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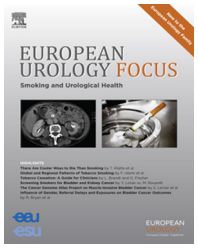

Review – Prostate Cancer

Variability in Outcomes for Patients with Intermediate-risk Prostate Cancer (Gleason Score 7, International Society of Urological Pathology Gleason Group 2–3) and Implications for Risk Stratification: A Systematic Review

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Abstract

Context: Optimal management for patients with intermediate-risk (IR) prostate cancer (PCa) remains controversial. Clinical metrics provide guidance on appropriate management options.
Objective: To report estimates for clinically relevant outcomes in men with IR PCa based on clinical and pathological features.
Evidence acquisition: PubMed and programs from key 2015 uro-oncology congresses were searched using the terms "intermediate", "Gleason 3 + 4", "Gleason 4 + 3", "active surveillance", "treatment", "adverse pathology", AND "prostate cancer." Articles meeting prespecified criteria were retrieved. Bibliographies were scanned for additional relevant references.
Evidence synthesis: Men with IR PCa have a wide range of predicted clinically relevant outcomes. Within the IR category, estimate ranges for adverse surgical pathology and 5-yr disease progression are 15–64% and 21–91%, respectively. Clinical parameters and predictive nomograms refine these estimates, but do not uniformly differentiate favorable and unfavorable IR PCa. Variations in study design and data quality in source manuscripts mandate caution in interpreting results.
Conclusions: Outcomes in IR PCa are heterogeneous. Refinements in personalized risk assessment are needed to better select IR PCa patients for surveillance.
Patient summary: Current and future risk stratification tools may provide additional information to identify men with intermediate-risk prostate cancer who may consider active surveillance.

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1. Introduction

Prostate cancer (PCa) has a protracted natural history [1]. Few men diagnosed with low-risk PCa (Gleason score [GS] ≤6, prostate-specific antigen [PSA] ≤10 ng/ml, clinical stage ≤T2a) will die from the disease [2]. Active surveillance (AS) has gained traction as a valid management option for these men. AS avoids the morbidity of immediate treatment

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but maintains the option of deferred treatment, with high cure rates for patients who subsequently elect for treatment [3,4].

Historically, all GS7 PCa has been considered intermediate risk (IR). However, an increasing proportion of Gleason pattern 4 in biopsy GS7 (bGS7) and pathological GS7 (pGS7) disease has adverse implications [5–7]. Estimation of percentage GS4 in biopsies is challenging, subject to interobserver variability, and rarely reported [8,9]. Furthermore, a significant proportion of men with bGS7 PCa are found to have a different pGS at radical prostatectomy (RP) [10].

National Comprehensive Cancer Network (NCCN) risk groups [11] and other commonly used PCa-specific nomograms incorporate bGS, serum prostate-specific antigen (PSA), clinical stage, PSA density (PSAD), and other parameters. The prognostic utility (measured as a c index) of PCa nomograms ranges between 0.59 and 0.79, depending on the study population and outcome of interest [12–14]. This variability in predictive power is reflected in the wide range of outcomes for patients with IR PCa derived from the Memorial Sloan-Kettering nomogram (www.mskcc.org/nomograms/prostate/pre-op) (Table 1).

Men with bGS7 have traditionally been excluded from AS [15]. However, some centers have included select men with bGS3 + 4 IR PCa in AS protocols and have reported favorable outcomes [16,17]. The 2016 NCCN guidelines suggest that AS may be an option for men with favorable IR PCa [11]. In this systematic review, we review clinical and pathologic metrics used to predict outcome in men with IR PCa; this information may guide decisions on AS for IR PCa.

2. Evidence acquisition

2.1. Literature search strategies

PubMed was searched using Medical Subject Headings (MeSH) keywords relating to IR PCa including AS, radiotherapy, brachytherapy, surgery, biochemical recurrence (BCR), adverse pathology (AP), metastasis, and mortality. Boolean operators were used to narrow search results. The results were refined by applying the following filters: English-language, human studies, and only experimental and observational study designs. The search strategy is summarized in Figure 1. We adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Articles were excluded if: (1) they did not include IR PCa; (2) no analysis of individual clinical factors contributing to IR PCa status was included; and/or (3) they were case reports, reviews, editorials, letters, comments, or other correspondence.

Bibliographies for articles meeting the inclusion criteria were searched. Abstracts from the 2015 meetings of the American Society of Clinical Oncology (ASCO), the American Urological Association (AUA), and the European Association of Urology (EAU) were searched using the same terms as above.

Table 1 – Intermediate-risk prostate cancer calculator derived from the Memorial Sloan-Kettering Cancer Center nomogram (www.mskcc.org/nomograms/prostate)

	Pre-RP characteristics					Post-RP characteristics			
	Low (65 yr, PSA 0.1, GS3 + 4, T1c, 1/12 cores +)	"Low" but GS4 + 3	High (65 yr, PSA 20, GS4 + 3, T2c, 12/12 cores +)	"High" but GS3 + 4	GS3 + 3, PSA 10.1, T1c, 1/12 cores +	GS3 + 3, PSA 20, T2c, 12/12 cores +	Low (65 yr, preRP PSA 0.1, GS3 + 4; PM, ECE, SV, LN − at T_0)	"Low" but GS4 + 3	High (65 yr, preRP PSA 20, GS4 + 3; PM, ECE, SV, LN − at T_0)	"High" but GS3 + 4
CSS postRP							RFS status postRP			
10 yr	99%	99%	99%	99%	99%	99%	2 yr	99%	97%	82%	95%
15 yr	99%	99%	98%	98%	99%	99%	5 yr	98%	92%	65%	88%
PFS postRP							7 yr	97%	89	57%	84%
5 yr	99%	97%	21%	46%	92%	65%	10 yr	96%	85%	48%	79%
10 yr	98%	95%	12%	31%	87%	49%	CSS postRP				
OCD	64%	57%	15%	19%	62%	29%	15 yr	99%	99%	98%	99%
ECE	36%	42%	82%	78%	37%	68%					
LNI	1%	4%	33%	13%	1%	5%					
SVI	1%	3%	34%	17%	1%	9%					

CSS = cancer-specific survival; ECE = extracapsular extension; GS = Gleason score; LNI = lymph node involvement; OCD = organ = confined disease; PFS = progression-free survival; PM = positive margins; PSA, prostate-specific antigen (ng/ml); RFS = recurrence-free survival; RP = radical prostatectomy; SVI = seminal vesicle invasion; T_0 = time zero.

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