INTRODUCTION

Gleason scoring for prostatic carcinoma is probably the oldest and most established grading system for any malignancy [1]. It is a powerful predictor of prognosis in numerous well-validated series. Gleason grading runs from 1 (‘well-differentiated’) to 5 (‘poorly differentiated’). Many tumours show grade heterogeneity and Gleason devised the score, which takes the two most common grades to give a score from 2 to 10. However, as it presently stands, the Gleason grading system is misleading for clinicians and patients.

Gleason scoring has become universal because the classic diagram Gleason provided gives an easy reference chart for pathologists. However, it gives the erroneous impression of de-differentiation between grades, and more seriously, it takes no account of the fact that low grades are extremely rare. In Gleason’s series, score 2 (1 + 1) represented only 0.5% of tumours [1]. With the benefit of hindsight and modern immunohistochemistry, most of these lesions have been shown to be atypical adenomatous hyperplasia (AAH) [2], a lesion common in the transition zone, similar to Gleason score 2 (1 + 1) [3]. Also, biopsy scoring frequently underestimates the score at radical prostatectomy (RP) and therefore scores of 4 (2 + 2) or less are not recommended on prostate biopsies [4].

This, and other factors in interpretation, has resulted in what Albertsen et al. [5] described as the ‘Will Rogers phenomenon’. This derives from an old joke that ‘when the Okies [migrant farmers from Oklahoma] moved to California, the IQ of both states went up’. Thus when Gleason 4 (2 + 2) score tumours are reclassified as Gleason 6 (3 + 3), both survival curves show an improvement. Therefore, for a given grade or score, results appear deceptively better than 10 or 20 years ago. Therefore, the grading of prostate carcinoma has changed radically in 30 years. Because it is nearly impossible to diagnose low-score tumours on biopsies, their diagnosis is limited to RP specimens and TURP chips. However, as they are usually completely excised by TURP or RP, the reason for reporting them seems very dubious, even if they actually exist. Therefore, the diagnosis of low-grade Gleason score has diminished substantially through the 1990s. Scores in contemporary series show that Gleason 2 (1 + 1) was not diagnosed in pooled data from four large centres providing biopsies, and was only reported in one case of 2004 in the matched RP [6].

Historical papers report low-grade lesions relatively frequently (often much more than Gleason did) but will contain many lesions which would now be considered AAH. Recent papers on Gleason grade/share and survival either do not make the diagnosis of Gleason 2 (1 + 1) or make it so rarely that statistics are inapplicable and valid survival curves cannot be generated. There is considerable doubt that this so-called ‘malignancy’ has ever led to progression, metastasis or death. As all these lesions are completely excised at TURP (unless all the borders of the lesion can be seen, the diagnosis of Gleason 2 (1 + 1) cannot be made) any progression seen during the follow-up is likely to be due to an entirely unrelated lesion in the prostate peripheral zone.

A recent consensus conference for Gleason scoring [7] did not preclude the existence of Gleason 2 (1 + 1) lesions, merely claiming they were rare and should only be diagnosed by specialist uropathologists. The continued presence of Gleason grades 1 and 2 will mean that they will continue to be diagnosed, or more likely, misdiagnosed. There are few convincing images published for Gleason 3 (3 + 3) tumours; one web-based tutorial avoids images of score 2 (1 + 1) completely [8]. If there is difficulty among uropathologists in reliably diagnosing these entities, then they cannot remain a diagnostic entity.

Thus survival curves suffer from similar problems as those encountered for the lowest grades; diagnosis is only possible in TURP and RP specimens, making the diagnosis of doubtful value. We are left with the possibility that a grading system running initially from 2 to 10, in reality, runs only from 6 to 10. A problem with analysing reports on this subject is that scores are often combined inconsistently. Some papers report on the survival for patients with scores from 2 to 4, compared with scores 5 and 6; others compare scores of 4 and 5 with 6.

Patients are unaware of this background; most men, particularly so in countries with a screening programme, will be told they have a...
'Gleason 3 + 3 = 6 carcinoma.' They are told they have a tumour that is 6 on a scale from 2 to 10 in severity. This is surely taken by most patients to represent a medium-risk tumour, as they presume that the risk rises equally with the score, and that each score is well established and common. However, the moderate pathology equates with an excellent prognosis. The largest study of clinically localized conservatively treated prostate cancer was published recently [10]. No cases of Gleason grade 1 were diagnosed, and patients with a Gleason 6 (3 + 3) tumour and a PSA level of <4 ng/mL had only a 10% risk of dying from prostate cancer within 10 years.

Despite reassurances from the urologist, it is not surprising that some might opt for radical treatment and refuse conservative treatment, thinking they have a 'moderate' cancer. Also, while Gleason grade 1 is still an entity, higher grades will be misdiagnosed as 2 (1 + 1), and patients will be given erroneous information on the risks of recurrence. The removal of the low-score lesions from the Gleason system would aid clinicians and patients in their interpretation of results, and lead to a grading system that would honestly reflect the current understanding of prostate carcinoma. The Gleason system would then remain robust and comprehensible to clinicians and patients.

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CONFLICT OF INTEREST

None declared.

REFERENCES


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Abbreviations: RP, radical prostatectomy; AAH, atypical adenomatous hyperplasia.

IS OBESITY A RISK FACTOR FOR PROSTATE CANCER?

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INTRODUCTION

Obesity is reaching epidemic proportions, affecting >30% of the population in the USA [1] and becoming a growing problem worldwide. While obesity has recognized links with various chronic disease states, including diabetes, hypertension and cardiovascular disease, it might be a factor in the causes of prostate cancer. However, attempting to identify obesity as a risk factor from other related factors, e.g. dietary intake, socioeconomic status and genetic susceptibility, is extremely difficult, necessitating multivariate analysis of large-scale epidemiological studies. Therefore, whether obesity is a causal factor or merely associated with prostate cancer is a matter of continued debate. Confirmation of a link could have enormous implications for prostate cancer management and quality of life issues.

The precise biological processes linking obesity and prostate cancer are unknown, but there are several possible mechanisms proposed. Obesity is associated with several hormonal alterations, including lower levels of sex hormone-binding globulin that might increase the fraction of biologically available testosterone. Certainly androgens have been implicated as a potential cause of prostate cancer and endocrine aberrations might have a role in progression to clinically significant disease. Obesity is associated with diabetes, the metabolic syndrome with insulin resistance and hyperinsulinaemia; exposure to elevated levels of insulin and circulating IGF-1 might facilitate the progression of prostate cancer. Increased levels of leptin and decreased levels of adiponectin may also be important. The mitogenic effects of leptin on prostate cancer cells, combined with increased expression of growth factors, might be more likely to contribute to the progression of prostate cancer. Therefore, obesity associated with high leptin levels should be considered a risk factor in patients with prostate cancer [2]. Mistry et al. [3] suggested that adiponectin and its receptors might contribute to the molecular association between obesity...