Treatment of Low-risk Prostate Cancer with Radical Hypofractionated Accelerated Radiotherapy with Cytoprotection (HypoARC): An Interim Analysis of Toxicity and Efficacy

MICHAEL I. KOUKOURAKIS[1], GEORGE KYRGIAS[2], AIKATERINI PAPADOPOULOU[1], MARIANTHI PANTELIADOU[1], ALEXANDRA GIATROMANOLAKI[3], EFTHIMIOS SIVRIDIS[3], SOPHIA MAVROPOULOU[4], KRITON KALOGERIS[5], PAVLOS NASSOS[5], NICOLAOS MILIOUDIS[5] and STAVROS TOULOUPIDIS[6]

Departments of [1]Radiotherapy – Oncology,
[3]Pathology, [6]Urology, Democritus University of Thrace,
University Hospital of Alexandroupolis, Alexandroupolis, Greece;
[2]Department of Radiotherapy – Oncology,
University of Thessalia, University Hospital of Larissa, Larissa, Greece;
Departments of [4]Pathology, [5]Urology, Xanthi General Hospital, Xanthi, Greece

Abstract. *Aim: Radiobiological analysis of clinical data suggests that prostate cancer has a low α/β ratio, implying that large radiotherapy fractions may better control the disease. Acceleration of radiotherapy may be also of importance in a subset of tumors. In this study we assessed the feasibility and efficacy of a highly accelerated and hypofractionated scheme of radiotherapy (HypoARC), for the treatment of localized low risk prostate cancer. Patients and Methods: Fifty-five patients with prostate cancer (T1-2 stage, Gleason score <7 and prostate specific antigen (PSA) <10 ng/ml) were treated with localized conformal 4-field radiotherapy to the prostate and seminal vesicles: 51 Gy were delivered (3.4 Gy/fraction, within 19 days). The biological dose to the prostate ranged from 67.9-91.7 Gy. Amifostine (0-1000 mg depending upon tolerance) was delivered daily for cytoprotection. The median follow-up of patients is 30 (6-69) months. Results: Early toxicity was overall low, proctitis being the most frequent side-effect (23.6% grade II). High dose amifostine significantly protected against proctitis (p=0.005). Grade 2 frequency and dysurea occurred in 1.8% and 3.7% of cases, respectively. There was no late toxicity*

≥grade 2. Amifostine significantly protected against chronic frequency (p=0.02). Within a median follow-up of 30 months, one patient (1.8%) experienced a biochemical relapse. Conclusion: HypoARC is feasible and safe for patients with low-risk prostate cancer and, considering also the high efficacy noted, a strong rationale is provided for the further evaluation of HypoARC in randomized trials.

Radiobiological analysis of clinical data show that prostate cancer has very low α/β ratio values (0.8-2.2 Gy) (1-3). Although Fowler *et al.* insists that α/β ration for prostate cancer is between 1.3-1.8 Gy (4), studies performed by Wang *et al.* and Kal *et al.* suggest a slightly higher α/β ratio of 3.1 Gy (5, 6). Large radiotherapy fractions are, therefore, expected to improve local control rates compared to the 2 Gy fractions used in standard radiotherapy. The old concept on tumors sharing a high α/β value seems not to apply in prostate cancer as well as in other tumors, such as breast and colon cancer (7, 8).

Prostate cancer is considered a slowly proliferating tumor (9). In an early analysis the overall radiotherapy time seemed not to affect the outcome in prostate cancer (10). However, a high proliferation index is often noted (11-13). Moreover, a high Ki-67 index has been linked to poor local control with radiotherapy, high biochemical relapse and poor overall survival (14, 15). It is, therefore, postulated that acceleration of radiotherapy may, in fact, affect the post-radiotherapy outcome in subsets of prostate carcinomas.

In this study we present our experience in treating early prostate cancer with hypofractionated accelerated radiotherapy

Correspondence to: Michael I. Koukourakis, MD, Department of Radiotherapy Oncology, Democritus University of Thrace, PO BOX 12, Alexandroupolis 68100, Greece. Tel: +302551074622, Fax: +302551030349, e-mail: targ@her.forthnet.gr

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(HypoARC), targeting cancer cells with low α/β value and tumors with increased clonogen repopulation. Radiobiological analysis of the theoretical basis of the regimen has been previously reported (16). In an attempt to reduce the overall acute and late toxicity expected by the aggressiveness of the schedule, amifostine was used at high daily dose as previously described (17).

Patients and Methods

A total of 55 patients (PS 0-1) with histologically diagnosed low-risk prostate cancer, after transrectal needle biopsy, were recruited in this phase II study. Patients were of T1-2 stage, without extracapsular or seminal vessel invasion or node involvement at CT/MRI pelvic examination, Gleason score <7 and maximum PSA <10 ng/ml. Patient and disease characteristics are shown in Table I. Patients with major lung, kidney or liver disease, and patients with psychiatric diseases were excluded from the protocol. The follow-up of patients ranges from 6-69 months (median 30 months).

End points. The end points of the current study is the evaluation of the early and short term late radiation toxicity of the HypoARC scheme, as well as the short term biochemical control of the disease.

Radiotherapy technique. Patients were treated with localized radiotherapy to the prostate and seminal vesicles. The whole therapy was given with a conformal simple 4-field technique (antero-posterior and latero-lateral; Figure 1a, b). Lateral fields comprised less than 35% of the rectal area and less than 1/3 of the bladder. The daily dose to the 95% isodose was 3.4 Gy. Five fractions per week were administered to a total of 15 fractions. The physical dose delivered was 51 Gy, within 19 days. The dose volume histogram of a typical radiotherapy plan is shown in Figure 1c.

Radiobiological considerations. The physical dose was corrected according to the Macejewski formula (18) defining the so called normalized total dose: $NTD=D((\alpha/\beta+d)/(\alpha/\beta+2))$, where D is the total physical dose, d the dose per fraction and α/β is the tissue specific ratio. NTD provides the dose that a conventionally fractionated scheme (2 Gy per fraction) would give to a tissue, so that the biologic effect is equal to the one induced by the scheme under consideration (fractionation other than 2 Gy).

Correction of the NTD for overall treatment time was performed using a previously proposed formula (19), $NTD(T)=D((\alpha/\beta+d)/(\alpha/\beta+2))+\lambda(Tc-To)$, where Tc is the number of days required for the delivery of the NTD using a conventionally fractionated scheme, To is the number of days required for the delivery of the accelerated scheme, and λ is the estimated daily dose consumed to compensate for rapid tumor repopulation.

We assumed that α/β was 4 Gy for late responding normal tissues (rectum and bladder) and 1.5-3 Gy for prostate cancer cells, as suggested by Fowler *et al.* and Wang *et al.* respectively) (4, 5). We also assumed a range of λ values for cancer cells, between 0.1-0.4 Gy. Such values are suggested by potential doubling times of between 10-40 days (9). Within this range should fall half of prostate carcinomas, considering that the median doubling time is 42 days as suggested by Haustermans and Fowler (20).

Although it is not clear whether by reducing the overall treatment time the toxicity of late responding tissues increases, it seems that

Table I. *Patient and disease characteristics.*

No patients	55
Age (years)	
Median	71
Range	57-81
WHO PS	
Median	0
Range	0-1
T-stage	
pT1*	31
pT2*	24
cN-stage **	
N0	55
Gleason score	
4	31
5-6	24
PSAmax*	
Range	3.3-9.9
Median	7.2

*Pathological staging from prostate biopsy; **CT/MRI staging; ***Maximum PSA before hormonal therapy

such an increase is far lower as compared to rapidly repopulating tissues (21, 22). We, therefore, assumed a λ value of 0.2 Gy for normal tissues (23-25).

Biological dose calculation. The physical dose delivered to the prostate and seminal vesicles was 51 Gy using 3.4 Gy daily fractions. The NTD for prostate cancer ($\alpha/\beta=1.5-3$ Gy) was therefore 65.3-78.1 Gy. Thus, the acceleration of therapy compared to a standard fractionation scheme delivering this NTD, was between 26-34 days. Assuming a λ value of 0.1-0.4 Gy, the biologic dose to the prostate ranged from 67.9-91.7 Gy, depending upon individual α/β tumor value and doubling time.

The proximal to the prostate, rectal and bladder, tissues were included in the full dose region, receiving 3.4 Gy for 15 fractions, thus 51 Gy. The NTD for $\alpha/\beta=4$ Gy was therefore 62.9 Gy, delivered within 19 days. Assuming a λ-value of 0.2 Gy and an acceleration of 24 days, the biological dose to this rectal/bladder region was 67.7 Gy.

Administration of amifostine. A dose of 1000 mg of amifostine was delivered before each radiotherapy fraction. This was reached gradually (first day 500 mg, second day 750 mg and third day 1,000 mg) using a previously published algorithm (17).

Hormonal therapy. Forty-three patients (78.2%) were under hormonal therapy with LH-RH analogs and anti-androgens, for 2 months before the onset of radiotherapy and continued hormonal therapy for 12-18 months thereafter. The remaining 12/55 (21.8%) did not receive any hormonal treatment untill recurrence.

Assessment of toxicity. Radiation toxicity was monitored daily during radiotherapy, weekly for 1 month following the end of radiotherapy, monthly for 4 months and 3-monthly thereafter. The NCI (National Cancer Institute) Common Toxicity Criteria Version 2 scale was used to assess chemotherapy and acute radiation toxicity (26). The LENT-SOMA toxicity scale was used to assess late radiation sequel (27).
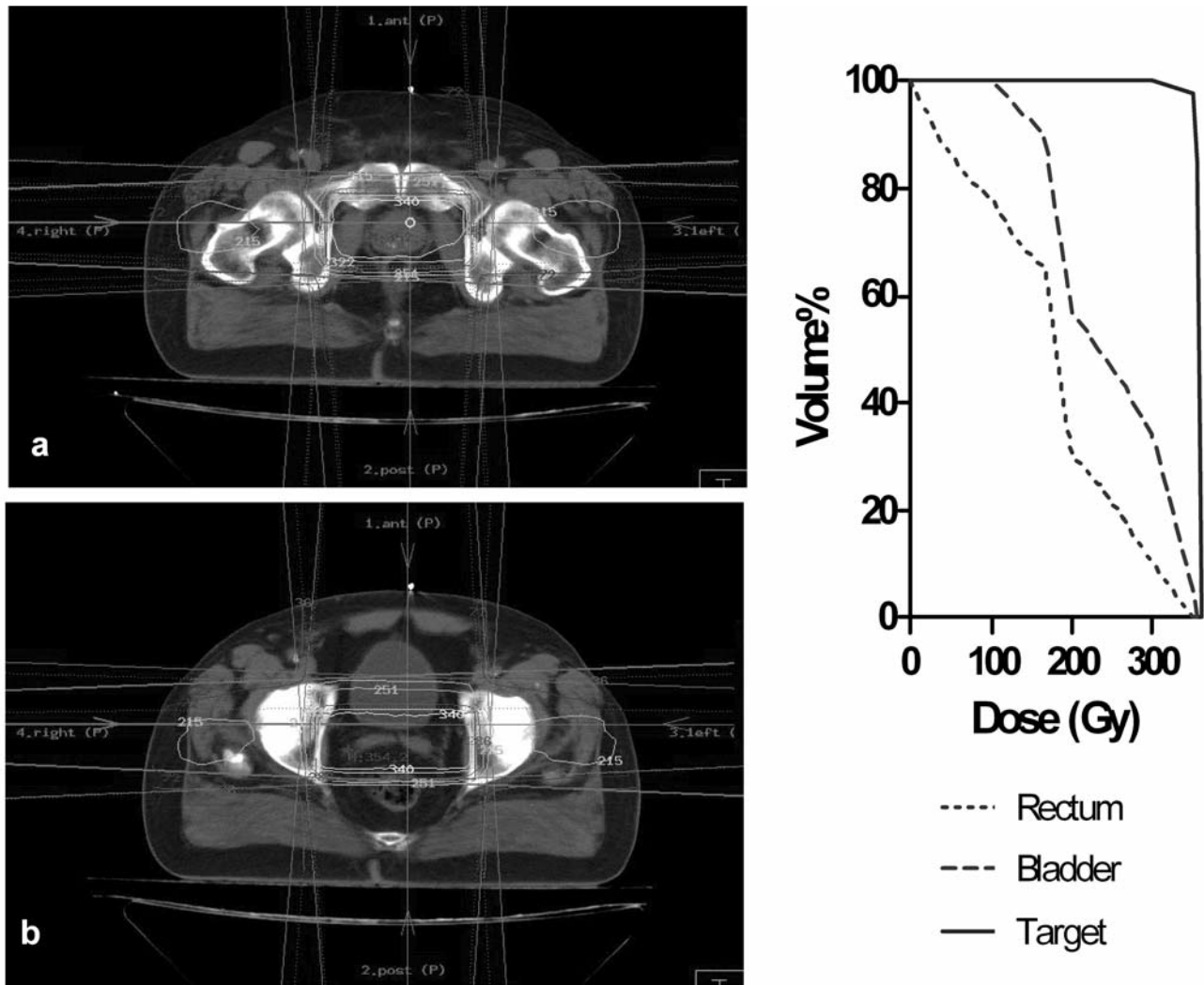
Figure 1. *Radiotherapy planning showing the dose distribution to the prostate cancer (a) and seminal vesicles (b), using the proposed HypoARC regimen, and dose volume histograms (c).*

Statistical analysis. The statistical analysis and graphical presentation of survival curves was performed using the GraphPad Prism 5.00 version and the GraphPad Instat package (GraphPad Software, CA). The Fisher's exact test or the unpaired two-tailed *t*-test was used to compare categorical variables, as appropriate. Survival curves were plotted using the Kaplan-Meier method, and the log-rank test was used to determine statistical differences between life tables. *p*-Values <0.05 were considered to be statistically significant.

Results

Amifostine tolerance. Using the dose individualization algorithm, 31/55 (56.4%) patients received 1,000 mg of amifostine, 13/55 (23.6%) 750 mg and 6/55 (10.9%) 500 mg. Another 5/55 (9.1%) patients did not tolerate the dose of 500 mg, due to unacceptable fatigue and/or vomiting and

amifostine was interrupted. Fever and/or rash symptomatology appeared in 9/55 (16.4%) patients (1/6, 3/13 and 5/31 patients receiving 500, 750 and 1,000 mg, respectively; *p*=0.90).

Overall treatment time. All 55 cases recruited in the HypoARC trial completed therapy: 46/55 (83.6%) patients accomplished therapy without delay due to early radiation sequelae. Acute toxicities, however, resulted in a 4 to 7-day (median 5 days) delay in 9/55 (16.4%) patients. Even in this latter case, the overall treatment time was reduced by 10-26 days compared to patients that would have received the same biological dose with standard fractionation.

Early radiation toxicity. Early toxicity was overall low (Table II). Proctitis was the most frequent and troublesome side

Table II. *Early pelvic toxicity assessed with the NCI (National Cancer Institute) Common Toxicity Criteria in patients treated with HypoARC.*

		No. of pts 55 (%)
Dysuria		
0.	None	29 (52.7)
1.	Mild	24 (43.6)
2.	Relieved with analgesics	2 (3.7)
3.	Persistent – requiring catheter	0 (0)
Urinary frequency		
0.	None	46 (83.6)
1.	Up to 2 x normal	8 (14.6)
2.	>2 x Normal but < hourly	1 (1.8)
3.	>hourly, requiring catheter	0 (0.0)
Bladder infection		
0.	None	55 (100)
Proctitis		
0.	None	25 (45.5)
1.	Mild rectal discomfort	17 (30.9)
2.	Requires medication	13 (23.6)
3.	Pads - parenteral support	0 (0.0)
4.	Necrosis – life threatening bleeding	0 (0.0)
Hemorrhoid bleeding*		
0.	None or minor bleeding	53 (96.4)
1.	Episode of substantial bleeding	1 (1.8)
2.	Bleeding affecting the Hb levels	1 (1.8)
3.	Bleeding demanding hospitalization	0
Diarrhea		
0.	<4 Stools	46 (83.6)
1.	4-6 Stools	9 (16.4)
2.	>7 Stools, incontinence	0 (0.0)
3.	Requiring hospitalization	0 (0.0)
Dermatitis		
0. None		55 (100)

*Proposed by authors (not included in NCI scale).

effect for the patients. This more frequently appeared at the end of therapy (after the 15th day). It was negligible or mild for 45.5% and 30.9% of patients, respectively. In 23.6% of patients, however, it produced significant discomfort that demanded narcotic analgesics and local steroid medication. The duration of symptoms was 1-2 weeks after the end of therapy. Bleeding from hemorrhoids when occurring was minor, while one episode of substantial bleeding was reported by 3.6% of patients.

Mild grade 1 urinary frequency/urgency and dysurea was common, noted in 14.6% and 43.6% of patients. More severe grade 2 urgency and dysurea were, however, rare (1.8% and 3.7% respectively), while no case of grade 3-4 toxicity was noted. Diarrhea was infrequent and when appeared in 16.4% of patients, and was of grade 1. No dermatitis was noted.

Amifostine dose, early toxicities and RT delays. Table III shows the early toxicities according to the amifostine dose.

Amifostine significantly reduced proctitis, but this effect was evident only at the highest (1,000 mg) dose level (p=0.005). Four out of ten patients who received 0-500 mg of amifostine experienced grade 1 diarrhea *vs*. 5/44 in patients receiving 750-1000 mg of amifostine, which was statistically significantly different (p=0.04). No effect of amifostine on dysurea and urinary urgency, nor on bleeding from hemorrhoids was noted. Radiotherapy delay due to early toxicities was more frequent in patients who did not receive amifostine (2/5 *vs*. 7/50) but a proper comparison was not possible because of the low number of cases that did not receive amifostine.

Late radiation toxicity. Within a median follow-up of 30 months patients treated with HypoARC showed a low incidence of severe late sequelae. There was no grade 2 or higher toxicity noted. Urinary frequency grade 1(less than 4-hourly) was noted in 9/55 patients (16.4%) and mild dysurea grade 1 in 5/55 (9.1%). No bladder incontinence or hematurea was noted. Persistent diarrhea of grade 1 (less than 4 stools) was noted in 1/55 (1.8%) patients and occasional tenesmus in 1/55 (1.8%). Amifostine at doses of 500-1000 mg significantly protected against increased frequency of urination (3/5 *vs*. 6/50; p=0.02).

Biochemical control – Survival. Within a median of 30 months (6-69 months) of follow-up 1/55 (1.8%) patients showed a biochemical rise of PSA value above 2 ng/ml from the nadir reached after radiotherapy. Figure 2a shows the biochemical relapse-free survival curve for patients with Gleason score 4 *vs*. those with score 5-6 (p=0.25). None of the patients has died from their disease. Two patients died from other causes (one from heart infarction, one from chronic renal insufficiency).

Biochemical response. In 12 patients who had not received hormonotherapy before RT, we were able to monitor the radiotherapy related PSA changes (Figure 2b). Within 2 months after HypoARC, there was a sharp drop of PSA from a median of 7.15 (3.3-9.8) to 0.70 (0-8) ng/ml. At 4 months this dropped to 0.06 (0.0-2.2) ng/ml and further decreased to 0.0 (0.0-0.9) ng/ml at 8 months, which seemed to be the nadir for most patients. There was a shallow rise to a median of 0.34 (0.01-0.89) ng/ml at 24 months.

A similar sharp drop of PSA was seen within 2 months after radiotherapy in patients receiving hormonal therapy (started 2 months before radiotherapy). The median PSA value dropped from a median of 0.18 (0.0-24) to 0.01 (0.0-4.0) ng/ml. The PSA was maintained at 0.13 (0.0-1.07) ng/ml at 24 months (Figure 2c).

Discussion

Radical radiotherapy is an alternative to radical prostatectomy in patients with prostate cancer, although the superiority of the one method over the other is an issue of debate. In a large

Table III. *Early radiation toxicity and amifostine dose.*

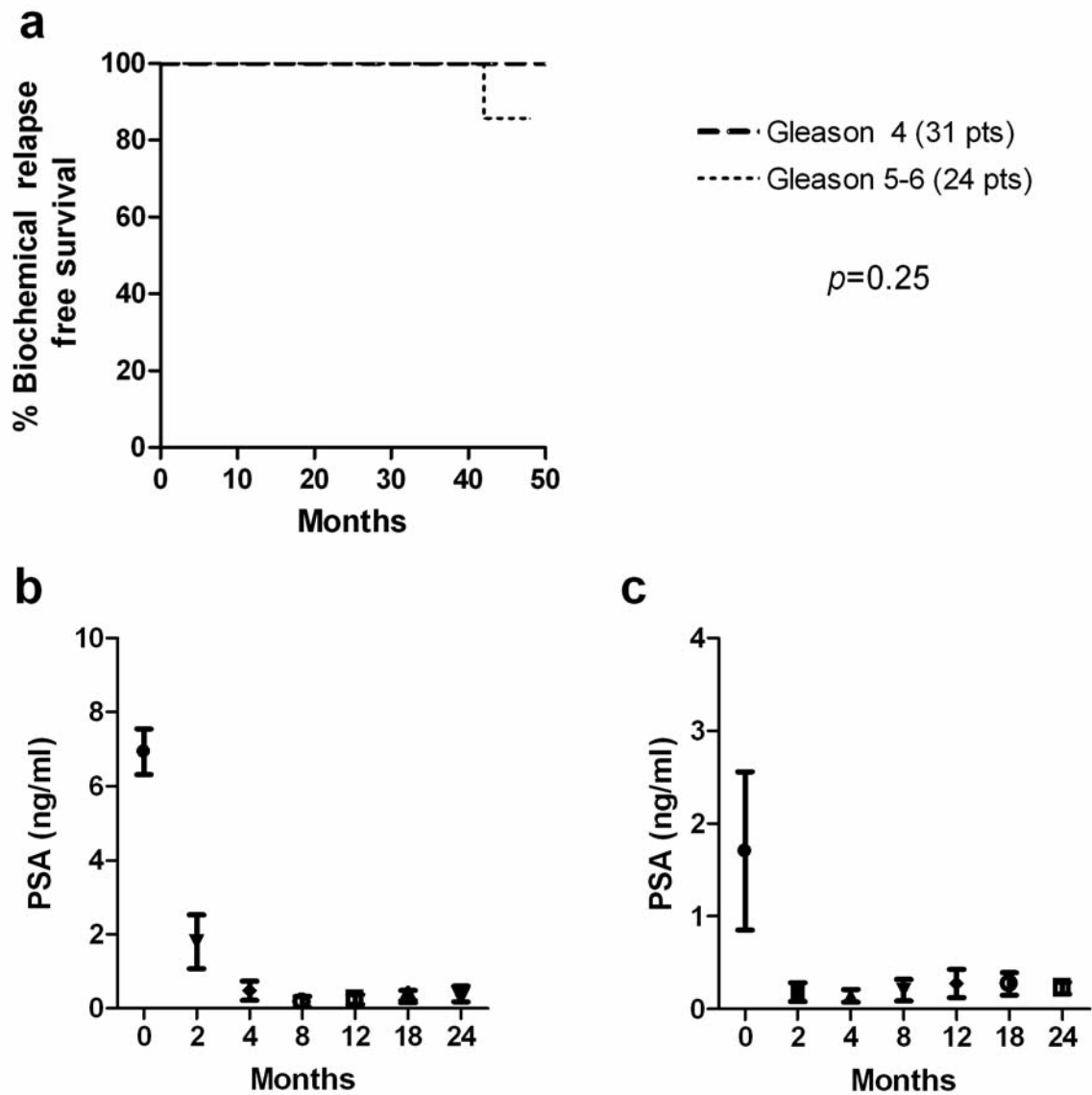| Amifostine dose (mg)	Dysuria			Frequency of urination			Proctitis			Hemorrhoids			Diarrhea			RT Delays	
	0	1	2	0	1	2	0	1	2/3	0	1	2	0	1	2/3	No	Yes
A 0 (5 pts.)	2	2	1	5	0	0	1	2	2	4	1	0	3	2	0	3	2
B 500 (6 pts.)	3	3	0	6	0	0	2	3	1	5	1	0	4	2	0	6	0
C 750 (13 pts.)	9	4	0	11	2	0	4	2	7	11	2	0	11	2	0	10	3
D 1000 (31 pts.)	15	15	1	24	6	1	18	10	3	25	4	2	28	3	0	27	4
p-Value	>0.41			>0.76			0.005*			>0.94			0.04**			>0.24	

*A+B+C *vs*. D, ** A+B *vs*. C+D.

Figure 2. *Biochemical relapse-free survival curves according to the Gleason score (a). PSA level kinetics following HypoARC in patients receiving radiotherapy without hormonotherapy (b) and in patients receiving combined hormonotherapy and HypoARC (c).*

study on 1865 patients with early stage prostate cancer, RTOG reported a slight benefit of prostatectomy over radiotherapy for patients with Gleason score >6 and PSA values >10 ng/ml, but this difference shifted towards a superiority of radiotherapy when the radiotherapy dose increased to more than 72 Gy (28). Nowadays, radical radiotherapy for prostate cancer with doses higher than 75 Gy using conformal or IMRT techniques is a standard approach.

The low α/β values of prostate cancer suggest that large radiotherapy fractions may be more effective. In a previous radiobiological analysis we suggested that using hypofractionation and acceleration of radiotherapy, very high biological doses of 77-93 Gy are feasible to the prostate tumor without producing excess damage to normal tissues (16). During the last 5 years data from clinical trials on hypofractionated radiotherapy are becoming available. Rene *et al*. reported a 5-year actuarial control of 98%, in favorable risk prostate cancer patients, using 22 fractions of 3 Gy, but genitourinary and gastrointestinal late toxicity ≥grade 2 was quite high (32% and 25%, respectively) (29). In a randomized trial, Arcangeli *et al*. found an 87% 3-year biochemical control in patients receiving hypofractionation (3.1 Gy × 20 fractions) compared to 79% in patients receiving conventional radiotherapy (30) with a similar, but still substantial, 11% and 14% genitourinary and gastrointestinal late toxicity in both groups (31). The large experience reported from the Cleaveland Clinic (32) on a relatively mild hypofractionation scheme (2.5 Gy × 28 fractions) showed an 82% 5-year biochemical relapse free interval and low early (grade 2 toxicities of 18%) and late (grade 2 toxicities <6%) *sequelae* (32).

In the current study we used a simple box conformal (non IMRT) technique to deliver a daily dose of 3.4 Gy to the prostate and seminal vesicles. The total biological dose was estimated to be 67.9-91.7 Gy, depending upon tumor characteristics. A reduction of the overall treatment time by 26-34 days compared to an equivalent conventionally fractionated scheme was feasible for 83.6% of patients with minor early toxicities, mainly proctitis (grade 2: 23.6%). Other grade 2 toxicities (dysurea, increased urinary frequency) were rare (<4%), which compares favorably to the genitourinary and gastrointestinal toxicities reported from other trials on hypofractionated radiotherapy (27-30). Amifostine may have accounted for this effect. In fact, high amifostine dose (1,000 mg) significantly reduced grade 2 proctitis to less than 10% and also reduced the incidence of diarrhea.

Although a longer follow-up is demanded to reliably assess late radiation sequelae, within a follow-up of 30 months, no grade 2 genitourinary or gastrointestinal toxicity was noted, which compares favorably to the toxicities reported by other centers (29-32). Amifostine may account for these results. Indeed, amifostine significantly protected against frequency of urination even when used at a low dose of 500 mg.

The 5-year projected biochemical control of the disease was 100% for Gleason score 4 cases and 85.7% for Gleason score 5-6, which is similar to the results of previous studies (29-32). Of interest, the response of PSA was sharp at 2 months following radiotherapy completion, reaching a nadir at 8 months and exhibiting a shallow rise thereafter.

It is concluded that HypoARC with amifostine is feasible and safe for patients with low risk prostate cancer. Apart from grade 2 proctitis noted in one fourth of patients, which was significantly reduced when high amifostine dose was administered, no other grade 2 toxicities were noted, and late toxicities were of surprisingly low frequency. Limitations of the study are the lack of control groups receiving conventional radiotherapy or the HypoARC regimen without amifostine. The encouraging results, however, in terms of toxicity and efficacy provide a strong basis to evaluate HypoARC in randomized trials.

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