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Salvage Conformal Radiotherapy for Biochemical Recurrent Prostate Cancer after Radical Prostatectomy

Carlos R. Monti, Ricardo A. Nakamura, Robson Ferrigno, Aristides Rossi Jr, Neusa S. Kawakami, Felipe A. Trevisan

Radiotherapy Department, Radium Oncology Institute, Campinas, Sao Paulo, Brazil

ABSTRACT

Objective: Assess the results of salvage conformal radiotherapy in patients with biochemical failure after radical prostatectomy and identify prognostic factors for biochemical recurrence and toxicity of the treatment.
Materials and Methods: From June 1998 to November 2001, 35 patients were submitted to conformal radiotherapy for PSA ≥ 0.2 ng/mL in progression after radical prostatectomy and were retrospectively analyzed. The mean dose of radiation in prostatic bed was of 77.4 Gy (68-81). Variables related to the treatment and to tumor were assessed to identify prognostic factors for biochemical recurrence after salvage radiotherapy.
Results: The median follow-up was of 55 months (17-83). The actuarial survival rates free of biochemical recurrence and free of metastasis at a distance of 5 years were 79.7% e 84.7%, respectively. The actuarial global survival rate in 5 years was 96.1%.The actuarial survival rate free of biochemical recurrence in 5 years was 83.3% with PSA pre-radiotherapy ≤ 1, 100% when > 1 and ≤ 2, and 57.1% when > 2 (p = 0.023). Dose > 70 Gy in 30% of the bladder volume implied in more acute urinary toxicity (p = 0.035). The mean time for the development of late urinary toxicity was 21 months (12-51). Dose > 55 Gy in 50% bladder volume implied in more late urinary toxicity (p = 0.018). A patient presented late rectal toxicity of 2nd grade.
Conclusions: Conformal radiotherapy showed to be effective for the control of biochemical recurrence after radical prostatectomy. Patients with pre-therapy PSA ≤ 2 ng/mL have more biochemical control.

Key words*: prostatic neoplasms; prostate-specific antigen; salvage therapy; radiotherapy*
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INTRODUCTION

Amongst the treatments used for the salvage of patients with biochemical recurrence after radical prostatectomy that can offer cure to the patients, radiotherapy is the most interesting therapeutic modality, if not, the only one (1). The rates of biochemical control in 5 years with salvage radiotherapy vary from 10% to 58% (2,3) due to the great difficulty in selecting patients with non-metastatic disease after radical prostatectomy. It is not yet established in literature the best moment to offer radiotherapy, either as an adjuvant or as a salvage therapy, which should be the extension of radiotherapy field, the dose of radiation, the use of neoadjuvant, concomitant and/or adjuvant of androgenic suppression, and which patients distant disease free that would benefit of loco-regional treatment. Retrospective studies (3,4) have observed better recurrence results of adjuvant radiotherapy over salvage radiotherapy in high risk patients. Bolla et al.

(5), in a randomized study comparing adjuvant radiotherapy or not with radiotherapy in high risk recurrence patients after radical prostatectomy, have observed a superiority in adjuvant treatment in relation to the survival rate free of biochemical recurrence and disease progression. Even though there is an occurrence of more toxicity grade 2 and 3 in the group of adjuvant treatment, the late toxicity greater or equal to grade 3 occurred in only 4.2% of the patients. The present article aims at reporting the results of conformal salvage radiotherapy in prostate cancer with biochemical recurrence after radical prostatectomy performed in a sole institution, and identify variables associated to biochemical control and the toxicity of the treatment.

MATERIALS AND METHODS

Patient's Population

From June 1998 to November 2001, 35 patients were submitted to conformal salvage radiotherapy for PSA ≥ 0.2 ng/mL in progression after radical prostatectomy for prostate adenocarcinoma in a sole institution, and they were retrospectively analyzed. All patients were staged according to the staging system of 2002 American Joint Committee on Cancer. All had bone scintigraphy without the evidence of metastatic disease previous to the salvage radiotherapy. All patients signed an informed consent previous to treatment.

Patients Characteristics before Salvage Radiotherapy

Median age was 65 years (52-74). Median pre-radiotherapy PSA was 1.5 ng/mL (0.2-8.98). Eight patients had a nodule in prostatic fossa at digital rectal examination and/or at the computerized tomography. The median time between biochemical recurrence after surgery and the radiotherapy was 2.3 months, which is low, being possible to indicate distant disease. All patients were considered as a sole high-risk group for systemic dissemination, for they presented biochemical recurrence, and thus, 5 patients that did not have pathologic results of radical prostatectomy were included in the study; for statistical analysis, these patients were considered as negative margin so that radiotherapy could not benefit. Urinary incontinence and urethral stenosis were considered as postoperative complications. Other patients' characteristics are listed in Table-1.

Characteristics of Salvage Treatment

Fourteen patients received neoadjuvant hormone therapy, 17 at the same time and 2 adjuvant in relation to radiotherapy. For salvage radiotherapy, patients were oriented to ingest 300 mL of liquid and void 1 hour before the simulation and treatment procedures. Patients were simulated in dorsal decubitus, in a CTE General Electric helicoidal tomography with venous and urethra contrast, with 5 mm thickness. Images were acquired by the software "Med Crane". The treatment targets were delineated in the tomography slices in the following way: a) prostatic bed - delineated the anastomotic junction between the membranous urethra and the vesical trigone; b) seminal vesicles bed - delineated seminal residual vesicles or the region that supply seminal vesicles; c) drainage - delineated lymph nodes of the internal and external iliac veins starting from the caudal part of the sacroiliac articulation, and obturatory lymph nodes, excluding lateral perirectal lymph nodes. As margins for target movement and positioning errors 10 mm were given in all dimensions and 3 mm afterwards. The risk organs were outlined in the following way: a) bladder - outlined all its volume through the external muscular layer; b) rectum - outlined its entire volume trough the external layer, from the anal-rectal transition zone until the rectal-sigmoid transition. Energies of 6 or 15 MeV, and 5 fields of radiation were utilized. Radiotherapy treatment was divided in phases: in the first phase the pelvis, the seminal vesicle region and the prostatic bed were irradiated; afterwards, the volume of treatment was restricted to the seminal vesicle region and to the prostatic bed; and in the end, the field of treatment has embodied only the prostatic bed. When no pelvic irradiation occurred, treatment was performed in only 2 phases, the irradiation of the seminal vesicle region the prostatic bed, and afterwards only the prostatic bed (Figure-1). Pelvic irradiation, the doses in the seminal vesicle

Table 1 – *Characteristics of patients submitted to salvage conformal radiotherapy in biochemical recurrence after radical prostatectomy.*

Variable	**Category**	**N Patients** (%)
Positive Margin	Yes	15 (42.9)
	No	20 (57)
Postoperative tumor extension	T2a	5 (14.3)
	T2b-T2c	10 (28.6)
	T3a-T3b	15 (42.9)
	Undetermined	5 (14.3)
Gleason score	≤ 6	20 (57.1)
	7	9 (25.7)
	≥ 8	4 (11.4)
	Undetermined	2 (5.7)
PSA pre-radiotherapy	≤ 1	12 (34.3)
	> 1 - ≤ 2	11 (31.4)
	> 2	12 (34.3)
Postoperative complications	Yes	13 (37.1)
	No	22 (62.9)
Co-morbidity	Yes	11 (31.4)
	No	24 (68.6)
Time between surgery and radiotherapy	Median (months)	23
	Variation	1.7-183

region and in the prostatic bed were performed according to the radiotherapist decision. Fifteen patients received pelvic radiotherapy without any association to hormone therapy. Eight received pelvic radiotherapy concomitant to hormone therapy. The dose of median radiotherapy in pelvis for the patients that were submitted to pelvic irradiation was 4840 cGy (4680-5040). Afterwards information regarding the treatment was transferred to the linear accelerator Mevatron MD-2 Siemens and the treatment was performed with a dose 180 cGy per day, 5 days a week. Other characteristics of the treatment are listed on Table-2.

Patients Follow-up

After salvage radiotherapy patients were monitored with total serial PSA between 3 and 6 months, and image studies were requested when specific complaints were filed. All patients were contacted by telephone to update data regarding biochemical control and toxicity at the moment of the analysis.

Acute toxicity was considered up to 3 months after the end of the salvage radiotherapy. Acute and late toxicities were assessed for rectum and bladder and were graded according to "Common Terminology Criteria for Adverse Effects version 3" (6).

Biochemical failure was considered after 3 consecutives increases of the total PSA (7) or the beginning of anti-androgen therapy due to total PSA increase after salvage radiotherapy.

Statistical Analysis

Descriptive statistics methods based on frequency tables for qualitative variables and measurement calculation for central tendency and dispersion were utilized, besides the Kaplan-Meier method, when applied to quantitative variables. Analytical statistics utilized for the comparison of proportions either the qui-square method or Fisher's exact test, ac-

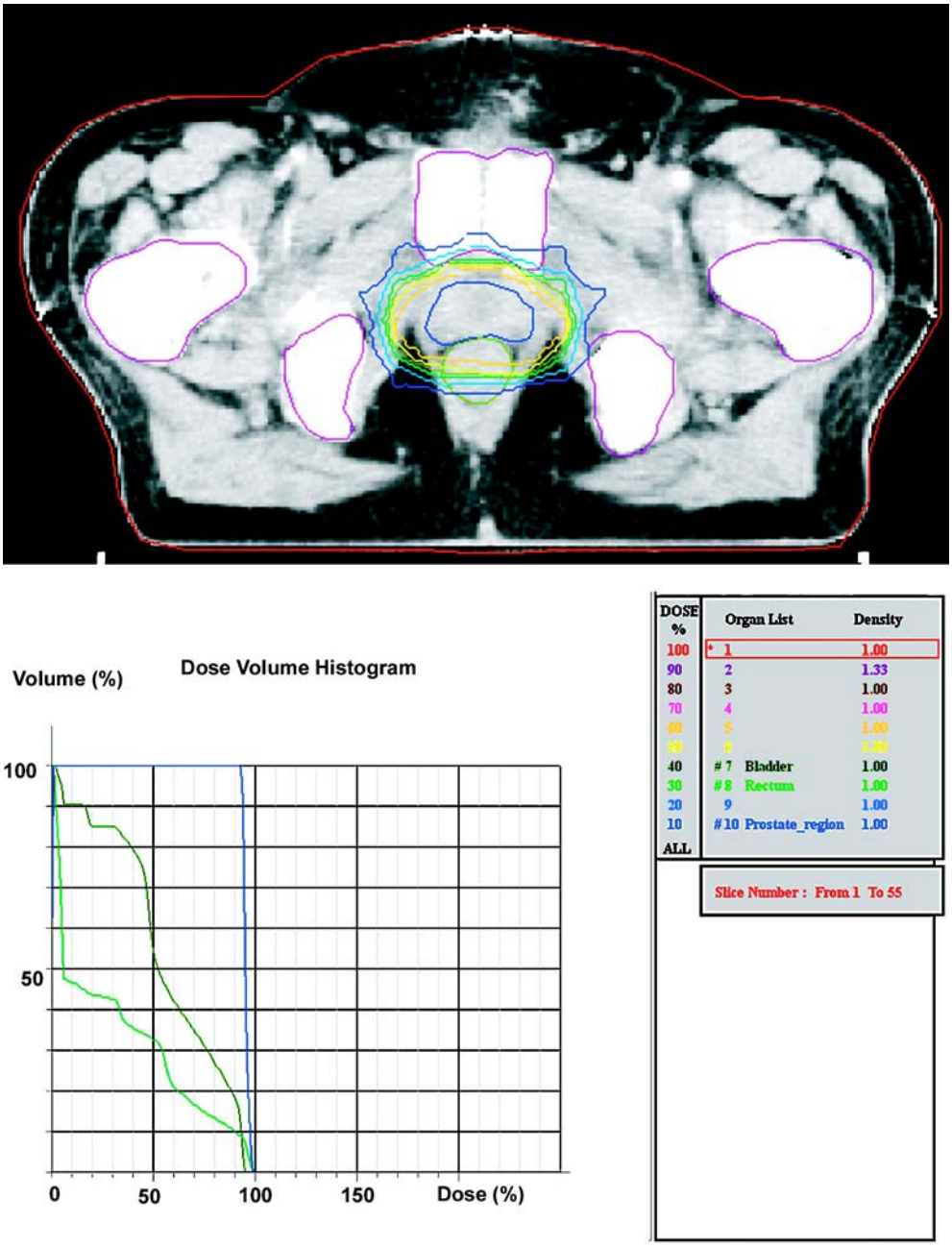

Figure 1 – *Prostatic bed outline in axial cut and histogram dose volume of the target volume and risk organs.*

cording to the case, in contingency tables. For the association among quantitative variables the Pearson correlation coefficient was utilized. The comparison of quantitative variables among the groups considered in each case was done based on the log-rank. $P < 0.05$ was considered statically significant.

Table 2 – *Characteristics of salvage conformal radiotherapy in biochemical recurrence after radical prostatectomy.*

Variable	Median (cGy) Variation
Radiation dose at the seminal vesicle region	6660 4680-7740
Radiation dose at the prostatic bed region	7740 6840-8100
Radiation dose at 50% of the bladder	5482 2246-7137
Radiation dose at 30% of the bladder	6580 3254-7709
Radiation dose at 50% of the rectum	4832 1759-6880
Radiation dose at 25% of the rectum	6430 2920-7702
Radiation dose at 15% of the rectum	6937 3618-7979
Radiation dose at 5% of the rectum	7403 5783-8176
Time of treatment with radiotherapy	2.4 1.2-3.3

RESULTS

Biochemical Control

Mean follow-up was 55 months (17-83). Actuarial survival rate of biochemical recurrence and free of metastasis in 5 years were 79.7% and 84.7%, respectively (Figures-2 and 3). The mean time for the development of biochemical recurrence after radiotherapy was 15 months, and there was no biochemical recurrence after 36 months. One patient died due to prostate cancer 48.1 months after radiotherapy. Actuarial global survival rate in 5 years was 96.1%.

Actuarial survival rate free of biochemical recurrence in 5 years was 83.3% when pre-radiotherapy PSA ≤ 1, 100% when pre-radiotherapy PSA > 1 and ≤ 2, and 57.1% when pre-radiotherapy PSA > 2 ($p = 0.023$) (Figure-4). Neoadjuvant hormone therapy either concomitant or adjuvant, co-morbidity , radiation dose in seminal vesicle and prostrate bed, age, radiation treatment time and time between surgery and radiotherapy did not influence biochemical control. Other variables analyzed were not significant for the biochemical control (Table-3).

Acute and Late Toxicities

Four patients presented acute urinary toxicity grades 2 and 3 (Table-4). Dose > 70 Gy at 30% of the bladder volume implied in a more acute urinary toxicity ($p = 0.035$).

Six patients (17%) presented late urinary toxicity grades 2 and 3 (Table-4). One patient with late urinary retention and the patient with late hematuria did not have their complications solved until the moment of the analysis. Actuarial survival rate free from late urinary toxicity grade 2 and 3 in 5 years was 80.6%. The mean time for the development of late urinary toxicity was of 21 months (12-51). Dose > 55 Gy at 50% bladder volume implied in a higher late toxicity ($p = 0.018$) (Figure-5). Treatment time with radiation did not influence acute urinary toxicity, however, patients that received radiotherapy in a shorter space of time presented more late urinary toxicity ($p = 0.019$). In the multivariate linear regression analysis, only dose > 55 Gy at 50% of the bladder volume was significant for late urinary toxicity ($p = 0.021$). Age, co-morbidity, neoadjuvant hormone therapy, radiation dose in seminal vesicle and prostrate bed did not influence the toxicity of the treatment. Other variables analyzed were not relevant for acute and late urinary toxicity (Table-5).

DISCUSSION

Radical prostatectomy is a highly efficient treatment in localized prostate cancer therapy. However, disease-free survival rate is only 37-70% when

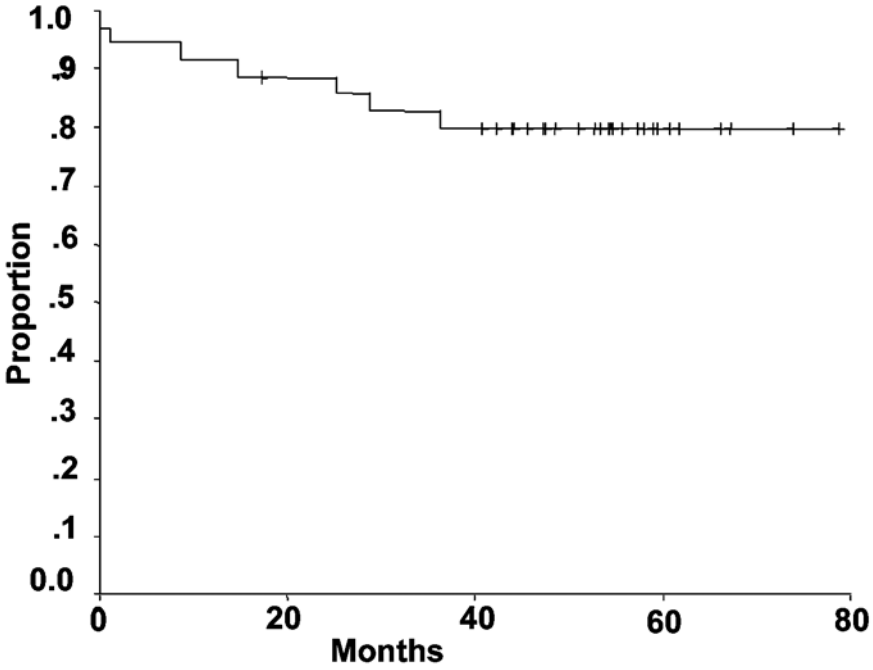

Figure 2 – *Actuarial survival rate free from biochemical recurrence after salvage conformal radiotherapy.*

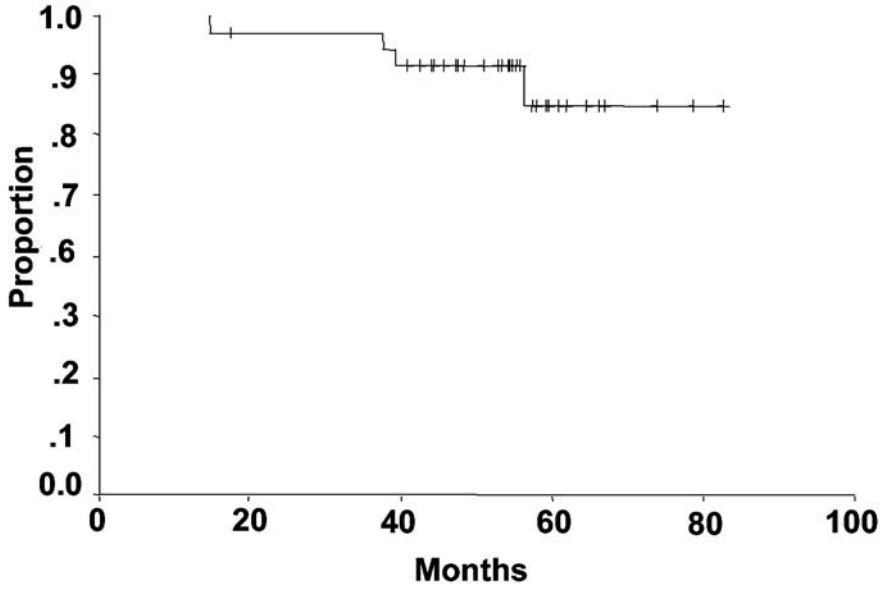

Figure 3 – *Actuarial survival rate free from distant metastasis after salvage conformal radiotherapy.*

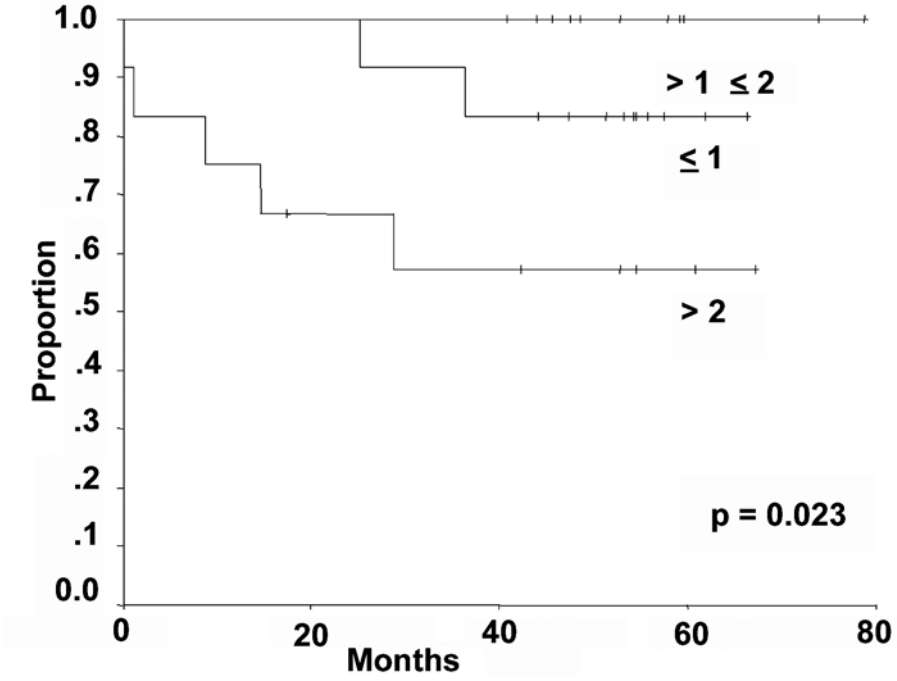

Figure 4 – *Actuarial survival rate free from biochemical recurrence after survival conformal radiotherapy for groups of patients with pre-radiotherapy PSA ≤ 1, > 1 ≤ 2, > 2 ng/mL.*

Table 3 – *Univariate analysis of variables associated to biochemical recurrence free survival rate in 5 years after salvage conformal radiotherapy.*

Variable	Category	Probability of Biochemical Recurrence in 5 Years	p Value
Positive margin	Yes	80%	0.967
	No	79.4%	
Postoperative tumor stage	≤ T2c	80%	0.148
	T3a-T3b	66.7%	
Gleason score	≤ 6	84.7%	0.288
	≥ 7	69.2%	
Pre-radiotherapy PSA	≤ 1	83.3%	0.023
	> 1 - ≤ 2	100%	
	> 2	57.1%	
Prostatic nodule	Yes	75%	0.679
	No	81%	
Radiotherapy in pelvis	Yes	78.2%	0.788
	No	83.3%	
Radiotherapy in pelvis associated to hormone therapy	Yes	88.8%	0.482
	No	76.4%	

Table 4 – *Late and acute toxicities.*

Acute Toxicity	Hematuria grade 2	1
	Dysuria grade 2	1
	Urinary incontinence grade 2	1
	Urinary retention grade 3	1
	Rectal bleeding grade 1	1
Late Toxicity	Hematuria grade 2	1
	Dysuria grade 2	1
	Urinary incontinence grade 2	1
	Urinary retention grade 3	3
	Rectal bleeding grade 2	1

there is extension of the disease beyond the prostatic capsule or there is impossibility of surgery with negative margins (8). We estimate that 65% of the patients with biochemical recurrence after prostatectomy will develop bone metastasis in 10 years (9). However, some patients with total PSA in progression after a radical prostatectomy will have a disease initially confined to the pelvis with a subsequent systemic dissemination. Salvage radiotherapy becomes interesting for this group of patients, being the best-studied treatment that can offer cure (1).

In our country there are no statistic data on the number of patients sent to a second treatment with radiotherapy. However, in the United States, less than 50% receive salvage radiotherapy treatment (9). There is a disseminated perception that the majority of biochemical recurrent patients have a hidden metastatic disease impeding any well-succeeded local salvage therapy, especially if the recurrence is precocious. This is because some series of salvage radiotherapy for biochemical failure have reported recurrence-free survival rates as low as 0% to 19% (4). Another current conception is that postoperative radiotherapy can cause actinic toxicities as high as 41% (10). However, conformal techniques have minimized bladder and rectum volume included in the field of treatment with radiation and allow the liberation of high doses of radiation with acceptable toxicity. Even though conformal salvage radiotherapy studies in biochemical recurrent prostate cancer are few, biochemical and

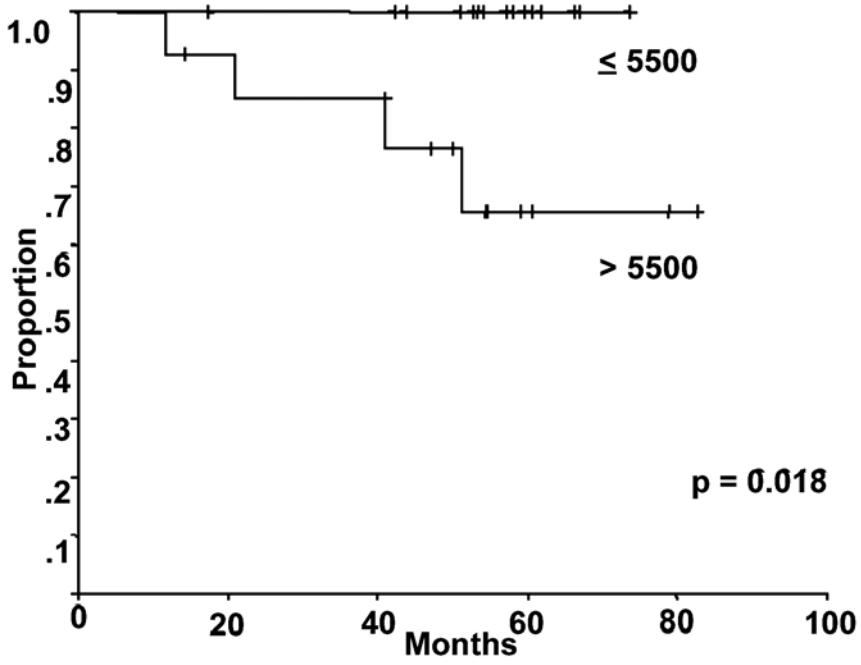

Figure 5 – *Actuarial survival rate free from late urinary toxicity grades 2 and 3 after salvage conformal radiotherapy due to the radiation dosage of 5500 cGy in 50% of the bladder volume.*

Table 5 – *Univariate analysis of variables associated to late urinary toxicity-free survival rate grades 2 and 3 after survival conformal radiotherapy in 5 years.*

Variable	Category	Probability of Late Urinary Toxicity-Free Survival Rate in 5 years	p Value
Post-surgery complications	Yes	67.3%	0.142
	No	90%	
Radiotherapy in pelvis	Yes	76.0%	0.407
	No	90%	
Radiotherapy in pelvis associated to hormone therapy	Yes	88.8%	0.560
	No	76.9%	
Radiation dose in 50% bladder volume	≤ 55Gy	100%	0.018
	> 55Gy	65.6%	
Radiation dose in 30% bladder volume	≤ 70Gy	88.2%	0.314
	> 70Gy	76.1%	

toxicity control results have revealed long-lasting responses with low toxicity (3,11). Katz et al. (11) have reported actuarial biochemical control of 77% in 4 years with late urinary toxicity grade 2 and 3 in 4 years 9% and 10%, respectively. Tsien et al. (3) have reported biochemical control rates in 5 and 8 years of 58% and 37%, with rectal and urinary complications probability rates ≥ grade 2 in 5 years of 6.3% and 8.9%, respectively. The present series have obtained similar actuarial rates in relation to the disease-free, metastasis-free and global survival rate, with acceptable acute and late complications rate and similar to the studies with the conformal technique and high radiation doses (3,11).

Katz et al. (11) reported that patients with positive margins have the smaller probability of biochemical control with salvage radiotherapy, however, median doses used in biochemical recurrence and in tumor recurrence in their series were 66.6 Gy and 70.2 Gy, respectively. In the present series, positive margins or the presence of a palpable nodule in prostatic fossa do not influence biochemical failure, probably because of the high radiation dose liberated in prostatic bed (median dose of 77.4 Gy).

Efficient salvage radiotherapy dose for biochemical control after surgery has not been established in literature. In patients submitted to radiotherapy exclusively for prostate cancer with locally advanced disease, high PSA and Gleason value have benefited from higher radiotherapy doses (≥75.6 Gy) (12,13). In salvage radiotherapy, we have also suggested that higher radiation doses (> 64.8 Gy) have obtained a better biochemical control (14). Series with high radiation doses have reported biochemical recurrence-free actuarial survival rates in 4 and 5 years of 77% (11) and 81% (15) in selected patients. In the present series, radiation dose was not a significant factor for the control of the disease, probably because the median radiation dose in prostatic bed was high and only 2 patients received a dosage inferior to 70 Gy.

Roach et al. (16) have reported that in prostate cancer patients not operated, pelvic radiotherapy associated to hormone therapy have proportioned a greater biochemical recurrence-free survival rate in patients with more that 15% risk of lymph node involvement, suggesting that pelvic lymph node prostate cancer is sensible to radiation when utilized at the same time as hormone therapy. The extension of the radiotherapy field in post-surgery salvage is not established in retrospective studies and not even there are randomized studies proving or not its benefit. However, lymph nodes attacked by prostate cancer

have been reported as post-surgery PSA production sources and based on Roach et al. findings (16), concomitance between radiotherapy and hormone therapy can benefit those patients. In the present series, the use of pelvic radiotherapy and hormone therapy did not influence biochemical control, probably by the relative small number of patients.

The extension of the disease to seminal vesicles has been reported as an important prognostic factor to biochemical failure after salvage radiotherapy in post-surgery biochemical failure (11). In the present series, it was not possible to correctly assess the importance of the seminal vesicles invasion by prostate cancer due to pathological charts that did not inform the situation of the seminal vesicles or the failure to completely remove them during surgery. Radiation dose was high at the seminal vesicles region with a median dose of 6660 cGy, and probably adequate for the control of the disease in this region, not influencing biochemical control.

Many series have associated pre-radiotherapy PSA values higher than 1 ng/mL and higher than 2 ng/mL with less probability of biochemical control (14,17). In this series pre-radiotherapy PSA ≤ 1 and between 1 and 2 were presented as similar groups, not revealing significant statistical difference between them, even though there was a difference in percentage. However, pre-radiotherapy PSA > 2 ng/mL implied in a higher biochemical recurrence ($p = 0.023$), suggesting that the most benefit is achieved when the treatment is preformed precociously.

Gleason value is being considered a factor related to biochemical recurrence in patients submitted to salvage radiotherapy in post-surgery biochemical recurrence (3). The reported series did not find any association between Gleason value and biochemical failure.

Adjuvant conventional radiotherapy series or in salvage of post-surgery biochemical recurred prostate cancer have reported toxicity grade 3 varying from 5% to 14% (18,19). Maier et al. (15) have treated 149 patients with a median dose of 68 Gy and 21 patients with a dose of 78 Gy, and reported 19% and 33% gastrointestinal and genitourinary toxicity grade 2, and 3% and 6% of gastrointestinal and genitourinary toxicity grade 3, respectively. Katz et al. (11) reported annual actuarial rates in 4 years of late genitourinary toxicity grades 2 and 3 of 9% and 10%, respectively, and late gastrointestinal toxicity grades 2 and 3 of 12% and 0%, respectively. Tsien et al. (3) reported urinary and rectal complication probability rates ≥ grade 2 in 5 years of 6.3% and 8.9%, respectively. In the present series, a patient has presented acute rectal toxicity grade 1 and a late rectal toxicity grade 2, not allowing any statistical analysis. Margins of 3 mm in prostatic bed for the rectum to compensate organ movement and positioning errors during radiotherapy applications have probably helped low rectal morbidity and did not compromise biochemical control. Acute and late genitourinary toxicities were acceptable, even though not irrelevant. However, we can identify which dose > 70 Gy in 30% bladder volume implied in a higher acute urinary toxicity, and dose > 55 Gy in 50% of the bladder volume implied in a higher late urinary toxicity, suggesting that the restriction of radiation dose in these volumes would minimize the radiotherapy effects. In the present series, a shorter time of treatment with radiation resulted in higher late genitourinary toxicity; however, this factor was not relevant to multivariate linear regression analysis. This finding has not been found in other salvage radiotherapy series in literature, being possible to be a sample error.

CONCLUSION

Conformal radiotherapy showed to be effective in the salvage of patients with biochemical recurrent prostate cancer after prostatectomy (79.7% of biochemical recurrence-free actuarial survival rate). Patients with pre-radiotherapy PSA ≤ 2 ng/mL have more biochemical control. We suggest reducing radiotherapy dose < 70 Gy in 30% of the bladder volume and < 55 Gy in 50% of the bladder volume to reduce the probability of acute and late urinary toxicity, respectively.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Carlos Roberto Monti
Av. Heitor Penteado, 1780, Taquaral
Campinas, SP, 13087-000, Brazil
Fax: + 55 19 3753-4166
E-mail: monti@radium.com.br

EDITORIAL COMMENT

Unfortunately, there is no homogeneity in the works that compare salvage and adjuvant radiotherapies after radical prostatectomy. In the first group (adjuvant) all individuals are treated with radiotherapy, i.e., both favorable and unfavorable cases, however, in the second group (salvage only the cases with recurrence of the disease), are irradiated, obviously unfavorable cases and those with a higher risk of progression. This methodological problem presents an important bias, limiting the scientific relevance of these study designs.

Dr. Marcos Dall'Oglio
Division of Urology
University of Sao Paulo, USP
Sao Paulo, SP, Brazil
E-mail: marcosdallogliouro@terra.com.br