External radiotherapy for prostate cancer with or without androgen deprivation: Geneva, 1991 to 2004

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Summary

Questions under study/principles: A retrospective assessment of long-term results on a single centre, single author experience in treating prostate cancer with high dose curative radiotherapy (RT) with or without androgen deprivation (AD).

Methods: Between 1991 and 2004, 408 patients with clinically localised prostate cancer were treated with RT (±AD) at the University Hospital of Geneva. RT alone was delivered to 229 patients whereas AD associated to RT was given to 179 patients. The latter was most frequently delivered to those patients with worse prognostic factors at diagnosis (high PSA values, high Gleason scores, stage T3–T4; p <0.001). Patient's biochemical failure was established at the time of PSA progression above the post-treatment nadir value +2 ng/ml. Late urinary, rectal, and sexual side effects were assessed and scored according to the Radiotherapy Oncology Group grading system.

Results: Ten-year overall survival (OS) and cancer specific survival were 93% and 62% (p = 0.10), and 94% and 71% (p = 0.19) for patients treated with RT with and without AD respectively (p = 0.10). Ten-year biochemical disease-free survival (bDFS) was 61% and 50% for patients treated with RT with and without AD, respectively (p = 0.14). On Cox regression analysis, PSA at diagnosis and treatment modality correlated significantly with OS, whereas PSA at diagnosis, Gleason score, and treatment modality correlated significantly with bDFS. Mostly high-risk patients (PSA >20 ng/ml and/or Gleason 8–10) benefited from neo-adjuvant AD+RT compared to patients treated with RT alone (67% versus 32%, 5-year bDFS; p <0.001). The 5-year probability of moderate to severe late urinary and low-GI toxicities was 15% and 7% respectively. Regarding sexual toxicity, the 5-year risk of complete failure of erections after treatment was 57%.

Conclusions: AD+RT significantly improved both 10-year OS and bDFS, especially in patients with high-risk disease at diagnosis. Patients treated with RT alone presented with continuous failures during the 10-year interval of observation, thus questioning the wisdom of proposing RT alone at doses below 74 Gy, especially for patients with long life expectancies.

Key words: prostate cancer; radiotherapy; androgen deprivation

Introduction

Prostate cancer, nowadays the most frequent cancer in Western males, is a special paradigm in oncology since it can be managed successfully with surgery, radiotherapy (RT) or a simple watchful waiting policy [1, 2]. Localised tumours are the object of exhaustive clinical research programmes in radiation oncology, aiming to improve cure rates while preserving the quality of life of this most frequently symptom-free and relatively old patient population. Questions about the best treatment method (external RT or brachytherapy); technical improvements allowing for better accuracy; dose escalation; and the role of postoperative RT are among the key questions regarding the role of RT in the contemporary treatment of prostate cancer.

One of the more frequently addressed questions in clinical research on the curative treatment of prostate cancer is the role of androgen deprivation (AD) in association to radical RT with the aim to cure, especially for those patients with locally advanced disease for which “standard” RT doses (up to 70 Gy) may be considered suboptimal [3]. Although most studies so far do confirm a role for AD regarding improvement in biochemical failure, not all show a definitive improvement in survival [4–9]. It has been suggested that AD may compensate for what are currently consid-
Radiotherapy with or without hormones for prostate cancer

The purpose of the present report is to present retrospective long-term data on a single centre, single author results in treating prostate cancer patients with high dose curative RT (median dose, 74 Gy) with or without AD (neo-adjuvant + concomitant ± adjuvant) between the years 1991 and 2004.

Methods and materials

Between 1991 and 2004, 408 consecutive patients with clinically localised prostate cancer were treated at the University Hospital of Geneva in an attempt to cure with RT (aAD). Median age at diagnosis was 68.5 years (range 42–87.5). In 1991 and 1992 RT was delivered according to 2D treatment techniques (29 patients), while from 1993 to 2004 all the remaining 379 patients were treated with 3D conformal RT (CRT). A dose to the pelvic nodes of 30.4 Gy was delivered to 110 patients, 90 of whom were treated according to the RT+AD protocol. Pelvic RT was delivered to patients with a risk of nodal disease above 15% (though not all patients with this risk of nodal involvement received pelvic irradiation). The dose to the prostate was 67–70 Gy, 70–74.4 Gy, and 74.4–78.4 Gy in 48, 246, and 114 patients, respectively. Radiotherapy alone was delivered to 229 patients and neo-adjuvant AD associated to RT was given to 179 patients.

Hormonal treatment aimed to deliver an oral anti-androgen (flutamide 250 mg tid or bicalutamide 50 mg qd) for 30 days and monthly or trimestral orientations of LH-RH analogues (leuprolide or goserelin) starting 10–15 days after the first day of anti-androgens. Hormones started in every case 2–4 months before RT, continued during the usual 8-week period of RT and thereafter for a limited number of high-risk patients. Indeed, AD lasted 4, 6, 12, and 24 months in 35, 120, 6, and 18 patients, respectively. More patients in the combined treatment protocol were treated during the period 1998–2004 compared to 1991–1997 (p <0.001). Patient age did not correlate with treatment option (p = 0.597). The policy of adding AD to RT was not standard and changed over time. Recommendations from clinical trials were adopted into corresponding binary indicators, have been considered: age at diagnosis (up to 60 years vs >60 to 70 vs >70), period of treatment (91–97 versus 98–04), months from diagnosis to radiotherapy (≤3 vs >3–6 vs >6–12 vs >12), clinical T-stage (1–2 vs 3–4), transurethral resection of the prostate (TURP) (yes vs no), grade (grade 1 or Gleason 2–6 vs Grade 2 or Gleason 7 vs grade 3 or Gleason 8–10), PSA at diagnosis (<10 ng/ml vs 10–20 ng/ml vs >20 ng/ml), type of radiotherapy (RT only vs RT+AD), pelvic radiation (yes vs no), and the dose of RT to the prostate (≤74.4 Gy vs >74.4 Gy). All reported probability values are for two-sided tests.

Overall survival (OS) and cancer-specific survival (CSSV) were calculated from the date of diagnosis to death from any cause or from any cancer-related event respectively. Biochemical disease-free survival (bDFS) was computed as time to biochemical failure, considered at the time of PSA progression above the post-treatment nadir value +2 ng/ml (Phoenix consensus) [16], or to metastases or to death, whichever occurred first; deaths from any cause other than cancer were censored.

Late urinary, rectal, and sexual treatment-related side effects were assessed and scored according to the RTOG/EORTC grading system [17]. Four hundred patients were evaluated for both late rectal and urinary toxicities, while only 186 patients with no erection dysfunction at diagnosis were assessed for post-treatment sexual late effects. Kaplan Meyer curves were obtained for time to toxicities ≥grade-1 (any), ≥grade-2 (moderate and severe), and ≥grade-3 (only severe). Age, type of treatment, pelvic irradiation, RT dose, TURP, and treatment period were assessed for toxicity and their potential prognostic significance was evaluated by the Cox logistic regression method.
Results

Five-year and 10-year OS was 96% (±2%, SE) and 93% (±3%, SE) for patients treated with AD+RT, and 91% (±2%, SE) and 62% (±6%, SE) for patients treated with RT alone (p = 0.103) (fig. 1). Five-year and 10-year CSSV was 96% (±2%, SE) and 94% (±3%, SE) for patients treated with AD+RT, and 94% (±2%, SE) and 71% (±5%, SE) for patients treated with RT alone (p = 0.188) (fig. 2). Five-year and 10-year bDFS was 70% (±4%, SE) and 61% (±6%, SE) for patients treated with AD+RT, and 63% (±4%, SE) and 50% (±5%, SE) for patients treated with RT alone (p = 0.136) (fig. 3). On multivariate analysis (MVA), PSA at diagnosis and treatment modality correlated significantly with OS (table 2), whereas PSA at diagnosis, Gleason score, and treatment modality correlated significantly with bDFS (table 3). An exploratory analysis was performed to study the possible differential effect of AD+RT according to risk category: patients were stratified into three groups with different risks of biochemical failure based on PSA at diagnosis and Gleason score on biopsies (table 4). Only patients in the “high-risk” group (i.e., PSA >20 ng/ml and/or Gleason 8–10) benefited significantly from neo-adjuvant AD+RT compared to patients treated with RT alone (67% versus 32%, 5-year bDFS; p <0.001). It is however worth noting that the significance of this interaction between risk group and treatment with or without AD was not confirmed in the MVA which included the variables listed in the methods section (except PSA and Gleason which are part of the risk group definition). Among AD treated patients, a PSA ≤0.1 ng/ml at the time of...
Radiotherapy with or without hormones for prostate cancer

Table 2
Factors selected by the Cox regression analysis for 381 patients with complete data to correlate with overall survival.

<table>
<thead>
<tr>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA (ng/ml) at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>1</td>
<td>reference</td>
</tr>
<tr>
<td>10–20</td>
<td>3.4</td>
<td>1–11.6</td>
</tr>
<tr>
<td>&gt;20</td>
<td>4.2</td>
<td>1.3–13.5</td>
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<tr>
<td>RT±AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT only</td>
<td>1</td>
<td>reference</td>
</tr>
<tr>
<td>AD+RT</td>
<td>0.3</td>
<td>0.1–0.9</td>
</tr>
</tbody>
</table>

PSA: prostate specific antigen; RT: radiotherapy; AD: androgen deprivation; HR: hazard ratio; CI: confidence intervals

Table 3
Factors selected by the Cox regression analysis for 381 patients with complete data to correlate with biochemical disease-free survival.

<table>
<thead>
<tr>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA (ng/ml) at diagnosis</td>
<td></td>
<td></td>
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<tr>
<td>&lt;10</td>
<td>1</td>
<td>reference</td>
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<tr>
<td>10–20</td>
<td>2.8</td>
<td>1–5.0</td>
</tr>
<tr>
<td>&gt;20</td>
<td>6.2</td>
<td>3.6–10.6</td>
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<tr>
<td>Grade/Gleason</td>
<td></td>
<td></td>
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<tr>
<td>I/&lt;7</td>
<td>1</td>
<td>reference</td>
</tr>
<tr>
<td>II/=7</td>
<td>1.8</td>
<td>1.1–2.8</td>
</tr>
<tr>
<td>III/&gt;7</td>
<td>2.3</td>
<td>1.1–4.9</td>
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<tr>
<td>RT±AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT only</td>
<td>1</td>
<td>reference</td>
</tr>
<tr>
<td>AD+RT</td>
<td>0.3</td>
<td>0.2–0.5</td>
</tr>
</tbody>
</table>

PSA: prostate specific antigen; RT: radiotherapy; AD: androgen deprivation; HR: hazard ratio; CI: confidence intervals

Table 4
5-year biochemical disease-free survival (%) and risk groups (see text).

<table>
<thead>
<tr>
<th>Nb patients</th>
<th>RT</th>
<th>AD+RT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk (PSA, &lt;10 ng/ml; Gr-I/Gleason &lt;7)</td>
<td>58</td>
<td>87</td>
<td>NE*</td>
</tr>
<tr>
<td>Intermediate-risk (PSA, 10–20 ng/ml; Gr-II/Gleason = 7)</td>
<td>189</td>
<td>67</td>
<td>74</td>
</tr>
<tr>
<td>High-risk (PSA, &gt;20 ng/ml; Gr-III/Gleason &gt;7)</td>
<td>157</td>
<td>32</td>
<td>67</td>
</tr>
</tbody>
</table>

PSA: prostate specific antigen; RT: radiotherapy; AD: androgen deprivation

Starting RT (28 patients) correlated with a trend for a better bDFS (but not OS) than patients with higher PSA values at the time of RT (151 patients) (p = 0.085).

Overall survival was similar for patients treated with or without pelvic RT, while bDFS did not benefit from pelvic irradiation either, with a better outcome for patients treated exclusively to the prostate only on univariate analysis (p = 0.05), probably translating the more favourable risk of the later patients.

The 5-year probability of grade-2 late urinary and low-GI toxicities (moderate to severe, requiring medical or surgical interventions) was 15% (±2%, SE) and 7% (±1%, SE), respectively, for the whole group of patients in the study (fig. 3a and 3b). In addition, a 5-year probability of irreversible failure of erections (unresponsive to sildenafil or analogues, grade 3) was observed in 57% (±4%, SE) of patients, as shown in fig. 4.

In the MVA, late urinary toxicity (grade-2) was significantly correlated with high RT dose (HR: 1.8, 95% CI 1.1–3.0) and pre-treatment TURP (HR: 1.9, 95% CI 1.2–3.0). Late rectal toxicity (grade-1) was significantly correlated with high RT dose only (HR: 1.6, 95% CI 1.1–2.5). Post-treatment erection dysfunction (grade 3) was correlated with treatment modality (AD+RT, HR: 3.4, 95% CI 2.2–5.4) and patient age at treat-
Discussion

This is a single centre, single author (RM) experience in the curative treatment of prostate cancer with RT (with or without AD) during a 14-year period. Almost all patients were treated with CRT and relatively high doses (median, 74 Gy). AD was prescribed most frequently to those patients with unfavourable prognostic factors such as elevated PSA at diagnosis or high Gleason scores on tissue specimens. Despite those negative prognosticators, both long-term (10 years) OS and bDFS were significantly better among patients treated with the AD+RT association. Most patients (155/179, 85%) were treated with ≤6 months AD.

An appealing hypothesis that may explain, at least in part, the better results with AD before RT is the hypoxic status of aggressive prostate cancer at diagnosis [18]. This may potentially be improved with AD, since treatment-related tumour cell destruction may improve the oxygenation status of the tumour cells in the prostate, rendering them more radio-responsive at the time of RT [19, 20]. In addition, an optimal PSA nadir before RT may be a surrogate for a better response after RT, suggesting that AD before RT should be continued until reaching the lowest possible PSA value [21, 22].

When stratifying by risk groups, only patients with the worse prognosticators had a significantly better 5-year bDFS when treated with AD+RT (table 4). RT alone was associated with a 5-year bDFS of 87% in low-risk patients, which compares favourably with similar reports in the literature on patients treated with 3-D conformal RT to doses <80 Gy or after radical prostatectomy [23-26]. Nevertheless, even for low-risk patients treated with RT alone, failures continued to be diagnosed after 5 years (bDFS dropping to 70% at 10 years). In a recent analysis of the Geneva tumour registry on patients treated for prostate cancer between 1989 and 1998, cancer-specific survival was similar at 5 years for patients treated by RT alone when compared to those treated by radical prostatectomy (93% versus 94% respectively) [27]. However, at 10 years cancer-specific survival was significantly better for patients treated with prostatectomy, 83% (73–93% 95%CI) dropping...
Radiotherapy with or without hormones for prostate cancer

played a role in preserving erections after treat-
case. with RT alone [29], this was not observed in our
rectal late effects than their counterparts treated
by RT+AD associations presented worse
to other authors who have suggested that patients
widely used 4-field “box” techniques. In contrast
much of the rectal wall compared with more
the prescribed dose respectively) which may spare
through optimisation of rectal dose distribution,
since most of our patients were treated with
6 fields (2 lateral and 4 oblique, delivering 50% of
the prescribed dose respectively) which may spare
much of the rectal wall compared with more
widely used 4-field “box” techniques. In contrast
to other authors who have suggested that patients
treated by RT+AD associations presented worse
rectal late effects than their counterparts treated
with RT alone [29], this was not observed in our
case.

Erectile dysfunction was strongly correlated
with the addition of AD to RT. Age, however, also
played a role in preserving erections after treat-
ment. Indeed, 71% (±8%, SE) of patients <60
years were free of severe erection dysfunction
(grade 3) five years after treatment. For patients
aged 60–70 and above the age of 70, the 5-year
probability of being free of severe erectile dys-
function was 53% and 55%, respectively. Thus,
the benefit of adding AD to RT with its well
proven effect for patients with high-risk disease,
must be balanced against the severe toxicity ob-
served in sexual function (47% 5-year free of any
erectile dysfunction for patients treated with RT
only, but only 17% for their AD+RT counter-
parts) for an HR of 2.4 (1.7–3.5, 95%CI) in
favour of RT alone. Furthermore, an increased
risk of incident diabetes, dyslipidaemia and car-
diovascular disease, in addition to other well
known side effects such as osteoporosis, loss of
lean body mass, sweating, fatigue, and depression,
have recently been reported in prostate cancer pa-
tients on long-term AD, reinforcing a defensive
attitude in recommending AD for those patients
without a clear benefit and rather favouring short
treatment periods whenever possible [30, 31].

In summary, associating AD for four months
or more to curative RT improved both 5- and 10-
year OS and bDFS. This benefit was usually sig-
nificant for patients with unfavourable risk factors
diagnosis. Patients treated with RT only (re-
gardless of the risk group) presented with contin-
uous failures without flattening of the OS curve
for the whole 10-year observation period, thus
questioning the wisdom of proposing RT alone at
doses below 74 Gy, especially for patients with
long life expectancies. The low late rectal toxicity
incidence observed was probably related to a
dose-sparing effect of the rectal wall due to an op-
timal conformation with the 6-field 3-D confor-
mal RT technique. Sexual function was severely
impaired in the group of patients treated with
AD+RT.

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