The risk of locally recurrent prostate cancer (PCa) remains substantial despite the continuous development of innovative radiotherapy (RT) techniques, including image-guided RT, three-dimensional conventional RT, intensity-modulated conformal RT, and low-dose brachytherapy (BT). Various studies reported on a 10–25% clinical local failure rate following external beam RT (EBRT) and low-dose rate BT of clinically localized PCa. Secondary local salvage therapy with curative intent is basically justified in all patients with a true local recurrence and without evidence of locoregional lymph node or visceral systemic metastases. When counseling patients for local salvage therapies, primary treatment goals should be considered based on the patient. Treatment goals are (1) local cancer control and prevention of local complications, (2) eradication of poorly differentiated PCa clones with metastasizing capabilities, (3) minimization of treatment-related morbidities, and (4) maintenance of quality of life. Among the various treatment options, salvage radical prostatectomy (SRP), salvage cryosurgery of the prostate (SCP), and salvage BT represent the most commonly applied and the most reliable treatment options. However, even now, the majority of men who experience relapses after RT are treated with androgen deprivation therapy [1], as has been shown in a recent retrospective analysis of the Cancer of the Prostate Strategic Urological Research Endeavour (CaPSURE) database.

In the current manuscript, Wenske et al. [2] report on the midterm, but not long-term, follow-up data of 328 patients who underwent SCP for locally recurrent PCa following EBRT ($n = 259; 79\%$), low-dose BT ($n = 49; 15\%$), and cryosurgery ($n = 20; 6\%$). The authors are to be congratulated for this large, retrospective study (1) that highlights the fact that local salvage procedures can be highly effective; (2) that creates more evidence to support SCP in men with clinically localized, radiorecurrent PCa; (3) that helps identify patients who might benefit from local salvage procedures; and (4) that highlights the fact that radiorecurrent PCa, even now, is a clinically significant phenomenon largely ignored by the radio-oncologic and urologic communities.

After a mean follow-up of nearly 4 yr, the 5- and 10-yr disease-free survival (DFS) was 63% and 35%, respectively. Interestingly, 55 (17%) patients underwent focal SCP of the affected lobe, which resulted in 5- and 10-yr DFS rates of 47% and 42%, respectively. According to the authors’ data, treatment-associated complication rates were rare, with urethral strictures and bladder outlet obstruction representing the most common side effects in 4.6% and 3.4% of patients, respectively. Rectourethral fistulas represented the most serious side effect and developed in about 2% of the patients. The authors concluded that SCP results in an excellent survival outcome and that it is associated with a minimal treatment-related morbidity.

There are several aspects associated with the presented study that need some attention to analyze the data correctly:

1. **How is the ideal candidate for salvage cryosurgery of the prostate identified?**

Secondary local treatment of radiorecurrent PCa can be performed for cure and/or for the prevention of local complications. If performed for cure, it is evident that only men with organ-confined radiorecurrent PCA are ideal candidates for either SCP or SRP. Predictors that can be obtained preoperatively are needed to identify patients who
will benefit most from local salvage procedures. In the current study [2], prostate-specific antigen (PSA) nadir after SCP was the only significant predictive factor; it was associated with a 2.46 relative risk (RR) of disease recurrence. In other large retrospective studies, however, preradiation PSA serum level, presalvage PSA, and a presalvage biopsy Gleason score ≥8 were identified as significant risk factors associated with disease recurrence [3,4]. In the current study, presalvage PSA was only associated with a marginally increased RR of 1.06 for disease recurrence, which might be due to the relatively low median serum level of 4.0 ng/ml at time of SCP, as compared to other studies with a median PSA of 7–8 ng/ml. A presalvage PSA <5 ng/ml and a presalvage PSA >10 ng/ml were associated with a 10-yr DFS of 64% versus 6.7%. A presalvage biopsy Gleason score ≥8 was associated with a 1.92 RR of PCa relapse as compared to a biopsy Gleason score ≤6 [3,4].

In the presence of unfavorable risk factors, SCP should not be abandoned, since several retrospective studies have demonstrated an impressive local cancer-control rate, thereby preventing local progression of PCa and its associated complications [5]. However, the patient has to be informed about the high likelihood of biochemical relapse and the need for future systemic treatment. The intraprostatic location of the relapsing PCa might represent another predictor of post-SCP failure. Ng et al. demonstrated that the majority of postcryosurgery failures were located in the apex and, to a lesser extent, in the base of the prostate and the seminal vesicles. The apex, especially, represents an area of less aggressive freezing due to the close proximity of the external urethral sphincter and the rectum. Knowledge of the intraprostatic distribution of cancer foci will be of significant importance for treatment planning, and this information can be best retrieved from a transperineal saturation prostate biopsy [6].

Therefore, patients with presalvage PSA <5 ng/ml, a presalvage biopsy Gleason score ≥7, and a nonapical recurrence might be the best candidates for SCP in terms of a curative intent.

2. How are patients suitable for focal salvage cryotherapy identified?

According to the data of the Wenske et al. study [2], 17% of the patients underwent focal cryotherapy of the primarily affected lobe, and after a median follow-up of approximately 3 yr, 53% already had experienced biochemical relapse, compared to 37% of patients who underwent full-gland SCP. Also, complications increased significantly after focal SCP, especially the development of rectourethral fistulas, which represent high-impact complications. Based on the limited number of patients, the short follow-up period, and the lack of a stringent follow-up protocol, including a full biopsy protocol together with a high PSA relapse rate, focal SCP should be used with caution and the patient has to be thoroughly informed about the experimental character of this procedure. Detailed patient information is even more important considering the fact that about two-thirds of all recurrent PCa develop in the periurethral region, where cryosurgeons usually attempt to protect the urethral wall from deep freezing [7]. Furthermore, nearly three-fourths of all radiorecurrent PCa demonstrate bilateral prostate involvement, even in patients with a mean pretreatment PSA <4 ng/ml [8].

3. How is oncologic efficacy and postsalvage failure defined?

Whereas an undetectable, postoperative, PSA serum level is the major indicator of complete local PCa eradication after SRP and any PSA increase >0.2 ng/ml represents relapsing disease [9], no established definition of failure exists following SCP [5]. Gowardhan et al. [10] used a PSA threshold level of 0.5 ng/ml to define treatment failure and the authors reported a 1-yr biochemical failure rate of 39%. In another series, Spiess et al. [11] analyzed the outcome of 450 SCPs and defined SCP biochemical failure as a total serum PSA >0.5 ng/ml. After a median follow-up of 3.4 yr, 34% of the patients experienced biochemical relapse. In the current study, Wenske et al. [2] applied the Phoenix criteria to define relapse, which is used in several other studies. Considering the fact that post-SCP PSA levels >1 ng/ml were associated with a RR ratio of 6.63 for disease recurrence and were associated with a 5-yr DFS of only 3% in the retrospective study of Williams et al. [3], it might be clinically more useful to define absolute threshold levels to define post-SCP relapse as it is done for SRP.

4. How is the most suitable salvage procedure, cryosurgery or radical prostatectomy, identified?

SCP and SRP are guideline-recommended local treatment options for radiorecurrent PCa. The indication for either one should be based on (1) cancer characteristics to achieve the best oncologic outcome possible, (2) the surgeon’s experience to guarantee optimal oncologic efficacy and tolerable treatment-associated morbidity, and (3) the patient’s choice.

Biochemical DFS probabilities range between 34% and 58% after SCP and between 54% and 87% after SRP if one considers only series published between 2007 and 2012. This approach ensures encompassing modern RT techniques and modern cryosurgical and surgical techniques. Until now, there has been only one case–control study comparing both therapies in patients with clinically organ-confined, locally recurrent PCa following RT stratified by PSA level and cancer grade [12]. Median follow-up was 7.8 yr and 5.5 yr in the SRP and SCP groups, respectively. Whereas the disease-specific survival was nearly identical between both groups (96% for SCP vs 98% for SRP), patients undergoing SRP had a significantly better biochemical DFS at 5 yr (24% for SCP vs 61% for SRP; p = 0.01) using stringent criteria of PSA progression. With regard to Gleason score, SRP was significantly superior to SCP in terms of PSA increase and overall survival in eight patients.

Based on these findings, SRP might be the superior treatment option in men with longer life expectancy and a
poorly differentiated cancer. Furthermore, patients with recurrent cancer foci at the apex might be best treated by a surgical approach, since this area is frozen less aggressively and most of the postcryosurgery relapses are located in this area. Taking these data into consideration, thorough diagnostic exploration of patients with suspected, locally recurrent PCa after RT is mandatory, including transperineal mapping biopsies and, eventually, 3.0 Tesla magnetic resonance imaging.

The surgeon’s experience plays an important role in the outcome of both techniques, especially in terms of treatment-related complications. The frequency of rectal injuries has decreased to between 2% and 8%, and the frequency of stress urinary incontinence has decreased to about 20%, in modern series of SRP [13,14]. In modern series of SCP, rectourethral fistulas are reported in about 3% of patients [5]. Incontinence and obstruction necessitating surgical interventions are described in 8–40% and in 4–11% of patients, respectively. The low frequency of complications reported in the current study [2] have to be interpreted with caution because the authors did not apply validated questionnaires to evaluate posttreatment incontinence and erectile dysfunction. Furthermore, complications were not classified according to objective tools, such as the Clavien-Dindo classification system.

Conflicts of interest: The author has nothing to disclose.

References