groups. Although the present study was not randomized, neoadjuvant LHRH + EMP therapy followed by RP might reduce the risk of biochemical recurrence.

Keywords High-risk prostate cancer · Prostatectomy · Neoadjuvant therapy · Extended lymph node dissection

Introduction

Individuals with prostate-specific antigen (PSA) levels of ≥20 ng/mL, Gleason scores (GSs) of ≥8, or tumors of clinical stage T2c/T3 are defined as high-risk prostate cancer (Pca) patients [1]. Treatment options for high-risk Pca include external-beam radiation therapy (RT) with androgen-deprivation therapy (ADT); trimodal therapy with a combination of brachytherapy, external-beam RT, and ADT; and radical prostatectomy (RP) with neoadjuvant or adjuvant therapy. To date, sufficiently large-scale, prospective, randomized clinical trials that compare the above-mentioned treatment options have not been conducted. Therefore, optimal management strategies for high-risk Pca patients have not been established.

Pelvic lymph node dissection (PLND) is one of the accurate methods used for determining the nodal stage in Pca; however, the indications, optimal extent, and therapeutic benefits of PLND remain unclear. The current guidelines recommend extended PLND (e-PLND) for selected intermediate- and high-risk patients treated with RP [2–4]. Previous retrospective studies suggested that e-PLND might confer a survival benefit not only for

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patients with node-positive Pca but also for those with node-negative Pca [5–7]. In addition, an increase in the number of dissected nodes was also correlated with a positive impact on biochemical recurrence (BCR) or cancer-specific survival (CSS) [8]. On the other hand, the e-PLND might have several disadvantages, including longer operation time or increased rates of peri- or postoperative e-PLND-related complications [9–11].

Several studies have reported similar results in high-risk Pca patients with neoadjuvant combination therapies, including docetaxel [12, 13]. Although various trials aimed to prolong BCR-free survival (BRFS), the PSA-free survival rates remained low [14]. We previously reported the efficacy and safety of combined luteinizing hormone-releasing hormone (LHRH) plus low-dose EMP (LHRH + EMP) therapy in patients with high-risk Pca [15, 16].

The aim of this study was to evaluate whether neoadjuvant LHRH + EMP or e-PLND conferred clinical benefits for high-risk Pca using the Michinoku Urological Cancer Study Group database.

Methods

Study population

The Michinoku Urological Cancer Study Group database contained preoperative and postoperative data for 2403 consecutive Pca patients who were treated with RP between March 2000 and December 2014 at Hirosaki University, Tohoku University, Akita University, and Miyagi Cancer Center. The study was approved by each institutional review board, and all participating sites provided the necessary institutional data-sharing agreements before study initiation. The preoperative information included the patient age, height, weight, preoperative serum PSA level, clinical stage, biopsy GS, and the number and percentage of cancer-positive biopsy cores. The pathological T and N stages of the surgical specimens were recorded along with the GS and the presence of extraprostatic extension, seminal vesicle invasion, and positive surgical margins. All tumors were staged according to the 2002 American Joint Committee on Cancer Staging Manual [17].

High-risk Pca was defined as clinical stage T2c or T3 disease, initial PSA levels of $\geq$20 ng/mL, and/or a biopsy GS of $\geq$8 according to the D'Amico risk stratification system [1]. The eligibility criteria for receiving neoadjuvant LHRH + EMP therapy (neoadjuvant group) were as follows: histologically confirmed high-risk Pca without evidence of radiologic lymph node or distant metastases; an Eastern Cooperative Oncology Group performance status of 0–1; adequate bone marrow function (absolute neutrophil count $\geq$1500/m^3 and platelet count $\geq$100,000/m^3); adequate renal function (creatinine <2.0 mg/dL and/or creatinine clearance >40 mL/min); and adequate hepatic function (total bilirubin <1.5 mg/dL) [15, 16].

Treatment

In patients who received neoadjuvant LHRH + EMP, all patients received an LHRH agonist (11.25 mg of leuprolide or 10.8 mg of goserelin acetate) every 3 months and EMP (280 mg/day) for 6 months before RP [15, 16]. All patients who received neoadjuvant LHRH + EMP underwent the same lymphadenectomy procedure, which included removal of the bilateral obturator node chains (l-PLND; neoadjuvant therapy with l-PLND group).

In patients who underwent RP and e-PLND (e-PLND group), the minimum extent of e-PLND included obturator, external iliac, and hypogastric lymph nodes [8].

Pathological analysis

All prostatectomy specimens were sectioned according to the whole-mount technique and were evaluated according to the ISUP 2005 guidelines [18]. The apex of the prostate was shaved perpendicular to the prostatic urethra. The bladder neck margin was coned from the specimen and sectioned perpendicularly. The remaining prostate tissue was completely sectioned at 3-mm intervals along a plane perpendicular to the urethral axis.

Follow-up schedule

Following surgery, all patients were assessed at 3-month intervals according to their serum PSA and testosterone levels. The date of disease recurrence or PSA failure was defined as the date the serum PSA level exceeded 0.2 ng/mL. If the PSA level did not decrease to <0.2 ng/mL after the surgery, the date of RP was defined as the date of disease recurrence.

Endpoints and statistical analysis

The primary endpoint was the BRFS. Data were analyzed using the IBM SPSS 20 (IBM Corp, Armonk, NY, USA). The neoadjuvant therapy with l-PLND and e-PLND groups was compared using the Pearson Chi-square test for categorical variables and the Student's *t* test or Wilcoxon rank-sum test for continuous variables. The BRFS after RP was analyzed using the Kaplan–Meier method. The relationship between survival and the subgroup classification was analyzed using the log-rank test. The multivariate analysis was performed using a Cox proportional hazard model.

All P values were two-sided, and P values <0.05 were considered statistically significant.

Results

Patient characteristics

The demographic data of the patients who were classified into two groups according to treatment modalities are listed in Table 1. In the e-PLND group, we identified 238 high-risk Pca patients who underwent RP and bilateral e-PLND at four institutions between April 2000 and December 2014. In the neoadjuvant therapy with l-PLND group, 280 high-risk Pca patients received LHRH + EMP for 6 months and subsequently underwent RP and bilateral l-PLND at the Hirosaki University hospital between September 2005 and June 2014. The median patient age was 68 years (interquartile range [IQR] 64–72 years). The median follow-up duration was 51 months (IQR 36–72 months).

Surgical outcomes

In the neoadjuvant therapy with l-PLND group, 230 and 50 patients underwent open RP and robot-assisted RP (RARP), respectively. In the e-PLND group, 218 and 20 patients underwent open RP and RARP, respectively. The median operating time was 126 min (IQR 101–158 min) in the neoadjuvant therapy with l-PLND group and 309 min (IQR 267–351 min) in the e-PLND group ($P < 0.0001$). The median estimated blood loss was 640 mL (IQR 248–1050 ml) in the neoadjuvant therapy with l-PLND group and 737 mL (IQR 448–1150 mL) in the e-PLND group ($P = 0.3097$). All complications were grade ≤2 in both groups according to the Clavien–Dindo classification [19].

Pathological outcomes

The pathological evaluation data of the enrolled patients are listed in Table 2. In the e-PLND group, the number of lymph nodes removed, lymph node involvement, and positive surgical margins was significantly higher than that for the neoadjuvant therapy with l-PLND group. It is noteworthy that 8% of the patients in the neoadjuvant therapy with l-PLND group had pathological stage pT0 tumors.

Oncological outcomes

During the follow-up period, PSA relapse without clinical recurrence occurred in 45 (15%) patients in the neoadjuvant group and 90 patients (38%) in the e-PLND group. None of the enrolled patients developed clinical recurrences during the follow-up period. The 5-year BRFS rate was 84.9% in the neoadjuvant group (95% confidence interval [CI] 80.4–89.4) and 54.7% in the e-PLND group (95% CI 53.9–62.5; $P < 0.001$; Fig. 1).

Table 1 Patient characteristics

	Neoadjuvant therapy with l-PLND[a] group ($N = 280$)	e-PLND[b] group ($N = 238$)	P
Age (median, year, IQR[c])	69 (64–72)	68 (64–72)	0.683
Initial PSA[d] (median, ng/mL, IQR)	10.4 (6.9–21.9)	10.3 (6.6–21.0)	0.787
Clinical stage, number (%)			0.045
T1c	85 (30)	73 (31)	
T2a	36 (13)	39 (16)	
T2b	20 (7)	29 (12)	
T2c	44 (16)	40 (17)	
T3	96 (34)	56 (23)	
Gleason score, number (%)			<0.001
≤6	5 (2)	15 (6)	
7	55 (20)	81 (34)	
≥8	221 (78)	142 (60)	
Follow-up period (median, months, IQR)	61 (42–84)	44 (27–60)	0.001

[a] *l-PLND* limited pelvic lymph node dissection

[b] *e-PLND* extended pelvic lymph node dissection

[c] *IQR* interquartile rate

[d] *PSA* prostate-specific antigen

Table 2 Pathological outcomes

	Neoadjuvant therapy with l-PLND[a] group ($N = 280$)	e-PLND[b] group ($N = 238$)	P
Pathological stage, number (%)			<0.001
T0	23 (8)	0 (0)	
T2a	57 (20)	14 (6)	
T2b	25 (9)	36 (15)	
T2c	68 (24)	58 (24)	
T3a	65 (23)	68 (29)	
T3b	43 (15)	53 (22)	
T4	0 (0)	9 (3.8)	
LN[c] count, median (IQR[d])	6 (2–9)	16 (13–21)	<0.001
LN involvement, number (%)	4 (1.4)	27 (11)	<0.001
Positive surgical margins, number (%)	26 (9)	101 (42)	<0.001

[a] *l-PLND* limited pelvic lymph node dissection

[b] *e-PLND* extended pelvic lymph node dissection

[c] *LN* lymph node

[d] *IQR* interquartile range

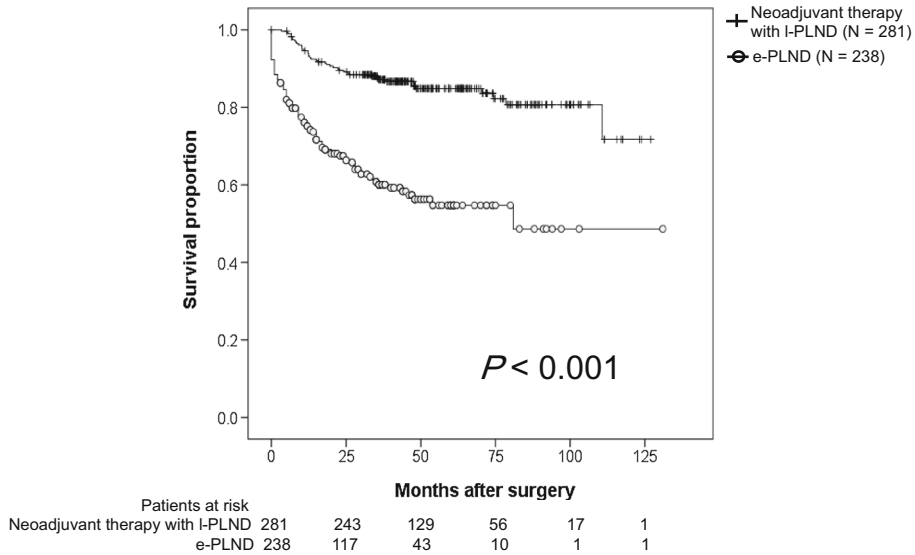

Fig. 1 Kaplan–Meier estimate of the biochemical recurrence-free survival (BRFS) for high-risk prostate cancer patients who underwent radical prostatectomy (RP) and limited pelvic lymph node dissection with neoadjuvant luteinizing hormone-releasing hormone plus estramustine (neoadjuvant therapy with l-PLND) or RP and extended pelvic lymph node dissection (e-PLND). The 5-year BRFS rate was 84.9% for patients who received neoadjuvant therapy with l-PLND and 54.7% for patients who underwent e-PLND ($P < 0.001$)

On multivariate analysis, neoadjuvant therapy with l-PLND and initial PSA was significantly associated with BCR (Table 3).

Discussion

Definitive therapy, often requiring a multimodal approach, appears to confer a relatively long-term survival advantage in patients with high-risk Pca. However, there is no current consensus regarding the optimal treatment for high-risk, non-metastatic Pca, and the oncologic outcomes associated with Pca are heterogeneous [2].

Historically, the levels of LN drainage of Pca have been segregated into hypogastric, obturator, external iliac, and presacral regions [10]. Autopsy studies suggested that the predominant region for LN metastasis is the external ileac LN chain [20]. However, several studies reported primary spread of Pca to the hypogastric LN chain rather than the obturator region [21, 22]. The presacral region has also been identified as the initial site of LN drainage in a small proportion of the patients with Pca [23]. Therefore, it is difficult to standardize the definition of the e-PLND. Currently, many studies adopt that the l-PLND includes the obturator LN chains and e-PLND includes the obturator, external iliac, and hypogastric LN chains [10].

Table 3 Multivariate analysis for biochemical recurrence-free survival

	Risk factors	Odds ratio	95% CI[a]	*P*
Neoadjuvant therapy with l-PLND[b] versus e-PLND[c]	e-PLND	5.0	3.4–7.5	<0.001
Initial PSA[d] (ng/mL)	≥20	3.8	2.6–5.5	<0.001
Clinical *T* stage	≥cT2c	1.4	1.0–2.1	0.046
Biopsy Gleason score	≥8	1.4	0.9–2.0	0.104
Age (years)	≥68	0.9	0.6–1.3	0.505

[a] *CI* confidence interval

[b] *l-PLND* limited pelvic lymph node dissection

[c] *e-PLND* extended pelvic lymph node dissection

[d] *PSA* prostate-specific antigen

PLND is associated with increased operative time, especially in case an e-PLND is performed [10]. In this study, the operative time in the e-PLND group was significantly longer than that in the neoadjuvant therapy with l-PLND group. Davis et al. suggested that the extended template required roughly doubled the operative time with no significant impact of surgeon experience or learning curve [21]. While the incidence rate of PLND-related complications ranged 4.1–19.8% [11], the most frequent complication after PLND was pelvic lymphocele, with an estimated incidence rate of 5–10.3% [11, 24]. Briganti et al. [22] reported that the incidence rate of pelvic lymphocele was 10.3% in the e-PLND cohort compared to 4.6% in the L-PLND cohort ($P = 0.01$). Tyritzis et al. [25] reported that PLND was associated with an eightfold and a sixfold higher risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) events, respectively, compared to no PLND. In this study, no grade 3/4 operation-related complications occurred. It is necessary to keep in mind that e-PLND during RP might increase the incidences of PLND-related complications, in particular those of DVT and PE.

The therapeutic effect of e-PLND on the outcome of Pca remains to be elucidated. Bivalacqua et al. [6] showed that patients undergoing e-PLND had better oncological outcomes at 10-year follow-up compared to their counterparts who underwent l-PLND. In a recent prospective randomized trial comparing e-PLND to standard PLND (defined as lymphatic tissue removal around the obturator and external lymph nodes; s-PLND), the BRFS rates after s-PLND and e-PLND were 73.1 and 85.7% ($P = 0.042$), respectively, in intermediate-risk patients, and 51.1 and 71.4% ($P = 0.036$), respectively, in high-risk patients [7]. On the other hand, Kim et al. [25] analyzed the outcomes of 464 patients with intermediate- or high-risk Pca who underwent RP with e-PLND or s-PLND. Patients who underwent e-PLND had more lymph nodes removed than those who underwent s-PLND (21 vs. 12, respectively; $P < 0.001$), and a greater proportion of those who underwent e-PLND were identified with lymph node metastases than those who underwent s-PLND (12.1 vs. 5.0%, respectively; $P = 0.033$). However, no significant difference in BRFS was noted between patients who underwent e-PLND and s-PLND (77 vs. 73%, respectively; $P = 0.497$). The e-PLND might improve the outcome of Pca by eliminating micrometastatic nodal disease that might progress to systemic dissemination [24]. However, eradicating all Pca cells, including the circulating tumor cells, appears to be impossible.

A subset of high-risk Pca patients is at a higher risk of BCR and cancer-related mortality due to micrometastases at the time of surgery. Therefore, in order to eradicate the risk of micrometastases outside the surgical field, it is important to administer early systemic therapy. In this study, the patients who received neoadjuvant LHRH + EMP therapy before surgery had significantly higher BRFS rates than did patients who were treated with e-PLND. Additionally, the administration of neoadjuvant LHRH + EMP achieved a relatively high pT0 rate (8%). Therefore, neoadjuvant LHRH and low-dose EMP therapy might achieve relatively long PSA-free survival corresponding to that in low- or intermediate-risk patients treated with RP alone [26].

The present study had several limitations. Firstly, owing to its retrospective nature, the study had an inherent potential for bias. Secondly, we acknowledge the lack of a centralized pathology review involving the biopsy GS. Thirdly, a relatively small number of patients were enrolled in this study, and the follow-up period was relatively short.

The BRFS rate was higher in high-risk Pca patients who received neoadjuvant LHRH + EMP followed by RP and l-PLND than in those who received RP and e-PLND. Neoadjuvant LHRH + EMP therapy with subsequent RP might reduce the risk of BCR. A prospective randomized study is warranted to determine the clinical implications of the present neoadjuvant therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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