

Recurrence rate of localized prostate cancer after radical prostatectomy according to D'amico risk classification in a tertiary referral hospital: association study

Tasa de recurrencia del cáncer de próstata localizado después de la prostatectomía radical según la clasificación de riesgo de D'amico, en un hospital terciario de referencia: estudio de asociación

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Abstract

Objective: The objective of the study was to determine the recurrence rate of localized prostate cancer after radical prostatectomy according to the D'Amico classification. **Methods:** This was a observational and 5-year comparative retrospective cohort study. Data were obtained from clinical records of patients with localized prostate cancer who underwent radical prostatectomy and the recurrence rate of the disease was evaluated. It was analyzed with descriptive and comparative statistical tests, $p < 0.05$ was considered significant. **Results:** One hundred and eight patients were analyzed, and the average age was 65.3 years. About D'Amico's risk classification, 33.33% low risk, 55.56% intermediate risk, and 11.11% high risk. The prostate-specific antigen (PSA) recurrence rate was 14.81%. Low-risk patients had recurrence of 13.89%, intermediate risk 18.33%, and high risk had no recurrence. Regarding surgical pieces, 25.93% presented adverse characteristics. The post-operative Gleason scale shows an increase of 44.44% in low risk, 26.67% in intermediate risk, and 41.67% in high risk. **Conclusions:** Radical prostatectomy offers adequate control of localized prostate cancer. The PSA recurrence rate was lower than other international reports. Likewise, the biochemical recurrence of low, intermediate, and high risk was similar to the global trend.

Key words: Prostate cancer. Recurrence localized. Prostate cancer. Radical prostatectomy. Prostatic specific antigen.

Resumen

Objetivo: Determinar la tasa de recurrencia del cáncer de próstata localizado después de la prostatectomía radical según la clasificación D'Amico. **Métodos:** Estudio de cohorte retrospectivo comparativo de 5 años. Se obtuvieron datos de registros clínicos de pacientes con cáncer de próstata localizado, que se sometieron a prostatectomía radical y se evaluó la tasa de recurrencia de la enfermedad. Se analizó con pruebas estadísticas descriptivas y comparativas. Una $p < 0.05$ se consideró significativo. **Resultados:** Se analizó 108 pacientes, la edad promedio 65.3 años. Acerca de la clasificación de riesgo de D'Amico, 33.33% de bajo riesgo, 55.56% riesgo intermedio y 11.11% alto riesgo. La tasa de recurrencia de APE fue 14,81%. Los pacientes de bajo riesgo tuvieron recurrencia del 13.89%, riesgo intermedio 18.33% y alto riesgo no tuvieron recurrencia.

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Sobre piezas quirúrgicas, el 25.93% presentaron características adversas. La escala de Gleason postoperatoria muestra un aumento de 44.44% en bajo riesgo, 26.67% en riesgo intermedio y 41.67% en alto riesgo. Conclusiones: La prostatectomía radical ofrece un control adecuado del cáncer de próstata localizado. La tasa de recurrencia del APE fue menor que otros informes internacionales. Asimismo, la recurrencia bioquímica del riesgo bajo, intermedio y alto fue similar a la tendencia global.

Palabras clave: Cáncer de próstata. Recurrencia de cáncer de próstata localizado. Prostatectomía radical. Antígeno prostático específico.

Introduction

Prostate cancer is the most common non-cutaneous cancer in older men (> 70 years old), with an accumulative risk by 8.3% and a mortality of 4.27%. In México, the incidence of accumulative risk for prostate cancer is 41.6%¹⁻³. Prostate cancer is the most common cause of mortality from malignant tumors with an incidence of 16% in México. The most recent data published by the National Institute of Cancerology in México (INCan) indicate a mortality rate of 13 deaths per 100.000 men. In 2013, a mortality rate of six deaths was observed for every 100.000 men of 20 years old or more⁴. By the other hand, in the USA, the National Institute of Cancer (NIH) reports that at the time of diagnosis, 78% of cases are confined to the organ, with a relative survival of 100% to 5 years⁵.

Localized prostate cancer rarely causes symptoms; moreover, the presence of symptoms is frequent in locally advanced prostate cancer with a high growth rate or with metastatic disease^{6,7}. The intervention of patients with localized prostate cancer should be made on time to provide a positive impact on the evolution of the disease; this approach could even be potentially curative^{2,6}. Localized prostate cancer should be classified according to the risk group to develop recurrence of disease, using the D'Amico Classification^{8,9}.

At present day, the radical prostatectomy is the only treatment for localized prostate cancer that shows benefits in global survival and specific cancer survivorship⁷. Different studies compare the radical prostatectomy with the conservative treatment (active surveillance); particularly, in a 15-year follow-up study SPCG-4 the authors founded a reduction of mortality (relative risk [RR] of 0.75). In another study, the radical prostatectomy was associated with a reduction in mortality of localized prostate cancer with a RR of 0.62^{10,11}. In the 10-year follow-up study PIVOT, the subgroups analysis showed that in low-risk patients of prostate cancer, radical prostatectomy did not increase significantly the mortality by any cause (hazard ratio [HR]=1.15); At intermediate risk, radical prostatectomy reduced mortality of all causes

(HR=0.69); in high-risk tumors, radical prostatectomy did not reduce significantly total mortality (HR=0.40)¹¹⁻¹³. Another study for Gleason score >8, the biochemical progression-free survival at 5 and 10 years of follow-up ranges was between 35-61% and 24-39%, respectively, while the 5, 10, and 15-year specific cancer survival rate was 96%, 84-88%, and 66%, respectively². In a cohort study on biochemical recurrence after radical prostatectomy stratification according to the risk classification of D'Amico, the accumulative incidence of biochemical recurrence of 10 years was 17.9%, 31.9%, and 47.9% for low, intermediate, and high-risk patients, respectively¹⁴.

High-risk localized prostate cancer is more likely to have early recurrence of prostate-specific antigen (PSA), with the need for secondary treatment, as well as a metastatic progression and death from prostate cancer. However, not all high-risk patients have bad prognostics after radical prostatectomy. The incidence of tumor limited to the organ is 26-31%¹⁵. The aim of the study was to evaluate the recurrence rate in patients with localized prostate cancer who underwent radical prostatectomy, according to the different risk groups in a third-level hospital.

Materials and Methods

Study design and settings

This was a observational, descriptive, comparative, and 5-year retrospective study of prevalence conducted in Bajío Regional High Specialty Hospital. The institution is a referral hospital, which provides tertiary care in the central region of Mexico.

Data collection

Data were collected from clinical records of patients with localized prostate cancer who underwent to radical prostatectomy in our institution. Patients were diagnosed with prostate cancer by transrectal biopsy or transurethral resection of the prostate, and then were

referred to our hospital. The diagnosis of localized prostate cancer was made with extension studies, such as bone scintigraphy. Patients were evaluated with specific prostate antigen levels, digital rectal examination, and histopathological result. With this information, all patients were evaluated according to D'Amico classification. A radical prostatectomy was indicated and performed in these patients. In the follow-up, patients should remain stable without recurrence or persistence of the antigen. All clinical, surgical and pathological data were collected from medical records of the patients to analyze variables as sex, age, prostate biopsy, date of surgery, kind of surgery performed, transoperative findings, pathology report, and PSA outcome.

Statistical analysis

For numerical variables, measures of central tendency and dispersion were calculated, and representative values were reported, according to the type of data distribution. For qualitative variables, proportions in percentage rates were determined. Contingency tables were constructed for independent and dependent variables. For qualitative variables, they were compared with the Chi-square test or Fisher's exact probability test, depending on the distribution of the expected values of the contingency table. For quantitative variables, the Student's t-tests were used to compare two non-correlated samples or their non-parametric equivalent if the data did not show normal distribution. The tests were performed considering a level of significance $\alpha=0.05$

Ethics Committee Approval

This article was submitted for review by the Hospital's research and ethics committees, and after its approval it was executed. The agreements of the Declaration of Helsinki of the World Medical Association on ethical principles for medical research in human beings were followed. Each and every one of the data obtained was safeguarded; the identification data and any other personal data of the patient were not exposed.

Results

STUDY POPULATION

A total of 108 patients with prostate cancer undergoing radical prostatectomy were analyzed according to

Table 1. General description of patients

Variable	n (%)	n=108
Age	65.3 ± 5.91	
Sex		
Male	108 (100%)	
Background		
DM*	17 (15.74%)	
AH**	32 (29.63%)	
Other	60 (55.56%)	
Pathological diagnosis performed by		
Transrectal prostate biopsy	100 (92.59%)	
Transurethral resection of prostate	8 (7.41%)	
Gleason prior to surgery		
2+2	4	3 (2.78%)
2+3	5	1 (0.93%)
3+2	5	1 (0.93%)
3+3	6	67 (62.04%)
3+4	7	25 (23.15%)
4+3	7	10 (9.26%)
3+5	8	1 (0.93%)
Recurrence risk groups according to D'Amico		
Low	36 (33.33%)	
Intermediate	60 (55.56%)	
High	12 (11.11%)	
Surgical approach		
Retropubic	64 (59.26%)	
Retropubic + pelvic lymphadenectomy	32 (29.63%)	
Laparoscopic	12 (11.11%)	
Surgical bleeding	842.03 ± 600.20	
Gleason post-surgical		
3+2	5	1 (0.93%)
3+3	6	53 (49.07%)
3+4	7	30 (27.78%)
4+3	7	12 (11.11%)
4+4	8	7 (6.48%)
3+5	8	1 (0.93%)
5+3	8	0 (0%)
4+5	9	2 (1.85%)
5+4	9	1 (0.93%)
5+5	10	1 (0.93%)

*DM: Diabetes mellitus, **AH: Arterial hypertension.

their risk group. Overall, the average age was 65.3 ± 5.91 years. About the comorbidities, diabetes mellitus occurred in 15.74%, hypertension in 29.63%, and other medical, surgical, and traumatic comorbidities in

Table 2. Results by risk groups according to D'Amico for persistence and recurrence of PSA, characteristics of the surgical piece and adjuvant treatment

Risk groups	Low	Intermediate	High	Total	χ ²	P	Cramer's V
Adverse characteristics of the surgical piece							
Adverse	5 (13.89%)	17 (28.33%)	6 (50%)	28 (25.93%)	6.52	0.0434*	0.246
No adverse	31 (86.11%)	43 (71.67%)	6 (50%)	80 (74.07%)			
Persistence of PSA							
Persistence	4 (11.11%)	2 (3.33%)	3 (25.00%)	9 (8.33%)	6.69	0.0302*	0.249
No persistence	32 (88.89%)	58 (96.67%)	9 (75.00%)	79 (91.67%)			
Recurrence of PSA							
Recurrence	5 (13.89%)	11 (18.33%)	0 (0%)	16 (14.81%)	2.7	0.3309*	0.158
No Recurrence	31 (86.11%)	49 (81.67%)	12 (100%)	92 (85.19%)			
Adjuvant treatment							
Treatment	16 (44.44%)	22 (36.67%)	8 (66.67%)	46 (42.59%)	3.76	>0.05	0.186
No treatment	20 (55.56%)	38 (63.33%)	4 (3.33%)	62 (57.41%)			

*Fisher exact probability test. PSA: prostate-specific antigen.

55.56% of patients. The pathological diagnosis was made in 92.59% patients by transrectal prostate biopsy, while 7.4% were made by transurethral resection of the prostate (Table 1).

Risk classification analysis

Regarding the classification of the risk of recurrence according to the D'Amico scale, the following was observed: thirty-six patients (33.33%) presented low risk, 60 patients (55.56%) presented intermediate risk, and 12 patients (11.11%) were identified as high risk. According to surgical management, open retropubic radical prostatectomies were performed in 64 patients (59.26%) of these 40 patients with intermediate risk, no pelvic lymphadenectomy was performed due to the calculated probability of lymph node involvement <5%, high-risk patients underwent pelvic lymphadenectomy, in another group of patients open retropubic prostatectomy plus pelvic lymphadenectomy were performed in 32 patients (29.63%), and laparoscopic radical prostatectomy in 12 patients (11.11%) who were classified as low risk. The average bleeding was 842.03 ± 600.20 ml. One death from acute myocardial infarction was identified 15 days after surgery. These and other descriptive patient data are shown in detail

Surgical piece analysis

In the surgical piece analysis, 28 patients (25.93%) were found to have adverse characteristics; six patients (50%) corresponded to the high-risk group,

17 patients (28.33%) to the intermediate group, and five patients (13.89%) to the low-risk group.

Persistence of PSA

In the clinical course of patients with PSA control, found out that nine (8.33%) patients presented persistence of PSA; four patients (11.11%) had low risk, two patients had intermediate risk (3.33%), and three patients (25%) had high risk in the D'Amico scale.

Recurrence of PSA

About the recurrence of PSA, we found 16 (14.81%) patients; five patients had low risk (13.89%), and 11 patients had intermediate risk (18.33%). No patient with high risk had recurrence.

Adjuvant treatment

During the following time after surgery, 46 (42.59%) patients received adjuvant treatment with radiotherapy (76-81 Gy) and/or hormonal treatment. Of these patients, 16 (44.44%) were evaluated as low risk, 22 (36.67%) as intermediate risk, and eight (66.67%) as high risk. All this data are shown detailed in Table 2.

Post-surgical Gleason score analysis

About the increase of post-surgical Gleason score, it was observed in 16 (44.44%) patients evaluated as

Table 3. Variation of Gleason score following radical prostatectomy by risk group according to D'Amico classification

Risk groups	Gleason						
	Increase				χ^2	p	Cramer's V
	n (%)	Decrease	Same	Total			
Low	16 (44.44)	n (%)	n (%)	n (%)			
Intermediate	16 (26.67)	0 (0)	20 (55.56)	36 (100)	1.86	0.172	0.1518
High	5 (41.67)	13 (21.66)	31 (51.67)	60 (100)	2.74	0.0978	0.179
Total	37 (34.26)	1 (8.33)	6 (50)	12 (100)		0.392*	0.0533
*Fisher exact probability test		14 (12.96)	57 (54.29)	108 (100)			

low risk by D'Amico scale; moreover, in 16 (26.67%) patients evaluated as intermediate risk and in 5 (41.67%) patients evaluated as high risk (Table 3).

Discussion

This study evaluated 108 patients with localized prostate cancer who underwent radical prostatectomy. They were classified into risk groups according to D'Amico scale, the most prevalent was the intermediate risk (55.56%). We found a PSA recurrence rate of 14.81%, lower than the reported in international studies (23-34%); moreover, the mortality reported in the follow-up was 6%². In our hospital, only one death was identified (acute myocardial infarction), 2 weeks after surgery; no deaths were identified in the follow-up of localized prostate cancer disease after radical prostatectomy, neither in patients who merited adjuvant treatment. In our study, in the high-risk group, no patients had recurrence, possibly due to the sample size; nevertheless, we cannot underestimate the effect of patient selection before surgery in the institution, specifically in their risk classification. It was observed that the average age was 65.3 ± 5.91 years, similar to the reported in other studies (63-68 years)¹⁶⁻¹⁸. The main comorbidities were also evaluated, being type 2 diabetes mellitus (15.74%) and arterial hypertension (29.63%) the most frequent; considering that the metabolic syndrome is associated in different studies to increasing risk of prostate cancer¹⁹.

The pathological diagnosis of localized prostate cancer was performed in 92.59% by transrectal biopsy, while 7.4% were performed by transurethral resection of the prostate. In international studies, it was found that prostate cancer was diagnosed in 98.7% by transrectal biopsy and the rest by

transurethral resection of the prostate². In Mexico, prostate cancer is diagnosed by transrectal prostate biopsy in 77% of the patients and by transurethral resection of the prostate in 17% of the patients²⁰. The results of our hospital are similar with international studies; but, comparing with Mexico, the percentage decreases by transrectal prostate biopsy, because patients do not have a screening and come for obstructive prostatic hyperplasia performing transurethral resection of the prostate. Surgical management of patients was performed by open and laparoscopic surgery. Open surgery was the most frequent technique in the present study, with retropubic radical prostatectomy in 64 patients (59.26%), retropubic radical prostatectomy plus pelvic lymphadenectomy in 32 patients (29.63%), and laparoscopic surgery in 12 patients (11.11%) who were classified as low risk. Lymphadenectomy is not necessary in patients with low-risk prostate cancer since the risk of positive lymph node involvement does not exceed 5%. In intermediate risk, lymphadenectomy is performed if the positive lymph nodes are >5% and in those of high risk it should be performed to all².

The decision to perform lymphadenectomy in radical prostatectomy uses the nomograms of the Memorial Sloan Kettering Center, Briganti nomograms representing a discriminating power superior to the Partin tables². Therefore, 40 patients classified as intermediate risk before surgery did not undergo pelvic lymphadenectomy because it was <5% of the calculated probability of lymph node involvement. All patients classified as high risk underwent lymphadenectomy. Average bleeding was 842.03 ± 600.20 mL.

Radical prostatectomy represents one of the treatments of choice for patients with localized prostate cancer and it is associated with good long-term outcomes². However, more than 30-35% of contemporary

patients treated with radical prostatectomy will present adverse features to the disease (extracapsular extension, invasion of seminal vesicles, or positive margins) in the final pathology exam²⁰. We found 28 patients (25.93%) that presented adverse characteristics in the surgical piece, being lesser than the international reports. In the present study, we found the following results: about 13.89%, 28.33%, and 50% for low, intermediate, and high-risk groups, respectively; on the other hand, results of information in the international literature show 16%, 41%, and 66% for low, intermediate, and high-risk groups, respectively. These percentages are higher, but the ratio of distribution is similar to the literature²¹.

While evaluating the persistence of PSA, it was found that nine patients (8.33%) presented persistence of it, being low-risk four patients (11.11%), intermediate-risk two patients (3.33%), and high-risk three patients (25%). In different international articles, biochemical persistence occurs in approximately 20% of patients^{22,23}, comparing with our study, only 8.33% were low. After surgery, PSA is expected to become undetectable at approximately 6 weeks postoperatively. However, up to 20% of patients with adverse pathologic features do not achieve an undetectable PSA level after radical prostatectomy²³.

Adjuvant treatment after radical prostatectomy is to add to the primary therapy to decrease the risk of relapse. Adjuvant treatment to radical prostatectomy is performed with radiation therapy with or without androgen deprivation therapy. The combination of radiation therapy with androgen deprivation therapy has been shown to be superior to radiation therapy alone.

All prostate cancer patients high-risk should be given multimodal treatment (androgen deprivation therapy and/or radiotherapy)².

Adjuvant therapy should be offered to the surgical field to patients with a higher risk of local relapse: pT3 pN0 with positive margins (greater impact) and/or invasion of the seminal vesicles. Patients can be offered pN + adjuvant therapy: (1) androgen deprivation therapy by pN + and (2) androgen deprivation therapy with additional radiotherapy².

In patients with high risk or adverse features in the surgical piece, surgery alone may not provide adequate long-term oncologic control. Therefore, a multimodal approach including radiotherapy with or without hormone deprivation therapy should be considered. Adjuvant radiation therapy is defined as the administration of radiation therapy to the prostate bed, seminal vesicle bed, and pelvic lymph node area

that is typically administered 1-6 months after surgery in the absence of signs of recurrence. Prospective randomized trials support the role of radiotherapy in the risk reduction of biochemical recurrence. However, more than 40% of patients treated with initial observation will not resort to 10 years follow-up. Possible short- and long-term side effects associated with adjuvant radiotherapy, as well as the inconvenience and expense should be considered in the oncological benefit. Consequently, adjuvant radiotherapy is administered in approximately 20% of patients in contemporary series with adverse pathological features in first world countries²⁰. In our study, 46 patients (42.59%) received adjuvant treatment as part of the complementary treatment, being more than double when compared with first world countries. Adjuvant was given to those patients with adverse characteristics to the surgical specimen, those who presented persistence or recurrence of the disease. Therefore, a multimodal approach was given that included: radiotherapy with or without hormone deprivation therapy to the 46 patients who received complementary treatment. We observed that the adjuvant treatment is higher in low-risk patients (44.44%), it is expected that in this risk group the percentage is low; this may be due to the elevation of the Gleason score that was obtained in low-risk patients. This may be a bad result of the prostate biopsy to have the different cores in quality and quantity, not getting adequate results and this influence the result of the biopsy. With 66.67% of high-risk patients receiving adjuvant treatment, this trend was found in the international literature, where they receive complementary treatment after surgery. In different international studies, the increase in the total Gleason score after surgery is 52-54% with an increase in the primary grade of Gleason with or without the increase in the total score of Gleason²⁴. Our study showed a 34.26% increase in the total Gleason score after surgery, being low compared to international studies. Therefore, Gleason score after surgery was evaluated, divided into risk groups, finding that 16 patients (44.44%) of low-risk increased the Gleason score, 16 patients (26.67%) of intermediate-risk increased the Gleason score after surgery, and five patients (41.67%) of high-risk increased Gleason score. The low-risk patients' percentage was higher; this could be due to a poor classification of the risk group, a poor pathology report or a poor sampling when performing transurethral prostate biopsy, which influences the patient's risk classification.

Our institution provides free medication to patients with a health insurance government program, as well as radiotherapy, being an advantage in treatment and prevents abandonment, because most of the population attended is of low socioeconomic and educational level. We cannot deny that the retrospective nature affects the data collected about the disease evolution and some patients were lost in the monitoring of the disease by many reasons, such as migration or living in remote areas. Patients are routinely asked about urinary incontinence and erectile dysfunction, complications expected in radical prostatectomy, but some records did not report the evolution of these complications. In national and international studies, urinary incontinence after radical prostatectomy varies between 27% and 35% and erectile dysfunction in 25% and 75% of cases following surgery²⁵. Prospective longitudinal studies on urinary incontinence and erectile dysfunction following radical prostatectomy may be performed in the future, as well as evaluating the survival of patients.

Conclusions

Based on our results, we consider important to make an adequate risk classification of patients with prostate cancer located before surgery. This action provides an appropriate oncological management. We consider that an adequate classification and selection of patients who received medical and surgical treatment allowed us to obtain low recurrence rates. The recurrence rate of PSA was lower compared to international studies, probably due to the adequate selection of patients in the institution. No death from prostate cancer was reported in the follow-up of the disease. In high-risk patients, no recurrences were observed, possibly due to a small sample size, but we consider important to state that 42.59% of patients received adjuvant treatment, and 25.93% of patients had adverse characteristics in the surgical piece.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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