



# Magnetic resonance-guided stereotactic body radiation therapy (MRgSBRT) for oligometastatic patients: a single-center experience

Giuditta Chiloire<sup>1</sup> · Luca Boldrini<sup>1</sup> · Angela Romano<sup>1</sup> · Lorenzo Placidi<sup>1</sup> · Huong Elena Tran<sup>1</sup> · Matteo Nardini<sup>1</sup> · Mariangela Massaccesi<sup>1</sup> · Francesco Cellini<sup>1</sup> · Luca Indovina<sup>1</sup> · Maria Antonietta Gambacorta<sup>1</sup>

Received: 19 December 2022 / Accepted: 27 March 2023 / Published online: 20 April 2023  
© Italian Society of Medical Radiology 2023

## Abstract

**Purpose** Stereotactic body radiotherapy is increasingly used for the treatment of oligometastatic disease. Magnetic resonance-guided stereotactic radiotherapy (MRgSBRT) offers the opportunity to perform dose escalation protocols while reducing the unnecessary irradiation of the surrounding organs at risk. The aim of this retrospective, monoinstitutional study is to evaluate the feasibility and clinical benefit (CB) of MRgSBRT in the setting of oligometastatic patients.

**Materials and methods** Data from oligometastatic patients treated with MRgSBRT were collected. The primary objectives were to define the 12-month progression-free survival (PFS) and local progression-free survival (LPFS) and 24-month overall survival (OS) rate. The objective response rate (ORR) included complete response (CR) and partial response (PR). CB was defined as the achievement of ORR and stable disease (SD). Toxicities were also assessed according to the CTCAE version 5.0 scale.

**Results** From February 2017 to March 2021, 59 consecutive patients with a total of 80 lesions were treated by MRgSBRT on a 0.35 T hybrid unit. CR and PR as well as SD were observed in 30 (37.5%), 7 (8.75%), and 17 (21.25%) lesions, respectively. Furthermore, CB was evaluated at a rate of 67.5% with an ORR of 46.25%.

Median follow-up time was 14 months (range: 3–46 months). The 12-month LPFS and PFS rates were 70% and 23%, while 24-month OS rate was 93%. No acute toxicity was reported, whereas late pulmonary fibrosis G1 was observed in 9 patients (15.25%).

**Conclusion** MRgSBRT was well tolerated by patients with reported low toxicity levels and a satisfying CB.

**Keywords** Magnetic resonance-guided radiation therapy · Oligometastatic disease · Stereotactic body radiation therapy · Online adaptive radiation therapy

## Introduction

The use of stereotactic body radiation therapy (SBRT) in the metastatic setting has been widely discussed in the literature, especially regarding its feasibility and efficacy in both poly- and oligometastatic diseases. Oligometastatic disease is considered an intermediate stage between localized (usually 1 to 5 lesions) and diffused disease, amenable to local ablative treatment. Over time, many efforts have been made to characterize and classify it [1, 2].

A major topic of debate is the precise definition of the oligometastatic disease (e.g. the cut-off number of metastases for the definition of oligo disease, their size, the impact of tumour type and metastatic site, etc.) and the actual benefit of ablative treatments on survival and local control [3].

Very often, surgery or other local metastases-directed therapies are not feasible and so different strategies need to be implemented. SBRT represents one of the main treatment options for oligometastatic disease located in critical body sites due to its potential to deliver a high dose while minimizing organs at risk (OARs) exposure. Results from the randomized phase II SABR-COMET trial supported the evidence of an oligometastatic disease status that may be amenable of curative treatment.

SBRT was associated with an improved overall survival (OS) and progression-free survival (PFS) when compared

✉ Angela Romano  
angela.romano1@guest.policlinicogemelli.it

<sup>1</sup> Fondazione Policlinico Universitario “A. Gemelli” IRCCS,  
Largo Agostino Gemelli 8, 00168 Rome, Italy

to standard palliative therapy [4]. Although the results were very promising and new trials have been designed, concerns about acute and late toxicities remain. SABR-COMET reported 29% grade  $\geq 2$  toxicities and 3 fatal events [4].

In recent years, technological advances in radiotherapy (RT) have demonstrated the safety and feasibility of applying SBRT, but more attention needs to be drawn to the risk of toxicity when treating potentially long-surviving patients.

Furthermore, the advent of the COVID-19 pandemic has had a major impact on the diagnosis and treatment of cancer, with hypofractionated RT and, consequently, SBRT becoming increasingly important to reduce access to hospital and the risk of infection and proving to be a valid and safe treatment option [5].

Hybrid accelerators with integrated magnetic resonance (MR-Linac) have been recently developed, leading to the introduction of magnetic resonance-guided radiotherapy (MRgRT) in clinical practice. The main concept of this technology is to obtain improved soft tissue visualization, advanced gating protocols, and the possibility to safely deliver stereotactic MR-guided online adaptive radiotherapy (SMART) [6].

The recalled features allow for a more precise identification of therapy volumes improving the reliability of the segmentation purposes and allowing to use smaller safety margins due to direct real-time target tracking.

Furthermore, SMART allows re-contouring and re-optimization of the daily dose distribution on the patient's anatomy just before starting the RT session, thereby enabling dose escalation protocols and improving OAR sparing. This technology is particularly suitable for the treatment of lesions located in critical anatomical areas (e.g. upper gastrointestinal tract, which is characterized by the presence of very radiosensitive healthy organs, such as the small bowel or the duodenum) that undergo a physiological daily positional change due to the respiratory cycle and organ filling [6]. Hence, the goal of this single-institutional study is to present a case series of oligometastatic patients with visceral metastases only, undergoing MRgSBRT in order to demonstrate its efficacy and safety.

## Materials and methods

Data from oligometastatic patients treated with MRgRT from February 2017 to March 2021 at Policlinico Universitario “Agostino Gemelli” IRCCS of Rome, Italy, were retrospectively collected and analysed. All patients were treated using a 0.35 T MRgRT unit (MRIdian, ViewRay Inc., Mountain View, CA, USA), initially using the Cobalt-60 version, consisting of a tri-cobalt-60-ringed gantry with on-board MRI imaging [7]. Its updated Linac version, which couples a 0.35 T MRI scanner with a 6-MV

flattering filter-free (FFF) Linac [8], was used after an upgrade that took place in February 2018.

Patients  $\geq 18$  years old, with the Eastern Cooperative Oncology Group (ECOG) performance score 0–2, presenting up to five inoperable metastases, eligible for MRgSBRT, and able to sign an informed consent were included. Patients who had already undergone RT on the same anatomical site with overlap with the previously treated radiation volume were excluded. No size-related cut-off thresholds for the lesion size were established.

All patients underwent dedicated treatment simulation on the MRIdian system.

Patients with abdominal metastases were instructed to fast at least 3 h before the simulation and therapy sessions to increase the reproducibility of the treatment. All patients were immobilized in a supine position using a customized immobilization device Fluxboard (Fluxboard™, MacroMedics, The Netherlands). True fast imaging (TRUFI) MR scans were acquired with different acquisition protocols, either free breathing (FB) 25-s MR scans or breath-hold inspiration (BHI) 17- or 25-s MR scans, to assess tumour and OAR motion.

A real-time sagittal cine TRUFI MRI sequence (4/8 frames/s) was used to assess reproducibility and patient tolerance to gating. If the patient was unable to tolerate simulation under BHI conditions, he/she was considered for FB treatment.

In this phase, several parameters were defined in order to customize the treatment, such as the gating target structure (which could be the lesion itself or a surrogate), the boundary values, tracking algorithms, confidence rating, and percentage of region of interest (ROI%).

A standard simulation CT scan was performed with the same immobilization system to obtain the electron density information for the dose calculation. After a deformable coregistration of the CT on the simulation MR used as primary imaging, contouring was performed according to the RTOG guidelines [9, 10], using the information obtained from coregistered diagnostic imaging (MR, CT, or  $^{18}\text{F}$ FDG PET-CT).

The GTV was considered equal to the CTV, and the CTV-PTV margin was set at 3–5 mm, depending on clinical judgement and intrafraction motion. Planning was performed with the MRIdian treatment planning system (ViewRay Inc., Mountain View, CA, USA) through a Monte Carlo calculation algorithm with a step-and-shoot intensity-modulated radiation technique [11], including the influence of 0.35 T on the dose calculation.

PTV coverage was assessed according to ICRU 83 [12] or ICRU 91 [13] recommendations, and AAPM Task Group 101 [14] constraints were used for dose evaluation to OARs.

Prior to each treatment fraction, a new 17- or 25-s MR scan was acquired, either FB or BHI, depending on the case,

to assess patient alignment and make set-up corrections if needed.

If the indication for SMART was given by attending physician, deformable contour registration, contour adjustment, dose prediction, treatment plan re-optimization, and secondary Monte Carlo-based quality assurance (QA) were performed, as described previously [15, 16]. After selecting the most appropriate sagittal plane for gating and setting the recalled parameters defined in the simulation phase, the treatment was delivered through daily online cine-MR monitoring.

Toxicities were considered acute if recorded up to 90 days after the end of treatment or late if afterwards. The Common Terminology Criteria for Adverse Events (CTCAE) scale version 5.0 was used for their scoring [17].

Local and systemic response to treatment were assessed according to RECIST criteria, according to a follow-up schedule that included instrumental re-evaluation every 3–6 months with contrast-enhanced MRI, contrast-enhanced CT, or  $^{18}\text{F}$ FDG PET-CT, depending on clinical judgement [18]. Clinical and dosimetric data were also collected.

The conformity index (CI) and the homogeneity index (HI) of lesions representing the conformity between the prescribed dose area and PTV and the degree of uniformity within the target were calculated according to the RTOG definitions [19].

Furthermore, patients were classified according to the status of metastatic disease as defined by Guckenberger et al. [20]. OS was calculated from the date of primary tumour diagnosis to the date of the last follow-up or death. Overall and local progression-free survival (PFS and LPFS) were calculated from the date of end of RT treatment to the date of overall and local progression, respectively. OS, PFS, and LPFS were estimated using the Kaplan–Meier method.

The objective response rate (ORR), including complete response (CR) and partial response (PR), was evaluated for the irradiated lesions. Clinical benefit (CB) included ORR and stable disease (SD).

The analysed variables were patient-dependent (e.g. age, gender, ECOG), disease-dependent (e.g. site of primary cancer, site of treated metastasis, oligometastatic disease or induced oligometastatic disease, synchronous or metachronous metastatic presentation, subsequent combined treatments), and treatment-dependent (e.g. SMART application, gating phase, BED, GTV volume) (see supplementary materials for complete datasets). These parameters were correlated with each survival outcome on “per-lesion” basis using the univariate analysis with the Kaplan–Meier method. Then, Cox regression multivariate analysis was performed using the variables that resulted statistically significant from the univariate analysis. Statistical significance was defined as  $p\text{-value} < 0.05$ . Results were reported as odds ratio with 95% confidence interval.

## Results

Eighty metastatic lesions from 59 patients were evaluated for this retrospective analysis.

The clinical characteristics of the patients and metastatic lesions are shown in Table 1. Median age was 71 years (38–83), and 55.9% were female. The most common primary tumour was colorectal cancer (CRC) (35%), and the most common site treated was the liver (42%). Table 2 summarizes the dosimetric parameters of the treated lesions.

All patients completed the planned treatment without interruption.

Forty-six patients (77.97%) treated a single lesion, while 13 patients (22.03%) treated more than one lesion, either sequentially or simultaneously. Among the latter, four (6.78%) patients underwent re-irradiation of newly occurring oligometastatic lesions. Figure 1 shows the case of a patient affected by uveal melanoma who underwent sequential irradiation of three liver metastases and one adrenal gland metastasis. The three liver lesions were treated with 50 Gy/5 fractions prescribed at 80% isodose (in orange colourwash), and the adrenal lesion was treated with 35 Gy/5 fractions prescribed at 80% isodose (in yellow colourwash).

Eleven different fractionations were used, depending on the clinical characteristics, location, and volume of the lesion. Particularly, the most commonly used one was 50 Gy in 5 fractions (40%) and the median  $\text{BED}_{\alpha/\beta=10}$  achieved was 99.4 Gy (range 42.8–143.8). Nine (11.25%) of the treatments were performed with SMART technique for the treatment of 5 peritoneal nodules, 2 adrenal lesions, and 2 medial liver lesions. Daily SMART was performed to improve improved target coverage and optimize OARs irradiation. Following RT treatment, chemotherapy (CHT) was performed in 57.5% of cases, while in 28.75% of the cases, a following course of SBRT or RT was performed.

Complete response (CR), PR, and SD of the treated lesions were observed in 30 (37.5%), 7 (8.75%), and 17 (21.25%) lesions, respectively, reaching a 67.5% CB rate with a 46.25% of ORR.

Median follow-up was 14 months (range: 3–46 months). The 24-month OS rate was 93%, while the 12-month actuarial PFS and LPFS rates were 23% and 70%, respectively (Fig. 2).

Primary pancreatic cancer was shown to have a negative effect on OS, PFS, and LPFS after univariate and multivariate analysis, whereas primary lung carcinoma had a negative effect on OS only.

On the contrary, the presence of metachronous metastatic disease  $\geq 12$  months in general and in the case of treated lesions were found to have improved OS after both

**Table 1** Clinical characteristics of patients and lesions

|   |                  |            | N (%)      |
|---|------------------|------------|------------|
| Patients  |                  |            | 59 (100)   |
| Lesions   |                  |            | 80 (100)   |
| MRIIdian  |                  |            |            |
| Tri-cobalt-60   |                  |            | 12 (15)    |
| Linac   |                  |            | 68 (85)    |
| Age at RT time, years   |                  |            | 71 (38–83) |
| Median (range)  |                  |            |            |
| Gender  |                  |            |            |
| Male  |                  |            | 26 (44.1)  |
| Female  |                  |            | 33 (55.9)  |
| ECOG performance status   |                  |            |            |
| 0–1   |                  |            | 56 (94.9)  |
| 2   |                  |            | 3 (5.1)    |
| Primary tumour  |                  |            |            |
| NSCLC   |                  |            | 7 (8.8)    |
| Pancreas  |                  |            | 11 (13.6)  |
| Melanoma  |                  |            | 6 (7.6)    |
| Colorectal  |                  |            | 28 (35)    |
| Gynaecological malignancies                                       |                  |            | 16 (20)    |
| Other   |                  |            | 12 (15)    |
| Metastasis site   |                  |            |            |
| Adrenal   |                  |            | 7 (8.8)    |
| Liver   |                  |            | 42 (52.5)  |
| Pancreatic  |                  |            | 1 (1.3)    |
| Lung  |                  |            | 25 (31.2)  |
| Peritoneal  |                  |            | 5 (6.2)    |
| Timing-treated lesion   |                  |            |            |
| Synchronous   |                  |            | 4 (5)      |
| Metachronous  |                  |            | 17 (21.3)  |
| Metachronous > 12 months  |                  |            | 59 (73.7)  |
| Primary tumour control  |                  |            |            |
| Yes   |                  |            | 66 (82.5)  |
| Not   |                  |            | 14 (17.5)  |
| Primary chemotherapy  |                  |            |            |
| Yes   |                  |            | 64 (80)    |
| Not   |                  |            | 16 (20)    |
| Oligometastatic status (according to Guckenberger classification) |                  |            |            |
| Induced   | Oligopersistence | 9 (11.25)  | 13 (16.25) |
| Repeat  |                  | 4 (5)      |            |
| Induced   | Oligoprogression | 11 (13.75) | 35 (43.75) |
| Metachronous  |                  | 7 (8.75)   |            |
| Repeat  |                  | 17 (21.25) |            |
| Induced   | Oligorecurrence  | 5 (6.25)   | 28 (35)    |
| Metachronous  |                  | 17 (21.25) |            |
| Repeat  |                  | 6 (7.5)    |            |
| Synchronous   | Oligometastasis  | 4 (5)      |            |

NSCLC non-small cell lung cancer; RT radiotherapy; ECOG Eastern cooperative oncology group

univariate analysis and multivariate analysis. Univariate analysis also revealed that patients aged > 65 years with approximately 1-year PFS had a positive impact on OS.

Furthermore, subsequent RT or SBRT treatments had a statistically significant impact on PFS with both univariate

**Table 2** Dosimetric characteristics of treated lesions

|   | <i>N</i> (%)       |
|---|--------------------|
| Median total dose (range) (Gy)                                  | 48 (24–55)         |
| Median fraction number (range)                                  | 5 (3–6)            |
| Fractionation regimes (Gy/fx)                                   | 3 (3.75)           |
| 24/3  | 4 (5)              |
| 30/5  | 2 (2.5)            |
| 30/3  | 7 (8.75)           |
| 35/5  | 19 (23.75)         |
| 40/5  | 1 (1.25)           |
| 42/3  | 2 (2.5)            |
| 48/6  | 3 (3.75)           |
| 48/4  | 32 (40)            |
| 50/5  | 4 (5)              |
| 54/6  | 3 (3.75)           |
| 55/5  |                    |
| Normalization   | 29 (36.25)         |
| Dmean   | 51 (63.75)         |
| 80% isodose   |                    |
| Median BED <sub><math>\alpha/\beta=10</math></sub> (range) (Gy) | 99.4 (42.8–143.8)  |
| Median CI (range)   | 0.98 (0.3–1.16)    |
| Median HI (range)   | 14.14 (4.82–58.04) |
| GTV size  | 44 (55)            |
| < 5 cc  | 36 (45)            |
| > 5 cc  |                    |
| Gating  | 64 (80)            |
| BHI   | 16 (20)            |
| FB  |                    |
| Online adaptive treatment                                       | 9 (11.25)          |
| Yes   | 71 (88.75)         |
| Not   |                    |

*BHI* breath-hold inspiration; *FB* free breathing; *BED* biologically effective dose; *CI* conformity index; *HI* homogeneity index; *GTV* gross tumour volume; *Fx* fraction

and multivariate analyses, whereas subsequent CHT had a significant impact on PFS after univariate analysis only.

In addition, treatment-related data indicated that a GTV volume > 5 cc negatively affected PFS in univariate analysis

and LPFS in both univariate and multivariate analyses. The univariate analysis also showed an extension of LPFS for lung metastases when compared to the others, which was in contrast to the application of the online adaptive workflow, which was found to be unfavourable. Only 9 (11.25%) patients were treated with the SMART approach, out of which 5 presented peritoneal nodules. Overall, oligometastatic disease status according to the Guckenberger classification showed no statistically significant differences for the considered outcomes.

Table 3 shows the statistically significant variables predicting OS, PFS, and LPFS on a per-lesion basis.

No patients developed acute toxicity, whereas 9 (15.25%) patients developed late G1 toxicity (mild pulmonary fibrosis requiring no treatment).

## Discussion

To the best of our knowledge, this study represents the largest monoinstitutional series of visceral oligometastases treated with MRgSBRT, having collected data from 59 patients with 80 lesions.

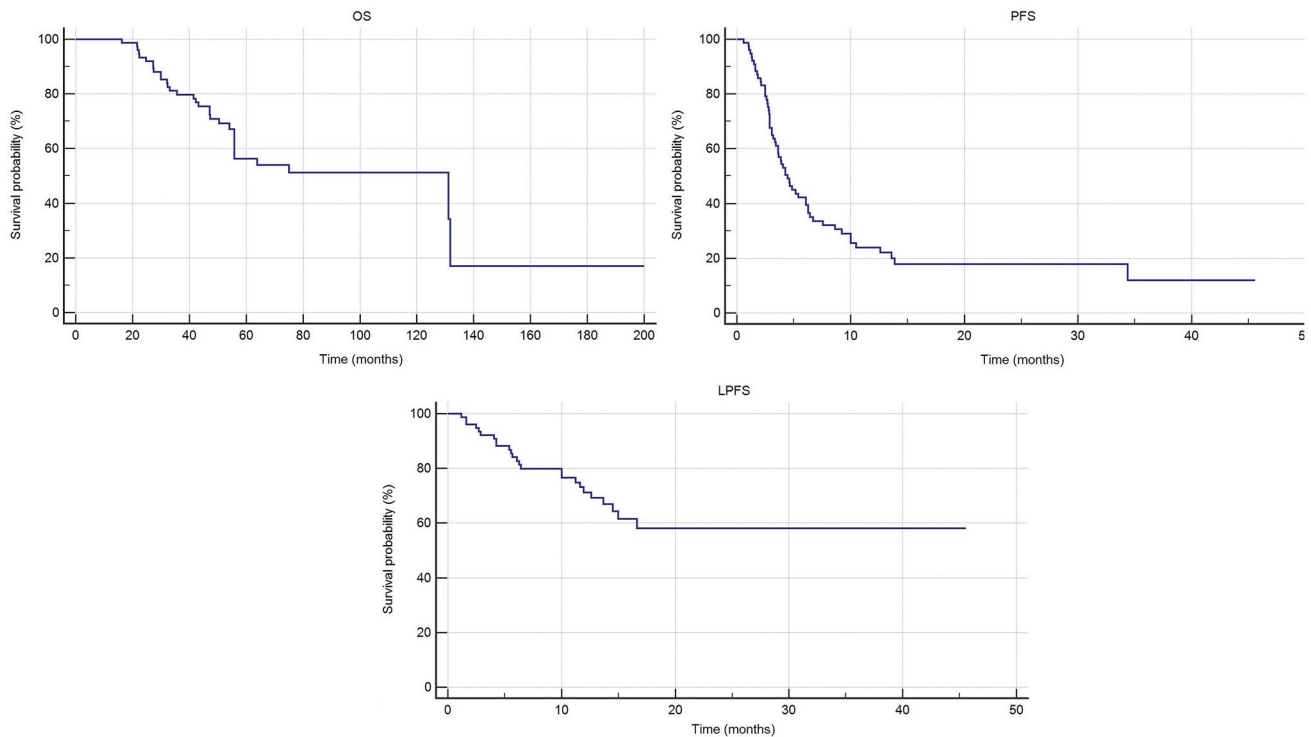
MRgRT is considered to be one of the most promising techniques used to deliver ablative RT doses in challenging anatomical locations, safely and effectively, and may play a pivotal role in the treatment of oligometastatic disease [21]. Recent reports from other monoinstitutional retrospective studies that implemented the SMART approach in primary and secondary malignancies demonstrated a high tolerance profile with G3 toxicity rates ranging from 0 to 8% and no G4 toxicity, with promising disease control rates [6, 22–26].

Although the SMART approach was used in only 9 (11.25%) cases in our study, our results confirm this high tolerance level, reporting no acute toxicity and only 15.25% late G1 toxicity grade among the entire cohort, considering



**Fig. 1** Sequential irradiation of three liver lesions and one adrenal lesion under inspiratory breath-hold (BHI) conditions





**Fig. 2** OS, PFS, and LPFS rates of the overall patient cohort. OS: overall survival; PFS: progression-free survival; LPFS: local progression-free survival

that 13 patients (22.03%) underwent SBRT on more than one lesion.

However, the unfavourable impact of SMART found on univariate analysis must be interpreted with caution, considering that 5 of the 9 lesions treated with the SMART approach were peritoneal nodules that were confirmed to be an aggressive disease condition that negatively affects the LPFS even on multivariate analysis.

This is probably correlated to the better visualization of the target volumes offered by on-board MRI and the effective direct gating for treatment delivery that allowed minimizing the exposure of OARs. Moreover, the efficacy and feasibility of SBRT have been described in several reports and in a recent meta-analysis, with rates of 1-year LC 94.7%, 1-year OS 85.4%, and 1-year PFS 51.4% [27]. However, the obtained data are not entirely comparable due to the difference in patient selection because the authors also included patients with bone and/or spine (44.8%) and lymph nodes (12.2%) lesions. Our results are encouraging with reports of 70% 1-year LC and 100% 1-year OS [27]. Furthermore, reaching a median  $BED_{\alpha/\beta=10}$  of 99.4 Gy (range 42.8–143.8), the 24-month OS rate was 93% and the 12-month actuarial PFS and LPFS rates were 23% and 70%, respectively.

These results appear to be consistent with those reported by a recent multi-institutional study performed by Kutuk

et al. and confirm the promising potentialities of this therapeutic approach [28]. The authors collected data from 96 patients with 108 lesions (48.1% abdominal/pelvic lymph nodes) undergoing MRgRT with a median  $BED_{\alpha/\beta=10}$  of 100 Gy, reporting 1-year freedom from local progression (FFLP), freedom from distant progression (FFDP), and PFS and OS rates of 92.3%, 41.1%, and 39.3% e 89.6%, respectively. Although these results seem to be similar to ours, the local and global disease control outcomes differ from those reported in our study, as the authors also included lymph node metastases, which are known to have a higher response to SBRT, compared to parenchymal metastases [29].

Interestingly, our analysis showed that the factors negatively impacting OS, PFS, and LPFS were primary pancreatic cancer and lung cancer, which may be due to their intrinsic aggressiveness, while the presence of metachronous disease  $\geq 12$  months was found to be a protective factor.

Another factor negatively affecting OS from the univariate analysis was the presence of uncontrolled primary tumour. The potential for metastatic spread, prognosis and treatment options differ between synchronous and metachronous diseases, as well as the precise time cut-off for the definition of metachronous (usually a time interval of 3–6 months from diagnosis of primary tumour to diagnosis of metastasis) [3]. A subsequent course of RT/SBRT referred to as “post-SBRT treatment” was found to

**Table 3** Univariate and multivariate analysis of variables predicting OS, PFS, and LPFS on per-lesion basis, using Kaplan–Meier and Cox regression analysis, respectively

| Variable  | n<br>(80) | OS                   |               |                       | PFS                  |                     |                     | LPFS                      |                     |                      |
|---|-----------|----------------------|---------------|-----------------------|----------------------|---------------------|---------------------|---------------------------|---------------------|----------------------|
|   |           | Univariate           |               | Multivariate          | Univariate           |                     | Multivariate        | Univariate                |                     | Multivariate         |
|   |           | HR<br>(95% CI)       | p             | HR<br>(95% CI)        | HR<br>(95% CI)       | p                   | HR<br>(95% CI)      | p                         | HR (95% CI)         | p                    |
| Patient characteristics                         |           |                      |               |                       |                      |                     |                     |                           |                     |                      |
| Age ≥ 65  | 60        | 0.46 (0.19 to 1.10)  | <b>0.028</b>  |                       | 0.92 (0.50 to 1.69)  | 0.776               |                     | 0.54 (0.20 to 1.43)       | 0.1414              |                      |
| Primary cancer characteristics                  |           |                      |               |                       |                      |                     |                     |                           |                     |                      |
| Lung cancer                                     | 7         | 2.53 (0.64 to 9.99)  | <b>0.0452</b> | 7.22 (2.19 to 23.81)  | <b>0.0012</b>        | 1.67 (0.63 to 4.40) | 0.1934              | 0.83 (0.22 to 3.16)       | 0.7983              |                      |
| Pancreatic cancer                               | 11        | 7.28 (1.51 to 35.17) | <b>0.0001</b> | 12.60 (4.45 to 35.71) | <b>&lt;0.0001</b>    | 2.94 (1.04 to 8.29) | <b>0.0008</b>       | 3.8887 (1.8860 to 8.0181) | <b>0.0003</b>       | 2.65 (0.66 to 10.73) |
| Gyn cancer                                      | 16        | 0.19 (0.09 to 0.41)  | <b>0.0076</b> |                       | 1.11 (0.57 to 2.20)  | 0.7326              |                     | 0.82 (0.30 to 2.23)       | 0.7129              |                      |
| Metachronous metas-<br>tasis ≥ 12 months        | 37        | 0.30 (0.15 to 0.61)  | <b>0.0005</b> | 0.29 (0.11 to 0.75)   | <b>0.0108</b>        | 1.01 (0.61 to 1.69) | 0.9606              | 0.68 (0.28 to 1.66)       | 0.4426              |                      |
| Uncontrolled<br>primary cancer                  | 14        | 3.33 (1.08 to 10.31) | <b>0.0009</b> |                       | 1.29 (0.65 to 2.567) | 0.4218              |                     | 0.39 (0.14 to 1.07)       | 0.1793              |                      |
| Target metastasis characteristics               |           |                      |               |                       |                      |                     |                     |                           |                     |                      |
| Lung metastasis                                 | 25        | 0.58 (0.283 to 1.19) | 0.1588        |                       | 0.70 (0.41 to 1.17)  | 0.1921              |                     | 0.39 (0.17 to 0.86)       | <b>0.0477</b>       |                      |
| Peritoneal<br>metastasis                        | 5         |                      |               |                       | 1.24 (0.41 to 3.76)  | 0.6799              |                     | 5.34 (0.62 to 45.77)      | <b>0.0005</b>       | 8.16 (2.58 to 25.82) |
| SMART   | 9         | 0.46 (0.16 to 1.31)  | 0.2566        |                       | 0.98 (0.45 to 2.14)  | 0.9571              |                     | 3.77 (0.87 to 16.33)      | <b>0.0022</b>       |                      |
| GTV volume > 5 cc                               | 36        | 1.64 (0.81 to 3.32)  | 0.1499        |                       | 1.77 (1.05 to 3.01)  | <b>0.0228</b>       |                     | 2.20 (0.99 to 4.90)       | <b>0.0462</b>       | 2.76 (1.20 to 6.33)  |
| BED > 70  | 68        | 0.79 (0.32 to 1.94)  | 0.5639        |                       | 2.77 (1.53 to 5.04)  | <b>0.0108</b>       |                     | 1.84 (0.70 to 4.89)       | 0.3104              |                      |
| Metachronous-<br>treated metastasis ≥ 12 months | 59        | 0.24 (0.083 to 0.68) | <b>0.0001</b> |                       | 1.24 (0.70 to 2.19)  | 0.4702              |                     | 1.94 (0.80 to 4.69)       | 0.2108              |                      |
| Post-SBRT procedures/outcome                    |           |                      |               |                       |                      |                     |                     |                           |                     |                      |
| CHT post-SBRT                                   | 46        | 1.53 (0.71 to 3.27)  | 0.2723        |                       | 2.03 (1.21 to 3.40)  | <b>0.0113</b>       |                     | 1.78 (0.79 to 4.04)       | 0.2075              |                      |
| RT/SBRT post-SBRT                               | 23        | 0.85 (0.38 to 1.90)  | 0.6954        |                       | 1.85 (1.02 to 3.35)  | <b>0.018</b>        | 1.90 (1.11 to 3.28) | <b>0.0211</b>             | 0.78 (0.35 to 1.74) | 0.5464               |
| CR-treated lesion                               | 30        | 0.80 (0.39 to 1.62)  | 0.528         |                       | 0.50 (0.30 to 0.82)  | <b>0.0101</b>       |                     |                           |                     |                      |
| ly PFS  | 21        | 0.33 (0.16 to 0.70)  | <b>0.0268</b> |                       |                      |                     |                     |                           |                     |                      |

Statistically significant values are highlighted in bold

OS overall survival; PFS progression-free survival; LPFS local progression-free survival; HR hazard ratio; CI confidence interval; SMART stereotactic MR-guided online adaptive radiation therapy; RT radiation therapy; SBRT stereotactic body radiation therapy; GTV gross tumour volume; BED biological effective dose; CHT chemotherapy; CR complete response; PD progression disease

have a positive role on PFS. This could be probably true for the treatment of a disease that has been confirmed to be oligometastatic with no signs of local or systemic advancement. Moreover, the variables with the greatest impact on LPFS were found to be the treatment of peritoneal nodules and a GTV volume > 5 cc. However, tumour size has been confirmed to be a prognostic factor for response to therapy [30, 31].

Indeed, peritoneal nodules are often placed closely to bowel loops, making ablative doses difficult to reach for a disease with considerable biological aggressiveness [32]. MRgRT appears to be a very promising technique, especially for very challenging targets such as peritoneal nodules, taking advantage of online adaptive radiotherapy in terms of target coverage and sparing of organs at risk. With this approach, the potential for high-dose prescription, together with appropriate patient selection, may lead to improved survival outcomes in future [33].

This analysis describes results from a heterogeneous population treated by different fractionation schedules, which together with the overall short follow-up time and the retrospective nature of the study, may be considered a study limitation.

Nevertheless, the technological setting is of certain interest, as the use of MRgRT is growing and the results of early reports are promising [34].

To date, there are still no reports that compare the benefits of MRgRT versus CT-based technology, also considering the introduction of online adaptive workflow for X-ray-based machines [35]. Therefore, data derived from further studies including prospective randomized and phase III trials will be required to confirm the benefits of MRgRT.

## Conclusions

MRgRT has been shown to be a safe and effective treatment modality for parenchymal lesions of oligometastatic patients characterized by favourable survival and local control rates. However, further studies are required to confirm the benefits of this technology and to explore further potential treatment options in this particular setting.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s11547-023-01627-4>.

**Author contributions** All authors contributed to the study conception and design. G.C., A.R., L.B., L.P., H.E.T., M.N., M.M., F.C., L.I., and M.A.G. acquired the data and wrote the manuscript. All authors read and approved the final manuscript.

**Funding** The authors declare that no funds, grants, or other supports were received during the preparation of this manuscript.

## Declarations

**Competing interests** Dr. Luca Boldrini has active research agreements with ViewRay Inc., Mountain View, CA, USA and received speaker honoraria for scientific presentations and travel reimbursements. Dr. Lorenzo Placidi reports a consulting agreement and research grants with ViewRay Inc., Mountain View, CA, USA, outside the submitted work.

**Ethics approval and consent to participate** This research study was conducted retrospectively in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study did not require approval by the Ethics Committee.

**Consent to participate** Informed consent was obtained from all individual participants included in the study.

**Consent for publication** All patients recruited in the study will sign informed consent regarding publishing their data.

## References

1. Hellman S, Weichselbaum RR (1995) Oligometastases. *J Clin Oncol* 13:8–10. <https://doi.org/10.1200/JCO.1995.13.1.8>
2. Tree AC, Khoo VS, Eeles RA et al (2013) Stereotactic body radiotherapy for oligometastases. *Lancet Oncol* 14:e28–e37. [https://doi.org/10.1016/S1470-2045\(12\)70510-7](https://doi.org/10.1016/S1470-2045(12)70510-7)
3. Lievens Y, Guckenberger M, Gomez D et al (2020) Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. *Radiother Oncol* 148:157–166. <https://doi.org/10.1016/j.radonc.2020.04.003>
4. Palma DA, Olson R, Harrow S et al (2019) Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 393:2051–2058. [https://doi.org/10.1016/S0140-6736\(18\)32487-5](https://doi.org/10.1016/S0140-6736(18)32487-5)
5. Piras A, Venuti V, D'Aviero A et al (2022) Covid-19 and radiotherapy: a systematic review after 2 years of pandemic. *Clin Transl Imaging* 10:611–630. <https://doi.org/10.1007/s40336-022-00513-9>
6. Henke L, Kashani R, Robinson C et al (2018) Phase I trial of stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen. *Radiother Oncol* 126:519–526. <https://doi.org/10.1016/j.radonc.2017.11.032>
7. Mutic S, Dempsey JF (2014) The ViewRay system: magnetic resonance-guided and controlled radiotherapy. *Semin Radiat Oncol* 24:196–199. <https://doi.org/10.1016/j.semradonc.2014.02.008>
8. Klüter S (2019) Technical design and concept of a 0.35 T MR-Linac. *Clin Trans Radiat Oncol* 18:98–101. <https://doi.org/10.1016/j.ctro.2019.04.007>
9. Jabbour SK, Hashem SA, Bosch W et al (2014) Upper abdominal normal organ contouring guidelines and atlas: a radiation therapy oncology group consensus. *Pract Radiat Oncol* 4:82–89. <https://doi.org/10.1016/j.prro.2013.06.004>
10. Kong (Spring) F-M, Ritter T, Quint DJ et al (2011) consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs,



- and brachial plexus. *Int J Radiat Oncol Biol Phys* 81:1442–1457. <https://doi.org/10.1016/j.ijrobp.2010.07.1977>
11. Placidi L, Nardini M, Cusumano D et al (2021) VMAT-like plans for magnetic resonance guided radiotherapy: addressing unmet needs. *Phys Med* 85:72–78. <https://doi.org/10.1016/j.ejmp.2021.05.002>
  12. Hodapp N (2012) The ICRU Report 83: prescribing, recording and reporting photon-beam intensity-modulated radiation therapy (IMRT). *Strahlenther Onkol* 188:97–99. <https://doi.org/10.1007/s00066-011-0015-x>
  13. Wilke L, Andrasschke N, Blanck O et al (2019) ICRU report 91 on prescribing, recording, and reporting of stereotactic treatments with small photon beams: statement from the DEGRO/DGMP working group stereotactic radiotherapy and radiosurgery. *Strahlenther Onkol* 195:193–198. <https://doi.org/10.1007/s00066-018-1416-x>
  14. Benedict SH, Yenice KM, Followill D et al (2010) Stereotactic body radiation therapy: the report of AAPM Task Group 101. *Med Phys* 37:4078–4101. <https://doi.org/10.1118/1.3438081>
  15. Bohoudi O, Bruynzeel AME, Senan S et al (2017) Fast and robust online adaptive planning in stereotactic MR-guided adaptive radiation therapy (SMART) for pancreatic cancer. *Radiother Oncol* 125:439–444. <https://doi.org/10.1016/j.radonc.2017.07.028>
  16. Placidi L, Romano A, Chiloiri G et al (2020) On-line adaptive MR guided radiotherapy for locally advanced pancreatic cancer: clinical and dosimetric considerations. *Tech Innov Patient Support Radiat Oncol* 15:15–21. <https://doi.org/10.1016/j.tipsro.2020.06.001>
  17. National Institutes of Health (2010) Common terminology criteria for adverse events (CTCAE). Version 4:196
  18. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 45:228–247. <https://doi.org/10.1016/j.ejca.2008.10.026>
  19. Shaw E, Kline R, Gillin M et al (1993) Radiation therapy oncology group: radiosurgery quality assurance guidelines. *Int J Radiat Oncol Biol Phys* 27:1231–1239. [https://doi.org/10.1016/0360-3016\(93\)90548-a](https://doi.org/10.1016/0360-3016(93)90548-a)
  20. Guckenberger M, Lievens Y, Bouma AB et al (2020) Characterisation and classification of oligometastatic disease: a European society for radiotherapy and oncology and european organisation for research and treatment of Cancer consensus recommendation. *Lancet Oncol* 21:e18–e28. [https://doi.org/10.1016/S1470-2045\(19\)30718-1](https://doi.org/10.1016/S1470-2045(19)30718-1)
  21. Chetty IJ, Doerner AJ, Dolan JL et al (2022) MRI-guided radiotherapy (MRgRT) for treatment of oligometastases: review of clinical applications and challenges. *Int J Radiat Oncol Biol Phys* S0360–3016(22):00745–00753. <https://doi.org/10.1016/j.ijrobp.2022.07.027>
  22. Rosenberg SA, Henke LE, Shaverdian N et al (2019) A multi-institutional experience of MR-guided liver stereotactic body radiation therapy. *Adv Radiat Oncol* 4:142–149. <https://doi.org/10.1016/j.adro.2018.08.005>
  23. Ugurluer G, Mustafayev TZ, Gungor G et al (2021) Stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of liver metastases in oligometastatic patients: initial clinical experience. *Radiat Oncol J* 39:33–40. <https://doi.org/10.3857/roj.2020.00976>
  24. Weykamp F, Hoegen P, Klüter S et al (2021) Magnetic resonance-guided stereotactic body radiotherapy of liver tumors: initial clinical experience and patient-reported outcomes. *Front Oncol* 11:610637
  25. Henke LE, Olsen JR, Contreras JA et al (2019) Stereotactic MR-guided online adaptive radiation therapy (SMART) for ultracentral thorax malignancies: results of a phase I trial. *Adv Radiat Oncol* 4:201–209. <https://doi.org/10.1016/j.adro.2018.10.003>
  26. Finazzi T, Haasbeek CJA, Spoelstra FOB et al (2020) Clinical outcomes of stereotactic MR-guided adaptive radiation therapy for high-risk lung tumors. *Int J Radiat Oncol Biol Phys* 107:270–278. <https://doi.org/10.1016/j.ijrobp.2020.02.025>
  27. Lehrer EJ, Singh R, Wang M et al (2021) Safety and survival rates associated with ablative stereotactic radiotherapy for patients with oligometastatic cancer: A systematic review and meta-analysis. *JAMA Oncol* 7:92–106. <https://doi.org/10.1001/jamaoncol.2020.6146>
  28. Kutuk T, Herrera R, Mustafayev TZ et al (2022) Multi-institutional outcomes of stereotactic magnetic resonance image guided adaptive radiation therapy with a median biologically effective dose of 100 Gy10 for non-bone oligometastases. *Adv Radiat Oncol* 7:100978. <https://doi.org/10.1016/j.adro.2022.100978>
  29. O’Cathail SM, Smith T, Owens R et al (2020) Superior outcomes of nodal metastases compared to visceral sites in oligometastatic colorectal cancer treated with stereotactic ablative radiotherapy. *Radiother Oncol* 151:280–286. <https://doi.org/10.1016/j.radonc.2020.08.012>
  30. Borm KJ, Oechsner M, Schiller K et al (2018) Prognostic factors in stereotactic body radiotherapy of lung metastases. *Strahlenther Onkol* 194:886–893. <https://doi.org/10.1007/s00066-018-1335-x>
  31. Allibhai Z, Taremi M, Bezjak A et al (2013) The impact of tumor size on outcomes after stereotactic body radiation therapy for medically inoperable early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 87:1064–1070. <https://doi.org/10.1016/j.ijrobp.2013.08.020>
  32. Boldrini L, Romano A, Placidi L et al (2020) Case report: first in human online adaptive mr guided sbt of peritoneal carcinomatosis nodules: a new therapeutic approach for the oligo-metastatic patient. *Front Oncol* 10:601739. <https://doi.org/10.3389/fonc.2020.601739>
  33. Cuccia F, Rigo M, Gurrera D et al (2021) Mitigation on bowel loops daily variations by 1.5-T MR-guided daily-adaptive SBRT for abdomino-pelvic lymph-nodal oligometastases. *J Cancer Res Clin Oncol* 147:3269–3277. <https://doi.org/10.1007/s00432-021-03739-8>
  34. Baptist Health South Florida (2022) A feasibility study of stereotactic MRI-guided adaptive radiation therapy (SMART) in one fraction for inoperable primary or metastatic carcinoma (SMART ONE). [clinicaltrials.gov](https://clinicaltrials.gov)
  35. Mao W, Riess J, Kim J et al (2022) Evaluation of auto-contouring and dose distributions for online adaptive radiation therapy of patients with locally advanced lung cancers. *Pract Radiat Oncol* 12:e329–e338. <https://doi.org/10.1016/j.prro.2021.12.017>

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.