Radiation Oncology Approaches in Liver Malignancies

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OVERVIEW

Radiation therapy plays an increasingly important role in the treatment of hepatic malignancies. There is convincing evidence of safety and efficacy employing brachytherapy (yttrium-90), three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, stereotactic body radiotherapy (SBRT), and proton beam therapy (PBT) in all stages of primary and metastatic involvement in the liver. Technologic advances in tumor imaging, real-time tracking of moving targets during radiotherapy delivery, and superb radiation dose deposition control have enabled treatment of previously unapproachable lesions. Recently completed and ongoing clinical trials are refining optimal dose fractionation schedules for SBRT as monotherapy. Radioembolization as part of first-line therapy in metastatic colorectal tumors is being tested in large international trials combined with FOLFOX6 and bevacizumab, as well as in hepatocellular carcinoma with sorafenib. PBT is becoming more available as new facilities open in many countries providing particle beam therapy, which delivers unparalleled control of radiation dose close to critical structures. A major point of research is understanding how best to safely destroy tumors in the background of often fragile hepatic function from cirrhosis or heavily pretreated chemotherapy liver parenchyma. Fortunately, serious complications from radiotherapy are rare, acute toxicities are typically Common Terminology Criteria for Adverse Events v4.0 grade 1–2, with consistent response rates of 50% to 97% in the modern era.

The liver is a frequent site of both primary malignancies (e.g., example, hepatocellular carcinoma [HCC] and solid tumor metastases). The incidence and mortality of HCC continues to increase worldwide, making it the third most common cause of cancer death globally, with an estimated 564,000 new cases annually.[1] In the United States, HCC mortality has been rising steadily for more than 2 decades with no plateau yet reached.[2] A dismal overall 5-year survival rate of only 5% is achieved, and more than 70% of patients present with advanced disease that cannot be approached with curative intent—that is, transplantation, resection, or tumors of less than 3 cm that can be ablated.[3]

The liver is also one of the most frequent sites of metastases for a variety of malignancies, including colorectal cancer, breast cancer, cutaneous and ocular melanoma, and neuroendocrine tumors. Although resection is suitable for a minority of patients, most patients with these malignancies do not qualify for surgery either because of medical contraindications, an excessive burden of hepatic disease, or insufficient liver functional reserve. Most patients with liver metastases have occult diffuse micrometastases, which are incurable despite any liver-directed therapy. However, some patients have only radiographically detected metastases, or oligometastases, which are the only sites of disease. In these individuals, local control of the metastases may improve overall survival.

Nonsurgical local therapies are viable options for selected patients. These approaches include hepatic arterial embolization with or without chemotherapy and local ablative therapies such as radiofrequency ablation (RFA), laser-induced interstitial thermotherapy, and ionizing radiation via brachytherapy. The variety of techniques used to deliver radiation therapy (RT) to liver tumors achieve outcomes ranging from palliation to cure. Despite these efforts, many patients will die from liver disease, and additional approaches have enriched the current armamentarium. Use of traditional permanent interstitial-seed brachytherapy, ^{125}I, has been successful in controlling selected colorectal liver metastases, as has high-dose afterloading of ^{192}Ir with ultrasound or CT guidance.[4,5] Unfortunately, these specialized nonsurgical local interventions are difficult to provide en mass, and thus investigators continue to search for additional approaches that can treat even more patients.

RT has a growing role to play in treatment of both HCC and liver metastases. In the past 20 years, normal liver tolerance to RT has become better understood, such that post-treatment liver toxicity is no longer inevitable but instead an uncommon occurrence. Technical challenges in delivering focused RT to the liver are rapidly being overcome, and a number of new technologies make liver-directed therapies more conducive to improved outcomes. Advances in imaging, radiation planning, and image guidance allow safe delivery of ablative doses of RT to focal liver tumors. Although radiation doses that can be delivered to hepatic tumors are

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limited by the tolerance of the liver and adjacent tissues, several radiation strategies—intensity modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), particle beam therapy (protons, carbon ions), and brachytherapy (yttrium-90 [^{90}Y], iodine-125 [^{125}I], ^{192}Ir)—are clinically important in current practice.

RT techniques, including both external and internal (brachytherapy) strategies, are dependent on state-of-the-art imaging to define the liver target volume. Quality assurance for most techniques involves sophisticated patient immobilization, organ motion management, and specialized training and equipment. All techniques require collaboration with other members of the hepatobiliary team. Both HCC and liver metastases have variable RT dose responses, but the optimal dose and fractionation (individual applications of RT) for these heterogenous tumors is not clearly defined. The most common nonsurgical approaches for the treatment of localized HCC remain hepatic artery-delivered particles laden with chemotherapy (transarterial chemoembolization [TACE]) or radioactive microparticles (transarterial radioembolization [TARE]).[6] External beam RT (EBRT) has been an effective option in many parts of the world for selected patients with HCC but now has an expanded role with stereotactic and proton beam technologies.

RT at doses above 50 Gy is effective in destroying tumors when concurrent chemotherapy is given— usually 5-fluorouracil. Advanced technologic strides in RT planning and delivery, use of three-dimensional conformal RT (3DCRT), IMRT, SBRT may benefit an increasing number of patients with liver metastases.[7-12] The key limitation in this treatment is the tolerance of normal liver parenchyma to radiation; the maximum acceptable dose to the whole liver of 35 Gy is far below that which is required to destroy adenocarcinoma metastases, estimated at 70 Gy or more. Several important factors must be evaluated before proceeding to either external or internal RT; a partial list is in the sidebar.

KEY POINTS

- Normal liver parenchymal radiation tolerance is far below required tumoricidal doses of radiation.
- External beam radiation techniques of intensity-modulated radiotherapy and stereotactic body radiotherapy (SBRT) increase safety and ability to deliver high doses of radiation.
- SBRT and proton beam therapy use is rapidly increasing worldwide and becoming available in all major cancer treatment regions.
- Intraarterial radiation delivery (yttrium-90 [^{90}Y]) is supported by level 1 medical evidence in unresectable metastatic colorectal cancer unresponsive to chemotherapy.
- ^{90}Y can often be used—when all other liver-directed therapies cannot—as salvage monotherapy or in first-/second-line therapy with concurrent chemotherapy.

SIDEBAR. Key Factors in Eligibility for Hepatic Radiotherapy

- Liver function test trend (total bilirubin, albumin)
- Child-Pugh score 5-9; $>$ 9
- Estimated volume normal liver not receiving any radiation
- Post-radiation functional liver volume ($>$ 700 mL recommended)
- Spatial distribution of tumors (focal/diffuse)
- Total number of tumors targeted
- Parallel structure of normal liver and dose/volume constraints
- Tumor location in relation to stomach/duodenum

BRACHYTHERAPY

Radioembolization

One approach for multiple liver metastases that has been in clinical use for more than 40 years is implantation of radiation sources into the tumor (brachytherapy) via ^{90}Y carrying microspheres.[13-15] Radioembolization using radioactive ^{90}Y-labeled microspheres has level 1 evidence supporting its use in colorectal cancer hepatic metastases and level 2 evidence for efficacy and safety in HCC, neuroendocrine, and breast cancer metastases.[13,16] The expanding literature reveals good and encouraging results in both retrospective and prospective reports as demonstrated by low acute and late toxicity and consistent response rates. ^{90}Y is a pure-beta emitter that decays to stable zirconium-90 with an average energy of 0.94 MeV via a half-life of 2.67 days (64.2 hours). Key to normal liver protection is that high doses of radiation only penetrate 2.5 mm (maximum range of 1.1 cm) from the source. There are two commercially available ^{90}Y microspheres with the radioactive source permanently embedded within either glass or resin structure. The diameters of the microspheres allow them to become permanently embolized in the terminal arterioles of tumor. No significant amount of ^{90}Y leaches from the microspheres. [17]

Eligibility

Patients with liver-predominant disease, adequate liver function and reserve, and an Eastern Cooperative Oncology Group performance status of 0 to 2 have benefited the most from this therapy, even with portal vein thrombosis. Pretreatment assessments hepatic angiogram and technetium-99m macroaggregated albumin scan ensure that only patients in whom radioactive microspheres will be captured in the tumors and will not pass through arteriovenous fistulae to the lungs or other arteries to the gastrointestinal track will proceed to treatment.

Toxicity

Because the ^{90}Y used in microspheres is a beta emitter with a relatively short half-life, radiation safety issues are not problematic and are without specific post-treatment constraints. Toxicity is increased in patients with advanced HCC and impaired liver function (Child-Pugh B or C). In the largest HCC

^{90}Y experience to date, acute toxicity in the first 3 to 7 days post-treatment is as follows: grade 0, 65%; grade 1, 23% mostly fatigue and upper abdominal pain; grade 2, 6% fatigue; grade 3, 2% gastritis and overt gastric ulceration, with biopsy proof of microspheres in the mucosa; and grade 4, 1%.[18,19] Late complications of ascites, worsening liver dysfunction, and elevated total bilirubin are uncommon (range, 1% to 4%). Liver failure within 90 days in the absence of tumor progression—termed radioembolization-induced liver disease—leads to death in 1% of these very ill patients. Similar toxicity rates are seen in patients with metastatic tumors receiving radioembolization.[20]

Results

By the end of 2014 worldwide, it is estimated that approximately 40,000 patients will have received radioembolization treatment since 2001. In addition to HCC, metastatic colorectal tumors (mCRC) and metastatic neuroendocrine tumors represent the majority of tumor types treated. Radioembolization can often be used when all other liver-directed therapies cannot and can be given as salvage monotherapy or in first-/second-line therapy with concurrent chemotherapy. It has also been shown that in patients with mCRC, advanced age (older than 70) is not a contraindication to treatment, with comparable toxicity and efficacy to younger patients.[21]

EBRT

EBRT has been used effectively for selected patients with HCC in many parts of the world.[22,23] Its role has recently been expanded by the advent and proliferation of stereotactic photon beam therapy and proton beam facilities. The use of EBRT for liver metastases continues to be of interest from data showing combined chemotherapy with EBRT and EBRT monotherapy can be highly effective in controlling solid tumors while respecting the critical parallel structure of the liver and sparing sufficient normal tissue from radiation. Although beyond the scope of this report, clinically based mathematical models of normal tissue complication probabilities (NTCP) from RT have enabled dose escalation and expansion of eligible patients considered for EBRT.[24,25]

3DCRT/IMRT

3DCRT and IMRT have been mainstays of advanced treatment delivery using CT-based datasets to target tumors while sparing normal surrounding tissues. Both 3DCRT and IMRT have shown a number of benefits, mostly for patients with good hepatic function, in tumor control, palliation, and increased progression-free survival.[6-10] Very high-dose RT may be used safely and effectively if a small volume of the liver ($< 25\%$) is irradiated. In particular, RT—and especially 3DCRT—may be used to manage medically unfit patients or those with an unresectable metastatic liver lesion. Employing 3DCRT can provide at least two important advantages over traditional (two-dimensional) radiation methods: (1) 3DCRT permits the tumor to be treated with higher doses and minimizes the dose to the uninvolved liver areas and surrounding critical organs; and (2) the dose-volume histograms, which are integral to 3DCRT planning, permit a quantitatively better understanding of the relationship among dose, volume, and risk of complications in treated target tissues and surrounding critical counterparts. A surgical rule of thumb used during hepatic resection is that only 25% to 40% of the normal liver is needed to sustain life. The logic of efforts to treat hepatic metastases with higher RT doses builds on both this surgical rule and the assumption that tumors may be controlled safely with 3DCRT doses beyond 30–35 Gy.

With conventional three-dimensional treatment planning, the entire target is typically encompassed within each beam. Further, each RT beam typically delivers a relatively homogeneous dose throughout the target. With IMRT, a portion of each beam is modulated to provide a unique intensity to each region of the tumor.[26] The clinician can thus adjust the dose to normal tissue within the path of the beam. The purposefully nonuniform intensities from several beam orientations combine to deliver the desired three-dimensional dose.

SBRT

SBRT is still being formulated with very promising early results. It was first introduced in the mid-1990s and constituted a dramatic change in the way radiation had been previously delivered— both biologically and in terms of process. This modality primarily exploited modern technologic innovations to achieve geometric avoidance of high doses to normal tissues in localized liver irradiation. The use of hypofractionated delivery can result in biologic effects very different from conventionally fractionated radiation.

In the past decade, this specialized form of 3DCRT, which administers single or hypofractionated large-radiation doses (up to five total fractions), has shown benefits to patients with a variety of tumor types, both in the primary and metastatic setting.[27] Proper patient selection is paramount, as the risk of harm to patients is also present due to much larger fraction sizes used with few opportunities to make corrections. SBRT may be given as a cytoreductive therapy for metastatic liver disease that either eliminates or greatly reduces whole body disease burden in patients with a good performance status and limited burden of systemic disease. These requirements often are found in patients with colorectal cancer with metastases to the liver. A heightened awareness of the importance of safety and efforts to improve safety processes and technologies are constantly ongoing. There are many challenges in using EBRT for HCC, with successes being realized using image-guided RT (IGRT) to assist in the delivery of 3DCRT, IMRT, and SBRT, along with respiratory motion compensation and tumor visualization.[28,29]

Procedure/Process

SBRT involves a brief, intensified regimen of tightly focused external RT that targets one or more discrete extracranial lesions. In hepatic SBRT, organ motion during breathing must be accounted for, and there are a variety of ways to do this. These range from respiratory manipulation (i.e., "gating"), real-time tracking of tumor as it moves (e.g., CyberKnife), or enlarging the volume treated to ensure the tumor is always in the beam at the cost of more normal liver being irradiated. Delivery times of photons in SBRT are typically longer than standard fractions due to the significant dose delivered in 1-5 fractions total compared to 28-35 fractions in IMRT. All patients are treated with IGRT for each fraction—often with continuous tracking during treatment delivery. Figure 1 illustrates a typical radiation dose distribution for SBRT.

Results

There is strong interest in pursuing SBRT for HCC and metastatic tumors due to the increased ability to spare normal liver tissue from receiving tolerance doses of radiation. The available prospective studies and retrospective reports from 2006 to 2011 involve a range of eight to 60 patients and are limited to single institutions. Despite the lack of larger, randomized, controlled data, the positive outcomes in all stages of HCC are proven with a wide array of fraction sizes and total doses. Excluding the one study with a sample of only eight patients, the remaining three used at least five different fractionation schedules adjusted for Child-Pugh A or B classes. One-year survival ranged from 48% to 79% in these heterogeneous groups.[30-32] In mCRC, two phase I/II studies have been reported that provide a solid basis for patient selection and expected outcomes.[12,33] Kavanagh limited eligibility in 36 patients with mCRC to lesions smaller than 6 cm and delivered 60 Gy in three fractions resulting in 1-year local control of 92%.[12] Rusthoven reported on 47 patients with mCRC with relatively small tumor volumes treated with 36-60 Gy in three fractions resulting in 95% 1-year local control.[33]

PROTON BEAM THERAPY

The use of proton beam RT (PBT) represents a different type of energy (charged particle) than photons (electromagnetic energy wave). The physical characteristics of this modality can achieve superior dose deposition compared to 3DCRT.[34,35] Because of increased control of radiation dose deposition at any depth in the body, there has been intense interest in using PBT for HCC.[36] Dawson has suggested that photon beams (3DCRT, IMRT, SBRT) might be best employed in patients with Child-Pugh A with tumors in the right lobe near the dome and of smaller than 6 cm. Protons may be best used in Child-Pugh B, tumors larger than 8 cm, and in those that are central/medial in the liver.[28,36] Only level 2a evidence supports any form of radiation in HCC; however, combined with the retrospective reports of hundreds of patients, there is a significant amount of evidence supporting RT in all stages of HCC.[9,10,22,23,28,29,30,32,34,35]

Eligibility

A challenge for eligible patients in North America is the relative scarcity of PBT centers; currently about 14 are in operation, with 10 more planned by 2020. There is not more or less stringent eligibility for PBT than for SBRT. As with 3DCRT/IMRT, PBT can have a meaningful role in all stages of HCC, with a proven ability to sterilize tumors similarly to other local ablative approaches such as RFA.[37] In the Barcelona Clinic Liver Cancer classification, patients with stage 0 and early stage A disease who cannot undergo surgical resection, transplant, or RFA are candidates for curative intent

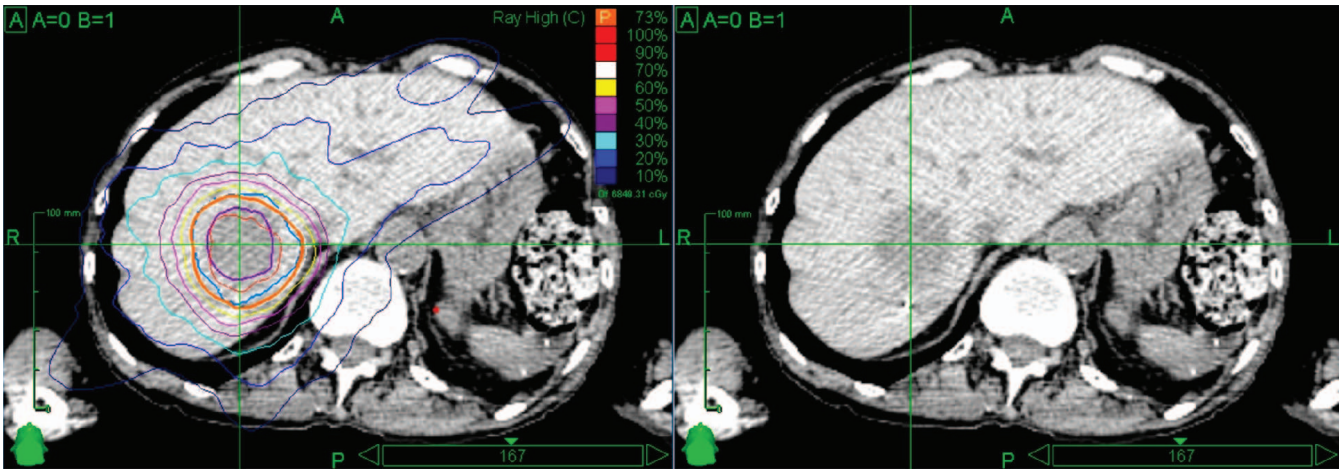

FIG 1. Axial CT image from stereotactic body radiotherapy (SBRT) treatment planning system with colored isodose lines (left) and without (right). Each line represents a three-dimensional calculated absorbed dose of radiation. Note the tightly conformed high-dose lines around the tumor, with rapid fall off of radiation dose in the normal liver tissue only a short distance away. This patient received 50 Gy in five fractions of 10 Gy for metastatic colon cancer lesion. At 12 weeks post-SBRT, the lesions was necrotic and lacked enhancement with IV contrast. The patient did not experience any side effects or late toxicity.

RT. Patients with potentially transplantable disease can benefit from PBT as a bridge to transplant while on the wait list. In stage B and C, 3DCRT/IMRT but not PBT has proven efficacy in situations where TACE has been ineffective or is unsuitable. This is particularly important in patients with portal vein invasion where TACE is contraindicated and where TARE may not be possible or ineffective.[28,29]

Toxicity

There is now more than a decade of experience with 3DCRT/IMRT, SBRT, and PBT 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. Growing evidence reveals that strategies using aggressive or ablative adjunctive local therapies with systemic therapy might achieve improvements in overall outcome as long as they are administered safely.[38] The main and most worrisome toxicity is radiation-induced liver disease leading to irreversible dysfunction, decompensation, and liver failure. Although careful patient selection and use of NTCP models, it is difficult to know by using available labs and imaging the true health of a liver before treatment.

Results

Prospective studies to date using PBT have been positive regarding toxicity and tumor control, with encouraging overall survival rates in selected groups of patients with HCC in Eastern and Western populations.[39-42] Compared to SBRT, there are more prospective studies (10), with each study reporting sample sizes ranging from 76 to 318 patients. It is not known whether SBRT or PBT is superior or equivalent in outcomes of patients with HCC. Likely, these techniques will be complementary to each other based on factors such as tumor size, distribution, and location in the liver.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Relationships marked "U" are uncompensated.

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Keywords: hematological malignancies, nanoparticles, translational medicine. Introduction.Â Figure 2 miRNA-based approaches in cancer therapy. Abbreviation: miRNA, micro ribonucleic acid.Â Nanotechnology can be applied not only in chemotherapy, but also in radiation oncology, by combining radiobiology with experimental pharmacology. Malignant cells are sensitive to ionizing radiation emitted by various radioactive metals.81 By delivering such substances to the primary tumor site, we may improve current radiotherapy or brachytherapy protocols. Chanda et al82 have conjugated gum arabic glycoproteins to gold nanoparticles and tested this new assay on a murine model of prostate cancer. Hepatic radiation toxicity restricts irradiation of liver malignancies. Better knowledge of hepatic tolerance dose is favourable to gain higher safety and to optimize radiation regimes in radiotherapy of the liver. In this study we sought to determine the hepatic tolerance dose to small volume single fraction high dose rate irradiation. 23 liver metastases were treated by CT-guided interstitial brachytherapy. MRI was performed 3 days, 6, 12 and 24 weeks after therapy. MR-sequences were conducted with T1-w GRE enhanced by hepatocyte-targeted Gd-EOB-DTPA. All MRI data sets were merged with 3D-do