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Review

Retreatment for prostate cancer with stereotactic body radiation therapy (SBRT): Feasible or foolhardy?

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ABSTRACT

The most popular therapeutic option in the management of radio-recurrent prostatic carcinoma is represented by the androgen deprivation therapy, that however should be considered only palliative and hampered by potential adverse effects of testosterone suppression. Local therapies such as surgery, cryoablation or brachytherapy might be curative choices for patients in good conditions and with a long-life expectancy, but at cost of significant risk of failure and severe toxicity. The administration of stereotactic body radiation therapy (SBRT) in this setting have come about because of tremendous technologic advances in image guidance and treatment delivery techniques that enable the delivery of large doses to tumor with reduced margins and high gradients outside the target, thereby reducing the volume of rectum which already received significant doses from primary radiotherapy. So far, very modest data are available to support its employment. Rationale, clinical experience, and challenges are herein reviewed and discussed.

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1. Background

In the dose escalation era, primary external beam radiotherapy (EBRT) ± hormonal therapy for localized prostate cancer (PCa) registered excellent outcomes, equivalent to those reported in the largest surgical series.^{1–4} Nevertheless, a proportion of patients develop biochemical failure, defined as PSA rising 2 ng/ml above the nadir.^{5–8} Among them, while a

significant percentage will harbor occult micrometastases,⁹ a subset will present with a truly localized recurrence within the prostate only. The PSA doubling time (PSA-DT)¹⁰ is an important parameter to identify potential candidates for local re-treatments, as the local failure is generally associated with a PSA-DT ≥ 6 months. Along with this data, emerging technologies in the diagnostic work up employing molecular imaging techniques, such as positron emission computed tomography (PET-CT) with radio-labeled choline (11C- and

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18F-choline)^{11–13} and/or functional imaging techniques, such as dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), diffusion-weighted imaging (DWI) and proton magnetic resonance spectroscopy imaging (MRSI)^{14–16} play a crucial role in both detecting local recurrence and excluding the presence of metastatic disease, due to a higher sensitivity and specificity than the standard imaging modalities. In most of the cases however, confirmatory biopsies are still warranted prior to any local procedures with curative intent,¹⁷ although associated with problems of timing and sampling errors that can make difficult their interpretation. Indeed, the accuracy of post radiation biopsies ranges from 62% to 76%, with undetected cancers ranging from 12% to 26% and biopsies missed up to 20% of tumors.¹⁸ Currently, there is a lack of high level evidence supporting the use of salvage therapies after primary radiation,¹⁹ and the majority of reports are retrospective single institution studies. For this reason, there is no established standard of care in this setting, as the potentially available options are considered grade B recommendations according to recent guidelines.²⁰ The choice of a salvage modality mainly depends on clinical and individual factors that may influence the outcome of this type of treatment. About 92% of patients who previously received RT are usually managed with androgen deprivation therapy (ADT) alone as secondary treatment on PSA progression, or with no salvage procedures.²¹ Nevertheless, hormonal blockade is considered only a palliative option and its potential benefit must be weighed against the adverse effects of testosterone suppression.^{22–25} Patients with radio-recurrent PCa may still be selected for curative treatment, especially those in good clinical conditions and long life expectancy.

2. Local treatments

Therapeutic options include local procedures such as salvage prostatectomy (RP), cryotherapy, interstitial brachytherapy and high intensity focused ultrasound (HI-FU).^{26–56} None of them is carried out without significant risk of failure and severe (grade ≥ 3) genitourinary and gastrointestinal toxicities are observed in up to 30% of the patients⁵⁷ (Table 1). The disappointing outcomes of salvage techniques make these choices highly demanding and might explain the lack of large prospective trials in the recent literature. Prostatic re-irradiation for local recurrence in patients who already received primary radiotherapy represents a challenging option. A basic,

longstanding principle of radiotherapy is that once definitive EBRT has been administered further RT cannot be given because it would likely exceed normal tissue tolerances. Tremendous technological advances from the diagnosis to the treatment planning and delivery of radiation therapy have aroused interest in assessing the appropriateness of a re-irradiation in the management of radio-recurrent PCa. In this setting brachytherapy, allowing flexible radiation dose sculpting, is expected to deliver a relatively small dose to the surrounding tissues, thus having the potential for a better rectal sparing compared to conventional EBRT. This has recently prompted the Radiation Therapy Oncology Group (RTOG) to evaluate the role of brachytherapy for locally recurrent prostatic adenocarcinoma in an ongoing phase II prospective trial (RTOG 0526).⁵⁸ The primary drawback however is that brachytherapy is an invasive procedure associated with non-negligible risks of infection and thromboembolism, which make its choice unsuitable for many patients. Meanwhile, early data consistently show that stereotactic body radiation therapy (SBRT) is a safe and effective treatment modality in the re-irradiation situation for various anatomical sites.⁵⁹ SBRT is a novel EBRT modality that is becoming popular also in the treatment of primary prostate cancer⁶⁰ where is currently being evaluated in an ongoing randomized non-inferiority phase II trial (RTOG 0938).⁶¹ SBRT allows to deliver steep dose gradients that resemble brachytherapy dose distributions, with the further advantages of avoiding hospitalization, catheterization and the discomfort of delivery needles inserted for an extended time period (in the case of LDR-implants) or the need of managing the indwelling transperineal HDR catheters and dealing with their attendant pain.⁶² Highly focused radiation beams can therefore minimize the radiation-associated rectal toxicity – which must be considered even more dose-limiting in the salvage setting – by reducing the volume of rectum receiving high radiation doses.⁶³ Moreover, exploiting the favorable therapeutic ratio offered by the low α/β of prostate cancer, SBRT allows a dramatic reduction in the number of fractions and overall treatment time making possible the irradiation with few fractions of very large doses. The delivery of such treatment regime certainly requires the adoption of techniques with multiple non-coplanar fields or intensity modulated arc therapy. In addition, minimal clinical target volume (CTV) to planning target volume (PTV) margins, and a daily patient repositioning with correction for the inter- and intra-fraction organ movements are mandatory to improve the treatment

Table 1 – Complications of salvage local procedures for radio-recurrent prostate cancer after ≥ 24 months of follow up.

Type of treatment	Total no. of pts	Median FU Months (range)	Late toxicities					
			Incontinence		Stricture		Recto-urethral fistula	
			%	Range %	%	Range %	%	Range %
Surgery ^{26–38}	762	49 (24–120)	41	(0–79)	19.3	(0–40)	NR	
Brachytherapy ^{45–52}	236	66 (30–86)	10.4	(0–31)	NR		7	(2–12)
Cryotherapy ^{39–44}	1126	61.5 (22–120)	8.5	(4.4–13)	NR		1.8	(1–3.4)
HIFU ^{53–56}	211	39 (24–50)	33.7	(18–49.5)	NR		3	(1–5)

HIFU: high intensity focused ultrasound; NR: not reported; FU: follow up.

accuracy. SBRT can be carried out with several devices, such as CyberKnife® (Accuray Incorporated, Sunnyvale, CA), or modern Linac-based systems like True Beam™, Varian Trilogy™ (Varian Medical Systems, Inc., Palo Alto, CA), TomoTherapy Hi-Art® System (Accuray Incorporated, Sunnyvale, CA), or VERO® (Brainlab AG, Germany), each of them clearly having its strength and weakness. According to this potential, SBRT holds sufficient promise to warrant broader investigation in the setting of post-radiotherapy local salvage treatment, but currently there are very modest data to support its employment.

3. SBRT re-irradiation

Recently, some reports on stereotactic prostate re-irradiation have been published.^{64–66} Vavassori et al.⁶⁴ documented the first 6 patients with locally recurrent prostate cancer after primary EBRT with 70–80 Gy, who underwent re-irradiation with CyberKnife SBRT for a total dose 30 Gy in 5 fractions over 5 consecutive days. After a median follow-up of 11.2 months (range, 9.6–18.6 months), none of the patients had clinical evidence of tumor persistence in the prostate and all of them were alive without severe urinary or rectal acute morbidity. The early findings of this report were then updated by Jereczek-Fossa et al.⁶⁵ in a subsequent study where nine more patients were added. In their experience, 15 patients with biopsy-proven isolated intraprostatic recurrence were treated with the same CyberKnife SBRT schedule; 6/15 also received systemic therapy. Complete biochemical response was obtained in six out of nine patients treated with SBRT alone (no systemic therapy), confirming the potential radiosensitivity of intraprostatic recurrence. The pattern of failure was out-field in 80%. Actuarial 3-year progression-free survival was 22%. Interestingly, no acute or late rectal toxicity was registered. Urinary toxicity included five acute events (only one grade 3) and three late events (only one grade 3). Ricchetti et al.⁶⁶ reported four patients with local recurrence after definitive radiotherapy for prostate, bladder and rectal carcinoma, who were re-treated with helical tomotherapy. The total prescribed dose was 60 Gy in 3 patients and 50 Gy in 1 patient. After a median follow up of 9 months, re-irradiation was well tolerated, with negligible rates of acute and late toxicity. Although in its infancy and still being considered experimental, SBRT is a feasible approach to isolated intraprostatic recurrence, offering excellent in-field tumor control and a low toxicity profile, regardless the treatment delivery system adopted. A further interesting issue is that local recurrences are located predominantly at the primary lesion site,^{67,68} as the surviving macroscopic tumor received a too low radiation dose from the primary treatment. This, in conjunction with greater accuracy in diagnostic imaging and radiation treatment planning/delivery, opens the way to focus the target volume to the recurrent macroscopic lesion alone, avoiding an unnecessary exposure of a substantial proportion of surrounding healthy tissues, and allowing a partial re-irradiation.⁶⁹ In addition, this strategy has the potential for the retreatment of another area of locally recurrent disease which may be discovered again during the follow up in long-term survivors. In the latter fashion, the employment of a focal salvage therapy raises the question on whether it should be

considered curative rather than turn recurrent PCa into the perspective of a chronic disease.⁷⁰ SBRT prostate re-irradiation could also benefit from a tool which can reduce the dose to the rectum, that already have received high doses with the primary treatment: the transperineal ultrasound (TRUS)-guided injection of a self absorbable hydrogel into the prostate–rectal interface has been shown to result in significant dose reductions to the rectum across the entire dose range for >90% of patients undergoing EBRT for prostate cancer⁷¹ and to successfully preserve the rectal wall in prostate SBRT.⁷² The physical rectal sparing obtained by temporarily pushing away the rectum from the high-doses area may allow the safe delivery of a second course of radiation, and has resulted in an improved therapeutic ratio also when re-irradiation has been administered with high dose rate brachytherapy [73]. Coupled with the SBRT treatment technique, this device is expected to reduce rectal toxicity rates even more in the salvage setting, where the need for preserving the integrity of rectal wall become crucial.

4. Future insights

Most of the series so far published reported on PCa patients often diagnosed with locally advanced (stage T2c–T4N0) disease who received initial RT in the conventional or lower dose era (≤ 70 Gy). Currently outcomes with dose escalation have indicated significant gains^{1–4} compared with the lower doses of RT, and men are less likely to present with such advanced disease. These improvements in disease presentation and RT delivery, would theoretically make the risks of local relapse less likely. On the other hand, since patients are now usually treated with higher radiation doses for their primary therapy (75–80 Gy), it is still unknown whether morbidity from a salvage local therapy will be more severe and thus overcome the potential benefit of a re-irradiation course. In conclusion, some caveats should be placed in extrapolating biological effects to very large fraction size, as well as monitoring long term tolerance, particularly of the urethra which is an unavoidable organ at risk. These latter uncertainties need to be addressed by appropriate randomized trials with a sufficiently long follow-up. At present, since no clear evidence has yet emerged from randomized trials, there is a lack of data regarding the better therapeutic option for post-radiation recurrent disease. In this scenario, patients selection performed on individual bases could be considered a reliable criterion to identify the most appropriate treatment modality, including a pioneering approach such as re-irradiation with cutting-edge techniques. Enrollment of these patients in clinical trials is highly warranted.

Conflict of interest

None declared.

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