Conformal Hypofractionated and Accelerated Radiotherapy with Cytoprotection (HypoARC) for High Risk Prostatic Carcinoma: Rationale, Technique and Early Experience

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Abstract. Recent radiobiological analysis of the radiotherapy results for prostate cancer revealed that prostate carcinoma behaves as a late responding tissue, sharing an α/β ratio lower than 2Gy. These findings suggest that hypofractionation may be more effective. Reduction of the overall treatment time could further increase response by abrogating the effect of rapid tumor repopulation. In the present study we report a conformal technique applied (to pelvis and prostate) for the treatment of high-risk prostate cancer, using hypofractionated and accelerated radiotherapy (3.4Gy x 15 consecutive fractions) supported with high-dose daily amifostine (1000mg subcutaneously) to protect normal tissues against early and late effects. The biological dose delivered to the prostate cancer by this HypoARC (hypofractionated accelerated radiotherapy with cytoprotection) technique is estimated to be 71.4Gy (α/β=1.5 Gy). The time-adjusted biological dose is estimated to 77-94 Gy. Amifostine tolerance was excellent. All seven patients recruited up to now have accomplished their treatment with grade 0-1 cystitis or diarrhoea (5/7 grade 0). The study is ongoing to assess efficacy and late effects of HypoARC.

Low radiation dose per fraction (1.2-2Gy) during standard or hyperfractionated radiotherapy is used on the assumption that tumors behave like early responding normal tissues sharing high α/β ratio values (>8Gy). However, not all tumors have high α/β values as, even under experimental conditions, a very low α/β ratio has been reported for a variety of tumor types including lung cancer, head and neck cancer melanomas or sarcomas (1,2).

In contrast to our overall belief regarding tumor radiobiology, it has been recently suggested that prostate cancer behaves as a late responding tissue. In 1999, Brenner and Hall reported an analysis of two mature data sets on the outcome of prostate cancer following external beam radiotherapy or permanent seed implants (3). Using the standard linear quadratic model, the authors suggested that the α/β ratio value is as low as 1.5Gy (0.8-2.2), indicating that large radiotherapy fractions are more appropriate to treat prostatic carcinoma. In a subsequent analysis of 17 clinical papers on the radiotherapy outcome of prostate cancer, Fowler et al. also found very low α/β values between 1.49 and 1.9Gy (4). In a more recent analysis of the results from a protocol combining external beam radiotherapy and HDR (high-dose rate) implants for prostate cancer, Brenner et al. confirmed an α/β value of 1.2Gy (5). Even if the relative failure of small radiation doses per fraction to control prostate cancer is due to hypoxia and not to low α/β values (6), it is becoming clear that hypofractionation is a more appropriate radiotherapy option for prostate cancer.

On the other hand, the overall treatment time also seems to play an important role in the efficacy of radiotherapy in prostatic cancer (7). Despite the generally accepted assumption that prostate cancer is a poorly-proliferating neoplasm, experimental studies show that large prostatic tumors (T3,4-stage) and poorly-differentiated neoplasm share a quite high cancer cell proliferation index (8-10). Acceleration of the hypofractionated radiotherapy regimen could therefore become even more effective since it also targets prostatic carcinomas with a potentially high clonogen repopulation ability.

Although radiotherapy protocols include prostate and seminal vesicles, the therapeutic importance of pelvic lymph node irradiation should not be underestimated, for
Figure 1. a. Isodose curves displaying the daily dose delivered with HypoARC, plotted on a CT-tomogram at the area of prostate. b. 3D-reconstruction of the pelvic tissues (red area: prostate and seminal vesicles; yellow area: rectum; grey area: bladder; blue area: femur, and pink area: pelvic bones). Noted the anterior field located to the pelvis and the lateral located to the prostate and seminal vesicles. c. View of the anterior field located to pelvis and prostate, shaped by a multileaf collimator. d. Lateral field located to the prostate and seminal vesicles, with a multileaf collimator shaping these areas minimizing the dose to the bladder and rectum.
high Gleason score (>7) or advanced T-stage are linked with 25-45% incidence of lymphatic spread of the disease (11-13). The development of hypofractionated and accelerated techniques for the irradiation of the prostate and the regional lymph node area is therefore of immediate clinical relevance. In this study, we report the rationale and the radiobiology of a technique developed to treat high-risk prostatic cancer with a hypofractionated and accelerated conformal radiotherapy technique combined with cytoprotection with high-dose, subcutaneously administered, amifostine. The early experience of the ongoing study is also reported.

**Patients and Methods**

**Patients.** Since January 2003, seven patients have been treated with hypofractionated and accelerated radiotherapy with cytoprotection (HypoARC), at the department of Radiotherapy and Oncology, Democritus University of Thrace, Greece. All patients were under hormonal therapy with LH-RH agonists. Five patients had high-risk prostatic cancer (T3-stage) and one patient had a double prostate/bladder cancer. Pelvic CT-scans revealed node involvement in none of the patients. Mild dysuria was reported by 4/6 and complete obstruction (permanent Foley catheter) in 1/6 patients. One additional young patient (46 years old) with stage T3N0M1 disease (metastatic to left iliac and pubic bones presented with pain and bladder obstruction) was also treated with HypoARC.

**The radiotherapy / cytoprotection technique.** The radiotherapy technique comprised two anteroposterior fields delivering a daily dose of 2.7Gy and two lateral fields localized to the prostate and seminal vesicles, delivering a booster dose of 0.7Gy (4 fields treated per fraction). The whole planning was performed following CT-simulation and conformal 3D-elaboration of data (Plato, Nucletron system) (Figure 1). Using these fields, 14 consecutive fractions (5 fractions per week) were delivered, while an additional fraction of 3.4Gy was given through the localized lateral fields.

For the patient with double prostate/bladder cancer, the whole bladder was included in the lateral fields. For the patient with left pelvic bone involvement, antero-posterior fields, extended to cover the whole area of left pelvic bones and hip were used for the first 7 fractions (3.4Gy per fraction). Thereafter, treatment was localized to the prostate and seminal vesicles, using 4 fields and a daily fraction of 3.4Gy, for 8 consecutive days.

Twenty to 30 minutes before each radiotherapy fraction, amifostine was subcutaneously administered at a dose of 1000mg.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Fraction (Gy) x No fractions</th>
<th>Physical dose (Gy)</th>
<th>NTD (Gy)</th>
<th>Acceleration (days)</th>
<th>NTD-T (Gy)</th>
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<tr>
<td>Prostate cancer</td>
<td>3.4 x 15</td>
<td>51</td>
<td>71.4</td>
<td>29</td>
<td>77.2-94.6</td>
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<tr>
<td>Prostate cancer in lymph nodes</td>
<td>2.7 x 14</td>
<td>37.8</td>
<td>45.3</td>
<td>10</td>
<td>47.3-53.3</td>
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<td>Proximal bladder and rectum areas</td>
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<td>62.9</td>
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<td>(late toxicity)</td>
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<tr>
<td>Proximal bladder and rectum areas</td>
<td>3.4 x 15</td>
<td>51</td>
<td>56.9</td>
<td>18</td>
<td>71.3</td>
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<tr>
<td>(early toxicity)</td>
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</tr>
<tr>
<td>*Distal bladder and rectum areas</td>
<td>3 x 14</td>
<td>42</td>
<td>49</td>
<td>12</td>
<td>51.4</td>
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<td>(early toxicity)</td>
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<tr>
<td>Other pelvic tissues</td>
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<td>42.2</td>
<td>8</td>
<td>48.6</td>
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*These areas are included in the 300cG isodose.

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**Table I. Physical dose, normalized total dose (NTD) and time-corrected NTD-T delivered to prostate cancer, early and late responding normal pelvic tissues.**

Koukourakis et al: HypoARC for High Risk Prostatic Carcinoma
(500mg diluted in 2.5 ml sterile water for injection to the right and 500mg to the left shoulder).

**Radiobiological analysis.** The normalized total dose (NTD) was calculated using the formula proposed by Maciejewski (16), NTD = D/((α/β + d)/(α/β + 2)), where D is the total physical dose, d the dose per fraction and α/β is the tissue specific ratio. The NTD corrected for overall treatment time was calculated using a previously proposed formula (17), NTD(T) = D/((α/β + d)/(α/β + 2) + λ(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 current scheme, and λ is the estimated daily dose consumed to compensate for rapid tumor repopulation. For prostate cancer an α/β ratio equal to 1.5Gy was considered (for prostate tumor and node metastatic deposits). We assumed that α/β is 4Gy for late responding normal tissues (bladder, rectum and other pelvic tissues) and 10Gy for early responding normal tissues (intestinal and bladder mucosa).

We also assumed that the λ value for prostate cancer cells ranges between 0.2-0.8Gy. Such values were obtained in a previous study of ours in non-small cell lung carcinomas (17). Time-values between 0-3-0.6Gy have been reported for HNC (18) and in bladder cancer (19), but a relevant analysis is not available for prostate cancer. 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 (20). We therefore assumed a λ value of 0.2Gy for late responding normal tissues and 0.8Gy for early responding tissues. Although the HypoARC scheme herein described is delivered within 19 days, we considered that ‘To’ was the 21st day, assuming that the onset of the rapid tumor repopulation is evident after the 3rd week of therapy. Therefore, the HypoARC scheme introduces a significant 29-day reduction of the overall treatment time compared to a conventionally fractionated scheme, that would deliver an NTD of 72Gy (50 days) to prostate cancer.

**Follow-up of patients.** Patients were examined daily during therapy and amifostine / radiation toxicities were recorded. Following treatment completion, patients were examined weekly for a period of 4 weeks. Clinical examination was repeated monthly for 4 months and every 3 months thereafter.

**Results**

The physical dose and biological normalized total dose (NTD) calculated for prostate cancer (α/β=1.5Gy) and normal tissue late effects (α/β=4Gy), as well as the NTD corrected for time-factors NTD-T (λ=0.2-0.8), are shown in Table 1.

Amifostine tolerance was very good with grade 0/1 nausea noted in 6/7 patients and emesis grade 2 in 1/7. Grade 1 asthenia and somnolence was noted in 3/7 patients at some point of the treatment. Intramuscular injection of 8mg dexamethazone was administered in these patients (once a week during therapy), which improved tolerance. No other systemic toxicity was noted. Limited rash, around the area of amifostine injection, was noted in 2/7 patients.

None of the patients treated developed any grade bladder toxicity, including the patient with double prostate/bladder cancer. Diarrhoea grade 1 was noted in 2/7 patient, while 1/7 patients complained of constipation throughout the treatment. Grade 1 skin toxicity (limited dry desquamation) was noted in 1/7 patients, while no perineal skin toxicity was noted. Mild abdominal pain or cramps during the 2 weeks following radiotherapy completion were reported by 3/7 patients. Painful proctitis though with a known history of haemorrhoids (operated 5 years before RT), developed in 1/7 patients During the follow-up period of 3-13 months no other toxicities have been recorded.

Cancer-related dysuria was completely resolved in all 7 patients and almost complete response of the bone pain was noted in the patient with iliac bone metastasis.

**Discussion**

The use of hypofractionated and accelerated radiotherapy for the treatment of prostate cancer is gradually becoming an appealing radiotherapy option due to the recent evidence regarding the radiobiological behavior of prostate cancer that resembles that of late responding tissues (3,4,5). In 1990, Collins et al. reported the experience of the St. Thomas Hospital, UK on the radiotherapy outcome of 232 patients with prostate cancer treated with six large radiotherapy fractions over a 3-week period (14). The efficacy and late radiotherapy morbidity seemed to be at least as good as that expected from standard radiotherapy protocols. Recently, a large retrospective analysis of 705 patients with prostate cancer treated with hypofractionated/accelerated radiotherapy (16 daily fractions of 3.13Gy over 22 days), confined to the prostate and seminal vesicles, was reported from Christie Hospital, UK (15). The efficacy was high and, despite the no-conformal radiotherapy technique used, the late radiotherapy sequel were quite low to justify further dose escalation.

In the present study we described a conformal radiotherapy technique aiming to treat patients with high-risk prostate carcinoma. Radiotherapy is directed to both the prostate and regional pelvic lymph nodes. As the rate of lymph node involvement is as high as 45% in patients with high-grade and relatively advanced T-stage disease, pelvic irradiation is an essential step to guarantee good chances of local control. The hypofractionated and accelerated technique herein described gives a high biological dose to the prostatic carcinoma and nodes, while the dose to normal tissues is maintained at an acceptable level. This is mainly achieved by: (a) the very low α/β value of prostatic cancer that allows a sharp differential increase of the biological damage induced by large radiotherapy fractions to cancer cells compared to normal tissues and, (b) the use of conformal booster irradiation to the prostate and seminal
vesicles through lateral fields that further minimizes the exposure of normal pelvic tissues to radiation.

An important factor that further contributes to the selective protection of normal pelvic tissues is the administration of high-dose amifostine before each radiotherapy fraction. The adoption of a high amifostine dose schedule is based on experimental data suggesting that the higher the dose of amifostine, the better the cytoprotective efficacy (16). Such an optimal protection should be sought in radiotherapy schedules delivering a dose intensity higher than the prescribed in conventional radiation schemes. Using a simple subcutaneous administration procedure, the daily dose of 1000mg of amifostine was well tolerated and effectively contributed to the protection of normal pelvic tissues; none out of 7 patients herein described presented higher than grade 1 diarrhoea, while no cystitis or skin toxicity was noted despite the highly accelerated irradiation technique applied.

It is concluded that hypofractionated accelerated conformal radiotherapy is feasible in prostate cancer and that amifostine provides impressive protection against early radiotherapy pelvic toxicities. Studies with a large number of patients and long follow-up are necessary to assess the efficacy and late sequel of the regimen.

References


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