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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-

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ered the low RT doses of the first studies addressing the role of AD [10]. D'Amico et al. published what are so far among the best results on survival, with 6 months' AD associated to 70 Gy to the primary tumour [11]. Although several studies are ongoing there is at present no randomised published data on AD with doses of RT of 74 Gy and above. Such studies might help to underscore the benefit of higher doses of RT with the adjunction of AD.

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 (±AD). 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 50.4 Gy was delivered to 110 patients, 90 of whom were treated according to the RT+AD association. 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 injections 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 with the publication of their results. During the first period (1991 to 1997) AD+RT was delivered to patients with PSA values superior to 50 ng/ml, this threshold being diminished later on, and since 1998 most patients on AD+RT presented with PSA values ≥15 ng/ml at diagnosis. Nonetheless, patients selected for AD+RT presented not only with higher PSA values at diagnosis, but also with higher Gleason scores, and higher T-stage disease compared to the group of patients treated with RT alone (p <0.001, *chi*-square) (table 1). Indeed, all but one patient out of 58 "low-risk" patients were treated with RT alone, while 71/189 patients (40%) with "intermediate risk" and 107/157 "high-risk" patients (60%) received the association of AD and RT.

Table 1

Disease-related characteristics and treatment arm among the 408 patients in the study.

	RT only	AD+RT	p-value
PSA (ng/ml) at diagnosis			
<10	135	24	
10–20	51	62	
>20	40	91	<0.001
Grade/Gleason			
I/<7	107	41	
II/=7	104	105	
III/>7	8	31	<0.001
T-stage			
1 and 2	145	62	
3 and 4	80	112	<0.001

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

Percentages of events of interest over time have been calculated by the Kaplan-Meier method [12] and their corresponding standard errors (SE) with Greenwood's formula [13]. For the comparison of survival experiences the p-values from the log-rank test are reported for each comparison considered [14]. Cox regression (forward selection on 381 patients with complete data) has been used to assess the simultaneous effect of covariates on the outcomes of interest [15]. The following variables, coded 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

Figure 1

Overall survival (Kaplan-Meier, log-rank test) for the 229 patients treated by radiotherapy alone (Rx only) and for the 179 patients treated by neoadjuvant and concomitant androgen deprivation plus radiotherapy (Rx and Hormones). Patients at risk at the start of each two-year period are also given.

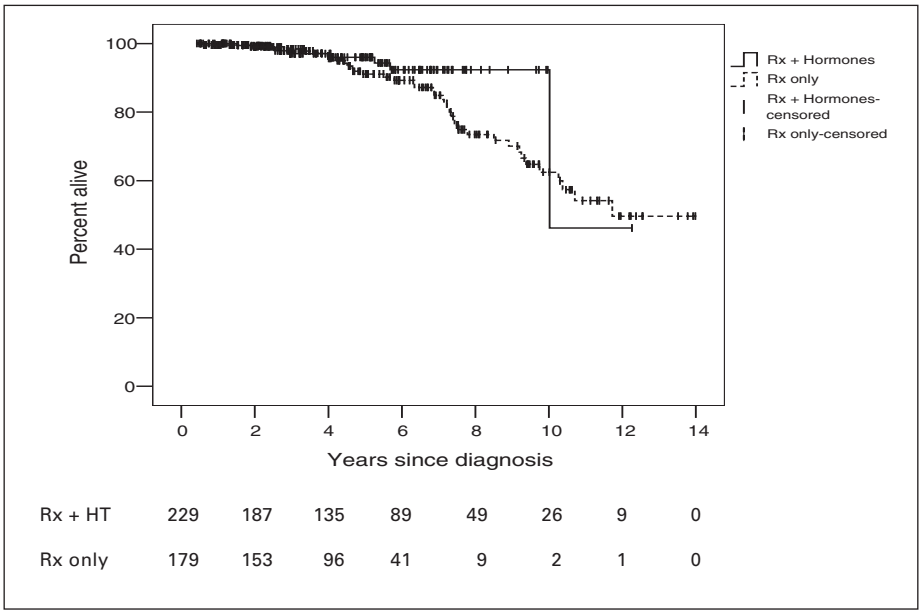

Figure 2

Cancer specific survival (Kaplan-Meier, log-rank test) for the 229 patients treated by radiotherapy alone (Rx only) and for the 179 patients treated by neoadjuvant and concomitant androgen deprivation plus radiotherapy (Rx and Hormones). Patients at risk at the start of each two-year period are also given.

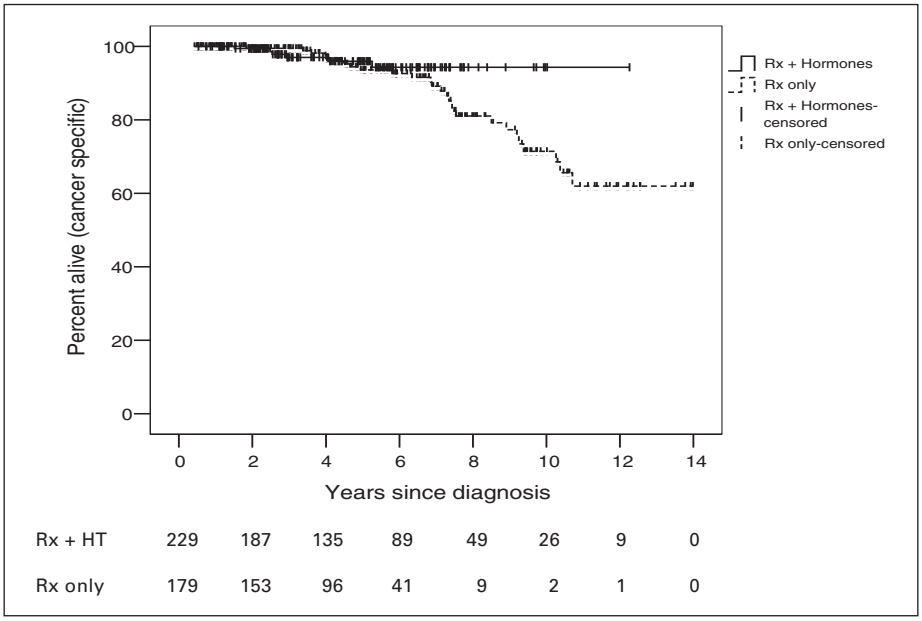

Figure 3

Biochemical disease-free survival (Kaplan-Meier, log-rank test) for the 229 patients treated by radiotherapy alone (Rx only) and for the 179 patients treated by neoadjuvant and concomitant androgen deprivation plus radiotherapy (Rx and Hormones). Patients at risk at the start of each two-year period are also given.

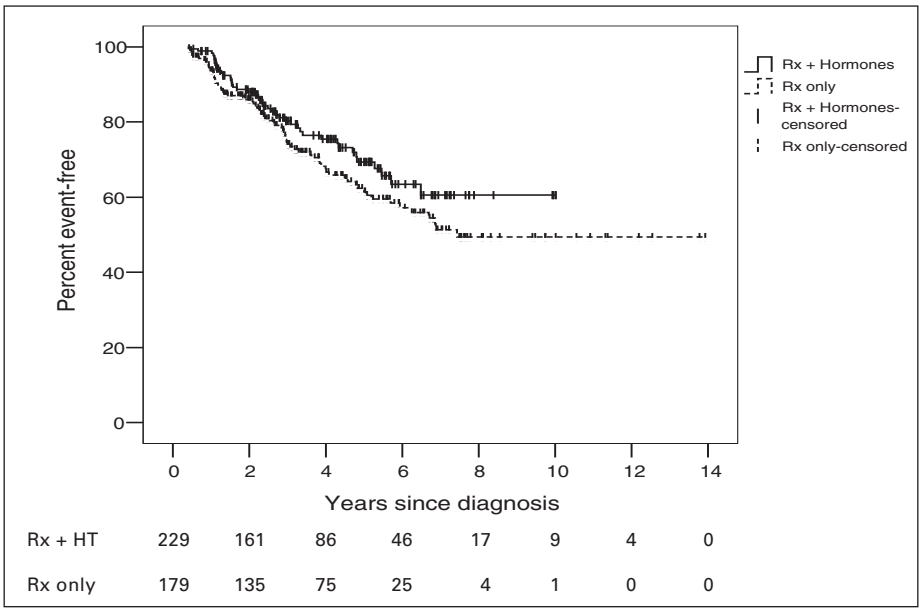

Table 2

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

	HR	95%CI	p-value
PSA (ng/ml) at diagnosis			
<10	1	reference	–
10–20	3.4	1–11.6	0.052
>20	4.2	1.3–13.5	0.017
RT±AD			
RT only	1	reference	–
AD+RT	0.3	0.1–0.9	0.039

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.

	HR	95%CI	p-value
PSA (ng/ml) at diagnosis			
<10	1	reference	–
10–20	2.8	1–5.0	<0.001
>20	6.2	3.6–10.6	<0.001
Grade/Gleason			
I/<7	1	reference	–
II/=7	1.8	1.1–2.8	0.015
III/>7	2.3	1.1–4.9	0.029
RT±AD			
RT only	1	reference	–
AD+RT	0.3	0.2–0.5	<0.001

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

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-

Table 4

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

	Nb patients	RT	AD+RT	p-value
Low-risk				
(PSA, <10 ng/ml; Gr-I/Gleason <7)	58	87	NE*	–
Intermediate-risk				
(PSA, 10–20 ng/ml; Gr-II/Gleason = 7)	189	67	74	0.42
High-risk				
(PSA, >20 ng/ml; Gr-III/Gleason >7)	157	32	67	<0.001

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

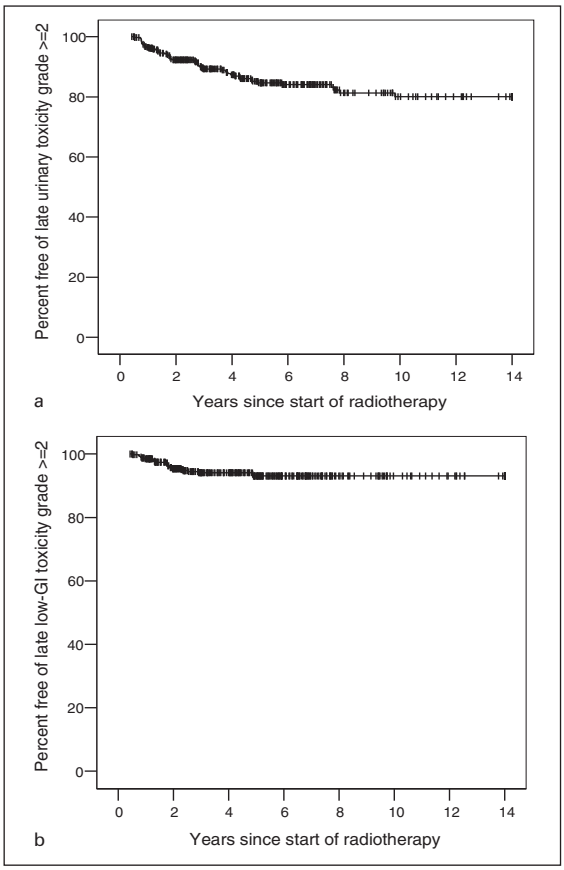

Figure 4

Cumulative survival free of genito-urinary (a) and low gastro-intestinal (b) ≥grade-2 toxicity (Kaplan-Meier).

ment (<60 years old, reference; 60–70 years old, HR: 2.3, 95%CI 1.1–4.7; >70 years old, HR: 2.6, 95%CI 1.2–5.6). Although not selected by the Cox model, pelvic irradiation did correlate with ≥grade-2 late urinary toxicity on the *log-rank* test (predicting almost twice the risk than in patients treated without including pelvic lymph nodes in the treatment fields). A similar observation was made for ≥grade-1 low-GI toxicity as it also correlated with pelvic RT in the univariate analysis only: 39% versus 27% 5-year risk for ≥grade-1 late low-GI toxicity for patients with and without RT to the pelvic nodes (p = 0.037).

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

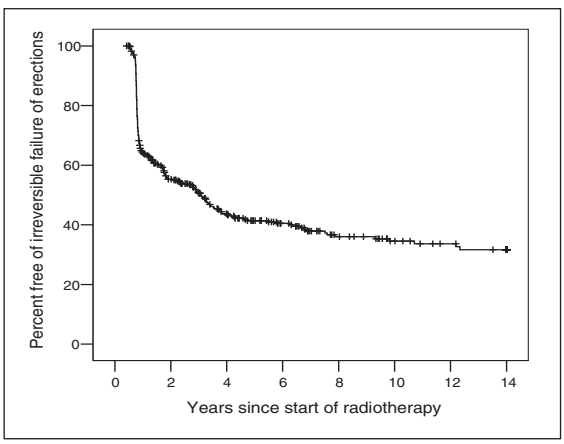

Figure 5

Cumulative survival free of sexual grade 3 toxicity (complete loss of erections) (Kaplan-Meier).

to 73% (65–81%, 95%CI) for those treated with RT alone, a hazard ratio of 2.3 (1.2–4.4, 95%CI) in favour of prostatectomy after adjusting for age, period, stage, and other disease-related risk factors. AD added a survival benefit for all patients treated with RT in our series (10-year, 95% CSSV) which is probably better than the 10-year, 69% CSSV for patients treated with radical prostatectomy in Geneva, as reported by the same tumour registry study and regardless of the "negative" selection with worse prognosticators for patients treated with AD+RT [27].

The 5-year risk of ≥grade-2 urinary late effects was 15%, similar to the late urinary toxicity risk reported in the literature for patients treated with 3-D conformal RT to doses of 74–78 Gy [28]. The prescribed RT dose and a TURP preceding irradiation significantly correlated with the risk of urinary late effects. All our patients were treated with "empty" bladders, trading a potential reduction in target motion (bladder-filling related) against a suboptimal sparing of the bladder in the high-dose region.

The 5-year risk of moderate to severe rectal late toxicity was 7%, which is significantly lower than the usually 20% reported in the literature for patients treated with 3-D CRT to doses of 74–78 Gy [26]. Indeed, only a "high" dose to the prostate (>74.4 Gy) correlated with any (≥grade-1) rectal toxicity level in the MVA. The fact that this was not also observed in patients with more severe toxicity levels can be explained by the few events with grade-2 or grade-3 toxicities in the present series. The dose factor, however, may still explain the low rectal toxicity risk in our patients, possibly 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 treatment. 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 dysfunction 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 observed in sexual function (47% 5-year free of any erectile dysfunction for patients treated with RT only, but only 17% for their AD+RT counterparts) 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 cardiovascular 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 patients 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 significant for patients with unfavourable risk factors at diagnosis. Patients treated with RT only (regardless of the risk group) presented with continuous 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 optimal conformation with the 6-field 3-D conformal RT technique. Sexual function was severely impaired in the group of patients treated with AD+RT.

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