45–49 yr would break down in this study to only 4922 men with a second PSA value 6 yr later. Finally, 1369 men were found to have PCa; of those, 241 had metastasis (M+ or N+), and only 162 died from PCa in the observation period. Therefore the paper derives its conclusions from 162 deaths in 21 277 men (<0.8%). The difference between registry information on death from PCa and chart review information was nearly 20%. Thus a certain number of patients probably were missed by using only registry and chart data. If this is the 20% of 162 men who died from PCa, there were about 30 more deaths.

Second, baseline and subsequent PSA values were highly correlated (C = 0.71). This poses the question of whether a second PSA value is necessary at all. The authors argue that 28% and 18% of men at 45–49 and 50–55 yr of age, respectively, with baseline PSA values below the median (<0.68 ng/ml and <0.85 ng/ml, respectively) had PCa metastases 27 yr later. Thus the authors recommended screening until 60 yr of age. These diverging figures show the disadvantages of using PSA alone for risk assessment. This is substantiated by the fact that only 44% of deaths from PCa could be detected in the men in the highest risk group (45–49 yr with PSA >1.6 ng/ml). In spite of a rather good definition of the so-called high-risk group, this translates to putting 46% of patients at unnecessary risk, with all its emotional and medical consequences.

Third, the paper does not answer the question whether a high PSA value at a young age is predictive of an aggressive cancer, which would be needed to recommend early treatment and prevent death. If a high PSA at age 45 simply correlates to PCa at age 80, it would not alter the recommendation not to screen. If a high PSA at age 45 would lead to death from PCa at age 55, however, treatment recommendations certainly would be different.

This important paper adds very useful information to the literature and provides the basis for a risk-adapted screening approach. The paper not only identifies a high-risk group at ages 45–49 yr but even better defines a very low-risk group at this young age. These are men with a PSA <1.0 ng/ml at age 45–49 who will thereby harbor a risk of developing metastases from PCa 25 yr later (at age 70–74) of only approximately 1%. In our view, this is even more useful information for men who want assurance they will not have to worry about PCa when they opt for a baseline PSA value at age 45–49.

However, a prospective evaluation of this strategy is necessary. German Cancer Aid recently decided to fund a large randomized trial to test a risk-adapted screening strategy in 50 000 men. This trial will deliver important results not only on the prediction of risk groups but also on the current incidence of PCa at a young age [2]. In collaboration with the International Cancer Genome Consortium regarding early onset PCa, this research will enhance our knowledge concerning early onset PCa [3].

Conflicts of interest: The authors have nothing to disclose.

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Re: Comparative Effectiveness of Alternative Prostate-specific Antigen–Based Prostate Cancer Screening Strategies: Model Estimates of Potential Benefits and Harms
Gulati R, Gore JL, Etzioni R

Ann Intern Med 2013;158:145–53

Expert's summary:
The effects of different prostate-specific antigen (PSA) screening strategies were compared using microsimulation modeling. The strategies varied by starting age (40–50 yr), ending age (69–74 yr), screening interval (every 1, 2, or 4 yr), and biopsy indication (PSA of 4 ng/ml, 2.5 ng/ml, or age-specific threshold, with or without a PSA velocity threshold). The probability that a screening participant would be overdiagnosed varied from 1.3% to 6.0% among different strategies. The probability that a man would avoid prostate cancer ranged from 0.41% to 0.85%. Most of the benefits of screening could be retained but a proportion of the harms were avoided by age-specific biopsy thresholds or by using longer screening intervals for men with lower PSA.

Expert's comments:
PSA screening can be implemented in a number of different ways, with variations in starting and stopping age, biopsy criteria, and screening interval. Given the large number of possible permutations of screening and the likely small differences among them, alternative strategies cannot realistically be compared empirically—to do so would take decades and millions of patients—and we must rely on statistical simulations such as those of Gulati et al.

Many of the findings are well in keeping with those from studies such as the European Randomized Study of Screening for Prostate Cancer [1], for instance, that men with lower PSA can have less frequent screenings. However, in some instances, there are important inconsistencies

between the findings of Gulati et al. and the best empirical evidence. Two of the screening strategies compared, for example, are similar; however, for one, biopsy is performed on the basis of a PSA >4 ng/ml or a PSA velocity >0.35 ng/ml per year, and for the other, biopsy is performed for men with PSA >2.5 ng/ml only. Gulati et al. suggest that the latter strategy results in a relative 4% reduction in life-years gained from screening. However, in a direct empirical comparison of the two strategies using data from the large, randomized Prostate Cancer Prevention Trial, the PSA >2.5 ng/ml strategy led to detection of about 60% more high-grade cancers and 35% more clinically significant cancers [2]. Similarly, although the European randomized trial did not find a benefit from screening men in their 70s [1] and both the Scandanavian Prostate Cancer Group 4 trial [3] and the Prostate Cancer Intervention Versus Observation Trial (PIVOT) [4] showed little value for treatment in this age group, Gulati et al. reported much lower death rates for screening that ended at 74 yr compared with 69 yr.

Most of us would agree with the call of Gulati et al. to "screen smarter," and there is no realistic alternative to modeling studies to help us do so. But microsimulation models will require continual updating and modification to keep abreast of the developing research literature.

On a final note, we should all support academic studies of screening; indeed, that is a lot of what I do personally. But it is questionable whether changing age ranges by 5 yr or switching to biennial rather than annual screens will have a large impact on patient outcome. Far more influential will be a much greater reliance on active surveillance and ending the common practice of screening men who are very old. These are predominately issues of policy rather than empirical research.

Conflicts of interest: The author has nothing to disclose.

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Re: Prospective Randomized Phase II Trial of a Single Early Intravesical Instillation of Pirarubicin (THP) in the Prevention of Bladder Recurrence After Nephroureterectomy for Upper Urinary Tract Urothelial Carcinoma: The THP Monotherapy Study Group Trial
Ito A, Shintaku I, Satoh M, et al.

J Clin Oncol 2013;31:1422–7

Experts' summary:
Ito et al. performed a prospective randomized phase 2 trial evaluating the efficacy of a single postoperative intravesical instillation of pirarubicin (THP) for the prevention of intravesical recurrence after radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC). Eligible patients were randomized to receive (n = 39) or not to receive (n = 38) a single instillation of THP (30 mg in 30 ml of saline) into the bladder within 48 h of RNU. The primary end point was intravesical recurrence-free survival; median follow-up was 25 mo and 13.7 mo in the THP and placebo groups, respectively. Significantly fewer patients in the THP group experienced intravesical recurrence compared with the control group (1 yr: 16.9% vs 31.8%; 2 yr: 16.9% vs 42.2%; p = 0.025). There were no serious adverse events in either group. In multivariable analysis, THP instillation (hazard ratio [HR]: 0.26; 95% confidence interval [CI], 0.07–0.91; p = 0.035) and open (vs laparoscopic) surgery (HR: 0.28; 95% CI, 0.09–0.84; p = 0.024) were independently associated with a reduced risk of intravesical recurrence after RNU.

Experts' comments:
Intravesical recurrence after RNU for UTUC is a frequent event, occurring in 20–50% of patients, with most in the first postoperative year [1,2]. This study represents the third prospective randomized trial assessing the effect of an immediate postoperative intravesical instillation of chemotherapy on the risk of intravesical recurrence after RNU. In 2001, Sakamoto et al. failed to demonstrate the efficacy of a combination of mitomycin C (MMC) and cytosine arabinoside in 27 patients treated with RNU for UTUC [3]. Conversely, O'Brien et al. recently demonstrated that a single postoperative administration of 40 mg of intravesical MMC reduces the probability of intravesical recurrence following RNU by 11% (absolute risk reduction). In other words, nine patients need to be treated to prevent one intravesical recurrence (ODMIT-C trial) [4]. In the current study, Ito et al. confirmed this finding and showed, for the first time, that intravesical chemotherapy is associated with a lower intravesical recurrence rate, even after adjusting for the effects of standard predictors. These later two studies provide level 1 evidence for the safety and efficacy of intravesical single postoperative chemotherapy for patients treated with RNU for UTUC.

Nonetheless, some questions remain unanswered. First, the three trials published to date used three different drug