REVIEW ARTICLE

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Early stage prostate cancer: biochemical recurrence after treatment

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ABSTRACT

Objectives: To identify retrospectively through chart analysis the biochemical recurrence frequency of localized prostate cancer at diagnosis of patients submitted to surgery or radiotherapy; to correlate diagnostic characteristics associated with higher risk of biochemical recurrence.
Materials and Methods: Retrospective analysis of 483 patients treated in a single center, from March 2000 to December 2009 in order to verify factors associated with biochemical recurrence.
Results: Biochemical recurrence was more frequent in patients with higher initial PSA levels and those with higher risk disease. Recurrence was more frequent in patients with high risk (25.9%) than those with intermediate risk (10.7%) and low risk (5.5%). There was no significant statistical difference of biochemical recurrence between patients submitted to radiotherapy or radical prostatectomy. Biochemical recurrence was diagnosed in only 11 of 73 patients (15%) submitted to conformal radiotherapy using tridimensional technique.
Conclusion: Radiotherapy and radical prostatectomy have similar treatment results. Tridimensional conformal radiotherapy used nowadays is more efficient than earlier forms of radiation therapy (cobalt therapy and bidimensional linear accelerator therapy).

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INTRODUCTION

Prostate cancer is the second more prevalent malignant tumor in men (skin cancer other than melanoma being the first); in 2008 it was estimated 900.000 cases and 258.000 deaths due to the disease (1).

In 2012 it was estimated nearly 60.000 new patients with prostate cancer in Brazil: 62 new cases for every 100.000 men (2). It is the most prevalent malignant tumor in the Southeast region (78/100.000); in Midwest 75/100.000, in South 68/100.000, Northeast 43/100.000 and in North region 30/100.000 (2).

Treatment options for localized disease include radical prostatectomy and radiotherapy, with similar results (3).

Biochemical recurrence is characterized by PSA elevation following primary treatment. It usually precedes often for many years, clinical recurrence and progression of the disease.

MATERIAL AND METHODS

From March 2000 to December 2009, 819 patients with prostate cancer were treated at Cancer Hospital of Cascavel - UOPECCAN. From these, 483 had non-metastatic disease at diagnosis and were treated with curative purposes (radiotherapy or radical prostatectomy) and were followed in an out-patient basis at the institution.

The present study is a retrospective analysis of the evolution of these 483 patients, in order to identify biochemical recurrence and related factors.

Radical prostatectomy (RP) was performed by a trained group of urologists and radiotherapy (RT) evolved along the years, being divided in three phases: first phase, from March 2000 to September, 2004, it was used cobalt radiotherapy (RTCo). From October 2004 to August 2008, patients were submitted to bidimensional linear accelerator radiotherapy (RT2D) and from September 2008 on it was used conformal tridimensional RT linear accelerator (RT3D).

Patients were divided in three risk groups concerning biochemical recurrence: low risk (PSA < 10ng/mL and Gleason ≤ 6), intermediate (PSA between 10 and 20 ng/mL or Gleason = 7) and high risk (PSA > 20ng/mL or Gleason 8 to 10). The first group (low risk) encompasses patients with very low risk and low risk cited in previous studies (4).

Biochemical recurrence was considered when it was observed a rise of PSA following PR in two different occasions (> 0.2ng/mL).

Biochemical recurrence in patients submitted to RT was considered when the PSA level exceeded 2ng/mL from the lowest post-treatment value (nadir).

Diagnostic characteristics (PSA, Gleason score, risk categories) and treatment modalities (RP or RT) were submitted to statistical analysis in order to identify the risk of biochemical recurrence using the chi-square or Fisher tests (when the sample was small) and the t-Student test. Significance level was 5% (p = 0.05).

RESULTS

Four hundred eighty-three patients were treated with localized disease at diagnosis. Age varied from 41 to 90 years (median = 68 years). Time between diagnosis and treatment varied from two to 621 days (median = 54 days). Table-1 shows the distribution according to Gleason score, serum PSA and risk stratification.

Table 1 - Patients characteristic before treatment.

Characteristics	Total patients (%)
Gleason < 7	353 (73)
Gleason = 7	100 (21)
Gleason 8-10	030 (6)
PSA < 10	200 (41.4)
PSA 10 - 20	155 (32.1)
PSA > 20	128 (26.5)
Low risk	155 (32.1)
Intermediate risk	184 (38.1)
High risk	144 (29.8)

PSA = Prostatic Specific Antigen

Table-2 shows the classification of patients according to risk factors and treatment modality.

PSA was higher in patients submitted to RT than those submitted to RP ($p < 0.05$). There was also a higher number of high risk patients among those submitted to RT ($p < 0.05$). Table-3 shows the risk factors and biochemical recurrence prior treatment.

Biochemical recurrence was identified in 180 patients (37.3%). It was more frequent in patients with higher PSA, higher Gleason and high risk stratification. It was observed in 60% of patients with Gleason score 8-10, 50% of those with Gleason 7 and in 31.7% of patients with Gleason ≤ 6 ($p < 0.05$).

Recurrence was more frequent in patients with PSA higher than 20ng/mL(61.2% of patients), when compared to those with PSA 10-20ng/mL (30.3%) and below 10ng/mL (27%)($p < 0.05$).

More recurrence episodes were also observed in patients with high risk (61.1%) than those

Table 2 - Risk factors and modality of treatment.

Characteristics	Total of patients (n = 483)	RP (n = 227)	RT (n = 256)	P value
Gleason < 7	353	163	190	0.55
Gleason = 7	100	054	046	0.06
Gleason 8-10	30	010	020	0.12
PSA < 10	200	123	077	< 0.05
PSA 10 – 20	155	076	079	0.54
PSA > 20	128	028	100	< 0.05
Low Risk	155	097	058	< 0.05
Intermediate risk	184	094	090	0.16
High risk	144	036	108	< 0.05

PSA = Prostatic Specific Antigen; **RP =** Radical Prostatectomy; **RT =** Radiotherapy

Table 3 - Pre-treatment risk factors and biochemical recurrence.

Treatment modality	Total of patients	Total of recurrences(%)	p value
PTR	227	078 (34.4)	0.25
RT	256	102 (39.8)	
RTCo	033	017 (51.5)	
RT2D	150	074 (49.3)	< 0.05
RT3D	073	011 (15.1)	

RP = Radical Prostatectomy; **RT =** Radiotherapy; **RTCo =** Cobalt Radiotherapy; **RT2D =** Conformal Bidimensional Radiotherapy; **RT3D =** Tridimensional Conformal Radiotherapy

with intermediate risk (31%) and low risk (22%) $p < 0.05$.

The differences between recurrence levels of different treatment modalities are shown on Table-4 and Figure-1.

There was no statistical difference ($p = 0.25$) in recurrence between patients submitted to RP (34.4%) or RT (39.8%).

Median time of follow-up of patients submitted to RP (n = 227) was 1427 days (54 to 3431 days). Time between surgery and biochemical recurrence (n = 78, 34.4%) varied from 53 to 2451 days (median 502 days, Figure-2). There were more recurrence episodes in patients with Gleason score 8-10, higher initial PSA and those of high risk group.

Recurrence was more frequent in patients with Gleason 8-10 (90% versus 48% and 26%, $p < 0.05$), PSA > 20ng/mL (68% versus 30 and 29%, $p < 0.05$) and in high risk group (72% vs. 31 and 28%, $p < 0.05$) - Table-5.

The primary treatment of 256 patients was RT; the first 33 patients were treated with cobalt radiotherapy; 147 patients were treated with RT2D and 73 patients received RT3D.

Table 4 - Biochemical recurrence according to treatment.

Characteristic	Total of patients	Biochemical recurrence(%)	p value
Gleason < 7	353	112 (31.7)	
Gleason = 7	100	050 (50)	< 0.05
Gleason 8-10	030	018 (60)	
p value		< 0.05	
PSA < 10	200	054 (27)	
PSA 10 - 20	155	047 (30.3)	< 0.05
PSA > 20	128	079 (61,2)	
p-value		< 0.05	
Low risk	155	034 (21.9)	
Intermediate risk	184	058 (31.5)	< 0.05
High risk	144	088 (61.1)	
p-value		< 0.05	

RP = Radical Prostatectomy; **RT =** Radiotherapy

Figure 1 - Disease-free survival curves (Kaplan-Meier estimates) for RP and RT

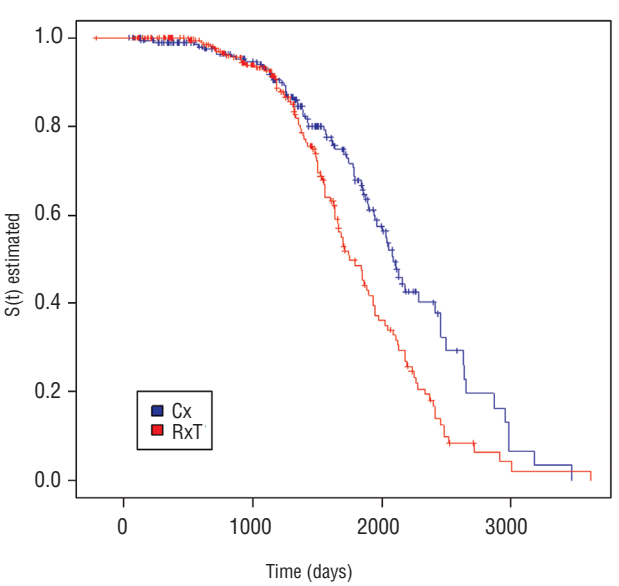
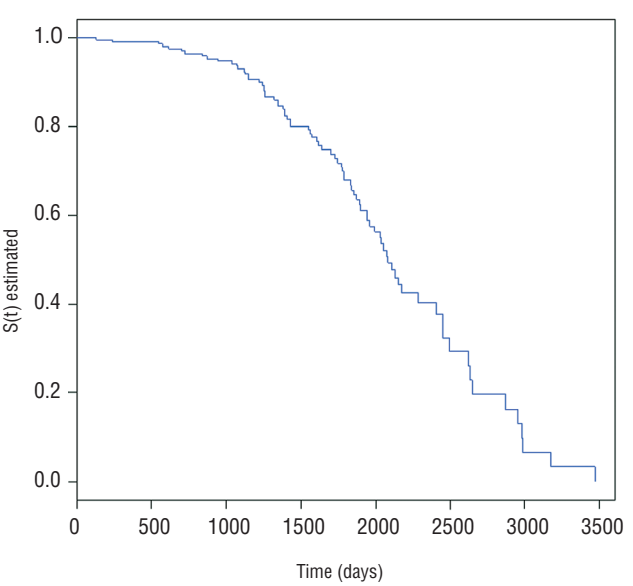


Figure 2 - Disease-free-survival curve (Kaplan-Meier estimates) for RP.



Cx = Prostatectomy; RxT: Radiotherapy.
Mantel-Haenzel test between RP and RT
X^2 = 9.5, freedom grade=1 and p-value= 0.0021*

Table 5 - Biochemical recurrence after RP.

Characteristics	Total	Recurrence		p value
		Yes (%)	No (%)	
Gleason < 7	163	043 (26.3)	120 (73,6)	< 0,05
Gleason = 7	54	026 (48.1)	028 (51.8)	< 0.05
Gleason 8-10	10	009 (90)	001 (10)	< 0.05
p value		< 0.05	< 0.05	
PSA < 10	123	036 (29.2)	087 (70.7)	0.1
PSA 10 -20	76	023 (30.2)	053 (69.7)	0.4
PSA > 20	28	019 (67.8)	009 (32.1)	< 0.05
p value		< 0.05	< 0.05	
Median PSA		10.36	9.00	< 0.05
Low risk	97	023 (23.7)	074 (76.3)	< 0.05
Intermediate risk	94	029 (30.8)	065 (69.1)	0.4
High risk	36	026 (72.2)	010 (27.7)	< 0.05
p value		< 0.05	< 0.05	

PSA = Prostatic Specific Antigen; **RP =** Radical Prostatectomy

Follow-up varied from 115 to 3638 days (median 1296 days). Median follow-up of patients treated with cobalt radiotherapy was 1811 days and those submitted to RT2D was 1421 days. As expected, median of follow-up of patients treated with RT3D was lower (1026 days).

There were 102 recurrences after RT (39.8%, Figure-3). Time between treatment and recurrence varied from 350 to 2532 days (median 685 days). Recurrence was identified in 17 patients treated with RTCo (51.5%), in 74 with RT2D (50.8%) and in 11 with RT3D (15.1%). These differences are significant ($p < 0.05$), Table-4 and Figure-4.

Table-6 shows the risk factors and biochemical recurrence after radiotherapy. The stratification of patients according to PSA level showed more recurrences in patients with PSA ≥ 20ng/mL and intermediate and high risk patients.

More recurrences were identified in patients treated with cobalt radiotherapy (55%) and

Figure 3 - Disease-free survival curve (Kaplan-Meier estimates) for RT.

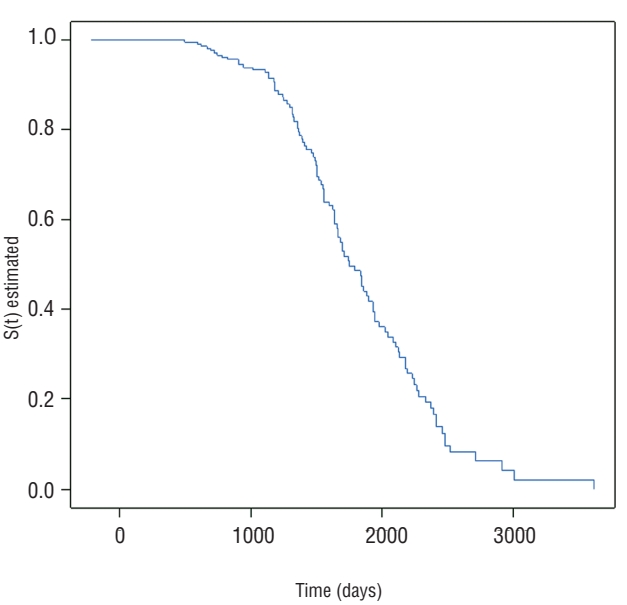
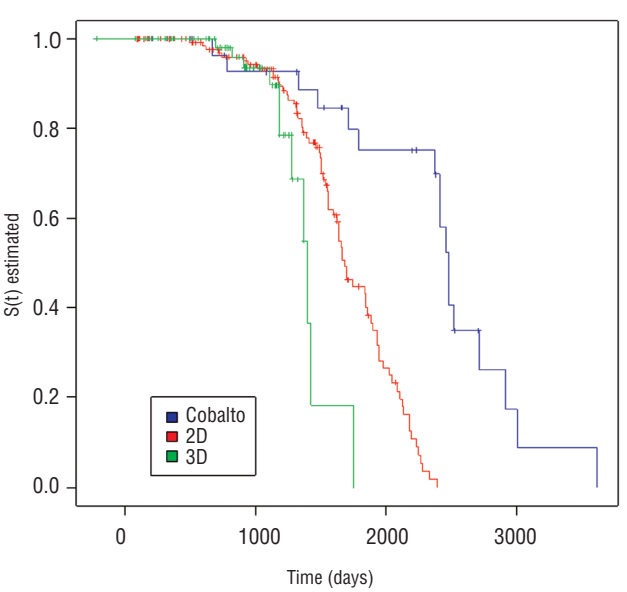


Table 6 - Biochemical recurrence after radiotherapy.

Characteristics	Total	Recurrence		p value
		Yes (%)	No (%)	
Gleason < 7	190	069 (36.3)	121 (63.6)	< 0.05
Gleason = 7	46	024 (52.1)	022 (47.8)	0.67
Gleason 8-10	20	009 (45)	011 (55)	0.52
p value		0.12	0.12	
PSA < 10	77	018 (23.3)	059 (76.6)	< 0.05
PSA 10 - 20	79	024 (30.3)	055 (69.6)	< 0.05
PSA > 20	100	060 (60)	040 (40)	< 0.05
p value		< 0.05	< 0.05	
Median PSA		28.97	12.20	< 0.05
Low risk	58	011 (18.9)	047 (81)	< 0.05
Intermediate risk	90	029 (32.2)	061 (67.7)	< 0.05
High risk	108	062 (57.4)	046 (42.6)	< 0.05
p value		< 0.05	< 0.05	

PSA = Prostatic Specific Antigen

Figure 4 - Disease-free survival curves (Kaplan-Meier estimates) for Rtco, RT2D and RT3D treatments.



Mantel-Haenzel test among Co, 2D and 3D
X^2 = 37.6, freedom grade = 2 and p-valu e = 0.000*

RT2D (51%) than those treated with RT3D (16%), p < 0.05, Table-7.

There was no influence of risk factors (Gleason score, PSA and risk stratification) in biochemical recurrence incidence of patients treated with cobalt radiotherapy.

Among patients treated with RT2D, recurrence rate was higher in patients with PSA ≥ 20ng/mL (43/56 patients, 77%) and intermediate risk (22/54 patients, 41%) and high risk (45/63 patients, 71%).

Biochemical recurrence was identified in 11 of 73 patients submitted to RT3D (15%). Analysis of pre-treatments characteristics did not show any statistical difference among patients classified as high risk (25.9%), intermediate (10.7%) and low risk (5.5%).

DISCUSSION

Prostate cancer is frequent and responsible for cancer associated morbidity and mortality. When treated initially, RP of RT are curative (1).

Table 7 - Biochemical recurrence according to RT modality of treatment.

	RTCo patients/ recurrence	RT2D patients/ recurrence	RT3D patients/ recurrence	p value	
Total of patients	33/17	150/74	73/11	< 0.05	
Characteristics					
Gleason <7	026/015	104/046	060/008	< 0.05	
Gleason =7	004/001	033/020	009/003	0.18	0.26
Gleason 8-10	003/001	013/008	004/0	0.08	
p value	0.4	0.17	0.25		
PSA < 10	008/003	049/014	020/001	0.06	
PSA 10 -20	008/004	045/017	026/003	< 0.05	0.48
PSA > 20	017/010	056/043	027/007	< 0.05	
p value	0,61	< 0.05	0.11		
Median PSA	23.0	21.2	28.5	--	
Low risk	007/003	033/007	018/001	0.09	
Intermediate risk	008/004	054/022	028/003	< 0.05	0.53
High risk	018/010	063/045	027/007	< 0,05	
p value	0.84	< 0.05	0.14		

PSA = Prostatic Specific Antigen; **RTCo =** Cobalt radiotherapy; **RT2D =** Bidimensional conformal radiotherapy; **RT3D =** Tridimensional conformal radiotherapy

Sustained elevation of PSA in any moment after treatment is related to the existence of viable prostatic tissue anywhere. Biochemical recurrence precedes the beginning of clinical disease in the majority of cases (5-7).

The concept of biochemical recurrence is not consensual in literature and varies according to the primary treatment (RP or RT) (8-10).

A widely accepted definition of biochemical recurrence after surgery is of a serum PSA greater than 0.2ng/mL in two different consecutive samples after treatment (11-13). Biochemical recurrence following radiotherapy is defined at present when serum PSA is equal or greater than 2ng/mL above the original lower level of PSA (nadir) following radiotherapy (14).

The present study analyzed a great number of patients with localized prostate cancer submitted to RP or RT in a single institution.

The criteria of biochemical recurrence after RP was PSA > 0.2. Although many authors consider PSA > 0.4, PSA > 0.2 is widely used in literature and probably more suitable due to more precise and sensitive detection methods (8-12).

Results showed that prognostic factors at diagnosis, PSA level and high risk stratification were associated with higher level of biochemical recurrence. These results are in accordance to literature (15-21).

Biochemical recurrence following RP was more frequent in patients with Gleason score 8-10, higher PSA level and those considered of high

risk, also in accordance to literature (5,7,22-25).

Three different radiotherapy techniques were used throughout the study: RTCo, RT2D and RT3D. The three groups of patients were compared and there were a lower number of recurrences in patients submitted to RT3D. The use of RT3D allows the use of higher doses associated to better therapeutic results (26-28).

Biochemical recurrence was identified in only 15% of patients submitted to RT3D. The low number of recurrences in this group of patients probably did not allow the identification of a relationship between recurrence level and associated risk factors.

The lower level of recurrence in patients submitted to RT3D is not explained by different pre-treatment characteristics among patients. They were uniformly distributed among the three modalities of radiotherapy. However, it is important to observe that the time of follow-up was lower in those patients than those treated with cobalt or RD2T radiotherapy; eventually during a longer follow-up more recurrence episodes will be identified.

The comparison of RT and RP did not show any statistical difference regarding biochemical recurrence. Available data in literature cannot conclude that one treatment is better than the other in any risk group of disease (3).

CONCLUSIONS

RT and RP have similar results. Today RT is more efficient than those previously used. Risk factors and treatment results are in accordance to literature data.

CONFLICT OF INTEREST

None declared.

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