CRITICAL REVIEW

RADIOTHERAPY FOR LIVER METASTASES: A REVIEW OF EVIDENCE

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Over the past decade, there has been an increasing use of radiotherapy (RT) for the treatment of liver metastases. Most often, ablative doses are delivered to focal liver metastases with the goal of local control and ultimately improving survival. In contrast, low-dose whole-liver RT may be used for the palliation of symptomatic diffuse metastases. This review examines the available clinical data for both approaches. The review found that RT is effective both for local ablation of focal liver metastases and for palliation of patients with symptomatic liver metastases. However, there is a lack of a high level of evidence from randomized clinical trials.   © 2012 Elsevier Inc.

Stereotactic body radiation therapy, Conformal radiotherapy, Brachytherapy, Selective internal radiotherapy, Whole liver radiotherapy, Liver metastases.

INTRODUCTION

The liver is a common site of metastases. In particular, lung, breast, and gastrointestinal cancers frequently give rise to liver metastases, and for some patients, the liver may be the only site of disease. In general, systemic therapy is the preferred therapy for liver metastases. However, selected patients with limited involvement of the liver may be suitable for surgical resection, minimally invasive focal ablation, or radiotherapy (RT), delivered with the goal of improving the time to progression and overall survival. In contrast, low-dose whole-liver radiotherapy (WLRT) may be delivered to patients with symptoms from diffuse liver metastases refractory to systemic therapy, with the primary goal of reducing symptoms and improving quality of life (QL).

METHODS AND MATERIALS

This review was performed by the Liver Metastases Consensus Group, a subcommittee under the Clinical Affairs and Quality Committee of the American Society for Radiation Oncology (ASTRO), in coordination with the Third International Consensus Conference on Palliative Radiotherapy held at the ASTRO 51st Annual Meeting in 2009. Members were appointed by ASTRO, the European Society for Therapeutic Radiology and Oncology, the Canadian Association of Radiation Oncology, and the Trans Tasman Radiation Oncology Group.

The expert group was commissioned to review the current literature and give an overview report on the role of RT for ablation of focal liver metastases, using stereotactic body radiotherapy (SBRT), conformal radiotherapy (CRT), brachytherapy, and selected internal radiotherapy (SIRT), and for palliation of symptomatic liver metastases by WLRT.

The review was based on a literature search of Medline with the Medical Subject Heading term "liver metastases" combined with the key words "stereotactic body radiation therapy," "conformal radiation therapy," "brachytherapy," "selected internal radiation therapy," "whole liver radiation therapy," and so on, from January 1990 to July 2010. The Medline search was combined with back tracking based on published reference lists.

RATIONALE FOR FOCAL ABLATIVE, RADICAL-INTENT TREATMENT OF LIVER METASTASES AND FOR LOW-DOSE WLRT

Does surgical resection or ablative therapy improve survival in liver metastasis patients?

Hellman and Weichselbaum (1) suggested that cancer progression has a multistep nature with a state of oligometastases between the stages of purely localized and widely metastatic disease. This is supported by retrospective studies showing favorable 5-year survival rates of 25% to 47% in patients treated with surgical resection for colorectal (CRC) liver metastases (2–6). However, there are no randomized studies comparing resection with no resection in patients with potentially resectable liver metastases. Multiple prognostic criteria related to survival have been identified, including number of lesions, size, satellite lesions, surgical margins, extrahepatic disease, age, preoperative carcinoembryonic antigen (CEA), primary (CRC) tumor stage, and disease-free interval between resection of the primary tumor and appearance of metastases (2, 4, 5, 7).

Patients unsuitable for surgical resection for technical or medical reasons may be treated by radiofrequency ablation (RFA), cryotherapy, laser-induced thermotherapy, and high-intensity focal ultrasound (8). The EORTC (European Organisation for Research and Treatment of Cancer) 40004-CLOCC Phase II trial randomized patients with unresectable CRC liver metastases to chemotherapy folinic acid, fluorouracil (5-FU) and oxaliplatin [FOLFOX]) plus bevacizumab and RFA or to systemic therapy alone (9). Combined therapy was associated with improved progression-free survival (17 months vs. 10 months), but the statistical power was low and did not allow comparison of survival. An American Society of Clinical Oncology review on RFA for CRC liver metastases found a large variability in 5-year survival rates (14–55%) and local tumor recurrence rates (3.6–60%) (10). Tumor size of 3 cm or greater or location close to large vessels was associated with reduced local control, whereas multiple and extrahepatic metastases were associated with poor survival.

Surgical resection of non-CRC liver metastases may be considered in selected indolent non-CRC cases. In a large French, multi-institutional, retrospective study, long-term outcome was analyzed in 1,452 patients with non-CRC, non-neuroendocrine liver metastases. The most common primary sites were breast, gastrointestinal, and urologic. The 5- and 10-year survival rates were 36% and 23%, respectively, with breast cancer having the best survival and melanoma and squamous cell carcinoma the poorest survival (11). Favorable survival has also been observed after hepatic resection of neuroendocrine liver metastases (12).

Is there a need for palliative WLRT for symptomatic liver metastases?

Liver metastases often cause symptoms such as pain, discomfort, night sweats, and nausea (13, 14). Low-dose WLRT can benefit patients with symptomatic liver metastases, and the relief may be prompt and the treatment given with few side effects (13, 14). RT is used far less often for the palliation of liver metastases than it is for the palliation of bone, brain, or lung metastases, possibly because of an incorrect belief that hepatic irradiation inevitably leads to radiation liver toxicity.

Summary

Historical studies show long-term survival in patients with CRC liver metastases treated with surgical resection or ablation, which would otherwise not be expected, and there is growing evidence for resection or ablation of non-CRC metastases. Symptoms from unresectable liver metastases may be palliated by WLRT, which appears to be well tolerated.

ENDPOINTS FOR TREATMENTS OF LIVER METASTASES

Which endpoints should be considered for clinical trials of RT for liver metastases?

In general, symptom control and quality of life (QL) are considered the most valid endpoints to be used in palliative RT. However, the use of these endpoints alone is not appropriate for both of two very different scenarios in which RT is used: (*1*) tumor ablation with the goal of improving survival and (*2*) relief of symptoms. For the former, patients are generally in a relatively good prognostic group with longer survival expectancy and usually without local symptoms from metastases. Overall survival and progression-free survival are primary endpoints for these patients, with QL being a secondary endpoint. In the latter palliative scenario, patients are generally nearing the end of life. In these patients symptom control and short-term QL are primary endpoints.

General QL has been assessed by patient-completed questionnaires (*e.g.*, EORTC QL-30). Two cancer-specific questionnaires, the QLQ-LMC21 (http://groups.eortc.be/qol/) and the FACT-Hep (http://facit.org), have been developed for patients with liver metastases from CRC. Side effects of treatments should be assessed by use of the standard measures with a particular focus on detecting treatment-associated liver injury.

Summary

Primary endpoints on trials on ablation of liver metastases include survival, progression-free survival, and local control of treated tumors. Primary endpoints for RT delivered with the goal of symptom relief only are symptom control and short-term QL.

RT FOR ABLATION OF LIVER METASTASES

Stereotactic body radiotherapy

SBRT refers to the delivery of large doses of highly conformal radiation with steep dose gradients toward the surrounding normal tissue over a limited number of fractions (1 to 6 fractions) to extracranial tumor sites (15). SBRT was historically derived by use of the principles of stereotactic brain radiosurgery, and initial attempts were performed using a fixed body frame for patient immobilization. However, extracranial tumors and organs may move and change

Table 1. Overview of prospective studies of SBRT for liver metastases

Primary author	Design	No. of patients with mets	Tumor volume	Type of mets	RT dose	Toxicity	Outcomes
Herfarth (32), 2004	Phase I–II	35	1–132 mL (median, 10 mL)	Not reported by patient	Dose escalation, 14–26 Gy (1 frx)	No significant toxicity reported	1–yr LC, 71% 18–mo LC, 67% 1–yr OS, 72%
Méndez Romero (30), 2006	Phase I–II (HCC and mets)	25 (17 liver mets)	1.1–322 mL (median, 22.2 mL)	CRC (14) Lung (1) Breast (1) Carcinoid (1)	30–37.5 Gy (3 frx)	2 Grade 3 liver toxicities	2-yr LC, 86% 2-yr OS, 62%
Hoyer (41), 2006	Phase II (CRC oligomets)	64 (44 liver mets)	1–8.8 cm (median, 3.5 cm)	CRC (44)	45 Gy (3 frx)	1 liver failure 2 severe late GI toxicities	2-yr LC, 79% (by tumor) and 64% (by patient)
Rusthoven (37), 2009	Phase I–II	47	0.75–97.98 mL (median, 14.93 mL)	CRC (15) Lung (10) Breast (4) Ovarian (3) Esophageal (3) HCC (2) Other (10)	Dose escalation, 36–60 Gy (3 frx)	No RILD Late Grade 3/4 <2%	1-yr LC, 95% 2-yr LC, 92% Median survival, 20.5 mo
Lee (33), 2009	Phase I–II	68	1.2–3,090 mL (median, 75.9 mL)	CRC (40) Breast (12) Gallbladder (4) Lung (2) Anal canal (2) Melanoma (2) Other (6)	Individualized dose, 27.7–60 Gy (6 frx)	No RILD 10% Grade 3/4 acute toxicity No Grade 3/4 late toxicity	1-yr LC, 71% Median survival, 17.6 mo
Ambrosino (39), 2009	Prospective cohort	27	20–165 mL (median, 69 mL)	CRC (11) Other (16)	25–60 Gy (3 frx)	No serious toxicity	Crude LC rate 74%
Goodman (35), 2010	Phase I (HCC and liver mets)	26 (19 liver mets)	0.8–146.6 mL (median, 32.6 mL)	CRC (6) Pancreatic (3) Gastric (2) Ovarian (2) Other (6)	Dose escalation, 18–30 Gy (1 frx)	No dose–limiting toxicity 4 cases of Grade 2 late toxicity (2 GI, 2 soft tissue/rib)	1-yr local failure, 23% 2-yr OS, 49% (mets only)

Abbreviations: SBRT = stereotactic body radiotherapy; mets = metastases; RT = radiotherapy; LC = local control; OS = overall survival; HCC = hepatocellular carcinoma; CRC = colorectal; RILD = radiation-induced liver disease; frx = fractions; GI = gastrointestinal.

shape between and within fractions, relative to the external anatomy or a reference frame. Thus image-guided radiotherapy (IGRT) techniques are now used in SBRT to improve target localization. The ultimate success of a SBRT program requires rigorous quality assurance and coordinated teamwork by radiation oncology, medical physics, medical dosimetry, and radiation therapy teams (15).

Which techniques are regarded as standards in planning, delivery, and follow-up after SBRT?. SBRT planning requires at least a planning computed tomography (CT) simulation scan with intravenous contrast for appropriate target definition. Multimodal imaging by use of positron emission tomography/CT or contrast-enhanced magnetic resonance imaging can improve the ability to accurately define metastatic targets (16, 17). Breathing-related liver motion may be assessed by four-dimensional CT, cine–magnetic resonance imaging, or two-dimensional kilovoltage (kV) fluoroscopy to determine appropriate planning target volume margins.

Treatment planning for SBRT typically results in highly conformal dose distributions, with multiple beams using both coplanar and non-coplanar geometries. The nominal doses prescribed during SBRT planning reflect the isodose lines that encompass the planning target volume. Intensity-modulated RT can improve the conformality for concave targets (*e.g.*, target volumes wrapping around the luminal gastrointestinal organs) but has less benefit in spherical targets (18).

Immobilization of the liver by use of controlled breath holds (19), shallow breathing, abdominal compression devices (20), gating of the RT beam during certain phases of the respiratory cycle (21), and tumor tracking via implanted fiducial markers (22, 23) may reduce the uncertainty related to internal motion during treatment delivery. Baseline shifts

in liver position relative to the vertebral bodies can be as large as 1 cm from fraction to fraction (24). IGRT based on megavoltage orthogonal imaging (19, 25), kV fluoroscopy (26), ultrasound (27), or CT housed into the accelerator (megavoltage CT/TomoTherapy (Accuray, Madison WI) or megavoltage or kV cone beam CT) can reduce the adverse effect of day-to-day internal motion and ensure more accurate SBRT delivery (28). The methods are based on onboard imaging of the liver or surrogates such as implanted markers or air–diaphragm or air–rib interfaces.

Assessment of tumor response after SBRT may be challenging because of radiation-induced changes in both tumor and surrounding liver. However, on follow-up CT scan, distinct patterns of contrast enhancement, shrinkage of hypodensity, and displacement of vessels are indicative of local control (29). Some groups have found that magnetic resonance imaging may better distinguish between viable tumor and normal tissue reaction (30), whereas positron emission tomography does not, so far, provide additional tumor response information (29).

Summary. SBRT involves immobilization and high accuracy and precision of highly conformal, high-dose RT, delivered in a limited number of fractions. Multimodal imaging, IGRT, advanced planning, and motion management improve the accuracy of the treatment.

Which tumors and patients should be considered candidates for SBRT?. Table 1 illustrates the prospective and Table 2 the retrospective SBRT studies of liver metastases. No randomized Phase III data have been reported. Among the reviewed studies of SBRT for liver metastases, there is significant heterogeneity concerning patient selection (CRC vs. other primary subtypes), tumor volumes, total dose, dose per fraction, and dosimetric planning criteria.

Table 2. Overview of retrospective studies of SBRT for liver metastases

Primary author	No. of patients	Tumor volume	Type of mets	RT dose	Toxicity	Outcomes
Blomgren (34), 1995	14	3–260 mL	CRC (11) Anal canal (1) Kidney (1) Ovarian (1)	7.7–45 Gy (1–4 frx)	2 cases of hemorrhagic gastritis	50% response rate
Wada (44), 2004	5	NR	NR	45 Gy (3 frx)	No serious toxicity	2–yr LC, 71.2%
Wulf (36), 2006	44 (39 liver mets)	9–355 mL	CRC (23) Breast (11) Ovarian (4) Other (13)	30–37.5 Gy (3 frx) 26 Gy (1 frx)	No Grade 2–4 toxicity	1–yr LC, 92% 2-yr LC, 66% 1-yr OS, 72% 2-yr OS, 32%
Katz (40), 2007	69	0.6–12.5 cm (median, 2.7 cm)	CRC (20) Breast (16) Pancreas (9) Lung (5) Other (19)	30–55 Gy (5–15 frx)	No Grade 3/4 toxicity	10-mo LC, 76% 20-mo LC, 57% Median survival, 14.5 mo
van der Pool (42), 2010	20	0.7–6.2 cm (median, 2.3 cm)	CRC (20)	30–37.5 Gy (3 frx)	2 Grade 3 late liver enzyme changes 1 Grade 2 rib fracture	1-yr LC, 100% 2-yr LC, 74% Median survival, 34 mo

Abbreviations: SBRT = stereotactic body radiotherapy; mets = metastases; RT = radiotherapy; CRC = colorectal; NR = not reported; LC = local control; OS = overall survival; frx = fractions.

In general, most SBRT studies used doses ranging from 30 to 60 Gy in 1 to 6 fractions, for 5 metastases or fewer, with maximal tumor sizes of 6 cm. CRC liver metastases comprise the most frequent group. However, an increasing number of patients with breast and lung cancer are included in more recent series. In general, outcomes are best in patients with non-CRC metastases (31–33), perhaps because most patients with CRC liver metastases have been heavily pretreated with other local and systemic treatments before being referred for SBRT.

Summary. Ideal candidates for liver metastasis SBRT have a good performance status (Eastern Cooperative Oncology Group 0–1), possess adequate hepatic function, have no extrahepatic disease, and have an uninvolved liver volume of 700 mL or greater.

What are the expected local control and survival outcomes after SBRT?. Local control of liver metastases by use of SBRT is favorable, with rates ranging from 70% to 100% at 1 year and 60% to 90% at 2 years, largely dependent on tumor volume, prior therapy, and RT dose (Tables 1 and 2) (30, 33–41). Median overall survival after SBRT ranges from 10 to 34 months, with 2-year overall survival rates ranging from 30% to 83%, with occasional long-term survivors (42). However, out-of-field metastatic progression develops in a substantial proportion of patients; therefore there is a strong rationale to combine SBRT with systemic treatments.

Prognostic factors related to improved local control include smaller tumor volumes (33, 37, 38, 43, 44), potentially non-CRC metastases, metachronous liver metastases (41), and absence of previous chemotherapy (41).

Summary. The reported 2-year local control and survival rates after SBRT for liver metastases range from 60% to 90% and from 30% to 83%, respectively. Patients included in Phase I/II SBRT studies have generally been heavily pretreated, and as a result, it is difficult to compare survival outcomes with other local modalities used for liver metastases. Phase III trials have not been performed with SBRT of liver metastases.

Does intensification of radiation dose improve the treatment outcome in SBRT?. The radiobiology and cell killing effects have not been fully understood for fraction doses over 8 Gy, and conversion of SBRT dose schedules to equivalent doses in 2-Gy fractions (ED_{50Gy}) by use of the linear–quadratic model should be done with awareness of substantial uncertainty (45). One retrospective study showed that higher doses of 36 to 37.5 Gy in 3 fractions or 26 Gy in 1 fraction (prescribed at the 65% isodose line) resulted in improved local control compared with lower doses (36). An analysis from a group from the University of Colorado showed that both increased nominal dose and equivalent uniform dose improved local control (43). A Canadian study of 6-fraction SBRT for large metastases documented improved local control with higher doses on univariate analysis (33), and a dose-escalation Phase I study from Texas found a similar dose-dependent effect on local control (46). Finally, a pooled multi-institutional analysis suggested that to achieve a 90% rate of local control at 1 year for CRC metas-

tases, the 3-fraction SBRT dose required is in the range of 48 to 52 Gy (47).

Summary. A dose response for local control exists, although there is uncertainty in the optimal threshold dose beyond which local control is improved. A total prescription dose of 48 Gy or higher in 3 fractions is recommended when possible.

What toxicity can be expected after SBRT?. Severe toxicity related to SBRT is uncommon. The risk of radiation-induced liver disease (RILD) in SBRT is low (41). Transient Grade 3 elevation of liver enzyme levels developed within 3 months of treatment in 2 patients treated in a Phase I/II SBRT study with 30 to 37.5 Gy in 3 fractions (30). There has been 1 reported death from hepatic failure 7 weeks after SBRT, possibly—but not definitely—related to RT (60% of the liver received >10 Gy in 3 fractions; median total liver dose was 14.4 Gy) (41). In the study by Lee *et al.* (33), no RILD was seen in 68 patients (median mean liver dose of 16.9 Gy [range, 3–22 Gy] in 6 fractions). In a Phase I/II study by Rusthoven *et al.* (37), no RILD was seen in 47 patients, using a critical dose–volume model allowing no more than 700 mL of uninvolved liver to receive 15 Gy or greater in 3 fractions in accordance with the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) recommendations on liver (48).

Other toxicity related to SBRT that has been uncommonly reported is luminal gastrointestinal and soft-tissue/bone complications. Duodenal ulceration was seen in 2 patients and colonic perforation in 1 patient—all with maximum doses to portions of the bowel of greater than 30 Gy in 3 fractions (41). Grade 3 soft-tissue toxicity was observed in 1 patient after receiving 48 Gy in 3 fractions to a region of subcutaneous tissue (37). Nontraumatic rib fractures were seen in 2 patients treated to maximum doses to 51.8 Gy and 66.2 Gy in 6 fractions to 0.5 cm^3 of rib (33). Constraints used in clinical trials or recommended by experts are listed in Table 3.

Summary. Grade 1 or 2 toxicity is common after SBRT, but severe toxicity (Grade $\geq$3) is uncommon. Toxicity is more likely in patients receiving a high dose to the bowel or to large volumes of the liver.

Conformal RT

What is the expected outcome after CRT for liver metastases?. Using a conformal 3-dimensional technique, a group from Ann Arbor treated 22 patients with CRC liver metastases with conventional CRT with concomitant hepatic arterial infusion (HAI) of fluorodeoxyuridine (49). With total doses of 48 to 73 Gy in 1.5- to 1.65-Gy fractions given twice daily, the response rate was 50%, but only 25% of the patients were without hepatic progression within 1 year. In a risk-adapted normal tissue complication probability model (NTCP) based dose-escalation study on CRT of primary and secondary liver cancer using a median total dose of 60.75 Gy (range, 40 to 90 Gy), 1.5 Gy twice daily, and concomitant fluorodeoxyuridine, the response rate for CRC patients was 60% and median survival was 17 months (50, 51). Patients included in this study generally had very large tumors.

Table 3. Constraints proposed for 3-fraction SBRT schedule

Organ at risk	Wulf *et al.* (36)	Rusthoven *et al.* (37)	Hoyer RAS–Trial (www.cirro.dk)	RTOG 0236 SBRT lung (www.rtog.org)	QUANTEC (48)
Liver (CTV excluded)	30% <21 Gy* 50% <15 Gy*	700 mL < 15 Gy	700 mL < 15 Gy	NA	700 mL ≤15 Gy D_{mean} < 15 Gy
Stomach	$D_{5\ mL}$ <21 Gy	D_{max} ≤30 Gy	$D_{1\ mL}$ <21 Gy	NA	D_{max} <30 Gy ($D_{5\ mL}$ <22.5 Gy)
Bowel	$D_{5\ mL}$ <21 Gy	D_{max} ≤30 Gy	$D_{1\ mL}$ <21 Gy	NA	D_{max} <30 Gy
Esophagus	$D_{5\ mL}$ <21 Gy	NA	$D_{1\ mL}$ <21 Gy	D_{max} ≤27 Gy	NA
Kidney	NA	Total kidney $D_{35\%}$ <15 Gy	Total kidney $D_{35\%}$ <15 Gy	NA	NA
Spinal cord	NA	D_{max} ≤18 Gy	D_{max} <18 Gy	D_{max} ≤18 Gy	D_{max} ≤20 Gy
Heart	$D_{5\ mL}$ <21 Gy	NA	$D_{1\ mL}$ <30 Gy	D_{max} ≤30 Gy	NA

Abbreviations: SBRT = stereotactic body radiotherapy; RTOG = Radiation Therapy Oncology Group; CTV = clinical target volume; NA = not available; Dx % = dose to x%; Dx mL = dose to x mL; D_{max} = maximum dose.

* Liver including clinical target volume.

Summary. Studies have shown high response rates after CRT, but these are not directly comparable to results of SBRT studies, because patient selection is different, generally including larger metastases.

Brachytherapy

What is the expected outcome after brachytherapy for liver metastases?. Brachytherapy based on CT-guided insertion of ^{192}iridium high–dose rate sources in the liver with after-loading technique offers a favorable dose distribution. Generally, brachytherapy is restricted by its invasive nature and a dose distribution that only allows treatment of small tumors (although tumors up to 13.5 cm in diameter have been treated) (52).

A dose-finding study has shown that single doses of 25 Gy can be administered with acceptable toxicity and with only 1 local recurrence in 33 treated tumors (53). In a feasibility study on combined HAI and interstitial brachytherapy, 76% of the metastases were controlled (54).

Severe complications, such as intrahepatic bleeding, abscess, pneumothorax, or pleural effusion, were reported in 6% to 9% of the procedures (54).

Summary. Brachytherapy is associated with a high probability of local control in selected patients with liver metastases. Severe complications have been reported, which emphasizes that brachytherapy should be limited to experienced centers.

Selective internal RT

What is the expected outcome after SIRT?. SIRT is performed by embolization of ^{90}yttrium-containing microbeads into the arterial supply of the tumor-involved liver and is used in therapy of focal and diffuse liver metastases. A randomized Phase III trial showed no difference in overall survival; however, there was significant prolongation of hepatic progression-free survival (9.7 months vs. 15.9 months, p = 0.001) for patients receiving SIRT in combination with HAI administration of floxuridine vs. HAI alone (55). Recently, a multicenter Phase II study on SIRT as salvage therapy for inoperable CRC liver metastases showed a promising median survival of 12.6 months and a 2-year survival of 19.6% in a high-risk, heavily treated population (56). How-

ever, a Cochrane review concluded that the results of the studies were inconclusive because of insufficient power (57).

Toxicities such as neutropenic sepsis, liver abscess, and moderate RILD have been observed after SIRT. Gastric perforations due to nontargeted deposition of radioactive spheres have been reported (58).

Summary. Tumor regression has been demonstrated after SIRT, especially after treatment of tumors with a diameter of less than 3 cm. Some severe toxicities have been reported. The patient selection for SIRT varies tremendously, as do the doses delivered to the tumors.

LOW-DOSE PALLIATIVE RT FOR SYMPTOMATIC LIVER METASTASES

RT may also be used with the goal of palliation of symptomatic diffuse liver metastases. Most often, it is given as low-dose WLRT with a simple opposing-field technique.

What is the expected palliative outcome after WLRT for liver metastases?

A number of studies have investigated palliative WLRT either alone or combined with systemic therapy (Tables 4 and 5). In all studies WLRT resulted in symptom relief (13, 14, 59–66). Pain relief, the most frequently reported endpoint, ranged from 55% to 80% in studies on WLRT alone. The Radiation Therapy Oncology Group (RTOG) pilot study used dose-fractionation schedules ranging from 21 to 30 Gy in 7 to 19 fractions to treat 109 patients (14). Responses were seen for abdominal pain (55%), nausea and vomiting (49%), fever and night sweats (45%), ascites (33%), anorexia (28%), abdominal distension (27%), jaundice (27%), and night sweats/fever (19%), with complete response rates for individual symptoms ranging from 7% to 34%. Performance status improved in 25%. Leibel *et al.* (67) found an 80% response for pain (complete in 54%) and improved performance status in 28%. Pain relief occurred quickly and had a median duration of 13 weeks.

Summary. Prospective studies show considerable palliative effect after low-dose palliative RT, with pain relief in 55% to 80% of cases after WLRT.

Does WLRT improve survival in patients treated for liver metastases?

There has been one randomized trial comparing WLRT vs. regional chemotherapy alone, and this was closed early because of slow accrual (with no statistically significant difference between the two arms) (65). Median survival in 3 studies with over 100 patients receiving WLRT ranged from 11 to 17 weeks. The studies were not designed to detect a survival advantage from WLRT.

Summary. There are no clinical data indicating that low-dose WLRT offers a survival advantage, and it should be reserved for symptom control.

Which doses and fractionation schedules should be used for WLRT?

A range of schedules are well tolerated. Russell *et al.* (66) reported a multi-institutional (RTOG) dose-escalation study of WLRT in 173 patients. No dose–response relationship for symptom control was found in patients received WLRT with doses ranging from 27 to 33 Gy in 1.5-Gy fractions twice daily, and 33 Gy was associated with a 10% rate of late liver injury.

Symptom control can be achieved with hypofractionated WLRT over few fractions with relatively low total doses. The Trans Tasman Radiation Oncology Group study using 10 Gy in 2 fractions achieved symptom improvements for one-half to two-thirds of patients (13). Preliminary results from another Phase II study suggest that doses as low as 8 Gy in 1 fraction may be effective for palliation of symptoms (68).

Summary. Low-dose WLRT over few fractions is recommended when the only goal of therapy is palliation of symptoms. WLRT is well tolerated if given with equivalent doses in 2-Gy fractions of up to 30 to 35 Gy.

Should WLRT be combined with systemic therapy?

A number of reports describe attempts to improve the results of WLRT with the use of concurrent radiosensitizers or chemotherapy (63, 64, 67, 69–76). A randomized, multi-institutional (RTOG) study with 187 patients treated with WLRT with 21 Gy in 7 fractions with or without misonidazole did not show any differences in outcomes (67). In a number of small, non-randomized reports on WLRT with systemic or regional chemotherapy, the outcomes appear to be only modestly superior to RT alone and associated with increased toxicity.

Summary. There is no evidence for combining WLRT with radiosensitizers.

What toxicities can be expected after WLRT?

The liver tolerates WLRT in doses below 30 Gy in 2-Gy fractions (67) or 21 Gy in 7 fractions or 10 Gy in 2 fractions (13). At least one (functioning) kidney should be excluded from the treatment volumes, and supportive medication such as high-dose steroids and antiemetic drugs should be administered prior to therapy.

Summary. With low-dose WLRT and pretreatment antiemetics, expected toxicity rates are very low.

DISCUSSION

Liver metastases present a unique opportunity for radiation oncologists, because RT appears to be underused in both the radical and palliative settings. A multidisciplinary team approach in the management of patients with liver metastases is of utmost importance (77, 78), and radiation oncologists should be active members.

An uncommon role of liver RT is for palliation of symptoms from diffuse liver metastases. RT appears to be underused in this situation, in contrast to the frequent and effective use of

Table 4. Studies using WLRT/low-dose palliative radiotherapy alone for liver metastases

Primary author	Design	No. of patients	Dose fractionation	Main results of study	Median survival
Phillips (59), 1954		36	20–37.5 Gy	26/36 (72%) with complete pain relief; other symptoms also often improved	NA
Turek–Maischeider (60), 1975		11	25 Gy in 1.5– Gy frx	8/11 (72%) with response	NA
Prasad (61), 1977		20	19–31 Gy	19/20 (95%) with pain relief	NA
Sherman (62), 1978		55	24 in 3–Gy frx	90% symptomatic improvement	20 wk
Borgelt (14), 1981	Multi-institutional	109	21–30 Gy in 1.6- to 3–Gy frx	Symptoms improved from 55% (pain) to 19% (fatigue) and performance status improved in 25% but aggravation of nausea occurred in 19%	11 wk
Russell (66), 1993	Multi-institutional dose-escalation study	173	27, 30, and 33 Gy in 1.5–Gy frx bid	No RT dose response for survival Acute Grade 3/4 toxicity in 6% and late in 8% at 33 Gy	17 wk
Bydder (13), 2003	Multi-institutional	28	10 Gy in 2 frx	Improvement in baseline symptoms in approximately 50% to 66% Pain relief in 65% Acute Grade 3/4 toxicity in 7%, no late	10 wk

Abbreviations: WLRT = whole-liver radiotherapy; NA = not available; frx = fractions; bid = twice daily.

Table 5. Studies using WLRT/low-dose palliative radiotherapy combined with chemotherapy/radiosensitizers for liver metastases

Primary author	Design	No. of patients	Dose fractionation and chemotherapy/radiosensitizer	Main results of study	Median survival
Webber (64), 1978		25	25 Gy	Improved survival with combined chemotherapy and WLRT compared with WLRT alone (historical cohort)	54 wk vs. 20 wk
Herbsman (69), 1978		11	25–30 Gy in 1.67- to 2–Gy frx and HAI floxuridine, 5 patients also had MTX	Mild acute toxicity Duodenal ulcer and pylorus stenosis	65 wk
Friedman(70), 1979	Multi-institutional	22	13.5–21 Gy in 3–Gy frx and HAI 5-FU and DOX	Imaging response in 55%	15+ wk
Leibel (63), 1981	Multi-institutional (RTOG)	42	21 Gy in 3–Gy frx and misonidazole	Pain response (complete) in 63% Improved fever/night sweats in 83%, performance status improved in 47%	17 wk
Lokich (71), 1981		16	25–30 Gy in 10–12 frx and regional 5-FU/FUdR	10/16 (63%) responded on imaging	
Byfield (73), 1984		28 colon primary	20–30 Gy and intra-arterial 5-FU/FUdR	1 fatal liver toxicity	36 wk if LFTs >2× ULN, 109 wk if LFTs <2× ULN
Rotman (74), 1986	Retrospective	23 colorectal primary	Mean of 27.25 Gy in 1.5- to 2–Gy frx and intravenous 5–FU wk 1, 3, and 5	19/23 (82%) achieved subjective response No Grade 3/4 toxicities	30 wk
Leibel (67), 1987	Randomized, multi-institutional (RTOG)	214 (187 evaluable)	WLRT with 21 Gy in 3–Gy frx ± misonidazole	No effect of metronidazole Pain relief in 80% (complete in 54%); ECOG performance status improved in 28%, but aggravation of nausea occurred in 6%	17 wk
Wiley (65), 1989	Randomized	37	HAI 5-FU ± WLRT with 25.5 Gy in 1.5–Gy frx	No benefit of hepatic RT over regional chemotherapy alone: diarrhea, 42% vs. 17%, and pain, 26% vs. 26%	24 wk (WLRT) 32 wk (no WLRT)
Witte (76), 2001	Randomized, multi-institutional (ECOG)	168 colorectal primary	5-FU or 5-FU + LV ± WLRT with 20 Gy in 2–Gy frx	No difference in survival or time to disease progression 1 (2%) fatal liver toxicity	58 wk (WLRT –chemotherapy)

Abbreviations: WLRT = whole-liver radiotherapy; HAI = hepatic arterial infusion; MTX = methotrexate; 5-FU = 5-fluorouracil; DOX = doxorubicin; RTOG = Radiation Therapy Oncology Group; FUdR = floxuridine; LFTs = liver function tests; ULN = upper limit of normal; RT = radiotherapy; ECOG = Eastern Cooperative Oncology Group; LV = levamisole.

RT for palliation of metastases in other sites such as the brain or bone. A number of studies have shown high efficacy and low toxicity of WLRT (Tables 4 and 5). Low-dose WLRT should be considered in patients with symptomatic liver metastases refractory to standard therapies. Randomized clinical studies of low-dose WLRT for these patients are warranted.

In patients in whom resection for liver metastases is unsuitable, focal ablative RT may be used with the goal of improving survival, and long-term survivors after focal SBRT have been reported. Patients with CRC as well as non-CRC liver-confined metastases should be considered for RT. Patients should have a good performance status. There is not an absolute maximum number or size of the metastases, but RT should spare at least 700 cm of normal liver. In general, the risk of occult diffuse metastases increases as the number of metastases increases, especially for non-CRC metastases, and the best results are found in patients with 3 or fewer metastases, ideally less than 6 to 8 cm in maximum diameter. Most published reports on radical RT for liver metastases describe technical developments and retrospective cohort studies. However, there are now a number of Phase I and II studies available for patients with liver oligo-metastases. This review shows low to moderate toxicity and high efficacy of RT with local control rates of 70% to 100% at 1 year and 60% to 90% at 2 years, which are comparable to the best results achieved in studies on RFA.

The optimal combination of systemic and local therapies is yet to be determined. Surgical resection combined with perioperative chemotherapy for CRC liver metastases yielded superior survival compared with surgery alone (79). There are no similar published studies for nonsurgical ablation, but clinical trials combining SBRT with systemic therapy are ongoing. Examples are the Princess Margaret Hospital trial on SBRT and sorafenib in the treatment of unresectable liver metastases (http://clinicaltrials.gov/ct2/show/NCT00892424) and the MD Anderson Cancer Center trial on ^{90}yttrium radioembolization and chemotherapy (http://clinicaltrials.gov/ct2/show/NCT00766220). Head-to-head comparisons of local therapies, including RT, are urgently needed. The RAS-Trial (RFA vs. SBRT) (http://clinicaltrials.gov/ct2/show/NCT01233544) may be the first to test the efficacy of two different modalities. Such trials will be challenging to conduct, because they will require inclusion of large numbers of patients in international multicenter settings and they need to consider the continuously changing systemic therapies available for CRC and non-CRC.

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