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Image guided SBRT for multiple liver metastases with ExacTrac® Adaptive Gating

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ABSTRACT

Aim: To report the outcome and toxicity of sequential stereotactic body radiotherapy (SBRT) for multiple liver metastases in patients treated with ExacTrac Adaptive Gating.

Background: In selected patients with a limited number of liver metastases, SBRT has been evaluated as a safe and effective treatment, with minimal toxicity and high rates of local control.

Materials and methods: From April 2008 to October 2013, 21 patients with multiple (3–14) liver metastases ($n = 101$) were treated sequentially with SBRT at our institution. Maximum tumor diameter was 7.5 cm. Prior to treatment, internal markers were placed inside or near the tumor. CT or PET-CT simulation was used for the definition of gross tumor volume (GTV). Median planning target volume was 32.3 cc (3.6–139.3 cc). Treatment consisted of 3 fractions (12–20 Gy/fraction) or 5 fractions (10 Gy/fraction), prescribed to the 90–95% of the PTV volume. Daily intra-fraction image guidance was performed with ExacTrac Adaptive Gating. Regular follow-up included CT or PET-CT imaging.

Results: After a median of 23.2 months, the estimated local control rate was 94.4%, 80.6%, 65% and 65% after 1, 2, 3 and 4 years; the median overall survival was 62 months (95% CI 49.12–74.87) and the actuarial survival reached at 60 months was 57.6%. The univariate data analysis revealed that only primary histology other than colorectal adenocarcinoma was shown as an independent significant prognostic factor for local control ($p = 0.022$). Number of treated metastases did not modify significantly the overall survival ($p = 0.51$). No toxicity higher than G3 (1 patient with chest wall pain) and no radiation-induced liver disease were observed.

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Conclusions: Sequential SBRT with ExacTrac Adaptive Gating for multiple liver metastases can be considered an effective, safe therapeutic option, with a low treatment-related toxicity. Excellent rates of local control and survival were obtained.

1. Background

The liver is a common site of metastases from most solid malignancies. Improvements in systemic therapy, including chemotherapy and molecularly targeted agents, have led to improved survival, although they rarely eradicate metastases in a permanent way. In an "oligo-metastatic" scenario (patients with single or limited metastases), local therapies may improve overall survival.[1] For colorectal liver metastases, resection series have yielded 5-year survival rates of 50–60%,[2] leading to a cure of selected cases. However, most patients with liver metastases are unfit for surgery because of unfavorable tumor factors or their poor general conditions, and treatment strategies focusing on effective local treatment may be indicated after proper patient selection.

Historically, radiation therapy has had a limited role in the treatment of hepatic metastasis because of the low tolerance of the liver to radiation. A major concern is the risk of radiation-induced liver disease (RILD).[3] However, the liver obeys the parallel architecture model of radiobiology and the risk of RILD is proportional to the mean dose of radiation delivered to normal liver tissue; therefore, it becomes safe to treat small hepatic lesions with high doses, limiting the mean dose to normal liver.[4]

In the past decade, improvements in tumor imaging, radiation therapy planning, delivery, and motion management, have contributed to the development of stereotactic body radiation therapy (SBRT). Intensification of tightly focused radiation to small lesions, while significantly limiting dose to the surrounding tissues, in either a single or limited number of dose fractions have resulted in the delivery of a highly biological effective dose. SBRT requires a high level of accuracy, and recommendations and treatment quality control guidelines have been established.[5,6]

For liver SBRT, integration of imaging (CT, MRI, PET-CT) is required in order to properly define the metastases, as is highly conformed dosimetry to further minimize radiation dose to healthy liver and surrounding tissues. Due to uncertainty of liver positioning during the breathing, the effectiveness and safety of SBRT depends on the accuracy to treat a moving organ. Various image-guided methods, the use of internal markers, breathing control and intra-fraction control of tumor position (Gating or Tracking) increase SBRT precision, allowing the delivery of cytotoxic high dose to the metastases, while maintaining whole-liver doses within acceptable limits.[7,8]

The feasibility and potential utility of SBRT in selected patients with liver metastases, has been evaluated with encouraging results. SBRT has resulted as a safe and effective treatment, with minimal toxicity and high rates of local control.[9–16] Therefore, it can be considered a noninvasive treatment to deliver ablative treatments.[17–19] Most of the retrospective and prospective clinical experiences and studies of liver metastases (using high-dose SBRT) have generally selected patients with a limited number of lesions. However, there are also patients with more than 3 liver metastases or patients with liver oligo-progression that in the course of their disease could be treated safely and benefit from ablative local treatments with sequential SBRT, thus improving their metastatic sites, decreasing morbidity and prolonging survival.

2. Aim

The purpose of the present article is to report the efficacy and safety of high-dose sequential SBRT in oligo-metastatic patients with multiple liver metastases (3 or more), not eligible for surgery. Patients were treated with Novalis ExacTrac Adaptive Gating, based on the accuracy of the irradiation of the lesions in a selected area of the respiratory cycle, with an intra-fraction control of the tumor position guided by internal markers.

3. Materials and methods

3.1. *Eligibility*

From April 2008 to October 2013, 21 oligo-metastatic patients with multiple liver lesions (3 or more), not eligible for surgery after discussion in a multidisciplinary tumor-board, were treated with high-dose SBRT, with Novalis ExacTrac Adaptive Gating, at our institution.

Pretreatment evaluation in all patients consisted of physical examination, laboratory tests, including blood counts and liver enzymes, computed tomography (CT) scan of the thorax and abdomen with i.v. contrast and in selected patients whole body positron emission tomography (PET) with [^{18}F]-fluorodeoxyglucose (FDG) on a dedicated combined PET/CT scanner.

Inclusion criteria for the analysis were: patients with 3 or more liver metastases considered not suitable for surgery, because of being technically or medically inoperable or because of patient refusal; minimum age 18 years; Karnofsky Performance Status $\geq$70; no evidence of untreated or progressive gross disease outside the liver; maximum tumor diameter less than 8 cm, normal liver volume >1000 cm^3 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 amynotransferase (ALT) less than 3 times the upper limit of normal). Chemotherapy was allowed 14 days before or after SBRT and written informed consent was required.

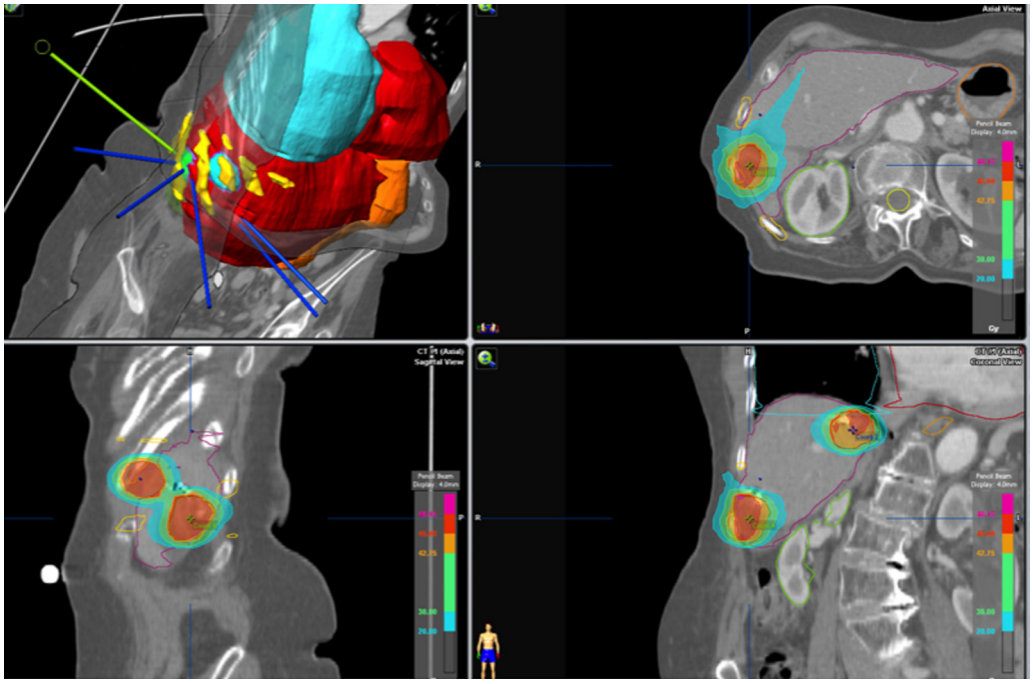

Fig. 1 – Treatment plan for a patient treated with stereotactic body radiation therapy for multiple liver metastasis. Visualization of dose distribution on the planning target volumes.

3.2. SBRT

Prior to treatment, in order to use them as a point of reference and measure for ExacTrac Adaptive Gating, 1–3 fiducial internal markers (Visicoil®0.75 mm × 30 mm) were implanted into the liver, guided by CT scan, with local anesthesia and using a preloaded needle.

CT or [^{18}F]-FDG PET-CT scans, with i.v. contrast, were performed with breath-holding, (3 mm slice thickness), and with external markers located on the patient's surface. The external markers were used as a reference of position and later tracking with the infrared cameras of the ExacTrac system. Patients were immobilized with a custom-formed vacuum cushion or wing board. No 4D CT scan was performed.iPlan (Brainlab^{TM}) v3 and v4 were used for contouring and planning. Planning CT images were in some cases co-registered with magnetic resonance imaging (MRI) or [^{18}F]-FDG PET-CT for a better identification of the gross tumor volume (GTV). The clinical target volume (CTV) was defined as equal to the GTV. The planning target volume (PTV) was generated from either the GTV-CTV by adding an overall isotropic margin of 5 mm, for attending the set-up margin (3 mm) and the internal margin (2 mm). No internal target volume (ITV) was defined.

SBRT (Fig. 1) was delivered using multiple coplanar beams and 3-D highly conformal dosimetry.[6] IMRT (Intensity modulated radiation therapy) was performed in 5 patients (23.8%) to avoid adjacent organs at risks (OARs).

The prescripted dose was 36 Gy, 45 Gy or 60 Gy in 3 fractions of 12 Gy, 15 Gy or 20 Gy, respectively, separated by at least 48 h, or 50 Gy in 5 daily fractions, prescribed to the 90–95% of the PTV volume. Previously reported critical dose volume model was applied to fulfill the constraints for organs at risk (OAR): V15 Gy (volume receiving 15 Gy) < (total liver volume < 700 cm^3) for healthy liver, D0.1 cm^3 for spinal cord <18 Gy (dose at a volume of 0.1 cm^3 should be <18 Gy), V15 Gy <35% for both kidneys, V21 Gy <1% for the duodenum, small bowel, esophagus, and stomach, V30 Gy <1% for the heart and D30 cm^3 <30 Gy for the ribs. In the case of an overlap between the PTV and the duodenum or stomach, the priority was given to the OAR. Due to liver dose tolerance limitation, no more than 4 liver metastases were treated at the same time.

Patients were treated with SBRT in a Novalis (Brainlab^{TM}), a 6MV mono-energetic LINAC, adapted to stereotactic treatments. Intra-fraction image guided radiation therapy (IGRT) was performed with the Novalis ExacTrac Adaptive Gating. During patient set-up, the external markers on the patient's skin were tracked with the ExacTrac infrared cameras for automatic patient positioning (guided by the Novalis robotic 6D coach), and for tracking the respiratory cycle of the patient during the treatment. Three pairs of ExacTrac stereoscopic X-rays localized the internal marker subrogated to the external markers, in the different phases of the respiratory cycle (inspiration, gating reference level and exhalation). The location of the internal marker was correlated with the PTV isocenter, in order to quantify the tumor motion and determined a gated area ("beam on area") for irradiation. Beam on area never exceeded 2 mm above and 2 below the gating reference level, due to the prior established PTV isotropic margin of 5 mm, taking into account the 3 mm set-up margin. Intra-fraction stereoscopic X-rays were performed during the treatment, in order to verify the position of the markers and the accuracy of the irradiation during the "beam on area".

3.3. Study end points and follow-up

The primary end-point for this retrospective study was to assess infield local control. Secondary end points were to define the value of CT and [^{18}F]-FDG PET-TC for the assessment of tumor response, radiation treatment-related toxicity, overall survival and progression free survival.

Patients were monitored by physical examination and a basal blood, coagulation and serum liver parameters were analyzed at the beginning of the SBRT. During treatment, all patients were monitored for acute treatment related toxicity. After conclusion of SBRT, patient's follow-up included an interview, clinical exams and blood tests one month after the treatment and every 3 months.

Acute and late toxicity were scored by the Common Terminology Criteria for Adverse Events (CTCAE version 3.0). Any increase in grade from baseline was considered toxicity related to the treatment.

Assessment of tumor response was based evaluated, with CT-iv contrast scan, 3 months after radiotherapy and every 3–6 months, based on European Organization for Research and Treatment of Cancer Response Evaluation Criteria In Solid Tumors (EORTC-RECIST) criteria version 1.1.[20,21] Complete response (CR) was defined as disappearance of all target lesions; partial response (PR) as at least a 30% decrease in the sum of diameters of target lesions; and progressive disease (PD) as at least a 20% increase in the sum of diameters of target lesions. Progressive disease was scored depending on whether it was intra- or extrahepatic. In selected patients with more than 4 liver metastases or sequential SBRT treatments[^{18}F]-FDG PET-TC- iv contrast scans were performed at 3 months, 6 months and 12 months for assessment of tumor response was based also on Choi criteria and PERCIST criteria.[22]

3.4. Statistical considerations

All enrolled patients were included in the statistical evaluation. V.20 Statistical Packege for Social Science (SPSS Inc. Chicago, IL), was used for the statistical analysis. Actuarial LC and OS curves were generated by using the Kaplan–Meier method and Log Rank Test was used for the univariate comparatives. When differences were found, Cox proportional hazards regression was used to measure the HRs. The results were considered statistically significant when $p \leq 0.05$.

4. Results

This ongoing study included 21 enrolled patients with 101 liver metastases from solid tumors treated between April 2008 and October 2013. The median follow-up was 23.2 months (range 3–66 m). Baseline patients and treatment characteristics are summarized in Tables 1 and 2. No patient received any prior directed liver therapies. The mean D95% was 97.9% (range 88.8–100%) for PTV. The Mean GTV diameter was 3.4 cm (1.14–7.5 cm). The Mean PTV volume was 32.6 cc (3.6–139 cc). The Mean liver volume was 1.344.3 cc (range 747–2.223 cc).

Seventy-seven lesions (70.4%) received 48–60 Gy (3 × 15–20 Gy BED_{10}, >120 Gy), 6 lesions (5.9%) 50 Gy (5 × 10 Gy, BED_{10} = 100 Gy) and 24 metastasis (23.8%) 36 Gy (3 × 12 Gy, BED_{10} < 100 Gy).

Table 1 – Patient characteristics.

Age	
Mean 64.14	(Range 42–80)
Sex	
Male 12 (57%)	Female 9 (43%)
Number of lesions per patient	
3	6 patients (28.6%)
4	8 patients (38.1%)
5	3 patients (14.3%)
6	1 patient (4.8%)
7	1 patient (4.8%)
9	1 patient (4.8%)
14	1 patient (4.8%)
No. of internal markers	
1	6 patients (28.6%)
2	13 patients (61.9%)
3	2 patients (8.5%)
Histology	
Colorectal Adenocarcinoma	13 (61.9%)
Breast cancer	2 (9.5%)
Pancreas cancer	2 (9.5%)
Others	4 (19.1%)
Lesion size	
<5 cm	86 (85.1%)
>5 cm	15 (14.9%)
Extra-hepatic disease	
No 19 (90.5%)	Yes 2 (9.5%)
Systemic treatments	
Chemotherapy 1 line	7 (33.3%)
Chemotherapy 2 lines	8 (38.1%)
Chemotherapy ≥3 lines	6 (28.6%)

Table 2 – Treatment characteristics.

Lesions	Fractions	Total Dose	Dose per fraction
24 (23.8%)	3	36 Gy	12 Gy
45 (44.6%)	3	45 Gy	15 Gy
1 (1%)	3	48 Gy	16 Gy
3 (3%)	3	54 Gy	18 Gy
22 (21.8%)	3	60 Gy	20 Gy
6 (5.9%)	5	50 Gy	10 Gy

Three patients (14.3%) were treated with one single SBRT course, and 18 patients (85.7%) received a median of 2 sequential SBRT treatments (range: 2–8). The median number of lesions treated each course was 2 (range: 1–4). Median time between two consecutive SBRT treatments was 8 months (range: 3–29), and the elapsed time between the first and the last treatment was 15 months (range 3–51).

4.1. Local control

The radiographic crude response rate of the radiated lesions was: 42.6% complete response (n = 43), 29.7% partial response (n = 30) and 6.9% stable disease (n = 7). In-field progression was observed in 21 lesions (20.8%), mean time 19 months (Table 3).

Actuarial local control rates for treated lesions were 94.4%, 80.6%, 65% and 65% at 12, 24, 36 and 48 months respectively, the median for local control has not been reached yet (Fig. 2).

Table 3 – Patterns of treatment response.

In-field response	Lesions no./(%)
Complete response	43 (42.6%)
Partial response	30 (29.7%)
Stable disease	7 (6.9%)
Progressive disease	21 (20.8%)

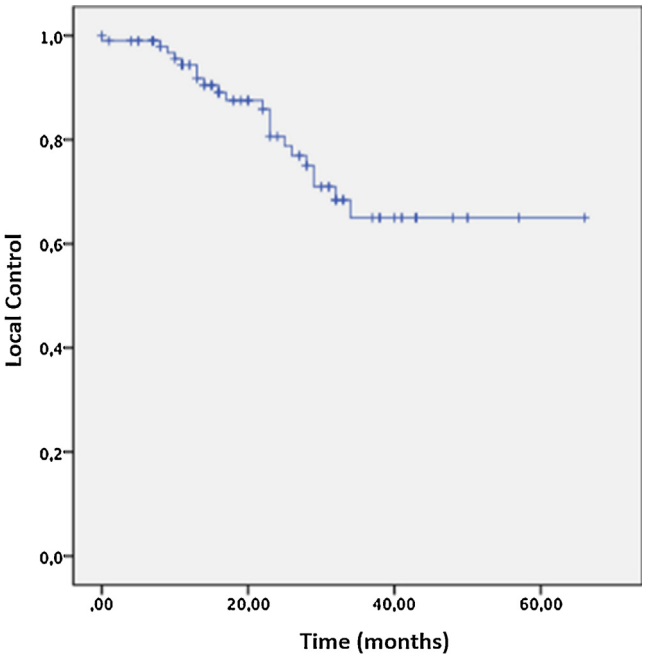

Fig. 2 – In-field local control after SBRT for multiple liver metastases.

The univariate analysis showed that only metastases from colorectal adenocarcinoma showed significantly poor local control when compared with other primary tumors ($p = 0.022$; HR 0.26), having 3.8 more probabilities of local relapse (Fig. 3).

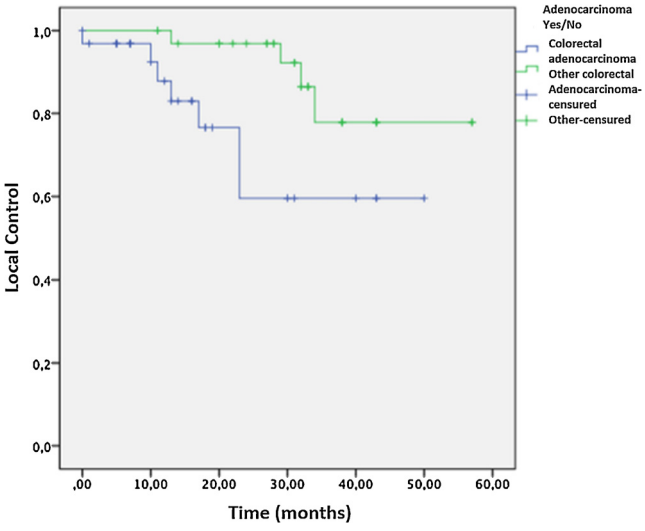

Fig. 3 – Local control according to type of lesion, colorectal adenocarcinoma versus other primary tumors.

Table 4 – Patterns of failure.

Site of failure	Patients no./%
No progression after SBRT	4 (19%)
Progressive disease after SBRT	17 (81%)
Intra-hepatic progression	12 (70.5%)
Extra-hepatic progression	5 (29.5%)

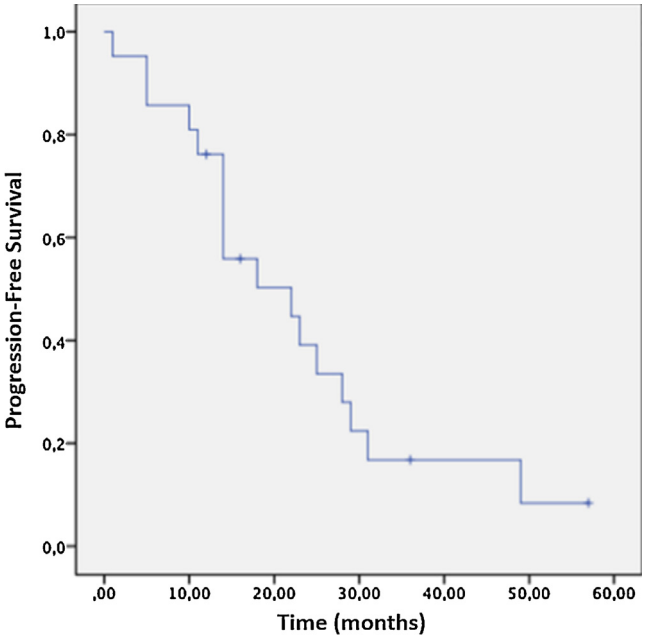

Fig. 4 – Progression free survival after SBRT for multiple liver metastases.

4.2. *Assessment of tumor response*

A sub-analysis of 20 liver metastasis on complete response after 2 years of follow up were evaluated, both by CT and [^{18}F]-FDG-PET-TC scans. Imaging studies were performed at 3 months, 6 months and 12 months after SBRT. At contrast-enhanced CT scans, both size (cm) and attenuation coefficient (UH) of the lesions were evaluated. At PET-TC scans [^{18}F]-FDG uptake (SUV) of the lesion was evaluated. The comparative of both techniques, showed that at 3 and 6 months [^{18}F]-FDG-PET-CT was much more sensitive to detect complete response (100% with RECIST 1.1 criteria), than CT (50% with RECIST 1.1 criteria and 90% with Choi criteria), and at 12 months the sensitivity of CT to assess response increased, reaching 80% following RECIST 1.1 criteria and 100% Choi criteria.

4.3. *Progression free survival*

At the time of the analysis, 4 patients (19%) were free of disease and 17 patients (81%) had progressive disease, 12 (70.5%) with intra-hepatic progression and 5 (29.5%) with extra-hepatic disease (Table 4). The median progression free survival was 22 months (95% CI 6.1–37.8). Estimated progression free survival at 12, 24 and 36 months was 76.2%, 39.1% and 16.8%, respectively (Fig. 4).

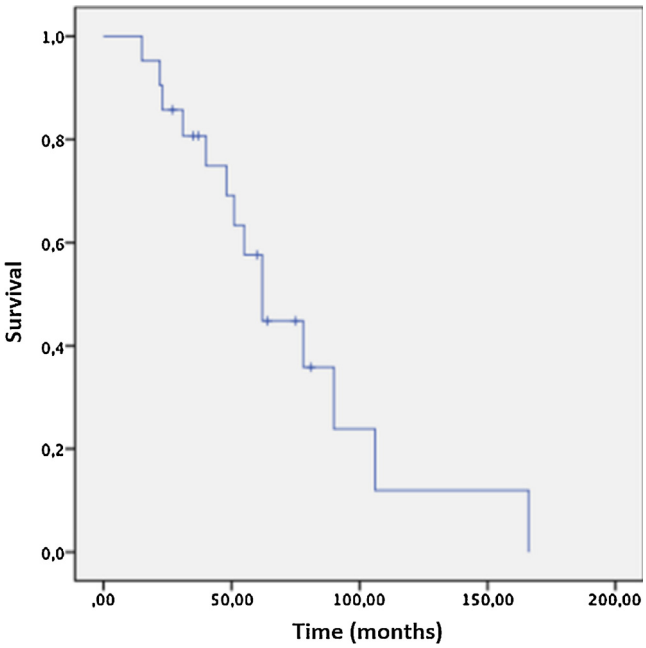

Fig. 5 – Overall survival after SBRT for multiple liver metastases.

4.4. *Survival*

At the time of analysis, 14 patients (66.6%) had died, of these, 9 (64.3%) had died of disease-specific causes, whereas 5 (35.7%) of other causes.

The median OS rate was 62 months (95% CI 49.12–74.87). Actuarial survival at 12, 24, 36 and 60 months was 95%, 85.7%, 80.7% and 57.6%, respectively (Fig. 5).

Number of treated metastases did not modify significantly the overall survival ($p = 0.51$) nor did the other analyzed factors (age, sex, histology of the primary tumor, SBRT doses, number of SBRT treatments, other metastases, or systemic treatment).

4.5. *Toxicity*

The treatment was very well tolerated with only grade 1 acute side effects, predominantly mild fatigue during the days of treatment. Due to the puncture procedures for the implantation of internal markers, one case of liver peri-hepatic hematoma grade 1 was reported.

No relevant long-term complications (grade 4 or 5) were reported. Only 2 patients experienced late toxicity with grade 1 and 3 chronic chest wall pain that regressed with conservative treatment.

5. Discussion

The liver is a common site of metastases from most solid malignancies and in many cases it is the only site. Chemotherapy and new molecularly targeted agents, have led to improved survival, although surgical resection is still considered the gold standard treatment to eradicate liver metastases. However, most patients with liver metastases are unfit for surgery because of unfavorable tumor factors or their poor general conditions and in a "oligo-metastatic" scenario, with single or limited metastases, local ablative therapies may improve overall survival.

Historically, radiation therapy has had a limited role in the treatment of liver metastasis, but in the last decade, advances in tumor imaging, radiation therapy planning, delivery, and motion management, have contributed to improve the accuracy of the treatments and to the development of SBRT, thus allowing the ablative irradiation of liver lesions and limiting the dose to healthy liver and other surrounding organs.

However, for moving lesions such as liver lesions, problems with accuracy still remain and assessment of tumor motion in liver can be approached in different ways. Quantification of tumor motion can be measured and an ITV (internal target volume) can be deduced using a 4D-CT scan during the different respiratory phases. However, it has been found that respiratory motion can often range up to 50 mm, meaning the ITV deduced from extreme respiratory phases is sometimes overestimated, resulting in too much healthy liver tissue included in the PTV and unnecessarily irradiated.[10–13] In the liver the major dose-limiting concern is the risk of radiation-induced liver disease (RILD), proportional to the mean dose of radiation delivered to normal liver tissue and this considerably limits the number of patients that can benefit from SBRT due to the number or size of their liver lesions.

We retrospectively analyzed a subgroup of patients treated of multiple (3 or more) liver metastases with ExacTrac Adaptive Gating, irradiating the tumor during a selected phase of the respiratory cycle, and verifying tumor position in real time with ExacTrac stereoscopic X-rays in an effort to decrease the PTV margin and save as much healthy liver and surrounding organs as possible.

Previous works have demonstrated the efficacy and security of SBRT for the treatment of liver metastases (Table 5). The University of Heidelberg[9] reported one of the earliest prospective studies to use single fraction SBRT (dose, 14 to 26 Gy) for the treatment of liver metastases, with local control rate of 66% at 18 months.

Rochester University[10] reported the experience with SBRT in 69 patients with a total of 174 metastases (20 patients with colorectal liver metastases) treated with a median total dose of 48 Gy in 8 or more fractions. Local control rate was of 76% and 57% at 10 and 24 months respectively.

A prospective, multicenter phase I/II study[11] evaluated 47 patients with 63 liver metastases, dose was escalated from 36 Gy to 60 Gy in three fractions, in 6 Gy increments, without dose-limiting toxicity [11]. Lesions with maximum diameter of 3 cm or less achieved a 2-year local control of 100% compared with 77% for lesions greater than 3 cm ($p = 0.015$).

Chang[12] reported the results of the study of a pooled patient cohort treated with SBRT for colorectal liver metastases (1–4 lesions, 1–6 fractions of SBRT), including 65 patients with 102 lesions from 3 institutions. The median follow up was 1.2 years. Total dose, dose per fraction and BED all correlated with local control. The estimated dose range needed for 1-year local control >90% was 46–52 Gy in 3 fractions.

Scorsetti[13] in the phase II trial reported 61 patients with 76 lesions treated with 3 fractions up to 75 Gy; they observed excellent local control and survival at 1 year (both >80%).

Table 5 – Clinical studies in the literature studying SBRT in liver metastases.

Ref.	Design	N° patients	SBRT dose	Toxicity	Outcomes
Herfarth, 2001[9]	Phase I–II	35	Dose escalation 14–26 Gy (in 1 fraction)	No significant toxicity	1-yr, LC 71% 18-mo, LC 67% 1-yr OS 72%
Katz, 2005	Retrospective	69	48 Gy (in 8 or more fractions)	No grade ≥3 toxicity	10-mo, LC 76% 24-mo, LC 57%
Rusthoven, 2009[11]	Phase I-II	47	Dose escalation 45–60 Gy (in 3 fractions)	No RILD Grade ¾ toxicity: 2%	1-yr, LC 95% 2-yr, LC 92% Median survival 20.5 months
Chang, 2011[12]	Prospective multicentric	65	46–52 Gy (in 3 fractions)	Grade ¾ toxicity: 3%	1-yr, LC >90%
Scorsetti, 2013[13]	Phase II	61	75 Gy (in 3 fractions)	No RILD 1 patient Grade 3 (Chest wall pain)	1-yr, LC 94% 22-mo, LC 90.6%
Berber, 2013[14]	Multicentric database	153	37.5 ± 8.2 Gy (in 5 ± 3 fractions)	Grade ¾ toxicity: 3%	1-yr, LC 62% 1-yr OS 51%
Hernando, 2013[18]	Retrospective	47	36–60 Gy (in 3 fractions)	No grade ≥3 toxicity	2-yr, LC 87.3%
Andratschke, 2015[16]	Retrospective	74	5–12.5 Gy per fraction (in 3–5 fractions)	No grade ≥3 toxicity	1-yr, LC 74.7% 2-yr, LC 48.3% 3-yr, LC 48.3%

In a recent multicenter database from 4 academic medical centers in the United States[14] the total dose was 37.5 ± 8.2 Gy in 5 ± 3 fractions, with a median follow-up of 25 months, they reported on 153 patients (363 tumors) a local control rate of 62% with one-year survival of 51%. Grade 3 and 4 toxicity was observed in 3% of patients.

We previously reported our initial experience on the treatment of lung and liver lesions with Gating SBRT; in the liver metastases set,[15] 47 patients with 74 liver metastases (48 colorectal liver metastases) where treated. Dose prescription was 36–45–60 Gy in three fractions. Median follow up was 13.6 months and 2-year local control rate was 87.3%. No Grade 3 toxicity was described.

Andratschke,[16] in a recent publication reported the experience with SBRT in 74 patients with 91 liver metastases, treated with 5–12.5 Gy per fraction in 3–5 fractions, with a median follow-up of 15 months. They reported a local control rate of 74.7%, 48.3% and 48.3% at 1, 2 and 3 years. Only the BED to GTV was a significant factor for local control in multivariate analysis, with 100% of local control in those receiving minimal BED > 120 Gy to GTV. Median overall survival was 25 months, GTV volume was a significant prognostic factor for overall survival in multivariate analysis. No acute Grade 3–5 and no late Grade 4–5 toxicity was observed.

Here we report a long-term follow-up group of patients with multiple liver metastases (3 or more) treated with sequential SBRT from 2008 to 2013 (median follow up: 23.2 months). Similar to other published studies, the local control was very high, 94.4%, 80.6%, 65% and 65% at 12, 24, 36 and 48 months, respectively, even considering that we treated more lesions (71.4% of the patients had more than 3 metastasis) and with a considerable size (14.9% > 5 cm). Local control was mainly influenced by lesion size and radiation dose in other studies. In our patients we only found colorectal adenocarcinoma histology as a predictive factor for local control in univariate analysis.

In our sub-analysis for assessment of tumor response in 20 liver metastasis on complete response after 2 years of follow up, with CT and [^{18}F]- PET-TC scans, we found that 18-FDG-PET-CT was much more sensitive to detect complete response than CT on the first 6 months, probably due to early radiological changes induced by ablative doses of irradiation, and in certain patients [^{18}F]-FDG PET-CT may be necessary for the confirmation of a possible local control, although this data need to be confirmed in further studies.

As expected, when we analyzed patients with multiple liver metastases, our crude PFS rate was low 19%, only 4 patients were free of disease after SBRT. The median PFS was 22 was months. While 29.5% of the patients developed metastases in other organs, the majority (70.5%) progressed with new liver metastases that were treated sequentially with new courses of SBRT whenever possible. Eighteen patients (85.7%) received a median of 2 sequential SBRT treatments (range: 2–8) and the median time between two consecutive SBRT treatments was 8 months (range: 3–29), reaching long periods of time between SBRT courses (median of 15 months, range 3–51).

The overall survival reached a median time of 62 months, with estimated survival at 5 years of 57.6%. This overall survival is longer than achieved in other studies, this could be explained by the selection of patients for sequential SBRT treatments that were performed during their disease evolution. To our knowledge, this sequential SBRT courses have not been referred previously for the management of liver metastases.

Although further studies also need to be done to confirm these results, the toxicity that we found with sequential SBRT treatments for multiple liver lesions are very acceptable and similar to those published in the literature and no relevant long-term complications (grade 4 or 5) were reported. The implantation of internal markers in the liver did not represent a major concern and gave us the accuracy for treating these patients with the Exactrac Adaptive Gating.

6. Conclusions

Our findings confirm that SBRT provides an effective local ablation with low toxicity profile even in patients with multiple liver metastases in whom disease control and survival

can be prolonged with sequential SBRT treatments. Exactrac Adaptive Gating with intra-fraction tumor motion control have demonstrated to be a safe and accurate SBRT technique for liver metastases treatment. Prospective controlled trials are needed to confirm this results.

Conflicts of interest

None declared.

Financial disclosure

None declared.

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