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Original Research Article

# Daily adaptive MR-guided stereotactic ablative re-irradiation (re-SABR) in oligometastatic liver disease: A single-institution retrospective analysis

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ABSTRACT

*Objective:* Stereotactic ablative body radiotherapy (SABR) is an established treatment option in oligometastatic liver disease. Limited data exist on liver SABR re-irradiation (re-SABR). MR-guided SABR with daily plan adaptation and deformable image registration (DIR) allows organ-at-risk (OAR) sparing and dose accumulation in a re-irradiation setting. We report the safety and efficacy of MR-guided re-SABR in oligometastatic liver disease, alongside a DIR-based workflow for cumulative OAR dose calculation.

*Methods:* MR-guided re-SABR to oligometastatic liver disease was retrospectively analysed. Key inclusion criteria included: prior liver SABR, MR-guided re-SABR to $\leq$ 4 liver metastases, Child Pugh Score (CPS) $\leq$ B7, and a minimum prescribed dose of 30 Gy in 5 fractions. Lesions were classified according to the ESTRO-EORTC re-irradiation consensus. Acute and delayed toxicity, local control (LC), local progression-free survival (LPFS), and overall survival (OS) were reported, overall and by primary tumour type. Cumulative OAR doses were estimated using a DIR-based as compared to a non-DIR-based workflow.

*Results:* Between October 2020 and April 2024, twelve patients underwent MR-guided re-SABR to 18 liver metastases. While the majority (12/18) were colorectal in origin, other primaries included pancreas, breast, oesophagogastric, and ovary. 50% of lesions were type-1 re-irradiation (including 3 repeated target irradiations). Median prescription $BED_{10}$ was 100 Gy (range 72–151 Gy) for initial SABR and 100 Gy (range 48–132 Gy) for re-SABR. 50 Gy in 5 fractions (BED10 100 Gy) was delivered in 8 out of 12 re-SABR cases. With a median follow-up of 10 months (range 3–33) from re-SABR, no acute $\geq$ G2 toxicity was seen. 12-month PFS was 92 % (95 % CI 54–99).

Median, 1-year, and 2-year OS were 36 months (range 12–37), 100 % (95 % CI 54–99) and 91 % (95 % CI 51–99) for SABR and 22 months, 68 % (95 %CI 28–89) and 34 % (95 % CI 5–67) for re-SABR. DIR-based workflow estimates predicted significantly higher MLD and D700cc ($p < 0.01$) and smaller uninvolved liver volumes ($p < 0.05$).

*Conclusion:* With the limitation of relatively low patient numbers and mixed tumour histology, MR-guided re-SABR to oligometastatic liver disease appeared well tolerated, achieving high LC rates. DIR-based workflow predicted higher cumulative OAR doses, potentially further improving the safety of liver re-SABR.

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## 1. Introduction

Liver metastases represent a common site of disease spread from multiple primary tumours, most notably, colorectal and breast cancer [1]. Several liver-directed treatment (LDT) options exist, including surgical resection, percutaneous thermal ablation (radiofrequency ablation [RFA] or microwave ablation [MWA]) as well as chemo- and radioembolization (TACE/TARE) [2].

Stereotactic ablative body radiotherapy (SABR) offers a non-invasive LDT option, achieving high local control (LC) rates of 85 % and 75 % at 1 and 2 years, respectively, with an acceptable toxicity profile [3,4]. Its use has expanded due to its ability to spare healthy liver tissue better than conventional radiotherapy, reducing the risk of radiation-induced liver disease (RILD), a potentially fatal complication [5].

Whilst in-field disease control rates with SABR remain high, up to 50 % of patients experience out-of-field intrahepatic disease progression [6]. With improvements in novel systemic therapies (ST) and consequent increase in life expectancy of patients with oligometastatic liver disease (OMD), the potential role of liver re-SABR is expanding. Despite this, there exists a paucity of published data on the safety and efficacy of re-SABR in oligometastatic liver disease. Most liver re-irradiation studies have focused on hepatocellular carcinoma (HCC) [7–12] with only a small number of series including metastatic liver disease [13–15].

While liver re-SABR may offer a salvage option to patients experiencing intra-hepatic disease progression following SABR [13], its utility is often limited by high cumulative organ-at-risk (OAR) doses including dose to normal liver parenchyma and visceral structures. Attempts at reducing OAR doses may, in turn, lead to reduction in target coverage and subsequent reduction in LC. These challenges may be the reason for limited utilisation of liver re-SABR on conventional, non-adaptive CT based linac platforms.

Stereotactic MR-guided adaptive radiotherapy (SMART) represents a significant advancement in precision radiotherapy delivery, providing superior soft-tissue visualization, target and OAR contour adaptation to daily anatomy, on-set plan re-optimization, real time target tracking and beam gating for advanced motion management. This allows for accurate delineation of liver metastases, reduction in treatment margins, improvement in target coverage and safe dose-escalation within tolerance constraints of OARs [16–18]. Initial reports of re-SABR in oligometastatic liver disease are promising [15].

In the re-irradiation setting, deformable image registration (DIR) workflows may enhance dose accumulation accuracy and improve clinical decisions in adaptive radiotherapy [19]. Here, we report our institutional experience of daily adaptive MR-guided re-SABR in oligometastatic liver disease, focusing on feasibility as well as early toxicity and efficacy.

## 2. Methods

### 2.1. Study design and population

A retrospective, single institution study of daily-adaptive MR-guided re-SABR to liver metastases was conducted. Inclusion criteria included prior SABR to liver metastases, daily adaptive re-SABR to $\leq$ 4 liver metastases in a single plan and a minimum prescribed dose of 30 Gy in 5 fractions. We imposed no limit on maximum tumour size, provided volume of uninvolved liver (liver minus all gross tumour volumes-GTVs) $\geq$ 700 cc. All cases were reviewed in specialist SABR multidisciplinary meeting (MDM). Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and Child-Pugh score $\leq$ B7.

Re-irradiation was defined and classified according to the European Society for Radiotherapy and Oncology (ESTRO) and European Organisation for Research and Treatment of Cancer (EORTC) consensus guidelines [20,21].

### 2.2. SABR planning and delivery

Online adaptive MR-guided re-planning, including motion tracking with automatic beam gating, was utilised for all patients (*6 MV 0.3 5 T MRIdian Linac, ViewRay Systems Inc, Oak-wood Village, OH*).

Simulation included a true fast imaging with steady-state free precession (TRUFISP) MRI acquisition with Primovist® liver-specific contrast and a computed tomography (CT) scan. Additional diagnostic MRI sequences and/or PET-CT images were rigidly registered in MIM Maestro® (version 7.2.8, MIM Software, Cleveland Ohio), as required, to assist with target contour delineation. Within the MRIdian planning system, the planning CT was deformably registered to the MR to provide electron density information for dose calculation.

GTV was defined by the practitioner; contouring peer review by a radiation oncologist was mandatory, with optional hepato-pancreato-biliary (HPB) radiologist peer review. If requested by the practitioner, the CTV was defined as a 6 mm geometrical expansion of the GTV, cropped to anatomical boundaries to microscopic spread such as the liver and gallbladder. The PTV was CTV + 3 mm.

The tumour was identified and tracked through cine MR imaging to permit gated treatment. For lesions with poor image contrast or lesions $\leq$ 1 cm in diameter, the whole liver was selected as a surrogate tracking structure, with increased PTV margins to account for motion uncertainty.

Treatment plans were generated with step-and-shoot IMRT with the following dosimetric aims; PTV V(100 %) $\geq$ 95 %, V(95 %) $\geq$ 98 %, Dmax(0.1 cc) $\geq$ 110 % and $\leq$ 140 %, with hotspots inside the GTV. To account for unavoidable underdosing of the PTV in proximity to dose-limiting OAR, an optimisation volume was created as PTV minus OARs with a 6 mm margin expansion to allow for dose fall-off. This was undertaken to maximise prescription dose coverage while ensuring compliance with mandatory recovery-adjusted OAR dose constraints. The minimum PTV V(100 %) threshold was defined as $\geq$ 70 %.

Dose constraints were from the UK SABR Consortium [22](Table S1).

Re-irradiation OAR dose constraints were calculated using the methodology outlined in United Kingdom SABR Consortium Guidance for SABR re-irradiation [23]. In brief, this involved converting doses from all SABR courses to effective dose in 2 Gy (EQD2) with suitable alpha–beta ($\alpha/\beta$) ratios [24]. To account for tissue repair over time, a recovery factor was applied to the dose received in the first course, taking into consideration the time interval between courses. Cumulative dose limits for OARs were then adjusted based on the estimated degree of normal tissue recovery occurring between radiotherapy courses. Specifically, for the liver, we delineated an 'uninvolved liver' region of interest (ROI) by subtracting all prior and current GTVs from the deformed, cumulative liver contour. This enabled calculation of recovery-adapted cumulative constraints for mean liver dose (MLD) and D700cc using deformable image registration (DIR)-based dose accumulation, accounting for anatomical changes between SABR courses. The Appendix 1 shows a calculation example for determining the remaining tolerance after previous radiotherapy.

### 2.3. Deformable dose accumulation (DIR)-based cumulative OAR dose calculation workflow

As an alternative to the method above, a DIR-based workflow was created in MIM® to assess cumulative doses from primary and re-irradiation SABR courses. Fusion accuracy was visually assessed using DIR grey-value assessment, focusing on the liver. Prior to dose accumulation, voxel-by-voxel conversion to EQD2 was performed with a suitable ($\alpha/\beta$) ratio [24] and a tissue recovery factor applied to account for the time since the previous SABR. Doses were transferred to the most recent image set for accumulation. An 'uninvolved liver' region of interest (ROI) was created by subtracting the GTVs from all liver SABR courses from the deformed liver contour, which served as the basis of cumulative MLD and D (700 cc) calculation. We carried out a

comparison of cumulative OAR doses using DIR-based and the UK SABR Consortium workflows [25] (Fig. 1).

### 2.4. Toxicity and response evaluation

Institutional follow-up assessment was conducted 7–10 days after treatment completion. In cases, where subsequent follow-up was conducted outside our institution, clinical and imaging data was requested from the referring oncologist. Treatment toxicity was divided into acute (<3 months) and late (>3 months) and graded using the Common Terminology Criteria for Adverse Events (CTCAE v5.0) scale.

LC and distant disease progression were assessed based on radiographic findings on restaging imaging performed at 8–12 weeks and subsequently every 3 to 4 months after treatment completion. Local treatment response was classed as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). In cases of uncertainty in response assessment, imaging studies were re-reviewed independently by a specialist HPB radiologist.

### 2.5. Statistical analysis

Descriptive data was presented as median (range) for continuous variables, and percentage for categorical and dichotomous variables. All time-to-event analyses were measured from day 1 of SABR and day 1 of re-SABR. Cases where the event did not occur were censored at the time of last follow-up. Patients lost to follow-up were censored at the date of last contact.

Kaplan-Meier method was used to estimate survival outcomes. Outcomes over time were calculated for all patients combined and subsequently stratified by primary tumour type (CRC versus others) using log-rank test. Paired t-tests were used to assess dosimetric differences between the DIR-based and non-DIR based treatment plans. All analyses were conducted using software package Stata® (version 18.5).

## 3. Results

### 3.1. Patient demographics

Between October 2020 and April 2024, twelve patients received daily adaptive MR-guided re-SABR to 18 liver metastases. Median age was 62 years (range 40–84), 50 % of patients were male. CRC was the most frequent primary cancer (66.7 %). 75 % of patients were treated on the MR Linac during initial liver SABR, with the remainder of patients treated on CT-based or Cyberknife® based platforms. 58.3 % of patients underwent additional LDT, including surgery (n = 4), RFA (n = 1), or both (n = 1) (Table 1).

**Table 1**
Demographic parameters and treatment characteristics.

| Table 1. **Demographic parameters** | | | |
|---|---|---|---|
| | **N** | | 12 |
| | **Age, median (range)** | | 62 (40–84) |
| | **Gender, n (%)** | | |
| | **Male** | | 6 (50 %) |
| | **Female** | | 6 (50 %) |
| **PRIMARY** | **Histology** | | |
| | **CRC** | | 8 (66.7 %) |
| | **Pancreas** | | 1 (8.3 %) |
| | **Breast** | | 1 (8.3 %) |
| | **Oesophagus-gastric** | | 1 (8.3 %) |
| | **Ovary** | | 1 (8.3 %) |
| | **Prior ablative treatments (multimodality approach)** | | |
| | **Liver Surgery** | | 5 (3 of them more than one) |
| | **RFA** | | 2 |
| **Intercourses Time (months) median (range)** | | | 16.5 (3–37) |
| **SECONDARY** | **Progression characteristics** | | |
| | **Lesions (N)** | | 18 |
| | **Re-biopsy** | | 3 (25 %) |
| | **Oligoprogression classification*** | | |
| | **De-novo** | | 0 (0 %) |
| | **Repeat** | **Oligorecurrence** | 4 (33.33 %) |
| | | **Oligoprogression** | 1 (8.3 %) |
| | | **Oligopersistance** | 1 (8.3 %) |
| | **Induced** | **Oligorecurrence** | 4 (33.33 %) |
| | | **Oligoprogression** | 1 (8.3 %) |
| | | **Oligopersistance** | 1 (8.3 %) |
| | **Reirradiation Classification†** | | |
| | **Type 1** | | 9 (50 %) |
| | **Type 2** | | 9 (50 %) |

*N: number; CRC: colorectal cancer; Gy: gray; RFA: radiofrecuency*
**According ESTRO-EORTC consensus, Nicolaus Andratschke et al. Lancet Oncol 2022; 23: e469–78*
*†According to ESTRO-EORTC. Matthias Guckenberger et al. Lancet Oncol 2020; 21: e18–28*

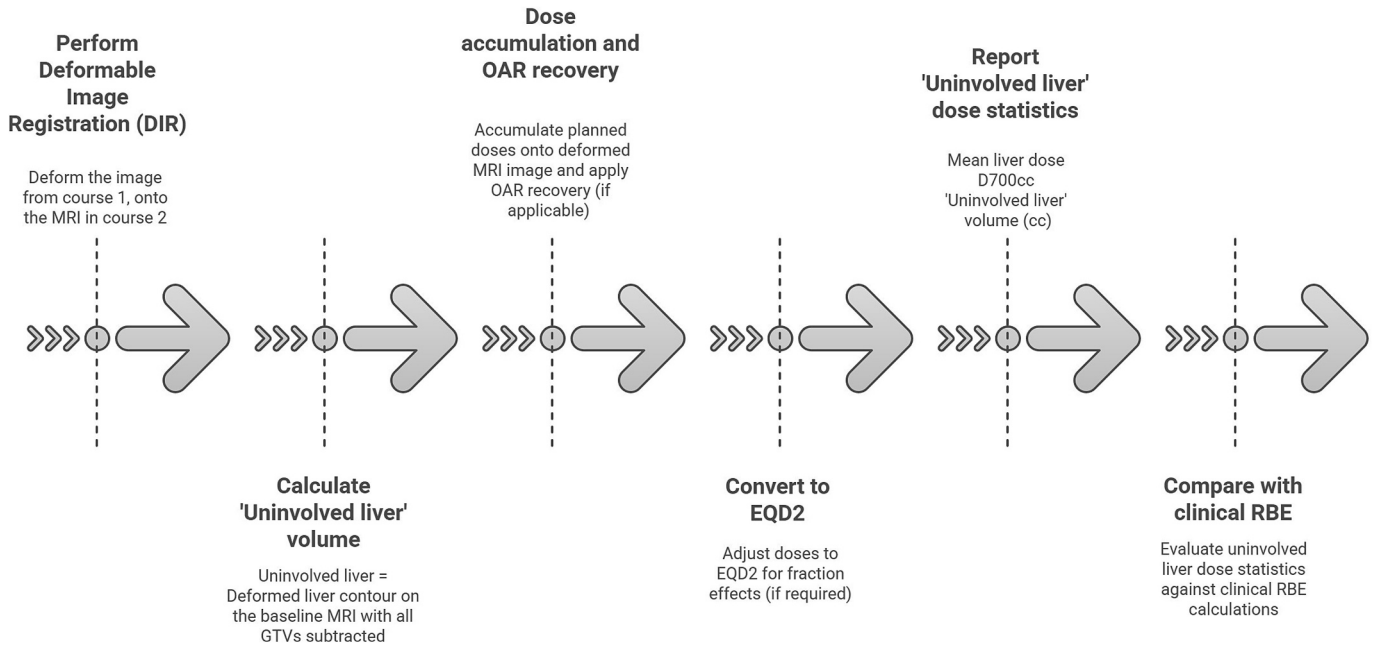


**Fig. 1.**

At a median interval between SABR courses of 16.5 months (range 6–37), nine treatments were classified as type-1 re-irradiation (including 3 cases of repeated target irradiation) and another nine as type 2 re-irradiation according to the ESTRO-EORTC consensus classification [20,21] (Fig. 2).

33.3 % of patients were receiving systemic therapy (ST) at the time of re-irradiation, with re-SABR delivered to oligo-progressive or oligo-persistent disease. In the remainder of cases re-SABR was delivered to oligo-metastatic disease with the aim to defer ST and/or time to poly-metastatic progression (with repeat and induced oligorecurrence being the most common types of OMD) (Table 1).

### 3.2. Dosimetric parameters

Mean GTV and PTV volumes were 12.7 cc (SD ± 22.1) and 44.1 cc (SD ± 44.7) for the first SABR and 11.4 cc (SD ± 16.7) and 37.4 cc (SD ± 33.3) for re-SABR courses.

The mean uninvolved liver volume was 1568.3 cc (SD ± 342.5) and 1472.2 cc (SD ± 363;) respectively.

Median prescription $BED_{10}$ was 100 Gy (range 72–151 Gy) for initial SABR and 100 Gy (range 48–132 Gy) for re-SABR. 50 Gy in 5 fractions ($BED_{10}$ 100 Gy) was delivered in 8 out of 12 re-SABR cases. All mandatory OAR constraints were met (Table 2 **and S2**).

### 3.3. Toxicity

With a median follow-up from re-SABR of 10 months (range 3——33), no G2 or higher acute toxicity was observed. Cumulative incidence of acute grade 1 toxicity was 50 %, with fatigue being the most common side effect (41.7 %). Late toxicity was reported in one case, with a G4 colo-hepatic fistula, occurring 15 months post 40 Gy in 5# re-SABR (type 1 re-irradiation), with sequential liver resection and RFA, in a setting of disease progression. There were no reports of liver decompensation and increase in Child-Pugh Score in this cohort.

### 3.4. Survival outcomes

Following the first SABR, median OS, 1-year OS, and 2-year OS were 36 months (range 12–37), 100 % (95 %CI 54–99), and 91 % (95 %CI 51–99) (Fig. 3a).

58 % of patients were alive at the time of analysis. 12-month LPFS after re-SABR was 92 % (95 % CI 54—99). N = 9 lesions displayed a degree of radiological response (n = 2 CR, n = 7 PR), n = 2 lesions demonstrated SD, and one lesion exhibited features of in-field disease progression (patient with KRAS mt CRC who received two courses of SABR with geometric overlap to 50 Gy in 5# and 35 Gy in 5# with a 24-month interval).

Out-of-field intra-hepatic progression was the main pattern of failure (9 cases, 75 %), whilst distant extra-hepatic progression occurred in 7 (58 %) cases, most commonly in the lung in 5 (41.7 %) cases. Median PFS was 2.8 months (range 1–5; 95 % CI 1.2–3.9). Median OS, 1-year OS, and 2-year OS was 22 months, 68 % (95 %CI 28–89) and 34 % (95 %CI 5–67) following re-SABR (Fig. 3b). There was no statistical difference in PFS and/or OS between CRC and other primary tumour sites (Fig. 3c-d and Table 3).

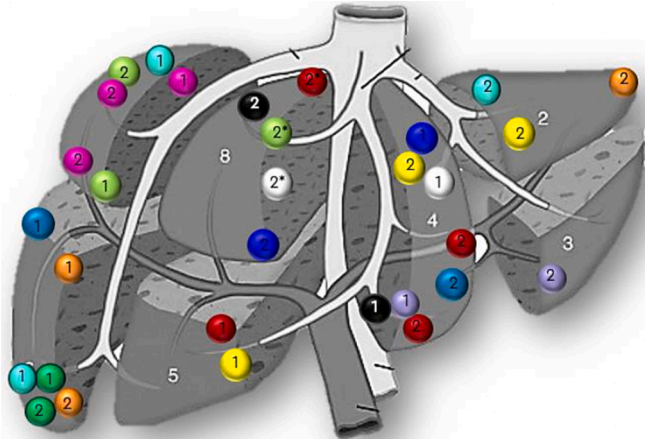

**Fig. 2.** Lesions distribution per hepatic segment. The figure 2 represents the location of each analysed lesion. Each color represents a patient. Treatment courses are indicated as 1 (first SABR) and 2 (Mr-guided reirradiation). Lesions marked with an asterisk (*) represent those repeat target radiation.

**Table 2**
Key dosimetric characteristics of the initial SABR and re-SABR treatment course.

| Table 2. Dosimetry characteristics | | |
|---|---|---|
| **PRIMARY** | **Total dose (Gy), median (range)** | 50 (40–60) |
| | **EQD2, median (range)** | 83.3 (60–126) |
| | **$BED_{10}$, median (range)** | 100 (72–151) |
| | **Fractions prescribed, range** | 3–5 |
| | **Cumulative GTV Vol (cc), median (range)** | 8.12 (2.76–98.5) |
| | **PTV vol (cc), median (range)** | 40.9 (13.4–180.5) |
| | **Max Lesion Diameter (cm), median (range)** | 3.4 (2–9) |
| | **MLD (Gy), median; SD (range)** | 7.9; 3.5 (4.2–16.5) |
| | **Liver D (700 cc) median; SD (range)** | 6.21; 4.0 (0.5–13.2) |
| **SECONDARY** | **Total dose (Gy), median (range)** | 45 (30–60) |
| | **EQD2, median (range)** | 83.33 (40–110) |
| | **$BED_{10}$, median (range)** | 100 (48–132) |
| | **Fractions prescribed, range** | 3–5 |
| | **Normal liver remaining vol (cc), median (range)** | 1445.3 (851.4–2247.54) |
| | **Cumulative GTV Vol (cc), median (range)** | 13.1 (1.87–71.8) |
| | **PTV vol (cc), median (range)** | 33.4 (9.8–141.1) |
| | **Max Lesion Diameter (cm), median (range)** | 3.5 (1.7–9) |
| | **PTV D(95 %) (Gy), median; SD (range)** | 40; 11.4 (20.7–61.4) |
| | **PTV D(98 %) (Gy), median; SD (range)** | 38.4; 12.0 (16.6–59.9) |
| | **PTV V(100 %) (%), median; SD (range)** | 95; 7.6 (74.3–97.9) |
| | **GTV D(0.1 cc) (Gy), median; SD (range)** | 59.7; 18.4 (6.6–82) |
| | **MLD (Gy), median, SD (Range)** | 6.1; 3.1 (2.8–13.5) |
| | **Liver D (700 cc) (Gy), median; SD (range)** | 1.9; 2.5 (0.2–8) |
| | **DLT** | 5/12 (viscerals) |

*Gy: gray; BED: Biological Effective Dose; Equivalent Dose in 2 Gy Fractions vol: volume; MLD: mean liver dose; GTV: Gross Tumour Volume; PTV: Planning Target Volume; DLT: Dose Limiting Toxicity; DLT: Dose Limiting Toxicity*

### 3.5. Comparison of DIR-based and non-DIR-based workflow

The mean estimated uninvolved liver volume was significantly smaller when estimated using DIR-based as compared to non-DIR-based workflow (1384 cc vs. 1472.2 cc; $p < 0.05$). Additionally, the DIR-based approach predicted significantly higher cumulative MLD (14.43 Gy vs. 6.65 Gy; $p < 0.01$) and D700cc (9.04 Gy vs. 2.74 Gy, $p < 0.01$) as compared to the non-DIR-based workflow (**Table S2**).

## 4. Discussion

This retrospective single-institution series of patients with oligometastatic liver disease who have undergone daily adaptive MR-guided re-SABR demonstrated high LC rates as well as a low acute toxicity profile. These findings underscore the potential of re-SABR as a feasible LDT option for patients who develop intra-hepatic disease progression following initial SABR.

Historically, liver re-SABR has been considered challenging due to concerns about cumulative radiation dose to the uninvolved liver parenchyma and adjacent visceral OARs. Additionally, difficulties in

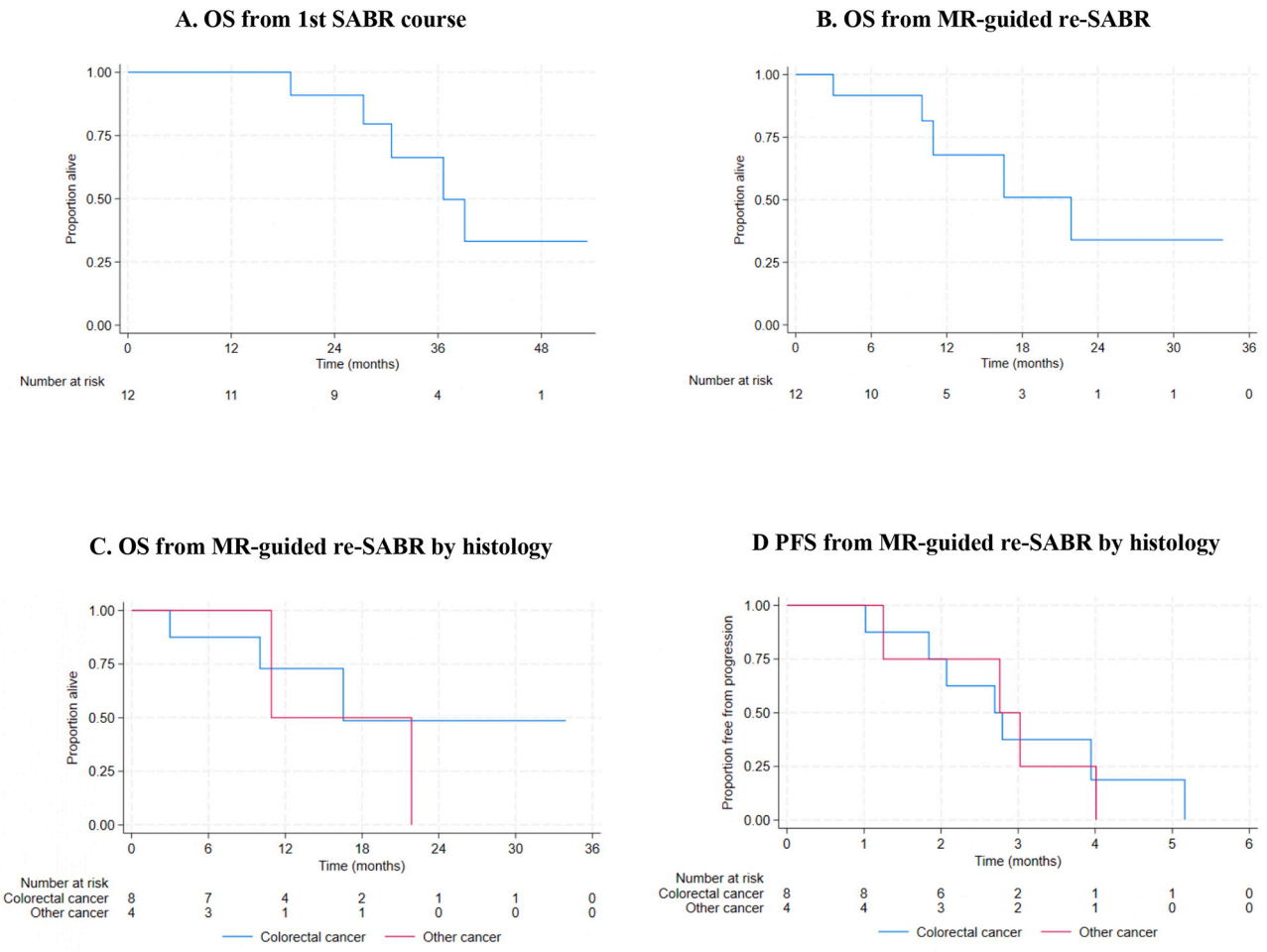


**Fig. 3.** Kaplan-Meier function for (A) overall survival (OS) from first stereotactic radiotheraphy (SABR) course. (B) OS from stereotactic MR-guided radiotheraphy (SMART) reirradiation. (C) OS from SMART reirradiation by histology subgroups (Colorectal cancer versus other histologies). (D) Progression-free survival (PFS) from SMART reirradiation treatment by histology subgroups.

**Table 3**
Key oncological outcomes in our cohort in reference to published series of re-SABR in oligometastatic liver disease (including mixed population cohorts).

Table 3. **Key outcomes compared to the most relevant reports of Liver SABR reirradiation**

| **Platform** | **Adaptive approach, MRI-Linac** | | **Non-Adaptive approach, CT-based** | |
|---|---|---|---|---|
| | **Current cohort** | **REPAIR** (15) | **McDuff** (13) | **Gkika** (14) |
| **Patients (lesions)** | 12 (18) | 18 (25)(20 Liver) | 49 (64)(23 mets) | 24 (30)(12 mets) |
| **Histology** | Mets<br>66.7 % CRC | Mets<br>23.1 % CRC | HCC/CCC/Mets<br>52 % CRC | HCC/CCC/Mets |
| **LINAC/RMM** | MRIdian®Tracking, Gating | 89 % MRIdian®Tracking, Gating | Cyclotron (10 %) or photons (90 %) | Abdominal compression/ 4D-CT |
| **Dose regimens, Gy/# (range)** | 45/3–5# (30–50) (BED $_{10}$ = 100, range 48–132) | 41/5 (16–50)<br>(mean BED10 = 92) | 67 % SABR:50/5; 54/6.<br>24 % IMRT/3D: 67.5/15 ($EQD2_{10}$ = 65) | 48/3–12 (27–66), ($EQD2_{10}$ = 71) |
| **Survival Parameters *(calculate from SABR reirradiation)*** | | | | |
| **Median FU, months** | 10 | 10.7 | 10.5 | 14 |
| **LC, %** | 94.4 | NR | 1y 53.6 % †<br>(39 % for mets) | NR |
| **PFS, months** | 2.8 (median) | 1y 50 %†. | NR | NR |
| **G3-5 toxicity, %** | 8.3 % G4 (1pt) | 0 | 4.1 % G3 | 1pt G3 bleeding |
| **RILD** | 0 | 0 | %* | 0 % |

*BED: Biological Equivalent Dose (alpha/beta of 10);CCC: Cholangiocarcinoma; CRC: colorectal cancer; HCC: Hepatocellular carcinoma; ITV: Interval Target Volume; LINAC: Linear accelerator; LC: Local Control; Linac: linear accelerator; LPFS: Local Progression Free Survival; MRIdian®=6 MV 0.35 T MRI-Linac ViewRay Systems' NR: not reported; OS: Overall Survival; PBT: Proximal Bronchial Tree; PFS: Progression Free Survival; PTV: Planning Target Volume; RILD: Radiation-induced liver disease; RMM: respiratory motion management; SABR: Stereotactic Ablative Radiation Therapy; UC: Ultra-central; VMAT: Volumetric modulated arc therapy*

*#: fractions, y: year(s)*

*† Entire cohort (no discrimination by groups)*

**HCC*

accurately calculating residual OAR tolerances, combined with the limitations of non-adaptive, CT-based SABR in terms of target delineation, motion management, and daily anatomical variation, have further restricted re-SABR adoption in the treatment of oligometastatic liver disease. This is reflected in the paucity of published data available [13–15].

Advances in modern RT technologies have led to an increase in precision and adaptive delivery, facilitating OAR sparing and safe dose escalation. This is of particular importance in the setting of re-irradiation, where high cumulative OAR doses may limit PTV coverage and lead to a reduction in prescription dose, which in turn can negatively impact LC rates and/ or toxicity profile.

Through the elimination of internal target volume (ITV) and online target tracking, daily adaptive MR-guided SABR can reduce the volume of re-irradiated uninvolved liver parenchyma [26]. This is particularly relevant in the setting of liver re-irradiation, where previous LDTs, including surgical resections, catheter-based ablations, and radiation-induced changes, can significantly alter liver anatomy over time, leading to a reduction in functional liver volume [27].

Daily adaptive MR-guided SABR has been shown to be the optimal platform for delivering SABR to mobile targets in the upper abdomen with a favourable toxicity profile [16]. In a series of 11 patients, MR-guided re-SABR to abdominal and pelvic targets demonstrated a 1-year LC rate of 89 % with no acute or late $\geq$ G2 toxicity; however, there were no cases of liver re-irradiation in this cohort [28]. A series of liver re-SABR on conventional CT-based linacs in a mixed population (n = 49) of primary and metastatic liver tumours [13], reported a median OS of 14 months with a median follow-up of 10.5 months. The 1-year local failure rate were 61.0 % for liver metastases and 32.5 % for HCC. G3 toxicity occurred in 4.1 % of patients. The relatively lower LC rate may be attributed to a lower re-SABR prescription dose (median $EQD2_{10}$ 65 Gy), despite a similar uninvolved mean liver dose to the dose reported in our cohort (EQD2 10.5 Gy). This finding may be a function of non-adaptive, non-gated treatment necessitating larger treatment margins, which in turn increase OAR exposure and restrict dose escalation.

A recent publication reporting the use of MR-guided re-SABR in the treatment of liver metastases showed similar results to our study with 1-year OS of 73 %, 1-year PFS of 50 % and no grade $\geq$ 3 toxicities observed [15] (Table 3). The authors proposed a novel classification system of re-irradiation based on the overlap of radiation fields and specific isodoses. In contrast, our study followed the ESTRO-EORTC classification [20], aiming towards standardization. According to this framework, Type I re-irradiation involves overlapping target volumes, raising concern for potential cumulative toxicity, especially liver necrosis, when critical dose thresholds are exceeded. To address this, all repeated and Type I cases in our cohort were retrospectively reviewed by an experienced radiologist, who confirmed the absence of radiological evidence of necrosis, supporting the feasibility of safe retreatment when guided by careful dosimetric constraints.

Conversely, Type II re-irradiation, involving adjacent but non-overlapping volumes, presents a distinct challenge: the need to spare the remaining healthy liver, especially the region previously irradiated. In these cases, achieving an acceptable mean liver dose (MLD) was technically more difficult. We now emphasize the importance of subtracting the previously irradiated volume from the planning target volume when evaluating dose constraints in Type II settings to better preserve hepatic function.

Lastly, we highlight those anatomical changes over time (including liver shape deformation, regeneration, or motion variability) can further complicate accurate dose reconstruction and adaptive planning. The temporal gap between irradiations introduces uncertainties in organ motion and target localization.

Historically, re-irradiation has been limited to doses of 40–60 Gy $EQD2_{10}$ to minimize toxicity risk due to cumulative OAR doses. However, these modest doses are not associated with durable LC [29]. In liver metastases in particular, a dose–response relationship has been observed in studies, with $BED_{10} > 100$ Gy linked to improved LC [30] MR-guided, daily adaptive SABR enables dose escalation, which in turn may translate to improved LC. In our cohort, the median prescribed re-irradiation dose was 83.33 Gy $EQD_2$ (range: 40–110 Gy) equating to median $BED_{10}$ 100 Gy (48–132). A prescription dose $BED_{10} \geq 100$ Gy was unachievable in 4 out of 12 re-SABR cases due to visceral constraints (Table S2).

Re-irradiation poses inherent toxicity risk due to prior OAR treatment exposure. Our study demonstrated an acceptable safety profile, with no reported acute grade $\geq$ 2 toxicities. Despite a history of prior LDTs in 58.3 % of patients, no cases of liver decompensation were observed in our cohort.

Ensuring the safety of liver re-SABR requires an individualised approach, with dose prescription carefully tailored to the treatment goal and clinical context, particularly considering cumulative OAR tolerances and volume of uninvolved liver (**Table S2 and S3**).

While clear dose constraints exist for primary liver SABR, guidance for re-SABR remains limited. Dose constraints for primary SABR vary across guidelines. AAPM TG101 recommends MLD < 9 Gy for 3-fraction and < 13 Gy for 5-fraction regimen and limiting the liver volume receiving > 15 Gy to < 700 cc [31]. The UK SABR consortium guidelines [22] recommend a MLD < 15 Gy and < 15.2 Gy for 3 and 5 fractions alongside a D700cc < 15 Gy and a V10Gy < 70 % for 5-fraction regimen. The Princess Margaret Cancer Centre guidelines emphasize an individualized approach, incorporating factors such as Child-Pugh score, platelet count, MLD, and Liver D800cc to guide safe dose delivery.

Given the lack of standardized dose constraints for upper abdominal re-irradiation, our practice involves calculating individualised re-irradiation constraints applying EQD2 conversion, suitable a/b ratios [24,31], and tissue recovery factor to account for the primary SABR course (Appendix 1). In addition, we developed a DIR-based workflow to allow for dose conversion and accumulation. This method has demonstrated more conservative estimates of uninvolved liver and MLD. We highlight those temporal anatomical changes (including liver shape deformation, regeneration, or motion variability) increase the uncertainties of dose mapping and uninvolved liver volume calculations [32]. Therefore, rigid registrations were not considered within this proof-of-concept workflow, given DIR considers changes in liver shape between treatments and provides a more representative assessment of functional liver remnant [25]. While our results showed that DIR improved the accuracy of dose accumulation estimation, its integration into clinical decision-making remains to be validated prospectively.

Whilst we observed high in-field LC rate, given relatively short follow-up and high rates of intrahepatic out-of-field disease progression and distant metastatic relapse, the magnitude of meaningful clinical benefit remains unclear. These patterns of metastatic spread, as well as differential responses to MR-guided SABR, may be influenced by the heterogeneity of primary tumour types included in our cohort, which introduces potential biological and treatment-related confounders. While no statistically significant differences in LPFS or OS were observed between CRC and non-CRC subgroups in our cohort (Fig. 3c-d), the generalizability of our efficacy outcomes should nevertheless be interpreted with caution.

We must acknowledge limitations in our analysis, including the inherent biases of a single-institution retrospective study, a heterogeneous patient cohort, and variability in dose fractionation schedules. In addition, the small sample size and mixed tumour histology limit the generalisability of our findings. Nevertheless, our results are consistent with previously published work (Table 3), contributing to the growing body of evidence in this field. We also recognise the relatively short median follow-up period; however, it was long enough to assess tolerability, safety and tolerability of this technique. Given the follow-up duration, the primary focus of our study was on treatment feasibility and tolerability, with emphasis on acute and delayed acute toxicity. Longer-term surveillance will be required to capture late effects comprehensively.

Whilst there is potential for missing follow-up data, especially since most patients were not monitored within our institution, every effort was made to obtain robust and detailed follow-up information, which included imaging reports, blood test results, and clinic letters. Finally, we acknowledge that the statistical power of this analysis is limited by the cohort size.

Despite these limitations, we believe our data contribute to the body of evidence supporting the safety and feasibility of MR-guided, daily adaptive liver metastases re-SABR.

## 5. Conclusion

Our study suggests that daily adaptive MR-guided re-SABR is a feasible non-invasive treatment option for selected patients with oligometastatic liver disease, associated with high LC rates and low acute toxicity. The integration of MR-Linac treatment offers potential for safe dose escalation in the re-irradiation setting, particularly for patients with limited alternative local treatment options. Further prospective studies with standardised outcome reporting and patient-reported outcome measure (PROM) incorporation are warranted in this area.

## 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.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2025.101082.

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