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A single-institutional experience with low dose stereotactic body radiation therapy for liver metastases

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ABSTRACT

Aim: This study reports a single-institutional experience treating liver metastases with stereotactic body radiation therapy (SBRT).
Materials and methods: 107 patients with 169 lesions were assessed to determine factors predictive for local control, radiographic response, and overall survival (OS). Machine learning techniques, univariate analysis, and the Kaplan-Meier method were utilized.
Results: Patients were treated with a relatively low median dose of 30 Gy in 3 fractions. Fractions were generally delivered once weekly. Median biologically effective dose (BED) was 60 Gy, and the median gross tumor volume (GTV) was 12.16 cc. Median follow-up was 7.36 months. 1-year local control was 75% via the Kaplan-Meier method. On follow-up imaging, 43%, 40%, and 17% of lesions were decreased, stable, and increased in size, respectively. 1-year OS was 46% and varied by primary tumor, with median OS of 34.3, 25.1, 12.5, and 4.6 months for ovarian, breast, colorectal, and lung primary tumors, respectively. Breast and ovarian primary patients had better OS ($p < 0.0001$), and lung primary patients had worse OS ($p = 0.032$). Higher BED values, the number of hepatic lesions, and larger GTV were not predictive of local control, radiographic response, or OS. 21% of patients suffered from treatment toxicity, but no grade ≥3 toxicity was reported.
Conclusion: Relatively low-dose SBRT for liver metastases demonstrated efficacy and minimal toxicity, even for patients with large tumors or multiple lesions. This approach may be useful for patients in whom higher-dose therapy is contraindicated or associated with high risk for toxicity. OS depends largely on the primary tumor.

1. Introduction

Stereotactic body radiation therapy (SBRT), or stereotactic ablative radiotherapy (SABR), is a radiation therapy technique that delivers high doses of radiation in generally up to five treatments. Expanding use of this technique has allowed for the treatment of metastatic disease, resulting in local control and even survival benefit in carefully selected patients.[1–3] Metastases to the liver are common, especially in colon cancer patients.[4] Surgery remains the standard of care for resectable tumors, but many patients are deemed to be poor surgical candidates.[5–8] Though chemotherapy has been used to downstage lesions and allow more patients to undertake surgical resection, only 10–20% of metastases can be safely resected.[9,10] Other patients may consider alternative treatment approaches, including radiofrequency ablation.[11,12]

Radiation-induced liver disease (RILD) remains the dose-limiting toxicity for liver SBRT, but the RILD risk is proportional to the mean dose delivered to the liver.[13–15] For this reason, small hepatic lesions can be treated without significant risk for RILD if there is at least 700 cc of liver receiving less than 15 Gy total dose.[13,16–19] Though liver SBRT is generally well tolerated, other general gastrointestinal (GI) toxicity is possible.[20]

Prospective trials have published encouraging outcomes for liver SBRT, with multiple trials demonstrating 1-year local control rates over 90%. Toxicity profiles have also been quite low, with multiple studies finding no cases of RILD after multiple years of follow-up.[13,17,21–27] Follow-up of these patients has identified that World Health Organization (WHO) performance sta-

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tus, extrahepatic disease control, increased radiation prescription dose (>54–60 Gy), and increased biologically effective dose (BED) (>100–150 Gy) were considered to be positive prognostic factors. There have been a variety of dose-fractionation schemes in these studies, which is partly explained by the differences in size of the gross tumor volume (GTV) between patients. Other key factors of heterogeneity in these studies include different primary sites of the tumor, prior chemotherapeutic status, and the number of hepatic lesions being treated.[28–31] Liver function tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (AP), have also been investigated as factors to predict the development of liver metastases or even the outcome of SBRT, but results have been mixed.[32–34] These differences perhaps serve to underscore the wide range of patients who suffer from hepatic metastases and their correspondingly varied outcomes.

The purpose of this study is to report on a single institutional experience of treating liver metastases in non-surgical candidates with relatively low-dose SBRT. 107 patients with 169 total lesions were analyzed with the specific purpose of determining factors predictive for local control, radiographic response, and overall survival (OS), including dosimetric characteristics, primary disease site, and liver function tests. Machine learning techniques were used for this purpose, in addition to univariate analysis and the Kaplan-Meier method. Toxicity data was also reported to demonstrate the safety of this treatment modality.

2. Materials and methods

2.1. Patient eligibility

All patients treated with SBRT for liver metastases at our institution from October 2007–January 2018 were considered for inclusion. There were no significant changes to the treatment approach over this time period. Inclusion criteria included histology-proven solid tumor, and patients who were deemed not to be optimal surgical candidates. Retrospective tumor characteristics, including the use of chemotherapy within the previous six months, the number of hepatic lesions, and the site of the primary tumor were collected through a retrospective chart review. None of these characteristics were used as exclusion criteria. Patient data was anonymized and chart review was implemented to record dosimetric data, including prescription dose, number of fractions, GTV, planning target volume (PTV), and the %GTV and %PTV receiving the prescription dose of radiation. BED was calculated using the linear quadratic model: BED = total dose*(1 + dose per fraction / α/β). The α/β for the tumor volume was chosen to be 10 Gy. AST, ALT, and AP data were also recorded before and after treatment when available. This analysis was exempt by the institutional review board and conducted in accordance with their tenets.

2.2. Endpoints

Tracking follow-up data was completed through a standardized protocol. The two primary endpoints of the study were overall survival and local control. In order to further describe the disease process, extrahepatic progression, hepatic progression, radiographic response, duration of follow-up, and time to local failure were all recorded as secondary endpoints. Radiographic response was scored as decrease, stability, or increase in the lesion size. Local failure was defined as an increase in the size of the metastatic lesion after SBRT according to post-treatment imaging, such as CT, MRI, or PET-CT scans. The duration of local control was calculated from the time of completion of SBRT. The time between the pre-treatment lab values and the start of treatment and the time between the end of treatment and post-treatment lab values were also recorded. Pre-treatment labs were generally recorded about two months prior to the start of treatments, and post-treatment labs were recorded approximately two months after the completion of treatment. Patients were generally followed with imaging every two-three months. Follow-up appointments primarily consisted of medical oncologists and radiation oncologists.

2.3. Treatment

All patients were positioned with a full-body vacuum-driven immobilization device custom fit at the time of 4-dimensional CT simulation. After delineation of the GTV by the attending radiation oncologist, an internal target volume (ITV) was constructed from the 4DCT scan to account for motion of the tumor. Doses were prescribed to the ITV. The treatment delivery techniques included 3D forward planned non-coplanar static field apertures and non-coplanar static arcs. Intensity-modulated radiation therapy and volumetric modulated arc therapy inverse planned delivery techniques were also considered. Treatments were delivered using 6 MV X-ray beams on a stereotactic radiosurgical linear accelerator with a microleaf collimator (2.5 mm–4 mm leaf width) and a six degrees of freedom robotic couch for localization using cone-beam CT image guidance. Cone-beam CT was used prior to the start of treatment to assist with alignment of the patient and tumor. Cone-beam CT was also used during treatment as needed to correct for intra-fraction motion. Radiation therapy was generally delivered in once-weekly fractions in an effort to reduce toxicity.

2.4. Statistics

Statistical analyses were conducted for each treated lesion for the endpoints of radiographic response and local control, whereas data was analyzed by patient for determination of factors predictive for overall survival. Techniques used during analysis included: decision tree analysis, K-nearest neighbors, linear discriminant analysis, Gaussian naïve Bayesian classifier, support-vector machine, and linear and logistic regression. Kaplan-Meier analyses were used for time-dependent variables, including overall survival. Only treatments with imaging follow-up were included in the Kaplan-Meier analysis for local control. Such analyses were conducted for each distinct primary site for the liver metastasis and for other variables potentially predictive of local control (e.g. BED, GTV, and number of lesions). T-tests were conducted for binary variables, and an alpha value of 0.05 was used to signify statistical significance. Acute and late toxicity findings were tabulated according to the Common Terminology Criteria for Adverse Events v5.0.

3. Results

3.1. Patients

107 patients with 169 lesions were included in the analysis. 87 of these patients had received chemotherapy within the previous six months. The primary disease site was quite varied, including at least 19 patients with breast, lung, and colorectal primary tumors. The number of lesions per patient ranged from one to four. 68 of 107 patients had only one lesion; 20 patients had two lesions; 14 patients had three lesions; and 5 patients had four lesions (Table 1).

3.2. Dosimetric characteristics

Patients were treated with a median 30 Gy (18–45) in 3 fractions (3–5). The most common treatment regimens were 30 Gy in 3 fractions (27%), 36 Gy in 3 fractions (27%), and 24 Gy in 3 fractions (18%). There was an average of 5.19 days between fractions. Median

Table 1
Patient demographics and characteristics are tabulated.

Characteristic	Number	Rate
Total patients	107	
Male	44	41%
Female	63	59%
Chemotherapy in the past 6 months	87	81%
Median age (years)	69	
Primary site: colorectal	23	21%
Lung	22	21%
Breast	19	18%
Gynecologic	19	18%
Genitourinary	10	9%
Other	14	13%
Lesions: Total	169	
Mean lesions per patient	1.59 (1–4)	
Patients with 1 lesion	68	64%
Patients with 2 lesions	20	19%
Patients with 3 lesions	14	13%
Patients with 4 lesions	5	5%

Table 2
Dosimetric characteristics are considered in detail.

Dosimetric characteristic	
Median dose (Gy)	30 (18–45)
Median fractions	3 (3–5)
Median BED (Gy)	60 (28.8–112.5)
Mean days between fractions	5.19
Median GTV (cc)	12.16 (0.46–300)
Median PTV (cc)	46.5 (7.2–586.09)
Median %GTV receiving prescription dose	100 (96.1–100)
Median % PTV receiving prescription dose	96.74 (73.95–100)
Median PTV maximum cGy / fraction	1099 (598–1746)
Median PTV mean cGy / fraction	1053 (546–1643)
Median PTV minimum cGy / fraction	912 (285–1455)

Table 3
Outcomes regarding survival, tumor progression, local control, and radiographic response are displayed.

Outcome	Number	Rate
Patients alive	16	15%
Patients deceased	91	85%
Median overall survival (months)	9.43 (0.1–64.43)	
Hepatic progression	55	60%
No hepatic progression	36	40%
Extrahepatic progression	78	80%
No extrahepatic progression	20	20%
Patients with clinical follow-up	94	88%
Lesions with imaging follow-up	143	85%
Median follow-up time (months)	7.36	
Local failure	25	15%
Radiographic response: size decreased	61	43%
Lesion stable	57	40%
Lesion size increased	25	17%
Median time to failure (months)	4.60	

BED was 60 Gy (28.8–112.5), and since there were no restrictions regarding tumor size, the GTV was quite varied, with a median of 12.16 cc (0.46–300). Other dosimetric characteristics, including PTV, PTV maximum, mean, and minimum, as well as the %GTV and PTV receiving the prescription dose were recorded (Table 2).

3.3. Outcomes

Median OS was 9.4 months after a median follow-up time of 7.36 months (Fig. 1). There were 25 total cases of local failure (Table 3). Using Kaplan-Meier analysis, 1-year OS was 46%, and 1-year local control was 75%. 2-year local control was 73%, and local control at the median follow-up time of 7.36 months was 81%. Local failure occurred at a median 4.60 months after the completion of SBRT. 8 local failures occurred within 3 months and 23 total within 1 year. Imaging follow-up was obtained in 88% of patients and after 85% of treatments. Treatments without imaging follow-up were not included in the Kaplan-Meier analysis. This resulted in the elimination of one patient from the subsequent analysis. 61 lesions (43%) decreased in size, 57 (40%) remained stable, and 25 (17%) increased in size. Imaging follow-up showed that 55 patients (60%) had some hepatic progression, and 78 (80%) had extrahepatic progression.

3.4. Predictive factors

Kaplan-Meier analysis was conducted to determine predictive factors for OS, local control, and radiographic response. Patient median survival varied by primary tumor, with median OS of 34.3, 25.1, 12.5, and 4.6 months for ovarian, breast, colorectal, and lung primary tumors, respectively (Fig. 2). Breast and ovarian primary patients had a statistically significant increase in OS relative to the rest of the patient cohort, and lung primary patients had worse overall survival. Colorectal primary patients had no difference in OS relative to the rest of the cohort. A similar analysis was conducted for local control, again demonstrating improved local control for breast primary tumors and decreased local control for lung primary tumors (Fig. 3). OS and local control between breast and lung primary tumors were also directly compared, showing improved results in breast primary tumors (Fig. 4, $p < 0.0001$ and 0.032, respectively).

There was no significant difference in local control rates with higher BED values or the number of hepatic lesions, and there was no significant difference between larger (GTV > 30 cc) or smaller lesions ($p = 0.19$). These variables were considered as continuous variables, and specific thresholds (e.g. BED > 50 or 60 Gy) were also employed in this analysis. Even so, no statistically significant predictors were found using these variables. Radiographic response also showed no differences between treatments with higher BED values, treatments for larger vs. smaller tumors, or the number of hepatic lesions. None of these factors were predictive of increase or decrease on radiographic follow-up.

Machine learning techniques were utilized in order to attempt to derive a predictive model for local failure. First, importance testing was conducted, and pre-treatment lab values (AP, AST, and ALT) consistently showed the highest variable importance factors for predicting local failure. Mean pre-treatment AP, AST, and ALT values and their corresponding ranges were found to be 103.13 (43–253), 31.96 (14–113), and 29.93 (4–113), respectively, and mean post-treatment values were 156.90 (32–748), 43.88 (14–144), and 37.82 (3–168), respectively. These lab values increased after 74%, 62%, and 59% of treatments, and in 72%, 56%, and 51% of patients after treatment. Pre-treatment labs were obtained a median 2.60 months prior to treatment, and post-treatment labs were reported at a median 1.68 months after treatment. Six different machine learning techniques were used to determine whether these values were predictive of local failure, and the corresponding area under the curve and accuracy of each model were as follows: classical machine learning for logistic regression (0.5, 0.83), decision tree analysis (0.57, 0.78), K-nearest neighbors (0.59, 0.79), linear discriminant analysis (0.5, 0.84), Gaussian naïve Bayesian classifier (0.45, 0.64), and support-vector machine (0.5, 0.84). None of these models offered sufficient predictive power to conclusively denote these laboratory values as predictive factors.

3.5. Toxicity

Toxicity was quite low after treatment, with 23 patients (21%) suffering from either a grade 1 or 2 toxicity, and 36 total instances of toxicity (21%) recorded for all analyzed treatments. Only 3

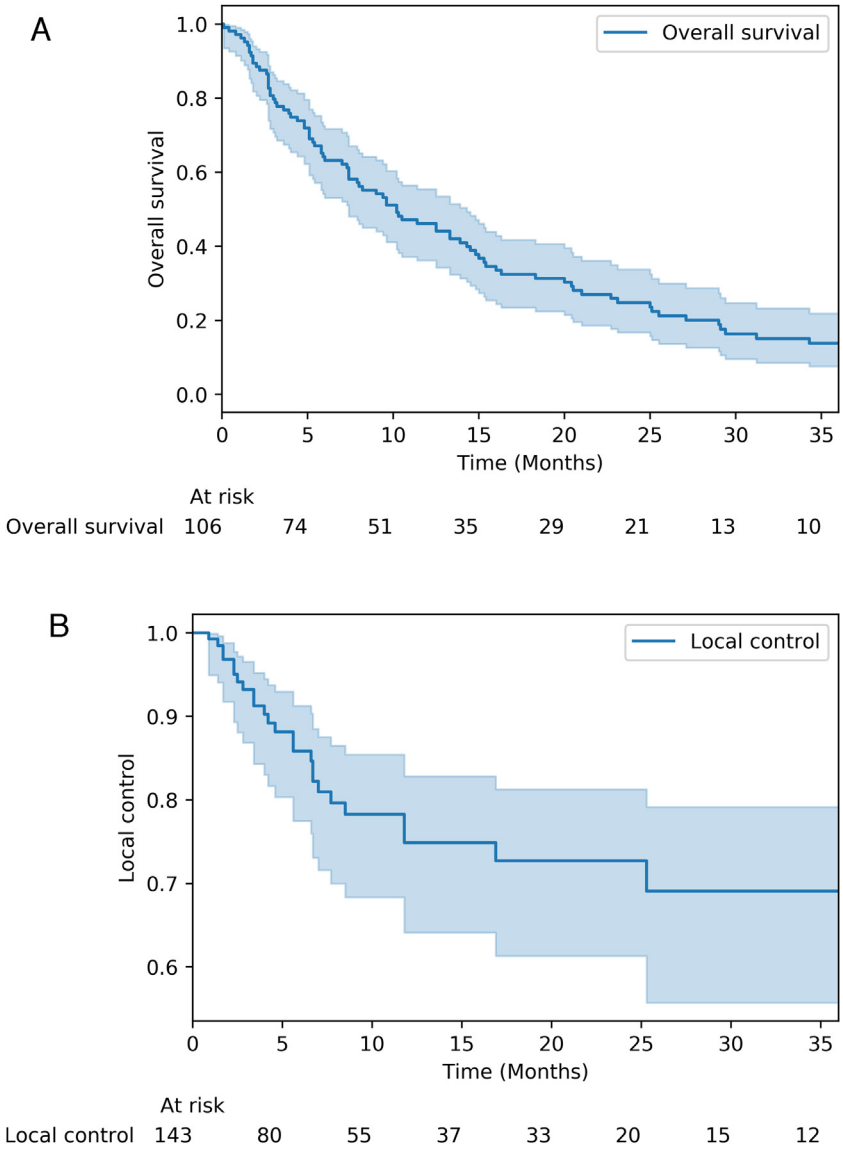

Fig. 1. The Kaplan-Meier method was utilized to demonstrate overall survival (a) and local control (b).

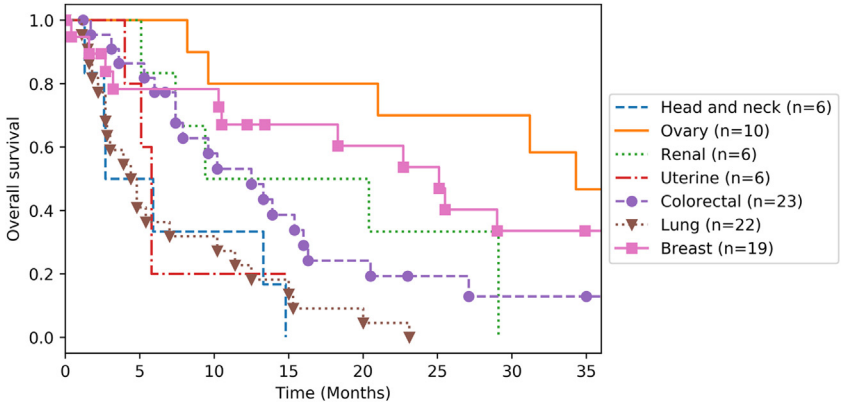

Fig. 2. Overall survival was stratified by all major primary tumor types.

patients suffered from grade 2 toxicity, and no grade ≥3 toxicity was reported. The most common toxicities were six patients (6%) suffering from pain (1 grade 2) and four patients (4%) suffering from nausea (all grade 1). 3 patients noted decreased appetite or early satiety and two experienced diarrhea. Two patients noted increased fatigue. There were no reported cases of pneumonitis or RILD, and no other specific side effect was experienced by more than one patient.

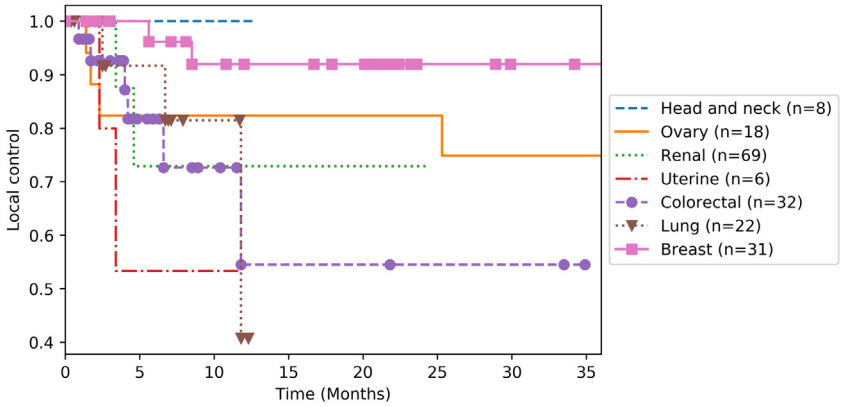

Fig. 3. Local control was demonstrated for all major primary tumor types.

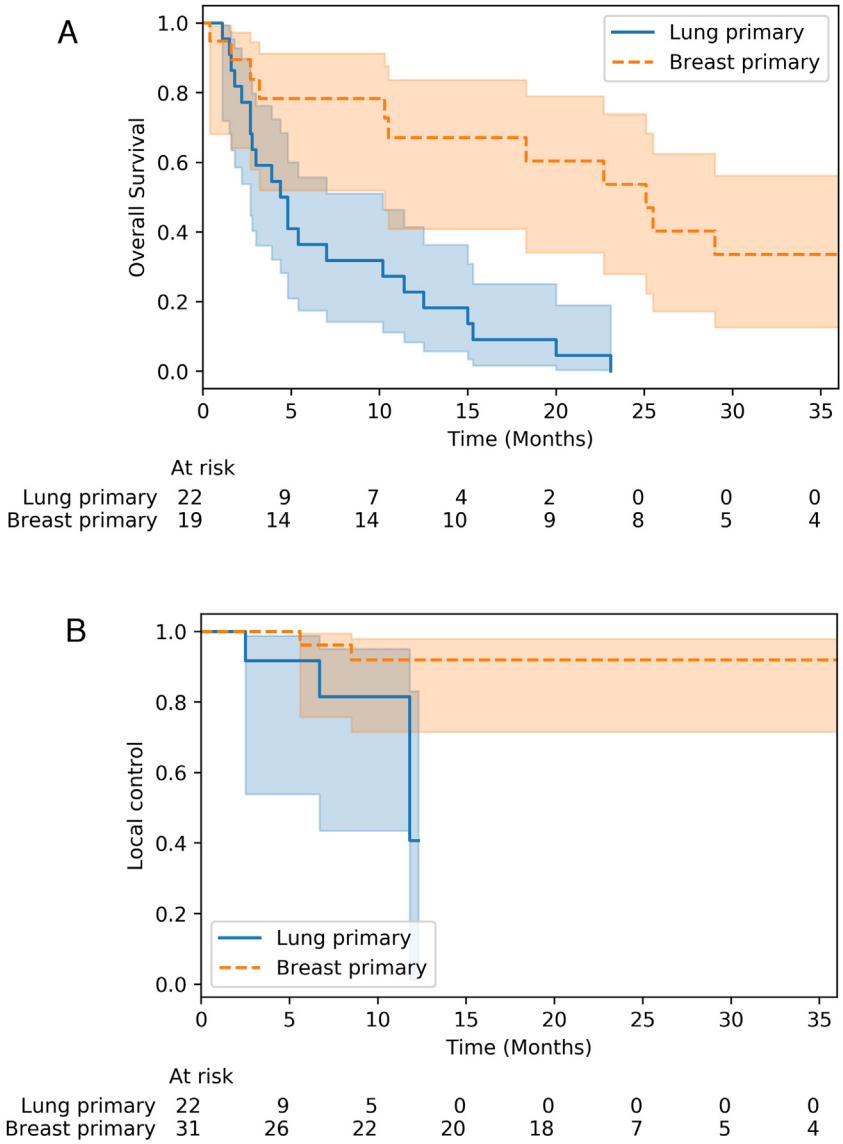

Fig. 4. Overall survival (a) and local control (b) were improved with a breast primary tumor, relative to a lung primary tumor ($p < 0.0001$ and $p = 0.032$, respectively).

4. Discussion

This study demonstrated 1-year local control of 75% with minimal toxicity in the setting of relatively low BED SBRT for liver metastases. These results were not dependent on GTV, BED, the number of treated lesions, or liver function tests, indicating that non-surgical candidates may be considered for low-dose SBRT.

This analysis considered a relatively ill patient cohort, with 81% of patients having received chemotherapy in the past 6 months and a median age of 69 years. Further, 39 patients were treated for at least two distinct lesions, and 73% of patients went on to experience extrahepatic progression of the primary malignancy. In this setting, it is unsurprising that the patients demonstrated a relatively low median overall survival of 9.4 months. Other studies have also found that overall survival is dependent on primary tumor site.[10,16] This patient cohort had a higher number of patients with a primary lung tumor (20.6%), who experienced a median overall survival of merely 4.6 months while patients with colorectal and breast primary tumors experienced overall survival which more closely approximates values previously reported in the literature (12.5 and 25.1 months, respectively).

Local control rates from previous studies have ranged from 71%–92%, and the local control rate here was 75% at one year via the Kaplan-Meier method.[10,13,17,21–23] Two variables have often arisen as predictive of local failure: dose and tumor volume (as measure by GTV or lesion size). Further, the number of treated lesions has often been discussed, with guidelines often recommending treating with SBRT only up to 3 lesions.[31] In this study, none of these factors were found to be predictive of local failure or overall survival. In fact, five patients were included with four lesions, and no restrictions were made regarding GTV or lesion size. For this reason, though the median GTV was only 12.16 cc, patients up to a GTV of 300 cc were included. Other studies have noted improved local control with small lesions of maximal diameter of 3 cm or less than 40 cc.,[13,10] Even with a higher number of large lesions treated in this study, no lesion size or GTV threshold was found to be predictive of treatment. This indicates that low-dose SBRT could be considered in carefully selected patients with large or multiple lesions.

Many studies have pointed towards higher doses as predictive of local control, including analyses ranging from single-fraction to six fraction treatment.[21,22,28] Most authors have pointed towards 48–60 Gy delivered in three fractions as an optimal regimen, but others have questioned whether the dose-fractionation scheme may also depend on the primary tumor histology.[10] Due to the significant differences in outcomes between the different primary tumors found in this analysis, we agree that this hypothesis merits further study. Outcomes in this study closely mirror those previously reported in the literature, and therefore 30 Gy in three fractions may also be an effective dose-fractionation scheme in selected patients for whom surgical resection and/or higher dose therapy may be contraindicated. One potential limitation of this study is that there may have been too few patients with high BED treatments in order to detect improved local control at high BED thresholds. For instance, this analysis would not have demonstrated improved local control with BED > 100 Gy since only two patients receiving treatment with >100 Gy. Even so, we demonstrate encouraging results that may serve as a foundation for further study.

Very low toxicity was noted with treatment. No cases of RILD were noted, and there were no cases of grade ≥3 toxicity. While previous studies have noted similarly encouraging results,[25,31] other have noted instances of grade ≥3 toxicity. Bae et al. reported grade 3 or 4 complications in 7% of patients; however, a higher dose of 45–60 Gy in 3 fractions was utilized.[28] The relatively low median BED of 60 Gy and the prolonged mean days between treatments of 5.19 likely contributed to the minimal toxicity reported in this study. In fact, only 4 grade 2 toxicities were reported among all treatments. These findings indicate that in settings in which the prescription dose may be limited (e.g. previous radiation or concern for toxicity), treatment may still be considered.

No conclusive results have been noted in the literature regarding whether or not liver function tests are predictive of treatment efficacy or toxicity.[32–34] Though a number of machine learning algorithms were applied to the outcomes data, it was difficult to construct a robust model due to the few local failures reported in the cohort. Importance testing did consistently point towards pre-treatment ALT, AST, and AP as predictive of local failure, but this result is insufficient to conclusively state whether or not these values should impact treatment decisions. Further study is recommended. In particular, a patient cohort specifically focused on considering patients who have had local failure of liver SBRT would be best suited to answer this question.

This analysis is primarily limited by the short duration of follow-up and high fraction of patients who were lost to follow-up. This is chiefly the result of the patients presenting with advanced stages of disease and following up with a range of providers at different facilities, including palliative care and primary care physicians. This also served to limit the duration of imaging follow-up. Additionally, patients were treated with a range of dose-fractionation schemes. A more consistent approach would have improved the subsequent analysis. Finally, the delineation of local failure as an increase in size on imaging is an imprecise measure. Because many of these patients suffered from heavy disease burdens and poor health status, biopsy was not commonly pursued. Even so, a more regimented approach to distinguishing local failure would have proven beneficial.

5. Conclusions

This study demonstrated safety and efficacy in a large set of 169 liver lesions treated with SBRT, showing impressive local control even for patients with large tumors or multiple lesions. This points towards the utility of low-dose treatment for non-surgical patients in whom higher-dose therapy may be contraindicated or associated with high risk for toxicity. In carefully selected patients, however, dose escalation may be advisable. Overall survival depends largely on the primary tumor.

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Data sharing statement

Research data are stored in an institutional repository and will be shared upon reasonable request to the corresponding author

Conflicts of interest/Competing interests

The wife of Dr. Kowalchuk is a senior technical product manager at GE Healthcare. No other authors have any conflicts or interests, competing interests, or disclosures.

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