

3D conformal external beam radiation therapy for prostate carcinoma: an experiment of Instituto do Radium de Campinas with 285 patients*

Radioterapia externa conformada 3D para o carcinoma de próstata: experiência do Instituto do Radium de Campinas com 285 pacientes

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Abstract **OBJECTIVE:** To report the outcomes of 3D conformal radiation therapy for prostate cancer in a single institution. **MATERIALS AND METHODS:** From July 1997 to January 2002, 285 consecutive patients with prostate cancer were submitted to 3D conformal radiation therapy receiving a median dose of 7920 cGy to the prostate, and were retrospectively evaluated. The patients distribution according to the level of risk was the following: low risk – 95 (33.7%); intermediate risk – 66 (23.4%); high risk – 121 (42.9%) patients. **RESULTS:** Median follow-up of 53.6 months (3.6–95.3 months) demonstrated 85.1% actuarial five-year overall survival, 97.0% specific cause survival, 94.2% five-year distant metastasis-free survival, and 75.8% five-year biochemical recurrence-free survival. Rates of five-year actuarial survival free from late rectal and urinary toxicity were 96.4% and 91.1% respectively. Pre-3D conformal radiation therapy transurethral resection of the prostate and doses > 70 Gy in 30% of the bladder volume implied a higher grade 2-3 late urinary toxicity in five years ($p = 0.0002$ and $p = 0.0264$, respectively). **CONCLUSION:** The first experiment with 3D conformal radiation therapy reported in Brazil allowed high radiation doses with acceptable levels of urinary and rectal toxicity. Pre-3D conformal radiation therapy transurethral resection of prostate may determine a higher risk for post-irradiation grade 2-3 late urinary toxicity. At the tomography planning, the reduction of the radiation dose to ≤ 70 Gy in 30% of the bladder volume may reduce the risk for late urinary complications. **Keywords:** Prostate; Cancer; Radiotherapy; Toxicity; Prognostic factors.

Resumo **OBJETIVO:** Reportar resultados de tratamentos do câncer de próstata com radioterapia conformada 3D realizados em uma única instituição. **MATERIAIS E MÉTODOS:** De julho de 1997 a janeiro de 2002, 285 pacientes consecutivos com câncer de próstata foram submetidos a radioterapia conformada 3D com dose mediana de 7.920 cGy na próstata e analisados retrospectivamente. A distribuição segundo o grupo de risco foi a seguinte: baixo risco – 95 (33,7%); risco intermediário – 66 (23,4%); alto risco – 121 (42,9%) pacientes. **RESULTADOS:** Em seguimento mediano de 53,6 meses (3,6–95,3 meses), sobrevidas atuariais global, causa específica, livre de metástases a distância e livre de recidiva bioquímica em cinco anos foram de 85,1%, 97,0%, 94,2% e 75,8%, respectivamente. Sobrevidas atuariais livre de toxicidade retal e urinária tardias em cinco anos foram de 96,4% e 91,1%, respectivamente. Ressecção transuretral pré-radioterapia conformada 3D e doses > 70 Gy em 30% do volume da bexiga implicaram maior toxicidade urinária tardia grau 2-3 em cinco anos ($p = 0,0002$ e $p = 0,0264$, respectivamente). **CONCLUSÃO:** A primeira experiência relatada de radioterapia conformada 3D no Brasil permitiu altas doses de radiação, com toxicidades retal e urinária aceitáveis. A existência de ressecção transuretral de próstata pré-radioterapia conformada 3D pode sinalizar maior risco de toxicidade urinária tardia grau 2-3 após irradiação. Restrição da dose ≤ 70 Gy em 30% do volume da bexiga à tomografia de planejamento pode reduzir complicações urinárias tardias. **Unitermos:** Próstata; Câncer; Radioterapia; Toxicidade; Fatores prognósticos.

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INTRODUCTION

Prostate cancer is the most frequent form of cancer in men, except for non-

melanoma skin cancer, with estimation of 49,530 new cases in 2008 in Brazil, corresponding to 52 new cases/100,000 men⁽¹⁾. The disease can be approached in a number of ways such as surgery, external beam radiation therapy, brachytherapy with iodine seeds, high-dose rate brachytherapy⁽²⁾, androgen suppression therapy, prostate-specific antigen (PSA) monitoring alone,

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and cryotherapy. However, only surgery, external beam radiotherapy, brachytherapy and cryotherapy, or an association of these therapeutic modalities can provide a cure for these patients.

Three-dimensional conformal radiation therapy (3DCRT), a technique of external beam radiotherapy, utilizes high technology with powerful computers and complex softwares, allowing a more accurate localization of the radiotherapy target and organs at risk, with the delivery of high doses to the target volume and better control over the radiation dose in healthy structures. The high radiation dose for prostate cancer has allowed a better biochemical control in prospective randomized studies although without resulting in increased overall survival^(3,4) and with an increase in toxicity⁽⁵⁾. However the high doses released with 3DCRT generate lower toxicity as compared with conventional radiotherapy with conventional radiation doses⁽⁶⁾.

The present study was aimed at reporting the outcomes of the treatment for localized prostate cancer with 3DCRT performed in an institution were more than 1,000 patients have already been treated up to the present moment, and evaluating prognostic factors for the management of the disease and toxicity of the therapy.

MATERIALS AND METHODS

In the period between July 1997 and January 2002, 285 consecutive patients with localized prostate adenocarcinoma diagnosed by means of transrectal biopsy were submitted to 3DCRT for curative purposes in a single institution, and were retrospectively evaluated. The median follow-up was of 53.6 months (3.6–95.3 months). All the patients were staged in compliance with the staging system of the American Joint Committee on Cancer (2002). Information on the testosterone levels at the beginning of the treatment was not available. All the patients signed a term of free and informed consent before being submitted to the treatment. Other characteristics of the patients are shown on Table 1.

Treatment characteristics

Concomitant and/or adjuvant, neoadjuvant androgen suppression and type of sup-

pressor drug were defined by decision of the urologist and/or radiotherapist. Simulation was performed with the patient in dorsal decubitus in a helical CT equipment with venous and urethral contrast-enhancement and 5 mm-thick slices. The Med-Crane software was utilized for images acquisition.

The therapy targets were delineated on the tomographic slices as follows: a) prostate – whole volume delineation (gross tumor volume – GTV); b) seminal vesicles – whole extent delineation (GTV, when affected; clinical target volume – CTV in subclinical disease); c) drainage – lymph nodes of internal and external iliac vessels from the caudal region of the sacroiliac joint, and lymph nodes of the obturator vessels, excluding the lateral perirectal lymph nodes (CTV in high-risk patients). Margins for target displacement and positioning errors measured 10 mm for all the dimensions and 3 mm posteriorly (PTV). Organs at risk were delineated as follows: a) bladder – whole volume by the outer muscular layer; b) rectum – whole volume and contents by the outer layer, from the rectoanal transition to the rectosigmoid transition. Energies of 6 or 15 MV and five radiation fields were utilized.

The radiotherapy treatment was divided into phases, as follows: in the first phase, pelvis, seminal vesicles and prostate were irradiated (PTV1); following, the treatment volume was restricted to the seminal vesicles and prostate (PTV2); and, finally, the treatment field covered only the prostate with respective margins (PTV3). In the absence of pelvic irradiation, the treatment was comprised of two phases, irradiation of seminal vesicles and prostate (PTV1), and following, only the prostate (PTV2). Restriction of doses in healthy tissues corresponded to: a) rectum: 50% < 50 Gy, 25% < 70 Gy; b) bladder: 50% < 50 Gy, 30% < 70 Gy; c) femoral heads: < 55Gy; the prescription dose corresponded to 95%. Figure 1 represents the dose and volume histogram, and an axial CT view in a 3DCRT planning for prostate cancer. Transference of the planning data to the linear accelerator was the next step, the treatment being performed with a dose of 180 cGy/day five times a week. The patients were evaluated on a weekly basis or more frequently as

necessary. Weekly check-films were utilized for quality control. Other treatment characteristics are shown on Table 1.

Patients follow-up

After the 3DCRT, the patients were followed-up with serial total PSA between three and six months, and image studies were requested in case of specific complaints. By the time of the analysis, data on the management of the disease and toxicity of the treatment were updated through phone conversations with the patients.

Toxicity

Late toxicity was evaluated for the rectum and bladder and rated according to the Common Terminology Criteria for Adverse Effects version 3⁽⁷⁾.

Biochemical failure

The presence of biochemical failure was considered after three consecutive increases in total PSA levels⁽⁸⁾ or introduction of therapy with androgen suppression for any reason.

Statistical analysis

The patients were evaluated as a single group for management of the disease and late toxicity, and as three different groups for management of the disease according to the initial total PSA levels, Gleason score and clinical T-stage, as follows: low-risk group including patients with initial total PSA < 10 ng/ml, Gleason score ≤ 6 and stage ≥ T2a; intermediate risk group with initial total PSA ≥ 10 and < 20 ng/ml or Gleason score = 7 or stage T2b-T2c; and the high-risk group with initial total PSA ≥ 20 and/or Gleason score ≥ 8 and/or stage T3, or two or more characteristics of the intermediate risk group.

The patients with late urinary or rectal toxicity may have had one or more types of toxicity, and the data and degree considered for the survival calculation were respectively the most recent and the highest.

Death for prostate cancer was defined as death of the patient with distant metastasis.

Association between categorical variables on contingency tables was evaluated by means of the chi-squared test and, in cases where at least one expected frequency was < 5 on 2 × 2 tables, the exact

Table 1 Patients and treatment characteristics.

Variable	Category	No. of patients (%)	Median (variation)
Age		285	70 (47-86)
Prostate weight (g)		212	35.3 (11-123)
Gleason score	≤ 6	196 (69.26)	
	7	60 (21.20)	
	≥ 7	27 (9.54)	
Positive fragment	≤ 50%	154	2 (1-11)
	> 50%	73	
Total PSA level	< 10	140 (49.30)	10 (1.4-304)
	10 < 20	89 (31.34)	
	≥ 20	55 (19.37)	
Clinical T-stage	≤ T2a	200 (70.18)	
	T2b-T2c	46 (16.14)	
	T3a-T3b	39 (13.68)	
Risk level	Low	95 (33.69)	
	Intermediate	66 (23.40)	
	High	121 (42.91)	
Neoadjuvant androgen suppression	Yes	123 (43.16)	
	No	162 (56.84)	
Concomitant androgen suppression	Yes	146 (51.23)	
	No	139 (48.77)	
Adjuvant androgen suppression	Yes	8 (2.81)	
	No	277 (97.19)	
Comorbidity	Yes	143 (50.18)	
	No	142 (49.82)	
Radiotherapy time	Days		71 (40-205)
Pelvic 3DCRT	Yes	51 (17.89)	
	No	234 (82.11)	
Seminal vesicles 3DCRT	Yes	244 (85.61)	5040 cGy (4500-7740)
	No	41 (14.39)	
3DCRT prostate dose		285	7920 cGy (7020-8460)

Fisher test was adopted. The significance level of 5% was considered for all the tests.

Overall survival was defined as the interval between date of the treatment beginning and the date of death or last information for censored observations. The period of disease recurrence of biochemical failure was measured from the beginning of the 3DCRT to the date of recurrence.

Overall survival and recurrence-free survival were estimated by the Kaplan-Meier test, and the logrank test was applied to compare survival curves with 95% confidence interval. The gross and adjusted relative risk of death was estimated by the Cox regression model. The whole statistical analysis was performed with the Stata 7 software package (StataCorp.; Texas, USA).

RESULTS

Actuarial overall survival

Actuarial overall five-year and seven-year survival rates were, respectively, 85.1% and 77.0%. Age > 65 years ($p = 0.0458$) and absence of seminal vesicles irradiation ($p = 0.0125$) resulted in lower rates of overall survival (Table 2). Association between radiation dose in seminal vesicles and increase in overall survival could not be observed. Other variables

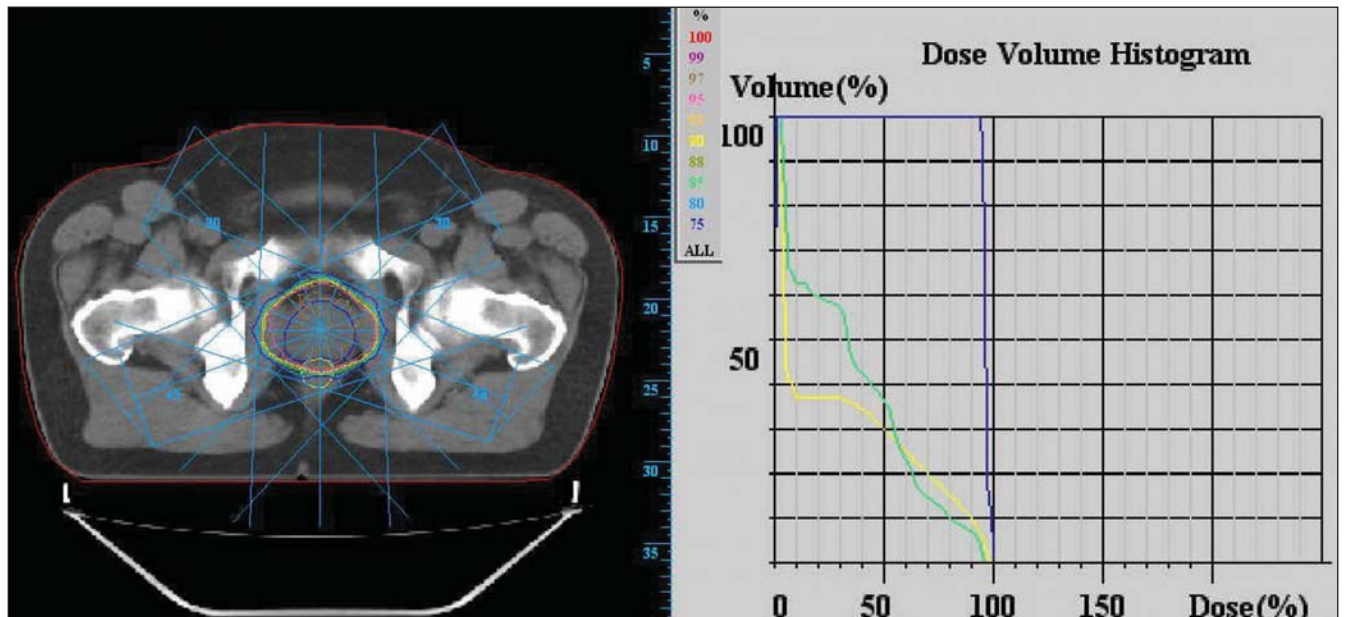


Figure 1. Axial CT view for 3DCRT planning for prostate cancer with respective dose-volume histogram showing the dose rate in prostate (blue), bladder (green) and rectum (yellow).

analyzed (see Table 2) did not influence the actuarial overall survival.

Actuarial cause-specific survival

The five-year and seven-year actuarial cause-specific survival rates were respectively 97% and 94.5%. Gleason score ($p = 0.0179$), percentage of positive fragments ($p = 0.0222$), clinical T-stage ($p = 0.0006$), biochemical recurrence ($p < 0.0001$) and pre-3DCRT transurethral resection ($p =$

0.0206) constituted prognostic factors for death for prostate cancer. The analysis of risk groups demonstrated a tendency towards statistical significance ($p = 0.0677$). However, as the risk groups were separately analyzed, a same p value was found for risk groups 1 and 2 ($p = 0.2403$) and the group 1 demonstrated longer cause-specific survival than group 3 ($p = 0.0327$). Other characteristics analyzed are shown on Table 2.

Actuarial metastasis-free survival

The five-year and seven-year actuarial metastasis-free survival rates were respectively 94.2% and 93.1%. Seventeen patients presented distant metastasis. Age ≤ 65 years ($p = 0.0220$), Gleason score ($p = 0.0005$), clinical T-stage ($p = 0.0041$), risk group ($p = 0.0033$), biochemical recurrence ($p < 0.0001$), pr \acute{e} -3DCRT transurethral resection ($p = 0.0039$) and a period > 5 months

Table 2 Characteristics related to the patient, to the tumor, and to the 3DCRT in terms of actuarial overall and cause-specific survival.

Variable	Category	No. of patients	Overall survival			Cause-specific survival		
			5 years (%)	7 years (%)	p -value	5 years (%)	7 years (%)	p -value
Age range (years)	≤ 65	80	93.50	77.43	0.0458	94.69	87.68	0.1626
	> 65	205	81.80	77.36		98.18	98.18	
Comorbidity	Yes	143	80.44	78.24	0.1099	95.96	95.96	0.5709
	No	142	89.73	76.99		97.92	93.66	
Gleason score	≤ 6	196	86.20	81.13	0.3076	98.83	95.88	0.0179
	7	60	80.99	24.43		88.68	88.68	
	≥ 8	27	84.68	76.21		100.00	100.00	
Positive fragment	≤ 50	154	88.24	81.94	0.3902	100.00	100.00	0.0222
	> 50	73	83.18	78.69		93.94	93.94	
Total PSA	< 10	140	86.40	79.97	0.7525	97.94	92.78	0.8010
	$10 < 20$	89	85.06	76.36		96.48	96.48	
	≥ 20	55	81.81	70.12		95.24	95.24	
Clinical T-stage	$\leq T2a$	200	86.94	85.43	0.2980	100.00	100.00	0.0006
	T2b-T2c	46	82.18	60.26		89.29	89.29	
	T3a-T3b	39	79.94	65.41		92.61	75.77	
Risk level	Low	95	87.18	87.18	0.7916	100.00	100.00	0.0677
	Intermediate	66	83.31	78.92		98.41	98.41	
	High	121	84.13	67.05		94.00	94.00	
Pre-3DCRT transurethral resection	Yes	37	81.95	81.95	0.4912	89.83	89.83	0.0206
	No	247	85.55	76.59		98.07	95.34	
Neoadjuvant androgen suppression	Yes	123	86.79	77.37	0.2082	96.14	88.12	0.4716
	No	162	83.98	76.57		97.71	97.71	
Concomitant androgen suppression	Yes	146	87.56	77.38	0.1365	96.52	89.63	0.6643
	No	139	82.36	76.14		97.38	97.38	
Adjuvant androgen suppression	Yes	8	74.04	74.04	0.4990	87.50	87.50	0.0916
	No	277	85.63	77.34		97.32	94.83	
Pelvic 3DCRT	Yes	51	84.92	44.23	0.2578	94.52	70.89	0.0804
	No	234	85.12	81.61		97.61	97.61	
Seminal vesicles 3DCRT	Yes	244	87.45	78.24	0.0125	97.53	94.79	0.1091
	No	41	69.59	69.59		93.36	93.36	
3DCRT prostate dose	≤ 7600 cGy	31	75.00	68.18	0.0587	100.00	100.00	0.3293
	> 7600 cGy	254	86.30	78.32		96.69	93.35	
Biochemical recurrence	Yes	69	83.40	68.89	0.6644	88.90	80.82	< 0.0001
	No	216	85.74	80.15		100.00	100.00	
Grade 2-3 late urinary toxicity	Yes	22	100.00	100.00	0.0609	100.00	100.00	0.4475
	No	263	83.89	75.48		96.70	94.12	
Grade 2-3 late rectal toxicity	Yes	10	90.00	90.00	0.8021	100.00	100.00	0.6683
	No	275	85.02	76.64		96.89	94.34	
Time between diagnosis and 3DCRT	≤ 5 months	231	86.63	79.74	0.2337	97.43	97.43	0.0671
	> 5 months	54	77.87	58.40		95.12	71.34	

between diagnosis and introduction of 3DCRT ($p = 0.0016$) constituted prognostic factors for the development of distant metastasis (Table 3).

Actuarial biochemical recurrence-free survival

Actuarial five-year and seven-year biochemical recurrence-free survival rates were respectively 75.8% and 64.0%. Sixty-nine patients presented biochemical recur-

rence (24.21%). Gleason score ($p = 0.0004$), percentage of positive fragments $> 50\%$ ($p = 0.0211$), initial total PSA ($p < 0.0001$), clinical T-stage ($p = 0.0204$) and risk group ($p < 0.0001$) implied higher rates of biochemical failure in the univariate analysis (Table 3). In the multivariate analysis, pre-3DCRT initial total PSA and Gleason scores constituted independent prognostic factors ($p < 0.0001$ and $p = 0.0011$, respectively) (Table 4).

Pelvic 3DCRT

Patients submitted to pelvic radiotherapy presented lower actuarial biochemical recurrence-free and metastasis-free survivals. However, these patients had more aggressive tumors, allowing a sampling error in the statistical analysis.

Low-risk group

Actuarial seven-year overall and biochemical recurrence-free survival rates for

Table 3 Characteristics related to the patient, to the tumor, and to the 3DCRT in terms of actuarial metastasis-free and biochemical recurrence-free survival.

Variable	Category	No. of patients	Metastasis-free survival			Biochemical recurrence-free survival		
			5 years (%)	7 years (%)	p-value	5 years (%)	7 years (%)	p-value
Age range (years)	≤ 65	80	89.82	86.43	0.0220	74.08	74.08	0.7372
	> 65	205	95.98	95.98		76.20	58.88	
Comorbidity	Yes	143	93.54	91.61	0.4979	72.37	62.19	0.1791
	No	142	94.94	94.94		79.16	65.97	
Gleason score	≤ 6	196	97.87	96.39	0.0005	81.47	71.50	0.0004
	7	60	84.53	84.53		62.95	53.26	
	≥ 8	27	88.81	88.81		59.54	40.52	
Positive fragment	≤ 50	154	98.70	96.53	0.0524	82.05	66.12	0.0211
	> 50	73	92.73	92.73		67.87	52.52	
Total PSA	< 10	140	97.05	94.71	0.0545	87.91	85.60	< 0.0001
	10 < 20	89	94.34	94.34		66.17	48.72	
	≥ 20	55	86.84	86.84		61.20	40.27	
Clinical T-stage	≤ T2a	200	97.43	95.68	0.0041	79.35	65.45	0.0204
	T2b-T2c	46	84.70	84.70		61.47	49.33	
	T3a-T3b	39	89.21	89.21		74.83	74.83	
Risk	Low	95	100.00	89.21	0.0033	91.21	87.83	< 0.0001
	Intermediate	66	96.97	96.67		73.56	59.22	
	High	121	88.17	88.17		64.59	49.01	
Pre-3DCRT transurethral resection	Yes	37	83.60	83.60	0.0039	61.71	61.71	0.1883
	No	247	95.81	94.52		77.85	64.30	
Neoadjuvant androgen suppression	Yes	123	90.83	90.83	0.0699	72.61	60.76	0.1970
	No	162	96.87	94.97		78.21	66.23	
Concomitant androgen suppression	Yes	146	92.28	92.28	0.2686	73.96	57.84	0.3819
	No	139	96.34	94.27		77.89	68.32	
Adjuvant androgen suppression	Yes	8	87.50	87.50	0.4996	62.50	—	0.3628
	No	277	94.45	93.28		76.14	63.97	
Pelvic 3DCRT	Yes	51	81.78	81.78	0.0001	62.92	62.92	0.0353
	No	234	96.95	95.59		78.66	65.27	
Seminal vesicles 3DCRT	Yes	244	94.97	93.72	0.2448	76.88	64.65	0.3186
	No	41	89.53	89.53		67.71	57.29	
3DCRT prostate dose	≤ 7600 cGy	31	100.00	92.00	0.5068	84.22	74.31	0.1123
	> 7600 cGy	254	93.56	93.56		74.86	63.04	
Biochemical recurrence	Yes	69	76.57	73.09	< 0.0001	—	—	—
	No	216	100.00	100.00		—	—	
Grade 2-3 late urinary toxicity	Yes	22	86.36	86.36	0.1105	59.53	59.53	0.4017
	No	263	94.91	93.72		77.15	64.56	
Grade 2-3 late rectal toxicity	Yes	10	100.00	100.00	0.4277	57.27	57.27	0.4339
	No	275	94.02	92.86		76.33	64.23	
Time between diagnosis and 3DCRT	≤ 5 months	231	96.49	95.19	0.0016	77.50	64.09	0.2197
	> 5 months	54	84.47	84.47		68.28	68.28	

Table 4 Independent prognostic factors for biochemical failure in the multivariate analysis.

Variable	Category	Relative gross risk (95% CI)	Relative multivariate risk (95% CI)
Initial total PSA level	< 10 ng/ml	1.0 (reference)	1.0 (reference)
	10 < 20 ng/ml	3.39 (1.9–6.2)	3.05 (1.7–5.6)
	≥ 20 ng/ml	3.96 (2.1–7.5)	3.43 (1.8–6.6)
Gleason score	≤ 6	1.0 (reference)	1.0 (reference)
	7	2.44 (1.4–4.2)	2.17 (1.2–3.8)
	≥ 8	2.63 (1.4–5.0)	1.90 (1.0–3.7)

CI, confidence interval.

patients in the low-risk group were, respectively, 87.2% and 87.8%. Prognostic factors implying lower survival rates for this group of patients were not identified. Only a tendency to longer actuarial overall survival with doses > 76 Gy in the prostate ($p = 0.0524$) was observed. In account of the low incidence of deaths for prostate cancer and distant metastasis, actuarial cause-specific and distant metastasis-free survival rates could not be evaluated for this group.

Intermediate-risk group

Actuarial seven-year overall and biochemical recurrence-free survival rates were, respectively 78.9% and 59.2%. Irradiation of seminal vesicles resulted in longer actuarial overall and biochemical recurrence-free survival ($p = 0.0034$ and $p = 0.0301$, respectively). No association was found between the other variables. Because of the low incidence of deaths for prostate cancer and distant metastasis, actuarial cause-specific and distant metastasis-free survival rates could not be evaluated for this group.

High-risk group

Actuarial seven-year overall and biochemical recurrence-free survival rates were respectively 67.1% and 49.0%. Neoadjuvant and concomitant androgen suppression resulted in higher actuarial overall survival rates ($p = 0.0217$ and $p = 0.0238$, respectively), and irradiation of seminal vesicles resulted in higher actuarial biochemical recurrence-free survival rates ($p = 0.0040$). Other variables were not statistically significant. Because of the low incidence of deaths for prostate cancer and distant metastasis, actuarial cause-specific and distant metastasis-free survival rates could not be evaluated for this group.

Late rectal toxicity

The rate of actuarial seven-year survival free of late rectal toxicity (grade 2-3) was 96.38%. Three patients presented late rectal toxicity grade 2 and seven, grade 3 (Table 5). Associated prognostic factors could not be identified because of the low number of patients with late rectal toxicity.

Late urinary toxicity

The rate of actuarial seven-year survival free of late urinary toxicity (grade 2-3) was 89.97%. Seven patients presented late urinary toxicity grade 2, and 15 grade 3 (Table 5). Pre-3DCRT transurethral resection and doses > 70 Gy in 30% of the bladder volume implied a higher late urinary toxicity grade 2 and 3 (respectively ($p = 0.0002$ and $p = 0.0264$)). Other variables were not statistically significant.

DISCUSSION

Treatment characteristics associated with the therapy results

In low-risk patients with clinical T1 and T2a stages, long term outcome from conventional external beam radiotherapy have been similar to the ones from radical pros-

tatectomy^(9,10). However, in patients with locally advanced disease, the local management of the primary tumor with conventional external beam radiotherapy is unsatisfactory, with 30% to 40% local recurrence in ten years and, after 10 and 15 years, only 35% to 45% and 18% to 27% respectively are alive⁽¹⁰⁾.

Retrospective studies have associated local management with radiation dose in prostate adenocarcinoma^(10,11). However, the delivery of doses > 70 Gy with the technique of conventional radiotherapy has implied severe complications (grades 3 and 4) in 3.5% to 6.9% of cases⁽¹²⁾.

With the technological development, the association of computed tomography with linear accelerator became feasible by means of complex software packages. This association has allowed an extremely reliable visualization of the therapeutic target as well as of adjacent healthy structures, and the estimation of the radiation dose in the target volume and structures at risk. As a result, since the beginning of the nineties, dose scaling protocols have been developed and, in cases of prostate cancer, a higher biochemical control with acceptable late toxicity has been achieved^(3,4). In the present series, the actuarial five-year biochemical recurrence-free survival for low, intermediate and high-risk patients was, respectively, 91.40%, 73.29% and 64.25%, similarly to the results from 3D radiotherapy⁽¹³⁾ and radical prostatectomy⁽⁸⁾.

Already published series with dose scaling^(3,4,13) report a higher biochemical control with higher radiation doses, although without increasing the overall survival. However, the follow-up of these patients is still relatively short, and a longer follow-up may demonstrate benefits in terms of overall survival. In the meantime a decrease in biochemical failure may result in measurable benefits to the patients, with longer actuarial cause-specific and metastasis-free survival as reported by the present series, besides reducing the necessity of androgen suppression in the biochemical failure.

Gleason score, clinical T-stage and initial total PSA level can predict the risk for seminal vesicles involvement⁽¹⁴⁾ that, depending on the risk level, must be treated. However, irradiation of seminal vesicles may drastically increase the volume of

Table 5 Late urinary and rectal toxicity.

Complication	Grid	No. of patients
Cystitis	2	2
	3	3
Urinary retention	2	1
	3	8
Hematuria	3	7
	2	4
Urinary incontinence	2	4
	3	5
Rectal bleeding	2	3
	3	5
Rectal pain	3	1
	2	1
Intestinal obstruction	3	1
	2	1

healthy tissues irradiated and, consequently increase the risk for late toxicity. In the present study, irradiation of seminal vesicles resulted in longer actuarial overall and biochemical recurrence-free survival in patients of the intermediate risk group, and increased the biochemical recurrence-free survival in patients of the high-risk group, without increasing the toxicity.

Several prospective randomized studies associating androgen suppression with radiotherapy have been developed, demonstrating benefits in terms of overall survival, disease-free survival, cause-specific survival, biochemical recurrence-free survival, distant metastasis-free survival, and local management^(15,16). In the present series, the utilization of neoadjuvant and concomitant androgen suppression resulted in longer overall survival in high-risk patients. Patients at intermediate and low risks did not benefit from the procedure. The number of patients submitted to adjuvant androgen suppression was small and did not allow statistical analysis.

In the present study, patients submitted to pelvic radiotherapy presented shorter actuarial biochemical recurrence-free and distant metastasis-free survival. However, patients submitted to this treatment presented more aggressive tumor characteristics, causing distortion in findings confirmed in the cases where statistically significant was not observed among patients of a same risk group submitted or not to pelvic radiotherapy.

Patients' characteristics associated with treatment results

The relevance of several tumor-related prognostic factors, particularly Gleason score, clinical T-stage and initial total PSA level, has been identified in the literature⁽¹⁴⁾. In the present series, Gleason score, clinical T-stage and initial total PSA level constituted prognostic factor for cause-specific and biochemical recurrence-free survival. For metastasis-free survival, Gleason score and clinical T-stage were significant; initial total PSA level was marginally significant ($p = 0.0545$). The division into risk groups associating initial total PSA level, Gleason score and clinical T-stage in the present series was significant for biochemical recurrence-free and distant metastasis-

free survival, and marginally positive for cause-specific survival. However, as the risk groups are separately evaluated, a same p value was found for risk groups 1 and 2 and the group 1 demonstrated longer cause-specific survival than group 3.

In the literature, the role of pre-3DCRT transurethral resection in the management of prostate cancer is controversial^(17,18). In the present series, pre-3DCRT transurethral resection resulted in shorter cause-specific and metastasis-free survival, suggesting that the procedure may reduce the 3DCRT effectiveness.

After the diagnosis of prostate cancer, patients who had to wait for more than three months to have the 3DCRT started presented a tendency to a shorter metastasis-free survival ($p = 0.0763$). However, when the wait was extended for more than five months from the diagnosis, the distant metastasis-free survival was significantly longer ($p = 0.0016$), suggesting that prostate cancer should be treated in less than five months after the diagnosis.

Probably, patients with > 65 years of age present less aggressive tumors, considering that they presented longer metastasis-free survival than those with ≤ 65 years of age, suggesting that patients with > 65 years can benefit from less debilitating treatments.

In the present series, patients with $\leq 50\%$ of positive fragments presented longer cause-specific and biochemical recurrence-free survival and a tendency to longer metastasis-free survival ($p = 0.0524$), suggesting that this is significant prognostic factor to be taken into consideration in the treatment individualization, as reported in the literature⁽¹⁹⁾.

Late toxicity

Three-dimensional conformal radiation therapy for the treatment of prostate cancer reduces late effects grade ≥ 3 as compared with conventional 2D radiation therapy. The rate of late toxicity grade ≥ 3 for 78 Gy to the PTV in the study RTOG 94-06-group 1 (six cases) was significantly lower in relation to the historical expected 18.2 control cases (RTOG 7506 and RTOG 7706) ($p = 0.0042$)⁽⁶⁾.

In several studies, late rectal toxicity has been strongly associated with the rectal volume irradiated with a determined radia-

tion dose⁽²⁰⁾. It is recognized that there is not a single point of radiation dose in the volume of a healthy organ resulting in late rectal toxicity, but there is a continuum of relations between dose and volume. Studies developed at the M.D. Anderson Cancer Center associating absolute radiation dose with percentage of rectal volume have been of aid to the clinical practice for adding safety to the radiotherapy treatment. In a retrospective study including 163 patients submitted to 3DCRT at the M.D. Anderson Cancer Center, Huang et al.⁽²⁰⁾ have suggested that doses of 60 Gy, 70 Gy, 75.6 Gy and 78 Gy should be restricted to respectively 40%, 25%, 15% and 5% of the rectal volume. In the present study, probably because of the small number of patients with grade ≥ 2 late rectal toxicity, the authors could not observe any relation between this variable and the radiation dose to a determined rectal volume or its association with any other variable.

Liu et al.⁽²¹⁾ have evaluated 1,192 patients submitted to radiotherapy and observed that coexisting genitourinary disease, transurethral resection of the prostate or transurethral resection of vesical tumor and the presence of acute urinary toxicity during radiotherapy were significant factors for late urinary toxicity grade 3. In the present series, doses > 70 Gy to 30% of bladder volume implied a higher late urinary toxicity (grade 2-3). Patients submitted to pre-3DCRT transurethral resection of the prostate presented higher late urinary toxicity. However, the finding may result from a sampling error probably because of the selection of patients with a higher propensity to urinary toxicity, considering the previous necessity of transurethral resection of the prostate.

CONCLUSIONS

The firstly reported Brazilian experiment with 3DCRT utilizing high radiation doses has shown the effectiveness of this method in the management of patients with prostate cancer and low late rectal and urinary toxicity, as reported in the literature. Despite the retrospective character and the relatively limited number of patients, the present study suggests recommendations for the clinical practice. The irradiation of

seminal vesicles may be beneficial for intermediate-risk patients, as the study suggests, considering that there was an increase in the overall and biochemical recurrence-free survival. The utilization of neoadjuvant and concomitant androgen suppression in high-risk patients may extend the actuarial overall survival and irradiation of seminal vesicles may result in longer biochemical recurrence-free survival. Pre-3DCRT transurethral resection of the prostate may impair the management of the tumor and increase the late urinary toxicity (grade 2-3). The data presented herein suggest that the restriction of the radiation dose < 70 Gy in 30% of the bladder volume may reduce grade 2-3 late urinary toxicity.

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