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CLINICAL INVESTIGATION **Genitourinary Cancer**

HYPOFRACTIONATED CONCOMITANT INTENSITY-MODULATED RADIOTHERAPY BOOST FOR HIGH-RISK PROSTATE CANCER: LATE TOXICITY

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Purpose: To report the acute and late toxicities of patients with high-risk localized prostate cancer treated using a concomitant hypofractionated, intensity-modulated radiotherapy boost combined with long-term androgen deprivation therapy.

Methods and Materials: A prospective Phase I-II study of patients with any of the following: clinical Stage T3 disease, prostate-specific antigen level ≥20 ng/mL, or Gleason score 8–10. A dose of 45 Gy (1.8 Gy/fraction) was delivered to the pelvic lymph nodes with a concomitant 22.5 Gy prostate intensity-modulated radiotherapy boost, to a total of 67.5 Gy (2.7 Gy/fraction) in 25 fractions within 5 weeks. Image guidance was performed using three gold seed fiducials. The National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, and Radiation Therapy Oncology Group late morbidity scores were used to assess the acute and late toxicities, respectively. Biochemical failure was determined using the Phoenix definition.

Results: A total of 97 patients were treated and followed up for a median of 39 months, with 88% having a minimum of 24 months of follow-up. The maximal toxicity scores were recorded. The grade of acute gastrointestinal toxicity was Grade 0 in 4%, 1 in 59%, and 2 in 37%. The grade of acute urinary toxicity was Grade 0 in 8%, 1 in 50%, 2 in 39%, and 3 in 4%. The grade of late gastrointestinal toxicity was Grade 0 in 54%, 1 in 40%, and 2 in 7%. No Grade 3 or greater late gastrointestinal toxicities developed. The grade of late urinary toxicity was Grade 0 in 82%, 1 in 9%, 2 in 5%, 3 in 3%, and 4 in 1% (1 patient). All severe toxicities (Grade 3 or greater) had resolved at the last follow-up visit. The 4-year biochemical disease-free survival rate was 90.5%.

Conclusions: A hypofractionated intensity-modulated radiotherapy boost delivering 67.5 Gy in 25 fractions within 5 weeks combined with pelvic nodal radiotherapy and long-term androgen deprivation therapy was well tolerated, with low rates of severe toxicity. The biochemical control rate at early follow-up has been promising. Additional follow-up is needed to determine the long-term biochemical control and prostate biopsy results.

Prostatic neoplasms, Radiotherapy, Intensity-modulated radiotherapy, Hypofractionation, Radiation injuries.

INTRODUCTION

High-risk, locally advanced, prostate cancer has been associated with poor outcomes, necessitating a multimodality approach to therapy. Currently, one of the standard treatment options for high-risk disease is the combination of radiotherapy (RT) with long-term androgen deprivation therapy (ADT) (1, 2). In studies not using long-term ADT, dose-escalated RT in conventional 1.8–2-Gy fractions has been shown to improve biochemical disease-free survival (bDFS) (3, 4).

During the past decade, evidence has emerged suggesting that prostate cancer has a low α/β ratio, estimated in the range of 1–3 Gy (5, 6). As a result, prostate cancer has a greater sensitivity to large fraction sizes. Comparatively, the dose-limiting organs at risk (OAR) have been classically thought to have an α/β ratio of 3–4. The lower α/β ratio of prostate cancer relative to the adjacent OARs has been the

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basis for the potential of hypofractionation to improve tumor control without increasing the risk of late effects.

Most prostate hypofractionation trials have focused on RT of the prostate gland itself. However, patients with locally advanced disease have a high risk of nodal involvement. Although the use of pelvic lymph node RT has continued to be controversial, randomized data have supported its use (7). In addition, most of the randomized trials showing the benefit of combining long-term ADT and RT have used whole pelvis RT (1, 2).

The present report describes the late toxicity of a prospective, Phase I-II trial combining whole pelvis RT, a dose-intensified hypofractionated prostate boost, and long-term ADT in patients with localized, high-risk prostate cancer. The acute toxicity was previously reported for the initial cohort treated with pelvic three-dimensional conformal radiotherapy (3D-CRT) and a concomitant intensity-modulated radiotherapy (IMRT) boost to the prostate (8). In the present study, we report the late toxicity, with the addition of another cohort of patients treated with a single-phase IMRT technique.

METHODS AND MATERIALS

Study design

This was a single-institution, prospective, Phase I-II clinical trial. The research ethics board of the Sunnybrook Health Sciences Centre approved the study, and all eligible patients provided written informed consent.

Patient population

Eligible patients had histologically confirmed prostate cancer with at least one of the following high-risk features: clinical Stage T3 (2002 American Joint Committee on Cancer staging system), prostate-specific antigen level ≥20 but <100 ng/mL, and Gleason score 8–10. Exclusion criteria included lymph node involvement, distant metastases, previous RT to the pelvis, active collagen vascular disease, active inflammatory bowel disease, ataxia telangiectasia, bleeding diathesis or the use of anticoagulation therapy (precluding the insertion of gold seed fiducials into the prostate), or the presence of a hip prosthesis.

The pretreatment evaluation consisted of a complete history, digital rectal examination, whole body bone scan, computed tomography (CT) scan of the abdomen and pelvis, and blood work, including serum prostate-specific antigen and testosterone measurements and liver function tests.

Treatment planning

All patients underwent transrectal ultrasound-guided insertion of three gold fiducial markers (1.2 mm in diameter and 3 mm in length) into the prostate ≥1 week before CT simulation.

Two cohorts of patients were sequentially enrolled into the present study. The first cohort (3D+IMRT cohort) was treated with using a pelvic four-field 3D-CRT technique, with a concomitant boost using IMRT to the prostate and lower seminal vesicles (SVs). A second cohort of patients, treated with a single-phase IMRT technique (IMRT cohort) to the pelvic lymph nodes and prostate, was subsequently enrolled.

The patients were immobilized in the supine position with a vacuum-based device (VacLoc, Med-Tec, Orange City, IA). The 3D+IMRT cohort underwent treatment simulation and treatment with an empty bladder and rectum, according to institutional policy. In accordance with a change in practice, the patients in the IMRT cohort were instructed to have a comfortably full bladder and empty rectum. CT simulation was performed with 1.5-mm spacing and a 1.5-mm slice thickness.

The target volumes and OAR were similar for both cohorts. The OARs were contoured as solid structures and included the rectum, bladder, and femoral heads. The rectum was contoured from the inferior ischial tuberosities to the rectosigmoid flexure (typically 11 cm). In the 3D+IMRT cohort, the clinical target volume (CTV) for the pelvis (CTV_{pelvis}) included the distal common iliac, external iliac, internal iliac, upper presacral, and obturator lymph nodes, prostate gland, and SVs. Although not mandated by the protocol, contouring the pelvic vessels to aid in defining the field borders and shielding was performed by some physicians. However, the fields were not permitted to be smaller than described in the protocol according to the classic bony landmarks. An isotropic 10-mm margin added to the prostate and SVs was included in the pelvic RT. The CTV for the boost included the prostate and lower 10 mm of the SVs. If clinical involvement of either SV was found, both SVs were included in their entirety. In accordance with a previous study of intrafraction motion in the setting of daily image-guided RT (9), a uniform 4-mm margin was added to create the planning target volume (PTV) for the boost to the prostate.

In the IMRT cohort, the pelvic nodal volumes included in the CTV_{pelvis} were contoured according to Shih *et al.* (10) to encompass a 2.0-cm radial expansion around the distal common iliac and proximal external and internal iliac vessels. The prostate and SVs were included in the CTV_{pelvis}, with a uniform 10-mm margin. The PTV for the pelvis included a 6-mm margin around the CTV_{pelvis}. Also, the CTV and PTV boost volumes were the same as for the 3D+IMRT cohort.

Pelvic 3D-CRT with concomitant IMRT boost (3D+IMRT cohort)

Treatment planning for the 3D+IMRT cohort has been previously described (8). In brief, a four-field 3D-CRT plan was designed to deliver 45 Gy in 25 fractions to the pelvic lymph nodes using the classic bony landmarks. The IMRT prostate boost was created with seven to nine fields to concomitantly deliver an additional 22.5 Gy in 25 fractions to the prostate. Thus, the total dose to the prostate was 67.5 Gy in 25 fractions. Assuming an α/β ratio of 1.5 Gy, this would deliver a bioequivalent dose of approximately 81 Gy in 2-Gy fractions.

Single-phase IMRT technique (IMRT cohort)

For the IMRT cohort, IMRT plans using seven to nine fields were created using the Pinnacle system (Philips, Andover, MA). As for the 3D+IMRT cohort, the pelvic lymph nodes received 45 Gy in 25 fractions, and a concomitant IMRT boost of 22.5 Gy was delivered to the prostate.

RT planning objectives

The dose constraints for the 3D+IMRT cohort have been previously described (8). The objectives for the IMRT cohort were to ensure that 45 Gy was delivered to ≥99% of the CTV_{pelvis} and 42.8 Gy to ≥99% of the PTV for the pelvis. Similarly, 67.5 Gy was to be delivered to ≥99% of the CTV for the boost and 64.1 Gy to ≥99% of the PTV for boost. A maximal dose of 70.8 Gy was allowed to <5% of the PTV boost. The dose constraints for the