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Radiation Therapy for Liver Metastases

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Liver metastases are a common source of cancer morbidity and mortality and are often the only site of metastases. In the last 2 decades, major technological advancements in radiation treatment planning and delivery have resulted in resurgence in the use of radiation therapy (RT) as a treatment for liver tumors. With the advent of 3-dimensional conformal radiation treatment (CRT), partial liver irradiation became possible. Stereotactic body radiation therapy (SBRT) is a further enhancement, defined as highly focused, stereotactically localized and administered, high-dose RT delivered in a hypofractionated course. There is now more than a decade of experience with CRT and SBRT for the treatment of liver metastases. In selected patients, very high local control rates have been observed, with minimal toxicity. Patients most likely to benefit from RT are those with liver confined disease, focal distribution of metastases, and metastases more than 1.5 cm from luminal gastrointestinal organs. There is growing evidence that strategies using aggressive or ablative local therapies as an adjunct to systemic therapy might achieve improvements in overall outcome as long as they are administered safely.

The liver is a source of metastases from most common solid malignancies. This is especially common for cancers of the gastrointenstinal (GI) tract because their draining blood supply is funneled into the portal circulation. It has been estimated that 25% of colorectal cancer patients have hepatic metastases at diagnosis, and another 50% will have their tumor recur in the liver within 5 years.[1] Although improvements in systemic therapy have led to improved survival for patients with metastatic colorectal cancer,[2] chemotherapy and molecular-targeted agents rarely eradicate metastases permanently. For colorectal carcinoma liver metastases, selected resection series have yielded 5-year survival rates of 50% to 60%, showing that local therapy has the potential to cure "oligo" or isolated liver metastases.[3-9] Many patients are not suitable for resection because of medical or surgical reasons. The benefit of local therapy in noncolorectal liver metastases is less clearly defined, but long-term survival has been reported after the resection of liver metastases from sarcoma, breast cancer, and other tumor sites.[10]

Initially, radiation therapy (RT) for liver metastases from solid tumors was viewed exclusively as a palliative intervention because of the low whole-liver tolerance to RT. In the 1970s and 1980s, numerous studies suggested that low-dose whole-liver RT (approximately 21-30 Gy, in 2- to 3-Gy fractions) could palliate patients, but the associated survival rates were very low.[11-13] Subsequently, Bydder et al[14] showed in a cohort of heavily pretreated patients with limited life expectancy that 10 Gy in 2 fractions to the whole liver improved symptoms from liver metastases in 53% to 66% of patients at 2 weeks.

The dose-limiting toxicity from whole-liver RT is radiation-induced liver disease (classic RILD), initially called radiation hepatitis[15] and characterized pathologically by central vein occlusion as described by Reed and Cox.[16] Low-dose whole-liver RT remains an option for patients experiencing pain from extensive liver metastases that stretches the liver capsule; however, the safe doses that can be delivered are not associated with durable local control. With the advent of 3-dimensional conformal radiation treatment (CRT) planning and delivery technology that allows for partial liver irradiation, it was recognized that higher tumor doses could be delivered safely as long as the mean dose to the liver was kept to less than safely tolerated whole-liver doses. Pioneering investigators at the University of Michigan observed no cases of RILD after CRT for colorectal liver metastases when the mean liver dose was <31 Gy in 1.5 Gy twice a day. This group also found the Lyman normal tissue complication probability model useful as a means of relating dose-volume histogram data to risk of liver toxicity.[17] In recent years, the application of stereotactic body radiation therapy (SBRT) has allowed even more intensive tumor dose escalation in a hy-

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pofractionated schedule with increased conformality and steep dose gradients outside the planning target volume that reduce the dose to the liver usually well below the threshold above which severe RILD is observed.[18] The present review focuses on the role of CRT and SBRT in the setting of liver metastases.

Rationale for Treatment of Oligometastases

Until fairly recently, cancer metastases were thought to represent an incurable state, occurring late in the natural history of malignancy and warranting palliative care only. It is now recognized that some patients with "oligo," or few sites of metastases, may have isolated sites of metastases that can be potentially cured with local therapy. The term "oligometastases" was coined to refer to this stage of distant metastases.[19] Typically, the entire burden of disease can be recognized as a finite number of discreet lesions. Although there is no strict definition of oligometastases, it is commonly interpreted to be no more than 5 or 6 metastatic sites. For patients with oligometastases, locally ablative therapies such as surgical resection, radiofrequency ablation, or SBRT might prove "curative" or extend survival, especially when combined with effective systemic therapy to address occult micrometastases. The classic model of "oligometastases" in which local therapy can lead to a cure of metastases is in patients with liver metastases from colorectal carcinoma in which surgery alone can cure a substantial subset of patients.[4,20,21]

Surgical resection, considered the ultimate locally ablative therapy, has been the gold standard against which less invasive emerging modalities must compare. Most of the liver resection literature to date has been retrospective, with overall survival most commonly reported and local control less consistently reported. Some large series have shown high 5-year survival rates. Fong et al[4] have the largest reported experience of liver resection for metastatic CRC, and in a favorable subgroup with solitary small (<5 cm) metastases, long (>1 year) disease-free intervals, low carcinembryonic antigen (CEA) values (<200 ng/mL), and negative surgical margins, they observed a 5-year overall survival of 60%. These patients had de novo cases of oligometastases because none of these patients had received prior systemic chemotherapy. In contrast, the group with all 5 risk factors (tumors >5 cm, disease-free interval <1 year, CEA >200 ng/mL, positive surgical margins, and more than 1 metastasis) had a 5-year survival of only 14%. Christodouleas and Marks emphasized the importance of distinguishing the de novo oligometastatic state from that of the systemic therapy–induced oligometastatic state because the latter group is likely to have a much less favorable prognosis.[22,23]

The role of surgical resection in non-CRC is less clear. Lermite et al[24] recently summarized the literature to date in a review of surgical resection of liver metastases from breast cancer. Liver metastases from breast cancer generally portend a poor prognosis, at least in part because of lower responses with systemic therapy compared with bone or other soft-tissue metastases. The median survival after resection ranges from 27 to 63 months and the 5-year survival from 18.4% to 61%. The variability in prognosis of patients with metastatic breast cancer and in the systemic therapies they receive, which is more pronounced than CRC, makes these results challenging to interpret. Some patients may have indolent disease without treatment even in the presence of liver metastases. Patient selection for the resection of liver metastases from breast, neuroendocrine, and other non-CRC tumors requires further elucidation.

As more studies focus on the management of patients with oligometastases, it will be important to determine whether there is a threshold burden of metastatic disease beyond which death is inevitable regardless of the interventions applied. Quantitative metrics that characterize the relative severity of tumor burden or biology of disease to select patients might eventually help refine patient selection.[25,26] Milano et al[22] from the University of Rochester have also shown that the net tumor burden for patients with 5 or fewer sites of macrometastatic disease, treated on 2 prospective SBRT protocols, was an independent predictor of overall outcome.[22] Whether SBRT, as an adjunct to systemic therapy, to selected macroscopic metastases can influence overall survival by keeping the burden of disease below such a "lethal threshold" is being investigated.[27]

Patient Selection for Liver CRT or SBRT

The first reported experience of CRT and SBRT for liver metastases was more than 15 years ago.[28,29] As with most new treatments, the initial evaluation of RT for patients with metastatic disease was conducted in a very unfavorable prognostic group, with limited treatment options.[18,30-32] Tumors were generally inoperable and/or unresectable, with multiple metastases involving more than 1 organ or region (extrahepatic metastases and/or uncontrolled primaries) and short disease-free intervals; most had been heavily treated systemically. These patients are at an increased risk of metastatic progression and resultant death and the greater the burden the higher the risk.

Most trials and experiences reported to date have included many different primary cancer sites with varying risks of metastatic progression and response to systemic therapy, further clouding the interpretation of overall survival results. Reports of patients with limited life expectancy are problematic because toxicity might be underestimated and local control might be overestimated, despite censoring, because of competing risks. After these initial studies showing safety of CRT and SBRT, future studies will hopefully include patients with improved prognosis who are more likely to benefit from ablation of their liver metastases. In studies of favorable patients, we will better determine the late toxicity profile and long-term local control of more homogeneous patient populations. Optimal patients for such trials would be those with CRC or breast primary cancers, absence of extrahepatic disease, 3 or fewer liver metastases, 6 cm or less in size, more

than 1.5 cm from the luminal gastrointestinal organs, and no or minimal prior systemic therapy. Clearly, patients with only some of these characteristics may also benefit from liver metastases RT although the absolute benefits may be less.

Planning Techniques

There are several RT planning and delivery issues that are unique to the liver. Target delineation and image guidance can be especially challenging, because, in the absence of intravenous contrast, liver metastases are not well visualized on computed tomography (CT) scans or in-room volumetric imaging used for image guided radiotherapy (IGRT). The use of an intravenous contrast assists in target delineation, and the placement of radiopaque fiducial markers near the metastases is sometimes done to facilitate IGRT. The migration of fiducial markers is uncommon.[33] There is a small risk of bleeding, infection, and pneumothorax in the range of similar percutaneous procedures,[34] and serious toxicity such as cardiac embolization has been reported.[35] Details of fiducial-based IGRT and nonfiducial IGRT strategies are described by Brock in this issue (see pages 247-255).

In addition to the delivery of SBRT, there are several unique features involved in planning the treatment. Although a thorough review is beyond the scope of this report, at least 7 beams are necessary to produce steep dose gradients and conformality indexes associated with SBRT that reduce high dose to organs at risk.[36] For CRT, usually to lower biological doses than SBRT, fewer beams are sometimes appropriate, with beam angles chosen to minimize dose to the primary organs at risk (eg, liver or luminal GI structures).

There is motivation to keep the radiation treatment beam-on time as short as possible. Lengthy treatment times not only reduce throughput and patient convenience but also might increase the risk of intrafractional movement, especially if the patient experiences discomfort.[37] Advancements in linear accelerator design and control software, including specialized systems with increased monitor unit output and efficient modulated arc delivery platforms, may facilitate the rapid delivery of radiation, which may be particularly useful for hypofractionated SBRT.

Toxicity

The tolerance to SBRT of a cirrhotic liver is less than the tolerance of a normally functioning liver.[38] Fortunately, most patients with metastases do not have underlying cirrhosis or hepatitis, and the main hepatic toxicity that may occur is classic RILD, which can be avoided as long as the mean dose to the liver is $<$30 Gy in conventional fractionation.[17] Within the context of prospective phase I or phase I/II trials of liver SBRT for metastases in patients with good baseline liver function, various liver constraints have been applied.[18,31,32] In all of these studies, RILD was not a dose-limiting toxicity.

In the University of Colorado trial, it was shown to be safe to treat up to 3 liver metastases to 60 Gy in 3 fractions as long at least 700 mL of normal liver received a $<$15-Gy total dose in 3 fractions.[18,30] It was reasoned that the liver would retain adequate function as long as a certain minimum volume was protected. The initial estimate of the minimum volume that had to be spared was based on published surgical resection series in which it was observed that 75% to 80% of the normal noncirrhotic liver could be removed without causing liver failure.[20,21] Additional normal tissue constraints were applied to other organs in the vicinity of the liver. No more than 35% of the total kidney volume could receive 15 Gy or higher in 3 fractions, the maximum point dose to stomach or small intestine could be no more than 30 Gy, and the maximum total dose to the spinal cord had to be $<$18 Gy. Rule et al[32] from University of Texas Southwestern applied similar constraints in their phase I trial evaluating SBRT dose escalation from 30 Gy in 3 fractions to 60 Gy in 5 fractions delivered over 2 weeks. The liver constraint was similar to that used in the Colorado trial; at least 700 mL of normal liver had to receive $<$21 Gy. The maximum point doses to the spinal cord, esophagus, skin, stomach/duodenum, jejunum/ileum, and colon were 30, 35, 32, 32, 35, and 38 Gy, respectively. Twenty-seven patients with 37 lesions were enrolled. There was no grade 4 or 5 toxicity or treatment-related grade 3 toxicity after a median follow-up of 20 months. The maximum tolerated dose was not reached, but the predefined maximum dose was 60 Gy in 5 fractions.

A conceptually different approach to the prediction of liver toxicity from SBRT was used by Lee et al[31] from Princess Margaret Hospital, who applied the Lyman normal tissue complication probability model to guide the selection of tumor dose delivered in 6 fractions. The "risk" of hepatic toxicity was escalated from 5% to 10% to 20%. The lack of observation of any cases of radiation-induced liver disease in 68 patients treated suggests that the model was a useful tool to guide dose selection but not predict the actual risk of liver toxicity. One patient in the Princess Margaret Hospital trial experienced a grade 4 duodenal bleed resulting from a maximal total point dose to the duodenum of 33 Gy to 0.5 mL in 6 fractions. Note that this patient had progressive disease through the duodenum at the time that may have confounded the risk of bleeding.

Chest wall pain or rib fracture can occur from lung or liver SBRT. In a pooled analysis from 2 centers, Dunlap et al[39] identified the volume of the chest wall receiving 30 Gy in 3 to 5 fractions or higher (V30) as a robust predictor of the risk of pain requiring narcotic analgesics or rib fracture, with a substantially higher risk when the V30 exceeded 30 mL. Here, the chest wall was defined as all tissue (bony and soft) peripheral to the lung in the region treated. Focusing only on rib fractures, Pettersson et al[40] from Sahlgrenska University Hospital identified the minimum dose received by the 2 mL of rib receiving the highest dose (D_{2cc}) as a strong predictor of fracture, with an estimated risk of 50% for D_{2cc} of 49 Gy in 3 fractions.

Timmerman[41] nicely summarized conservative (but unvalidated) normal tissue dose constraints for single fraction as well as 3- and 5-fraction hypofractionated regimens. When treating the liver, the most relevant normal tissues at risk are the GI tract, chest wall, and liver. When the luminal GI tract is in close proximity, it is reasonable to use more protracted

fractionation regimens while still using SBRT techniques. Also, there is far less experience with <5-fraction SBRT with tumors larger than 6 cm in maximal diameter, so conventional fractionation or dose variable 6-fraction SBRT (similar to the Princess Margaret Hospital approach[31]) may be preferred in these cases.

Clinical Outcomes

CRT

In 1995, the University of Michigan reported on 22 patients with unresectable CRC liver metastases treated with concurrent hyperfractionated CRT (maximum dose of 72.6 Gy in 1.5-1.65 Gy per fraction) and intrahepatic fluorodeoxyuridine. A response rate of 50% was seen, with the remainder of patients having stable disease. The median survival was 20 months.[42] In the most recent report from the Michigan group, 128 patients were treated with CRT (median dose 60.75 Gy in 1.5 Gy twice a day) in combination with concurrent continuous-infusion hepatic arterial fluorodeoxyuridine in a prospective phase I/II trial. In 47 patients with CRC liver metastases, the median survival was 17.2 months. The 3-year freedom from extrahepatic progression was only 15.1%.[43,44] Patients treated with >70 Gy had an improved median survival (not reached, >16.4 months) versus those with lower doses (11.6 months). Others have also shown that CRT may be delivered safely to CRC liver metastases.[45] In another report of 45 patients with CRC liver metastases, survival was better in patients who received a boost (up to 60 Gy) versus those who received whole-liver RT alone (20-30 Gy) (median survival, 14 vs 4 months).[45]

SBRT

A wide variety of dose-fraction regimens have been used for liver SBRT, ranging from single-dose treatment to 3 to 10 fractions delivered on consecutive days or with at least 1 day between fractions. Few studies have examined dose escalation in a formal, structured phase I trial. The University of Colorado coordinated a multicenter phase I/II trial for liver metastases.[30] During phase I, doses were given in 3 fractions delivered in less than 1 week starting at 36 Gy. Doses were escalated by 6 Gy per dose cohort in a standard phase I design up to a predefined maximum of 60 Gy. Forty-seven patients with 63 lesions of median volume of 14.9-mL (range, 0.8-98.0 mL) size were treated.[18] The University of Colorado investigators found better local control for smaller tumors (100% for tumors ≤3 cm vs 77% for >3 cm). There was only 1 grade 3 or higher toxicity. The 2-year actuarial local control for the entire group who received 60 Gy in 3 fractions was 92%.

Recently, Rule et al[32] from the University of Texas Southwestern published their single-institution phase I experience in which they escalated dose from 30 Gy in 3 fractions to 50 Gy in 5 fractions to 60 Gy in 5 fractions. The authors' rationale for studying a 5-fraction as opposed to a 3-fraction regimen was based on concerns about treatment to lesions located near potentially more sensitive periportal biliary structures, where a slightly more protracted regimen might avoid treatment-induced fibrotic occlusion of such structures and the potential for late biliary toxicity. The authors note that although no such toxicity was observed, only 8 of 27 patients actually had lesions located near the liver hilum. Twenty-seven patients with 37 lesions were enrolled. The median follow-up was 20 months (range, 4-53). The 2-year actuarial local control rates were 56%, 89%, and 100% for the 30-, 50-, and 60-Gy cohorts, respectively.

Goodman et al[46] reported a phase I dose-escalation single-fraction trial for patients with liver metastases or intrahepatic cholangiocarcinoma. Doses were escalated in 4-Gy cohorts from 18 Gy up to 30 Gy in 1 fraction. Twenty-six patients with 40 lesions were treated. There was no dose-limiting toxicity. The median follow-up was 17 months, and this corresponded to a 12-month local control rate of 77%. The 2-year actuarial survival rate was 50.4%.

Sometimes, large liver metastases cannot be treated with highly potent doses safely despite the use of stereotactic techniques because of the increased volume of normal tissue required to be irradiated. Thus, a highly individualized 6-fraction SBRT treatment strategy was developed at Princess Margaret Hospital in which the dose was dependent on the volume of liver irradiated and the proximity to GI luminal structures.[31] In this phase I study, 68 patients with inoperable metastases (most were CRC and breast primaries) were treated using this risk-stratified approach. The median tumor volume was 75.2 mL (range, 1.19-3090 mL). There was no dose-limiting toxicity even in the highest RILD risk group. Local control at 1 year was 71%, corresponding to a median overall survival of 17.6 months.

Normal tissue changes seen on imaging for up to 3 to 6 months after ablative therapies can cloud response evaluation. Herfarth et al[47] were the first to describe multiphasic CT changes as a function of time after single-fraction SBRT. They found a median threshold dose of 13.7 Gy for inducing Housefield unit changes on CT images for patients treated to a median dose of 22 Gy at the isocenter. They divided these changes into 3 types depending on the time of observation after SBRT. Type I occurred up to 3 months, type II occurred at 3 to 6 months, and type III occurred more than 6 months after SBRT. The volume of the effect observed on CT imaging was largest early after SBRT and decreased with time from treatment. In other words, the low-density region, which is often of similar density as the original tumor, is larger than the pretreatment tumor because it corresponds to a dose below the prescription dose that tightly corresponds to the PTV. This large hypodense area is observed at a time within 3 months of treatment, a time when patients and treating oncologists are eager to determine whether SBRT has been effective. An awareness of transient treatment-induced changes on imaging is important because it allows us to advise patients, referring doctors, and radiologists of the imaging findings that are expected after treatment.

Despite the difficulties in evaluating liver RT for patients with liver metastases, published reports have shown 2-year actuarial local control rates ranging from 50% to 100% as summarized in Table 1. Higher doses are associated with

Table 1 SBRT for Liver Metastases: Outcomes

	Patients	Lesions	SBRT (PTV dose)	PTV	Time Point	Local Control Comments
Heidelberg, 2004[48]*	37	60	11-21 Gy × 1	GTV + 6 mm axial + 10 mm sup-inf	18 mo	
Wuerzburg, 2006[49]	39	51	7 Gy × 4 10 Gy × 3 12.5 Gy × 3 26 Gy × 1	GTV + 8 mm axial + 13 mm sup-inf	2 y	
Aarhus, Copenhagen, 2006[50]*	44	Not stated	10 Gy × 3	GTV + 5 mm axial + 10 mm sup-inf	2 y	79% All pts CRC 3 ulcers with intestinal dose >30 Gy
Erasmus U, Rotterdam, 2010[51]	17	34	10 Gy × 3 12.5 Gy × 3	GTV + 5 mm axial + 10 mm sup-inf	2 y	54% 15 pts CRC; 1 late portal HTN in multiply treated patient
Colorado/multi-institutional, 2009[30]*	47	63	12-20 Gy × 3	GTV + 5 mm axial + 10 mm sup-inf	2 y	≤3 cm: 100% >3 cm: 77% ($P = 0.015$)
PMH, 2009[31]*	68	141	Variable, NTCP-based Median 7 Gy × 66	GTV + 13 mm or more	1 y	71% Better for higher dose, smaller volume
Stanford, 2010[46]*	19	33	18-30 Gy × 1	ITV + 3-5 mm or GTV + 5-10mm without 4D-CT	1 y	77% Combined with 7 pts HCC or IHC MTD not reached
University of Texas Southwestern Medical Center, 2010[32]*	26	35	6 Gy × 5 10 Gy × 5 12 Gy × 5	ITV + 5 mm	2 y	56% 89% 100% MTD not reached

Abbrevations: PTV, planning target volume; ITV, internal target volume; MTD, maximum tolerated dose; HCC, hepatocellular carcinoma; IHC, intrahepatic cholangiocarcinoma; PMH, Princess Margaret Hospital; 4D, 4-dimensional; pts, patients; sup-inf, superior and inferior.

*Prospective study.

better local control. The best results thus far were obtained most recently by University of Texas Southwestern investigators who observed no local failures at 2 years after 60 Gy in 5 fractions delivered within 2.5 weeks.[32]

Studies to date have been small and confounded by broad eligibility criteria including varying primary sites, variable size and number of metastases, and number of lines of prior systemic therapy. Other than radiation dose, which has been shown to correlate with local control, it is difficult to draw conclusions about other prognostic factors based on the studies reported to date. Future trials of RT for liver metastases will require more homogeneous eligibility criteria while controlling for the intensity of pre-RT systemic therapy to further clarify prognostic factors that are correlated with local control.

Conclusions

Considerable experience with CRT and SBRT for liver metastases has shown favorable local control and acceptable toxicity. Further study in more favorable patients and longer follow-up will further elucidate the potential late toxicity profile and chances of long-term survival after liver metastases CRT or SBRT. Such studies will hopefully also help identify the patients most likely to benefit from this therapy.

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