Improved Toxicity Profile Following High-Dose Postprostatectomy Salvage Radiation Therapy With Intensity-Modulated Radiation Therapy

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Urinary incontinence

**Abstract**

**Background:** With salvage radiation therapy (SRT) in the postprostatectomy setting, the need to deliver sufficient radiation doses to achieve a high probability of tumor control is balanced with the risk of increased toxicity. Intensity-modulated radiation therapy (IMRT) in the postprostatectomy salvage setting is gaining interest as a treatment strategy.

**Objective:** Compare acute and late toxicities in patients treated with IMRT and three-dimensional conformal radiation therapy (3D-CRT) in the postprostatectomy salvage setting.

**Design, setting, and participants:** A total of 285 patients who were treated at our institution between 1988 and 2007 with SRT after radical prostatectomy for biochemical recurrence were identified. All medical records were reviewed and toxicity recorded. Median follow-up was 60 mo.

**Intervention:** All patients were treated with SRT with either 3D-CRT (n = 109) or IMRT (n = 176). A total of 205 patients (72%) were treated with doses ≥70 Gy.

**Measurements:** Late gastrointestinal (GI) and genitourinary (GU) toxicities were recorded using the Common Terminology Criteria for Adverse Events v. 3.0 definition.

**Results and limitations:** The 5-yr actuarial rates of late grade ≥2 GI and GU toxicity were 5.2% and 17.0%, respectively. IMRT was independently associated with a reduction in grade ≥2 GI toxicity compared with 3D-CRT (5-yr IMRT, 1.9%; 5-yr 3D-CRT, 10.2%; p = 0.02). IMRT was not associated with a reduction in risk of grade ≥2 GU toxicity (5-yr IMRT, 16.8%; 5-yr 3D-CRT, 15.8%; p = 0.86), urinary incontinence (5-yr IMRT, 13.6%; 5-yr 3D-CRT, 7.9%; p = 0.25), or grade 3 erectile dysfunction (5-yr IMRT, 26%; 5-yr 3D-CRT, 30%; p = 0.82). Of patients who developed late grade ≥2 GI or GU toxicity, 38% and 44%, respectively, experienced resolution of their symptoms prior to the last follow-up.

**Conclusions:** Our experience with high-dose IMRT in the postprostatectomy salvage setting demonstrates that the treatment can be delivered safely with an associated reduction in late GI toxicity.
Introduction

Radiation therapy (RT) in the postprostatectomy setting is the only potentially curative treatment option that exists for patients with prostate cancer following a biochemical recurrence [1–4]. However, the delivery of radiation doses sufficient to improve tumor control has been limited by the narrow therapeutic ratio. Understanding both the need for dose escalation and the concern about toxicity, the most recent American Society for Therapeutic Radiation and Oncology consensus guidelines, published in 1999, recommended that “the highest dose of RT that can be given without morbidity is justifiable” [5].

The advent of intensity-modulated RT (IMRT) has revolutionized radiation oncology [6]. IMRT techniques have the potential advantage of allowing inverse treatment planning with computer optimization, as well as computer-controlled intensity modulation of the radiation beam to allow more conformal treatment plans than three-dimensional conformal RT (3D-CRT) [7]. The technology has been harnessed in the treatment of prostate cancer in the definitive setting [8–15]. However, the role of IMRT in the postprostatectomy setting, in which lower doses are generally prescribed, has not been as well studied.

At Memorial Sloan-Kettering Cancer Center (MSKCC), we routinely treated patients after prostatectomy with doses of 66 Gy using 3D-CRT in the early 1990s. Since then, we have gradually increased our dose to 72 Gy, which we routinely deliver using IMRT. In this study, we review the acute and late genitourinary (GU) and gastrointestinal (GI) toxicity associated with the high-dose RT delivered in the postprostatectomy setting.

2. Patients and methods

Between January 1988 and March 2007, 301 patients developed biochemical recurrence following definitive radical prostatectomy and received salvage RT (SRT) at MSKCC; 285 of these patients were included in this study. Sixteen patients were excluded due to lack of MSKCC surgical pathology review (n = 1), follow-up after RT of <3 mo (n = 11), or discontinuation of RT less than halfway through the course of treatment due to rapid biochemical or clinical progression during treatment (n = 4). The median postprostatectomy prostate-specific antigen (PSA) prior to SRT was 0.4 ng/ml. Two hundred thirty-four patients (82%) had at least two consecutive increases in PSA before salvage RT, and 203 patients (71%) had a postprostatectomy PSA >0.2 ng/ml. Fourteen patients had a single detectable postprostatectomy PSA <0.2 ng/ml prior to SRT. 3D-CRT plans generally consisted of six-field coplanar beams with 15-MV photons, compared with IMRT plans that generally consisted of five-field coplanar beams with 15-MV photons.

We retrospectively reviewed all medical records, operative and pathology reports, and staging studies. Androgen-deprivation treatment (ADT) prescribed in connection with SRT was classified into three categories: neoadjuvant if treatment was given immediately before SRT, concurrent if given during SRT, and adjuvant if delivered immediately following completion of SRT. Acute GI and GU toxicities were retrospectively graded according to the Radiation Therapy Oncology Group (RTOG) classification system and were defined as symptoms occurring during or within 9 wk after treatment. Late GI toxicities, GU toxicities, urinary incontinence, and erectile dysfunction were separately graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0. International Prostate Symptom Scores were offered to patients beginning in 2003 at both the time of initial consultation and subsequent follow-up appointments after treatment. The Kaplan-Meier method was used to estimate the cumulative rate of late complications. For late toxicities, toxicity-free interval was defined as the interval from the date of the last RT treatment to the date of toxicity. For erectile function toxicity analysis, patients were censored at the time of initiation of ADT if initiated after completion of SRT. Event-time distributions were compared using log-rank tests. Multivariate regression analysis was used to evaluate the independent prognostic factors that were predefined for both acute and late toxicity. The covariates age, ADT, and treatment technique (IMRT vs 3D-CRT) were assessed for all toxicity analyses. Acute grade ≥2 toxicity was further considered in the analysis of late GI and GU toxicity. All multivariate analyses were adjusted for baseline characteristics. All tests were two-sided and were considered to be statistically significant at p < 0.05. Analyses were conducted using SPSS v.19 (IBM Corp., Armonk, NY, USA).

3. Results

Patient treatment characteristics are listed in Table 1. The median time from prostatectomy to SRT was 31 mo (range: 3 mo–16.7 yr), and the median follow-up time after SRT was 60 mo (range: 4–221 mo). Eighty percent of patients treated with doses ≥70 Gy were treated with IMRT, while 86% of patients treated with doses <70 Gy received 3D-CRT (p < 0.01). The overall 5-yr actuarial PSA relapse-free survival, distant metastasis-free survival, and overall survival following SRT with 3D-CRT was 38.4%, 85.0%, and 96.3% respectively, and following IMRT was 39.9%, 84.4%, and 96.0% respectively (p = 0.56, 0.80, and 0.18, respectively). On multivariate analysis, when considering both pretreatment PSA <0.4 ng/ml and treatment technique, IMRT was not associated with a statistical difference in PSA relapse-free survival (hazard ratio [HR]: 1.27; p = 0.16), distant metastasis-free survival (HR: 1.05; p = 0.88), or overall survival (HR: 0.50; p = 0.27).

3.1. Gastrointestinal toxicity

The overall rate of acute grade ≥2 GI toxicity was 9.8%. The rate of acute grade ≥2 GI toxicity was not associated with treatment technique on univariate analysis (IMRT, 7.6%; 3D-CRT, 13.2%; p = 0.14) or multivariate analysis (HR: 0.55; p = 0.15) (Table 2). There were no grade 3 acute GI toxicities. One patient (5.3%), who underwent treatment to the pelvic lymph nodes in addition to the prostate, developed an acute grade 2 toxicity.

The 2- and 5-yr actuarial rates of CTCAE grade ≥2 late GI toxicity were 2.2% and 5.2%, respectively (Fig. 1a). Patients treated with IMRT had a lower rate of grade ≥2 late GI toxicity at 5 yr than patients treated with 3D-CRT on univariate analysis (IMRT, 1.9%; 3D-CRT, 10.2%; p = 0.02; Fig. 1b) and multivariate analysis (HR: 0.29; p = 0.04) (Table 3). Six of the 16 patients who developed a grade 2 late GI toxicity had resolution of their symptoms with medical management.

There were four grade ≥3 late GI toxicities (1.4%), none of which occurred in patients whose pelvic lymph nodes were targeted during treatment. Three of the four patients had...
significant GI-related medical comorbidities prior to treatment placing them at high risk, including a history of ulcerative colitis, diverticulitis, and colorectal cancer.

3.2. Genitourinary toxicity

The overall rate of RTOG grade ≥2 acute GU toxicity was 16.3%. The incidence of grade ≥2 acute GU toxicity was not statistically different by treatment technique on univariate analysis (IMRT, 13.4%; 3D-CRT, 20.8%; \( p = 0.12 \)) or multivariate analysis (HR: 0.61; \( p = 0.15 \)) (Table 4).

There were 101 patients whose International Prostate Symptom Score (IPSS) was recorded both prior to and following RT. The median interval that IPSS was recorded following SRT was 4 mo. All of these patients were treated with IMRT. The average IPSS prior to SRT was 5.24 (range: 0–19), and the average maximum IPSS following SRT was 7.00 (range: 0–30). Seventy-six percent of patients who

**Table 1 – Patient treatment characteristics and prostate-specific antigen outcomes**

| Factor                        | IMRT  
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>63 (45–80)</td>
</tr>
<tr>
<td>Follow-up, mo</td>
<td>53 (4–121)</td>
</tr>
<tr>
<td>Pre-SRT PSA, maximum, ng/ml</td>
<td>0.24 (0.06–91.2)</td>
</tr>
</tbody>
</table>

**Table 2 – Acute gastrointestinal toxicity**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgen-deprivation therapy, no vs yes</td>
<td>0.40</td>
<td>0.63</td>
</tr>
<tr>
<td>Age, continuous</td>
<td>0.19</td>
<td>0.97</td>
</tr>
<tr>
<td>Treatment technique, 3D-CRT vs IMRT</td>
<td>0.14</td>
<td>0.55</td>
</tr>
</tbody>
</table>

HR = hazard ratio; 3D-CRT = three-dimensional conformal radiation therapy; IMRT = intensity-modulated radiation therapy.
developed an IPSS ≥2 points above their baseline had their scores normalize within 2 points of their baseline within 12 mo (Fig. 2).

The 2- and 5-yr actuarial risk of developing CTCAE grade ≥2 late GU toxicity was 7% and 17%, respectively (Fig. 3a). The incidence of grade ≥2 late GU toxicity was not statistically different by treatment technique on univariate analysis (IMRT, 16.8%; 3D-CRT, 15.8%; \( p = 0.86 \); Fig. 3b) or multivariate analysis (HR: 1.1; \( p = 0.76 \) (Table 5). Baseline urinary function grade ≥2 (HR: 2.7; \( p = 0.01 \)) and acute urinary toxicity grade ≥2 (HR: 2.01; \( p = 0.04 \)) were associated with increased grade ≥2 late GU toxicity on multivariate analysis. Of the 48 patients who developed grade ≥2 toxicity, 21 patients (44%) had resolution of their symptoms with medical management.

The 2- and 5-yr actuarial risk of developing CTCAE grade ≥2 stricture was 1.4% and 3.7%, respectively. The 5-yr stricture-free survival in patients treated with IMRT and 3D-CRT was 96.4% and 96.2%, respectively (\( p = 0.32 \)). The median time to development of urethral stricture following RT was 2.4 yr (range: 0.5–8.4 yr). Of 13 urethral strictures, 4 strictures occurred after 5 yr. Nine patients had resolution of their urinary complaints following treatment of the urethral stricture, three patients developed recurrent strictures, and one patient did not have follow-up after dilatation. Three patients who developed strictures following SRT had a history of strictures prior to SRT.

### Urinary incontinence

The overall 2- and 5-yr risk of CTCAE grade ≥2 urinary incontinence (defined as spontaneous incontinence requiring pads) in patients with a baseline CTCAE grade ≤1 (defined as not requiring pads) was 7.8% and 10.7%, respectively (Table 6). The 5-yr risk of grade ≥2 urinary incontinence was not associated with treatment technique on univariate analysis (IMRT, 13.6%; 3D-CRT, 7.9%; \( p = 0.25 \); Fig. 4) or multivariate analysis (HR: 1.7; \( p = 0.22 \). A poor baseline urinary incontinence function (CTCAE grade 1 vs CTCAE grade 0) was associated with an increased risk of developing grade ≥2 urinary incontinence on univariate analysis (grade 0, 4.5%; grade 1, 21.2%; \( p < 0.01 \)) and multivariate analysis (HR: 4.21; \( p < 0.01 \)). Baseline grade

### Table 3 – Late gastrointestinal toxicity

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( p ) value</td>
<td>( p ) value</td>
</tr>
<tr>
<td>Acute GI toxicity, grade &lt;2 vs ≥2</td>
<td>0.99</td>
<td>0.87</td>
</tr>
<tr>
<td>Androgen-deprivation therapy, no vs yes</td>
<td>0.25</td>
<td>1.76</td>
</tr>
<tr>
<td>Age, continuous</td>
<td>0.85</td>
<td>1.00</td>
</tr>
<tr>
<td>Treatment technique, 3D-CRT vs IMRT</td>
<td>0.02</td>
<td>0.29</td>
</tr>
</tbody>
</table>

HR = hazard ratio; GI = gastrointestinal; 3D-CRT = three-dimensional conformal radiation therapy; IMRT = intensity-modulated radiation therapy.

### Table 4 – Acute gastrourinary toxicity

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( p ) value</td>
<td>( p ) value</td>
</tr>
<tr>
<td>Androgen-deprivation therapy, no vs yes</td>
<td>0.53</td>
<td>1.22</td>
</tr>
<tr>
<td>Age, continuous</td>
<td>0.36</td>
<td>0.98</td>
</tr>
<tr>
<td>Baseline function at SRT, CTCAE grade ≤2 vs &gt;2</td>
<td>0.04</td>
<td>2.90</td>
</tr>
<tr>
<td>Treatment technique, 3D-CRT vs IMRT</td>
<td>0.12</td>
<td>0.61</td>
</tr>
</tbody>
</table>

HR = hazard ratio; SRT = salvage radiation therapy; CTCAE = Common Terminology Criteria for Adverse Events; 3D-CRT = three-dimensional conformal radiation therapy; IMRT = intensity-modulated radiation therapy.
2 urinary incontinence was associated with an increased risk of developing grade 3 urinary incontinence by 5 yr compared with patients with baseline grade 0 or grade 1 urinary incontinence (baseline grade 0, 0.8%; baseline grade 1, 4.3%; baseline grade 2, 13.9%; \( p = 0.04 \)). Six of the 17 patients (35%) who developed grade 3 urinary incontinence acquired their symptoms following the management of a urethral stricture.

3.4. Erectile function

In the IMRT cohort, patients were more recently treated and were more likely to have undergone a unilateral or bilateral nerve-sparing prostatectomy (62%) compared with patients treated with 3D-CRT (26%, \( p < 0.01 \)) and were more likely to be potent at the time of SRT, defined as CTCAE grade <3 (IMRT, 63%; 3D-CRT, 37%; \( p < 0.01 \)).

Table 5 – Late gastrourinary toxicity

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( p ) value</td>
<td>HR</td>
</tr>
<tr>
<td>Acute GU toxicity, grade &lt;2 vs ≥2</td>
<td>0.01</td>
<td>2.01</td>
</tr>
<tr>
<td>Androgen-deprivation therapy, no vs yes</td>
<td>0.77</td>
<td>1.1</td>
</tr>
<tr>
<td>Age, continuous</td>
<td>0.23</td>
<td>0.96</td>
</tr>
<tr>
<td>Baseline function at SRT, CTCAE grade ≤2 vs &gt;2</td>
<td>&lt;0.01</td>
<td>2.67</td>
</tr>
<tr>
<td>Treatment technique, 3D-CRT vs IMRT</td>
<td>0.86</td>
<td>1.10</td>
</tr>
</tbody>
</table>

HR = hazard ratio; GU = gastrourinary; SRT = salvage radiation therapy; CTCAE = Common Terminology Criteria for Adverse Events; 3D-CRT = three-dimensional conformal radiation therapy; IMRT = intensity-modulated radiation therapy.

Table 6 – Urinary incontinence

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( p ) value</td>
<td>HR</td>
</tr>
<tr>
<td>Androgen-deprivation therapy, no vs yes</td>
<td>0.10</td>
<td>0.48</td>
</tr>
<tr>
<td>Age, continuous</td>
<td>0.15</td>
<td>1.04</td>
</tr>
<tr>
<td>Baseline grade, CTCAE grade 0 vs 1</td>
<td>&lt;0.01</td>
<td>4.2</td>
</tr>
<tr>
<td>Treatment technique, 3D-CRT vs IMRT</td>
<td>0.25</td>
<td>1.70</td>
</tr>
</tbody>
</table>

HR = hazard ratio; CTCAE = Common Terminology Criteria for Adverse Events; 3D-CRT = three-dimensional conformal radiation therapy; IMRT = intensity-modulated radiation therapy.
Of the 99 patients who were potent at the time of SRT (CTCAE grade < 3) and not prescribed ADT, the 2- and 5-yr actuarial impotence-free survival was 82% and 73%, respectively. Five-year impotence-free survival was not associated with treatment technique on univariate analysis (IMRT, 74%; 3D-CRT, 70%; p = 0.82) or multivariate analysis (HR: 0.53; p = 0.21) (Table 7).

4. Discussion

Although IMRT has been shown to reduce toxicity in the definitive setting in the context of the higher doses that are routinely prescribed, the benefits have not been clearly elucidated in the setting of SRT. This study represents the largest single-institutional experience directly comparing long-term toxicity in patients treated with 3D-CRT and IMRT in the salvage setting following radical prostatectomy.

To our knowledge, we are the first to report that with IMRT, the risk of developing late GI toxicity with postprostatectomy salvage RT is significantly reduced compared with 3D-CRT. This reduction was seen despite the significantly larger average dose that was prescribed to patients being treated with IMRT. The 1.9% 5-yr rate of late grade ≥ 2 GI morbidity following SRT with IMRT compares favorably with the rates of GI morbidity presented in the literature in which patients are predominantly treated with 3D-CRT [7,12,16–25]. The largest previous postprostatectomy IMRT study, published by De Merleer et al. [10], reported a 16% rate of radiation-induced lower-intestinal toxicity grade ≥ 2. The increased toxicity in that series may be partially explained by the higher median dose, 75 Gy, that was prescribed. However, other studies have reported toxicity results with IMRT that are more similar to our series, which supports our finding that IMRT is beneficial in improving the therapeutic ratio of SRT.

Others have reported a benefit of IMRT in reducing acute GI toxicity and have further speculated that IMRT should result in a reduction in late GU toxicity [20,23,26]. We found no difference in either regard. It is possible that the higher doses that IMRT patients received in our study compared with 3D-CRT patients may have masked this theoretical benefit. Although we did not find a statistical difference between the rates of urinary incontinence based on treatment technique, our data support the notion that baseline urinary incontinence is the strongest predictor of long-term urinary continence following treatment. Our results are similar to those reported by Pearse et al, in which the rate of incidence of grade ≥ 2 urinary incontinence was 35% for patients with baseline urinary incontinence compared with 9.6% for patients with no baseline urinary incontinence [18].

Our study has several limitations. First, we were unable to independently assess the impact of dose from treatment technique, as IMRT patients almost exclusively received doses > 70 Gy. However, despite the higher doses, it is encouraging that patients treated with IMRT demonstrated reduced late GI toxicity. An additional possible confounding variable in this assessment is that patients treated with 3D-CRT were treated in an earlier era than patients treated with IMRT, reflecting the pattern of practice at MSKCC.

5. Conclusions

We present what is, to our knowledge, the largest comparison in the literature of late effects in patients treated with high-dose SRT using 3D-CRT or IMRT. We found that IMRT results in a significant reduction in late GI side effects. Despite the fact that patients treated with IMRT were more likely to be treated with a higher dose than patients treated with 3D-CRT, we did not see an increase in late GU toxicity, urinary incontinence, or erectile dysfunction. Our data support the idea that IMRT significantly improves the therapeutic ratio associated with SRT in the postprostatectomy setting.

Author contributions: Michael J. Zelefsky had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Goenka, Zelefsky.
Acquisition of data: Pei, Schechter, Goenka, Magsanoc, Zelefsky.
Analysis and interpretation of data: Goenka, Pei, Zelefsky.
Drafting of the manuscript: Goenka, Zelefsky, Pei.
Critical revision of the manuscript for important intellectual content: Kollmeier, Cox, Scardino, Eastham.
Statistical analysis: Pei.
Obtaining funding: None.
Administrative, technical, or material support: Pei, Schechter.
Supervision: Zelefsky.
Other (specify): None.

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References