Hypofractionated Radiotherapy with or without IGRT in Prostate Cancer: Preliminary Report of Acute Toxicity

MAURIZIO VALERIANI, FLAVIA MONACO, MATTIA FALCHETTO OSTI, VITALIANA DE SANCTIS, GIUSEPPE MINNITI and RICCARDO MAURIENRI

Operative Radiotherapy Unit, S. Andrea Hospital, La Sapienza University of Rome, Rome, Italy

Abstract. Background: To evaluate the acute tolerance to hypofractionated schedule of patients with prostate cancer. Methods: We treated 62 patients with intermediate risk prostate cancer. All patients were treated with a total dose of 43.8 Gy on seminal vesicles and 54.75 Gy on prostate, 3.65 Gy per fraction, three times a week for a total of 5 weeks. All patients underwent neoadjuvant, concomitant and adjuvant hormonal therapy. Thirty-six patients were submitted to image-guided radiation therapy (IGRT). Results: Median follow-up was 15 months (range 3-33 months). Toxicities during the treatment were: grade 1-2 gastrointestinal (GI) toxicity, 22.6%; grade 1-2 genitourinary (GU) toxicity, 51.6%. Toxicities 3 months after the end of the treatment were grade 1-2 GI 6.5%, grade 1-2 GU 9.7%. No statistical difference was observed comparing acute toxicity in patients treated with or without IGRT. Conclusion: This study showed that the hypofractionation schedule used is well tolerated, with a low rate of acute grade 1-2 GI toxicity and without major grade (≥3) acute toxicity. Longer follow-up is needed to determine if this low rate of acute toxicity will be translated in a low rate of late toxicity.

The different sensitivity of different tissues to fractionation changes can be quantified through the α/β ratio in the linear-quadratic model (1). The α/β ratio parameter is an indication of the fractionation sensitivity of a particular cell type. In general α/β is high (≥10 Gy) for early-responding normal tissues (skin and mucosa) and most tumors and low (<5 Gy) for late-responding normal tissue (spinal cord and bone). One implication of different α/β ratios for tumor cells and normal tissue is that it may be possible to increase the therapeutic ratio. Specifically, if α/β for prostate cancer is lower than the nearby normal tissues, then therapeutic advantage can be gained by using fewer, larger fractions (2). In 1999, Brenner and Hall (3) calculated the α/β ratio of prostate tumor after radiotherapy, using the linear-quadratic model and the obtained α/β value was 1.5 Gy (95% confidence interval, CI=0.8-2.2 Gy). Another matter is the α/β of the rectum and bladder. The α/β values of the rectal late-responding tissues have been found to be between 3 and 6 Gy, most probably around 5 Gy (4-5). Hypofractionation would, thus, reduce early side effects (if overall treatment time is left constant) or this gain in therapeutic index could be used to shorten overall treatment time. If the prostate tumor α/β ratio is lower than that for late rectal tissues, hypofractionated therapies could be designed with larger dose/fraction, fewer fractions, but not shortening the overall treatment too drastically, in order to maintain acute toxicity rates. It has been suggested that much rectal injury is actually a result of acute toxicity, which would fit in with a high α/β value for late rectal injury (7, 8).

According to these postulations, in 2007 we started a prospective study at our institution using an hypofractionated schedule (365 cGy for 15 fractions/3weeks) for patients with intermediate risk prostate cancer and here we have preliminarily analyzed the tolerance of this regimen in term of compliance and acute toxicity.

Patients and Methods

Between March 2007 and March 2010, 62 patients with intermediate risk (T1-T2c and Gleason score 7 and PSA ≤10 ng/ml or T1-T2c and Gleason score ≤7 and PSA 10-20 ng/ml) biopsy-proven carcinoma of the prostate were treated in our institution. The median age was 75 (range 55-85) years. Median PSA at diagnosis was 8.5 ng/ml (range 3.3-19 ng/ml). The distribution of T-stage, Gleason score and initial PSA is shown in Table I. Patients were extensively informed with an appropriate informed consent regarding the regimen of hypofractionation used in this study.

All patients underwent total body computed tomography (CT) with contrast medium, total-body scintigraphy and whole-blood count for systemic staging. The first 36 patients underwent trans rectal prostate ultrasonography and the last 26 patients diffusion,
perfusion, high resolution T2-weighted magnetic resonance (MR) of the prostate for local staging. All patients were submitted to CT with slides of 2.5 mm for the subsequent implementation of treatment planning.

The preparation for the implementation of CT involves the administration of a mini enema to the patient for rectal emptying, the patient was also invited to urinate and to drink 500 ml of water 30 minutes before the start of the procedure to fill the bladder. The patients were immobilized in the supine position during CT with a foot-block.

MR imaging (diffusion ADC map, diffusion series and axial high resolution T2-weighted) were fused with planning CT in the last 26 patients to help in clinical target volume (CTV) delineation and those patients were submitted to image guided radiation therapy (IGRT) for implementation in November 2008 of a linear accelerator with on board imaging (OBI) system. The CTV1 included the prostate plus the seminal vesicles (SV) and CTV2 only the prostate. The margins for the planning target volume (PTV1 and 2) were 8 mm in all directions except in the posterior direction, which was 6 mm in patients not submitted to IGRT and 5 mm in all directions for patients submitted to IGRT. The organs at risk contoured on the planning CT were: rectum from the sigmoid flexure to the anal canal, bladder and femoral heads. A 3-D conformal plan was executed in all cases using 5 coplanar fields (anterior, 2 lateral and 2 anterior-oblique). All patients were treated with 15 MV linear accelerator and received a total dose of 43.8 Gy at 3.65 Gy per fraction (12 fractions) to PTV1 and 54.75 Gy at 3.65 Gy per fraction (15 fractions) to PTV2, three times a week and the total duration of radiation treatment was 5 weeks. The first 36 patients were assessed during treatment daily by portal imaging matched with digitally reconstructed radiographs (DRRs), whereas for the last 26 patients, this was achieved with daily cone-beam CT.

The normalized total dose (NTD) of this fractionation for prostate cancer (α/β=1.5) was 79.5 Gy while for the late response in healthy tissue (α/β=3) it was 72 Gy (late effects). The choice of total duration of 5 weeks of treatment derived from extrapolations from studies focused on defining the optimal duration of treatment in tumors of head and neck (α/β=10) (9). Attributing an α/β ratios 10 to the mucosa, the acute biologically effective dose (BED) for this fractionation regimen was 54.5 Gy, lower than the 60 Gy that is the theoretical upper limit for high risk of serious acute reactions. The minimal (Dmin), mean (Dmean) and maximal dose (Dmax), delivered to the 95% of PTV1 and PTV2 volumes were analysed. The normal tissue dose–volume constraints were: V45 <35% and V52 <25% for the rectum and V40 <50% for the bladder (considering an α/β of 3 Gy for rectum and 5 Gy for bladder).

All patients underwent addition, neoadjuvant hormonal therapy, concomitant and adjuvant radiotherapy for a total of 9 months overall, starting 3 months before radiotherapy with antiandrogen (bicalutamide 150 mg) in 43/62 patients (69.4%) and luteinizing hormone-releasing hormone (LHRH) analogs in the other 19/62 (30.6%).

Acute toxicity was assessed by the physician using the RTOG/EORTC system (10) during the treatment, 1 month after the end of therapy and then every 3 months.

Results

The median follow-up for all patients was 15 months (range 3-33 months), with a median of 17 months (range 3-33 months) for patients treated without IGRT and 5 months (range 3-11 months) for those treated with IGRT. At the end of follow-up no grade 3 or 4 side effects were observed.

The toxicities during the treatment were: grade 1-2 gastrointestinal (GI) toxicity 22.6% (16.7% for non-IGRT and 30.8% for IGRT), grade 1-2 genitourinary (GU) toxicity 51.6% (52.8% for non-IGRT and 50% for IGRT). The toxicities 1 month after the end of the treatment were grade 1-2 GI 3.2% (5.6% for non-IGRT and 0% for IGRT), grade 1-2 GU 19.3% (27.8% for non-IGRT and 7.7% for IGRT). The toxicities 3 months after the end of the treatment were grade 1-2 GI 6.5% (5.6% for non-IGRT and 7.7% for IGRT), grade 1-2 GU 9.7% (16.7% for non-IGRT and 0% for IGRT).

The median PSA before the start of radiotherapy was 1.3 ng/ml (range 0.009-3.5 ng/ml), and that at the last follow-up was 0.21 ng/ml (range 0-1.37 ng/ml).

Table I. Characteristics of patients.

<table>
<thead>
<tr>
<th>T-Stage</th>
<th>Gleason Score</th>
<th>PSA (ng/ml) before any therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>5/62 (8.06%)</td>
<td>≥6</td>
</tr>
<tr>
<td>2a</td>
<td>21/62 (33.87%)</td>
<td>≤25</td>
</tr>
<tr>
<td>2b</td>
<td>16/62 (25.8%)</td>
<td>4+3</td>
</tr>
<tr>
<td>2c</td>
<td>20/62 (32.25%)</td>
<td>≥6</td>
</tr>
</tbody>
</table>

Statistical analysis. We used a nonparametrical test (Pearson chi-square) to compare the acute toxicity, considered as a dichotomized variable (presence or absence) in patients treated with or without IGRT. The toxicity was considered present if recorded in one of three times analyzed (during the treatment, at 1 and 3 months after the end of radiotherapy). No statistical difference was observed comparing acute GI and GU toxicity in patients treated with or without IGRT (p=0.448 and p=0.384, respectively; Chi-Square test).

For all patients, we respected the rectal constraint V52 ≤25%, but did not respect the rectal constraint V45 ≤35% in 4 patients (6.6%) and the bladder constraint V40 ≤50% in 14 cases (22.6%). Analyzing our data, there was a significant difference of acute toxicity if rectal V52 was <10% or ≥10%.
and a trend if rectal V45 was <20% or ≥20%. Rectal V52 ≤10% was obtained in 25/62 patients (40.3%) with grade 1 and grade 2 toxicity in 2/25 (8%) and 1/25 (4%) cases respectively; instead in patients with V52 >10% grade 1 and grade 2 toxicity was seen in 5/37 (13.5%) and 8/37 (21.6%) cases, respectively (p=0.03; Chi-square). Rectal V45 ≤20% was reached in 24 patients (38.7%) presenting grade 1 toxicity in 2/24 cases (8.3%) and grade 2 in 1/24 cases (4.2%). In patients with V45 >20%, grade 1 toxicity was seen in 5/38 cases (13.2%) and grade 2 in 8/38 cases (21.1%) (p=0.06; Chi-square). For bladder, there was no statistically significant difference in toxicity (V40 ≤30% vs. >30%, p=0.0965; V40 ≤20% vs. 20%, p=0.391). The acute effects were evaluated considering the worst grade scored at the three time point.

Discussion

Many authors have demonstrated a rising interest in hypofractionated schedules in the treatment of localized prostate cancer, with the aim of increasing the biological effect to the tumor, assuming an α/β value of 1.5 Gy (8, 11, 12) and reducing the toxicity for the organ at risk. With this consideration, in March 2007, we started to use hypofractionation treatment associated with neoadjuvant, concomitant and adjuvant hormone therapy in patients with intermediate-risk prostate cancer. We report the acute toxicity considering the short follow-up of these patients, especially those treated with IGRT.

During the treatment, grade 1-2 GI toxicity was 22.6% in all patients, 16.7% for patients treated without IGRT and 30.8% for those treated with IGRT. This toxicity ratio decreased 1 month after the end of the treatment (grade 1 GI 3.2%; 5.6% for patients treated without IGRT and 0% for those treated with IGRT) with no grade 2 acute effect, with a slight increase after 3 months (grade 1-2 GI 6.5%; 5.6% for patients treated without IGRT and 7.7% for those treated with IGRT). No grade 3-4 toxicity was reported.

In our study, the acute GI effect is low and similar to that reported by Rene et al. (13), despite the lower BED10 calculated using the BED formula (equation 1) with the correction for the time factor

\[
BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{\log e^2}{\alpha T} (T - T_k)
\]

as reported by Fowler et al. (9), and lower than other data reported in the Table II except for those reported by Lukka et al. (14).

Regarding the BED formula shown Fowler et al. used a simple linear quadratic (LQ) formula including cell proliferation (15). Specifically, the overall time was represented by T, with the first day designated Day 0, not
Day 1. The parameters were selected with a comprehensive review of clinical results from several dozen published schedules used for treating head and neck cancer (16). They included $a/b=10$ Gy; $\alpha/\beta=0.35$ Gy$^{-1}$; an onset time for repopulation in human oral mucosa of $T_1=7$ days (17); and an average doubling time of $2.5$ days thereafter. Although this formula is likely to be too simple in its representation of only two repopulation rates, zero and $T_D$, it has served well in comparing tumor BEDs in the head and neck schedules studied (16). Analyzing the data (Table II) many studies presented BED10 higher than 60, reporting a low rate of major acute toxicity.

The incidence of acute toxicity in our cohort is similar to that of other series. For instance, Soete et al. (18), using $56$ Gy in 16 fractions of $3.5$ Gy reported $75\%$ of grade 1-2 acute GU toxicity with no grade 3 toxicity, compared with $51.6\%$ of grade 1-2 GU toxicity in our series. There are some differences between these studies: Soete et al. used higher BED10 ($61.3 \text{ vs.} 54.5$), with different dose/fraction ($3.5 \text{ vs.} 3.65$ Gy) and the time of treatment was shorter than that of the current study ($3$ weeks vs. $5$).

It is, however, difficult to compare acute side-effects between different institutions because of differences in patient selection criteria, treatment technique and the scoring system used. In our study patients treated with IGRT presented acute GI toxicity similar (higher during treatment) to those treated without IGRT, despite the lower margin from CTV to PTV. This may be due to the low toxicity rate related to the radiobiological effect of the hypofractionated schedule used itself. Furthermore, the patients whose V52 was $<10\%$ presented statistically significant lower toxicity than other patients. This implies that the rectal dose constraint is the most important factor to reduce acute GI toxicity.

In conclusion, this study showed that the hypofractionation schedule used ($54.75$ Gy in 15 fractions for $3.65$ Gy per fraction) is well tolerated with a low rate of acute grade 1-2 gastrointestinal toxicity and without a major grade (23) acute toxicity. Longer follow-up is needed to determine outcomes in terms of disease control and if the low rate of acute toxicity is translated in a low rate of late toxicity.

References


3558

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