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CLINICAL INVESTIGATION

ULTRA-HIGH DOSE (86.4 GY) IMRT FOR LOCALIZED PROSTATE CANCER: TOXICITY AND BIOCHEMICAL OUTCOMES

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Purpose: To report toxicity and preliminary biochemical outcomes with high-dose intensity-modulated radiation therapy (IMRT) to a dose of 86.4 Gy for localized prostate cancer.

Methods and Materials: Between August 1997 and March 2004, 478 patients were treated with 86.4 Gy using a 5- to 7-field IMRT technique. To adhere to normal tissue constraints, the mean D95 and V100 for the planning target volume were 83 Gy and 87%, respectively. Toxicity data were scored according to the Common Terminology Criteria for Adverse Events Version 3.0. Freedom from biochemical relapse was calculated. The median follow-up was 53 months.

Results: Thirty-seven patients (8%) experienced acute Grade 2 gastrointestinal (GI) toxicity. There was no acute Grade 3 or 4 GI toxicity. One hundred and five patients (22%) experienced acute Grade 2 genitourinary (GU) toxicity and three patients (0.6%) had Grade 3 GU toxicity. There was no acute Grade 4 GU toxicity. Sixteen patients (3%) developed late Grade 2 GI toxicity and two patients (<1%) developed late Grade 3 GI toxicity. Sixty patients (13%) had late Grade 2 GU toxicity and 12 (<3%) experienced late Grade 3 GU toxicity. The 5-year actuarial PSA relapse-free survival according to the nadir plus 2 ng/mL definition was 98%, 85% and 70% for the low, intermediate, and high risk NCCN prognostic groups.

Conclusion: This report represents the largest data set of patients treated to ultra-high radiation dose levels of 86.4 Gy using IMRT for localized prostate cancer. Our findings indicate that this treatment is well tolerated and the early excellent biochemical control rates are encouraging. © 2007 Elsevier Inc.

Prostate cancer, Toxicity, Outcomes, IMRT, Dose escalation.

INTRODUCTION

The importance of dose escalation in the radiotherapeutic management of localized prostate cancer has been established for various prognostic risk groups. Improved outcomes were initially identified in single institution phase I/II dose escalation protocols (1, 2). More recently, four randomized controlled dose escalation trials have confirmed improved biochemical control outcomes with doses of 74–80 Gy compared to conventional doses of <70 Gy (3–6). Furthermore, improvements in distant metastases-free survival (DMFS) and cancer-specific survival (CSS) outcomes are emerging as the followup from these studies matures (7–10).

Improved tumor control with dose escalation has not come without a price. Dose escalation using conventional radiation techniques resulted in high morbidity, with up to 30% of

patients experiencing significant late toxicities (11–15). Three-dimensional conformal radiation therapy (3D-CRT) decreased the rates of serious toxicity, but moderate side effects remained relatively common (1, 2, 16, 17). With the implementation of intensity-modulated radiation therapy (IMRT) over the past decade, it has become possible to minimize the volume of normal tissue irradiated by producing steeper dose gradients and more effective exclusion of normal tissues from the high doses of irradiation. These important technologic advances have allowed for dose escalation to previously unattainable levels without an increase in toxicity. IMRT significantly decreases the rate of rectal morbidity even when high doses of radiation are used (18–20). Zelefsky *et al.* have shown minimal rectal toxicity in a large cohort of patients treated to 81 Gy using IMRT with eight years of followup (21). Recent publications have highlighted the need

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for appropriate rectal constraints in order to minimize late rectal toxicity (22-24).

Despite the progress that has been made with dose escalation, improvement is still needed as a significant number of patients continue to relapse. Even with doses of 78-81Gy, the 5-year biochemical failure rate for patients with intermediate-risk and high-risk disease remains 30-45% (4, 9, 21). Recent data from the Fox Chase Cancer Center (FCCC) dose escalation experience suggest that the dose response curve for prostate radiotherapy, especially in higher risk patients, continues beyond 80 Gy and that ultra-high radiation dose levels may be needed for optimal disease control (25).

As part of a Phase I dose escalation trial conducted at our institution, we investigated the feasibility of dose escalation to 86.4 Gy. We have previously reported our early experience with the first 74 patients treated to this dose level (26). In this report, we focus on the outcomes of almost 500 patients treated at our institution to a dose of 86.4 Gy with a minimum followup of three years. Our findings indicate that IMRT for the delivery of ultra-high radiation doses is well tolerated and associated with excellent biochemical control rates.

METHODS AND MATERIALS

Between August 1997 and March 2004, 478 consecutive patients with localized prostate cancer were treated with definitive IMRT to a dose of 86.4Gy at the Memorial Sloan-Kettering Cancer Center. The initial fifty patients were treated as part of a prospective phase I/II dose escalation protocol for patients with high-risk disease (27). This treatment regimen was then expanded to non-protocol patients due to the lack of increased toxicity in the first fifty patients, after a minimum followup of two years had elapsed.

The median followup for the cohort was 53 months. The median age of this patient cohort was 69 years (range, 46-85 years). All patients had a histologic diagnosis of prostate adenocarcinoma confirmed by a urologic pathologist at our institution. Pretreatment diagnostic evaluations were performed as previously described (28). Disease characteristics for the cohort are shown in Table 1. Patients were characterized into prognostic risk groups based on the NCCN classification system (www.nccn.com).

Patients were treated using a five- to seven-field IMRT plan. The details of this technique have been described (18, 20, 29). Briefly, patients were simulated in the prone position with a customized thermoplastic mold for immobilization. A CT scan was obtained at the time of simulation and images were then transferred to the treatment planning system. A PTV was contoured consisting of the prostate, seminal vesicles with a 1-cm margin in all directions except posteriorly at the prostate-rectal interface, where the margin was reduced to 0.6 cm. The bowel, rectal and bladder walls were contoured as critical normal tissue structures. For all patients, the rectal wall was contoured along the entire length of the PTV plus 0.5cm in the superior and inferior directions. Hot spots in the center of the gland were avoided (urethral area). Using an in-house treatment planning system and optimization algorithm, an IMRT plan was designed. The standard beam arrangement was: posterior (0), right posterior oblique (75), right anterior oblique (135), left anterior oblique (225) and a left posterior oblique field (285). When required to meet normal tissue and target dose criteria, two additional posterior obliques were added at 37 degree and 323 degrees to create seven field plans. Treatment plans were then optimized with an inverse

Table 1. Patient characteristics

	N	%
Age (years)		
Median		68.8
Mean		67.9
Range		46-85
Race		
White		381
Hispanic		32
Black		41
Other		24
Follow-up		
Median (months)		53
	N	%
Stage		
T1b	1	(<1)
T1c	217	(45)
T2a	104	(22)
T2b	34	(7)
T2c T3a	33	(7)
T3b	27	(6)
T4	37	(8)
Tx	0	
	25	(5)
Gleason score		
≤6	152	(32)
7	216	(45)
8-10	110	(23)
PSA		
<10	286	(60)
10-19.9	106	(22)
>20	86	(18)
Hormonal therapy		
Yes	314	(66)
No	164	(34)
NCCN Prognostic Group		
Low	100	(21)
Intermediate	192	(40)
High	186	(39)

Abbreviations: NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen.

optimization algorithm (30). Optimization was performed using dose or dose-volume constraints and penalties to control the PTV dose (with separate constraints applied to areas of rectal/PTV overlap), homogeneity within the PTV, and doses to critical structures.

Dose constraints were placed on the following normal structures: large bowel, rectal and bladder walls and PTV. The maximum point dose allowed to the large bowel was 60 Gy. We limited no more than 53% of the rectal and bladder walls to 47 Gy ($V_{47} < 53$) and no more than 30% of the rectal wall to 75.6 Gy ($V_{75.6} < 30$) (22, 23). In the areas of overlap between the PTV and rectum, the maximum point dose to the rectum was constrained to 99% of the prescription dose (8550 cGy). Once the intensity profiles of the five IMRT beams were determined, leaf motion files were created and dose distributions were generated. The dose distributions were normalized such that the maximum dose to the PTV did not exceed 110% of the prescribed dose. On average, this resulted in 87% of the PTV volume receiving the prescribed dose of 86.4 Gy or more (V_{100}) (standard deviation 6.5%) and an average dose to 95% of the PTV (D_{95}) of 83.1 Gy (standard deviation 2.1 Gy). PTV regions receiving less than the prescribed dose were limited to the prostate-rectal interface (to adhere to the rectal constraint) and sometimes superior regions of the seminal vesicles

(to adhere to the bowel constraint). All patients were treated using 15 MV photons to a dose of 8640 cGy in 48 fractions of 180 cGy. During the time period of the current study, prostate localization techniques were not used and patient position was verified with weekly port films. More recently, however, we have implemented a policy of routine fiducial marker placement and daily 2D-kV imaging for prostate localization in all patients receiving prostate IMRT.

Androgen deprivation therapy (ADT) was added at the discretion of the treating physician. Indications for ADT were cytoreduction or higher risk features. Patients usually received 3 months of neoadjuvant ADT and continued it during the course of treatment. High-risk patients continued on adjuvant hormone therapy for approximately six months.

Patients were seen in followup 3 months after the completion of treatment and then followed on a biannual basis for the next five years. The followup was reduced to an annual basis after five years. Early and late toxicity data were scored according to the NCI designated Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) Grade 1 - 4: Grade 1 – minimal side effects not requiring medications; Grade 2 – side effects requiring medications for symptom management (or increase in dose of pre-existing medication), Grade 3 – side effects requiring minor procedures (i.e., cauterization, catheterization, transfusions) to control or affecting activities of daily living; Grade 4 – life threatening toxicity requiring major surgery and hospitalization. Acute side effects occurred during the course of radiation or within 90 days of its completion. Urinary symptoms were monitored with the International Prostate Symptom Score and quality of life (QOL) questionnaire prior to treatment and at each followup visit. Erectile function was evaluated according to patient report at the time of each followup. Impotency was defined as the inability to achieve an erection sufficient for intercourse. Erectile dysfunction included any patient who noted a decrease in erectile strength after receiving radiation.

Disease status was determined at the time of analysis in March 2007. Freedom from biochemical relapse was analyzed with the American Society of Therapeutic Radiology and Oncology (ASTRO) consensus definition of three consecutive rises (31) and the nadir plus 2 ng/mL definition (32). The date of failure for the ASTRO analysis was backdated to the midpoint between the nadir PSA and the date of the first PSA rise. The date of failure for the nadir plus 2ng/mL was the date at which this level was reached. All endpoints were calculated from the radiation start date. For patients who did not receive hormonal therapy, PSA nadir was defined as the lowest post-treatment PSA value reached.

Distributions of PSA-relapse free survival were calculated by the Kaplan-Meier method. Univariate and multivariate analyses were

performed to determine predictors of biochemical relapse. Statistical significance was achieved when $p \leq 0.05$.

RESULTS

Acute toxicity

The acute side effects of radiotherapy in this cohort were well tolerated (Fig. 1). Grade 1 and 2 acute genitourinary (GU) toxicity occurred in 280 (59%) and 105 patients (22%), respectively. Three patients (0.6%) developed acute urinary retention requiring catheterization during the third to fourth week of treatment (Grade 3). All three of these patients had resolution of their symptoms after a brief treatment break with catheterization and went on to complete the full course of therapy without further incident. Acute gastrointestinal (GI) toxicity was minimal. Over half the patients (58%) did not experience any acute GI toxicity. Grade 1 and 2 rectal toxicity was identified in 165 (34%) and 37 (8%) patients, respectively. There was no acute Grade 3 or 4 rectal toxicity.

Late toxicity

The majority of patients had no long-term treatment related toxicity (Fig. 2). Specifically, 398 (83%) and 328 (69%) patients experienced no late GI or GU toxicity, respectively. Grade 1 and 2 late GU toxicity was identified in 78 (16%) and 60 (13%) patients, respectively. Twelve patients (<3%) developed late Grade 3 GU side effects. The majority of these patients developed urethral strictures requiring dilatation or radiation cystitis requiring cauterization. The median time to the development of Grade 3 GU toxicity was 26 months. There were no Grade 4 events. The 5-year actuarial risk of developing \geq Grade 2 GU toxicity was 16% (Fig. 3). Of the 437 patients who were completely continent prior to radiotherapy, 49 (11%) developed some degree of urinary leakage. The majority of these (82%) were Grade 1 urge incontinence which was infrequent and did not require the use of pads. Nine patients (1.8%) developed urinary urge incontinence requiring the use of 1-2 pads per day after radiation. No patient required more than 2 pads per day. The average time to the development of incontinence requiring pads was 17 months. Overall, most patients were happy

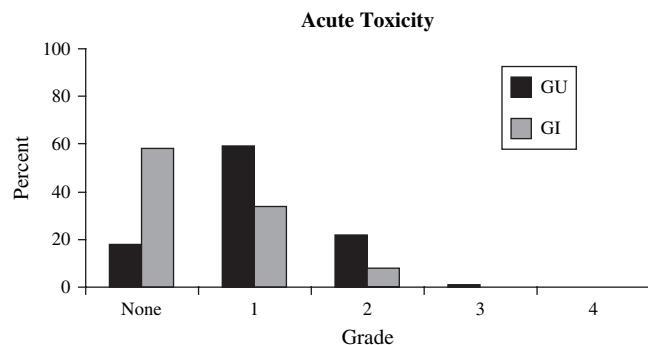


Fig. 1. Incidence of acute genitourinary (GU) and gastrointestinal (GI) toxicity.

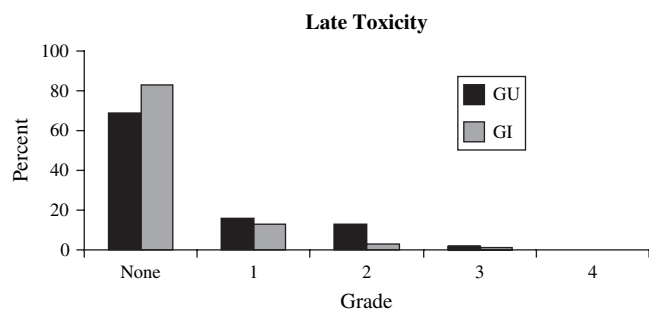


Fig. 2. Incidence of late genitourinary (GU) and gastrointestinal (GI) toxicity.

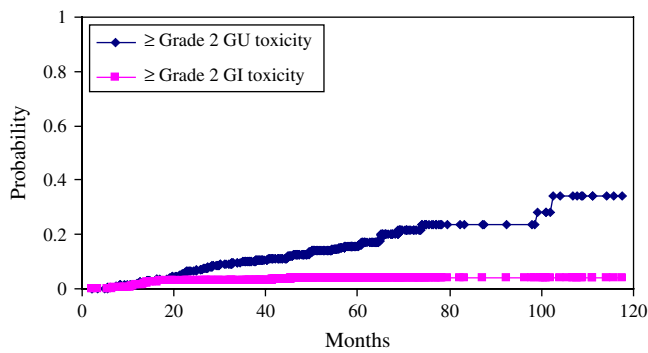


Fig. 3. Kaplan-Meier actuarial probability of \geq grade 2 late genitourinary (Gu) and gastrointestinal (GI) toxicity.

with their urinary quality of life (QOL) at the time of their last followup according to a validated QOL questionnaire. The average IPSS at time of last followup was 6 (range, 0–35), while the average QOL score was 1 (range, 0–6; 1=pleased). On univariate analysis, age >70 ($p = 0.02$), treatment with a GU medication prior to initiating radiation ($p = 0.001$) and the development of acute \geq Grade 2 GU toxicity ($p < 0.001$) were predictive for late GU toxicity. The use of hormone therapy and a history of diabetes were not associated with increased late toxicity. On a multivariate Cox regression (Table 2), only age >70 ($p < 0.005$) and treatment with a GU medication prior to treatment ($p = 0.003$) were significant for the development of late toxicity.

Late GI toxicity was uncommon (Fig. 2) with 63 (13%) and 16 (3%) patients experiencing Grade 1 and 2 late GI complications, respectively. Two patients (0.4%) experienced Grade 3 toxicity: one patient with brisk rectal bleeding from radiation proctitis requiring a red blood cell transfusion and one patient with intractable fecal incontinence affecting his daily activities. There were no Grade 4 events. The 5-year actuarial risk of developing Grade 2 or greater GI toxicity was 4% (Fig. 3). Fecal incontinence developed in 22 patients (5%) after completion of radiation. In 20 of these 22 patients, the incontinence was mild, infrequent and did not require the use of pads or medical treatment. One patient had Grade 2 incontinence requiring the use of pads and one patient had Grade 3 incontinence (as previously described). On univariate analysis, the only predictive factor for the

Table 2. Multivariate Cox regression of late toxicity.

	Late GU toxicity \geq Grade 2	Late GI toxicity \geq Grade 2	Erectile dysfunction
ADT	NS	NS	$p = 0.001$
Pre-RT GU Rx	$p = 0.003$	NS	NS
Age (>70)	$p = 0.005$	NS	$p < 0.001$
Diabetes	NS	NS	$p < 0.001$
Acute GU \geq Grade 2	NS	NA	NS
Acute GI \geq Grade 2	NA	$p = 0.03$	NS

Abbreviations: ADT = androgen deprivation therapy; GI = gastrointestinal; GU = genitourinary; NA = not applicable; NS = not significant; RT = radiotherapy; Rx = prescription medication.

development of late GI toxicity was the presence of acute \geq Grade 2 GI toxicity ($p = 0.009$). Age, prostate volume, use of ADT and diabetes did not have an impact on the development of late rectal toxicity. On multivariate analysis (Table 2), acute GI toxicity remained the only significant predictor for the development of late toxicity ($p = 0.035$).

Erectile dysfunction

Ninety-four patients were impotent prior to receiving any radiation treatment. Of the 384 patients who were potent prior to radiation, 115 patients (30%) became impotent; of these 115 patients, 92 (80%) received ADT. The 5-year actuarial risk of developing post-radiation impotence was 34% (Fig. 4). In addition to the 115 patients who became impotent, 100 patients (25%) experienced diminished erectile strength after radiation but were still able to engage in intercourse; among these 100 patients, 60 received ADT (60%). Therefore, a total of 215 patients (55%) experienced some degree of erectile dysfunction. Age >70 , a history of diabetes and the use of ADT were all predictive for the development of erectile dysfunction ($p < 0.001$) on both univariate and multivariate analyses (Table 2).

Biochemical tumor control rates

The 5-year actuarial PSA relapse-free survival according to the ASTRO definition was 99%, 79% and 72% for the low, intermediate and high risk groups, respectively ($p < 0.001$) (Fig. 5). The 5-year actuarial PSA relapse-free survival according to the nadir plus 2 ng/mL definition was 98%, 85% and 70% for the low, intermediate and high risk groups, respectively ($p < 0.001$) (Fig. 6). On multivariate analysis, Gleason 8–10 ($p = 0.001$) and pretreatment PSA >10 ng/mL ($p = 0.001$) were predictors of biochemical relapse according to both definitions. The use of hormonal therapy and clinical T-stage did not have a demonstrable impact on biochemical control rates.

DISCUSSION

This study represents the largest published experience using ultra-high IMRT doses for the treatment of clinically localized prostate cancer. These data show that dose escalation to a level of 86.4 Gy with IMRT is well tolerated in

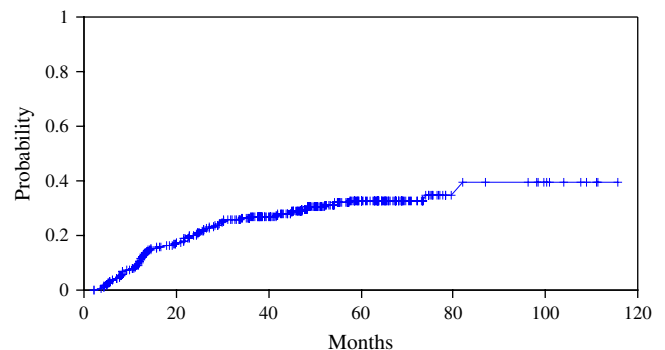


Fig. 4. Kaplan-Meier actuarial probability of radiation induced impotence in 384 men who were potent prior to treatment.

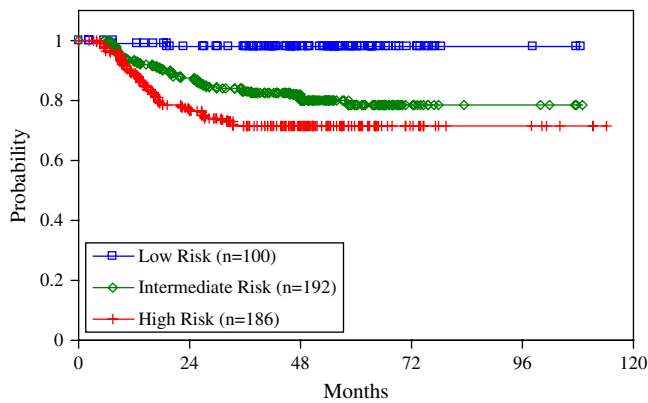


Fig. 5. Kaplan-Meier actuarial probability of achieving prostate specific antigen (PSA) relapse-free survival according to the ASTRO definition by NCCN risk group.

a large cohort of patients with a minimum followup of three years. Biochemical control rates are at least equivalent to previous dose escalation reports and are particularly encouraging for intermediate and unfavorable risk patients. This study did not intend to compare outcomes to lower dose levels delivered at our institution; our intent was to report the feasibility and tolerance of 86.4 Gy IMRT in a large cohort of patients. We recognize that longer followup will be necessary to corroborate the durability of the biochemical response and tolerance outcomes we report.

A dose response relationship has clearly been established in prostate radiotherapy. Convincing data from four randomized trials and several large, non-randomized reports have confirmed that doses of 74-81 Gy result in a 15-20% improvement in biochemical control compared to conventional doses of <70 Gy (2-4, 6, 33). Improvements in local control, defined by post treatment biopsies >2 years after treatment, have also been demonstrated with higher doses (2). Data from the most mature dose escalation series suggest that as the followup interval matures, improvements in biochemical control will translate into better DMFS and CSS (8, 10). A recent report from the Fox Chase Cancer Center showed that improvements in long-term local control with dose esca-

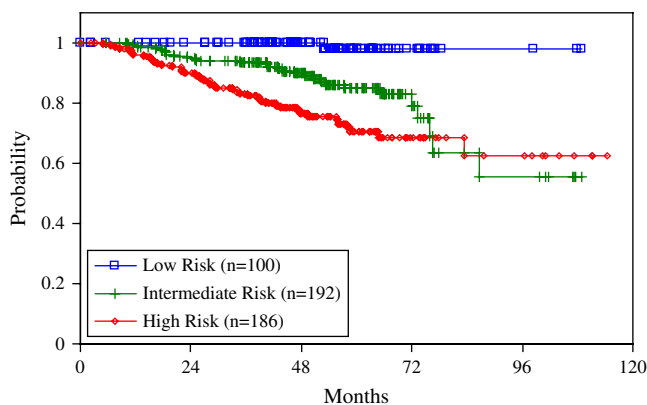


Fig. 6. Kaplan-Meier actuarial probability of achieving prostate specific antigen (PSA) relapse-free survival according to the nadir + 2 ng/ml definition by NCCN risk group.

lation led to a reduction in metastases (34). Equally impressive data exists in the brachytherapy literature regarding the impact of dose on clinical outcomes (35).

With the use of more conformal radiation techniques, high dose prostate radiotherapy has become feasible. In a prospective dose escalation trial conducted by the RTOG using 3D-CRT, late toxicity was significantly less than expected based on historical controls with conventional techniques. Furthermore, there were no differences in late toxicity rates between the dose levels (36, 37). In this trial, only 3% of patients who received 79.2 Gy experienced a Grade 3 toxicity and no patients experienced a Grade 4 or 5 toxicity. In the four aforementioned randomized trials, patients tolerated the high dose radiotherapy well despite the fact that a combination of conventional and 3D-CRT techniques were used. Late Grade 3 GU toxicity in these reports ranged from 1-7% and none of the trials showed an increase in late GU toxicity with the use of higher doses. In contrast, there was an increase in late GI toxicity for patients in the high dose arm of all four of the trials. Late Grade 2 GI toxicity ranged from 17-29% in the high dose arms of these trials versus 8-23% in the low dose arms. Grade 3 or greater GI toxicity increased from 1-2% in the low dose arms to 1-10% in the high dose arms. These results are comparable to the 3D-CRT dose escalation experience at MSKCC (2). Despite the overall low rate of serious complications in these trials, the increased incidence of late GI toxicity was of concern and was the primary motivation behind the implementation of IMRT at many institutions including our own.

The current report highlights the excellent tolerance of high dose radiotherapy when using a highly conformal treatment delivery such as IMRT. By producing steep dose gradients, IMRT is able to more effectively exclude normal tissues from the high doses of irradiation. A growing body of literature has demonstrated that this in turn leads to a reduction in treatment related morbidity compared to 3D-CRT. The major clinical advantage of IMRT has been its ability to decrease rectal toxicity (19, 20). The largest published series with IMRT reported a 4% incidence of late Grade 2 or greater proctitis in 772 patients treated at MSKCC to at least 81 Gy (26). In an update of this report, the 8-year actuarial risk of Grade 2 bleeding was <2% (21). A recent study from the University of Chicago comparing patients treated with conventional EBRT to patients treated with IMRT (median followup >2 years), reported very low rates of late rectal toxicity in the IMRT group (19). A dosimetric analysis in that study showed that IMRT significantly decreased the dose to the rectum, reducing the incidence of late Grade 1 GI toxicity from 25 to 8% and late Grade 2 or greater GI toxicity from 11 to 6%. In a study from Japan, patients treated with IMRT had better bowel quality of life outcomes compared to patients who received conventional/conformal RT, despite prescribing to a higher dose in the IMRT arm (38). In the current report, by adhering to appropriate constraints, we were able to deliver 86.4 Gy without causing an apparent increase in late GI toxicity compared to our previous experience with 81 Gy (26). The incidence of late Grade 3 GI and GU

complications in this report was <1% and 3%, respectively. This is similar to rates that have been reported with standard high dose IMRT (74-81 Gy) (19, 21, 39, 40). However, comparisons of patients across study cohorts are difficult and should be interpreted with caution.

Excellent long term biochemical control has been reported with the use of 78-81 Gy. The 5-year actuarial PSA relapse-free survival according to the nadir plus 2 ng/mL definition in this series was 98%, 85% and 70% for the favorable, intermediate and unfavorable NCCN prognostic risk groups, respectively. The 5-year actuarial PSA relapse-free survival in the current series is 99%, 79% and 72% for the respective prognostic groups. These results compare favorably to previous dose escalation series with this amount of followup and clearly represent an improvement compared to conventional doses (6, 9, 21). There are conflicting data in the literature as to which subsets of patients are most likely to benefit from dose escalation. Initial studies suggested that higher doses were only advantageous in intermediate and high risk patients (5). Recently, however, some investigators have shown that more favorable risk patients may also benefit from dose escalation (6, 7, 9, 17, 41-43). The current report shows excellent biochemical control across all the risk groups.

Eade *et al.* have advocated for the use of doses >80 Gy for localized prostate cancer (25). They suggest that doses of >80 Gy result in better local control and ultimately less distant failures than <80 Gy. In their report, each additional 1 Gy in this dose range decreased the risk of biochemical recurrence by 2.2%. The conclusion from this report was that most, if not all, patients could benefit from treatment to doses of ≥ 80 Gy and that the plateau on the dose response curve for prostate cancer lies well above 80 Gy. We believe that the current series demonstrates the feasibility of delivering such ultra-high doses with minimal toxicity with the use of IMRT. Only a randomized trial in this dose range will be able to determine whether these ultra-high doses offer a real benefit.

Multiple randomized trials have confirmed the benefit of androgen deprivation therapy for select groups of patients when used in combination with conventional doses of radiation (44-47). Two recent studies from The Netherlands (4) and the United Kingdom (3) were the first randomized dose escalation trials to include patients who received androgen deprivation therapy. The study from the Netherlands showed a biochemical control benefit for higher doses among intermediate and high risk patients, while the study from the UK showed a benefit across all the risk groups. In our report, hormonal therapy did not significantly impact on outcome. However, we acknowledge that in a retrospective series such as this, selection bias may have confounded the analysis. Furthermore, the impact of hormonal therapy may not

become apparent until the followup interval increases. We believe the role of hormone therapy in the setting of dose escalation needs to be evaluated in a randomized trial.

There are several limitations to our study. First, by virtue of being a retrospective chart review, we acknowledge that a selection bias exists. Patients at high risk for developing complications may have been advised to receive other treatment modalities or may have been treated to more conventional doses. Selective groups of unfavorable patients at MSKCC during this period received pelvic irradiation and were therefore excluded from this series. We acknowledge that the impact of hormone therapy cannot accurately be determined given the bias to treat more unfavorable patients with hormone therapy. In addition, toxicity was graded according to a physician-based assessment, which has inherent limitations. Erectile dysfunction was not collected prospectively by formal validated questionnaires in the majority of patients and therefore the results need to be interpreted with caution. An ongoing prospective quality of life study is ongoing at our institution to better evaluate this.

The current study does not provide evidence that 86.4 Gy is superior to doses of 78-81 Gy. However, the goal of this paper was not to compare these doses. Our intent, rather, was to report the acute and late toxicity in a large cohort of patients treated to a dose level that has never been reported. Although it seems that the 5-year biochemical control rates in this series are at least similar to those achieved with traditional dose escalation (4, 21, 33), we intentionally did not attempt to directly compare outcomes. Since the implementation of 86.4 Gy IMRT at our institution in the late 1990s, the majority of patients treated for localized prostate cancer at MSKCC have received this dose. As a result, patients treated to 81 Gy were treated in an earlier time period compared to 86.4 Gy leading due to a disparity in follow-up intervals between these cohorts. We recognize that only a randomized study can accurately compare outcomes between these two doses. However, a randomized trial in this dose range is unlikely in the immediate future. In the meantime, the current study demonstrates that such treatment is safe and well tolerated.

CONCLUSION

In conclusion, ultra-high dose radiotherapy to 86.4 Gy with IMRT for the treatment of localized prostate cancer is safe, well tolerated, and effective in a large cohort of patients. Biochemical control rates appear to be at least equivalent if not superior to previous dose escalation reports. Further followup is needed to determine the durability of tumor control and the full extent of late effects in this cohort of patients.

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