



SBRT-SG-01: final results of a prospective multicenter study on stereotactic body radiotherapy for liver metastases

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Abstract

Objective This study aimed to assess the efficacy and tolerability of stereotactic body radiation therapy (SBRT) for the treatment of liver metastases.

Methods Patients with up to 5 liver metastases were enrolled in this prospective multicenter study and underwent SBRT. Efficacy outcomes included in-field local control (LC), progression-free survival (PFS), and overall survival (OS). Acute and late toxicities were evaluated using CTCAE v.4.0.

Results A total of 52 patients with 105 liver metastases were treated between 2015 and 2018. The most common primary tumor was colorectal cancer (72% of cases). Liver metastases were synchronous with the primary tumor diagnosis in 24 patients (46.2%), and 21 patients (40.4%) presented with other extrahepatic oligometastases. All patients underwent intensity-modulated radiation therapy (IMRT)/volumetric-modulated arc therapy (VMAT) with image-guided radiation therapy (IGRT) and respiratory gating, and a minimum biologically effective dose (BED10Gy) of 100 Gy was delivered to all lesions. With a median follow-up of 23.1 months (range: 13.4–30.9 months) since liver SBRT, the median actuarial local progression-free survival (local-PFS) was not reached. The actuarial in-field LC rates were 84.9% and 78.4% at 24 and 48 months, respectively. The median actuarial liver-PFS and distant-PFS were 11 and 10.8 months, respectively. The actuarial median overall survival (OS) was 27.7 months from SBRT and 52.5 months from metastases diagnosis. Patients with lesion diameter ≤ 5 cm had significantly better median liver-PFS ($p=0.006$) and OS ($p=0.018$). No acute or late toxicities of grade ≥ 3 were observed.

Conclusions This prospective multicenter study confirms that liver SBRT is an effective alternative for the treatment of liver metastases, demonstrating high rates of local control and survival while maintaining a low toxicity profile.

Keywords SBRT · Liver metastases · Oligometastases

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Introduction

In recent years, the multidisciplinary management of oligometastatic cancer patients, incorporating new systemic regimens, surgery, and ablative local therapies, has significantly improved overall survival rates.

Liver metastases are frequently observed in oligometastatic disease from various cancers, and surgical resection remains the gold standard treatment, achieving 5 year survival rates of 50–60% in selected patients [1–3]. However, a substantial proportion of patients (70–90%) with liver metastases have unresectable disease or are deemed unfit for surgery due to poor clinical conditions or comorbidities.

In such cases, percutaneous thermal ablation techniques like radiofrequency or microwaves, and more recently, stereotactic body radiation therapy (SBRT), have emerged as viable alternatives for achieving a cure [4, 5].

An increasing number of prospective clinical trials have evaluated the safety and effectiveness of SBRT for liver metastases, demonstrating excellent clinical tolerance, high rates of local control (90–100% at 1 year and 80–70% at 2–3 years), and promising overall survival rates [6–10]. Most studies have employed SBRT dose schedules of 45–60 Gy delivered in 3–5 fractions. More recent phase II studies, employing doses up to 75 Gy in 3 fractions, have reported long-term rates of local control (78% at 5 years) and overall survival (median OS exceeding 27 months after SBRT). Furthermore, SBRT has exhibited a favorable tolerability profile, with low-grade 3 late complications (<5%) [11, 12].

These long-term results of SBRT have been reinforced by the SABR-COMET phase II randomized trial in oligometastatic patients, revealing a prolonged 5 year overall survival rate of 42.3% (95% CI 28–56%) in the SBRT arm compared to palliative standard of care [13].

The objective of this multicenter study is to provide prospective evidence on the safety and efficacy of SBRT for the treatment of liver metastases, specifically including patients with more unfavorable prognostic factors such as lesions larger than 5 cm and 3 or more metastases.

Materials and methods

Ethical statement

This study is a prospective, multicenter non-randomized clinical trial approved by the Institutional Review Boards of the Ethics Committees at the Fundación HM Hospitales (15.04.781-GHM) and Hospital Universitario de Navarra (Pyto2015/99). The study was conducted in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki. Informed consent was obtained from all participating subjects.

Endpoints

The primary endpoint was to evaluate in-field local control of liver metastases. The secondary endpoints included the analysis of treatment-related toxicity, intrahepatic progression-free survival, and overall survival.

Inclusion criteria

The inclusion criteria encompassed patients with a histological diagnosis of solid tissue cancer in an oligometastatic status or oligo-recurrences, with a restriction of no more than

five liver lesions, each measuring less than 7 cm in size for every individual lesion. Eligible patients were over 18 years old with an ECOG performance status of 0–1. Normal liver volume (> 1000 cm³) and adequate liver function (total bilirubin < 3 mg/dL, albumin > 2.5 g/dL, normal prothrombin time (PT)/partial thromboplastin time (PTT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than 3 times the upper limit of normal) were mandatory. Diagnostic imaging with abdominal computed tomography (CT), magnetic resonance imaging (MRI), or fluorodeoxyglucose (FDG)-positron emission tomography (PET)-CT was required. Following multidisciplinary tumor board discussion involving medical oncologists, hepato-biliary surgeons, radiologists, and radiation oncologists, patients who were not candidates for surgical resection or refused surgery were selected for SBRT. Prior local treatments of the liver (surgery or ablative therapies) were allowed. Extrahepatic disease was permissible if it was potentially treatable. Patients could receive systemic therapy before and after, but not concurrently (with at least a 2 week interval), with the radiation course. All patients provided informed consent prior to treatment.

Radiation treatment procedure

All patients were positioned in a stable supine position using a body vacuum cushion for simulation. Contrast-enhanced computed tomography (CT) with a slice thickness of 2–3 mm was acquired, employing respiratory control techniques. Three different respiratory control techniques were utilized: Dampening, Exactrac Adaptive Gating[®], and Breath Holding with ABC (Active Breathing Coordinator)[®]. Four-dimensional CT (4D-CT) was mandatory when abdominal compression (Dampening) was employed. Internal fiducial markers were placed via CT-guided liver puncture in all patients treated with the BrainLab Exactrac Adaptive Gating[®] system. CT images were acquired during free breathing and in deep inspiration breath-hold when the ABC (Active Breathing Coordinator) Elekta[®] system was used as a respiratory control technique.

CT images were co-registered with MRI or PET-CT images, whenever available, to enhance the definition of the gross target volume (GTV). The clinical target volume (CTV) was equivalent to the GTV. An internal target volume (ITV) was delineated and added to the CTV to create the planning target volume (PTV), defined as CTV/ITV + 5 mm margin in all directions.

The prescription dose was determined based on tumor size and the liver's proximity to organs at risk (OaR). For lesions with a CTV diameter ≤ 3 cm, the prescribed dose was 60 Gy in 3 fractions of 20 Gy (BED10 = 180 Gy) or 45 Gy in 3 fractions of 15 Gy (BED10 = 112.5 Gy), depending on the distance from an OaR (> 2 cm or < 2 cm, respectively).

Lesions measuring more than 3 cm but less than 5 cm in diameter received either 45 Gy in 3 fractions of 15 Gy or 50 Gy in 5 fractions of 10 Gy, depending on their proximity to an OaR (> 2 cm or < 2 cm, respectively). For lesions measuring 5–7 cm in diameter, a prescribed dose of 50 Gy in 5 fractions of 10 Gy (BED₁₀ = 100 Gy) was administered, regardless of the distance to an OaR. The minimum biologically equivalent dose (BED)₁₀ Gy for all treatment schedules was at least 100 Gy.

SBRT was delivered using an intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) technique with high conformity on Novalis (BrainlabTM), VERSA HD (ElektaTM), or Trilogy (VarianTM) linacs. Dosimetric planning parameters and dose constraints for OaRs are summarized in Table 1. Daily image-guided radiotherapy (IGRT) was mandatory, and intrafraction control of tumor position was achieved using 4D-Conebeam, BrainLab Exactrac Adaptive Gating[®] X-Ray, or Elekta[®] intrafraction Conebeam CT.

Evaluation and statistics

Patient monitoring and follow-up

During the SBRT treatment, patients underwent physical examinations, and baseline blood tests, including coagulation and serum liver parameters, were analyzed. Acute treatment-related toxicity was closely monitored. After the completion of SBRT, patients were followed up with clinical exams and blood tests one month after treatment and every 3 months thereafter. Acute and late toxicities were assessed

using the Common Terminology Criteria for Adverse Events (CTCAE version 4.0) [14].

Tumor response assessment

Treatment results were evaluated based on in-field local control and the occurrence of intrahepatic or distant recurrence. CT scans or abdominal MRI were performed at 3 months after SBRT and at 3 month intervals for the first 2 years, followed by evaluations every 6 months starting from the third year. If needed, an 18-FDG-PET-CT scan was performed. The follow-up period was considered from the end of treatment to the last evaluation date.

Tumor response was defined according to the European Organization for Research and Treatment of Cancer Response Evaluation Criteria In Solid Tumors (EORTC-RECIST) 1.1 or PERCIST criteria 1.0 [15, 16]. Local progression-free survival (LPFS) was estimated from the last day of SBRT until local progression. Patients who died from intercurrent disease without evidence of tumor were censored at the date of death. Overall survival (OS) was defined as the time interval between treatment and the date of death, regardless of the cause, or to the date of the last follow-up.

Statistical analysis

Statistical analysis was performed using SYSTAT, version 24.0 (SPSS, Chicago, IL). Actuarial LPFS and OS were calculated using the Kaplan–Meier method. Survival curves were compared using the log-rank test to assess prognostic factors, and the Chi-square test was used for comparisons between groups. A *p* value of less than 0.05 was considered statistically significant.

Table 1 Dosimetric Planning criteria and dose constraints for OaR

PTV planning criteria
95% of PTV should be covered by the prescription dose
D _{max} /D _{2%} ≤ 125% of the prescription dose in PTV
In PTV surrounding tissue, D _{max} < 105% should be considered
99% of PTV have to be covered by at least 90% of the prescription dose
Conformity index ≤ 1.5
Conformity index at 50% ≤ 4
Avoid > 50% dose at 2 cm distance from PTV
Dose constraints for OaR in 3 fractions
Healthy liver: volume receiving > 15 Gy > 700 cm ³ , V ₂₁ Gy < 30%
Duodenum, small bowel, esophagus, and stomach: D _{max} (0.03 cc) < 22.2 Gy, V _{16.5} Gy < 10 cc
Colon D _{max} (0.03 cc) < 28.2 Gy, V ₂₄ Gy < 20 cc
Ribs: D ₁ cc < 36.9 Gy, D ₁₀ cc < 30 Gy
Dose constraints for OaR in 5 fractions
Duodenum, small bowel, esophagus, and stomach: D _{max} (0.03 cc) < 35 Gy, V ₃₀ Gy < 5 cc
Colon D _{max} (0.03 cc) < 40 Gy, V ₂₅ Gy < 20 cc
Ribs: D ₁ cc < 43 Gy, D ₁₀ cc < 35 Gy

Results

Between June 2015 and October 2018, a total of 52 patients with isolated liver metastasis were enrolled in this prospective multicentric study. A total of 105 liver metastases treated with SBRT were analyzed. Of the enrolled patients, 34 (65%) were male and 18 (35%) were female, with a mean age of 69.7 years (62.2–75.2 years). Colorectal cancer was the most common primary tumor, followed by lung and breast cancer. Nineteen patients (36.5%) had received previous local liver metastasis treatments before SBRT, including surgery alone or combined with radiofrequency ablation in some cases (26.3%). Additionally, 21 patients (40.4%) had other oligo-extrahepatic metastases that had been previously treated. The majority of patients (90.4%) had undergone previous systemic therapy, including chemotherapy, targeted treatments, and hormonal therapy, with 57.4% of them receiving at least two different lines of treatment.

The median time from liver metastasis diagnosis to liver SBRT was 10.3 months (5.5–27.9 months). The number of treated liver metastases with SBRT was three or more in 15 patients (29%), two metastases in 14 patients (27%), and a single liver metastasis in 23 patients (44%). Fifteen patients (29%) received two or more courses of liver SBRT, ranging from 2 to 4 courses. Detailed patient characteristics and the SBRT doses delivered to the liver metastases are provided in Table 2.

Prior to SBRT, internal fiducial markers were safely placed in 28 patients (53.8%) using liver puncture guided by CT scan, without any associated adverse effects. The median diameter of the Gross Tumor Volume (GTV) was 2.8 cm (0.9–7.8 cm). Among the 105 liver lesions analyzed, 46 lesions (43.8%) had a GTV diameter > 3 cm, and 13 lesions (12.4%) had a GTV diameter > 5 cm. The median volume of the Planning Target Volume (PTV) was 7.5 cc (range 0.4–150.5 cc). Regarding the treatment doses, 46 lesions

(43.8%) received 60 Gy (3 × 20 Gy), 33 patients (31.4%) received 50 Gy (5 × 10 Gy), and 26 (24.8%) received 45 Gy (3 × 15 Gy). The median follow-up from the first liver SBRT was 23.1 months (13.4–30.6 months). After intra-hepatic recurrence, 15 patients (28.8%) received a median of 2 additional courses of SBRT (range 2–4) for different liver metastases, and 13 patients (25%) received further lines of chemotherapy after liver SBRT.

The median in-field progression-free survival (LPFS) from liver SBRT was not reached (Fig. 1A). The in-field LPFS rates at 12, 24, and 48 months were 95.6%, 84.9%, and 78.4% respectively, for all lesions. For lesions ≤ 5 cm, the LPFS rates were 97.1%, 91.2%, and 83.6% at 12, 24, and 48 months respectively (Fig. 1B). Lesions larger than 5 cm had LPFS rates of 88.9%, 53.3%, and 53.3% at 12, 24, and 36 months respectively.

The median liver progression-free survival (liver-PFS) was 11.0 months (5.5–16.5), and the median distant progression-free survival (D-PFS) was 10.8 months (4.7–17.0) (Fig. 1D, F).

The median overall survival time since liver SBRT was 27.7 months (20.3–35.1) (Fig. 1G), while the median overall survival time since liver metastases diagnosis was 52.5 months (37.2–67.9). The actuarial 2 year OS was 61.5%, and the actuarial 5 year OS was 26.3%. No significant differences in long-term survivals were identified.

Univariate analysis demonstrated that liver metastasis ≤ 5 cm, compared to those > 5 cm, was associated with significantly higher median liver-PFS (12.4 months vs. 3.8 months, $p=0.006$) and median OS (31.7 months vs. 22.8 months, $p=0.018$) (Fig. 1E, H). No significant relationship was found between LPFS and clinical or treatment-related factors, although a prescription of BED10Gy above 100 Gy ($p=0.061$) and lesions ≤ 5 cm ($p=0.053$) showed a tendency towards significance (Fig. 2).

Table 2 Patient characteristics and SBRT doses

	N (52 patients) (%)
Male/female	34 (65%)/18 (35%)
Mean age: 69.7 years (62.2–75.2)	
Primary tumor	
Colorectal cancer	38 (72%)
Lung cancer	5 (10%)
Breast cancer	4 (8%)
Pancreas cancer	3 (6%)
Others	2 (4%)
Synchronous metastases/metachronous metastases	24 (46%)/28 (54%)
Patient with other oligo extra-hepatic metastases	21 (40.4%)
Lung metastases	7 (33%)
Lymph node metastases	7 (33%)
Lung and lymph node metastases	1 (4.8%)
Bone + other metastases	2 (9.5%)
Brain + other metastases	2 (9.5%)
Adrenal metastases	1 (4.8%)
Ovarian metastases	1 (4.8%)
Size of the liver metastases (105 lesions)	
< 3 cm	59 (56.2%)
3–5 cm	33 (31.4%)
> 5 cm	13 (12.4%)
Number of metastases treated with SBRT / patient	
Single metastases	23 (44%)
2 metastases	14 (27%)
3 or more (3–8 metastases)	15 (29%)
Prescription dose per lesion	
60 Gy (3 × 20 Gy) BED _{10Gy} : 180 Gy	46 (43.8%)
45 Gy (3 × 15 Gy) BED _{10Gy} : 112.5 Gy	36 (24.8%)
50 Gy (5 × 10 Gy) BED _{10Gy} : 100 Gy	33 (31.4%)

Discussion

Stereotactic body radiation therapy (SBRT) has emerged as a promising treatment for liver metastases, and its role as an ablative alternative with radical intent in oligometastatic disease has been established in several clinical guidelines, including those of ESMO and NCCN [17–21].

SBRT enables the delivery of a highly focused and biologically effective radiation dose to liver metastases in a limited number of fractions, while minimizing the dose to the surrounding healthy liver and other tissues. The advancements in tumor imaging, such as the integration of CT, MRI, or PET-CT, have improved the definition of liver metastases. Additionally, modern delivery radiation techniques with image-guided radiotherapy (IGRT) and motion management

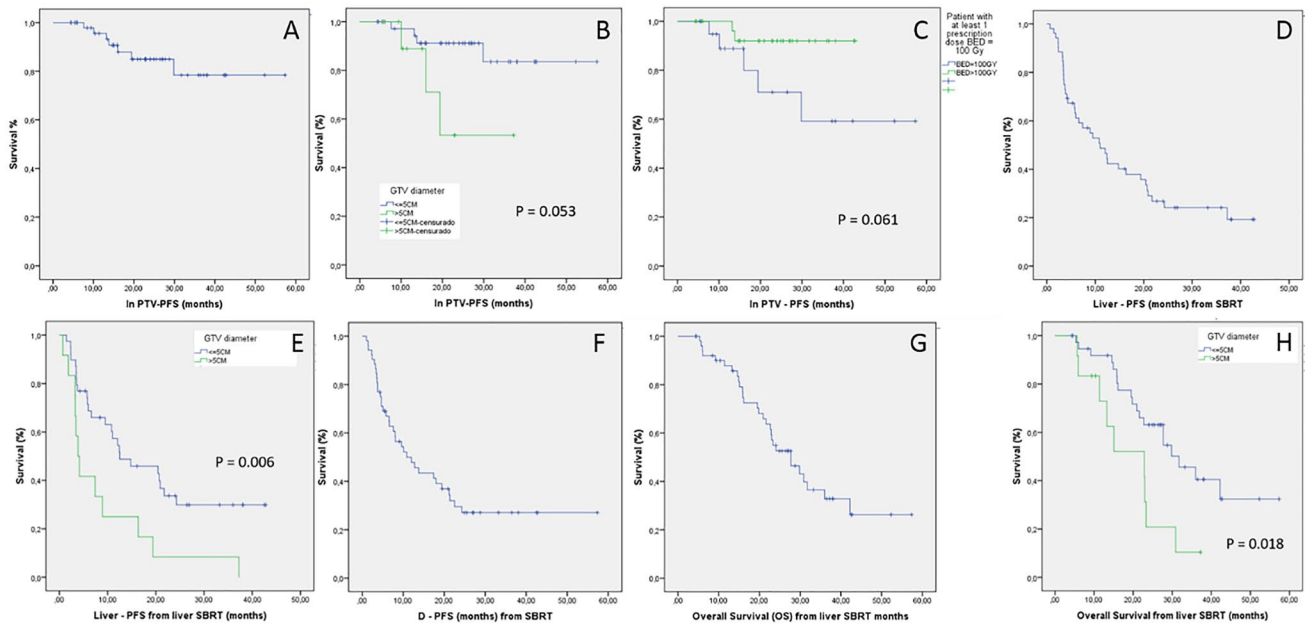


Fig. 1 **A** Progression-free survival (PFS) in the planning target volume (PTV) from liver SBRT. **B** PFS in the PTV based on gross tumor volume (GTV) diameter. **C** PFS in the PTV based on biologically effective dose (BED). **D** Liver progression-free survival (Liver-PFS)

in months following SBRT. **E** Liver-PFS based on GTV diameter. **F** Distant progression-free survival (D-PFS) in months following liver SBRT. **G** Overall survival (OS) from liver SBRT. **H** OS from liver SBRT based on GTV diameter

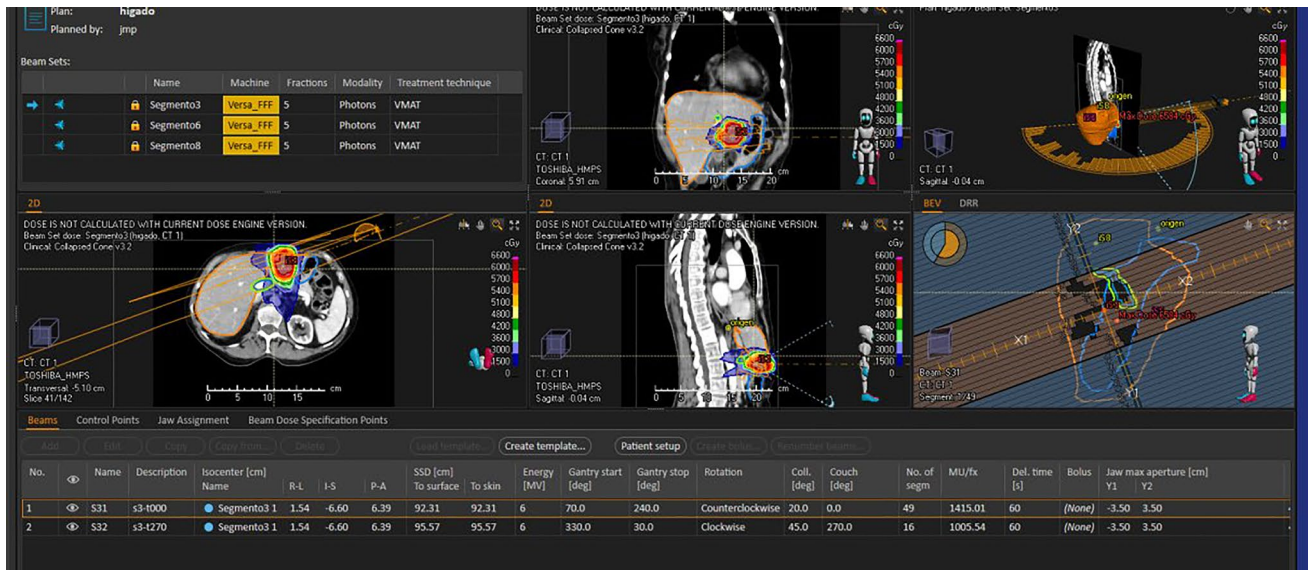


Fig. 2 Dosimetry of liver SBRT in the planning view

of the liver during irradiation have contributed to the development and implementation of SBRT [22, 23].

A growing number of prospective clinical trials have evaluated the safety and effectiveness of SBRT for liver metastases, demonstrating excellent clinical tolerance, high rates of local control, and promising overall survival. SBRT offers advantages over thermal ablation techniques by allowing

treatment of liver metastases located near critical structures such as the main biliary tree, blood vessels, gastrointestinal structures, or in subcapsular locations. Moreover, SBRT appears to be more suitable for larger tumors (> 3 cm) [24, 25].

Unlike surgery, SBRT does not require post-surgical recovery, can safely treat multiple tumor locations

simultaneously, and may induce an abscopal effect, particularly in "hot" tumors associated with a robust immune response [26].

This report summarizes the results of a prospective multicenter study that provides further evidence on the safety and efficacy of SBRT for the treatment of liver metastases, including patients with more unfavorable prognoses, such as lesions larger than 5 cm and three or more metastases.

In our study, the delivered dose was determined based on the tumor size, liver location of the metastases, and their proximity to organs at risk (OaR). Smaller lesions (≤ 5 cm) located at least 2 cm away from OaR received 45–60 Gy in 3 fractions (BED10 = 112.5–180 Gy), while larger lesions (5–7 cm) or those located less than 2 cm away from OaR received 50 Gy in 5 fractions (BED10 = 100 Gy). The minimum BED10Gy was 100 Gy for all lesions.

As the primary endpoint of our study was local progression-free survival (LPFS), we conducted a detailed analysis of this parameter. LPFS, defined as in-field (PTV) progression-free survival or liver progression-free survival, demonstrated a high rate of local control following liver SBRT. The in-field-PFS rates were 95.6% and 78.4% at 24 and 48 months, respectively, and the median actuarial in-field-PFS was not reached in our study. We observed that lesions larger than 5 cm had a lower in-field-PFS (53.3% at 24 and 36 months) compared to smaller lesions, although the difference was not statistically significant ($p=0.053$). The histology of the primary tumor and BED10Gy > 100 Gy were not identified as prognostic factors related to in-field-PFS ($p=0.61$). However, tumor size (lesions > 5 cm) was found to be a statistically significant ($p=0.006$) prognostic factor for liver progression-free survival, with a median liver-PFS of 3.8 months for lesions > 5 cm and 12.4 months for smaller lesions. To better analyze liver SBRT results in the future, we propose standardizing in-field-PFS as local control and liver-PFS as regional control.

Furthermore, we identified lesion size (> 5 cm) as an unfavorable prognostic factor related to overall survival, with a median overall survival of 31.7 months for patients with lesions ≤ 5 cm and 22.8 months for patients with lesions > 5 cm ($p=0.018$).

Several studies on liver metastases treated with SBRT have also investigated prognostic factors for local control and survival. The size of the metastases and the delivered radiation dose have been recognized as important prognostic factors. Smaller metastases and those receiving higher doses (BED10 > 100 Gy) have been associated with better local control [5, 6, 8]. A meta-analysis of prognostic factors following SBRT for colorectal liver metastases demonstrated that the total radiation dose, dose per fraction, and biologically effective dose were significantly associated with improved local control [27]. This prognostic factor was also validated in a large cohort of patients treated with various dose fractionation

schemes, where local control rates exceeding 90% were achieved with doses of 46–52 Gy in 3 fractions, and higher BEDs were associated with improved local control and survival, especially in larger tumors [28].

Some studies have suggested that the primary tumor histology may influence outcomes, with colorectal metastases showing lower local control rates compared to metastatic lesions from other primary sites [12, 29]. However, in our study, no significant difference in local control between primary tumor types was observed. This lack of significance may be attributed to factors such as patient selection (72% of our patients had colorectal cancer) or unreported factors, including the extent of systemic disease and varying use of systemic therapy.

In our study, SBRT for liver metastases was performed in heavily treated patients, with 90.4% having received multiple lines of chemotherapy. Additionally, 19 patients (36.5%) had previously undergone surgery or local ablative radiofrequency for liver metastases, and 21 (40.4%) had received local treatments for other oligo-extrahepatic metastases. Furthermore, 15 patients (29%) were treated with SBRT for three or more liver metastases, and 43.5% of the liver metastases were ≥ 3 cm in size. Despite these factors, the distant progression-free survival (D-PFS) was 10.8 months (4.7–17.0 months), and the actuarial median overall survival since liver SBRT was 27.7 months (20.3–35.1 months), with a median overall survival of 52.5 months (37.2–67.9 months) since liver metastases diagnosis. The actuarial 2 year overall survival rate was 61.5%, and the actuarial 5 year overall survival rate was 26.3%.

The excellent clinical tolerance of liver SBRT in our study was evident, with no observed acute or late toxicities grade ≥ 3 . This finding is consistent with previous studies on liver SBRT, where grade 3 or higher treatment-related toxicity is rarely reported [12, 30, 31]. For instance, in the Dutch-Belgian Registry of SBRT, grade 3 toxicity was observed in only 3.9% of 515 patients, and grade 5 toxicity was observed in just one patient (0.2%) [29].

While our study has some limitations, such as the relatively short median follow-up and the heterogeneity of patients, histologies, and treatments other than liver SBRT, we believe it provides robust evidence. Our results are comparable to previous studies (Table 3) and historical surgical series on liver metastases resection [3]. These findings can serve as a basis for future comparative studies and support the role of SBRT as a safe and effective local treatment for liver metastases. In the absence of phase III studies, Table 3 summarizes four recent key studies focusing on liver SBRT.

Conclusions

In conclusion, this prospective multi-institutional study provides strong evidence supporting the efficacy of liver SBRT as a treatment modality for patients with liver metastases.

Table 3 summarizes data of the four main studies published recently focussing on liver SBRT. Y: years

Study	Type study	Patients	N. lesions	Time	Median OS (months)	Local control (LC)	3 or 5 – years survival rate
Scorsetti 2018 (12)	Phase II	61	76	2010–2012	27.6	1y 94%; 3y 78%	18.0 ± 4.9%
RSSearch [®] patient registry (28)	Observational database	427	568	2005–2017	22	Median LC 51 months	< 10% estimated from Kaplan–Meier curve
DEGRO (30)	Observational database	474	623	1997–2015	24 after SBRT	1y 87%	15%
Dutch-belgian registry (29)	Observational database	515	668	2013–2019	–	1y 77% 2y 64%	44% at 3 years 30% estimated from Kaplan–Meier curve
This study	Prospective clinical trial	52	105	2015–2018	27.7 after SBRT	1y 95.6% 2y 84.9% 4y 78.4%	26.3%

The results demonstrate high rates of local control and overall survival, coupled with low toxicity. Importantly, liver SBRT offers an excellent local alternative for patients with multiple metastases and lesions up to 5 cm in size. These findings emphasize the potential of liver SBRT as an effective and well-tolerated treatment option for this patient population. Further research and long-term follow-up studies are warranted to validate these promising outcomes and optimize patient selection for liver SBRT.

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Data availability Data are available at rationale request.

Declarations

Conflict of interest The authors declare that there's no financial/personal interest or belief that could affect their objectivity, or if there is, stating the source and nature of that potential conflict.

Ethical approval This study is a prospective, multicenter non-randomized clinical trial approved by the Institutional Review Boards of the Ethics Committees at the Fundación HM Hospitales (15.04.781-GHM) and Hospital Universitario de Navarra (Pyto2015/99). The study was conducted in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki.

Informed consent Informed consent was obtained from all participating subjects before inclusion.

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