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Secondary Therapy, Metastatic Progression, and Cancer-Specific Mortality in Men with Clinically High-Risk Prostate Cancer Treated with Radical Prostatectomy

Ofer Yossepowitch, Scott E Eggener, Angel M. Serio, Brett S. Carver, Fernando J. Bianco Jr, Peter T. Scardino, and James A. Eastham*

Department of Surgery, Urology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Abstract

Objectives—Commonly used definitions for high-risk prostate cancer identify men at increased risk of PSA relapse after radical prostatectomy (RP). We assessed how accurately these definitions identify patients likely to receive secondary cancer therapy, experience metastatic progression, or die of prostate cancer.

Materials and methods—Among 5960 men with clinically localized or locally advanced prostate cancer who underwent RP, we identified eight different high-risk subsets, each comprising 40% of the study population. Estimates of freedom from radiation therapy, hormonal therapy, and metastatic progression after surgery were generated for each high-risk cohort with the Kaplan-Meier method, and hazard ratios (HR) were calculated with a Cox proportional hazards regression. The cumulative incidence and HR for prostate cancer-specific mortality (PCSM) were estimated with competing risk analysis.

Results—Each of the studied high-risk criteria was associated with increased hazard of secondary cancer therapy (HR = 1.3[en]5.2, $p < 0.05$) and metastatic progression (HR = 2.1[en]6.9, $p < 0.05$). However, depending on the definition, the probability of freedom from additional therapy 10 yr after

*Corresponding author. James A Eastham, MD, Department of Urology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021. Tel. 646-422-4390; Fax: 212-988-0759. E-mail address: easthamj@mskcc.org (J.A. Eastham).

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Ofer Yossepowitch
Scott E Eggener
Angel M Serio
Brett S Carver
Fernando J Bianco Jr
Peter T Scardino
James A Eastham

Take-home message Patients classified with high-risk prostate cancer by currently available definitions do not have a uniformly poor prognosis after RP. Most of these men are alive and many remain free of additional therapy or metastatic disease long-term after surgery.

surgery ranged from 35% to 76%. The 10-yr cumulative incidence of PCSM in high-risk patients ranged from 3% to 11% (HR = 3.2[en]10.4, $p < 0.0005$).

Conclusions—Commonly used definitions for high-risk prostate cancer identify men at increased risk of secondary cancer therapy, metastatic progression, and PCSM following RP. However, a substantial proportion of high-risk patients remain free from additional therapy or metastatic disease many years after surgery. The risk of PCSM within 10 yr of treatment is remarkably low, even for patients at the highest risk of recurrent disease.

Keywords

Radical prostatectomy; Risk assessment; Metastatic progression; Radiation therapy; Hormonal therapy; Prostate cancer[en]specific mortality

1. Introduction

For many years radical prostatectomy (RP) has been considered ill advised for men whose cancer may not be pathologically confined to the prostate (clinical stage T3 or, historically, stage C). These men were presumed to harbor clinically occult metastases at the time of diagnosis and consequently deemed incurable by surgery alone. Subjecting them to the daunting morbidities associated with surgery, namely urinary incontinence and erectile dysfunction, was considered unjustified. This philosophy still relegates patients with large-volume, high-grade tumors to radiation therapy [1] or, if local therapy is considered superfluous, to primary androgen-deprivation therapy [2].

To be clinically useful, criteria defining high-risk prostate cancer should reliably distinguish patients whose cancer is amenable to cure with local therapy alone from those who may require additional systemic therapy. While there is no consensus on what constitutes optimal treatment for the latter, the former can be safely offered surgery with curative intent. However, in light of the diversity of criteria defining high-risk prostate cancer [3], the historical tendency of discouraging these men from having surgical management, and the lack of randomized trials comparing the various local definitive therapies, treatment of men with high-risk prostate cancer is largely driven by physicians' experience and biases.

We previously reported on pathological characteristics and prostate-specific antigen (PSA) outcomes for patients with high-risk prostate cancer treated with RP alone [4]. To identify high-risk cohorts we examined eight different definitions commonly used in the medical literature. Depending on the definition used, clinically high-risk patients had cancers that were organ-confined in 22[en]63% of cases and 5-yr probability of freedom from PSA relapse ranging from 49% to 80%. Moreover, of the high-risk patients who had disease recurrence, 25% (across all definitions) relapsed more than 2 yr after surgery, and in 26[en]39% the PSA doubling time at recurrence was ≥ 10 mo, both considered surrogates for a more protracted clinical course following biochemical recurrence (BCR) [5]. Yet, while a rising PSA level after surgery may herald clinical disease progression, nearly a third of men with BCR never experience further PSA elevations or require additional therapy [6]. Moreover, because of competing mortality risks, the probability of dying from prostate cancer within 15 yr of BCR is similar to the likelihood of dying from other causes [7]. The latter is further accentuated by recent data indicating that long-term androgen-deprivation therapy may predispose patients to metabolic syndrome, myocardial infarction, and sudden cardiac death [8,9]. Thus, in an extension of our previous work, we sought to analyze patterns of secondary cancer therapy and risk of metastatic progression (MP) and cancer-specific mortality in patients with clinically high-risk prostate cancer treated with RP.

2. Methods

After obtaining institutional review board approval, we queried our multidisciplinary prostate cancer registry and identified 6421 patients with clinically localized or locally advanced prostate cancer (cT1[en]T3 N0 M0) treated with RP between 1985 and 2005 at Memorial Sloan-Kettering ($n = 5256$) or Baylor College of Medicine ($n = 1165$). Because our study end points were MP and overall and cancer-specific survival, and evidence from randomized trials showed no difference in PSA outcomes for patients treated with androgen deprivation before RP [10, 11], we included 815 patients (13%) who received a short course (median, 3.1 mo (interquartile range [IQR], 2.1[en]4.2)) of hormonal therapy before surgery. Most of these patients were treated prior to 2002 when the role of neoadjuvant hormonal therapy in patients undergoing radical prostatectomy was under investigation. We excluded 461 patients (7.1%) for whom preoperative data were missing because their preoperative risk stratification was unattainable. Complete information on PSA levels, primary and secondary biopsy Gleason grades, and 1992 TNM clinical stage was available for 5960 patients (Table 1). On the basis of preoperative characteristics, we used eight different definitions proposed to classify patients as high risk (Table 2) [3,12,13]. PSA velocity before surgery was calculated for the 3177 patients (53%) who had sufficient data available by a linear regression using all PSA values within 1 yr before surgery or before initiation of neoadjuvant androgen-deprivation therapy; the median interval between the last of these PSA values and surgery was 1 mo (IQR, 0.4, 2).

2.1. Follow-up

In general, patients were followed for recurrence with rectal examinations and serum PSA determinations every 3 mo for the first 3 yr, semiannually during years 4 and 5, and annually thereafter. Median follow-up from surgery was 5.5 yr (IQR, 2.3, 8). There were 2859 patients (48%) followed more than 5 yr and 914 (15%) more than 10 yr.

Secondary cancer treatment was instituted at the discretion of the treating physician. Postoperative radiation was administered to 410 patients, in 379 cases as salvage therapy and in 31 cases as adjuvant therapy because of adverse pathological features. Androgen-deprivation therapy (surgical or chemical castration with luteinizing hormone-releasing hormone agonists, antiandrogens, or a combination thereof) was given to 587 patients, all treated in a salvage setting following BCR. Metastatic disease (unequivocal bony, nodal, or visceral involvement by imaging or biopsy) was documented in 236 patients, 151 (64%) of whom were treated with hormonal therapy only after the first radiographic evidence of metastatic progression. Patients with a rising PSA who deferred hormonal therapy until MP were generally monitored carefully with diagnostic imaging studies and serial PSA measurements at intervals of 3[en]6 mo. At last follow-up 445 patients had died. Death certificates were used to ascertain or confirm the cause of each death. In 102 cases, death was attributed to widespread progressive castrate metastatic disease and was classified as death from prostate cancer.

2.2. Statistical methods

The Kaplan-Meier method was used to generate estimates of freedom from secondary therapies and freedom from MP for high-risk and non[en]high-risk patients. For these end points, patients were censored if they died of causes other than prostate cancer or were lost to follow-up. The log-rank test was used to compare estimates between high-risk and non[en]high-risk subsets. Univariate Cox proportional hazards regression was used for each of the tested definitions to estimate hazard ratios with 95% confidence intervals for secondary cancer treatment and MP in high-risk versus non[en]high-risk cohorts.

Because of the protracted clinical course of prostate cancer and relatively low number of patients who died from prostate cancer versus other causes, we used competing risk analyses

to generate estimates of the cumulative incidence of death from prostate cancer in high-risk and non[en]high-risk subsets. In this method, death from causes other than prostate cancer is considered a competing risk event and is censored in an informative manner (as opposed to censoring due to short follow-up). The association between each high-risk definition and prostate cancer[en]specific death was evaluated with the use of a proportional hazards regression model with adjustment for competing risk [14]. All statistical analyses were two-sided and performed with Stata, version 8.2 (Stata Corp, College Station, TX, USA) and R (R Foundation for Statistical Computing, www.r-project.org) with the *cmprsk* package, with $p < 0.05$ considered significant.

3. Results

Depending on the definition used, high-risk cohorts comprised 4[en]40% of the entire study population (Table 2). The 10-yr probability of postoperative radiation therapy in high-risk patients ranged from 14% (preoperative PSA velocity > 2 ng/ml/yr) to 26% (Gleason score ≥ 8) (Fig. 1 A). Similarly, the probability of receiving androgen-deprivation therapy within 10 yr after surgery ranged from 18% (preoperative PSA velocity > 2 ng/ml/yr) to 59% (cT3) (Fig. 1 B). Combined estimates of secondary cancer therapy (radiation, hormones, or both, whichever occurred first) are listed in Table 3. Compared with the non[en]high-risk patients, those at high-risk had a 1.3-fold (95%CI, 1.1, 1.5) to 5.2-fold (95%CI, 4.5, 6.0) increased hazard of being treated with secondary therapy. However, 35% (95%CI, 27, 44) to 76% (95%CI, 71, 80) of the high-risk patients were free from any type of secondary cancer treatment 10 yr after surgery.

Estimates of MP 5 and 10 yr after surgery are shown in Table 4. As indicated in the table, each of the studied high-risk criteria was associated with significantly higher rates of MP after surgery (hazard ratios ranging from 2.1 [95%CI, 1.3, 5.1] to 6.9 [4.7, 10.2], $p < 0.05$). Because the various high-risk subsets in our study are not mutually exclusive (ie, they contain, at least in part, some of the same patients), estimates of MP could not be compared between cohorts in a statistically valid manner. In general, however, definitions in which PSA level above 15 or 20 ng/ml was a sufficient criterion for a high-risk classification (definitions 2, 4, 6, and 7) were associated with lower rates of MP compared with those based solely on biopsy Gleason score 8[en]10 (definition 1) or clinical stage T3 (definition 3). It should also be noted that use of hormonal therapy for BCR before the first radiographic evidence of metastatic disease (in 47% of the patients with documented BCR in this series) may have skewed our estimates by virtue of delaying the progression to event.

Competing risk analyses were performed to assess whether each of the high-risk definitions was associated with increased likelihood of death from prostate cancer (Table 5, Fig. 2). Depending on the definition used, the 10-year cumulative incidence of prostate cancer[en]specific mortality in high-risk patients ranged from 3% (PSA velocity > 2 ng/ml/yr; 95%CI, 2, 6) to 11% (cT3; 95%CI, 7, 19). While estimates of dying from other causes did not differ significantly between high-risk and non[en]high-risk subsets (data not shown), those classified as high risk by seven of the eight definitions had a significantly increased risk of dying from prostate cancer (adjusted hazard ratios ranging from 3.2 [95%CI, 2.1, 4.8] to 10.5 [95%CI, 4.8, 22.9], $p < 0.05$). Noteworthy is that even among the high-risk patients the likelihood of dying from other causes was generally 2- to 3-fold higher than the likelihood of dying from prostate cancer (Fig. 2).

4. Discussion

Criteria that define high-risk prostate cancer are typically based on an increased likelihood of BCR following local definitive therapy [15]. BCR after RP, a cause of angst in both patient

and physician, often prompts the initiation of secondary therapies [16]. However, BCR can have a highly variable clinical course that does not inexorably culminate in MP and death from prostate cancer [6]. With the ultimate goal of identifying those who can be cured with surgery alone from those in whom monotherapy is likely to fail, it is imperative that clinical trials enrolling high-risk patients enable assessment of treatment efficacy using clinically meaningful end points. Further, given the range of toxicities associated with neoadjuvant therapies [3] and the substantial morbidity of long-term androgen deprivation [8,9], patients considering enrollment onto these trials must be provided with realistic expectations regarding the success of surgery monotherapy. With this in mind we endeavored to analyze risk of secondary cancer treatment, MP, and death from prostate cancer after RP among patients considered high risk by various definitions.

The current study demonstrates that commonly used definitions of high-risk prostate cancer are associated not only with an increased likelihood of PSA relapse[4] but also with significantly higher rates of secondary cancer therapy, MP, and death from prostate cancer. These results confirm the observations of others indicating that PSA > 20 at diagnosis and biopsy Gleason score 8[en]10 are pretreatment predictors of ultimately receiving additional cancer treatment after RP [17] and dying from prostate cancer [18]. Compared with non[en] high-risk patients, those at high-risk had a 1.3- to 5.2-fold increased hazard of being treated with secondary cancer therapy, a 2.1- to 6.9-fold higher probability of MP, and a 3.2- to 10.4-fold higher risk of dying from their cancer. However, equally important is the fact that 35[en] 76% of the high-risk patients were alive and free of additional cancer therapy 10 yr after surgery, highlighting the ability of surgery alone to control the disease in many of these men. Thus, while the currently available risk stratification systems are generally sensitive in determining patients at high risk for secondary cancer therapies, MP, and cancerspecific mortality, their lack of specificity leads to inclusion of many men whose disease is, in fact, amenable to cure with local therapy alone.

These findings can help guide clinical decision making. If, for example, a neoadjuvant trial is planned in which the drug has fairly minimal toxicity, it might be acceptable to use a definition of high-risk disease that is highly sensitive (ie, would encompass most patients in whom local therapy is likely to fail) at the expense of reduced specificity (ie, would also include a number of patients who could otherwise be cured by surgery alone). Definition 7 in our study (PSA \geq 15 or 1992 TNM \geq cT2B or biopsy Gleason score 8[en]10) might be applicable in this case. Conversely, in a trial in which the neoadjuvant drug has substantial expected toxicity, more stringent criteria to define high-risk candidates should be employed. One approach to risk assessment, as recently advocated by D'Amico et al [19], is to count the number of equally weighted categorical high-risk features, up to four, and relegate the patient to one of four risk groups (including 1, 2, 3, or all features). Another utilizes nomograms, which incorporate data from all relevant risk factors, both continuous and categorical, and proportionately weigh their relative contribution to the overall probability of treatment failure to allot a risk score. The latter approach is not only more accurate but also more appropriate for assigning risk to an individual patient [20]. While most current models are limited to predicting BCR following local therapy, enhanced nomograms developed on more mature cohorts will allow prediction of more meaningful clinical end points such as MP [21] and cancer-specific mortality. The addition of detailed biopsy data, magnetic resonance imaging findings, and, possibly, emerging molecular markers to the current risk-stratification tools might provide more precise information to guide clinical decision making and enable researchers to better target populations suitable for particular clinical trials. As currently classified, patients with "high-risk" prostate cancer by currently available definitions should not be categorically disqualified from having surgical therapy with curative intent despite their increased risk of treatment failure.

Regardless of definition, the optimal therapy for high-risk prostate cancer remains elusive. No study has provided persuasive evidence favoring one treatment modality over another. Radiation therapy has the advantage of avoiding the immediate morbidity of surgery, particularly since surgery for locally advanced cancers may be associated with a slightly higher complication rate than that for organ-confined cancers [22]. RP, compared with radiation therapy, may minimize late sequelae of local disease progression, although data supporting this conjecture are currently unavailable [23]. In an era of novel drug and multimodal strategies, surgery yields a tissue specimen for histological and molecular analyses. In fact, our observed 3[en]12% cumulative incidence of cancer-specific death at 10 yr after RP, depending on the definition used, is comparable or even superior to published estimates of cancer-specific mortality in high-risk patients treated by radiation with or without use of adjuvant hormonal therapy [24,25]. One may argue that our high-risk subsets represent a selected population of patients treated surgically. However, the proportion of high-risk patients in our study (23% by definition 4, the D'Amico criteria, and 16% by definition 6, the National Comprehensive Cancer Network guidelines) is comparable to contemporary radiation therapy series. Morgan and colleagues [26] classified 390 of their 1833 radiation-treated patients (21%) as high risk on the basis of a PSA \geq 20 ng/ml, clinical stage T3, or biopsy Gleason score \geq 8 (definition 6 in our study). Similar criteria were applied by Zelefsky et al [27] who identified 103 of their 561 contemporary patients treated with intensity-modulated radiation therapy (18%) as being high risk. Acknowledging the bias inherent in comparing treatment results across selected retrospective cohorts and understanding that optimal local control for high-risk cancers can only be determined in a well-designed clinical trial, our study clearly supports the notion that surgery is an option for high-risk patients.

Several limitations of our study are worth noting. First, while MP represents a clinically meaningful end point, lack of consistency in timing of androgen-deprivation therapy for PSA relapse may have rendered our estimates of metastasis-free survival somewhat inaccurate. The true risk of metastatic disease following RP failure can be assessed only by clinical trials in which use of secondary cancer therapies has been dictated by a predefined protocol. However, in the absence of uniform guidelines and standardized practice with respect to timing of radiation therapy or hormonal therapy for RP failures, our estimates of secondary therapy and metastatic progression reflect, in fact, a "real-world" practice. Second, given improvements in surgical technique and changes in grading of tumors overtime [28] as well as the lead time bias associated with widespread PSA screening [29], our findings may not be perfectly applicable to a contemporary era, and the actual risk of MP and cancer-specific mortality for high-risk patients treated with RP may be even lower than reported herein. Third, we included patients who received androgen-deprivation therapy prior to RP on the basis of evidence from randomized trials showing that a short course of hormonal therapy before surgery did not impact PSA outcomes [10,11]. However, it has also been suggested that a short course of hormonal therapy early in the course of disease may attenuate the response to salvage androgen-deprivation therapy administered after disease progression [30]. Thus, the true impact of neoadjuvant hormonal therapy prior to RP on the risk of prostate cancer[en]specific mortality requires further investigation. Lastly, because most prostate cancer deaths occur more than 10 yr after initial treatment, further follow-up is required to provide more robust estimates of prostate cancer[en]specific mortality and to confirm the long-term efficacy of surgery for disease control in clinically high-risk patients.

5. Conclusions

Patients classified with high-risk prostate cancer by currently available definitions do not have a uniformly poor prognosis after RP. While high-risk criteria for PSA relapse are also associated with increased risk of secondary cancer therapy, metastatic progression, and death from prostate cancer, most of these men are alive and many remain free of additional therapy

or metastatic disease 10 yr after surgery. The risk of prostate cancer[en]specific mortality within 10 yr of treatment is remarkably low, even for patients at the highest risk of recurrent disease on the basis of PSA, clinical stage, and tumor grade.

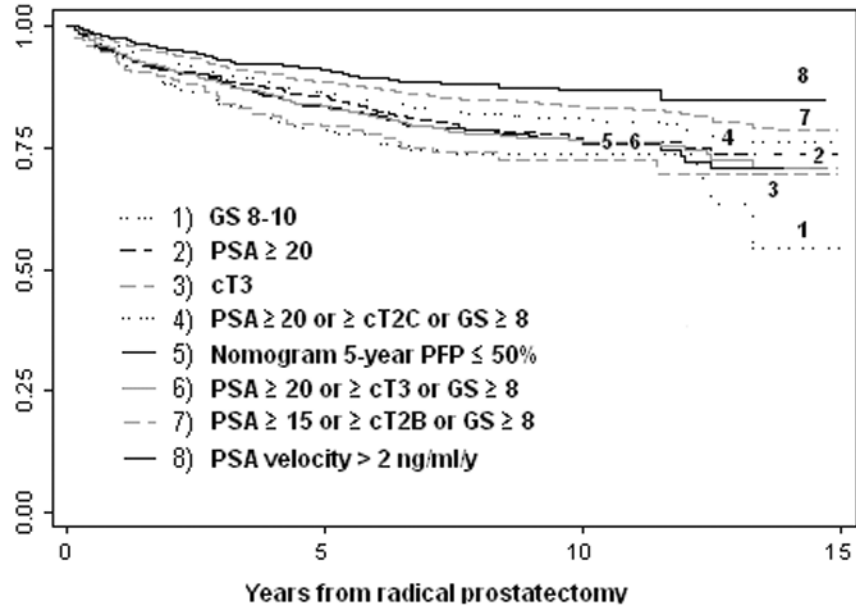
Acknowledgement

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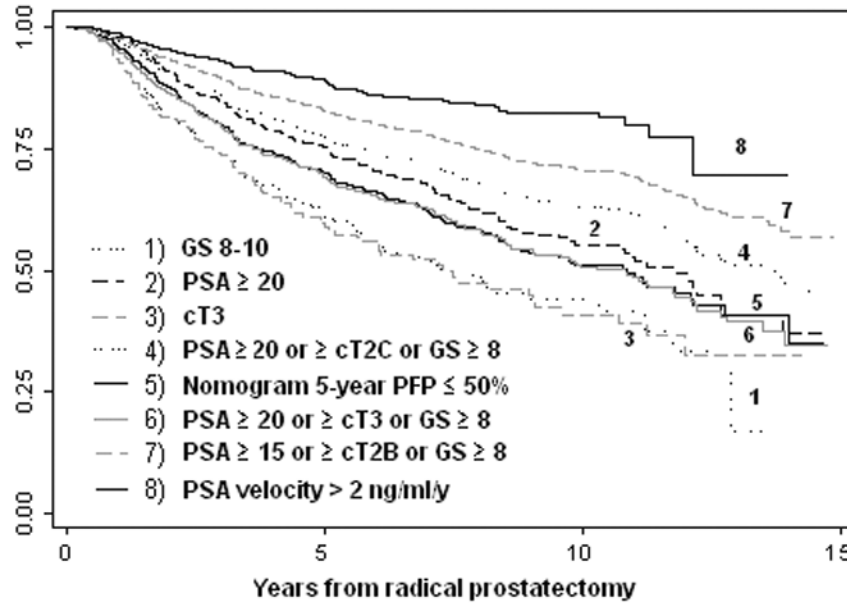
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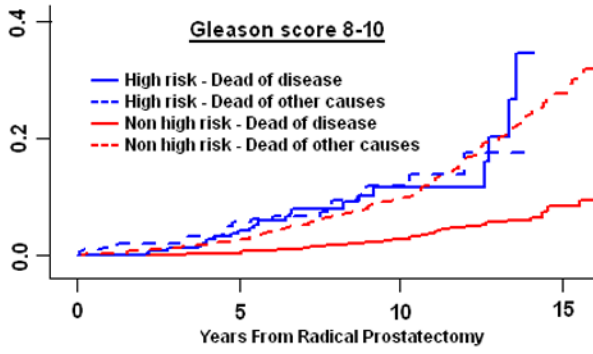
Number at risk :

	0	5	10	15
1) 401	244	141	83	35
2) 441	341	271	178	111
3) 243	169	109	61	43
4) 1359	1000	716	462	268
5) 606	441	316	207	122
6) 938	660	469	293	182
7) 2384	1792	1296	849	504
8) 1029	662	406	222	114



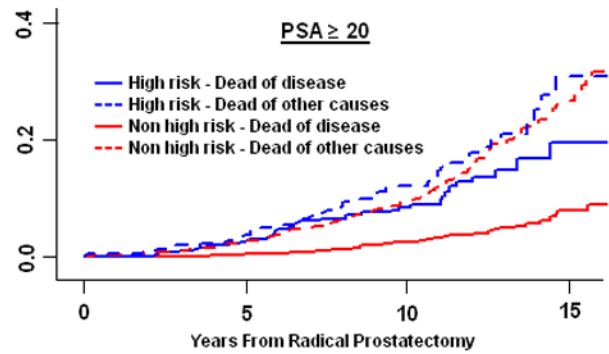
Number at risk:							
	0	5	10	15	20	25	30
1)	401	206	105	55	21	5	1
2)	441	317	242	152	80	28	5
3)	243	147	84	43	27	8	2
4)	1359	922	641	385	205	64	14
5)	606	403	279	171	86	31	4
6)	938	593	389	232	122	39	7
7)	2384	1688	1189	744	412	132	27
8)	1029	596	352	197	99	17	1

Fig. 1. (A) Radiation therapy-free survival in high-risk prostate cancer patients treated with radical prostatectomy. (B) Hormonal therapy-free survival in high-risk prostate cancer patients treated with radical prostatectomy.



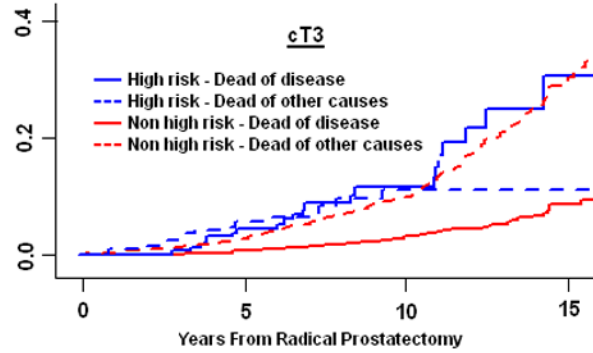
Numbers at risk :

High risk - Dead of disease	401	283	170	103	43	17	0
High risk - Dead of other causes	5559	4028	2689	1556	871	336	92



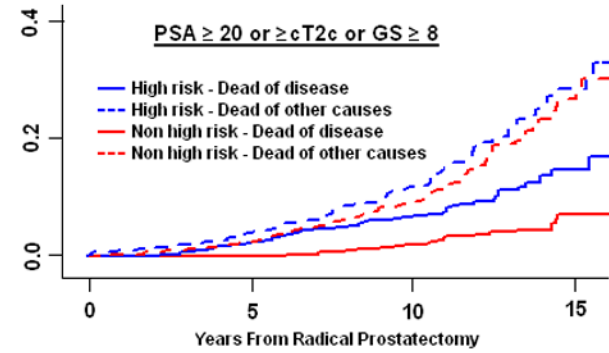
Numbers at risk :

High risk - Dead of disease	441	376	312	215	140	61	10
High risk - Dead of other causes	5519	3935	2547	1444	774	292	82



Numbers at risk :

High risk - Dead of disease	243	191	128	73	51	23	8
High risk - Dead of other causes	5717	4120	2731	1586	863	330	84



Numbers at risk :

High risk - Dead of disease	1359	1094	815	542	318	130	33
High risk - Dead of other causes	4601	3217	2044	1117	596	223	59

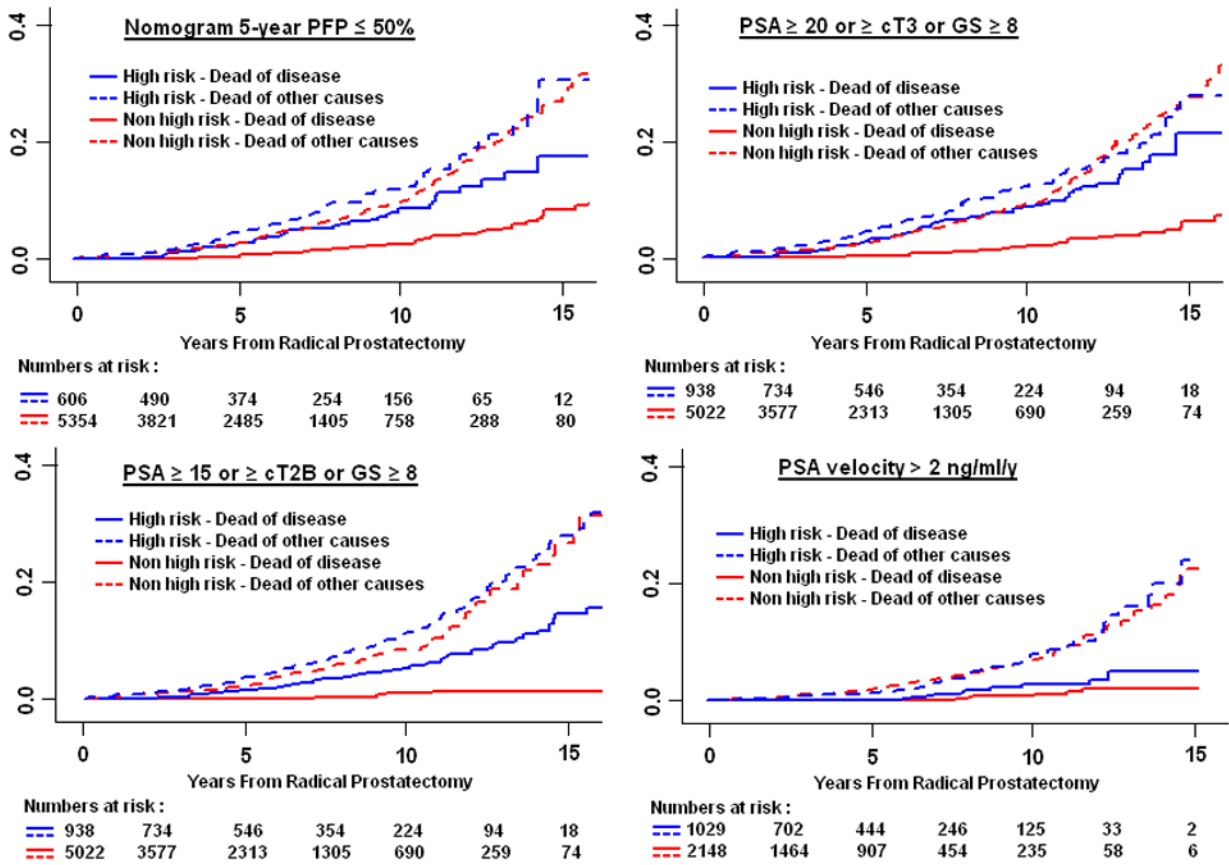


Fig. 2. (A) Prostate cancer-specific mortality in high-risk and non-high-risk patients treated with radical prostatectomy.

Table 1

[en] Preoperative and pathological characteristics of 5960 patients treated with radical prostatectomy for clinically localized prostate cancer

Characteristic	No. of patients (%)
Median age at surgery, yr (IQR)	61 (56, 66)
Median preoperative PSA, ng/ml (IQR)	6.34 (4.47, 9.60)
Median preoperative PSA velocity, ng/ml/yr (IQR) *	1.10 ([en]1.19, 3.83)
Biopsy Gleason sum	
2[en]6	3917 (66)
7 (3+4)	1175 (20)
7 (4+3)	467 (8)
8[en]10	401 (6)
1992 TNM clinical stage	
T1AB	122 (2)
T1C	2678 (45)
T2A	1260 (21)
T2B	1094 (18)
T2C	563 (10)
T3	243 (4)
Prostatectomy Gleason sum	
2[en]6	2125 (36)
7 (3+4)	1835 (31)
7 (4+3)	575 (9)
8[en]10	650 (11)
Not available **	775 (13)
Organ confined	3280 (70)
Extracapsular extension	1688 (27)
Positive surgical margins	1193 (20)
Seminal vesicle invasion	526 (9)
Lymph node involvement	254 (4)

IQR, interquartile range; PSA, prostate-specific antigen.

* Available for 3177 patients.

** Hormonal treatment effect.

Table 2 [en] Description of the eight high-risk prostate cancer definitions based on preoperative variables.

	High-risk definition	Description and references	No. (% of cohort)
1	bGS 8[en]10	Poorly differentiated cancer [3]	401 (6.7)
2	Preoperative PSA \geq 20 ng/ml	[3]	441 (7.4)
3	1992 TNM cT3	Locally advanced cancer [3]	243 (4.0)
4	PSA \geq 20 or 1992 TNM \geq cT2C or bGS 8[en]10	D'Amico's high-risk criteria [15]	1359 (22.8)
5	Nomogram 5-yr PFP \leq 50%	Preoperative nomogram [20]; a \leq 60% PFP is an entry criterion for CALGB Trial 90203	606 (10.2)
6	PSA \geq 20 or 1992 \geq TNM cT3 or bGS 8[en]10	NCCN guidelines for treatment and classification of clinically localized high-risk cancer [13]	938 (15.7)
7	PSA \geq 15 or 1992 TNM \geq cT2B or bGS 8[en]10	Entry criteria into neoadjuvant chemotherapy trials for high-risk patients [3]	2384 (40.0)
8	Preoperative PSA velocity $>$ 2 ng/ml/yr	Increased risk of prostate cancer[en]specific mortality after RP or radiotherapy [12]	1209 (32.4)*

bGS, biopsy Gleason score; PSA, prostate-specific antigen; PFP, progression-free probability; CALGB, Cancer and Leukemia Group B; NCCN, National Comprehensive Cancer Network; RP, radical prostatectomy.

* Percentage of the 3177 patients with calculable preoperative PSA velocity

[en] Estimates of freedom from secondary cancer therapy and hazard ratios in high-risk versus non[en]high-risk patients treated with RP

Table 3

Patient	High-risk definition	Freedom from 2nd cancer therapy (95%CI)			HR (95%CI)
		5-year	10-year		
1	Biopsy Gleason score 8[en]10				
	Yes	53 (47, 59)	40 (33, 47)	4.9 (4.1, 5.8)	
2	No	88 (87, 89)	78 (76, 80)		
	Preoperative PSA ≥ 20				
3	Yes	67 (62, 72)	47 (41, 53)	3.2 (2.7, 3.8)	
	No	87 (86, 88)	80 (78, 81)		
4	1992 TNM cT3				
	Yes	50 (43, 57)	35 (27, 44)	4.6 (3.8, 5.6)	
5	No	87 (86, 88)	78 (76, 80)		
	PSA ≥ 20 or 1992 TNM \geq cT2C or bGS 8[en]10				
6	Yes	70 (67, 72)	56 (53, 60)	3.7 (3.2, 4.3)	
	No	91 (90, 92)	84 (81, 86)		
7	Nomogram 5-yr PFP $\leq 50\%$				
	Yes	61 (57, 65)	43 (38, 48)	4.1 (3.6, 4.8)	
8	No	89 (88, 90)	81 (79, 83)		
	PSA ≥ 20 or 1992 TNM \geq cT3 or bGS 8[en]10				
9	Yes	61 (57, 64)	43 (39, 48)	5.2 (4.5, 6.0)	
	No	91 (90, 92)	84 (83, 86)		
10	PSA ≥ 15 or 1992 TNM \geq cT2B or bGS 8[en]10				
	Yes	76 (74, 77)	63 (61, 66)	4.5 (3.8, 5.4)	
11	No	94 (93, 95)	89 (86, 91)		
	Preoperative PSA velocity > 2 ng/ml/yr				
12	Yes	82 (79, 85)	76 (71, 80)	1.3 (1.1, 1.5)	
	No	86 (85, 87)	76 (74, 78)		

RP, radical prostatectomy; CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen; bGS, biopsy Gleason score; PFP, progression free probability.

High risk patients were significantly more likely to receive secondary therapy, irrespective of definition.

[en] Metastasis-free survival and hazard ratios for metastatic progression in high-risk versus non[en]high-risk patients treated with RP

Table 4

	High-risk definition	No. of events/no. of pts	Metastasis-free survival (95%CI)		HR (95%CI)
			5-year	10-year	
1	Biopsy Gleason score 8[en]10 Yes No	62/401 174/5559	85 (80, 89) 98 (97, 98)	76 (69, 82) 94 (93, 95)	6.1 (4.6, 8.2)
2	Preoperative PSA \geq 20 Yes No	65/441 171/5519	89 (86, 92) 97 (97, 98)	82 (77, 86) 94 (93, 95)	3.2 (2.4, 4.3)
3	1992 TNM cT3 Yes No	47/243 189/5717	85 (79, 89) 97 (97, 98)	72 (63, 79) 94 (93, 95)	5.4 (3.9, 7.4)
4	PSA \geq 20 or 1992 TNM \geq cT2c or bGS 8[en]10 Yes No	146/1359 90/4601	92 (90, 93) 99 (98, 99)	85 (83, 88) 95 (94, 96)	4.2 (3.2, 5.4)
5	Nomogram 5-yr PFP \leq 50% Yes No	78/606 158/5354	89 (86, 92) 98 (97, 98)	82 (78, 86) 94 (93, 95)	3.4 (2.6, 4.5)
6	PSA \geq 20 or 1992 TNM \geq cT3 or bGS 8[en]10 Yes No	140/938 96/5022	88 (85, 90) 99 (98, 99)	78 (75, 82) 96 (95, 97)	6.5 (5.0, 8.5)
7	PSA \geq 15 or 1992 TNM \geq cT2b or bGS 8[en]10 Yes No	206/2178 30/3546	94 (93, 95) 99 (98, 100)	88 (86, 90) 98 (97, 99)	6.9 (4.7, 10.2)
8	Preoperative PSA velocity $>$ 2 ng/ml/yr Yes No	32 / 1029 45 / 2148	98 (97, 99) 97 (95, 98)	91 (87, 93) 94 (91, 96)	2.1 (1.3, 5.1)

RP, radical prostatectomy; pts, patients; CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen; bGS, biopsy Gleason score; PFP, progression free probability.

High risk patients were significantly more likely to experience metastatic progression, irrespective of definition.

Table 5 Cumulative incidence estimates of prostate cancer-specific mortality and hazards ratios in high-risk versus non-high-risk patients treated with RP

	High-risk definition	No. dead of disease /pts	No. dead of other cause/pts	Estimated prostate cancer-specific mortality		
				5-year (95%CI)	10-year (95%CI)	HR (95%CI)
1	Biopsy Gleason score ≥ 8					
	Yes	23/401	47/401	4.2 (2.3, 7.8)	12 (7, 19)	5.1
	No	79/5559	398/5559	0.4 (0.3, 0.7)	3 (2, 4)	(3.2, 8.1)
2	Preoperative PSA ≥ 20					
	Yes	35/441	89/441	2.7 (1.5, 5.1)	9 (6, 13)	3.5
	No	67/5519	356/5519	0.5 (0.3, 0.8)	3 (2, 4)	(2.3, 5.4)
3	1992 TNM cT3					
	Yes	20/243	36/243	4.3 (2.1, 9)	11 (7, 19)	4.6
	No	82/5717	409/5717	0.5 (0.3, 0.8)	3 (2, 4)	(2.8, 7.5)
4	PSA ≥ 20 or ≥ 1992 TNM cT2C or bGS 8					
	Yes	36/1359	195/1359	2.3 (1.5, 3.4)	7 (5, 9)	3.9
	No	66/4601	250/4601	0.1 (0.0, 0.3)	2 (1, 3)	(2.6, 6.0)
5	Nomogram 5-yr PFP $\leq 50\%$					
	Yes	37/606	98/606	2.4 (1.3, 4.3)	8 (6, 12)	3.2
	No	65/5354	347/5354	0.4 (0.3, 0.7)	2 (2, 3)	(2, 1, 4.8)
6	PSA ≥ 20 or ≥ 1992 TNM cT3 or bGS 8					
	Yes	59/938	145/938	2.8 (1.8, 4.4)	8 (6, 11)	5.0
	No	43/5022	300/5022	0.2 (0.1, 0.4)	2 (1, 3)	(3.4, 7.5)
7	PSA ≥ 15 or ≥ 1992 TNM cT2B or bGS 8					
	Yes	95/2384	137/2384	1.4 (1, 2.1)	5 (4, 7)	10.4
	No	7/3576	308/3576	0	1 (0, 2)	(4.8, 22.7)
8	Preoperative PSA velocity > 2 ng/ml/yr					
	Yes	13/1029	56/1029	0.1 (0.0, 0.7)	3 (2, 6)	2.5
	No	10/2148	96/2148	0.2 (0.0, 0.9)	1 (1, 3)	(1.0, 5.7)

Pts, patients; CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen; bGS, biopsy Gleason score; PFP, progression free probability; RP, radical prostatectomy.

All hazard ratios (except for definition 8) were significant at the 0.0005 level.