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Biochemical Relapse in Low-risk Prostate Cancer Treated with Radical Prostatectomy and Bilateral Pelvic Lymphadenectomy

Cristina Dominguez-Bellini[1] José Gustavo Ramos[2] Luis Miguel Becerra[2] Rodolfo Varela[2,3]

[1] Department of Urology, Pontificia Universidad Javeriana, Bogotá, Colombia
[2] Department of Urology Oncology, National Cancer Institute of Colombia, Bogotá, Colombia
[3] National University of Colombia, Bogotá, Colombia

Address for correspondence Cristina Dominguez, MD, Department of Urology, Pontificia Universidad Javeriana, Carrera 1 este # 74-51 apt 603, Bogotá, Colombia (e-mail: Cristinadominguezb@gmail.com).

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Abstract

Introduction For low-risk prostate cancer (PCa), curative treatment with radical prostatectomy (RP) can be performed, reporting a biochemical relapse-free survival rate (bRFS) at 5 and 7 years of 90.1% and 88.3%, respectively. Prostatic specific antigen (PSA), pathological stage (pT), and positive margins (R1) are significant predictors of biochemical relapse (BR). Even though pelvic lymphadenectomy is not recommended during RP, in the literature, it is performed in 34% of these patients, finding 0.37% of positive lymph nodes (N1). In this study, we aim to evaluate the 10-year bRFS in patients with low-risk PCa who underwent RP and extended pelvic lymph node dissection (ePLND).

Methodology All low-risk patients who underwent RP plus bilateral ePLND at the National Cancer Institute of Colombia between 2006 and 2019 were reviewed. Biochemical relapse was defined as 2 consecutive increasing levels of PSA $>$ 0.2 ng/mL. A descriptive analysis was performed using the STATA 15 software (Stata Corp., College Station, TX, USA), and the Kaplan-Meier curves and uni and multivariate Cox proportional hazard models were used for the survival outcome analysis. The related regression coefficients were used for the hazard ratio (HR), and, for all comparisons, a two-sided p-value $<$ 0.05 was used to define statistical significance.

Results Two hundred and two patients met the study criteria. The 10-year bRFS for the general population was 82.5%, statistically related to stage pT3 ($p = 0.047$), higher Gleason grade group (GG) ($p \leq 0.001$), and R1 ($p \leq 0.001$), but not with N1. A total of 3.9% of the patients had N1; of these, 75% had R1, 25% GG2, and 37% GG3. Among the N0 (non-lymph node metástasis in prostate cáncer) patients, 31% of the patients had R1, 41% GG2, and 13% GG3.

Conclusions Our bRFS was 82.5% in low-risk patients who underwent RP and ePLND. With higher pT, GG, and presence of R1, the probability of BR increased. Those with pN1 (pathologicaly confirmed positive lymph nodes) were not associated with bRFS, with a pN1 detection rate of 3.9%.

Keywords
- prostate cancer
- low risk
- lymph node invasion
- nomogram
- pelvic lymphadenectomy
- radical prostatectomy
- relapse-free survival

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Details: In low-risk PCa, curative treatment with RP can be performed, reporting a bRFS rate at 5 and 7 years of 90.1% and 88.3%, respectively. Despite the fact that pelvic lymphadenectomy is not recommended during RP in clinical guidelines, in the literature, it is performed in 34% of these patients, finding 0.37% of N1. In this study, we report the 10-year bRFS in patients with low-risk PCa who underwent surgery.

Introduction

Pelvic lymph node dissection (PLND) at the time of radical prostatectomy (RP) for low-risk prostate cancer (PCa) is not recommended by clinical practice guidelines;[1] this is supported by patients with less than 2% of risk of lymphatic involvement in nomograms.[2] The European Association of Urology (EAU) guidelines recommend PLND, particularly extended pelvic lymph node dissection (ePLND), for patients with intermediate or high-risk cancers when the risk of positive lymph node extension may exceed 5%.[3] The clinical benefit and need for PLND during RP have been a subject of debate for several years.[4] The National Comprehensive Cancer Network (NCCN) guideline specifies that an extended dissection should always be performed when deciding to do it, as this dissection will reveal twice as many metastases as the limited pattern.[5] An European research study determined that 34.5%, 64.9%, and 91.2% of patients with low, intermediate, and high-risk PCa, respectively, underwent PLND during RP; however, positive lymph node involvement was detected in only 6.9% (122 patients) of the cohort, and within the low-risk group, positive lymph nodes (N1) = 0.37%.[6] Other studies in the literature have reported relapse-free survival rates at 5 and 7 years of 90.1% and 88.3% for patients undergoing ePLND versus patients who did not have ePLND of 82.4% and 82.4%, respectively ($p = 0.278$).[7]

The oncological outcome in many studies has been defined as the biochemical recurrence rate (BCR). The present study aims to evaluate the biochemical relapse-free survival (bRFS) rate at 10 years in patients with low-risk PCa who underwent RP and ePLND.

Methodology

Study Design

This is a retrospective study with data collected in the electronic charts from the National Cancer Institute of Colombia, and Institutional Review Board approval was obtained. All data were collected in a Microsoft Excel (Microsoft Corp., Redmond, WA, USA) database for which only researchers had access to it with a protected password. The authors attest that the study was conducted and monitored as specified in the protocol. Each patient provided a signed informed consent for the data collection on the day of the surgery. Five expert oncological urologists performed RP (open and robotic approach) with ePLND on all patients as established in the institutional guidelines. The anatomical template of ePLND included bilateral external iliac extending proximally to the crossing of the ureter and laterally to the genitofemoral nerve, obturator fossa nodes, hypogastric nodes, internal and common iliac, and Cloquet nodal stations.

Patient Selection

The inclusion criteria were patients with low-risk PCa defined by the D'Amico criteria, prostatic specific antigen (PSA) $\leq$ 10 ng/ml, Gleason group grade (GG) 1, clinical-stage (cT) $\leq$ cT2a, who underwent RP plus bilateral ePLND at the National Cancer Institute of Colombia between the years 2006 to 2019. Patients with a follow-up time shorter than 6 months were excluded. All biopsy and surgical specimens were processed by the highly trained pathologist in the institution. For those initial specimens done at other institutions, a thorough revision was done again in the National Cancer Institute of Colombia before surgery.

Study Endpoints

In this retrospective study, the primary endpoint was the bRFS rate. Biochemical relapse (BR) was defined as 2 consecutive increasing PSA levels >0.2 ng/mL. Follow up included serum PSA at 3-month intervals for the initial 2 years, every 6 months for the next 3 years and then annually thereafter. Secondary end-points involved the descriptive analysis of the number of lymph nodes resected, pathological margins, time until relapse, and following treatment after relapse. Patient with less thank 6 month follow-up were excluded.

Statistical Analysis

All statistical analyzes were performed using STATA 15 (Stata Corp., College Station, TX, USA). A descriptive analysis was performed for each variable. Survival analysis was performed for the oncological outcome (bRFS with Kaplan-Meier curves and uni and multivariate Cox proportional hazard models that were adjusted for preoperative and postoperative variables with a 10-year follow-up. The related regression coefficients were used to calculate the hazard ratio (HR), a specific relative risk index. For all comparisons, a two-sided *p*-value 0.05 was used to define statistical significance.

Results

A total of 212 patients were identified, 5 of whom were excluded because their follow-up was shorter than 6 months, and 5 due to initial substaging. The baseline characteristics of the population are specified in ►**Table 1**. We found 8 (3.9%) patients with positive lymph nodes; of these, 6 had positive

Table 1 Baseline characteristics

Variable	Nr/total nr (%)
Age (median [IQR])	64.5 (44–78)
PSA (median [IQR])	6.31 (1.3–9.9)
Clinical stage	
cT1a	1 (0.5)
cT1b	1 (0.5)
cT1c	128 (63.37)
cT2a	72 (35.64)
Pathological stage	
pT2	143 (70.8)
pT3a	50 (24.8)
pT3b	9 (4.5)
Pathological Gleason grade group	
1	92 (45.5)
2	84 (41.6)
3	24 (11.9)
4	1 (0.5)
5	1 (0.5)
# Lymph nodes resected (median [IQR])	22 (8–52)
pN1	8 (3.9)
R1	65 (32.2)
Undetermined margin	2 (1.0)
Biochemical relapse	
No	166 (82.2)
Yes	36 (17.8)
Time to relapse* (median [IQR])	4.69 (0–100)
Follow-up time months * (median [IQR])	79.69 (7–164)
Treatment when relapse	
Radiotherapy	22/36 (61.1)
ADT	7/36 (19.4)
Observation	7/36 (19.4)

Abbreviations: ADT, androgen deprivation therapy; cT, clinical stage; IQR, interquartile range; pT, pathological stage.
*Time in months.

margins (R1), 2 had GG2, and 3 had GG3; from these, 2 patients presented relapse at 1 and 18 months, receiving radiotherapy and androgen deprivation therapy (ADT) respectively. Of the total population, only 17.8% relapsed, with a median of 4.6 months. Of these patients with relapse ($n = 36$), 61.1% were treated with salvage radiotherapy, 19.4% with ADT, and 19.4% continue observation due to PSA doubling times 20 months. No patient in the cohort presented resistance to castration.

The 10-year bRFS for the general population was 82.5% (►**Fig. 1A**). A statistically significant difference was observed for bRFS between patients with stage pT3 ($p = 0.047$) as well as GG ($p \leq 0.001$) and R1 ($p \leq 0.001$) (►**Figs. 1B**, **1C** and **1D**). The Cox univariate analysis showed that PSA, GG, and R1 are associated with an increase in BR (►**Table 2**)

Discussion

Low-risk PCa has long been accepted as having a low probability of lymph node metastasis, and, therefore, PLND could be safely avoided.[7,8] Several studies have shown low incidences of lymph node metastases, such as 2.7%, regardless of PSA or clinical stage.[7] This correlates with our study, given the low incidence of lymph node metastasis of 4%.

The study of Naselli et al.[7] concluded that, compared with PLND, ePLND may have a higher incidence of lymph node metastasis, with a median of 11.6 versus 8.9 nodes, respectively, with extended dissection vs standard (p-value < 0.001). Other retrospective data have also indicated that ePLND improves staging with a 2-fold increase in lymph node metastasis.[9] Due to studies like these, ePLND is performed in all low-risk patients at this specific institution. Additionally, it can significantly increase disease-free survival in patients with a low lymph node metastasis burden and increase a significant benefit of bRFS[5,10]

Although not performing PLND in these patients is a globally accepted behavior, it should be taken into account that more than half of the patients are under-classified. In this series, all patients started with GG1, but the pathology showed that more than half of these patients upstage GG, which changes the classification for the majority of them to intermediate risk. This study does not evaluate the possible causes of this discordance. A previous study from our institution in 2016 reported substaging in 47% of the cases, from these, 35% in GG2, 7% in GG3 and 5% with a tertiary histological pattern[11] Additionally, performing PLND has a curative potential, with only 4% associated complications,[12] and overall complication rates are comparable between limited (7.3%) and extended PLND (6.4%).[9]

The presence of lymph node metastases in patients who had a clinically localized diagnosis of PCa sometimes leads to an increase in the BR rate after PLND; therefore, accurate diagnosis in these patients allows a more precise prognosis and may have an important meaning to start adjuvant or salvage therapy.[5] In this study, it was found that PSA, pathological stage (pT), GG, and R1 are associated with a higher risk of BR. The study by Fergany et al.[12] compares PLND vs no PLND, with a free rate of BRs at 4 years for the PLND group versus the control group of 91% and 97%, respectively ($p = 0.16$), and in the multivariate analysis, PLND was not an independent predictor of outcome ($p = 0.24$). Regarding the presence of R1, it has been shown that at a median follow-up of 53 months, 27% of these patients present BR compared with 4% R0, with a hazard ratio (HR) of 4.99 (95% confidence interval [CI] 2.425–10.296); $p < 0.0001$.[13] Concordant with this study that documents a HR 7.586 (95% CI 3.540–16.257); $p < 0.001$.

There are several important limitations to our study. First, there are the inherent limitations of retrospective analyses and, consequently, its sample size. Another limitation is that there were no specific data on complications, especially for

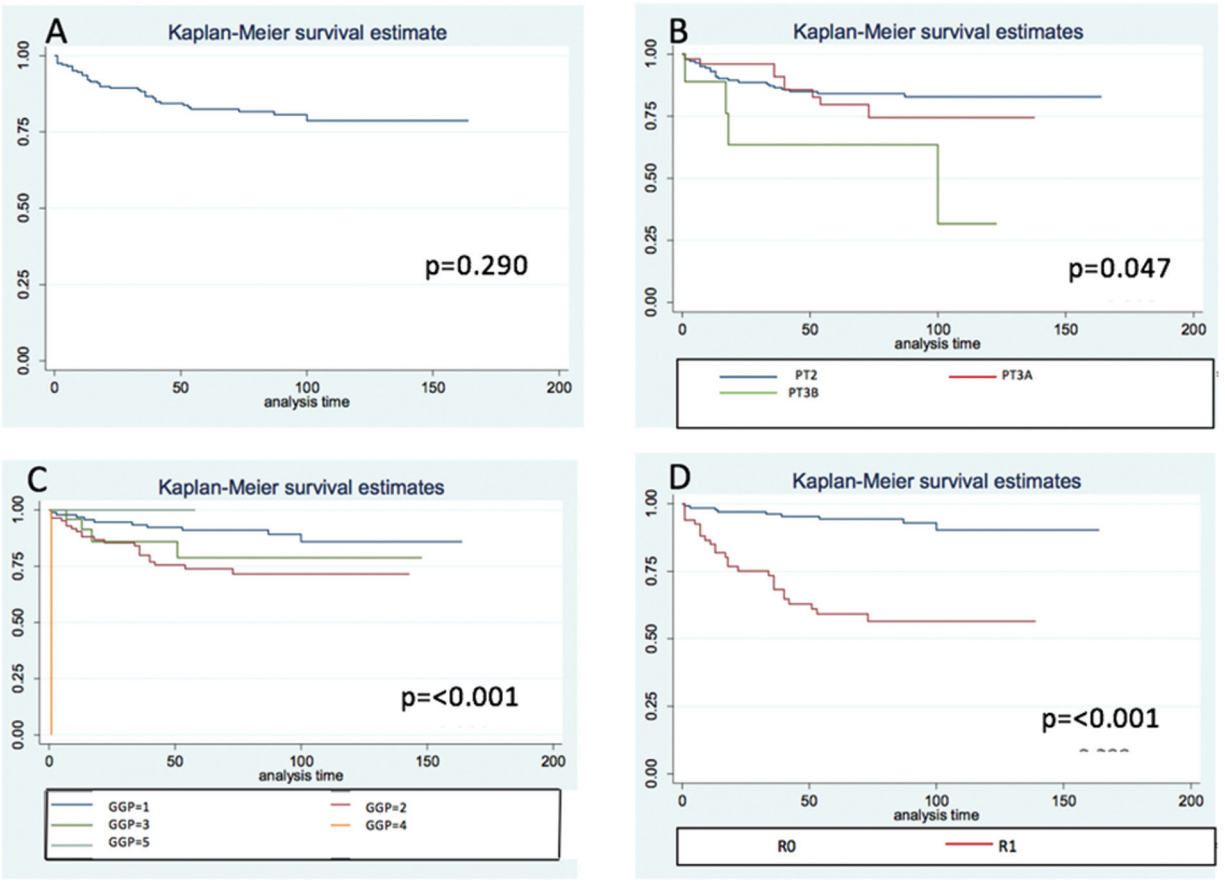

Fig. 1 Kaplan-Meier survival analysis A) general population B) pathological stages C) grade group D) positive margins.

Table 2 Univariate and multivariate analysis

	Univariate survival analysis		Multivariate survival analysis	
	HR (95% IC)	*P*-value	HR (95% CI)	*P*-value
Age	1.027 (0.976–1.082)	0.298		
PSA	1.217 (1.005–1.473)	0.044	1.200 (0.974–1.478)	0.087
cT*	1.053 (0.539–2.060)	0.878		
pT				
2	1.249 (0.577–2.705)	0.577	0.628 (0.270–1.463)	0.282
3	3.531 (1.218–10.240)	1.218	3.471 (1.096–10.990)	0.034
No. of lymph nodes	1.020 (0.988–1.054)	0.215		
N1	1.661 (0.655–4.210)	0.284		
GG				
2	2.810 (1.319–5.985)	0.007	1.702 (0.753–3.847)	0.201
3	2.012 (0.629–6.437)	0.239	0.657 (0.186–2.324)	0.516
4	94.100 (9.810–902.577)	< 0.0001	44.981 (4.036–501.239)	0.002
R1	7.586 (3.540–16.257)	< 0.0001	7.528 (3.396–16.689)	< 0.0001

Abbreviations: CI, confidence interval; cT, clinical stage; GG, grade group; HR, hazard ratio; N1, positive lymph nodes; PSA, prostatic specific antigen; Pt, patological stage; R1, positive margins.
*cT1 a, b, and c grouped in one group; cT2a the second group.

PLND, or information on relevant comorbidities. Additionally, there was no control group of patients who did not undergo PLND, which could lead to more solid results. However, our work consists of a large series with a reasonably long-term follow-up.

Conclusions

Whether performing PLND or not in low-risk PCa patients compromises oncological outcomes is still unknown. In this large single-center study, the detection rate for lymph node metastases was 4% in a low-risk group, with bRFS of 82.5%. Based on the current literature and on our results, the decision to perform PLND in these patients should be made individually and according to the expertise of the institution. In addition, a higher PSA, higher GG, and presence of R1 increase the probability of BR.

Conflict of Interests

The authors have no conflict of interests to declare.

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