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ORIGINAL ARTICLE

Robotic-assisted pelvic lymph node dissection for prostate cancer: frequency of nodal metastases and oncological outcomes

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ABSTRACT

Purpose Limited data are available regarding the oncologic efficacy of pelvic lymph node dissection (PLND) performed during robotic-assisted laparoscopic prostatectomy (RALP) for prostate cancer. We aimed to determine the frequency of pelvic lymph node metastasis and oncological outcomes following RALP with PLND in patients who did not receive adjuvant androgen deprivation therapy (ADT). Methods We retrospectively reviewed the records of 1740 consecutive patients who underwent RALP and extended PLND. The primary endpoint was biochemical recurrence (BCR). The estimated BCR probability was obtained using the Kaplan–Meier method. Cox proportional hazard regression models were used to assess for predictors of BCR. Results One hundred and eight patients (6 %) with positive LNs were identified. The median number of LNs removed was 17 (IQR 11–24), and median follow-up was 26 months (IQR 14–43). Ninety-one (84 %) patients did not receive adjuvant ADT of whom 60 % had BCR with a median time to recurrence of 8 months. The 1- and 3-year BCR-free probability was 42 and 28 %, respectively. Patients with ≤2 LN+ had significantly better biochemicalfree estimated probability compared to those with >2 LN+ (p = 0.002). The total number of LN+ (HR = 1.1; 95 % CI 1.01–1.2, p = 0.04) and Gleason 8–10 (HR = 1.96; 95 % CI 1.1–3.4, p = 0.02) were predictors of BCR on multivariate analysis.

Conclusion Among men with positive lymph nodes at time of robotic prostatectomy, those with two or fewer positive nodes and Gleason <8 exhibited favorable biochemical-free survival without adjuvant therapy.

Keywords

Prostate cancer · Radical prostatectomy ·Biochemical recurrence · Lymph node dissection · Robotics

Abbreviations

PCa Prostate cancer
RALP Robot-assisted laparoscopic prostatectomy
PLND Pelvic lymph node dissection
LN Lymph node
ADT Androgen deprivation therapy
BCR Biochemical recurrence
HR Hazard ratio
SD Standard deviation
CI Confidence interval

INTRODUCTION

The presence of lymph node (LN) metastases is an important prognostic factor for prostate cancer (PCa) [1].
Although the required extent remains a controversial topic, pelvic LN dissection (PLND) has proved to be the most accurate and reliable staging procedure in detecting positive LNs [2]. Moreover, by detecting micrometastatic disease earlier, PLND enables clinicians to counsel their patients regarding prognosis and potential adjuvant therapy, which may potentially provide a survival benefit in a subset of these patients [3].

In the era of robotic-assisted laparoscopic radical prostatectomy (RALP), large-volume centers have shown that robotic PLND is safe, effective and has equivalent lymph node yield compared to open surgery [4]. Over the last few years, 5-year oncological outcomes following RALP have been published, but only Liss et al. [5] described pathologic lymph node status. There is a paucity of data regarding the oncological efficacy of robotic PLND in patients with positive LNs.

Therefore, we aimed to investigate the oncological outcomes of patients with LN-positive PCa treated with RALP and PLND who did not receive immediate adjuvant androgen deprivation therapy (ADT).

MATERIALS AND METHODS

This was an institutional review board (IRB) approved study, and all patients gave their informed consent prior to their inclusion in the study. We conducted a retrospective study from our radical prostatectomy database including 3500 consecutive patients of which 1740 underwent RALP and PLND between March 2006 and December 2013. We queried our prospectively maintained institutional database to identify patients with positive LNs among those treated with RALP and extended PLND. The clinical information extracted included patient age, PSA, biopsy Gleason grade and clinical stage. Following surgery, we obtained the pathological stage, Gleason grade, surgical margin status, total number of LNs removed and number of positive LNs.

We excluded those who received adjuvant radiation therapy (n = 14) and/or androgen deprivation therapy (ADT) (n = 17) while having an undetectable postoperative PSA.

PLND selection criteria, surgical technique and nodal assessment

The criteria for selecting patients for PLND since the technique was established at our institution are as follows:
PSA > 10 ng/mL, palpable disease or presence of pattern 4 in the primary biopsy [4]. This is undertaken before the prostatectomy and after the posterior dissection of the seminal vesicles has been completed. We have had 21 % of upgrading to Gleason ≥7 during the last years, identifying two or more cores of Gleason 3+3 and more that 50 % of involvement as predictors [6]. Therefore, we have extended the criteria for undertaking a PLND to all patients who undergo RALP with the exception of those with 1 core of Gleason 3+3 with <50 % of involvement.

We routinely perform an extended pelvic lymph node dissection as described by Studer [7], and our institutional PLND template has been described elsewhere [4]. Briefly, the limits of dissection are anteriorly to the level of the external iliac artery and posteriorly the level of the pelvic floor. The caudal limit is the femoral canal and cephalad to the bifurcation of the common iliac vessels. The medial extent of the dissection is the medial umbilical ligament and laterally to the psoas muscle. All the lymphatic tissue is routinely placed into a laparoscopic bag, which is removed at the end of the procedure. Then, the nodes are submitted en bloc including left and right packages. After the lymph nodes are grossly examined by the attending surgeon, they are sent to pathology.

The nodes are evaluated following the recommendations of the International Society of Urological Pathology (ISUP) Consensus Conference [8]. Routinely, the macroscopically identifiable nodes are submitted. In cases that <8 nodes are visible in pelvic dissections, the additional fat is submitted for possible microscopical nodes.

Study variables and follow-up

The primary endpoint of the study was biochemical recurrence, defined as a PSA of 0.2 ng/mL or greater, with a second confirmatory level. Follow-up visits typically consisted of physical examination and PSA at 6 weeks postoperatively, then every 6 months for 5 years and yearly thereafter.

Statistical analysis

Kaplan–Meier method was used to estimate the biochemical recurrence-free probability stratified by number of involved LNs using the log-rank test. The impact of clinicopathological factors on outcome was analyzed using Cox proportional hazard regression models, obtaining the hazard ratio (HR) and 95 % confidence intervals (CI) associated with the dependent variables assessed. The statistical analysis was conducted using Stata 12 (StataCorp, College Station, TX, USA).

RESULTS

We identified 1740 consecutive patients treated with RALP and extended PLND. There were 122 (7 %) patients with positive LNs (Supplementary material 1: CONSORT diagram). After excluding those who received adjuvant radiation therapy (n = 14; 11 %), our final cohort consisted of 108 patients (6 %). Among patients with positive LNs, the median number of LNs removed was 17 (IQR 11–24).

Overall, 59 (64 %) patients had one, 16 (17 %) had two and 16 (17 %) had more than two positive LNs. The median time of follow-up was 26 months (IQR 14–43).

Fig. 1 Overall Kaplan–Meier estimated biochemical recurrence-free probability

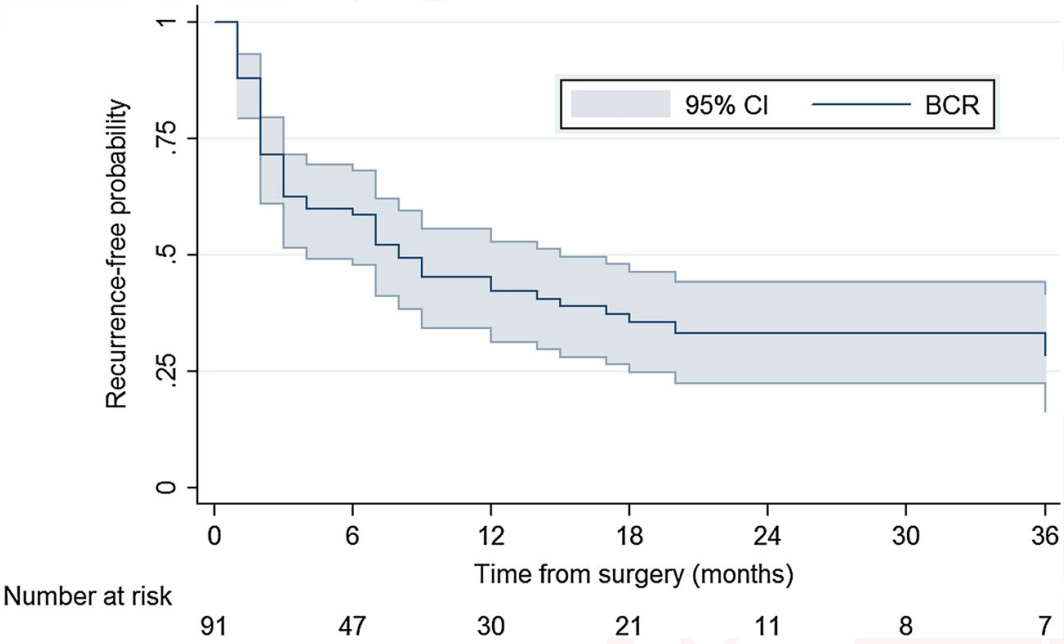
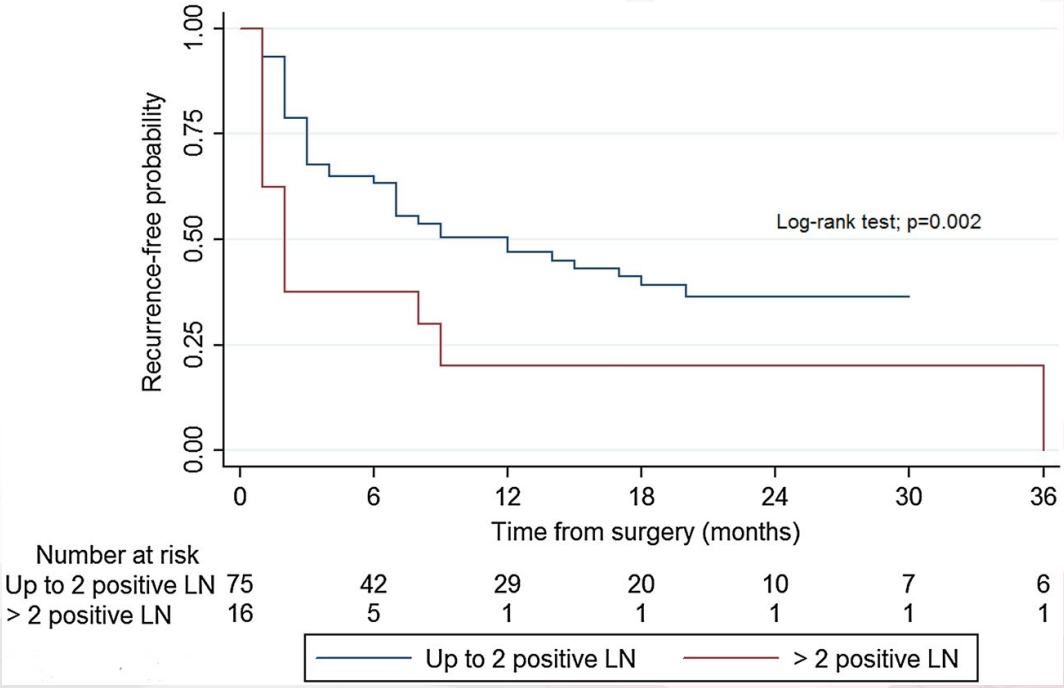


Fig. 2 Kaplan–Meier estimated biochemical recurrence-free probability stratified by the number of positive lymph nodes



Androgen deprivation therapy was administered in the setting of an undetectable PSA in 17 (15 %), while 91 (84 %) were followed expectantly (Supplementary material 2). Biochemical recurrence was observed in 60% (55/91) of the patients who did not receive immediate adjuvant ADT. The median time to recurrence was 8 months (Fig. 1). Overall, the 1- and 3-year BCR-free probability was 42 % (95 % CI 31–52) and 28 % (95 % CI 16–41), respectively. The median time to recurrence in patients with 1, 2 or more than 2 positive LNs was 12, 7 and 2 months, respectively. There was no difference in estimated BCRfree probability between 1 and 2 involved LN (log-rank test; p = 0.1). Men with two or fewer positive LNs had significantly better BCR-free probability compared to those with more than two positive LNs (Fig. 2 log-rank test; p = 0.002). For patients with more than two positive nodes, nearly all recurrences were observed in the first 6 months after surgery. The 12-month probability of freedom from BCR was 46 % (95 % CI 34–58) for those with up to two positive LNs and 18 % (95 % CI 4–43) for those with more than two positive LNs.

The BCR-free probability was also better in patients with pathologic Gleason <8 compared to those with Gleason score 8–10 (Fig. 3 log-rank test; p = 0.003).
On univariate analysis, the total number of positive LNs (HR = 1.1; 95 % CI 1.03–1.22, p = 0.004), presence of >2 positive LNs (HR = 2.5; 95 % CI 1.31–4.62, p = 0.005) and pathologic Gleason score 8–10 (HR = 2.2, 95 % CI 1.24–3.74, p = 0.006) were predictors significantly associated with biochemical recurrence (Table 1). On multivariate analysis, the total number of positive LNs (HR = 1.1; 95 % CI 1.01–1.2, p = 0.04) and pathologic Gleason score 8–10 (HR = 1.9; 95 % CI 1.1–3.4, p = 0.02) were independent predictors of BCR (Table 1).

Fig. 3 Kaplan–Meier estimated biochemical recurrence-free probability stratified pathological Gleason score

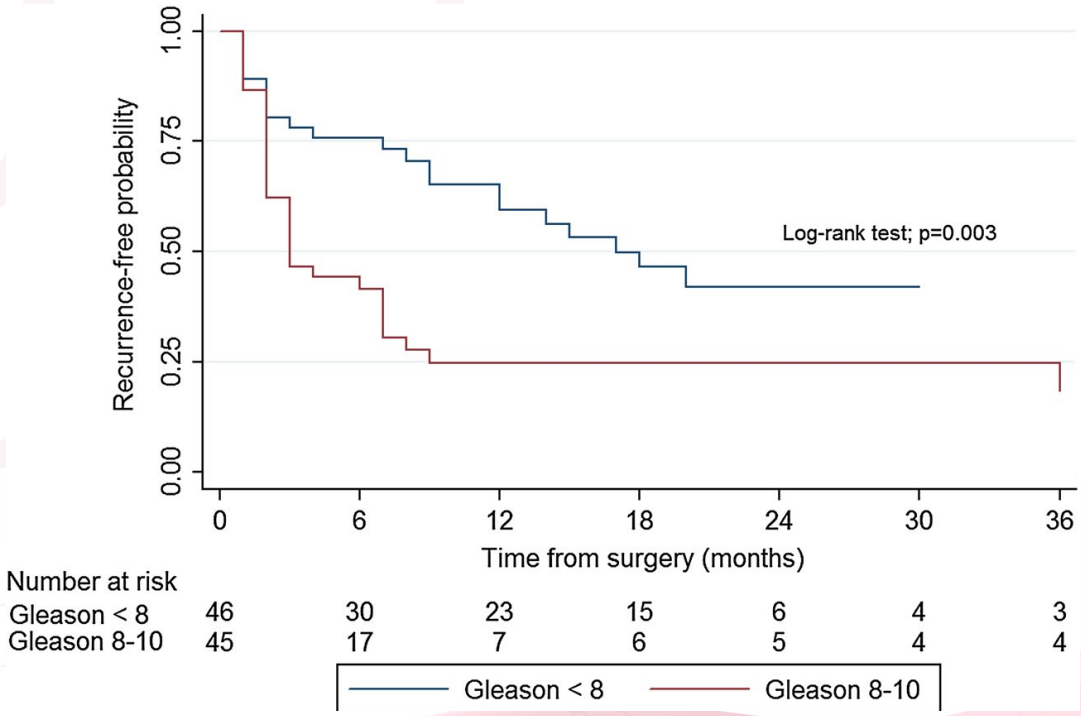


Table 1 Univariate and multivariate analysis of risk factors associated with BCR in patients with node-positive disease after surgery

Risk factor	Univariate			Multivariate		
	HR	95 % CI	*p*	HR	95 % CI	*p*
PSA (continuous, ng/mL)	1	0.98–1.03	0.4	1	0.98–1.02	0.6
No positive LNs (continuous)	1.1	1.03–1.22	**0.004**	1.1	1.01–1.2	**0.04**
Positive LNs						
≤2	1	Ref	**0.005**	1	Ref	0.07
>2	2.5	1.31–4.62		1.8	0.9–3.6	
Gleason						
≤7	1	Ref	**0.006**	1	Ref	**0.02**
>7	2.2	1.24–3.74		1.9	1.1–3.4	
Seminal vesicles involvement	1.6	0.94–2.73	0.08	1.17	0.8–2.4	0.2

Variables that were identifiedas independent predictor in the Cox model are in bold

DISCUSSION

We present, to our knowledge, the first report of the oncological outcomes of patients with positive lymph nodes treated with RALP and extended PLND. In the USA, RALP is nowadays the most commonly used technique to perform a radical prostatectomy (RP) [9]. During the early adoption of RALP (2003–2007), evidence from the Surveillance, Epidemiology and End Results (SEER) cancer registry data suggested that PLND was less likely to be performed in patients undergoing minimally invasive RP [10]. However, there has been a progressive increase in the experiences being reported from high-volume centers regarding the adoption of PLND during RALP [4, 11, 12]. More contemporary studies have shown robotic PLND to have comparable LN yields and complication rates when compared to the open approach.

Zorn et al. [4] reported the feasibility of sampling the anatomic boundaries of zones 1, 2 and 3 as described by Studer [7] during RALP, enabling the retrieval of 12.5 LN on average. Silberstein et al. [11] concluded that robotic PLND can yield a median of 16 nodes when the template systematically includes external iliac, obturator and hypogastric packets, comparable to the yield obtained with open PLND. In addition to these appealing results in nodal counts, these studies address an even more important question when analyzing the feasibility of this procedure. Robotic PLND is able to accomplish the goal of meticulously dissecting nodal landing zones. It is well recognized that the importance of performing an anatomic lymphadenectomy in PCa management includes external iliac, obturator and internal iliac nodes [2, 12]. Although the nomenclature used for the anatomic boundaries of PLND including this template varies among centers, by using an extended lymphadenectomy, also referred as standard for other centers, the detection

of positive LNs is more frequent than with more restricted templates [13, 14]. Moreover, a meticulous LN dissection is able to reveal higher rates of metastases [7]. Nonetheless, despite the role of improving diagnostic staging accuracy provided by extended PLND, its therapeutic role remains controversial [2].

Aside from data supporting the feasibility to dissect the required landing zones and attain equivalent nodal yield, there are several studies appraising the safety of the procedure. Zorn et al. [4] showed that complication rates were not significantly increased in patients undergoing PLND compared to those who did not undergo the procedure. More recently, Liss et al. demonstrated that complications were present in 16 % of the patients receiving an extended PLND including the common iliac packet and the rate of complication was not associated with the procedure or the extension of the lymphadenectomy. Most of the complications observed were Clavien I/II, and the rate of lymphocele requiring intervention was 3 % [15].

We aimed to study the oncologic efficiency of R-PLND performed during RALP given the paucity of published data. We found that 6 % of our cohort had at least one positive pelvic lymph node. Since we wanted to determine the natural course of the disease in men with positive lymph nodes after RALP and PLND, we stratified the patients and excluded those who received upfront adjuvant ADT from the analysis. Among 91 patients identified with positive lymph nodes who did not receive immediate adjuvant ADT, biochemical recurrence was detected in 60 % with a 2-year probability of being BCR-free of 32 %. Patients with up to two positive nodes had significantly improved BCR-free probability compared to those with more than two positive nodes, and the degree of lymph node involvement was a predictor of BCR on the Cox regression analysis. This may suggest a potential therapeutic advantage in patients undergoing extended PLND, albeit longer-term outcomes will help to answer this question.

The frequency of positive lymph nodes that we observed is similar to what has been described elsewhere. A contemporary series in 427 patients with clinically localized PCa treated with open RP found a rate of 8.2 % of LN metastases with a median number of 16 LNs removed from the external iliac, obturator and internal iliac zones [14]. In our study, we also report a median number of LNs removed of 16, having two-thirds of the patients with only one positive lymph node.

It has been previously described that in patients with positive LN, the disease may exhibit heterogeneous patterns of progression, having been reported that a subset of patients may remain free of PSA relapse for more than 10 years without adjuvant therapy [16]. Therefore, the identification of prognostic factors that influence disease progression in this group of patients may potentially assist clinical decision-making and management. In a retrospective review of 3264 patients conducted by Palapattu and colleagues, the percent of positive lymph nodes, pathological Gleason score and seminal vesicle invasion appeared to be predictors for increased risk of BCR among the 165 patients with lymph node metastases [17]. A series from the Mayo Clinic presented by Boorjian et al. [18] concluded that a subset of patients with LN-positive PCa may have long-term survival (86 % CSS at 10 years), and identified Gleason score, margin status, tumor ploidy and number of involved nodes as predictors of survival. In a more contemporary review from the Memorial Sloan Kettering Cancer Center

(MSKCC) including patients from 2000 to 2008 treated with open or laparoscopic RP and PLND including the external iliac, obturator and hypogastric nodes, the 24-month BCR-free probability was 55 %, demonstrating that a large subset of patients may have favorable prognosis, describing the number of positive LNs and Gleason grade as predictors of freedom from BCR [19]. In our study, to further illustrate the impact of several clinicopathological features in PSA relapse following surgery, we utilized the Cox proportional hazard regression model to corroborate their capability as predictors of BCR. In our univariate analysis, Gleason score higher than 7, total number of positive LNs and the presence of >2 positive LNs were predictors of biochemical failure. Conspicuously, the number of positive lymph nodes and Gleason score higher than 7 were confirmed as predictors of PSA relapse in a multivariate analysis.

Despite the evidence of the influence of lymph node involvement in the progression of PCa, the current 2010 American Joint Committee on Cancer (AJCC) staging system does not stratify patients according to the number of positive nodes [20]. In a multi-institutional experience that gathered a cohort of 703 patients with positive LNs treated with RP and extended PLND, Briganti et al. provided further evidence to bear the predictive value of the number of positive LNs in PCa progression. They concluded in this large series that the number of positive LNs represents a key variable for cancer-specific survival and patients with up to two metastatic LNs may experience excellent cancerspecific survival rate [21].

It is especially important to recognize that there may be variability in the pathological assessment of lymph nodes
and the final nodal count is a function pathological practice and surgical technique. In the ISUP conference's survey, 27 % of the pathologist sampled all the tissue submitted, 60 % only macroscopically identifiable nodal tissue and 8 % only a sample of each lymph node identified [8]. Notably, a consensus has not been reach yet, and only 3 % of the survey's responders generally report more than 15 lymph nodes.

There are several important limitations in our study. It represents a single-institution retrospective cohort and all the bias inherent to this type of design. Moreover, we acknowledge that the most important limitation of our study is our relatively short follow-up. In addition, we do recognize that there is selection bias and the patients who were recommended to be followed using a wait-and-see strategy may have a different risk profile than those who received immediate adjuvant therapy. However, there is a body of evidence that suggest that a selected subset of patients who are found to have minimal nodal disease at final pathology might achieve long-term biochemical control [16, 21]. This aforementioned observation needs to be addressed in the setting of a clinical trial in order to determine the most adequate strategy for the management of these patients. In spite of its limitations, this study has the strength of assessing a prospectively collected surgical case series with a consistently sampled template for lymph node metastases, displaying a contemporary high-volume practice.

CONCLUSION

Extended PLND during RALP enables the detection of lymph node-positive PCa. Among men with LN involvement, those with up to two positive LNs exhibited better biochemical-free estimated probability. To our knowledge, this is the first report of biochemical control in patients with positive LNs after undergoing RALP with PLND.

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

Ethical standard The manuscript entitled "Robotic-assisted pelvic lymph node dissection for prostate cancer: frequency of nodal metastases and oncological outcomes" was an investigation approved by the Internal Board Review committee of the University of Chicago (IRB number #13-031). Therefore, the manuscript has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. In addition, all patients gave their informed consent prior to their inclusion in the study.

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