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CLINICAL INVESTIGATION **Prostate**

INTENSITY-MODULATED RADIOTHERAPY OF PELVIC LYMPH NODES IN LOCALLY ADVANCED PROSTATE CANCER: PLANNING PROCEDURES AND EARLY EXPERIENCES

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Purpose: We present planning and early clinical outcomes of a study of intensity-modulated radiotherapy (IMRT) for locally advanced prostate cancer.
Methods and Materials: A total of 43 patients initially treated with an IMRT plan delivering 50 Gy to the prostate, seminal vesicles, and pelvic lymph nodes, followed by a conformal radiotherapy (CRT) plan delivering 20 Gy to the prostate and seminal vesicles, were studied. Dose–volume histogram (DVH) data for the added plans were compared with dose–volume histogram data for the sum of two CRT plans for 15 cases. Gastrointestinal (GI) and genitourinary (GU) toxicity, based on the Radiation Therapy Oncology Group scoring system, was recorded weekly throughout treatment as well as 3 to 18 months after treatment and are presented.
Results: Treatment with IMRT both reduced normal tissue doses and increased the minimum target doses. Intestine volumes receiving more than 40 and 50 Gy were significantly reduced (e.g., at 50 Gy, from 81 to 19 cm^3; $p = 0.026$), as were bladder volumes above 40, 50, and 60 Gy, rectum volumes above 30, 50, and 60 Gy, and hip joint muscle volumes above 20, 30, and 40 Gy. During treatment, Grade 2 GI toxicity was reported by 12 of 43 patients (28%), and Grade 2 to 4 GU toxicity was also observed among 12 patients (28%). With 6 to 18 months of follow-up, 2 patients (5%) experienced Grade 2 GI effects and 7 patients (16%) experienced Grade 2 GU effects.
Conclusions: Use of IMRT for pelvic irradiation in prostate cancer reduces normal tissue doses, improves target coverage, and has a promising toxicity profile. © 2008 Elsevier Inc.

Prostate cancer, Lymph node irradiation, Intensity-modulated radiotherapy, Inverse planning, Acute effects.

INTRODUCTION

Experience with conformal radiotherapy (CRT) for prostate cancer treatment has shown that reducing normal tissue irradiation leads to lower rates of gastrointestinal (GI) and genitourinary (GU) normal tissue toxicity (1–4). This has spurred efforts to achieve further sparing of organs at risk (OARs) to allow for dose escalation, in particular with the introduction of intensity-modulated radiotherapy (IMRT). Prostate cancer has been the major IMRT test site, mainly investigated as a treatment option for patients with localized disease where the prostate or prostate and seminal vesicles are the targets. For prostate cancer patients at high risk for involvement of pelvic lymph nodes, the Radiation Therapy Oncology Group (RTOG) 9413 trial documented an improved progression-free survival for these patients if the pelvic lymph nodes were irradiated (5). Compared with localized fields, however, pelvic irradiation carries the risk of increasing adverse effects rates, in particular for the intestine

(5–8). Although the typical shape of the lymph node target calls for use of IMRT (with the planning target volume very close to the intestine), relatively few institutions have yet reported on the application of IMRT for this subset of prostate cancer patients (9–14). We have implemented IMRT for this patient group with the aim of reducing the normal tissue doses and toxicity, in particular those related to intestine irradiation. In this report we present our procedures for target volume definitions, optimization criteria, and field arrangements as well as our early experiences in terms of resulting dose distributions and toxicities.

METHODS AND MATERIALS

Patients

Patient accrual to our prostate pelvic IMRT study started in September 2005; and as of January 2007, 43 patients had completed their RT course. Lymph node irradiation was indicated for patients with either stage T3 or N+ disease (15). The clinical staging of the

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primary tumor was performed according to the 2002 TNM classification for prostate cancer (16), and the histopathologic specimens were graded according to the Gleason pattern score (17). Patients with distant metastases were excluded if positive findings were present in the routine bone scan. All patients were at high risk according to the criteria of Zelefsky *et al.* (2) and were given endocrine therapy consisting of a 6-months course of luteinizing hormone–releasing hormone analogue and antiandrogen (maximal androgen blockade). Endocrine therapy commenced 2 to 3 months post-RT to exploit the reduction of the prostate volume, and continued 3 to 4 months after the start of RT (18). Relevant patient and tumor characteristics are shown in Table 1.

Computed tomographic scanning and definitions of targets and normal tissues

All patients underwent computed tomography (CT) scanning (Prospeed SX Power, GE Medical Systems, Milwaukee, WI) and were subsequently treated in supine position using knee and ankle fixation cushions (Sinmed BV, Reeuwijk, The Netherlands) for immobilization. The CT scans extended from the L3/L4 vertebrae down to the level of the perineum, with 5-mm thick slices with 5-mm intervals. Using our Eclipse treatment planning system (Varian Oncology Systems, Palo Alto, CA) the responsible oncologist contoured the prostate gland, the seminal vesicles, and the relevant lymph nodes, and produced two sets of clinical target volumes (CTV1 and CTV2) for the first and second treatment phases, respectively. Both CTV1 and CTV2 contained the prostate and the seminal vesicles, whereas CTV1 also included pelvic lymph nodes, defined individually in each patient. In most cases it encompassed the internal and external iliac vessels and a rim ~2.5 cm wide area along the pelvic wall between these vessels. The presacral nodes were not included. Positive para-aortic lymph nodes were considered as distant metastases. For both PTV1 and PTV2, a total margin of 15 mm was applied around the prostate and seminal vesicles, except posteriorly, where a 10-mm margin was used. No target localization technique was used during treatment, but a portal imaging protocol reducing systematic setup errors was followed, as explained later here. The lymph nodes that were encompassed in PTV1 were included with a 10-mm margin to account for delineation

uncertainty and setup accuracies; their internal motion was assumed to be negligible.

The responsible oncologist also outlined the relevant OARs, including intestine, bladder, rectum, penile bulb, hip joints, hip joint muscles (gluteus maximus and minimus) and bony structures. The intestine volume included all identifiable small and large intestine segments, not including the rectum. The bladder was outlined from apex to dome, whereas the rectosigmoid flexure was applied as the superior/cranial limit of the rectum and the anal verge as the inferior/caudal limit. Both the rectum and bladder were defined as the volumes within the respective outer wall contour, including contents. The outlined hip joint structure included 5 mm on both sides of the joint itself. The intestine, bladder, and rectum volumes were used actively in the optimization, as these were considered to be the dose-limiting OARs. All volumes were based on the planning scan situation only, and no attempts were made to account actively for the motion of these organs; this issue is the topic for ongoing projects at our institution.

Field arrangements and optimization criteria

The RT course for all patients consisted of an initial IMRT plan delivering 50 Gy to PTV1 (prostate, seminal vesicles, and lymph nodes with margins) followed by a four-field CRT plan delivering 20 Gy to PTV2 (prostate and seminal vesicles with margins), both plans delivered in daily 2-Gy fractions, 5 days per week. For the IMRT plan used in the first phase of the treatment (to 50 Gy), a seven-field beam arrangement with gantry angles 0°, 51°, 103°, 154°, 206°, 257°, and 309° was applied for all patients because of the complexity of the PTV shape, using in most cases 15-MV photon beam quality. A collimator angle of 2° was used for all beams to reduce tongue-and-groove effects. The same isocenter was used throughout treatment, including the four-field conformal plan used for the second phase (the last 20 Gy). All treatment planning and optimization was performed using Eclipse. Patients were treated on one of three Varian Clinacs, all equipped with a Millennium MLC-120 multileaf collimator. Intensity modulation was achieved using the sliding window technique.

During the optimization, the minimum PTV1 dose criterion was given the highest priority. To ensure adequate target coverage (aiming for a minimum point dose of 95% in the PTV1), the optimization criteria for PTV1 were applied on an enlarged volume, the PTV1 extended with 3 mm in the anterior/posterior/left/right directions and 5 mm in the superior/inferior directions. Good dose conformality was secured by reducing as far as possible the volume outside the extended PTV1 that received more than 95% of the target dose. For the main OARs (the intestine, bladder, and rectum), the optimization criteria were based on what could be achieved with a traditional conformal four-field plan for the PTV1. For all patients this conformal plan consisted of two opposing anterior and posterior beams and two opposing lateral beams (gantry angles 0°, 90°, 180°, and 270°), with the multileaf collimator shapes conforming to the projections of the PTV1. In the optimization we aimed to reduce the volumes of these organs receiving doses greater than 30, 40, and 50 Gy. For each individual patient we applied DVH points corresponding to 50%, 25%, and 25% volume reductions relative to this four-field CRT plan as initial DVH constraints for the intestine, rectum, and bladder, respectively, reflecting our aim to prioritize reduction of intestinal doses.

Analysis of dose–volume histograms

Dose–volume histograms (DVHs) were calculated for the IMRT plan up to 50 Gy, as well as for the total treatment plan (to 70 Gy),

Table 1. Characteristics of study patients

No. of patients	43
Median age (years)	66
Age range (years)	66
Concurrent cardiovascular disease	14 (33%)
Clinical stage	
T1	0
T2	3 (7%)
T3	36 (84%)
T4	3 (7%)
Tx	1 (2%)
Gleason sum	
≤6	7 (16%)
≥7	33 (77%)
Unknown	3 (7%)
PSA (ng/l)	
<4	2 (4%)
4–10	11 (26%)
10.1–20	11 (26%)
>20	19 (44%)
Endocrine treatment	43 (100%)

Abbreviation: PSA = prostate-specific antigen.

for all defined volumes (i.e., intestine, bladder, rectum, penile bulb, hip joints, and hip joint muscles) in the 15 patients treated consecutively between February and July 2006. To quantify the benefit of the IMRT plans actually applied, we also calculated the corresponding DVHs for the traditional conformal plan both for the initial phase and both phases combined, using the same dose prescription protocol.

Patient-specific quality assurance

For all patients included in this study we verified experimentally both the absolute dose in a dedicated IMRT phantom as well as the fluency of the individual treatment fields. To allow absolute dose verification, dose calculations were performed in Eclipse by transferring the treatment fields used for the patient onto a CT study of a dedicated IMRT phantom (Universal IMRT verification phantom, type 40020, PTW, Freiburg, Germany), positioning the fields to enable the active detector volume to be inside the high-dose volume. The gantry and collimator angles of all beams were reset to $0°$, and the absolute calculated dose resulting from each individual field was recorded. Absolute dose measurements were performed by delivering these IMRT fields when having a PTW 0.125 cm^3 ionization chamber in one of the detector slots, measuring the dose delivered by each individual field. All patients except 2 with marginal violations fulfilled the acceptance criteria of 4% used on the total absolute dose, with a mean dose difference of $-0.6\% \pm 1.5\%$. For the last 31 patients the dose calculation accuracy was improved, and the total dose measured in the initial attempt was within 3.2% of calculations and within 2% for 29 of these patients.

The fluency verification was performed field by field using the Varian Portal Vision amorphous silicone detector (aS500 and aS1000, Varian Medical Systems) positioned in 105-cm source-to-detector distance, and delivering the actual treatment beams onto the detector plate. The measured intensity distribution for each field was compared with the predicted fluency distribution, derived using the pencil beam Portal Dose Prediction software integrated in the Eclipse/Vision system (19). A gamma evaluation tool, incorporating both differences in dose relative to the maximum dose as well as distance to agreement, was used with acceptance criteria of 4% in dose difference and 4-mm in distance to agreement for 99% of the detector area. For some patients the comparison was performed after normalization of the fluencies because of problems with the calibration for one of the detectors. The acceptance criteria were then reduced to 3% and 3 mm. With this approach, these criteria were fulfilled in all patients except one field in 1 patient. Ion chamber verification alone was performed in 2 patients because of technical problems with one of the detectors.

Patient positioning

All patients followed the patient positioning procedures that we apply for all radically treated RT patients (except those receiving daily on-board imaging-based adaptive RT), with front and lateral electronic portal images acquired daily over the first four treatment fractions followed by weekly imaging for the remaining part of the treatment course. Bony structures in the portal images were matched to the bony anatomy in the digitally reconstructed radiographs.

Toxicity scoring

The RTOG toxicity scoring system was used to grade lower GI and GU morbidity during and after the course of treatment (20). Patients were scheduled for weekly assessments of symptoms during the course of therapy (after 10, 20, 30, 40, 50, 60, and 70 Gy) by the responsible oncologist in Weeks 3 and 6, and by the

radiographers at the treatment unit in the remaining weeks; consistency was secured by thorough instructions/training of the involved radiographers (by the responsible oncologist). For practical reasons, the acute effects were scored on average five times during treatment; 19 of the 43 patients were seen seven times. In addition patients were enrolled onto a 5-year follow-up scheme, with the first session scheduled 3 months after treatment. Anal symptoms were scored using the modified scoring system of Koper *et al.* (21), and were joined with the GI score. In general the GI or GU symptoms that needed medical prescriptions were scored as Grade 2 or greater toxicity. By end of July 2007, all cases had at least 6 months of follow-up time; 21 patients had been seen 12 months post-RT and 2 had been seen 18 months post-RT. The symptoms reported on these follow-up sessions will be presented here.

RESULTS

DVH analysis

The changes in normal tissue doses resulting from use of IMRT instead of CRT (for the first phase of treatment) are shown in Table 2, comparing DVH parameters for both phases of the treatment combined. Intestine, bladder, and rectum DVH constraints were included in the optimization, and hence the largest and most systematic changes were seen for these three organs as well as the hip joint muscles. For the intestine, the use of IMRT led to a considerable decrease in the absolute volumes receiving doses greater than 40 to 60 Gy; e.g., at 50 Gy, the average volume decreased from 81 to 19 cm^3 ($p < 0.001$). However there was an increase in the volumes receiving doses greater than 20 Gy. For the bladder, we also obtained considerable volume reductions for the doses in the range of 40 to 60 Gy (e.g., from 87% to 64% >50 Gy). For this organ, there was also a small but statistically significant increase in volumes receiving more than 70 Gy. The volumes of rectum above all dose levels from 20 Gy to 60 Gy were reduced with IMRT, and again the difference seemed to be largest at the level of 50 Gy. With either technique, only a very small part of the rectum received 70 Gy in approximately one third of the patients. Regarding the three other OARs that were not included in the optimization, use of IMRT led to a slight increase in doses to the penile bulb and the hip joints but reduced the doses to the hip joint muscles. For the penile bulb there was an increase in the volumes receiving more than 60 Gy, which probably resulted from the close proximity between this structure and the target volumes. For the hip joints, use of IMRT increased volumes receiving more than 40 to 50 Gy, whereas the volumes of the hip joint muscles receiving more than 20 to 40 Gy decreased considerably.

For the target volumes (both PTV1 and PTV2), use of IMRT increased the average minimum target doses (from 45.5 to 47.4 Gy for PTV1, $p < 0.001$, and from 62.2 to 64.6 Gy for PTV2, $p < 0.001$). The same mean dose was prescribed for both techniques, but as the dose was normalized to the ITV, the mean doses in the PTVs increased slightly after the improved coverage of the PTVs.

Table 2. Comparison of dose–volume histogram (DVH) parameters for intestine, bladder, rectum, penile bulb, hip joints and hip joint muscles for the total treatment (both phases) for conformal radiotherapy (CRT) versus intensity-modulated radiotherapy (IMRT) plans

DVH parameter	CRT	IMRT	*p* Value
Intestine (cm^3)			
Volume >20 Gy	264 (54-628)	281 (63–678)	0.005
Volume >30 Gy	177 (46–459)	182 (38–483)	0.13
Volume >40 Gy	139 (32–328)	89 (18–248)	<0.001
Volume >50 Gy	81 (2–214)	19 (0–77)	<0.001
Volume >60 Gy	3 (0–29)	2 (0–20)	0.043*
Volume >70 Gy	0	0	—
Bladder (%)			
Volume >20 Gy	100 (100–100)	100 (100–100)	0.32*
Volume >30 Gy	100 (95–100)	98 (94–100)	0.02
Volume >40 Gy	95 (79–100)	84 (67–100)	<0.001
Volume >50 Gy	87 (64–100)	64 (32–98)	<0.001
Volume >60 Gy	54 (21–95)	45 (18–83)	<0.001
Volume >70 Gy	0 (0–1)	1 (0–5)	0.007*
Rectum (%)			
Volume >20 Gy	98 (93–100)	97 (92–100)	<0.001
Volume >30 Gy	96 (89–100)	94 (85–99)	<0.001
Volume >40 Gy	84 (71–92)	75 (62–89)	<0.001
Volume >50 Gy	67 (45–88)	51 (34–67)	<0.001
Volume >60 Gy	36 (23–51)	29 (17–39)	<0.001
Volume >70 Gy	0 (0–5)	0 (0–1)	0.44*
Penile pulb (%)			
Volume >20 Gy	91 (50–100)	90 (45–100)	0.16
Volume >30 Gy	84 (40–100)	83 (36–100)	0.32
Volume >40 Gy	75 (31–100)	74 (27–100)	0.56
Volume >50 Gy	62 (18–100)	62 (16–100)	0.72
Volume >60 Gy	40 (1–99)	48 (6–99)	<0.001
Volume >70 Gy	0	0	—
Hip joint (%)			
Volume >20 Gy	99 (92–100)	100 (99–100)	0.03
Volume >30 Gy	86 (50–100)	87 (67–99)	0.49
Volume >40 Gy	44 (9–72)	51 (19–67)	0.06
Volume >50 Gy	6 (0–20)	11 (0–21)	0.04
Volume >60 Gy	0 (0–4)	0 (0–2)	0.77*
Volume >70 Gy	0	0	—
Hip joint muscles (%)			
Volume >20 Gy	66 (54–75)	40 (22–59)	<0.001
Volume >30 Gy	36 (14–54)	7 (1–18)	<0.001
Volume >40 Gy	7 (1–17)	0 (0–3)	<0.001
Volume >50 Gy	0	0	—

Data are means (ranges).

* Nonparametric Wilcoxon test applied; *p* values are derived from two-sided paired statistical tests.

As the second phase was delivered with the same (CRT) plan for both alternatives, the reduction in normal tissue doses obtained with IMRT was even clearer when comparing the first-phase plans separately (Fig. 1). For the first-phase plans, use of IMRT reduced intestine volumes receiving more than 40 to 50 Gy, rectum volumes receiving more than 20 to 50 Gy, and bladder volumes receiving more than 30 to 50 Gy. For example, the average intestine volume of more than 50 Gy was reduced from 48 to 3 cm^3, the average bladder volume of more than 40 Gy was reduced from 90% to 67%, and the average rectum volume of more than 40 Gy was reduced from 68% to 52%.

Adverse effects within 18 months post-treatment

No Grade 3 or higher GI adverse effects were observed among the patients. During the treatment course, acute Grade 2 GI effects were reported by 12 of 43 patients (28%), whereas Grade 1 GI adverse effects were reported by 22 patients (51%). These symptoms generally consisted of increased frequency of bowel movement, change in stool consistency, rectal discomfort, tenesmus, and urgency. Nine patients (21%) did not experience any GI adverse effects during treatment. Regarding acute GU effects, bladder catheterization was required in 1 patient during the third week of treatment, and this was scored as a Grade 4 effect. Otherwise, Grade 2 GU effects were observed among 12 of 43 patients (28%) and Grade 1 effects among 24 (56%). The symptoms reported included increased urinary frequency, urgency, dysuria, and nocturia. Six patients (14%) did not experience any GU adverse effects during treatment.

With a follow-up of 6 to 18 months post-RT (median, 12 months), the highest GI adverse effect score was Grade 2 in 2 patients (5%) and Grade 1 in 20 patients (47%). Apart from 1 patient who developed first renal and subsequently bladder cancer and had related GU symptoms (scored as Grade 3), Grade 2 was the highest score also for the GU effects and was observed in 7 patients (16%), and Grade 1 GU was scored in 13 patients (30%). Of the 21 patients seen 12 to 18 months post-RT, only 1 patient (5%) had Grade 2 GI effects and 1 patient (5%) had Grade 2 GU effects as of their last consultations.

DISCUSSION

In this report, we have presented our planning and verification procedures as well as our early clinical experiences from a study of prostate and lymph node IMRT. We found that use of IMRT reduces the doses to important OARs such as the intestine, bladder, and rectum when treating pelvic lymph nodes, while also improving target coverage. Clinical outcomes observed thus far are also promising, with a very low GI toxicity profile in particular.

A characteristic feature of IMRT and inverse planning is the trade-off between target coverage and normal tissue sparing. In this series we have given the highest priority to obtaining at least as good target coverage as in the standard plan, followed by reducing the doses to the intestine; this is also reflected in the DVH results. Although there are limited CT-based DVH constraints for the intestine (22, 23), it seems very likely that the reductions in intestine volumes that we obtained at both 40 Gy (from 139 to 89 cm^3) and 50 Gy (from 81 to 19 cm^3) are clinically meaningful. For example, according to Gallagher *et al.*, less than 78 cm^3 of the small intestine should receive more than 45 Gy, and less than 17 cm^3 should receive 50 Gy (22). The acute adverse effect outcome of the present IMRT series (28% of both Grade 2 GI and GU adverse effects) compare well with our previous CRT experience using the same prescription dose level, in which 40% of the CRT patients had acute Grade 2 GI and
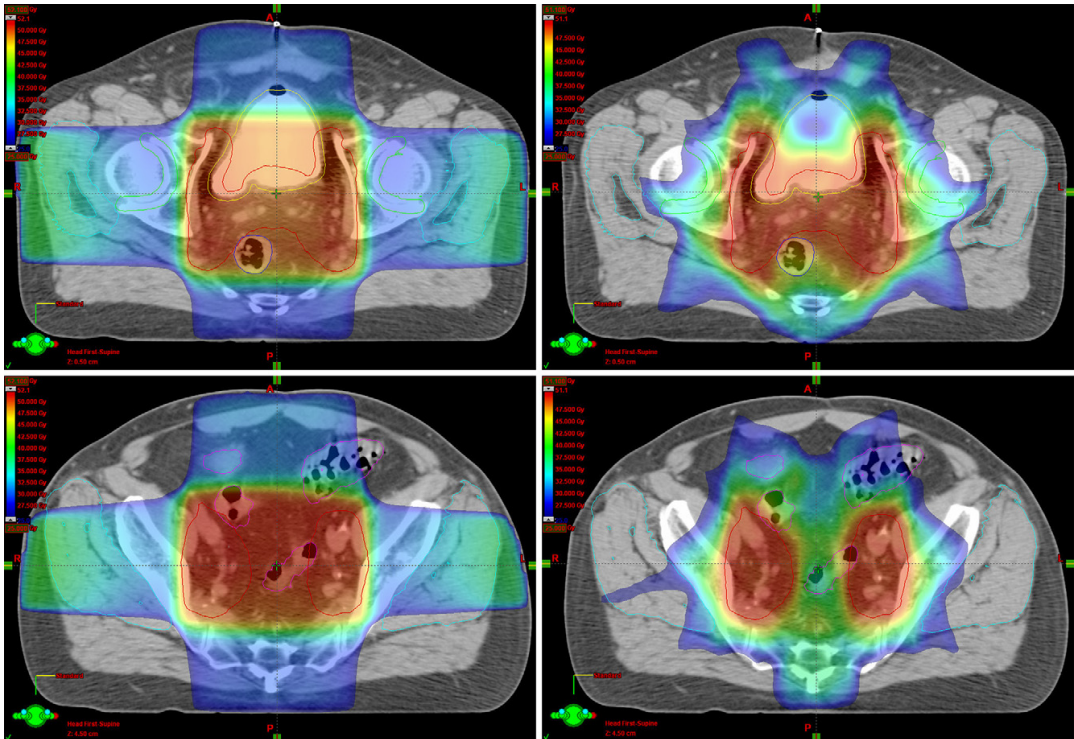
Fig. 1. Comparison of dose distributions of the first phase of the treatment with conformal radiotherapy (left) and intensity-modulated radiotherapy (right) in the upper (upper) and lower (lower) pelvis. Target volumes shown in red; intestine, pink; bladder, yellow; and rectum, blue. Dose color wash is from 25 Gy (dark blue) to ~50 Gy (red).

35% had acute Grade 2 GU adverse effects (6, 24). Also the late adverse effect rates observed at the first follow-up consultations after treatment seem reasonable, in particular for the GI effects. Again, comparing our previous CRT experience in which 11% of patients had at most Grade 2 late GI effects and 9% had at most Grade 2 late GU effects during their 6- and 12-month consultations, the corresponding values of 5% and 16% (with the same median follow-up times) in the present series seem comparable and, again, most favorable for the GI effects. These results also seem to be similar to those in previous IMRT studies in this patient group. In a retrospective study from the Memorial Sloan-Kettering Cancer Center in a series of 27 patients, of whom 13 actually had received IMRT, the average intestinal volumes receiving more than 45 Gy (i.e., the prescription dose to the lymph node volume) was reduced from 23% with CRT to 9% with IMRT, considering the first phase of treatment alone (14). Clinical outcomes for the IMRT patients were also good; in the acute phase, only 1 patient experienced acute Grade 2 GI effects and 4 patients experienced acute Grade 2 GU effects; there were no late Grade 2 effects observed among these patients, who all had more than 10 months of follow-up (14). In an IMRT planning study corresponding to the first phase in the current analysis, Nutting *et al.* also obtained considerable sparing of intestine,

bladder, and rectum using IMRT instead of CRT, e.g., a reduction from 18% to 5% of the intestine receiving more than 45 Gy (25). This planning study was also the basis for a clinical dose escalation study of pelvic IMRT cases at the Royal Marsden Hospital, where the doses to the two defined lymph node targets (negative and positive nodes) were increased in two 5-Gy steps. Initial clinical experience (with 50 Gy to the negative and 55 Gy to the positive lymph nodes) were more or less in line with our data, with 2 patients experiencing Grade 2 GU effects and 6 experiencing Grade 2 GI effects within a median follow-up of 7 months (26).

Although the pelvic anatomy obviously differs between men and women, considerable sparing of normal tissues has been documented also for pelvic irradiation in patients with gynecologic cancer, avoiding Grade 3 GI toxicity and reducing the rate of Grade 2 toxicity (27, 28).

Considering the definition and inclusion of lymph nodes for various stages of prostate cancer there are not yet any published consensus guidelines. The 2003 report from the RTOG 9413 study, which shows a clear benefit of lymph node irradiation for patients receiving adjuvant hormone therapy (5, 8), should increase the use of pelvic RT for these patients, and hence should also highlight the need for lymph node treatment guidelines (29). In addition, noninvasive methods such as magnetic resonance imaging with superparamagnetic

nanoparticle contrast, choline–positron emission tomography, and single photon emission computed tomography are now being used to define positive lymph nodes (7, 30–33). It should therefore become possible to test further refinement in the dose prescription pattern for the lymph nodes that could be delivered with IMRT.

The RT scheme used for the patient series described in this report involves two phases. A major advantage of IMRT is that it opens the possibilities for concomitant delivery of different doses to different target volumes, e.g., combining two-phase treatments using integrated boosts as well as local dose escalation (34–37). For the current patient group, we have recently introduced a Phase II study in which we simultaneously treat both the pelvic lymph nodes (with conventional fractionation, i.e., 2 Gy per fraction) combined with hypofractionated doses (2.4–2.7 Gy per fraction) to the prostate and seminal vesicles (38, 39). Following head-and-neck cancer practice, the doses prescribed to the pelvic lymph nodes could have been differentiated, with a higher dose to positive or radiologically suspect lymph nodes. It also seems justified to introduce yet another dose differentiation, as a higher dose could be prescribed to either the whole prostate (e.g., without margins) or to parts of the prostate, in the latter situation guided by magnetic resonance imaging or magnetic resonance spectroscopy (40, 41) or by positron emission tomography or computed tomography (42). In a recent study, Jacob *et al.* showed considerable benefit, in terms of biochemical control, from prescribing doses greater than 70 Gy to intermediate and high-risk prostate cancer patients (43). However attempts to derive alternative fractionation schedules using IMRT-delivered one-phase integrated boost approaches are complicated by their dependence on the currently unsettled radiobiologic parameters for prostate cancer, such as the sensitivity to changes in fraction sizes (i.e., the α/β ratio) as well as the sensitivity to changes in overall treatment time (i.e., T_k and D_{prolif}) (44–50). Such fractionation schedules should therefore be tested within the settings of carefully controlled trials.

The IMRT planning presented in this report is based on the planning CT scan only, which is typically acquired 1 week before the start of treatment. Given the considerable pelvic organ motion, this necessitated the use of relatively wide target volume margins. However we have used gold fiducials for localized prostate cancer patients for several years, and this procedure has now also been introduced for patients with locally advanced prostate cancer (within the above-mentioned simultaneous integrated IMRT protocol), allowing for a considerable margin reduction. In addition, basing the treatment on a single planning scan obviously leads to uncertainty in the normal tissue DVH parameters, and this is currently being investigated in a study at our institution in which repeated CT and OAR contour data are introduced. However, because of the good dose conformality obtained with IMRT, it seems reasonable to assume that the IMRT plans are still superior also when accounting for organ motion. Furthermore we are developing methods to account, in particular, for the intestine motion in pelvic IMRT. As an initial step we have quantified the size of intestine planning organ at risk volume margins (51). Because there seem to be distinct probability patterns (albeit individual) of the position/location of the intestine throughout the treatment course (51), we are currently initiating an investigation of the potential of the coverage probability concept (52) in planning pelvic IMRT. Ultimately such sophisticated planning methods should be combined with adaptive, image-guided radiation therapy–based methods through frequent acquisition of cone-beam CT scans during treatment.

As the follow-up time of this IMRT cohort increases, it will be interesting to see the time course of the late toxicity. The clinical outcome data collected will be compared with the results from a prospectively followed cohort of 247 patients with localized and locally advanced prostate cancer treated with CRT during 2000 to 2001, now with more than 5 years of follow-up.

CONCLUSION

Use of IMRT for treatment of pelvic lymph nodes in prostate cancer leads to considerably reduced irradiation of OARs such as the intestine, bladder, and rectum, while at the same time improving target coverage. The preliminary clinical outcomes experienced so far are also promising, and have encouraged us to pursue further target dose escalation for these patients.

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