Combining Local and Regional Therapeutic Modalities to Treat Hepatic Malignancies

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ABSTRACT

Hepatocellular carcinoma and metastatic colon cancer have proven to be challenging problems in oncology today. Currently multiple treatment options are available for treating patients with these diseases, and for this reason, a multimodality and multidisciplinary approach is needed to optimize the effectiveness of treatment. Local ablation techniques along with intra-arterial therapy may be complementary and therefore increase survival in patients being treated for hepatocellular carcinoma and metastatic colon cancer. With proper patient selection, further improvement in treatment outcomes can be achieved when these techniques are combined with surgical resection and multidrug systemic chemotherapy. Therefore, it is imperative that interventional radiologists work closely with our colleagues in other medical and surgical specialties to provide our patients with the best possible treatment options.

KEYWORDS: Ablation, hepatocellular carcinoma, combined therapy

Objectives: Upon completion of this article, the reader should understand the benefits of combination therapy when treating patients with hepatic malignancy.

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Interventional radiology provides important treatment options in some of the most challenging problems in oncology today: hepatocellular carcinoma (HCC) and metastatic colon cancer. As with most solid organ tumors, a multidisciplinary and multimodality approach is required to obtain optimal results. Just as surgery, chemotherapy, and radiation therapy are often combined in a single patient to improve outcomes, various local and regional image-guided techniques act synergistically to optimize results.

Image-guided therapy plays a central role in the treatment of hepatic malignancy and is showing promise in extrahepatic applications. Image-guided techniques allow for a targeted regional (organ-based) and/or a local approach to treating malignancy. From early in their development, it was clear that image-guided therapies could be combined with systemic therapy to obtain improved response rates and survival.

The combination of local ablation and intra-arterial therapies may be complementary on numerous

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levels. First, intra-arterial therapy can treat a liver segment or lobe with multiple lesions including those that cannot be localized for ablation; local ablation strategies (chemical, thermal, etc.) are more effective at treating localized disease that can be targeted by computed tomography (CT), ultrasound, or magnetic resonance imaging. Second, there is evidence that synergy exists between many image-guided techniques. For example, transarterial chemoembolization performed prior to radiofrequency ablation (RFA) can reduce tumor blood flow and decrease the heat-sink for a subsequent RFA. Finally, the likely zones of inadequate treatment for large tumors are opposite for ablation techniques (most likely to inadequately treat the periphery of the lesion) versus intra-arterial therapy (most likely to inadequately penetrate the hypovascular/necrotic center of a large tumor).

COMBINATION THERAPY FOR HCC

The treatment of HCC remains one of the most difficult problems in oncology today. Although surgical resection is considered curative, only ~20% of patients with HCCs are eligible for resection.¹ A large portion of patients with HCC have tumors that are not resectable due to location, poor hepatic reserve, or number of tumors. Additionally, recurrences in the remnant liver are relatively frequent and many of these patients die from recurrent HCC. For these reasons, numerous combination therapies to treat HCC have been studied. In a recent study of solitary HCC less than 7 cm, bland embolization in combination with ablation achieved similar survival rates when compared with surgical resection.²

For small HCC, local ablation strategies (percutaneous ethanol injection [PEI], RFA) have shown to be effective, and results can be improved when these local ablation techniques are combined with transarterial chemoembolization (TACE). In a prospective randomized study of 52 patients with HCC less than 3 cm, patients were randomized to PEI versus TACE/PEI. The local recurrence rate was significantly improved for combination therapy.³ Kamada et al⁴ reported decreased recurrence and improved survival in a series of 69 patients with HCC less than 3 cm treated with TACE plus PEI ($n=32$) versus TACE alone ($n=37$). Combining FRA with chemoembolization has also shown excellent results (Fig. 1). Kitamoto et al¹ reported a significant increase in thermal lesion size when TACE was combined with RFA versus RFA alone. The results of combination therapy with TACE and RFA were reported in another series of 108 lesions in 64 patients with a significant number of lesions greater than 3 cm ($n=43$). Complete necrosis was achieved in all lesions with recurrence seen in only two infiltrative lesions and 1-year survival of 98%.⁵ This same group reported that

the risk of intrahepatic recurrence was significantly greater in tumors larger than 5 cm and in patients with multiple tumors. In a multivariate analysis, tumor number was the only independent factor having a significant impact on early intrahepatic recurrence using combination TACE and RFA.⁶ Percutaneous RFA can also be potentiated by administration of intravenous liposomal doxorubicin as reported by Goldberg et al.⁷

Another treatment option for patients with early stage HCC is liver transplantation. In the United States, the incidence of HCC is increasing as a result of the maturation of the cohort of patients with chronic hepatitis C. Waiting periods for a liver transplant in the range of 6 to 12 months are fairly common in the United States. As a result, many patients will progress without therapy and may no longer be candidates for transplant. In one study,⁸ 25% of patients awaiting transplant progressed in only 6 months and were no longer candidates for transplant. Therefore, either local ablation or targeted chemoembolization techniques can be used as a "bridge" to liver transplantation. In a study of 27 patients with HCC awaiting transplant,⁹ chemoembolization was performed and after a mean waiting period of 167 days all 27 patients underwent liver transplant, and there was no recurrence at a mean follow-up of 29.2 months. Whether local ablation techniques, TACE, or a combination of these modalities are optimal bridge therapy to transplantation is yet to be determined.

For advanced HCC, combination therapy treatment strategies have proliferated and have shown improved results over monotherapy. Because long-term survival can be achieved following surgical resection (especially in noncirrhotic patients) neoadjuvant combination therapies have been employed to downstage tumors, enabling surgical resection (Fig. 2). Lau et al¹⁰ reported downstaging 49 patients with unresectable HCC at presentation using neoadjuvant systemic chemotherapy, Y-90 microspheres, or combination therapy with a median survival of 86 months following resection. In addition, there has been promising results from the early trials of TheraSphere (Y-90 microsphere; MDS Nordion, Ottawa, Canada) embolization for nonresectable HCC.¹¹ TheraSphere is a form of internal radiation that can be delivered selectively to the tumor via the hepatic artery. The Y-90 particles then emit beta radiation to treat the tumor. Early data suggest similar survival and fewer side effects when compared with TACE.¹²

The use of adjuvant and neoadjuvant systemic and/or intra-arterial chemotherapy remains controversial in advanced HCC. A recent meta-analysis of various adjuvant therapies, following resection for HCC, showed improved survival with postoperative hepatic artery chemotherapy.¹³ However, another review of eight trials involving 548 patients concluded that there is presently no strong evidence that adjuvant or

Figure 1 (A,B) TACE of a right hepatic mass. (C,D,E) Ultrasound-guided RFA of the same tumor. (F) Contrast-enhanced axial CT demonstrating retained ethiodol from TACE with hypoattenuating periphery from RFA.

neoadjuvant therapy prolongs survival following liver resection.¹⁴

Multimodality management of large HCCs has shown excellent results even in patients with unresectable disease. Mok et al¹⁵ reported the results of multimodality therapy of 131 patients with HCC >10 cm: 75 patients underwent hepatic artery chemotherapy in-

fusion, TACE, and percutaneous acetic acid injection and were compared with 56 patients having surgical resection. Patients not undergoing resection had anatomically unresectable tumors or poor indocyanine green elimination. In 38 patients having three or more sessions of image-guided therapy; 1- and 3-year survival was not statistically different: 57% and 19%, respectively,

Figure 2 (A) Axial CT demonstrating a hypodense lesion in the right hepatic lobe, which was found to be a colon cancer metastasis. This was surgically resected successfully. (B,C) Positron emission tomography scan postresection demonstrates no increased activity within the liver. (D) Surveillance CT demonstrates a new metastasis in the left hepatic lobe. (E) Corresponding positron emission tomography scan confirms malignancy. (F,G) CT-guided cryoablation performed successfully.

for image-guided therapy versus 61% and 25%, respectively, for surgical resection. There was significantly greater extrahepatic disease in the surgical group.¹⁵ Combined TACE and PEI have also been studied in large HCCs. Dohmen et al compared with results of 52 patients with HCCs > 3 cm who were treated with a single session of TACE followed by PEI versus 68 patients undergoing TACE alone. Three- and 5-year survival rates were significantly better with combination therapy (59% and 32%, respectively, versus 27% and 17%, respectively).¹⁶

The combination of external beam radiation and TACE has also been evaluated for large HCCs. Guo and Yu reported 28 patients with HCCs 3 to 10 cm in size who were treated with TACE followed by "local irradiation." One- and 3-year survival was 82% and 42%, respectively.¹⁷ In another study, conformal radiation was combined with TACE and was performed in 45 patients with a median survival of 23.5 months. Nine patients developed radiation-induced liver disease.¹⁸

COMBINATION THERAPY FOR METASTASIS

Colorectal cancer is one of the leading causes of cancer death in the United States. Multimodality therapy has been the standard of care for metastatic colorectal cancer for many years with most patients receiving a combination of multidrug systemic chemotherapy, intra-arterial chemotherapy, resection, and/or ablation. Fig. 2 is an example of a patient with metastatic colon cancer whose treatment was optimized by using both surgical resection and percutaneous RFA and cryoablation. One agent, SIR-spheres (Y-90 microsphere; Sirtex Medical Limited, Lane Cove, NSW, Australia), is currently commercially available and is supported in a phase III study in which microspheres plus hepatic artery floxuridine (FUDR) produced a higher response rate and an improved survival rate when compared with hepatic artery FUDR alone.¹⁹ Taylor et al reported the results of surgical resection, chemotherapy, and external beam plus intra-operative radiotherapy with a 5-year survival of 49% in the subgroup of patients with locally advanced colon cancer.²⁰

CONCLUSION

The armamentarium of interventional oncologists is rapidly evolving and new image-guided technologies and procedures are being developed at a rapid rate. This rapid evolution makes systematic evaluation of various combinations of image-guided treatments difficult. However, it is clear that with proper patient selection, combinations of systemic, regional, and local therapies are improving survival in our patients. Inter-

ventional radiologists need to take a lead role in the future development and investigation of these techniques and work closely with our colleagues in medical, surgical, and radiation oncology to achieve the best outcomes possible for our patients.

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