Making the Case: Intra-arterial Therapy for Less Common Metastases

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Semin Intervent Radiol 2017;34:132–139.

Abstract

Intra-arterial therapies have high antitumor activity for both primary and secondary hepatic malignancies. Selective infusions allow increased delivery of cytoreductive therapy to the tumor bed while sparing the normal hepatic parenchyma. These therapies are now often applied in the outpatient setting or with short overnight hospital stays and have a growing role in the treatment of liver-dominant disease from metastatic colorectal cancer and from neuroendocrine tumors. Less commonly, intra-arterial therapies are applied to treat secondary hepatic malignancies from breast cancer, melanoma, pancreatic adenocarcinoma, and soft-tissue sarcomas. The available data are limited and generally retrospective observational cohort series of single institutions. The purpose of this article is to summarize the recent literature on outcomes for intra-arterial therapy in nonsurgical patients. Multi-institutional registries and prospective data are greatly needed, as intra-arterial therapies are increasingly applied in these patients to stop progression of chemorefractory tumors.

Keywords
- hepatic artery infusion chemotherapy
- chemoembolization
- radioembolization
- liver metastases
- interventional radiology

Objectives: Upon completion of this article, the reader will be able to discuss the available intra-arterial therapies and outcomes for liver metastases from breast cancer, melanoma, pancreatic adenocarcinoma, and sarcomas.

Accreditation: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Tufts University School of Medicine (TUSM) and Thieme Medical Publishers, New York. TUSM is accredited by the ACCME to provide continuing medical education for physicians.

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Liver metastases are found in approximately half of patients with metastatic cancer. The liver resembles a lymph node, in the sense that it has two vascular inputs (hepatic artery and the portal vein) and one outlet (hepatic vein), serving as a lint trap for hematogenous cancer cells. The liver is also highly structured and compartmentalized and has its own resident immune cells. Metastases may arise due to arterial circulation and lymphatic spread, but these are thought to occur less frequently than cells depositing in the liver via portal circulation. Common sources of liver metastases are cancers such as lung cancer (23–25%) and those carcinomas of the gastrointestinal tract including colon (13–16%), pancreas (11–18%), and stomach (6–11%). The liver is also a site of metastases from carcinomas of the breast (7–10%), uveal and cutaneous melanoma (2%), and rarely soft-tissue sarcomas.[1,2]

If a patient presents with an isolated lesion, it should be approached with surgical resection, if possible. Unfortunately, the vast majority of patients with metastatic liver tumors are not surgical candidates due to extrahepatic

Issue Theme Decision Making as a Growth Mechanism in Interventional Oncology; Guest Editor, Daniel B. Brown, MD, FSIR

DOI https://doi.org/10.1055/s-0037-1601852.
ISSN 0739-9529.

disease, the distribution and extent of liver involvement, or comorbidities that create unfavorable surgical risk. Moreover, the number, size, shape, or location of lesions precludes technically successful ablation in many patients. In these cases, intra-arterial therapy may be applied to stop the progression of hepatic disease. Tenets of intra-arterial therapy are as follows: (1) preferential arterial flow to tumors allowing increased delivery of therapeutics to the tumor tissues in comparison to normal hepatic tissue, (2) use of imaging to map the arterial anatomy and allow selective (lobar) or superselective (segmental) infusions of therapeutics to accomplish tumor coverage while minimizing treated liver volumes, (3) modification of hepatic arterial flow to prevent off-target deposition or occlusion of parasitized vessels to reestablish hepatic arterial flow to intrahepatic tumors, (4) assessment of imaging response for target disease in comparison to baseline imaging, (5) treat-to-response principle with repeat interventions in the setting of preserved eligibility.

Patient Selection

Prior to intra-arterial therapy, standard of care chemotherapy should be completed. The liver should be the dominant site of active disease, and liver metastases may result in abdominal pain. The best outcomes for intra-arterial therapy are observed in patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, preserved liver function (albumin, bilirubin, international normalized ratio within normal limits), and tumor burden of less than 25%. Moreover, patients must be able to undergo baseline and follow-up imaging as well as visceral arterial angiography with antegrade hepatic arterial flow. Lesions are ideally hypervascular, but hypovascular tumors can safely be treated as well.[3]

Intra-arterial Therapies

The goal of intra-arterial therapy is to infuse chemotherapy, embolotherapy, or radiotherapy into the tumor vasculature to achieve high locoregional tumor doses without the toxicity profile that would be observed for similar doses administered systemically. Hepatic arterial infusion chemotherapy (HAIC) involves the introduction of an indwelling catheter into the hepatic artery and surgical implantation of a chemotherapy pump that delivers sustained intra-arterial chemotherapy. Conventional transarterial chemoembolization (cTACE) involves the delivery of cytotoxic chemotherapeutic drug(s) often mixed with iodinated-oil (lipiodol) for visualization of tumor uptake on noncontrast computed tomography (CT). Some advocate particle or gelatin sponge (Gelfoam; 100–300, 300–500, and 500–700 μm) embolization to induce tumor ischemia and increase the dwell time of the drug–oil mixture. Transarterial embolization (TAE) with bland beads has also been applied. Chemoembolization with drug-eluting beads (DEBs) loaded with doxorubicin or irinotecan has been a newer approach for intra-arterial therapy. Yttrium-90 radioembolization (Y90) is a mechanistically different approach that delivers high doses of radiation therapy accomplished with hepatic arterial infusion of microembolic (20–40 μm) glass or resin microspheres that deliver β-radiation to the tumor bed. The rationale for intra-arterial therapies and technical considerations for these therapies have been previously described.[4–7] The purpose of this article is to summarize the recent literature on outcomes for these intra-arterial therapies that can be offered to nonsurgical patients with liver metastases.

Breast Cancer

More than half of patients with metastatic breast cancer develop liver metastases during the course of treatment, and liver lesions are commonly found (62–72%) on autopsy.[8–10] In patients with oligometastatic disease, there may be a role for locoregional therapy.[11] Liver tumors are difficult to treat with systemic chemotherapy, as the liver is the site of posttreatment progression in the majority of these cases, and these tumors will eventually progress on systemic chemotherapy.[9] Intra-arterial therapy may be applied during a break or switch in systemic chemotherapy for patients who have stable extrahepatic disease and progression of hepatic tumors. These interventions may temporarily arrest hepatic progression and preserve liver function in these cases. Moreover, intra-arterial therapy may allow for tumor debulking for palliation of abdominal pain from large masses. Given the available data in liver metastases from metastatic breast cancer, rates of progression of target disease are higher after chemoembolization than radioembolization, and a limited number of publications are available on hepatic artery infusion chemotherapy and DEB chemoembolization in these patients. The rationale for radioembolization in these heavily pretreated patients includes that the mechanism of action is not limited by chemoresistance providing high response rates, preservation of eligibility for systemic chemotherapy, and potential for combination with systemic chemotherapies such as capecitabine for control of extrahepatic disease.[12,13]

Hepatic Artery Infusion

Ang et al described hepatic artery infusion chemotherapy and combination systemic chemotherapy (irinotecan in seven of nine) in nine patients with metastatic breast cancer liver metastases.[14] Prior to HAIC, these patients had undergone a median of six lines of systemic chemotherapy. Patients were treated with floxuridine and dexamethasone 25 mg (+ mitomycin C in seven patients) on days 1 to 14 of 4-week cycles. Toxicities were grade 3/4 elevations in transaminases in four patients, one pump malfunction, and one hepatic arterial dissection complicated by occlusion of the common hepatic artery and pancreatitis. The overall response rate was 78%, similar to the 81% measured by Arai et al.[15] The median time to progression of liver disease was 6 months. The median overall survival (OS) was 17 months.

Conventional Transarterial Chemoembolization/Bland Embolization

Cho et al tailored chemotherapeutic drug (doxorubicin, cisplatin + gemcitabine, cisplatin, oxaliplatin) to patients' chemotherapy history in 10 patients who underwent chemoembolization.[16] Seven had nausea, vomiting, abdominal pain. Six had progressive disease per Response Evaluation Criteria In Solid Tumors (RECIST). The median OS was 12 months.

Vogl et al applied mitomycin C ± gemcitabine chemoembolization in 161 patients with breast cancer liver metastases being downstaged to laser-induced thermotherapy.[17] There were no early deaths or major complications reported. Progressive disease per RECIST occurred in 71 patients (44%). The median OS was 32.5 months.

Eichler et al treated 43 patients with gemcitabine chemoembolization.[18] Grades 1 to 2 nausea and vomiting were observed in 23 patients (56%). Progressive disease per RECIST occurred in 22 patients (51%). The median OS was 10.2 months.

Drug-Eluting Beads

Martin et al reported doxorubicin-based DEB chemoembolization in 40 patients.[19] At baseline, 30 (75%) patients had less than 25% liver burden and 22 (55%) had extrahepatic disease. Patients received 75-mg doxorubicin for each 2 cm^3 vial, and the operator determined the number of infused vials per session. The median number of treatments was two and the median cumulative doxorubicin dose was 250 mg. Adverse events were rare. One patient required cholecystectomy 6 weeks after treatment due to gallbladder embolization. All patients were alive at 3 months and 23 (57.5%) had an imaging response (endpoint was enhancement per mRECIST criteria). The median OS was 47 months.

Y90

Haug et al applied radioembolization in 58 patients.[20] Three (5.2%) had grade 3/4 bilirubin toxicity. Partial response was observed in 25.6% (11/43), and 11.6% (5/43) had progressive disease per RECIST. Based on ^{18}F-FDG positron emission tomography/computed tomography (PET/CT), the response rate was 51% (22/43) defined as a 30% decreased in SUV_{max}. The median OS was 11 months.

Cianni et al examined radioembolization in 52 patients.[21] Late complications included radioembolization-induced liver disease in two patients (3.8%) with more than 50% tumor burden and grade 3 gastritis (3.8%). A partial response rate of 56% was reported according to RECIST. PET/CT imaging response defined as any reduction in metabolic activity was 81%. The median OS was 11.5 months.

Saxena et al reported a series on 40 patients with ECOG 0 (82.5%) or 1 (17.5%).[22] Nausea and vomiting were observed in 25%, abdominal pain in 20%, and fatigue in 15%. The overall response rate was 31.6% (12/38) with progressive disease in 28.9% (11/38) per RECIST. Median OS was 13.6 months.

Gordon et al studied radioembolization with glass microspheres in 75 patients with breast cancer liver metastases and stable extrahepatic disease.[23] Clinical grade 3/4 toxicities were abdominal pain (6.1%), nausea (1.5%), and fatigue (1.5%). One patient required cholecystectomy for radiation cholecystitis, and the 30-day mortality rate was 4%. Partial response was observed in 35.3%. At baseline, hepatic tumor burden 25% or greater and elevated serum bilirubin more than 1.1 mg/dL were adverse prognosticators for OS. For patients with less than 25% tumor burden, the median OS was 9.3 months.

Fendler et al applied resin microspheres in 81 patients.[24] The most common grade 3/4 toxicities were transaminitis (39%) and elevated GGT (36%). Increased rates of nausea, elevated bilirubin, gastrointestinal ulceration, and radioembolization-induced liver disease (REILD) were observed with the whole liver technique in comparison to the accepted practice of sequential bilobar technique. The authors noted a 52% response rate with follow-up ^{18}F-FDG PET/CT defined as a 30% decrease in SUV_{max} for up to five treated lesions. Liver tumor burden was an adverse prognosticator for OS. The median OS was 8.2 months.

Pieper et al recently published cohort of 44 patients treated with radioembolization primarily with resin microspheres.[25] Thirteen patients (29.5%) had new or worsening ascites within 3 months, one patient (2.2%) had duodenal ulceration requiring surgery, and the 30-day mortality rate was 4.8%. Partial response (RECIST v1.1) was 39.5% in the treated liver. The median OS was 6.1 months.

Melanoma

Uveal melanoma frequently metastasizes to the liver (60%) and lungs (20%) at a median time of 5 years after enucleation.[26] The liver is more commonly a site of metastases from ocular melanoma (95%) than cutaneous melanoma (20%), and patients with liver metastases very rarely respond to systemic chemotherapies. Systemic therapies benefitting patients with cutaneous melanoma have been applied in uveal melanoma with less success, and historic overall response rates are usually 10% and almost always less than 20% for first-line therapies.[27] As a result of these low response rates, regional therapy for liver metastases from ocular melanoma has been the mainstay initial treatment approach. Surgical resection of liver tumors is the best approach for select patients; however, more than 90% of patients are not candidates for surgery. Recurrence after surgery occurs in 75% of patients.[28] Locoregional intra-arterial therapies frequently provide overall response rates exceeding 10% without reductions in OS.

Liver metastases from ocular melanoma tend to be hypervascular, and many authors report enhancement criteria for assessment of imaging response such as EASL (bidimensional) and mRECIST (unidimensional). However, generally it should be noted that these imaging criteria were specifically developed and validated for hepatocellular carcinoma. Moreover, intra-arterial therapies that are highly embolic may alter early arterial enhancement even in the setting of preserved tumor viability. Therefore, size-based criteria like WHO (bidimensional) and RECIST v1.1 (unidimensional) are more appropriate for reporting purposes because they have

been broadly applied in a variety of primaries and are often used in systemic chemotherapy trials.

Hepatic Artery Infusion

Leyvraz et al completed a phase III randomized controlled trial in 171 patients treated with intravenous (IV) or hepatic intra-arterial fotemustine for isolated liver metastases from uveal melanoma.[29] Median follow-up was 5.6 years. Patients received 100 mg/m^2 on days 1, 8, 15, and 22 (for HIA arm only) as induction therapy with maintenance every 3 weeks after a 5-week break postinduction. Patients treated with HIA had fewer systemic toxicities including reduced rates of grade 3/4 thrombocytopenia (21.2% vs. 42.1%) and neutropenia (28.7% vs. 62.6%). Device-related complications related to the implanted catheter occurred in 31.8% and included stenosis, thrombosis, dissection, or misperfusion; ultimately, 16.7% of patients discontinued treatment due to catheter dysfunction. HIA treatment with fotemustine did not translate into a significantly improved OS compared with IV treatment: the median OS was 14.6 versus 13.8 months for HIA compared with IV, respectively. However, HIA had better progression-free survival (PFS; 4.5 vs. 3.7 months) and response rate at 1 year (10.5% vs. 2.4%) compared with IV.

Conventional Transarterial Chemoembolization/Bland Embolization

In 2015, Gonsalves et al published a retrospective series on 50 patients with uveal melanoma liver metastases ($\geq$50% liver tumor burden) treated with 200 mg 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU) chemoembolization in patients without extrahepatic metastases.[30] Median PFS was 5.0 months and median OS was 7.1 months with stable disease and partial response in 66% and 4%, respectively (per RECIST).

Valsecchi et al reported a randomized phase II trial of immunoembolization (GM-CSF + bland embo) versus bland embolization (lipiodol + Gelfoam) in 52 patients with isolated liver metastases from uveal melanoma and less than 50% hepatic tumor burden.[31] Overall response rates were 21.2% and 16.7%, respectively, without grade 4/5 toxicity. With median follow-up of 19.1 months, the immunoembolization group demonstrated longer PFS (10.4 vs. 7.1 months) and longer OS (21.5 vs. 17.2 months).

Drug-Eluting Beads

Carling et al compared intra-arterial chemoembolization with 100 to 300 μm DEBs loaded with irinotecan (DEBIRI; $n = 14$) to IV infusion of dacarbazine ($n = 14$).[32] Pain and stasis are common after DEBIRI, and the intended irinotecan dose could not be delivered in half of the patients in this study. After treatment with DEBIRI, 64% (9/14) of patients experienced major complications, including liver dysfunction in 29% (4/14) and death in 7% (1/14). On imaging, 85% had RECIST v1.1 progression at 1.5-month follow-up. The median OS was 9.4 versus 4.6 months for DEBIRI versus IV dacarbazine, respectively ($p = 0.23$).

In a larger retrospective series, Valpione et al reviewed a 24-year period including 58 patients treated with DEBIRI chemoembolization with and without IV fotemustine as first-line therapy in comparison to historical controls treated with IV fotemustine alone.[33] Pain (typically epigastric) was a common problem, occurring in 72% of patients treated with DEBIRI and 84% of DEBIRI patients who received induction IV fotemustine within 3 weeks of chemoembolization. The partial response rate was 27.5%, and 72.4% had stable disease per RECIST v1.1.

Y90

Gonsalves et al applied yttrium-90 radioembolization with resin microspheres in 32 patients with ocular melanoma liver metastases who had progressed after treatment with immunoembolization or chemoembolization.[34] These patients were ECOG 0–2 and 78% had less than 25% tumor burden in the liver. Complete response, partial response, stable disease, and progressive disease were observed in 1 (3%), 1 (3%), 18 (56%), and 12 patients (38%), respectively, per RECIST criteria. The median OS was significantly longer at 10.5 months for patients with less than 25% tumor burden versus at 3.9 months for patients with greater tumor burden. The median OS was 10 months.

Memon et al also applied radioembolization with glass microspheres in 16 patients with liver metastases from treatment-refractory melanoma from various primaries (seven ocular, four cutaneous, three rectal, two unknown) progressing for systemic and locoregional therapy.[35] Imaging response was 31% per WHO and 25% per RECIST v1.1. The median hepatic PFS was 4.2 months for the overall cohort and the ocular primary subset. The median OS from first intra-arterial treatment was 7.6 months for the cohort and 5.9 months for the subset of patients with ocular primaries. These results compared well with those of Klingenstein et al, who found a 7-month median OS and RECIST v1.1 response of 62% after treating 13 patients with liver metastases from uveal melanoma using resin microspheres.[36] Response by FDG PET/CT was 23%, and there were five cases of discordance between PET imaging and RECIST response.

Pancreatic Adenocarcinoma

Adenocarcinoma of the pancreas frequently metastasizes to the liver, and this is generally considered a contraindication to resection. For first-line therapy, more aggressive combination therapy with addition of nab-paclitaxel to gemcitabine was superior to gemcitabine alone in the MPACT trial; overall response was 23% versus 7% and OS was 8.5 versus 6.7 months, respectively.[37] Moreover, the ACCORD 11 trial explored treatment without a gemcitabine backbone. It demonstrated that combination therapy in ECOG 0–1 patients with oxaliplatin, irinotecan, fluorouracil, leucovorin (FOLFIRINOX) was superior to gemcitabine with 32% versus 9% overall response and 11.1 versus 6.8 months OS.[38] There are limited data for second-line treatments at this time, with one prospective study demonstrating improved survival over supportive care with median OS ranging from 2 to 5 months.[39] Therefore, intra-arterial therapies for liver metastases showing 5+ months of median survival and

response rates of 20 to 30% would be expected to have benefit for patients when first-line treatments have failed. Moreover, MR imaging of liver metastases from pancreatic adenocarcinoma demonstrates lesions that are frequently hypervascular,[40] suggesting that imaging can be used to identify cases where intra-arterial therapy may have added value.

Hepatic Artery Infusion

Hepatic artery infusion chemotherapy has been used in the adjuvant setting to prevent hepatic recurrence after resection of pancreatic primaries.[41–43] Hashimoto et al described use of hepatic artery infusion chemotherapy in nine patients with liver metastases from pancreatic adenocarcinoma and in 42 patients without liver metastasis for prevention of hepatic metastases.[43] Overall, patients received a median of nine courses with a median duration of 89 days. Toxicities were hepatic arterial occlusion (2%), hepatic artery stenosis (19.6%), liver abscess or biloma (5.9%), catheter dislocation (5.9%), and wound infection (3.9%). With 1 g/m^2 5-FU infused continuously over 5 hours once weekly for 3 weeks in a 4-week cycle, two patients had complete response, two patients had partial response, and four patients had stable disease per RECIST v1.1 criteria. The median OS was 14.1 months for patients with liver metastases at the time of hepatic artery infusion chemotherapy.

Tajima et al described seven cases of hepatic artery infusion chemotherapy with gemcitabine with either 5-FU or S-1.[44] Catheter-related complications occurred in six patients. Three patients had partial response, three had stable disease, and one progressed as per RECIST v1.1. The median OS was 22.1 months.

Conventional Transarterial Chemoembolization/Bland Embolization

Kim et al applied lipiodol chemoembolization with cisplatin 2 mg/kg and gelatin sponge particle (Gelfoam) embolization in 15 patients with hepatic recurrence after pancreatic surgery for resection of pancreatic adenocarcinoma (Whipple, pancreaticoduodenectomy, pancreatectomy, distal pancreatectomy).[45] Liver tumors were treatment naive in 13 of 15 patients with two patients having received gemcitabine. Nine patients (60%) had early nausea and vomiting that resolved. Two patients had liver abscess (13%) attributed to bilioenteric anastomoses likely secondary to disruption or removal of the sphincter of Oddi. Response was evaluated by enhancement using mRECIST with a response rate of 40% (6/15). The median OS from TACE was 7.5 months.

Azizi et al treated 32 patients with liver metastases from pancreatic adenocarcinoma using triple drug lipiodol chemoembolization with mitomycin C (8 mg/m^2), cisplatin (40 mg/m^2), and gemcitabine (1 g/m^2) with degradable starch microsphere embolization.[46] Patients with concomitant chemotherapy or radiation therapy were excluded. The mean number of treatments was 3.2 (range: 2–4) per patient. Toxicity was not reported. Per RECIST v1.1, 9% (3/32) had partial response, 72% (23/32) had stable disease, and 19% (6/32) had progressive disease. The median OS from TACE was 16 months.

Drug-Eluting Beads

Kotoyan et al applied DEB chemoembolization to treat liver metastases in a mixed cohort of 10 patients with adenocarcinoma ($n = 6$) or neuroendocrine tumors ($n = 4$) of the pancreas.[47] All of the adenocarcinoma patients had previously received chemotherapy, and five had experienced neurologic or hematologic grade 3/4 toxicities on systemic chemotherapy. DEBIRI at 250 mg (range, 100–400 mg) was applied in the six adenocarcinoma patients with pain (two events), nausea (one event), and vomiting (one event) after the procedure. Response and OS were not reported separately.

Y90

Cao et al applied yttrium-90 radioembolization with resin microspheres in seven patients with ECOG 0 performance status.[48] Two patients died before imaging follow-up. Of the five remaining patients with imaging follow-up, two had partial response and one had stable disease per RECIST.

Gibbs et al completed a phase II prospective open-label trial in 14 patients with liver-dominant metastases from pancreatic adenocarcinoma treated with resin microsphere yttrium-90 radioembolization concomitant to 5-FU.[49] Eight patients (57%) had liver-only disease. Grade 3/4 toxicities within 60 days were hyperbilirubinemia (21%) and fatigue (14%). Three patients had a partial response, and ten had stable disease. Median OS was 5.5 months overall and 12.2 months for patients with liver-only disease.

Recently, Kim et al completed a retrospective series on yttrium-90 radioembolization with resin microspheres in ECOG 0–1 patients with pancreatic adenocarcinoma. Fifteen out of 16 patients also received systemic chemotherapy consisting of 5-FU ($n = 6$), gemcitabine ($n = 8$), or Abraxane ($n = 1$).[50] Liver burden was less than 25% in 81% (13/16). Among 13 patients with imaging follow-up, four had partial response (31%) and five had stable disease (38%) per RECIST v1.1. The median OS was 12.5 months after radioembolization.

Michl et al reviewed 17 patients with pancreatic adenocarcinoma liver metastases treated with yttrium-90 radioembolization with resin microspheres and evaluated response according to PET Response Criteria In Solid Tumors (PERCIST) after ^{18}F-FDG PET/CT.[51] Nine patients (53%) had liver-only disease. Toxicity was not reported in this series. Metabolic tumor response was as follows: 35% (6/17) complete response, 6% (1/17) partial response, and 59% (10/17) progressive disease according to PERCIST. The median OS was 8.8 months.

Sarcomas

Soft-tissue sarcomas often metastasize to the lung and less frequently involve the liver. Gastrointestinal stromal and retroperitoneal sarcomas are the most common soft-tissue sarcomas to involve the liver.[1] KIT-positive, gastrointestinal stromal tumors respond well to tyrosine kinase inhibitors such as imatinib, sunitinib, and regorafenib, but nilotinib has provided less benefit as a first-line agent.[52] Surgery and

ablation are mainstays of treatment, given that hepatic lesions often grow slowly and are initially confined to a single organ. When liver tumors are in a poor location, become too large, or are too numerous to be addressed with surgery or ablation, intra-arterial therapies may allow treatment of hepatic disease. However, there are few reports on this topic given the overall rarity of this presentation.

Maluccio et al applied hepatic artery embolization with bland particles in 24 patients with liver-dominant metastases from soft-tissue sarcomas.[53] Grade 3/4 toxicities were observed in two patients with liver abscess, in one patient with off-target embolization of the duodenum, and in one patient with bacteremia. The median OS was 21 months.

Takaki et al applied TAE in 11 patients after failing either imatinib ($n = 3$) or imatinib followed by sunitinib ($n = 8$).[54] The overall response rate was 27.3%. The median OS was 14.9 months for patients receiving second-line TAE and 23.8 months for those receiving third-line TAE after sunitinib.

Chapiro et al studied cisplatin, doxorubicin, and mitomycin cTACE in liver metastases from soft-tissue sarcoma in 30 patients (mean age: 55 years) with liver-dominant metastases.[55] Ninety percent of these patients had failed previous chemotherapy. No grade 3 or 4 toxicities were reported. After a mean of 2.6 chemoembolizations, one patient (4%) had a partial response and 20 (80%) had stable disease, and three (16%) had progressive disease. The median OS was 21.2 months, comparing well with the 20-month median OS observed by Rajan et al.[56]

Transue et al presented an abstract on their multi-institutional experience in 18 patients with liver metastases from soft-tissue sarcomas treated with yttrium-90 radioembolization.[57] Response rates were 38.9% and 55.6% at 3 and 6 months, respectively. The median OS was 26.2 months.

Conclusion

Intra-arterial therapy has an acceptable safety profile and provides high antitumor activity in the setting of chemotherapy refractory hepatic metastases from breast cancer, melanoma, pancreatic adenocarcinoma, and soft-tissue sarcomas. The majority of the available data are from heterogeneous cohorts studied retrospectively, with varying technique, patient selection, and response criteria. The available literature should guide prospective trial design and also highlight the need for oncology registries that allow institutions to share data and resources. These efforts are greatly needed, as many patients with metastatic disease in the liver are not candidates for surgery, and intra-arterial therapies are increasingly applied in these patients to stop progression of chemorefractory tumors.

Role of Funding
A.C.G. is a student of the Medical Scientist Training Program (T32GM008152).

References

1 Centeno BA. Pathology of liver metastases. Cancer Contr 2006; 13(1):13–26
2 Goodman ZD. Neoplasms of the liver. Mod Pathol 2007; 20(Suppl 1):S49–S60
3 Sato KT, Lewandowski RJ, Mulcahy MF, et al. Unresectable chemorefractory liver metastases: radioembolization with 90Y microspheres–safety, efficacy, and survival. Radiology 2008;247(2): 507–515
4 Lewandowski RJ, Geschwind JF, Liapi E, Salem R. Transcatheter intraarterial therapies: rationale and overview. Radiology 2011; 259(3):641–657
5 Hickey RM, Lewandowski RJ, Salem R. Rationale of transcatheter intra-arterial therapies of hepatic cancers. Hepatic Oncology 2014;1(3):285–291
6 Salem R, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: Technical and methodologic considerations. J Vasc Interv Radiol 2006;17(8): 1251–1278
7 Lewandowski RJ, Sato KT, Atassi B, et al. Radioembolization with 90Y microspheres: angiographic and technical considerations. Cardiovasc Intervent Radiol 2007;30(4):571–592
8 Zinser JW, Hortobagyi GN, Buzdar AU, Smith TL, Fraschini G. Clinical course of breast cancer patients with liver metastases. J Clin Oncol 1987;5(5):773–782
9 Atalay G, Biganzoli L, Renard F, et al; EORTC Breast Cancer and Early Clinical Studies Groups. Clinical outcome of breast cancer patients with liver metastases alone in the anthracycline-taxane era: a retrospective analysis of two prospective, randomised metastatic breast cancer trials. Eur J Cancer 2003;39(17): 2439–2449
10 Cummings MC, Simpson PT, Reid LE, et al. Metastatic progression of breast cancer: insights from 50 years of autopsies. J Pathol 2014;232(1):23–31
11 Pagani O, Senkus E, Wood W, et al; ESO-MBC Task Force. International guidelines for management of metastatic breast cancer: can metastatic breast cancer be cured? J Natl Cancer Inst 2010;102(7): 456–463
12 Hickey R, Mulcahy MF, Lewandowski RJ, et al. Chemoradiation of hepatic malignancies: prospective, phase 1 study of full-dose capecitabine with escalating doses of yttrium-90 radioembolization. Int J Radiat Oncol Biol Phys 2014;88(5):1025–1031
13 Gordon AC, Salem R, Lewandowski RJ. Yttrium-90 radioembolization for breast cancer liver metastases. J Vasc Interv Radiol 2016;27(9):1316–1319
14 Ang C, Jhaveri K, Patel D, Gewirtz A, Seidman A, Kemeny N. Hepatic arterial infusion and systemic chemotherapy for breast cancer liver metastases. Breast J 2013;19(1):96–99
15 Arai Y, Sone Y, Inaba Y, Ariyoshi Y, Kido C. Hepatic arterial infusion chemotherapy for liver metastases from breast cancer. Cancer Chemother Pharmacol 1994;33(1, Suppl):S142–S144
16 Cho SW, Kitisin K, Buck D, et al. Transcatheter arterial chemoembolization is a feasible palliative locoregional therapy for breast cancer liver metastases. Int J Surg Oncol 2010; 2010:251621
17 Vogl TJ, Naguib NN, Nour-Eldin NE, et al. Repeated chemoembolization followed by laser-induced thermotherapy for liver metastasis of breast cancer. AJR Am J Roentgenol 2011;196(1): W66-72
18 Eichler K, Jakobi S, Gruber-Rouh T, Hammerstingl R, Vogl TJ, Zangos S. Transarterial chemoembolisation (TACE) with gemcitabine: phase II study in patients with liver metastases of breast cancer. Eur J Radiol 2013;82(12):e816–e822
19 Martin RCG, Joshi J, Robbins K, et al. Hepatic intra-arterial injection of drug-eluting bead, irinotecan (DEBIRI) in unresectable colorectal liver metastases refractory to systemic chemotherapy:

results of multi-institutional study. Ann Surg Oncol 2011;18(1): 192–198
20 Haug AR, Tiega Donfack BP, Trumm C, et al. 18F-FDG PET/CT predicts survival after radioembolization of hepatic metastases from breast cancer. J Nucl Med 2012;53(3):371–377
21 Cianni R, Pelle G, Notarianni E, et al. Radioembolisation with (90) Y-labelled resin microspheres in the treatment of liver metastasis from breast cancer. Eur Radiol 2013;23(1):182–189
22 Saxena A, Kapoor J, Meteling B, Morris DL, Bester L. Yttrium-90 radioembolization for unresectable, chemoresistant breast cancer liver metastases: a large single-center experience of 40 patients. Ann Surg Oncol 2014;21(4):1296–1303
23 Gordon AC, Gradishar WJ, Kaklamani VG, et al. Yttrium-90 radioembolization stops progression of targeted breast cancer liver metastases after failed chemotherapy. J Vasc Interv Radiol 2014; 25(10):1523–1532, 1532.e1–1532.e2
24 Fendler WP, Lechner H, Todica A, et al. Safety, efficacy, and prognostic factors after radioembolization of hepatic metastases from breast cancer: a large single-center experience in 81 patients. J Nucl Med 2016;57(4):517–523
25 Pieper CC, Meyer C, Wilhelm KE, et al. Yttrium-90 radioembolization of advanced, unresectable breast cancer liver metastases-a single-center experience. J Vasc Interv Radiol 2016;27(9): 1305–1315
26 Kujala E, Mäkitie T, Kivelä T. Very long-term prognosis of patients with malignant uveal melanoma. Invest Ophthalmol Vis Sci 2003; 44(11):4651–4659
27 Buder K, Gesierich A, Gelbrich G, Goebeler M. Systemic treatment of metastatic uveal melanoma: review of literature and future perspectives. Cancer Med 2013;2(5):674–686
28 Agarwala SS, Eggermont AM, O'Day S, Zager JS. Metastatic melanoma to the liver: a contemporary and comprehensive review of surgical, systemic, and regional therapeutic options. Cancer 2014; 120(6):781–789
29 Leyvraz S, Piperno-Neumann S, Suciu S, et al. Hepatic intra-arterial versus intravenous fotemustine in patients with liver metastases from uveal melanoma (EORTC 18021): a multicentric randomized trial. Ann Oncol 2014;25(3):742–746
30 Gonsalves CF, Eschelman DJ, Thornburg B, Frangos A, Sato T. Uveal melanoma metastatic to the liver: chemoembolization with 1,3-Bis-(2-Chloroethyl)-1-nitrosourea. AJR Am J Roentgenol 2015; 205(2):429–433
31 Valsecchi ME, Terai M, Eschelman DJ, et al. Double-blinded, randomized phase II study using embolization with or without granulocyte-macrophage colony-stimulating factor in uveal melanoma with hepatic metastases. J Vasc Interv Radiol 2015;26(4): 523–32.e2
32 Carling U, Dorenberg EJ, Haugvik SP, et al. Transarterial chemoembolization of liver metastases from uveal melanoma using irinotecan-loaded beads: treatment response and complications. Cardiovasc Intervent Radiol 2015;38(6):1532–1541
33 Valpione S, Aliberti C, Parrozzani R, et al. A retrospective analysis of 141 patients with liver metastases from uveal melanoma: a two-cohort study comparing transarterial chemoembolization with CPT-11 charged microbeads and historical treatments. Melanoma Res 2015;25(2):164–168
34 Gonsalves CF, Eschelman DJ, Sullivan KL, Anne PR, Doyle L, Sato T. Radioembolization as salvage therapy for hepatic metastasis of uveal melanoma: a single-institution experience. AJR Am J Roentgenol 2011;196(2):468–473
35 Memon K, Kuzel TM, Vouche M, Atassi R, Lewandowski RJ, Salem R. Hepatic yttrium-90 radioembolization for metastatic melanoma: a single-center experience. Melanoma Res 2014;24(3): 244–251
36 Klingenstein A, Haug AR, Zech CJ, Schaller UC. Radioembolization as locoregional therapy of hepatic metastases in uveal melanoma patients. Cardiovasc Intervent Radiol 2013;36(1):158–165
37 Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369(18):1691–1703
38 Conroy T, Desseigne F, Ychou M, et al; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19): 1817–1825
39 Pelzer U, Schwaner I, Stieler J, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. Eur J Cancer 2011; 47(11):1676–1681
40 Danet IM, Semelka RC, Nagase LL, Woosely JT, Leonardou P, Armao D. Liver metastases from pancreatic adenocarcinoma: MR imaging characteristics. J Magn Reson Imaging 2003;18(2): 181–188
41 Sho M, Tanaka T, Yamada T, et al. Novel postoperative adjuvant strategy prevents early hepatic recurrence after resection of pancreatic cancer. J Hepatobiliary Pancreat Sci 2011;18(2):235–239, discussion 239–240
42 Hashimoto A, Tanaka T, Sho M, et al. Adjuvant hepatic arterial infusion chemotherapy after resection for pancreatic cancer using coaxial catheter-port system compared with conventional system. Cardiovasc Intervent Radiol 2016;39(6):831–839
43 Hashimoto A, Nishiofuku H, Tanaka T, et al. Safety and optimal management of hepatic arterial infusion chemotherapy after pancreatectomy for pancreatobiliary cancer. AJR Am J Roentgenol 2012;198(4):923–930
44 Tajima H, Kitagawa H, Tsukada T, et al. Hepatic arterial infusion chemotherapy with gemcitabine and 5-fluorouracil or oral S-1 improves the prognosis of patients with postoperative liver metastases from pancreatic cancer. Mol Clin Oncol 2013;1(5): 869–874
45 Kim JH, Choi EK, Yoon HK, Ko GY, Sung KB, Gwon DI. Transcatheter arterial chemoembolization for hepatic recurrence after curative resection of pancreatic adenocarcinoma. Gut Liver 2010;4(3): 384–388
46 Azizi A, Naguib NN, Mbalisike E, Farshid P, Emami AH, Vogl TJ. Liver metastases of pancreatic cancer: role of repetitive transarterial chemoembolization (TACE) on tumor response and survival. Pancreas 2011;40(8):1271–1275
47 Kotoyan R, Metzger T, Tatum C, Robbins K, Martin RCG II. Hepatic arterial therapy with drug-eluting beads in the management of metastatic pancreatic carcinoma to the liver: a multi-institutional registry. J Oncol 2012;2012:168303
48 Cao C, Yan TD, Morris DL, Bester L. Radioembolization with yttrium-90 microspheres for pancreatic cancer liver metastases: results from a pilot study. Tumori 2010;96(6):955–958
49 Gibbs P, Do C, Lipton L, et al. Phase II trial of selective internal radiation therapy and systemic chemotherapy for liver-predominant metastases from pancreatic adenocarcinoma. BMC Cancer 2015;15:802
50 Kim AY, Unger K, Wang H, Pishvaian MJ. Incorporating Yttrium-90 trans-arterial radioembolization (TARE) in the treatment of metastatic pancreatic adenocarcinoma: a single center experience. BMC Cancer 2016;16:492
51 Michl M, Lehner S, Paprottka PM, et al. Use of PERCIST for prediction of progression-free and overall survival after radioembolization for liver metastases from pancreatic cancer. J Nucl Med 2016;57(3):355–360
52 Blay JY, Shen L, Kang YK, et al. Nilotinib versus imatinib as first-line therapy for patients with unresectable or metastatic gastrointestinal stromal tumours (ENESTg1): a randomised phase 3 trial. Lancet Oncol 2015;16(5):550–560
53 Maluccio MA, Covey AM, Schubert J, et al. Treatment of metastatic sarcoma to the liver with bland embolization. Cancer 2006; 107(7):1617–1623

54 Takaki H, Litchman T, Covey A, et al. Hepatic artery embolization for liver metastasis of gastrointestinal stromal tumor following imatinib and sunitinib therapy. J Gastrointest Cancer 2014;45(4): 494–499

55 Chapiro J, Duran R, Lin M, et al. Transarterial chemoembolization in soft-tissue sarcoma metastases to the liver - the use of imaging biomarkers as predictors of patient survival. Eur J Radiol 2015; 84(3):424–430

56 Rajan DK, Soulen MC, Clark TW, et al. Sarcomas metastatic to the liver: response and survival after cisplatin, doxorubicin, mitomycin-C, Ethiodol, and polyvinyl alcohol chemoembolization. J Vasc Interv Radiol 2001;12(2):187–193

57 Transue DL, Hackworth J, Johnson MS, Habib A. Multi-institutional experience treating metastatic soft tissue sarcomas using yttrium-90 microspheres. J Vasc Interv Radiol 2015;26(2): S133