The Treatment Paradigm Shifts Again on Prostate Cancer

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Prostate cancer has frustrated and challenged clinicians for >100 yr. Although infrequently recognized until 1890, when Von Recklinghausen reported that bone metastases often originated from the prostate, advanced prostate cancer has historically been viewed as carrying a poor prognosis. Although Hugh Hampton Young is credited with developing the radical perineal prostatectomy during the early 1900s, he performed the surgery infrequently. The perineal approach to the prostate was much more widely used to implant radium pellets to shrink locally advanced disease. Bowel complications limited the dose that could be applied. Barringer, a prominent New York urologist, recognized that most men presented with advanced disease, and he advocated screening with regular digital rectal examinations so that the disease could be treated much earlier.

This paradigm changed following Huggins’ report in 1941 that prostate cancer was an endocrine-dependent tumor. For the first time, men with advanced prostate cancer could obtain relief from painful bone metastases and obstructive local disease. Growing interest in the appropriate management of prostate cancer led to the Veterans Administration Cooperative Urologic Research Group trials. These studies clarified the appropriate role for estrogen therapy in men with advanced disease but never accrued sufficient numbers of men for trials investigating localized disease. These efforts established the significance of the Gleason histology classification system and demonstrated the wide variability of disease progression. Men with well-differentiated disease often survived for many years without symptoms, whereas men with poorly differentiated disease generally had a poor prognosis.

Treatment paradigms changed again during the 1960s after Bagshaw reported improved clinical outcomes associated with external-beam radiation therapy. He argued that prostate cancer could be cured if all disease was irradiated. He recognized the importance of staging prostate cancer accurately and the need to treat disease localized both in the prostate and in pelvic lymph nodes. In the early 1980s, Walsh promoted this concept by popularizing the surgical treatment of this disease. He demonstrated techniques for controlling pelvic bleeding and for performing a more anatomical dissection. As morbidity associated with treatment declined, more men sought treatment. Unfortunately, surgeons still frequently encountered lymph node metastases and positive prostate margins.

Prostate-specific antigen (PSA) changed the treatment paradigm again in the late 1980s. Stamey and McNeal demonstrated that serum PSA levels correlated with tumor volume, and Catalona showed that men with PSA values >4.0 ng/ml had a high incidence of prostate cancer. Many clinicians advocated annual PSA testing based on the theory that early treatment of localized disease would lead to cure, thereby eliminating prostate cancer as a lethal disease. In North America, screening for PSA was rapidly adopted and the number of newly reported cases doubled in <1 decade. Declining prostate cancer mortality rates during the past several years have added support for this approach [1].

But several other changes have occurred in North America over the past 2 decades as a consequence of
annual PSA testing. The number of men found to have one or two cores positive for minimal quantities of disease with a Gleason score of 3 + 3 has increased dramatically. Furthermore, low-grade prostate cancers (Gleason scores 2–5) have effectively disappeared as pathologists have become hesitant to assign lower scores [2]. Data from the Finasteride chemoprevention trial revealed a high prevalence of prostate cancer among healthy men with normal PSA values [3]. The trial showed that, among men with serum PSA values <4.0 ng/ml, as many as 20% had microscopic evidence of prostate cancer, of which the majority was categorized as Gleason 3 + 3 disease. The evidence is now inescapable: Annual prostate cancer testing results in serious overdetection and overtreatment of this disease. As a consequence, some clinicians have questioned whether all men with incident prostate cancers require treatment, and they have advocated a new treatment paradigm of active surveillance for men diagnosed with low-volume, low-grade disease.

During the past 2 decades, Europeans have been more hesitant to embrace PSA screening. Rather than simply adopting annual PSA testing without proof of efficacy, many leaders in urology chose to participate in the European Randomized Study of Screening for Prostate Cancer (ERSPC) [4]. After >10 yr of follow-up, multiple publications have expanded our understanding of the natural history of this disease. This issue of European Urology adds to this impressive collection of research.

Van den Bergh et al have explored the outcomes of men diagnosed with low-volume disease with a Gleason score of 3 + 3 [5]. They applied previously suggested criteria for active surveillance protocols to a group of men diagnosed with prostate cancer between 1994 and 2007 as part of the ERSPC trial and tracked their outcomes. Their findings are consistent with previous reports, and they add a large number of patients to this growing body of literature [6]. Men with clinically localized disease, ≤2 positive cores, Gleason 3 + 3 disease or less, PSA levels ≤10 ng/ml, and PSA density ≤0.2 ng/ml at diagnosis had excellent outcomes. The 10-yr prostate cancer-specific survival was 100%, and the overall survival rate was 77%. By adopting this approach, one-quarter of the men diagnosed with low-volume, low-grade localized disease were spared intervention, and there were with no serious consequences for the remaining men over a period of 10 yr. Outcomes were not compromised among those men seeking delayed interventions. These data support the concept that not all men require immediate treatment for localized prostate cancer.

Equally important was the observation that about half of the men who initially embarked on this regimen chose to undergo either surgery or radiation within 2 yr of diagnosis. Most of these decisions reflected anxiety over disease progression rather than objective evidence of disease progression. This is also very similar to previous reports. Men are anxious about developing metastatic prostate cancer, even when the probability is very low. They also assume that treatment offers a significant benefit. How should we deal with these results?

First, we must increase our understanding of the natural history of prostate cancer detected by screening. We cannot simply assume that all cancers found on biopsies driven by an elevation of PSA level are lethal and that excellent outcomes are the result of intervention. Despite advances in genetic testing, the Gleason score is still the best predictor of long-term prognosis. Data from multiple observation series demonstrate that high-grade prostate cancer carries a significant risk of disease progression [7]. The natural history of contemporary Gleason 3 + 3 disease, however, appears to be much more benign. We need more data from active surveillance protocols to advise our patients confidently that low-grade prostate cancer (Gleason 3 + 3 or less) can be monitored successfully.

Second, we need more data from randomized trials to understand the relative impact of treatment. Claims that treatments such as surgery, radiation, or thermotherapy are effective simply because patients have no evidence of progression are not sufficient. The most recent report from the Swedish randomized trial limited to men aged <65 yr at diagnosis compared a cohort receiving radical prostatectomy with a cohort undergoing watchful waiting, and only a modest improvement with surgery was shown [8]. After 12 yr of follow-up, overall survival was not statistically different between the two cohorts. The rate of prostate cancer mortality was 13% in the treatment arm and 18% in the control arm, suggesting some effect from surgery, but the impact was modest. Would these same results be achieved in a population of men with screen-detected prostate cancer? Hopefully the ProtecT (Prostate Testing for Cancer and Treatment) trial will provide answers within the next decade [9].

Third, we need to examine our screening practices carefully. The ERSPC study is poised to provide important new data concerning the efficacy of testing PSA level. Whether the trial shows a benefit from a population-based perspective or not, patients and clinicians will continue to order serum PSA tests. Hopefully data from the ERSPC study will guide clinicians concerning who needs to undergo biopsy
and who can be monitored safely. Once a patient undergoes prostate biopsy and is told that he has cancer, it is very difficult to suggest doing nothing. Algorithms based on Gleason scores, PSA-level kinetics, and, hopefully, new biologic markers should help patients and clinicians choose optimal treatment pathways that include active surveillance as a treatment alternative.

Finally, we need to collect more population-based outcomes data. European health care systems are better suited for this purpose. Data from the US Surveillance, Epidemiology and End Results (SEER) program linked to Medicare files have provided important insights, but data are limited to men aged >65 yr and lack critical information such as accurate Gleason scores and PSA values [10]. Until recently, the management of prostate cancer has been guided by much heated opinion but relatively little information. Contributions by researchers such as van den Bergh et al [5] provide important new evidence that helps guide our efforts to treat patients appropriately.

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References


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In his editorial in this issue of European Urology, Peter Albertsen [1], who is a pioneer and expert in studying the natural course of prostate cancer, supports the conclusions in our paper [2] that not all men with screen-detected early prostate cancer should be treated radically at the outset. We feel honoured by this support from overseas, and we would like to briefly discuss some additional points of view on this important topic.

Screening advances the moment of diagnosis of prostate cancer. The lead time differs based on stage and grade of the disease that is detected [3]. The intuitive assumption that screening reduces mortality by bringing forward the moment of diagnosis and resulting reduction of the stage and grade of detected tumours must still be confirmed by potential evidence from ongoing randomised controlled trials, such as the European Randomised Study of Screening for Prostate Cancer (ERSPC) [4]. Yet, regardless of the outcomes of these trials, PSA testing will remain common practice.

Some of the tumours that are detected due to screening would have surfaced later during the life