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ORIGINAL ARTICLE

Improved decision making in intermediate-risk prostate cancer: a multicenter study on pathologic and oncologic outcomes after radical prostatectomy

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Abstract
Background Prognoses for intermediate-risk prostate cancer (PCa) remain heterogeneous. Improved substratification could optimize treatment and monitoring strategies. The objective was to validate this subclassification in a radical prostatectomy (RP) series.
Methods Between 2000 and 2011, 4038 patients who underwent RP for intermediate-risk PCa in seven French academic centers were included. Unfavorable intermediate-risk (UIR) PCa was defined as having a primary Gleason score of 4, ≥50% positive biopsy cores (PPBC), or more than one D'Amico intermediate-risk factor (i.e., cT2b, PSA 10–20, or Gleason score 7). Remaining PCa cases were classified as favorable. Main endpoints were pathologic results (pT stage, final Gleason score, surgical margin status), and oncologic outcomes were assessed according to PSA recurrence-free survival (PSA-RFS). Univariate and multivariate analyses were performed using the log-rank test and the Cox proportional hazards model.
Results Median follow-up was 48 months (95% CI = [45–49]). Patients with UIR had worse PSA-RFS (68.17 vs. 81.98% at 4 years, HR = 1.97, 95% CI = [1.71; 2.27], $p < 0.0001$) compared to those with a favorable disease. The need for adjuvant therapy was significantly greater for UIR patients (43.5 vs. 29.2%, $p < 0.0001$). In multivariate analysis, primary Gleason score of 4 (HR = 1.81, 95% CI = [1.55; 2.12], $p < 0.0001$) and PPBC ≥ 50% (HR = 1.26, 95% CI = [1.02; 1.56], $p = 0.0286$) were significant preoperative predictors for worse PSA-RFS.
Conclusions This study highlights the heterogeneity of NCCN intermediate-risk patients and validates (in a large RP cohort) the previously proposed subclassification for this group. This classification can significantly predict both pathologic and oncologic outcomes. This easy-to-use stratification could help physicians' decision making. Prospective study and new tools as genomic tests and novel molecular-based approaches can improve this stratification in the future for patient counseling.

Keywords Prostate cancer · Intermediate risk · Radical prostatectomy · Biochemical recurrence-free survival · Risk factors · Stratification

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Introduction

In Europe, prostate cancer (PCa) is the most common solid malignancy with an incidence rate of 214 cases per 1000 men, and the second cause of death attributable to cancer [1, 2]. In France, in 2011, the incidence rate was 53,913 men and specific mortality was 8893 [3]. Currently, most patients with clinically localized PCa treated with radical prostatectomy (RP) are affected by intermediate-risk PCa according to the D'Amico's classification (defined as a prostate-specific antigen [PSA] level of between 10 and 20 ng/mL at diagnosis, clinical stage cT2b, and/or a biopsy Gleason score of 7) [4, 5].

In these cases of intermediate-risk localized PCa, the optimal treatment algorithm remains a real challenge [6, 7]. Therefore, the need for a new subclassification system to enable effective treatment decisions is clinically relevant. Despite contemporary studies that report excellent long-term oncologic outcomes for patients with PCa, those with intermediate-risk PCa represent an extremely heterogeneous category [8]. Indeed, while some patients harbor aggressive characteristics at final pathology including extraprostatic disease, seminal vesicle invasion, and high-grade tumor, leading to an increased risk of early recurrence after surgery [9], others are affected by indolent PCa despite their initial risk assessment [10, 11]. Thus, more accurate stratification is needed to improve treatment management.

The primary Gleason score, percentage of positive biopsy cores (PPBCs), and the number of intermediate-risk factors (IRFs) have been shown to be independent predictors of outcomes for localized PCa, but are not included in the current classification systems [12–14]. Recently, Zumsteg et al. [15] have suggested stratifying intermediate-risk PCa into favorable and unfavorable categories based on these criteria to improve treatment recommendations. Unfortunately, although this subclassification has been predictive for oncologic outcomes during the follow-up periods, no final pathologic prognosis can be provided.

The objective of the present multicenter retrospective study was to validate this easy-to-use subclassification based on pathologic and oncologic outcomes in a large cohort that underwent RP.

Materials and methods

Selection of patients

Between 2000 and 2011, 4038 patients with intermediate-risk prostate cancer were treated by RP in seven tertiary referral institutions after our approval from our Institutional Review Board. Intermediate risk was defined according to NCCN criteria as a patient with clinical stage T2b, a Gleason score of 7, or a prostate-specific antigen (PSA) level of 10–20 ng/mL but without high-risk features (i.e., clinical stage T3a or higher Gleason score 8–10, or a PSA level >20 ng/mL) [12–14]. Overall, 617 patients were excluded because of incomplete follow-ups. In total, 3421 patients were analyzed.

We defined favorable intermediate-risk (FIR) PCa, according to Zumsteg et al.'s classification, as a patient with NCCN intermediate-risk disease and all of the following criteria: a single IRF, a Gleason score of $3 + 4 = 7$ (grade group 3) [15], and <50% of biopsy cores containing cancer. Remaining cases were classified as having an unfavorable intermediate risk (UIR).

Treatment

All patients were treated with RP associated or not with extended pelvic lymph node dissection.

Endpoint

All complete clinical and pathologic data were recorded, including age, year of surgery, preoperative PSA, clinical stage, biopsy Gleason score, number of biopsy cores, number of positive cores, percentage of positive biopsy cores, pathologic stage, pathologic Gleason score, seminal vesicle invasion, surgical margin status, and lymph node invasion. TNM stage was applied according to the 2002 American Joint Committee on Cancer staging system. PSA recurrence was defined as a patient having two consecutive PSA values of > 0.2 ng/mL after surgery.

Statistical analyses

Baseline and pathological characteristics were summarized using descriptive statistics. Categorical variables were presented as contingency tables, i.e., number and percentage for each category of variable, and number of missing data. Continuous variables were presented as median, range, and number of missing data. Comparisons between groups were performed using the Chi-squared or Fisher's exact test for categorical variables and the Mann–Whitney test for continuous variables.

PSA recurrence-free survival (PSA-RFS) was defined as the time between the date of the RP and the date of PSA recurrence. Patients without PSA recurrence at the last follow-up news were censored at this date. Survival data were summarized by the Kaplan–Meier method with 95% confidence intervals. Comparisons between groups were performed using the log-rank test for univariate analyses. A Cox proportional hazards model was used to generate

Table 1 Baseline clinical charateristics

	Favorable	Unfavorable	Total	*p* value
No. of patients	2005 (58.6%)	1416 (41.4%)	3421	–
Age (year)				
Median (range)	68 (44–92)	68 (46–92)	68 (44–92)	0.0281
<70 year	1254 (63.8%)	815 (60.0%)	2069 (62.3%)	0.0262
>70year	711 (36.2%)	543 (40.0%)	1254 (37.7%)	
Missing	40	58	98	
Clinical T stage				
T1b–c	1404 (70.7%)	729 (51.8%)	2133 (62.9%)	
T2a	501 (25.2%)	445 (31.7%)	946 (27.9%)	
T2b	82 (4.1%)	232 (16.5%)	314 (9.3%)	<0.0001
Missing	18	10	28	
Biopsy Gleason score				<0.0001
≤6	891 (44.4%)	88 (6.2%)	979 (28.6%)	
3 + 4	1114 (55.6%)	607 (42.9%)	1721 (50.3%)	
4 + 3	0 (0%)	721 (50.9%)	721 (21.1%)	
PSA (ng/ml)				
Median (range)	8.5 (0.1–20)	9.8 (0–20)	9 (0–20)	
≤10	1196 (59.7%)	736 (52.0%)	1932 (56.5%)	<0.0001
>10	809 (40.3%)	680 (48.0%)	1489 (43.5%)	<0.0001
PPBC				
Median (range)	14 (0–49)	27 (0–100)	17.5 (0–100)	
<50%	2005 (100%)	1065 (75.2%)	3070 (89.7%)	<0.0001
≥50%	0 (0%)	351 (24.8%)	351 (10.3%)	<0.0001
Number of RF				<0.0001
<1	2005 (100%)	646 (45.6%)	2651 (77.5%)	
>1	0 (0%)	770 (54.4%)	770 (22.5%)	

PSA prostatic-specific antigen, *PPBC* percentage of positive biopsy cores

hazard ratios (HR) and 95% confidence intervals (95% CI) for both univariate and multivariate analyses.

All reported *p* values are two-sided. For all statistical tests, differences were considered significant at the 5% level. Statistical analysis was performed using STATA version 13 software (Stata Corporation, College Station, TX, USA).

Results

The median follow-up was 48 months (95% CI = [45; 49] Mo).

Table 1 shows the cohort's characteristics at baseline (3421 patients). The distributions for FUR and UIR were 58.6% and 41.4%, respectively. The number of cores taken has no impact on this distribution. Median serum PSA levels were 8.5 and 9.8 ng/mL for patients with FIR and UIR, respectively ($p < 0.0001$). Most patients in the UIR group had more than one RF. Patients with FIR PCa were more likely to have a lower clinical stage and a Gleason score <7 (44.4 vs. 6.2%, $p < 0.0001$) than those with a UIR.

Table 2 shows the final pathologic characteristics of the RP specimens. All pathologic parameters showed more aggressive disease in the UIR group compared to the FIR group. Positive surgical margin, seminal vesicle invasion and extraprostatic disease were reported in 29.8 versus 21.8% ($p < 0.0001$), 15.4 versus. 5.9% ($p < 0.0001$), and 50.0 versus 28.4% ($p < 0.0001$) of the UIR and FIR groups, respectively. Lymph node involvement was noted in 5.6% and 1.0% ($p < 0.0001$) of the UIR and FIR groups, respectively. A Gleason score ≥7 was reported in 94.9% of UIR cases compared to 76.8% of the FIR group ($p < 0.0001$). Overall, the upgrade rate for the Gleason score was 24.2%. The need for adjuvant therapy was significantly higher in the UIR group (43.5 vs. 29.2%, $p < 0.0001$).

In the overall population, 794 patients presented a biochemical recurrence (23.2%). The 1-, 2-, 4-, 5-, and 7-year PSA-RFS rates were 91.04% (95% CI = [89.99; 91.99]), 85.11% (95% CI = [83.87; 86.35]), 76.30% (95% CI = [74.56; 77.94]), 72.58% (95% CI = [70.66; 74.39]), and 66.66% (95% CI = [64.43; 68.79]), respectively.

Table 2 Pathological characteristics in two groups (favorable and unfavorable) after radical prostatectomy

	Favorable	Unfavorable	Total	*p* value
No. of patients	2005 (58.6%)	1416 (41.4%)	3421	–
Type of RP				0.0014
Open	196 (9.8%)	178 (12.6%)	374 (10.9%)	
Laparoscopic	1060 (52.9%)	771 (54.5%)	1831 (53.6%)	
Robot assisted	735 (36.7%)	463 (32.7%)	1198 (35.0%)	
Perineal	14 (0.7%)	2 (0.1%)	16 (0.5%)	
Missing	0	2	2	
Pathological stage				<0.0001
pT2	1429 (71.6%)	706 (50.0%)	2135 (62.6%)	
pT3-4	568 (28.4%)	707 (50.0%)	1275 (37.4%)	
Missing	8	3	11	
VSI				<0.0001
No	1879 (94.1%)	1196 (84.6%)	3075 (90.2%)	
Yes	118 (5.9%)	217 (15.4%)	335 (9.8%)	
Missing	8	3	11	
Pathological GS				<0.0001
<7	456 (23.2%)	70 (5.1%)	526 (15.8%)	
≥7	1508 (76.8%)	1301 (94.9%)	2809 (84.2%)	
Missing	41	45	86	
Surgical margin status				<0.0001
Negative SM	1568 (78.2%)	994 (70.2%)	2562 (74.9%)	
Positive SM	436 (21.8%)	422 (29.8%)	858 (25.1%)	
Missing	1	0	1	
PLND				<0.0001
No	1192 (61.5%)	590 (42.8%)	1782 (53.7%)	
Yes	745 (38.5%)	789 (57.2%)	1534 (46.3%)	
Missing	68	37	105	
LNI				<0.0001
No	1011 (99.0%)	835 (94.4%)	1846 (96.9%)	
Yes	10 (1.0%)	50 (5.6%)	60 (3.1%)	
PNx	984	531	1515	
Salvage treatment				<0.0001
No	704 (70.8%)	468 (56.5%)	1172 (64.3%)	
Yes	291 (29.2%)	360 (43.5%)	651 (35.7%)	
Salvage RT	128	138	266	
Salvage ADT	29	61	90	
Salvage RT + ADT	46	86	132	
Other	88	75	163	
Missing	1010	588	1598	

RP radical prostatectomy, *GS* Gleason score, *SVI* seminal vesicle invasion, *SM* surgical margin, *PLND* pelvic lymph node dissection, *LNI* lymph node involvement, *RT* radiotherapy, *ADT* androgen deprivation therapy

Figures 1 and 2 show Kaplan–Meier curves of PSA-RFS according to the FIR and UIR groups and number of risk factors.

Table 3 shows results of univariate and multivariate analyses. PSA-RFS was significantly improved in the FIR group (68.17 vs. 81.98% at 4 years, HR = 1.97, 95% CI = [1.71; 2.27], $p < 0.0001$). Patients with only one RF had better PSA-RFS (80.14 vs. 62.86% at 4 years, HR = 2.21, 95% CI = [1.91; 2.56]) compared to those with more than one risk factor ($p < 0.0001$).

A primary Gleason score of 4 (HR: 1.81 [1.55; 2.12], $p < 0.0001$) and a PPBC ≥ 50% (HR = 1.26, 95% CI = [1.02; 1.56], $p = 0.0286$) were independent predictors for decreased PSA-RFS in multivariate analysis.

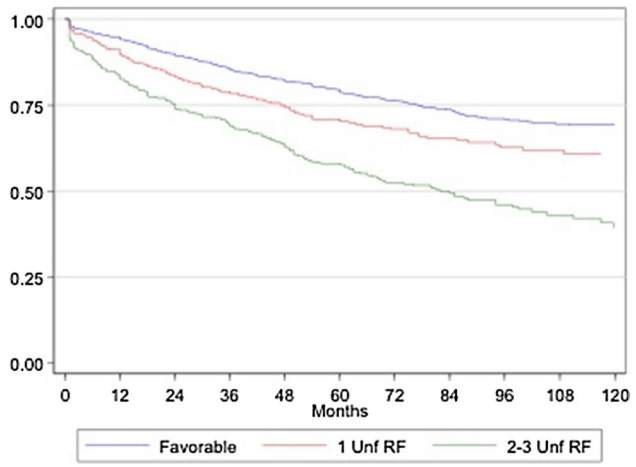

Fig. 1 A comparison of favorable versus unfavorable intermediate-risk prostate cancer patients undergoing RP showing significant differences in prostate-specific antigen (PSA) recurrence-free survival ($p < 0.001$)

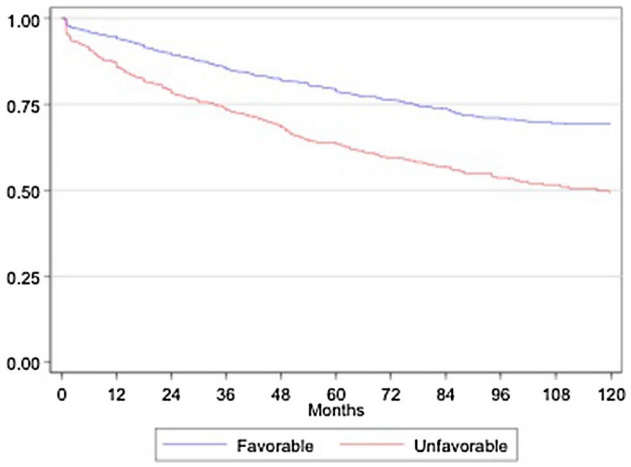

Fig. 2 Outcomes with no unfavorable risk factors (RFs), one unfavorable RF, or two or three unfavorable RFs (Gleason 4 + 3 = 7, PPBC > 50% of biopsy cores with cancer, or more than one intermediate-risk factor): prostate-specific antigen (PSA) recurrence-free survival ($p < 0.0001$)

Table 3 Univariate and multivariate analysis for prostate-specific antigen recurrence-free survival

	UVA		MVA	
	HR [95% CI]	*p* value	HR [95% CI]	*p* value
Risk factor >1	2.21 [1.91; 2.56]	<0.0001	–	–
FIR versus UIR	1.97 [1.71; 2.27]	<0.0001	–	–
Favorable	1	<0.0001	–	–
1 Unf RF	1.46 1.21; 1.77]			
2–3 Unf RF	2.45 [2.10; 2.87]			
Gleason score 4 + 3	1.71 [1.47; 2.00]	<0.0001	1.81 [1.55; 2.12]	<0.0001
PSA > 10 ng/ml	1.23 [1.07; 1.41]	0.0040	1.40 [1.21; 1.62]	<0.0001
cT1 versus cT2	1.44 [1.25; 1.65]	<0.0001	1.39 [1.20; 1.60]	<0.0001
PPBC > 50%	1.37 [1.12; 1.69]	0.0025	1.26 [1.02; 1.56]	0.0286

RF risk factor, *UIR* unfavorable intermediate risk, *FIR* favorable intermediate risk, *PPBC* percentage of positive biopsy cores, *UVA* univariate analysis, *MVA* multivariate analysis

Discussion

Improvements to individual risk prediction for patients with PCa remain subject to debate and are relevant to improve patient management. Our study is the largest to report on the pathologic and oncologic outcomes after RP in a group of patients with intermediate-risk PCa.

We found that the stratification proposed by Zumsteg et al. [15] (in a radiotherapy series) could be applied to our patients that had undergone RP. Our findings are in-line with those published and show that a subclassification into two groups could significantly predict the different risks of recurrence. Thus, our study, which was based on the analyses of RP specimens, has confirmed that intermediate-risk PCa remains heterogeneous with regard to its prognosis, but that this group can be easily separated into those with a favorable or an unfavorable prognosis based on simple risk factors.

Patients with UIR PCa had a twofold-increased risk of early PSA recurrence compared to patients with FIR, despite that the former often received more adjuvant therapy. Thus, taking into consideration this heterogeneity, it seems difficult to provide uniform therapeutic management for intermediate-risk PCa without obtaining a more definitive assessment of risk. Thus, it could be reasonable to consider patients with more than two risk factors as having a high risk of recurrence and, consequently, to adapt initial and adjuvant therapeutic decisions toward more invasive management. Conversely, in the FIR PCa group, the need for active surveillance, a lymphadenectomy with a RP, or the need for short-term androgen deprivation therapy combined (in some cases) with radiotherapy could be determined more specifically using this substratification.

One of the primary treatments recommended by urological and oncological guidelines is radical prostatectomy for intermediate-risk PCa patients who have a life expectancy >10 years. Extended pelvic lymph node dissection has been recommended for decades. Nevertheless, recent

guidelines propose that extended pelvic lymph node dissection is only useful if the estimated risk for positive lymph nodes involvement exceeds 5% [16]. Nomogram-integrated PPBC and the primary Gleason score were the foremost predictive factors for LNI in a validation study and were also the two independent predictors for oncologic outcome in our study [17]. We also found that the number of positive lymph nodes was very low in FIR, suggesting that extended pelvic lymph node dissection could be omitted in this subgroup.

In intermediate-risk PCa, short-term androgen deprivation therapy in association with external beam radiation therapy is the gold standards used by medical oncology communities. However, this approach is based on outdated clinical randomized trials [18, 19]. Furthermore, ADT is associated with significant morbidity, decreased in quality of life, and increased cardiac events; thus, re-definition of the risk stratification system for intermediate-risk PCa is needed. Thus, Zumsteg et al. concluded that omitting short-term ADT might be a reasonable option for patients with FIR and undergoing external beam radiation therapy especially for older men or those with cardiac comorbidities.

Currently, active surveillance is a treatment option for IR-PCa, although few prospective series have reported on the oncologic outcomes for this group. Most guidelines do not recommend active surveillance as a standard treatment. Nevertheless, recent articles show that active surveillance can be feasible and safe in selected IR-PCa patients [20–22].

To date, no direct prospective comparison has been made between FIR and low-risk PCa patients. A recent study on PCa FIR patients who were treated with brachytherapy found no significantly increased risk of prostate cancer-specific mortality when compared to men with low-risk PCa [23].

In contrast, we show that several unfavorable risk factors were strongly predictive of an aggressive disease. In patients with two or more risk factors, 38% experienced biochemical recurrence within 5 years. Patients with more than one IRF had a more than twofold increase in PSA recurrence compared to FIR patients. These results demonstrate, once again, the strong heterogeneity within these patients. Thus, it could be reasonable to consider patients with more than two risk factors as having a high risk of recurrence and, consequently, to adapt initial and adjuvant therapeutic decisions toward more invasive management.

A primary Gleason score of 4, the number of risk factors, and a PPBC of >50% have all been repeatedly shown to be independent predictors for an adverse outcome in PCa [12–14]. However, most of these studies are not contemporary and have included patients treated by radiation therapy.

Risk stratification nomograms have been previously published, but have not integrated these predictive factors and are not used in routine practice [24]. A new classification system is necessary to improve risk prediction, especially in patients with intermediate-risk disease.

Our study has several limitations. MRI was not achieved in all patients, because between 2000 and 2010, few patients had systematically preoperative MRI. Because of the heterogeneity encountered during our analysis period (non-systematic multiparametric-MRI), these data could not be analyzed. Our multiinstitutional design could have induced biases in patient selection, pathologic assessment, data collection, and the use of adjuvant therapies. Modification to the Gleason score grading system in 2005 could have also introduced biases. No centralized pathology was available between the different tertiary centers; however, only dedicated uropathologists reviewed the RP specimens in these referral cancer centers. Moreover, important confounders that could have a significant impact on oncologic outcomes have not been taken into account, due to the retrospective design of the study (BMI, surgeon experience, center experience). Median follow-up of the cohort was relatively short at the time of analysis, limiting the ability to analyze associations with progression variables since a large proportion of PSA failures occur beyond 3-year follow-up [25]. Moreover, biochemical recurrence rates and RFS were probably not the more relevant end points to address clinical conclusions in men undergoing RP. However, PSA failure and the time to biochemical progression are established to be associated with an increased risk of progression to metastatic disease and specific death [26].

Thus, the use of such a stratification prognostic approach should improve the accuracy of predicting pathologic and oncologic results. However, new tools as genomic test, novel molecular-based approaches and mpMRI are needed to improve the selection of our intermediate-risk PCa patients.

Conclusions

Our pathologic and oncologic data confirm that the heterogeneity encountered within intermediate-risk PCa can be easily and preoperatively divided into two separate risk groups that effectively predict different pathologic risks and oncologic outcomes. This new classification could improve risk management and lead to the promotion of active surveillance or focal therapy, as well as decrease the use of androgen deprivation therapy (associated with radiotherapy) in cases of PCa that have a favorable risk. Thus, this easy-to-use stratification could help physicians when making treatment decisions. Prospective study and new tools as genomic test and novel molecular-based approaches can improve this stratification in the future to counsel patients during daily practice.

Authors' contribution Beauval and Ploussard have contributed to protocol/project development, data collection or management, data analysis, and manuscript writing/editing. Cabarrou has contributed to data analysis. Roumiguié and Ouzzane have contributed to data collection or management, protocol/project development. Gas, Goujon, Marcq, and Mathieu have contributed to data collection or management. Vincendeau, Cathelineau, and Salomon have contributed to manuscript writing/editing, data collection or management. Soulié, de La Taille, and Rouprêt have contributed to manuscript writing/editing. Rozet has contributed to manuscript writing/editing, protocol/project development.

Compliance with ethical standards

This study was performed in accordance with ethical standards.

Conflict of interest The authors declare no conflicts of interest.

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