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LONG-TERM RESULTS OF A PHASE II TRIAL OF ULTRASOUND-GUIDED RADIOACTIVE IMPLANTATION OF THE PROSTATE FOR DEFINITIVE MANAGEMENT OF LOCALIZED ADENOCARCINOMA OF THE PROSTATE (RTOG 98-05)

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Purpose: To evaluate the long-term effectiveness of transrectal ultrasound–guided permanent radioactive I^{125} implantation of the prostate for organ confined adenocarcinoma of the prostate compared with historical data of prostatectomy and external beam radiotherapy within a cooperative group setting.

Methods and Materials: Patients accrued to this study had histologically confirmed, locally confined adenocarcinoma of the prostate clinical stage T1b, T1c, or T2a; no nodal or metastatic disease; prostate-specific antigen level of ≤10 ng/ml; and a Gleason score of ≤6. All patients underwent transrectal ultrasound–guided radioactive I^{125} seed implantation into the prostate. The prescribed dose was 145 Gy to the prostate planning target volume.

Results: A total of 101 patients from 27 institutions were accrued to this protocol; by design, no single institution accrued more than 8 patients. There were 94 eligible patients. The median follow up was 8.1 years (range, 0.1–9.2 years). After 8 years, 8 patients had protocol-defined biochemical (prostate-specific antigen) failure (cumulative incidence, 8.0%); 5 patients had local failure (cumulative incidence, 5.5%); and 1 patient had distant failure (cumulative incidence, 1.1%; this patient also had biochemical failure and died of causes not related to prostate cancer). The 8-year overall survival rate was 88%. At last follow-up, no patient had died of prostate cancer or related toxicities. Three patients had maximum late toxicities of Grade 3, all of which were genitourinary. No Grade 4 or 5 toxicities were observed.

Conclusions: The long-term results of this clinical trial have demonstrated that this kind of trial can be successfully completed through the RTOG and that results in terms of biochemical failure and toxicity compare very favorably with other brachytherapy published series as well as surgical and external beam radiotherapy series. In addition, the prospective, multicenter design highlights the probable generalizability of the outcomes.

Prostate, Brachytherapy, Low dose rate.

INTRODUCTION

The goal of Radiation Therapy Oncology Group (RTOG) protocol 98-05, which was written in 1998, was to evaluate the state-of-the-art brachytherapy technique (the preplanned I^{125} transperineal approach) in a multicenter protocol. This approach offered an outpatient, one-time treatment the cost and morbidity of which appeared to be reasonably low, at least from the perspective of single institutions. It was the multi-center approach that had not been tested. Given the rate at which prostate brachytherapy was being used across the United States, it was imperative that the multi-institutional trial be attempted to try to understand whether the single-institution trial results could be extended to multiple institutions.

The first report of this trial (1) was at a median follow-up of 5.3 years. At that time, 6% of the patients had biochemical failure and 5 patients had local failure, with 1 patient having evidence of distant failure. The 5-year overall survival (OS) rate was 96.7%. No patient had died of prostate cancer or related toxicities, and the maximum acute toxicity level was Grade 3, with no patient experiencing Grade 4 or 5 acute toxicity. Late toxicity reported at that time showed 2 patients

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with a maximum Grade 3 toxicity, in both cases related to genitourinary (GU) issues; no patient experienced Grade 4 or 5 toxicity. The initial report of the study suggested that this type of multi-institutional trial was successful, but the long-term results were not available.

The primary aim of this report is to evaluate the long-term effectiveness of transrectal ultrasound (TRUS)–guided permanent implantation of the prostate for organ-confined adenocarcinoma of the prostate compared with historical data for prostatectomy or external beam radiotherapy (EBRT) in a cooperative group setting. In addition, the long-term toxicity is an important aspect of this report because it allows the RTOG to prove its ability to safely and effectively evaluate brachytherapy protocols.

METHODS AND MATERIALS

Patient eligibility

Patients accrued to this trial had histologically confirmed locally confined adenocarcinoma of the prostate, clinical stage T1b, T1c, T2a, NX, N0 disease. They had a Karnofsky status of $\geq$70 and a prostate-specific antigen (PSA) that was $\leq$10 ng/ml. No patient had prior pelvic radiation, chemotherapy, or any hormonal therapy including 5α-reductase inhibitors. Maximum prostatic volume on TRUS was 45 cc. American Urological Association (AUA) obstructive sympton scoring was done and no patient was accrued to the study unless their voiding score was $\leq$18. A PSA and serum testosterone had to be done within 30 days before registration. The combined Gleason score for each patient accrued was $\leq$6. Patients were required to sign a study-specific consent form before registration. Patients who had radical surgery for their prostatic adenocarcinoma or a hip prosthesis were ineligible. Patients who had previous or concurrent cancers other than basal or squamous cell skin cancers were also ineligible unless disease free for $\geq$5 years. Patients with major medical or psychiatric illness that, in the investigators' opinion, would prevent completion of the treatment or would interfere with follow-up, were also ineligible.

No institution was allowed to enter more than 8 patients into this trial to ensure that the multi-institutional portion of the primary endpoint was satisfied. This part states that the effectiveness of TRUS-guided implantation of the prostate will be tested in the cooperative group setting, with data collection from multiple institutions to test dosimetric evaluation approaches and standard definitions and to establish quality assurance standards for future protocols.

Preimplantation ultrasound

Patients were to be placed in the dorsal lithotomy position, with care taken to ensure that the patient's spine was centered on the table and that the elevation of the legs was symmetric. TRUS was performed on each patient with a probe and stepping apparatus stabilized to the floor or to the table and the probe inserted into the rectum, such that the bottom row of the perineal template grid markers line up 1 to 2 mm inside the posterior prostate capsule. The probe was to be advanced until the base of the gland was visualized; this was designated the zero plane. Serial images of the prostate at 0.5-cm increments were to be obtained and the prostate capsule outlined on each. On each image, the grid position was to be evaluated to meet the following criteria: the grid pattern must bisect the prostate into equal right and left halves, the first row of the template position 1 to 2 mm inside the prostatic capsule at the mid gland, and the bottom row of the grid is outside of the rectal wall at all levels. Total gland volume was to be calculated automatically and displayed on the monitor. After serial imaging of the prostate, the pubic arch study was to be performed by moving the probe caudally until the pubic arch shadowing was visualized. The prostate was then traced from the image with the widest dimensions superimposed over the pubic arch image and grid lined up. The intersection of the pubic arch and the prostate cross section was then determined, and the amount of gland area that would be blocked by the pubic arch was estimated. Serial prostate images were to be mounted and delivered to the radiation physicist for dosimetric calculations.

Flexible cystoscopy, if advised by the urologist, was to be performed to check for urethral strictures or bladder pathology. Tumors had to be graded and a Gleason score provided as well as the results of pretreatment PSA and serum testosterone testing. A computed tomography (CT) scan of the pelvis was required. Lymph node evaluation was required by at least one of the following: CT or magnetic resonance imaging (MRI) of the pelvis, exploratory laparotomy, or laparoscopy with lymph node sampling. Only those lymph nodes evaluated by surgical sampling could be classified as N0; those evaluated by imaging were classified as NX. An AUA symptom score was obtained for each patient, and quality-of-life questionnaires had to be filled out before the implantation. The questionnaires used for this trial were Functional Assessment of Cancer Therapy - Prostate FACT-P and Sexual Adjustment Questionnaire SAQ; these results were described previously (2).

Radiation therapy

Target volume definitions were based on the ICRU report 58, dose and volume specification for reporting interstitial therapy (3). The clinical target volume (CTV) was defined as the pre-implant TRUS definition of the prostate. The planning target volume (PTV) was attained by enlargement of the CTV as follows:

1. Expand the TRUS definition of the prostate by 2 to 3 mm in the lateral dimension for each TRUS axial image. Thus the lateral dimensions of the prostate will be increased by approximately 5 mm.
2. Expand the transrectal definition of the prostate by 2 to 3 mm in the anterior dimension for each TRUS axial image.
3. Maintain the same posterior border of the prostate as defined by the TRUS.
4. Project and expand the most cephalad axial definition of the prostate to a plane 5 mm cephalad to the most cephalad TRUS plane.
5. Project and expand the most caudal axial definition of the prostate on ultrasound to a plane 5 mm caudal to the most caudad TRUS plane. Thus the PTV is approximately 10 mm longer in the cephalad caudad dimension than the CTV.

Evaluation target volume

The evaluation target volume (ETV) is defined as the postimplantation CT definition of the prostate (the ETV concept is not found in the ICRU report.)

Seed calibration handling

Only I^{125}, model 6711, seeds were to be used. The seeds were to be received and inventoried according to each institution's policies and procedures in a manner consistent with federal or state regulations. A random sampling of at least 10% of the seeds was to be calibrated in a manner such that there was a direct traceability to either the National Institute of Standards and Technology (NIST) or American Association of Physicists in Medicine (AAPM) Accredited Dosimetry Calibration Laboratory (ADCL) for the I^{125} seeds, as described by AAPM report TG40 (Task Group 40 of the AAPM),