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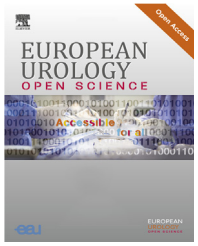

Brief Correspondence

Risk of Cancer-related Death for Men with Biopsy Grade Group 1 Prostate Cancer and High-risk Features: A European Multi-institutional Study

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Abstract

International Society of Urological Pathology grade group 1 (GG 1) prostate cancer (PCa) is generally considered insignificant, with recent suggestions that it should even be considered as "noncancerous". We evaluated outcomes for patients with GG 1 PCa on biopsy (bGG 1) and high-risk features (prostate-specific antigen [PSA] >20 ng/ml and/or cT3–4 stage) to challenge the hypothesis that every case of bGG 1 PCa has a benign disease course. We used the multi-institutional EMPaCT database, which includes data for 9508 patients with high-risk PCa undergoing surgery. We included patients with bGG 1 PCa (n = 848) in our analysis and divided them into three groups according to PSA >20 ng/ml, cT3–4 stage, or both. The estimated 10-yr cancer-specific survival (CSS) rate was 96% in the overall population, 88% in the group with both PSA >20 ng/ml and cT3–4 stage, 97% in the group with PSA >20 ng/ml alone, and 98% in the group with cT3–4 stage alone. Similar CSS outcomes were found in subgroups with GG 1 PCa on pathology (n = 502) and with GG 1 on biopsy diagnosed after 2005 (n = 253). Study limitations include the lack of magnetic resonance imaging (MRI) staging and MRI-targeted biopsies. In conclusion, patients with GG 1 and either PSA >20 ng/ml or cT3–4 stage have a low risk of dying from their cancer after surgery. However, patients with GG 1 PCa and both PSA >20 ng/ml and cT3–4 stage are at higher risk of cancer-specific mortality and active treatment should be discussed for this subgroup.
Patient summary: We assessed outcomes for patients diagnosed with low-grade prostate cancer on biopsy who also had one or two factors associated with high risk

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disease. Men with both of those risk factors had a higher risk of dying from their prostate cancer. Active treatment should be discussed for this subgroup of patients.

In recent years, prostate cancer (PCa) management has evolved significantly. In particular, for low-risk disease with biopsy International Society of Urological Pathology grade group 1 (bGG 1) and other low-risk factors such as prostate-specific antigen (PSA) <10 ng/ml and cT1–2a stage, recommendations have changed from active treatment options to active surveillance (AS). Historically, patients with GG 1 PCa were considered to have tumor with low malignant potential [1,2]. Currently, some claim that GG 1 should no longer be called cancer [3].

Traditionally, studies on GG 1 PCa focused primarily on cohorts with characteristics corresponding to low- or intermediate-risk classifications [4]. Consequently, the literature mainly reflects outcomes at the favorable end of the disease spectrum. However, it cannot be inferred that all patients with GG 1 disease have low-risk PCa. It is crucial to acknowledge the existence of a subset of patients with GG 1 PCa who may exhibit high-risk features and therefore may face less favorable prognosis [5].

In this context, our study goal was to refute the hypothesis that all cases of bGG 1 PCa follow a benign course without metastatic potential. We aimed to fill a critical knowledge gap by evaluating long-term cancer-specific survival (CSS) outcomes for patients with bGG 1 PCa and elevated PSA >20 ng/ml and/or locally advanced disease (cT3–4) on clinical staging (digital rectal examination). Our objective was to raise awareness of the caution needed when inferring an absence of metastatic potential for GG 1 and to promote a more personalized treatment approach.

We used the European Multicenter Prostate Cancer Clinical and Translational Research group (EMPaCT) retrospective database, which contains data for 9508 patients with high-risk PCa who underwent radical prostatectomy and lymph node dissection between 1989 and 2017 at 15 tertiary centers. Tumor T stage was based on digital rectal examination (DRE) as recommended in the 8th edition of the American Joint Committee on Cancer TNM staging system. Random biopsies were taken in the vast majority of patients, supplemented with targeted biopsies only if the tumor was palpable or visible on transrectal ultrasound. Patients were excluded if they were considered ineligible for surgery (physical reasons, local inoperability, patient/-surgeon preference) or if they received neoadjuvant treatment. (Supplementary Fig. 1). The final study cohort included 848 men. Patients were divided into three groups: men with (1) PSA >20 ng/ml, (2) men with cT3–4 stage, and (3) men with both PSA >20 ng/ml and cT3–4 stage. Descriptive analyses were performed. Kaplan-Meier survival plots were compared using a log-rank test. A subgroup analysis for patients with pathological GG 1 PCa (pGG 1) was performed. To account for the stricter Gleason scoring system introduced in 2005 [6], we also performed a subgroup analysis for patients diagnosed with bGG 1 PCa after 2005.

Baseline patient and tumor characteristics are summarized in Table 1. At median follow-up of 76 mo, 27 (3.2%) cancer-related deaths (CRDs) had occurred. The CRD rate was 8.1% in the group with both high-risk factors versus 3.1% in the group with just PSA >20 ng/ml and 1.9% in the group with just cT3–4 stage. The estimated 10-yr CSS rate was 96% (95% confidence interval [CI] 94–98%) in the total population, 88% in the group with both risk factors, 97% in the group with PSA >20 ng/ml alone, and 98% in the group with cT3–4 alone (Fig. 1). Cox regression analysis revealed that presence of both high-risk factors increased the risk of CRD four-fold (hazard ratio 4.1, 95% CI 1.27–13.48; Supplementary Table 1). Results for the pGG 1 (n = 502) and post-2005 bGG 1 (n = 253) subgroup analyses are presented in the Supplementary material.

Our findings have several important clinical implications. First, men with bGG 1 PCa and high-risk factors are at higher risk of unfavorable pathological findings and have a non-negligible risk of CRD. Second, 41% of men were upgraded at final pathology, which is similar to previous reports [7]. It is important to note that the proportion of patients with unfavorable pathological PCa features remained similar in the groups with and without upgrading (Supplementary Table 2). Similarly, unfavorable features such as lymph node invasion and positive surgical margins remained consistent between the group diagnosed after 2005 and the full cohort (Supplementary Table 3). Third, an important shift in Gleason scoring occurred after 2005, when it was decided that any percentage of the highest Gleason score should be included in the final Gleason sum score. A direct consequence was upgrading of many tumors graded as bGG 1 using the pre-2005 system to bGG $\geq$2 using the post-2005 system. The estimated 10-yr CSS rates were 96% for the overall bGG 1 cohort, 95% for the pGG 1 subgroup, and 97% for the subgroup with bGG 1 diagnosed after 2005. Finally, the occurrence of both high-risk factors was significantly correlated with higher risk of CRD in the overall cohort. This effect disappeared for patients diagnosed after 2005, probably because of the limited number of patients in the cohort with both risk factors (n = 11). Moreover, the estimated 10-yr CSS rate for men diagnosed with bGG 1 and both high-risk factors was 88%, but remained $\geq$97% for men with only one high-risk factor. Importantly, when interpreting these results it should be taken into account that all patients were treated with surgery ± adjuvant treatments. Therefore, these results cannot be extrapolated to patients treated conservatively (AS or watchful waiting) or with radiotherapy and androgen deprivation. It should be noted that the group with bGG 1 PCa and high-risk factors is a rare patient population in current European practice. However, our results are valid for this high-risk GG 1 patient group.

Table 1 – Clinicopathological characteristic of patients with biopsy GG 1 prostate cancer and high-risk factors

	All patients (*n* = 848)	PSA >20 ng/ml (*n* = 326)	cT3–4 stage (*n* = 411)	PSA >20 ng/ml and cT3–4 stage (*n* = 111)
Median age, yr (IQR)	66 (60–70)	66 (61–70)	65 (60–70)	67 (61.3–71)
Median PSA, ng/ml (IQR)	20.65 (8.1–27.7)	26.28 (23–34)	8 (5.6–11.6)	29.1 (24.9–43.2)
Year of radical prostatectomy, *n* (%)				
≤2005	595 (70.2)	264 (81)	231 (56.2)	100 (90.1)
>2005	253 (29.8)	62 (19)	180 (43.8)	11 (9.9)
PSA >20 ng/ml, *n* (%)	437 (51.5)	326 (100)	0 (0)	111 (100)
Median PSAD, ng/ml/cm^3 (IQR)	0.28 (0.17–0.60)	0.62 (0.41–0.84)	0.19 (0.12–0.29)	0.78 (0.54–1.04)
Clinical stage, *n (%)*				
cT1	114 (13.4)	114 (35)	0 (0)	0 (0)
cT2	212 (25)	212 (65)	0 (0)	0 (0)
cT3a	492 (58)	0 (0)	387 (94.2)	105 (94.6)
cT3b–4	30 (3.5)	0 (0)	24 (5.8)	6 (5.4)
Pathological stage, *n (%)*				
pT2	396 (46.7)	161 (49.4)	207 (50.4)	28 (25.2)
pT3a	294 (34.7)	98 (30.1)	156 (38)	40 (36)
pT3b	128 (15.1)	58 (17.8)	40 (9.7)	30 (27)
pT4	30 (3.5)	9 (2.8)	8 (1.9)	13 (11.7)
Pathological GG, *n (%)*				
GG 1	502 (59.2)	225 (69)	202 (49.1)	75 (67.6)
GG 2	228 (26.9)	60 (18.4)	145 (35.3)	23 (20.7)
GG 3	51 (6)	16 (4.9)	30 (7.3)	5 (4.5)
GG 4	47 (5.5)	17 (5.2)	24 (5.8)	6 (5.4)
GG 5	20 (2.4)	8 (2.5)	10 (2.4)	2 (1.8)
Positive surgical margin, *n* (%)	311 (37.1)	130 (40.5)	126 (31)	55 (49.5)
LN invasion, *n* (%)	111 (13.1)	49 (15)	33 (8)	29 (26.1)
Median LNs removed, *n* (IQR)	10 (6–16)	9 (6–13)	10 (6.25–17)	10 (7–13)
Median positive LNs in pN1 patients, *n* (IQR)	1 (1–2)	1 (1–2)	1 (1–2.75)	2 (1–4.25)
Upgrading at final pathology, *n* (%)	346 (40.8)	101 (31)	209 (50.9)	36 (32.4)
Salvage or adjuvant RT, *n* (%)	144 (17.8)	54 (17.4)	60 (15.2)	30 (28.3)
Salvage or adjuvant ADT, *n* (%)				
ADT monotherapy	213 (25.1)	86 (26.4)	79 (19.2)	48 (43.2)
ADT in combination with RT	96 (11.3)	37 (11.3)	39 (9.49)	20 (18)
Death from any cause, *n* (%)	144 (17)	51 (15.6)	62 (15.1)	31 (27.9)
Cancer-related death, *n* (%)	27 (3.2)	10 (3.1)	8 (1.9)	9 (8.1)
Median follow-up, mo (IQR)	75.5 (38–122)	85.5 (43–127)	64 (34–120)	84 (51–117.8)

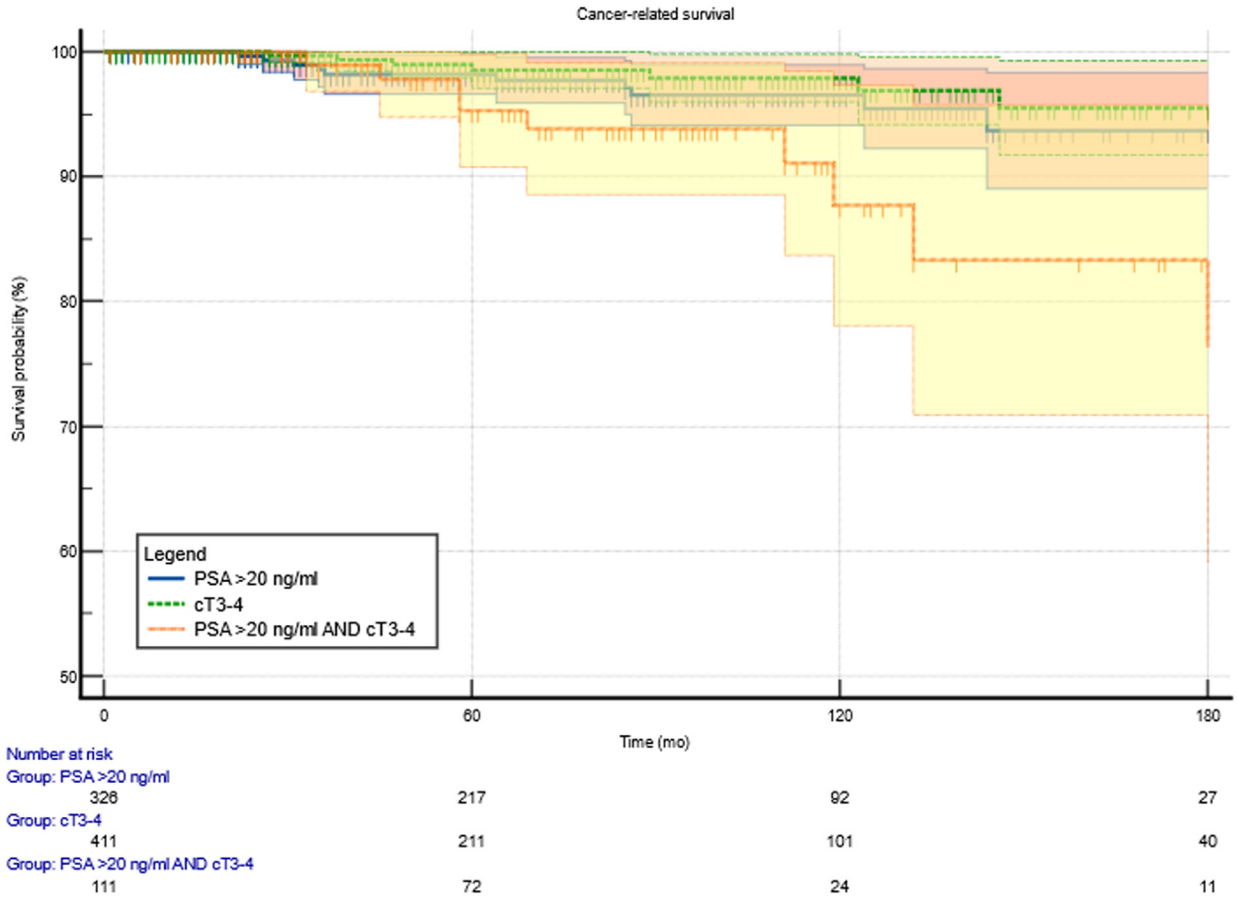
IQR = interquartile range; PSA, prostate-specific antigen; PSAD = PSA density according to transrectal ultrasound; GG = International Society of Urological Pathology grade group; LN = lymph node; RT = radiotherapy.

The current PRIAS protocol for decision-making on AS versus active treatment includes not only PSA and cT stage but also PSA density <0.2 ng/ml/cm^3 as a criterion for AS [8]. In our cohort, PSA density was calculated using the prostate volume estimated on transrectal ultrasound imaging. Overall, PSA density was >0.2 ng/ml/cm^3. Only patients with bGG 1 PCa and cT3–4 stage had median PSA density of 0.19 ng/ml/cm^3. Similar results were found for the subgroups with pGG 1 and bGG 1 diagnosed after 2005 (Supplementary tables).

Some limitations of our study should be mentioned. First, the EMPaCT database is a multi-institutional retrospective database and is inherently subject to several types of bias. There was no central review of histopathology, making the results sensitive to interobserver variability. However, all the participating institutions are tertiary centers with dedicated uropathologists. Information to address some important considerations was lacking. This included information about the timing of surgery (GG 1 PCa progressing on AS or de novo GG 1). However, we assume that the vast majority of patients underwent surgery for de novo high-risk PCa as recommended by the European Association of Urology guidelines [4]. Furthermore, some of the subgroup analyses involved relatively small numbers of patients, limiting the generalizability of the results to some extent.

Second, biopsy protocols have changed significantly over the years, moving from sextant biopsies to 12-core biopsies to targeted biopsies. As only tertiary centers were included in our study, biopsy protocols were compliant with international guidelines throughout the study period. As the database only included patients treated before 2017, the most important limitation is the lack of magnetic resonance imaging (MRI) use for clinical staging and the absence of MRI-targeted biopsies. It is likely that the use of MRI staging and MRI-targeted biopsies would have reduced the number of "undergraded" bGG 1 cases [9]. Of note, palpable and transrectal ultrasound–visible lesions were targeted during biopsy, which probably attenuated the lack of MRI data [10]. Third, there was an important change in Gleason scoring after 2005. A direct consequence was upgrading of many bGG 1 tumors diagnosed before 2005 to bGG ≥2. We performed a subgroup analysis for patients diagnosed after 2005 to account for this limitation, which revealed similar survival results.

While the literature has mainly focused on GG 1 PCa of low to intermediate risk, there is a group of patients with bGG 1 disease with high-risk features. We demonstrated that considering all bGG 1 disease as "noncancerous" may provide a false sense of safety. Moreover, the combination of high-risk features is associated with increasingly poor outcomes. Such



Groups	% 5-year CSS (95% CI)	% 10-year CSS (95% CI)
PSA >20 ng/ml	98.2 (96.6 – 99.8)	96.5 (94.1 – 98.9)
cT3-4	98.5 (97.1 – 99.9)	97.9 (96.0 – 99.8)
PSA >20 ng/ml AND cT3-4	95.3 (90.8 – 99.8)	87.7 (78.1 – 97.3)

Fig. 1 – Cancer-specific survival for patients with grade group 1 prostate cancer on biopsy and high-risk factors. PSA = prostate-specific antigen.

patients could represent a subgroup of GG 1 PCa with clonal features of lethal disease. Understanding whether primary tumor biopsies can be used for molecular stratification to guide PCa treatment remains a key question [11]. More studies with GG 1 biopsy tissue and with current targeted biopsy techniques are needed to confirm our findings.

In conclusion, not all GG 1 disease should be considered a "benign" variant of PCa. Patients with bGG 1 PCa and either PSA >20 ng/ml or cT3–4 stage have a non-negligible risk of dying from PCa after surgery. Moreover, patients bGG 1 with both PSA >20 ng/ml and cT3–4 stage—although rare in current practice—are at higher risk of PCa-specific mortality. Therefore, surgery should be part of the treatment discussion when patients diagnosed with bGG 1PCa have high-risk factors. Our findings corroborate observations from previous studies [12,13].

Author contributions: Steven Joniau had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2024.06.001.

References

[1] Eggener SE, Badani K, Barocas DA, et al. Gleason 6 prostate cancer: translating biology into population health. J Urol 2015;194:626–34.
[2] Nunez Bragayrac LA, Murekeyisoni C, Vacchio MJ, et al. Blinded review of archival radical prostatectomy specimens supports that contemporary Gleason score 6 prostate cancer lacks metastatic potential. Prostate 2017;77:1076–81.
[3] Eggener SE, Berlin A, Vickers AJ, Paner GP, Wolinsky H, Cooperberg MR. Low-grade prostate cancer: time to stop calling it cancer. J Clin Oncol 2022;40:3110–4.
[4] Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2021;79:243–62.
[5] Joniau S, Briganti A, Gontero P, et al. Stratification of high-risk prostate cancer into prognostic categories: a European multi-institutional study. Eur Urol 2015;67:157–64.
[6] Epstein JI. An update of the Gleason grading system. J Urol 2010;183:433–40.
[7] Epstein JI, Feng Z, Trock BJ, Pierorazio PM. Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factoring in tertiary grades. Eur Urol 2012;61:1019–24.
[8] Bokhorst LP, Valdagni R, Rannikko A, et al. A decade of active surveillance in the PRIAS study: an update and evaluation of the criteria used to recommend a switch to active treatment. Eur Urol 2016;70:954–60.
[9] Goel S, Shoag JE, Gross MD, et al. Concordance between biopsy and radical prostatectomy pathology in the era of targeted biopsy: a systematic review and meta-analysis. Eur Urol Oncol 2020;3:10–20.
[10] Ploussard G, Rouvière O, Rouprêt M, van den Bergh R, Renard-Penna R. The current role of MRI for guiding active surveillance in prostate cancer. Nat Rev Urol 2022;19:357–65.
[11] Mateo J, Seed G, Bertan C, et al. Genomics of lethal prostate cancer at diagnosis and castration resistance. J Clin Invest 2020;130:1743–51.
[12] Epstein JI, Kibel AS. Renaming Gleason score 6 prostate to noncancer: a flawed idea scientifically and for patient care. J Clin Oncol 2022;40:3106–9.
[13] Baboudjian M, Rouprêt M, Ploussard G. Redefining Gleason 6 prostate cancer nomenclature: the surgeon's perspective. J Clin Oncol 2023;41:1492–3.

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