ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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The Role of Radiation in Liver Cancer

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H&O For what categories of liver cancer is radiation used?

TL There are two general categories to consider regarding the role of radiation: cancer metastatic to the liver and cancer that starts in the bile ducts inside the liver or in liver cells, generally referred to as hepatobiliary cancer. Extrahepatic bile duct cancer is treated differently from intrahepatic bile duct cancer, and will not be addressed in this discussion.

The total number of patients in the United States with either primary hepatobiliary cancer or colorectal cancer with metastases confined to the liver is approximately 20,000 per year. Among these patients, only approximately 15–20% in each category have tumors that can be surgically resected. The remaining 80–85% of patients require other forms of treatment, which is where radiation therapy comes into play.

For primary hepatobiliary cancers that are not resectable, treatment options are very limited. There is some evidence that for patients with good performance status, transarterial chemoembolization, which involves injecting a chemotherapeutic agent into the liver and blocking the liver artery, may be effective, but the overall benefit from this approach is controversial. Systemic chemotherapy has been almost entirely unsuccessful in this setting, with several studies showing no benefit from this approach.

H&O How was radiation used in the treatment of primary hepatobiliary cancer in the past?

TL In the past, there were no proven techniques for successfully administering a high dose of radiation to patients with primary hepatobiliary cancer. Up until the late 1980s, the most common approach was to irradiate the entire liver. However, the sensitivity of the liver is such that only 30 Gy in 2-Gy fractions can be given safely; beyond this relatively low dose, patients experience liver damage. These early findings led many clinicians to conclude that radiation could not play a role in the treatment of liver cancer.

H&O How has this changed?

TL At our institution, we developed techniques for treating liver cancers with high-dose focal liver radiation using 3-dimensional conformal radiation therapy, and we have seen excellent results (Figure 1). There are two parts to this strategy. First, tumors are visualized using state-of-the-art imaging technology. When we first developed this technique, contrast-enhanced computed tomography was the imaging modality used. Now, we and some other groups are using magnetic resonance imaging. The information obtained through imaging can be incorporated into our radiation treatment planning systems, enabling us to arrange the radiation beams to target the tumor and avoid most of the normal liver.

The second part of this strategy entails the development of 3D treatment planning tools, such as dose volume histograms. For instance, we can divide the liver into 2,000 or so small "voxels" (volume elements) and calculate the dose to each of these units. This approach enables us to determine precisely how much radiation the normal liver is receiving.

H&O Why is it important to calculate the amount of radiation to the normal liver so exactly?

TL The main concepts behind this approach are to minimize and quantify the radiation administered to the normal liver. We have known for years that it is possible to surgically remove up to half (or even more) of the liver, as long as enough normal liver remains. We have been

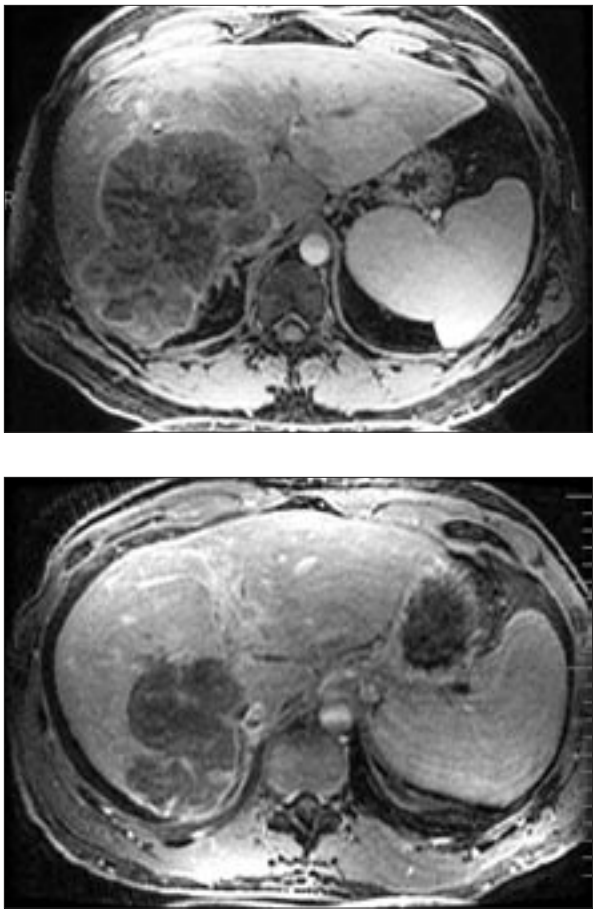

Figure 1. Serial magnetic resonance imaging (top: before; bottom: 9 months later) of a primary hepatocellular tumor treated with 3-dimensional conformal radiotherapy, with good response. Patient is now asymptomatic.

able to develop an analogous approach with radiation. By quantifying exactly how much of the normal liver is being treated and how much is being spared, we can provide a patient with the exact maximum radiation dose that he or she can safely receive.

H&O What have you found in studies evaluating this approach?

TL In studies that we have conducted over the past 10 years, every patient has received an individualized radiation dose based on how much of the normal liver can be spared. Of course, we aim to maximize that dose by minimizing the amount of normal liver that needs to be treated. A recent paper in the *Journal of Clinical Oncology* summarizes our experience over the last 6 years with approximately 130 patients. We found that the survival time among patients with primary hepatobiliary cancer and with primary colorectal cancer with unresectable metastases to the liver is approximately double that of historical controls. The key finding of this study was that patients who receive higher doses of radiation experience better outcomes.

H&O Did these patients receive radiation therapy alone or in combination with chemotherapy?

TL All patients received hepatic artery chemotherapy in addition to radiation therapy. Hepatic artery chemotherapy has been a standard approach for the treatment of intrahepatic cancers for many years, particularly for colorectal cancer metastatic to the liver. Combining chemotherapy with radiation therapy in this setting produces results that are greater than the sum of the parts because the agent used, floxuridine, has antitumor effects and also acts as a radiation sensitizer, enhancing the efficacy of the radiation therapy.

H&O Does the amount of radiation given depend on the size of the tumor?

TL One might assume that patients who are receiving higher doses of radiation are those with smaller tumors. However, this is not the case. A modest-size tumor located in the middle of the liver will receive the same dose as a large tumor on the edge of the liver. The dose is based not on the tumor size but on the volume of the normal liver that can be spared. Thus, we think that the improved outcomes among patients receiving higher doses are not due to the tumors being smaller, but rather because higher doses of radiation are more effective.

H&O What were the specific outcomes of the patients in your study?

TL According to our findings, it appears that a subgroup of patients, particularly those who are able to receive a radiation dose greater than 75 Gy, is curable. Among these patients, the survival rate at 3–4 years was 20%. Of course we want to increase this percentage; however, the fact that some patients are being cured is very encouraging.

H&O What side effects need to be considered with this approach?

TL Approximately 5–8% of patients experience serious side effects. If the tumor is touching the stomach, making it impossible to avoid delivering radiation to the stomach entirely, gastrointestinal bleeding may occur. In our study, no patients died from gastrointestinal bleeding.

Even though each patient receives what has been calculated to be a safe dose, a small percentage of patients

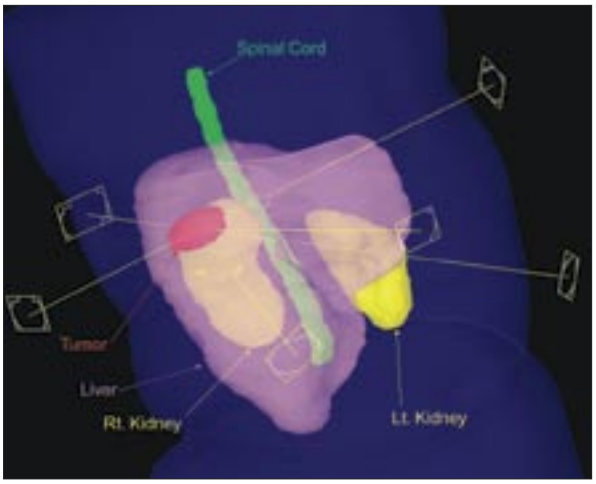

Figure 2. Example of stereotactic radiation treatment of a small, intrahepatic tumor.

experience liver damage. It may be that some patients have some genetic feature that makes them particularly susceptible to liver damage.

H&O What other high-dose focal radiation techniques are currently being explored in the setting of liver cancer?

TL Other groups are starting to employ this radiation strategy and to explore variations on the technique. Laura Dawson and colleagues at the University of Toronto are investigating the use of larger fractions of radiation, 6 Gy per treatment, instead of the small fractions that we have used, and not always with chemotherapy. The results seen thus far are very promising.

Intensity-modulated radiation therapy may enable us to match the dose of radiation to the tumor even more exactly than 3D conformal techniques allow, which our calculations show can increase the safe dose by 10 Gy or more. Research is ongoing to improve this approach.

Another strategy is to work with the surgeon to try to gain a clearer understanding of which portion of the tumor is rendering it unresectable. Generally, it is the central structures of the liver—the portal vein, the bile duct, etc—that cause the tumor to be unresectable. If we can identify this portion, we can deliver a higher dose of radiation to that specific area, with the goal of shrinking the tumor and converting it to a resectable state. This approach, which might have a better chance than chemoradiation alone for tumors larger than 10 cm that we often encounter, is in very early stages and no results are available.

Another area of ongoing research pertains to combining high-dose focal radiation with some of the newly developed systemic agents used in the treatment of colorectal cancer.

H&O What approaches are being developed for patients with small tumors?

TL While the majority of patients we have seen have tumors that are greater than 8–10 cm in diameter, another subgroup of patients may have several small tumors. Typically, these patients are treated with radiofrequency ablation or cryotherapy. We and others have been developing stereotactic radiation treatment techniques for administering one very high dose of radiation to these small tumors (in the range of 20–26 Gy; Figure 2). Such high doses can safely be administered to patients with small tumors without harming the liver. This approach needs more study in prospective trials, but hypothetically it should achieve the same results as radiofrequency ablation while avoiding an invasive procedure.

H&O Are there other patient subgroups for which specific techniques are being developed?

TL For patients with very diffuse disease, we have been studying the concept of radiation protection. Here, a particular agent—we have been using amifostine (Ethyol, MedImmune)—is used with the goal of protecting the normal liver from radiation. Preclinical evidence shows that amifostine is selectively processed by normal liver cells, therapy protecting these cells from radiation, whereas it does not protect malignant cells.

Suggested Reading

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.

Ben-Josef E, Lawrence TS. Radiotherapy for unresectable hepatic malignancies. *Semin Radiat Oncol.* 2005;15:273-278.

Dawson LA, Lawrence TS. The role of radiotherapy in the treatment of liver metastases. *Cancer J.* 2004;10:139-144.

Dawson LA, McGinn CJ, Lawrence TS. Conformal chemoradiation for primary and metastatic liver malignancies. *Semin Surg Oncol.* 2003;21:249-255.

Herfarth KK, Debus J, Lohr F, et al. Stereotactic single-dose radiation therapy of liver tumors: results of a phase I/II trial. *J Clin Oncol.* 2001;19:164-170.

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