

14 yr to 68 yr, but the results were reported without differentiating the outcome in adults and preadolescent boys. It is well known that the success rate of posterior urethroplasty in children is lower than in adults. The authors reported that prior urethral realignment failed in 12 cases but did not clarify whether the realignment was surgical or endoscopic.

Conflicts of interest: The author has nothing to disclose.

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Re: Mortality Results from a Randomized Prostate-Cancer Screening Trial

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Expert's summary:

The results of intention-to-screen analysis, which investigators in the Prostate, Lung, Colorectal, and Ovarian (PLCO) study initially conducted in their protocol, are presented, including some background data. The baseline contamination rates of prostate-specific antigen (PSA) screening during the 3 yr before trial entry was 44% in both cohorts. In other words, nearly half of the participants were prescreened with the PSA test at least once within the 3 yr before trial entry. If the baseline exposure rate is reset to 0%, the estimated contamination in the first year is 40% and increases to 52% in the 6 yr after trial entry.

While the amount of screening prior to randomization affected the event rate in both arms of the study, screening in the control arm affected the difference in event rates between arms. As a result, the number of patients diagnosed with prostate cancer in the screening cohort ($n = 3452$) was only 16% larger than that in the control cohort ($n = 2974$). This difference increased only slightly over time, with the lead time of the screening cohort being only 1.5–2.0 yr.

The stage distributions between the screening and control cohorts were identical. More important, even in the control cohort, the percentage of stage IV disease, which is strongly influenced by the level of exposure to PSA screening, was low at 2.7% (79 of 2974) and was almost the same as the screening cohort, which was 2.1% (73 of 3452). The crude number of patients with metastatic disease, which can be strongly related to death due to prostate cancer, was almost the same at the last follow-up in both cohorts. In fact, there was no significant difference in the development over time of the cumulative number of deaths due to prostate cancer between cohorts.

Expert's comments:

The main problem with the PLCO study could be contamination of the control cohort. It may have been impossible to conduct a proper screening trial in the United States because the exposure rate to PSA screening of men aged ≥ 50 yr was too high to start with and increased to about 75% during the time of recruitment [1]. The high contamination rates in the control cohort and the high rate of screening prior to randomization, which led to a decrease in advanced stages of prostate cancer in both arms of the study, resulted in a serious and uncontrollable flaw in the PLCO study. In Japan, where the exposure rate of screening was shown to be very low (between 5% and 10%) [2], 21% of patients present with distant metastases and 19% present with locally advanced disease (clinical stage T3b–4) [3]; therefore, the mortality due to prostate cancer has still increased, and there were estimated to be 9786 deaths in 2007 [4]. In addition, the percentage of metastatic prostate cancer cases in the control cohort in the PLCO study was $<3\%$. The control cohort in the PLCO study is clearly not appropriate as a nonscreening cohort. The cumulative exposure rate of PSA screening in the control cohort will increase in the future. Therefore, intention-to-screen analysis is not reasonable, and further follow-up in hope of reaching the end point of the study to show a difference in prostate cancer mortality does not make sense.

The PLCO study, however, may still have the potential to contribute to this important question if the data were analyzed as a nested case-control study. The case group comprises 94 patients who died due to prostate cancer within 7 yr after trial entry. One would then identify as a control group 94 age-adjusted men who were alive at the time that each corresponding case died. The PLCO manuscript indicated the number of men who had their PSA levels measured twice or more during the 3 yr before trial entry among patients who died due to prostate cancer within 7 yr after trial entry. In the case group, only 5 men had their PSA levels measured twice or more during the 3 yr before trial entry and 89 men were screened once or not at all by the PSA test. In contrast, it is estimated that 9 men in the control group had their PSA levels measured twice or more and 85 men did not because 9.6% of men were screened twice or more during the 3 yr before trial entry, as indicated in the paper.

The odds ratio is estimated to be 1.9 in favor of frequent PSA screening. This in itself is an important estimation. What we really want to know, however, is whether PSA screening affects mortality due to prostate cancer. Therefore, the authors could identify the number of men who were actually screened at least once during the 3 yr before trial entry among the 94 who died due to prostate cancer within 7 yr following trial entry. Thereafter, they could compare the risk of death due to prostate cancer for 7 yr after trial entry between men who were screened at least once and those were not screened at all during the 3 yr before trial entry.

Conflicts of interest: The author has nothing to disclose.

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Re: Selective Inhibition of CYP17 with Abiraterone Acetate is Highly Active in the Treatment of Castration-Resistant Prostate Cancer

Attard G, Reid AH, A'Hern R, et al

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Experts' summary:

In this single-center study from the Royal Marsden Hospital in London, 42 patients (median age: 70 yr; median serum prostate-specific antigen (PSA) level: 110 ng/ml) with progressive castration-resistant prostate cancer (CRPC) received 1000 mg abiraterone acetate once daily. The primary end point was a PSA decline $\geq 50\%$ at any time after 12 wk of treatment. Intermediate end points were radiologic assessment of measurable metastases and changes in circulating tumor cell counts. The median time to PSA progression in all 42 patients was 225 d (range: 162–287 d). A PSA decline $\geq 50\%$ was observed in 28 of 42 patients (67%) and a decline $\geq 90\%$ was observed in 8 of 42 patients (19%). Nine of 24 patients (38%) with measurable disease (with Response Evaluation Criteria in Solid Tumors [RECIST]) had a partial response. Furthermore, 33% of patients had a secondary PSA decline $\geq 50\%$ on addition of dexamethasone to abiraterone acetate. Side effects of treatment included hypokalemia (in 88% of patients), hypertension (40%), and fluid retention (31%), which could be managed by a mineralocorticoid receptor antagonist.

Experts' comments:

Since the introduction of nonsteroidal antiandrogens, studies on hormonal therapy of locally advanced or metastatic prostate cancer have focused on timing (immediate vs deferred, continuous vs intermittent, sequential) and clinical settings (neoadjuvant, adjuvant, palliative) rather than on evaluation of novel compounds [1]. This scenario might change now with the appearance of two “new kids on the block”: Data on the

clinical use of luteinizing hormone-releasing hormone (LHRH) antagonists and cytochrome P (CYP) 17 inhibitors are emerging.

The LHRH antagonist degarelix was approved by the US Food and Drug Administration (FDA) for treatment of advanced prostate cancer in December 2008. In a prospective, randomized phase 3 trial, degarelix was not inferior to leuprolide at maintaining low testosterone levels over a 1-yr treatment period [2]. Degarelix did not cause an initial testosterone surge; on the contrary, decline of testosterone and PSA was significantly faster than with the LHRH analog. Unlike its predecessor abarelix, there were no systemic allergic reactions. Specific disadvantages included local pain at injection site in up to 40% of patients and the fact that degarelix is currently available only as a 1-mo depot. Since LHRH antagonists are just another form of pharmaceutical castration, one would expect similar mid- and long-term sequelae for LHRH analogs (eg, osteoporosis, cardiovascular disease, diabetes mellitus). Therefore, the potential benefits of LHRH antagonists seem to be limited.

More promising is the design of CYP17 inhibitors [3]. CYP17 is a key enzyme in androgen and estrogen biosynthesis. There is evidence that despite elimination of gonadal androgens by surgical or medical castration, androgens originating from other sources (adrenal glands, intracrine de novo synthesis) continue to drive androgen receptor signaling. The antifungal agent ketoconazole is a nonspecific competitive inhibitor of several CYP17 enzymes. The drug exerts modest antitumor activity in CRPC, but its utility is limited by neurologic, respiratory, and hepatic toxicities [4]. Ketoconazole is not approved by the FDA for prostate cancer. The steroidal small molecule abiraterone acetate is a novel selective CYP17 inhibitor. This microsomal enzyme showed remarkable clinical effects in a recent phase 1 study [5]. The present phase 2 expansion could confirm these favorable results and is promising for