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Reevaluating the therapeutic role of extended lymph node dissection in the era of robot-assisted radical prostatectomy

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To elucidate the real-world oncological outcomes of robot-assisted radical prostatectomy (RARP) and effectiveness of extended pelvic lymph node dissection (ext-LDN) in the RARP era. Data from 8 194 patients who underwent RARP, including age, clinical T stage, prostate-specific antigen (PSA) before prostate cancer diagnosis (initial PSA), follow-up years, biopsied specimen grade group (GG), and whether they underwent lymph node dissection or not and presurgical androgen deprivation therapy, were recorded. Oncological outcomes among three risk groups (low, intermediate, and poor risks) were analyzed using Kaplan–Meier curves. In intermediate and poor risk cohorts, PSA failure-free, clinical recurrence-free, castration-resistant prostate cancer (CRPC)-free survival, and overall survival (OS) were compared between the ext-LDN groups and no or limited lymph node dissection (no-ltd-LND) groups before and after propensity matching for initial PSA, clinical stage, GG, and androgen deprivation therapy. Four survivals (PSA failure-free, clinical recurrence-free, CRPC-free survival, and OS) were noted among the three risk groups that generally reflected the risks. In comparison between ext-LDN and no-ltd-LND groups, propensity matching matched four factors. No significant difference was observed in the four survivals with or without ext-LDN. In the intermediate-risk, high-risk, and locally advanced cohorts (cT3–4), similar analyses were performed as the subanalyses; no significant difference was observed in the three subanalyses. We showed survival differences among the risk groups and that extended pelvic lymph node dissection has no oncological effectiveness using the largest patient cohort in the literature.

Robotic-assisted radical prostatectomy (RARP) for clinically localized prostate cancer has reduced the difficulty of complex maneuvers such as vesicourethral anastomosis compared to open or laparoscopic surgery, and it facilitates optional treatments including extended lymph node dissection (ext-LND)[1]. The National Comprehensive Cancer Network (NCCN) classification of prostate cancer is based on clinical T stage, pathological grade group of biopsied specimens (GG), and initial (pre-biopsy) prostate-specific antigen (iPSA). The clinical T stage is determined by digital rectal examination and/or multi-parametric magnetic resonance imaging (mpMRI), with mpMRI showing more accuracy[2,3]. In Japan, mpMRI and RARP are covered by the national insurance; therefore, most prostate cancer patients are risk-classified by mpMRI and treated by RARP,

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if indicated. The effectiveness of open and laparoscopic radical prostatectomy has been previously described[4–8]. However, only a few reports on such assessments are mentioned in literature in the mpMRI and RARP era. The oncological outcome can be assessed by biochemical recurrence-free, clinical recurrence-free, and castration-resistant prostate cancer (CRPC)-free survival as well as overall survival (OS), however the literature in the mpMRI and RARP era assessed only by biochemical recurrence with small number of patients[9–11].

The NCCN guidelines recommend undergoing ext-LND during prostatectomy for intermediate- and high-(including very high-) risk patients because of its diagnostic value rather than effectiveness[12]. According to a systematic review[13], although ext-LND represents the most accurate staging procedure, its direct therapeutic effect remains unproven. The review concluded that ext-LND results in worse intraoperative and perioperative outcomes, including increased operative time, blood loss, length of hospital stays, and postoperative complications, without significant improvements in the survival or cancer recurrence rates. Thus, the treatment effects of ext-LND in RARP have not been sufficiently studied.

We have developed a comprehensive database of patients with prostate cancer treated with RARP in Japan (https://www.urology.kuhp.kyoto-u.ac.jp/information/research_activities.html). Using the robust database, we initially aimed to compare the oncological outcomes of RARP among low-, intermediate-, and high-risk patients categorized based on the NCCN risk classification. Our secondary aim was to determine whether ext-LND is beneficial for patients with intermediate risk or higher by propensity score matching. Our study findings will not only facilitate making accurate predictions of treatment outcomes in the era where refined surgeries are performed via RARP but also clarify the controversy on the therapeutic effects of ext-LND.

Materials/subjects and methods

Data acquisition

We retrospectively collected the clinical data of 8 194 patients who underwent RARP from 2011 to 2023 at 25 tertiary care centers nationwide in Japan. (see Supplemental Methods; A word file, that describes affiliated institutions). All cases were allocated a patient ID for analyses. Ext-LND was performed on a case-by-case basis at each facility's preoperative conference and surgeon's decision.

Factors for analyses and their data cleaning

We performed data cleaning, and columns containing cleaned data were appended with "[corrected]" (data not shown). PSA failure was defined as follow-up PSA of ≥0.2 ng/ml with a confirmatory increase. Of note, in patients whose postoperative PSA was not <0.2 ng/mL, the surgical date was defined as the PSA failure date. Clinical recurrence was defined as the presence of recurrence on imaging studies, such as computed tomography or mpMRI. Limited lymph node dissection (ltd-LND) was defined as the dissection of the obturator fossa only, whereas ext-LND was defined as the dissection of the obturator fossa, external iliac, and internal iliac, including a more expansive template.

Data processing and cleaning for statistical analyses were performed as shown in Supplemental Methods. Briefly, data formats were corrected (e.g., mm/dd/yyyy data was changed to yyyy/mm/dd). The patients with lacking data and metastases in the lymph nodes and/or distant organs (cN1 and/or cM1) as well as those who were too young or old were removed. The categorical data were binarized. Thus, a total of 7 384 cases were analyzed.

Statistical analysis

We utilized Kolmogorov–Smirnov test, Kruskal–Wallis test with Dunn's post-hoc test, The Mann–Whitney U test, Fisher's exact tests, Kaplan–Meier method, log-rank test and Cox proportional hazards model for statistical analyses. Propensity matching was utilized for balancing groups. Detailed statistical methods are shown in Supplemental Methods.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (Approved Protocol Number R3168), and performed in accordance with the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. All study participants provided informed consent before participation in the study and had the right to withdraw voluntarily and without penalty.

Results

Comparisons of factors among low-, intermediate- and high-risk cases

To obtain a comprehensive overview of the entire database, we examined the patient characteristics within each risk category. Normality tests for age, iPSA, and years from surgery to the final observation indicated that these variables followed non-normal distributions (Supplemental Fig. 1). The median ages of the high- (70.0 [66.0–73.1] years), intermediate- (70.0 [65.0–73.0] years), and low-risk (69.0 [64.0–73.0] years) groups were significantly, although slightly, different from each other (Fig. 1A). The median iPSA for the high-, intermediate-, and low-risk groups decreased in that order (9.3 [6.3–16.0] ng/mL, 7.5 [5.5–10.6] ng/mL, and 6.1 [5.1–7.6] ng/mL, respectively; Fig. 1B). Follow-up periods were similar among the three groups (high-risk: 2.6 [1.4–4.5] years, intermediate-risk: 2.7 [1.3–4.5] years, low-risk: 2.9 [1.4–4.8] years; Fig. 1C). The proportion of patients who underwent ext-LND was significantly higher in the high-risk group (38.6%) than in the intermediate-(11.3%) and low-risk (3.1%; Fig. 1D). The median numbers of removed lymph nodes were 19 (interquartile range: 13–26) and 8 (5–13) in ext-LND and ltd-LND, respectively. The percentage of patients with pN1 after lymph node dissection was 6.82% for those with cN0, compared to 55.1% for those with cN1. All cases with grade group 4 or 5 were classified as high-risk group according to the risk classification (Fig. 1E) groups. The

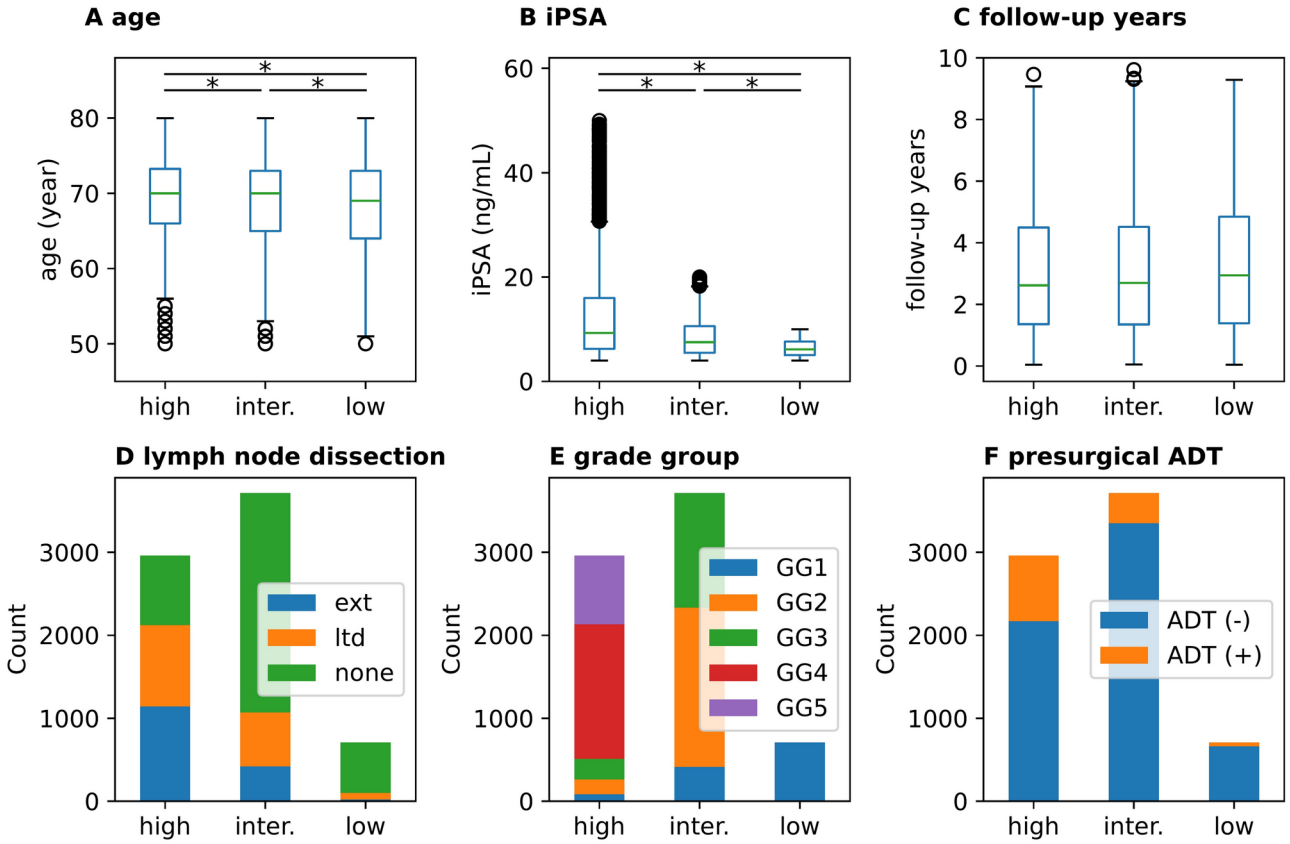


Fig. 1. Patient characteristics from the different risk groups. The distributions of age (**A**), initial PSA (iPSA, **B**), and follow-up years (**C**) among the high-, intermediate-, and low-risk groups. Asterisks (*) indicate statistically significant differences between groups by Dunn's method. **D**: The distribution of patients who underwent extended lymph node dissection (ext), those who underwent limited lymph node dissection (ltd), or those who did not undergo lymph node dissection (none). **E**: The distribution of patients diagnosed with grade groups 1–5 based on the results of the prostate biopsy pathology. **F**: The distribution of patients who underwent presurgical ADT.

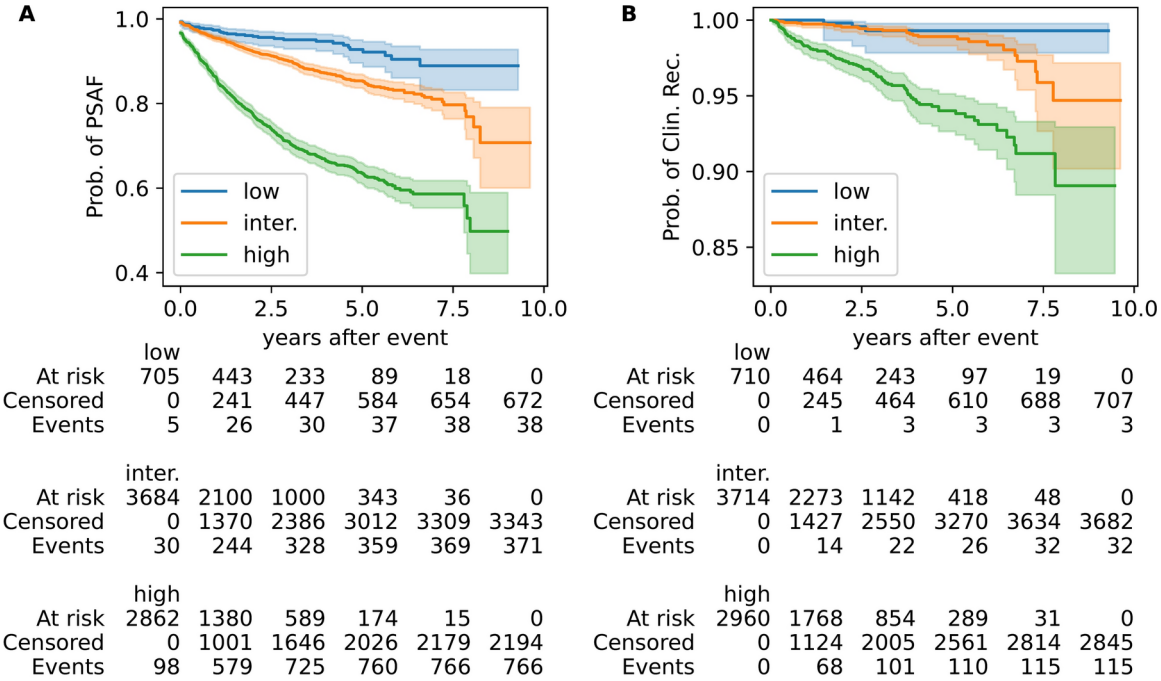
high-risk group was more likely to undergo presurgical androgen deprivation therapy (ADT) (26.7%) than the intermediate- (9.8%) and low-risk (6.8%) groups (Fig. 1F).

The survival probability for PSA failure was significantly different among the three groups ($p < 0.001$, log-rank test, Fig. 2A). The survival rates for clinical recurrence and CRPC were significantly different between the low- and high-risk groups and between the intermediate- and high-risk groups ($p < 0.001$), but not between the low- and intermediate-risk groups ($p = 0.159$ and 0.937, respectively; Figs. 2B and C). The OS was significantly different between the intermediate- and high-risk groups ($p = 0.037$), but not between the low- and intermediate-risk groups ($p = 0.703$) and between the low- and high-risk groups ($p = 0.119$, Fig. 2D).

Patient characteristics

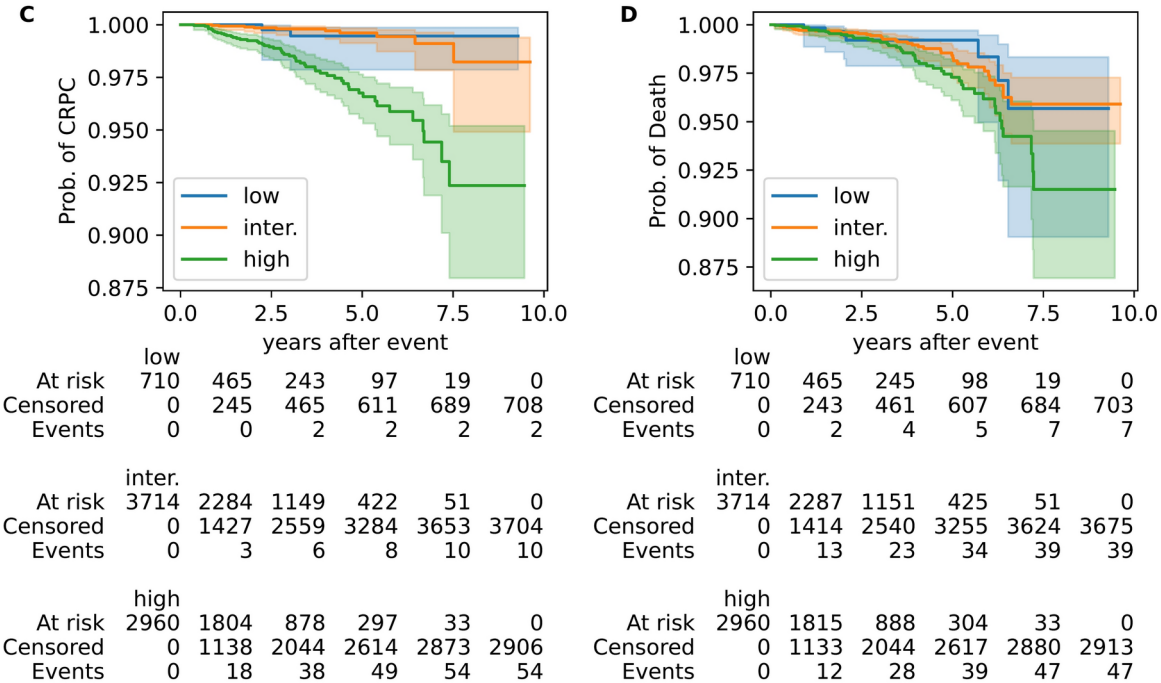
To analyze the effectiveness of ext-LND, we only conducted analyses on the intermediate- or high-risk groups (n = 6 674). We further compared the patient characteristics between the no-LND plus ltd-LND (no-ltd-LND) and ext-LND groups. The iPSA was significantly higher in the ext-LND group (9.8 [6.6–15.6] ng/mL) than in the no-ltd-LND group (7.8 [5.6–11.3] ng/mL, $p < 0.001$, Table 1). More patients with clinical T3–4 stage were included in the ext-LND group (21.5%) than in the no-ltd-LND group (6.8%, $p < 0.0001$, Fisher's exact test, Table 2). For the statistical analyses, the GGs (grades 1–5) were re-categorized into the following binary data: grade 1 vs. 2–5, grades 1–2 vs. 3–5, grades 1–3 vs. 4–5, and grades 1–4 vs. 5. Although all cases in the ext-LND group had higher GGs throughout all the binarized categories, the comparison of GG1–3 vs. GG4–5 showed the lowest p-value ($1.9\ 10^{-99}$), with the ratio of GG4–5 being 59.6% in the ext-LND group as compared to 29.7% in the no-ltd-LND group (Table 2). The ext-LND group (73.1%) has a higher proportion of high-risk patients than the no-ltd-LND group (35.6%, $p < 0.001$, Table 2). Overall, iPSA, ratio of clinical T stage (cT1–2 vs. cT3–4), ratio of high-grade biopsied specimens (GG1–3 vs. GG4–5), ratio of high-risk cases (intermediate vs. high-risk), which were the three factors defining risks, were significantly different between the ext-LND group and the no-ltd-LND group.

We utilized the values of the iPSA, clinical T stage, GG1–3 vs. GG4–5, and usage of preoperative androgen blockade for propensity matching. To find the best matched cohort, we calculated the p-values and SMDs of the matching factors using a range of caliper values (Supplemental methods and Supplemental Table 1). When using



low						
At risk	705	443	233	89	18	0
Censored	0	241	447	584	654	672
Events	5	26	30	37	38	38
inter.						
At risk	3684	2100	1000	343	36	0
Censored	0	1370	2386	3012	3309	3343
Events	30	244	328	359	369	371
high						
At risk	2862	1380	589	174	15	0
Censored	0	1001	1646	2026	2179	2194
Events	98	579	725	760	766	766

low						
At risk	710	464	243	97	19	0
Censored	0	245	464	610	688	707
Events	0	1	3	3	3	3
inter.						
At risk	3714	2273	1142	418	48	0
Censored	0	1427	2550	3270	3634	3682
Events	0	14	22	26	32	32
high						
At risk	2960	1768	854	289	31	0
Censored	0	1124	2005	2561	2814	2845
Events	0	68	101	110	115	115



low						
At risk	710	465	243	97	19	0
Censored	0	245	465	611	689	708
Events	0	0	2	2	2	2
inter.						
At risk	3714	2284	1149	422	51	0
Censored	0	1427	2559	3284	3653	3704
Events	0	3	6	8	10	10
high						
At risk	2960	1804	878	297	33	0
Censored	0	1138	2044	2614	2873	2906
Events	0	18	38	49	54	54

low						
At risk	710	465	245	98	19	0
Censored	0	243	461	607	684	703
Events	0	2	4	5	7	7
inter.						
At risk	3714	2287	1151	425	51	0
Censored	0	1414	2540	3255	3624	3675
Events	0	13	23	34	39	39
high						
At risk	2960	1815	888	304	33	0
Censored	0	1133	2044	2617	2880	2913
Events	0	12	28	39	47	47

Figure2

Fig. 2. Kaplan–Meier survival analysis. Survival probabilities for PSA failure (**A**), clinical recurrence (**B**), CRPC (**C**), and overall survival (**D**) among the high-, intermediate-, and low-risk groups.

a caliper of 0.00009, all factors had SMD of < 0.1 and p of > 0.2 in 945 cases in both groups. In fact, the values of the four factors were well balanced (Tables 1–2).

After the propensity matching, we performed survival analyses using pre- and post-matched case data (Fig. 3). The biochemical recurrence-free survival (PSA-Fail-Free Survival) was significantly higher in the no-ltd-LND group (5-year survival: 78.9%) than in the ext-LND group (5-year survival: 5.8%, HR: 1.77 [95% CI: 1.56–2.00], p < 0.001) in the pre-matched cohort (Fig. 3A). However, the PSA-Fail-Free Survival was similar between the

Cohort	Factors	Median [IQR] values before matching				Median [IQR] values after matching			SMD
		ext_LND (n=1563)	no_ltd_LND (n=5111)	p value		ext_LND (n=1113)	no_ltd_LND (n=1113)	p value	
int. & high (caliper=0.00002)	age (years)	70.0 [65.0–73.0]	70.0 [66.0–73.0]	0.183		69.0 [65.0–73.0]	70.0 [65.0–73.0]	0.280	0.060
	initial PSA (ng/mL)	9.8 [6.6–15.6]	7.8 [5.6–11.3]	<0.001	*	8.4 [6.1–12.3]	8.1 [5.9–11.7]	0.113	
	follow-up years	2.6 [1.4–4.5]	2.7 [1.3–4.5]	0.773		2.7 [1.5–4.8]	2.9 [1.5–5.0]	0.557	
		ext_LND (n=1143)	**no_ltd_LND (n=1817)**	**p value**		**ext_LND (n=1064)**	**no_ltd_LND (n=1064)**	**p value**	
high only (caliper=0.03)	age (years)	70.0 [66.0–73.0]	70.0 [66.0–74.0]	0.252		70.0 [66.0–74.0]	70.0 [66.0–73.0]	0.208	0.024
	initial PSA (ng/mL)	10.6 [7.1–18.3]	8.5 [6.0–14.2]	<0.001	*	10.1 [6.8–17.9]	10.2 [6.9–16.7]	0.729	
	follow-up years	2.6 [1.4–4.5]	2.7 [1.3–4.5]	0.825		2.7 [1.3–4.6]	2.6 [1.4–4.6]	0.703	
		ext_LND (n=420)	**no_ltd_LND (n=3294)**	**p value**		**ext_LND (n=362)**	**no_ltd_LND (n=362)**	**p value**	
int only (caliper=0.00004)	age (years)	70.0 [66.0–73.0]	69.0 [65.0–73.0]	0.023		69.0 [65.0–73.0]	70.0 [66.0–73.0]	0.134	0.007
	initial PSA (ng/mL)	7.5 [5.5–10.5]	7.8 [5.8–11.5]	0.015	*	7.3 [5.5–10.8]	7.3 [5.5–10.8]	0.951	
	follow-up years	2.7 [1.3–4.5]	2.9 [1.5–4.9]	0.235		3.0 [1.6–5.0]	3.1 [1.6–5.0]	0.252	
		ext_LND (n=333)	**no_ltd_LND (n=343)**	**p value**		**ext_LND (n=241)**	**no_ltd_LND (n=241)**	**p value**	
T34 only (caliper=0.003)	age (years)	70.0[65.0–73.0]	71.0 [67.0–74.0]	0.050		70.0 [66.0–73.0]	71.0 [66.0–74.0]	0.172	0.051
	initial PSA (ng/mL)	11.5 [7.9–19.5]	9.1 [6.3–16.3]	<0.001	*	10.5 [7.4–16.1]	10.2 [6.9–18.8]	0.725	
	follow-up years	2.6 [1.5–4.3]	3.0 [1.4–5.0]	0.051		2.8 [1.5–4.5]	3.0 [1.4–4.8]	0.550	

Table 1. Comparisons of prepoerative factors (continuous values) between ext_LND and no_ltd_LND in intermediate and high risk patients. ext_LND: patient group who performed extended lymph node dissection, no_ltd_LND: patient group who performed limited lymph node dissection or who performed neither limited nor extended lymph node dissection. *: p value was below.05, IQR: interquartile range, p value: Mann Whitney U tests, SMD: standardized mean difference. initial PSA was used for propensity matching.

no-ltd-LND (5-year survival: 79.3%) and ext-LND (5-year survival: 78.7%, HR = 1.07 [0.78–1.48], p = 0.672) groups in the post-matched cohort (Fig. 3B). Clinical recurrence-free survival was significantly higher in the no-ltd-LND group (5-year survival: 97.6%) than in the ext-LND group (5-year survival: 94.0%, HR: 2.69 [95% CI: 1.94–3.72], p < 0.001) in the pre-matched cohort (Fig. 3C). However, clinical recurrence-free survival was similar between the no-ltd-LND (5-year survival: 96.3%) and ext-LND (5-year survival: 95.9%, HR: 1.28 [0.56–2.93], p = 0.551) groups in the post-matched cohort (Fig. 3D). The survival before CRPC (CRPC-free survival) was significantly higher in the no-ltd-LND group (5-year survival: 98.7%) than in the ext-LND group (5-year survival: 97.2%, HR: 2.63 [95% CI: 1.61–4.32], p < 0.001 in the pre-matched cohort (Fig. 3E). However, the CRPC-free survival was similar between the ext-LND (5-year survival: 99.6%) and no-ltd-LND groups (5-year survival: 97.6%, HR: 0.33 [0.07–1.66], p = 0.159) in the post-matched cohort (Fig. 3F). The OS was significantly better in the no-ltd-LND group (5-year survival: 98.0%) than in the ext-LND group (5-year survival: 97.5%, HR: 1.62 [1.03–2.55], p = 0.034) in the pre-matched cohort (Fig. 3G), whereas the OS was not different between the no-ltd-LND (5-year survival: 97.5%) and ext-LND groups (5-year survival: 97.7%, HR: 1.91 [0.48–7.66], p = 0.351) in the post-matched cohort (Fig. 3H).

Survival analyses for high-risk-only, intermediate-risk-only, and clinical T3–4-only cohorts

For the subgroup analyses, we performed similar analyses in the high-risk-only, intermediate-risk-only, and locally advanced-only (cT3–4) cohorts. In the high-risk-only cohort, similar to the total cohort (intermediate- and high-risk cohorts), age and follow-up years were not different between the ext-LND and no-ltd-LND groups, but the iPSA was higher in the ext-LND group than in the no-ltd-LND group ("high-risk only" in Table 1). The ext-LND cohort had a higher number of patients with cT3-4 and a lower number of patients who underwent ADT, but the ratio of the high GG was not different between the two groups (Table 2). In the analysis to find the best caliper value, values were well balanced in age (p = 0.208), iPSA (p = 0.729) and follow-up years (p = 0.703) as depicted in Table 1 as well as in clinical T stage (p = 1.000), grade group (p = 1.000) and ADT (p = 0.438) as presented in Table 2 at the caliper value 0.03 (n = 1064, each; Supplemental Table 2). Differences were not observed in the four survival analyses in the post-matched cohort (Fig. 4). In the intermediate-risk-only cohort, age and follow-up years were not different between the ext-LND and no-ltd-LND groups, but the iPSA was higher in the ext-LND group than in the no-ltd-LND group ("int.-risk only" in Table 1). A smaller number of patients in the ext-LND cohort underwent ADT (Table 2). Values were well balanced in age (p = 0.134), iPSA (p = 0.951) and follow-up years (p = 0.252) as shown in Table 1 as well as in ADT (p = 1.000) as depicted in Table 2 at the caliper value 0.00004 (n = 362 each; Supplemental Table 1). No differences were observed in the four survival analyses in the post-matched cohort (Fig. 5). In the locally advanced-only cohort, similar to the other cohorts, age and follow-up years were not different between the ext-LND and no-ltd-LND groups, but the iPSA was higher in the ext-LND group (Table 1). The ext-LND group had a higher number of high-GG cases (p = 0.043) and a lower number of patients who underwent ADT (p < 0.001) (Table 2). Values were well balanced in age (p = 0.172), iPSA (p = 0.725) and follow-up years (p = 0.550) as shown in Table 1 as well as in GG (p = 1.000) and ADT (p = 0.700) as shown in Table 2 at the caliper value 0.003 (n = 241 each; Supplemental Table 1). No statistically significant differences were observed in the four survival analyses in the post-matched cohort (Fig. 6).

Cohort	Factors	Before matching						After matching					
		ext_LND [n=1563]		no_ltd_LND [n=5111]		p value		ext_LND [n=1113]		no_ltd_LND [n=1113]		p value	SMD
int. & high (caliper=0.00002)		**T3-4**	**T1-2**	**T3-4**	**T1-2**			**T3-4**	**T1-2**	**T3-4**	**T1-2**		
	clinical T	333 [21.3%]	1230 [78.7%]	343 [6.7%]	4768 [93.3%]	<0.001	*	122 [11.0%]	991 [89.0%]	106 [9.5%]	1007 [90.5%]	0.294	0.002
	group grade	**high**	**low**	**high**	**low**			**high**	**low**	**high**	**low**		
	1 vs 2–5	1527 [97.7%]	36 [2.3%]	4648 [90.9%]	463 [9.1%]	5.8E-23	*						
	1–2 vs 3–5	1262 [80.7%]	301 [19.3%]	2816 [55.1%]	2295 [44.9%]	2.4E-79	*						
	1–3 vs 4–5	932 [59.6%]	631 [40.4%]	1518 [29.7%]	3593 [70.3%]	1.9E-99	*,**	564 [50.7%]	549 [49.3%]	595 [53.5%]	518 [46.5%]	0.203	0.002
	1–4 vs 5	341 [21.8%]	1222 [78.2%]	487 [9.5%]	4624 [90.5%]	3.7E-34	*						
	ADT	**performed**	**not performed**	**performed**	**not performed**			**performed**	**not performed**	**performed**	**not performed**		
		277 [17.7%]	1286 [82.3%]	878 [17.2%]	4233 [82.8%]	0.620		173 [15.5%]	940 [84.5%]	171 [15.4%]	942 [84.6%]	0.953	0.036
	risk	**High**	**intermediate**	**High**	**intermediate**			**high**	**intermediate**	**high**	**intermediate**		
		1143 [73.1%]	420 [26.9%]	1817 [35.6%]	3294 [64.4%]	<0.001	*	701 [63.0%]	412 [37.0%]	680 [61.1%]	433 [38.9%]	0.382	
		ext_LND [n=1143]		**no_ltd_LND [n=1817]**		**p value**		**ext_LND [n=1064]**		**no_ltd_LND [n=1064]**		**p value**	
high only (caliper=0.03)		**T3-4**	**T1-2**	**T3-4**	**T1-2**			**T3-4**	**T1-2**	**T3-4**	**T1-2**		
	clinical T	333 [29.1%]	810 [70.9%]	343 [18.9%]	1474 [81.1%]	<0.001	*	269 [25.3%]	795 [74.7%]	270 [25.4%]	794 [74.6%]	1.000	0.002
	group grade	**high**	**low**	**high**	**low**			**high**	**low**	**high**	**low**		
	1–3 vs 4–5	932 [81.5%]	211 [18.5%]	1518 [83.5%]	299 [16.5%]	0.162	*	866 [81.4%]	198 [18.6%]	865 [81.3%]	199 [18.7%]	1.000	0.002
	ADT	**performed**	**not performed**	**performed**	**not performed**			**performed**	**not performed**	**performed**	**not performed**		
		246 [21.5%]	897 [78.5%]	545 [30.0%]	1272 [70.0%]	<0.001		234 [22.0%]	830 [78.0%]	250 [23.5%]	814 [76.5%]	0.438	0.036
		ext_LND [n=420]		**no_ltd_LND [n=3294]**		**p value**		**ext_LND [n=362]**		**no_ltd_LND [n=362]**		**p value**	
int only (caliper=0.00004)	ADT	**performed**	**not performed**	**performed**	**not performed**			**performed**	**not performed**	**performed**	**not performed**		
		31 [7.4%]	389 [92.6%]	333 [10.1%]	2961 [89.9%]	0.081		20 [5.5%]	342 [94.5%]	19 [5.2%]	343 [94.8%]	1.000	0.012
		ext_LND [n=333]		**no_ltd_LND [n=343]**		**p value**		**ext_LND [n=241**		**no_ltd_LND [n=241]**		**p value**	
T34 only (caliper=0.003)	group grade	**high**	**low**	**high**	**low**			**high**	**low**	**high**	**low**		
	1–3 vs 4–5	204 [61.3%]	129 [38.7%]	183 [53.4%]	160 [46.6%]	0.043	*	136 [56.4%]	105 [43.6%]	137 [56.8%]	104 [43.2%]	1.000	0.008
	ADT	**performed**	**not performed**	**performed**	**not performed**			**performed**	**not performed**	**performed**	**not performed**		
		102 [30.6%]	231 [69.4%]	139 [40.5%]	204 [59.5%]	<0.001		84 [34.9%]	157 [65.1%]	79 [32.8%]	162 [67.2%]	0.700	0.044

Table 2. Comparisons of prepoerative parameters [categorical values] between ext_LND and no_ltd_LND in intermediate and high risk patients. ext_LND: patient group who performed extended lymph node dissection, no_ltd_LND: patient group who performed limited lymph node dissection or who performed neither limited nor extended lymph node dissection. P values were calculated by Fisher exact test. *: p value was below.05, **: lowest p value among binarized values among group grade of biopsied pathological specimens (group grade). SMD: standardized mean difference. initial PSA was used for propensity matching. ADT: presurgical/neoadjuvant androgen deprivation therapy.

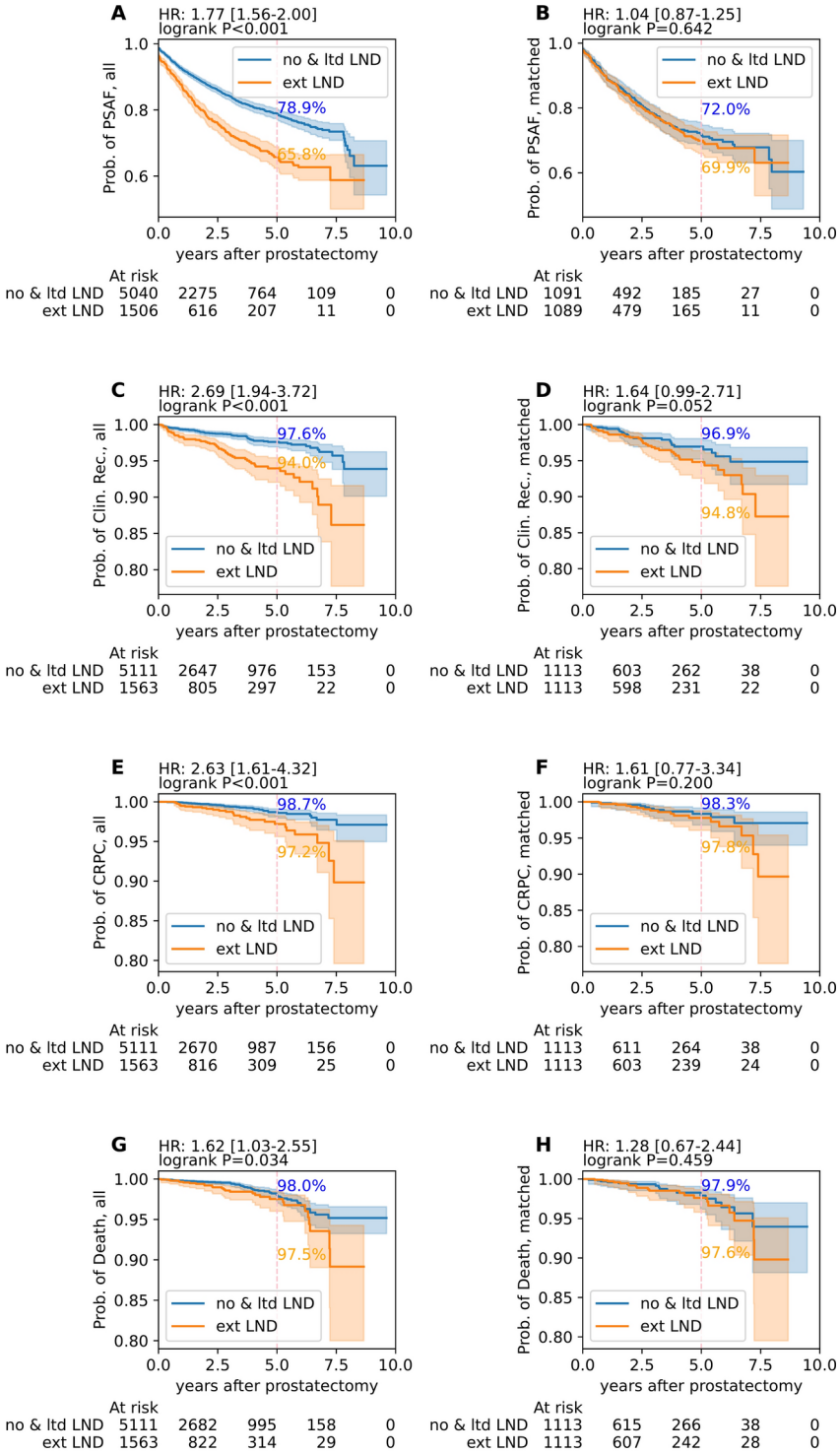


Fig. 3. Kaplan–Meier survival curves for the pre-matched and post-matched cohorts of the LND groups with intermediate and high risks. Survival probabilities for PSA failure (**A**, **B**), clinical recurrence (**C**, **D**), CRPC (**E**, **F**), and overall survival (**G**, **H**) in the pre-matched (**A**, **C**, **E**, **G**) and post-matched (**B**, **D**, **F**, **H**) cohorts among patients who did not undergo lymph node dissection (no-ltd-LND) and those who underwent extended LND (ext-LND). HR: hazard ratio and its 95% confidence interval (brackets), which was calculated by using the Cox proportional hazards model. Values highlighted in blue and orange represent 5-year survival. "no & ltd-LND" represent the survival curves of patients who did not undergo LND or those who underwent ltd-LND. "ext-LND" represents the survival curves of patients who underwent extended lymph node dissection.

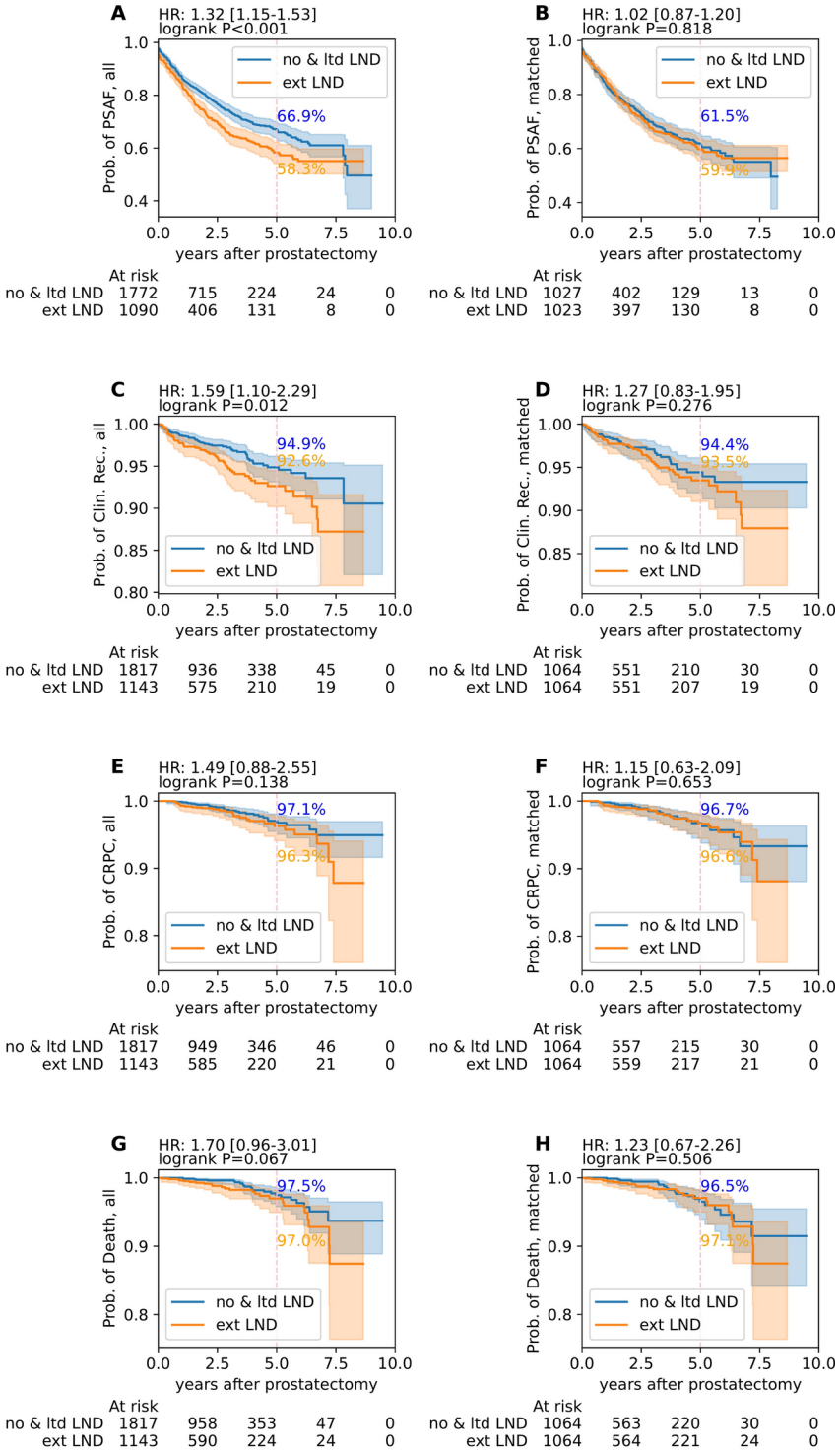


Fig. 4. Kaplan–Meier survival curves of the pre-matched and post-matched cohorts of the LND group with a high risk. Survival probabilities for PSA failure (**A**, **B**), clinical recurrence (**C**, **D**), CRPC (**E**, **F**), and overall survival (**G**, **H**) in the pre-matched (**A**, **C**, **E**, **G**) and post-matched (**B**, **D**, **F**, **H**) cohorts among patients who did not undergo lymph node dissection (no-ltd-LND) and those who underwent extended LND (ext-LND). HR: hazard ratio and its 95% confidence interval (brackets), which was calculated by Cox proportional hazards model. Values highlighted in blue and orange represent 5-year survival. "no & ltd-LND" represents the survival curves of patients who did not undergo LND or those who performed limited LND. "ext-LND" represents the survival curves of patients who underwent extended lymph node dissection.

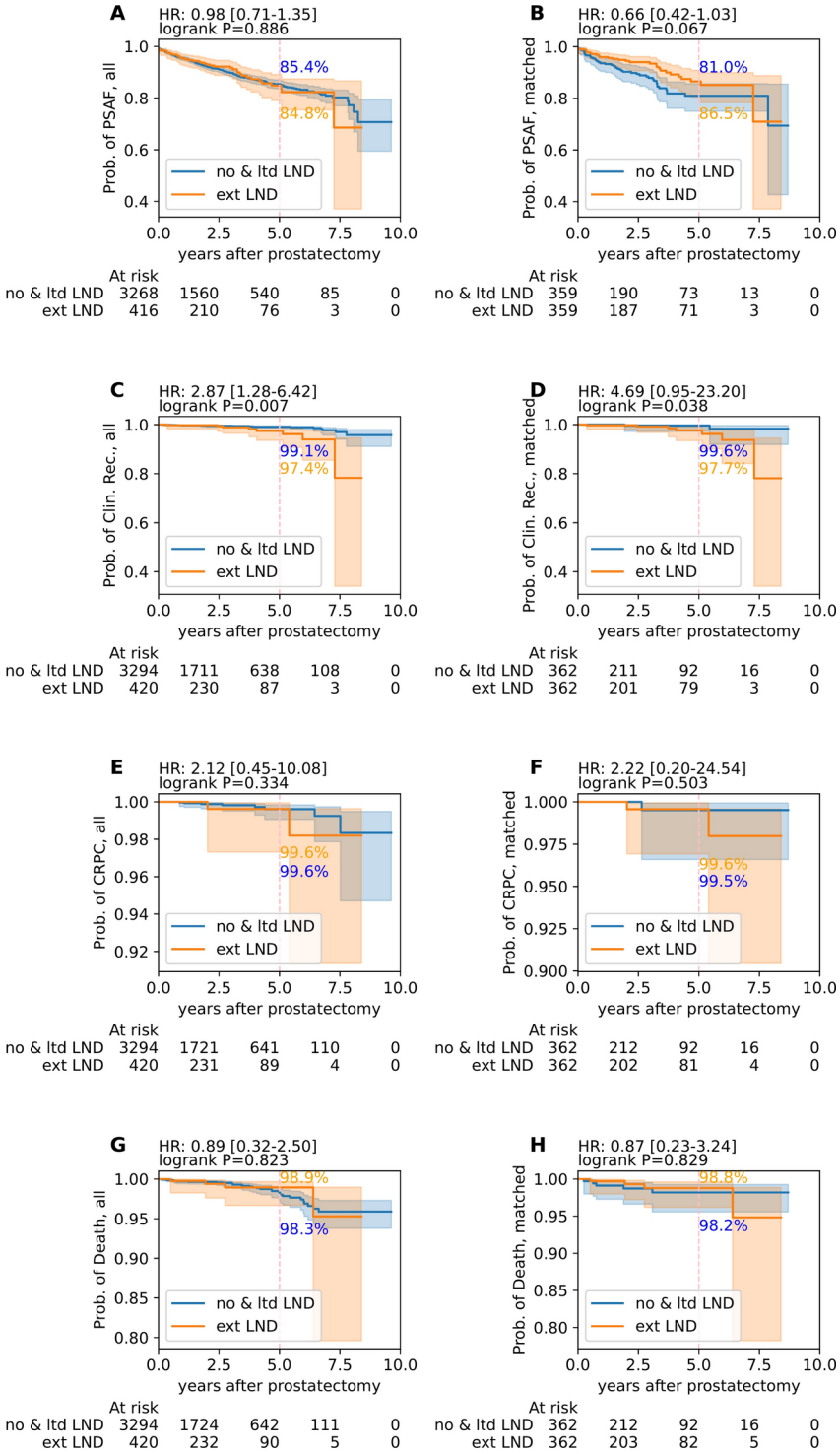


Fig. 5. Kaplan–Meier survival curves for the pre-matched and post-matched cohorts of LND groups with an intermediate risk. Survival probabilities for PSA failure (**A**, **B**), clinical recurrence (**C**, **D**), CRPC (**E**, **F**), and overall survival (**G**, **H**) in the pre-matched (**A**, **C**, **E**, **G**) and post-matched (**B**, **D**, **F**, **H**) cohorts among patients who did not undergo LND (no-ltd-LND) and those who underwent extended LND (ext-LND). HR: hazard ratio and its 95% confidence interval (brackets), which was calculated by using a Cox proportional hazards model. Values highlighted in blue and orange represent 5-year survival. "no & ltd-LND" represents the survival curves of patients who did not undergo LND or those who underwent ltd-LND. "ext-LND" represents the survival curves of patients who underwent extended lymph node dissection.

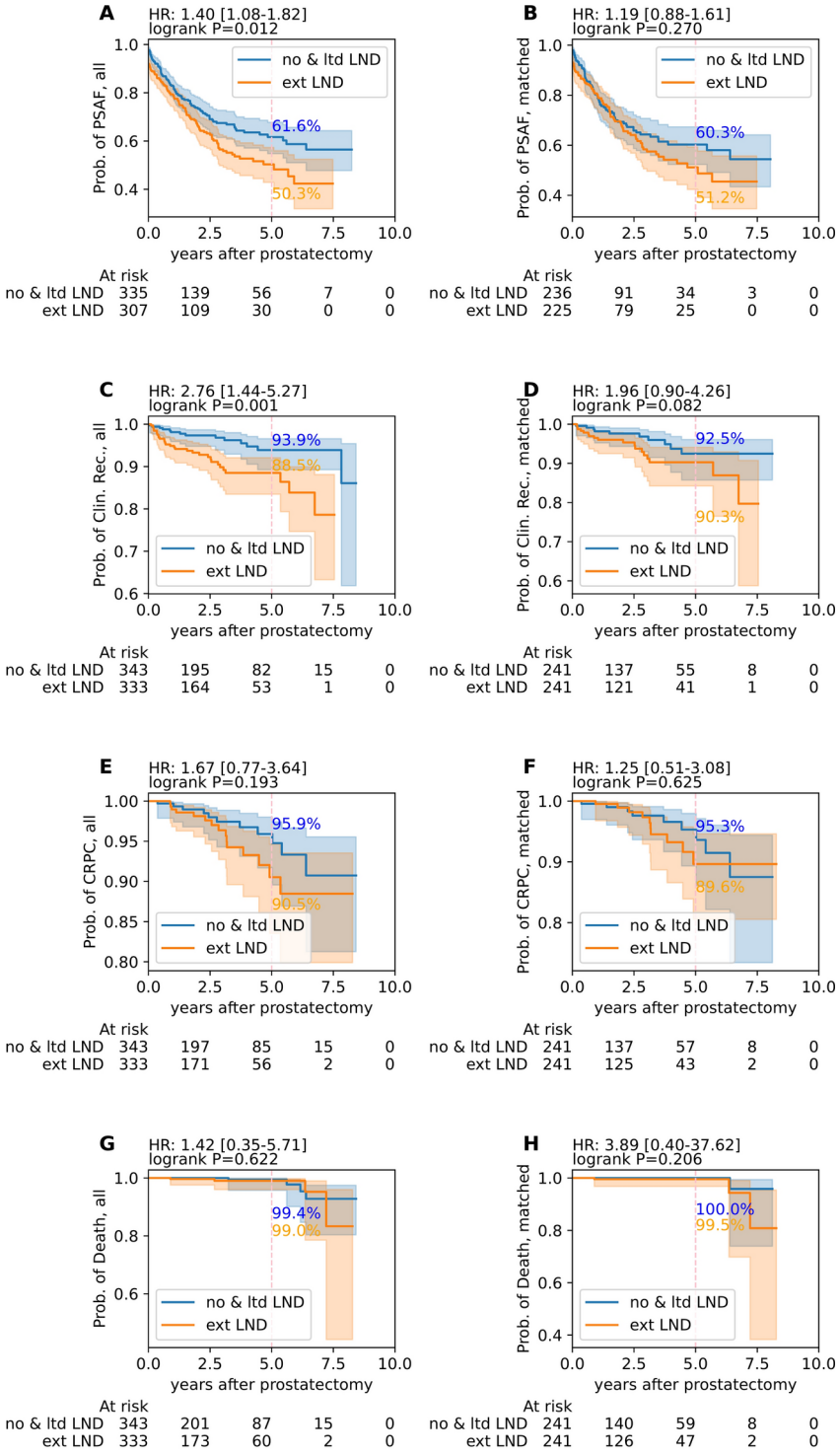


Fig. 6. Kaplan–Meier survival curves for the pre-matched and post-matched cohorts of the LND groups with clinical T3 or T4 on MRI. Survival probabilities for PSA failure (**A**, **B**), clinical recurrence (**C**, **D**), CRPC (**E**, **F**), and overall survival (**G**, **H**) in the pre-matched (**A**, **C**, **E**, **G**) and post-matched (**B**, **D**, **F**, **H**) cohorts among patients who did not undergo LND (no-ltd-LND) and those who underwent extended LND (ext-LND). HR: hazard ratio and its 95% confidence interval (brackets), which was calculated by using a Cox proportional hazards model. Values highlighted in blue and orange represent 5-year survival. "no & ltd-LND" represents the survival curves of patients who did not undergo LND or those who performed limited lymph node dissection. "ext-LND" represents the survival curves of patients who underwent extended lymph node dissection.

Discussion

We conducted several analyses using a comprehensive database of patients who underwent RARP. Although no significant difference was found in the OS among the risk categories, the other survival parameters (PSA failure, clinical recurrence, and CRPC) were different among the risk groups. Ext-LND did not lead to improved oncological outcomes, even in the era of RARP using the da Vinci system.

The oncological benefit at the time of radical prostatectomy (RP) has been reported in a previous systematic review[13]. Recently, a prospective randomized study involving 300 cases assessed the effectiveness of ext-LND and ltd-LND. Although it is unknown if the surgeries were performed by RARP or not, the surgeries were conducted by five selected expert surgeons. Similar to the findings of the current study, they showed no differences in the PSA-Fail-Free Survival, metastasis-free survival, and cancer-specific survival among the risk groups[14]. As RP is now mainly performed by robot-assisted surgery, LND can now be performed more delicately and precisely through high-resolution three-dimensional imaging and highly flexible articulated arms. Better PSA-Fail-Free Survival has been reported for ext-LND than for ltd-LND in Japanese patients; however, this study did not performing matching of a small cohort (n = 378)[15]. Another Japanese report showed similar analyses (small cohort and no matching), but they reported opposite results, stating that ext-LND did not improve the outcomes[16]. A previous report that performed analyses with propensity matching showed that the PSA-Fail-Free Survival was not improved by ext-LND[17]. Although robotic-assisted ext-LND achieved increased lymph node yield and higher detection rates of lymph node metastases, it did not improve the biochemical outcomes at the short-term follow-up[18].

The importance of LND in other cancers may raise intriguing questions. Previous systematic reviews and meta-analyses have indicated that ext-LND is associated with improved oncologic outcomes among bladder cancer cases[19,20]. However, a recent randomized controlled trial showed that ext-LND did not demonstrate a significant advantage over ltd-LND in terms of recurrence-free survival (primary endpoint), cancer-specific survival, and OS[21]. Similar concerns also arise in renal cell carcinoma (RCC), where the benefits of LND remain uncertain[22,23]. As with bladder cancer and RCC, we question the utility of LND in cancer control for prostate cancer. Reasons for this include the potential immunological benefits of preserving lymph nodes and the inherent difficulty in achieving cancer control through LND alone. Future research, including refined basic science studies and large-scale prospective clinical trials, is needed to resolve these doubts across various cancer types.

In conclusion, our study successfully demonstrated real-world survival differences among patients with localized prostate cancer by each risk category. Additionally, our analysis using large-scale propensity matching revealed that extended LND does not improve the survival outcomes of patients with prostate cancer even with robotic surgery.

Data availability

Data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. https://www.urology.kuhp.kyoto-u.ac.jp/information/research_activities.html.

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Author contributions

Conception and design: AS; Acquisition of data: AS, MK, TS, RS, RK, YS, HN, YS, RI, MN, KK, HI, NK, KS; Analysis and interpretation of data: AS, KN; Drafting of the manuscript: AS; Critical revision of the manuscript for important intellectual content: AS, KN, SA, TG; Statistical analysis: KN; Supervision: TK, TG, TK; Other: DaiCAD project administration: AS, SA, MK, RS, TG, TK.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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