REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 24 (2019) 472–480

Available online at www.sciencedirect.com

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Original research article

Multiparametric magnetic resonance imaging-guided salvage radiotherapy in prostate cancer

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ARTICLE INFO

Article history:
Received 1 May 2019
Received in revised form
12 June 2019
Accepted 10 July 2019
Available online 8 August 2019

Keywords:
Biochemical failure
Multiparametric MRI
Prostate cancer
Radical prostatectomy
Salvage radiotherapy

ABSTRACT

Aim: To analyse the efficacy and toxicity of postprostatectomy SRT in patients with a BCR evaluated with mpMRI.
Background: Multiparametric magnetic resonance imaging (mpMRI) has the ability to detect the site of pelvic recurrence in patients with biochemical recurrence (BCR) after radical prostatectomy (RP). However, we do not know the oncological outcomes of mpMRI-guided savage radiotherapy (SRT).
Results: Local, lymph node, and pelvic bone recurrence was observed in 13, 4 and 2 patients, respectively. PSA levels were significantly lower in patients with negative mpMRI (0.4 ng/mL [0.4]) vs. positive mpMRI (2.2 ng/mL [4.1], $p = 0.003$). Median planning target volume doses in patients with visible vs. non-visible recurrences were 76 Gy vs. 70 Gy. Overall, mean follow-up was 41 months (6–81). Biochemical relapse-free survival (bRFS) at 3 years was 82.3% and 82.5%, respectively, for the negative and positive mpMRI groups ($p = 0.800$). Three-year rates

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https://doi.org/10.1016/j.rpor.2019.07.008

of late grade ≥2 urinary and rectal toxicity were 14.8% and 1.9%, respectively; all but one patient recovered without sequelae.

Conclusion: SRT to the macroscopic recurrence identified by mpMRI is a feasible and well-tolerated option. In this study, there were no differences in bRFS between MRI-positive and MRI-negative patients, indicating effective targeting of MRI-positive lesions.

1. Background and aim

Salvage radiotherapy (SRT) is the treatment of choice in patients with prostate cancer (PCa) whose prostate-specific antigen (PSA) levels remain high after radical prostatectomy (RP) and in those who develop biochemical recurrence (BCR; PSA >0.2 ng/mL).[1] The outcome of SRT varied depending on the particular mix of known risk factors in each patient, including the initial and kinetic PSA values, Gleason score, tumour dissemination, and margin status. It is estimated that up to 50% of these patients will develop disease progression within 5 years.[2] However, these outcomes can be improved by early administration of SRT when the PSA is still low (<0.5 ng/mL).[3]

In patients with low PSA values, it is difficult to identify the site of recurrence with conventional imaging studies, such as bone scintigraphy and computed tomography (CT). However, more advanced imaging techniques, such as multiparametric magnetic resonance imaging (mpMRI) and positron-emission tomography (PET)-CT with choline or prostate-specific membrane antigen (PSMA) tracers, can more effectively identify the location—whether local, nodal, or distant—of the recurrence.[4,5] At present, it is not known whether the presence of local recurrence detected by these imaging techniques is a predictor of worse prognosis. However, a key benefit of these advanced modalities is that they can help to accurately determine the topography of the lesion(s), thus allowing the clinician to contour with high precision volumes to deliver high dose radiation to eradicate the local disease and, thereby, prevent or delay distant progression. In patients with nodal and/or distant oligometastatic recurrence, metastatic lesions can be irradiated with or without concurrent androgen deprivation therapy (ADT).[5] Although dose escalation (up to 70 Gy) to the prostate bed is associated with increased urinary toxicity, studies suggest that this only minimally impacts the quality of life.[6] The available data indicate that more conformal radiotherapy techniques, such as IMRT or volumetric arc therapy (VMAT), allow for higher doses to the prostate bed with acceptable toxicity.[7]

In this context, the aim of this study was to analyse the efficacy and toxicity of postprostatectomy SRT in patients with a biochemical relapse evaluated with mpMRI.

2. Materials and methods

2.1. Patients

This retrospective, observational study included the first 57 consecutive patients at our institution with post-prostatectomy BCR (PSA > 0.2 ng/mL, with two consecutive rises) who underwent mpMRI prior to SRT planning. All patients were treated between the years 2010 and 2014. We included all patients with a local macroscopic recurrence in the prostatectomy bed and those with nodal and/or pelvic bone oligo-recurrence (<5 metastases). Due to the presence of risk factors associated with disseminated disease, 19 patients underwent bone scans and/or choline PET-CT. In 3 of these 19 cases, the imaging scans identified multiple distant metastases; consequently, these patients were excluded from the final analysis, leaving a total of 54 patients.

In all cases, testosterone levels measured ≤30 days prior to the mpMRI were within normal limits. The maximum time between mpMRI and treatment initiation (SRT ± ADT) was 15 days.

The study was approved by the Clinical Research Ethics Committee of the Quirónsalud Madrid University Hospital, Spain (approval code: CEIm-FJD, November 27, 2018; act no. 21/18).

2.2. MRI protocol and image analysis

The mpMRI protocol has been described in detail elsewhere.[8] Briefly, we used 3T-MRI (Signa HDxt 3.0 T G.E. Healthcare; Milwaukee, WI, USA) at a gradient strength and slew rate, respectively, of 33 mT/m and 120 T/m/s. The surface coil was an 8-channel array (Torso phased array). T1- and T2-weighted sequences were used for morphological imaging. The functional studies included both DCE and DWI imaging.

The apparent diffusion coefficient (ADC) map was calculated using DWI and *b*-values of 0 and 1000 s/mm^2, respectively. Gadolinium contrast was used for DCE imaging. A qualitative review of the DCE was performed. The uptake patterns of suspicious lesions were classified by curve type, as follows: type 1 (slow, continuous uptake), type 2 (initial uptake followed by a plateau), or type 3 (strong initial uptake followed by washout). A radiologist with expertise in urologic oncology retrospectively reviewed the mpMRI images. Radiological findings were scored as follows: negative finding (absence of recurrence; score = 1), indeterminate findings (score = 2), and positive findings (presence of recurrence, score = 3). Local recurrence (LR) was considered positive when ≥2 sequences were abnormal. Lymph node recurrence (LNR) was considered pathological when the short axis diameter was >8 mm, the MRI signal was heterogeneous, and there was an irregular contour. Bone metastases (BM) were considered pathological when T2 and DWI showed evidence of abnormalities.

2.3. Salvage treatment

IMRT was used to deliver the salvage treatment in all cases. The planning CT was performed in the supine position. Patients were instructed to arrive with a full bladder and empty rectum. Target contouring was done in accordance with the Radiation Therapy Oncology Group (RTOG) atlas for SRT for PCa[9] and for pelvic lymph node delineation.[10] However, due to difficulties with anatomical reproducibility of the rectum and bladder, automatic fusion of the mpMRI and simulation CT could not be performed in all patients. In these cases, tumour contouring was performed by an experienced uro-radiologist to ensure an adequate margin of safety around the tumour recurrence site. The planning target volume (PTV) was created by expanding the clinical target volume (CTV) 7 mm posteriorly and 1 cm in all other directions in the prostate bed, and 7 mm in the LNR and the BMs. Patients with postoperative BCR but without a visible lesion on the imaging scans received SRT to the whole prostate bed at doses ranging from 64 to 72 Gy. Higher doses to the whole prostate bed (64–80 Gy) were prescribed in the case of macroscopic local recurrences. In cases with pelvic LNR, IMRT was administered to the pelvic lymph nodes (52.8 Gy, 1.6 Gy/fraction) and to the prostatectomy bed (66 Gy, 2 Gy/fraction). A simultaneous integrated boost (SIB) was administered to the affected lymph nodes (72.6 Gy, 2.2 Gy/fraction). Pelvic BMs were included within the IMRT treatment volume with SIB (72.6 Gy, 2.2 Gy/fraction). In some cases, the prescribed dose was de-escalated due to non-compliance of the dose volume histograms. ADT was prescribed at the discretion of the clinician. All patients underwent close monitoring of testosterone levels. After suspending ADT, all patients had normal testosterone levels at the last follow-up.

2.4. Follow-up

Follow-up visits were performed weekly during the treatment phase after which the follow-up schedule was as follows: every 3 months for the first 2 years, then every 6 months until year 5, and annually from then on. PSA values were obtained and a digital rectal exam (DRE) was performed at all follow-up visits.

Biochemical failure after SRT was defined as nadir PSA level +0.2 ng/mL.[1] Imaging scans were performed in all patients who had developed biochemical failure. Acute toxicity (defined as any toxicity occurring ≤3 months after SRT) and late toxicity were evaluated according to the Common Toxicity Criteria for Adverse Events, version 4.0.

2.5. Statistical analysis

The study characteristics were described as median and interquartile range [IQR] or mean and standard deviation (SD). Qualitative factors were described with absolute (n) and relative (%) frequencies.

Patient characteristics at baseline were compared using the Chi-square test and the Fisher's exact test for categorical variables and Student's t test or the U Mann–Whitney test for continuous variables. The Kaplan–Meier method was applied to evaluate biochemical relapse-free survival (bRFS). The log-rank test with 95% confidence intervals (CI) was used to test for differences among groups. A Cox proportional hazards multivariate analysis was performed to identify independent prognostic factors for biochemical relapse-free survival (bRFS). Statistical significance was set at $p < 0.05$. All of the statistical analyses were performed with the SPSS program, v.21 (IBM Inc., Armonk, NY; USA).

3. Results

3.1. MRI results

Visible tumour recurrence on the mpMRI was detected in 18 of the 54 patients (33.3%). Locally-recurrent BMs were observed in 13 patients while PLN and pelvic bone metastases were observed in 4 and 2 patients, respectively (Table 2). The median PSA prior to mpMRI was 0.4 ng/mL [1.6]. PSA levels were significantly higher in patients with a positive mpMRI than in those with a negative mpMRI: 2.2 [4.1] vs. 0.4 [0.4] ng/mL ($p = 0.003$). The mpMRI was positive in 38.9% of the 37 patients with PSA ≤ 1 ng/mL and in 61.1% of cases with PSA > 1 ng/mL (Table 1).

3.2. Treatment

The median [IQR] time elapsed from RP to BCR was 13.5 months [39.5]. The median SRT dose in patients with negative mpMRI findings was 70 Gy (range, 64–74) vs. 76 Gy (range, 64–80) in those with a positive mpMRI. Seventeen patients (31.5%) received adjuvant ADT; of these, 8 had a positive mpMRI. The median duration of ADT was 10 [18] months. The mean time elapsed from the final ADT administration to the last follow-up was 28.2 [14.6] months.

3.3. Survival

All survival outcomes are shown in Table 3. Mean follow-up was 41 months (range, 6–81). Median post-SRT PSA nadir was 0.04 ng/mL (range, 0.003–3.89). After SRT, 20.4% (11/54) of patients developed biochemical failure. Survival rates for the whole cohort at 3-years were as follows: cancer-specific survival (CSS), 98% (95% CI, 94.1–100); overall survival (OS), 92.5% (95% CI, 85.3–99.6; bRFS, 82.3% (95% CI, 71.7–92.9). There was no significant difference in 3-year bRFS between the patients with negative and positive mpMRI scans (82.3% vs. 82.5%, $p = 0.8$); however, bRFS was significantly better in patients with a post-SRT PSA nadir ≤0.04 ng/mL (94.1% vs. 38.9%, $p < 0.001$), Fig. 1. On the univariate analysis, the only independent prognostic factor associated with bRFS was post-SRT PSA nadir (Tables 4). Among the patients achieving a PSA nadir ≤0.04 ng/mL, 65% (26/40) did not receive hormone treatment compared to those receiving ADT 35% (14/40).

3.4. Toxicity

Acute genitourinary (GU) ≥grade 2 was observed in 3.7% of the patients (2/54). No cases of acute gastrointestinal (GI) toxicity ≥grade 2 were observed. Late GU and GI toxicity rates ≥grade 2 were, respectively, 14.8% (8/54) and 1.9% (1/54) (Table 3), which resolved without any sequelae in eight of these nine patients

Table 1 – Patient and treatment characteristics for the entire cohort and stratified according to MRI findings.

Variables	All patients[b] (N = 54)	Negative MRI (N = 36)	Positive MRI (N = 18)	p-value[a]
Age, years	66.1 ± 6.4	65.2 ± 6.3	68 ± 6.3	0.126
Preoperative PSA, ng/mL	8 [5.3]	8 [5.8]	8 [4.5]	0.897
Pathologic T stage, *n* (%)				1.000
T2	40 (74.1)	27 (75)	13 (72.2)	
T3a	10 (18.5)	7 (19.4)	1 (5.6)	
T3b	3 (5.6)	2 (5.6)	1 (5.6)	
T4	1 (1.9)	0	1 (5.6)	
Pathologic N stage, *n* (%)				0.111
N0	20 (37.0)	16 (44.4)	4 (22.2)	
N1-Nx	34 (63.0)	20 (55.6)	14 (77.8)	
Pathologic Gleason score, *n* (%)				0.482
6	16 (29.6)	12 (33.3)	4 (22.2)	
7	25 (46.3)	17 (47.2)	8 (44.4)	
8–10	13 (24.1)	7 (19.4)	6 (33.3)	
Surgical margins after RP				0.847
Negative, *n* (%)	29 (53.7)	19 (52.8)	10 (55.7)	
Positive, *n* (%)	25 (46.3)	17 (47.2)	8 (44.4)	
Persistently positive PSA after RP				0.847
No, *n* (%)	28 (51.9)	19 (52.8)	9 (50.0)	
Yes, *n* (%)	26 (48.1)	17 (47.2)	9 (50.0)	
Time to first PSA recurrence, months	13.5 [39.3]	13.5 [32.5]	15.5 [48.3]	0.673
Time from surgery to MRI, months	23.5 [50.3]	16 [42.0]	38.5 [63.8]	0.393
Highest PSA before mpMRI and SRT, ng/mL	0.4 [1.6]	0.4 [0.4]	2.2 [4.1]	**0.003**
Highest PSA before RT				
≤1 ng/mL	37 (68.5)	30 (83.3)	7 (38.9)	**0.001**
>1 ng/mL	17 (31.5)	6 (16.7)	11 (61.1)	
PSA doubling time, months	7 [10.8]	6 [7.5]	9 [14.0]	0.170
ADT with SRT, *n* (%)	17 (31.5)	9 (25.0)	8 (44.4)	0.147
ADT duration, months	10 [18.0]	6 [18.0]	18 [16.8]	0.595
RT dose (EBD; Gy)	70 [8.0]	70 [4.0]	76 [0.6]	**<0.001**
SRT target volume				**0.004**
Prostate bed alone, *n* (%)	47 (87.0)	35 (97.2)	12 (66.7)	
Prostate bed + pelvis, *n* (%)	7 (13.0)	1 (2.8)	6 (33.3)	

MRI, magnetic resonance imaging; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy; EBD, equivalent biological dose; SRT, salvage radiation therapy.

[a] Significant differences are shown in bold text.

[b] All values are given as medians with IQR unless otherwise indicated.

(Table 5). On the univariate analysis, no independent factor was associated with late GU toxicity ≥grade 2 (Table 4).

4. Discussion

The management of BCR after radical prostatectomy presents a significant therapeutic challenge for clinicians. According to European treatment guidelines, the recommended treatment for BCR is early SRT (≥66 Gy) to the prostate bed when the PSA is still low (<0.5 ng/mL).[11] Spratt et al.,[12] recently developed a decision-making framework based on the findings from two key clinical trials (RTOG 9601[13] and GETUG-AFU-16[14]) to help guide the use of ADT with SRT. However, the imaging techniques used in those trials to identify the recurrence—CT and bone scans—have a poor capacity to detect the site of recurrence in patients with PSA levels <1 ng/mL; as a result, it is not clear whether those recommendations can be extrapolated to patients with evidence of macroscopic recurrence on the imaging tests.[15] In this sense, two national surveys conducted recently in Spain[16] and Switzerland,[17] concluded a high variability in the treatment of pelvic macroscopic recurrence after RP.

Traditionally, patients with biochemically-recurrent disease but with an undetectable lesion have been treated "blindly" using the contouring guidelines for SRT established in the literature.[9,10,18] However, in 20–25% of these patients, the recurrence is located outside of the CTV,[19,20] which implies a higher risk of treatment-related toxicity. For this reason, it is essential to accurately determine—when possible—the location of the recurrent lesion in patients with low PSA levels. Fortunately, the development of advanced imagining modalities, such as mpMRI has improved our capacity of detecting the site of recurrence in these patients.[4]

Despite the low median PSA (0.4 ng/mL) in our cohort, the pelvic mpMRI detected the location of the recurrence in 33% of the patients, a finding that is consistent with previously-reported detection rates (20–40%) for patients with low PSA values.[4]

However, it is worth noting that other imaging modalities, such as PET-CT with 68 Ga-PSMA have been shown to detect recurrences in 60–70% of patients with PSA < 1 ng/mL.[21,22] Nevertheless, choline PET-CT might be useful in patients with

Table 2 – Distribution of macroscopic pelvic recurrences detected by mpMRI.

Local recurrence	Pelvic lymph nodes	Pelvic bone metastases	Total
No	No	No	36
		Yes	1
	Yes	No	4
		Yes	0
Yes	No	No	12
		Yes	1
	Yes	No	0
		Yes	0

elevated PSA to detect pelvic recurrence and distal metastasis in a similar detection rate as mpMRI, as previously described by our group.[23]

In our study, SRT planning was based on the mpMRI findings, thus ensuring that the macroscopic tumour was included within the CTV. Moreover, the data provided by the mpMRI allowed us to limit the size of the target volume, thus allowing for dose escalation and a better therapeutic ratio, which may explain why we found no differences in bRFS between the mpMRI-positive and mpMRI-negative patients. This hypothesis is further supported by Dirix et al.,[19] who evaluated 183 patients who underwent MRI prior to SRT. In that study, patients with evidence of pelvic macroscopic recurrence on the MRI had significantly worse bRFS than those without such evidence (2-year bRFS: 62.5% vs. 81.3%), which those authors attributed to two main factors: (1) the macroscopic recurrence was located outside the postoperative CTV in 25% of patients and (2) those patients did not receive an escalated radiotherapy dose. Additional support for this hypothesis is provided by the recent study by Schmidt-Hegemann et al.[24] Those authors used a similar study design to ours, except for the imaging technique (PSMA PET/CT), to evaluate patients ($n = 90$) prior to SRT. The following doses were administered: 70 Gy (range, 67.2–72 Gy) to the local macroscopic tumour, 66 Gy (range, 59.4–70.2 Gy) to the prostatic fossa, 60.8 Gy (range, 54–66 Gy) to PET-positive lymph nodes, and 50.4 Gy to the lymphatic pathways. The 2-year bRFS was 78%, with no significant differences between patients with PET-positive or PET-negative pelvic macroscopic recurrences (78% vs. 82%, $p = 0.392$), findings that are in line with our results. In another dose escalation study, Zilli et al. administered 74 Gy to the site of the local macroscopic recurrence detected on MRI. The results of that study were similar to ours, with no significant differences in 3-year bRFS rates between the MRI-positive and MRI negative patients.[25]

Our outcomes (3-year bRFS: 82%) are highly encouraging, especially considering that nearly one-fourth (13/54) of the patients in our study presented a macroscopic local recurrence and several patients also had nodal ($n = 4$) or pelvic bone ($n = 2$) oligo-recurrence. Moreover, these results compare favourably to the findings of studies that did not use image-guided SRT (2-year bRFS: 55–70%; 3-year bRFS: 54–63%),[26,27] as well as those that have used image-guided (MRI or PSMA PET) SRT (2y-bRFS: 78%; 3y-bRFS: 64%).[19,24,25] It is important to emphasize that the optimal treatment (either SBRT or radiotherapy to the whole pelvis with a boost to the lymph nodes) for patients with pelvic node oligo-recurrence remains unclear, although the results of the STORM trial (NCT03569241) are expected to clarify this question in the near future.

Nonetheless, it seems increasingly clear that patients with oligometastatic PCa are likely to benefit from local treatment (surgery or radiotherapy) to the metastatic lesion(s). In this regard, Palma et al. recently presented the findings of the

Table 3 – Efficacy and toxicity results after salvage radiotherapy based on mpMRI findings.

	All patients ($N = 54$)	Positive MRI ($N = 18$)	Negative MRI ($N = 36$)	p-value
Median follow-up	40 (6–81)	38.5 (6–55)	41 (17–81)	
PSA nadir	$n = 52$	$n = 16$	$n = 36$	
PSA nadir, median	0.04 (0.003–3.890)	0.04 (0.008–3.890)	0.04 (0.003–0.790)	
PSA ≤ 0.04 ng/mL	76.9%	62.5%	83.3%	0.153
PSA ≤ 0.1 ng/mL	80.8%	62.5%	88.9%	0.052
PSA ≤ 0.2 ng/mL	84.6%	75.0%	88.9%	0.231
Clinical Progression	$n = 54$	$n = 18$	$n = 36$	
Biochemical recurrence	11 (20.4%)	3 (16.7%)	8 (22.2%)	0.733
Mortality	$n = 53$	$n = 17$	$n = 36$	
Cancer-specific	1 (1.9%)	None	1 (2.8%)	0.321
Overall	4 (7.5%)	3 (17.6%)	1 (2.8%)	0.092
Acute toxicity ≥ 2	$n = 54$	$n = 18$	$n = 36$	
GU	2 (3.7%)	None	2 (5.6%)	0.547
GI	None	None	None	
Acute toxicity ≥ 3	$n = 54$	$n = 18$	$n = 36$	
GU	None	None	None	
GI	None	None	None	
Late toxicity ≥ 2	$n = 54$	$n = 18$	$n = 36$	
GU	8 (14.8%)	2 (11.1%)	6 (16.7%)	0.704
GI	1 (1.9%)	None	1 (2.8%)	0.998
Late toxicity ≥ 3				
GU	4 (7.4%)	2 (11.1%)	2 (5.6%)	0.594
GI	1 (1.9%)	None	1 (2.8%)	0.998

MRI, magnetic resonance imaging; GU, genitourinary; GI, gastrointestinal.

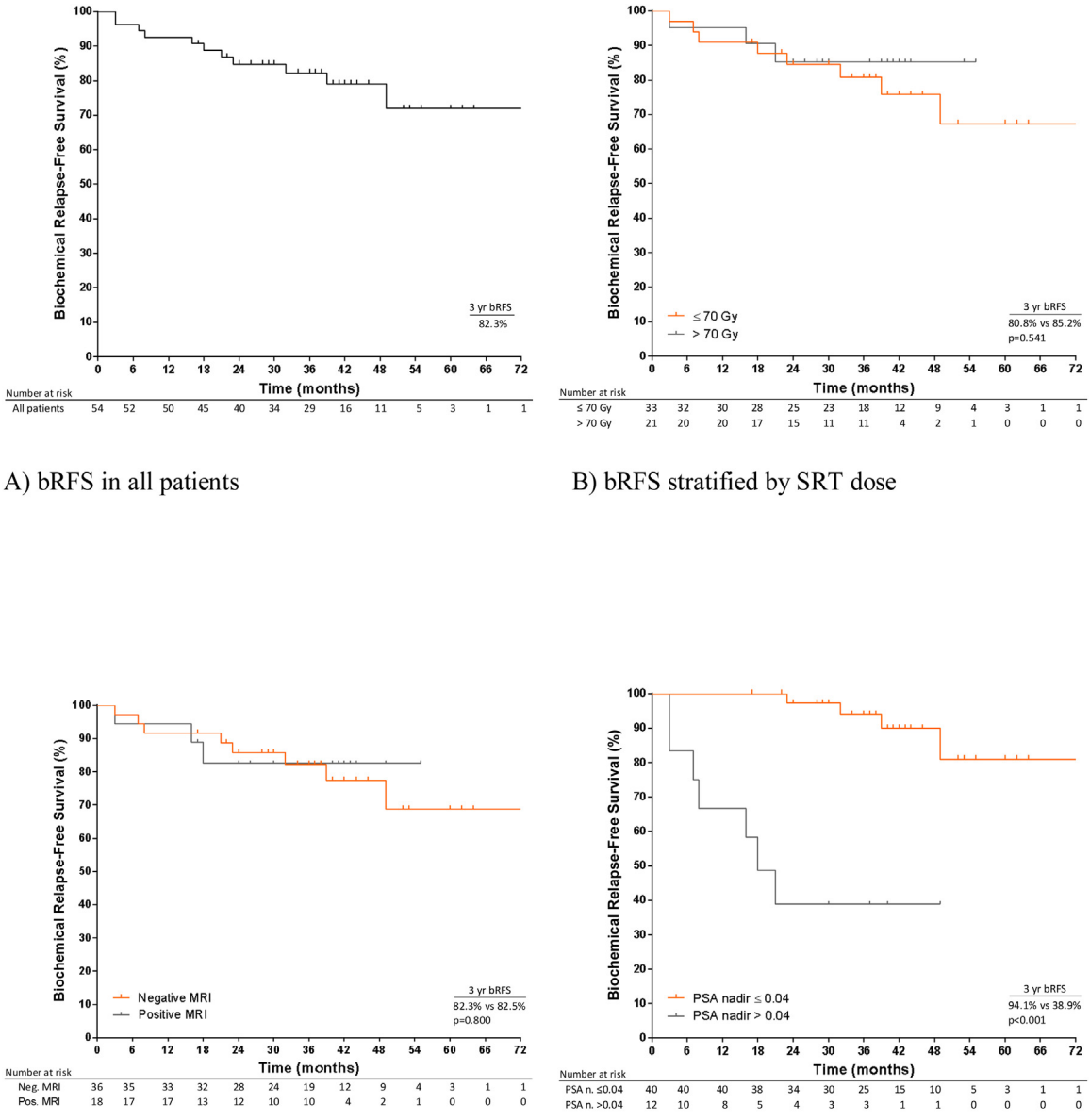

Fig. 1 – Biochemical relapse-free survival (bRFS).

SABR-COMET trial at the 2018 congress of the American Society for Radiation Oncology (ASTRO).[28] That trial included 99 patients (16 with PCa) with oligometastatic disease. Although the inclusion criteria allowed for up to 5 metastatic lesions, the majority (93%) had only 1–3 lesions. Patients with similar baseline characteristics were randomized to receive SBRT plus standard palliative care or palliative care alone (control group). At a median follow-up of 27 months, progression-free survival was 12 months in the SBRT arm vs. 6 months in the palliative care arm ($p = 0.001$). Median OS was 41 months (95% CI, 26—upper limit not reached) in the SBRT group vs. 28 months (95% CI, 19–33 months) in the control group ($p = 0.09$).

On the other hand, our results confirm that a low PSA nadir following SRT (≤0.1; ≤0.2; ≤0.04 ng/mL) is an important prognostic factor associated with better bRFS, similar to the findings of previous studies.[29,30] A recent study found that patients who achieve an undetectable post-SRT PSA nadir have lower rates of metastasis and better OS.[30]

Despite the use of IMRT in our cohort, 14% of the patients developed late GU toxicity ≥grade 2, perhaps due to the high doses (median dose, 70 and 76 Gy, respectively, in MRI-negative and MRI-positive patients). Goenka et al.[31] compared 285 patients treated with 3D-CRT or IMRT, finding that IMRT was associated with lower rates of grade 2 GI toxicity (10.2% vs. 1.9%: $p = 0.02$) but without significant differences in GU toxicity between 3D-CRT and IMRT (15.8% vs. 16.8%). Importantly, in our study, the toxicity event resolved in 7 of the 8 cases. We were unable to find an association between late GU toxicity and any of the clinical- or treatment-related factors (not even high-dose radiation) evaluated in our study. However, based

Table 4 – Univariate analysis for association of baseline characteristics and treatment-related variables with bRFS and GU late toxicity ($n = 54$).

Variable	bRFS		Late GU toxicity ≥ 2	
	HR (95% CI)	p	HR (95% CI)	p
Age, years ($n = 54$)	–	–	0.922 (0.815–1.043)	0.195
Preoperative PSA ≥10 ($n = 18$) [ref: <10 ($n = 36$)]	1.923 (0.497–7.444)	0.344	–	–
Pathological T stage pT3–pT4 ($n = 14$) [ref: pT2 ($n = 40$)]	1.091 (0.245–4.856)	0.909	–	–
Pathological N stage pN1–pNx ($n = 34$) [ref: pN0 ($n = 20$)]	3.24 (0.624–16.83)	0.162	–	–
Surgical margins Positive ($n = 25$) [ref: Negative ($n = 29$)]	1.516 (0.401–5.735)	0.540	–	–
Postoperative PSA (ng/mL) >0.2 ng/mL ($n = 26$) [ref: < = 0.2 ng/mL ($n = 28$)]	1.38 (0.365–5.215)	0.635	–	–
PSA prior to SRT (ng/mL) >1 ng/mL ($n = 17$) [ref: ≤1 ng/mL ($n = 37$)]	0.777 (0.178–3.386)	0.292	–	–
Pathologic Gleason score ≥7 ($n = 38$) [ref: ≤6 ($n = 16$)]	2.172 (0.413–11.421)	0.36	–	–
ADT added to SRT Yes ($n = 17$) [ref: No ($n = 37$)]	0.777 (0.178–3.386)	0.737	4.722 (0.977 –22.821)	0.053
SRT target volume Prostatic bed + Pelvis ($n = 7$) [ref: prostatic bed ($n = 47$)]	3.656 (0.682–19.601)	0.130	2.733 (0.43–17.386)	0.287
Time to first recurrence by PSA (months) ≥12 ($n = 31$) [ref: <12 ($n = 23$)]	0.520 (0.134–2.013)	0.830	–	–
Time from surgery to MRI (months) ≥12 ($n = 36$) [ref: <12 ($n = 18$)]	0.520 (0.134–2.013)	0.344	–	–
PSADT (months) ≥6 ($n = 29$) [ref: < 6 ($n = 19$)]	1.111 (0.232–5.314)	0.895		
RT dose 70 ($n = 21$) [ref: ≤ 70 ($n = 33$)]	0.521 (0.121–2.24)	0.381	0.474 (0.086–2.605)	0.390
>74 ($n = 14$) [ref: ≤ 74 ($n = 40$)]	0.521 (0.121–2.24)	0.381	0.363 (0.041–3.245)	0.364
MRI Positive ($n = 18$) [ref: Negative ($n = 36$)]	0.7 (0.161–3.037)	0.381	0.625 (0.113–3.461)	0.364
PSA nadir after SRT ≤0.1 ng/mL (n=) [ref: >0.1 ng/mL (n=)]	0.075 (0.020–0.277)	<0.001	–	–
≤0.2 ng/mL (n=) [ref: >0.2 ng/mL (n=)]	0.077 (0.021–0.281)	<0.001	–	–
≤0.04 ng/mL (n=) [ref: >0.04 ng/mL (n=)]	0.090 (0.026–0.316)	<0.001	–	–
Diabetes Yes ($n = 8$) [ref: No ($n = 46$)]	–	–	2.222 (0.362–13.658)	0.389
Arterial hypertension Yes ($n = 30$) [ref: No ($n = 24$)]	–	–	0.422 (0.09–1.983)	0.275
Intestinal comorbidity Yes ($n = 8$) [ref: No ($n = 46$)]	–	–	0.796 (0.084–7.51)	0.842
Bladder V70 ($n = 54$)	–	–	1.015 (0.958–1.074)	0.622
Absolute bladder volume (cc) ($n = 54$)	–	–	1.015 (0.958–1.074)	0.622
GU toxicity prior to SRT ≥2 ($n = 3$) [ref: < 2 ($n = 51$)]	–	–	–	–
Acute GU toxicity ≥2 ($n = 2$) [ref: < 2 ($n = 52$)]	–	–	–	–

bRFS, biochemical relapse-free survival; GU, genitourinary; PSA, prostate-specific antigen; ADT, androgen deprivation therapy; MRI, magnetic resonance imaging; SRT, salvage radiation therapy; PSADT, prostate-specific antigen doubling time; Bladder V70, volume of the bladder receiving 70 Gy.

on these toxicity outcomes, to minimize the risk of treatment-related toxicity, we now escalate the dose only to the site of the local macroscopic recurrence, and not to the whole prostate bed.

Ultimately, we have two messages for readers. First, as we all know, advance imaging has the potential to play a role in detecting distant metastases and/or local or nodal recurrence. If the results may change your subsequent treatment

Table 5 – Late GU and GI toxicity in the entire cohort.

Grade	GU		GI	
	Cases *n* (%)	Resolved *n* (%)	Cases *n* (%)	Resolved *n* (%)
0	28 (51.9)	–	46 (85.2)	–
1	18 (33.3)	10 (55.6)	7 (13)	6 (85.7)
2	4 (7.4)	4 (100)	0	–
3	4 (7.4)	3 (75)	1 (1.9)	1 (100)
Total	54 (100)	17 (65.4)	54 (100)	7 (87.5)

GU, genitourinary; GI, gastrointestinal.

(use of ADT, RT volumes or dosage), we strongly recommend the performance of an mpMRI and a PSMA-PET/CT to all patients with a PSA level >0.2 ng/mL. However, the second message is not to wait for a macroscopic recurrence, which could have an impact on toxicity and survival outcomes. The recommendation is to perform early SRT with a PSA trigger <0.5 ng/mL, regardless of whether it detects a macroscopic recurrence or not in the mpMRI. In this regard, a recent study, in which 69 patients with a macroscopic LR were analysed after RP, with a median pre-SRT PSA of 2.7 ng/mL, concluded that delayed SRT with dose escalation (72–74 Gy), provides a lower tumour control compared to early intervention.[32] So, until data from randomized trials become available, the recommended approach continues to be the application of early SRT, regardless of whether or not a macroscopic recurrence is detected on imaging tests.

The main limitations of this study are those associated with the retrospective study design, the short follow-up, the small sample size, and heterogeneities in ADT use. Patients in the positive mpMRI group had a significantly higher median PSA before salvage treatment 2.2 vs. 0.4 ($p = 0.003$) and received a longer course of ADT in combination with salvage radiotherapy (18 vs. 6 months), compared to the negative mpMRI group. The delivery of a longer duration of ADT in the positive mpMRI patients has likely balanced the higher risk of metastatic spread in this group. In fact, in our cohort, the mean follow-up was 41 months (range 6–81) and patients with shorter follow-up may not have enough time to develop a biochemical failure. However, it is necessary to clarify that all patients had regained their normal testosterone levels at the last follow-up.

5. Conclusion

SRT to the pelvic macroscopic recurrence identified by mpMRI is a feasible and well-tolerated treatment option. In this study, there were no differences in bRFS between MRI-positive and MRI-negative patients, indicating that MRI-positive lesions were targeted effectively.

Conflicts of interest

None declared.

Financial disclosure

None declared.

Acknowledgments

The authors wish to thank Bradley Londres for his excellent work in translating and editing this manuscript.

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