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Review

## Management of local relapse after prostate cancer radiotherapy: Surgery or radiotherapy?



### Prise en charge d'une récidive locale d'un cancer de la prostate après une radiothérapie : chirurgie ou réirradiation ?

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## ABSTRACT

Isolated local relapse after prostate cancer radiotherapy corresponds to 40% of biochemical failure. The management of these relapses is not well defined. Several strategies are available including surgery, high-intensity focused ultrasounds (HIFU), cryotherapy and reirradiation. Radical prostatectomy is the historical approach; biochemical control is obtained in 50 to 80% at 5 year. However, morbidity is higher after irradiation than as a first line treatment. Some limited series of HIFU and cryotherapy have been published with interesting results, but again the risk of urinary and rectal toxicity is high. However, new generation technologies could decrease the complication rate. Reirradiation could be performed with brachytherapy and more recently with stereotactic radiation therapy. The results of salvage low-dose-rate brachytherapy have been reported in some series with a 5-year biochemical control rate of 34 to 88%. High-dose rate brachytherapy seems to be better tolerated, but the number of patients treated and reported is too low to draw firm conclusions. This is the same for stereotactic radiation therapy salvage treatment. A prospective trial of salvage brachytherapy (CAPRICUR) is now open in France and inclusion in this trial is recommended.

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## R É S U M É

Les récidives locales d'un cancer prostatique après radiothérapie représentent schématiquement 40 % des récidives biochimiques. La prise en charge de ces récidives est mal codifiée. Plusieurs stratégies sont proposées : chirurgie, ultrasons focalisés de haute intensité (*high-intensity focused ultrasounds* [HIFU]), cryothérapie et réirradiation. La prostatectomie totale représente la technique historique ; elle permet d'obtenir un contrôle biochimique dans 50 à 80 % des cas à 5 ans. Cependant, sa morbidité n'est pas négligeable, plus importante qu'après une chirurgie première. Quelques données existent sur l'efficacité du traitement par ultrasons focalisés de haute intensité ou de la cryothérapie, mais là encore la morbidité de ces techniques n'est pas nulle. Ces techniques bénéficient de technologies de troisième génération, qui pourraient diminuer les effets secondaires. Une réirradiation est possible, soit par curiethérapie, soit par radiothérapie en conditions stéréotaxiques. Il a été obtenu dans quelques séries de curiethérapie de bas de débit de dose un taux de contrôle biochimique à 5 ans de 34 à 88 %. La curiethérapie de haut débit de dose paraît mieux tolérée, mais les résultats carcinologiques sont encore mal connus, de même que les résultats de la radiothérapie stéréotaxique. Un essai prospectif de curiethérapie (Capricur) débute en France, dans lequel il est conseillé d'inclure les patients.

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## 1. Introduction

After external beam radiation therapy or brachytherapy, biochemical relapse is defined by a rise of prostate specific antigen blood concentration [PSA] 2 ng/ml or more above the nadir [1]. Although these treatment modalities are very efficient for localized prostate cancer, more than the half of the patients would experience a biochemical recurrence within 10 years [2,3]. The rate of biochemical relapse varies widely according to the initial prognostic group. At 5 year, survival without metastases has been reported to be only 47% with a specific mortality of 18% [4]. Among these patients, about 20 to 40% would present an isolated local recurrence [5], for which most of the physicians would choose androgen-deprivation therapy as the cornerstone of the therapy management [6]. But androgen-deprivation therapy remains a palliative treatment, which significantly impacts quality of life [7]. Furthermore, tumour sensitivity to androgen-deprivation therapy is transient and cancer would eventually become castration-resistant.

Therefore, preventing or delaying the introduction of androgen-deprivation therapy for PSA failure appears as a major challenge. The first step in the decision-making process in front of a biochemical recurrence is to define the localization of the relapse. PET-scan (with [<sup>18</sup>F]-choline tracer and sooner [<sup>68</sup>Ga]-PSMA) coupled with multiparametric prostate MRI are required to define an isolated local relapse. Systematic or image-guided prostate biopsies are also mandatory to confirm the relapse before any local salvage treatment could be considered.

Local salvage procedures such as radical prostatectomy, high-intensity focused ultrasounds (HIFU) ablation, cryosurgery or prostate reirradiation are therapy alternatives that can be offered to highly selected patients [8–11]. In spite of their encouraging results, very few patients benefit from these treatment options [6,12].

## 2. Salvage prostatectomy

Prostatectomy is the historical procedure for local relapse after radiotherapy. Some retrospective series has now a long follow-up. Morbidity of prostatectomy is higher after irradiation than as a first treatment.

Selection of patients and their information is essential: no associated comorbidity, information of potential side effects, local relapse histologically confirmed, curable disease before radiotherapy or brachytherapy (tumour stage less than cT3b, preoperative [PSA] < 10–15 ng/ml, Gleason score < 8, cNO), PSA doubling-time longer than 12 mois and delay between radiotherapy and relapse higher than 2 years or at least 3 years after brachytherapy, no major urinary symptoms or incontinence [13].

Survival without biochemical relapse after salvage prostatectomy ranges from 47% to 83% and 28–53%, respectively at 5 and 10 years [14]. Ten-year specific and overall survivals are 70 to 83% and 54 to 89%, respectively. Gleason score and [PSA] level before surgery are the main prognostic factors [15]. The rate of incontinence ranges from 21 to 91%, rectal injury from 2 to 9% and anastomotic stricture from 11 to 41%. This complication rate seems to be lower in the most contemporary series.

The French societies for urology and for radiotherapy (AFU/SFRO) recommendations proposed that salvage prostatectomy must be considered in case of local relapse for a good prognostic disease.

## 3. Salvage high-intensity focalized ultrasounds (HIFU) or cryotherapy

For HIFU, one French series reported 290 patients with a local relapse after radiotherapy; 50% received an androgen deprivation

associated with the procedure. At 7 years, specific survival and survival without metastases were de 80%. Five-year progression-free survival were 45%, 31% et 21%, according to the initial prognostic group. A special configuration must be used to decrease urinary morbidity [16,17].

After salvage cryotherapy, survival without biochemical relapse was reported at 5 years between 50 and 70%, with sustained responses in 50% of the patients. In a review, compiling the results of 450 patients, biochemical relapse rates are 33% at 5 years and 66% at 10 years [18]. New third generation technologies decrease the rate of post-operative complications: incontinence (8 to 12%), urinary blockade (4 to 7%), pelvic pain, rectovesical fistulae (1 to 3,4%) [19–21]. Salvage cryotherapy is indicated for patients with no comorbidities, a life expectancy higher than 10 years, a localised disease with [PSA] < 10 ng/ml and a long PSA doubling time.

## 4. Prostate reirradiation

Prostate reirradiation was mainly done with low-dose-rate brachytherapy using seeds, with mixed results on efficacy and toxicity [11,22,23]. However, recent improvement in radiotherapy devices such as high-dose rate brachytherapy and stereotactic body radiotherapy allow delivering higher ablative dose in a smaller target volume with better sparing of surrounding critical organs at risk [24]. Actually, available data on postradiation salvage high-dose rate brachytherapy and stereotactic body radiotherapy are very sparse and heterogeneous.

## 5. Salvage prostate brachytherapy

Salvage prostate brachytherapy may provide another attractive option for attaining disease control in patients with prostate cancer local failure. Uro-GEC group recently published a Delphi consensus on salvage brachytherapy for prostate cancer relapse after radiotherapy [25]. Using a perineal template, radioactive seeds (low-dose rate brachytherapy) or catheters (high dose rate brachytherapy) are inserted into the prostate. A transrectal ultrasound allows for visualization of the prostate, the urethra and the surrounding tissue. It also guides catheter and needle insertion. Assessment and optimization of dose distribution can be obtained intraoperatively using radioactive seeds (iodine-125 or palladium-103) or postoperatively, using CT planning, by dwell location and time variation of the high dose rate source. Dose distribution optimization help to maximize radiation dose to the prostate while sparing the rest of organ at risk tissues.

Multiple studies of salvage low-dose brachytherapy have been reported in the post-PSA era, although the published reports comprise fewer than 100 patients [26]. Grado et al. presented the results of the largest clinical experience reported to date (49 patients) using radioactive seeds [27]. With a median follow-up of 64 months, 3- and 5-year biochemical control rates were 48% and 34%, respectively. Late complications included gross haematuria (4%), dysuria (6%) and rectal ulcers (4%). The rate of hematochezia requiring surgical intervention was of 2% and the rate of urinary incontinence requiring a prostate transurethral resection was of 6%. Results of salvage brachytherapy published in the literature show a 5-year disease-free survival ranging from 20% to 67% (Table 1). Nguyen et al. reported rates of incontinence and fistula formation around 6% and 3% respectively with a risk of grade 3/4 genitourinary complications of 17% [31]. Salvage brachytherapy, when combined with careful patient selection, seems to be at least as effective as other salvage options with comparable or potentially fewer treatment-related morbidity.

The use of high-dose rate brachytherapy as a salvage procedure was a more recent procedure. Chen et al. used a high dose rate

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