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Selecting lymph node–positive patients for adjuvant therapy after radical prostatectomy and extended pelvic lymphadenectomy: An outcome analysis of 100 node-positive patients managed without adjuvant therapy

Ashwin Sunil Tamhankar, Saurabh Patil, Shanky Singh, Danny Darlington Carbin, Smruti Mokal, Puneet Ahluwalia, Gagan Gautam*

Urologic Oncology and Robotic Surgery, Max Institute of Cancer Care, New Delhi, India

Abstract

Objective: The aim of the study is to evaluate the effect of deferred androgen deprivation therapy on biochemical recurrence (BCR) and other survival parameters in node-positive prostate cancer patients after robot-assisted radical prostatectomy with bilateral extended pelvic lymph node dissection (RARP + EPLND).

Materials and methods: Of the 453 consecutive RARP procedures performed from 2011 to 2018, 100 patients with no prior use of androgen deprivation therapy were found to be lymph node (LN) positive and were observed, with initiation of salvage treatment at the time of BCR only. Patients were divided into 1 or 2 LNs (67)—and more than 2 LNs (33)—positive groups to assess survival outcomes.

Results: At a median follow-up of 21 months (1–70 months), the LN group ($p < 0.000$), preoperative prostate-specific antigen (PSA, $p = 0.013$), tumor volume (TV, $p = 0.031$), and LND ($p = 0.004$) were significantly associated with BCR. In multivariate analysis, only the LN group ($p = 0.035$) and PSA level ($p = 0.026$) were statistically significant. The estimated BCR-free survival rates in the 1/2 LN group were 37.6% (27%–52.2%), 26.5% (16.8%–41.7%), and 19.9% (9.6%–41.0%) at 1, 3, and 5 years, respectively, with a hazard of developing BCR of 0.462 (0.225–0.948) compared with the more than 2 LN-positive group. Estimated 5-year overall survival, cancer-specific, metastasis-free, and local recurrence-free survival rates were 88.4% (73.1%–100%), 89.5% (74%–100%), 65.1% (46.0%–92.1%), and 94.8% (87.2%–100.0%), respectively, for which none of the factors were significant. Based on cutoff values for PSA, TV, and LND of 30 ng/mL, 30%, and 10%, respectively, the 1/2 LN group was substratified, wherein the median BCR-free survival for the low- and intermediate-risk groups was 40 and 12 months, respectively.

Conclusions: Nearly one fourth and one fifth of 1/2 node-positive patients were BCR-free at 3 and 5 years after RARP + EPLND. Further substratification using PSA, TV, and LN density may help in providing individualized care regarding the initiation of adjuvant therapy.

Keywords: Adjuvant therapy; Extended pelvic lymph node dissection; Prostate cancer; Robotic radical prostatectomy

1. Introduction

Radical prostatectomy (RP) is a leading treatment option for localized prostate cancer and has grown in popularity in recent times because of the decreased morbidity afforded by the robotic approach. Pelvic lymph node dissection (PLND) is an inherent part of this procedure, and the decision for the same can be facilitated by the use of tables and nomograms, such as those of Partin, Memorial Sloan Kettering Cancer Center and Briganti, which predict the probability of lymphatic invasion based on several preoperative factors, such as prostate-specific antigen (PSA) level, clinical stage, and biopsy grade group (GG).[1–4] As per the European Association of Urology (EAU) guidelines, PLND is recommended for patients undergoing RP if the nomogram-predicted probability of harboring pelvic lymph node (LN) metastasis is greater than 5% (Briganti nomogram).[5] The controversy regarding the extent of PLND also seems to have been resolved to a large extent, with most current recommendations aligning toward bilateral dissection of the external iliac, internal iliac, and obturator groups as the minimal acceptable template in all cases where extended pelvic lymph node dissection (EPLND) is performed.[5,6]

The importance of pelvic lymphadenectomy stems from the fact that no preoperative imaging investigation has matched its accuracy in detecting LN invasion in prostate cancer.[5] This information has critical value in prognosticating the disease and has implications for decision making regarding adjuvant and salvage treatments after surgery. There may also be a therapeutic benefit of lymphadenectomy in some clinical situations, which may improve long-term outcomes in a certain cohort of patients.[6] In light of the above, clinicians may face a conundrum regarding the best mode of management of patients found to be LN-positive during RP. Should they be observed with additional treatment being deferred until biochemical recurrence (BCR) is detected? Should all LN-positive patients be started on

*Corresponding Author: Dr. Gagan Gautam, Urologic Oncology and Robotic Surgery, Max Institute of Cancer Care, New Delhi, 110017, India. E-mail address: gagangg@gmail.com (G. Gautam).

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immediate androgen deprivation therapy (ADT) with or without radiation therapy (RT)?

In a landmark clinical trial, Messing et al.[7,8] tilted the scales in favor of immediate ADT by demonstrating that overall survival (OS) and cancer-specific survival (CSS) were better in the immediate ADT group than in the observation group. However, as a potential pitfall, patients in the observation cohort were not subjected to ADT at the time of BCR, and the deferred therapy was initiated at the time of detection of metastases or symptomatic recurrence only. Hence, the findings of this study may not be applicable in the current real-world scenario, where advanced imaging and ultrasensitive PSA testing may provide ample opportunities to initiate additional therapy at earlier stages of relapse. The study by Messing et al.[8] also suffered from inadequate accrual (against a planned sample size of 220), because PSA testing developed around the same time, and physicians and patients found it difficult to ignore rising PSA values during follow-up. Other similar studies have evaluated the role of ADT in this scenario,[9–15] and it is now considered the standard of care for node-positive disease detected in RP. The National Comprehensive Cancer Network® panel strongly recommends (category 1) ADT after RP in patients with node positivity.[6] On the other hand, EAU guidelines also provide an option of deferring immediate ADT and continuing with a period of observation in patients with more than or equal to 2 positive nodes on EPLND with favorable histology.[5] As per evidence accumulated from observational studies, a subgroup of these node-positive patients may achieve long-term control or potential cure with RP + EPLND and may be spared the toxic effects of ADT[16] with or without RT.[9–11] To explore this aspect in depth, we analyzed the outcomes of 100 consecutive prostate cancer patients found to be LN-positive on EPLND performed during robot-assisted radical prostatectomy (RARP) by a single surgical team over a 7-year period, as well as the impact of several preoperative and postoperative parameters such as BCR, OS, CSS, local recurrence-free survival (LRFS), and metastasis-free survival (MFS), with a specific focus on the number of positive nodes on histopathology.

2. Materials and methods

From our prospectively maintained database, the records of 453 consecutive patients who underwent RARP between October 2011 and July 2018 were evaluated. Of these, 38 patients (8.3%) did not undergo LN dissection and were excluded from further analysis. Of the remaining 415 patients, 114 were LN-positive on EPLND and were subjected to further analysis. Of these, 14 patients received neoadjuvant ADT before surgery and were not considered further. Hence, the final cohort consisted of 100 patients. All procedures were performed by a single surgical team consisting of fellowship-trained console surgeons with dedicated bedside assistance while running a concurrent robotic urologic oncology fellowship program. All patients were thoroughly counseled regarding the procedures and outcomes. Extended pelvic lymph node dissection was performed in these 100 patients, which consisted of bilateral dissection of the obturator, external iliac, and internal iliac groups of LN.[17] Nodes were sent as 2 separate packets, one for each side. A consistent team of pathologists adequately experienced in uropathology reported the final histopathology of the specimens. Postoperatively, the first PSA level measurement was performed 4 weeks after procedure. Prostate-specific antigen was followed-up every 3 months in the initial 2 years, every 6 months in years 3–5, and annually thereafter in cases without BCR. Biochemical recurrence was defined as a PSA level greater than 0.2 ng/mL or the initiation of adjuvant therapy, whichever occurred earlier. On BCR, treatment decisions regarding the options of ADT alone (continuous vs. intermittent) or ADT with salvage RT were made on a case-to-case basis with frequent involvement of a multidisciplinary tumor board. The patients were thoroughly

Table 1

Demographic details and clinicopathological findings of the cohort.

Variables	n = 100
Age, median (range), yr	65.5 (49–78)
BMI, median (range), kg/m^2	27 (21–37)
PSA levels, median (range), ng/mL	23.5 (1–>100)
Console time, median (range)min	180 (110–307)
Estimated blood loss, median (range), mL	150 (50–500)
Length of stay, median (range), d	2 (1–6)
Catheter removal day, median (range)	9 (6–21)
LN yield, median (range)	19.5 (6–59)
LN density, median (range), %	10 (2–70)
LN positivity, n (%)	
1	45 (45)
2	22 (22)
>2	33 (33)
Grade group on final histopathology, n (%)	
1	1 (1)
2	19 (19)
3	22 (22)
4	38 (38)
5	20 (20)
Pathological T stage, n (%)	
2	7 (7)
3a	32 (32)
3b	61 (61)
Extraprostatic extension, n (%)	
Yes	93 (93)
No	7 (7)
Seminal vesicle invasion, n (%)	
Yes	61 (61)
No	39 (39)
Tumor volume, median (range), %	40 (2–85)
Margin positivity, n (%)	57 (57)
Multifocal	35 (35)
Unifocal	22 (22)
BCR, n (%)	
Yes	75 (75)
No	25 (25)
Local recurrence, n (%)	
Yes	2 (2)
No	98 (98)
Metastasis, n (%)	
Yes	8 (8)
No	92 (92)
CRPC, n (%)	
Yes	5 (5)
No	95 (95)
Death, n (%)	
Yes	3 (3)
No	97 (97)
Complications (Clavien-Dindo grade), n (%)	
1	4 (4)
2	2 (2)
3a	0 (0)
3b	1 (1)
4	1 (1)
5	0 (0)

BCR = biochemical recurrence; BMI = body mass index; CRPC = castration-resistant prostate cancer; LN = lymph node; PSA = prostate-specific antigen.

Table 2

Estimated survival parameters at 1, 3, and 5 years based on Kaplan-Meier analysis.

	1 yr	95% LCI	95% UCI	3 yr	95% LCI	95% UCI	5 yr	95% LCI	95% UCI	*p*
BCRFS overall	26.3%	18.5%	37.6%	18.6%	11.6%	29.8%	13.9%	6.7%	29.1%	
BCRFS (1/2 LN+)	37.6%	27.0%	52.2%	26.5%	16.8%	41.7%	19.9%	9.6%	41%	**<0.001**
BCRFS (>2 LN+)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
OS overall	98.8%	96.5%	100.0%	97.3%	93.6%	100.0%	88.4%	73.1%	100.0%	
OS (1/2 LN+)	100%	100%	100.0%	97.6%	93.0%	100.0%	81.3%	56.7%	100.0%	0.085
OS (>2 LN+)	96.6%	90.1%	100.0%	96.6%	90.1%	100.0%	96.6%	90.1%	100.0%	
MFS overall	97.8%	94.8%	100.0%	93.9%	86.2%	100.0%	65.1%	46.0%	92.1%	
MFS (1/2 LN+)	98.2%	94.7%	100%	98.2%	94.7%	100.0%	81.8%	63.4%	100.0%	0.083
MFS (>2 LN+)	97.0%	91.3%	100.0%	86.2%	67.9%	100%	43.1%	18.7%	99.3%	
LRFS overall	98.7%	96.3%	100.0%	94.8%	87.2%	100.0%	94.8%	87.2%	100.0%	
LRFS (1/2 LN+)	98.1%	94.5%	100.0%	98.1%	94.5%	100.0%	98.1%	94.5%	100.0%	0.64
LRFS (>2 LN+)	100.0%	100.0%	100.0%	88.9%	70.6%	100.0%	88.9%	70.6%	100.0%	
CSS overall	100.0%	100.0%	100.0%	98.4%	95.4%	100.0%	89.5%	74.0%	100.0%	
CSS (1/2 LN+)	100.0%	100.0%	100.0%	97.6%	93.0%	100.0%	81.3%	56.7%	100.0%	0.24
CSS (>2 LN+)	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	

Significant values in bold ($p < 0.05$).

BCRFS = biochemical recurrence-free survival; CSS = cancer-specific survival; LN = lymph node; LRFS = local recurrence-free survival; LCI = lower confidence interval; MFS = metastasis-free survival; OS = overall survival; UCI = upper confidence interval.

counseled at every step of the treatment course and provided with information regarding available options. In recent years, with the widespread availability of gallium prostate-specific membrane antigen positron emission tomography, most patients have undergone this imaging modality to assess any obvious local or distant uptake, which may impact the choice of treatment modality.

Lymph node-positive patients were divided into 1, 2, or more than 2 positive LN groups. Because of the lack of differences between the only 1 or 2 positive LN groups, these 2 cohorts were combined and later compared with the more than 2 positive LN group. Outcome-related parameters, which were evaluated, were BCR, OS, CSS, LRFS, MFS, and the development of castration-resistant prostate cancer state (CRPC). For causal association, the preoperative parameters considered were age, body mass index, preoperative PSA levels, biopsy GG, percentage of positive cores, percentage of maximum core involvement, and clinical T stage. From the final pathology report, the parameters considered for evaluation were the final biopsy GG, number of positive LN (group-wise distribution), lymph node dissection (LND), extraprostatic extension, seminal vesicle invasion (SVI), unifocal and multifocal margin positivity, overall pathological T stage, and percentage of tumor volume (TV) in the main specimen. The percentage of TV in the RP specimen was calculated by microscopically assessing the percentage of tumor involvement in each section of the specimen and averaging

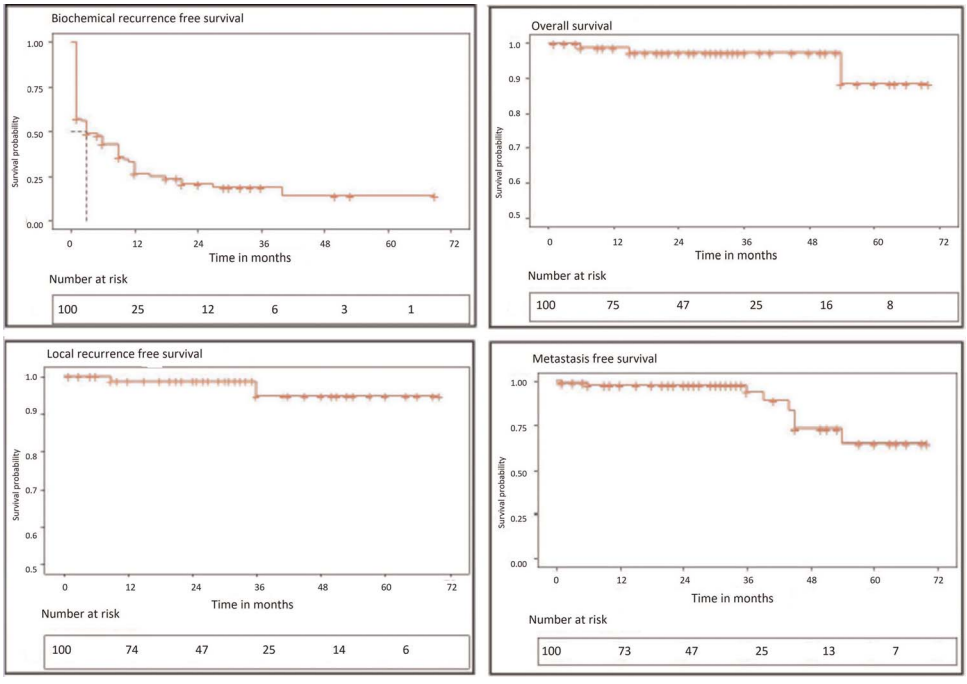

Figure 1. Kaplan-Meier survival curves for oncological outcomes.

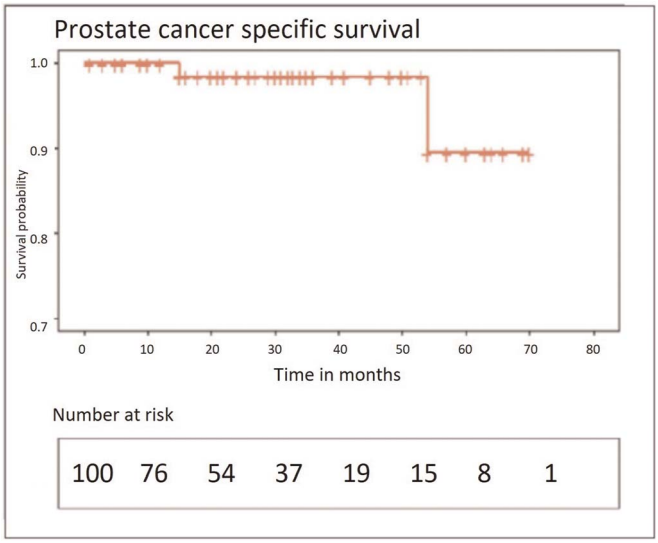

Figure 2. Prostate cancer–specific survival.

by dividing the number of sections assessed.[18] Univariate and multivariate Cox proportional hazards regression models were used to estimate causal associations. Statistical significance was set at a p value less than 0.05. Kaplan-Meier analysis was performed to estimate survival curves for BCR, CSS, OS, LRFS, and MFS. Secondary evaluation was performed to assess the demographic details and perioperative outcomes in terms of console time, estimated blood loss, length of stay, catheter removal day, and 30-day complication rates (Clavien-Dindo scale [CD]).[19] For substratification of patients with only 1 or 2 positive LNs, recursive partitioning analysis, which uses a classification approach through a decision tree, was performed, including parameters that were significant for BCR in univariate analysis.

3. Results

The 100 evaluable patients had a median age of 65.5 years (range, 49–78 years) and median body mass index of 27 kg/m^2 (range, 21–37 kg/m^2; Table 1). The median preoperative PSA level was 23.5 ng/mL (range, 1–>100 ng/mL). All patients underwent surgery using the da Vinci Si® and subsequently the Xi® systems (Intuitive Surgical, Sunnyvale, Calif), without open conversion. The median console time was 180 minutes (range, 110–307 minutes), and the estimated blood loss was 150 mL (range, 50–500 mL). The median length of stay and median number of days for catheter removal were 2 days (range, 1–6 days) and 9 days (range, 6–21 days), respectively. The median LN yield was 19.5 (range, 6–59) and LND was 10% (range, 2%–70%). The median TV was 40% (range, 2%–85%). The longest follow-up period for the entire cohort was 70 months with a median follow-up of 21 months. These LN-positive patients were divided into 2 cohorts for analysis: 1 or 2 nodes positive (n = 77; 1 LN-positive, n = 45; 2 LN-positive, n = 22) and more than 2 nodes positive (n = 33). The distribution of the GG in the final pathology was 1 (1%), 2 (19%), 3 (22%), 4 (38%), and 5 (20%), respectively. pT2 disease comprised only 7% of the cases, whereas 93% of the patients had pT3 disease. Extraprostatic extension and SVI were present in 93% and 63% of the patients, respectively. Overall and multifocal margin positivity was observed in 57% and 35% of individuals, respectively. Margin-positive male patients received treatment only when they developed BCR. Overall (CD, 1–5) and major (CD, 3–5) complication rates were 8% and 2%, respectively. Two patients had local recurrence, whereas distant metastases were detected in 8 patients. Five patients developed CRPC during long-term follow-up after starting ADT for BCR. Until the longest follow-up, 3 patients had died, 2 of whom died because of prostate cancer metastases (Table 1).

At a median follow-up of 21 months (range, 1–70 months), 25% of the patients were free of BCR. The overall BCR-free probabilities at 1, 3, and 5 years were 26.3% (confidence interval [CI], 18.5%–37.6%), 18.6% (CI, 11.6%–29.8%), and 13.9% (CI, 6.7%–29.1%), respectively (Table 2, Fig. 1). Comparison between 1 and 2 positive nodes did not show any significance (p = 0.130); however, a comparison between 2 or less than 2 LNs and more than 2 LNs showed higher BCR rates for the more than 2-LN group (p < 0.000). The estimated BCR-free survival rates in the first group were 37.6% (CI, 27%–52.2%), 26.5% (CI, 16.8%–41.7%), and 19.9% (CI, 9.6%–41.0%) at 1, 3, and 5 years, respectively. In contrast, in the second group, none of the patients were free of BCR at 1 year. The estimated median BCR-free survival was 9 months (range, 6–18 months) and 1 month (range, 1–3 months) for these 2 cohorts. Among the 75 patients who received ADT, 17 (22.7%) received intermittent ADT. The median time for the off-phase of ADT was 15 months (range, 6–54 months). Estimated 1, 3, and 5 year OS rates were 98.8% (CI, 96.5%–100.0%), 97.3% (CI, 93.6%–100.0%), and 88.4% (CI, 73.1%–100.0%), respectively (Table 2, Fig. 1). Estimated 1-, 3-, and 5-year MFS rates were 97.8% (CI, 94.8%–100.0%), 93.9% (CI, 86.2%–100.0%), and 65.1% (CI, 46.0%–92.1%), respectively. Estimated 1-, 3-, and 5-year LRFS rates were 98.7% (CI, 96.3%–100.0%), 94.8% (CI, 87.2%–100.0%), and 94.8% (CI, 87.2%–100.0%), respectively (Table 2, Fig. 1). Estimated 1-, 3-, and 5-year CSS rates were 100.0% (CI, 100.0%–100.0%), 98.4% (CI, 95.4%–100.0%), and 89.5% (CI, 74%–100.0%), respectively (Table 2, Fig. 2). On univariate cox analysis, factors that had significant association with BCR were biopsy GG (p = 0.046), LN group (1 or 2 vs. ≥2, p < 0.000), preoperative PSA levels (p = 0.013), TV (≤30% vs. >30%, p = 0.031), and LND (p = 0.004; Table 3). A unit increase in LND and PSA increased the hazard of BCR by 1.021 (CI, 1.006–1.036) and 1.006 (CI, 1.001–1.010), respectively (Table 3). However, on multivariate analysis, only the LN group (p = 0.035)

Table 3

Univariate and multivariate analyses for association with BCR.

	Univariate				Multivariate			
	HR	95% LCI	95% UCI	p	HR	95% LCI	95% UCI	p
Grade group in biopsy >2 (Ref.) ≤2	0.624	0.392	0.993	**0.046**	0.746	0.459	1.213	0.238
LN group >2 LN+ (Ref.) 1–2 LN+	0.404	0.244	0.669	0.000	0.462	0.225	0.948	**0.035**
PSA	1.006	1.001	1.010	**0.013**	1.006	1.001	1.011	**0.026**
Tumor volume ≤30% (Ref.) >30%	1.797	1.054	3.061	**0.031**	1.405	0.793	2.489	0.243
LN density	1.021	1.006	1.036	**0.004**	1.001	0.980	1.023	0.911
SVI	0.613	0.375	1.004	0.052				

Significant values in bold (p < 0.05).

HR = hazard ratio; LCI = lower confidence interval; LN = lymph node; PSA = prostate-specific antigen; SVI = seminal vesicle invasion; UCI = upper confidence interval.

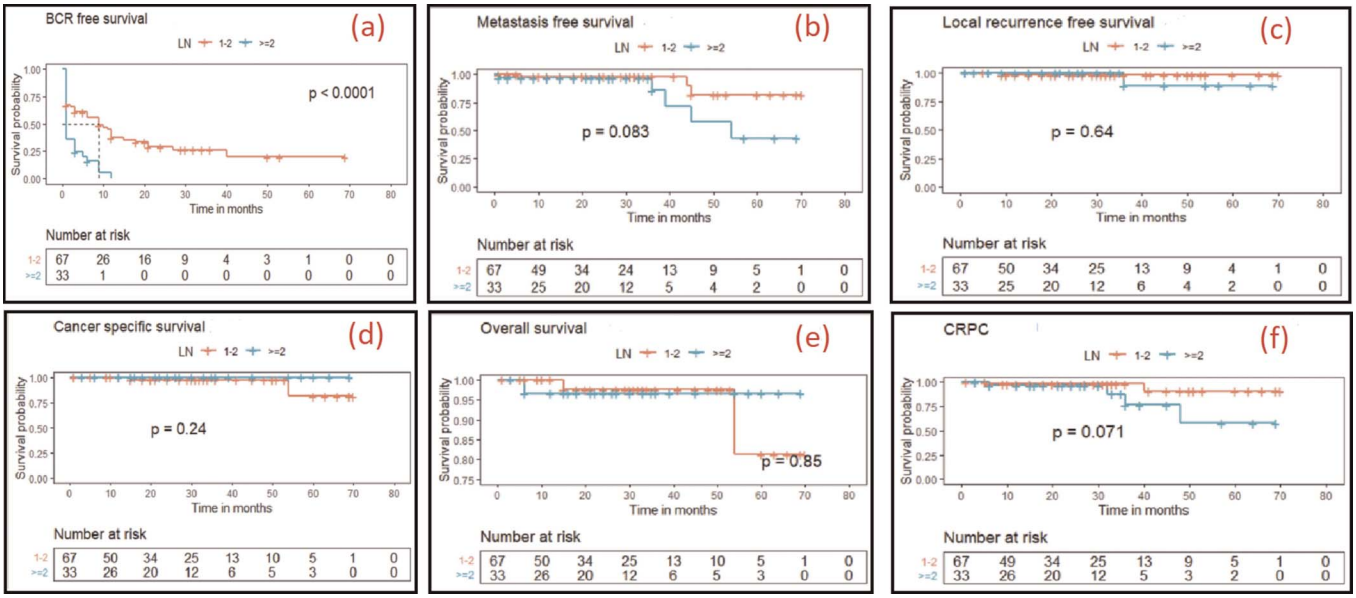

Figure 3. Kaplan-Meier survival curves with respect to the LN groups. BCR = biochemical recurrence; CRPC = castration-resistant prostate cancer state; LN = lymph node.

and PSA level ($p = 0.026$) were predictors of BCR. The hazard ratio (HR) for BCR for patients with 1 or 2 positive LNs was 0.462, compared with more than 2 positive LNs (HR, 0.462; CI, 0.225–0.948; $p = 0.035$; Fig. 3). On multivariate analysis, a one-unit increase in PSA increased the risk of BCR by 1.006 ($p = 0.026$; HR, 1.006, CI, 1.001–1.011; Table 3). None of the evaluated parameters, including the LN group and PSA, were found to be associated with CSS, OS, MFS, or LRFS (Table 4, Fig. 3). For the CRPC status, biopsy GG and final pathology GG were the only significant factors (Table 4).

One or 2 positive LN groups ($n = 67$) were substratified based on cutoffs of PSA 30 ng/mL, 30% TV, and 10% LND into low-, intermediate-, and high-risk groups, respectively (Fig. 4, Table 5). The high-risk group comprised patients with either a PSA level greater than 30 ng/mL or with a PSA level less than 30 ng/mL, but TV more than 30% and LND more than 10%. The patients with PSA less than 30 ng/mL and TV less than 30% constituted the low-risk group for which 1- and 3-year BCR-free survival rates were 56.9% (CI, 37.8%–85.6%) and 50.6% (CI, 31.6%–80.9%), respectively. The intermediate-risk group was comprised individuals with PSA levels less than 30 ng/mL, TV greater than 30%, and LND less than 10%. The estimated BCR-free survival rates in the intermediate group were 44.0% (CI, 25.1%–77.2%), 27.5% (CI, 11.5%–65.9%), and 27.5% (CI, 11.5%–65.9%) at 1, 3, and 5 years, respectively. The median time free of BCR was 40 and 12 months in the low- and

Table 4

Association of perioperative and postoperative factors with different types of survival.

Variables	BCR	Metastasis-free survival	Overall survival	Cancer-specific survival	Local recurrence-free survival	CRPC status-free survival
Age, yr	0.734	0.844	0.944	0.944	0.453	0.869
BMI, kg/m^2	0.393	0.997	0.660	0.629	0.178	0.838
PSA, ng/mL	**0.013**	0.814	0.231	0.235	0.799	0.167
Positive cores, %	0.065	0.934	0.606	0.618	0.642	0.493
Maximum core involvement, %	0.455	0.834	0.991	0.943	0.919	0.951
cT stage	0.287	0.897	0.863	0.863	0.157	0.596
Grade group biopsy	**0.046**	0.261	0.243	0.978	0.836	**0.009**
Grade group final HPR	0.195	0.072	0.059	0.433	0.639	**0.020**
pT stage	0.107	0.391	0.338	0.338	0.807	0.224
LN group	0.000	0.104	0.850	0.516	0.649	0.098
EPE	0.389	0.800	0.381	0.381	0.592	0.756
SVI	0.052	0.240	0.801	0.801	0.238	0.222
Margin positivity	0.190	0.265	0.401	0.401	0.884	0.524
Multifocal margin positivity	0.080	0.236	0.835	0.435	0.281	0.935
Unifocal margin positivity	0.614	0.951	0.424	0.944	0.226	0.343
Tumor volume	**0.031**	0.160	0.435	0.980	0.419	0.245
LN density	**0.004**	0.127	0.593	0.597	0.601	0.221

Significant values in bold ($p < 0.05$).

BCR = biochemical recurrence; BMI = body mass index; CRPC = castration-resistant prostate cancer; EPE = extraprostatic extension; HPR=Histopathology report; LN = lymph node; PSA = prostate-specific antigen; pT=pathological Tumour stage; SVI = seminal vesicle invasion.

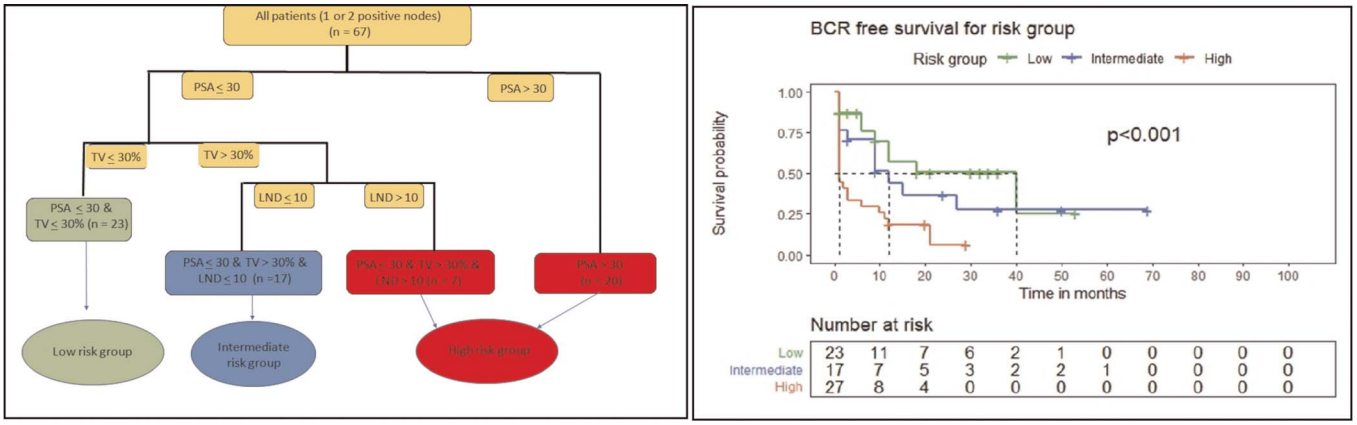

Figure 4. Decision tree analysis for substratification of patients with up to 2 positive nodes. BCR= biochemical recurrence; LND= lymph node dissection; PSA= prostate-specific antigen; TV= tumor volume.

intermediate-risk groups, respectively. The difference in BCR between each of the 3 groups was highly significant ($p < 0.001$), wherein the high group had a higher probability of BCR.

4. Discussion

While the utility of EPLND during RP in terms of facilitating pathological staging and prognostication is well established, controversy remains regarding its therapeutic benefit.[7–15] Considering the genetic heterogeneity and varied disease biology between individuals, immediate use of adjuvant treatment, especially ADT, may be difficult to justify in all patients found to be LN-positive on RP. Indeed, this "one-size-fits-all" approach may expose patients to unnecessary toxicity—avoidable by following a more nuanced selection strategy. Currently, there seems to be a paucity of data regarding the natural course of the disease in LN-positive patients after RARP, as most of them are automatically started on adjuvant ADT, with or without RT. The limited studies available mostly explore datasets with small numbers and nondiverse ethnicities.[9–15] Hence, currently, it may be difficult to generalize and apply their conclusions to other patients worldwide. Moreover, most of the data available thus far include patients operated via open or laparoscopic techniques and may not reflect more recent surgical advancements, especially pertaining to RARP.[7–9,11]

After excluding patients who had received neoadjuvant ADT, we evaluated 100 consecutive patients found to be LN-positive on RARP + EPLND and followed them without any adjuvant treatment until BCR (defined as postoperative PSA >0.2 ng/mL), at which point salvage treatment (ADT, with or without RT) was initiated. We found that approximately one third (37.6%), one fourth (26.5%), and one fifth (19.5%) of patients with either 1 or 2 positive LNs were free of BCR at 1, 3, and 5 years, respectively. The median BCR-free survival was 9 months (range, 6–18 months). This is similar to a publication from Switzerland, wherein BCR-free survival at 5 years was 24.7% and 11.8% for patients with 1 and 2 positive LNs, respectively.[11] Most studies that have addressed the outcomes of pN+ patients after RP have reported that in nearly 80% of LN-positive patients, only 1 or 2 LNs are involved.[9,10] Our study had a higher proportion of patients (33%) with more than 2 positive nodes, which is similar to the Swiss cohort.[11] Extrapolating the results of the trial by Messing et al.,[7,8] if all of the pN+ patients are subjected to immediate long-term ADT, it would potentially lead to overtreatment in a significant proportion of patients with minimal LN involvement (1/2 positive nodes)—a cohort that actually constitutes the bulk of patients with node-positive disease after RP (66%–80%). In addition, among the pN+ patients, the probability of remaining free of BCR at 10 years was 81% if they were free of recurrence for 5 years, thereby implying that a subset of pN+ patients can likely be cured by surgery alone.[10]

Although the National Comprehensive Cancer Network guidelines provide a category 1 recommendation for adjuvant ADT for pN+ patients after RP,[6] all other guidelines approach this clinical situation with greater caution.[20,21] The Australian Council

Table 5

Substratification of 1 or 2 LN-positive patients in risk groups with BCR-free survival rates.

Risk group	Classification parameters	Median BCR-free survival in months (range)	1-yr BCR-free survival rates (95% CI)	3-yr BCR-free survival rates (95% CI)	5-yr BCR-free survival rates (95% CI)	*p*
Low	PSA ≤ 30 and TV ≤ 30%	40 (12–not achieved)	56.9% (37.8%–85.6%)	50.6% (31.6%–80.9%)	-	**<0.001**
Intermediate	PSA ≤ 30 and TV > 30% and LND ≤ 10%	12 (9–not achieved)	44% (25.1%–77.2%)	27.5% (11.5%–65.9%)	27.5% (11.5%–65.9%)	
High	PSA > 30 or PSA ≤ 30 and TV > 30% and LND > 10%	1 (1–10)	18.5% (8.4%–40.9%)	-	-	

Significant values in bold ($p < 0.05$).

*Data for longer follow-up beyond the longest follow-up period mentioned were not available.

BCR = biochemical recurrence; CI = confidence interval; LN = lymph node; LND = lymph node density; PSA = prostate-specific antigen; TV = tumor volume.

provides a grade C recommendation for the use of ADT after RP + lymphadenectomy; however, the guidelines advise clinicians to consider the potential adverse effects of ADT in the decision-making process.[21] The EAU panel recommends observation as an option for patients with less than or equal to 2 nodes positive with microscopic nodal involvement (nodal metastasis ≤0.2 cm, absence of extranodal extension) and a follow-up PSA of less than 0.1 ng/mL.[5]

In view of the above, there is a need for additional data for substratification of node-positive cases based on the number of positive nodes and/or other high-risk pathology findings. In our analysis, we found that preoperative PSA and biopsy GG, and postoperative TV, LND, and LN group (based on the number of LN found to be involved) were significantly associated with BCR in univariate analysis. However, in multivariate analysis, only the PSA and LN groups were found to have a significant association. This is in agreement with a few other studies wherein the Gleason score (GS), number of positive LN, and LND have been found to correlate with the probability of BCR.[9–11] von Bodman and colleagues[9] found that patients with GS of 7 or less and only 1 positive LN were more likely to be free of recurrence compared with those with more than or equal to 2 positive nodes and GS greater than 7. Another study identified a combination of GS less than 8 and less than 2-node positive and negative surgical margins to be predictive of the most favorable outcome.[10] Similarly, LND greater than 15%, GS greater than 7, SVI, and margin positivity have been shown to result in relatively poor prognosis, with an increased risk of BCR.[22] Cancer-specific survival has also been found to correlate with the number of LN involved, with patients having more than or equal to 2 positive LNs having a nearly 2-fold increased risk of adverse outcomes in this regard compared with those with single LN involvement.[13] Similarly, the size of the metastasis in the LN and the presence of micrometastasis also have prognostic value in predicting the outcomes of pN+ patients.[14,15]

As per the evidence from other studies on this subject and our analysis, it is reasonable to assume that management decisions only based on the number of LN involved would likely be a gross oversimplification. Hence, using the parameters found to be significant in univariate analysis, we further substratified patients with 1 or 2 positive LNs using recursive partitioning analysis. We found that patients with a preoperative PSA level greater than 30 ng/mL or those with lower PSA levels but TV greater than 30% and LND greater than 10% had a median BCR-free survival of only 1 month and were unlikely candidates for a successful surveillance strategy. On the other hand, more than half of the patients with a PSA level less than 30 ng/mL and TV less than 30% were free of BCR at 1 and 3 years after surgery and would likely be best managed with observation alone.

The need for individualized and rational adjuvant treatment protocols for LN-positive patients further stems from the fact that these patients have been shown to have a long natural history with a likely prolonged locoregional phase of prostate cancer. In our study, the estimated 5-year CSS and OS rates for all LN-positive patients were 89.5% (CI, 74%–100.0%) and 88.4% (CI, 73.1%–100.0%), respectively. This is in congruence with 2 other studies on deferred ADT after RP, which included 369 and 122 LN-positive patients. The 5- and 10-year CSS rates were 84.5% and 60% and 94% and 72%, respectively.[10,11] Given the above, and in light of the known long-term toxicity of ADT,[16] it would be prudent to make any decisions regarding adjuvant treatment with utmost care and with the utilization of all available evidence in this regard.

Our study has some limitations. This was a retrospective analysis from a single institution and, as a result, is limited in terms of the number of patients, duration of follow-up, and lack of a control arm. However, we believe that it has the potential to contribute significantly to this understudied topic by exploring several new dimensions. First, standardizing the extent of EPLND, the approach (robotic), and sample retrieval (one packet for each side) results in a degree of uniformity that may not be available in multi-institutional cohorts. As mentioned earlier, variations in the approach, technique, and extent of LN dissection can have a significant impact on the outcomes, and our single-team standardized approach is likely to yield benefits in this regard. To the best of our knowledge, our study represents the largest cohort of LN-positive patients managed with observation alone after a robotic approach to RP and EPLND. Second, we have also been able to present a substratified risk classification of patients with minimal LN (1 or 2) involvement using readily available parameters, such as PSA, LND, and TV. Not only is this likely to help in the further prognostication of LN-positive patients after surgery, but it can also be used to make clinical decisions regarding the initiation or otherwise of adjuvant treatment in the postoperative period. Third, our study explores this facet of prostate cancer in a cohort of South Asian (Indian) men, a population that is grossly underrepresented in the current literature emerging primarily from Western databases.

We believe that further exploration of this topic is warranted with the incorporation of genetic biomarkers,[23] multi-institutional collaboration, and randomized trials so that the previously mentioned findings can be confirmed and post-RP adjuvant therapy for LN-positive prostate cancer patients can be instituted using a more targeted and patient-specific approach.

5. Conclusions

A significant proportion of prostate cancer patients were found to have minimal LN involvement (1 or 2 positive LNs) on RP and EPLND and remained free of BCR without any adjuvant treatment. Substratification of these patients based on preoperative PSA, TV on final histopathology, and LND may help in identifying the patients best suited for a surveillance strategy vis-à-vis adjuvant therapy. Further studies, including those incorporating genetic biomarkers, may further elucidate this and help establish a more individualized approach to adjuvant therapy for patients in this clinical situation.

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Statement of ethics

Ethical approval was waived by the local Ethics Committee in view of the retrospective nature of the study, and all the procedures being performed were part of the routine care. All patients underwent standard treatment and consented for the same. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest statement

No conflict of interest has been declared by the authors.

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Author contributions

All the authors contributed for the final manuscript draft, including data collection, data analysis, conceptualization, manuscript writing, and manuscript editing.

References

[1] Tosoian JJ, Chappidi M, Feng Z, et al. Prediction of pathological stage based on clinical stage, serum prostate-specific antigen, and biopsy Gleason score: Partin Tables in the contemporary era. *BJU Int* 2017;119(5):676–683.

[2] Cagiannos I, Karakiewicz P, Eastham JA, et al. A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. *J Urol* 2003;170(5):1798–1803.

[3] 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(3):480–487.

[4] Cimino S, Reale G, Castelli T, et al. Comparison between Briganti, Partin and MSKCC tools in predicting positive lymph nodes in prostate cancer: A systematic review and meta-analysis. *Scand J Urol* 2017;51(5):345–350.

[5] Mottet N, van den Bergh RCN, Briers E, et al. EAU Guidelines. Edn. Presented at the EAU Annual Congress Amsterdam 2020. ISBN 978-94-92671-07-3. Available at: https://uroweb.org/guideline/prostate-cancer/#11. Accessed on May 17, 2020.

[6] Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate cancer, version 2. 2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2019;17(5):479–505.

[7] Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med* 1999;341(24):1781–1788.

[8] Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol* 2006;7(6):472–479.

[9] von Bodman C, Godoy G, Chade DC, et al. Predicting biochemical recurrence-free survival for patients with positive pelvic lymph nodes at radical prostatectomy. *J Urol* 2010;184(1):143–148.

[10] Touijer KA, Mazzola CR, Sjoberg DD, Scardino PT, Eastham JA. Long-term outcomes of patients with lymph node metastasis treated with radical prostatectomy without adjuvant androgen-deprivation therapy. *Eur Urol* 2014;65(1):20–25.

[11] Schumacher MC, Burkhard FC, Thalmann GN, Fleischmann A, Studer UE. Good outcome for patients with few lymph node metastases after radical retropubic prostatectomy. *Eur Urol* 2008;54(2):344–352.

[12] Briganti A, Karnes JR, Da Pozzo LF, et al. Two positive nodes represent a significant cut-off value for cancer specifics survival in patients with node positive prostate cancer. A new proposal based on a two-institution experience on 703 consecutive N+ patients treated with radical prostatectomy, extended pelvic lymph node dissection and adjuvant therapy. *Eur Urol* 2009;55(2):261–270.

[13] Boorjian SA, Thompson RH, Siddiqui S, et al. Long-term outcome after radical prostatectomy for patients with lymph node positive prostate cancer in the prostate specific antigen era. *J Urol* 2007;178(3 Pt 1):864–70.

[14] Fleischmann A, Schobinger S, Schumacher M, Thalmann GN, Studer UE. Survival in surgically treated, nodal positive prostate cancer patients is predicted by histopathological characteristics of the primary tumor and its lymph node metastases. *Prostate* 2009;69(4):352–362.

[15] Carlsson SV, Tafe LJ, Chade DC, et al. Pathological features of lymph node metastasis for predicting biochemical recurrence after radical prostatectomy for prostate cancer. *J Urol* 2013;189(4):1314–1318.

[16] Zhao J, Zhu S, Sun L, et al. Androgen deprivation therapy for prostate cancer is associated with cardiovascular morbidity and mortality: A meta-analysis of population-based observational studies. *PLoS One* 2014;9(9):e107516.

[17] Fossati N, Willemse PM, Van den Broeck T, 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(1):84–109.

[18] Vollmer RT. Percentage of tumor in prostatectomy specimens: A study of American veterans. *Am J Clin Pathol* 2009;131(1):86–91.

[19] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240(2):205–213.

[20] Dasgupta P, Davis J, Hughes S. NICE guidelines on prostate cancer 2019. *BJU Int* 2019;124(1):1.

[21] Gardiner RA, Sweeney C, Chambers S, et al. For men with locally advanced prostate cancer, is there a role for peri-operative hormone therapy in the following situations: Neoadjuvant setting, post-radical prostatectomy short duration, post-radical prostatectomy long duration? Available at: https://wiki.cancer.org.au/australiawiki/index.php?oldid=90211. Accessed August 4, 2019. Available at: https://wiki.cancer.org.au/australia/Clinical_question:For_men_with_locally_advanced_prostate_cancer,_is_there_a_role_for_peri-operative_hormone_therapy_in_the_following_situations:_neoadjuvant_setting,_post-radical_prostatectomy_short_duration,_post-radical_prostatectomy_long_duration%3F.

[22] Palapattu GS, Allaf ME, Trock BJ, Epstein JI, Walsh PC. Prostate specific antigen progression in men with lymph node metastases following radical prostatectomy: Results of long-term follow up. *J Urol* 2004;172(5 Pt 1):1860–1864.

[23] Heck MM, Retz M, Bandur M, 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(10):2342–2349.

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