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CLINICAL INVESTIGATION **Prostate**

HYPOFRACTIONATED VERSUS CONVENTIONALLY FRACTIONATED RADIOTHERAPY FOR PROSTATE CARCINOMA: FINAL RESULTS OF PHASE III RANDOMIZED TRIAL

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Purpose: To evaluate the long-term efficacy and toxicity of a hypofractionated (55 Gy in 20 fractions within 4 weeks) vs. a conventionally fractionated (64 Gy in 32 fractions within 6.5 weeks) dose schedule for radiotherapy (RT) for localized carcinoma of the prostate.

Methods and Materials: A total of 217 patients were randomized to either the hypofractionated (n = 108) or the conventional (n = 109) dose schedule. Most patients (n = 156) underwent RT planning and RT using a two-dimensional computed tomography method. Efficacy using the clinical, radiologic, and prostate-specific antigen data in each patient was evaluated before RT and at predetermined intervals after RT until death. Gastrointestinal and genitourinary toxicity using the modified Late Effect in Normal Tissue - Subjective Objective Management Analytic (LENT-SOMA) scales was also evaluated before and at intervals after RT to 60 months.

Results: The whole group has now been followed for a median of 90 months (range, 3–138). Of the 217 patients, 85 developed biochemical relapse (nadir prostate-specific antigen level + 2 μg/L), 36 in the hypofractionated and 49 in the conventional group. The biochemical relapse-free, but not overall, survival at 90 months was significantly better with the hypofractionated (53%) than with the conventional (34%) schedule. Gastrointestinal and genitourinary toxicity persisted 60 months after RT and did not differ between the two dose schedules. Multivariate analyses revealed that the conventional schedule was of independent prognostic significance, not only for biochemical failure, but also for an increased risk of worse genitourinary symptoms at 4 years.

Conclusions: A therapeutic advantage of the hypofractionated compared with the conventional dose schedule for RT of prostate cancer was evident at 90 months in the present study.

Radiotherapy, Prostate carcinoma, Hypofractionation, Late Effect in Normal Tissue - Subjective Objective Management Analytic toxicity scales, Quality of life.

INTRODUCTION

Although evidence of a higher dose fraction sensitivity relative to the surrounding late responding normal tissues in radiotherapy (RT) for prostate cancer has continued to accumulate (1–4), debate about whether the data are sufficiently robust for hypofractionated dose schedules to be implemented for the treatment of low- and intermediate-risk disease persists (5). Prospective data from Phase III studies of hypofractionated vs. conventionally fractionated RT for localized prostate carcinoma, including our own, have been limited by either the lack of long-term (>5 years) follow-up of patients or the use of physician-based recording of gastrointestinal toxicity (6–9), such as the Radiation Therapy Oncology Group system. The Radiation Therapy Oncology Group does not include an evaluation of anorectal symptoms such as urgency of defecation or fecal incontinence (10, 11). The lack of Level II evidence of a long-term therapeutic advantage for hypofractionated compared with conventional RT dose schedules for prostate cancer is a major obstacle to the adoption of hypofractionated dose schedules in clinical

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practice (5), particularly with the higher radiation doses prescribed with newer techniques of three-dimensional (3D) conformal RT involving intensity modulation.

We have previously reported the updated results of this Phase III randomized study comparing the efficacy and toxicity of hypofractionated vs. conventionally fractionated RT for localized prostate carcinoma (6). The original population of 217 patients has now been followed for a median of 90 months (range, 3–138). The present study reports on more mature efficacy and toxicity data and also provides new information, including freedom from biochemical relapse (FBR) using the Phoenix definition of failure and androgen suppression (hormonal)-free survival rates.

METHODS AND MATERIALS

As previously reported, the 217 patients (median age, 69 years; range, 44–82) with Stage T1-T2N0M0 (International Union Against Cancer 1992) prostate carcinoma were recruited for this single-institutional study between July 1996 and August 2003 (6).

Patient randomization was done using blocked computer-generated numbers administered by data managers to one of two radiation dose schedules (55 Gy in 20 fractions within 4 weeks; n = 108) and 64 Gy in 32 fractions within 6.5 weeks (n = 109), even after the department acquired 3D-conformal RT capability in 2001. The margins around the prostate gland for the 61 patients treated using 3D-RT were the same as for the (n = 156) patients treated with 2D RT (see below). Also, the patient numbers assigned to the two dose schedules in this subgroup were balanced (32 for the hypofractionated group and 29 for the conventional fractionation group). Because the study was initiated before categorization into the three prognostic risk groups became standard clinical practice, the patients were not stratified into the risk groups, nor was it standard practice then to use androgen deprivation therapy for high-risk disease.

RT planning

Radiotherapy planning was done using computed tomography scan data for all patients. For the patients receiving 2D-RT, the prostate was encompassed by 1.5-cm 95% isodose margins in the transverse and coronal planes (in the sagittal plane, the beam edges were set at 2 cm beyond the most cranial and caudal computed tomography slice identified anatomically as the prostate gland by the diagnostic radiologist). For the patients receiving 3D-RT, the planned target volume was derived by applying the same 1.5-cm margins around the contoured prostate gland as for 2D-RT but using the automatic expansion tool of the planning system (ADAC Pinnacle) (6). Although multileaf collimators were used to shape each radiation beam for 3D-RT, only anterior block shielding of the bowel was allowed for 2D-RT (6).

The dose was prescribed to the isocenter of the computer-generated plan for all patients, and the treatment was delivered using a predominately four-field (anteroposterior and lateral fields) external beam, megavoltage (6–23 MV) photon technique (6).

Protocol

The patients were followed at 1 month after RT completion, at 3-month intervals for the next 2 years, and at 6-month intervals for another 3 years. At 5 years after RT, the interval between follow-up visits was extended to yearly until death. Gastrointestinal (GI) and genitourinary (GU) symptoms were evaluated before RT and at each visit after RT to 5 years. Venous blood was obtained before RT and at each of 3-month, 6-month, and annual visits after RT completion for assay of the serum prostate-specific antigen (PSA) level (Abbot AXSym, Abbot Park, IL). All patients provided written, informed consent, and the Human Research Committee of the Royal Adelaide Hospital approved the study protocol.

Study method

The following GI symptoms were assessed by questionnaire: stool frequency, stool consistency, rectal pain, rectal mucous discharge, urgency of defecation, and rectal bleeding.

The scoring of each GI symptom was done using a 5- point categorical scale (0–4), or a modification of LENT-SOMA scales as previously reported (6). The effect of GI symptoms on the daily activities of the patients after RT completion was graded as follows: 0, no effect; 1, little effect but a change noted; 2, moderate effect requiring changes to daily activities; and 3, severe, practically housebound (10).

The following GU symptoms were evaluated: diurnal frequency of micturition, nocturia, hematuria, urgency of micturition, and dysuria. The scoring of each GU symptom and the effect the GU symptoms had on the daily activities of the patients after RT, was graded the same as for the GI symptoms (10).

Data analysis

The mean ± standard error and the median and range of the serum PSA level was calculated for all patients and according to the RT schedule at baseline and annually after RT. The mean ± standard error and the median and range of the nadir serum PSA level was also derived for the total patient population and for each RT schedule. The patient numbers for each of the three pretreatment PSA of <10, 11–20, and >20 μg/L and histologic prognostic subgroups of Gleason scores of 2–6, 7, and 8–10 were retrospectively determined for all patients and according to the assigned RT schedule, as previously reported (6).

The median and range of the individual and total GI and GU symptom scores were calculated for all the patients at baseline and at 1 month and annually after RT. The percentage of patients who had increases in the total GI and GU symptom scores after RT and their effect on daily activities was also determined.

Statistical analysis

The serum PSA levels at baseline, the nadir PSA and PSA levels annually after RT was analyzed using two-way repeated measures analysis of variance with a comparison of the mean values. The Friedman repeated measures analysis of variance on ranks was used to evaluate the individual and total GI and GU symptom scores at baseline and after RT and the effect GI and GU symptoms had on the daily activities of patients after RT. The unpaired t test and Mann-Whitney U test was used to compare the serum PSA values and the individual and total GI and GU symptom scores between the treatment groups, respectively. The chi-square test was used to compare the distribution of patients in each of the three pretreatment PSA and histologic prognostic sub-groups according to the assigned RT schedule and the proportion of patients with increased GI and GU symptoms after RT according to the dose schedule and treatment (2D vs. 3D) technique.

The actuarial 90-month (7.5-year) FBR (using both the Phoenix and American Society for Therapeutic Radiology Oncology (ASTRO) definitions of biochemical failure) and androgen suppression (hormonal)-free and overall survival rates for all patients was determined using the Kaplan-Meier method. The log–rank test was used