Prostate Cancer: Is it all just hype?

Prostate cancer, its screening using prostate-specific antigen (PSA) and management are among the most controversial topics in medicine today. The prominence of this disease and the interest it generates stem from a few important facts. Prostate cancer is the most common non-skin cancer diagnosed in men in the USA, where the lifetime risk of diagnosis is nearly 16% with a 2.8% lifetime risk of dying from it. In the USA, nearly 100,000 radical prostatectomies are done every year and over 85% of these are robotic. In fact, radical prostatectomies are the major drivers of robotic systems in most hospitals. US Medicare reimbursements for androgen-deprivation therapy using gonadotrophin-releasing hormone (GnRH) agonists cost over US$ 1 billion in 2001, which was the second largest expenditure for Medicare Part B that covers outpatient prescription drugs, and is steadily increasing. Without doubt medical research, literature and practice patterns around the world are largely driven by what happens in the USA.

Prostate cancer is asymptomatic in its early, curable stages. It can only be diagnosed through biopsies in those who are clinically suspected to have cancer. This suspicion may be aroused by the findings on digital rectal examination—a low sensitivity test. The discovery of PSA, and the associated detection of early prostate cancer on biopsies triggered by an elevated PSA, led to a rapid increase in its clinical use. However, PSA itself has a low specificity and leads to a large number of negative biopsies, up to 80% in men with PSA levels of 4–10 ng/ml. An elevated PSA results in anxiety and biopsies are associated with complications. This has led to questions regarding the utility of PSA in screening for prostate cancer.

The other issue relates to the need and benefit of intervention in patients with prostate cancer. The natural response of both patients and physicians to a diagnosis of cancer would be to make every attempt possible to remove the disease and achieve cure. For prostate cancer, the answer is not so simple. This is because prostate cancer is a frequent occurrence, does not always progress and certainly does not always kill. The majority of deaths from this cancer occur in men above the age of 75 years. Independent autopsy studies by Rich and Franks noted that pathological prostate cancer was common and existed in nearly all men by the age of 99 years. The high prevalence with low mortality suggests that the disease rarely kills. The inevitable question then is: Does it need to be treated? The question becomes even more relevant because the methods of treatment, radical prostatectomy or radiation, are expensive and associated with significant complications that limit quality of life. If it is simply a condition that ‘peacefully coexists’, there may be no need to treat it and therefore no need to make any attempt to diagnose it.

Two contradictory papers on the natural history of prostate cancer that were published at almost the same time highlight the dilemma. In 2004, Johansson et al. reported outcomes of 21 years of follow-up of untreated, early stage prostate cancer. These men, with clinically diagnosed early stage prostate cancer, did not receive any treatment until they developed metastasis; 223 men who fulfilled the eligibility criteria were followed up until the end of study or death with no loss to follow-up. Forty percent patients had disease progression, 91% died during the study period with 16% due
to prostate cancer, suggesting significant morbidity and mortality due to untreated disease. These data were different from their earlier report on 15 years of follow-up of the same cohort and showed that prostate cancer becomes an important cause of mortality in men who survive 15 years beyond the diagnosis. Further, they noted significant local morbidity due to disease progression and concluded that early treatment should be recommended for men with longer life expectancy. The other study in 2005 looked retrospectively at the 20-year survival data for conservatively managed localized prostate cancer in Connecticut, USA. Among 767 subjects, the authors noted no difference in mortality rates from prostate cancer before or after 15 years after adjusting for histology. Men with low-grade disease had minimal disease-specific mortality in 20 years while those with high-grade disease had high mortality within the first 10 years. The authors concluded that data were still unclear on the need for surgery in men with prostate cancer and hoped that three ongoing trials would resolve the issue. Data from all the three trials are now available but, unfortunately, these simply confound the issue further.

One of the first reports comparing radical prostatectomy with observation alone was published in 2005. This study of 695 men with clinically localized prostate cancer who were randomized to radical prostatectomy or observation, at a mean of 8.2 years, reported a 44% reduction in disease-specific mortality, 40% reduction in distant metastasis and 67% reduction in local progression after radical surgery. Radical surgery appeared beneficial at 10 years of follow-up and was likely to provide greater advantage to men who lived longer than 10 years after diagnosis, a conclusion supported by their more recent report on longer follow-up. In the PSA era, the Prostate Cancer Intervention versus Observation Trial (PIVOT) study is the largest trial attempting to address this issue. For 8 years (1994–2002), investigators at 52 centres in the USA randomized 731 men with localized prostate cancer suitable for radical prostatectomy to surgery or observation. All-cause mortality was assessed as the primary outcome with prostate cancer-specific mortality as the secondary outcome. At the end of the study, with a median follow-up of 10 years, mortality in the surgery group (47%) was no different from that of the observation group (49.9%; HR 0.88; 95% CI 0.71–1.08). Prostate cancer-specific mortality was non-significantly lower in the surgery group (5.8% vs. 8.4%; HR 0.63; 95% CI 0.36–1.09). Risk reduction for all-cause mortality in men with PSA >10 ng/ml was 13.2% (HR 0.67; 95% CI 0.48–0.94). This reduction was 31% for men with intermediate-risk tumours (HR 0.69; 95% CI 0.49–0.98). The authors concluded that there was no advantage of surgery over observation in reducing all-cause or prostate cancer-specific mortality in men with localized prostate cancer as a whole but suggested a potential benefit of surgery in men with higher PSA (>10 ng/ml) and high-risk disease.

The large amounts of time and money spent on prostate cancer despite publications that doubt its necessity and the much lower incidence in other parts of the world including India (9/100 000 population) have been an ideal recipe for debate and denunciations. The PIVOT study, along with the two PSA screening studies and a recent report by the US Preventive Services Task Force (USPTF) recommending against routine PSA screening in all men has fuelled this debate.

So, does this mean that prostate cancer needs no treatment? There are a number of problems in generalizing the results of the PIVOT study, the most important being the population that it addresses. The subjects were recruited from US Veterans, 90% were >60 years of age and suffered from a number of comorbid conditions (45% had Charlson comorbidity score of >0). This is reflected in the overall high mortality in both arms of the study (47%–49.9%). Since a large proportion of men were dying of competing causes within 10 years of treatment, there was little opportunity to show the benefit of surgery which is uniformly recommended only if the patient is likely to survive beyond 10 years. The study also excludes younger men who are diagnosed with cancer in their forties and fifties and may benefit the most from intervention. The authors aimed to recruit over 2000 subjects but had to stop at 731 men due to poor participation. The revised statistical calculations did not allow detection of smaller benefits. Despite these limitations, there was a trend towards benefit for men with
intermediate- and high-risk disease and a statistical advantage for men with PSA >10 ng/ml.12

What does seem clear from these data is that a large proportion of prostate cancer that is detected does not need treatment. Low-grade disease in men with limited life expectancy deserves observation and even those with 15 years or more to live may be appropriately managed with surveillance. This, in fact, is a well-established clinical paradigm reflected in all major treatment guidelines for prostate cancer.19,20 The problem is primarily with younger men and those with aggressive disease that is localized to the prostate. While the existing data point to an advantage of surgery in these men, no study answers these questions directly. The PIVOT trial did not recruit enough fit, young men to address it while data from the earlier natural history studies would suggest that men, with life expectancy of >10–15 years, are most likely to suffer disease progression or death.9

If we accept that some men do need treatment for their prostate cancer, how do we identify them? PSA continues to be the only test that can identify at least a cohort that is more likely to have cancer than the general population. Despite its limitations, is it justifiable to discard the test simply because it is not perfect? A more pragmatic approach would be to understand its limitations and harness it to the best possible use. The current debate centres on the word ‘screening’ that has public health and policy implications. Accepting ‘screening’ would mean offering it to all eligible individuals and a potential liability for healthcare providers who do not do so. It also means that insurance firms and governments are obliged to reimburse for it. The question of screening is most pertinent in the USA and other western countries where the incidence of prostate cancer is 20 times more than that in India. The low incidence in India clearly rules out any question of screening.21

If we outright reject screening for the Indian population, should we be resigned to diagnosing only advanced or metastatic disease? The answer lies in the recommendations of the USPTF itself that did not recommend routine PSA screening.1 The primary requirement is for physicians to understand the limitations of the test and be willing to discuss these with their patients for informed decision-making before offering it. The test will continue to be used for ‘screening’ as the patient is asymptomatic but would differ from the public health meaning of the term. Methods are required to subselect a PSA-screened population which has a higher likelihood of intervention-requiring disease. Ongoing efforts to improve case selection for biopsy may take time to mature. The use of additional tools such as PSA density, free PSA, metabolomics, magnetic resonance spectroscopy and predictive nomograms aim to select a population that will benefit most from biopsy and treatment.22,21 No doubt these tools are far from perfect and overtreatment continues to happen. However, it seems unjustified that we wait another 20 years for a randomized study in intermediate- and high-risk disease groups before offering treatment when the present evidence points in that direction.

REFERENCES


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