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Original Research

Prostate cancer outcomes of men with biopsy Gleason score 6 and 7 without cribriform or intraductal carcinoma

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Abstract ***Aim of the study:*** Gleason score (GS) 3 + 4 = 7 prostate cancer patients with presence of cribriform or intraductal carcinoma (7^+) have a worse disease-specific survival than those without. The aim of this study was to compare the clinicopathologic characteristics and patient outcomes of men with biopsy GS 3 + 4 = 7 without cribriform or intraductal carcinoma (7^-) to those with GS 3 + 3 = 6.

Materials and methods: We included all patients from the first screening round of the European Randomized Study of Screening for Prostate Cancer (1993–2000) with a revised GS ≤ 3 + 4 = 7 (n = 796) following the 2014 International Society of Urological Pathology criteria. Relations with biochemical recurrence after radical prostatectomy or radiotherapy were analysed using log-rank testing and multivariable Cox regression analysis.

Results: In total, 486 patients had GS 6 and 310 had GS 7, 54 of whom had GS 7^+ (17%). During a median follow-up of 15 years, biochemical recurrence was seen in 61 (20%) GS 6, 54 (21%) GS 7^- and 22 (41%) GS 7^+ patients (41%). Both biopsy GS 7^- and 7^+ patients had significantly higher prostate-specific antigen levels, mean tumour percentage, percentage of positive cores and ≥cT3 than those with GS 6 (all P < .001). GS 7^- patients did not have a poorer biochemical recurrence-free survival (BCRFS) after radical prostatectomy than GS 6 patients (log-rank P = .13), whereas those with GS 7^+ had (log-rank P = .05). In multivariable analyses, biopsy GS 7^- was not associated with poorer BCRFS after radical

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prostatectomy (hazard ratio [HR], 1.3; 95% confidence interval [CI]: 0.67–2.4; P = .47) or radiotherapy (HR, 0.88; 95% CI: 0.51–1.5; P = .63). GS 7^+ was independently associated with poorer BCRFS after radical prostatectomy (HR, 3.0; 95% CI: 1.1–7.8; P = .03), but not after radiotherapy (HR, 1.2; 95% CI: 0.58–2.3; P = .67).

Conclusions: Men with biopsy GS 7^- prostate cancer have similar BCRFS after radical prostatectomy or radiotherapy to those with GS 6 and may be candidates for active surveillance as long as other inclusion criteria such as on PSA and tumour volume are met.

1. Introduction

The use of prostate-specific antigen (PSA) testing has led to substantially increased detection of insignificant prostate cancers in the past two decades [1]. Active surveillance has gradually emerged as a valuable alternative treatment option for these men. While active surveillance has the benefit of avoiding overtreatment, it also retains the option for active treatment in case of disease progression. Although most active surveillance protocols are limited to Gleason score (GS) 3 + 3 = 6, some institutions have extended their criteria to include biopsies containing small amounts of Gleason grade 4 [2–5]. Contemporary Gleason grade 4 prostate cancer represents a heterogeneous group of various growth patterns comprising ill-formed, fused, cribriform and glomeruloid glands. While Gleason grade 4 is not subclassified in daily practice, recent studies have suggested that among Gleason grade 4 growth patterns, cribriform growth is associated with worse clinical outcome, while fused, glomeruloid and ill-formed glands are not [6–9].

In recent years, the clinical relevance of intraductal carcinoma of the prostate cancer – a high-risk lesion defined as malignant epithelium filling large acini or ducts with preservation of basal cells – has been acknowledged. Although not included in the Gleason grading system, intraductal carcinoma has been associated with high GS, advanced tumour stage, biochemical relapse and distant metastasis [10–15]. Intraductal carcinoma can microscopically mimic invasive cribriform carcinoma, and immunohistochemistry is often required for their distinction. Recently, our group has shown that biopsy GS 3 + 4 = 7 patients without cribriform or intraductal carcinoma (7^-) have comparable disease-specific survival rates to those with GS 3 + 3 = 6, while those with cribriform or intraductal carcinoma in their biopsies (7^+) had significantly worse outcomes [16]. Although various studies have shown the adverse prognostic value of invasive cribriform and intraductal growth in GS 7 prostate cancer patients, it is not yet clear to what extent the outcome of men with GS 7^- differs from those with GS 6 prostate cancer. Since GS 3 + 4 = 7 prostate cancer patients generally undergo active treatment, identifying low-risk GS 3 + 4 = 7 tumours could offer a rationale for active surveillance in this large subgroup of prostate cancer patients. The aim of this study was to compare the clinicopathologic characteristics and long-term outcomes of men with biopsy GS 3 + 3 = 6 or GS 3 + 4 = 7 without invasive cribriform or intraductal prostate cancer.

2. Materials and methods

2.1. Patient selection

We identified all 1078 men from the first screening round of the Dutch part of the European Randomized Study of Screening for Prostate Cancer (ERSPC), who had been diagnosed with prostate cancer between November 1993 and March 2000 in Erasmus Medical Centre, Rotterdam, The Netherlands. The trial protocol has been published previously [17,18]. After pathologic review of all available slides (n = 1055) according to the 2014 International Society of Urological Pathology (ISUP) recommendations, we selected all patients with a highest biopsy GS 3 + 4 = 7 or lower for the current study (n = 803) [19,20]. Exclusion criteria were presence of a lymph node or distant metastasis at time of diagnosis (n = 7). The final selection included 796 patients, 486 of whom had GS 3 + 3 = 6 and 310 had 3 + 4 = 7.

2.2. Pathological evaluation

Three investigators (C.F.K., I.P.K., G.v.L.), who were blinded to patient information and outcome, revised all histopathological slides. For each biopsy core, we recorded GS and presence of cribriform pattern or intraductal carcinoma. Since invasive cribriform and intraductal carcinoma often coexist and separate classification is challenging, we combined both patterns to one group (invasive cribriform [CR]/intraductal carcinoma [IDC]). The mean tumour percentage per patient was defined as the sum of total tumour length (mm) divided by the sum of total biopsy length (mm). The label 7^+ was given to patients with GS 3 + 4 = 7 who either had invasive cribriform carcinoma, intraductal carcinoma or both, 7^- to those who had neither. Gleason grading was done according to the 2014 ISUP recommendations [19,20]. The 2009 TNM classification was used to assess pT stage [21]. A positive surgical