Treating Prostate Cancer: Where Do We Draw the Line?

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Source:

The article by Drs. Lepor and Donin is a provocative look at a timely topic in urologic oncology.[1] There is little debate among experts in the field that we are overtreating prostate cancer at the current time. Studies are ongoing to evaluate active surveillance as an option for low-risk tumors, even in men with very long life expectancies. However, in this review, the authors have overreached in suggesting that no Gleason 6 tumor needs to be treated. I believe one can look at the same data they review and reach a slightly different conclusion.

It is well known that microscopic evidence of prostate cancer will develop in most men if they live long enough. In the cystoprostatectomy series cited, occult prostate cancer was detected in 49.6% of men, and the Gleason score was 6 or lower in 87%. [2] Most important, the tumor volume was less than 0.5 mL in 98%. Patients who harbor such low-grade, low-volume tumors probably do not need to be treated. Ideally, these tumors would never be detected, but if identified they would be best served by active surveillance. As I will describe, men with such tumors are not the majority of patients in whom cancer is being detected by systematic biopsies.

The ability of a systematic prostate biopsy to predict final pathologic findings after prostatectomy is an area of major concern. In our series of patients who underwent radical prostatectomy, Gleason 6 tumors at biopsy were upgraded after radical prostatectomy 63% of the time.[3] Drs. Lepor and Donin cite their institution’s study (by Mufarrij et al)[4] of men who met active surveillance criteria but were treated with radical prostatectomy. In other words, these men had primarily small-volume Gleason 6 tumors. Nearly 50% of men with Gleason 6 tumors on biopsy had pattern 4 or 5 disease at prostatectomy, and approximately 10% had extracapsular extension. How are we to predict the pathology of these tumors, which are often multifocal and often heterogeneous between foci? Drs. Lepor and Donin refer to the use of magnetic resonance imaging (MRI) to rule out high-grade disease. I would submit that multiparametric MRI is an emerging technology that holds great promise. However, I do not believe that it has reached the point at which it can detect significant prostate cancer with the needed degree of certainty and predict the biologic potential of these tumors.

Even if we could rule out the presence of pattern 4 and 5 disease in biopsy specimens, it is doubtful that all Gleason 6 tumors follow a benign course. In the New York University (NYU) Gleason 6 prostatectomy series cited in the article, there were very few biochemical recurrences.[5] Yet it is not clear whether this means that the tumors would have followed an indolent course if left untreated. In this study 7% of patients had tumor in more than 20% of the specimen. Furthermore, 7% of the tumors exhibited extracapsular extension. These are different tumors from those seen at autopsy. In other tumor grading systems, there is evidence for progression from low-grade lesions to invasive carcinoma. The progression of colon cancer from polyp to invasive carcinoma through an accumulation of genetic mutations has been well documented.[6] An equally plausible conclusion from the NYU study would be that patients with significant-volume Gleason 6 disease have a limited window of curability with surgery before local extension or metastatic disease develops.

Finally, the pattern of cell growth (which the Gleason score reflects) is a relatively crude predictor of tumor behavior. Molecular profiling of tumors is becoming a reality. This profiling will soon allow us to assess the growth and metastatic potential of prostate cancers in ways that would have seemed inconceivable only a few years ago. This technology will allow us to stratify tumors in more meaningful ways. Not only will we observe more tumors, but in addition, treatments will be based on these profiles.

In the meantime, how are we to proceed? While there is no doubt that many indolent prostate cancers have been treated, it is unclear where one should draw the line between indolent and aggressive tumors. Numerous groups have defined clinical parameters that describe characteristics of patients with tumors similar to those found at autopsy (ie, Gleason 6 tumors of < 0.5 mL).[7,8]
This seems an appropriate place to start for now. These patients should be placed on active surveillance protocols, ideally associated with clinical trials. Unfortunately, for the time being, these patients need to be followed up with serial biopsies because of the inexact targeting of systematic biopsies and our inability to predict the natural history of even small tumors. Many of these active surveillance studies have specimen repositories that will allow correlations between long-term clinical outcomes and biomarkers in the blood, urine, and prostate tissue. Such correlations will one day allow us to expand the indications for active surveillance.

In the very near future there is hope that the current paradigm will change. We need better screening tests, which will detect clinically significant cancers but not small indolent tumors. Many new blood and urine markers are being evaluated. We need better imaging, which will show us the regions of interest and allow targeted biopsies. Multiparametric MRI with the technology to fuse MRI and ultrasound images is here. Finally, we need molecular markers that will be better predictors of tumor behavior. Many are in various stages of evaluation. The paradigm will change sooner than most think. Then we will be able to accurately draw the line between those who should be treated and those who should be observed.

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References:

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