ANTICANCER RESEARCH *40*: 5901-5907 (2020)
doi:10.21873/anticanres.14610

Predictors of Local Control for Stereotactic Ablative Radiotherapy (SAbR) in Pulmonary Oligometastases from Gastrointestinal Malignancies

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Abstract. *Background/Aim: To assess predictors of local control (LC) for stereotactic ablative radiotherapy (SAbR) in pulmonary oligometastatic disease (OMD) from gastrointestinal (GI) malignancies. Patients and Methods: Patients with pulmonary OMD treated with SAbR from January 2016 to December 2018 were included in this observational analysis. Primary endpoint was LC. Uni- and multivariate analyses to assess variable correlations were conducted. Results: Thirty-seven patients and 59 lung metastases were evaluated. The delivered dose was 30-60 Gy in 3-8 fractions. After a median follow-up of 23.0 months (range=6.3-50.4 months), LC rate at 1/2 years was 89.7%/85.0%, and increased to 96.0%/91.0% for lesions treated with a biologically effective dose (BED_{10}) ≥100 Gy (p=0.03). RECIST response at 6 months was predictive for LC (p=0.002). Conclusion: SAbR is an effective option for pulmonary OMD from GI malignancies. A BED_{10} ≥100 Gy and radiological response at 6 months can affect LC.*

Oligometastasis, a term first introduced in 1995, refers to a limited metastatic state with a small number of lesions and involved organs (1). The notion of oligometastatic disease (OMD) has dramatically changed the concept and therapeutic approach to metastatic cancer (2). Even if systemic therapy remains essential, these patients seem to benefit from local therapy (*e.g.* surgery and radiation therapy), and multimodality approach is considered potentially able to improve oncological outcomes in selected OMD cases (3). Lung parenchyma represents a common site for oligometastatic seeding. Notably, in a series of 575 patients and 708 lung metastasectomies, 35.6% resulted from gastrointestinal (GI) tumors (4). Surgery represents a mainstay of treatment for lung oligometastasis, resulting in long-term disease control and survival (5). More recently, stereotactic ablative radiotherapy (SAbR), also referred to as stereotactic body radiotherapy (SBRT), has emerged as a consistent alternative to surgery, with reported promising local control and acceptable toxicity (6-15).

Based on this background, we aimed at performing a novel analysis of the efficacy of using SAbR in a cohort of pulmonary OMD from GI malignancies. Factors potentially affecting LC were analyzed.

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Key Words: SAbR, lung metastases, oligometastatic disease, gastrointestinal tumors.

Patients and Methods

Study design. Patients treated with SAbR for lung OMD from GI cancers between January 2016 and December 2018 were included in this analysis. Each case was discussed by the institutional multidisciplinary tumor board including dedicated Radiation Oncologists, Medical Oncologists, Thoracic and General Surgeons, Pathologists and Diagnostic Radiologists. Indications for SAbR were as follows: oligometastasis and oligorecurrence, treatment of all pulmonary lesions (≤5 lung lesions); oligoprogression and oligopersistence, treatment only of progressive/active lesions after chemotherapy (≤5 lung lesions). In the latter case, the treatment goal was to obtain local control and prevent or delay any change in systemic therapy (CST). All treated patients gave written consent for SAbR and data collection.

Table I. *Baseline characteristics*.

Characteristic	No.	%
No. of patients	37	
No. of lesions	59	
Gender		
Male	21	56.8
Female	16	43.2
Age, years		
Median (range)	72 (40-91)	
Primary tumor		
CRC	25	67.6
EG	5	13.5
Pancreas	3	8.1
CC	3	8.1
Anus	1	2.7
Distribution of metastasis (for patient)		
Lung only	19	51.4
Extrapulmonary and lung	18	48.6
Presentation of metastasis (for patient)		
Oligometastasis	2	5.4
Oligorecurrence	24	64.9
Oligoprogression/oligopersistence	11	29.7
Time since primary tumor diagnosis, months		
Median (range)	25.6 (0-108.6)	
Pre- SAbR numbers of chemotherapy regimens		
Mean (range)	1 (1-4)	
0	5	13.5
1	16	43.2
2	11	29.7
≥3	5	13.5

CRC: Colorectal cancer; EG: esophageal and gastric cancer; CC: cholangiocarcinoma; SAbR: stereotactic ablative radiotherapy.

Table II. *SAbR treatment details*.

Characteristic	No.	%
Treated lung metastases for SAbR course		
Median (range)	1 (1-4)	
1	27	
2	11	
3	2	
4	1	
Total course of SAbR (for patient)		
1	34	91.9
2	3	8.1
Location of lung metastasis		
Lower lobes	30	50.8
Other lobes	29	49.2
Volume, ml		
GTV, median (range)	2.0 (0.3-28.1)	
PTV, median (range)	11.0 (3.8-68.4)	
Number of SAbR fractions		
3	28	47.5
4	2	3.9
5	28	47.5
8	1	1.7
SAbR delivery		
RapidArc®	52	88.1
TomoTherapy®	7	11.9
Delivered Dose PTV, Gy		
Median (range)	45 (30-60)	
BED_{10} PTV, Gy		
Median (range)	112.5 (48-151.2)	
≥100 Gy	54	91.5
<100 Gy	5	8.5
Fractionations		
45 Gy/3 fx	15	25.4
50 Gy/5 fx	24	40.7
60 Gy/8 fx	1	1.7
45 Gy (ITV SIB 54 Gy)/3 fx	14	23.7
30 Gy (ITV SIB 40 Gy)/5 fx	1	1.7
32 Gy (ITV SIB 50 Gy)/5 fx	1	1.7
40 Gy (ITV SIB 50 Gy)/5 fx	3	5.1

SAbR: Stereotactic ablative radiotherapy; GTV: gross tumor volume; PTV: planning target volume; Gy: gray; BED10: biological equivalent dose; fx: fractions; SIB: simultaneous integrated boost.

SAbR procedure. Patients were immobilized in supine position with arms over the head. All patients underwent a 4-dimensional non-contrast chest simulation computed tomography (CT) using 1.5-3 mm slices to account for intra-fractional respiratory motion. To give respiratory feedback to the patients a Real-Time Position Management® system (Varian Medical Systems, Palo Alto, CA, USA) was used. The gross tumor volume (GTV) was defined on a free breathing scan and then expanded on five respiratory phases to generate the internal target volume (ITV). An ITV to planning target volume (PTV) isotropic margin of 5 mm was applied. SAbR was delivered using a hypofractionated schedule of 3 to 8 fractions, and dose and fractionation were defined according to metastases location, number and dimension. The dose was prescribed to cover 95% of the PTV and dose constraints to organs at risk (OARs) were accepted according to current reports (16). The goal was to prescribe a biologically effective dose (BED_{10}) of 100 Gy, with an appropriate reduction in case of close proximity to OARs. The SAbR was delivered using RapidArc® Technology (Varian Medical Systems) or TomoTherapy® System (Accuray, Sunnyvale, CA, USA), and daily on-line volumetric image-guided radiotherapy (cone beam or megavoltage CT) was performed before each treatment fraction.

Restaging and follow-up. Follow-up examination was performed with CT every 3 months after completion of SAbR for 2 years and every 6 months thereafter. Response evaluation was performed using response evaluation criteria in solid tumors (RECIST) (17). Complementary positron emission tomography/computed tomography (PET/CT) was used if local disease progression was suspected. SAbR acute and late toxicity data were collected during follow-up according to common terminology criteria for adverse events (CTCAE) version 4.0 (18).

Endpoints and statistical analysis. Primary endpoint was local control (LC). Secondary endpoints were overall survival (OS), progression-free survival (PFS) and toxicity. Survival estimates were calculated with Kaplan-Meier's method and compared by the log-rank test. Risk factors for LC, OS and PFS were further investigated in univariate and multivariate Cox regression model. The LC was calculated from the end of SAbR to the date of local failure, death or last follow-up, whichever came first. Acute and late toxicities were defined as those occurring within 90 days and >90

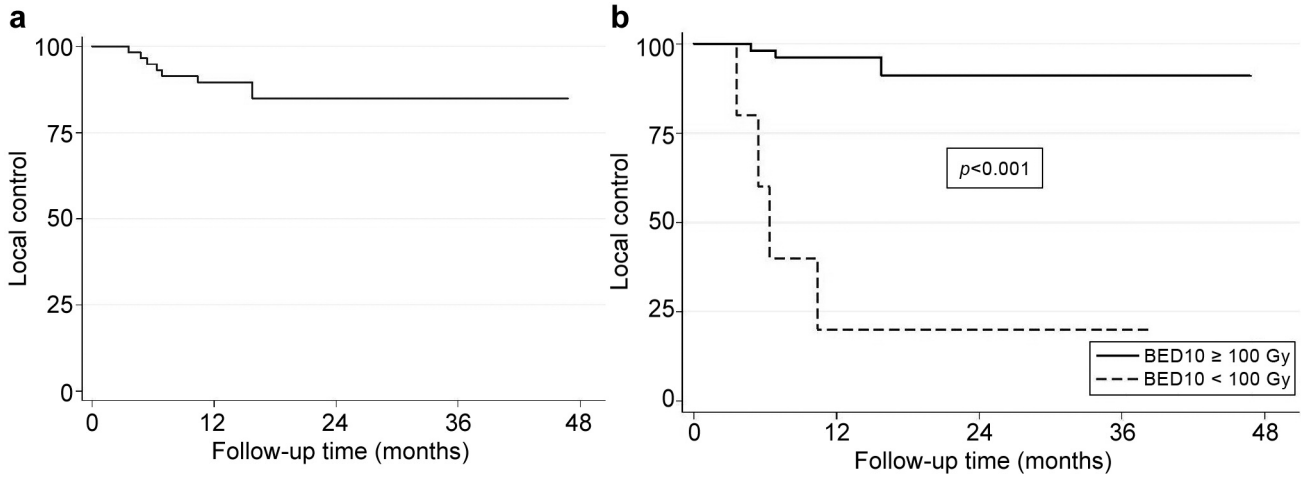

Figure 1. *Local control (a) for all metastases and (b) by biologically effective dose (BED_{10}).*

days from SAbR completion, respectively. The OS and PFS were defined as the time between the end of SAbR and last follow-up or death or progression disease, respectively. Statistical significance was set at p-value <0.05, and data were analyzed using Stata software version 14 (StataCorp, Lakeway, TX, USA).

Results

Baseline characteristics. Thirty-seven patients and 59 lung metastases were included in the analysis. Baseline characteristics are outlined in Table I. The most common site of primary GI tumor was colorectal (64.9%). The median number of treated lesions in each course was 1 (range=1-4), and 3 (8.1%) patients were treated with a second course of SAbR after the first treatment. The median GTV and PTV volume were 2.0 ml (range=0.3-28.1 ml) and 11.0 ml (range=3.8-68.4 ml), respectively. A BED_{10} ≥100 Gy to the PTV was prescribed in 54 (91.5%) lesions, and in 20 (33.9%) a simultaneous integrated boost (SIB) to the ITV was planned. Of 5 patients with BED_{10} <100 Gy, 3 had lesions close to the heart and 2 to the esophagus. SAbR treatment details are described in Table II.

LC and radiological response. The median follow-up was 23.0 months (range=6.3-50.4 months). The overall LC rate was 86.4% for the 59 treated lesions, with a 1- and 2- year LC rate of 89.7% (95%CI=82.2-97.9%) and 85.0% (95%CI=75.7-95.3%), respectively (Figure 1a). At the first radiological evaluation (median time 2.8 months after SAbR, range=1.8-4.3 months), 39 (66.1%) lesions showed a RECIST partial response to SAbR, while the remaining were classified as stable disease. The second CT evaluation was performed 6.3 months after SAbR (range=4.7-10.3 months) and showed additional response in 24 (40.6%) lesions (of which 15.3% as complete response), and local failure (LF) in 5 (8.4%) lesions. The maximum percentage change in lesions dimension is reported in Figure 2. At the last follow-up, LF occurred in 8 (13.6%) lesions, with a median time to LF of 6.8 months (range=3.8-16.0 months) after SAbR. The longest duration of radiographic LC after SAbR was 46.8 months. A multiparametric Cox analysis showed that the only significant variables in predicting LC were BED_{10} ≥100 Gy and RECIST response at 6 months (Table III). In addition, an analysis of radiological lung parenchymal changes after SAbR according to well-established scoring systems was also performed (19, 20). Acute and late SAbR-related CT changes are reported in Figure 3.

OS and PFS. At the time of analysis, death was observed in 7 (18.9%) patients. One- and 2-year OS rates were 94.6% (95%CI=87.6-100%) and 84.6% (95%CI=72.0-98.2%), respectively, and the comparable PFS rates were 45.5% (95%CI=31.3-66.1%) and 32.7% (95%CI=19.9-53.8%), respectively. The first site of progression was lung (new lesions), lymph nodes and liver in 51.4%, 16.2% and 13.5%, respectively. A BED_{10} ≥100 Gy was a significant predictor of PFS (HR=0.30, 95%CI=0.09-1.04, p=0.04), but had no significant impact on OS (p=0.33).

Toxicity. Treatment was well-tolerated, no acute or late G≥3 toxicities were reported and no patients required SAbR interruption due to SAbR-related adverse events. Overall grade 2 radiation pneumonitis and lung atelectasis were observed in 2 (5.4%) and 3 (8.1%) patients, respectively.

Discussion

We report the results of an observational study demonstrating the efficacy of SAbR for the treatment of patients with oligometastatic pulmonary disease from gastrointestinal (GI)

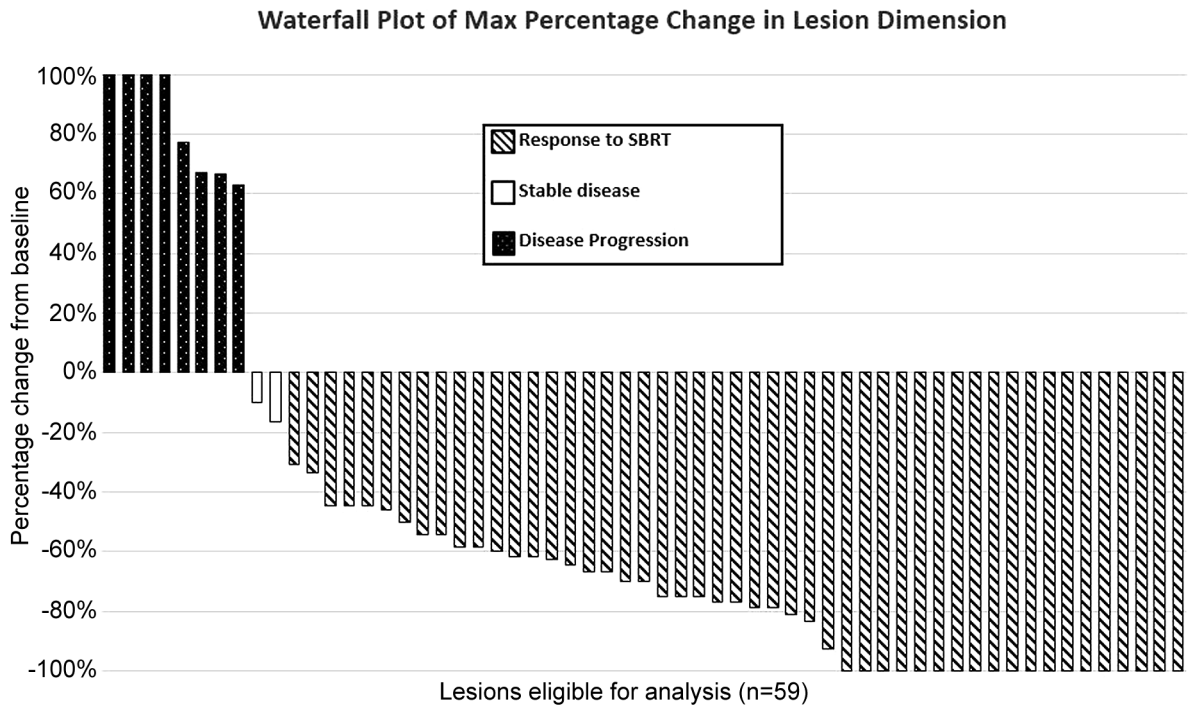

Figure 2. *According to RECIST Criteria, 49 lesions (83.1%) had a partial/complete response after SAbR (at least 30% decrease in target lesion dimension from baseline), while 2 (3.3%) lesions had stable disease, for an overall local control rate of 86.4%. Local progression occurred in 8 (13.6%) lesions (>20% increase of target lesion).*

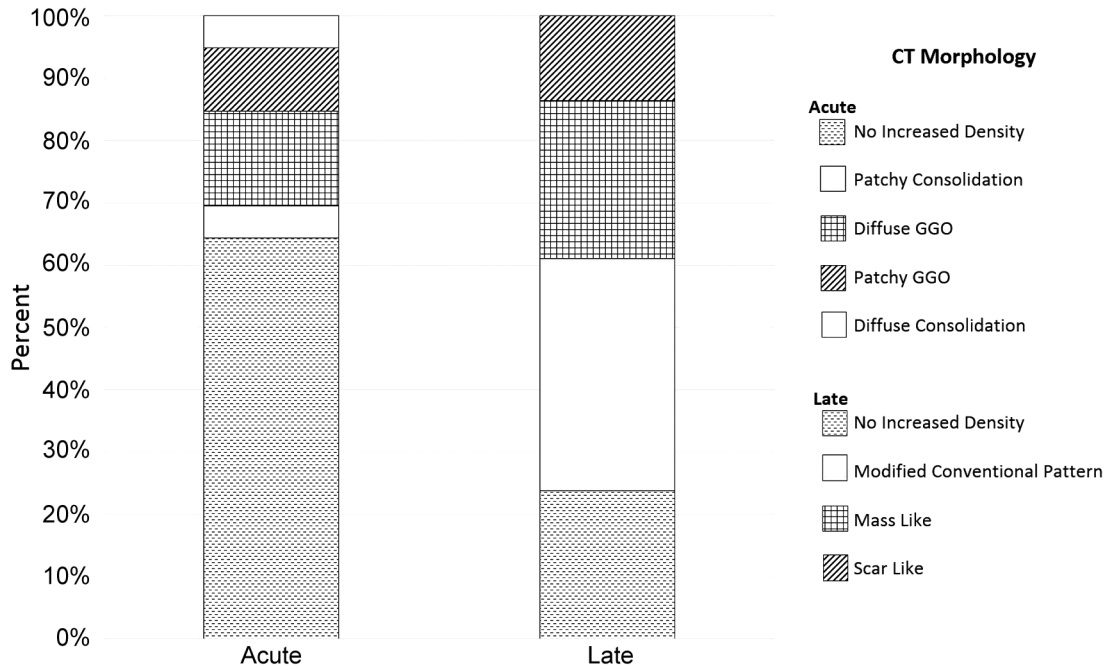

Figure 3. *Pattern of computed tomography (CT) changes after stereotactic ablative radiotherapy (SAbR) by follow-up period. Acute changes occuring <6 months, while late changes ≥6 months after the end of SAbR. GGO: Ground glass opacity.*

Table III. *Univariate and multivariate hazard ratios and 95%CIs of factor associated with local control (LC).*

	Univariable analysis		Multivariable analysis	
Variable	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age				
<65	1			
≥65	0.76 (0.19-3.03)	0.69		
Gender				
Male	1			
Female	1.69 (0.40-7.09)	0.47		
BED10				
<100 Gy	1		1	
≥100 Gy	0.05 (0.01-0.20)	**<0.001**	0.16 (0.03-0.85)	**0.03**
Primary				
CRC	1			
Non CRC	0.55 (0.06-4.90)	0.59		
OMD state				
Recurrence	1			
Progression/Persistence	0.54 (0.11-2.69)	0.45		
Treated lung metastases				
1	1			
≥1	2.64 (0.29-23.65)	0.34		
GTV				
<2.0 ml	1			
≥2.0 ml	0.85 (0.21-3.40)	0.82		
PTV				
<11.0 ml	1			
≥11.0 ml	1.76 (0.39-6.77)	0.44		
RECIST evaluation at 3 months*				
nr	1			
r	0.52 (0.04-6.47)	0.62		
RECIST evaluation at 6 months#				
nr	1		1	
r	0.002 (0.0001-0.06)	**<0.001**	0.001(0.00-0.08)	**0.002**
RECIST evaluation at 12 months°				
nr	1			
r	0.02 (0.002-0.22)	**0.001**		

BED_{10}: Biologically effective dose; Gy: gray; CRC: colorectal cancer; OMD: oligometastatic disease; GTV: gross tumor volume; PTV: planning target volume; nr: not response; r: response. Bold values indicate significant correlations. *median time re-evaluation after SBRT 2.8 months (range=1.8-4.3 months); #median time re-evaluation after SBRT 6.3 months (range=4.7-10.3 months); °median time re-evaluation after SBRT 12.2 months (range=9.6-14.9 months).

malignancies. For the 59 pulmonary treated lesions, local control (LC) at 1 and 2 years was 89.7% and 85.0%, respectively. No acute or late G≥3 toxicity occurred during follow-up.

The results of this study may lead to different considerations. High doses (BED_{10} ≥100 Gy) appeared to be associated with better LC (p=0.03 in multivariate Cox analysis). Notably, we found a 2-year LC rate of 91.0% *versus* 20.0% for lesions treated with a BED_{10} ≥100 Gy *versus* <100 Gy, respectively (Figure 1b). Although SAbR radiobiology is not yet fully understood (21), this result is consistent with previous experiences reported in the literature, in which the administration of ablative doses had the biggest influence on LC (14). At present, the optimal SAbR dose for pulmonary metastases has yet to be determined, and is generally conditioned by the size, number and site of treated lesions, as well as by the respect of organs at risk's dose constraints. Since the excellent toxicity profile of SAbR was confirmed in our study, we can postulate that prescribing ablative doses (BED_{10} ≥100 Gy) represents a clinical priority, even if a reasonable increased risk of toxicity may be foreseen. When a BED_{10} ≥100 Gy cannot be prescribed, alternative local strategies should be considered.

Correlation between RECIST response, LC and CT parenchymal changes after SAbR were analyzed. Interestingly, we found that radiology re-assessment at 6 months was predictive for LC (p=0.002 in multivariate Cox

analysis). Similarly, Li *et al*. observed a strong correlation between the radiology evaluation at 5.3 months and final local effect of SAbR for 105 colorectal lung metastases (22). This confirms the relatively slow but continuous shrinkage of the lesion size over months after SAbR and the fallibility of a too early CT re-evaluation. However, the incidence of lung parenchymal modifications increases over time after the end of SAbR. Dahele *et al*. reported a cumulative incidence of SAbR-related CT changes of 54%, 56%, 73% and 87% at <6, 6, 12 and 24 months, respectively (23). In our series, acute radiological lung changes were seen in 35.6% of cases, and continued to increase during follow-up up to 76.3% for late modifications (Figure 3). Thus, radiological assessment could be influenced by SAbR-induced parenchyma modifications at the time interval maximally predictive of LC. This underlines the importance of a multidisciplinary evaluation of CT images by a dedicated board, and the strategic role of PET/CT if local failure is suspected. Indeed, metabolic information might be crucial to differentiate tumor progression from SAbR-related fibrotic changes (24).

In our study LC was not influenced by other evaluated factors, such as size and number of treated lesions or OMD state. Differently, some authors reported lower LC for higher lesion dimension (25) or extent of metastatic disease (26). This could be in part explained by the fact that 91.5% of lung metastases in our experience received a BED_{10} ≥100 Gy and by the relatively low number of LFs, thus definitive conclusions cannot be drawn.

Furthermore, we found that a BED_{10} ≥100 Gy may improve PFS (p=0.04 in multivariate Cox analysis). The SABR-COMET trial has recently reported, in oligometastatic patients, an improved OS and PFS in the SAbR arm compared to palliative standard of care treatments alone (control group) (27). Although in the present study a significance was not achieved even for OS, the prolonged PFS further confirms the importance of using metastasis-directed ablative doses to prevent or delay any CST. For the patient, this can be translated into a “therapeutic holiday” or in avoiding the start of the next line of chemotherapy, with an improvement in the quality of life.

Our study presents some limitations. The design is observational, with a relatively small sample size, although consistent with other experiences reported in the literature. In addition, since the indication to SAbR was defined case-by-case, as a distinctive characteristic of our clinical practice, our results can be biased by the patient selection process. Finally, this analysis included different histologies and type of OMD (“true” *versus* “induced”), which potentially add heterogeneity to the outcomes measured.

A significant number of patients with GI tumors experience limited metastatic disease to the lungs during their illness history. The efficacy of systemic therapy in this setting is increasing, potentially expanding the indication for SAbR in selected patients belonging to the spectrum of oligometastatic disease. The excellent LC and toxicity profile observed in this and other series, confirm that SAbR is an effective alternative to surgery in this scenario. A BED_{10} ≥100 Gy and RECIST response at 6 months may represent the main factors affecting LC, therefore a proper SAbR prescription dose and radiological re-assessment should be planned.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors’ Contributions

Conceptualization, NS and RMi; methodology, NS and RMi; data curation and statistical analysis, GR, MGG and MP; validation, MM and RMa; writing – original draft preparation, NS, RMi, GR, MGG and MP; writing – review and editing, AM, NLVC, MDL, SG and CC; supervision, MM and RMa; all Authors have read and agreed to the published version of the manuscript.

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Received July 23, 2020
Revised August 6, 2020
Accepted August 7, 2020