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Results with radical conformal radiotherapy in prostate cancer

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Abstract

Background: *Prostate cancer (PCa) is the most common malignant tumor in men in Mexico. There are two treatments with curative potential, such as radical prostatectomy (RP) for localized disease and radical radiotherapy (R-RT). Control rates are determined by the prognostic factors present.* **Objective:** *The objective of this study was to determine the control and survival rate with radical conformal radiotherapy (R-CR) in PCa.* **Methods***: The 8.5-year results of an institutional series are presented using Cox proportional hazards analysis and Kaplan-Meier survival.* **Results:** *One hundred and fifty-one cases were analyzed with a mean age of 67.5 years, treated with R-CR at doses of 72-75 Grays (Gy). The Gleason score was the main predictor of biochemical recurrence (BR) (hazard ratio [HR] 1.69, p = 0.005), followed by prostate-specific antigen (PSA) (HR 1.013, p < 0.001). The biochemical recurrence-free survival in low risk was 100%, intermediate risk 86.7%, and 72.4% in high-risk. Cause-specific survival (CES) of the series was 92.7% and overall survival (OS) was 83.5%.* **Conclusions:** *R-CR achieved high control rates in PCa. Radiotherapy is the treatment modality best adapted to the locoregional nature of the clinical disease.*

Keywords: *Prostate cancer. Biochemical recurrence. External beam radiotherapy.*

Introduction

PCa is the second most common malignant tumor in morbidity and the fifth most common in mortality for men worldwide[1]. In Mexico, it represents the first place in morbidity and mortality in men[2].

Control and survival are in relation to the present prognostic factors and the extent of the disease, thus for localized disease a 5-year OS is reported > 90%, for locoregional disease 60-80%, and in metastatic disease 30-40%[3,4].

In the context of clinical staging, recognized predictors for control are clinical T stage, PSA, and Gleason score[5-8]. These factors constitute the basis of the prognostic models of risk groups for BR proposed by D'Amico[9] and the National Comprehensive Cancer Network (NCCN)[10] with the recognition of inherent limitations due to both the underestimation of the disease and its heterogeneity clinical and pathological.

There are 2 treatment modalities with curative potentials, such as RP for localized disease and R-RT in localized and regional disease, with 8-year biochemical control rates for external radiotherapy of 80-90% in low risk[5,6,11], of 65-80% in intermediate risk,[11-13] and 48-75% at 10 years for high-risk[7,14,15].

Methods

An institutional series of PCa patients treated with R-CR in the period 2014-2015 is presented with clinical staging variables, extension studies of abdominopelvic tomography, and complete bone scan. The risk group prognostic model proposed by D'Amico was used due

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to the best fit to the available data, and the NCCN model was used for descriptive purposes. The cutoff date was December 2023.

R-CR treatment was administered with simulation and 3D planning, with a radical dose of 72-75 Gy to the prostate, with a prescription for 95% of the planning volume, with the inclusion of pelvic lymph nodes at doses of 45-50 Gy at the consideration of the radiation oncologist based on the present factors and fractionation of 1.8-2 Gy/day. In the first phase, a conventional 4-field technique was used with the upper limit at L4-5 and the restriction doses to risk organs were those suggested in QUANTEC[16]. Androgen deprivation therapy (ADT) was a short course of 4-6 months in intermediate risk and a long course of 2-3 years in high risk before the start of radiotherapy.

The primary outcome was BR with the definition of ≥ 2 ng/mL above the PSA nadir or initiation of ADT before meeting the criterion[17]. The time to the BR was from the end of the R-CR to the date of compliance with the criterion. Secondary outcomes were CES (death due to cancer progression) and OS (death from any cause). The statistical analysis was using the Cox regression model with a statistical significance value of 5%, and Kaplan–Meier survival analysis. The SPSS-27 statistical program was used.

Table 1: Characteristics of the disease (n = 151)

Factor	F (%)
Clinical stage T	
T1	60 (39.8)
T2	85 (56.3)
T4	2 (1.3)
Tx	4 (2.6)
PSA (ng/ml)	
≤ 10	22 (14.6)
10.1-20	62 (41.1)
> 20	67 (44.4)
PSA median (range)	18.5 (4.7-281)
Gleason score	
6	37 (24.5)
7 (3+4)	55 (36.4)
7 (4+3)	18 (11.9)
8	31 (20.5)
9	9 (6.0)
10	1 (0.7)
Group/Risk D'Amico	
Low	4 (2.6)
Intermediate	60 (39.8)
High	87 (57.6)
Group/Risk NCCN	
Low	4 (2.6)
Favorable intermediate	26 (17.2)
Unfavorable intermediate	35 (23.2)
High	62 (41.1)
Very high	24 (15.9)

Results

There were 151 cases with a mean age of 67.5 years (53-85).

The baseline characteristics of the disease and risk groups are shown in table 1.

Treatment characteristics are shown in Supplementary Table S1. The radical dose range was 72-75 Gy. In the intermediate-risk group, 78.3% received pelvic lymph node treatment and 98.8% in the high-risk group. ADT was administered in 86% of the intermediate-risk group and 100% of the high-risk group.

In the univariate analysis of the predictors of BR of the entire series, it was observed that age in years (p = 0.013), the initial PSA value in ng/mL (p < 0.001), and the Gleason score (p = 0.001) were significant but not the clinical stage T by D'Amico risk group categories (p = 0.28).

Table 2 shows the results of the multivariate Cox regression analysis.

In the analysis by prognostic groups for the intermediate risk group, age confirmed its significant value (p = 0.045, HR 0.90, 95% CI 0.819-0.998). The ADT (p = 0.264) and the comparison of doses < 75 Gy versus 75 Gy (p = 0.295) did not show to be significant for the biochemical control.

Table 2. Multivariate analysis of predictive factors of BR (n = 151)

Factor	HR	95% CI	p-value
Age[1]	0.92	0.875-0.984	0.012
PSA[2]	1.013	1.007-1.018	< 0.001
Gleason score[1]	1.69	1.177-2.439	0.005

[1]Discrete variable.
[2]Continuous variable.
BR: biochemical recurrence; HR: hazard ratio; CI: confidence interval.

In the high-risk group, the PSA in ng/mL (p ≤ 0.001, HR 1.011, 95% CI 1.006-1.017) and the Gleason score (p = 0.015, HR 1.74, 95% CI 1.113-2.742) were confirmed to be independent variables for BR, but not age (p = 0.120) and dose < 75 versus 75 Gy (p = 0.121).

Table 3 shows the control rate of the total series by D'Amico risk group.

Supplementary Table S2 shows the biochemical control rate by NCCN risk group.

Table 3. Biochemical control at 8.5 years by risk group

Risk group	Biochemical recurrence	Control rate (%)
Low	0/4 (0%)	100
Intermediate	8/60 (13.3%)	86.7
High	24/87 (27.6%)	72.4
Total	32/151 (21.2%)	78.8

The average time to BR of the total series was 39 months (9-101). 25% of recurrences occurred in the intermediate-risk group, with a mean of 48 months (9-101), while in high risk 75% presented with an average of 36 months (10-63). In intermediate risk, 25% of BRs occurred in the first 2 years, 50% at 4, and 75% at 5 years; while in high risk, 29% occurred in the first 2 years, 58% at 3 years, 71% at 4 and 95% at 5 years. The documented recurrence patterns of the series are described in Supplementary Table S3.

The Kaplan–Meier Survival Analysis shows the difference in biochemical recurrence-free survival at 8.5 years in the prognostic risk groups (Fig. 1).

Regarding mortality, there were 25 deaths, 14 due to a different or competent cause (56%) and 11 related to PCa (44%). The overall mortality rate was 16.5%. The causes of death of the total series are shown in Supplementary Table S4.

The OS of the total series was 83.5% and the CES was 92.7% at 8.5 years. In the intermediate-risk group, four deaths occurred due to competent causes (6.6%) and two due to PCa (3.3%). The causes of death not related to PCa were 2 due to COVID-19, myocardial infarction, and multiple myeloma. The OS for the group was 90% and the CES 96.7%. The OS of the group without BR was 92.3%, while that of the recurrence group was 75%. In the high-risk group, there were 10 deaths not related to PCa (11.5%), the causes of which were four due to myocardial infarction, two due to cerebrovascular disease, two due to complications of gastroesophageal surgery, one due to multi-pathology, and one due to digestive bleeding while there were nine deaths due to PCa (10.3%). The OS of the group was 78.2% while the CES was 89.7%. In the BR-free group, the OS was 84.1%, while in the recurrence group, it was 62.5%.

There were five cases of second primary cancers (bladder carcinoma at 2.7 years, rectal carcinoma at 3 years, renal carcinoma at 3.4 years, lung carcinoma at 3.8 years, and multiple myeloma at 8.3 years).

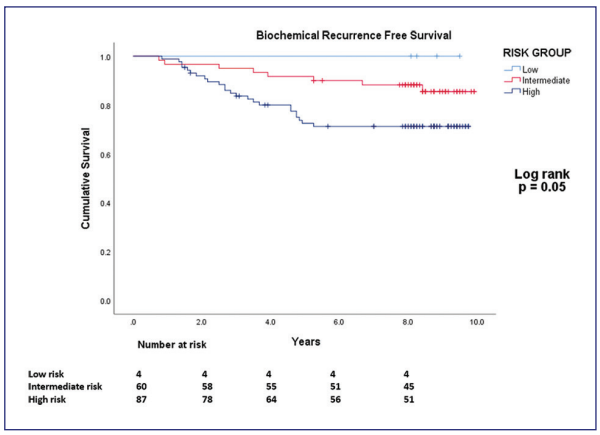

Figure 1. Kaplan–Meier survival curve for biochemical control in D'Amico risk groups.

An incidence of grade 3-4 late proctitis and/or cystitis of < 5% was observed.

The mean follow-up of cases without BR was 8.7 years (7.8-9.9).

Discussion

In the review of our data, a heterogeneous distribution of prognostic clinicopathological factors is observed, which in part explains the limitations of the predictive value of the risk models, as well as a predominance of high-risk disease, unlike other series where intermediate risk prevailed[6-8].

In relation to the predictive factors of BR, we confirmed that the Gleason score was the main independent factor for BR, followed by the PSA, data consistent with other series[5,7,8]. The T stage was not shown to be a predictive factor in our series due to a bias in the initial clinical record. ADT did not prove to be an independent factor in intermediate risk and the difference < 5 Gy in the dose comparison in both the intermediate and high-risk groups did not allow detecting a difference in control of approximately 5-10% for every 5 Gy scaling as reported in the literature[5-7,11,13].

To compare results, it is necessary to recognize the heterogeneity in the designs and their reporting in the literature series. In the intermediate risk, 87% received a radical dose of 73.8-75 Gy, with which we obtained a biochemical control rate of 86.7% at 8.5 years; our design is more similar to 3 series that report control rates of 79, 72, and 65-80%, respectively[11-13]. Compared to the mean, we observed an absolute benefit of 14% in biochemical control, possibly in part due to formal

pelvic lymph node treatment. In the high-risk group, 95% received a radical dose of 73.8-75, achieving biochemical control at 5 years of 73.5% and at 8.5 years of 72.4%. Biochemical control at 5 years in series of similar design, all including pelvic lymph nodes, is reported to be 70-95%[7,18,19] and 48-75% at 10 years[7,14,15]. Our small number of low-risk cases does not allow us to do analysis.

In relation to the radiotherapy technique and the inclusion of pelvic lymph nodes, it is necessary to consider that although the historical series in intermediate risk did not have the intention of including them[6,12,13,20], it is observed that having used predominantly conformal technique and according to their field sizes, it follows that at least the first levels were included. Current prediction methods based on nomograms and formulas[21,22] have an average of 25-30% underestimation of the pathological disease and even with the practice of systematic sampling (≥ 10 biopsies), there is an underestimation of the highest Gleason score of 21-38%[23-25]. These inherent diagnostic biases and the multifocal nature of the disease must be considered in radical treatment at low and intermediate risks. Because these historical series did not include a detailed study of recurrences, we do not have precise information on their patterns and their correlation with the technique, to consider lymph node exclusion safe. There are no specialized studies in this regard based ideally on positron emission tomography; only in the study by Spratt et al., an approximation to the pelvic lymph node component of recurrences at intermediate risk is reported using conventional studies[26].

Regarding BR, we observed a later trend in the intermediate risk with a mean of 48 months compared to 36 for the high risk. There was a temporal distribution like that reported in the series by Kuban et al., where the highest risk it was in the first 3.5 years[5]. In the intermediate risk we observed a trend similar to that described in the same series, of an incidence of 3.5-4.5% of annual recurrences after the first 5 years; in the high-risk, we did not observe this distribution. In the intermediate risk, there was a tendency towards locoregional recurrence, while distant and predominantly bone recurrence for the high-risk, similar to what was reported by Nabid et al., in the high-risk, where 67% had a bone component[15].

In relation to survival, in the intermediate risk group, the probability of dying from PCa was 3.3% and 10% for general causes at 8.5 years. The impact of recurrence on OS was 17.3%. In the high-risk group, the probability of dying from PCa was 10.3% and 21.8% from general mortality. The impact of recurrence on group survival was 21.6%.

The limitations of the study were the retrospective documentation of variables, the number of cases from an institutional series, and the detection rates of conventional studies for initial subclinical disease and recurrences since only 19% of these were studied by emission tomography of positrons.

It is concluded that PCa is a disease with high clinical and pathological heterogeneity that must be considered in the approach of radical treatment. A specialized and analytical study of the pattern of recurrences and its relationship with the treatment technique is required that includes all risk groups. R-CR achieved high control rates in PCa. Radiotherapy is the treatment modality best adapted to the loco-regional nature of the clinical disease.

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Conflicts of interest

The authors declare no conflicts of interest.

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 have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

Supplementary data

Supplementary data are available at DOI: 10.24875/CIHR.M24000008. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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