Two Different Intensity-modulated Radiotherapy Strategies for Patients with High-risk Prostate Cancer

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Abstract. Aim: To compare toxicity profiles of two different intensity-modulated radiation therapy (IMRT) strategies in patients with high-risk prostate cancer. Patients and Methods: From May 2010 to September 2012, 43 patients with high-risk prostate cancer were treated with IMRT and concurrent hormone therapy; 23 patients were treated by conventional fractionation (IMRT/C) and 20 patients by simultaneous integrated boost (IMRT/SIB). Acute and late toxicities were compared for each group. Results: Severe acute genitourinary toxicity was recorded in 8.6% and 2% of patients in the IMRT/C and IMRT/SIB group, respectively. Genitourinary toxicity G2 was observed in 39.1% (IMRT/C group) and 25% (IMRT/SIB group) of patients. Severe acute gastrointestinal toxicity was not observed; Grade 2 acute gastrointestinal toxicity was recorded in 21.7% (IMRT/C group) and 10% (IMRT/SIB group). Grade 2 late genitourinary toxicity was observed in 26% (IMRT/C group) and 15% (IMRT/SIB group), whereas G2 late gastrointestinal toxicity in 34.5% and 30% of patients, respectively. No significant differences in incidence and severity of genitourinary and gastrointestinal toxicity were detected between the two IMRT treatment strategies. Conclusion: IMRT/SIB was well-tolerated with favorable rates of acute and late toxicity, both genitourinary and gastrointestinal. Compared to IMRT/C, IMRT/SIB maintained the same efficacy and reduced the overall treatment time.
Radiation therapy technique. All patients were simulated and treated supine, with a comfortably full bladder. A foot support was used for immobilization of the legs. Patients were treated using 6-MV photons and treatment was given in five daily fractions per week. The intensity-modulated beams were delivered with a multileaf collimator, using the step and shoot technique. Treatment verification was performed using electronic portal imaging device once a week. Treatment-planning computed tomographic (CT) scan with a 2 mm slice thickness from L3 to 1 cm below the ischium was obtained. The planning target volume 1 (PTV1) was defined as the entire prostate gland, complete seminal vesicles and pelvic lymph nodes (internal iliacs, external iliacs, obturator). PTV2 included the prostate gland and the seminal vesicles, and PTV3 the entire prostate gland only. Because two different fractionation strategies have been studied, using the same technique, the arm of the conventional fractionation was named IMRT/C, whereas the group of patients treated by SIB was named IMRT/SIB. In the IMRT/C group, the prescribed dose was 50.4 Gy in daily fractions of 1.8 Gy for PTV1 plus 20 Gy in daily fractions of 2 Gy for PTV2. For IMRT/SIB, the prescription dose was 45 Gy in 1.8 Gy/fraction to PTV1, concurrently with 56.25 Gy in 2.25 Gy/fraction to PTV2 and 68.75 Gy in 2.75 Gy/fraction to PTV3.

Follow up. All patients were routinely followed during the RT, at one month after the end of treatment, and then every three months. Acute and late toxicities were graded according to National Cancer Institute Common Toxicity Criteria version 3.0 (8). Hormone therapy was proposed to all patients and was typically begun two months prior to the start of RT.

Statistical analysis. Toxicity data were compared using Fisher’s test. All reported p-values were considered to be statistically significant at less than 0.05 from two-sided tests. Statistical analysis was performed with MATLAB, version 7.5.0.342 (Rome, Italy).

Results
A total of 43 patients with high-risk prostate cancer were treated between May 2010 and September 2012. The IMRT/C group consisted of 23 patients and the IMRT/SIB group included 20 patients. All patients received the prescribed course without treatment delays. The median follow-up of all patients was 25 months (range=12-28 months).

Acute toxicity. We observed severe acute genitourinary toxicity in 8.6% and 2% of patients in the IMRT/C and IMRT/SIB group, respectively. No application of urinary catheter was required. Genitourinary toxicity G2 was recorded in 39.1% (IMRT/C group) and 25% (IMRT/SIB group) of patients. Patients started alpha-blocker medications and after two weeks of treatment; symptoms in all patients had improved to Grade 1.

Considering all enrolled patients, the most common genitourinary symptom was urinary frequency/urgency [65.7% 95% confidence interval (CI)=43.3-80.8%], followed by cystitis [43.1%; 95% CI=23.9-60.4%]. Symptoms persisted for more than four weeks in 35% (IMRT/C group) and 33% (IMRT/SIB group) of patients. Symptoms were present 12 weeks after the end of treatment in 13% (IMRT/C group) and 10% (IMRT/SIB group) of patients. Severe acute gastrointestinal toxicity was not observed. Grade 2 acute gastrointestinal toxicity was recorded in 21.7% (IMRT/C group) and 10% (IMRT/SIB group) and it persisted for more than four weeks only in two patients of the IMRT/C group. The maximal acute gastrointestinal toxicity was G1 in 60.8% (IMRT/C group) and 55% (IMRT/SIB). The most common toxicity was diarrhoea [43.1%; 95% CI=19.4-53.9%]. No significant differences in terms of incidence and severity of genitourinary and gastrointestinal toxicity were detected between the two different IMRT treatment strategies. The baseline and acute toxicities are shown in Figure 1.

Late toxicity. Severe late genitourinary toxicity was not recorded. Grade 2 genitourinary toxicity was observed in 26% (IMRT/C group) and 15% (IMRT/SIB group), whereas G1 toxicity in 56.5% and 45% of patients, respectively. The most common late symptom was frequency/urgency (47.3%; 95% confidence interval 22.7-64.3%). Only one patient

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Table I. Patients' characteristics.

<table>
<thead>
<tr>
<th></th>
<th>IMRT/C</th>
<th>IMRT/SIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Mean age (range), years</td>
<td>65.9 (47-80)</td>
<td>67.5 (48-79)</td>
</tr>
<tr>
<td>Stage, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>10 (43.5%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>T2c</td>
<td>11 (47.8%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>T3a</td>
<td>2 (8.7%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Gleason score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-7</td>
<td>5 (21.7%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>8-9</td>
<td>14 (60.8%)</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>PSA, ng/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>2 (8.7%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>10-20</td>
<td>10 (43.5%)</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>11 (47.8%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Hormone therapy, n (%)</td>
<td>23 (100%)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>Total dose RT, Gray</td>
<td>70.4</td>
<td>68.75</td>
</tr>
<tr>
<td>Duration of RT, fractions</td>
<td>38</td>
<td>25</td>
</tr>
</tbody>
</table>

IMRT: Intensity-modulated radiotherapy; SIB: simultaneous integrated boost; PSA: prostate-specific antigen; RT: radiation therapy.
treated by IMRT/C presented severe rectal toxicity. He described rectal discomfort and bleeding 11 months after treatment that required endoscopic intervention. In the IMRT/SIB group, no G3 gastrointestinal toxicity was recorded. Grade 2 late gastrointestinal toxicity was observed in 34.5% (IMRT/C group) and 30% (IMRT/SIB group) of patients, and included diarrhoea and proctitis.

Discussion

In light of the unsatisfactory local control and survival results in prostate cancer with past treatments, over the last 10 to 15 years, there has been a significant interest in dose escalation for prostate RT (9-10). Moreover, to improve outcome, the use of hormone treatment combined with external beam irradiation have been examined and became the standard for high-risk patients (11-13). IMRT is a technique increasingly used due to its potential reduction of normal tissue toxicities, particularly proctitis and dysuria resulting from irradiation of the rectum and bladder, respectively. Excellent candidates for IMRT include patients with high-risk disease, because of pelvic nodal irradiation. The high-dose gradients, the highly conformal plans and the lower alpha/beta ratio of prostate cancer tissue compared to the adjacent organs at risk have been the basis for the hypofractionation schemes to maintain tumour control without increasing toxicity (14). SIB technique allows the simultaneous delivery of different dose prescriptions to different target volumes in the same treatment fraction. The potential benefit of the SIB concept is that it reduces the overall treatment time and increases the fraction size to the boost volumes (15). In the past, different hypofractionation schemes have been examined in phase III trials, but results cannot be definitively validated due to the inappropriate total dose delivered (16). To address this problem, single-centre series have tested hypofractionated RT protocols, using recent techniques, such as IMRT or image-guided RT, to ensure adequate biological equivalent dose to the target.

Figure 1. Baseline and maximal acute genitourinary (GU) and gastrointestinal (GI) toxicities. IMRT/C: Conventional fractionation; IMRT/SIB: simultaneous integrated boost.
volumes (17-22). The purpose of this study was to compare the toxicity and efficacy of two different fractionation strategies used to design IMRT plans in patients treated with concomitant hormone therapy for high-risk prostate cancer. To our knowledge, no prospective or retrospective studies exist comparing IMRT conventional fractionation strategy versus SIB for the treatment of this sub-group of patients. Results showed that IMRT/SIB was well-tolerated with favourable rates of acute and late toxicity, both genitourinary and gastrointestinal. Compared to IMRT/C, IMRT/SIB maintained the same efficacy and reduced the overall treatment time (5 vs. 8 weeks).

Despite lack of similar trials, we have compared our results with IMRT techniques reported in other series. In the last analysis of a prospective phase I-II trial combining whole-pelvis RT, dose-intensified hypofractionated prostate boost, and long-term hormone therapy in patients with high-risk prostate cancer by Quon et al., there was an additional cohort of 30 patients treated with a single-phase IMRT technique (23). In the sub-group IMRT cohort analysis, G2 acute genitourinary and gastrointestinal toxicity was reported in 46.4% and 32.1% of patients, respectively. Compared to those rates, both G2 acute genitourinary (25%) and gastrointestinal (10%) toxicity was improved in our study. Moreover, the rate of G2 or greater genitourinary and gastrointestinal toxicity in our series compared favourably with that reported by Arcangeli et al., in which patients with grade 2 acute genitourinary and gastrointestinal toxicity were 37% and 29%, respectively (18). McCammon et al. performed a retrospective toxicity analysis in 30 consecutive patients with intermediate to high-risk prostate cancer treated definitively with pelvic IMRT-SIB (20). Our rate of gastrointestinal toxicity (diarrhoea) was slightly greater than that reported in their series (43.1% vs. 36.7%). In the trial by McDonald et al., the hypofractionated simultaneous RT regimen resulted in 44% of patients with early urinary complications and 36% with early rectal complications but no differences in toxicity grade were found (21). According to our clinical data, the majority of late events of G2, and G3 toxicity was recorded in a very small percentage of patients, but the median follow-up (3.7 years) of McDonald et al. was definitely longer than ours (25 months) and makes these results difficult to compare. Focussing on the evaluation of the late adverse effects, the absence of G3 or greater late toxicity in our series was comparable to that reported in the series of Quon et al. (23), in which a similar median follow-up period (27 months) was reported for the IMRT cohort.

Although this study has shown both safety and efficacy with the use of IMRT/SIB for high-risk prostate cancer, it is important to note the limitations of this analysis. Firstly, this study is limited by its relatively small number of patients, with a median follow-up time of 25 months, although this was adequate to detect differences in acute and late toxicity. Moreover, well-defined inclusion criteria helped to minimize bias. Toxicity data were recorded at the time of patient presentation in a standardized manner to ensure quality and they were correlated with toxicity grading to reduce the rate of underreported events. A longer follow-up will be required to determine if the different regimens have an effect on biochemical control. However, the proposed IMRT/SIB technique demonstrates a non-inferiority and offers potential advantages such as better sparing of critical structures and shorter treatment duration.

## Conclusion

There is no definite consensus on how to treat patients with high-risk prostate cancer. Current evidence suggests a multimodality therapy, combining hormone therapy with RT. The optimal RT technique to reduce excessive treatment-related toxicities is IMRT, but the best IMRT fractionation strategy is still debate. In this study, IMRT/SIB was a safe regimen and was associated with favourable toxicity profile, with less genitourinary and gastrointestinal toxicity compared with conventional IMRT fractionation. Altered fractionation RT seems to be efficient, delivering the same biological dose in a shorter period of time.

## References

De Felice et al: IMRI and IMRT/SIB in High-risk Prostate Cancer Patients


Received March 2, 2014
Revised May 5, 2014
Accepted May 8, 2014