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CLINICAL INVESTIGATION **Prostate**

INTENSITY-MODULATED RADIOTHERAPY AS PRIMARY THERAPY FOR PROSTATE CANCER: REPORT ON ACUTE TOXICITY AFTER DOSE ESCALATION WITH SIMULTANEOUS INTEGRATED BOOST TO INTRAPROSTATIC LESION

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Purpose: To report on the acute toxicity of a third escalation level using intensity-modulated radiotherapy for prostate cancer (PCa) and the acute toxicity resulting from delivery of a simultaneous integrated boost (SIB) to an intraprostatic lesion (IPL) detected on magnetic resonance imaging (MRI), with or without spectroscopy.

Methods and Materials: Between January 2002 and March 2007, we treated 230 patients with intensity-modulated radiotherapy to a third escalation level as primary therapy for prostate cancer. If an IPL (defined by MRI or MRI plus spectroscopy) was present, a SIB was delivered to the IPL. To report on acute toxicity, patients were seen weekly during treatment and 1 and 3 months after treatment. Toxicity was scored using the Radiation Therapy Oncology Group toxicity scale, supplemented by an in-house–developed scoring system.

Results: The median dose to the planning target volume was 78 Gy. An IPL was found in 118 patients. The median dose to the MRI-detected IPL and MRI plus spectroscopy-detected IPL was 81 Gy and 82 Gy, respectively. No Grade 3 or 4 acute gastrointestinal toxicity developed. Grade 2 acute gastrointestinal toxicity was present in 26 patients (11%). Grade 3 genitourinary toxicity was present in 15 patients (7%), and 95 patients developed Grade 2 acute genitourinary toxicity (41%). No statistically significant increase was found in Grade 2-3 acute gastrointestinal or genitourinary toxicity after a SIB to an IPL.

Conclusion: The results of our study have shown that treatment-induced acute toxicity remains low when intensity-modulated radiotherapy to 80 Gy as primary therapy for prostate cancer is used. In addition, a SIB to an IPL did not increase the severity or incidence of acute toxicity. © 2008 Elsevier Inc.

Intensity-modulated radiotherapy, IMRT, Prostate cancer, Simultaneous integrated boost, SIB, Intraprostatic lesion, Acute toxicity.

INTRODUCTION

For prostate cancer (PCa), several randomized trials have shown better biochemical no evidence of disease (bNED) with greater doses (1–7). At a dose >68 Gy, the absolute gain in the bNED rate when increasing the dose to the prostate by 8–10 Gy has varied from 10% (3) to 23% (7) at 5–10 years. Nevertheless, prostate-specific antigen failure is observed in 8–27% of patients treated to greater doses, with actuarial local failure rates of ≤33% (2). Isolated local failure is of clinical importance, because a relationship between local control and distant metastasis (8, 9) and survival (10) has been suggested.

On the basis of these data, we started to treat the prostate to greater doses. Between 1996 and 2001, two prescriptions were launched: 74 Gy and 76 Gy as a median dose to the planning target volume (PTV) of the prostate with or without the seminal vesicles. Both dose levels have been proved safe in terms of acute and late toxicity and provide excellent biochemical control (11–13). We initiated a third dose-escalation level in 2002, in which we treated the PTV to 78 Gy while keeping the maximal rectal dose at 76 Gy (hard constraint, IMRT_78_R76).

Cellini *et al.* (14) demonstrated that intraprostatic failure mainly originates at the initial tumor location as a result of intrinsic resistance of a fraction of the tumor clones. Consequently, we hypothesized that targeting this location with even greater doses could increase local control. Therefore, we delivered IMRT_78_R76 plus a simultaneous integrated boost (SIB) to the intraprostatic lesion (IPL). Few data have been published on the planning feasibility of delivering

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a SIB to the IPL (15, 16). We have demonstrated the feasibility of implementing a SIB to a magnetic resonance imaging (MRI)-detected IPL (IPL_M), without compromising the dose to the rest of the PTV and without increasing the dose to the surrounding organs at risk (17).

In this paper, we report on the acute toxicity after a dose escalation to IMRT_78_R76 and the acute toxicity after IMRT_78_R76 with a SIB to the IPL.

METHODS AND MATERIALS

Between January 2002 and March 2007, 230 patients were treated with IMRT_78_R76 as primary therapy for PCa Stage T1-T4N0M0 at Ghent University Hospital.

The T stage was determined by digital rectal examination and the 1997 American Joint Committee on Cancer staging criteria (18). Additional T-stage information obtained from MRI was not used, because MRI staging has not yet been incorporated into the TNM staging system. Adjuvant androgen deprivation, consisting of a luteinizing hormone-releasing hormone analogue, was given for 6 months for intermediate-risk PCa (Gleason score 6 or 7 [3+4] or prostate-specific antigen level $\geq$10.0 ng/mL but <20 ng/mL or Stage T2a) and for 2–3 years for poor-risk PCa (Gleason score $\geq$7 [4+3], a prostate-specific antigen level of $\geq$20.0 ng/mL, or Stage T2b-T4). The details have been previously published (19, 20).

Pretreatment imaging consisted of computed tomography (CT) in all patients and MRI in all but 9 patients. Details concerning the pretreatment imaging modalities have been previously published (11, 12).

Pelvic phased-array coil MRI

The MRI scans used for image fusion and planning were acquired on a 1.5 Tesla MRI scanner (Magnetom Symphony, Siemens, Erlangen, Germany), using T_1-weighted gradient echo localizer sequences, followed by 4-mm-thick transverse, sagittal, and coronal T_2-weighted turbo-spin echo images (repetition time/excitation time, 4,600/89 ms) using a pelvic phased-array coil. To facilitate image fusion for delineation, all patients were scanned in the treatment position, with the pelvis positioned in the isocenter of the magnet and with the same preparation as for CT (*i.e.,* after active emptying of the rectum) (21) and with a filled bladder. The diagnostic criteria suggestive of malignancy on the T_2-weighted images were an inhomogeneous, irregular, low-signal intensity lesion with unclear margins or diffuse extension and mass effect. Linear, wedge-shaped, or oval low-signal intensity lesions were considered nonmalignant (22).

Magnetic resonance spectroscopy with endorectal coil

All spectroscopic data were acquired on the same 1.5 Tesla scanner using a combined pelvic phased-array coil with a balloon-covered endorectal coil (MRInnervu, Medrad, Pittsburgh, PA) inflated with 60 cm^3 of air. The fast T_2-weighted imaging parameters were as follows: 4-mm thickness without an interslice gap, transverse, coronal, and sagittal orientation, repetition time/excitation time of 4,400/139 ms. Three-dimensional chemical shift imaging magnetic resonance spectroscopy (MRS) was performed using a nominal voxel size of $6 \times 6 \times 6$ mm^3, matrix size of 16^3, and repetition time/excitation time of 650/120 ms (23). The spectra were postprocessed, and spectral maps were obtained. Two or more adjacent voxels at which the height of the choline+creatine peak was higher than the citrate peak were suggestive of an IPL. In contrast, voxels at which the choline+creatine peak was equal to or smaller than the citrate peak were considered normal (24). Because of the negative effect of androgen deprivation on the cellular metabolism of the prostate and PCa cells, MRS examinations were only performed in the absence of, or before, any form of androgen deprivation (25). The clinical target volume (CTV), PTV, and organs at risk were defined as previously described (11, 26). Using the Syntegra software packet for image fusion (Syntegra, version 1.2b, Philips Medical Systems, Cleveland, OH), the CT and MRI scans were fused with alignment determined by the pelvic bone structures and prostate anatomy.

For the MRS images, an off-line fusion with the CT scans was performed. To define an IPL, the MRI and MRS films were used. The IPL was referred to as IPL_M or IPL_S when it was defined on ''morphologic'' MRI or ''spectroscopic'' images, respectively. Figure 1 shows the number of patients who underwent MRI and MRS and the number of patients in whom an IPL_M and/or IPL_S was detected. The detected IPL was used for delineation and SIB.

The CTV was delineated using the fused MRI and CT images in consensus reading with a radiologist. The PTV was created using an isotropic expansion of 4 mm. Identical to the delineation of the CTV and organs at risk, the delineation of the IPL was done in consensus reading with the same radiologist.

In all cases, three beams around the PTV with gantry angles of 0°, 116°, and 244° were used, and the dose was described as a median dose to the PTV of 78 Gy in 38 fractions (third escalation level). The maximal rectal dose was set as a hard constraint at 76 Gy. The planning endpoints were achieved using anatomy-based beam segmentation (27) and direct aperture and weight optimization (SOWAT) (28, 29). The organs at risk were the rectum, sigmoid colon, bladder, small bowel, and femoral heads (26). Details concerning the planning constraints for the CTV, PTV, and organs at risk are listed in Table 1.

When an IPL was delineated, three additional beams (gantry angles of 0°, 116°, and 244°) were created around the IPL with 8-mm margin. If more than one IPL was present, these three additional beams were created per IPL, unless these beam outlines interacted in the beam's eye view. In such a situation, the beam aperture encompassed the different IPLs. SOWAT (29) was also applied to the IPL beams. We prescribed 80 Gy as a median dose to the IPL, to be delivered in 38 fractions (Fig. 2).

All patients were treated with a step-and-shoot technique using 18-MV photons and an Elekta linear accelerator (Crawley, UK) equipped with a multileaf collimator. For all patients, daily ultrasound-based prostate positioning was used to correct the prostate positioning (30). All patients were treated in the supine position, with the knees and ankles fixed (Sinmed, Cablon Medical, Leusden, The Netherlands). The patients were instructed to use a daily rectal suppository and to have a comfortably filled bladder (21).

At the patients' first admission to our department, a fixed questionnaire was used to register the medical and surgical history (Crohn's disease, colitis, irritable bowel disease, diabetes, hypertension, nicotine abuse, hemorrhoids, and previous—nonprostate-related—abdominal surgery) and pretreatment lower intestinal/rectal and urinary symptoms. To score the acute RT-induced toxicity, the patients were seen weekly during RT and at 1 and 3 months after RT. The gastrointestinal (GI) and genitourinary (GU) toxicity was recorded at each visit using the Radiation Therapy Oncology Group (RTOG) toxicity scale (31), supplemented by an in-house–developed symptom scale (11). Even if a symptom occurred only once during treatment, we scored it as a RT-induced toxicity. This is in discordance with other groups, who registered a symptom as RT-induced toxicity only if the event occurred twice or more (4).

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