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ORIGINAL ARTICLE

A hypofractionated radiotherapy schedule with 57.75Gy in 21 fractions for T1-2N0 prostate carcinoma: Analysis of late toxicity and efficacy

Vassilis Kouloulias[1], Anna Zygogianni[2], Ioanna Kantzou[3], Maria Tolia[1], Kalliopi Platoni[1], Christos Antypas[2], Demetrios Chaldeopoulos[1], Panagiotis Pantelakos[1], Argyrios Siatelis[4], Michael Chrysofos[4], Ivelina Beli[1], Maria Dilvoi[1], Ioannis Georgakopoulos[1], George Sarris[3], John Kouvaris[2], Nikolaos Kelekis[1]

[1]Kapodistrian University of Athens, Medical School, 2nd Radiology Department, Radiotherapy Unit, Attikon Hospital, Athens; [2]Kapodistrian University of Athens, Medical School, 1st Radiology Department, Radiotherapy Unit, Aretaieion Hospital, Athens; [3]1st Radiotherapy Department, Metaxa Cancer Hospital, Piraeus; [4]Urology Department, Attikon University Hospital, Athens, Greece

Summary

Purpose: *The primary endpoint was to assess the late toxicity of a hypofractionated radiotherapy schedule in relation to radiation parameters concerning the rectum and bladder. The second endpoint was to assess a composite of biochemical and clinical failure.*

Methods: *Sixty-four prospectively selected patients diagnosed with localized low risk prostate cancer, Gleason score (GS) <7, PSA <10, and T1-2N0, were treated with external 3- dimensional conformal radiotherapy (3D-CRT). Patients received 57.75 Gy in 21 daily fractions of 2.75 Gy/fraction.*

Results: *Late gastrointestinal (GI) toxicity was as follows: grade 0: 47 (73.4 %) patients, grade 1: 12 (19.2 %), grade 2: 4 (6.3%), and grade 3: 1 (1.6%). There was a significant correlation between D50, V70 and EORTC/RTOG late rectal toxicity score (p<0.001 and p=0.006, respectively). Grade 1 and 2 late bladder toxicity was seen in 4.7 and 1.6% of the patients, respectively. With a median follow up of 18 months no biochemical relapse was observed.*

Conclusion: *The present study supports the use of hypofractionated radiation therapy which showed a high therapeutic ratio with acceptable toxicity and no biochemical relapse during follow-up.*

Key words: *D50, hypofractionation, prostate cancer, radiotherapy ,V70, rectum toxicity*

Introduction

Prostate cancer belongs to tumors for which a radiation dose–response has been established by several dose escalation trials [1,2].

Moreover, prostate cancer has also come to the forefront of clinical radiobiological research with great relevance to clinical practice and for the design of trials evaluating new biologically driven strategies [3,4].

The aim of this study was to assess the late toxicity of a hypofractionated radiotherapy schedule in relation to radiation parameters concerning the rectum and bladder. Thus, the primary endpoint was the monitoring of late toxicity, while the second endpoint was to assess a composite of biochemical and clinical failure.

Methods

Patient characteristics

Sixty-four patients with locally advanced prostate cancer (T1-T2) were studied prospectively. Patients were classified into prognostic risk groups (low risk and intermediate risk) according to pretreatment PSA, GS and clinical T classification. High risk patients (PSA>20, GS 8-10, T3-T4) were not included in this study. Factors characterizing the low risk group were:

Correspondence to: Vassilis Kouloulias, MS, MD, PhD. Attikon University Hospital, Rimini 1, 124 62 Haidari, Athens, Greece.
Tel: +30 210 5831860, E-mail: vkouloul@ece.ntua.gr
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PSA< 10, GS ≤6, T1-T2a prostate cancer and those for the intermediate group: PSA:10-20, GS=7, T2b-T3 prostate cancer. In addition, patients were ineligible if they had undergone previous pelvic radiotherapy, neoadjuvant androgen deprivation therapy, or radical prostatectomy, had lymph node metastatic involvement, distant metastases, or had a hip prosthesis. Patients under antiandrogen treatment were excluded from study. The median age was 65 years (range: 56-74). All patients had good Eastern Cooperative Oncology Group (ECOG) performance status (0–1) [5] (Table 1).

Table 1. Patient characteristics

Characteristics	*N (%)*
Age, years, median (range)	65 (56-74)
Stage	
T1	28 (44)
T2	36 (56)
ECOG PS	
0	49 (77)
1	15 (23)

Radiotherapy

All patients underwent a computerized tomography (CT) based treatment planning (5mm slice thickness) in the supine position with a triangle sponge placed under their knees. The bladder was full during the CT scan. Target volumes such as clinical target volume (CTV) and planning target volume (PTV) along with the relevant organs at risk (OAR), i.e. rectum, bladder and femoral heads were contoured according to the ICRU recommendations [6].

Two clinical target volumes (CTV1 and CTV2) were identified for treatment planning purposes. The CTV1 included the entire prostate, bilateral seminal vesicles, periprostatic tissues and all known areas of tumor extension. The PTV1 was created by adding a 10mm margin to CTV1 in all directions except 5mm posterior margin and 15mm anteriorly. CTV2 included the prostate and proximal seminal vesicles while PTV2 was created by adding the same margins as previously. Rectum was contoured from the anal verge to recto-sigmoid flexure as a solid organ. Bladder was contoured as a whole organ including the cavity. The small intestine was contoured from the promontorium downward [5,6].

All patients were assigned to receive a hypofractionated radiotherapy schedule. The PTV1 was prescribed by 46.75 Gy of 2.75Gy per day for a total 17 fractions while PTV2 was prescribed by 11Gy of 2.75Gy per day for a total 4 fractions. The fractions were delivered daily and the whole treatment lasted for 29 days. The prescription dose was defined at the isocenter of PTV. No attempt was made to electively irradiate the draining pelvic lymph nodes.

We used linear-quadratic (LQ) modeling in order to equate this hypofractionation schedule to the normalized total dose (NTD) if delivered in 2Gy-fractions [7]. Thus, NTD represents the dose given in 2Gy fractions that would give the equivalent biologic effect to the new hypofractionated dose:

$$NTD = D_{new}\frac{d_{new}+\alpha/\beta}{2+\alpha/\beta}$$

where Dnew and dnew are the total dose and dose per fraction respectively, for a suggested hypofractionation scheme. The α/β ratio stands for the point in the survival curve, where the phenomenon of repair for sublethal damages is equivalent to the death related to hit from ionizing radiation [7]. NTD has been calculated and tabulated for both prostate (α/β=1.5Gy) and late reacting tissues (α/β=3Gy) [8]. The total dose was 57.75 Gy. Considering that a/β=1.5, NTD was 70.1 Gy and by a/β=3, NTD was 66.4 Gy.

Dose calculations were performed using either the treatment planning system ECLIPSE (Release 6.5, Varian Associates, Palo Alto, CA) or PLATO (Nucletron, version 2.8, the Netherlands), or Masterplan ONCENTRA (Nucletron, the Netherlands) to deliver the prescribed dose to the International Commission on Radiation Units and Measurements (ICRU) reference point with a minimum dose of 95% and a maximum dose of 107% to the PTV [6].

The beam arrangement consisted of 4 beams, where the beam angles, apertures, weights and dynamic wedges were optimized by standard forward planning. Treatments were delivered with either a 15 MV photon beam generated by a Clinac 2100 C Varian accelerator or a 6MV SIEMENS ONCOR Impression (MLC optifocus). A typical image with isodose distribution is shown in Figure 1.

Treatment plan evaluation was based on 3-dimensional dose distributions and dose-volume histograms. Dose constraints for rectum, the bladder and femoral heads were adopted from published references [5,6,8] (Figure 2).

The dose constraints for the OARs are described below:

Bladder: V75 <25%, V70 <35%, V65 <25–50%, V55 <50%, V40 <50%.

Rectum: V75 <15%, V70 <20–25%, V65 <17%, V60 <40%, V50 <50%, V40 <35–40%; D50<50Gy.

Femoral heads: V50 <5%.

Small bowel: V52 = 0%.

Penile bulb: Mean dose <52.5 Gy

where Vx means the volume that has the x dose deposited, and D50 the dose at the 50% of the volume.

Monitoring of patients and follow up

Clinical follow up was defined as the interval from the starting date of radiotherapy to the last known pa-

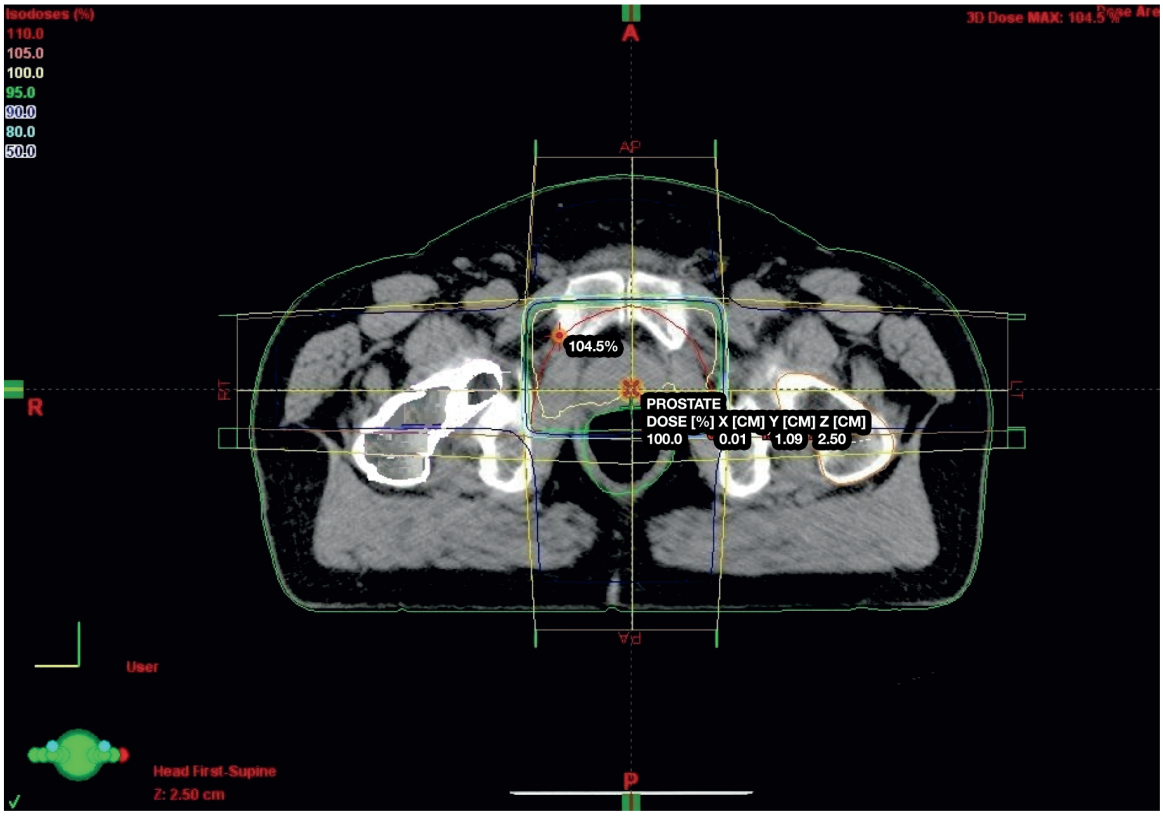

Figure 1. Isodose distribution in central plan in a T1N0 prostate cancer patient.

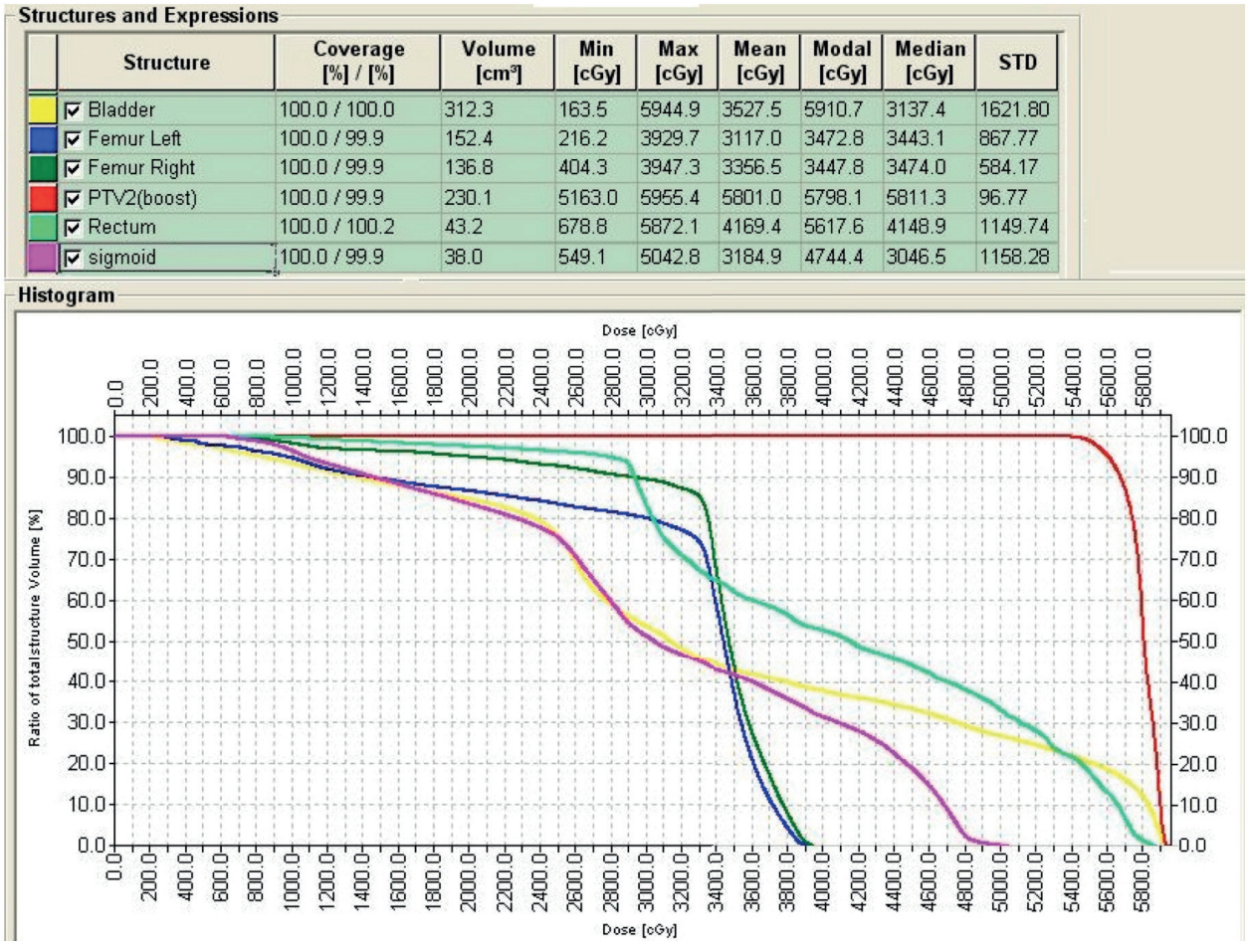

Figure 2. Treatment plan evaluation based on 3D dose distribution and dose-volume histograms.

Table 2. Late gastrointestinal and genitourinary toxicity

Grade 0	*Grade 1*	*Grade 2*	*Grade 3*
Late gastrointestinal toxicity			
47/65 (73.4%)	12/64 (19.2%)	4/64 (6.3%)	1/64 (1.6%)
Late genitourinary toxicity			
60/64 (93.7%)	3/64 (4.7%)	1/64 (1.6%)	-

tient contact. Follow up included history, physical examination, and PSA values at 3-month intervals during the first 2 years and every 6 months from the 2nd to the 5th year. Rectosigmoidoscopies were also asked at the completion of radiotherapy and 12 months thereafter. Late toxicity was defined as an event occurring more than 3 months after treatment. Bladder toxicity and GI toxicity were defined according to the RTOG/EORTC late radiation morbidity scoring system [9] (Table 2).

PSA was monitored every 3 months post irradiation.

Statistics

The statistical analysis was performed by using the SPSS software (Version 10, IL, USA). The evaluation of the correlation between dosimetric parameters and the rectal toxicity was performed with the Spearman's rho non parametric test. The significance level was set at 0.05. Descriptive statistics were done for the incidence of toxicity grading.

Results

The incidence of late moderate and severe toxicity was negligible as monitored with the clinical evaluation of EORTC/RTOG criteria and rectosigmoidoscopy (1 year after radiotherapy). Concerning GI toxicity there were 47 (73.4 %) patients with grade 0, 12 (19.2 %) with grade 1, 4 (6.3%) with grade 2 and 1 (1.6%) with grade 3 toxicity. Concerning the 4 patients with grade 2 GI toxicity, mucus was observed during defecation. One patient had bloody stools due to radiation-induced enteritis. The treatment administered for the radiation toxicity included non steroid anti-inflammatory drugs and steroids for rectal irritation, pain, and bleeding. There was a significant correlation between D50, V70 and EORTC/RTOG late rectal toxicity score in terms of rho=0.59 ($p<0.001$) and rho=0.38 ($p=0.006$), respectively.

Twelve months after the completion of radiotherapy, 3 patients (4.7%) presented microscopic hematuria as grade I toxicity, while one patient (1.6%) presented grade II toxicity with moderate frequency and intermittent macroscopic hematuria. No significant correlation was noted between the grades of toxicity and any of the dosimetric parameters for the bladder. With a median follow up of 18 months (range 12-24), no biochemical relapse was observed. All patients were disease free.

Discussion

The last two decades have witnessed important improvements in treatment outcomes, in general, due to major advances in planning and treatment delivery technologies and in multidisciplinary therapeutic approaches.

Results that challenged traditional beliefs on the radiobiology of "generic tumors" were provided by dose-fractionation parameter studies in prostate cancer. These tumors usually proliferate very slowly and this, when in early low-risk stages, makes them suitable candidates for active surveillance strategies [10]. This has raised the question as to whether prostate cancer, which proliferates as slowly as many late responding normal tissues, is characterized by pronounced fractionation sensitivity, i.e. by a low α/β ratio. Indeed, data from several retrospective studies on clinical brachytherapy and external-beam radiotherapy provide clinical evidence for low α/β values of the order of only 1.5 Gy for prostate cancer [11,12]. This is lower than α/β ratios for rectal wall and urinary bladder, thereby providing a rationale for the use of hypofractionation in prostate cancer, which, in combination with high-precision radiotherapy techniques, is currently under investigation in several clinical studies [13].

Lukka et al. studied 936 men with early-stage prostate cancer who were randomized to receive a hypofractionated radiation treatment schedule of 52.5 Gy in 20 fractions over 28 days, or a conventional treatment schedule of 66 Gy in 33 fractions over 45 days [14]. The probability of biochemical and clinical failure in the conventional treatment arm was 52.95%, but it was 59.95% in the hypofractionated arm, over 5 years. Acute toxicity was slightly higher in the hypofractionated arm (11.4%) rather than the conventional arm (7%), whereas late toxicity was similarly low (3.2%) in both arms. These results raised the possibility that a hypofractionated regimen to a higher total dose may compare more favorably to the conventional schedule.

Arcangeli et al. randomized 168 high-risk prostate cancer patients to receive either 3D conformal hypofractionated external beam radiation therapy with 62 Gy in 20 fractions of 3.1 Gy, or conventional external beam radiation therapy 80 Gy in 40 fractions of 2.0 Gy, in combination with hormone treatment. An α/β value for prostate

of 1.5 Gy was used. After a median follow-up of 32 months in the hypofractionation arm and 35 months in the conventional fractionation arm, there was a statistically significant improvement in the 3-year freedom from biochemical failure from 79% for the conventional fractionation to 87% for the hypofractionation. At the same time, there was no significant difference in grade 2 GI and genitourinary toxicities. These results support the role of hypofractionation in increasing tumor control rate, while not increasing toxicity [15].

Kupelian et al. treated 770 consecutive patients with ultrasound-guided intensity modulated radiotherapy (IMRT) 2.5 Gy per fraction to 70 Gy in 5 weeks. The median follow-up in this prospective trial was 3.75 years. The actuarial 5-year biochemical relapse free survival rate was 95, 85, and 68% for low-, intermediate-, and high-risk disease, respectively. The late GI RTOG grade 2, 3, and 4 toxicities were 3.1, 1.3, and 0.1%, respectively. The corresponding data for late genitourinary toxicity were 5.1 0.1, and 0%, respectively [16].

Tsuji et al. studied 201 patients who received 3.3 Gy per fraction to 66 Gy in 5.6 weeks. The median follow-up was 30 months; no grade 3 or higher toxicities in the rectum and bladder were observed. The incidence of grade 2 rectal morbidity was only 1%. The overall 5-year biochemical relapse free survival was 83.2% without any local recurrence [17].

Marzi et al. treated 162 patients with localized prostate cancer with conformal radiotherapy. The patients were randomly assigned to 80 Gy in 40 fractions over 8 weeks (arm A) or 62 Gy in 20 fractions over 5 weeks (arm B). The median follow-up was 30 months and the incidence of late rectal toxicity in both schedules was evaluated. The incidence of grade 2 or higher late rectal toxicity was 14 and 12% for arm A and arm B, respectively. For arm A, volumes receiving ≥ 50 Gy (V50) and 70 Gy (V70) were 38.3 ± 7.5% and 23.4 ± 5.5%; for arm B, V38 and V54 were 40.9 ± 6.8% and 24.5 ± 4.4%. In conlusion the late toxicities in both arms were comparable, indicating the feasibility of hypofractionated regimes in prostate cancer. The α/β ratio was found close to 3 Gy for late rectal toxicity [18].

Yeoh et al. randomized 217 patients with localized prostate carcinoma to an hypofractionated (108 patients) or a conventional (109 patients) dose schedule. They delivered 55 Gy in 20 fractions for 4 weeks vs a conventional fractionation of 64 Gy in 32 fractions for 6.5 weeks. With a median follow-up of 48 months GI and genitourinary toxicity persisted 5 years after radiotherapy and did not differ between the two dose schedules other than in regard to urgency of defecation which was worse in the hypofractionated arm. There was no difference in biochemical failure or overall survival [19].

In addition, there are at least 4 randomized prospective clinical trials [20-23] which address the efficacy and safety of hypofractionated external beam radiation therapy regimens in prostate cancer. Pollack et al. [24] randomized 300 intermediate and high-risk prostate cancer patients to 76 Gy in conventional 2 Gy fractions vs 70.2 Gy in 2.7 Gy fractions, with IMRT. This study has completed accrual and the authors reported the preliminary acute toxicity results in the first 100 patients treated; it was noted that the hypofractionated regimen was generally well-tolerated, with only a slight but significant increase in GI toxicity during weeks 2–4 of treatment. The clinical data has not matured, and the primary endpoint of the study, 5-year freedom from biochemical failure, has not yet been reported.

Of note, the following 3 studies from the Medical Research Council (MRC), the National Cancer Institute of Canada (NCIC) and RTOG are still accruing patients. The MRC randomized 2100 low and intermediate risk prostate cancer patients to a conventional arm of 70 Gy in 2 Gy fractions vs two hypofractionated arms of 57 Gy in 3 Gy fractions, or 60 Gy in 3 Gy fractions [21].

The NCIC studied 1204 intermediate risk prostate cancer patients and randomized them to a conventional fractionation scheme of 78 Gy in 2 Gy fractions, vs a hypofractionated scheme of 60 Gy in 3 Gy fractions [22].

Lastly, the RTOG 0415 study randomized 1067 low-risk prostate cancer patients to a conventional external beam radiation therapy arm of 73.8 Gy in 1.8 Gy fractions vs a hypofractionated external beam radiation therapy arm of 70 Gy in 2.5 Gy fractions. Both 3D conformal radiotherapy and IMRT were permitted for the RTOG study [23]. It was observed that dose escalation contributes to reduction of biochemical recurrence [21-23].

However, rectal toxicity appears to be the most clinically relevant and rectum is the dose-limiting organ for prostate radiotherapy [25]. The probability of late rectal complications has been reported to increase with larger volumes irradiated to target dose levels. Radiation induced toxicity to the rectum according to the percentage of rectal volume exposed to doses higher than 70 Gy [26,27].

In our study it was observed one case of rectal bleeding due to the anatomical structure of the patient and non compliance of the dietary guidelines during radiotherapy. However, it should be mentioned that, especially for GI toxicity, our study showed one of the lowest levels reported in the current literature. We believe that this is due to the high quality assurance programme [28] in our departments concerning verification portals twice a week and the close clinical monitoring of patients, and secondly the administration of arginine and glutamine against radiation-induced enteritis [29]. Moreover, the radiation-induced cystitis was really very low mainly due to the restrictions concerning the dosimetric parameters for bladder. Nakamoura et al. [30] already reported that the incidence of radio-cystitis is significantly reduced if the V70 of the bladder in as low as 30% of the organ. In our study the V70 was really less than 25% in all cases.

In conclusion our results are in accordance with the current literature supporting the use of hypofractionated radiation therapy. A high therapeutic ratio was observed along with acceptable short-term levels of toxicity. The main disadvantage of the current study is the small number of patients. The results remain to be proven with controlled studies with more patients.

We should be careful in utilizing empirical models of α/β in guiding treatment for prostate cancer while data from randomized clinical trials continue to mature. The practical advantages in several settings, such as prostate brachytherapy and hypofractionated stereotactic radiosurgery, have been well defined. However, in the next years, it seems that the data emerging from ongoing clinical trials will show more clearly the potential benefits of hypofractionation.

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