

Intraarterial Liver-Directed Therapies: The Role of Interventional Oncology

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Background: Since the early 1990s, the minimally invasive image-guided therapies used in interventional oncology to treat hepatocellular carcinoma have continued to evolve. Additionally, the range of applications has been expanded to the treatment of hepatic metastases from colorectal cancer, neuroendocrine tumors, cholangiocarcinoma, breast cancer, melanoma, and sarcoma.

Methods: We searched the literature to identify publications from 1990 to the present on various image-guided intraarterial therapies and their efficacy, as well as their role in the management of primary and secondary liver malignancies.

Results: Chemoembolization and radioembolization are considered a standard of care in treating, delaying progression of disease, and downstaging to bridge to liver transplantation. Progression-free survival and overall survival outcomes are promising in patients with colorectal cancer and neuroendocrine tumors with liver metastases. Applications in the treatment of hepatic metastases from cholangiocarcinoma, breast cancer, melanoma, and sarcoma also show potential.

Conclusion: Interventional oncology and its image-guided intraarterial therapies continue to gain recognition as treatment options for primary and secondary liver cancers. Growing evidence supports their role as a standard of care alongside medical oncology, surgery, and radiation oncology.

Keywords: Chemoembolization–therapeutic, gastrointestinal neoplasms, neoplasm metastasis, radiology–interventional, yttrium radioisotopes

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INTRODUCTION

Evidence supporting the role of image-guided transarterial cancer therapies for palliation and as a bridge to resection or transplant continues to increase. Additionally, some interventional oncology therapies have garnered significant evidence to gain inclusion in standards of care.^{1,2} The range of treatments and applications for image-directed therapy has expanded to meet the growing demand from referring clinicians. Interventional oncology progressively continues to establish itself as a key pillar of cancer care, alongside medical oncology, surgery, and radiation oncology.

Different modalities are available in the interventional oncology armamentarium for the locoregional treatment of primary and metastatic liver tumors: hepatic artery embolization (HAE), transarterial chemoembolization (TACE), transarterial radioembolization (TARE) using yttrium-90 (Y-90), and chemoinfusion therapy. Intraarterial treatments of hepatic neoplasms take advantage of the liver's dual blood supply, in which primary liver tumors and metastatic tumors derive up to 95% of their blood supply from the hepatic arterial system, while the majority of blood supply (up to

75%) to normal hepatocytes is derived from the portal vein.^{3,4} Therefore, a significantly higher concentration of chemotherapeutic drugs (up to 16 times higher) can be delivered to the tumor via the hepatic arterial system with less consequential systemic side effects than conventional chemotherapy.⁴

The goal of HAE is tumor ischemia via terminal arterial obstruction using particles. TACE—either with ethiodized oil (Lipiodol) (conventional TACE [cTACE]) or with drug-eluting beads (DEB-TACE)—combines targeted delivery of chemotherapeutic agents with embolization of the tumor arterial supply. Radioembolization's mechanism of action is delivery of internal radiation to liver tumors without significant embolic phenomenon. Chemoinfusion therapy selectively delivers local chemotherapeutic drugs in high concentrations, greater than can be safely administered systemically and with fewer systemic side effects.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is one of the principal causes of cancer-related mortality and is currently the

primary cause of death in patients with cirrhosis.⁵ Locoregional intraarterial cancer therapies, aimed at a cure or palliation, are well established in the treatment of HCC and play an integral role in hepatic transplantation for HCC by downsizing or controlling the tumor growth while patients await liver transplant surgery.⁶

In the PRECISION V trial, the first international, multicenter, randomized study designed to evaluate the safety and efficacy of cTACE compared with DEB-TACE in the treatment of HCC, DEB-TACE showed a trend toward higher response rates in complete and partial response and disease control compared to cTACE.⁷ Additionally, the DEB-TACE cohort demonstrated better tolerability without increased liver toxicity, especially for higher risk patients, despite higher doses of chemotherapy administered in the DEB-TACE arm. The improved tolerability of DEB-TACE allows quicker repeat doses to achieve tumor control, if necessary.⁷

In 2016, the PREMIERE trial demonstrated that TARE with Y-90 glass microspheres had significantly longer time to progression (26 months vs 6.4 months) compared to the current standard of practice with cTACE. Although longer time to progression did not produce a significant difference in overall survival, TARE achieved improved local tumor control and decreased dropout from transplant wait listing compared to cTACE.^{8,9} TARE had previously been advocated for patients with intermediate stage HCC who responded poorly to TACE, based on large tumor burden or vascular invasion.¹⁰ However, the PREMIERE trial demonstrated a potential role for transplant bridging in HCC with a longer time to progression and delayed transplant waitlist dropout.^{8,9} Similarly, the SARAH trial demonstrated no survival benefit between Y-90 resin microspheres and sorafenib in patients with locally advanced HCC.^{11,12} However, similar to the findings in the PREMIERE trial, participants receiving Y-90 resin microspheres in the SARAH trial had reduced side effects, better quality of life, higher response rates, and improved tumor progression in the liver compared to the patients who received sorafenib.¹²

COLORECTAL CANCER LIVER METASTASIS

The most common neoplasm identified in the liver is related to metastatic disease. In cases of colorectal metastasis, the liver is frequently the first and only metastatic site. Up to 80% of patients with colorectal cancer will have a liver metastasis, 50% at initial presentation.¹³ While surgical resection remains the standard of care for select patients with limited liver metastases, <20% of patients are candidates for resection, and recurrence rates are as high as 75%.¹⁴ Patients who are not candidates for resection are typically treated with systemic 5-fluorouracil (5-FU) and leucovorin, with a mean survival time of approximately 12 months.¹⁵ Median survival time is longer, up to 19.5 months, with oxaliplatin and infused fluorouracil plus leucovorin (FOLFOX).¹⁶

Regional intraarterial liver therapies can be used as a neoadjuvant therapeutic regimen to reduce tumor size, and the tumor can later be percutaneously ablated or surgically resected for definitive treatment. The SIRFLOX trial demonstrated the value of TARE with Y-90 resin microspheres in combination with first-line chemotherapy in patients with

unresectable liver-only or liver-dominant metastatic colorectal cancer. Patients were randomized to receive TARE with Y-90 resin microspheres (SIR-Spheres) in combination with modified FOLFOX chemotherapy (\pm bevacizumab) or modified FOLFOX chemotherapy (\pm bevacizumab) alone. Analysis of progression-free survival in the liver revealed that treatment with radioembolization showed improvement from 12.6 to 20.5 months and a decreased risk of tumor progression of 31%.¹⁷ Despite higher response rates and improved liver-specific progression-free survival with the addition of Y-90 to first-line chemotherapy, no improvement in overall survival or overall progression-free survival was seen in patients with liver-only and liver-dominant metastatic colorectal cancer.¹⁸ As of the latest update of the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for colon and rectal cancer, treatment with Y-90 resin microspheres is included as a Category 2A recommended treatment for patients with liver-dominant, chemotherapy-resistant colorectal disease.²

Similar to TARE, drug-eluting bead treatment with irinotecan (DEBIRI) results in median survival of approximately 15-25 months. This median survival is comparable to outcomes from standard systemic chemotherapy and may be useful in downstaging unresectable metastatic disease to resectable status with minimal toxicity.¹⁹ Additionally, DEBIRI showed improvement in disease-free survival, with partial and complete response rates ranging from 36%-78%, based on Response Evaluation Criteria In Solid Tumors criteria, and durable response to 12 months.¹⁹ However, when compared to TARE, patients treated with DEBIRI experienced worse postembolization syndrome and required a total of 4 sessions to complete 1 cycle of treatment.²⁰

NEUROENDOCRINE TUMORS

Neuroendocrine tumors (NETs) represent a large heterogeneous spectrum of disease that arises from embryonic neural crest tissue and can be functioning or nonfunctioning.^{21,22} NETs are characterized by their site of origin and the ability to make biologically active peptides. These tumors range from medullary thyroid carcinomas, pancreatic NETs (islet cell carcinomas), carcinoid tumors, pheochromocytomas/paragangliomas, and poorly differentiated small cell/large cell NETs.²¹ Liver resection is associated with prolonged overall survival of approximately 10 years. However, resection is not curative, with recurrence rates up to 94% at 5 years.^{23,24} Symptomatic patients with liver-dominant NET metastases who are treated with HAE, TACE, or TARE with Y-90 show 90%-100% symptom response.²⁵ While studies have shown a higher response rate for HAE compared to TACE, whether TACE offers any therapeutic benefit compared to particulate embolization alone remains uncertain.²⁶⁻³¹ In patients with carcinoid tumors, no improvement in overall survival or progression-free survival was shown when intraarterial chemotherapy was added to embolization. However, in patients with islet cell carcinomas, a tendency toward prolonged survival (31.5 months vs 18.2 months) and improved response rate (50% vs 25%) was observed in patients who received TACE as opposed to HAE, although the differences did not reach statistical significance.³⁰ No significant differences were seen in complications or severe toxicities between HAE and TACE.³⁰ To date, no clear advantage of one embolotherapy

has been established in the literature. The Randomized Embolization Trial for NeuroEndocrine Tumor Metastases to the Liver (RETNET) will estimate the duration of hepatic progression-free survival in participants treated with HAE, cTACE, and DEB-TACE. The primary hypothesis is that chemoembolization will be nearly twice as durable as bland embolization.³²

TARE with Y-90 microspheres is safe with high response rates, even with extensive tumor burden of the liver.³³ Median survival has been demonstrated up to 70 months, with a low incidence of acute and delayed toxicity.³³ The advent of peptide receptor radionuclide therapy (PRRT) has raised concerns about possible added toxicity to the liver from excessive radiation, but in a cohort of 20 patients, sequential treatment with TARE and PRRT was considered safe.³⁴ Despite TARE being considered safe, 2 cases of delayed toxicity to the liver have been reported.^{35,36} Prospective randomized trials are needed to evaluate the long-term effects of Y-90. A study presented in 2016 that evaluated the survival outcomes for cTACE, DEB-TACE, and Y-90 TARE suggests significant survival benefits with cTACE and supports the therapeutic decision for cTACE as the mainstay intraarterial therapy option for NET liver metastases.³⁷

CHOLANGIOCARCINOMA

Cholangiocarcinoma, either intrahepatic or extrahepatic, is a rare malignancy with poor prognosis even for patients undergoing surgery. The 5-year overall survival rate for patients with cholangiocarcinoma is <5%.³⁸ Only 30% of patients present at a resectable stage, and recurrence is common even after complete resection.³⁹ Transarterial therapies are safe and effective for treating unresectable intrahepatic cholangiocarcinoma. Response rates are similar for TARE, TACE, and chemoinfusion, even though higher rates of partial and stable response were reported with TARE. The overall and 1-year survival rates were also similar between chemotherapy and radiotherapy approaches.⁴⁰ Median overall survival for intraarterial therapies was 13 months, which is higher than median overall survival of 11 months for systemic chemotherapy.⁴¹ Randomized studies are needed to evaluate the efficacy of combined intraarterial therapies and systemic therapies in the treatment of cholangiocarcinoma.

BREAST CANCER

Breast cancer is the second most common cancer in the United States and worldwide, as well as the second leading cause of cancer death, following lung cancer.⁴² Up to 48% of women with metastatic breast cancer develop liver metastasis, and the median overall survival is 14.2-16.8 months if they present with extrahepatic metastases and 22.7-27.1 months if metastasis is confined to the liver.⁴³ The use of Lipiodol-based cTACE with various chemotherapeutic agents has been compared in several studies to the use of DEB-TACE with doxorubicin.⁴⁴⁻⁴⁷ Treatment with either DEB-TACE with doxorubicin or TACE with mitomycin C plus gemcitabine shows compelling support for their use in the treatment algorithm for breast cancer, with overall survival rates up to 47 and 35 months, respectively.^{46,47} Evaluation of TARE with Y-90 in patients with progressive liver metastases on standard polychemotherapy reveals median survival of 2.6-14 months.⁴⁸⁻⁵⁰

MELANOMA

Ocular melanomas, the most common intraocular tumor in adults, and cutaneous melanomas generally metastasize to the liver.⁵¹ Median survival is usually poor with liver involvement, only averaging 2-7 months.⁵²⁻⁵³ While the verdict is still out on whether TACE offers greater benefit than standard immunotherapy and targeted therapies, several studies show that responders perform significantly better and TACE should be considered as a treatment option for patients with bulky uveal melanoma hepatic metastases.⁵⁴⁻⁵⁶ The overall survival in patients who received hepatic arterial infusion, TACE, or immunoembolization as first-line treatment ranges from 6-21 months.⁵⁷ TARE demonstrated superior overall survival and is a safe and effective salvage therapy for limited metastasis of uveal melanoma. Additional studies are needed to determine whether TARE should be used as a first-line alternative for hepatic metastasis of uveal melanoma.⁵⁷

SARCOMA

Metastatic soft tissue sarcomas are an uncommon group of malignancies and are particularly difficult to treat. The outcome for unresectable metastatic sarcoma is poor, with a median overall survival of 12-16 months.⁵⁸ Systemic chemotherapy is the standard of care. However, systemic toxicity frequently limits its use. Although data are limited, intraarterial-directed therapy has been found to be safe and effective in the treatment of unresectable liver sarcomas, achieving local control of the target lesion in >65% of cases, with the highest rates of complete remission seen with TARE and radiofrequency ablation.⁵⁸ TARE using Y-90 has demonstrated improved safety as well as a median survival of 26.2 months, suggesting its use as a favorable alternative therapeutic option compared to systemic chemotherapy.⁵⁹

CONCLUSION

Interventional oncology continues to establish itself as a pillar of cancer care because of its rapid advancement and innovative applications. Growing evidence supports image-guided intraarterial liver-directed therapies in the treatment of both primary and secondary liver malignancies. These outcome-changing therapies allow for an increasing number of patients with HCC who are eligible for transplant. Patients with metastatic colorectal cancer after Y-90 therapy can become surgical candidates for potential curative intent or benefit from consolidation treatment after first-line chemotherapy. Multiple therapeutic options that prolong overall survival exist for NETs. Exciting times are on the horizon for interventional oncology with improvements in imaging technologies, development of new delivery platforms, and the advent of precision medicine with new drugs that target tumors as well as immune oncology.

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