# Active breathing control guided stereotactic body ablative radiotherapy for management of liver metastases from colorectal cancer

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## Abstract

***Background:*** **Liver metastases may occur during the course of several cancer types and may be associated with significant morbidity and mortality. There is paucity of data regarding the utility of Active Breathing Control (ABC) guided Stereotactic Ablative Body Radiotherapy (SABR) for management of Liver Metastases from Colorectal Cancer (LMCC). Our aim is to investigate the role of ABC guided SABR for management of liver metastases**

***Patients and methods:*** **42 liver metastases of 29 patients treated with ABC guided SABR between February 2015 and October 2018 were retrospectively assessed for local control (LC), overall survival (OS), and toxicity outcomes. Primary endpoint was LC. Secondary endpoints were OS and treatment toxicity.**

***Results:*** **At a median follow up duration of 16 months (range: 9-74 months), median OS was 20 months and 3 patients were still alive at last follow up. 1-year OS was 83% and 2-year OS was 28%. LC rates were 92% and 61% at 1 and 2 years, respectively. Comparative analysis of Biological Effective Dose (BED) values revealed that higher BED10 values were associated with higher LC rates (p=0.007). While LC rates for BED10 ≥ 100 Gray (Gy) were 94% and 86% at 1 and 2 years, corresponding LC rates for BED10 < 100 Gy were 89% and 36%, respectively with statistical significance (p=0.007). Assessment of acute and late toxicity outcomes revealed that most common toxicity was fatigue, however, no patients had ≥ grade 3 toxicity.**

***Conclusion:*** **ABC guided SABR is an effective and safe treatment modality for LMCC management.** (Acta gastroenterol. belg., **2022,** 85, **469-475**).

**Keywords**: Active breathing control, stereotactic body ablative radiotherapy, colorectal cancer, liver metastases.

**Abbreviations:** LMCC: Liver metastases from colorectal cancer; ABC: Active Breathing Control; SABR: Stereotactic Ablative Body Radiotherapy; LC: Local control; OS: Overall survival; BED: Biological effective dose; Gy: Gray.

## Introduction

Liver metastases may occur during the course of several cancer types and may be associated with significant morbidity and mortality in overwhelming majority of affected patients (1-4). Colon and tumors of the proximal rectum are among the most common causes of liver metastases due to portal venous drainage. While approximately 20% of colorectal cancers are metastatic at the time of diagnosis, metachronous metastasis may also occur in 25% of the patients (1). Synchronous metastases may portend a poorer prognosis compared to metachronous metastases (2-4). The liver is a very common metastatic site, and it has been reported that up to 80% of stage 4 colorectal cancer patients have metastatic liver disease (5). Curative surgical resection may be performed in approximately 12% to 36% of patients with limited number of metastatic lesions in the liver and no extrahepatic metastases (6). Combination of hepatic metastasectomy and systemic chemotherapy confers 5-year survival rates of 50% to 60%, and surgery remains to be the standard treatment modality for management of liver metastases (7). However, surgical resection may be performed only in 25-30% of patients due to inappropriate tumor location, poor performance status, presence of extrahepatic disease, or insufficient normal liver volume after resection (8). Non-surgical ablative approaches for management of isolated liver metastases include radiofrequency ablation (RF), cryosurgery ablation and transarterial chemoembolization (9). Stereotactic Ablative Body Radiotherapy (SABR) may also be utilized as a non-invasive treatment modality for management of liver metastases in selected patients as an alternative and relatively newer local treatment method. The rationale for SABR is that high ablative doses can be delivered to relatively small and well defined target volumes while preserving surrounding healthy liver tissue. SABR serves as a viable radiotherapeutic modality for management of several cancers with high precision and accuracy under robust immobilization and image guidance. Breathing induced tumor motion poses a formidable challenge for radiotherapeutic management of thoracoabdominal tumors. In this context, management of respiratory motion is a critical aspect of SABR for liver metastases. Active Breathing Control (ABC) system has been introduced as a viable method for management of respiratory motion in thoracoabdominal tumors. Several studies have reported the safety and efficacy of ABC guided SABR for management of several thoracoabdominal tumors including lung cancer, adrenal and pulmonary metastases (10,11). However, there is paucity of data regarding the utility of ABC guided SABR for management of liver metastases. Herein, we report our tertiary cancer center

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experience with ABC guided SABR for management of liver metastases from colorectal cancer (LMCC).

## Materials and Methods

### *Study Population*

Patients who underwent SABR for LMCC between 2015 and 2018 were retrospectively assessed. Inclusion criteria were as follows:

1-Patients with Karnofsky performance status (KPS) > 70,
2-Maximum diameter of metastases <5 cm,
3-Minimum patient age 18,
4-No active connective tissue disease,
5-No liver cirrhosis,
6-No previous radiotherapy treatment to the affected site

Histological confirmation was not mandatory and clinical diagnosis of liver metastases was established by imaging of the liver region by computed tomography (CT), PET/CT or magnetic resonance imaging (MRI). Written informed consents of all patients were taken before treatment with institutional tumor board approval at our tertiary cancer center, and the study was performed in compliance with the Declaration of Helsinki principles and its later amendments.

### *Treatment technique for ABC guided SABR*

Patients were informed about the ABC device (ABC, Elekta, UK) before CT simulation with thorough explanation of the rationale and potential benefits of using this system. Moderate deep inspiration (60-75% of maximum inspiratory capacity) thresholds have been individually determined for each patient to assure reproducible breath holds for 20-25 seconds. CT simulation was performed after achieving optimal patient compliance.

BODYFIX (Bluebag, Elekta) has been used for robust patient immobilization, and planning CT images with 1.25 mm slice thickness were acquired at the CT simulator (GE lightspeed RT, GE Healthcare, Chalfont st. Giles, UK) at moderate deep inspiration breath holding with the ABC system. IV contrast material was used for CT simulation provided that patients had no allergy to contrast media and could tolerate contrast administration. After image acquisition, planning CT images were transferred to the contouring workstation via the network. Advantage SimMD (Elekta, UK) software was used for delineation of critical structures and target volumes at appropriate window-level values. Organs at risk (OARs) included the normal liver (excluding the PTV), kidneys, spinal cord, stomach, esophageus, heart, duodenum, and rib cage. Along with planning CT images, registered imaging modalities including PET/CT and MRI were also used for optimal definition of gross tumor volume (GTV). PTV was generated by expanding the GTV by 5-10 mm isotropically. After completion of the delineation procedure, structure sets were tsent to SABR planning system (ERGO++ Planning system, Elekta, UK). Treatment planning was performed by using dynamic conformal arc technique and 95% of the PTV received 95% of the prescribed dose in all patients. The following normal tissue constraints were used (12): Threshold maximum doses for spinal cord, heart and esophagus were 30 Gy, 38 Gy and 35 Gy respectively. Maximum doses for stomach, duodenum and bowel were 32 Gy and 35 Gy, respectively. It was mandated that minimum 700 cc of healthy liver (liver minus PTV) had to receive a total dose of less than 21 Gy in five fractions. Dose fractionation scheme was individually determined for each patient considering the lesion location and association with critical structures. All SABR procedures were performed in 5 fractions delivered in alternating days for all patients. SABR treatment delivery was performed by Elekta Synergy Linear Accelerator (Synergy, Elekta, UK) with dynamic multileaf collimator (DMLC) using 6 MV photons. Treatment set-up verification was performed by matching of reference planning CT images with the kilovoltage cone beam CT (kv-CBCT) images using the XVI program (XVI version 4.0, Elekta, UK) before delivery of each treatment fraction.

### *Study endpoints and assessment of treatment response and toxicity*

Primary endpoint was local control (LC). Secondary endpoints were overall survival (OS) and treatment toxicity. European Organization for Research and Treatment of Cancer Response Evaluation Criteria in Solid Tumors (EORTC RECIST) were used for treatment response assessment (13). According to these criteria, the categories were defined as: (i) the disappearance of all target lesions (complet response), (ii) at least a 30% decrease in the sum o the longest diameter of the target lesions (partial response) (iii) a response ranging from a 30% decrease to a 20% increase in the sum of the longest diameter of the target lesions (stabl disease), and (iv) a 20% increase in the sum of the longest diamete of the target lesions (progressive disease). Common terminology criteria for adverse events (CTCAE) version 4.0 was used for evaluation of acute and late treatment toxicity.

### *Statistical analysis*

Statistical Package for the Social Sciences, version 28.0 (v 28.0 IBM, Armonk, NY, USA) software was used for statistical analysis with the level of significance set at $p < 0.05$. Mean, standard deviation and range of median values were calculated as descriptive statistics. LC was calculated from the date of first SABR fraction to disease progression, and OS was calculated from the date of first SABR fraction until death. LC and OS curves were generated by using the Kaplan Meier method. Biological

effective dose (BED) calculation was performed for comparative assessment of dose fractionation schemes. Formula for BED calculation was BED (Gy) = n X d (1+d/a/b). n corresponded to number of fractions and d corresponded to fraction dose, a/b value for tumor was considered as 10 Gy. BED refers to a measure of the true biological dose delivered by using a particular combination of dose per fraction and total dose to a particular tissue characterized by a specific a/b ratio. Within this context, BED10 is a critical radiobiology concept which is based on a linear quadratic model of radiation effect that accounts for the radiosensitivity of irradiated tissues, total dose, and dose per fraction. Log-rank statistics was used for comparative evaluation of LC with respect to tumor size and BED10.

## Results

### *Patient characteristics*

In this study, 42 liver metastases of 29 patients treated with SABR between February 2015 and October 2018 were assessed. Patient and tumor characteristics are summarized in Table 1.

Out of the total 29 patients, 13 patients (45%) were female and 16 patients (55%) were male. Median patient age was 61 (range: 37-82) years. KPS was ≥ 70 in all patients and median KPS was 90. 41% and 59% of patients had synchronous and metachronous metastases, respectively. History of previous liver directed therapy was present in 8 patients (28%) while majority (72%) of the study population did not receive previous liver directed therapies. RF constituted half of the previous local treatments, followed by cryotherapy in 37.5% and transarterial chemoembolization in 12.5% of the patients, respectively. 17 patients (59%) had controlled primary colorectal cancer. In addition to liver metastases, 6 patients (21%) also had other metastases in a different organ.

### *Treatment characteristics and results*

While 5-fraction SABR was used for treatment of all patients, most frequently (52%) utilized dose fractionation scheme was 10 Gy x 5 fractions. BED10 equivalent dose was lower than 100 Gy in approximately half (48%) of the patients. Mean GTV of the treated lesions was 10.4 cc (0.3-36.2) while mean PTV was 22.1 cc (3.2-68). Median prescribed isodose line was 93%. Treatment characteristics are summarized in Table 2. At a median follow up duration of 16 months (range: 9-74 months), median OS was 20 months and 3 patients were still alive at last follow up. 1-year OS was 83% and 2-year OS was 28% (figure 1). LC rates were 92% and 61% at 1 and 2 years, respectively (figure 2). Comparative analysis of BED values revealed that higher BED10 values were associated with higher LC rates (figure 3). While LC rates for BED10 ≥ 100 Gy were 94% and 86% at 1 and 2 years, corresponding LC rates for BED10 < 100 Gy were 89% and 36%, respectively with statistical significance

Table 1. — **Patient characteristics**

| **Characteristics** | **N (%)** |
|---|---|
| Gender | |
| Female<br>Male | 13 (45)<br>16 (55) |
| Primary tumor control | |
| Yes<br>No | 17 (59)<br>12 (41) |
| Presence of extrahepatic disease | |
| Yes<br>No | 6 (21)<br>23 (79) |
| Prior liver directed therapy | |
| Yes<br>No | 8 (28)<br>21 (72) |
| Timing of metastasis | |
| Synchronous<br>Metachronous | 12 (41)<br>17 (59) |
| No. of SABR lesions | |
| 1<br>2<br>3 | 17 (59)<br>11 (38)<br>1 (3) |
| Maximum diameter of lesion | |
| <3 cm<br>≥3 cm | 33 (79)<br>9 (21) |

N: number; SABR: Stereotactic Ablative Body Radiotherapy; cm: centimeter.

Table 2. — **Treatment characteristics**

| **Characteristic** | **N** |
|---|---|
| SABR dose (Gy)/fraction-BED10 (Gy) | |
| 10 x 5-BED10 (100 Gy)<br>9 x 5-BED10 (85.5 Gy)<br>8 x 5-BED10 (72 Gy)<br>7 x 5-BED10 (59.5 Gy) | 22<br>4<br>11<br>5 |
| GTV (cc) | |
| Range<br>Mean | 0.3-36.2<br>10.4 |
| PTV (cc) | |
| Range<br>Mean | 3.2-68<br>22.1 |
| Isodose line (%) | |
| Range<br>median | 90-94<br>93 |

N: number; SABR: Stereotactic Ablative Body Radiotherapy; BED: Biological effective dose; Gy: Gray; GTV: Gross tumor volume; PTV: Planning target volume.

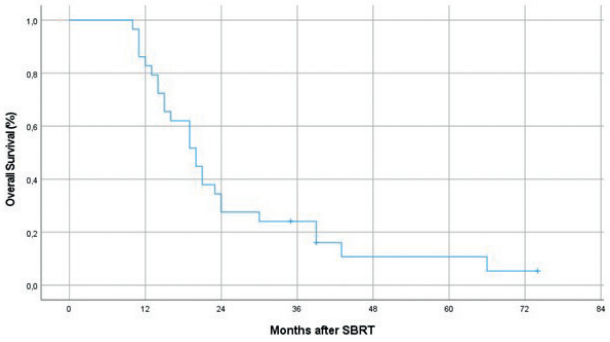


Figure 1. — Overall survival.

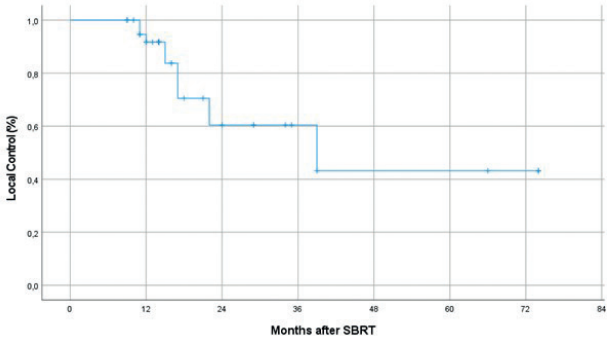


Figure 2. — Local control.

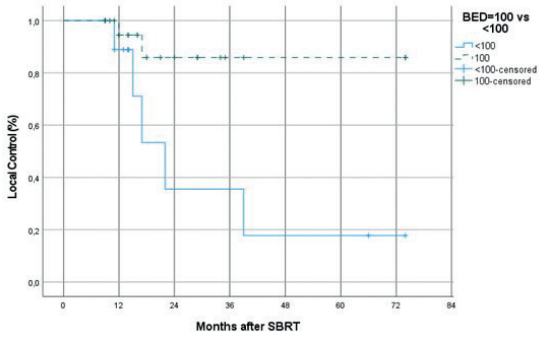


Figure 3. — Local control of liver metastases by Biological effective dose 10.

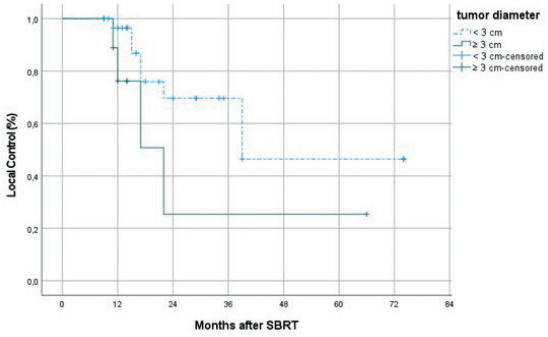


Figure 4. — Local control of liver metastases by size.

(p=0.007). Comparative analysis with respect to tumor size revealed that 1 and 2 year LC rates were 76% and 25% respectively for tumor size ≥ 3 cm and corresponding 1 and 2 year LC rates were 96% and 70% respectively for tumor size < 3 cm (figure 4). Statistical analysis revealed no statistically significant difference although LC was better for smaller tumor sizes (p = 0.106). Assessment of acute and late toxicity outcomes revealed that the most common toxicity was fatigue, however, no patients had ≥ grade 3 toxicity.

## Discussion

SABR serves as a viable radiotherapeutic modality used for treatment of various extracranial targets throughout the human body. While it allows ablative doses to be delivered to the tumor under robust immobilization and image guidance, normal tissue protection is optimal due to steep dose gradients around the target. In the context of liver metastases from colorectal cancer, systematic reviews have reported encouraging clinical outcomes with SABR (14,15). Also, ESMO guidelines currently include SABR as an ablative therapeutic option for patients not suitable for other local treatments such as surgery or RF (16). However, respiratory motion is a significant challenge for SABR of liver metastases since little margins are used for optimal sparing of surrounding normal tissues while delivering high ablative doses to the tumor for improved therapeutic efficacy. While several trials have addressed the utility of SABR, there is paucity of data regarding ABC guided SABR for LMCC and our study significantly adds to the literature from this aspect. Indeed, respiratory motion management for irradiation of thoracoabdominal tumors by use of ABC system is not a novel concept, and initial studies of ABC date back to 2 decades ago (17). Since then, many studies have reported on the utility of ABC system for elimination of internal margins with effective respiratory motion management and optimal normal tissue protection (10,11,18-21). Although less frequently addressed, ABC system has also been used in combination with SABR procedures as well. At our tertiary cancer center, ABC guided SABR is utilized for management of liver metastases as well as for other indications including adrenal metastases, pulmonary metastases and early stage lung cancer treatment (10,11) Clearly, utilization of ABC system offers a viable method for respiratory motion management as evident from previously published studies (18-21).

In the study by Stera et al., a pooled multi-platform liver-SABR-database was analyzed for clinical outcomes (18) LC, progression-free interval (PFI), OS, predictive factors and toxicity were assessed for 135 patients with 227 metastases receiving gantry-based SABR by (deep inspiratory breath-hold-gating; n = 71) and robotic-based SBRT (fiducial-tracking, n = 156). Mean GTV BED10 dose was 146.6 Gy. LC was 90% and 68.7% at 1 and 5 years, respectively. Median OS was 20 months while OS was 67% and 37% at 1 and 2 years, respectively. Acute

Table 3. — **Selected series of Stereotactic Ablative Body Radiotherapy for liver metastases**

| Study/Design | Patients/Lesions | SABR dose Gy /fx | LC (year) % | OS (year) % | Toxicity ≥grade3 % | MFU (months) |
|---|---|---|---|---|---|---|
| Chang retrospective (22) | 65/102 | 22-60/1-6 | 1-62%<br>2-45% | 1-72%<br>2-38% | %3 | 14 |
| Vautravers-Dewas retrospective (23) | 30/62 | 40/4<br>45/3 | 2-86% | 2-58% | 0 | 14.3 |
| Stintzing Prospective (24) | 30/35 | 24-26/1 | 1-85%<br>2-%80 | Median 34.4 months | 0 | 23.3 |
| Berber Retrospective (25) | 153/363 | 37.5±8.2 /5±3 | 1-62% | 1-51% | %3 | Mean 25.2±5.9 |
| Liu Retrospective (26) | 62/106 | 20/3<br>50/5 | 1-93%<br>2-82% | 1-81%<br>2-52% | 0 | 18 |
| Van De Voorde retrospective (27) | 33/39 | EQD2 62-150/3-10 | - | 1-85%<br>2-68% | 0 | 21 |
| Scorsetti phase 2 (28) | 42/52 | 75/3 | 2-91% | 2-65% | 0 | 24 |
| Ahmed Retrospective (29) | 33/38 | 50-60/5 | 1-79%<br>2-59% | 1-100%<br>2-73% | - | 21.2 |
| Goodman Retrospective (30) | 81/106 | 54/3-5 | 1-96%<br>2-91% | 1-89%<br>2-68% | 4.9 | 33 |
| Méndez Romero retrospective (31) | 40/55 | 37.5-50.25/3 | 2-74%<br>2-90% | 2-69%<br>2-81% | 0 | 26-25 |
| Doi Retrospective (32) | 24/39 | 71.7-115.5/4-33 | 2-35%<br>2-62% | 2-45%<br>2-87% | 0 | 16 |
| Joo Retrospective (33) | 70/103 | 45-60/3-4 | 2-52%<br>2-83%<br>2-89% | 2-75% | 0 | 34 |
| McPartli phase 1-2 (34) | 60/105 | 22.7-62.1/6 | 1-50%<br>2-32% | 1-63%<br>2-26% | 2 | 28 |
| Present study retrospective | 29/42 | 35-50/5 | 1-92%<br>2-61% | 1-83%<br>2-28% | 0 | 16 |

SABR: Stereotactic Ablative Body Radiotherapy; Gy: Gray; LC: Local control; OS: Overall survival; MFU: Median follow up; EQD2: Equivalent dose in 2Gy fractions.

toxicity was mild and infrequent, and rate of chronic grade III/ IV toxicity was 1.1%. The authors concluded that patient selection, time to SABR and use of adequate doses were essential for achieving optimal treatment outcomes by SABR with active motion compensation.

Bloemen-van Gurp et al. assessed utilization of 3-dimensional ultrasound imaging (3DUS) and ABC as an image guidance tool for liver SABR (19). 3DUS image guidance was analyzed for 11 patients with 88 treatment fractions. 3DUS imaging was combined with ABC in 5 patients. Combined uncertainty of US scanning and matching (inter- and intraobserver) was 4 mm, and use of ABC reduced the uncertainty by 1.7 mm in the superior-inferior direction. The authors concluded that ABC-based breath holding at midventilation during 3DUS imaging could reduce the uncertainty of US-based 3D table shift correction.

Lu et al. evaluated intra- and interfractional motions of liver and lung tumors with ABC in a study including 19 patients with liver cancer and 15 patients with lung cancer receiving SABR (20). All patients underwent a series of 3 CTs at simulation to analyze breath-hold reproducibility. Centroids of whole livers and of lung tumors from the 3 CTs were compared to evaluate intra-fraction variability. Liver intra-fractional systematic/random errors were found as 0.75/0.39 mm, 1.36/ 0.97 mm, and 1.55/1.41 mm at medial-lateral (ML), anterior-posterior (AP), and superior-inferior (SI) directions, respectively. Substantial intra-fraction motion (>3 mm) was found in 26.3% of liver cancer patients and most inter-fractional systematic and random errors were larger than corresponding intra-fractional errors. Nevertheless, kV CBCT-guided soft tissue alignment provided correction of inter-fractional errors. The authors concluded that patient-specific

treatment planning margins should be utilized rather than recipe based margins, and intra-fractional motion should be the key to establish the planning margins since inter-fractional motion could be compensated by daily gated soft tissue imaging guidance with kV-CBCT.

Mast et al. from the Radiotherapy Department of Haaglanden Medical Center, Netherlands reported their 2 years' experience with liver SABR in combination with inspiration breath-hold by using the ABC method (21). Median follow-up and median OS were 12 months. Actuarial 2-year OS was 31% and median progression free survival was 4 months, Actuarial 6-month LC was 92%, and LC was 57% at 1 and 2 years. No ≥ grade 3 acute clinical toxicity was observed. Only one patient experienced gastrointestinal bleeding episode 1 year after the SABR procedure. The authors concluded that image guided SABR served as an effective non-invasive treatment modality with low toxicity for patients with small inoperable liver metastases.

The literature includes several retrospective, phase I or phase II trials about SABR for liver metastases (22-34). There is wide diversity among the studies addressing radiotherapeutic management of liver metastases with respect to primary cancers, tumor volumes and SABR dose fractionation schemes. Encouraging treatment outcomes from selected published series of SABR for liver metastases are summarized in Table 3. LC rates in these studies range between 50% and 96% at 1 year and 32% and 91% at 2 years (Table 3).

In our study, LC rate was 92% and 61% at 1 and 2 years, respectively. Factors affecting LC have been evaluated in many studies with most commonly assessed parameters being the tumor size and BED10 values. Mendez-Romero et al. reported a 2 year LC rate of 74% for patients receiving a total dose of 37.5 Gy in 3 fractions and 2 year survival of 90% for patients receiving a total dose of 50.25 Gy in 3 fractions(31). Joo et al. reported 2 year LC rates of 52%, 83%, and 89% for BED ≤ 80 Gy, 100-112 Gy, and > 132 Gy, respectively (33). In our study, 1 and 2 year LC rates were 94% and 86% for BED10 ≥ 100, and corresponding LC rates were 86% and 36% for BED10 < 100 Gy, with statistical significance (p=0.007). Our results are consistent with the literature.

Studies have reported variable OS rates ranging between 51% and 100% for 1 year and 26% and 87% for 2 years. Our study revealed an OS rate of 83% and 28% at 1 and 2 years, respectively which is consistent with the literature. Lower 2 year OS rates in our study may partly be explained with high number of patients with synchronous metastases and uncontrolled primary tumors.

Several studies of SABR for liver metastases reported low rates of toxicity with ≥ grade 3 toxicity rates ranging between 1% and 10%. Grade 1-2 fatigue and transient elevation of transaminase were reported as most frequent acute toxicities while grade 3-4 toxicity rate was 8.7%, and 3 patients suffered from treatment related death (14). Toxicity outcomes in our study are consistent with the literature. Treatment compliance and tolerance was well, and most common toxicity was fatigue without any ≥ grade 3 toxicity.

We acknowledge the limitations of this study including its retrospective nature and small number of patients. Nevertheless, our study adds to the literature given the paucity of available data regarding ABC guided SABR for liver metastases from colorectal cancer.

In conclusion, our tertiary cancer center experience confirms the safety and efficacy of ABC guided SABR for management of liver metastases from colorectal cancer. This sophisticated radiotherapeutic modality may serve as a viable alternative treatment option for selected patients.

## Conflict of interest

The authors declare that they have no conflict of interest.

## Informed consent and ethical statement

This study has been performed in compliance with the Declaration of Helsinki principles and its later amendments, and written informed consents of all patients were taken before treatment with institutional tumor board approval.

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