Re: Overdiagnosis and Overtreatment in Cancer: An Opportunity for Improvement

Esserman LJ, Thompson IM, Reid B

JAMA 2013;310:797–8

Expert's summary:

One of the major goals of improving the survival rate for many common cancers has been seeking an earlier diagnosis. The concept has been that if we can diagnose cancers earlier, we can treat them before metastasis occurs, and the survival rates will increase. Unfortunately, despite the rapid introduction and use of prostate-specific antigen (PSA) testing, chest and abdominal imaging, mammography, and so forth, there has been an increase in diagnosis of cancers but not a corresponding improvement in survival rates. Too many "indolent" cancers are being found, with a significant amount of overtreatment. The viewpoint editorial by Esserman et al. (one of the authors, I.M. Thompson, is a urologist) presents a summary from a National Cancer Institute (NCI) brainstorming conference held in March 2012.

The authors made some important recommendations. First, physicians, patients, and the general public must understand the problem and consequences of overdiagnosis related to cancer screening. The authors specifically mention prostate screening, along with breast and thyroid screening, as a problem. Second, the term *cancer* may not be justified or appropriate for some of these "lesions" we now identify as cancer. The latter term should be reserved for lesions with a reasonable chance of lethal progression if left untreated. Of course, the authors advocate for molecular markers that would differentiate between benign-acting neoplasms and neoplasms that have the potential to invade and metastasize (ie, cancers). Until such reliable markers arrive, the nomenclature might be changed. The authors suggest that some of these lesions could be called *indolent lesions of epithelial origin*, or *IDLE*. They site the grade 1 papillary tumor now called a PUNLMP (papillary urothelial neoplasm of low malignant potential) as a prime example of avoiding the "C" word. Third, large observational data sets or registries should be created for these lesions of low malignant potential to further emphasize the low risk of active surveillance (AS). Fourth, overdiagnosis should be mitigated by focusing screening on high-risk populations and avoiding detection of inconsequential neoplasms.

Expert's comments:

I was delighted to see the NCI take the lead in bringing this topic to the forefront. After this viewpoint was released, it was the lead story in the U.S. evening news, and there was a lead article on the front page of the *New York Times.* The topic of overdiagnosis and overtreatment is open for broad discussion now more than ever.

It is my view that the opportunity for change in this area is more likely to occur in countries that have a national health care system with recommendations on treatment given certain clinical details than in a less controlled environment like that of the United States, where there are fewer limitations on what the physician can do and receive compensation for. For example, a patient can receive proton-beam irradiation ($100 000) or external-beam irradiation ($\geq$$20 000) for a small focus of Gleason score 6 prostate cancer (PCa) regardless of his age or comorbidity, and insurance will pay for it. Patients with a history of a low-grade small papillary bladder tumor may be taken to the operating room for resection of a small, apparently low-grade, new tumor and then undergo cystoscopy every 3 mo indefinitely regardless of the development of additional tumors. The alternative treatment for this IDLE lesion would be office fulguration or AS and further monitoring, depending on the growth and appearance of new lesions.

Urology should promptly enter this discussion. We identify and manage three common tumors that fall into the category of lesions with low malignant potential: small-volume Gleason 6 PCa, low-grade (grade 1) Ta papillary bladder tumors, and small renal masses. I am not stating that we can accurately predict in each case that AS is the best option for all patients with these lesions, but the possibility should enter the discussion with all these lesions.

There is ample evidence, for example, that low-grade bladder tumors rarely metastasize, and patients who develop these tumors infrequently develop a new tumor that is high grade and invades the bladder, thus threatening the life of the patient. Guidelines now indicate that AS is an alternative for the small, recurrent, low-grade papillary tumor [1,2]. Office cautery is a reasonable alternative. Trips to the operating room should be avoided because of the expense and added morbidity of transurethral resection. Bacillus Calmette-Guérin should be avoided as first-line adjuvant therapy. Upper tract monitoring is unnecessary. These are but a few examples of areas in which urologists have taken the lead in one particular IDLE lesion. It is hoped that these recommendations will be followed by all urologists as we emphasize the important issues of how to effectively screen for high-grade, potentially lethal bladder cancer (BCa), consider neoadjuvant chemotherapy for cT3 BCa, and accelerate the delay between diagnosis of high-grade muscle-invasive BCa and cystectomy or chemotherapy and/or irradiation.

Although the subject of AS for low-volume Gleason 6 PCa has its proponents and ever-increasing data from several institutions indicate the very low chance of metastasis and death in men who enter an AS program, there are those practitioners who stress that early diagnosis and treatment remain the standard of care because of the inability of current techniques to exclude a higher-grade cancer in these patients [3]. The dialogue should continue, and patients should hear both sides of the discussion. Often they do not [4].

The use and misuse of PSA has been played out in the academic arena, at our national meetings, and in the popular press. My view is that PSA and some of the other markers of PCa are imperfect, but they are wonderful tools to allow us to identify and cure men with high-grade clinically localized PCa and many men with high-volume Gleason grade 6 cancer who would not have been so fortunate in the pre-PSA era. The discussion needs to concentrate, as it has more recently, on how to avoid the morbidity of overdiagnosis and overtreatment. The recently released American Urological Association guidelines on PSA are a move in that direction [5].

Conflicts of interest: The author has nothing to disclose.

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Re: Use of Advanced Treatment Technologies Among Men at Low Risk of Dying from Prostate Cancer

Jacobs BL, Zhang Y, Schroeck FR, et al.

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Expert's summary:
Using the Surveillance Epidemiology and End Results database, Jacobs et al. evaluated the use of high-tech treatment modalities in men with prostate cancer (PCa) at low risk for disease-specific mortality. Risk categorization was based on having low-risk tumor variables or significant competing comorbidity. The use of either intensity-modulated radiotherapy or robotic prostatectomy among low-risk men increased from 13% of treatments in 2004 to 25% of treatments in 2009. These increases largely represented substitution for prior standard treatments rather than an expansion of the number of patients undergoing treatment.

Expert's comments:
The forces underlying changes in disease management are multiple and interrelated. Improved outcomes, new technologies, evolving understanding of disease biology, patient demand, and/or physician self-interest are among the potential contributors. In the past decade, most, if not all, of these variables have factored into changes in PCa patient management.

Against this backdrop, what role does the physician play in the change process? It is the physician who serves as the lens through which these variables are focused onto the patient so as to arrive at a management approach. The physician, having the knowledge, influence, and opportunity, ultimately "colors the light" in a way that hopefully serves the needs of the patient. This is a powerful role, one that has brought physicians to the upper echelons of societal status.

Unfortunately, today this role and stature are threatened. Real or perceived abuse of influence for provider self-interest is eroding patient confidence and prompting governmental regulation. Self-referral, equity interests in treatment facilities, adoption of unproven technologies for market expansion, and the continued application of curative therapies to low-risk patients serve as examples. While the degree to which self-interest has contributed to the use of expensive new technologies is unclear, the application of these costly treatments to low-risk patients is troubling. Some studies suggest that the expansion of high-tech curative therapies, beyond simply serving as a substitute for arguably inferior approaches, is occurring against a backdrop of stable, if not declining, disease incidence [1].

The potential for physician behavior to be seen as self-serving is a corrosive force threatening to undermine the legitimacy of our profession. We have an obligation to ensure that the interests of the patient are paramount. As such, a proactive role for our societies in addressing physician self-interest is critical, not only for our specialty but also for the broader field of medicine.

Conflicts of interest: The author has nothing to disclose.

Reference

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Re: Long-term Outcomes of Patients with Lymph Node Metastasis Treated with Radical Prostatectomy Without Adjuvant Androgen-deprivation Therapy

Touijer KA, Mazzola CR, Sjoberg DD, Scardino PT, Eastham JA

Eur Urol 2014;65:20–5

Experts' summary:
In a recently published paper in *European Urology*, Touijer and coworkers noted that pathologic Gleason score, as well as the number of positive nodes, was significantly correlated with prostate cancer (PCa) outcome in one of the largest retrospective series of node-positive patients after radical prostatectomy (RP) without adjuvant therapy (369 consecutive patients). The study showed that for each year without biochemical recurrence (BCR), the probability of BCR-free survival increases annually to approximately 80% after 5 yr. The Gleason score and the number of positive nodes were important predictors of metastasis-free and BCR-free survival on multivariate analysis. The main message of the paper by Toujier and coworkers is that node-positive patients can have