



Editorial – referring to the article published on pp. 37–44 of this issue

## Prostate Cancer: Are We Over-Diagnosing— or Under-Thinking?

J. Stephen Jones\*

9500 Euclid Ave St. A100, Cleveland, OH 44195, United States

Until the last two decades, detection of prostate cancer was so poor that early disease usually remained unrecognized, and approximately half of patients were incurable at presentation [1]. Following the advances of prostate-specific antigen (PSA) [2], systematic biopsy [3], extended biopsy [4], laterally focused biopsy [5], and population-based screening [6], we now have the tools to diagnose the overwhelming majority of significant prostate cancers at a curable stage. However, the success of these advancements has met with significant controversy or outright disapproval. Concern regarding “over-diagnosis” dominates most consideration of prostate cancer screening and detection, including the review published in this issue [7].

Exactly what is over-diagnosis? A literal interpretation would be diagnosis in excess of the actual disease under consideration. We certainly do not identify more cancer than exists and still leave many cases undetected with even the most aggressive screening and diagnostic strategies. The concept of over-diagnosis is literally unachievable—there is only diagnosis or misdiagnosis. However, unlike the past, the cancers we miss now are usually small and will probably be curable if or when detected during subsequent surveillance.

The preceding review accurately describes the controversy and absence of level 1 evidence to conclusively support population-based screening. Nevertheless, as noted in the review, screening is now common and is often expected by patients even

in countries with an official policy discouraging its use. Moreover, the individual patient comes to us with one question, “Do I have cancer?” Our job is to answer that question—*honestly*. Failure to offer that answer using available diagnostic strategies is tantamount to deception. For example, reassuring a man with a PSA of 3.1 that he does not have cancer is inaccurate. He actually has a 26.9% chance of sextant biopsy identifying prostate cancer [8]. Telling a man with an elevated PSA that has undergone a single negative sextant biopsy that he does not have cancer is just as deceptive. He has a 39% chance of finding prostate cancer using an extended biopsy [9]. Regardless of the nobility of underlying intentions, can we really justify these misdiagnoses?

It has been said that “ignorance is bliss,” but rarely does the field of medicine strive for failure by intentionally overlooking a cancer diagnosis. Doing so without allowing the patient to make a fully informed decision based on his individual risk undermines the trust our patients put in us. Failing to provide patients with information required to make a decision on screening and diagnosis invites scrutiny of the legal system for intentional failure to diagnose cancer. Hoping we overlook the “right” cancer instead of missing the dangerous one is a step on a slippery slope.

A number of studies have sought to determine the risk of over-detection. Graif et al recently concluded that there was a 1.3–7.1% risk (which they termed “over-diagnosis”) in 2126 patients who underwent

radical prostatectomy. However, they also found a 20–30% chance of under-diagnosis in their heavily screened series, demonstrating that more significant cases elude early detection than do low-risk cases that are treated with radical prostatectomy [10].

Until diagnostic strategies arise that limit identification to “clinically significant” (whatever that means—consensus has been elusive) cases, it is not acceptable to simply hope that we fail to find prostate cancer. Doing so unilaterally is equivalent to treating our patients as children. Keeping your child from knowing that dangerous people lurk in your city may be acceptable. Telling your adult patient that no dangerous cancer lurks inside his prostate when the data clearly define a risk is not.

But why would one object to detection of all prostate cancers? The answer lies in the fact that most of these cancers will never become harmful. In contrast, treatments administered may certainly cause harm, and even the knowledge of the cancer’s existence may harm the patient (through anxiety or unnecessary diagnostic tests and treatments) who would have otherwise been in ignorant bliss. Thus, although *over-diagnosis* is impossible, concern for *over-detection* has unequivocal merit, and risk of *over-treatment* is all too real.

So how do we move forward? I believe it is by taking the advice of Carroll, who espoused the concept of “unlinking detection and treatment, as they are separate processes” [11]. Critics of active screening and diagnostic strategies may dismiss this solution by accurately observing that the overwhelming majority of men diagnosed with prostate cancer are promptly treated, and even those who initially embark on a strategy of active surveillance often proceed to treatment. Sometimes the reason for exiting the surveillance group into active treatment is disease progression, but often it is based on nonspecific reasons such as doctor or patient anxiety, resulting in potentially unnecessary treatment [12]. In either case, failure to think through the actual risk of treatment versus that of disease progression may lead to improper treatment.

Critics note that the data on active surveillance strategies are limited. Considering it took almost a century before the first randomized controlled trial demonstrated a survival advantage for radical prostatectomy, criticism of supporting evidence for active surveillance should be tempered [13]. Klotz demonstrated a 99% 8-yr disease-specific survival using an active surveillance strategy in 299 low-risk patients, an oncologic success that would create a rush toward adoption if the strategy were a new operation or chemotherapeutic agent. I presently observe approximately one fourth of

newly diagnosed cases of prostate cancer, and the majority of those remain on an active surveillance protocol, avoiding treatment and its attendant morbidity. I have yet to observe a patient under careful surveillance progress to an incurable stage, although this risk is disclosed to each one.

A common concern with active surveillance regards irrational fear of medicolegal risk. Our responsibility is to interpret all the information that should drive every medical decision. Excluding active surveillance from the options offered for management of low-risk localized prostate cancer is at least as medicolegally hazardous as is insisting on treatments associated with significant impact on quality of life without clear evidence of improvement in overall survival. Moreover, the same physicians fearing litigation if active treatment is foregone are often ironically comfortable with missing the diagnosis of prostate cancer as described above.

As a middle ground between no treatment and radical treatment, significant interest has developed for subtotal (or focal) treatment. Hall et al found that pathologic evaluation of the index tumor accurately predicted the clinical behavior of the entire gland regardless of synchronous tumors in > 90% of patients [14]. Villers et al showed that 80% of secondary tumors are < 0.5 cc, a common criterion for depiction of clinical insignificance [15]. Rukstalis et al found that the median ancillary lesion size was only 0.3 cc and concluded that 79% of men would likely have significant cancer eradicated if the index cancer was targeted [16]. To date, only very small case series using subtotal cryotherapy or high-intensity focused ultrasound (HIFU) have been published, but a significant increase is expected in the foreseeable future [17,18].

So what is the right approach now to prostate cancer screening and diagnosis? I believe the answer must incorporate more honesty toward ourselves and our patients. We should:

- Acknowledge that prostate cancer is present in a significant portion of the male population, increasing with age [19], but will remain asymptomatic and harmless in the overwhelming majority of cases whether it is detected or not [20].
- Concede that screening often leads to biopsy, further diagnostic tests, and treatments associated with significant morbidity with limited, albeit growing, evidence of an impact on survival.
- Conclude that there is no legitimate PSA cut-off point.
- Demand that our laboratories eliminate any artificial PSA cut-off value when reporting results. A threshold is scientifically and statistically

baseless in the screening or diagnosis setting and is completely meaningless for any patient who has undergone treatment for prostate cancer. Flagging PSA results as “normal” or “abnormal” is no longer justifiable.

- Acknowledge the limitations of our ability to determine which cancers might cause morbidity or mortality instead of hoping the cancers we miss were the ones we wanted to miss.
- Allow patients armed with the above knowledge to determine whether they would wish to know if prostate cancer is present.
- Inform patients who choose screening of their individual probability of harboring prostate cancer based on PSA level interpreted in a broad clinical context, including age, race, family history, digital rectal examination, prostate size, results of prior biopsy, and use of 5 $\alpha$ -reductase inhibitors. Only then should they consent to biopsy.
- Offer all viable management options to patients with a positive biopsy, but include full disclosure of side effects of treatment and data showing that the overwhelming majority of prostate cancers will not be clinically threatening, regardless of treatment.
- Offer active surveillance as a viable management strategy for more patients with Gleason sum  $\leq 6$ , and plan for delayed intervention based on a change in their risk of clinical impact such as PSA or biopsy-proven change in Gleason score or tumor volume. This approach for patients with Gleason sum  $\leq 7$  potentially carries more risk, but may be appropriate in selected cases.
- Think more!

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