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Stereotactic Ablative Radiotherapy to Treat Colorectal Liver Metastases: Ready for Prime-Time?

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Abstract

Background: Stereotactic Ablative Radiotherapy (SABR) is a non-invasive treatment option for patients with Colorectal Liver Metastases (CRLM) ineligible for resection or thermal ablation. The aim of our study was to evaluate local control, disease progression, toxicity, complications and survival after SABR of CRLM. We also discuss the place of SABR in the treatment algorithm of CRLM.

Methods: Patients with CRLM, ineligible for resection or thermal ablation and suitable for SABR, were included in our database and retrospectively analyzed. Patients with oligometastases <5 cm without the presence of other organs in the target area are eligible for SABR. Follow-up imaging was conducted at 3 and 6 months following SABR and 6-monthly thereafter. Total delivered dose per lesion was 54-60 Gy, divided over 3-12 fractions, depending on the dose constraints of normal tissues.

Results: Ten patients with 13 lesions were treated with SABR. Complete local control was achieved in eight patients with 11 lesions, with a median follow-up of 20.4 months (range 7-38). Two patients showed possible local progressive disease after 12 and 25 months. No toxicity > grade 2 as a result of treatment was reported. Eight patients had died at time of analysis; median survival was 26 months.

Conclusion: SABR of CRLM is safe, feasible and effective in achieving local control in patients ineligible for resection or thermal ablation. Although SABR is currently offered in a late and often palliative stage, it deserves a higher profile as a possible local treatment option and its place in the treatment algorithm should be re-evaluated.

Keywords: Liver neoplasms/radiotherapy; Liver neoplasms/secondary; Radiotherapy/adverse effects; Stereotaxic techniques; Liver/radiation effects

Introduction

Colorectal cancer is the second leading cause of cancer-related death in the USA and Europe [1]. Approximately 40-60% of the patients develop Colorectal Liver Metastases (CLRM) within 2 years of primary diagnosis, making the liver the most frequent, and often only, metastatic site. CRLM are a common source of cancer morbidity and mortality [2].

Resection has long been regarded as the only curative treatment option in patients with CRLM, even with limited extrahepatic disease. However, 70-80% of patients are ineligible for surgery due to tumor size, site or number, liver dysfunction and/or co-morbidity [3,4]. The 5-year survival rate following resection of CRLM varies from 24% to 58%, depending on the number of lesions resected [5-8].

Thermal ablative therapies, such as Radiofrequency Ablation (RFA), have emerged as a well-accepted and well-documented treatment option for selected patients with unresectable CRLM. Recent literature suggests that RFA may achieve full tumor clearance, with 5-year survival rates of 18% to 43% [9-11]. The main area of concern following RFA is the presence of remnant tumor tissue in the ablation zone of larger lesions, leading to higher local recurrence rates. Due to the heat-sink effect of large vessels and the therefore increased risks of incomplete ablation and heat injury, tumor tissue close to vital structures such as large vessels or bile ducts is a less suitable target for RFA [12-14].

Stereotactic Ablative Radiotherapy (SABR), previously called stereotactic body radiotherapy, offers an alternative, non-invasive ablative approach to the local treatment of oligometastases of the liver when ineligible for resection or thermal ablation [15,16]. In the past, the value of radiation therapy for primary and secondary liver cancer has been limited due to dose-limiting radiation-associated liver injury. Recent technological advances in radiation therapy led to the development of SABR. SABR involves the delivery of extremely high biological doses to limited liver volumes, with high precision and in a few fractions, thus minimizing normal tissue toxicity and maximizing local control. The software used in treatment planning incorporates data from respiration-correlated CT images to more precisely define the motion of target volume and normal tissues [17]. A number of prospective phases I and II studies as well as retrospective studies are available that evaluate the effect of SABR in the treatment of CRLM [18-20]. Although all studies include a small number of patients, they show promising results with very high local control rates in selected patients, with minimal toxicity [19-22].

The use of SABR for colorectal liver metastases is not yet common practice in most hospitals. In clinics that do offer SABR, it is often only used for recurrent local disease after previous local treatment and if no other local treatment options exist. The aim of this study was to evaluate our experience regarding local control, disease progression, toxicity

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and survival after SABR of CRLM, and discuss the place and future of SABR in the treatment algorithm of CRLM.

Material and Methods

Patients

This study was conducted with the approval of the Institutional Science Board. All patients diagnosed with CRLM between August 2007 and August 2011 that was treated with SABR were included in our database and retrospectively analyzed. All patients with CRLM were evaluated by a multidisciplinary liver tumor board consisting of an oncological surgeon, interventional and imaging radiologist, medical oncologist, hepatologist, radiation oncologist, pathologist and a nuclear medicine physician. The decision to treat was made based on imaging with 18F-fluorodeoxyglucose Positron Emission Tomography (FDG-PET) and contrast enhanced CT and from 2007 onwards, with integrated FDG PET-CT and a diagnostic contrast enhanced CT (ceCT). SABR was indicated in cases with a limited number of unresectable CRLM, unsuitable for RFA due to size or proximity to large vessels, bile ducts or the diaphragm. Patients with liver-dominant disease (e.g. minimal extrahepatic disease) and with recurrent disease after previous treatment by resection or RFA were also included. Contra-indications for SABR were the presence of the stomach, intestines or oesophagus in the targeted area.

Imaging procedure

The 4-Dimensional Computed Tomography (4DCT) scanning procedure used at our center has been reported in detail previously [23,24]. In brief, while during a normal diagnostic CT procedure only one image is taken at every table position with maximum inspiration, during a 4DCT multiple images are taken at every table position during the full respiratory cycle. After sorting of the images, movie loops of the moving tumor and normal tissues can be reconstructed. In our center, respiration-gated 4DCT scans were performed during normal respiration using the Real-Time Position Management system (RPM, Varian Medical Systems, Palo Alto, CA), in combination with a 16-slice CT scanner (Light speed 16 GE Medical Systems, Waukesha, WI), or using an in-line 64-slice hybrid time of flight 4D PET/CT scanner (Philips Gemini 64 TF; Philips Medical Systems) in treatment position. The 4DCT scans were performed with intravenous contrast to facilitate the delineation of the target volume [25].

Generating target volumes

Internal target volumes (ITV; ICRU 62) were delineated using the 4DCT and FDG-PET images, including all motion. Isotropic safety margins of 3-10 mm were used to derive the Planning Target Volume (PTV) from the ITV (Figure 1). No separate margins were used to account for microscopic tumor extension [26].

Dose schemes and treatment delivery

All included patients were treated using a risk-adapted scheme of 3 to 12 fractions to a total dose of 54-60Gy, prescribed at the 80% PTV encompassing isodose. Total overall treatment time for all schedules was 2-3 weeks. The fractionation schedule was based on dose constraints of normal tissues. Two patients were treated using a gated treatment technique with 9 or 10 static beams, meaning that these patients were treated only during the end-expiration phases of the respiratory cycle, to spare bowel tissue. The other patients were treated using intensity-modulated arc therapy (RapidArc, Varian Medical Systems, and Palo Alto, USA) during the full respiratory cycle. Patient position was checked and corrected before each treatment fraction in all patients using cone beam CT, integrated in the treatment machine. No prophylactic anti-emetics or steroids were used.

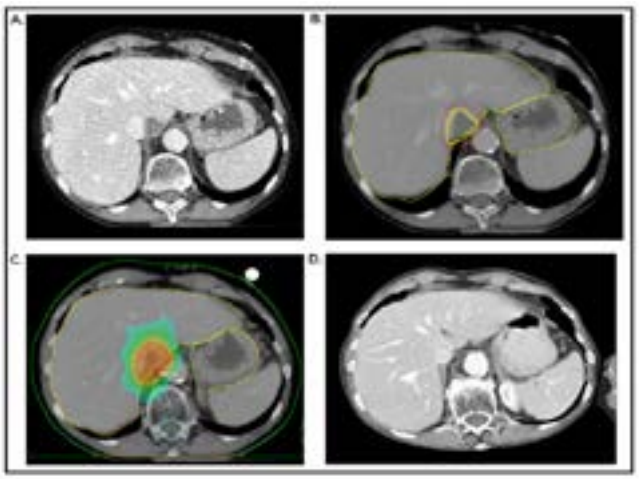

Figure 1: A. ceCT image before treatment. **B.** Target Volume. The inner yellow line represents the tumor, the red line indicates the tumor including margins. **C.** Scan used for planning. Different colors showing the level of received radiation in the targeted area (50% and higher). **D.** CT Follow-up 14 month's post-SABR.

Follow-up

Adverse events were documented during the five days of radiation and at all scheduled visits to the outpatient clinic during follow-up (radiation, surgery and medical oncology department). The files were retrospectively analyzed. A four-phase CT or FDG PET-CT scan was used during follow-up. Treatment results were evaluated at 3 and 6 months, and 6-monthly thereafter. Follow-up was conducted in a number of different referring hospitals but all images were re-examined and scored by one experienced radiation oncologist in our center (CJAH). If necessary, additional clinical follow-up information was obtained from the general practitioner and/or referring physician. Local failure was defined as an increase in size of the treated lesion or tumor growth on a per lesion basis. Follow-up continued regardless of development of new intra- or extrahepatic disease progression. Progressive disease was subdivided in local failure, new intrahepatic- and extrahepatic disease. Complications and toxicity were defined according to the Common Toxicity Criteria (CTC) version 3.0 (http://ctep.cancer.gov).

Statistical analysis

Baseline characteristics, local control and progressive disease, complications, toxicity and survival were analyzed. Survival was estimated based on the interval between first SABR treatment and death or last follow-up using the Kaplan Meier method. All calculations were performed using SPSS 20.0.0 (IBM SPSS Statistics, USA) and Microsoft® Office Excel 2003 (Microsoft Corp., Redmond, WA) software.

Results

Patients

Between August 2007 and August 2011, 10 patients with 13 lesions were treated with SABR in an attempt to obtain local control. These patients were prospectively included in our database and analyzed. Demographic and tumor characteristics are summarized in Table 1.

Median age (yr) (range)		67 (51-83)
Gender	Male / Female	5/5
Previous treatment		
	RFA	4
	Resection	2
	Chemotherapy	6
WHO performing stage		
	0	7
	1	2
	2	1
Primary tumor site		
	Colon	6
	Rectum	4
Tumor size		
	Median (mm)	28
	Range (mm)	11-63
Synchronous/metachronous		4/6
Tumor site (Couinaud segment)		
	1	1
	3	1
	4	3
	5	2
	8	4
	Hilus	2

Table 1: Demographic and tumor characteristics.

In 9 patients, the metastases were not amenable to resection or RFA due to an unfavourable location and/or recurrence after previous surgical intervention. A non-invasive procedure without a requirement for general anaesthesia was preferred for one patient suffering from multiple sclerosis. Five patients were primarily treated with SABR; in three patients, the tumor was ineligible for resection or RFA due to location, and two patients were unfit for general anaesthesia due to poor general health (multiple sclerosis or recovering from complications due to earlier surgery). SABR was administered to five patients as a second-line treatment after one or more previous local treatments (Table 1). In one patient, extrahepatic disease was already present at time of SABR (intra-abdominal lymph nodes). The median interval between diagnosis of CRLM and first liver SABR treatment was 13 months (range 3-36).

Local control and recurrent disease

Complete local control of 11 lesions in 8 patients was achieved, resulting in a 1-year actuarial local recurrence-free survival rate of 85.7%. Median follow-up was 20.4 months. Median disease free survival in the complete group was 7.4 months (range 0-25 months). Possible local failure occurred in 2 lesions in 2 patients after 12 and 25 months, respectively. Local failure in these patients was diagnosed by PET-CT and appeared as an enlarged hypodense lesion on CT, with increased FDG uptake on PET. These two patients also had new hepatic metastases outside the treated area (Figure 2). Five patients developed new intrahepatic metastases outside the treatment area (outfield failure), resulting in a 1-year actuarial outfield recurrence-free survival rate of 54.9%. Seven patients developed new extrahepatic metastases after a median time of 8.8 months (range 2-24). The actuarial distant metastases-free survival rate was 41.7%. Two patients could be retreated for hepatic recurrence with resection and RFA, and one patient received radiotherapy for extrahepatic disease. The 1-year disease-free survival rate was 22.2%. Most patients also received palliative chemotherapy at some stage in their disease.

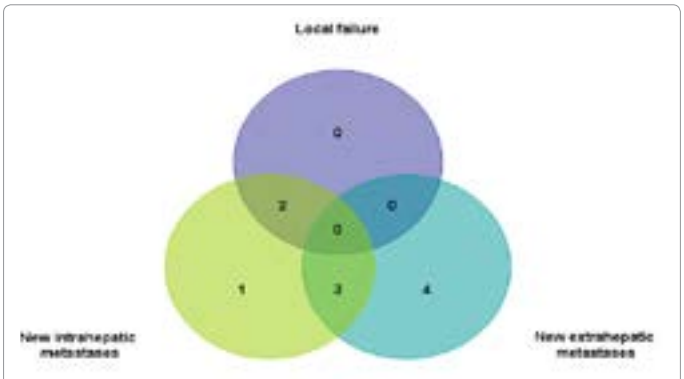

Figure 2: Results of 4-phase CT or FDG PET-CT follow-up scans for 10 patients regarding local failure, new intra- and extrahepatic malignancies.

Survival

At the time of analysis, 8 out of 10 patients had died of extensive new intra- and/or extrahepatic disease. Median survival was 26 months (range 7-38 months). Actuarial 1- and 2-year survival rates were 78.8% and 56.3%, respectively.

Toxicity and complications

No patients developed acute or late toxicity grade 3 or higher (CTC version 3.0) following SABR treatment. This includes no mortality. Seven patients reported no side-effects related to SABR. Three patients reported mild acute symptoms; 1 patient experienced tiredness, 1 patient reported pyrosis, and 1 patient reported both tiredness and mild dysphagia.

Discussion

Our study shows that SABR is safe, feasible and effective as a local treatment of patients with CRLM not amenable to surgical resection or RFA. Eight of the 10 patients showed complete local control of 11 lesions after a median follow-up of 20.4 months. None of the patients suffered from SABR-based toxicity grade >2. The predominant sites of failure were distant metastases and new metastases in the liver outside the treated area.

Local control, and not survival, is currently the most important endpoint in studies concerning SABR, due to the large variation in cancer stage and patient population. In studies evaluating the use of SABR in patients with unresectable CRLM, the reported 1- to 2-year lesion-based local control varies from 72% to 79% [18,22,27,28] (Table 2). Although not all factors associated with the local failure of SABR are known, previous research has shown that local control of CRLM is dose-dependent. SABR, with doses equal to or above 48 Gy in 3 fractions, provides better local control than doses below 48 Gy [29]. However, with multiple lesions or lesions >5 cm in diameter, this dose may not always be achieved because of an increased risk of radiation-induced liver disease or other toxicities. SABR is therefore especially suitable for the treatment of patients with a limited number of metastases.

The effects of SABR were monitored with FDG-PET, PET-CT or ceCT imaging. There are reasons to believe that the actual local control achieved by SABR is higher than has been reported. Local control is often defined as the lack of progression of the treated lesion on imaging, either by size increase or by metabolic activity [29]. However, tissue and imaging responses to SABR are unpredictable and assessment of the images can be challenging. An increase in lesion size observed with CT,

Author	# Patients	# Lesions	Patient based Local control	Lesion based local control	Actuarial survival	Total dose (Gy)	Fractions
Van der Pool et al. [22]	20	31	NR	100% (1yr) 74% (2 yrs)	83% (2 yrs)	37,5 45	3
Hoyer et al. [18]	44	NR	63% (2yrs)	79% (2 yrs)	22% (3 yrs) 13% (5 yrs)	45	3
Kress et al. [27]	11	14	NR	72% (1 yr)	26% (2 yrs)	16-42	2-5
Rusthoven et al. [28]	15	NR	93% (2yrs)	NR	NR	36-60	3

Table 2: Studies in which SABR was performed on a comparable patient group. All data shown are specific for liver metastases of colorectal origin.

as well as increased FDG-PET uptake, could be due to local radiation effects rather than lack of local control. An increased hypodense area around the tumor location, due to radiation, is often observed on CT and is most pronounced on imaging after a median of 2 months [30]. Because no histology was obtained from our patients at the time of possible local recurrence, lesions may have been erroneously scored as tumor recurrence, meaning that SABR may potentially be even more effective in local control than could be shown here. Even when including possible local recurrences, local control was high and these promising local control rates suggest that SABR could achieve survival benefit in patients with CRLM when applied in an earlier phase.

Survival following the treatment of CRLM has improved over past decades, with 5-year survival rates now at around 24–58% [5-8]. Tumor eradication is the main contributor to this improvement, and therefore surgical resection is generally considered the gold standard for local treatment of patients with CRLM, although only a minority of these patients are primarily eligible for surgery [31]. Neo-adjuvant chemotherapeutics are able to downstage metastases and increase the number of patients in which surgical resection is possible [32]. To achieve tumor eradication in unresectable CRLM, RFA is gaining popularity, reaching 5-year survival rates between 18-30% [9,33]. Complete tumor eradication is also aimed for when treating CRLM with SABR, but current median survival rates cannot be compared to those of other local treatment modalities due to patient selection. The patients enrolled in these studies were the most (negatively) selected of all patients treated for CRLM in our hospital. They represent a group with a generally poor prognosis, with tumors ineligible for surgery or RFA due to tumor size or location near centrally situated vessels or vital organs. These unresectable tumors may often show a less favourable biological behaviour than resectable CRLM [5,34]. Half of the patients in our group were, sometimes heavily, pre-treated prior to SABR. This creates a major bias when comparing the outcomes of SABR for hepatic metastases to those of RFA and surgical resection. The median survival in our group after SABR is comparable to the survival after chemotherapy [35,36]. In addition, follow-up in most retrospective and prospective SABR studies, including ours, has been relatively short.

SABR appears to be a safe and feasible technique, confirmed by groups that studied patients with liver metastases from a variety of origins and by our own results. SABR is often well-tolerated and hepatic or non-hepatic toxic effects grade 3 or higher, including mortality, are rare [19,20,22,28,37,38]. Only two fatal events have been reported in literature, both related to radiation-induced liver disease [18,38].

SABR is an attractive alternative for patients who are ineligible for general anesthesia and major surgery due to poor lung or cardiac function. It is possible to perform RFA of liver tumors under local anesthetic, but our experience indicates that patients do suffer from pain. This causes the patient to move, with a risk of incomplete ablation.

It should be stressed that SABR is an addition to the existing treatment options for selected patients with CRLM. It has proven to be a patient-friendly, non-invasive treatment option and it is also deliverable on an outpatient basis, with no requirement for anaesthesia. Our results indicate that SABR is safe, feasible and effective in terms of local control in patients with CRLM. Different stereotactic radiation treatment platforms from different vendors are used for the treatment of colorectal liver metastasis [39]. All have their own pros and cons, especially in terms of treatment delivery time and the need for invasive markers. However, the achieved dose distributions are comparable so there is no expected difference in treatment outcome between different stereotactic radiation techniques.

The exact position of SABR in the treatment algorithm of CRLM has yet to be established. However, with growing experience, it proves to be a valuable contribution to the treatment armamentarium of CRLM. One study compared stereotactic radiotherapy to RFA in a matched patient population and found a significantly longer local disease free survival than in the patients treated with RFA [40,41]. These findings should be confirmed by larger prospective trials. We suggest that SABR should not only be used as a treatment of last resort or palliative treatment option, but that it should be considered earlier in the process of determining the appropriate treatment policy. Overall awareness of SABR as a possible local treatment option should be raised, especially for tumors too large for safe resection or RFA and for tumors located < 1cm from central arteries, veins or bile ducts, which precludes safe resection or thermal ablation. We advise that the multidisciplinary consultation regarding treatment of CRLM include an attending or consulting radiation oncologist with experience in SABR when assessing the role of SABR in individual patients.

Most studies of SABR for colorectal liver metastases, including our own, have included a limited number of patients and a relatively short follow-up. Future studies should provide more extensive information on follow-up and survival. We believe that our results, and those of others, justify and provide a rationale for a prospective study comparing SABR to other local treatments in comparable patient groups with CRLM. We note that such a study has already been initiated by the International Liver Tumor Group and is currently recruiting participants (clinicaltrial.gov: NCT01233544).

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