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.*

The clinical trial was registered in the registry of research projects of Sapienza University of Rome, 2012 (no. C26A12SBYM).

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Prostate cancer represented the major public health problem in the male population, with an eximated new cases of 238.590/year in 2012 (1). Concurrent hormone therapy and radiation therapy (RT) remains the standard-of-care for high-risk prostate cancer (2). Intensity-modulated radiation therapy (IMRT) nowadays is preferred to 3D-conformal RT due to target volume adequacy of coverage and widespread organs at risk (3). But the treatment volume for patients affected with high-risk prostate cancer continues to be a controversial topic. The debate regarding the RT field is still ongoing and the inclusion of the pelvic lymph nodes remains controversial (4). Pre-treatment prostate-specific antigen (PSA) value, clinical stage disease and biopsy Gleason score are validated nomograms which accurately predict the risk of positive pelvic lymph nodes (5). The benefit of pelvic irradiation depends on the real likelihood of there being positive lymph nodes. The accurate estimation of the risk of regional lymph node metastases is better evaluated by the Yale formula, which correlates PSA, Gleason score and T stage (6). Patients at high risk for lymph node-positive disease were differentiated using a >15% risk as a cut-off; for these patients, pelvic irradiation is recommended (2).

The aim of the present study (approved by the Sapienza University of Rome) was to compare two different IMRT treatment strategies used at our Institution for patients with high-risk prostate cancer treated with concurrent hormone therapy. The first treatment strategy was a conventional fractionation strategy, the second was a simultaneously integrated boost (SIB). We predicted that feasibility and toxicity of the SIB regimen for high-risk prostate cancer would be non-inferior to those of the conventional regimen.

Patients and Methods

Study design. In this single-Institute clinical study, all patients treated between May 2010 to September 2012 for high-risk prostate cancer were enrolled. Inclusion criteria were: high-risk adenocarcinoma; treatment with a curative intent; and treatment with hormone therapy. Patients were excluded if treated in the

adjuvant postoperative setting or for tumour recurrence. No patients included in the study had known metastatic disease at presentation. The results are based on a final follow-up as of September 2013. This study was approved by the Sapienza University of Rome in the context of research about the quality of practice.

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, esternal 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.

Patients' characteristics. Patient demographic data are shown in Table I. Clinical staging determinations were made according to the seventh edition of the American Joint Commitee on Cancer staging criteria (7). The cancer lymph node risk was evaluated using Yale formulae (6). Hormone therapy was proposed to all patients and was typically begun two months prior to the start of RT.

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)

Statistical analysis. Toxicities 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.

Table I. *Patients' characteristics*.

	IMRT/C	IMRT/SIB
Patients (n)	23	20
Mean age (range), years	65.9 (47-80)	67.5 (48-79)
Stage, n (%)		
T2b	10 (43.5%)	10 (50%)
T2c	11 (47.8%)	8 (40%)
T3a	2 (8.7%)	2 (10%)
Gleason score, n (%)		
≤6	5 (21.7%)	2 (10%)
7	4 (17.4%)	6 (30%)
8-9	14 (60.8%)	12 (60%)
PSA, ng/ml		
<10	2 (8.7%)	1 (10%)
10-20	10 (43.5%)	11 (55%)
>20	11 (47.8%)	8 (40%)
Hormone therapy, n (%)	23 (100%)	20 (100%)
Total dose RT, Gray	70.4	68.75
Duration of RT, fractions	38	25

IMRT: Intensity-modulated radiotherapy; SIB: simultaneous integrated boost; PSA: prostate-specific antigen; RT: radiation therapy.

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

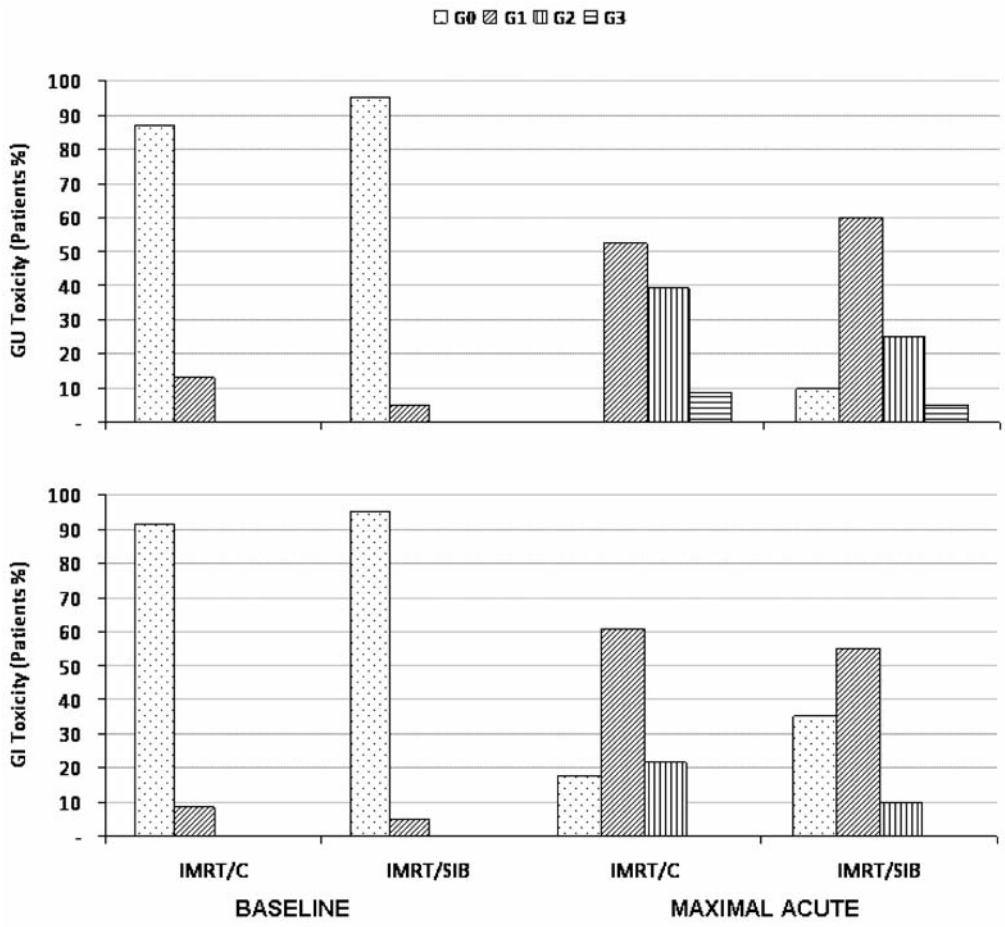

Figure 1. *Baseline and maximal acute genitourinary (GU) and gastrointestinal (GI) toxicities. IMRT/C: Conventional fractionation; IMRT/SIB: simultaneous integrated boost.*

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

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.

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