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Prostate brachytherapy

Results of high dose-rate brachytherapy boost before 2D or 3D external beam irradiation for prostate cancer

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ABSTRACT

Background and purpose: To evaluate biochemical control and treatment related toxicity of patients with localized adenocarcinoma of the prostate treated with high dose-rate brachytherapy (HDRB) combined with conventional 2D or 3D-conformal external beam irradiation (EBI).

Material and methods: Four-hundred and three patients treated between December 2000 and March 2004. HDRB was delivered with three fractions of 5.5–7 Gy with a single implant, followed by 45 Gy delivered with 2D or 3D conformal EBI.

Results: The median follow-up was 48.4 months. Biochemical failure (BF) occurred in 9.6% according to both ASTRO and Phoenix consensus criteria. Mean time to relapse was 13 and 26 months, respectively. The 5-year BF free survival using the ASTRO criteria was 94.3%, 86.9% and 86.6% for the low, intermediate and high risk groups, respectively; using Phoenix criteria, 92.4%, 88.0% and 85.3%, respectively. The only predictive factor of BF in the multivariate analysis by both ASTRO and Phoenix criteria was the presence of prostate nodules detected by digital palpation, and patients younger than 60 years presented a higher chance of failure using Phoenix criteria only.

Conclusions: Treatment scheme is feasible and safe with good efficacy.

Prostate cancer is the most common malignant neoplasia affecting men in Brazil, after non-melanoma skin cancer. For 2010, estimates of the Brazilian National Cancer Institute pointed out that 52,350 new cases of prostate cancer would be diagnosed in Brazil; an incidence of 54/100,000 men [1]. Besides the high worldwide incidence, prostate cancer presents a low mortality rate, comprising 3.8% of all deaths due to cancer in the world, 6.8% of deaths in men [2].

The results of radiotherapy of prostate cancer are highly related to radiation dose, mainly for patients with intermediate or high risk disease [3–5]. However, dose-escalation is associated with a higher risk of complications and several techniques have been developed to improve the outcome with minimal complications [3,6]. These include 3D-conformal and intensity modulated radiation therapy (IMRT) and brachytherapy (high or low dose-rate) alone or combined with external beam irradiation. A combination of high dose-rate brachytherapy (HDRB) with conventional external beam irradiation is an attractive option for a safe dose-escalation [7–13], allied with the advantage of fewer days of treatment.

The purpose of this study was to evaluate biochemical control of patients with localized adenocarcinoma of the prostate treated with conventional 2D or 3D-conformal external beam irradiation (EBI) combined with HDRB, validate one of the common biochemical failure criteria (ASTRO or Phoenix) for this population, and define prognostic factors associated to biochemical control, as well as to treatment related toxicity.

Materials and methods

A retrospective study of 455 patients with localized adenocarcinoma of the prostate, treated with HDRB combined with EBI from 2000 to 2004 was performed. Patients had to be from 50 to 90 years-old, present a Karnofsky performance status above 70, stage T1 to T3 (AJCC 5th ed.) and a prostate volume below 100 cm^3. Previous pelvic irradiation or the history of other cancer except non-melanoma skin cancer and metastatic disease were exclusion criteria. Of the 455 patients, 403 with a minimum follow-up of 2 years were selected for this study. The remaining 52 (11%) were lost to follow-up. This study has been approved by the appropriate ethical committees related to the institutions in which it was performed and the subjects gave informed consent to the work.

The treatment protocol included HDRB followed by EBI with about 15 days interval. Patients with initial prostate volume of

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above 50 cm^3 received neoadjuvant hormone therapy, cyproterone acetate 50 mg orally three times a day for 3 months.

HDRB was administered with a single implant, in 3 fractions over a 24-h period with a minimum interval of 6 h between each fraction. Patients were stratified into three groups, according to the following risk factors: PSA between 10 and 20 ηg/ml, Gleason score greater than or equal to 7, and the presence of bilateral palpable prostate nodule or visible at ultrasound system (Mount Sinai grouping scheme [11]).Thus: low risk patients presented no risk factor among the above; Intermediate Risk, one risk factor among the above, and high risk, PSA > 20 ng/ml and/or Gleason score 8–10, and/or stage ⩾ T2c or two or more risk factors among the above. Brachytherapy doses were 3×5.5 to 6 Gy for low risk, 3×6 to 6.5 Gy for intermediate risk, and 3×6.5 to 7 Gy for high risk patients, respectively. Brachytherapy needles were placed with transretal ultrasound guidance. Calculation was based on semi-orthogonal radiographs reconstruction, using geometrical optimization. Nucletron Plato brachytherapy planning system (BPS) version 13.7 (Nucletron Corporation B.V., Veenendaal, The Netherlands) was used. Hundred percent isodose (minimal peripherical dose) was normalized to a 5–6 mm margin lateral to the prostatic capsule at the median plane. The quality of the implant was assessed by the analysis of the isodoses and of the volumes receiving 100% (V100) and 150% (V150) of the prescribed dose. The relationship V150/V100 was kept lower than or equal to 1/3, and the urethral dose was kept lower than or equal to 120% of the prescription dose. Treatment was delivered with the microSelectron-HDR equipment (Nucletron®, Netherlands).

A dose of 45 Gy (1.8 Gy/day, five times per week) was delivered with EBI, either with conventional technique (4 fields in "box") or three-dimensional conformal irradiation, including the prostate and seminal vesicles. The four-field box technique was based on bone landmarks. The fields were 9×9 cm with the lower limit defined at the inferior border of the ischial tuberosities and the anterior limit at the midportion of the pubic symphysis. Dose was calculated at the isocenter. Most patients (81%) were treated with this technique. When conformal radiotherapy was used, a 1.0 cm margin was defined for the PTV, except posteriorly, where a 0.7 cm margin was defined. The software MEVIS-CAT3D was used for calculation (MEVIS Informática Médica Ltda, Brazil, www.mevis.com.br). The dose was prescribed at the 95% isodose, normalized at the isocenter. The patients were treated with a 6 MV linear accelerator (Varian Clinac 600C®).

Follow-up including clinical evaluation and PSA dosage was performed at 2, 6, 10, and then, every 6 months after treatment, unless clinical signs or symptoms lead patients to seek medical attention. Biochemical failure free survival was analyzed according to the ASTRO criteria [14] and the PHOENIX consensus [15]. Time for biochemical relapse was considered from the end of irradiation. The following variables were studied and correlated to treatment outcome and complications: age, PSA level at diagnosis, histological Gleason score, prostate volume, stage, risk group, prior hormone therapy, prior transurethral resection, the presence of prostate nodules on rectal digital examination, dose of brachytherapy, type of EBI (two or three dimensional), and the presence of comorbidities, such as diabetes or hypertension. Technical variables, such as V100 and V150 and the urethral dose were also studied. With a median age of 68 years, ranging from 42 to 89 years, low risk patients represented the largest risk group (44%), with PSA < 10 ηg/ml, Gleason score < 7 and T1 or T2a,b disease. Neoadjuvant hormone therapy was delivered to 64% of the cases and 3D conformal EBI in 19%. Table 1 summarizes patients' characteristics.

Early toxicity was considered until 6 months after the end of irradiation and a period of at least 1 year after irradiation was defined to evaluate late toxicities. Urinary and rectal toxicities were evaluated according to the Radiation Therapy Oncology Group (RTOG) early and late toxicity scores [16]. Sexual function was assessed according to the score defined by Stock et al., grading from 0 to 3 [17,18].

Patients who did not respond to treatment were classified as having initial failure and were not included in the analysis of biochemical failure free survival and toxicity.

Statistical analysis

The data were submitted to descriptive and frequency analyses. The end-points were initial failure (patients not responding to treatment, identified as not presenting PSA decrease) and biochemical failure free survival defined either by the ASTRO or PHOENIX criteria. The Kaplan–Meier method, univariate analysis and a regression model were used for the survival analyses. Evaluation of the equality of the survival functions was performed by the log-rank test. Multivariate analysis was performed by the Cox model of proportional hazards. The variables of interest were selected by a regression model using the "forward stepwise" method, with scores test for inclusion of the variables and Wald test for exclusion. The significance level was set at 5% ($p < 0.05$). The softwares SAS 8.0 and R 1.8.1 were used for the statistical analysis.

Results

The mean follow-up of the 403 patients was 50 months (median of 48.4 months), ranging from 24 to 113 months, and was similar for all risk groups (Table 1). The 2 and 5 years biochemical failure free survival were, respectively, 93% and 90% for the ASTRO definition, and 95% and 89% using the Phoenix definition. Considering the risk group, the 5-year biochemical failure free survival according to the ASTRO criteria was 94.3%, 86.9% and 86.6% for the low, intermediate and high risk groups, respectively (Fig. 1), and using the Phoenix criteria, 92.4%, 88.0% and 85.3%, respectively (Fig. 2). There were 8 (2.2%) patients that presented initial failure and distant metastasis occurred in 13 (3.2%) patients in a median time of 22 months (2–60 months). With a median survival of 22 months, ranging from 1 to 82 months, 18 (4.5%) patients died, only 4 due to prostate cancer.

Among the patients who presented response to treatment, 9.6% had biochemical failure using the ASTRO criteria, in a median time of 13 months (4–31 months). Using the PHOENIX criteria, also 9.6% presented biochemical failure, in a median of 26 months (6–76 months).

PSA at diagnosis above 20 ηg/ml ($p = 0.009$), Gleason score equal to or higher than 7 ($p = 0.011$), use of hormone therapy ($p = 0.010$), high dose treatment schedule (3×700 cGy) ($p = 0.017$) and high risk group ($p = 0.007$) were associated with initial failure on univariate analysis. On multivariate analysis, only PSA ($p = 0.034$) and Gleason score ($p = 0.029$) remained as independent significant factors associated to initial failure.

Only three variables were predictive of biochemical failure by the ASTRO criteria in the univariate analysis: the presence of nodules in the prostate ($p = 0.011$), high risk group ($p = 0.050$) and stage ($p = 0.020$). Using the PHOENIX criteria, the presence of nodules ($p = 0.011$) and stage ($p = 0.017$) were also selected. In the multivariate analysis, only the presence of prostatic nodules ($p = 0.014$) was significantly correlated to failure by the ASTRO criteria, and the presence of nodules ($p = 0.005$) and younger age (60 years or less) ($p = 0.023$), by the PHOENIX criteria.

Overall early and late urinary toxicities were observed in 40.8% and 20.7% of the patients, respectively, and rectal toxicities in 26.6% and 5.5%, respectively. Most toxicities were of grade 1 or 2 (Table 2).