HHS Public Access

Author manuscript

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2022 May 01.

Local Control After Stereotactic Body Radiation Therapy for Liver Tumors

Nitin Ohri, MD[*], **Wolfgang A. Tomé, PhD**[*], **Alejandra Méndez Romero, MD**[†], **Moyed Miften, PhD**[‡], **Randall K. Ten Haken, PhD**[§], **Laura A. Dawson, MD**[‖], **Jimm Grimm, PhD**[¶], **Ellen Yorke, PhD**[#], **Andrew Jackson, PhD**[#]

[*]Department of Radiation Oncology, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York [†]Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands [‡]Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, Colorado [§]Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan [‖]Radiation Medicine Program, Princess Margaret Cancer Centre and Department of Radiation Oncology, University of Toronto, Ontario, Canada [¶]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University, Baltimore, Maryland [#]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York

Abstract

Purpose: To quantitatively evaluate published experiences with hepatic stereotactic body radiation therapy (SBRT), to determine local control rates after treatment of primary and metastatic liver tumors and to examine whether outcomes are affected by SBRT dosing regimen.

Methods and Materials: We identified published articles that reported local control rates after SBRT for primary or metastatic liver tumors. Biologically effective doses (BEDs) were calculated for each dosing regimen using the linear-quadratic equation. We excluded series in which a wide range of BEDs was used. Individual lesion data for local control were extracted from actuarial survival curves, and data were aggregated to form a single dataset. Actuarial local control curves were generated using the Kaplan-Meier method after grouping lesions by disease type and BED (<100 Gy_{10} vs >100 Gy_{10}). Comparisons were made using logerank testing.

Results: Thirteen articles met all inclusion criteria and formed the dataset for this analysis. The 1-, 2-, and 3-year actuarial local control rates after SBRT for primary liver tumors (n = 431) were 93%, 89%, and 86%, respectively. Lower 1- (90%), 2- (79%), and 3-year (76%) actuarial local control rates were observed for liver metastases (n = 290, logerank $P = .011$). Among patients treated with SBRT for primary liver tumors, there was no evidence that local control is influenced by BED within the range of schedules used. For liver metastases, on the other hand, outcomes

Reprint requests to: Wolfgang A. Tomé, PhD, FAAPM, FASTRO, Department of Radiation Oncology, Montefiore Medical Center and Albert Einstein College of Medicine, 1300 Morris Park Ave, Block Building Room 106, Bronx, NY 10461. Tel: (718)-430-3188; wtome@monteflore.org.

Conflict of interest: none.

were significantly better for lesions treated with BEDs exceeding 100 Gy_{10} (3-year local control 93%) than for those treated with BEDs of 100 Gy_{10} (3-year local control 65%, $P < .001$).

Conclusions: Stereotactic body radiation therapy for primary liver tumors provides high rates of durable local control, with no clear evidence for a doseeresponse relationship among commonly utilized schedules. Excellent local control rates are also seen after SBRT for liver metastases when BEDs of >100 Gy_{10} are utilized.

Summary

The authors quantitatively evaluated published experiences with hepatic SBRT to determine local control rates for primary and metastatic liver tumors and examined whether outcomes are affected by SBRT dosing regimen. For primary liver tumors, SBRT provides high rates of durable local control, with no clear evidence of a doseeresponse relationship for commonly utilized schedules; whereas for liver metastases after SBRT, excellent local control rates are seen when utilizing biologically effective doses above 100 Gy_{10}.

1. Clinical Significance

The liver is a common location for both primary and metastatic malignancies. Options for local therapy may include surgical resection, ablative procedures, intra-arterial therapy, and radiation therapy (RT). Historical experiences using large-field hepatic RT have had limited success, because tolerable doses of whole-liver RT (approximately 30 Gy) are insufficient to control most carcinomas (1–3). Higher doses of whole-liver RT are associated with a significant risk of radiation-induced liver damage.

More recent experiences have demonstrated that high-dose partial liver RT may be safer and more effective than whole-liver RT for patients with primary and metastatic liver tumors (4–9). In recent years, technological advances in target definition, treatment planning, and setup verification have allowed radiation oncologists to implement hypofractionated stereo-tactic body radiation therapy (SBRT) for liver tumors. Potential benefits of SBRT include decreased normal tissue irradiation, delivery of increased biologically effective doses to target tissues, shortening of the overall treatment duration, and exploitation of tumoricidal mechanisms that may not be active when standard fractionation is used (10).

Numerous dosing and fractionation schedules have been used to treat hepatic tumors with SBRT. In other settings (eg, SBRT for early-stage lung cancer), doseeresponse relationships and tumor control probability (TCP) models are available to guide dose selection (11, 12). There are few data, however, to indicate whether similar doseeresponse relationships apply to hepatic SBRT. We herein report the results of a systematic quantitative review of published experiences with liver SBRT to determine whether there is a relationship between liver SBRT dosing and clinical outcomes.

2. Endpoints

The primary endpoint examined in this study was local control. For patients who received simultaneous treatment for several lesions, each lesion was treated as an individual data point. Local control was based on serial imaging in all of the studies incorporated in this

analysis. Imaging protocols varied slightly between studies but almost always included computed tomography and/or magnetic resonance imaging every 3 months. Response evaluations were mainly performed using guidelines that included RECIST (13), modified RECIST (14), World Health Organization (15), and European Association for the Study of the Liver (16) criteria. Local control was evaluated using actuarial statistical methods; data were right-censored when patients were lost to follow-up or died without local progression.

3. Challenges Defining and Segmenting Anatomic Volumes

Target definition protocols varied between studies. Gross tumor volumes were typically defined using contrast-enhanced computed tomography, often with magnetic resonance imaging fusion. In many series, implanted fiducials were used for treatment planning and setup verification (17–22). In 1 series in which SBRT was used to treat cholangiocarcinoma, biliary stents served as fiducial markers (23). In some hepatocellular carcinoma (HCC) series, lipiodol from prior chemoembolizations was used for target definition and as a fiducial marker (24, 25). Clinical target volume expansions ranged from 0 to 10 mm (17–22, 25–29). Planning target volume (PTV) margins varied according to immobilization technique and how respiratory motion was managed. We are unable to make specific recommendations regarding motion management strategies and margin sizes on the basis of available data. We strongly recommend that liver SBRT be performed under the guidance of clinicians with expertise in this area, because there is likely a learning curve in the implementation of this new tool.

4. Review of Outcomes Data

Study selection

We performed PubMed searches for the terms “SBRT and liver” and “SABR and liver” on November 16, 2013. Abstracts of all hits were reviewed. Studies that did not report clinical outcomes for patients treated with hepatic SBRT were excluded. Review articles and case reports were also excluded, as were studies in which SBRT was used as a bridge to liver transplant. Because the primary purpose of this analysis was to correlate SBRT dosing with tumor control, we also excluded series in which a wide range of doses were used and outcomes data were not provided for various dose levels. When more than 1 publication describing the same group of patients was identified, we used the article with the most recent or complete data.

Data extraction

Data extraction was conducted by the lead investigator (N.O.) and reviewed by a second investigator (W.A.T.). For articles that met all inclusion criteria, individual lesion data were extracted from Kaplan-Meier local control curves, as described by Guyot et al (30). We also tabulated the following information from each study: first author’s name, year of publication, disease treated, sample size, SBRT schedule, and median follow-up. For each SBRT dosing schedule, a biologically effective dose (BED) for the prescription dose was calculated using the standard linear-quadratic model and $\alpha/\beta = 10$ Gy. It is important to optimize values of α/β in future studies, but currently it has still been common to use $\alpha/\beta =$

3 Gy for some normal tissues and α/β =10 Gy for some fast turnover tissues, such as tumors whose cell survival curves do not exhibit a pronounced shoulder (31, 32).

Search results

Our initial search yielded 201 hits. Forty-eight of these articles provided local control data after hepatic SBRT. Twenty-one series were excluded from this analysis because they included patients treated with a wide range of BEDs and did not report outcomes in subgroups based on BED. Eleven articles were excluded because they reported outcomes for patient populations that overlapped with patients included in subsequent articles. Two remaining series did not report separate outcomes for primary and metastatic liver tumors, and 1 reported on the use of SBRT as a bridge to transplant for HCC. The remaining 13 articles met all inclusion criteria and formed the dataset for this analysis. The composite sample size was 721 tumors (642 patients). Stereotactic body radiation therapy was used to treat HCC in 5 studies (n = 394) (17, 18, 24–26), to treat liver metastases in 6 studies (n = 290) (20–22, 27–29), and to treat cholangiocarcinoma in 2 studies (n = 37) (19, 23). The most common histology for patients with liver metastases was colorectal cancer, which accounted for 32% to 100% of the treated lesions in the articles we analyzed (overall 56% of liver metastases). Stereotactic body radiation therapy doses ranged from 24 to 60 Gy, delivered in 1 to 5 fractions of 7 to 26 Gy. Median BED was 88 Gy_{10}, with an interquartile range of 72 to 125 Gy_{10}. Seventy-nine local failures were observed. Study details are summarized in Table 1.

5. Factors Affecting Outcomes

The individual lesion data extracted from each article were aggregated to form a single dataset. Factors that we explored as predictors of outcomes were diagnosis and BED. Separate Kaplan-Meier curves for local control were generated for HCC, cholangiocarcinoma, and liver metastases. For each diagnosis, additional Kaplan-Meier curves were also generated for the subsets of patients treated with BED > 100 Gy_{10} versus patients treated with BED ≤ 100 Gy_{10}. Logerank testing was used to compare actuarial local control results. Tumor diameters or volumes were often not reported for each study subject, so these potentially important factors could not be incorporated into our analysis.

Local control by tumor type

Median follow-up for patients with primary liver tumors was 18 months (interquartile range, 11–29 months). The 1-, 2-, and 3-year actuarial local control rates after SBRT for primary liver tumors were 93%, 89%, and 86%, respectively. Median follow-up for patients with liver metastases was 14 months (interquartile range, 8–23 months). The 1-, 2-, and 3-year actuarial local control rates for liver metastases were 90%, 79%, and 76%, respectively. Kaplan-Meier curves for local control after SBRT are shown in Figure 1.

Local control by tumor type and SBRT dose

For primary liver tumors, the data presented here suggest that there might not be a doseeresponse relationship within the range of reported schedules (33–60 Gy, 3–5 fractions, BED 60–180 Gy_{10}). Actuarial local rates at 1, 2, and 3 years for lesions treated with BED ≤

100 Gy were 94%, 89%, and 86%, respectively. Similar local control rates (92%, 89%, and 86%) were seen in lesions treated with BED > 100 Gy_{10} (logerank $P = .972$). These results are displayed graphically in Figure 2. The same finding held true when other BED cutoffs between 60 and 180 Gy_{10} were explored (data not shown). This, however, does not mean that a doseeresponse relationship either as a function of tumor volume or tumor stage does not exist, but simply points to the limitation of our analysis in taking these factors into account. In particular, 2 recent studies have shown the importance of tumor volume on expected local tumor control (33, 34). Although Yamashita et al (33) noted no difference in local control after SBRT for a median BED of 100 Gy_{10} for HCC and liver metastases in their cohort of 130 patients, they did note a dependence of the local control rate on tumor volume, observing that local control rate was significantly different for tumors having a maximum diameter of >30 mm versus ≤30 mm (64% vs 85%, $P = .040$). Therefore, if one would be able to take the variables of tumor volume and tumor stage into account, a definite doseeresponse relationship might well emerge.

In contrast, BED was a significant predictor of local control after SBRT for liver metastases. Treatment with BED > 100 Gy_{10} yielded higher 1- (96% vs 84%), 2- (93% vs 70%), and 3-year (93% vs 65%) local control than treatment with lower doses (logerank $P < .001$; Fig. 3).

6. Mathematical/Biological Model

As mentioned above, a BED was calculated for each lesion treated with SBRT. In cases in which examination of Kaplan-Meier curves suggested a doseeresponse relationship, TCP modeling was performed. Data were sorted into 4 groups according to BED, and the actuarial 2-year local control for each group was calculated. These 4 data points were fit to a standard TCP model using least-squares optimization:

$$TCP(d) = \frac{100\%}{1 + exp\left(\frac{TCD_{50} - d}{k}\right)} \quad (1)$$

where d is BED, TCD_{50} is the BED required to achieve 50% tumor control, and k is a fitting constant that is equal to 25 divided by $Slope_{50}$ of the TCP curve (35), where $Slope_{50}$ is an estimate for the expected percent increase in TCP for each additional delivered gray to the tumor. We used a bootstrap resampling method to characterize the distributions of model parameters and formulate 95% confidence bounds for the TCP curve (36). A total of 5000 iterations were performed. All analyses were performed using MATLAB (The Mathworks, Natick, MA).

Tumor control probability modeling results for the treatment of liver metastases are depicted in Figure 4. Modeling using the full dataset provided optimal model parameters of 16 Gy for the TCD_{50} and 74 Gy for k.

Incorporating bootstrap resampling results, the estimated 2-year local control for a BED of 80 Gy_{10} (eg, 10 Gy × 4) is 70% (95% confidence interval 64%−77%). For a BED of 100 Gy_{10} (eg, 10 Gy × 5), this increases to 76% (70%−82%), and using a BED of 180 Gy_{10} (eg, 20 Gy × 3), TCP is 90% (85%−95%). It may be noted that the TCP model shown in

Equation 1 approaches 100% as BED increases, but in clinical practice it is known that for various reasons the actual 100% is rarely achieved. However, the highest clinical data point in Figure 4 is at 94%, and our model only mildly increases this to 97%, and at a BED of 300 Gy_{10} the model is still below 99%, so in this case the model matches clinical observations quite well. In fact, the R^2 for the model generated using the full dataset was 0.98.

7. Special Situations

The doseeresponse analyses presented in this report were based on SBRT prescription doses. In some series these doses were applied to the isocenter. In other reports, doses were prescribed to a PTV or an isodose line between 65% and 80%. Separate analyses were performed after accounting for these differences. These adjustments did not meaningfully alter our results (data not shown). Further analysis using dosimetric data from individual lesions would allow comparisons of isocenter dose, PTV dose, and other measures, such as equivalent uniform dose (37), as predictors of tumor control.

Metastases from colorectal cancer have been shown to be relatively resistant to SBRT in some settings (38, 39). Tools to quantify radio-sensitivity across wider ranges of histologies are also being developed (40). Although more than half of the liver metastases included in the present analysis were in patients with colorectal cancer, very few of the articles we reviewed compared local control after SBRT for colorectal metastases against outcomes for other malignancies. Although the outcomes for liver metastases from different sites tend to be rather heterogeneous, and the heterogeneity of primary tumor locations will have an impact on the expected tumor control of liver metastases, we are unable to take this heterogeneity into account in our analysis. Furthermore, for the same reason we could not examine the effect of histology on the likelihood of tumor control or whether the disparate control rates seen in primary and metastatic liver tumors were driven by colorectal metastases.

The local control results and doseeresponse relationships reported in this analysis are applicable to primary and metastatic liver tumors treated with SBRT. Our findings cannot be translated to other forms of delivering high-dose RT, such as selective internal RT with ^{90}Y, which is more often used in patients with multifocal disease. Our findings may also be limited by the sensitivity and specificity of existing imaging tools to diagnose local disease progression after SBRT. Posttreatment changes seen on imaging may be difficult to interpret, leading clinicians to misdiagnose local control or local recurrence (41). This could confound the doseeresponse relationships demonstrated in this analysis.

Because many patients die without local tumor progression after SBRT for primary or metastatic liver tumors, Kaplan-Meier estimates of local control may be significantly biased. Future studies should use competing risks methodology, which has been used in very few studies on this topic to date.

8. Recommended DoseeVolume Objectives

Primary liver tumors

We found no evidence that local control after SBRT for primary liver tumors is improved when more intense dosing regimens are used. This was because excellent local control rates were seen in cases in which HCC and cholangiocarcinoma were treated with relatively low-dose SBRT regimens. This may be viewed as an unexpected finding, because HCC has historically not been considered to be a particularly radiosensitive tumor. A quantitative review has demonstrated that the radiosensitivity of HCC is comparable to that of other carcinomas commonly treated with RT (42). Our results are consistent with excellent local control rates observed in a prospective trial in which a wide range of SBRT doses was used to treat HCC (43). One possible explanation for our findings is that SBRT is often used to treat HCC after administration of other local, regional, or systemic treatments. The viable tumor burden in lesions treated with SBRT may therefore be lower than that existing in comparable metastatic liver tumors, contributing to the excellent local control rates observed after SBRT. Another concern is possible latent confounding by variables, such as tumor size, that may be associated with BED and could affect control rates after SBRT. Patient-level data will be required to explore this possibility.

In the use of SBRT for primary liver tumors, in which underlying liver dysfunction may increase the risk of radiation-induced liver damage, several groups now advocate the use of normal tissue complication probability modeling to select a prescription dose that does not exceed an acceptable risk level (44, 45). This approach has been used in large, prospective, single-institution trials (43) and is being used in an ongoing cooperative group study (NCT01730937). Although this strategy may be critical to the successful implementation of SBRT for patients with liver disease, it may confound further study of dosee response relationships in this setting.

Among the 227 lesions in this analysis that were treated with BEDs of between 60 and 72 Gy_{10} (approximately half of the dataset), actuarial local control was 90% at 2 years. We therefore believe that it is reasonable to use relatively conservative SBRT schedules, such as 8 to 10 Gy × 5 fractions, in this patient population. More aggressive schedules should be used with caution, especially in patients with underlying liver disease.

Metastatic liver tumors

For metastatic tumors involving the liver, we observed excellent local control rates in the subset of patients treated with BEDs exceeding 100 Gy_{10}. Tumor control probability modeling revealed that the 2-year local control is expected to increase progressively with BED, reaching 76% for a BED of 100 Gy_{10} and 90% for a BED of 180 Gy_{10}. Similar effects have been seen in the treatment of primary lung tumors (11, 12) and spine and other metastases (46, 47) with hypofractionated RT. Hence, relatively aggressive SBRT schedules delivering a BED 100 Gy_{10} should be considered for patients with liver metastases.

9. Future Studies

Future analyses with complete patient-level data will be needed to determine whether tumor histology modulates the TCP curve for liver metastases. Studies exploring the mechanisms underlying the efficacy of SBRT, which may modulate the tumor microenvironment (48) and engage the immune system (49) more effectively than conventional RT, will be critical in advancing our field. Moreover, the potential for improved tumor control from selective boosting of tumor subvolumes could also be explored, particularly in conjunction with fluorodeoxyglucose, fluoromisonidazole, or other positron emission tomography radiotracers to overcome tumor metabolic activity or hypoxia (50, 51).

On the basis of a thorough review of available data, we have determined that SBRT can be extremely effective in achieving local tumor control for patients with primary or metastatic liver tumors. High-level data demonstrating that liver SBRT provides clinical benefit in comparison with or as an adjunct to other local and systemic treatments, however, are still lacking. Randomized trials incorporating SBRT into the treatment of primary and metastatic liver tumors will be critical in establishing liver SBRT as an accepted treatment modality.

10. Reporting Standards for Outcomes

In this analysis we were able to extract local control data for individual lesions from published Kaplan-Meier curves. By excluding series in which wide BED ranges were used, we were able to ascribe a BED to each patient and evaluate for doseeresponse relationships. Other factors that may significantly influence local control, such as metastasis histology and tumor size, could not be analyzed quantitatively owing to limitations in the available data. Improved reporting of these and other factors, perhaps as supplemental information accompanying published articles, will facilitate a better understanding of predictors of disease control in the future (52).

Acknowledgments

A.J. was supported in part by grant nos. 1RO1CA129182 and P30 CA008748 from the National Cancer Institute. E.Y. was supported in part by grant no. P30 CA008748 from the National Cancer Institute.

References

1. Stillwagon GB, Order SE, Guse C, et al. 194 hepatocellular cancers treated by radiation and chemotherapy combinations: Toxicity and response: A Radiation Therapy Oncology Group Study. Int J Radiat Oncol Biol Phys 1989;17:1223–1229. [PubMed: 2557307]
2. Leibel SA, Pajak TF, Massullo V, et al. A comparison of misonidazole sensitized radiation therapy to radiation therapy alone for the palliation of hepatic metastases: Results of a Radiation Therapy Oncology Group randomized prospective trial. Int J Radiat Oncol Biol Phys 1987;13:1057–1064. [PubMed: 3597149]
3. Russell AH, Clyde C, Wasserman TH, et al. Accelerated hyper-fractionated hepatic irradiation in the management of patients with liver metastases: Results of the RTOG dose escalating protocol. Int J Radiat Oncol Biol Phys 1993;27:117–123. [PubMed: 8365932]
4. Seo YS, Kim JN, Keum B, et al. Radiotherapy for 65 patients with advanced unresectable hepatocellular carcinoma. World J Gastroenterol 2008;14:2394–2400. [PubMed: 18416468]
5. Park W, Lim DH, Paik SW, et al. Local radiotherapy for patients with unresectable hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2005;61:1143–1150. [PubMed: 15752895]

6. Seong J, Park HC, Han KH, et al. Clinical results and prognostic factors in radiotherapy for unresectable hepatocellular carcinoma: A retrospective study of 158 patients. Int J Radiat Oncol Biol Phys 2003;55:329–336. [PubMed: 12527045]
7. Robertson JM, Lawrence TS, Walker S, et al. The treatment of colorectal liver metastases with conformal radiation therapy and regional chemotherapy. Int J Radiat Oncol Biol Phys 1995;32: 445–450. [PubMed: 7751185]
8. Dawson LA, McGinn CJ, Normolle D, et al. Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. J Clin Oncol 2000;18: 2210–2218. [PubMed: 10829040]
9. Ben-Josef E, Normolle D, Ensminger WD, et al. Phase II trial of high-dose conformal radiation therapy with concurrent hepatic artery floxuridine for unresectable intrahepatic malignancies. J Clin Oncol 2005;23:8739–8747. [PubMed: 16314634]
10. Park HJ, Griffin RJ, Hui S, et al. Radiation-induced vascular damage in tumors: Implications of vascular damage in ablative hypofractionated radiotherapy (SBRT and SRS). Radiat Res 2012;177:311–327. [PubMed: 22229487]
11. Ohri N, Werner-Wasik M, Grills IS, et al. Modeling local control after hypofractionated stereotactic body radiation therapy for stage I non-small cell lung cancer: A report from the Elekta collaborative lung research group. Int J Radiat Oncol Biol Phys 2012;84: e379–e384. [PubMed: 22999272]
12. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: Updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94. [PubMed: 17603311]
13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–247. [PubMed: 19097774]
14. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52–60. [PubMed: 20175033]
15. Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. Cancer 1981;47:207–214. [PubMed: 7459811]
16. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421–430. [PubMed: 11592607]
17. Dewas S, Bibault JE, Mirabel X, et al. Prognostic factors affecting local control of hepatic tumors treated by stereotactic body radiation therapy. Radiat Oncol 2012;7:166. [PubMed: 23050794]
18. Kwon JH, Bae SH, Kim JY, et al. Long-term effect of stereotactic body radiation therapy for primary hepatocellular carcinoma ineligible for local ablation therapy or surgical resection. Stereotactic radiotherapy for liver cancer. BMC Cancer 2010;10:475. [PubMed: 20813065]
19. Barney BM, Olivier KR, Miller RC, et al. Clinical outcomes and toxicity using stereotactic body radiotherapy (SBRT) for advanced cholangiocarcinoma. Radiat Oncol 2012;7:67. [PubMed: 22553982]
20. Mendez Romero A, Wunderink W, Hussain SM, et al. Stereotactic body radiation therapy for primary and metastatic liver tumors: A single institution phase I-II study. Acta Oncol 2006;45:831–837. [PubMed: 16982547]
21. Stintzing S, Grothe A, Hendrich S, et al. Percutaneous radio-frequency ablation (RFA) or robotic radiosurgery (RRS) for salvage treatment of colorectal liver metastases. Acta Oncol 2013;52: 971–977. [PubMed: 23409768]
22. Vautravers-Dewas C, Dewas S, Bonodeau F, et al. Image-guided robotic stereotactic body radiation therapy for liver metastases: Is there a dose response relationship? Int J Radiat Oncol Biol Phys 2011;81:e39–e47. [PubMed: 21377292]
23. Kopek N, Holt MI, Hansen AT, et al. Stereotactic body radiotherapy for unresectable cholangiocarcinoma. Radiother Oncol 2010;94: 47–52. [PubMed: 19963295]
24. Jang WI, Kim MS, Bae SH, et al. High-dose stereotactic body radiotherapy correlates increased local control and overall survival in patients with inoperable hepatocellular carcinoma. Radiat Oncol 2013;8:250. [PubMed: 24160944]

25. Sanuki N, Takeda A, Oku Y, et al. Stereotactic body radiotherapy for small hepatocellular carcinoma: A retrospective outcome analysis in 185 patients. Acta Oncol 2014;53:399–404. [PubMed: 23962244]
26. Honda Y, Kimura T, Aikata H, et al. Stereotactic body radiation therapy combined with transcatheter arterial chemoembolization for small hepatocellular carcinoma. J Gastroenterol Hepatol 2013;28: 530–536. [PubMed: 23216217]
27. 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]
28. Scorsetti M, Arcangeli S, Tozzi A, et al. Is stereotactic body radiation therapy an attractive option for unresectable liver metastases? A preliminary report from a phase 2 trial. Int J Radiat Oncol Biol Phys 2013;86:336–342. [PubMed: 23433800]
29. Wulf J, Guckenberger M, Haedinger U, et al. Stereotactic radio-therapy of primary liver cancer and hepatic metastases. Acta Oncol 2006;45:838–847. [PubMed: 16982548]
30. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: Reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9. [PubMed: 22297116]
31. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 1989;62:679–694. [PubMed: 2670032]
32. Kavanagh BD, Schefter TE, Cardenes HR, et al. Interim analysis of a prospective phase I/II trial of SBRT for liver metastases. Acta Oncol 2006;45:848–855. [PubMed: 16982549]
33. Yamashita H, Onishi H, Matsumoto Y, et al. Local effect of stereo-tactic body radiotherapy for primary and metastatic liver tumors in 130 Japanese patients. Radiat Oncol 2014;9:112. [PubMed: 24886477]
34. Andratschke NH, Nieder C, Heppt F, et al. Stereotactic radiation therapy for liver metastases: Factors affecting local control and survival. Radiat Oncol 2015;10:69. [PubMed: 25889512]
35. Okunieff P, Morgan D, Niemierko A, et al. Radiation dose-response of human tumors. Int J Radiat Oncol Biol Phys 1995; 32:1227–1237. [PubMed: 7607946]
36. Deasy JO, Chao KS, Markman J. Uncertainties in model-based outcome predictions for treatment planning. Int J Radiat Oncol Biol Phys 2001;51:1389–1399. [PubMed: 11728700]
37. Thomas E, Chapet O, Kessler ML, et al. Benefit of using biologic parameters (EUD and NTCP) in IMRT optimization for treatment of intrahepatic tumors. Int J Radiat Oncol Biol Phys 2005;62:571–578. [PubMed: 15890602]
38. Baschnagel AM, Mangona VS, Robertson JM, et al. Lung metastases treated with image-guided stereotactic body radiation therapy. Clin Oncol (R Coll Radiol) 2013;25:236–241. [PubMed: 23352916]
39. Singh D, Chen Y, Hare MZ, et al. Local control rates with five-fraction stereotactic body radiotherapy for oligometastatic cancer to the lung. J Thorac Dis 2014;6:369–374. [PubMed: 24688781]
40. Ahmed KA, Caudell JJ, El-Haddad G, et al. Radiosensitivity differences between liver metastases based on primary histology suggest implications for clinical outcomes after stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2016;95:1399–1404. [PubMed: 27319288]
41. Sanuki-Fujimoto N, Takeda A, Ohashi T, et al. CT evaluations of focal liver reactions following stereotactic body radiotherapy for small hepatocellular carcinoma with cirrhosis: Relationship between imaging appearance and baseline liver function. Br J Radiol 2010;83: 1063–1071. [PubMed: 21088090]
42. Wigg AJ, Palumbo K, Wigg DR. Radiotherapy for hepatocellular carcinoma: Systematic review of radiobiology and modeling projections indicate reconsideration of its use. J Gastroenterol Hepatol 2010;25:664–671. [PubMed: 20074152]
43. Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol 2013;31:1631–1639. [PubMed: 23547075]
44. Normolle D, Pan C, Ben-Josef E, et al. Adaptive trial of personalized radiotherapy for intrahepatic cancer. Per Med 2010;7:197–204. [PubMed: 20448804]

45. Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol 2008;26: 657–664. [PubMed: 18172187]

46. Laufer I, Iorgulescu JB, Chapman T, et al. Local disease control for spinal metastases following "separation surgery" and adjuvant hypofractionated or high-dose single-fraction stereotactic radiosurgery: Outcome analysis in 186 patients. J Neurosurg Spine 2013; 18:207–214. [PubMed: 23339593]

47. Stinauer MA, Kavanagh BD, Schefter TE, et al. Stereotactic body radiation therapy for melanoma and renal cell carcinoma: Impact of single fraction equivalent dose on local control. Radiat Oncol 2011; 6:34. [PubMed: 21477295]

48. Garcia-Barros M, Paris F, Cordon-Cardo C, et al. Tumor response to radiotherapy regulated by endothelial cell apoptosis. Science 2003; 300:1155. [PubMed: 12750523]

49. Hodge JW, Guha C, Neefjes J, et al. Synergizing radiation therapy and immunotherapy for curing incurable cancers: Opportunities and challenges. Oncology (Williston Park) 2008;22:1064–1070. [PubMed: 18777956]

50. Tome WA, Fowler JF. Selective boosting of tumor subvolumes. Int J Radiat Oncol Biol Phys 2000;48:593–599. [PubMed: 10974480]

51. Popple RA, Ove R, Shen S. Tumor control probability for selective boosting of hypoxic subvolumes, including the effect of reoxygenation. Int J Radiat Oncol Biol Phys 2002;54:921–927. [PubMed: 12377346]

52. Williamson J, Das S, Goodsitt M, et al. Introducing the medical physics dataset article. Med Phys 2017;44:349–350. [PubMed: 28205310]

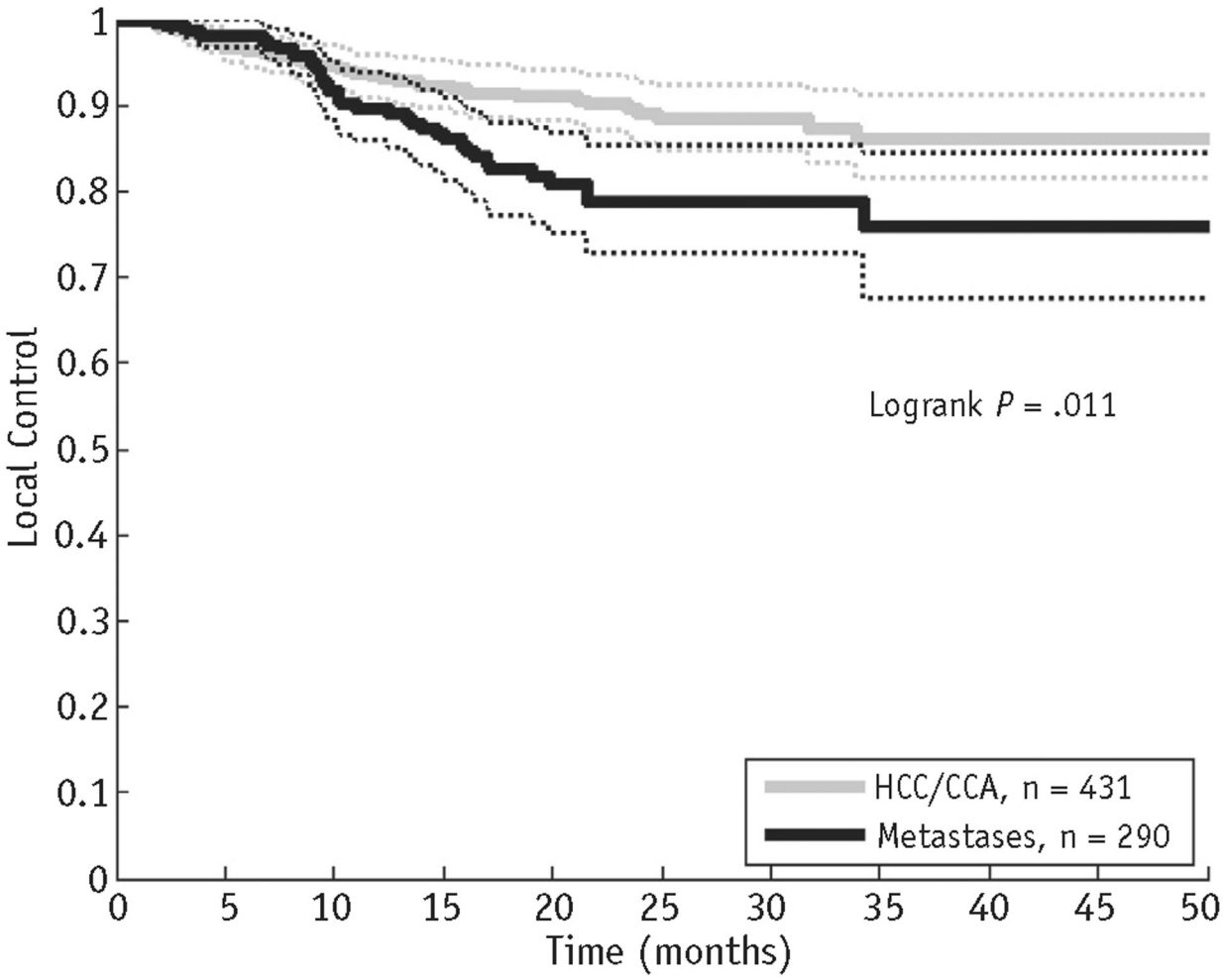

Fig. 1.

Kaplan-Meier curves for local control of primary and metastatic liver tumors after stereotactic body radiation therapy. *Abbreviations*: CCA Z cholangiocarcinoma; HCC Z hepatocellular carcinoma.

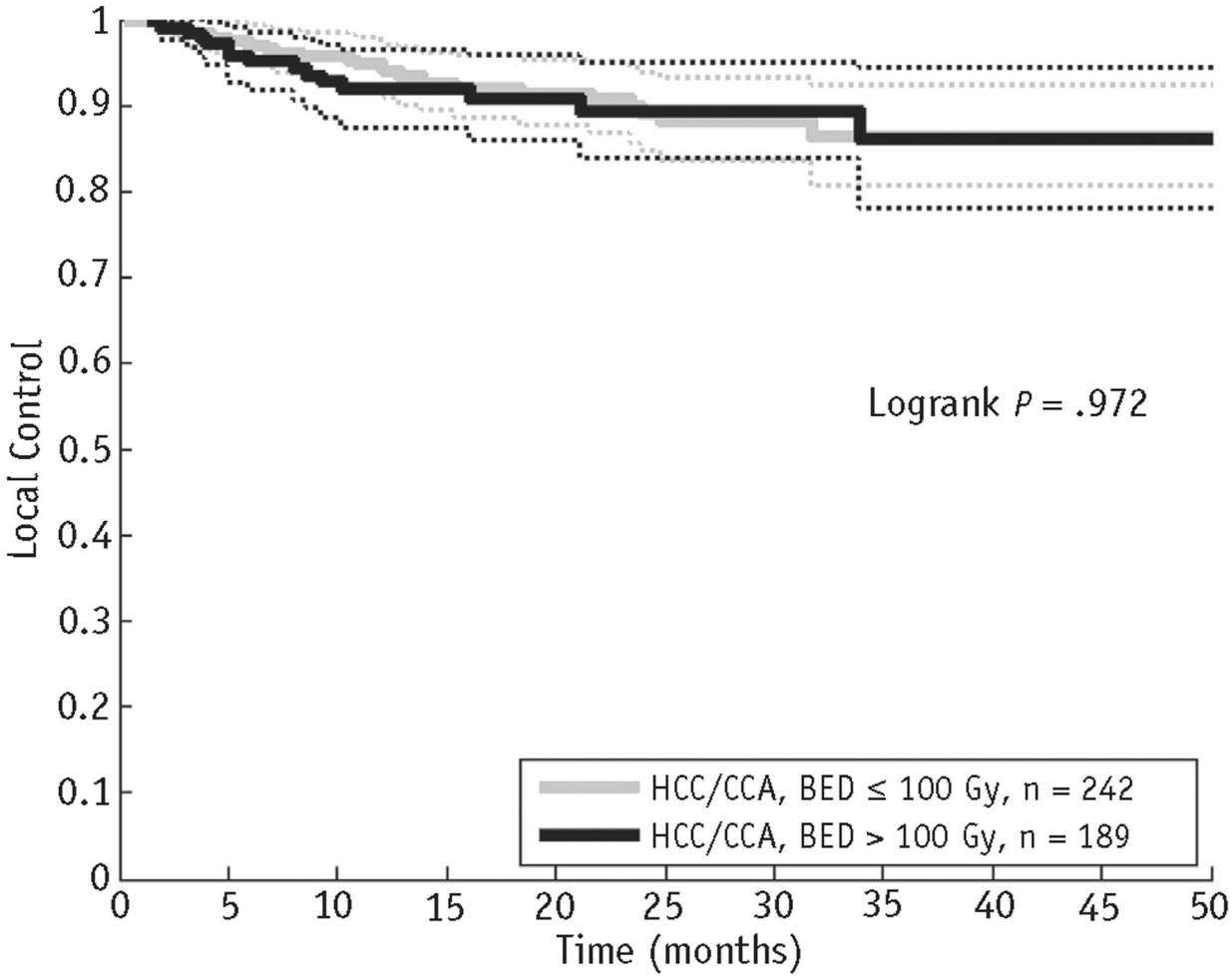

Fig. 2.

Kaplan-Meier curves for local control of primary liver tumors after stereotactic body radiation therapy, after grouping patients by biologically effective dose (BED).

Abbreviations: CCA Z cholangiocarcinoma; HCC Z hepatocellular carcinoma.

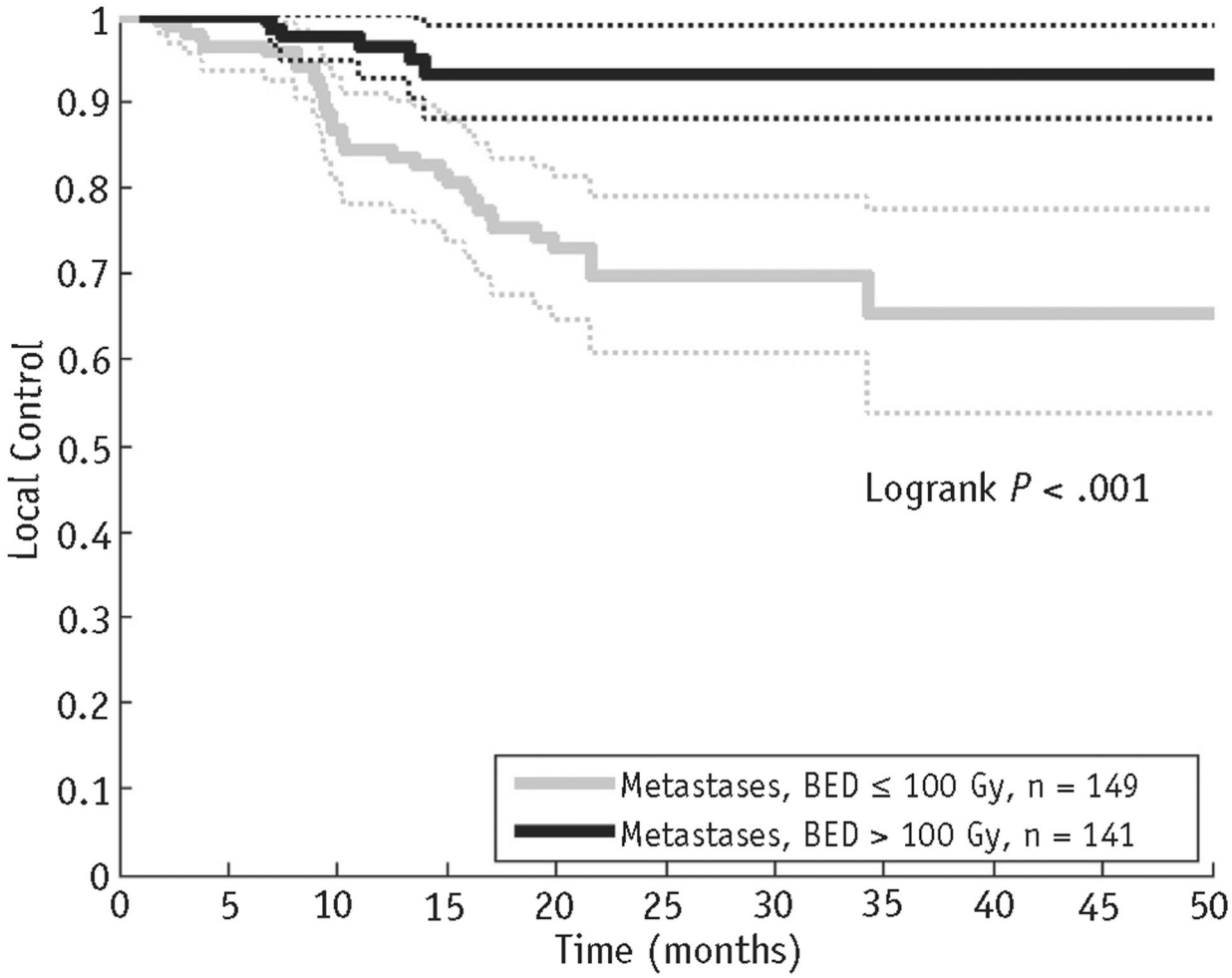

Fig. 3.

Kaplan-Meier curves for local control of meta-static liver tumors after stereotactic body radiation therapy, after grouping patients by biologically effective dose (BED).

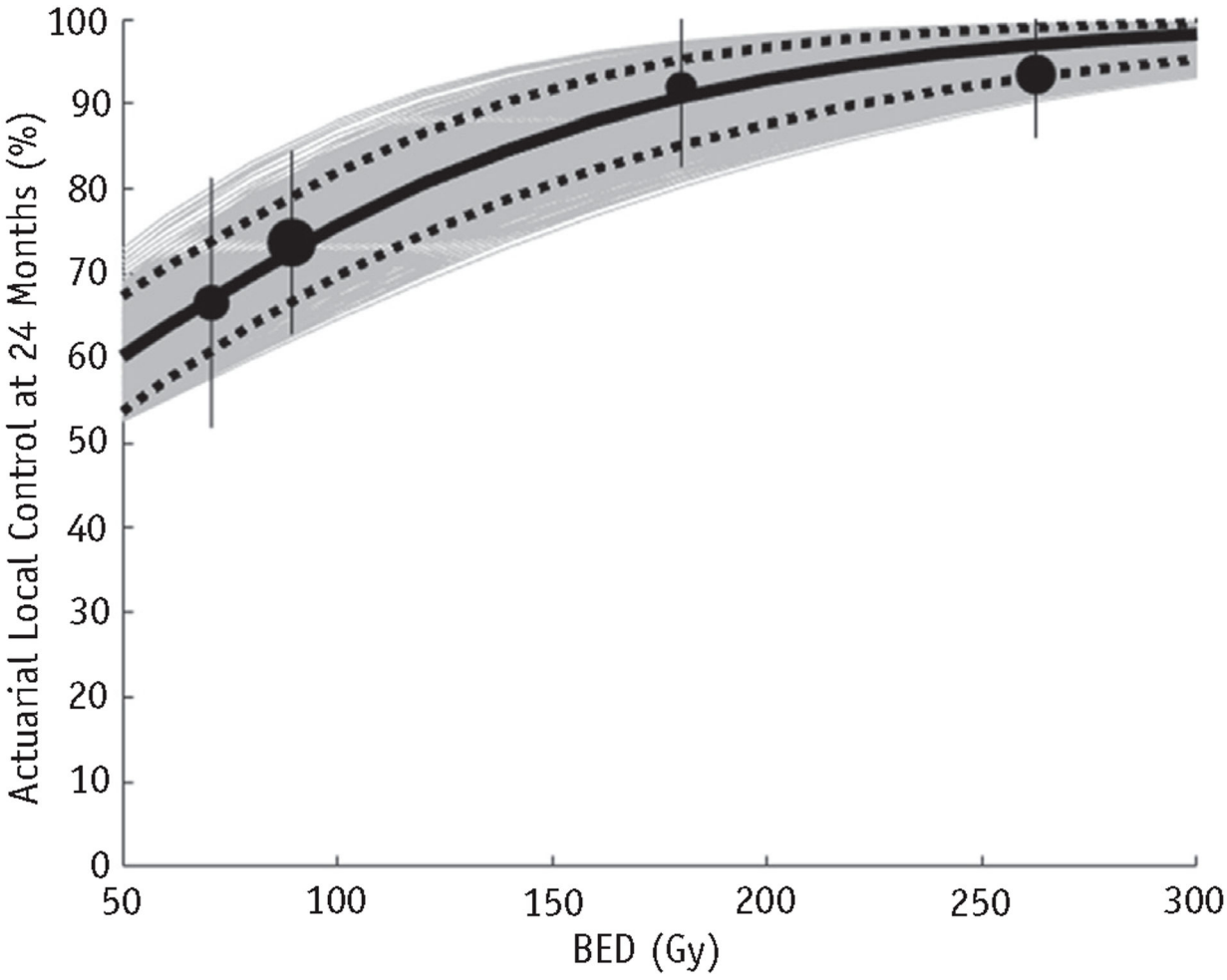

Fig. 4.

Tumor control probability modeling results for actuarial local control of metastatic liver tumors two years after stereotactic body radiation therapy. Black circles represent mean biologically effective dose (BED) and 2-year actuarial local control for 4 groups after sorting by BED. Circle size is proportional to sample size, and vertical lines span 95% confidence intervals for 2-year actuarial local control in each group. The solid curve depicts the results of model fitting using all available data. Grey lines represent model fitting results for 5000 bootstrap iterations. Dotted black lines indicate 95% confidence bounds for tumor control probability as a function of BED.

Table 1

Characteristics of the 13 studies included in the present analysis

First author (country) (reference)	Disease	Sample size	SBRT schedule	Prescription point/ volume	Median (range) follow-up
Dewas (France) (17)	HCC	42 patients,* 48 lesions*	Median 45 Gy, 3 fx	PTV (80% IDL)	15 mo
Honda (Japan) (26)	HCC	30 patients*	Median 48 Gy, 4 fx	Isocenter	12 (6–38) mo
Jang (Korea) (24)	HCC	82 patients, 95 lesions	<45 Gy, 3fx(n = 11) 45–54 Gy, 3 fx (n = 47) >54 Gy, 3 fx (n = 57)	PTV (70–80% IDL)	30 (4–81) mo
Kwon (Korea) (18)	HCC	42 patients	Median 33 Gy, 3 fx	PTV (70–85% IDL)	29 (8–49) mo
Sanuki (Japan) (25)	HCC	185 patients	35 Gy, 5 fx (n = 48) 40 Gy, 5 fx (n = 137)	PTV (70–80% IDL)	25† (3–80) mo
Barney (United States) (19)	CCA	9 patients,* 10 lesions*	45–60 Gy, 3–5 fx	NR	14 (2–26) mo
Kopek (Denmark) (23)	CCA	27 patients	45 Gy, 3 fx	Isocenter	5.4 (2.3–8.6) y
Mendez Romero (The Netherlands) (20)	Mets (82% CRC)	17 patients,* 34 lesions*	Median 37.5 Gy, 3 fx	PTV (65% IDL)	13 (1–31) mo
Rusthoven (United States) (27)	Mets (32% CRC, 21% lung)	36 patients,* 49 lesions*	60 Gy, 3 fx	PTV (80–90% IDL)	16 (6–54) mo
Scorsetti (Italy) (28)	Mets (48% CRC)	61 patients, 76 lesions	75 Gy, 3 fx	PTV	12 (2–26) mo
Stintzing (Germany) (21)	Mets (100% CRC)	30 patients, 35 lesions	24–26 Gy, 1 fx	70% IDL	35 (6–96) mo
Vautravers-Dewas (France) (22)	Mets (67% CRC)	42 patients, 62 lesions	40 Gy, 4 fx (n = 29) 45 Gy, 3 fx (n = 16)	80% IDL	14 (2–23) mo
Wulf (Germany) (29)	Mets (45% CRC)	39 patients, 51 lesions	Median 30 Gy, 3 fx (n = 25) Median 37.5 Gy, 3 fx (n = 26)	PTV (65% IDL)	15 (2–85) mo

Abbreviations: CCA = cholangiocarcinoma; CRC = colorectal cancer; fx = fractions; HCC = hepatocellular carcinoma; IDL = isodose line; Mets = liver metastases; NR = not reported.

*Subset of larger cohort included in present analysis.

†Estimate.