Increase of the Incidence of Biochemical Recurrence after Radical Prostatectomy in an Uro-Oncology Training Center in Brazil: Are More Advanced Diseases undergoing Surgery?

doi: https://doi.org/10.32635/2176-9745.RBC.2022v68n3.2483

Aumento da Incidência de Recidiva Bioquímica após Prostatectomia Radical em um Centro de Formação em Urologia Oncológica no Brasil: Doenças mais Avançadas estão sendo submetidas à Cirurgia?

Aumento de la Incidencia de Recurrentes Bioquímicos Después de Prostatectomía Radical en un Centro de Capacitación en Urología Oncológica en Brasil: ¿Enfermedades más Avanzadas están siendo sometidas a Cirugía?

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ABSTRACT

Introduction: Prostate cancer is the most common cancer in men representing 29% of diagnoses of the disease in Brazil according to the National Cancer Institute José Alencar Gomes da Silva (INCA). If digital rectal examination presents alterations and/or altered serum level of prostate-specific antigen (PSA) total is detected, there is suspicion of prostate cancer, but the definitive diagnosis occurs only with histopathological study. **Objective:** To correlate clinical and pathological parameters after radical prostatectomy with biochemical recurrence during follow-up. **Method:** Retrospective observational study of clinical parameters (age, initial PSA, digital rectal examination, histopathological classification of the International Society of Urological Pathology (ISUP), D'Amico scale and clinical stage) and pathological (ISUP degree of the surgical specimen, surgical margins, extracapsular tumor extension and presence of positive lymph nodes) of 177 patients who underwent radical prostatectomy in an uro-oncology service from June 2010 to May 2018. **Results:** Biochemical recurrence occurred in 44.1% of the cases within a mean follow-up time of 34.9 months. Univariate analysis showed that baseline PSA>9 ng/mL, altered rectal examination, pathological ISUP classification 4 and 5, high D'Amico risk, and clinical TNM stage T3 are risk factors for biochemical recurrence. Surgical margins were positive in 46.3%, and in 47.7% extracapsular extension was identified. Positive lymph nodes were detected in 10.9% and positive seminal vesicles occurred in 21.8%. **Conclusion:** Clinical and pathological factors can be predictors of biochemical recurrence. In these cases, it was identified a more aggressive clinical pattern than the literature in general. In addition, it should be considered the learning curve of surgeons in training at the service, which can result in higher rates of positive surgical margins.

Key words: prostatectomy; prostatic neoplasms; neoplasm recurrence, local.

RESUMO

Introdução: O câncer de próstata é a neoplasia maligna mais incidente em homens, representando 29% dos diagnósticos da doença no Brasil, segundo o Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA). Esse câncer é suspeito em alterações do toque retal e/ou do nível sérico do antígeno prostático específico (PSA) total, sendo o diagnóstico definitivo feito por estudo histopatológico. **Objetivo:** Verificar a associação entre parâmetros clínicos e anatomopatológicos após prostatectomia radical com recidiva bioquímica ao longo do seguimento. **Método:** Estudo retrospectivo observacional dos parâmetros clínicos (idade, PSA inicial, toque retal, classificação histopatológica da *International Society of Urological Pathology* (ISUP), escala de D'Amico e estádio clínico) e anatomopatológicos (grau ISUP da peça cirúrgica, margens cirúrgicas, extensão extracapsular tumoral e presença de linfonodos acometidos), de 177 pacientes submetidos à prostatectomia radical em serviço de uro-oncologia de junho/2010-maio/2018. **Resultados:** A recidiva bioquímica ocorreu em 44,1% dos casos no tempo de seguimento médio de 34,9 meses. A análise univariada demonstrou PSA inicial >9 ng/mL, toque retal alterado, classificação patológica ISUP 4 e 5, risco D'Amico alto e estágio clínico TNM T3 como fatores diretamente associados à recidiva bioquímica. As margens cirúrgicas foram positivas em 46,3%; em 47,7%, identificou-se extensão extraprostática tumoral. Linfonodos positivos em 10,9% e vesículas seminais comprometidas ocorreram em 21,8%. **Conclusão:** Fatores clínico-patológicos podem ser preditores de recidiva bioquímica. Nesses casos, foi identificado padrão clínico pré-tratamento supostamente mais agressivo em comparação à literatura em geral. Além disso, deve-se considerar a curva de aprendizado dos cirurgiões em formação no serviço, o que pode resultar em maiores taxas de margens cirúrgicas positivas.

Palavras-chave: prostatectomia; neoplasias da próstata; recidiva local de neoplasia.

RESUMEN

Introducción: El cáncer de próstata es lo más incidente en hombres representando 29% de los diagnósticos de enfermedades en Brasil según Instituto Nacional del Cáncer José Alencar Gomes da Silva (INCA), se sospecha en tacto rectal y/o en el nivel de análisis del antígeno prostático específico (PSA) total alterado, y el diagnóstico definitivo se realiza mediante el estudio histopatológico. **Objetivo:** Correlacionar los parámetros clínicos y patológicos después de la prostatectomía radical con la recurrencia bioquímica a lo largo del seguimiento. **Método:** Estudio observacional retrospectivo de parámetros clínicos (edad, PSA inicial, tacto rectal, clasificación histopatológica de la *International Society of Urological Pathology* (ISUP), escala D'Amico y estadio clínico) y patológicos (grado ISUP de la muestra quirúrgica, márgenes quirúrgicos, extensión capsular tumoral extra y ganglios linfáticos positivos) de 177 pacientes sometidos a prostatectomía radical en servicio de uro-oncología de junio/2010-mayo/2018. **Resultados:** La recurrencia bioquímica ocurrió en el 44,1% de los casos en un tiempo de seguimiento promedio de 34,9 meses. El análisis univariado demostró que el PSA inicial >9 ng/mL, alteración del tacto rectal, clasificación patológica ISUP 4 y 5, alto riesgo de D'Amico y estadificación TNM clínico T3 como factores de riesgo para recurrencia bioquímica. Los márgenes quirúrgicos fueron positivos en el 46,3%, y en el 47,7% se identificó una extensión extra capsular adicional. Los ganglios linfáticos positivos fueron detectados en 10,9% y las vesículas seminales positivas ocurrieron en el 21,8%. **Conclusión:** Los factores clínicos y patológicos pueden ser predictores de recurrencia bioquímica. En estos casos, fue identificado un patrón más agresivo que la literatura en general. Además, se debe considerar la curva de aprendizaje de los cirujanos en formación en el servicio, lo que puede resultar en mayores tasas de márgenes quirúrgicos positivos.

Palabras clave: prostatectomía; neoplasias de la próstata; recurrencia local de neoplasia.

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INTRODUCTION

Radical prostatectomy has clinical and oncological benefits in patients with prostate cancer clinically significant with high metastasis-free and global survival[1]. In tumors with low risk of progression, nearly 85% of the patients submitted to surgery do not show evidences after 5-years and two thirds, after ten years[2]. However, the incidence of post-surgery biochemical recurrence, defined as elevation of the prostate-specific antigen (PSA) above 0.2 ng/ml in two consecutive measures has contrasting results in the literature[3,4].

The clinical evolution of this group of patients varies, some of them with biochemical recurrence have fast progression to metastasis while for others the elevated PSA may not affect the oncological survival. Ten-years survival data comparing patients with and without diagnosis of biochemical recurrence do not show difference of global survival[2]. Regardless of the uncertain correlation between biochemical recurrence and specific cancer survival, the elevation of the PSA indicates persistence of tumor cells and raises discussion about adjuvant treatment and its respective adverse events, in addition to anxiety the patient experiences[2].

Understanding the local epidemiological, clinical-pathological profile of patients treated in public oncology hospitals and possible correlation with the oncological clinical outcome is necessary. The objective of the study was to correlate the clinical and pathological parameters with the oncological outcome (cure or biochemical recurrence) post radical prostatectomy and define risk factors for radical prostatectomy.

METHOD

Observational, retrospective study with 179 patients submitted to radical prostatectomy at "*Hospital São Vicente*" a single High Complexity Oncological Unit (Unacon) in Curitiba (PR), one of the references of Brazil's Southern region for oncological patients of the National Health System (SUS) from June 2010 to May 2018. The data were retrospective through the analysis of electronic charts of the institution. The Institutional Review Board of "*Hospital São Vicente*, Curitiba (PR) approved the study, report number 3.589.604, CAAE (Submission for Ethical Review) 19429019.1.0000.0020, in compliance with scientific and ethical requirements of Ordinance 466/2012[5] of the National Health Council.

The clinical data evaluated were: age, initial PSA, characteristic of the digital rectal exam of the prostate (altered or normal), histopathological grade of the diagnostic biopsy (grades 1 to 5) according to the International Society of Urological Pathology (ISUP), D'Amico risk classification[6] − combines PSA, Gleason's score and clinical staging of Malignant Tumors Classification (TNM)[7] −, and classified as low, intermediate or high risk. The surgical pathological data were: ISUP histopathological grade of the surgical piece, TNM pathological staging, surgical margins (yes or no), extracapsular tumor extension (yes or no), seminal vesicles (yes or no) and presence of positive lymph nodes. The TNM classification is utilized to classify separately the individual tumor (T), lymph node (N) and metastatic elements (M) and group them in stages. The objectives of TNM classification are to aid the clinician in planning the treatment, give some indication of the prognosis, and assist in the evaluation of the results of the treatment[7].

The inclusion criteria were patients diagnosed with local or locally advanced prostate cancer with indication of curative surgical treatment, submitted to radical prostatectomy at the oncological urology service of "*Hospital São Vicente*" in Curitiba (PR) and who accepted to sign the Informed Consent Form (ICF). Electronic charts with missing data and patients who refused to sign the ICF were excluded.

The study results were described as means, standard-deviation, medians, minimal and maximal values (quantitative variables) or by frequencies and percentages (categorical variables). To determine the cutoff for initial PSA associated with biochemical recurrence, the curve receiver operating characteristic (ROC) was adjusted, which is defined as a plot of test sensitiveness of a diagnostic test *versus* its specificity or false-positive rate[8]. Cox regression models, a semiparametric for characterizing the associations between covariables[9], were adjusted to analyze the association of recurrence-free time (univariate and multivariate analysis). Wald's test was utilized to find out if each variable is significant, a non-parametric test to evaluate restrictions of statistic parameters[10]. By means of the stepwise backward model of selection of variables (significance $p<0.20$ was excluded), the initial PSA variables, rectal exam, compromised margin and extraprostatic extension were analyzed. Hazard ratio (HR) was the measure of association estimated, a relative risk of occurrence of the event as a function of time[11], for which confidence intervals of 95% were established (CI 95%). Values of $p<0.05$ indicated statistical significance. The data were analyzed with the software Stata, version 14.1, by StataCorpLP, USA.

RESULTS

Of the 179 patients, 177 had complete pathological and clinic data for analysis. The mean age of the

population was 63.7 years of age and mean follow-up of 34.9 months.

Digital rectal exam was altered in 60.1% of the cases (104/177). ISUP classification of the diagnostic biopsy was 48.2% for group 1, 23.5% for group 2, 16.5% for group 3 and 11.8% for groups 4 and 5 grouped. The D'Amico risk classification showed 28.9% of low-risk patients, 43.4% at intermediate risk and 27.7% at high risk (Table 1).

The surgical pathological study revealed that 71.7% had clinically significant tumors with ISUP from 2 to 5. Pathological TNM showed that 34.5% of the cases were classified with disease pT2 (tumor confined to the prostate) and 37.9% classified as pT3a, 16.7%, pT3b and 10.9%, pN1 (Table 1).

As Graph 1 shows, half of the patients had biochemical recurrence in 40 months. Pathological staging pT3 or pN1, positive surgical margin, compromised seminal vesicles and extracapsular tumor extension were variables that are correlated to risk of biochemical recurrence.

PSA cutoff of 9 ng/ml (Graph 2) was demonstrated by ROC curve . The area under the curve was 0.70 (p<0.001). Values of PSA >9 ng/ml are associated with recurrence with sensitivity of 72% and specificity of 67%.

The univariate analysis concluded that the relevant factors correlated with biochemical recurrence were: initial PSA >9 ng/ml (p<0.001; HR 3.19), altered digital rectal exam (p=0.027; HR 1.74), high D'Amico risk (p<0.001; HR 4.34), clinical staging T3 (p<0.001; HR 3.65), ISUP 3 of the surgical piece (HR 2.11; p=0.021), ISUP 4 or 5 (p=0.004; HR 2.54) and pN1 (p<0.001; HR 6.65), compromised margins (p<0.001; HR 2.92), positive seminal vesicles (p<0.001; HR 3.26), extraprostatic tumor extension (p<0.001; HR 3. 06) as shown in Table 2.

The multivariate analysis revealed the association of the following variables with biochemical recurrence: ISUP 4 or 5 (p=0.136; HR 1.85), compromised margins (p=0.073; HR 1.72), compromised seminal vesicles (p=0.527; HR 1.24) and extraprostatic extension (p=0.022; HR 2.05).

With the stepwise approach (p<0.20 to exclude the variable from the model), initial PSA >9 ng/ml (p=0.017; HR 2.06), altered digital rectal exam (p=0.030; HR 1.92), compromised margin (p=0.029; HR 1.92) and extraprostatic extension (p=0.009; HR 2.2) correlated with higher risk of biochemical recurrence (Table 3).

Table 1. Clinical and pathological variables of the 177 patients investigate

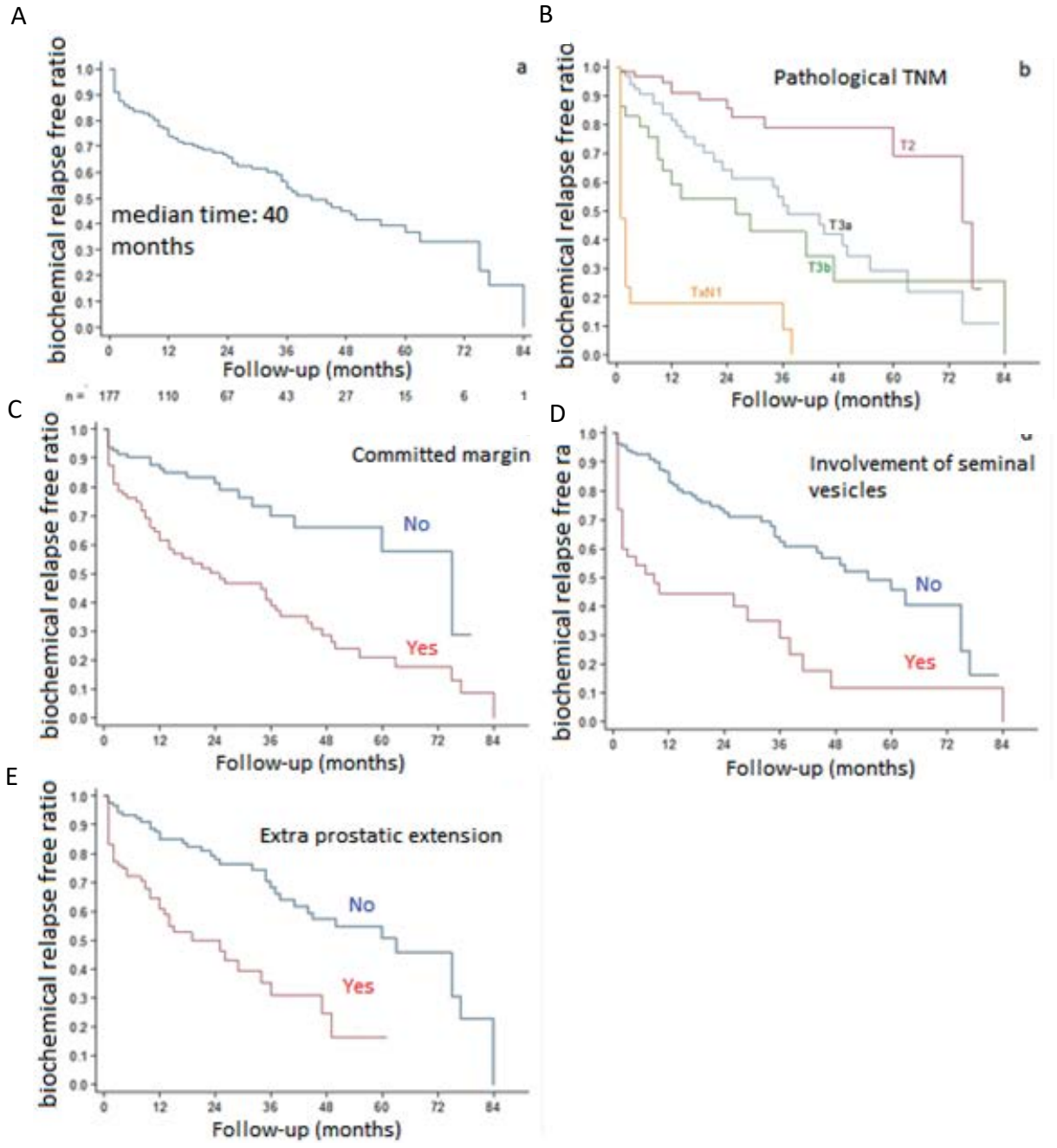
Variable	Classification	n (%)
Digital rectal exam	Altered	104 (60.1)
	Normal	69 (39.9)
ISUP grade of prostate biopsy	1	82 (48.2)
	2	40 (23.5)
	3	28 (16.5)
	4	11 (6.5)
	5	9 (5.3)
D'Amico	Low	50 (28.9)
	Intermediate	75 (43.4)
	High	48 (27.7)
Clinic TNM	T1c	68 (38.4)
	T2a	48 (27.1)
	T2b	24 (13.6)
	T2c	18 (10.2)
	T3	19 (10.7)
ISUP grade of the surgical piece	1	49 (28.3)
	2	55 (31.8)
	3	33 (19.1)
	4	14 (8.1)
	5	22 (12.7)
Pathological TNM	T2	60 (34.5)
	T3a	66 (37.9)
	T3b	29 (16.7)
	TxN1	19 (10.9)
Compromised margin	No	94 (53.7)
	Yes	81 (46.3)
Compromised vesicles	No	136 (78.2)
	Yes	38 (21.8)
Extraprostatic extension	No	92 (52.3)
	Yes	84 (47.7)

Captions: ISUP = International Society of Urological Pathology; TNM = Classification of Malignant Tumors.

DISCUSSION

The study showed the clinical evolution of the patients submitted to radical prostatectomy at a Brazilian oncological public service. During 34.9 months of follow-up, postoperative prostate cancer biochemical recurrence occurred in 44.1% of the cases, higher than described in similar studies of the literature. Aguilera et al.[12] reported 37.2% of biochemical recurrence, while other study[13] with 400 patients submitted to radical prostatectomy found a rate of 32%.

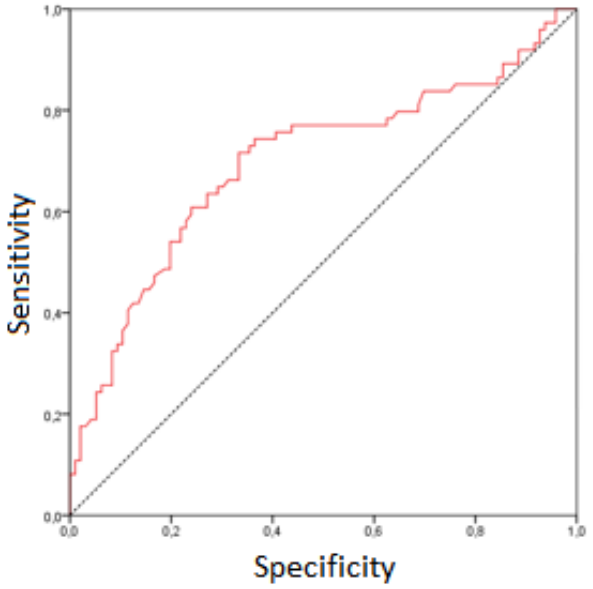
Digital rectal exam revealed alteration in 60.1% of the cases and was an independent factor for biochemical recurrence (p=0.03; HR 1.92). In comparison, a Spanish study with 276 patients submitted to prostatectomy for prostate cancer showed that 93 (33%) had altered exam[12]. PSA above cutoff was also determinant for unfavorable



Graph 1. Curves of biochemical recurrence-free survival during follow-up in months according to surgical pathological variables. A) Overall curve of biochemical recurrence-free survival of the 177 patients investigated; B) Biochemical recurrence-free survival associated with TNM pathological staging; C) Biochemical recurrence-free survival associated with compromised surgical margin; D) Biochemical recurrence-free survival associated with compromise of seminal vesicles; E) Biochemical recurrence-free survival associated with extraprostatic extension

outcome ($p<0.017$), with high incidence of recurrence in patients with initial PSA >9 ng/mL, an important predictive factor of postoperative biochemical recurrence.

Of the patients investigated, 10.9% had positive lymph nodes on the pieces of pelvic lymphadenectomy performed during prostatectomy. The percentage of lymph node compromised according to the literature is variable[14,15]. Abdollah et al.[14] analyzed 5,274 patients with prostate cancer treated with extended pelvic lymphadenectomy and found 13.8% of compromised lymph nodes (N+). The authors affirmed that the mean was higher than other American studies, possibly because the lymphadenectomy was more extended than in other studies which would require bigger sample of lymph nodes[14]. In another multicenter study, 130,800 patients submitted to radical prostatectomy were reported between 1988 and 2006. The mean of lymph node compromise reduced along the time from 10.7% in the beginning of the study to 3.1%



Graph 2. ROC curve associating initial total PSA total value with risk of biochemical recurrence

at the end. This decrease may be related to small sampling of lymph nodes during the period[15].

The percentage of positive surgical margins was 46.3% and its presence was related to the multivariate analysis with biochemical recurrence (p=0.029). In a study with 1,250 patients submitted to radical prostatectomy clinically localized, 23.84% of the cases had positive surgical margins[16]. The compromised margins indicated higher risk of biochemical recurrence. The rates of prostatectomy failure were from 45% to 55% in patients with positive margins when compared from 15% to 25% of those with free margins[16]. Another study with 74 patients submitted to radical prostatectomy and pathological staging T3a showed positive surgical margin of 49.3%[17]. The multivariate analysis, presence of ISUP 4 or higher at the compromised margin larger than 3 mm and the presence of two or more areas of compromised margin were strongly correlated with biochemical recurrence[18]. The variability of the rates of compromised surgical margins according to the literature can be the result of sample heterogeneity of the clinical standard before the surgery, further to the heterogeneity of surgical techniques and experience of the surgical team.

One of the hypothesis for the elevated incidence of positive surgical margins is the fact that surgeons still in formation (resident and specialized) participate actively of the surgeries. The learning curve of the surgeons can elevate the incidence of positive margins. A study[19] which proposed to investigate the learning curve of radical prostatectomy showed that after 20 surgeries, a significant decrease of operation time from 150 to 120 minutes was found and that after the 29th surgery, the necessity of blood transfusion decreased from 9% to 3%. However, the percentage of compromised surgical margins remained stable during the learning curve, suggesting an elevated number of operated cases to reduce the incidence[19].

Another hypothesis is that patients of the group investigated were at more advanced clinical and pathological stage. All the patients were consulted at SUS and issues like access and late diagnosis suggest that socioeconomic status is an independent factor of biochemical recurrence[20]. An Australian study showed the socioeconomic impact on the overall survival of oncologic patients and its results revealed that the population with stomach, colorectal, liver, lungs, breast and prostate cancer living in underserved economic areas had worst outcomes[21]. Freeman et al.[22] conducted a similar study whose focus was prostate cancer where worst socioeconomic status was significantly associated with lower cancer-specific survival for the American population.

Some of the limitations of the study are the retrospective design of data collection, which may result in poor uniformity of the data recorded in the electronic chart. The sample was collected in one institution alone, which is an obstacle for the generalization of the results reached, so future national multicenter studies are necessary.

The interpretation of data of the public healthcare network, the source of medical care for great part of the Brazilian population, can help developing strategies to reduce the impact of prostate cancer and its post-treatment repercussions. Initiatives as expanding the scope of the information provided to the patients and the healthcare team about early diagnosis and effective treatment can help to increase postoperative biochemical recurrence-free survival.

CONCLUSION

For a population whose source of care is a public oncological service at Brazil's Southern region, a more aggressive pathological pattern was found and consequentially, a higher rate of biochemical recurrence in comparison with the literature.

Oncologic diagnosis delay and learning curve of in-training surgeons are possible factors associated with the results.

ACKNOWLEDGMENT

To Márcia Olandoski for the contribution to statistical analyzes.

CONTRIBUTIONS

All the authors contributed substantially to the study design, acquisition, analysis and interpretation of the

Table 2. Univariate analysis of clinical and pathological factors associated with biochemical recurrence

Variable	Classification	n***	Biochemical recurrence		p*	HR (CI 95%)
			No	Yes		
Age (years)			64.1±6.2 (51-79)	63.1±6.1 (51-77)	0.865	1.00 (0.97-1.04)
Initial PSA **			9±5 (1.4-34.9)	16.2±16.4 (3.5-105)	<0.001	1.04 (1.02-1.05)
	≤9 ng/ml (ref.)	83	62 (74.7)	21 (25.3)		
	>9 ng/ml	94	34 (39.1)	53 (60.9)	<0.001	3.19 (1.91-5.33)
Length of hospital stay			2.7±1.1 (1-7)	3.4±1.5 (2-11)	0.081	1.14 (0.98-1.31)
Digital rectal exam	Normal (ref.)	69	46 (66.7)	23 (33.3)		
	Altered	104	52 (50)	52 (50.0)	0.027	1.74 (1.06-2.87)
ISUP grade of prostate biopsy	1 (ref.)	82	51 (62.2)	31 (37.8)		
	2	40	26 (65.0)	14 (35.0)	0.694	1.14 (0.60-2.14)
	3	28	14 (50.0)	14 (50.0)	0.021	2.11 (1.12-3.99)
	4 or 5	20	5 (25.0)	15 (75.0)	0.004	2.54 (1.35-4.80)
D'Amico Risk	Low (ref.)	50	38 (76)	12 (24.0)		
	Intermediate	75	44 (58.7)	31 (41.3)	0.041	2.00 (1.03-3.91)
	High	48	14 (29.2)	34 (70.8)	<0.001	4.34 (2.24-8.43)
Clinic TNM	T1c (ref.)	68	42 (61.8)	26 (38.2)		
	T2a	48	33 (68.8)	15 (31.3)	0.699	1.13 (0.60-2.15)
	T2b	24	12 (50.0)	12 (50.0)	0.557	1.24 (0.61-2.53)
	T2c	18	9 (50.0)	9 (50.0)	0.183	1.68 (0.78-3.61)
	T3	19	3 (15.8)	16 (84.2)	<0.001	3.65 (1.95-6.84)
ISUP grade of the surgical piece	1 (ref.)	49	33 (67.4)	16 (32.7)		
	2	55	35 (63.6)	20 (36.4)	0.098	1.76 (0.90-3.42)
	3	33	21 (63.6)	12 (36.4)	0.013	2.69 (1.23-5.89)
	4 or 5	36	9 (25.0)	27 (75.0)	0.001	2.96 (1.57-5.56)
Pathological TNM	T2	66	36 (54.6)	30 (45.5)		
	T3a	60	48 (80.0)	12 (20.0)	0.003	0.36 (0.18-0.70)
	T3b	29	12 (41.4)	17 (58.6)	0.237	1.44 (0.79-2.66)
	TxN1	19	2 (10.5)	17 (89.5)	<0.001	6.65 (3.51-12.6)
Compromised margin	Não (ref.)	94	72 (76.6)	22 (23.4)		
	Sim	81	27 (33.3)	54 (66.7)	<0.001	2.92 (1.77-4.82)
Compromised vesicles	Não (ref.)	136	88 (64.7)	48 (35.3)		
	Sim	38	11 (29)	27 (71.1)	<0.001	3.26 (2.00-5.30)
Extraprostatic extension	Não (ref.)	92	57 (62)	35 (38)		
	Sim	84	42 (50)	42 (50)	<0.001	3.06 (1.87-4.99)

Captions: HR = hazard ratio; CI 95% = confidence intervals of 95%; PSA = prostate specific antigen; ISUP = International Society of Urological Pathology; TNM = Classification of Malignant Tumors; ref. = reference.
(*) Cox regression model and Wald's test , p<0.05.
(**) Cutoff indicated by the adjustment of the ROC curve (area below the curve: 0.70 with statistical significance p<0.001). Sensitivity of the cutoff = 72%; specificity of the cutoff = 67%.
(***) Total number of patients of the sample investigated (n=177).

Table 3. Multivariate analysis stepwise backward

Variable	Classification	p*	HR (CI 95%)
PSA (ng/ml)	≤9		
	>9	0.017	2.06 (1.14-3.74)
Digital rectal exam	Normal		
	Altered	0.030	1.92 (1.07-3.47)
Compromised margin	No		
	Yes	0.029	1.92 (1.07-3.46)
Extraprostatic extension	No		
	Yes	0.009	2.20 (1.22-3.99)

Captions: HR = hazard ratio; CI 95% = confidence intervals of 95%; PSA = prostatic specific antigen.
(*) Values of p of the statistical tests and estimated values of HR with respective confidence intervals of 95% (CI95%) for the final model.

data, wording and critical review. They approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

FUNDING SOURCES

None.

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Recebido em 11/1/2022
Aprovado em 21/3/2022

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