Postoperative Pelvic Hypofractionated Accelerated Radiotherapy with Cytoprotection (HypoARC) for High-risk or Recurrent Prostate Cancer

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Abstract. *Aim: We evaluated the feasibility and efficacy of postoperative hypofractionated and accelerated radiotherapy supported with amifostine cytoprotection (HypoARC) in patients with high-risk or recurrent prostate cancer. Patients and Methods: Fourty-eight patients were recruited (median follow-up=41 months; range=12-84 months). Twenty-one received HypoARC after surgery and 27 at biochemical relapse. Radiotherapy was given with a 3D-conformal technique, delivering 2.7 Gy/day to the pelvis and 3.4 Gy to the peri-prostatic region for 14 fractions. A 15th fraction increased the total dose to the peri-prostatic area to 51 Gy (15×3.4 Gy) in 19 days. Amifostine was delivered before each radiotherapy fraction at an individualized (by tolerance) dose (0-1000 mg). Results: Amifostine was delivered subcutaneously at 1000 mg in 35/48 (72.9%) patients, while lower doses were tolerated by the remaining patients. Twenty-six (54.2%) patients accomplished therapy without delays, while acute toxicities enforced 1 to 2 week delays in 11/48 patients (22.9%). Grade 2 proctitis was noted in 18.7%, while substantial bleeding occurred in 8.3% of patients. Grade 1 dysurea was noted in 27.1%, while diarrhea grade 2 appeared in 10.4% of patients. High amifostine dose was linked to a significant reduction of proctitis (p=0.04). No severe late toxicities were noted. Within a median of 41 months, 7/48 (14.6%) patients exhibited post-radiotherpy biochemical failure (in four due to metastasis). High-dose (1000 mg) amifostine defined a significantly better outcome (p=0.004), an effect sustained on multivariate analysis. Conclusion: Postoperative HypoARC is feasible with low-grade early and late toxicities, and emerges as a candidate for evaluation in randomized trials. The three-fold reduction of the overall treatment time renders HypoARC appealing for busy radiotherapy departments.*

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Prostate cancer is the most commonly diagnosed malignancy in men. The existing treatment options are radical prostatectomy, radiotherapy and hormonal therapy. Although radical prostatectomy is an effective treatment when the disease is confined to the prostate gland, 15%-20% of patients have positive surgical margins, demanding for additional radiotherapy (1). The excellent 5-year disease-free survival rates that exceed 90% are severely compromised by such a histological finding, which goes along with biochemical relapse rates of up to 50% within 5 years. In this instance postoperative radiotherapy represents an option as adjuvant treatment, reducing the risk of recurrence by about 50% (2). Capsular invasion and/or seminal vesicle involvement also demand for postoperative radiotherapy. On the other hand, post-prostatectomy biochemical recurrence occurs in 10%-40% of the patients, and for these the use of salvage radiotherapy remains the only effective therapeutic option (3).

Although standard fractionation of radiotherapy (1.8-2.2 Gy/fraction) is widely applied in the treatment of prostate cancer, recent radiobiological data suggest that prostate cancer tissues have a low α/β ratio, indicative of a higher sensitivity to large radiotherapy fractions (4). Hypofractionated treatment schemes may therefore be more effective. Indeed, several randomized trials show a benefit of hypofractionated radiotherapy over the standard fractionation, without altering the toxicity profiles of therapy (5, 6).

Although the above applies for localized prostate cancer the role of hypofractionated postoperative radiotherapy addressed to pelvic lymph nodes has been poorly explored. Similarly, the role of acceleration of radiotherapy (shrinkage of the overall treatment time) on prostate cancer control is

Table I. *Patients' and disease characteristics,*

No of patients	48
Age (years)	
Median	66
Range	52-72
WHO PS	
Median	0
Range	0-1
Reason for postoperative RT	
Positive surgical margins	10
Extracapsular invasion/seminal vescicles	11
Biochemical failure	26
Gross local failure	1
Hormonal therapy during RT	
No	25
Yes	23
Duration of hormonal therapy (months)	
6	8
12	11
18	4
Gleason score	
<7	22
≥7	26
PSA before RT (mean; range)	
A	2.2; (0-31)
B	0.18 (0.03-1.6)

A: Patients treated with radiotherapy for postoperative failure; B: patients treated with adjuvant RT.

unknown. In this study we provide evidence that accelerated and hypofractionated radiotherapy, involving prostate-related and pelvic node areas, is well-tolerated and highly effective in a postoperative setting or after biochemical relapse.

Patients and Methods

A total of 48 patients with histologically-diagnosed prostate cancer, after radical prostatectomy, were recruited in a phase II study. Patients' and disease characteristics are shown in Table I. The median follow-up of patients was 41 months (range 12-84 months). Written informed consent was obtained from all patients and the study was approved by the institutional Scientific and Ethical Committees.

End-points. The end-points of the current study were the evaluation of the efficacy in terms of biochemical and clinical control of the disease, as well as the early and short term late radiation toxicity of the Hypofractionated and Accelerated Radiotherapy with Cytoprotecton (HypoARC) scheme in a postoperative setting.

Radiotherapy technique. Patients were treated with pelvic radiotherapy and concomitant booster dose to the previous prostate and seminal vesicle area. A conformal technique was used [not Intensity Modulated Radiotherapy (IMRT)] based on a 3D-planning on images obtained from a computerized-tomography (CT)-simulator. No specific technique was applied to follow or stabilize the prostate movements during respiration, so calm slow breathing was recommended to patients during the treatment of fields.

The pelvic radiation was given through a four-field technique comprising the previous prostate area/seminal vesicles (Figure 1a) and the pelvic lymph nodes (Figure 1b), delivering a daily dose of 2.7 Gy for 14 consecutive fractions (37.8 Gy within 18 days). Two additional lateral fields delivered a booster dose of 0.7 Gy, increasing the daily dose to the prostate and seminal vesicles to 3.4 Gy (Figure 1b). An additional 15th fraction of 3.4 Gy was delivered with these fields on day 19. In this way the total physical dose to the prostate area was 51 Gy within 19 days. The dose was calculated to the 95% isodose curve.

Radiobiological considerations. The physical dose, delivered to any point of interest, is corrected for the α/β value, according to the Macejewski formula (7), 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 (2Gy per fraction) would give to a tissue, so that the biological effect is equal to the one of the scheme under consideration (fractionation other than 2 Gy).

Correction of the NTD for overall treatment time is performed using a previously proposed formula (8), $NTD_{(T)}=D\ [(\alpha/\beta+d)/(\alpha/\beta+2)]+\lambda(T_c-T_o)$, 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 is 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 (9, 10)]. We also assumed a range of λ values for cancer cells, between 0.2-0.4 Gy. Such values are suggested by potential doubling times of between 10-40 days and within this range should include half of all prostate carcinomas, considering that the median doubling time is 42 days, as suggested by Haustermans and Fowler (11).

Although it is not clear whether by reducing the overall treatment time the toxicity of late responding tissues increases, it seems that such an increase is far lower as compared to rapidly repopulating tissues (12). We, therefore, assumed a λ value of 0.2 Gy for normal tissues (13).

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 (α/β=1.5-3 Gy) was, therefore, 65.3-78.1 Gy. The acceleration of therapy compared to a standard fractionation scheme delivering this NTD was between 26-34 days. Assuming a λ value of 0.2-0.4 Gy, the biological dose to the prostate ranged from 67.9-91.7 Gy, depending upon the individual α/β tumor value and doubling time.

The physical dose to the microscopic disease in the lymph nodes was 37.8 Gy using 2.7-Gy daily fractions. The NTD for these prostate cancer cells (α/β=1.5-3 Gy) was therefore 43.1-45.3 Gy, delivered within 18 days. Thus the acceleration of therapy compared to a standard fractionation scheme delivering this NTD was between 12-13 days. Assuming the above details for acceleration, the biological dose, corrected for time-factors, was between 44.3-50.5 Gy.

The physical dose to the pelvic tissues was 37.8 Gy using 2.7 Gy daily fractions. The NTD for α/β=4 Gy was therefore 42.2 Gy, delivered within 18 days. Thus, acceleration was 11 days. The biological dose corrected for λ=0.2 Gy is, therefore 44.4 Gy. The rectal tissue proximal to the prostate, however, was included in the

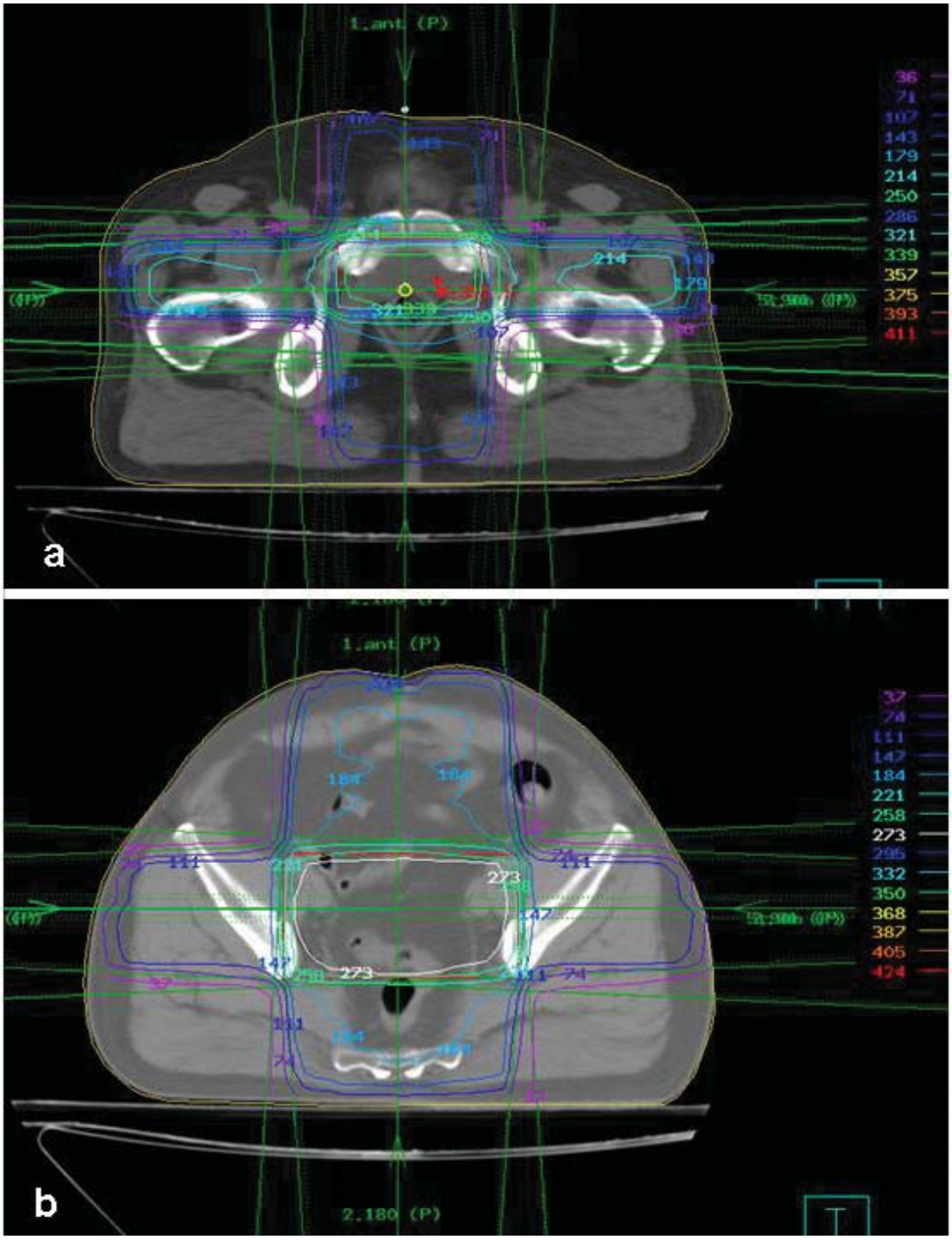

Figure 1. *Conformal 3D-treatment planning at the level of the prostate (1a; six-field technique) and at the level of the iliac nodes (1b; four-field technique).*

full dose region, receiving 3.4 Gy for 15 fractions, thus 51 Gy. The NTD for α/β=4 Gy is 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 region was 67.7 Gy.

Administration of amifostine. Ondasetron of 8 mg was administered per os, 30-60 min before daily amifostine injections, as antiemetic policy. Amifostine of 1000 mg was diluted in 5 ml water for injection and was injected into two sites (usually the right and left

shoulder), with the patient being at a sitting position. Blood pressure assessment was not performed, as this is not necessary when amifostine is given subcutaneously (14). The higher dose of amifostine (1000 mg instead of 350-500 mg used in other studies) applied in the protocol, was chosen in order to better protect tissues against the large fractions of radiotherapy in the HypoARC scheme. The dose of 1000 mg was reached gradually (day 1 500 mg, day 2 750 mg and day 3 1000 mg) using a previously published algorithm (14). The tolerance to amifostine was recorded daily using a scoring system (14). According to this scale the tolerance of amifostine is scored as good/acceptable, poor or unacceptable for each dose level. If at any point of therapy patients exhibit poor tolerance (unacceptable nausea/emesis or fatigue), dexamethasone at 8 mg was administered intramuscularly immediately before injection of amifostine and tolerance was re-assessed the following day. If good tolerance was confirmed, amifostine administration continued as prescribed. If not, the dose was reduced to 750 mg and, if necessary, to 500 mg. If patients did not tolerate the dose of 500 mg well, amifostine was interrupted. No more than 2 dexamethasone injections were allowed per week of radiotherapy, otherwise the dose of amifostine was reduced. Fever/rash attributed to amifostine (or to any other drug) was followed by immediate and permanent interruption of amifostine and by oral administration of corticosteroids and antihistamines for two to three days (14).

Statistical analysis. The statistical analysis and graphical presentation of survival curves was performed using the GraphPad Prism 5.0 version and the GraphPad Instat packages (La Jolla, CA, USA). The chi-square or the Fisher's exact test was used to test categorical groups. Survival curves were plotted using the Kaplan Meier method, and the log-rank test was used to determine statistical differences between life tables. Patient and treatment-related variables were analyzed in a multivariate stepwise logistic regression model to determine which contain independently significant information. *p*-Values <0.05 were considered to be statistically significant.

Results

Amifostine tolerance. Using the dose individualization algorithm, 35/48 (72.9%) patients received 1000 mg of amifostine, 8/48 (16.7%) 750 mg and 4/48 (8.3%) 500 mg. One 1/48 (2.1%) patient did not tolerate the dose of 500 mg, due to unacceptable fatigue and vomiting and amifostine was interrupted. Fever and/or rash appeared in 7/48 (14.6%) patients (5/35, 1/8 and 1/4 patients receiving 1000, 750 mg and 500 mg, respectively; p=0.83). This appeared within a median of five days of therapy (range=3-11 days). Amifostine was permanently interrupted then patients received oral methylprednisolone (16 mg twice-a-day) and anti-histamines for two to three consecutive days and symptomatology completely resolved. No case of necrolytic syndrome, clinical hypotension or hypoglycemia was noted. At the established individualized dose, patients had an excellent tolerance.

Overall treatment time. All 48 cases recruited in the HypoARC trial accomplished therapy. Twenty-six (26/48; 54.2%) patients accomplished therapy without delays from early radiation sequelae. Acute toxicities, however, resulted in less than one week delay in 11/48 (22.9%) and in up to 2 weeks delay in 11/48 patients (22.9%). Even in this latter case, for the prostate area, the overall treatment time was reduced by at least 16 days compared to receiving the same biological dose with standard fractionation.

Table II. *Early pelvic toxicity assessed with the National Cancer Institute Common Toxicity Criteria, in patients treated with Hypofractionated and Accelerated Radiotherapy with Cytoprotection (Hypo ARC).*

	No. of patients= 48 (100%)
Frequencyof urination	
0: None	42 (87:5)
1: Up to 2 × normal	6 (12:5)
2: > 2 × normal but < hourly	0 (0:0)
3: > hourly, demands catheter	0 (0:0)
Dysuria	
0: None	35 (72:9)
1: Mild	13 (27:1)
2: Relieved with analgesics	0 (0:0)
3: Persistent demand of catheter	0 (0:0)
Bladder infection	
0: None	73 (100)
Proctitis	
0: None	14 (29:2)
1: Mild rectal discomfort	25 (52:1)
2: Requires medication	9 (18:7)
3: Pads – parenteral support	0 (0:0)
4: Necrosis – life threatening bleeding – colostomy	0 (0:0)
Hemorrhoid bleeding (*)	
0: None or minor bleeding	44 (91:7)
1: Episode of substantial bleeding	4 (8:3)
2: Bleeding affecting the Hb levels	0 (0:0)
3: Bleeding demanding hospitalization	0 (0:0)
Diarrhea	
0: < 4 Stools	35 (72:9)
1: 4-6 Stools	8 (16:7)
2: >7 Stools – incontinence	5 (10:4)
3: Hospitalization	0 (0:0)
Dermatitis	
0: None	42 (87:5)
1: Faint erythema/dry desquamation	6 (2:5)
2: Notable erythema/patchy moist desquamation	0 (0:0)
3: Confluent moist desquamation	0 (0)
4: Skin necrosis	0 (0)

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

Early radiation toxicity. Early toxicity was overall low (Table II). Proctitis was the most frequent and bothersome side effect for the patients. This more frequently appeared at the end of therapy (after the 15th day). It was negligible or mild for 29.2% and 52.1% of patients, respectively. In 18.7% of

patients, however, it produced significant discomfort that demanded narcotic analgesics and local steroid medication. Symptoms persisted for up to one to two weeks after the end of therapy. Bleeding from haemorrhoids was frequent but minor in most cases, while at least one episode of substantial bleeding was reported by 8.3% of patients.

Mild grade 1 urination and dysurea were noted in 12.5% and 27.1% of patients, respectively. Diarrhea grade 1 and 2 appeared in 16.7%, 10.4% of patients, respectively. Dermatitis grade 1 was noted in 2.5% of patients.

Analysis according to the amifostine dose level showed a significant reduction of grade 1-2 proctitis in patients treated with 1000 mg (22/35 *vs*. 12/13; p=0.04). No other difference was evident.

Late radiation toxicity. Within a median follow-up of 41 months, there was no late toxicity greater than grade 1. Increased frequency of urination grade 1 (less than 4-hourly) was noted in 4/48 (8.3%) and mild grade 1 dysurea in 4/48 (8.3%) patients. Incontinence, pre-existing before radiotherapy deteriorated in 1/48 patients (2.1%). Persistent diarrhea grade 1 (lower than 4 stools) was noted in 2/48 (4.2%) patients and occasional tenesmus in 3/48 (6.2%). There was no case of bladder incontinence or haematurea. There was no association of late effects with the dose level of amifostine.

Biochemical response kinetics. In 24 patients who had not received hormonotherapy before radioterapy, we were able to monitor the prostate specific antigen (PSA) changes. The kinetics of PSA-drop following radiotherapy are shown in Figure 2. Within two months after HypoARC, there was a sharp drop of PSA from a median of 0.58 (0.00-1.60) to 0.24 (0.0-0.70) ng/ml. This further decreased to 0.12 (0.00-1.08) at 8 months, which seemed to be the nadir time point for most patients.

Biochemical control. Within a median of 41 months (12-84 months) of follow-up 7/48 (14.6%) patients exhibited a biochemical rise of PSA following an initial regression, while in the remaining patients the PSA levels stabilized at a certain nadir point reached (median=0.04, range=0.0-0.84). In 3 patients bone scintigraphy confirmed metastatic relapse and in two it revealed paraortic node involvement, while for three patients there was no disease confirmation. For these latter patients, local relapse was considered the cause of PSA rise (local relapse rate within 41 months 6.25%).

The Kaplan Meier biochemical relapse-free survival, stratified for the setting of irradiation, are shown in Figure 3a; there was no significant difference (p=0.40) observed. Analysis according to Gleason score did not reveal a statistical difference (Figure 3b; p=0.31).

We further analyzed the effect of amifostine on the biochemical relapse-free survival to assess the effect of the drug on tumour protection. Surprisingly, patients receiving a high dose (1000 mg) of amifostine had a significantly better outcome (Figure 3c; p=0.004). In a multivariate Cox regression model, including amifostine, Gleason score and reason of radiotherapy, amifostine maintained its predictive role (p=0.005, hazard ratio=7.1).

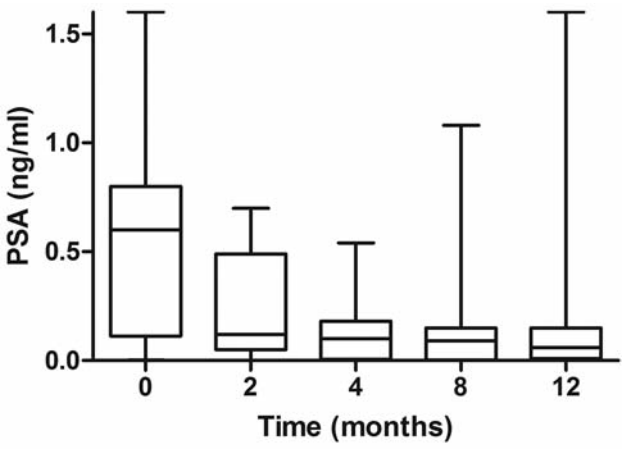

Figure 2. *Post-radiotherapy time course of PSA levels in 24 patients with postoperative biochemical failure. These patients were not receiving hormonal therapy.*

Discussion

Radiobiological analysis of clinical data provided evidence that prostate cancer has low overall α/β values, suggesting that a higher biological dose can be achieved by applying large radiotherapy fractions (9, 10). Hypofractionation of radiotherapy could, therefore, be the schedule of choice for prostate carcinoma. Indeed, several studies found a significantly improved local control in patients undergoing hypofractionated radiotherapy, with no increase of the genitourinary and gastrointestinal toxicity (5, 6).

Postoperative radiotherapy in high risk prostate cancer with positive surgical margins or extracapsular invasion, with or without involvement of the seminal vesicles, demands for irradiation of the pelvic nodes as well as the prostate-related areas. Similarly, treatment of patients with biochemical failure demands irradiation of the whole pelvic area to eradicate growing cancer cell foci in the prostate-related area or the pelvic nodes. The importance of pelvic irradiation in patients with high risk prostate cancer has been recently raised (15). In a recent study, a higher dose of radiotherapy to the pelvic node region was revealed as an important prognostic factor in patients with high-risk prostate cancer (16). If hypofractionation is more effective than standard fractionation, then such a regimen applied to the pelvic region may prove of importance in the postoperative treatment of high-risk or recurrent cases.

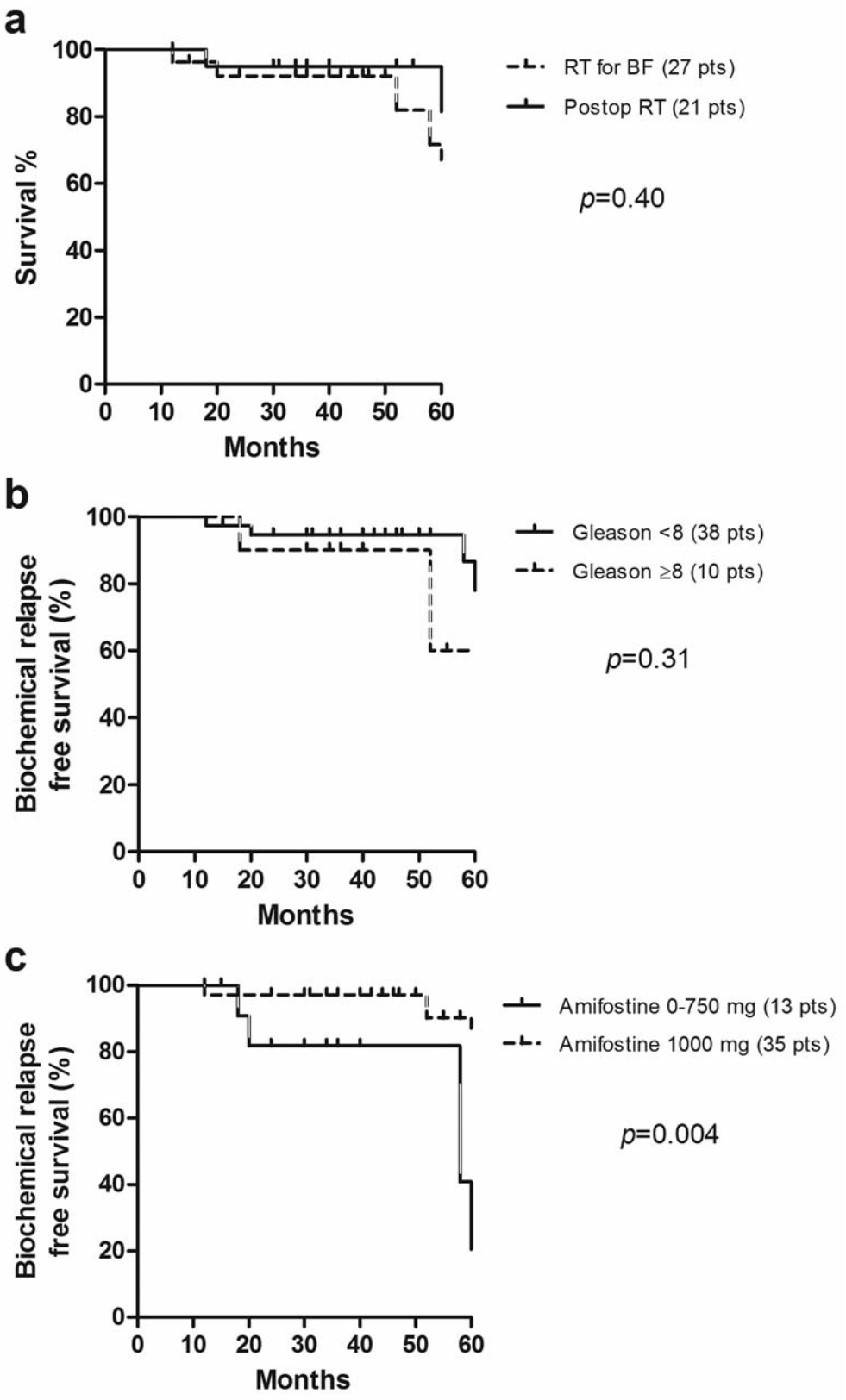

Figure 3. *Kaplan Meier survival curves stratified for the setting of radiotherapy [postoperative vs. at-biochemical failure (BF); (a), for Gleason score (b) and for amifostine administration (c).*

The current study is probably the first phase II study examining the tolerance and efficacy of pelvic hypofractionated radiotherapy, while at the same time applying an intense acceleration of the overall treatment time. Amifostine, a potent cytoprotective agent, was concurrently administered to improve tolerance. Although prostate cancer is considered a slowly-proliferating tumour, high proliferation indices are often reported and, when so, they relate to poor radiotherapy local control, high frequency of biochemical relapse and poor overall survival (17,18). Higher than expected λ values may, therefore, apply in certain prostate tumors, so that acceleration of radiotherapy could prove of importance in the treatment of high-risk prostate cancer.

Despite the large radiotherapy fractions to the prostate-related area, together with the mild hypofractionation for pelvic nodes and the intense acceleration of the overall treatment time, the regimen had an excellent tolerance. The assessment of late toxicity within a median of 41 months of follow-up also showed very low complication rates. The concurrent administration of amifostine may have contributed to this, as indeed, high doses seemed to significantly protect against proctitis, which is the major acute side-effect of prostate radiotherapy.

Recording of the PSA kinetics in patients non-receiving hormonal therapy, showed that rapid reduction of PSA was achieved within two months in most patients, and these reached a nadir at eight months after irradiation. Within a median of 41 months, the biochemical or clinical relapse rate was 14.6%. This was clearly due to metastatic recurrence in 4/7 cases, so that the local failure rate is estimated to be as low as 6.25%.

Further analysis showed that neither the Gleason score nor the reason for radiotherapy (postoperative or at relapse) were linked to the risk of post-radiotherapy biochemical failure. The usage of amifostine, in contrast to worries on an eventual tumour protective effect, showed significant beneficial effects by improving the relapse free interval. Although reduction of proctitis and avoidance of long delays of radiotherapy may underlie the finding, a direct effect of the drug on angiogenic pathways or immunological activation of cytotoxic lymphocytes cannot be excluded (19, 20).

It is concluded that HypoARC for high-risk prostate cancer, including the prostate-related area and pelvic regional nodes, is feasible, well-tolerated and produces a low incidence of late radiation events. These results are obtained with simple conformal non-IMRT techniques and can be applied even at centers without IMRT-like facilities. The eventual role of amifostine in further reducing toxicity when combined with IMRT, or even in allowing further radiation dose escalation, is proposed for further investigation. HypoARC, with or without amifostine, emerges as a candidate for evaluation in randomized trials. The drastic (three-fold) reduction of the overall treatment time and of the number of fractions, renders HypoARC appealing for busy radiotherapy departments with long waiting lists as well as for patients residing at a distance form radiotherapy centers.

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