There is no doubt that prostate cancer kills, but only a minority of men who are given this diagnosis, die from prostate cancer. In the developed world we are now over-diagnosing and, more importantly, overtreating prostate cancer, a fact for which we will be criticized in generations to come. As well-intentioned urologists, we should have no trouble in justifying our radical therapy for pathologically moderate to high grade, Gleason 7–10 cancers. Despite the opinions of some urological luddites, careful active surveillance is slowly becoming the standard for Gleason 6, particularly for those with low volume disease associated with low serum PSA values, however, many patients with Gleason 6 still receive radical treatment. We (and others) would like to hypothesize, at least for the sake of discussion, that Gleason 6 pattern prostate pathology is not in itself a lethal prostate cancer, but rather can be associated with a higher risk of potentially lethal prostate cancer (e.g. Gleason 7 or higher) or, alternatively, is a precursor to such prostate cancer. This change in thinking would mean that patients with Gleason 6 scores would not be labelled with a ‘lethal’ cancer diagnosis and would be less anxious about the appropriate treatment plan of active surveillance. Many patients drop out of active surveillance and pursue radical treatment, not because of rising PSA levels, biopsy results or other forms of disease progression, but because of anxiety. There may be less morbidity (and cost) if patients were not given the ‘cancer-label’ until they had Gleason 7 disease. Certainly high volume Gleason 6 disease warrants concern, closer follow-up or perhaps pre-emptive therapy.

So why do we treat Gleason 6 as lethal cancer? Although, probably never examined for specifically, most pathologists will be able to find a strong association between Gleason 7–10 cancers and the presence of Gleason 6 cancers in radical prostatectomy specimens (e.g. areas of Gleason 6 in prostates removed for Gleason 7–10 cancer). We also find areas of Gleason 7–10 cancers in prostates removed with only biopsy-proven Gleason 6 pattern. Furthermore, although not studied, one could hypothesize that increased volume of Gleason 6 may be more likely to be associated with higher grade pathology. Gleason 6 pattern is usually multicentric, much like aggressive prostate cancer, and the features of Gleason 6 are pathologically intermediate between benign prostatic epithelium and aggressive prostate cancer. The actual pathological characteristics of Gleason 6 (3 + 3) do not look that ominous, but one could certainly speculate that it could progress into a more dangerous looking Gleason 7 (or higher) pattern. If we speculate that Gleason 6 pattern is not a true cancer, it cannot instead be considered truly benign. Molecular, morphometric, genetic and immunohistochemical observation indicate that Gleason 6 pattern is more closely related to higher grade invasive carcinoma than to benign epithelium, but the same statement could have been made with respect to high grade intraepithelial neoplasia, another benign but possible precursor of prostate cancer, and more recently for atypical small acinar proliferation. These observations, when looked at from a different point of view, could suggest that Gleason 6 pattern is either associated with a higher risk of independent development or, alternatively, is an early precursor to Gleason 7–10 prostate cancer.

It is the clinical characteristics of Gleason 6 pattern that evoke the hypothesis that this might be a benign, but risky, condition. It is extremely hard to find any evidence that many patients die with a proven diagnosis of Gleason 6 at time of death of Gleason 6 pattern pathology. That is not to say that patients diagnosed with Gleason 6 pattern may not die of higher grade prostate cancers sometime after initial diagnosis. The patients originally diagnosed with Gleason 6, who eventually succumb, invariably die from invasive or metastatic prostate cancer, almost always Gleason 7–10 (not Gleason 6) and they die for one of two reasons. The first is that a higher Gleason grade corresponding to malignant cancer was not diagnosed earlier (missed diagnosis of Gleason 7 or higher) and the second is that patients progressed from a precursor lesion (Gleason 6 pattern?) to a lethal cancer over time. Would it be better, therefore, for patient care worldwide if Gleason grade 6 cancer were considered a non-lethal or even ‘benign’ disease? The data would suggest that, as long as we did not forget the association of Gleason 6 with potential risk of concurrent or future ‘real’ prostate cancer, there would be much less cost, morbidity, anxiety and, in the long run, better male population-based health.

So if Gleason 6 pattern is benign and not really a lethal cancer, what lessons can we learn? Well to start with, our present technology (PSA, PCA-3, and even biopsies) cannot confirm that we are really dealing with only Gleason 6. Until we discover and validate new biomarkers of lethal prostate cancer, we must be very careful not to miss higher Gleason grade prostate cancer in our active surveillance population by close
monitoring and planned biopsies in patients who have a quality life expectancy that would be affected by such a higher grade diagnosis. Alternatively, analysis of maturing data from our active surveillance cohorts (using the tools we presently have) should help us and our patients make informed decisions as to whether radical therapy for selected patients with Gleason 6 pattern pathology warrants consideration for early intervention (e.g. before they develop potentially lethal cancer), e.g. for those patients with a strong family history of prostate cancer.

Whether Gleason 6 is really a cancer or not is a mute point, one that can only be debated, at this time. We continue to over-diagnose and subsequently over-treat unfortunate men who are labelled with a ‘lethal’ cancer, when in fact they will probably never die from it. It is a fact, however, that some men continue to die from prostate cancer, so we must try and direct our therapies to those men, a task that will only be possible through enlightened discussion coupled with basic and clinical research. We need to change our paradigm when dealing with Gleason 6 pattern diagnosis, whether it is a low-risk cancer, a benign disease associated with a high risk of developing real potentially lethal cancer, or a true prostate cancer precursor. Let’s find a way to treat only those men who are destined to die from this serious cancer and relieve some of the psychological burden and significant morbidity from those men who should never have been labelled as having a lethal cancer in the first place. Let us make the case and put in the effort to develop improved prostate cancer screening for the higher grade prostate cancers, while at the same time relegating low volume Gleason 6 to the status of no more than a significant risk factor. Let us decide as a profession to stop the push for inappropriate, expensive, inopportune and perhaps even unethical radical therapies for a condition that by itself does not kill our patients.

CONFLICT OF INTEREST

None declared.

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