



# Tailored treatment including radical prostatectomy and radiation therapy + androgen deprivation therapy versus exclusive radical prostatectomy in high-risk prostate cancer patients: results from a prospective study

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## ABSTRACT

**Purpose:** To evaluate outcomes of patients with high risk prostate cancer (PCa) who underwent radical prostatectomy (RP) in a context of a multidisciplinary approach including adjuvant radiation (RT) + androgen deprivation therapy (ADT).

**Materials and Methods:** 244 consecutive patients with high risk localized PCa underwent RP and bilateral extended pelvic lymph node dissection at our institution. Adjuvant RT + 24 months ADT was carried out in subjects with pathological stage  $\geq$  T3N0 and/or positive surgical margins or in patients with local relapse.

**Results:** After a median follow-up was 54.17 months (range 5.4-117.16), 13 (5.3%) subjects had biochemical progression, 21 (8.6%) had clinical progression, 7 (2.9%) died due to prostate cancer and 15 (6.1%) died due to other causes. 136 (55.7%) patients did not receive any adjuvant treatment while 108 (44.3%) received respectively adjuvant or salvage RT+ADT. Multivariate Cox proportional hazard analysis showed that pre-operative PSA value at diagnosis is a significant predictive factor for BCR (HR: 1.04,  $p < 0.05$ ) and that Gleason Score 8-10 (HR: 2.4;  $p < 0.05$ ) and PSMs (HR: 2.01;  $p < 0.01$ ) were significant predictors for clinical progression.

Radical prostatectomy group was associated with BPFs, CPFS, CSS and OS at 5-years of 97%, 90%, 95% and 86% respectively, while adjuvant radiation + androgen deprivation therapy group was associated with a BPFs, CPFS and CSS at 5-years of 91%, 83%, 95% and 88%, without any statistical difference.

**Conclusions:** Multimodality tailored treatment based on RP and adjuvant therapy with RT+ADT achieve similar results in terms of OS after 5-years of follow-up.

## ARTICLE INFO

### Key words:

high-risk; prostate cancer; radical prostatectomy; androgen deprivation therapy; radiation therapy; multimodality

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## INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed non-dermatologic malignancy among American men, and it remains the second most fatal cancer. Similar incidence and mortality

figures are reported by the European Association of Urology (EAU) (1).

The goal of PCa screening is to detect potential fatal cancers at a time when they may still be curable. The downside of screening is the diagnosis and overtreatment of tumours destined

to pose no threat to the man during his lifetime. The upside of screening is the detection of high-risk cancers while still clinically localized. In a heavily screened population, this “high-risk” group accounts for 15% of men with clinically localized disease and likely a higher percentage in less heavily screened population (2).

In the presence of adverse clinical or pathologic features connoting high-risk disease, results of local treatment alone are disappointing and there is increasing recognition of the need for a multimodal approach to treatment (3,4). The optimal sequence and constituents of such a strategy, however, remain controversial. The use of external-beam RT as primary therapy in conjunction with androgen-deprivation therapy (ADT) is supported by the results of several randomized controlled trials (RCTs) (5-8). Alternatively, surgery may be employed as the definitive initial treatment. While radical prostatectomy (RP) has not been traditionally recommended for high-risk disease in the past, its use in this setting is increasing, as evidenced by several large, modern, single-institution series (9-12). Currently, multimodality approaches, including surgery, adjuvant radiotherapy and androgen deprivation therapy are proposed for high risk prostate cancer.

The aim of this study is to evaluate outcomes of patients with high risk prostate cancer who underwent RP in a context of a multidisciplinary approach including surgery alone or adjuvant or salvage radiation therapy + androgen deprivation therapy.

## MATERIAL AND METHODS

### Study Population

From January 2003 to December 2006, 244 consecutive patients with high risk localized PCa (PSA greater than 20 ng/mL, and/or cT3-4 and/or biopsy Gleason Score 8-10) who underwent retropubic radical prostatectomy (RP) and bilateral extended pelvic lymph node dissection (eLND) at a single institution were enrolled in this prospective study.

The protocol was approved by the Internal Institutional Review Board and an informed written consent was obtained from each man before initiation of the study.

Clinical stage was assigned according to the 2002 TNM and prostate biopsy was performed

under transperineal ultrasound guidance. Preoperative staging with CT and bone scan showed no signs of metastases. None of the patients received neoadjuvant ADT. All patients underwent extended lymph node dissection including bilateral dissection of the right and left common iliac vessels, the right and left internal iliac vessels, the right and left external iliac vessels, and the right and left obturator fossa ( $\geq 20$  lymph node).

Follow-up included DRE and serum PSA every 3 months, CT and bone scan annually or when clinically appropriate; TRUS + biopsy of the prostatic bed when clinically required. The baseline information, Charlson Comorbidity Index (CCI), the pathologic Gleason score, surgical margin (SM) status, seminal vesicle invasion (SVI), and the follow-up information were recorded for each subject.

### Postoperative therapy

Postoperative therapy was considered adjuvant therapy if it was begun before PSA or clinical progression. Patients with pathological pelvic lymph node metastases were excluded.

Adjuvant radiotherapy + 24 months ADT was carried out in subjects with pathological stage  $\geq T3N0$  and/or positive surgical margins at 4 to 6 weeks after surgery while salvage RT + 24 months ADT in patients with local relapse confirmed after biopsy of the prostatic bed. Radiotherapy was performed with intensity-modulated technique using 18-MV photons of an Elekta linear accelerator (Elekta AB, Crawley, UK) equipped with a multileaf collimator. The clinical target volume (CTV) consisted of the postoperative prostate and seminal vesicle bed. To create the planning target volume (PTV), an isotropic, 3-dimensional, 7-mm expansion of the CTV was performed. Treatment was delivered in 37 fractions with a median 76-Gy dose to the PTV (range: 70-79 Gy). ADT consisted of triptorelin 11.25 mg administered every 3 months as LHRH analogue.

Biochemical progression after surgery was defined as the first occurrence of two consecutive PSA levels above 0.2ng/mL at follow-up. Clinical progression was defined as either local recurrence or distant metastasis. Local recurrence was defined as histologically confirmed evidence of cancer cells

in targeted biopsies at the prostatic bed. Distant metastasis was defined as a positive finding on bone scan or imaging examination. Prostate Cancer Specific Mortality (PCSM) was defined as the time from RP to death for PCa or disease related complications while Other-Cause Mortality (OCM) as the time from RP to death not depending for PCa. Prostate Cancer-Specific Survival (PCSS) was defined as the time from RP to PCSM while overall survival (OS) was defined as the time from RP to death from any cause.

### Statistical analysis

All statistical analyses were completed using *SPSS* v. 19 software (SPSS Inc, IBM Corp, Somers, NY, USA). Cox univariate and multivariate regression models were carried out to identify variables for predicting biochemical recurrence (BCR), clinical progression (CP), prostate cancer specific mortality (PCSM) and other-cause mortality (OCM) from preoperative variables including age, PSA levels, clinical T stage, biopsy Gleason score and from postoperative variables including pathological Gleason score, positive margin status, seminal vesicle invasions, and adjuvant treatment conditions. Biochemical progression-free survival (BPFS), clinical progression-free survival (CPFS), prostate cancer-specific survival (PCSS) and overall survival (OS) were determined using the Kaplan-Meier method and curves were tested with the log-rank test. Life-tables of each subgroup were analyzed using the Wilcoxon (Gehan) test. For all statistical comparisons significance was considered as  $p < 0.05$ .

### RESULTS

Table-1 lists the baseline characteristics of the subjects included in this study. Median of pre-operative PSA level was 20ng/mL (range 1-82), median of age of patients was 68 (range 48-78) and CCI was respectively  $< 2$  and  $\geq 2$  in 159 (65.2%) and 85 (34.8%) subjects. Upstaging and upgrading was found in 72 (29.1%) and 49 (20.08%) patients and median follow-up was 54.17 months (range 5.4-117.16), 13 (5.3%) subjects had biochemical progression, 21 (8.6%) had clinical progression, 7

(2.9%) died due to prostate cancer and 15 (6.1%) died due to other causes. 136 (55.7%) patients did not receive any adjuvant treatment while 108 (44.3%) received respectively adjuvant or salvage RT+ADT.

Multivariate Cox proportional hazard analysis showed that pre-operative PSA value at diagnosis is a significant predictive factor for BCR (HR: 1.04;  $p < 0.05$ ) and that Gleason Score 8-10 (HR: 2.4;  $p < 0.05$ ) and PSMs (HR: 2.01 (0.75-3.12);  $p < 0.01$ ) were significant predictors for clinical progression (Table-2). None of the pre-operative and post-operative variables were predictors of PCSM and OCM. Kaplan-Meier curves showed no significant differences between groups when considering BPFS, CPFS, CSS and OS. (Figure-1). The over-all 5-years BPFS, CPFS, PCSS and OS were respectively 94%, 85%, 95% and 87%. Radical prostatectomy alone was associated with BPFS, CPFS, CSS and OS at 5-years of 97%, 90%, 95% and 86% respectively, while adjuvant radiation + androgen deprivation therapy was associated with a BPFS, CPFS and CSS at 5-yr of 91%, 83%, 95% and 88% (Table-3).

### DISCUSSION

In the past, RP was not considered an acceptable treatment in patients with high-risk prostate cancer. However, thanks to the improvements in surgical techniques and technologies, RP and adjuvant treatments are now increasingly being used in selected patients.

The exact definition of high risk is a matter of debate. High-risk, clinically localised disease was classically defined by D'Amico et al. as any combination of the following factors: a prostate-specific antigen (PSA) score  $> 20$ ng/mL, a Gleason score of 8-10, or clinical stage T2c or greater (13). More recently, the National Comprehensive Cancer Network and EAU have modified this definition to include any combination of a clinical T3, a PSA score  $> 20$ ng/mL, or a Gleason score of 8-10.

Several authors suggest the use of a combination of PSA, Gleason score, and clinical stage to predict outcomes after radical prostatectomy (RP) in patients with a PSA  $\geq 20$ ng/mL, assuming that the use of a single criterion may overestimate the risk of recurrence and may not identify the

**Table 1 - Clinical and pathological characteristics of patients.**

	Overall (n = 244)	Exclusive RP (n = 136)	RT+ADT (n = 108)	p-value
Median (range) age, years	68 (48-78)	68 (53-78)	67 (48-78)	0.40
Median (range) PSA at baseline, ng/mL	20 (1-82)	14 (1-69)	21 (3-82)	0.03
<b>CCI, n (%)</b>				0.11
< 2	159 (65.2)	83 (61.0)	76 (70.4)	
≥ 2	85 (34.8)	53 (39.0)	32 (29.6)	
<b>Clinical stage, n (%)</b>				0.27
T1c	16 (6.6)	12 (8.8)	4 (3.7)	
T2	206 (84.4)	112 (82.4)	94 (87.0)	
T3a	22 (9.0)	12 (8.8)	10 (9.3)	
<b>Biopsy Gleason score, n (%)</b>				0.14
≤ 6	48 (19.7)	32 (23.5)	16 (14.8)	
7	43 (17.6)	20 (14.7)	23 (21.3)	
8-10	153 (62.7)	84 (61.8)	69 (63.9)	
<b>Pathological Gleason score, n (%)</b>				0.01
≤ 6	30 (12.3)	20 (14.7)	10 (9.3)	
7	105 (43.0)	66 (48.5)	39 (36.1)	
8-10	109 (44.7)	50 (36.8)	59 (54.6)	
<b>Pathological stage, n (%)</b>				< 0.01
pT2	80 (32.8)	64 (47.1)	16 (14.8)	
pT3a	104 (42.6)	46 (33.8)	58 (53.7)	
pT3b-4	60 (24.6)	26 (19.1)	34 (31.5)	
Upgrading, n (%)	49 (20.08)	25 (18.38)	24 (22.22)	0.09
Upstaging, n (%)	72 (29.1)	34 (25.0)	37 (34.26)	0.10
PSMs, n (%)	86 (35.2)	60 (55.6)	26 (19.1)	< 0.01
SVI, n (%)	65 (26.6)	0 (0.0)	28 (26.6)	< 0.01

true high-risk patient (14). In fact, men with a high level of PSA and a Gleason grade ≤ 7 had very low risk for cancer progression. Alternatively, men with multiple high-risk features (i.e., PSA > 20ng/mL, biopsy Gleason score 8-10, or clinical stage T3 disease) had poor outcomes despite sur-

gery (15).

Data from the randomized controlled trial EORTC 22911 demonstrated that conventional postoperative irradiation significantly improves biochemical progression-free survival and local control compared with a wait-and-see policy at 5

**Table 2 - Multivariate cox regression analysis of preoperative and pathological predictors of biochemical recurrence and clinical progression.**

	Biochemical Recurrence		Clinical Progression	
	Multivariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Patient age, years	1.03 (0.89-1.19)	0.68	1.10 (0.94-1.28)	0.23
PSA level, ng/mL	1.04 (1.00-1.06)	0.04	0.68 (0.98-1.05)	0.68
<b>Clinical T stage</b>				
T1c	1.00 (Ref.)		1.00 (Ref.)	
T2	2.78 (0.10-4.63)	0.97	1.42 (0.1-6.69)	0.96
T3-4	4.00 (0.10-6.68)	0.96	2.97 (0.2-6.31)	0.97
<b>Biopsy Gleason Score</b>				
≤ 6	1.00 (Ref.)		1.00 (Ref.)	
7	3.07 (0.1-3.27)	0.95	3.14 (0.18-77.76)	0.48
8-10	6.57 (0.2-6.94)	0.95	4.25 (1.10-5.77)	0.38
<b>Pathological Gleason Score</b>				
≤ 6	1.00 (Ref.)		1.00 (Ref.)	
7	1.48 (0.50-4.80)	0.53	1.2 (1.1-1.4)	0.04
8-10	2.57 (0.48-4.22)	0.58	2.4 (1.0-2.8)	0.03
<b>Pathological Stage</b>				
T2	1.00 (Ref.)		1.00 (Ref.)	
T3a	1.44 (1.12-2.56)	0.55	2.36 ( 1.74-3.56)	0.50
T3b-T4	2.23 (0.32-15.54)	0.41	3.23 (2.02-4.50)	0.30
PSMs, yes vs. no	1.46 (0.84-1.98)	0.72	2.01 (0.75-3.12)	< 0.01
SVI, no vs. yes	0.87 (0.2-2.66)	0.74	0.83 (0.04-2.65)	0.64

and 10 years follow-up (16,17).

In addition, results from the SWOG 8794 showed that adjuvant radiotherapy within 18 weeks after radical prostatectomy in a men with pT3N0M0 prostate cancer significantly reduces the risk of PSA recurrence, metastasis and the need for hormonal therapy, and significantly increases survival (18).

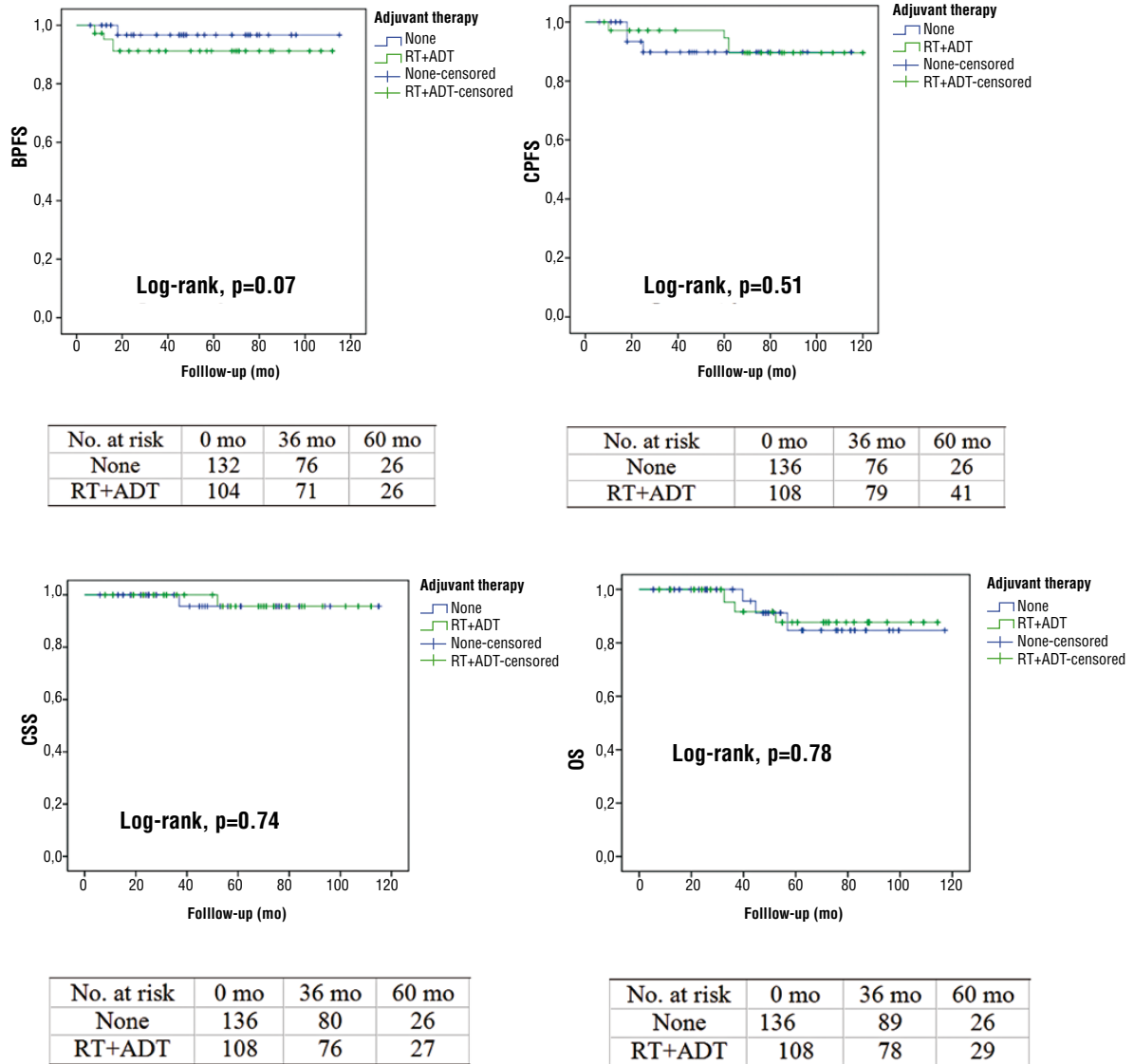
More recently, in a retrospective study of Ost et al., it has been showed that adjuvant RT + ADT significantly improved biochemical and clin-

ical progression rates after a median follow-up of 5 years in patients with unfavourable pathological findings (19,20).

In our study, good oncological outcomes seem to be obtained even in patients with worse pathological characteristics (i.e. pathological stage ≥ T3N0 and/or positive surgical margins) who needed adjuvant or salvage treatment like RT + ADT, with an estimated BPFs, CPFs, PCSS and OS of 94%, 85%, 95% and 87% respectively.

Androgen deprivation given in combina-

**Figure 1 - Kaplan-Meier curve analysis of BPFs, CPFS, PCSS and OS between groups.**



**Table 3 - Life tables comparison of BPFs, CPFS, PCSS and OS between both groups.**

	BPFs at 5-years		CPFS at 5-years		PCSS at 5-years		OS at 5-years	
	Cumulative Survival Rate	P-value	Cumulative Survival Rate	P-value	Cumulative Survival Rate	P-value	Cumulative Survival Rate	P-value
Adjuvant		0.20		0.64		0.83		0.90
Exclusive RP	97%		90%		94%		86%	
RT+ADT	90%		80%		94%		87%	



tion with RT in men with high risk prostate cancer demonstrates clinical benefits. The advantages appear to be related both to the ability of androgen deprivation to make prostate cancer more susceptible to radiation induced death and by killing or suppressing cancer cells that might have escaped from the prostate gland.

The role of lymph node dissection was addressed by Engel et al., who compared outcomes in LN positive patients with or without RP. They showed a survival benefit for local treatment even in positive lymph node disease, suggesting that RP may result in improved outcomes. However, these results must be viewed with caution given the greater proportion of prostatectomy abandonment in patients with unresectable and therefore more advanced disease (21). In our series, extended lymph node dissection was considered as integral part of the treatment.

Despite the different pathological characteristics of these patients, these tailored multimodality approach could offer benefits, with substantial survival gains of the RT+ADT group. In fact, we did not observe statistically differences in term of BPFs, CPFS, CSS and OS between groups. Certainly, the adjuvant or salvage therapy uniforms the survival rate to those patients who underwent exclusive RP.

However, the crucial question whether the optimum initial strategy should include radiation combined with androgen deprivation therapy at the time of RP, or surgery followed by selective radiation on the basis of pathological findings is still open (22).

Finally, to the best of our knowledge, this is the first study that report similar benefits in term of OS in high-risk prostate cancer patients who underwent a tailored treatment based on pathological features including RP alone and adjuvant or salvage therapy including RT+ADT when clinically required. However, our study contains potential limitations that need to be considered.

One possible limitation is the identification of high-risk prostate cancer patients based on D'Amico definition despite possible favorable features at pathological specimens after surgery.

Moreover, the short follow-up might have underestimated the overall risk of relapse and

mortality, because it is well known that PCa progresses slowly and our median follow-up could be considered insufficient (23). Finally, recent observations demonstrated the importance of comorbidities, evaluated as Charlson Comorbidity Index (CCI), when showing long-term survival in high-risk prostate cancer patients (24). In this context, the role of radical prostatectomy even in patients with high risk prostate cancer should be cautious, due to the limited life expectancy. However, the small sample size and the impact of comorbidity on patient survival might have been underestimated in our analyses.

## CONCLUSIONS

Although the heterogeneous pathological characteristics of our cohort of high-risk prostate cancer multimodality, tailored treatment based on RP and adjuvant or salvage therapy with RT+ADT achieved similar results in terms of BPFs, CPFS, CSS and OS after 5-years of follow-up.

## CONFLICT OF INTEREST

None declared.

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