Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2018 March 15; 100(4): 950–958. doi:10.1016/j.ijrobp.2017.12.014.

Comparison of Stereotactic Body Radiation Therapy and Radiofrequency Ablation in the Treatment of Intrahepatic Metastases

William C. Jackson, MD*, Yebin Tao, PhD*, Mishal Mendiratta-Lala, MD†, Latifa Bazzi, BA*, Dan R. Wahl, MD, PhD*, Matthew J. Schipper, PhD*, Mary Feng, MD‡, Kyle C. Cuneo, MD*, Theodore S. Lawrence, MD, PhD*, and Dawn Owen, MD, PhD*

*Departments of Radiation Oncology, University of Michigan, Ann Arbor, Michigan

†Departments of Radiology, University of Michigan, Ann Arbor, Michigan

‡Department of Radiation Oncology, University of California, San Francisco, San Francisco, California

Abstract

Purpose: Stereotactic body radiation therapy (SBRT) and radiofrequency ablation (RFA) are widely used therapies for the treatment of intrahepatic metastases; however, direct comparisons are lacking. We sought to compare outcomes for these 2 modalities.

Methods and Materials: From 2000 to 2015, 161 patients with 282 pathologically diagnosed unresectable liver metastases were treated with RFA (n = 112) or SBRT (n = 170) at a single institution. The primary outcome was freedom from local progression (FFLP). The effect of treatment and covariates on FFLP was modeled using a mixed-effects Cox model with application of inverse probability treatment weighting to adjust for potential imbalances in treatment modality.

Results: The median follow-up period was 24.6 months. Patients receiving SBRT had larger tumors than those treated with RFA (median, 2.7 cm vs 1.8 cm; $P < .01$). On univariate analysis, tumor size was associated with worse FFLP for RFA (hazard ratio [HR], 1.57; 95% confidence interval [CI], 1.15–2.14; $P < .01$) but not for SBRT (HR, 1.38; 95% CI, 0.76–2.51; $P = .3$). The 2-year FFLP rate was 88.2% compared with 73.9%, favoring SBRT ($P = .06$). For tumors ≥ 2 cm in diameter, SBRT was associated with improved FFLP (HR, 0.28; 95% CI, 0.09–0.93; $P < .01$). On multivariate analysis, treatment with SBRT (HR, 0.21; 95% CI, 0.07–0.62; $P = .005$) and smaller tumor size (HR, 0.65; 95% CI, 0.47–0.91; $P = .01$) were associated with improved FFLP. The 2-year overall survival rate was 51.1%, with no difference between groups ($P = .8$). Grade 3 treatment-related toxicity was rare, with no difference between SBRT (n = 4) and RFA (n = 3).

Conclusions: Treatment with SBRT or RFA is well tolerated and provides excellent and similar local control for intrahepatic metastases < 2 cm in size. For tumors ≥ 2 cm in size, treatment with SBRT is associated with improved FFLP and may be the preferable treatment.

Reprint requests to: Dawn Owen, MD, PhD, Department of Radiation Oncology, University of Michigan Medical Center, 1500 E Medical Center, Dr, Ann Arbor, MI 48109-0010. Tel: (734) 763-9513; dawnowen@med.umich.edu.

Conflict of interest: none.

Introduction

Surgical resection is the gold-standard treatment for intrahepatic oligometastases (1). However, the majority of patients with intrahepatic metastases are not candidates for surgical resection (2), often because of an unresectable tumor location, inadequate hepatic reserve, or other comorbidities. For patients with liver metastases from colorectal cancer, surgical resection of oligometastases is associated with improved overall survival (OS) and occasionally results in cure (2, 3), highlighting the importance of intrahepatic local control for patients with limited or controlled systemic disease.

For the majority of patients who are not surgical candidates, liver-directed therapies to provide local control include hepatic artery infusion chemotherapy, transarterial chemoembolization or radioembolization, percutaneous or laparoscopic radiofrequency or microwave ablation, and stereotactic body radiation therapy (SBRT), among others (4). For patients with a limited number of metastases, SBRT and radiofrequency ablation (RFA) are widely used focal liver therapies, as both have prospectively been shown to provide good local control, frequently with reported local recurrence rates <20% (5–8). Results from EORTC (European Organisation for Research and Treatment of Cancer) 40004, which randomized patients with unresectable colorectal liver metastases to systemic therapy with or without RFA, suggest that the addition of RFA improves progression-free survival and OS (9), advocating a role of focal intrahepatic therapy for patients with unresectable metastases. Unfortunately, there are no randomized data to guide the decision between RFA and SBRT for patients with a limited number of liver metastases who are not surgical candidates.

We previously compared the efficacy of SBRT and RFA in a cohort of patients with nonmetastatic inoperable hepatocellular carcinoma treated at our institution, demonstrating excellent local control for both modalities when treating lesions <2 cm in diameter and improved local control with SBRT for larger tumors (10). As it is unclear whether there is an advantage to either RFA or SBRT for patients with a limited number of metastases to the liver, we sought to compare outcomes of patients treated with either modality at our institution from 2000 to 2015. On the basis of our previous comparison of RFA and SBRT when treating hepatocellular carcinoma (10), we hypothesized that both modalities would provide excellent local control for small-diameter metastases, with an advantage favoring SBRT when treating larger metastases.

Methods and Materials

Patient selection

From 2000 to 2015, 161 patients with 282 pathologically diagnosed unresectable liver metastases were treated with RFA or SBRT at a single institution; they form the cohort for this retrospective analysis, which was approved through the local institutional review board. Patients were allowed to have received prior liver-directed therapy or systemic therapy. Most commonly, patients had limited (<5 cm) or stable extrahepatic disease.

Treatment and follow-up

All patients received treatment with SBRT or RFA. Treatment modality was determined after cases were presented to a multidisciplinary tumor board. In general, SBRT was favored over RFA for tumors abutting vasculature or major bile ducts, which could act as heat sinks, or hollow viscera. RFA was delivered percutaneously or laparoscopically with ultrasonographic guidance. Patients received 1 dose of intravenous prophylactic antibiotic (1 dose of intravenous ampicillin and sulbactam, 3 g). All percutaneous ultrasonography guided ablations were performed with patients under general anesthesia with continuous monitoring by an anesthesiologist or certified registered nurse anesthetist. Ultrasonography was used for real-time positioning of the RFA electrode into the lesion. All cases were performed with the Cool-Tip ablation system (Covidien, Minneapolis, MN), with a generator allowing up to 200 W of power. At least 2 grounding pads were placed on the skin of each patient. RFA electrodes were 18 gauge in diameter, and once satisfactory placement of up to 3 electrodes was achieved, ablations were performed according to manufacturer protocol, for an ablation defect aimed to be 5 mm larger than the maximum tumor diameter. Intratumoral temperature was monitored throughout the ablation by a thermocouple present in each probe, with minimum temperatures achieved at 60°C. Ultrasonographic imaging after ablation confirmed ablation of the visualized tumor margin. For any tumor >2.5 cm, a follow-up ablation session was considered. Post-ablation imaging was performed 4 to 6 weeks after the initial ablation session.

For SBRT, all patients underwent magnetic resonance imaging (MRI) and/or computed tomography (CT) simulation. Percutaneously placed fiducial markers for targeting were placed by the interventional radiology department if deemed clinically necessary. Patients were immobilized with a custom body mold. Liver motion was accounted for and minimized with the use of active breathing control or similar spirometric-based breath holdbased technology when tolerated by the patient; otherwise, a 4-dimensional CT scan was used. Daily imaging for tumor localization was used, with daily cone beam CT imaging used in patients without fiducials and used most commonly in patients with fiducials as well. Three-dimensional treatment planning (n = 148, 87%) or intensity modulated radiation therapy (n = 22, 13%) was used for all patients and delivered using 6- to 16-megavolt photons.

The gross tumor volume was defined using the planning CT or MRI scan. There was no planned clinical target volume expansion. If a free-breathing simulation was performed, an internal target volume was created to encompass the range of respiratory-related tumor motion. A 0.5-cm uniform planning target volume (PTV) expansion from gross tumor volume or internal target volume was typically used.

Dose was prescribed to an isodose surface encompassing 99.5% of the PTV, most commonly the 80% isodose surface (75%–85%), with a minimum PTV dose of 90% required, although underdosing of the PTV was permitted if necessary to meet normal tissue constraints. SBRT was delivered in 2 to 3 weekly fractions, with 1 day between any 2 treatments. The most common fractionation was 50 Gy in 5 total fractions (10 Gy/fraction), used in 43% of treated lesions. The next most common regimens were 60 Gy in 3 fractions (20 Gy/fraction), 30 to 45 Gy in 5 fractions (6–9 Gy/fraction), 24 to 54 Gy in 3 fractions (8–18 Gy/fraction),

and 55 to 60 Gy in 5 fractions (11–12 Gy/fraction), used in 19%, 13%, 12%, and 10%, respectively.

Patients were followed up clinically with imaging, most commonly performed in 3-month intervals with CT and/or MRI starting approximately 3 months after treatment. Follow-up was consistent between the 2 groups. Decisions regarding the use of CT and/or MRI were made on a patient-by-patient basis and were usually dependent on how easily visualized the initial metastases and subsequently treated lesion were on CT imaging.

Endpoints

Freedom from local progression (FFLP) was defined as the time from the start of local therapy until local progression of the treated lesion. Local progression was assessed using standard Response Evaluation Criteria in Solid Tumors (RECIST). Censoring for FFLP occurred at the earliest of the following: last hepatic scan, liver transplant, or initiation of systemic therapy (to prevent biases on local control possibly introduced by initiation of systemic therapy). FFLP was evaluated at the lesion level. If residual tumor was observed on initial post-RFA imaging, repeat ablation was allowed, and this did not constitute local progression. OS was measured at the patient level as the time from the start of first focal therapy to death from any cause, with censoring at the last follow-up date. Treatment-related toxicity was graded using the Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

To compare patient characteristics, we used *t* tests, Wilcoxon (Mann-Whitney) tests, *z* tests and χ^2 tests for normal variables, ordinal but nonnormal variables, 2-sample proportions, and nominal categorical variables, respectively. Treatment groups were compared at the tumor level using FFLP and at the patient level using OS. The effect of treatment and other covariates on local progression was modeled using a mixed-effects proportional hazards (Cox) model with patient-level random effects to adjust for the correlation between tumors in the same patient (11). We applied inverse probability of treatment weighting (IPTW) to the Kaplan-Meier method and Cox models for FFLP to adjust for potential imbalances in treatment modality (12). The treatment probabilities were calculated using logistic regression with a set of covariates likely related to the original treatment decisions, including age, sex, race, tumor size, performance status, and number of prior treatments. All of these variables were included, regardless of statistical significance. To assess whether the treatment effect on FFLP was modified by tumor size, we included a treatment by tumor size interaction term in the mixed-effects Cox model. Analyses were performed using R (version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria) with use of the “coxme” package to perform the mixed-effects Cox models.

Results

Patient, tumor, and treatment characteristics

Patient-, tumor-, and treatment-related characteristics can be found in Table 1. In total, 69 patients were treated with RFA to 112 metastases, and 92 patients were treated with SBRT to

170 metastases. The median follow-up period was 24.6 months. Seventy-seven percent of patients were treated between 2008 and 2015. Patients treated with RFA had a statistically significantly longer median follow-up period than patients treated with SBRT (30.5 months vs 20.2 months, $P = .001$), in part due to patients receiving SBRT being treated more recently (median year of treatment, 2010 for SBRT vs 2008 for RFA). The median age at the time of treatment was 60 years in both groups. Patients treated with RFA had improved performance status compared with patients receiving SBRT. The most common histology was colon and/or rectal adenocarcinoma (28% of lesions overall), with the second being tumors of pancreaticobiliary origin (23% of lesions overall). Most patients had received 1 prior liver-directed treatment. Patients receiving SBRT had larger tumors than those treated with RFA (median, 2.7 cm vs 1.8 cm; $P < .001$). While tumors treated with RFA ranged in size from <1 cm to 11 cm, the interquartile range (IQR) was 1.2 to 2.5 cm, and only 4 lesions >5 cm were treated with RFA. The IQR for SBRT-treated lesion size was 1.8 to 4 cm. The median SBRT dose was 50 Gy (IQR, 48–55 Gy) delivered over 5 fractions (IQR, 3–5 fractions). Eighty-one percent of patients received a total biologically equivalent dose >80 Gy assuming an α/β ratio of 10.

Local control

Figure 1 shows Kaplan-Meier analysis of FFLP with IPTW for patients treated with SBRT and RFA. SBRT was associated with numerically improved FFLP, although this did not reach statistical significance (hazard ratio [HR], 2.66; 95% confidence interval [CI], 0.97–7.25; $P = .057$). The FFLP rates at 1 and 2 years after treatment were 74.7% and 60.6%, respectively, for RFA compared with 96% and 88.2%, respectively, for SBRT. Progression elsewhere in the liver and extrahepatic progression were common, occurring in 58% and 64% of patients, respectively, at any point during follow-up, with no difference between SBRT and RFA (both $P > .1$).

Univariate analysis for predictors of FFLP is reported in Table 2. Of note, for patients treated with RFA, when we adjusted for tumor size and histology, there was not a statistical difference in local control when comparing patients treated intraoperatively and those treated percutaneously (HR, 0.19; 95% CI, 0.03–1.40; $P = .1$). Year of treatment was not associated with FFLP (HR, 1.004/year; $P = .96$). There was no statistically significant interaction between treatment (RFA vs SBRT) and tumor histology on FFLP. For all treated lesions, increasing tumor size was the only statistically significant predictor of decreased FFLP (HR, 1.57; 95% CI, 1.15–2.14; $P = .004$) other than age. However, when we independently analyzed patients treated with RFA and SBRT, increasing tumor size remained predictive of decreasing FFLP for patients treated with RFA, with a nearly 2-fold risk of local progression with each centimeter increase in tumor size (HR, 1.95; 95% CI, 1.05–3.62; $P = .035$), whereas this association was not present for patients treated with SBRT (HR, 1.38; 95% CI, 0.76–2.51; $P = .294$). To further characterize the relationship between tumor size, treatment modality, and FFLP, we modeled the HR of RFA versus SBRT against tumor size, with size stratified by quintile (Fig. 2). This suggested a significantly higher HR associated with RFA as compared with SBRT for tumor sizes 2.0 cm (HR, 3.54; 95% CI, 1.08–11.6; $P < .01$). For lesions <2 cm in size, there was no difference in FFLP when RFA and SBRT were compared (HR, 2.18; 95% CI, 0.34–13.8; $P = .4$).

On multivariate Cox proportional hazards analysis (Table 3), when we controlled for treatment modality, patient age, performance status, tumor size, and tumor histology, treatment with SBRT (HR, 0.21; 95% CI, 0.07–0.62; $P = .005$) and smaller tumor size (per centimeter) (HR, 0.65; 95% CI, 0.47–0.91; $P = .01$) were associated with improved FFLP.

Overall survival

Median OS was 24.5 months for all patients, and this did not vary by treatment, with a 25.9-month median OS for RFA versus 24.5 months after SBRT ($P = .6$). Figure 3 shows Kaplan-Meier analysis of OS with IPTW stratified by treatment modality. OS at 1 and 2 years was 75.0% and 50.2%, respectively, for SBRT and 63.1% and 52.3%, respectively, for RFA (both $P > .1$). Five-year OS was approximately 20% in the entire cohort, and this was similar between treatments. On multivariate analysis, treatment modality was not associated with OS.

Treatment-related toxicity

Grade 3 treatment-related toxicity was rare, with no difference in toxicity between SBRT ($n = 4$) and RFA ($n = 3$). SBRT-related toxicity was related to grade 3 gastrointestinal bleeding ($n = 2$) or grade 3 biliary stricture ($n = 2$), whereas RFA-related toxicity was most commonly due to procedure-related infection or visceral perforation (hemorrhagic pericardial effusion [$n = 1$], hemoperitoneum while receiving enoxaparin sodium [$n = 1$], or hepatic abscess [$n = 1$]). There were no cases of radiation-induced liver dysfunction.

Discussion

For patients with a limited number of unresectable intrahepatic metastases, SBRT and RFA are commonly used focal liver therapies; however, direct comparisons of these modalities have been lacking. We have demonstrated that treatment of intrahepatic metastases < 2 cm in size with SBRT or RFA results in excellent local control. For tumors ≥ 2 cm in size, treatment with SBRT was associated with superior local tumor control and therefore may be the preferable treatment option in this setting. There was no difference in OS when SBRT and RFA were compared, and both treatments were well tolerated. Improved local control likely did not translate into improved OS as only approximately 20% of patients with liver metastases die of isolated intrahepatic progression (13) and, as such, we would not expect to detect a difference in a study of this size.

Our 1- and 2-year rates of local control achieved with SBRT, 96% and 88.2%, respectively, are comparable to findings of modern prospective analyses assessing the utility of SBRT in the treatment of liver metastases (Table 4) (5–7, 14, 15). A prospective multi-institutional phase 1–phase 2 trial of SBRT for liver metastases, in which 49 treated lesions were available for analysis, showed local control rates of 95% and 92% at 1 and 2 years after treatment, respectively, when most commonly treating with 60 Gy in 3 fractions (6). A phase 1 trial from Princess Margaret Hospital treated 68 patients with metastatic liver lesions with liver SBRT (27.7–60 Gy over 6 fractions), with a 1-year local control rate of 71% (5). The numerically lower rate of local control in this analysis was likely due to some patients receiving insufficient treatment dose to provide durable local control, particularly given the

larger tumor sizes treated in this trial, as increasing dose was associated with improved local control (5). Scorsetti et al (7) performed a phase 2 trial of SBRT for inoperable liver metastases, treating with 75 Gy delivered over 3 fractions, with 75 Gy representing the mean dose delivered to the PTV. In total, 52 lesions were treated, with a 2-year local control rate of 91% (7). Last, prospective dose-escalation trials of multifraction and single-fraction SBRT performed at the Memorial Sloan Kettering Cancer Center similarly demonstrated local control in excess of 80% when treating intrahepatic metastases (14, 15). In sum, prospective series support the excellent local control rate offered by SBRT in our analysis when treating intrahepatic metastases and suggest that our results are generalizable.

RFA has consistently been shown to provide excellent local control for tumors up to 3 cm in diameter. Indeed, 3 cm is the most commonly reported threshold associated with decreased efficacy of RFA for liver metastases (16, 17), likely driven by the fact that most ablative probes can create approximately 4-cm-diameter ablation zones, and as such, lesions >3 cm are at increasing risk of insufficient treatment margins (18). Analysis of local control after RFA on EORTC 40004, which randomized patients with unresectable colorectal liver metastases to systemic therapy with or without RFA, showed that the risk of local recurrence was >7-fold greater for tumors >3 cm compared with those <3 cm (19). While most analyses of local control following RFA have assessed the impact of tumor size as a categorical variable with a 3- to 3.5-cm threshold, analyses of tumor size as a continuous variable have suggested that there is a continuum of decreasing local control with increasing tumor size (20), and as such, our findings are consistent with the reported literature. It should be emphasized that our analyses did not attempt to assess the ideal size threshold associated with local control after RFA but rather assessed at what threshold SBRT was associated with improved local control when compared with RFA. We demonstrate that SBRT and RFA provide similar local control for lesions <2 cm in size, with SBRT offering improved local control for lesions larger than this, consistent with the overall size limitations associated with RFA. One method by which to overcome the size restriction associated with RFA may be through the use of microwave ablation, as theoretically microwave ablation is able to create larger ablation volumes and does not have the same electrical insulation and heat sink limitations associated with RFA (21). Retrospective analyses support this notion, showing improved local control at 2 years (93% vs 82%) when treating liver metastases with microwave ablation versus RFA (21).

The results of our analysis are also consistent with our previous comparison of SBRT and RFA in the setting of treatment of hepatocellular carcinoma (10). In this analysis SBRT and RFA likewise provided similar local control for tumors <2 cm, with SBRT resulting in improved local control for hepatocellular carcinomas ≥ 2 cm (10). Despite the differences in histologies in these 2 analyses, the 1- and 2-year rates of local control with SBRT were quite similar (96% vs 97.4% and 88.2% vs 83.8%, respectively). The ablative treatment doses delivered with SBRT provide local control rates that rival those achieved with surgical resection, and they do so with minimal impact from tumor histology. Analysis of local recurrence rates after resection of liver metastases on EORTC 40983, which randomized patients with 4 resectable isolated colorectal liver metastases to surgical resection with or without perioperative FOLFOX (folinic acid, 5-fluorouracil, and oxaliplatin), showed an overall local recurrence rate of 5.5%, with a median time from resection to recurrence of 1.1

years in patients receiving perioperative FOLFOX (19). Rates of local recurrence with SBRT in our analysis were similar, albeit slightly higher, with a 2-year rate of 11.8%, although our analysis was performed in a significantly less favorable population, as the majority of patients in this analysis had received prior systemic and focal liver-directed therapy and were not receiving systemic therapy.

Although individual lesion local control for RFA and SBRT is high, intrahepatic progression outside of the treated lesion remains a major clinical problem. The combination of these treatments with systemic therapy earlier in the course of treatment, as has been done with surgical resection, would be a promising next step in improving therapy. EORTC 40983 demonstrated improved progression-free survival with the addition of systemic therapy to surgical resection of hepatic metastases as a result of improved intrahepatic control (22). Regional liver therapy with selective internal radiation therapy (SIRT) with yttrium 90 radioembolization has also been evaluated in conjunction with first-line chemotherapy for patients with colorectal liver metastases. Combined analysis of 3 prospective trials with 1103 patients demonstrated no improvement in OS or progression-free survival with the addition of SIRT, and as such, SIRT is perhaps best reserved for patients with liver metastases refractory to systemic therapy not amenable to focally ablative therapy (23). The strongest data in support of aggressive upfront treatment of hepatic metastases in combination with systemic therapy come from EORTC 40004. In this trial, patients with up to 10 unresectable colorectal liver metastases received systemic therapy with or without aggressive local treatment with RFA with or without surgical resection (9). Aggressive focal treatment of liver metastases resulted in a statistically significant improvement in OS, with the 5-year OS rate increasing from 30.3% to 43.1%, driven by improved progression-free survival (9). On the basis of the improved OS associated with aggressive treatment of liver metastases observed in EORTC 40004 and our finding of improved local control with SBRT compared with RFA, we would anticipate that the upfront use of SBRT plus systemic therapy would improve outcomes compared with systemic therapy alone.

Our analyses are not without limitation. Foremost, our analysis is limited by its retrospective nature, and prospective validation in a randomized clinical trial remains necessary. Furthermore, patients were treated over a 15-year period, during which treatment techniques for both RFA and SBRT have improved. Patients treated with RFA had longer follow-up than patients treated with SBRT. It is possible that with additional follow-up, an increasing number of local recurrences would have been observed in patients treated with SBRT. However, follow-up for patients treated with SBRT approached the median OS of our population, and as such, our 2-year rates of FFLP are likely valid. In addition, radiographic evidence of local progression is easier to assess after RFA than after SBRT, as imaging responses to SBRT evolve over time. We attempted to limit this bias by allowing for repeat RFA after initial posttreatment imaging if there was evidence of residual disease and not considering this local progression. Intrahepatic progression at sites distant to treated lesions was also common, in part reflective of most patients having received prior systemic and liver-directed therapy. Last, <25% of patients treated with SBRT had lesions >4 cm, and as such, our reported rates of local control may not apply to tumors >4 cm.

In closing, treatment with SBRT or RFA is well tolerated and provides excellent and similar local control for intrahepatic metastases <2 cm in size. For tumors ≥ 2 cm in size, treatment with SBRT is associated with improved FFLP and may be the preferable treatment option. Clinical trials assessing aggressive focal treatment of unresectable oligometastatic liver disease with SBRT in combination with systemic therapy near the time of diagnosis are warranted.

References

1. Mayo SC, Pawlik TM. Current management of colorectal hepatic metastasis. *Expert Rev Gastroenterol Hepatol* 2009;3:131–144. [PubMed: 19351284]
2. Cummings LC, Payes JD, Cooper GS. Survival after hepatic resection in metastatic colorectal cancer: A population-based study. *Cancer* 2007;109:718–726. [PubMed: 17238180]
3. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007;25:4575–4580. [PubMed: 17925551]
4. Mahnken AH, Pereira PL, de Baere T. Interventional oncologic approaches to liver metastases. *Radiology* 2013;266:407–430. [PubMed: 23362094]
5. Lee MT, Kim JJ, Dinniwell R, et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. *J Clin Oncol* 2009; 27:1585–1591. [PubMed: 19255313]
6. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol* 2009;27:1572–1578. [PubMed: 19255321]
7. Scorsetti M, Comito T, Tozzi A, et al. Final results of a phase II trial for stereotactic body radiation therapy for patients with inoperable liver metastases from colorectal cancer. *J Cancer Res Clin Oncol* 2015;141:543–553. [PubMed: 25245052]
8. Wong SL, Mangu PB, Choti MA, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. *J Clin Oncol* 2010;28:493–508. [PubMed: 19841322]
9. Ruers T, Van Coevorden F, Punt CJ, et al. Local treatment of unresectable colorectal liver metastases: Results of a randomized phase II trial. *J Natl Cancer Inst* 2017;109:djx105.
10. Wahl DR, Stenmark MH, Tao Y, et al. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. *J Clin Oncol* 2016;34:452–459. [PubMed: 26628466]
11. Ripatti S, Palmgren J. Estimation of multivariate frailty models using penalized partial likelihood. *Biometrics* 2000;56:1016–1022. [PubMed: 11129456]
12. Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: Concepts and analytical approaches. *Annu Rev Public Health* 2000;21:121–145. [PubMed: 10884949]
13. Adam R, Wicherts DA, de Haas RJ, et al. Patients with initially unresectable colorectal liver metastases: Is there a possibility of cure? *J Clin Oncol* 2009;27:1829–1835. [PubMed: 19273699]
14. Meyer JJ, Foster RD, Lev-Cohain N, et al. A phase I dose-escalation trial of single-fraction stereotactic radiation therapy for liver metastases. *Ann Surg Oncol* 2016;23:218–224. [PubMed: 25963478]
15. Rule W, Timmerman R, Tong L, et al. Phase I dose-escalation study of stereotactic body radiotherapy in patients with hepatic metastases. *Ann Surg Oncol* 2011;18:1081–1087. [PubMed: 21046264]
16. Shady W, Petre EN, Gonen M, et al. Percutaneous radiofrequency ablation of colorectal cancer liver metastases: Factors affecting outcomes—a 10-year experience at a single center. *Radiology* 2016; 278:601–611. [PubMed: 26267832]
17. Gillams A, Goldberg N, Ahmed M, et al. Thermal ablation of colorectal liver metastases: A position paper by an international panel of ablation experts, the interventional Oncology Sans Frontières meeting 2013. *Eur Radiol* 2015;25:3438–3454. [PubMed: 25994193]

18. Pathak S, Jones R, Tang JM, et al. Ablative therapies for colorectal liver metastases: A systematic review. *Colorectal Dis* 2011;13:e252–e265. [PubMed: 21689362]
19. Tanis E, Nordlinger B, Mauer M, et al. Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983. *Eur J Cancer* 2014;50:912–919. [PubMed: 24411080]
20. Bleicher RJ, Allegra DP, Nora DT, et al. Radiofrequency ablation in 447 complex unresectable liver tumors: Lessons learned. *Ann Surg Oncol* 2003;10:52–58. [PubMed: 12513961]
21. Correa-Gallego C, Fong YM, Gonen M, et al. A retrospective comparison of microwave ablation vs. radiofrequency ablation for colorectal cancer hepatic metastases. *Ann Surg Oncol* 2014;21:4278–4283. [PubMed: 24889486]
22. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): Long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013;14:1208–1215. [PubMed: 24120480]
23. Sharma RA, Wasan HS, Van Hazel GA, et al. Overall survival analysis of the FOXFIRE prospective randomized studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer [abstract]. *J Clin Oncol* 2017; 35(Suppl.):3507.

Summary

Stereotactic body radiation therapy and radiofrequency ablation provide excellent local control when treating small liver metastases. For larger metastases, treatment with stereotactic body radiation therapy results in superior local control.

Fig. 1. Freedom from local progression (FFLP) by treatment modality. Abbreviations: CI = confidence interval; HR = hazard ratio; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy.

Fig. 2.

Freedom from local progression (FFLP) by treatment modality stratified by tumor size. The solid central line denotes hazard ratio estimates, with the dashed lines representing 95% confidence intervals. The x-axis is stratified by tumor-size quintiles. *Abbreviations:* RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy.

Fig. 3. Overall survival (OS) by treatment modality. *Abbreviations:* RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy.

Table 1

Patient characteristics

Characteristic	RFA	SBRT	P value
No. of patients	69	92	-
Age, y			
Median	60.0	60.4	.32
Range	33.0–86.0	23.0–82.3	
Male sex	34 (49.3)	44 (47.8)	.86
Race			
White	65 (94.2)	78 (84.8)	.06
Other or unknown	4 (5.8)	14 (15.2)	
ECOG score			
<2	106 (96.4)	142 (86.1)	.005
2	4 (3.6)	23 (13.9)	
Histology			
Colon and/or rectal adenocarcinoma	46 (41.0)	33 (19.4)	<.001
Pancreaticobiliary	17 (15.2)	47 (27.6)	
Sarcoma	6 (5.4)	26 (15.3)	
Neuroendocrine and/or small cell tumors	20 (17.9)	10 (5.9)	
Esophageal and/or gastric adenocarcinoma	2 (1.8)	19 (11.2)	
Breast adenocarcinoma	12 (10.7)	8 (4.7)	
Squamous cell carcinoma	0(0)	12 (7.1)	
Melanoma	0 (0)	6 (3.5)	
Other	9 (8.0)	9 (5.3)	
No. of tumors	112	170	
Tumor maximal diameter, cm			
Median	1.8	2.7	<.001
Range	0.0–11.0	0.0–9.2	
No. of active liver tumors at time of treatment			
Median	2	2	.31
Range	1–7	1–10	
No. of prior liver therapies			
Median	1	1	.18
Range	0–6	0–8	
No. of lines of prior systemic therapies			
Median	1	1	.008
Range	0–11	0–10	
RFA type			
Percutaneous	63 (56.3)	-	
Intraoperative	49 (43.7)	-	
Fiducials	-	59 (34.7)	
SBRT dose, Gy			

Characteristic	RFA	SBRT	P value
Median	-	50	
Range	-	24–61	
Follow-up for all patients, mo			
Median	30.5	20.2	.001
Range	0.5–131.7	0.3–102.4	
Follow-up for living patients, mo			
Median	41.7	28.2	.15
Range	0.5–131.7	0.3–102.4	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy. Data are presented as number (percent) unless otherwise noted. Only age and sex are presented at the patient level; all other variables are presented at the tumor level. Unless otherwise noted, all variables are presented at baseline (ie, time of treatment).

Table 2

Univariate analysis of variables predictive of local progression

Variable	All lesions			RFA			SBRT		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Treatment: RFA vs SBRT	2.66	0.97–7.25	.057	-	-	-	-	-	-
Age	1.06	1.01–1.10	.018	1.09	1.06–1.14	<.001	1.03	0.93–1.15	.562
Tumor size	1.57	1.15–2.14	.004	1.95	1.05–3.62	.035	1.38	0.76–2.51	.294
ECOG score	2.42	0.21–27.8	.480	4.94	0.57–43.1	.147	0.92	0.03–27.7	.960
Histology	0.56	0.18–1.82	.340	0.17	0.03–1.11	.064	2.50	0.25–24.7	.430
No. of prior liver therapies	0.96	0.77–1.18	.670	0.63	0.31–1.28	.201	1.45	0.85–2.47	.171
No. of prior systemic therapies	1.08	0.60–1.92	.801	0.92	0.74–1.14	.428	1.36	0.66–2.77	.406
SBRT dose	-	-	-	-	-	-	0.98	0.86–1.12	.749

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy.

Age (per year), tumor size (per centimeter), ECOG score (2 vs < 2), histology (colon and/or rectal adenocarcinoma vs other), number of prior liver therapies (per therapy), number of prior systemic therapies (per therapy), and SBRT dose (per gray) were treated as continuous variables. Data under “All lesions” have been corrected for treatment modality.

Table 3

Multivariate Cox proportional hazards analysis of factors associated with local progression

	HR	95% CI	P value
Treatment: RFA vs SBRT	4.75	1.60–14.1	.005
Age (per year)	1.05	1.00–1.11	.053
Tumor size (per centimeter)	1.53	1.10–2.14	.011
ECOG score (2 vs < 2)	1.69	0.24–10.6	.638
Histology (colon and/or rectal adenocarcinoma vs other)	0.65	0.20–2.11	.470

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy.

Table 4

Comparison of our analysis with select modern prospective trials of liver-only SBRT for intrahepatic metastases

Trial	Patients (lesions)	% Colorectal	Fractions	Dose/fraction, Gy	Total dose, Gy	BED ($\alpha/\beta = 10$)	Median diameter, cm	1-y LC	2-y LC	Median OS
Meyer et al (14)	14 (17)	21.4%	1	35–40	35–40	157.5–200	Approximately 2.8 [*]	100%	100%	>36 mo
Scorsetti et al (7)	42 (52)	100%	3	25	75 (mean PTV)	262.5	3.5 (mean)	95%	91%	29.2 mo
Rule et al (15)	27 (37)	44.4%	3–5	10–12	30–60	60–132	2.5	~ 88% [†]	~ 84% [†]	37 mo
Lee et al (5)	68 (approximately 143)	59%	6	4.6–10	27.7–60	40.4–120	5.2	71%	71%	17.6 mo
Rusthoven et al (6)	47 (63)	32%	3	12–20	36–60	79.2–180	2.7	95%	92%	20.5 mo
Our analysis	92 (170)	62%	3–5	8–12	24–61	43.2–132	2.7	96%	88.2%	24.5 mo

Abbreviations: BED = biologically equivalent dose; LC = local control; OS = overall survival; PTV = planning target volume; SBRT = stereotactic body radiation therapy.

^{*} Calculated from PTV assuming a uniform 5-mm PTV expansion.

[†] Estimated.