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Regional therapies for the treatment of primary and metastatic hepatic tumors: A disease-based review of techniques and critical appraisal of current evidence

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ABSTRACT

The practice of hepatic surgery has become increasingly complex as additional therapeutic options emerge to treat both primary and metastatic tumors of the liver. Liver-directed therapy options include selective internal radiation therapy (SIRT), stereotactic body radiation therapy, chemoembolization, bland embolization, hepatic artery infusion chemotherapy (HAIC), and ablative techniques such as microwave or radiofrequency ablation. Hepatocellular carcinoma has been treated with many of these therapies for palliation of symptoms, definitive treatment, and as a bridge to transplantation. Intrahepatic cholangiocarcinoma, particularly patients with unresectable disease, have demonstrated clinical responses to both SIRT as well as HAIC. Colorectal liver metastases have been treated with all of these techniques with varying degrees of success depending on the clinical scenario. A detailed understanding of these technologies and the evidence supporting their use is essential for the modern hepatic surgeon to properly sequence therapies and provide salvage options when first-line treatment has failed. This review describes these techniques and their appropriate usage based on the disease of interest and the respective evidence currently available.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) comprises the majority of primary hepatic tumors, constituting 90% of primary cancers of the liver. It has a worldwide incidence of 850,000 cases per year. Surgical treatment remains the standard of care when applicable, either via resection or orthotopic liver transplant (OLT).[1] Among well-matched patients, OLT appears to offer better disease-free survival, but with similar overall survival rates.[2–4] For patients diagnosed with HCC who are deemed unresectable or are outside of OLT criteria, ablation techniques have been used as a bridge to resection or transplant.[5]

Thermal ablation

Radiofrequency ablation (RFA) utilizes electromagnetic energy at electrodes to disseminate heat around tumors resulting in their destruction. Microwave ablation (MWA) utilizes dielectric hysteresis to create energy transmitted to the target tissue through an interstitial antenna resulting in tissue destruction around the antenna which can be manipulated in shape and volume by the type of probe and settings used. While MWA has theoretical advantages including less susceptibility to heat-sink, shorter time to target temperatures, and larger ablation zones, comparative studies are limited in scope and quality with apparent equivalent efficacy.[6] RFA has been shown to be a safe and effective treatment for small HCC.[7] Three prospective randomized controlled trials have compared radiofrequency ablation with surgical resection for small HCC. Two of these trials demonstrated equivalent survival, though one showed higher local recurrence with ablation, while the largest of the three showed improved overall and disease-free survival with resection.[8–10] Though resection remains the standard of care over ablation in patients fit for surgery, many patients with HCC suffer

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from other co-morbidities and the percutaneous or laparoscopic approach offered by ablation is a safe and effective alternative.

Transarterial chemoembolization

Transvascular therapy allows for targeted chemotherapeutic delivery combined with disruption of arterial supply to tumors. A number of strategies have been employed including transarterial (bland) embolization (TAE), transarterial chemoembolization with macroparticles (TACE), and TACE with drug-eluting beads which are microparticles (DEB-TACE). RFA appears to be favorable when compared with TACE in the setting of small volume tumors, however, TACE can be used to treat lesions in close proximity to blood vessels.[11] DEB-TACE may provide improved response rates when compared with conventional TACE in patients with unresectable HCC as evidenced by the PRECISION V study, though this did not translate into a survival advantage.[12] Several smaller studies suggest similar results. In high-risk patients, TAE offers a reasonable alternative to TACE or DEB-TACE and is superior to best supportive care.[13] A recently published randomized controlled trial comparing RFA and TACE combination therapy to resection for HCC within the Milan criteria showed improved survival and decreased recurrence in the resection group, albeit with higher morbidity rates with surgical resection.[14] TACE can be used in tumors with limited portal vein involvement but is contraindicated in patients with Child's class C cirrhosis.[1]

Selective internal radiation therapy

Selective internal radiation therapy (SIRT), also referred to as transarterial radioembolization, delivers high-dose beta radiation to tumor capillary beds via glass or resin microparticles loaded with yttrium-90. The growth of SIRT has been evident by an increasing number of reports within the literature, though high-quality data are limited. A meta-analysis of retrospective studies comparing TACE and SIRT demonstrated comparable survival with less pain following SIRT.[15] The PREMIRE trial, a small phase II study, was conducted demonstrating improved time to progression for patients treated with SIRT versus TACE, though the results are muddied by the small sample size and nearly half the patients had these therapies utilized as a bridge to transplantation.[16] Two recent phase III trials comparing systemic therapy with sorafenib to SIRT demonstrated equivalent survival but fewer adverse events with SIRT suggesting this is perhaps a reasonable alternative to systemic therapy in select patients.[17,18] Caution is advised for patients with total bilirubin greater than 2 mg/dL as these patients are at increased risk of radiation-induced liver disease.[1]

Radiation therapy

Advances in radiation delivery including intensity-modulated radiation therapy, stereotactic body radiation therapy (SBRT), and proton beam therapy have led to interest in this non-invasive modality for treating HCC. Limited data suggest adequate disease control in patients pre-treated with TACE.[19] While a single-center retrospective study demonstrated comparable treatment outcomes for SBRT when compared with RFA in the first-line setting for unresectable HCC, a recent analysis of data from the National Cancer Database found RFA to be associated with superior overall survival.[20,21] High-quality randomized controlled trials are needed to define the ideal utilization for radiation therapy in HCC.

Intrahepatic Cholangiocarcinoma

Intrahepatic Cholangiocarcinoma (ICC) is the second most prevalent primary liver tumor. It arises from the epithelium of the intrahepatic biliary tree, and accounts for between 10 and 20% of primary biliary tumors.[22] ICC is often unresectable at diagnosis, but operative management remains the gold standard for management when the disease is amenable as it offers the only potentially for cure. Even with resection, however, ICC displays frequent local recurrence.[23] ICC tumors are supplied by the hepatic artery, and while classically less vascular than HCC, transvascular techniques allow for utilization of the dual blood supply to the liver and are not limited by the anatomic restrictions that affect resection. The rarity of the disease and heterogeneity of presentation has resulted in relatively minimal high-quality evidence to guide management.

Thermal ablation

Data surrounding local ablative therapies for ICC are sparse, consisting mostly of database reviews or single institution series. An analysis of NCDB data showed a survival benefit for Stage I disease with RFA when compared to no local therapy.[24] In a series composed of 107 patients with a total of 171 ICC tumors ≤ 5 cm diameter who underwent percutaneous MWA between 2009 and 2016, median progression-free survival was 8.9 months.[25] This compares favorably with historic retrospective series of other modalities. Local ablative techniques for ICC appear to be safe, and can be effective for small tumors, but high-level evidence to guide their use is still lacking.

Transarterial chemoembolization

Both conventional TACE and DEB-TACE have been utilized for ICC with chemotherapeutic agents including gemcitabine, cisplatin, doxorubicin, mitomycin-C and irinotecan.[1] Multiple retrospective, primarily single-institution, studies support that TACE is safe and can be utilized in the adjuvant setting for resection or in combination with other ablative techniques.[26] TACE and DEB-TACE appear to be associated with similar survival in limited experience.[27]

Selective internal radiotherapy

SIRT has demonstrated promising results in small series of patients with ICC. As with other liver-directed therapies, its role is in unresectable ICC, either to convert to resection or as definitive treatment. Reports of down-staging unresectable patients to surgery have described encouraging outcomes.[28,29] A meta-analysis of retrospective studies demonstrated patients receiving SIRT to have a median survival of 12–14 months which was comparable to TACE and DEB-TACE in the unresectable setting.[30]

Hepatic artery infusion chemotherapy

Hepatic artery infusion chemotherapy (HAIC) allows for continuous infusion of chemotherapy directly to the liver via the hepatic artery. This is typically performed by implanting a pump device in the subcutaneous tissues of the abdominal wall with the catheter placed within the gastroduodenal artery though other techniques are described. All collateral vessels must be ligated to ensure no extrahepatic perfusion of the drug. The most commonly used drug has been floxuridine (FUDR) due to its favorable pharmacologic profile with >95% hepatic first-pass metabolism. This allows for up to a 400-fold increase in tumor exposure to drug when compared to systemic chemotherapy, with relative absence of systemic symptoms.[31] Hepatotoxicity can occur and typically manifests as elevations in liver function testing due to biliary sclerosis. The incidence of hepatotoxicity is increased in patients

receiving concurrent bevacizumab.[32]

A meta-analysis including 657 patients who did not receive systemic chemotherapy compared the effectiveness and toxicity of arterial-based therapies and showed prolonged survival in patients treated with HAIC when compared to TACE, DEB-TACE, and SIRT.[30] HAIC was, however, associated with higher toxicity rates than the percutaneous techniques. Retrospective analysis of patients treated at Memorial Sloan Kettering Cancer Center (MSKCC) with unresectable ICC confined to the liver or regional lymph nodes demonstrated improved survival for HAIC over systemic chemotherapy alone (30.8 months vs. 18.4 months $p < 0.001$).[33] These results were echoed by another single center series of patients with multi-focal ICC where arterial-based therapies were associated with equivalent survival to surgical resection, though HAIC appeared most promising.[34] Overall, no regional therapeutic modality has produced comparable survival data to HAIC in the treatment of ICC though prospective data are needed and results of a multicenter trial are eagerly awaited (NCT01862315).

Radiation therapy

Radiation has been used in both the adjuvant setting and as definitive therapy for patients with localized, unresectable tumors.[35] In the aforementioned NCDB review, radiation therapy was associated with increased survival in Stage I and III disease in comparison with patients receiving no local therapy.[24] Further prospective, controlled trials are needed for this modality as well.

Colorectal liver metastases

Colorectal cancer ranks third in incidence among cancers and is the second leading cause of mortality globally, with an estimated 881,000 deaths in 2018.[36] Among the disease processes presented in this review, colorectal liver metastases (CRLM) has been the most thoroughly evaluated. Liver metastases will be diagnosed in approximately one in four patients within five years of diagnosis of primary colorectal cancer, and 30–50% will develop them at some point in their disease course.[37,38] The standard for treatment of these patients is surgical resection with curative intent combined with systemic chemotherapy.[39] While advances in perioperative techniques have increased utilization of resection, technical limits exist including a future liver remnant consisting of at least two contiguous liver segments of adequate functional status. Only about 25% of patients are amenable to standard resection at diagnosis.[37]

Thermal ablation

RFA and MWA have been performed for CRLM both as monotherapy and as an adjunct to resection. Though prospective data are lacking, RFA or MWA combined with hepatic resection demonstrated good short- and long-term outcomes in two large, multicenter retrospective studies and compares favorably to two-stage hepatectomy.[40,41] There is a growing interest that ablation could replace resection in specific subsets of patients as ablative techniques appear to be associated with reduced morbidity without compromising survival.[42] Two large European trials, the COLLISION (NCT03088150) and LAVA trials, will seek to answer this question more definitively for small CRLMs.[43,44]

Transarterial chemoembolization

The best developed evidence for TACE in the setting of CRLM is for DEB-TACE with irinotecan (DEBIRI) which has been utilized in two randomized controlled trials. The first compared DEBIRI versus systemic chemotherapy with FOLFIRI in patients presenting with unresectable CRLM who progressed to second- or third-line therapy.[45] This study showed prolonged median overall survival (22 vs 15 months, $p = 0.031$) in the DEBIRI arm. The second trial compared modified FOLFOX with bevacizumab with and without DEBIRI.[46] The study showed no difference in overall survival, but did show an increase in response rate, rate of downstaging to resection, and progression-free survival after resection for patients who received DEBIRI. As DEB-TACE is well tolerated and has not led to treatment delays, this represents a viable treatment option, particularly to downsize tumors involving major hepatic vascular structures.

Selective internal radiotherapy

SIRT has been shown to be a promising treatment of chemorefractory CRLM, though data originates from retrospective reviews and is limited by selection bias.[47] The excitement for SIRT led to three large, randomized, phase III clinical trials (FOXIRE, SIRFLOX, FOXFIRE-Global) for utilization of this modality in combination with systemic chemotherapy versus systemic chemotherapy alone in the first-line treatment of CRLM.[48,49] The planned combined analysis demonstrated a lack of improvement in overall or progression-free survival though SIRT was associated with improved hepatic progression-free survival.[50] Though not advisable in the first-line setting, SIRT can be a safe and effective salvage option for advanced disease confined to the liver.

Hepatic artery infusion chemotherapy

The use of catheter-directed therapy via the hepatic artery for metastatic colon cancer dates to at least the 1960s, when a description of twenty-one patients with advanced liver neoplasms (nine of colorectal primary) were treated with HAIC therapy via a surgically placed catheter.[51] Current application of HAIC includes: 1) unresectable CRLM for definitive therapy or to downstage to resection, 2) as salvage treatment, and 3) as adjuvant therapy following hepatic resection.

In a randomized controlled trial comparing HAIC versus systemic chemotherapy in 135 patients with unresectable CRLM, HAIC showed improved survival and response rates, and was associated with improved physical function.[52] A more recent phase II trial (OPTILIV) has shown conversion to resectability in 29.7% by using HAIC with 5-fluorouracil, oxaliplatin, and irinotecan whereas systemic chemotherapy would typically convert only 15%.[53] Conversion to resectability has been suggested as the most appropriate endpoint for trials focused on cure, as resection rate directly correlates with response rate and survival.[54,55] A prospective phase two trial demonstrated conversion to resection in 47% at a median of 6 months following combined HAIC and systemic chemotherapy.[56] Long-term follow-up of this trial demonstrated chemotherapy-naive patients had high response rates and a 5-year overall survival of 51%, while patients who were converted to resection had 5-year survival of 63%.[57]

As a salvage therapy, HAIC still appears to offer a survival advantage over modern systemic chemotherapy alone.[58] Even for patients who have been refractory to all standard systemic chemotherapy, HAIC with floxuridine offers a response rate of 33%[59] HAIC has also been compared to SIRT with yttrium-90 for patients with isolated unresectable liver metastases.[60] Though retrospective, the groups were well matched and median overall survival was 31.2 months in the HAIC group versus 16.3 months in the SIRT group.

HAIC as adjuvant therapy following liver resection for CRLM is the only modality, including systemic chemotherapy, to demonstrate a survival benefit in a randomized controlled trial.[61] Though this trial pre-dated the era of modern chemotherapy, subsequent

long-term follow-up from MSKCC demonstrates a continued survival benefit on propensity score matched comparison of HAIC versus systemic chemotherapy alone.[62] So, while many have felt that improvements in systemic chemotherapy would make HAIC obsolete, there still appears to be an advantage to arterial chemotherapy. HAIC should be delivered at experienced centers in the setting of a multidisciplinary team and further multi-center trials are warranted to determine the appropriate role and timing for HAIC, particularly in the setting of unresectable CRLM.

Other metastatic tumors to the liver

Neuroendocrine tumor

Gastro-entero-pancreatic neuroendocrine tumors (NET) have an annual incidence of 3.65 cases per 100,000, and frequently follow an indolent course, with overall 5-year survival of 68.1%.[63] Commonly described liver-directed therapies utilized for tumors not amenable to resection are SIRT, TACE, and TAE.[64] Ablative therapy is often used as an adjunct to resection. A review of SIRT performed in 870 patients with NET described improvement in nearly 70% of patients with clinical symptoms of carcinoid syndrome.[65] Prior systematic review and expert consensus indicated symptom palliation was similar between TAE, TACE and SIRT, but that SIRT is associated with improved quality of life due to fewer side effects and treatment sessions.[66]

Breast cancer

Liver metastases are diagnosed in 6–25% of patients with metastatic breast cancer with a historically described survival of 1–14 months. Though systemic therapy often offers excellent disease control, liver-directed therapy is of growing interest for oligometastatic disease. Percutaneous RFA has demonstrated some success in local control and may offer an opportunity for chemotherapy holiday, though the impact on survival is unclear.[67,68] Prospective trials investigating SBRT and surgical metastasectomy are ongoing (NCT02364557). Isolated retrospective reports of SIRT and HAIC have been published from single institutions but selection bias for these series significantly limits the conclusions.[69,70] Given the high efficacy of systemic therapy for breast cancer, patients considered for liver-directed therapy should be rigorously screened in a multi-disciplinary setting or placed on a clinical trial protocol.

Conclusion

Liver-directed therapies have undergone a relative boom over the past two decades. While these are advancing patient care, many of these options have been propagated without high-level clinical evidence. However, these options have allowed us to tailor our clinical approach to the individual based on their disease status and clinical condition. With an increasing number of options available for treatment, comparative trials need to be undertaken to better define the role for and sequence of these therapies used in combination with the standard pillars of surgery and systemic therapy. This will require suspension of bias among key stakeholders but is crucial to advancing the science of modern cancer care.

Conflict of interest

The authors have no conflict of interest or sources of funding to disclose.

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