

Dosimetric comparison of brachyablation and stereotactic ablative body radiotherapy in the treatment of liver metastasis

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ABSTRACT

PURPOSE: We compared the dosimetry of brachyablation (BA) and stereotactic ablative radiotherapy (SABR) in the treatment of liver metastases.

METHODS AND MATERIALS: Treatment plans for 10 consecutive liver metastasis patients, treated with SABR, were replanned for BA. BA treatment was planned using five 12 Gy fractions to the same planning target volume (PTV) used for SABR. Dosimetric parameters were compared using a Student's paired *t* test.

RESULTS AND CONCLUSIONS: BA and SABR plans had similar mean volume receiving 100% of the prescribed dose (94.1% vs. 93.9% of PTV, $p = 0.8$). Mean volume receiving 150% of the prescribed dose for BA was 63.6%, whereas for SABR it was 0. The minimum dose to the PTV was 65.8% for BA, whereas for SABR it was 87.4% ($p = 0.0002$).

Liver volume receiving ≥ 15 Gy was similar for BA and SABR (278 vs. 256 cc, $p = 0.3$). Small bowel mean dose, as percent prescription dose, was higher for BA (10.8% vs. 7.1%, $p = 0.006$). Stomach mean dose was similar (4.9% vs. 4.8% of prescription dose, $p = 0.98$). Right kidney mean dose was greater for BA (6.7% vs. 4.2%, $p = 0.07$).

BA leads to a higher target dose, similar dose to organs at risk, but potentially with lower target coverage compared with SABR. Further work is needed to determine ideal suitability for mono vs. combination therapy with this approach. © 2015 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords:

Stereotactic body radiotherapy; SABR; Brachyablation; Liver metastasis; Image guided brachytherapy

Introduction

A variety of treatment modalities are available for managing oligometastatic liver lesions. They include surgery, multiple ablative modalities (high-intensity frequency ultrasound, radiofrequency ablation, and cryotherapy), chemotherapy, and radiation therapy.

Advances in radiation treatment delivery and imaging have expanded the role of external beam radiation therapy to include stereotactic ablative radiotherapy (SABR). SABR for oligometastatic liver lesions has a mature clinical

experience, with multiple studies demonstrating considerable promise (1). The successful delivery of this treatment relies on strict patient immobilization and accounting for organ motion (four-dimensional CT simulation, respiratory gating, and/or fiducial marker seed localization).

Brachyablation (BA) represents an advance in brachytherapy treatment delivery and through collaboration with interventional radiology allows brachytherapy catheters to be inserted directly into the tumor. By having catheters directly placed into the target, a smaller volume can be treated compared with SABR, as one does not need to account for a planning target volume (PTV). The dose heterogeneity of brachytherapy can also allow for dose escalation, which may be advantageous in larger targets.

Although several series of patients treated with BA have been published, these articles neither do fully characterize the specific advantages or disadvantages of this technique nor do address how or why this technique compliments SABR. In our dosimetric analysis, we provide the first comparison of

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these technologies and suggest directions for future investigation.

Methods and materials

Ten consecutive patients treated with SABR (by PPL) for hepatic metastases were selected for comparative BA dosimetric analysis. Planning used identical structure sets and prescription (12 Gy \times five fractions) for each analysis. An interventional radiologist (CL) selected the number and trajectory of catheters for virtual insertion into the target lesion (Fig. 1). A treatment plan was created for each patient (by SJP) using high-dose-rate brachytherapy planning software (Oncentra Masterplan, version 4.3; Nucletron, Veenendaal, The Netherlands) to simulate BA treatment of these lesions and reviewed by a radiation oncologist with brachytherapy expertise (MK). Inverse planning simulated annealing was used to come up with an initial plan followed by manual graphical optimization. The planning goal was to match the PTV receiving 100% of the prescribed dose to the SABR plan.

Planning was for high-dose-rate brachytherapy using an iridium-192 afterloader. CT simulation would follow

catheter insertion. After the catheters are secured in place using a drain tie, they would be marked and checked for migration before treatment. There would be a 6 hour treatment interval between fractions. CT simulation would need to be performed before each subsequent fraction to assess catheter displacement.

Dose–volume histograms were generated for each plan and used for comparative analysis. Comparison was by paired two-tailed Student's *t* test. We compared target coverage parameters (volume receiving 100% of the prescribed dose [$V_{100\%}$]; volume receiving 150% of the prescription dose [$V_{150\%}$]; percentage of the prescription dose covering 90% of the volume of the PTV; average, mean, and minimum percentage of the prescription dose), dose falloff (ratio of the volume receiving 50% of the prescription dose to the volume of the PTV [$R_{50\%}$]), and dose to organs at risk (liver volume receiving 15 Gy or more and mean dose to small bowel, stomach, and right kidney). For one of the 10 patients, we were not able to develop a feasible BA plan because the tumor target was located in a position that was safe, and adequate access with catheters was not felt to be possible. This patient was excluded from further analysis.

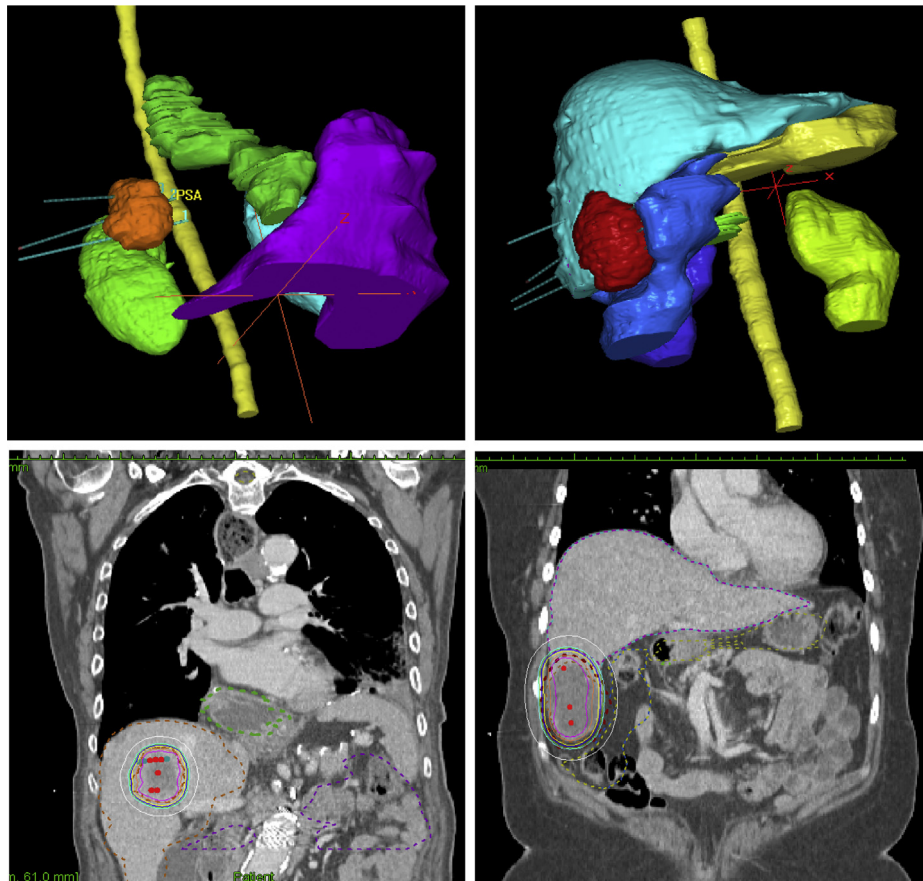


Fig. 1. Examples of two brachyablation (BA) plans are shown. Patients treated with stereotactic ablative radiotherapy were replanned for BA treatment using virtual catheters placed into the lesion. Catheters are pictured in relation to tumor and organs at risk.

Results

The average volume of the target and liver was 68 and 1418 cc, respectively. In terms of target coverage, BA and SABR plans had similar PTV V_{100} (94.1% vs. 93.9%, $p = 0.8$). Mean percentage of the prescription dose covering 90% of the volume of the PTV for BA vs. SABR was 107.9% vs. 101.0% ($p = 0.001$), demonstrating greater dose heterogeneity for the BA group. Similarly, mean $V_{150\%}$ for BA was 63.6%, whereas for SABR it was 0%, indicating significant dose escalation within the PTV with BA. Minimum dose, as a percentage of prescription dose for the lowest dose voxel in each plan, was 66% for BA and 88% for SABR ($p = 0.0002$).

Dose falloff was not significantly different for BA vs. SABR, with $R_{50\%}$ of 3.5 vs. 3.91 ($p = 0.109$).

For organs at risk, liver volume receiving 15 Gy or more was not significantly different for BA compared with SABR (278 vs. 256 cc, $p = 0.3$). Mean dose, as a percentage of prescription dose, for the small bowel (10.8% vs. 7.1%, $p = 0.006$) and kidney (6.7% vs. 4.2%, $p = 0.07$) was significantly higher for BA vs. SABR. Stomach mean dose was not significantly different between BA and SABR (4.9% vs. 4.8%, $p = 0.98$).

Discussion

There is a wide range of appropriate local therapies available for the management of liver metastasis. Selection of the ideal local therapy is best determined through discussion at a multidisciplinary tumor board. With respect to radiation options, SABR is the most commonly used method to treat liver metastasis. To the best of our knowledge, there are no clinical reports on BA for the treatment of liver metastasis in the United States, but there are multiple reports from other countries.

BA has both advantages and disadvantages compared with SABR (Table 1). The greatest potential advantage is that the treatment is typically delivered in a single fraction, does not require a PTV margin, and is delivered using a heterogeneous dose distribution. On the other hand, there are advantages to SABR that include improved access and expertise to deliver this type of treatment, it is noninvasive, and most of the data that exist use this technique.

There has not been an analysis of the dosimetric differences between BA and SABR. We compared the dosimetry of simulated BA vs. actual SABR treatment plans for 10 patients treated with liver metastases to better understand the similarities and differences between these two treatment approaches. Nine of 10 cases had lesions amenable to brachytherapy catheter insertion. Among the nine cases that simulated plans could be generated, we found that for equal $V_{100\%}$ s between BA and SABR that the V_{150} of BA plans was significantly higher than SABR. This dose heterogeneity led to a significantly higher mean dose (Dmean 205% for

Table 1

Comparison of the advantages and disadvantages of brachyablation vs. SABR for treating liver metastasis

Brachyablation	SABR
Advantages	
No PTV so smaller treatment volume	Noninvasive Technology and expertise available in most clinics
Ability to biopsy tissue for genomic analysis	Most data using this approach
Typically done in 1 treatment	
Higher mean dose to target	
Disadvantages	
Minimally invasive	Organ motion management needed
Technology and expertise not available in most clinics	Larger volumes to account for organ motion
Not all cases eligible	Commonly multiple treatments
Perfect target coverage difficult (lower minimum dose than SABR)	Difficulties with daily setup Dose is standardly delivered as homogeneous

SABR = stereotactic ablative radiotherapy; PTV = planning target volume.

BA vs. 104% for stereotactic body radiotherapy) being delivered to the target. This dose escalation was achieved for similar doses to the organs at risk. Although there were some statistically significantly higher mean doses to organs at risk with BA compared with SABR, they were only a few percent higher and not thought to be clinically meaningful. On the other hand, BA plans had a lower minimum dose to the target compared with SABR plans demonstrating the potential difficulties of BA being able to cover the entirety of the target. The other finding from this dosimetry study was that the R_{50} for the BA and SABR plans was not significantly different. This is remarkable as one of the advantages of brachytherapy has always been the perception that the dose falloff cannot be matched by an external approach. In our study, this is not true as the $R_{50\%}$ s were the same between the two plans. Although it is true that the SABR approach will deliver a greater low-dose spill compared with BA, it is not known if this is a clinically relevant concern. Based on our dosimetric analysis, it appears that the main advantage of BA is the dose escalation that can be achieved within the target for about the same dose to organs at risk that can be achieved with SABR.

Although not commonly done in the United States, there are multiple clinical series using BA to treat liver metastasis from Europe. Major toxicities were associated primarily with percutaneous access (e.g., hemorrhage, abscess), whereas radiation-associated major complications including obstructive jaundice secondary to tumor-related edema and gastric ulcer have been reported in a low percentage of BA patients (Table 2). Minor complications including pain and nausea are associated with this procedure in some series.

One case series included 36 patients with liver metastasis treated with BA alone or in combination with thermal ablation (2). A range of prescription doses from 10 to

Table 2
Clinical summary of trials using brachyablation to treat liver metastasis

Study	Histology	Patients	Dose	Major complications
Ricke, 2004a (2)	Metastatic (36) and cholangiocarcinoma (1)	37	10–20 Gy	1 acute liver failure (concurrent capecitabine) and 1 obstructive jaundice
Ricke, 2004b (3)	Metastatic (19) and cholangiocarcinoma (1)	20	12–25 Gy	1 hemorrhage and 1 obstructive jaundice
Mohnike, 2010 (4)	HCC (140)	83	15–25 Gy (114 lesions), 12–15 Gy × 2, bimonthly (12 patients)	9 complications in 124 interventions: 5 bleeding, 3 abscess, and 1 gastric ulcer
Ricke, 2010 (5)	Colorectal metastases (199)	73	15, 20, or 25 Gy	2 occult bleeding, 2 gastric ulcer, 1 pleural effusion, and 1 anaphylaxis to contrast
Rühl, 2010 (6)	Colorectal metastases (18), breast metastasis (1), and HCC (1)	20	15–25 Gy, retreated 2–4 times	No Grade 2 hematologic toxicity, and no acute or chronic liver dysfunction
Wieners, 2011 (7)	Breast (115)	41	15–25 Gy	1 hemorrhage through puncture site
Colletini, 2012 (8)	HCC (5–12 cm)	35	15–20 Gy	None
Tselis, 2012 (9)	Metastatic (23), HCC or cholangiocarcinoma (8)	31 (42 procedures)	7–32 Gy total in 4–10 Gy BID or 7–14 Gy daily (1–5 fractions)	2 intra-abdominal hemorrhage
Colletini, 2013 (10)	Colorectal (16), breast (9), and other (7)	32	20 Gy	1 biliary abscess
Sharma, 2013 (11)	Metastatic (12)	10	20 Gy	None
Tselis, 2013 (12)	Metastatic (40) and primary liver tumors (10)	41	7–32 Gy total in 4–10 Gy BID or 7–14 Gy daily	2 intra-abdominal hemorrhage and 1 gram-negative sepsis
Brinkhaus, 2014 (13)	HCC (21), colorectal (17), cholangiocarcinoma (9), breast (8), pancreas (6), gastric (3), and other (5)	69	10–20 Gy	Biochemical markers of liver function normalized at 6 wk
Colletini, 2014 (14)	Colorectal metastases (179)	80	15–20 Gy	None

HCC = hepatocellular carcinoma; BID = twice a day.

20 Gy was used. At 6 months, the local control rate was 73% for combination therapy and 87% for BA alone.

An additional series from the same group reported on 20 patients with 19 liver metastases and one cholangiocarcinoma that were either >5 cm or adjacent to the hilum (3). All patients were treated with BA alone to prescription doses ranging from 12 to 25 Gy. In patients with tumors >5 cm, primary local control was 74% at 6 months and 40% at 12 months. In patients with perihilar tumors, primary local control was 100% and 71%, respectively. Of note, all but one local recurrence was treated successfully with additional BA, producing a primary-assisted local control rate of 93% at 12 months.

Colletini *et al.* (10) reported on 32 consecutive patients with 34 metastatic lesions treated with BA to a dose of 15–20 Gy. Doses of 15 Gy were given if dosimetric constraints showed that 20 Gy was not achievable. After a mean followup of 18.75 months, 11.8% experienced local recurrence, and median overall survival was 20.24 months. The same group has reported a larger series (with some

overlap) of 80 patients with 179 unresectable colorectal metastases (14). Local progression was seen in 12.9% of patients, whereas 62.5% experienced systemic progression.

Finally, it appears that histology impacts outcomes as in one series of 41 patients with 115 liver metastases treated with doses ranging from 15 to 20 Gy had an 18-month local control rate of 93.5% (7). In another series of 73 patients with 199 colorectal liver metastases, local control was lower and significantly correlated with the dose received (5). Metastases were initially assigned to BA target doses of 15 ($n = 64$ metastases), 20 ($n = 67$), and 25 Gy ($n = 68$). There was significant crossover in this study, driven by dose limits to organs at risk or excessive irradiation time, and 38 lesions were reassigned to low-dose arms. Based on final assignment to intended dose, there were significantly fewer recurrences in the group assigned to 25 Gy (1 of 33 lesions) than in the group assigned to 20 Gy (15 of 68) or in the group assigned to 15 Gy (34 of 98) ($p < 0.05$). Underdosing was noted in many treatments, and no recurrences were seen in metastases where

the true dose was more than 23 Gy. These data demonstrate a strong dose dependence for BA of colorectal liver metastases.

These data suggest similar local control and toxicity rates of BA relative to SABR but leaves unanswered questions regarding when one technique should be used over another. It appears that the greatest advantages of BA and SABR are the heterogeneous dose distribution and high target coverage, respectively. We speculate that for carefully selected cases, the dose escalation advantages of BA could help improve local control compared with SABR alone. This is especially in light of the pooled analysis of patients with colorectal liver metastases demonstrating local control was 84% for total doses given in three fractions greater than or equal to 42 Gy vs. 43% for total doses under 42 Gy (15). It may be that a combination of BA with SABR may be ideal in cases where escalated dose is necessary but cannot be achieved through SABR alone. Further work is needed to define more precisely which tumor locations and morphologies might be optimal for BA boost. The optimal sequence of BA and SABR is likewise unclear. Tumors responding favorably to one modality may become smaller and more favorable for boost using the other.

Clinical experience with BA is lesser than that of SABR; however, the literature does allow us to make some comparisons with respect to recommended dose. We assume an α/β ratio of 10 for tumor. We use the linear quadratic equation while acknowledging limitations of this model for ablative doses (16, 17).

Chang's (15) pooled analysis of SABR results from three institutions recommends a dose of at least 48 Gy delivered in three fractions. This represents a biological equivalent dose (BED) of 125 Gy or an equivalent dose in 2 Gy per fraction of 104 Gy. Lanciano's (18) analysis of patients treated for liver metastases in Philadelphia concluded that a BED of >100 Gy should be used when possible. Analysis of BA dose delivered in a single fraction for liver metastases by Ricke *et al.* (5) found a superior level of local control for 25 Gy when possible. This corresponds to a BED of 88 Gy or an equivalent dose in 2 Gy per fraction of 73 Gy.

These results are broadly in agreement given the imprecision inherent in the underlying estimations required by these calculations and limitations of the linear quadratic model. Conceptually, local tumor control will be maximized with higher doses; our ability to deliver dose is limited by toxicity to surrounding tissues. Given differing profiles of normal tissue dose delivered for comparable doses of SABR and BA, we speculate that BA may hold value in providing a boost to tumors in locations where SABR is unable to deliver sufficient dose because of normal tissue constraints.

Another possible advantage of BA is its ability to assist in advancing personalized medicine. Increasingly, personalization in cancer treatment is driven by biological characteristics of tumors. A biopsy of tumor tissue could easily

be performed at the time of brachytherapy catheter placement. This tissue could be sent for molecular or genomic analysis to assist with appropriate targeted therapy selection. This is an important advantage as most patients will achieve local control but progress in other sites.

In the developing world, some centers have used BA for lesions that would more likely be treated with SABR in the United States. For example, Sharma *et al.* (11) reported a small series of patients in New Delhi with liver metastases treated with BA. In such settings, with access to interventional radiology services and an iridium-192 afterloader, liver BA could hold promise to expand treatment options.

There are some limitations to this analysis including the fact that the brachytherapy catheters were virtually placed, and it is possible that they may not actually be able to be inserted exactly as planned. We used the SABR PTV to plan the BA cases. We decided to do this as the CTVs were sometimes difficult to confidently identify on the CT scans, and therefore, we decided to plan to the PTV. This means that the BA plans could have underestimated the advantages of brachytherapy as a margin for organ motion and treatment setup was included. Our results suggest that brachytherapy can result in dose escalation to the target with similar doses to organs at risk compared with SABR. We compared the dosimetry of SABR using volume modulated arc therapy planning and noted that with advances in external beam planning, for example, 4π noncoplanar planning, the differences between BA and SABR may be less pronounced (19, 20).

Conclusion

In common use in the United States, SABR will likely continue to be the primary treatment modality for radiotherapy of liver lesions. BA should be investigated further in the setting of combination therapy with SABR. Examination of resource utilization factors, such as cost and equipment availability, could elucidate relative advantages of BA in some settings where SABR is limited in availability or unavailable.

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