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A prospective study assessing the pattern of response of local disease at DCE-MRI after salvage radiotherapy for prostate cancer☆

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ABSTRACT

Background: To assess the pattern of response of presumed local lesions at dynamic contrast enhancement magnetic resonance imaging (DCE-MRI) after salvage radiotherapy (sRT).

Methods: This is a prospective study conducted at a single Institution accruing patients with one or more local failures at DCE-MRI after radical prostatectomy between August 2017 and June 2020. Patients underwent exclusive sRT delivering 66–69 Gy and 73.5 Gy in 30 fractions to the whole prostatic fossa and to the local failure (s) seen at DCE-MRI, respectively.

Patients were offered DCE-MRI at 3 months intervals after sRT until complete disappearance (CR) of the lesion(s) or up to a maximum of 4 revaluations.

Results: 62 patients with 72 nodules were enrolled. All patients underwent the 1st revaluation, and 33 patients (53.2%) showed a CR. The median time to CR was 4.7 months. Four patients did not undergo further testing before achieving a CR and even considering these patients as no responses, the vast majority (87.1%, 95%CI: 78.5–94.4%) of lesions would have completely disappeared by 12 months from the end of sRT.

The volume of the lesion at pre-sRT DCE-MRI was an independent predictor of CR at the 1st revaluation (OR: 0.076, 95%CI: 0.009–0.667; p = 0.020) along with time elapsed from sRT (OR: 3.399, 95% CI: 1.156–9.993, p = 0.026).

Conclusions: The present study documents the complete disappearance of the vast majority of local lesions after dose-escalated sRT though this requires several months after sRT; timing of CR is at least in part predictable based on the volume of the lesion.

Trial registration: Clinicaltrials.gov NCT04703543, registered July 15 2020, retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT04703543.

Introduction

The proper evaluation of response to therapy is crucial in cancer treatment evolution and amelioration. Acknowledging the presence of residual disease after a local therapy helps to tailor treatment intent and its aggressiveness.

After exclusive salvage radiotherapy (sRT) for a presumed local failure following radical prostatectomy, about 30–40% of patients show further biochemical progression at 5 years [1–3]. However, serum prostate specific antigen (PSA) measurement lacks spatial information and the pattern of failure of patients in this clinical scenario remains unclear for the majority of them [2–5]. The paucity of data on the local response rate to sRT is partly due to the fact that none of the above studies requested a detailed imaging study of the prostatic fossa before sRT consistently with the recommendations [6] and the limitations of the imaging modalities [7] at the time these studies were undertaken. An

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exception is the SAKK trial, though MRI of the prostatic fossa was done in only about a third of the patients and multiparametric sequences were not required per protocol [1]. If the prostatic fossa is not properly staged before sRT, response cannot be obviously assessed.

At our Institution multiparametric magnetic resonance is part of the restaging process for patients with a biochemical failure after radical prostatectomy (RP) and it is systematically performed in patients who are candidates for sRT [8]. As part of a prospective study enrolling patients with a presumed local failure at restaging MRI and undergoing exclusive sRT [9], local response was assessed at regular intervals with dynamic contrast enhancement magnetic resonance imaging (DCE-MRI) during follow up, providing unique data on local response of prostate cancer to sRT.

Material and methods

The present prospective study was conducted at a single Institution between August 2017 and June 2020 (Clinicaltrials.gov NCT04703543). The study was approved by the Institutional Review Board (RS 946/17) and specific written informed consent was obtained by each patient before enrollment. Selection criteria as well as other methodological aspects of the study have been reported previously in details [9]. In order to be eligible, patients had to have a history of localized prostate cancer treated with RP, followed by an undetectable (<0.1 ng/ml) PSA and a subsequent biochemical recurrence (2 consecutive PSA rises up to 0.2 ng/ml or higher). At restaging with DCE-MRI, all patients had to harbor a presumed local failure defined as an early/fast enhancing discrete lesion on DCE-MRI possibly with a T2w hyperintense lesion [8,9]. The location of each detected lesion was classified as per Connolly et al in perianastomotic, bladder neck and retrovesical [10]. Patients with known nodal or distant metastatic disease at PET CT were excluded. All scans were obtained at our Institution and details can be found elsewhere [9].

All patients then underwent sRT, consisting in an intensity modulated approach to the whole prostatic bed to 66–69 Gy in 30 fractions. Presumed local failures at DCE-MRI were prescribed 73.5 Gy with a simultaneous integrated boost technique. The presumed site of local failure at DCE-MRI was outlined as clinical target volume (CTV) after co-registration to the planning computed tomography [11]. The CTV was enlarged by an 8 mm isotropic margin to the planning target volume (PTV). When treated [9], the pelvic nodes (bilateral internal, external and common iliac lymph nodes as well as presacral lymph nodes) were prescribed 54 Gy in 30 fractions. According to internal guidelines [8], patients with [1] a risk of nodal involvement greater than 15% according to the Roach formula at original surgery and/or [2] disease-free interval shorter than 12 months or PSA doubling time < 6 months and/or [3] Gleason sum score >3 + 4 were considered for pelvic node irradiation. Details on treatment planning and delivery have been reported previously [8].

All patients were offered repeated DCE-MRI (rDCE-MRI) at our Institution as described above and interpreted by the same single observer (L.B.). Response was assessed exclusively on DCE sequences and defined with a qualitative method as it follows: complete response (CR) as the complete disappearance of the target lesion at DCE-MRI; partial response (PR) as any reduction of the size of the area/volume of early/fast enhancement; no response (NR) as no change in size/volume of the target lesion at DCE-MRI.

The first rDCE-MRI was planned at 3 months after sRT completion. In patients without a complete response, imaging was repeated at 3 month intervals until complete disappearance or a maximum of 4 repeated scans. In case of complete response, no further scans were offered.

The endpoint of the study is the achievement of a CR at rDCE-MRI during the follow up. Therefore, responses were further dichotomized in CR and noCR, that includes both PR and NR. For patients with multiple local lesions, CR implied the complete disappearance of *all* lesions seen before sRT. The analysis was initially set for a complete database (no missing observations during the follow up). Unfortunately, some patients did not undergo all planned examinations. Therefore, the analysis has been carried in terms of both actual cumulative incidence (the number of new CRs divided by the total number of individuals at risk) and actuarial cumulative incidence using the Kaplan Meier estimate censoring for patients who did not undergo further testing at the date of last examination. Groups were compared with the chi-squared test, the Mann–Whitney rank test or the log-rank test when appropriate. For proportions, confidence intervals (CI) were computed with the Wilson score method without continuity correction.

Univariable/multivariable binary logistic regression analyses on CR were performed considering the Gleason Grade Grouping at RP (1–2 vs 3 vs 4–5), the PSA value at failure (continuum), the PSA doubling time at failure (continuum), the nodule volume at pre-sRT MRI (continuum), the number of failures at pre-sRT MRI (1 vs multiple), the time interval between RP and sRT (continuum), the time interval between the end of sRT and rDCE-MRI (continuum), the percent decrease of PSA at the 5th week of sRT (continuum) and the location of the failure, anastomotic (yes vs no), in the bladder neck (yes vs no) and retrovesical (yes vs no). For patients with multiple lesions, the total volume was computed by adding up each nodule volume. The area under the receiver operating characteristic curve (AUC) and Hosmer-Lemeshow goodness-of-fit test (HL) were used to assess the performance of the logistic regression multivariable analysis.

PSA recurrence after sRT was defined as a 0.2 ng/ml PSA rise above the nadir after treatment [12]. Statistical significance was claimed for p values < 0.05. All statistical tests were performed using GraphPad (version 8.0.1, GraphPad Software Inc., San Diego, CA) and SPSS (version 25, IBM, Armonk, USA).

Results

Patients and scans

Sixty-two patients with 72 lesions were enrolled. Selected patient characteristics have been reported before in details [9] and are summarized in Supplementary Table 1. Briefly, 9 patients were found to harbor multiple local failures: 8 patients had 2 lesions; 1 patient, 3 lesions. All patients underwent sRT and no one received androgen deprivation until biochemical failure after sRT. At the time of analysis, median follow up is 27.1 months (IQR: 19.5–33.3 months).

As shown in Table 1, all patients underwent the 1st repeated DCE-MRI at a median time of 3.3 (IQR: 3.1–4.1) months after treatment completion. Of the patients without a complete response at the 1st revaluation, 1 was implanted a cardiac device and was unable to undergo further MRI scans. Three more patients declined additional testing after the 1st (N = 2) or the 2nd (N = 1) revaluation due to issues related to the COVID-19 pandemia.

Overall, at the 1st observation all patients showed a decline in serum PSA compared to pre-sRT (median percent decrease: 83.6%, IQR: 69.2%-91.8%). The percent decrease of PSA was higher for patients with CR vs patients with noCR (86.0% vs 77.8% for CR vs noCR, p = 0.04).

Regarding the 4 patients lost to revaluation before achieving a CR, 3 are biochemically controlled at the last follow up (27.0, 24.5 and 14.1 months after sRT, respectively). The 4th patient had a PSA progression while showing a local PR: the biochemical failure was recorded at 4.23 months after sRT and both revaluation #1 (3.67 mths) and #2 (7.63 mths) revealed a partial response. After the second revaluation he was started on androgen deprivation and declined further MRI testing.

Responses

Responses at each revaluation are summarized in Table 1 and illustrated for each patient in Supplementary Fig. 1.

Fig. 1 shows both the actual and the actuarial cumulative rates of CR. The difference between the two approaches is negligible and for both

Table 1
Summary of findings at rDCE-MRI.

	A	B	A-B				
Re-ev #	Patients due for scanning	noCR not further evaluated	# patients actually scanned	Median time (mths) of scan after sRT (IQR)	Complete Response	No Response	Partial Response
	(#)	(#)	(#)	(months)	(#)	(#)	(#)
1st	62	0	62	3.3 (3.1–4.1)	33	2	27
2nd	29	1	28	6.8 (6.5–7.6)	20	0	8
3rd	9	3	6	10.7 (10.6–12.6)	4	0	2
4th	5	4	1	16.7	1	0	0

Abbreviations: Re-ev: revaluation.

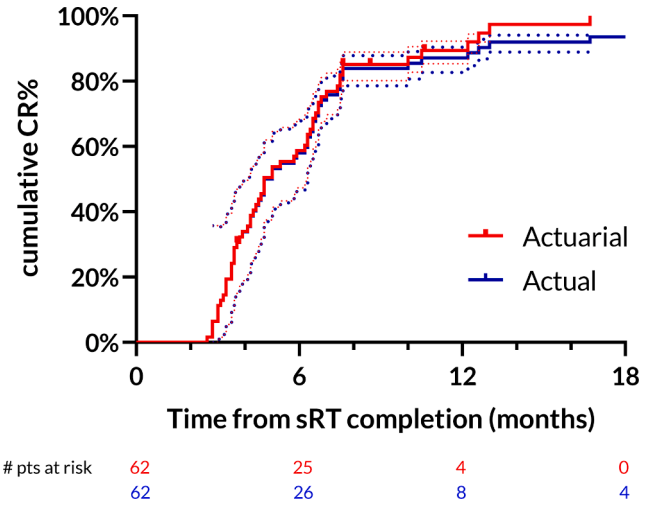

Fig. 1. Estimated cumulative incidence rates (95%CI) of CR after sRT. The actuarial method (red line) censors for the 4 patients who were lost to follow up before achieving a CR while the actual method (blue line) treats lost observations as persisting incomplete responses. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

approaches the median time to CR was identical at 4.7 months (95%CI: 3.4–6.0 mths and 3.8–5.6 mths for the actual and the actuarial methods, respectively). Even in the more conservative scenario (actual method), the vast majority (87.1%, 95%CI: 78.5–94.4%) of lesions would have completely disappeared by 12 months from the end of sRT.

Predictors of response

At the first revaluation, 33 patients (53.2%; 95%CI: 41.0–65.1%) were found to be without evidence of local disease. Results of logistic regression on CR at the 1st revaluation are summarized in Table 2. Independent predictors were the volume of the presumed local lesion at pre-sRT MRI and the time elapsed between sRT and the revaluation. Due to both missing observations and the limited (<10) number of events at the subsequent revaluation time points, no further logistic regression testing was performed.

The AUC of the multivariable logistic regression is 0.811 (95%CI: 0.705–0.917), $p < 0.001$, and the Hosmer-Lemeshow chi-squared value is 6.613, $p = 0.579$.

We categorized baseline lesion volumes at DCE-MRI according to tertiles and the cumulative incidences of CR in each subgroup are illustrated in Fig. 2. All 4 incompletely evaluated lesions belong to the subset of lesions larger than 4.5 cc at baseline. Nevertheless, both the actuarial and the actual methods provide identical median times to CR for all sub-groups: 3.6 months (95%CI: 3.3–3.8 mths), 4.7 months (95%

Table 2
Logistic Regression on CR at 1st revaluation.

			Univariable			Multivariable		
Covariate	Strata	# patients	OR	95%CI	p value	OR	95%CI	p value
Volume @ baseline MRI (cc)	Continuum	62	0.207	0.045–0.958	0.044	0.076	0.009–0.667	0.020
PSADT (mths)	Continuum	62	0.977	0.948–1.006	0.120			
PSA @ fail (ng/ml)	Continuum	62	0.843	0.558–1.274	0.418			
Site failure Anastomosis	No	25	1					
	Yes	37	1.422	0.513–3.940	0.498			
Site failure Bladder Neck	No	45	1					
	Yes	17	0.512	0.165–1.588	0.246			
Site failure Retrovesical	No	47	1					
	Yes	15	1.437	0.441–4.682	0.547			
Site + number	Single VUA	30	1					
	Single BN	14	0.574	0.159–2.066	0.395			
	Single RV	9	0.956	0.213–4.284	0.953			
	Multiple Any	9	0.956	0.213–4.284	0.953			
Time RP/sRT (mths)	Continuum	62	0.991	0.980–1.002	0.117			
GGG	1–2	29	1					
	3	25	0.880	0.301–2.574	0.816			
	4–5	8	0.813	0.169–3.895	0.795			
Time from sRT (mths)	Continuum	62	2.472	1.050–5.818	0.038	3.399	1.156–9.993	0.026
PSA decrease @ wk 5 (%)	Continuum	62	1.026	1.003–1.049	0.024	1.025	0.999–1.050	0.058
PSA decrease @ 1st ev (%)	Continuum	62	1.025	0.998–1.052	0.067			
# Failures	1	53	1					
	2–3	9	1.116	0.269–4.622	0.880			
Pelvic node coverage	No	33	1					
	Yes	29	0.893	0.328–2.427	0.824			

Abbreviations: OR (odds ratio); MRI (magnetic resonance imaging); PSADT (prostate specific antigen doubling time); mths (months); PSA (prostate specific antigen); GGG (Gleason Grade Group); sRT (salvage radiotherapy).

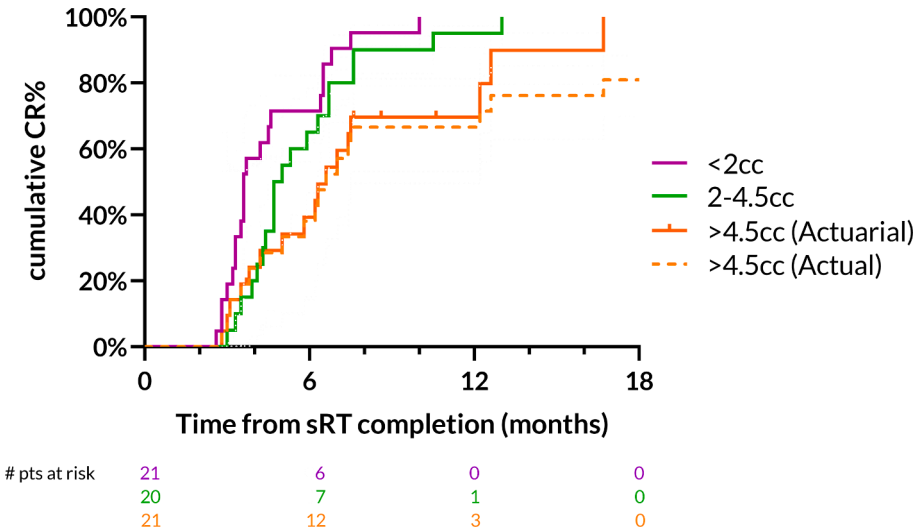

Fig. 2. Estimated cumulative incidence rates (95% CI) of CR by baseline volume at DCE-MRI. For lesions up to 4.5 cc, both the actuarial and the actual methods provide identical results since there are no censored observations: for lesions larger than 4.5 cc, both approaches (actuarial, solid line and actual, dashed line) are shown. The difference among both actuarial and actual curves is highly significant (p = 0.009 and p = 0.003 for the former and the latter ones, respectively).

CI: 4.0–5.4 mths) and 6.6 months (95%CI: 5.5–7.7 mths) for lesions<2 cc, between 2 and 4.5 cc and larger than 4.5 cc at diagnosis, respectively. The difference among subgroups is highly significant (p = 0.009 and p = 0.003 according the actuarial and the actual approaches, respectively).

For lesions up to 4.5 cc before sRT we were able to document their complete disappearance by 13 months from the end of treatment (Fig. 2). Conversely, out of lesions larger than 4.5 cc only slightly more than 2/3 would have completely disappeared by 12 months (66.7%, 95%CI: 45.4%-82.8% and 69.6%, 95%CI: 49.4%-89.8% according to the actual and the actuarial methods, respectively).

Discussion

About 50% of patients undergoing RP for localized prostate cancer develop a biochemical failure despite a window of PSA undetectability. While there is some discussion on which PSA threshold best predicts further metastases, both the American and the European Urology as well as Radiation Oncology associations agree to offer 'early' salvage radiotherapy in case of 2 consecutive PSA rises above 0.2 ng/ml [13,14]. The optimal dose of sRT remains controversial, with 64–66 Gy at 2 Gy per fraction considered the minimum prescribed dose to the whole prostatic fossa [14,15]. However, even if sRT is started at PSA levels below 0.5 ng/ml, up to 50% of patients harbor one or more visible lesions in the prostatic bed at high resolution DCE-MRI [9,16,17]. Though a minority of the detected lesions may be falsely positives [8,18,19] and the detection of a local lesion per se is a favorable prognostic factor [12,16,20], there are concerns on the appropriateness of such limited dosages of radiation. Indeed, in a recent randomized trial comparing two dose levels of sRT, local recurrence alone or in combination with other sites represented 21.6% of all first events of clinical progression after 64 Gy [1]. Moreover, a systematic review showed that each Gy improves the biochemical-free survival after sRT by 2.6% suggesting that a total dose above 70 Gy should be administered [21]. It has been prospectively shown that local treatment may in turn impact distant metastasis rates in the postoperative setting [22]. In order to limit the risk of toxicity associated with dose escalation [14], it seems reasonable to limit the highest prescribed dose level to the site of presumed local disease. We have systematically pursued this strategy in patients undergoing sRT at our institution and here we confirm that the vast majority of local lesions disappears completely after 73.5 Gy in 30 fractions [8].

Prostate cancer response to radiotherapy is monitored usually throughout serum PSA values [23] and little is known on both the clinical/instrumental response rate of prostate cancer along with its timing after radiotherapy [8,24]. Pilepich and Hederman in the post-radiation evaluation of 262 patients in the pre-PSA era showed CR rates at 12 months similar to those reported in Fig. 1 with smaller primary tumors regressing somewhat faster than larger ones at digital rectal exam [25].

While DCE-MRI, and in particular changes in apparent diffusion coefficient, have been used to assess the response of prostate cancer to primary radiotherapy [26,27], the post-RP/pre-sRT setting is different due to the lack of normal prostate tissue surrounding the lesion and the presence of anatomical changes due to surgery [28]. Though in previously untreated prostate cancer the diagnostic role of DCE-MRI is marginal [29], it represents the most important sequence in the detection of recurrent disease after RP [30] since recurrent tumor neoangiogenesis is composed by disorganized and permeable blood vessels that result in an early hyperintense focal lesion [28]. Even if early radiation-induced changes may actually increase vessel permeability and thus potentially increase tumor flare [28], successful radiotherapy leads to fibrosis and decreased blood flow/permeability that has been associated with pathologically complete responses in various cancer sub-sites [31–34].

We have found that sRT is highly effective in obtaining the complete resolution of local lesions, though longer follow up is needed to confirm these results. Interestingly, response was found to be a time-dependent process even within the same revaluation window (Table 2) and, as shown in Fig. 1, assessment of response at DCE-MRI should be deferred several months after sRT end. Moreover, despite DCE is a functional test, we found the lesion volume to be the only additional independent predictor of response at multivariable analysis. Surprisingly, none of the factors potentially correlated with tumor aggressiveness (i.e. Gleason score) were found to predict the timing of response. On the other hand, microvessel density, that is a surrogate of angiogenesis, has been inconsistently correlated to pathologic tumor stage and Gleason score in prostate cancer [35]. Limitations of the present study include the fact that the time interval of revaluation was delayed by a few months due to issues related to the COVID-19 pandemia (Table 1). In particular, the 3rd revaluation took place on average at 10.7 months instead of 9 months, even if this has minimal impact on the interpretation of the results (Fig. 1). More importantly, 4 (6.4%) patients were lost before achieving a CR and this prevents us to draw firm conclusions on the long term response of larger lesions. However, the cumulative incidence for lesions larger than 4.5 cc are quite similar up to 12 months regardless the method used for computation of rates, suggesting that until this time

point results are not impacted by censoring. Moreover, as discussed elsewhere [9], we assumed all detected local lesions to be prostate cancer-related at baseline despite an estimated rate of false positives for multiparametric MR up to 10% [8,18]. Therefore, the goal of 100% for the cumulative incidence of CR might be unrealistic in absence of a baseline positive biopsy though false positive lesions usually remain unchanged after sRT as discussed elsewhere [8].

Conclusions

The present prospective study documents the complete disappearance of the vast majority of presumed local lesions after dose-escalated sRT though this requires several months after treatment completion. The timing of CR is at least in part predictable based on the volume of the lesion with smaller lesions responding quicker and within ≈1 year from treatment end.

Declarations

Ethics approval and consent to participate: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the 'Regina Elena' National Cancer Institute (protocol code 946/17) and approved 13 June 2017.

Consent for publication: Informed consent was obtained from all subjects involved in the study.

Data availability: https://gbox.garr.it/garrbox/index.php/s/aJGRXorIc8ItRFy.

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CRediT authorship contribution statement

Marta Bottero: Data curation, Writing – original draft, Writing – review & editing. **Adriana Faiella:** Validation, Resources, Data curation. **Diana Giannarelli:** Methodology, Software, Formal analysis. **Alessia Farneti:** Validation. **Pasqualina D'Urso:** Validation. **Luca Bertini:** Validation, Writing – review & editing. **Valeria Landoni:** Software. **Patrizia Vici:** Investigation. **Giuseppe Sanguineti:** Conceptualization, Methodology, Software, Investigation, Writing – original draft, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.04.010.

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