Research Square

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Extended and Sufficient Pelvic Lymph Node Dissection at Robotic Prostatectomy for High-risk Prostate Cancer Benefits Biochemical Recurrence-free Survival: A Single-center, Propensity Score-matched Analysis

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Abstract

Background: A recent randomized controlled trial failed to demonstrate oncological benefit from extended pelvic lymph node dissection (PLND) during radical prostatectomy, while subgroup analysis suggested a potential benefit in high grade prostate cancer (PCa). We evaluated early survival outcome in contemporary PCa patients using propensity score (PS)-matched analysis.

Methods: Three hundred and seventy-eight patients with high-risk PCa were enrolled. They were determined to have a lymph node (LN) involvement probability of greater than 5%. The National Comprehensive Cancer Network classification and Johns Hopkins University criteria were used as risk stratification. Clinical stage was determined by assessing digital rectal examination and multiparametric magnetic resonance imaging. Biochemical recurrence (BCR)-free survival was compared between the two groups divided by the threshold of LN yield, which was set at 15.

Results: The mean LN yield was 23.9 and 3.4, and the positive LN rate was 20.1% and 2.0% in the sufficient and insufficient LN yield groups, respectively. In the entire unmatched cohort, the estimated curve was 15.6% superior in 3-year BCR-free survival for sufficient LN yield (hazard ratio [HR] 0.62, 95% confidence interval [CI] 0.40-0.94; *p*=0.025). The PS-matched cohort was converged in each LN yield group to 117 patients, and the difference in the 3-year BCR-free survival widened to 24.8% (HR 0.43, 95% CI 0.26-0.74; *p*=0.002). In the PS-matched analyses of subgroups, the statistical difference was consistent in both standard high-risk PCa (HR 0.43, 95% CI 0.20-0.93; *p*=0.033) and very high-risk PCa (HR 0.45, 95% CI 0.21-0.96; *p*=0.040).

Conclusions: Our results possibly demonstrate the therapeutic role of PLND in high-risk PCa. The benefit of PLND depends on the surgeon complying with the extended template and removing a sufficient number of LNs in selected patients with an optimal risk-range.

Background

Since 2015, prostate cancer (PCa) has become the most prevalent malignant disease and is categorized as the 6th to 7th top cause of death in Japanese men [1]. Over the last decade, radical prostatectomy has become a first-line therapy, and robotic surgery is now a standard method for patients with a localized stage PCa. Simultaneously, a paradigm shift in the surgical approach has resulted changes in the extent or boundaries of pelvic lymph node dissection (PLND) including both better and worse results.

In the early era of minimally invasive prostatectomy done by robotic surgery, a drastically reduced rate was reported for those undergoing a PLND procedure compared to open prostatectomy, and the trend was observed in both minimally invasive and open surgery. The reasons were speculated to be complicated and affected by academic status of institutions, surgeon volume, economic issues, and regional differences [2, 3]. When viewed at a national level, this trend is still observed in Japan and in the United States [4]. In an analysis using the National Cancer Data Base, nearly 40% of patients with unfavorable risk disease did not receive PLND [5].

Oncologic principles should require us to transcend surgical modality and provide surgery of the same quality. The recent rates for the PLND procedure and LN yield appear to have increased with improvements in safety and feasibility in proportion to the surgical volume [6]. However, there are pros and cons in systematic reviews regarding the direct benefit of PLND on oncological outcome. Even if this is the case, the majority of the results are only for biochemical recurrence (BCR)-free survival [7–10], and it is consistent that expanding the template results in more complications [11]. A long-awaited randomized controlled trial (RCT) did not demonstrate better oncological outcomes for extended PLND during radical prostatectomy, despite suggesting the potential benefits of BCR-free survival in high-grade PCa [12]. Thus, for over the last decade the therapeutic role of PLND has remained unclear.

PLND cannot be established as a standard surgical management if the oncological benefit does not outweigh negative impacts on patients. This study focused on early survival outcome, especially on BCR-free survival as an endpoint, and the therapeutic impact of extended and sufficient PLND during robotic prostatectomy, which was evaluated in contemporary patients with high-risk PCa at a single-center and investigated with propensity score (PS)-matched analysis.

Methods

Patient enrollment

A total of 943 patients underwent robot-assisted radical prostatectomy (RARP) between October 2012 and May 2021 at our prostate center. Clinical and pathologic findings were prospectively recorded in a computer database in a stand-alone environment. Of these patients, 378 with high-risk PCa who were determined to have a LN involvement probability of greater than 5% on the Briganti 2012 nomogram were enrolled in the study [13].

National Comprehensive Cancer Network (NCCN) classification was used for entries for the entire high-risk cohort. Clinical stage in all patients was determined by assessing digital rectal examination (DRE) and multiparametric magnetic resonance imaging (MRI) findings, and the appropriate staging was used for risk stratification and nomogram. In the cohort of this study, very few patients underwent MRI targeted biopsy. No cancer was detected in the target core alone, and the statistical data was processed in cores obtained by multiple systematic biopsies.

Patients diagnosed with clinically distinct positive LN (cN1) or with a total biopsy number less than 10 were excluded, while those that received preoperative androgen-deprivation therapy (ADT) were not excluded. Neoadjuvant ADT was not used as a strategy because of high-risk cancer, and it was left to the judgment of the patient and the attending physician. These included cases of hesitation in local radical treatment, cases of change in treatment policy, and cases of receiving preoperative ADT due to anxiety while waiting for surgery. All patients had no plans for radiotherapy and intended for surgery. The median duration of ADT was 6.5 months (interquartile range 3.0-11.8), and there was no difference between the groups compared later ($p = 0.572$).

Robotic prostatectomy and pelvic lymph node dissection

RARP followed by PLND was carried out using an intraperitoneal anterior approach by six surgeons, and the extended PLND template was applied from August 2015. The extended PLND template included the bilateral intrapelvic regions, such as obturator, external iliac, internal iliac, and common iliac up to the ureter crossing. Tissues in the Marcille triangle as the obturator region and lateral vesical fat tissue as the internal iliac region were included from February 2018. All our surgeons performed a mandatory self-assessment of the quality of PLND when the PLND was done according to the extended template. Prostatectomy specimens and LNs separated by regions were submitted for pathological evaluation.

Postoperative follow-up

After robotic surgery, patients that received preoperative ADT did not continue any hormonal therapy. Prostate-specific antigen (PSA) levels combined with general blood test and physical status were examined every three months, and adjuvant treatment such as radiotherapy or ADT was not performed until a judgement of BCR, although the pathological results show positive surgically resected margins or LN metastases.

BCR was defined as a PSA level greater than 0.2 ng/mL with a subsequent increase, and the occurrence of BCR was the first date of confirmation. Detectable PSA greater than 0.2 ng/mL on the first checkup after surgery was also followed the same criteria, and the occurrence was determined to be the date of surgery.

Patient characteristics of high-risk entire cohort and subgroups

The endpoints for the entire high-risk cohort and subgroups were BCR-free survival as an early oncological outcome. This study applied the 2013 Johns Hopkins University criteria to stratify the entire PCa cohort into subgroups as a standard high-risk (SHR) and very high-risk (VHR) PCa cohort. VHR criteria was defined as multiple individual NCCN high-risk features, > 4 biopsy cores with a Gleason grade sum of 8 to 10, or a primary Gleason grade pattern 5 [14, 15].

Our retrospective analysis found the lower limit for the LN yield was around 15 in high quality PLND as determined by our surgeons' self-assessment, which consisted of the degree of LN dissection in each part in the template and the reason when omitted. Accordingly, we tentatively set a threshold of a sufficient LN number at 15, and compared estimated BCR-free survival between extended PLND with a sufficient LN yield group (sufficient LN yield group, $n = 174$) and other (insufficient LN yield group, $n = 204$) in the entire and subgroup cohort (Tables 1,3,4).

The insufficient LN yield group included patients that underwent standard- (n = 36, 17.6%), limited- (n = 74, 36.3%), unilateral- (n = 10, 4.9%) and omitted-PLND with various reasons (n = 84, 41.2%); the reasons of omission were inexperienced operative technique at the early stage of robot introduction, spending time

to remove adhesions in the abdominal cavity, and concerns about old age or complications of extended PLND.

The covariate factors used in the PS-matching were age, body mass index, PSA, MRI measured prostate volume, clinical T-stage, number of biopsy cores, number of positive cores, biopsy ISUP grade groups proposed by the 2014 International Society of Urological Pathology [16], and preoperative ADT. In this study, the findings for multiparametric MRI were read by specialists in urologic radiology, to determine whether or not there were typical suspicious lesions for malignancy, and histopathologie were evaluated by specialists in urologic pathology.

Statistical analyses

The quantitative and qualitative data were compared using Student's *t*-test and a chi-squared test or Fisher's exact, respectively. The covariate factors used at PS-matched analysis included the preoperative variables mentioned above. Survival was estimated using Kaplan–Meier analysis, and differences were compared with the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox regression analysis, which was also used for conventional multivariate analyses.

All statistical analyses were performed with EZR, which is a graphical user interface for R (2020 The R Foundation for Statistical Computing, version 1.54). All statistical tests were two-sided, with a *p*-value of less than 0.05 considered as statistically significant.

Results

Pathological outcomes in high-risk entire cohort

The mean (median) LN yield and the number (%) of patients with a positive LN were 23.9 (22) and 35 (20.1%) in the sufficient LN yield group, respectively.

Synchronized with the distribution bias of the pathological T-stage, the positive resection margin rate was significantly higher in the sufficient LN yield group than the counterpart (35.1 versus 24.5%, $p = 0.031$). The inequality of these postoperative pathological factors other than the results related to LNs was resolved with an adjustment PS-matching of preoperative factors (Table 2).

The ISUP grading in patients that received preoperative ADT remains for reference. Furthermore, the LN yield in patients that received preoperative ADT was consistently lower than those in hormone naïve patients (24.7 versus 19.7, $p = 0.002$).

BCR-free survival in high-risk entire cohort

After a mean follow-up of 40.3 months in the unmatched cohort, BCR was observed in 31 (17.8%) and 74 patients (36.3%) in the sufficient and insufficient LN yield group, respectively. The estimated curve was 15.6% superior in the 3-year BCR-free survival for sufficient LN yield (77.5 versus 61.9%). Median BCR-free

survival was not reached in either sufficient and insufficient LN yield groups (log rank, $p = 0.021$) (hazard ratio [HR] 0.62, 95% confidence interval [CI] 0.40–0.94; $p = 0.025$) (Fig. 1).

There were some differences in preoperative factors associated with biopsy, stage distribution, and ADT. PS-matching was adjusted for these background differences and converged each LN yield group to 117 patients (Table 1). The difference in the 3-year BCR-free survival widened to 24.8%. Median BCR-free survival was not reached in either the sufficient and insufficient LN yield groups (log rank, $p = 0.001$) (HR 0.44, 95% CI 0.25–0.74; $p = 0.002$) (Fig. 1).

The BCR-free survival was analyzed also in patients group divided by statistical measures. When the entire cohort was stratified by median LN number of 11 and mean LN number of 13, the difference in 3-year BCR-free survival in PS-matched cohort remained at 12.0% (log rank, $p = 0.161$) (HR 0.71, 95% CI 0.43–1.16; $p = 0.174$) and 14.5% (log rank, $p = 0.098$) (HR 0.65, 95% CI 0.39–1.10; $p = 0.108$), respectively.

BCR-free survival in high-risk subgroups

In the SHR unmatched cohort, the estimated curve showed a 12.4% advantage in 3-year BCR-free survival for sufficient LN yield (84.8 versus 72.4%, log rank, $p = 0.042$) (HR 0.50, 95% CI 0.26–0.99; $p = 0.047$). After adjusting for differences in patient age and biopsy-related factors, the PS-matched cohort was converged in each LN yield group to 75 patients (Table 3), and showed a consistent statistical difference in 3-year BCR-free survival (84.5 versus 67.8%, log rank, $p = 0.027$) (HR 0.43, 95% CI 0.20–0.93; $p = 0.033$) (Fig. 2A).

In the VHR cohort, 3-year BCR-free survival for a sufficient LN yield showed a 29.9% advantage in the unmatched cohort (65.7 versus 35.8%, log rank, $p = 0.037$) (HR 0.57, 95% CI 0.33–0.99; $p = 0.048$). The PS-matched cohort was converged in each LN yield group to 35 patients (Table 4), and showed a similar statistical difference in 3-year BCR-free survival (70.0 versus 34.2%, log rank, $p = 0.028$) (HR 0.45, 95% CI 0.21–0.96; $p = 0.040$) (Fig. 2B).

BCR-free survival in cohort excluding patients with PSA > 0.2 ng/mL on the first checkup

Thirty (7.9%) patients were interpreted as detectable PSA greater than 0.2 ng/mL on the first checkup after surgery, and the distribution was equivalent in 13 (7.5%) patients with sufficient LN yield and 17 (8.3) patients with insufficient LN yield. These are clearly different patient groups, which may also include many metastatic stage diseases. Analysis was performed in PS-matched cohort excluding patients with PSA > 0.2 ng/mL on the first checkup to confirm the effect of extended PLND in patients at risk of delayed recurrence. The difference in 3-year BCR-free survival was apparent at 20.8% (log rank, $p = 0.005$) (HR 0.39, 95% CI 0.20–0.78; $p = 0.007$) (Fig. 3A).

BCR-free survival in cohort stratified by timeframe

The extended PLND approach improved around February 2018 with a median LN yield increasing from 4 to 19.5. Analysis was performed in PS-matched cohort between groups stratified according to that timeframe. Although the analysis was mixture of patients with and without complying with the extended PLND, the difference in 3-year BCR-free survival was significant trend as 15.4% (log rank, $p = 0.077$) (HR 0.63, 95% CI 0.37–1.06; $p = 0.084$) (Fig. 3B).

Predictive postoperative factors for BCR in multivariate analysis

Conventional multivariate analysis was also performed on the model with LN yield and postoperative pathological factors. A LN yield of less than 15 and all unfavorable pathological factors, such as T3-4, N1, ISUP grade group 4–5, large index tumor volume, and positive resection margin were statistically significant predictors for BCR in univariate analysis, and those, except for the positive resection margin, showed an independent predictive value in multivariate analysis (Table 5).

Surgical parameters and complications

The mean operating time on the robotic console was 43 minutes longer (184 vs. 141minutes, $p < 0.001$), while the mean blood loss including urine (219 vs. 224mL, $p = 0.786$) did not increase due to the LN yield procedure.

There were no postoperative complications classified as Clavien-Dindo grade IV or V and no statistical difference in frequency of grade III complications. There was adhesive ileus, paralytic ileus, or infectious lymphocele that required radiographic intervention or surgery in three patients of the sufficient LN yield group. There was adhesive ileus or infectious lymphocele that required radiographic intervention in two patients of the insufficient LN yield group.

Discussion

This study enrolled high-risk PCa patients with estimated LN involvement of 21.6% on average. PS-matching followed by survival analysis using preoperative factors showed a statistically significant value of extended PLND with a promising hazard ratio. Attempts to analyses in limited cohorts, such as in cohort excluding patients with PSA > 0.2 ng/mL on the first checkup and in cohort stratified by timeframe with different LN yield, to reduce potential bias as much as possible also supported the existence of oncological benefits of extended PLND. In addition, Cox regression multivariate analysis using postoperative factors showed its independent predictive value. These results definitely indicate the superiority of extended PLND for BCR-free survival and the optimal risk-range setting for patients enrolled in the study.

After safety and feasibility was established, extended PLND became the gold standard for providing accurate nodal staging [17]. Guidelines from both the American Urological Association and European Association of Urology recommend PLND with an extended template in patients with intermediate- and high-risk PCa as an expert opinion under situations without distinct evidence of the oncological benefits

of PLND [18, 19]. Some systematic reviews and meta-analysis referred to oncological outcomes, but most consisted of reports with low levels of evidence, and furthermore, there are considerable variations in the LN yield and the positive rate of metastasis [7–10]. However, recent reports found a modest superiority for PLND regarding the effects of BCR-free survival with hazard risks of approximately 0.6–0.7 [8, 9].

The first attempt of a RCT to determine the oncological benefit of extended PLND unfortunately failed to show a statistically significant difference, despite the study being precisely designed to expect a 15% advantage in BCR-free survival [12]. The report is an important reference in the field of PLND. However as pointed out in correspondence, there was a favorable cancer profile characterized by more than one-third of patients having an ISUP grade group 1, and the estimated risk of LN involvement was 11 to 12%, which might be due to incorrect patient selection that reduced the effect of extended PLND [20]. On the contrary, a recent RCT to determine the role of prophylactic pelvic irradiation for high-risk, locally advanced PCa successfully showed improved disease-free survival [21]. Although one cannot compare the different treatment modalities on the same basis, the crucial difference is that the enrolled patients had a higher risk PCa in the latter RCT; and the estimated risk of LN involvement was more than 20%. Therefore, careful planning prior to a study is essential for the selection of patients and risk-range setting, especially when shedding light on the therapeutic role of PLND.

There is an attractive report regarding molecular LN staging that may alter patient risk stratification and thus affect PLND application or efficient adjuvant therapy in the near future. Molecular LN analysis is determined by prostate-specific expression of Kallikrein 3 (KLK3) using a quantitative polymerase chain reaction that detect LN metastases with a higher sensitivity and the risk of BCR than histopathology [22]. The study group later proposed a combined KLK3/ transmembrane serine protease 2 panel as a diagnostic and prognostic tool for molecular LN analysis [23]. Interestingly, patients with pN0/molecular N1 were observed at the same proportion or slightly more that those with pN1/N1, and this implies that the PLND removes unrecognized micro metastases by histopathology to varying degrees.

The interpretation of this study suggests unique characteristics and limitations. Primarily, the current study enrolls PCa patients whose clinical stage has been determined by a combination of DRE and multiparametric MRI. The use of an MRI finding leads to a significant upstaging of clinical T-stage and risk grouping, and further affects treatment intensification in around 30% of patients. These effects arise as MRI shows higher sensitivity and lower specificity compared to DRE [24]. Recent reports suggest that MRI staging has advantages in the established risk grouping and LN involvement nomograms originally developed with DRE staging in contemporary PCa patients; to determine a locally advanced high-risk group in the European Association of Urology (EAU) risk group and to improve model performance both at Memorial Sloan Kettering Cancer Centre 2018 and Briganti 2012 nomograms [25, 26].

Whereas, in our cohort, the re-classification to high-risk from the intermediate-risk was only 4.7% (12/253 patients) and to VHR from SHR subgroup was 20.0% (25/125 patients). For all, the risk migration remained less than 9.8%. This is probably because the staging did not rely solely on MRI, and the NCCN classification with T3 or higher as one of the high-risk criteria was used in the risk stratification. Actually,

the concordance rate between MRI and DRE was high in determining clinical T3 stage in our cohort. Nevertheless, the measured values of BCR-free survival cannot merely be compared to those in other reports since the Will Rogers phenomenon arising from the risk migration has occurred often [27]

Secondly, many previous studies set patients that received preoperative ADT as one of the exclusion criteria, while this study does not. In the real-world practice, considerable preoperative ADT is still performed, and the rate increases at higher disease stages. We took into consideration that multiple biases in patient selection or confounding of background would be unavoidable, whether these patients were included or excluded. Nevertheless, it is well acknowledged that preoperative ADT has no significant effect on BCR-free survival [28], and recent findings include no significant effect even on resection margin positivity [29]. These are the rationale for deciding the patients to be enrolled in this study, and naturally preoperative ADT was adjusted in the PS-matched analysis; the reduction of positive resection margin was not observed, while the independent predictive value for BCR was lost in the Cox regression analysis.

A statistical approach using the rigorous application of a causal inference framework and the concept of causal mediation analysis has attracted attention, which is frequently used analysis in the field of psychology. Although its effectiveness as an analytical method for lymph node dissection in the field of oncology is still immature, this method may clearly quantify the direct effect and the indirect effect of PLND on survival. A recent report indicated that the impact of extended PLND was not restricted to a staging benefit, but also involved a therapeutic benefit of reducing BCR or second-line therapy experience at approximately 30% [30]. When a well-designed RCT is not feasible due to ethical issues, such methodology may resolve the analytical challenges for exploring oncological benefits of PLND.

Despite that data were collected prospectively, and PS-matching adjusted the differences in known background factor, the study design is a retrospective analysis of outcomes by multiple surgeons at a single institution, the comparison with patients ranged from without to standard PLND, the short follow-up periods, and small number of patients would limit the oncological impact of the results. Despite such limitations, this report should serve as a reference indicating the positive therapeutic role of PLND.

Conclusion

There should be PCa patient benefit from PLND that is performed with the extended template and removal of a sufficient number of LNs. We are concerned about the current disadvantage for many high-risk PCa patients who should originally receive extended PLND solely because there is no high level of evidence for oncological benefits outweighing negative impacts. Our study potentially demonstrates the therapeutic role of PLND in high-risk PCa that may harbor both recognizable and unrecognizable metastases. The benefit of PLND depends on the study design, selection of patients with an optimal risk-range, and the surgeon complying with the extended template and removing a sufficient number of LNs.

Declarations

Ethics and patient consents

This study was conducted in accordance with the Helsinki Declaration and was approved by the institutional ethical review boards at Dokkyo Medical University Hospital: Approval number #28010 including the responsibility to report the results of this study for further clinical evaluation. In addition, each patient signed an INFORMED CONSENT form regarding the storage of their information for the purpose of research and acknowledged that the results of this study did not affect the subsequent clinical course.

Consent to publish

NOT APPLICABLE

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None

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

Mya, Myo and TKa initiated this study, participated in its design and coordination, carried out the study and drafted the manuscript. GN, TU, IS, KS and DN performed the statistical analysis. MYa, IS, and TKi were surgeons of robot-assisted radical prostatectomy and carried out the study. KI and YK were uropathologist and uroradiologist, respectively, and advised the manuscript design. All authors read and approved the final manuscript.

Availability of Data and Material

The authors declare that the informed consent was obtained for publication of patient data as additional supporting files uploaded in the supplementary material.

References

1. Cancer Information Service, N.C.C. Cancer Registry and Statistics. (Vital Statistics of Japan). 2021; Available from: https://ganjoho.jp/reg_stat/statistics/stat/summary.html.

2. Prasad SM, Keating NL, Wang Q, Pashos CL, Lipsitz S, Richie JP, et al. Variations in surgeon volume and use of pelvic lymph node dissection with open and minimally invasive radical prostatectomy. Urology. 2008; 72: 647-652. doi: 10.1016/j.urology.2008.03.067.
3. Feifer AH, Elkin EB, Lowrance WT, Denton B, Jacks L, Yee DS, et al. Temporal trends and predictors of pelvic lymph node dissection in open or minimally invasive radical prostatectomy. Cancer. 2011; 117: 3933-3942. doi: 10.1002/cncr.25981.
4. Wang EH, Yu JB, Gross CP, Smaldone MC, Shah ND, Trinh QD, et al. Variation in pelvic lymph node dissection among patients undergoing radical prostatectomy by hospital characteristics and surgical approach: results from the National Cancer Database. J Urol. 2015; 193: 820-825. doi: 10.1016/j.juro.2014.09.019.
5. Kodiyan J, Guirguis A, Ashamalla H. Radical prostatectomy without pelvic lymph node dissection is widely practiced in high-risk patients despite poorer survival. Clin Genitourin Cancer. 2020; 18: 395-401. e8. doi: 10.1016/j.clgc.2020.03.008
6. Yuh BE, Ruel NH, Mejia R, Wilson CM, Wilson TG. Robotic extended pelvic lymphadenectomy for intermediate- and high-risk prostate cancer. Eur Urol. 2012; 61: 1004-1010. doi: 10.1016/j.eururo.2012.01.048.
7. Fossati N, Willemse PM, Van den Broeck T, van den Bergh RCN, Yuan CY, Briers E, et al. The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: A systematic review. Eur Urol. 2017; 72: 84-109. doi: 10.1016/j.eururo.2016.12.003.
8. Choo MS, Kim M, Ku JH, Kwak C, Kim HH, Jeong CW. Extended versus standard pelvic lymph node dissection in radical prostatectomy on oncological and functional outcomes: A systematic review and meta-analysis. Ann Surg Oncol. 2017; 24: 2047-2054. doi: 10.1245/s10434-017-5822-6.
9. García-Perdomo HA, Correa-Ochoa JJ, Contreras-García R, Daneshmand S. Effectiveness of extended pelvic lymphadenectomy in the survival of prostate cancer: a systematic review and meta-analysis. Cent European J Urol. 2018; 71: 262-269. doi: 10.5173/ceju.2018.1703.
10. Gao L, Yang L, Lv X, Bu S, Wan F, Qian S, et al. A systematic review and meta-analysis of comparative studies on the efficacy of extended pelvic lymph node dissection in patients with clinically localized prostatic carcinoma. J Cancer Res Clin Oncol. 2014; 140: 243-256. doi: 10.1007/s00432-013-1574-2.
11. Cacciamani GE, Maas M, Nassiri N, Ortega D, Gill K, Dell'Oglio P, et al. Impact of pelvic lymph node dissection and its extent on perioperative morbidity in patients undergoing radical prostatectomy for prostate cancer: A comprehensive systematic review and meta-analysis. Eur Urol Oncol. 2021; 4: 134-149. doi: 10.1016/j.euo.2021.02.001.
12. Lestingi JFP, Guglielmetti GB, Trinh QD, Coelho RF, Pontes J Jr, Bastos DA, et al. Extended versus limited pelvic lymph node dissection during radical prostatectomy for intermediate- and high-risk prostate cancer: Early oncological outcomes from a randomized phase 3 trial. Eur Urol. 2021; 79: 595-604. doi: 10.1016/j.eururo.2020.11.040.
13. Briganti A, Larcher A, Abdollah F, Capitanio U, Gallina A, Suardi N, 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: 480–487. doi: 10.1016/j.eururo.2011.10.044.

14. Sundi D, Wang VM, Pierorazio PM, Han M, Bivalacqua TJ, Ball MW, et al. Very-high-risk localized prostate cancer: definition and outcomes. Prostate Cancer Prostatic Dis. 2013; 17: 57-63. doi: 10.1038/pcan.2013.46.
15. Sundi D, Tosoian JJ, Nyame YA, Alam R, Achim M, Reichard CA, et al. Outcomes of very high-risk prostate cancer after radical prostatectomy: Validation study from 3 centers. Cancer. 2019; 125: 391–397. doi: 10.1002/cncr.31833.
16. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA; Grading Committee. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: Definition of grading patterns and proposal for a new grading system. Am J Surg Pathol. 2016; 40: 244-252. doi: 10.1097/PAS.0000000000000530.
17. Yıldız A, Anıl H, Akdemir S, Aksaray EE, Ateş M, Arslan M. Extraperitoneal laparoscopic versus transperitoneal robot-assisted laparoscopic approaches for extended pelvic lymph node dissection during radical prostatectomy. J Laparoendosc Adv Surg Tech. 2022; 32: 355-359. doi: 10.1089/lap.2021.0174.
18. Sanda MG, Cadeddu JA, Kirkby E, Chen RC, Crispino T, Fontanarosa J, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part II: Recommended approaches and details of specific care options. J Urol. 2018; 199: 990-997. doi: 10.1016/j.juro.2018.01.002.
19. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent. Eur Urol. 2017; 71: 618-629. doi: 10.1016/j.eururo.2016.08.003.
20. Briganti A, Gandaglia G, Graefen M, Joniau S, Karnes RJ, Montorsi F. Re: Jean FP, et al. Extended versus limited pelvic lymph node dissection during radical prostatectomy for intermediate- and high-risk prostate cancer: Early oncological outcomes from a randomized phase 3 trial: Time for a change? clinically meaningful reasons why we will continue performing extended pelvic lymph node dissection in selected patients with prostate cancer. Eur Urol. 2021; 79: e154-e156. doi: 10.1016/j.eururo.2021.02.024.
21. Murthy V, Maitre P, Kannan S, Panigrahi G, Krishnatry R, Bakshi G, et al. Prostate-only versus whole-pelvic radiation therapy in high-risk and very high-risk prostate cancer (POP-RT): Outcomes from phase III randomized controlled trial. J Clin Oncol. 2021; 39: 1234-1242. doi: 10.1200/JCO.20.03282.
22. Heck MM, Retz M, Bandur M, Souchay M, Vitzthum E, Weirich G, et al. Molecular lymph node status for prognostic stratification of prostate cancer patients undergoing radical prostatectomy with extended pelvic lymph node dissection. Clin Cancer Res. 2018; 24: 2342-2349. doi: 10.1158/1078-0432.CCR-17-3771.
23. Lunger L, Retz M, Bandur M, Souchay M, Vitzthum E, Jäger M, et al. KLK3 and TMPRSS2 for molecular lymph-node staging in prostate cancer patients undergoing radical prostatectomy. Prostate Cancer Prostatic Dis. 2021; 24: 362-369. doi: 10.1038/s41391-020-00283-3.

24. Draulans C, Everaerts W, Isebaert S, Gevaert T, Oyen R, Joniau S, et al. Impact of magnetic resonance imaging on prostate cancer staging and European association of urology risk classification. Urology. 2019; 130: 113-119. doi: 10.1016/j.urology.2019.04.023.
25. Soeterik TFW, Hueting TA, Israel B, van Melick HHE, Dijksman LM, Stomps S, et al. External validation of the Memorial Sloan Kettering Cancer Centre and Briganti nomograms for the prediction of lymph node involvement of prostate cancer using clinical stage assessed by magnetic resonance imaging. BJU Int. 2021;128: 236-243. doi: 10.1111/bju.15376.
26. Soeterik TFW, van Melick HHE, Dijksman LM, Biesma DH, Witjes JA, van Basten JA. Multiparametric magnetic resonance imaging should be preferred over digital rectal examination for prostate cancer local staging and disease risk classification. Urology. 2021;147: 205-212. doi: 10.1016/j.urology.2020.08.089.
27. Gofrit ON, Zorn KC, Steinberg GD, Zagaja GP, Shalhav AL. The Will Rogers phenomenon in urological oncology. J Urol. 2008; 179: 28-33. doi: 10.1016/j.juro.2007.08.125.
28. Scolieri MJ, Altman A, Resnick MI. Neoadjuvant hormonal ablative therapy before radical prostatectomy: a review. Is it indicated? J Urol. 2000; 164: 1465-1472.
29. Kim SH, Park EY, Joo J, Joung JY, Seo HK, Chung J, et al. Effect of neoadjuvant hormone therapy on resection margin and survival prognoses in locally advanced prostate cancer after prostatectomy using propensity-score matching. Biomed Res Int. 2018: 4307207. doi: 10.1155/2018/4307207.
30. Wettstein MS, David LA, Pazhepurackel C, Qureshi AA, Zisman A, Nesbitt M, et al. Benefit of a more extended pelvic lymph node dissection among patients undergoing radical prostatectomy for localized prostate cancer: A causal mediation analysis. Prostate. 2021; 81: 286-294. doi: 10.1002/pros.24105.

Tables

Tables 1 to 5 are available in the Supplementary Files section

Figures

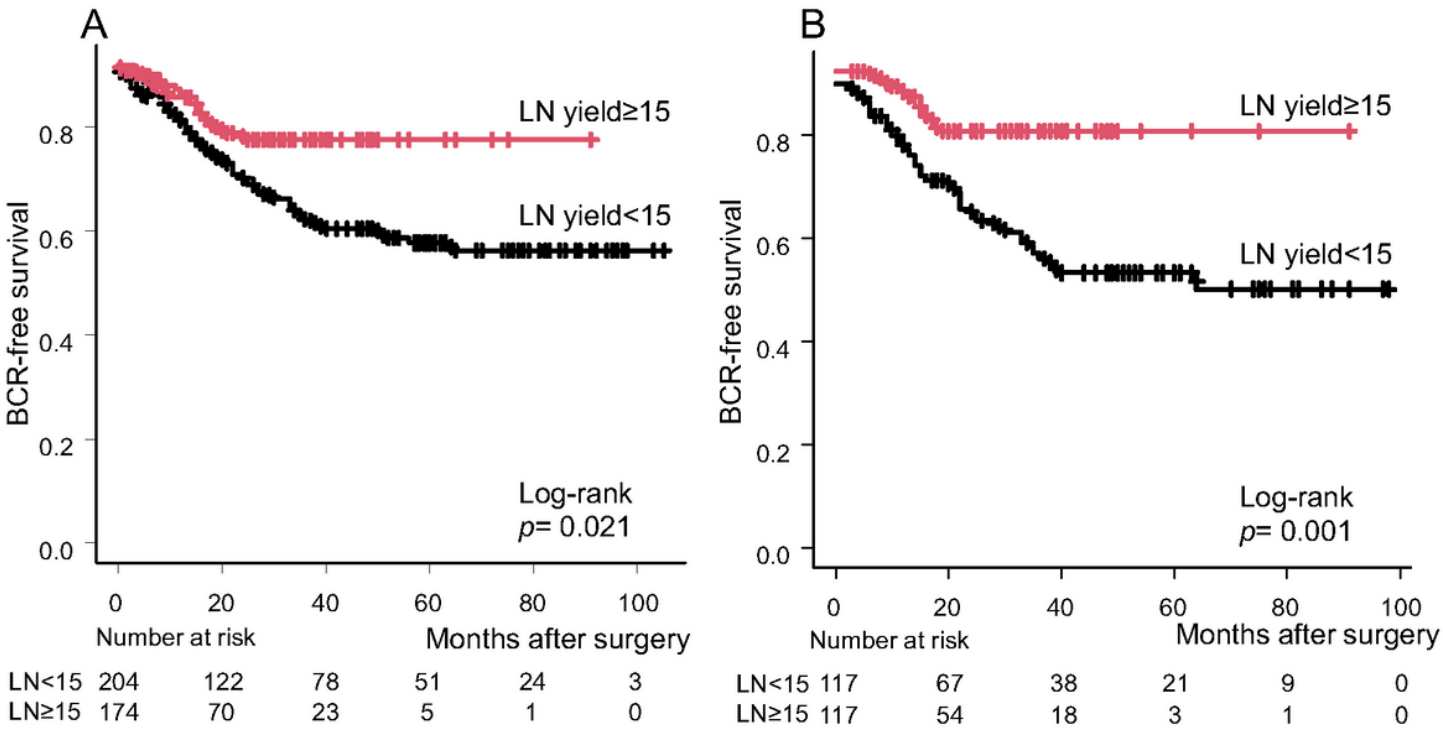


Figure 1

Kaplan–Meier estimates biochemical recurrence-free survival in entire unmatched cohort (A) and propensity score-matched cohort (B).

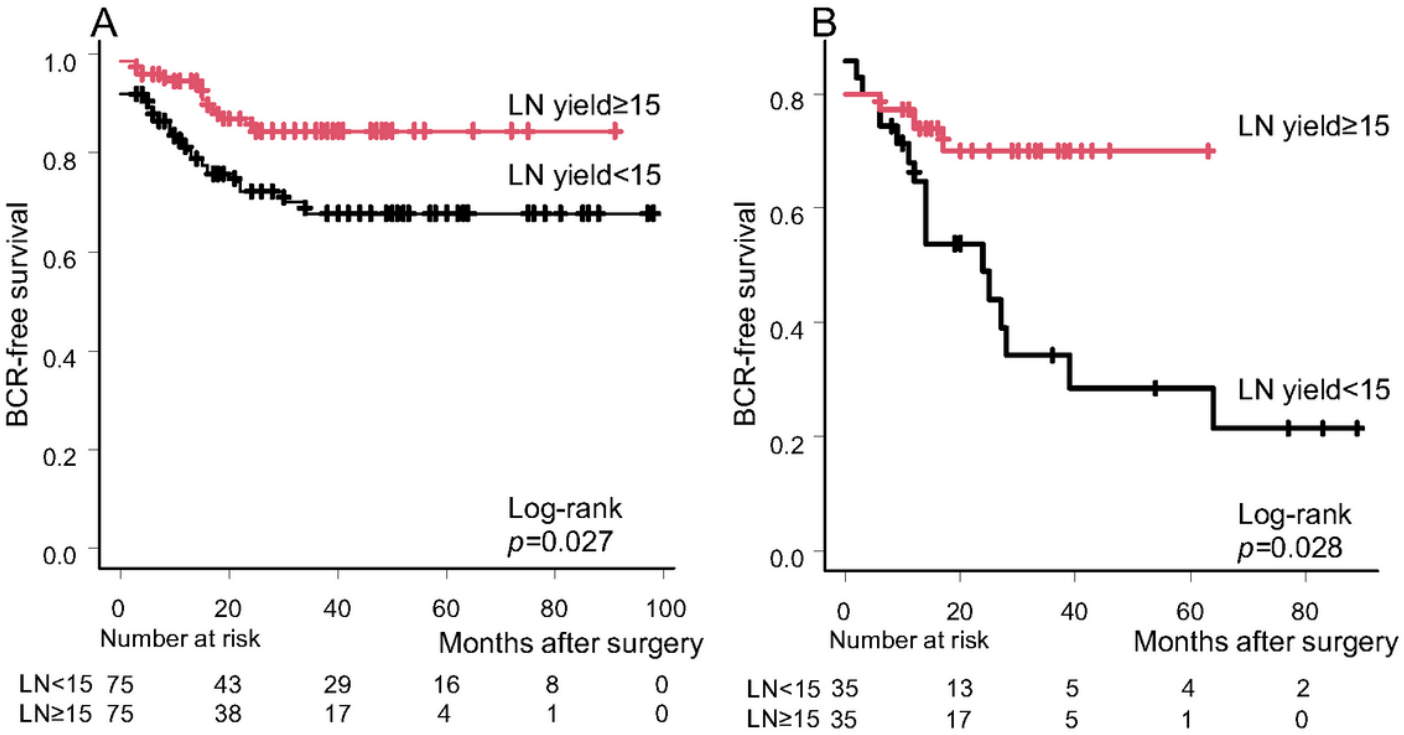


Figure 2

Kaplan–Meier estimates biochemical recurrence-free survival in propensity score-matched standard high-risk (A) and very high-risk cohort (B).

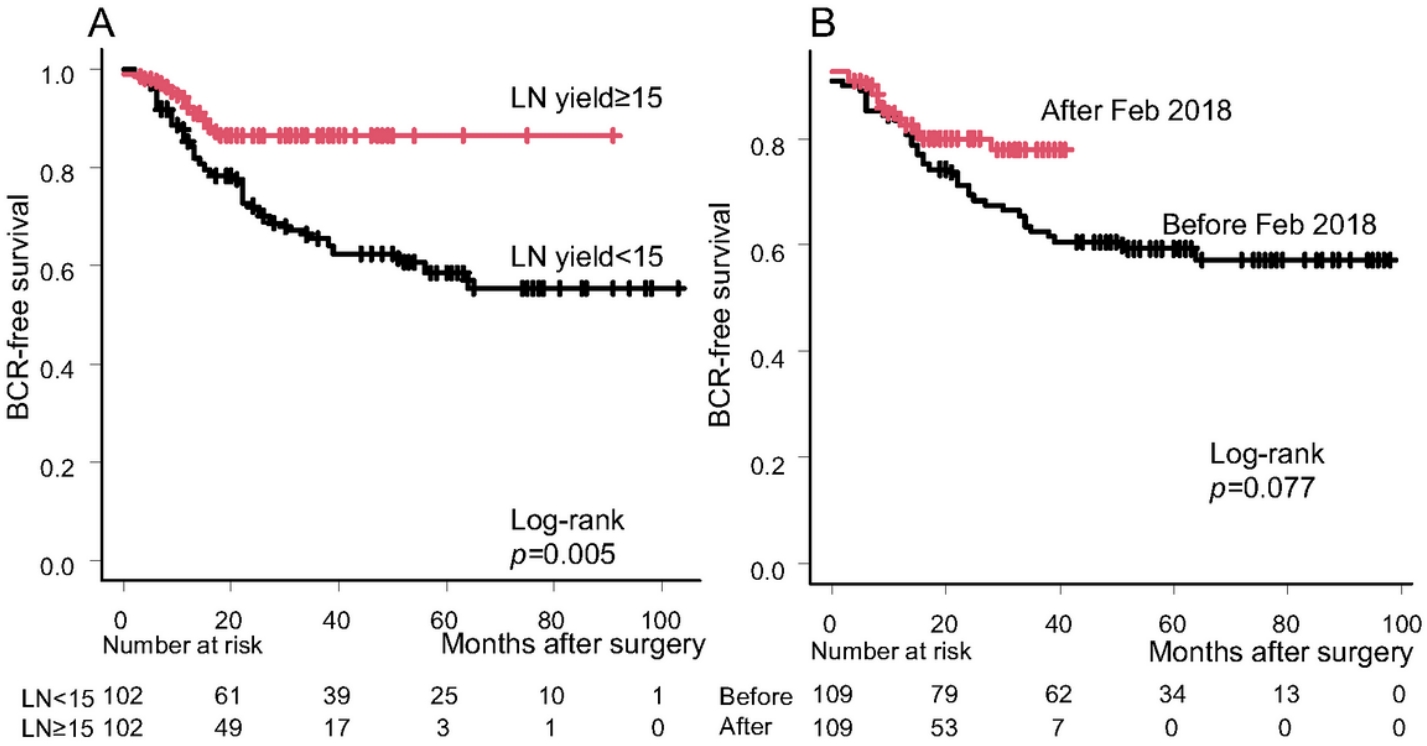


Figure 3

Kaplan–Meier estimates biochemical recurrence-free survival in propensity score-matched entire high-risk cohort excluding patients with PSA>0.2 ng/mL on the first checkup (A) and those stratified by timeframe (B).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.pdf
- Table2.pdf
- Table3.pdf
- Table4.pdf
- Table5.pdf
- Rawdataforentirecohort.csv

- Rawdataforstandarhighrisk.csv
- Rawdataforveryhighrisk.csv