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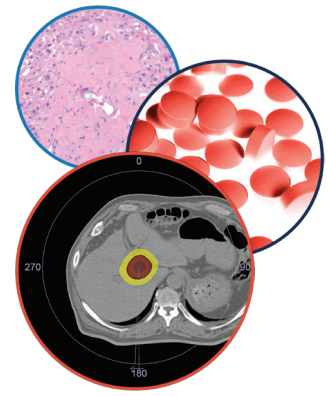

Hepatic Oncology

Rationale of transcatheter intra-arterial therapies of hepatic cancers

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Practice points

- Transcatheter locoregional therapies for the treatment of primary and metastatic disease to the liver include bland embolization, chemoembolization with and without drug-eluting beads, and radioembolization.
- Each of the transarterial therapies have shown favorable results in the treatment of a variety of malignancies, including hepatocellular carcinoma, metastatic neuroendocrine tumors, colorectal carcinoma, as well as select additional malignancies.
- Transarterial locoregional therapies are a part of the overall cancer treatment paradigm for patients with primary and metastatic malignancies of the liver. Treatment should be coordinated with other oncologic specialists, including medical, surgical and radiation oncologists.

SUMMARY: Transcatheter, intra-arterial therapies for primary and metastatic hepatic malignancies comprise angiographically guided procedures that provide for the administration of tumoricidal agents directly to liver tumors. These locoregional therapies have demonstrated encouraging clinical outcomes for liver tumors that are otherwise not amenable or not responsive to standard surgical or systemic treatments. This article provides a review of transcatheter therapies for hepatic cancers and reported clinical outcomes.

Locoregional, selective transarterial treatment options for primary and metastatic disease to the liver include bland embolization, chemoembolization with or without drug-eluting beads, and radioembolization. These therapies rely on the selective administration of antitumoral agents directly to hepatic tumors via the tumor's nutrient artery, inducing local tumoricidal effects with relative sparing of the uninvolved hepatic parenchyma.

Bland embolization causes a distal arterial blockade that results in tumor ischemia. Chemoembolization, with or without drug-eluting beads, combines the ischemic effects of embolization with targeted delivery of high-dose chemotherapeutics. With radioembolization, microscopic radioactive particles are preferentially deposited within tumor tissue, resulting in high-dose internal radiation of the tumor. Because hepatic tumors derive the majority of their blood supply from hepatic arteries, as opposed to uninvolved liver parenchyma predominantly supplied by the portal vein, transarterial administration of these agents favors deposition within the hepatic tumors rather than uninvolved liver parenchyma [1,2].

Bland embolization

Bland embolization refers to the transarterial administration of an embolic agent, without an additional pharmacologic or radioactive agent, with the intent of causing tumor ischemia by occluding the distal nutrient arterioles. Several embolic agents have been described, including gelfoam, polyvinyl alcohol and various acrylic copolymer particles. Particles should be larger than 40 µm,

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as smaller particles have been shown to cross hepatic sinusoids and intratumoral arteriovenous shunts into the systemic circulation [3,4].

A retrospective review of bland embolization for the treatment of hepatocellular carcinoma (HCC) in 46 patients reported actuarial survival rates of 50% at 1 year and 33% at 2 years. While the procedure was generally well tolerated, 81% of patients experienced postembolization syndrome [5].

In a subsequent prospective, randomized controlled trial of 80 patients comparing bland embolization to symptomatic treatment, tumor growth was slowed in patients receiving embolization, although there was no overall survival difference between the two groups [6].

In one of the largest series of bland embolization in 322 patients with unresectable HCC, the 1-, 2- and 3-year survival rates were 66, 46 and 33%, respectively, with a median overall survival from first treatment of 21 months [7].

Bland embolization of neuroendocrine metastases to the liver offers substantial symptomatic and morphologic responses. Symptomatic response has been reported in 64–93% of patients treated. Objective response rates range from 37 to 74%, with an additional 19% demonstrating stable disease. These response rates, as well the duration of response and survival rates, have been shown to be comparable with response rates achieved with chemoembolization [8,9].

Chemoembolization

Chemoembolization, namely the infusion of a chemotherapeutic agent followed by an embolic agent, has been described using a wide variety of both chemotherapeutic and embolic agents. According to the Society of Interventional Radiology guidelines, chemoembolization is currently defined as the infusion of a mixture of chemotherapeutic agents with or without iodized oil, followed by embolization with particles [10]. Embolization of the tumor following administration of the chemotherapeutic not only induces tumor ischemia but also prevents washout of the chemotherapeutic agent by arterial inflow. The iodized oil, such as lipiodol, is both a contrast agent as well as an emulsifier for chemotherapeutic agents. The iodized oil has been shown to remain within liver tumors longer than uninvolved liver parenchyma when administered via the hepatic artery [11,12], resulting in increased tumor retention of the chemotherapeutic agent [13–15].

In 2002, two landmark studies were published providing level I evidence for the use of conventional chemoembolization in the treatment of HCC. Llovet *et al.* prospectively randomized patients with unresectable HCC to bland embolization, chemoembolization with doxorubicin or conservative management. The study was terminated early after interim analysis demonstrated a statistically significant survival benefit for the patients receiving chemoembolization compared with conservative therapy [16]. Lo *et al.* prospectively randomized patients with unresectable HCC to chemoembolization with cisplatin or symptomatic treatment. Patients receiving chemoembolization had statistically significant improved overall survival at 1-, 2- and 3-years compared with patients in the conservative therapy arm [17]. Based on these trials, chemoembolization is the recommended first-line therapy in intermediate-stage disease (Barcelona Clinic Liver Cancer [BCLC] stage B) and considered standard of care [18].

Chemoembolization has been shown to be an effective treatment option for hepatic neuroendocrine metastases not only related to morphologic tumor responses but also due to long-term palliation and effective reduction in the biochemical symptoms caused by neuroendocrine tumors, particularly carcinoid syndrome [19–21]. Liapi *et al.* reported mean survival of 78 months despite objective imaging responses seen in less than 30% of patients [20], whereas another study of 123 patients reported partial response in greater than 60% of patients with 3-, 5- and 10-year survival rates of 59, 36 and 20%, respectively [22].

Outcomes following chemoembolization for the treatment of unresectable colorectal metastases to the liver have been varied. Despite evidence of favorable objective response rates with chemoembolization [23], an early study indicated that the addition of chemoembolization using doxorubicin, cisplatin and mitomycin-C to a systemic chemotherapy regimen of 5-fluorouracil (5-FU) failed to provide response rates greater than those seen with systemic therapy alone, limiting the adoption of chemoembolization in standard treatment regimens [24]. More recent studies have indicated that chemoembolization using a variety of chemotherapeutic agents can offer survival benefits for patients with colorectal metastases refractory to systemic chemotherapy, with 1- and 2-year survival rates ranging from 43 to 62% and 10 to 28%, respectively, time to liver

tumor progression of 5 months, and median survival rates ranging from nearly 8 to 14 months [25–27]. Better survival rates were seen in patients who received chemoembolization after first- or second-line chemotherapy compared with patients receiving chemoembolization after three or more lines of chemotherapy [27].

Chemoembolization for hepatic metastases of breast cancer has demonstrated limited survival benefits, often because of extrahepatic disease progression. While chemoembolization has been shown to provide symptomatic relief for a substantial portion of treated patients [28], progression-free survival and overall survival are often not substantially altered [28,29].

Approximately 90% of systemic metastases from ocular melanoma involve the liver [30], as opposed to less than 20% of cutaneous melanoma metastases [31]. While there is a lack of effective systemic therapies for hepatic metastases of ocular melanoma, chemoembolization has demonstrated objective responses. Overall response rates range from 0 to 46% with median survival times ranging from 5 to 11 months [32–39]. Chemoembolization has provided disease stabilization in 47% of patients with median overall survival of 7.7 months for hepatic metastases of cutaneous melanoma[40].

Chemoembolization with drug-eluting beads

Chemoembolization with drug-eluting beads expands on the principles of chemoembolization by loading polyvinyl-alcohol-based microspheres with the chemotherapeutic agent in order to release the chemotherapeutic agent in a sustained manner. Compared with standard chemoembolization, chemoembolization with drug-eluting beads has shown a significant reduction in the peak plasma concentration of the agent, indicating that more of the chemotherapeutic remains localized to the tumor rather than redistributing to the systemic circulation [41].

A randomized trial comparing conventional chemoembolization to chemoembolization with doxorubicin-loaded, drug-eluting beads for unresectable HCC demonstrated a trend toward but not statistically significant improvement in tumor response rates. There was no survival difference between the two groups. The patients receiving chemoembolization with drug-eluting beads did have a reduction in serious liver toxicity and lower rate of doxorubicin-related side effects [42].

Outcomes following chemoembolization of colorectal metastases using drug-eluting beads loaded with irinotecan have been more favorable. A randomized trial comparing chemoembolization with drug-eluting beads loaded with irinotecan to systemic 5-FU and irinotecan demonstrated a statistically significant improvement in survival for the patients receiving chemoembolization with drug-eluting beads (22 vs 15 months), as well as a significantly prolonged duration of improvement in quality of life [43].

Chemoembolization with drug-eluting beads has been reported as an acceptable alternative to conventional chemoembolization in the treatment of metastatic neuroendocrine tumors. In one study, 57% of treatment cycles produced an objective response at intermediate-term follow up with median time to tumor progression of 419 days [44]. In another study, chemoembolization with doxorubicin-eluting beads provided a partial response in 80% and stable disease in 15% of patients at 3-month follow up. Median time to tumor progression was 15 months [45]. A third study reported similar response rates although with a substantial incidence of biliary injury [46].

Chemoembolization with drug-eluting beads has been reported to provide favorable outcomes for patients with liver-dominant metastatic breast cancer. Hepatic progression-free survival was reported as 26 months with median overall survival of 47 months [47].

Response rates for hepatic metastases of melanoma following chemoembolization with drug-eluting beads loaded with doxorubicin have been favorable with median survival of approximately 12 months [48]. Early results from a study of the use of drug-eluting beads loaded with irinotecan for the treatment of uveal melanoma indicated an objective response in all patients [49].

However, reports of biliary complications, specifically biliary necrosis and bilomas, following chemoembolization with drug-eluting beads are becoming more prevalent with the increasing use of drug-eluting beads. While there have been reports of biliary necrosis and biloma formation following conventional chemoembolization, the rates are consistently less than 10% and appear to be more common in patients with metastatic disease to the liver compared with patients with HCC and cirrhosis [50,51]. Bhagat *et al.* reported biloma formation in 54% of patients with neuroendocrine tumors

treated with drug-eluting beads [46]. Guiu *et al.* compared rates of biliary injuries in patients receiving chemoembolization with drug-eluting beads to conventional chemoembolization and found that the occurrence of liver or biliary injuries was significantly associated with drug-eluting beads (odds ratio: 6.63), regardless of the tumor type treated, occurring in 30% of treated patients [52]. Suggested causes of the biliary complications include over-embolization of the drug-eluting beads and increased local toxicity due to prolonged exposure of the biliary tissue to the slowly eluted, highly concentrated chemotherapy [46,52].

Radioembolization

Radioembolization refers to the selective injection of micrometer-sized particles loaded with the radioisotope ^{90}yttrium (Y^{90}). Because radioembolization provides an internal source of radiation, it is considered brachytherapy. Normal liver parenchyma has a low tolerance to external beam radiation, with rates of severe radiation-induced liver disease as high as 50% for doses greater than 35–40 Gy, whereas the preferential delivery of radioactive particles to tumor tissues as a result of radioembolization allows for the safe delivery of doses in excess of 150 Gy [53–56].

While there is no randomized study comparing radioembolization to chemoembolization for the treatment of HCC, a comparative effectiveness report of outcomes following radioembolization and chemoembolization in a 245-patient cohort indicated that adverse events, clinical toxicities, response rate and time to tumor progression were improved with radioembolization compared with conventional chemoembolization. There was no difference in overall survival between the two groups, possibly related to the competing risks of death of HCC and cirrhosis. *Post-hoc* analyses concluded that a sample size larger than 1000 patients would be required to provide the power necessary to establish survival equivalence between conventional chemoembolization and radioembolization [57].

For patients with intermediate and advanced HCC, time to tumor progression and median overall survival rates after radioembolization are approximately 10 to 11 months and 15 to 16 months, respectively [58,59]. Long-term survival outcomes stratified by BCLC stage have indicated survival rates following radioembolization of 24.4, 16.9 and 10.0 months for BCLC A, B and C stages, respectively [60]. Stratified by Child-Pugh class, survival rates of 17.2, 7.7 and 5.6 months have been reported for Childs-Pugh class A, B and Childs-Pugh class B patients with portal vein thrombosis, respectively [61].

Radioembolization has been shown to be more effective than conventional chemoembolization in downstaging patients with HCC to transplantation, surgical resection or ablation. In one study, 66% patients were successfully downstaged to transplantation, surgical resection or ablation following radioembolization [62]. In another study, 58% of patients treated with radioembolization were downstaged from UNOS T3 disease (outside of transplant criteria) to T2 disease compared with 31% of patients treated with conventional chemoembolization [63].

Radioembolization causes significant volumetric changes of the liver, with volumetric reduction of the treated lobe and simultaneous volumetric increases in the untreated lobe. This atrophy–hypertrophy complex, referred to as radiation lobectomy, has been shown to induce volumetric changes comparable with those seen in the future liver remnant following portal vein embolization, while also offering local tumor control and limiting hepatic progression. This ability to hypertrophy the future liver remnant while simultaneously treating the hepatic tumor has important implications for the use of radioembolization as a bridge-to-resection therapy [64].

Radioembolization has shown favorable results in the treatment of hepatic metastases of colorectal cancer. The addition of radioembolization to chemotherapy has demonstrated significant increases in the time to tumor progression compared with chemotherapy alone (15.9 vs 9.7 months; $p = 0.001$ [65]; 18.6 vs 3.6 months; $p < 0.0005$ [66]) with a trend toward prolonged 2-year survival in one of the studies (39 vs 29%; $p = 0.06$ [65]) and a significantly longer median survival in a second study (29.4 vs 12.8 months; $p = 0.02$ [66]). In an additional randomized control trial, the addition of Y^{90} radioembolization to 5-FU compared with a control arm of 5-FU alone resulted in a statistically significant improvement in time to tumor progression compared with the control group (4.5 vs 2.1 months; $p = 0.03$). While the increase in overall survival (10 vs 7.3 months; $p = 0.8$) did not reach statistical significance, survival data is confounded by 40% of the patients in the control arm crossing over to receive radioembolization following disease progression [67].

Radioembolization for metastatic neuroendocrine tumors has resulted in favorable imaging and clinical responses. In a multicenter study of hepatic neuroendocrine tumors treated with either glass and resin ^{90}Y microspheres, partial response or stable disease was reported in 92 and 94% of patients, respectively, with median survival times of 22 and 28 months for glass and resin microspheres, respectively [68]. In a more recent study, patients with hepatic neuroendocrine metastases that were refractory to systemic therapy treated with Y^{90} radioembolization had a response rate of 62.7% with 1-, 2- and 3-year overall survival rates of 72.5, 62.5 and 45%, respectively [69].

Radioembolization may be an option for patients with hepatic metastases of breast cancer who have progressed on multiple chemotherapies. A study of 27 women with chemorefractory liver metastases of breast cancer treated with radioembolization reported an objective response rate of 39% with stable disease achieved in 52% of patients at 90 days. Median overall survival was 6.8 months for patients with Eastern Cooperative Oncology Group performance status of 0 compared with 2.6 months for Eastern Cooperative Oncology Group performance status 1, 2 or 3 [70]. In a more recent study of 40 women with chemorefractory liver metastases of breast cancer treated with radioembolization, 31% had objective response (complete or partial response), while 39% of patients demonstrated stable disease. Median overall survival was 13.6 months [71].

Patients with hepatic metastases of ocular melanoma who had failed chemoembolization or immunoembolization demonstrated encouraging overall survival and hepatic progression-free survival of 10 and 4.7 months, respectively, following radioembolization [72].

Conclusion & future perspective

Selective transarterial therapies for unresectable primary and metastatic hepatic malignancies are locoregional therapies that target malignant tumors directly. These therapies are well tolerated and have demonstrated encouraging clinical outcomes. Further prospective studies providing level I data are required; however, in order to more clearly define the optimal role and timing of each of these therapies in the treatment of primary and metastatic diseases of the liver.

Financial & competing interests disclosure

RJ Lewandowski and R Salem serve on the advisory boards for Boston Scientific and BTG. RJ Lewandowski is a consultant for Cook Medical. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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