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How Best To Use Our Tools?

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Last October, the US Preventive Services Task Force stunned the urologic community by suggesting that screening for prostate cancer (PCa) using prostate-specific antigen (PSA) testing provided few benefits and caused considerable harm [1]. The task force's analysis claimed that excessive numbers of men were being subjected to transrectal ultrasound (TRUS) and biopsies and that too many men were being diagnosed with PCa that did not appear to carry any lethal potential. The task force concluded that we may be lowering PCa mortality in a few men, but the collateral damage is excessive.

These findings came as no surprise to many epidemiologists. They have learned that the seductive concept of early diagnosis and treatment frequently does not achieve the goals intended. One famous study based on this concept was the South-East London Screening Study [2]. This study was set up by the UK Ministry of Health in response to a movement supported by public health practitioners to provide multiple screening studies to middle-aged adults in general practice offices. The study randomized approximately 7000 participants into two groups: One group received two screening checks 2 yr apart, and the other group received no screening. All participants underwent a health survey at the end of the study. Detailed analysis of the data showed no significant differences between the two groups in terms of their morbidity, hospital admissions, sickness, or mortality. The only difference the UK ministry could detect was the difference in costs. Screening cost an additional £142 million. The conclusion: Just because screening should work does not mean that it does. Several cancer-screening trials have also failed to show a significant impact on disease-specific mortality.

What tools do we use to screen men for PCa? Primarily two: PSA kinetics and prostate biopsies. We have learned that these two tools work well in a population of men that

has a high prevalence of advanced disease, but the tools' performance declines markedly when used in screening programs in which the prevalence of disease is only 1–3%. The positive predictive value of PSA testing was only 24% for the men presenting for screening in the European Randomized Study of Screening for Prostate Cancer (ERSPC). The PSA test leads to too many false-positive results. The subsequent confirmatory test, TRUS and prostate biopsy, also has problems. The test either finds too many indolent low-grade cancers or misses the high-grade cancers located in the anterior region of the prostate or surrounding the apex.

During the last decade, the urologic community recognized that PSA testing has led to an excessive number of men being diagnosed with PCa. The Prostate Cancer Prevention Trial revealed that there is an enormous pool of low-grade PCa present in men with normal PSA values [3]. We often tap into this pool as PSA values rise in men. Historically, we have viewed all these cancers as potentially lethal, but there is a growing recognition that many of these lesions are indolent. Both the ERSPC study and the Göteborg study have shown that PSA testing leads to significant increases in the number of men diagnosed with PCa [4,5]. Most of the additional cases are classified as Gleason 6 disease. This disease grade carries the lowest potential for progression. The number of men who present with Gleason ≥ 7 disease is almost comparable in both arms of these studies. In the ERSPC study, after 8.8 yr, 5.1% of men in the control arm and 5.2% of men in the screened arm had Gleason 7 cancers or higher. In the Göteborg study, after 14 yr the numbers were 5.0% and 5.7%, respectively.

Given that PSA testing identifies an excessive number of men with potentially indolent Gleason 6 tumors, how has the urologic community responded? Several researchers have proposed the concept of active surveillance— withholding treatment from men who are deemed to have

disease that is unlikely to progress. What tools do we use to monitor this group of patients? Precisely the same tools that we know work poorly in a population of men with low prevalence of disease. Do the tools work any better among men choosing active surveillance? Ideally, we should obtain an answer from a randomized trial, but because such a trial is unlikely to occur, we look for insights from case series reports such as the one published by Bul et al. [6]. They looked at outcomes for 2079 men enrolled in the Prostate Cancer Research International: Active Surveillance (PRIAS) program. This is an online registry of men who meet the criteria to be enrolled in an active surveillance program. Bul et al. analyzed a subset of this case series, a group of 446 men who had undergone radical prostatectomy a median of 1.3 yr after enrolling in the program. These patients were advised to undergo surgery because they met a pathologic or PSA kinetic criterion of disease progression. The authors found that approximately 70% of these patients had organ-confined disease, but 30% of the patients had unfavorable disease characteristics: pT3–4, Gleason 4 + 3. Because the repeat evaluations occurred within a relatively short time after the initial diagnosis, presumably these results reflect a reevaluation of 22% of the PRIAS men who were felt to have progressed.

How should we interpret these findings? We can either conclude that we have a relatively good method for identifying men who are candidates for active surveillance because most men had organ-confined disease or we can conclude that we have an imperfect method that fails to identify men with clinically significant PCa. The astute epidemiologist will recognize that we are arguing a sensitivity/specificity problem. Increasing the sensitivity of the method (ie, more extensive and frequent biopsies) will risk overtreatment of indolent PCa, which is precisely what active surveillance tries to avoid. Increasing the specificity will miss more clinically significant cancers. We are essentially back where we started because we have failed to understand the natural history of screening-detected disease and are unsure which patients need treatment.

The main message coming from the paper by Bul et al. is that we have relatively poor tools to identify clinically significant PCa. While trials have shown that screening reduces PCa mortality, the absolute reduction is modest. In the ERSPC study, after 8.8 yr, mortality was 0.365% in the control arm compared with 0.294% in the screening arm—a difference of fewer than 1 man of every 1000 men screened. After 14 yr, the difference was somewhat greater. The mortality rate in the Göteborg study was 0.784% in the control arm and 0.442% in the screened arm—a difference of approximately 3.4 men of every 1000 men screened.

What should we do? We must continue to learn from the randomized screening trials. It is hoped that the ERSPC and Göteborg studies will define a population of men in whom

PSA testing will lead to dramatic declines in PCa mortality during the next decade. We must stop screening older men who are unlikely to benefit from PSA testing, or we risk losing funding for screening, similar to the South-East London Screening project. Fortunately, two major studies currently being conducted in the United Kingdom—the Prostate Testing for Cancer and Treatment (ProtecT) trial, which has enrolled >1500 men, and the Comparison Arm for ProtecT (CAP) screening trial, which has enrolled >400 000 men—should provide additional insights into the natural history of screening-detected disease when they report results in 2016 [7].

In the interim, we should explore other ways to use our tools. PSA may be a good initial screening tool, but the confirmatory tool, TRUS, is not sufficiently selective. Maybe we should consider imaging the prostate first and limit our biopsies to men who have evidence of clinically significant nodules. Maybe imaging, rather than PSA kinetics and repeat biopsies, should be the tool to monitor men on active surveillance. Many researchers are currently exploring these concepts. In the end, however, these approaches will need to be tested in a randomized trial, because that is the only way we can understand the real value of any diagnostic tool or treatment or screening program.

Conflicts of interest: The author has nothing to disclose.

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