As more and more men undergo radical prostatectomy as their primary treatment for prostate cancer, it is becoming evident that not all of them will enjoy a prostate-specific antigen (PSA)-free status for the rest of their life. As presented in other series with long-term follow-up, the risk for biochemical recurrence continued to increase over time in a large European series from Hamburg [1]. The 2-, 5-, and 8-yr biochemical-free survival rates (PSA < 0.1 ng/ml) were 84%, 70%, and 61%, respectively.

The importance of a PSA relapse after radical prostatectomy has been described in detail by Simmons et al [2] in this issue of European Urology. By reviewing the current literature, the authors propose a cut-off point for defining biochemical recurrence. Also, they suggest a clinical useful algorithm to handle patients with PSA failure after radical prostatectomy. This algorithm suggests the use nomograms as proposed by Pound [3] or Freedland [4] for postoperative risk prediction and Cowen et al [5] to calculate life expectancy to better define the group of patients who will be in the real need for active treatment for their biochemical failure (Table 3 in the article). For patients having a life expectancy of >5–10 yr and a high risk of progression, the authors suggest that the outcome data presented by Stephenson et al [6] be used to define the subgroup of high-risk patients who might benefit from salvage radiation therapy. For patients who are not expected to benefit from salvage radiation therapy they suggest hormonal therapy or, if the patients have low-risk features or shorter life expectancy, observation only.

Simmons et al make a strong case for using a cut-off point of >0.4 ng/ml and repeated determinations to define biochemical failure after radical prostatectomy. This is higher than the >0.2 ng/ml suggested in the European Association of Urology (EAU) prostate cancer guidelines [7]. Their main reason to suggest the higher cut-off value is that this better correlates to clinical progression than lower values; that is, some patients with values between 0.2 and 0.4 ng/ml will not continue to progress within the reasonable future. One could argue a great deal about the optimal cut-off level but I would suggest the following implications of this for PSA follow-up after radical prostatectomy:

1. There is no use of ultrasensitive PSA assays in the routine follow-up of patients after radical prostatectomy.
2. Even if one does not believe that >0.2 ng/ml is a valid definition of biochemical failure, I would strongly suggest that patients with a reasonably long life expectancy who have reached this PSA level be kept under closer surveillance because the PSA window of opportunity for second-line curative radiotherapy is rather narrow.
**Fig. 2** in the article depicts the suggested algorithm for treatment of biochemical recurrence after prostatectomy. One thing that immediately separates this algorithm from the current European recommendations is the suggested need for a full metastatic evaluation (including chest radiograph (!) and bone scan) in all patients with biochemical failure only. Such a strategy seems to represent a use of health care resources more common in the United States than in Europe. The authors have themselves suggested use of the nomogram of Dotan et al[8] to determine the risk for a positive bone scan after radical prostatectomy. One of the conclusions from Dotan et al was that low-risk patients do not need a metastatic evaluation and that omitting this would create large cost savings [8].

In accordance with EAU guidelines, my interpretation is that the vast majority of asymptomatic patients with early biochemical recurrence only do not need a metastatic work-up before a decision on second-line treatment strategy is made. The occasional exception would be symptomatic men or those with very high-risk features, such as nodal involvement.

Simmons et al emphasise the fact that there is no place for routine imaging or biopsy of the prostatic fossa before eventual second-line therapy is started and this is in line with the current EAU guidelines. The second thing with the algorithm worth pointing out is that patients with a life expectancy of >5–10 yr and at low risk for clinical progression and prostate cancer mortality should be recommended observation only hormonal therapy or clinical trials in the case of progression. Most urologists would feel that this is adequate for many men, but for the very young patient (<60–65 yr of age) a second attempt at curative radiation must be more attractive than only watching a slowly rising PSA. The long life expectancy of these men means that also low risk may be a real risk during their expected life span and because the “window of opportunity” for successful radiotherapy is closed when PSA has passed 1–2 ng/ml, I would find it hard to suggest only hormonal therapy in the case of a continuous rise in PSA. I would suggest that the readers take out a pencil and add another arrow from “Progression” to “Salvage RT” in the algorithm to not deny these young men a second chance for cure.

In another study with a group of patients showing close similarity to the one in Simmons et al, Bolla and coworkers showed that giving immediate postoperative radiotherapy to patients with high-risk features (extracapsular extension or positive surgical margin or seminal vesical invasion but without taking PSA failure into consideration) was better than watchful waiting and delayed therapy [9]. However, only a few men in the watchful waiting arm were offered second-line radiotherapy as suggested above. Also, by not waiting for a confirmed biochemical recurrence, there could be a significant risk for over-treatment when all patients are given immediate radiation, illustrated by the fact that 40% of the patients in the watchful waiting arm did not show biochemical progression after 9 yr of observation (projected data) [9].

The authors are to be congratulated for their successful effort to gather knowledge about a
difficult subject that is becoming increasingly common in everyday urology practice. Their approach (possibly with some respects to the comments given above) gives a balanced view of what a biochemical failure really means to the patients and a possible way to handle the problem for the clinician in their efforts to give the right therapy to those who really need it.

References


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Patients with postprostatectomy biochemical recurrence (BCR) pose a complicated clinical problem. Although we are eager to be aggressive to stem the progression of a smoldering tumor, we must temper this impulse with the knowledge that our secondary therapy may not benefit the patient at all and may, in fact, harm him.

We appreciate Dr. Aus’s remarks [1] and agree that full radiographic assessment of potential metastases for all patients may be somewhat excessive. Patients with low prostate-specific antigen (PSA) levels and slow doubling times are unlikely to have meaningful information gleaned from such studies. However, it is reasonable to perform a bone scan at the time of BCR as a baseline study to facilitate interpretation of subsequent follow-up scans in patients with higher risk of metastatic progression.

We wish to disagree with the suggestion that all younger men with BCR should be offered salvage radiotherapy because of their long life expectancy. We believe that an evidence-based approach based on published nomograms that restrict secondary therapy to patients most likely to benefit is superior to choosing patients based on age or other non-validated factors. Radiotherapy has acute, chronic, and late toxicities, and though it is tempting to offer younger patients the hope of driving the PSA to undetectable levels with salvage radiation in the short term, those with the longest life expectancy will be most at risk for late urethral, bladder, and bowel dysfunction and the appearance of radiation-induced secondary malignancies. Surely a detectable PSA with a slow doubling time that carries little risk for clinical progression or prostate cancer-specific mortality is preferable to loss of bladder or rectal function due to these late effects; it is incumbent on us to counsel patients not only about the short-term psychological gain of an undetectable PSA, but also to make our best judgments about who may actually have a biologic need for secondary therapy and to not overlook the potential for late toxicity or the need for long-term monitoring for their occurrence, a burden that is often overlooked.

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