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Stereotactic body radiation therapy for liver metastases and primary liver tumors: treatment results and toxicity

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The aim of our research was to evaluate the efficacy and toxicity of stereotactic body radiotherapy (SBRT) for the liver in all patients diagnosed with either primary liver tumor or metastases from other primary malignancies since its initial application at a single institution. A retrospective analysis of the prospective designed registry included 105 patients with 133 liver metastases or primary tumors treated with SBRT from the introduction of the technique in March 2018 until November 2023. The main objectives of the study were to evaluate treatment toxicity, disease control, and survival rates. At a median follow-up of 24 months, a complete response to treatment was achieved in 86.7% of patients. During irradiation, only one patient experienced grade 3 abdominal discomfort, while the other 34.3% of patients experienced only mild acute adverse events (AEs), the majority of which were nausea. After completion of SBRT, 36.2% of patients reported AEs, but only grade 1 and 2 toxicity was observed. The one-, two-, and five-year LC rates were 89.2%, 84.9%, and 84.9%, respectively. DFS rates were 54.7%, 42.9%, and 25.8%; DSS rates were 94.9%, 81.1%, and 46.8%; and OS rates at one, two, and five years were 93.1%, 79.6%, and 43.2%, respectively. In the multivariate analysis, only the number of lesions presented independent prognostic value. In conclusion, SBRT offers effective disease control and survival rates with minimal toxicity, side by side with surgical options as a curative treatment for liver tumors.

Key words: stereotactic body radiotherapy; liver; outcome; toxicity

The liver is a common site of metastasis, especially of colorectal carcinomas [1–2]. Primary liver tumors such as hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma occur less frequently, but the incidence is increasing [3–4].

Regardless of the type of cancer, liver metastases represent an advanced disease with a poor prognosis [5]. For many metastases, systemic treatment with palliative intent may be considered. In some patients with one or few metastases (oligometastatic disease, OMD), a better prognosis can be expected with more intensive local treatment [6–7].

Surgery is the traditional treatment for liver metastases and is associated with improved survival in many cases [8–13]. Unfortunately, only 10–25% of metastases are resectable, depending on the type of primary tumor. Furthermore, despite advances in surgery, liver resection remains associated with significant morbidity and mortality. Many patients are also unsuitable for surgery due to their performance status and/or comorbidities or they decline surgery due to many concerns and other factors [14–15].

Several local treatment options are available for these patients, including the newer approach of stereotactic body radiation therapy (SBRT) [16–17].

SBRT of the liver is technically difficult because of respiratory movement and movement due to the different filling of the gastrointestinal organs. It is also close to other organs with low radiation tolerance, and liver metastases are difficult to detect during irradiation as they are not visible on cone-beam computed tomography (CBCT). Precision is achieved through effective immobilization, image-guided irradiation, and restriction of organ movement. Four-dimensional computed tomography (4D-CT) is used to assess target displacement, which can be up to 4 cm in the cranio-caudal direction [18]. Strategies are used to restrict mobility, such as abdominal compression or breath-holding techniques [19]. The problem of poor visibility of lesions on CBCT is solved

by placing radiopaque fiducial markers in the liver parenchyma near the target [20].

There is growing evidence for the role of SBRT in the treatment of liver metastases and primary liver tumors. Although there are no randomized phase III trials evaluating the use of SBRT in the treatment of liver metastases, several prospective phase I and phase II trials and retrospective case series have shown promising results in terms of better overall survival (OS), local control (LC), and toxicity profile, and proving that SBRT is at least comparable to other local treatment modalities [21–22]. SABR-COMET was the first randomized trial to show a survival benefit in patients with OMD treated with standard palliative treatment plus SBRT compared to standard palliative treatment alone (8-year OS 27.2% vs. 13.6%, p=0.008) [23].

SBRT treatment has also been shown to be effective in the treatment of primary liver tumors. In the treatment of HCC, the approach is at least comparable to surgery or other ablative therapy modalities. It is also successfully used as a bridging therapy until liver transplantation [24–26]. The primary treatment for intrahepatic cholangiocarcinoma is surgery plus chemotherapy, which has a 5-year OS rate of 20–40% but is only feasible in one-third of patients. SBRT has been shown to be useful in the treatment of inoperable tumors or local recurrence, with a 1-year LC rate of 49–100% with minimal toxicity rates [27].

In our article, we present the results of liver treatment with the SBRT technique at the Institute of Oncology Ljubljana since its introduction in 2018 for patients with liver metastases of various primary tumors or primary liver tumors.

Table 1. Patients' inclusion criteria.

Cytological/histological confirmation of cancer from metastases or primary tumor or confirmation of new liver lesions by imaging (CT, MR, PET-CT)
Presented at the Multidisciplinary tumor board
Oligometastatic disease (1–5 metastases) or primary liver tumor
WHO PS 0-2
Lesion diameter ≤6 cm (optimally <3 cm)
≤5 lesions (optimally ≤3)
≥700 cm^3 healthy liver parenchyma (optimally >1,000 cm^3)
Child's Pugh liver function score A or B in case of liver cirrhosis
Lesion ≥5–8 mm distant from the esophagus, stomach, duodenum, and intestine
No or limited proven extra-liver disease that can be treated
Expected survival ≥6 months
Last administration of systemic therapy ≥2 weeks ago, with some exceptions in agreement with the treating oncologist (e.g., anti-HER-2 therapy)
Patients ≥18 years old

Abbreviations: CT-computed tomography; MR-magnetic resonance; PET-CT - positron emission computed tomography; PS-performance status; WHO-World Health Organisation; HER-2-human epidermal growth factor receptor-2

Patients and methods

Patients. We conducted a retrospective analysis of the prospective registry of patients with liver metastases and primary liver tumors treated with SBRT to determine treatment success and toxicity. The clinical protocol was approved by the Ethics Committee (approval number: ERIDEK-0108/2019) and the Clinical Trials Protocol Review Committee (approval number: ERID-KSOPKR-0091/2019). We included all patients who were treated with SBRT since the introduction of the technique in March 2018 until November 2023 and underwent at least 2 consecutive diagnostic procedures with CT and/or MR. All included patients were discussed in a multidisciplinary team before starting treatment, where SBRT treatment was indicated according to the inclusion criteria (Table 1).

The technical suitability of the patient for SBRT was usually assessed by two radiotherapists on the basis of diagnostic imaging performed within 6 weeks prior to the planned treatment.

Treatment protocol. If the lesions were not clearly visible on CT due to their location or characteristics (e.g., HCC), the radiologist placed fiducial markers in 3 dimensions (above, below, and next to the lesion, at least 2–3 cm apart) by ultrasound at least 1 week before the simulation.

On the CT simulator, the patient was positioned supine on a vacuum cushion with his arms raised behind his head and immobilized. Abdominal compression and 4D-CT were performed to assess the movement of the target volume due to respiration. To improve the accuracy, MR simulation was performed in all patients with the same settings and immobilization as for CT simulation. All patients were given a proton pump inhibitor and instructed not to eat for three hours before SBRT.

The target volumes and organs-at-risk (OAR) were delineated on the CT and MR images. The gross tumor volume (GTV), which represents the radiologically visible lesion, the internal target volume (ITV), which represents the GTV with shifts in all respiratory phases, and the planning target volume (PTV), which represents the ITV with a margin of 5 mm were contoured. The contoured target volumes and OAR were reviewed by two radiation oncologists to ensure the quality of the contouring.

The dose per target was determined according to the size of the lesion. A tumor smaller than 3 cm received a total dose of 54 Gy in 3 fractions and a tumor larger than 3 cm received a total dose of 60 Gy in 3 fractions. If the OAR doses were exceeded (especially with larger tumors), the dosage regimen was adjusted (lower total dose or a hypofractionated regimen in several fractions (e.g., 50 Gy in 5 fractions). Volumetric-modulated arc therapy (VMAT) was the most commonly used irradiation modality. After two physicists reviewed and revised the plan, two radiation oncologists reviewed and approved the plan to ensure that it conformed to the protocol.

Radiation was delivered every other day and the total duration of the treatment was no more than 5 days for three fractions.

Patients were monitored in the outpatient clinic once at the end of treatment, and then after 1 month, and every 3 months during the first 2 years. After the second year, clinical and laboratory examinations were performed every 6 months and imaging examinations once a year. Acute toxicity data, defined as any toxicity that occurred during SBRT or up to three months after treatment, were documented in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, 2017. Imaging tests were evaluated according to the RECIST (Response Evaluation and Criteria in Solid Tumors) criteria.

Statistical analysis. For the statistical analysis, we used the Statistical Package for the Social Sciences, version 26.0 (SPSS Inc., Chicago, IL, USA). For statistical processing, we used the basic frequency statistics of data distribution.

The main objectives of the study were to assess treatment toxicity, LC, disease-free survival (DFS), OS, and disease-specific survival (DSS), the latter calculated using the Kaplan-Meier technique. The log-rank test was used to evaluate the influence of the individual prognostic factors on the analyzed endpoints. The independent prognostic values of the factors that appeared statistically significant in the univariate analysis, were tested using the multivariate Cox regression analysis model. Two-sided tests were used and differences at $p<0.05$ were considered statistically significant.

Results

The study included 105 patients with 133 liver lesions who met the predefined inclusion criteria. The median follow-up time after SBRT was 24 months (6–72 months). Baseline patient and treatment characteristics are summarized in Table 2. Fiducial markers were inserted in 63 patients (60%) before the start of radiotherapy. One patient experienced grade 1 intrahepatic hemorrhage after fiducial markers insertion, which was treated conservatively and resolved spontaneously.

Toxicity during irradiation. Acute toxicity occurred in 36 patients (34.3%) during irradiation, with nausea being the predominant AE; 16.2% of patients reported grade 1 nausea and 5.7% reported grade 2 nausea. Vomiting occurred in 3.8% of patients (grade 1) and 1.9% (grade 2), while 9.5% of patients reported fatigue (grade 1). Abdominal pain occurred in 6.7% of patients (grade 1) and in 2.9% (grade 2); in addition, one patient (1%) reported grade 3 abdominal discomfort. Patients rarely reported inappetence (1%, grade 1) or back pain (1%, grade 1).

Acute toxicity after irradiation. Acute adverse reactions were reported by 38 (36.2%) patients (Supplementary Figure S1). Only grade 1 and 2 toxicities were observed. Abdominal pain was the most common side effect, followed by fatigue and nausea. One patient had a rib fracture and myositis of the chest wall muscles in the immediate vicinity of the irradiated area, a complication that was treated conservatively. In this case, SBRT was performed following a multidisciplinary team's decision for a 9 cm metastasis, as it was the only active oncologic lesion in a young patient after several resections and systemic lines of treatment.

Acute toxicity assessed in laboratory tests. We observed a change in laboratory test results in 72 patients (68.6%). The most common finding was a transient increase in liver function tests, even if this was clinically insignificant. The

Table 2. Baseline patient and treatment characteristics.

Characteristics	Number	Percent (%)
Age (years) Mean (min-max)	67.7 (32.5-88)	
Sex		
Male	67	63.8
Female	38	36.2
No. of liver lesions		
1	82	78.1
2	20	19
3	2	1.9
5	1	1
Primary tumor		
Colorectal cancer	39	37.1
HCC	20	19
Breast cancer	9	8.6
Intrahepatic Cholangiocarcinoma	8	7.6
GIST	5	4.8
Lung cancer	4	3.8
Melanoma	4	3.8
Head and neck carcinoma	4	3.8
Ovarian cancer	2	1.9
Sarcoma	2	1.9
Hürthle cell carcinoma	2	1.9
Unclassified	2	1.9
Anal cancer	1	1
Uterine cancer	1	1
Penile cancer	1	1
Gastric cancer	1	1
Lesion diameter Mean (min-max)	3.2 cm (0.6-9.8 cm)	
≤ 3 cm	64	61
> 3 cm	41	39
Prior liver-directed therapy[1]		
Yes	44	41.9
No	61	58.1
Fractionation		
3 fractions	64	61
5 fractions	41	39
TD Median (min-max)	54 Gy (35-60)	
BED (α/β = 10, BED10) Median (min-max)	151.2 Gy (59.5-180)	

Note: [1]local treatment of liver lesions (surgery, radiofrequency ablation-RFA, microwave ablation-MWA, transcatheter arterial chemoembolisation-TACE, electrochemotherapy) prior to SBRT
Abbreviations: HCC-hepatocellular carcinoma; GIST-gastrointestinal stromal tumor; TD-total dose; BED-biologically effective dose; Gy-Gray

most common finding was an increase in gamma-glutamyl transferase levels. No cases of radiation-induced liver disease (RILD) or coagulopathy were observed in the patients (Supplementary Table S1).

Local control. The one-, two- and five-year LC rates were 89.2%, 84.9%, and 84.9%, respectively (Figure 1). A complete response was observed in 91 patients (86.7%), while an incomplete response occurred in 10 patients (9.5%). Response to the treatment could not be assessed in 4 patients (3.8%), due to rapid and marked disease progression, characterized by multiple liver metastases in three cases, while one patient underwent liver transplantation within six months of SBRT. We observed differences in LC according to fractionation, BED, lesion size (Supplementary Figure S2), and histologic type (Supplementary Figure S3).

Disease-free survival. Disease progression was observed in 62 patients (59%) during the follow-up period. Twenty-one patients (20%) showed disease progression in the liver outside the irradiated lesion, while two cases (1.9%) showed progression within the irradiated lesion. In 34 patients, representing 32.4% of the cohort, disease progression was predominantly systemic. Five patients (4.8%) had isolated progression of the primary tumor, including three with colorectal and two with gynecologic carcinoma (ovarian and uterine carcinoma).

The median DFS was 14.3 months, with a 95% confidence interval (CI) of 9.5–19 months. The DFS rates for one, two, and five years were 54.7%, 42.9%, and 25.8%, respectively (Figure 1).

Disease-specific and overall survival. During the follow-up period, 32 patients (30.5%) died. Most of these deaths (29 patients; 27.6%) were attributed to systemic progression of the oncologic disease. One patient died due to the progression of liver cirrhosis, another due to duodenal hemorrhage, and in one patient the cause of death is unknown. The median DSS was 48.5 months (95% CI; 42.2–54.9 months). The DSS rates at one, two, and five years were 94.9%, 81.1%, and 46.8%, respectively (Figure 2). The median OS was 46.8 months (95% CI; 40.5–53.1 months). The OS rates at one, two, and five years were 93.1%, 79.6%, and 43.2%, respectively, as shown in Figure 2.

Prognostic factors for survival. Univariate and multivariate analyses were performed on the prognostic factors (Table 3). In the multivariate model, we included the number of lesions, size of the lesions, fractionation, and BED. The sole statistically independent predictive factor for OS (p=0.037), DFS (p=0.008), and DSS (p=0.01) was the number of lesions.

Discussion

In this study, we report the first prospective cohort analysis in Slovenia of patients treated with SBRT for primary liver tumors and liver metastases. We observed minimal toxicity, favorable and durable LC, and satisfactory OS. Our results are consistent with those of other published studies, mostly retrospective and prospective phase 1–2 studies, as well as with a systematic review article, presented in Table 4 [28–35].

In our group, the majority of patients had colorectal carcinoma and in the majority of cases, only one lesion was treated, which is consistent with other series [29, 35].

In the German SBRT database, only one lesion was treated in 78.5% and 2–4 lesions in 21.5% of patients [29]. However, some authors also reported up to 6 [35] and even up to 14 treated lesions [36]. Prior to SBRT treatment, 41.9% of patients had received liver-targeted therapy, which is consistent with other authors [32].

Most lesions were treated with 3 fractions, the rest with 5 fractions. The median total dose was 54 Gy and the median BED_{10} was 151.2 Gy. A meta-analysis reported that researchers typically used a lower median SBRT dose of 48 Gy and BED_{10} of 100 Gy [35], while Italian authors used higher doses (75 Gy, BED_{10} 263 Gy) [32].

In our patient group, all local recurrences occurred within 1 year after completion of local treatment and the LC rates at

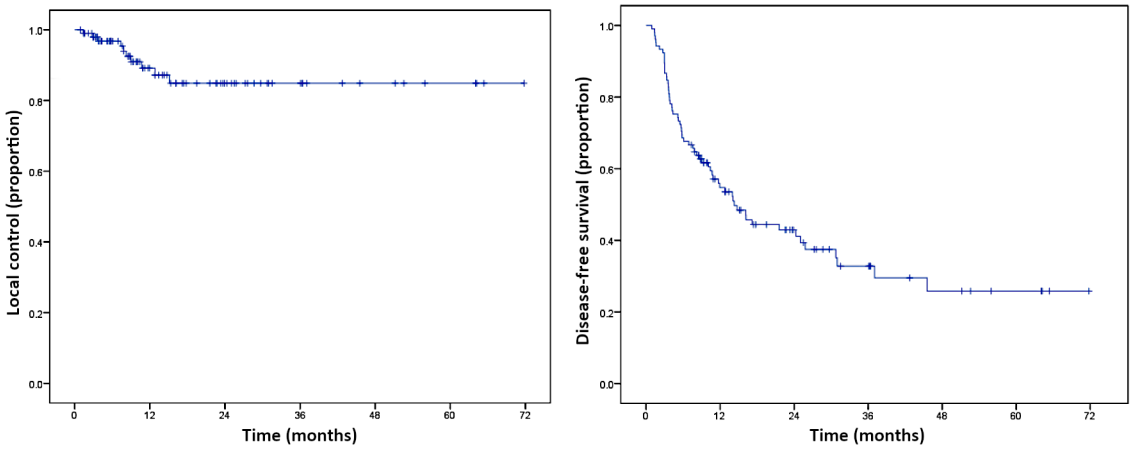

Figure 1. Local control (LC) and disease-free survival (DFS).

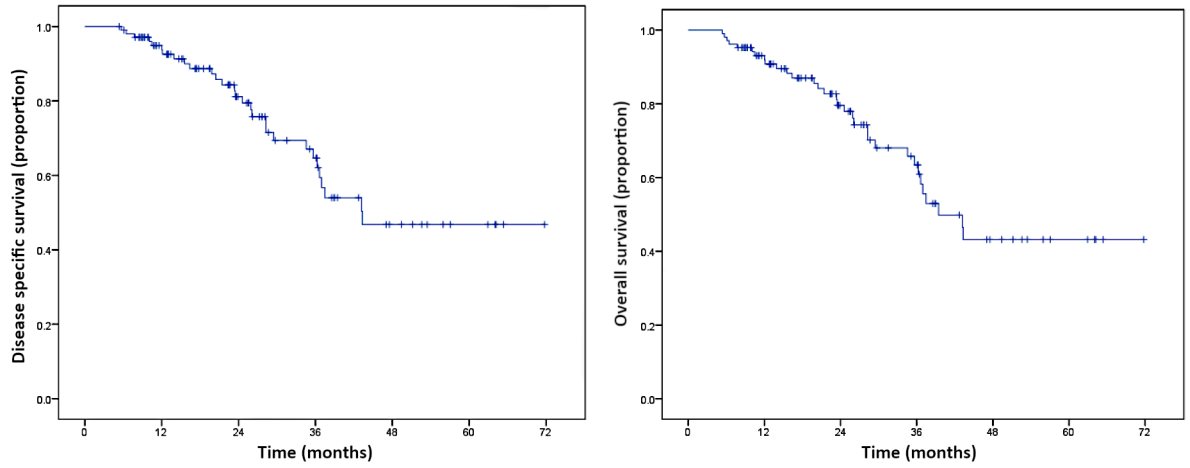

Figure 2. Disease-specific survival (DSS) and overall survival (OS).

Table 3. Prognostic factors for survival.

Factor	Group 1/ 2	Survival	% 1-year survival Group 1: 2		% 3-year survival Group 1: 2		p-value
Number of lesions	1 vs. >1	DFS	61	52.2	38.2	0	0.002
		DSS	98.8	86.2	66.1	60.1	0.026
Diameter of lesion	<4 cm vs. ≥4 cm	LC	92.9	77.4	90.1	67.8	0.029
		DSS	97.3	89.2	72	35.6	0.015
Fractionation	3 vs. 5	DFS	62.9	41.6	35.1	29.1	0.049
		DSS	96.8	91.4	72.9	47.4	0.038
		OS	95.3	89.2	71.8	46.2	0.047
BED (α/β = 10, BED10)	≥120 Gy vs. <120 Gy	LC	96.1	77.2	92.8	71.2	0.018
		DSS	96.7	92.1	74.4	47.9	0.036
		OS	95.1	90	73.2	46.8	0.047

Abbreviations: BED-biologically effective dose; LC-local control; DFS-disease-free survival; DSS-disease-specific survival; OS-overall survival, Gy-Gray

1, 2, and 3 years were 89.2%, 84.9%, and 84.9% compared to a systematic review and meta-analysis that reported pooled LC rates at 1, 2, and 3 years of 85%, 75%, and 68%, respectively [35]. For example, Italian authors using higher total SBRT doses and higher BED_{10} reported a 1-year LC of 94%, but their 3-year LC and reported OS were worse than in our study [32].

The 1-, 2-, and 5-year OS rates of our patients were generally better than those of other studies [28–29, 31–33, 35]. The reason for our better results could be the really careful selection of patients and strict adherence to the protocol. However, in a study comparing the efficacy of SBRT and RFA in recurrent small hepatocellular carcinoma, even better results were obtained. The 2-year OS rates were as high as 97.6% in the SBRT group and 93.9% in the RFA group [37].

In the univariate analysis, patients with a lesion of 4 cm in diameter or more and patients irradiated with a BED_{10} < 120 Gy had a worse LC. In addition, patients with more than 1 treated lesion had worse DFS. More than 1 treated lesion, a lesion diameter of 4 cm or more, the use of 5 fractions, and a BED_{10} of less than 120 Gy had a negative impact on DSS. Similar results were also reported by other researchers [28–30, 35]. Some of them reported a slightly altered disease volume or even a lower total dose or a BED of at least 100 Gy [35]. In addition, some researchers found that histology and motion management techniques may have an impact on LC and survival [29, 35].

In a meta-analysis, they found worse pooled LC rates at 1-, 2-, and 3-years of 80%, 66%, and 60% for colorectal metastases than for other histology types [35]. The radiosensitivity index was investigated by analyzing a 10-gene assay in metastatic liver lesions treated with SBRT. The authors indicated significant differences in radiosensitivity index according to histology, with gastrointestinal stromal tumors, melanomas, neuroendocrine, and colorectal adenocarcinomas being among the most radioresistant, compared to breast, lung, and pancreatic adenocarcinomas [38].

The German researchers also found that colorectal cancer metastases had a significantly worse control rate of treated metastases at one year (67%) than breast cancer (91%), NSCLC (88%), or other histologies (80%) [29]. Similar results have been reported by others [30, 33], while the

Table 4. Selected outcomes in published literature for SBRT of liver lesions.

Author, year	Design	No. pat./ No. met.	Fractionation	LC 1y/2y/5y	DFS 1y/2y/5y	OS 1y/2y/5y	Toxicity G3
Mendez Romero, 2020 [28]	P	515/668	3×18–20 Gy (36%) 5×11–12 Gy (25.5%) 8×7.5 Gy (31.8%) 12×5 Gy (6.7%)	87%/ 75%/ 68% (3y)	NR	84%/ 63%/ 44% (3y)	G3: 3.9 G4: 0.4 G5: 0.2
Andratschke, 2018 [29]	R	474/623	mBED102 Gy (before 2003) mBED134 Gy (after 2003)	76.1%/ 63.8%/ 55.7% (3y)	NR	70%/ 29% (3y)/ 15%	acute: <1% late: 1.4%
Mahadavan, 2018 [30]	R	427/568	m45 Gy (12-60) in m3 fractions	mLC 51m	NR	mOS 22m	0
McPartlin, 2017 [31]	P phase 1 and 2	51/93	mGTV 37.6 Gy in 6 fractions	50%/ 32%/ 26% (4y)	NR	63%/ 26%/ 9% (4y)	3 patients
Scorsetti, 2018 [32]	P phase 2	61/76	3×25 Gy (82%)	94%/ 78% (3y)/ 78%	NR	85.2%/ 31.1% (3y)/ 18%	1 patient
Clerici, 2019 [33]	R	202/268	3×25 Gy (57.9%)	92%/ 87%/ 84%	NR	79%/ 50%/ 15%	1 patient
Py, 2021 [34]	R	67/99	3×15 Gy (79.8%)	86.6%/ 72.4%/ 45.3%	81.9%/ 54%/ 13.1%	95.5%/ 81.4%/ 43.5%	3%
Franzese, 2024 [35]	Systematic review	3101/4437	/	85%/ 75%/ 68% (3y)	NR	79%/ 54%/ 37% (3y)	3%
Present study, 2024	P	105/133	mBED 151.2 Gy in 3–5 fractions	89.2%/ 84.9%/ 84.9%	54.7%/ 42.9%/ 25.8%	93.1%/ 79.6%/ 43.2%	0%

Abbreviations: R-retrospective design; P-prospective design; No. pat-number of patients; No. met-number of metastases; m-median; NR-not reported; BED-biologically effective dose; Gy-Gray; GTV-gross tumor volume; LC-local control; DFS-disease-free survival; OS-overall survival; G-grade

Dutch-Belgian registry of SBRT for liver metastases found no such differences [28]. We agree that the histological nature of the metastases determines the LC. Breast cancer and cholangiocarcinoma had a better LC in our analysis, followed by colorectal, HCC, and other carcinomas. GIST had the worst LC, but the sample was limited (5 patients). The poorer LC in colorectal carcinoma could be due to the heterogeneity of the tumor subtype and its higher radioresistance compared to breast cancer.

Radiotherapy centers have used different approaches and technologies for SBRT of the liver. Appropriate respiratory management is recommended. Traditionally, fiducial markers are used to guide the targeting of liver tumors during SBRT by breath holding on inspiration or expiration, an active breathing coordinate system, or abdominal compression. In our patients, we used an active breathing coordinate system or most commonly abdominal compression to restrict respiratory movement. The new approach to breath holding in SBRT utilizes real-time registration of the diaphragm. They reported that this new approach could improve the accuracy and precision of SBRT of the liver, thereby increasing treatment efficacy and reducing toxicity [39].

In our series, AEs occurred in 36 (34.3%) patients during radiotherapy, while 38 patients (36.2%) reported them after completion of treatment. No toxicity greater than grade 3 was observed. The German study reported that grade 1–2 toxicity was observed in 23% of patients and consisted mainly of fatigue, nausea, and diarrhea [29]. Grade 3 acute toxicity occurred in less than 1% of patients with gastric ulcers being the most serious AE. A meta-analysis reported that grade 3 and 4 treatment-related AEs occurred in 3%. Seven cases of RILD were reported by four investigators, 5/7 had grade 3 and 4 and 2/7 had grade 5 RILD [35]. Some investigators also reported hepatotoxicity-related deaths [28, 40]. One study indicated a correlation between GTV volume and maximum diameter with an increased risk of mortality [40], while another example involved a patient who received 60 Gy in three fractions to two adjacent metastases that had previously undergone RFA in segments 1 and 4a [28]. The central bile duct was located within the PTV and received

a maximum dose of 69.6 Gy. The patient developed biliary stenosis and died 1 year after treatment [28]. In general, toxicity is low and acceptable.

A limitation of our study is the rather small number of included patients with various tumor localizations to compare them with each other. In general, it would be useful to include a larger number of patients with a longer observation period.

In conclusion, SBRT has excellent disease control and survival rates with minimal toxicity, which is confirmed by our results.

Supplementary information is available in the online version of the paper.

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Stereotactic body radiation therapy for liver metastases and primary liver tumors: treatment results and toxicity

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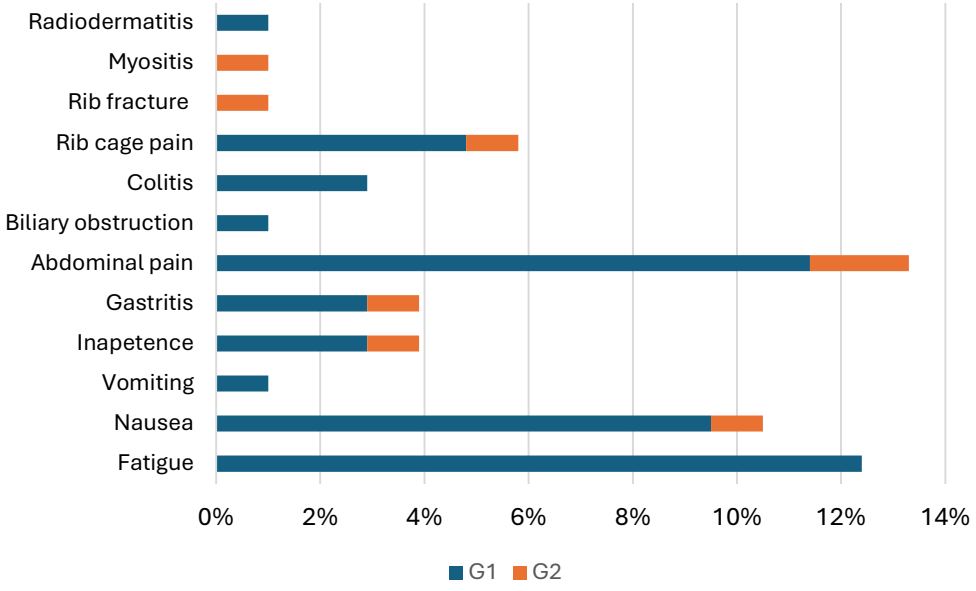
Supplementary Information

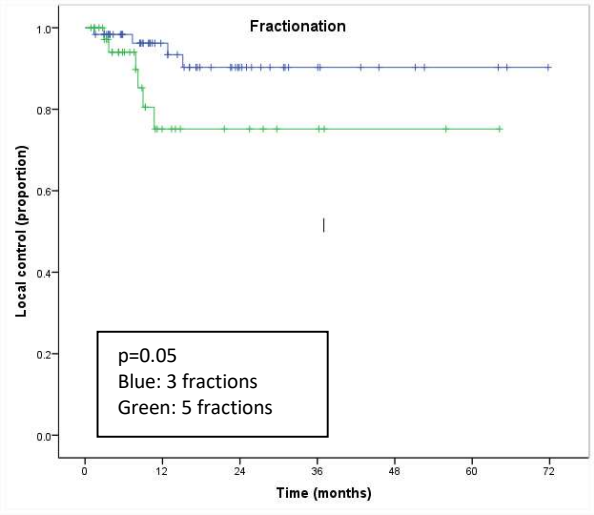


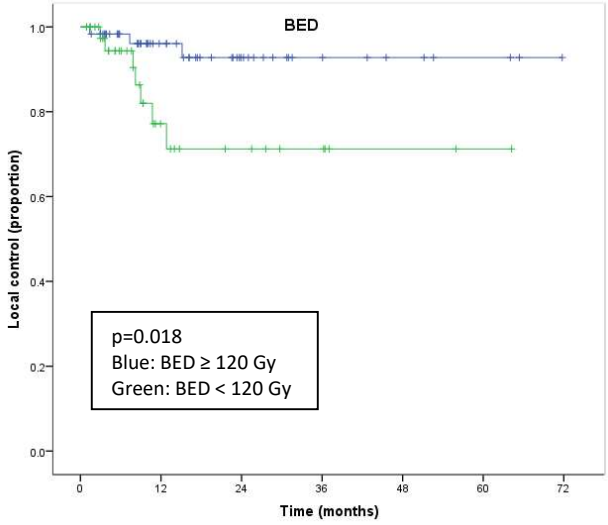
Supplementary Figure S1. Acute side effects after completion of irradiation. Abbreviation: G-Grade

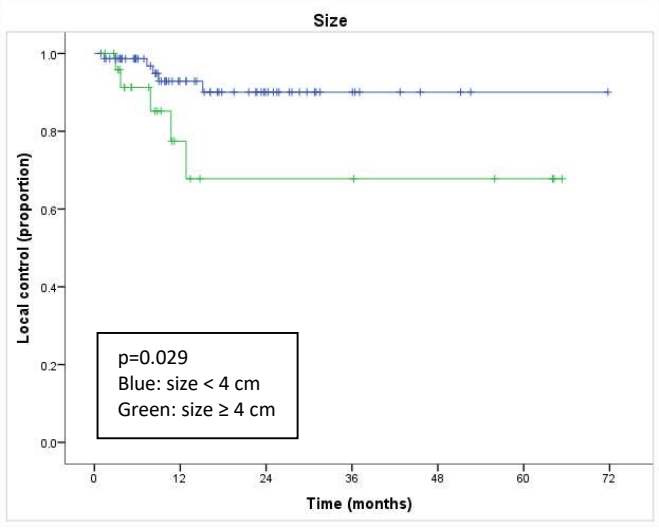
Supplementary Table S1. Acute toxicity assessed in laboratory tests.

Laboratory test/Grade (%)	0	1	2	3	4
AF	67.6	29.5	2.9	0	0
Gamma GT	49.5	37.1	7.6	5.7	0
ALT	68.6	29.5	1.9	0	0
AST	58.1	41	1	0	0
Hyperbilirubinemia	86.7	11.4	1	0	0

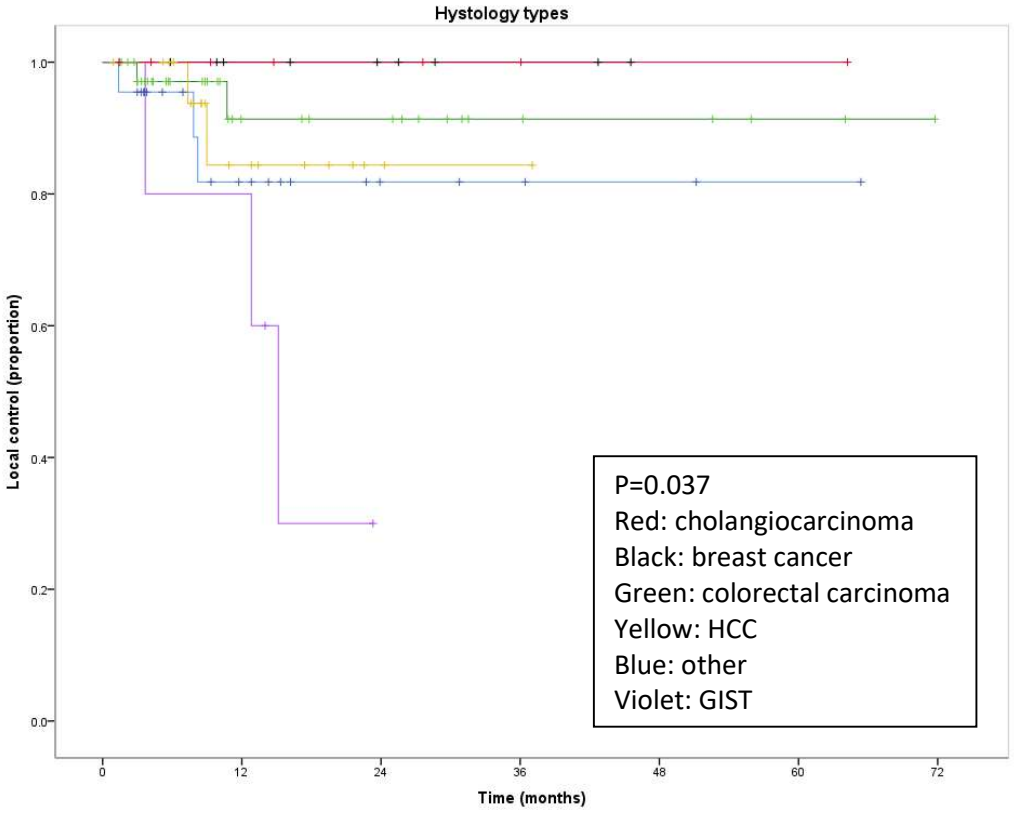
Abbreviations: AF-alkaline phosphatase; Gamma GT-gamma-glutamyl transferase; ALT-alanine transaminase; AST-aspartate transaminase







Supplementary Figure S2. Local control by fractionation, biologically effective dose (BED) and lesion size. Abbreviation: LC-local control



Supplementary Figure S3. Local control by different histology types. Abbreviations: LC-local control; HCC-hepatocellular carcinoma; GIST-gastrointestinal stromal tumor