



11C Choline PET Guided Salvage Radiotherapy with Volumetric Modulation Arc Therapy and Hypofractionation for Recurrent Prostate Cancer after HIFU Failure: Preliminary Results of Tolerability and Acute Toxicity

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The purpose of this work was to evaluate tolerance, feasibility and acute toxicity in patients undergoing salvage radiotherapy after high-intensity focused ultrasound (HIFU) failure. From 2005 to 2011 a total of 15 patients were treated with HIFU as primary radical treatment. Between July 2011 and February 2013, all 15 patients presented biochemical relapse after HIFU and 11C choline PET documenting intraprostatic-only failure. Salvage EBRT was performed with moderate hypofractionation schedule in 28 fractions with volumetric modulation arc therapy (VMAT). Genito-urinary (GU) and rectal and bowel toxicity were scored by common terminology criteria for adverse events version 4 (CTCAE V.4) scale. Biochemical response was assessed by ASTRO Phoenix criteria. Median age of patients was 67 years (range: 53-85). The median Gleason score was 7 (range: 6-9). The median prostate specific antigen (PSA) at the time of biochemical relapse after HIFU was 5.2 ng/mL (range: 2-64.2). Seven of the 15 patients received androgen deprivation therapy (ADT) started after HIFU failure, interrupted before 11C choline PET and radiotherapy. Median prescribed dose was 71.4 Gy (range: 71.4-74.2 Gy) in 28 fractions. No radiation related major upper gastrointestinal (GI), rectal and GU toxicity were experienced. GU, acute grade 1 and grade 2 toxicities were recorded in 7/15 and 4/15 respectively; bowel acute grade 1 and grade 2 toxicities in 4/15 and 1/15; rectal acute grade 1 and grade 2 toxicities in 3/15 and 2/15 respectively. No grade 3 or greater acute or late toxicities occurred. Biochemical control was assessed in 12/15 (80%) patients. With a median follow up of 12 months, three out of 15 patients, with biochemical relapse, showed lymph-nodal recurrence. Our early clinical results and biochemical data confirm the feasibility and show a good tolerance of the 11C choline PET guided salvage radiation therapy after HIFU failure. The findings of low acute toxicity is encouraging, but longer follow-up is needed to assess late toxicity and definitive outcomes.

Key words: PET; HIFU; Salvage radiotherapy; Prostate.

Introduction

Prostate cancer (PC) is the most common cancer in men and the second cause of cancer mortality, excluding primary lung cancer. Several local treatment approaches have been proposed for PC patients.

Abbreviations: ADT: Androgen Deprivation Therapy; CT: Computer Tomography; CTCAE V.4: Common Terminology Criteria for Adverse Events Version 4; CTV: Clinical Target Volume; ECOG: Eastern Cooperative Oncology Group; EBRT: External Beam Radiation Therapy; G: Grade; GU: Genito-urinary; HIFU: High-intensity Focused Ultrasound; OAR: Organ at Risk; PC: Prostate Cancer; PET: Positron Emission Tomography; PTV: Planning Target Volume; PSA: Prostate Specific Antigen; RA: RapidArc Technique; VMAT: Volumetric Modulation Arc Therapy; 3DCRT: 3-Dimensional Conformal Radiation Therapy.

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High-intensity focused ultrasound (HIFU) is a relatively new local treatment applied in cancer treatment. HIFU causes tissue ablation by means of intense ultrasound waves with focused heating of the targeted tissues. HIFU technique has been investigated for various decades in different sites. In prostate gland, HIFU has been originally proposed for benign diseases, but was then rapidly introduced as a non-invasive option for PC with a definitive or salvage intent (1-5). Several results, regarding biochemical (PSA decreasing) and pathological (high rate of negative biopsies or negative specimen of prostatectomy) data after HIFU have been published, evidencing its efficacy, but only in selected patients (1-5).

For more than two decades, external beam radiation therapy (EBRT) has been established as a standard option for the radical treatment of localized PC. EBRT has significantly evolved from 2-dimensional to 3-dimensional conformal radiation therapy (3D-CRT) and more recently intensity modulated radiation therapy (IMRT) and image guided radiation therapy (IGRT) has been introduced in radiation oncology departments. Based on the original investigation of Otto (6), Rapid-Arc technique (RA), as volumetric modulation arc therapy (VMAT), with IG integrated on RT delivery system, has been recently introduced in clinical practice after an intensive validation at planning level where it was compared to IMRT or other approaches, in a series of studies on various indications.

Over the last few years, hypofractionation has been adopted as a new strategy of EBRT fractionation in prostate cancer. The radiobiologic assumption is that PC cells have a higher sensitivity to fraction size, due to lower alpha/beta ratio, then late responding organs at risk (OAR) such as the rectum or bladder (7); thus, short schedules can represent a convenient and effective option for PC patients, and also a cost saving choice for health system (8).

The study described here is being reported because of the rare and atypical treatment approach including salvage irradiation after HIFU failure in PC patients. While the use of HIFU as salvage local treatment after RT is usual, there is a paucity of data in the literature on RT after HIFU (9-11). In the current study we retrospectively analyzed the feasibility and acute toxicity profile of PC patients treated with HIFU as primary treatment and, after biochemical failure and positive 11C choline for local relapse, with salvage RT using moderate hypofractionation and VMAT by means of RA technique. To the best of our knowledge, this is the first experience regarding the use of hypofractionation schedule in this setting of patients.

Materials and Methods

Fifteen patients were treated with HIFU from 2005 to 2011. Six of them were treated twice with HIFU to both lobes.

Between July 2011 and February 2013, all fifteen patients, presenting biochemical relapse after HIFU, underwent salvage EBRT. All patients were evaluated by radiation oncologists after a PSA failure following HIFU, and it was assessed based on Stuttgart definition (a PSA rising of 1.2 ng/mL above nadir). All patients were also submitted to 11C choline before EBRT. Intra-prostatic only pathologic accumulation of the tracer was documented for all cases. No biopsy on PET-positive intraprostatic region was performed. ADT after PSA failure following HIFU was prescribed in seven cases before radiation treatment, based on Urologist decision. However, ADT was interrupted in all cases before the 11C PET Choline, usually 6 months before, to have a basal treatment value and then to evaluate biochemical response after salvage RT without ADT influence. This treatment approach was applied in 7 out of 15 patients and duration of ADT before treatment ranged between 2 and 20 months (median 6). Patient data were prospectively collected and retrospectively evaluated for the present study. All patients had PC with clinical stage T1b-c, T2a-c; N0, M0, age <85 years, and eastern cooperative oncology group (ECOG) performance status 0-1. Pre-treatment evaluation consisted of documented history and physical examination, including performance status and digital rectal examination. IPSS score of 10 was considered the cut-off to exclude patients at risk for urinary symptoms (with this selection method two patients were previously excluded by the treatment procedure during first clinical evaluation).

Specific recommendations were suggested regarding daily preparation: comfortably full bladder (patients were request to drink 250-300ml of water just after having emptied the bladder and 30 min before each treatment session), and possibly empty rectum. Patients were submitted to planning CT in the treatment position (supine, arms on the chest, no cast or immobilizing device). Axial images were 3 mm spacing, adjacent, from L2 to 10cm below the level of ischiatic lower bone margin. Three permanent tattoos were marked on the skin at the time of planning CT scan. Delineation of the targets and organs at risk (OAR: rectum, bladder, intestinal cavity for bowel, femoral heads) were performed by the radiation oncologist.

The targets were the prostate and seminal vesicles in all cases. Pelvic lymph nodes were contoured in addition when risk of lymph node involvement at the moment of failure was superior to 15%, according to Roach formula calculated with the last value of PSA. Pelvic lymph node irradiation, delivered simultaneously to the prostate and seminal vesicles by simultaneous integrated boost (SIB), was performed in 8/15 patients. Clinical target volume (CTV) 1 included the prostate, CTV2 consisted of CTV1 plus the entire seminal vesicles, and CTV3 consisted of CTV2 plus pelvic lymph nodes. No boost of dose was prescribed on intraprostatic PET positive accumulation of tracer. However, all PET positive

findings were inside prostate gland, included in all cases on CTV1. Planning target volumes (PTV) were defined as CTV plus 8mm margin in all directions except cranial–caudal, where a 10mm margin was used; The median prescribed dose to PTV1 was 71.4Gy in 28 fractions (2.55 Gy per fraction). The range was between 71.4Gy and 74.2Gy. (2.55-2.65Gy per fraction). Median dose to the seminal vesicles was 65.5 (2.34 Gy per fraction), in the range between 61.6-65.5Gy (2.2-2.34 per fraction). The median dose to PTV3, volume irradiated in 8/15 patients, was 51.8Gy (1.85Gy per fraction), between 50.4 and 51.8 (1.8-1.85). Posteriorly, an overlap structure (Boolean intersection volume between PTV and rectum) was defined to receive a prescription dose of 65.5Gy, for respecting constraints of rectal volume. When pelvic lymph nodes had to be irradiated, an isotropic margin of 5-7mm from pelvic lymph node CTV was used. All patients were treated in 28 fractions with a moderate hypofractionated schedule for PC target.

Treatments have been performed with V-MAT (RapidArc[®]) technique (6). VMAT treatments were delivered with 6MV beams from either a Clinac DHX or a TrueBeam[®] facility, both equipped with a Millennium 120-MLC (multileaf collimators with 5mm leaves in the central 20cm). Plans were optimized with the progressive resolution optimizer in Eclipse (varian) treatment planning system, version 10, using two full arcs. For all PTVs, the planning objectives for targets were >95% of each prescribed dose (D95%). Maximum dose < 107% was requested for PTV1 only. OAR planning objectives were as follows: for rectum V50Gy < 45%, V60 Gy < 30%, V65 Gy < 20%, D_{max} < 70Gy; for bladder V60 Gy < 35%; for femurs (in particular femoral heads) D1cm³ < 50Gy.

Genito-urinary (GU) and rectal and bowel symptoms were scored prospectively during treatment and subsequently in the follow-up, using the common terminology criteria for adverse events version 4 (CTCAE V.4) scale. Biochemical response was assessed by ASTRO phoenix criteria (+2 from Nadir of PSA during follow-up). Follow-up visits were scheduled every week during the treatment at 4 and 12 weeks after the treatment.

Results

At initial diagnosis by biopsy, the median Gleason score was 7 (range: 6-9). The median PSA at the moment of HIFU was 11 (48-60). The median age of the patients at the time of HIFU was 63 years (range: 50-83). The median age of the patients at the time of RT was 67 years (range: 53-85). The median value of prostate specific antigen (PSA) at the time of biochemical relapse after HIFU (before Salvage RT) was 52ng/mL (range: 2-64.2). The median time between HIFU and RT was 30 months (8-70). The radiation treatment was

Table I

Demographic results at the time of HIFU and before Salvage RT.

	Median (range)	
Gleason score at biopsy before HIFU	Median (range)	7 (6-9)
Age (years) at HIFU	Median (range)	63 (50-83)
PSA at HIFU	Median (range)	11 (48-60)
Age (years) at RT	Median (range)	67 (53-85)
PSA at Salvage RT	Median (range)	4.59 (0.18-64.2)

well tolerated and completed by all patients. Hypofractionated RA treatments were completed in all 15 patients. No major radiation related gastrointestinal (GI) and GU toxicity were found. Demographic results at the time of HIFU and before Salvage RT are presented in Table I.

For the baseline status report, no rectal or bowel or GU symptoms were found during the recruitment before the beginning of Salvage RT. Acute toxicities ≤ 2 were common during the treatment or in early follow-up (within the first 3 months). According to CTCAE V.4 scoring, the acute adverse GU events in the population of study included cases of cystitis non-infective, hematuria, urinary frequency, urinary tract pain as follows: grade (G1) in 7/15 (47%) and G2 4/15 (27%) patients. One case of G2 urinary obstruction, with placement of urinary, suprapubic catheter placement, was found 2 weeks after the end of the treatment. No other cases of any grade of urinary incontinence, urinary tract obstruction or urinary retention were found; after this episode, the patient did not complain other acute or late urethral symptoms. Acute rectal (pain/tenesmus) G1 and G2 toxicities were 3/15 (20%) and 2/15 (13%) respectively; no other types of rectal events were found. The acute adverse bowel events in the subgroup of 8/15 irradiated simultaneously to the pelvic lymph node region included diarrhoea and abdominal pain as follows: G1 in 4/8 (50%) and G2 in 1/8 (12.5%) patients. No G3 or greater toxicities were found in acute setting. Late toxicities and outcomes are not the objective of this study. However, when the minimum follow-up was more than 6 months, toxicities (defined as “late”) were observed as rare and included urinary tract pain and hematuria \leq G2: 3 cases of G1 GU and 1 case of GU G2 with no cases of any type of upper GI or late rectal symptoms. No cases of additional urinary incontinence were recorded during follow-up. Considering that 6 patients were previously submitted to HIFU two times, we evaluated toxicity profile in this specific subgroup: only one case out of 6 presented acute G2, in GU, while another one presented late G2 rectum and GU toxicity.

Biochemical control was assessed in 12/15 patients. All patients were followed-up with PSA evaluation and 11C choline PET, prescribed in case of PSA following EBRT up to 1ng/mL. With a median follow-up of twelve months

(range: 2-20), three out of 15 patients, with biochemical relapse, showed recurrence and were treated: All three patients were treated with simultaneous pelvic lymph nodes regions irradiation, concomitantly to prostate and seminal vesicles, after HIFU. The first one was a 74 years old patients, with a diagnostic biopsy documenting Gleason score of 9, PSA before HIFU of 3.6 ng/mL and a PSA at relapse of 64 ng/mL. After further PSA relapse and PET documenting lymph node and bone metastases after salvage RT, was treated with hormone therapy and after further progression with Docetaxel; the second one was a 60 years old patients, with a Gleason score of 6, PSA before HIFU of 11 ng/mL and a PSA of 7.49 ng/mL at relapse before salvage RT. After a further PSA failure was re-staged with PET choline documenting an isolated pelvic lymph node recurrence. Thus, was included in a study for oligometastases, and treated with stereotactic body radiation therapy (SBRT) and then hormone therapy. The last one, was a 63 years old patients with a Gleason score of 8, initial PSA of 4.8 ng/mL and a PSA at relapse of 2.30 ng/mL, after PSA and imaging recurrence on sternal bone, was irradiated on this site and submitted to hormone therapy.

Clinical, pathological and radiological details of the patient population are summarized on Table II.

Discussion

Radiotherapy following prostatectomy is well tolerated as salvage treatment and offers a potentially curative effect for selected patients with biochemical or clinical failure after radical retropubic prostatectomy. On the contrary, salvage RT after HIFU failure has been rarely utilized and there is a paucity of data in recent years on this subject. However, given the increasing use of HIFU modality as primary treatment in patients who refuse or are not suitable for surgery, the referral of patients for salvage radiotherapy after HIFU is increasing and some experiences are recently available in the literature (9-11).

Pasticier *et al.* (9) investigated the role of RT as salvage treatment after HIFU relapse in 45 patients. A median dose of 71 Gy was delivered with daily fractions of 1.8-2 Gy. With a minimum follow up of 40 months and a minimum of 12 months between HIFU and EBRT. Only 1 patient (2.2%) experienced G3 toxicity, requiring endoscopic intervention because of hematuria. G1 urinary and G1 intestinal symptoms occurred in 60% and 46.7% of patients, respectively, while G2 was recorded in 8% and 13.3% respectively. No other major toxicities were found.

Table II
Details of the patient population analysed before and after HIFU and Salvage RT.

Patient number	Age	Gleason score at biopsy before HIFU	PSA at HIFU (ng/mL)	PSA at recurrence after HIFU (ng/mL)	Hormone therapy	PET choline on prostate	Time between HIFU and salvage RT (months)	Dose to the prostate/ seminal vesicles/ pelvic lymph nodes (Gy)	Clinical status at last follow-up control
1	78	7 (3 + 4)	4.8	4.00	Yes	Positive	45	71.4/65.5/-	Biochemical non-evidence of disease
2	63	7 (3 + 4)	60	10.46	No	Positive	59	74.2/65.5/51.8	Biochemical non-evidence of disease
3	72	7 (4 + 3)	4.76	6.28	Yes	Positive	22	74.2/65.5/51.8	Biochemical non-evidence of disease
4	60	6 (3 + 3)	11	7.49	No	Positive	43	74.2/65.5/51.8	Metastatic lymph node disease
5	85	7 (4 + 3)	9	7.64	Yes	Positive	37	74.2/65.5/51.8	Biochemical non-evidence of disease
6	63	8 (5 + 3)	4.8	2.30	Yes	Positive	14	71.4/65.5/51.8	Metastatic bone disease
7	74	9 (5 + 4)	3.16	64.02	Yes	Positive	8	71.4/65.5/51.8	Metastatic bone disease
8	67	6 (3 + 3)	12	27.86	No	Positive	71	74.2/65.5/51.8	Biochemical non-evidence of disease
9	62	7 (3 + 4)	21	2.00	No	Positive	13	71.4/65.5/-	Biochemical non-evidence of disease
10	65	6 (3 + 3)	3.3	6.74	No	Positive	20	71.4/65.5/-	Biochemical non-evidence of disease
11	71	7 (3 + 4)	4.5	4.50	Yes	Positive	34	74.2/65.5/51.8	Biochemical non-evidence of disease
12	68	7 (3 + 4)	5.75	4.59	No	Positive	10	74.2/65.5/-	Biochemical non-evidence of disease
13	53	6 (3 + 3)	5	3.04	No	Positive	38	71.4/65.5/-	Biochemical non-evidence of disease
14	70	6 (3 + 3)	35	3.60	No	Positive	25	71.4/65.5/-	Biochemical non-evidence of disease
15	65	6 (3 + 3)	11	5.25	No	Positive	30	71.4/65.5/-	Biochemical non-evidence of disease

Immediately after combined HIFU and EBRT, 7 additional patients (15%) developed urinary incontinence.

A large retrospective study of 100 patients, all submitted to RT after HIFU with local histologically proven recurrence, was conducted in several French departments (10). With a median range of 10 months between the two treatments and a median EBRT dose of 72 Gy, additional toxicity reported was mild. After salvage RT, G1, and G2 early urinary side effects were experienced in 22% and 29% respectively, while G1 and G2 early intestinal symptoms were recorded in 24% and 15%. G3 early urinary toxicity was found in 3% of the study population. Compared to the optimal acute toxicity profile, the severity of adverse events associated with salvage radiotherapy in patients failing HIFU in late setting remains similar for urinary (24% G1 and 23% G2) and was reduced for intestinal symptoms (10% G1 and 2% G2).

Ripert *et al.* (11) reported the study of 7 patients with local recurrence after HIFU treatment received salvage EBRT without adjunctive ADT and followed-up for a median of 37 months. The mean interval between the HIFU procedure and EBRT was 11.7 months. Two of the 7 patients experienced minor urinary symptoms and 1 patient experienced minor gastrointestinal symptoms. In 2 of these patients, symptoms persisted at 2 years. One patient experienced G3 GU toxicity after the first year post-EBRT and the patient required surgical management for cystitis.

With a minimum follow-up of 24 months, a total of 24 patients failing after HIFU, underwent salvage EBRT delivered by conventional 3DCRT technique and were retrospectively evaluated at Turin University (12). Acute GI toxicity $G \leq 2$ was 29.2%; acute GU toxicity $G \leq 2$ was 45.8%, with G3 in 8.3% of patients presenting. At 3 months urine incontinence was found as follow: G1 in 8.33%, G2 in 28.33%, and G3 in 4.16%. Also in this experience, salvage EBRT after HIFU failure was feasible and allowed to obtain satisfactory biochemical control rates.

If tolerability with salvage EBRT after HIFU with conventional fractionation and technique used in these published reports seems to be mild, still no data are available with hypofractionation and Intensity modulated techniques in this setting.

The current study is the first study to describe the feasibility of a moderate hypofractionation using VMAT by RapidArc. Despite treatment time being slightly reduced with hypofractionation schedule compared to conventional fractionation (28 fractions versus 33-40 fractions), the acute toxicity profile in our experience remains acceptable, in absence of G3 or greater acute local side effects. This good acute toxicity profile (also in the subgroup of patients submitted to HIFU two

times) can suggest the possible impact of VMAT technique in reducing surrounding healthy tissue involvement, confirming previous optimal data on pelvis irradiation with VMAT in our Institute and other recently published data on rotation IMRT technique (13-15). Obviously, with a short median follow-up as the present study, it is difficult to conclude that after HIFU, moderate hypofractionation with VMAT could be proposed as well as conventional fractionation. The main concern regards late toxicity, especially to urethra. Thus, to maximize the use of IMRT/VMAT a urethra sparing technique and a self-absorbable spacer between prostate and rectum, in order to reduce as low as possible the dose at these levels, can be possible strategies for a future prospective study.

In the present report, interestingly seems to be also the absence of incontinence compared to other similar series, with lower prescribed radiation doses to prostate gland (12). We believe that continence can be negatively affected by salvage RT. However, it can be similar to what happen usually in the setting of patients submitted to prostatectomy and subsequently irradiated, where urinary continence can be mainly influenced by the adopted surgical technique before RT and by experience of urologist. In the present case, we cannot exclude that the continence status can be affected by HIFU procedure and by the experience of the team performing the focused ablative procedure safely for urethra and bladder neck.

The here reported good GU profile of the patients after HIFU and salvage RT is also to correlate to a careful patient selection when a IPSS score cut off of 10 was considered to exclude patients at risk for urinary symptoms.

Clinical outcome was not the end point of the current study and it will be object of a further paper on this issue with a larger study population and longer follow-up. However, the presence of three cases of recurrences during follow-up opens a reflection into the correct selection of the patients suitable for salvage EBRT after HIFU. Adverse features, such as a high initial PSA, high Gleason score, high PSA velocity or a short disease-free interval should be seriously considered before local treatment selection and prospective trials are invoked to investigate this issue.

Although the level of evidence assessing efficacy outcomes of HIFU remains low for relative short follow-up experiences, and serious limitations for many patients, this ablative technique has been used in selected cases as primary treatment for localized PC (16). There are a lot of concerns regarding the modality to define a recurrence after HIFU: in fact no international consensus exists on objective response criteria. Obviously, it could also be the main criticism of the current study, where no re-biopsy was performed in biochemical failing patients

after HIFU. In the present study, the biochemical relapse after HIFU was assessed based on Stuttgart definition (17). This definition of biochemical failure, approved by European association of Urology in 2009, is specific to patients treated with HIFU and states that such failure occurs when the patient's PSA increases beyond the PSA nadir +1.2 ng/mL. Recently, the ASTRO Phoenix definition (PSA +2 ng/mL above nadir) for biochemical relapse used in radiotherapy, has been proposed. Considering that all fifteen patients were treated with HIFU from 2005 to 2011, in most of them Stuttgart definition has been used because of the absence of other significant definition criteria to define biochemical relapses. In our study the patients were also submitted to 11C choline PET before EBRT salvage treatment to confirm intraprostatic recurrence and exclude distant metastases. PET with radiolabeled choline (11C and 18F) or acetate tracers (11C acetate), is increasingly applied in PC restaging after biochemical relapse (18). PET can be considered more reliable since the biochemical relapse after primary therapy is associated with PSA values > 2 ng/mL (19-21), with a sensitivity ranging from 81% to 100% in identifying local relapses (31, 32). In all patients of our analysis PET showed local relapse on prostate gland. Even if choline PET is now frequently accepted and used by scientific community for restaging after primary treatment (including radical prostatectomy and radical radiotherapy), no data about its use in the specific setting of failure after HIFU are still available in literature. Potentially, PET could also have an interest not only for restaging but also for target definition in salvage EBRT and was used in selected cases (22-24). Nevertheless, PET for planning should still be considered an experimental procedure and it was not utilized with this end-point in the present study.

In our study no multi-parametric MRI was utilized to detect and describe failure after HIFU. Dynamic contrast-enhanced MRI, for example seems particularly accurate in this setting. Thus, these recent advances in (molecular and morphological) imaging could be integrated for intra-prostatic failure decisional algorithm and target definition and it may potentially improve the outcome of salvage therapies, including RT after HIFU (25).

In conclusion, our first clinical results seem to confirm the feasibility and good tolerance of PET guided salvage hypofractionated EBRT after HIFU failure. The EBRT course was completed in all patients with very low morbidity in acute setting. Biochemical outcomes are promising but a longer follow-up is needed to assess definitively the late tolerability and effectiveness of hypofractionated EBRT by VMAT as salvage therapy after HIFU failure. Nevertheless, this kind of approach is still to consider under investigation in this setting; several criticisms affect the present study: the first clear observation regards the small series investigated: 15 patients are few to be the study conclusive; the second is that the study is a

retrospective study, with the well known limits of this kind of evaluations; the crucial issue of the lack of histopathological assessment was previously discussed; other lacks also regard the need of more accurate grading scales and the needs to better assess the urinary and rectal basal condition before salvage RT (for example performing a rectoscopy before irradiation, etc.). A prospective study, considering all this pitfalls to avoid from the beginnings, could be advocated to obtain further data to confirm the feasibility and the possible effectiveness of the approach proposed in the present report.

Conflict of Interest

None for all authors.

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