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ABOUT COVER

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Metastatic disease to the liver: Locoregional therapy strategies and outcomes

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Abstract

Secondary cancers of the liver are more than twenty times more common than primary tumors and are incurable in most cases. While surgical resection and systemic chemotherapy are often the first-line therapy for metastatic liver disease, a majority of patients present with bilobar disease not amenable to curative local resection. Furthermore, by the time metastasis to the liver has developed, many tumors demonstrate a degree of resistance to systemic chemotherapy. Fortunately, catheter-directed and percutaneous locoregional approaches have evolved as major treatment modalities for unresectable metastatic disease. These novel techniques can be used for diverse applications ranging from curative intent for small localized tumors, downstaging of large tumors for resection, or locoregional control and palliation of advanced disease. Their use has been associated with increased tumor response, increased disease-free and overall survival, and decreased morbidity and mortality in a broad range of metastatic disease. This review explores recent advances in liver-directed therapies for metastatic liver disease from primary colorectal, neuroendocrine, breast, and lung cancer, as well as uveal melanoma, cholangiocarcinoma, and sarcoma. Therapies discussed include bland transarterial embolization, chemoembolization, radioembolization, and ablative therapies, with a focus on current treatment approaches, outcomes of locoregional therapy, and future directions in each type of metastatic disease.

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Core Tip: Locoregional percutaneous catheter-directed approaches have been associated with better tumor response, improved disease-free and overall survival, and decreased morbidity in metastatic disease to the liver compared to standard treatment. This review explores recent advances in liver-directed therapies for metastatic liver disease from primary colorectal, neuroendocrine, breast, and lung cancer, as well as uveal melanoma, cholangiocarcinoma, and sarcoma. Therapies discussed include bland transarterial embolization, chemoembolization, radioembolization, and ablative therapies, with a focus on current treatment approaches, outcomes of locoregional therapy, and future directions in each type of metastatic disease.

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INTRODUCTION

Metastatic disease to the liver is the most common malignant liver condition and a major cause of cancer-related morbidity and mortality[1]. While colon cancer represents the most common metastatic disease to the liver, other common primary tumors include lung and breast adenocarcinomas, neuroendocrine tumors, melanomas, and sarcoma[2]. Regardless of primary tumor type, liver metastasis generally represents advanced disease, and is typically associated with poor prognosis[3]. The goals of therapy at this stage are often palliative, but there is a growing interest in differentiating between oligometastatic disease characterized by limited metastasis from more widespread metastatic disease, as these classifications may carry prognostic value[4-7]. In some cases, curative treatment has been demonstrated in oligometastatic disease, encouraging aggressive local treatment in appropriate patients[8]. Traditional management options for patients with metastatic disease to the liver include surgical resection and systemic chemotherapy. However, the percent of patients who present with disease amenable to surgery ranges from 25% to less than 10% depending on the primary tumor[9,10]. While significant advances in complex liver surgery have been made over the past several decades, liver resections are nevertheless still associated with major morbidity and mortality[11]. These risks must be carefully balanced with the evidence for a survival benefit especially in the setting of metastatic disease[12].

On the other hand, most patients with liver metastases have unresectable disease, either because of anatomical limitations, presence of extrahepatic disease, or absence of evidence establishing a survival benefit for resection. Fortunately, novel liver-directed strategies are being used to downstage tumors for curative resection, reduce symptoms, and provide better tumor control[13-15]. In the last ten years, locoregional therapies in metastatic liver disease have demonstrated comparable outcomes with fewer side effects than current standards of care, leading to formal incorporation into treatment algorithms as first-line, adjunctive, or second-line therapy for various tumor types[16-19]. The development of new image-guided techniques and enhanced targeted pharmacologic and radiotherapeutics promise to improve upon the impressive tumor response, progression free survival (PFS), and overall survival (OS) rates that these therapies have already demonstrated. This review examines the recent advances in locoregional therapy for metastatic disease to the liver including transarterial embolization (TAE), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and ablative therapies in major cancer types.

LOCOREGIONAL THERAPIES

TAE, TACE, and TARE

Catheter-directed locoregional therapies are based on the principle that liver tumors recruit their blood supply from the hepatic artery, while hepatic parenchymal cells are primarily supplied by the portal vein. In this way, local therapies such as TAE, TACE, and TARE can be targeted to tumor cells while minimizing damage to normal liver tissue[20]. In all cases, the key branches of the hepatic artery supplying the tumor are identified before the introduction of embolic agents, chemotherapy, or radiotherapy to prevent non-target embolization[21] (Tables 1 and 2).

In TAE, particulate or liquid embolic agents are administered, resulting in cellular membrane disruption and ischemic cell death. Similarly, in TACE, tumor vessels are occluded, with the added benefit of local delivery of chemotherapeutic agents. In the conventional approach (c-TACE), a lipiodolized chemotherapeutic is introduced, followed by the embolic agent. More recently, drug-eluting beads (DEB-TACE) have been used as both chemotherapeutic and embolic agents allowing for the sustained release of chemotherapy with greater standardization compared to c-TACE. The most common complication of these procedures is postembolization syndrome (PES), which presents as self-limiting right upper quadrant pain, nausea, fever, and elevated liver function tests. PES is attributed to tumor necrosis and tissue ischemia and full recovery within seven to ten days is typical. Other risks include hepatic decompensation, renal injury, biliary injury, infection, and non-target embolization[21].

In a similar fashion, TARE uses 30-micron beads that have been embedded or coated with a radioisotope of yttrium (*i.e.*, ^{90}Y). Once introduced, ^{90}Y undergoes beta-decay causing radiation-induced damage to cellular DNA repair mechanisms and ultimately cell death. One benefit of TARE over TACE is that it can be delivered in the outpatient setting[22]. Unique complications of TARE include radioembolization-induced liver disease (REILD) and post-radiation syndrome. REILD is seen in up to 20% of patients treated with TARE and defined by jaundice and ascites that persist 1-2 mo after treatment without evidence of obstruction or tumor progression. In contrast, post-radiation syndrome is a set of non-specific symptoms including fatigue, nausea, anorexia, and fever generally requiring supportive management[23].

To assess response, follow up imaging and laboratory investigations are conducted 4-6 wk later, and every 3-6 mo thereafter to evaluate treatment success and monitor disease progression. Laboratory evaluation includes tumor markers such as CEA and CA19-9 for colorectal and cholangiocarcinoma[24] or chromogranin, pancreatic polypeptide, or pancreastatin for neuroendocrine tumors[25,26]. To evaluate response with imaging, multiple criteria have been created. One way to evaluate response is by assessing changes in tumor size with contrast-enhanced CT or MRI imaging, which is the basis of one commonly used set of response criteria, termed Response Evaluation Criteria in Solid Tumors (RECIST)[27]. Similarly, PET Response Criteria in Solid Tumors (PERCIST), was developed to measure changes in radiotracer uptake on positron emission topography imaging[28]. The development of novel therapies has led to the development of tumor-specific imaging criteria including the modified RECIST (mRECIST) criteria for hepatocellular carcinoma, Modified CT Response Evaluation (Choi) Criteria for gastrointestinal stromal tumors, and the European Association for Study of the Liver (EASL) criteria, among others[28-31]. These criteria were developed to take into account functional changes seen on imaging, such as contrast enhancement or density, when using therapies that may not lead to radiographic reductions in tumor size[32].

Ablative strategies

Ablative techniques include radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation (CA), irreversible electroporation (IRE), laser-induced interstitial thermotherapy (LITT), and high-intensity focused ultrasound (HIFU). Commonly used ablative techniques can be performed *via* intravascular approach, percutaneously, or in conjunction with surgical resection. While RFA is generally the most commonly studied method, alternate techniques such as MWA have become increasingly popular. In contrast, the use of CA has declined due to its increased post-procedure morbidity and local recurrence rates compared with other methods[33,34]. CA is associated with a number of other unique adverse effects including myohemoglobinuria leading to acute renal failure, cardiac dysrhythmias, and cryogenic shock, a cytokine-mediated syndrome of multi-organ failure, severe coagulopathy, and disseminated intravascular coagulation[21,35]. IRE, LITT, and HIFU remain less well-studied modalities for treatment of liver metastases but have demonstrated promise in clinical

Table 1 Summary of locoregional therapy options for metastatic disease to the liver

Modality	Techniques	Risks
TAE	Particulate or liquid embolic agents	PES, liver abscess, liver biloma, liver failure
TACE	Conventional emulsified chemotherapeutic agent (c-TACE) or drug-eluting beads (DEB-TACE)	PES, liver abscess, liver biloma, liver failure
TARE	Yttrium-90 radioisotope loaded on microspheres	REILD, PRS, liver failure, liver abscess, liver biloma
Ablation	Radiofrequency, microwaves, laser, cooling, alternating and direct current	PAS, bleeding, damage to surrounding structures

PES: Post-embolization syndrome; REILD: Radioembolization-induced liver disease; PRS: Post-radioembolization syndrome; PAS: Post-ablation syndrome; TAE: Transarterial embolization; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization.

Table 2 Applications and outcomes of locoregional therapies by tumor type

Modality	Applications and outcomes
TAE	First-line for unresectable symptomatic well-differentiated NELM refractory to medical therapy [19] Improved OS and PFS <i>vs</i> first-line chemotherapy in unresectable CRLM [39,40]
TACE	Comparable tumor response and OS <i>vs</i> first-line chemotherapy in neoadjuvant setting for CRLM [41] Improved OS and tumor control when used as adjunctive therapy in BCLM [42-44] Comparable overall survival to systemic chemotherapy in UMLM [45,46] In IHC, DEB-TACE and chemotherapy have comparable OS [47] and DEB-TACE improves OS when added to chemotherapy [48,49] TARE with first-line chemotherapy offers a survival benefit in CRLM [50], IHC [51]
TARE	Provides survival benefit in CRLM after failure of two lines of chemotherapy [52] TARE plus chemotherapy improves downstaging <i>vs</i> chemotherapy alone in CRLM [13,53], IHC [51] Increases OS in unresectable CRLM compared to chemotherapy alone [54]
Ablation	RFA [55] and MWA [56] have comparable OS to surgical resection in CRLM RFA with resection has comparable OS to two-stage hepatectomy in CRLM [57], NELM [58] Fewer adverse events, longer PFS, and comparable OS <i>vs</i> resection in BCLM [12,59]

NELM: Neuroendocrine cancer with liver metastasis, CRLM: Colorectal cancer with liver metastasis, BCLM: Breast cancer with liver metastasis, UMLM: Uveal melanoma with liver metastasis, IHC: intrahepatic cholangiocarcinoma, OS: Overall survival, PFS: Progression-free survival; TAE: Transarterial embolization; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization.

studies [21] (Tables 1 and 2).

RFA uses a locally introduced electrode to emit radiofrequency alternating current to generate thermal energy that results in tumor necrosis. It is most effective in small tumors (< 3 cm) and in metastases with fewer lesions and is less effective in tumors located close to the hilum and large blood vessel due to the heat sink effect of flowing blood [36,37]. To combat size limitations, multiprobe stereotactic RFA is a technique that shows promise for hepatic tumors up to 8 cm [38]. MWA similarly uses a locally introduced antenna to generate an electromagnetic field that aligns nearby water molecules, producing thermal energy. In contrast to RFA, MWA achieves target temperatures faster over a larger area, produces more uniform heating zones, and is less susceptible to heat sink effects. Further, MWA has the ability to perform multiple ablations simultaneously [39]. The newest form of ablation is irreversible electroporation (IRE). In contrast to thermal ablation techniques, IRE uses high-voltage electrical current to create permanent nanopores in the cell membrane, leading to apoptosis [40]. Serious complications common to ablative strategies include bleeding, damage to surrounding organs such as the diaphragm, GI tract, and gall bladder, and a self-limiting post-ablation syndrome (PAS) that presents with the same symptoms as

PES[41,42].

COLORECTAL CARCINOMA

Introduction to colorectal liver metastasis

Colorectal liver metastasis (CRLM) is the most common type of liver malignancy, and over one half of patients with colorectal cancer will develop metastasis to the liver[43]. Interestingly, in left-sided colorectal cancer, liver metastasis is less extensive with better overall survival. In contrast, metastasis to the liver in right-sided colorectal cancer is more extensive with worse survival[44]. Surgical resection remains the first-line treatment for CRLM, but only about 25% of patients are surgical candidates[9]. In recent years, there has been a substantial increase in evidence supporting local therapies for surgically untreatable CRLM. Current guidelines now support the use of local therapies after neoadjuvant systemic chemotherapy has failed to successfully downgrade a surgically unresectable tumor[45]. Currently, ablation is being explored as an alternative to surgical management in select cases of CRLM. Additionally, the benefits of TARE and TACE in conjunction with systemic chemotherapy and ablation are being actively explored.

TACE in CRLM

While c-TACE with doxorubicin is commonly employed for primary hepatocellular carcinoma, doxorubicin does not have the same efficacy against colorectal metastasis. In response, there has been growing interest in DEB-TACE with irinotecan (DEBIRI), a chemotherapeutic used primarily in the treatment of colorectal carcinoma. In 2012, Fiorentini *et al*[46] conducted the first randomized clinical trial on DEBIRI *vs* FOLFIRI (systemic irinotecan, fluorouracil, and leucovorin), which demonstrated the superiority of DEBIRI in terms of overall survival (22 *vs* 15 mo) and progression free survival (7 mo *vs* 4 mo). Metanalysis of studies since then have demonstrated an average tumor response rate of 62%, with median OS of 18 mo with DEBIRI, and 33 mo when DEBIRI is combined with FOLFOX[47]. DEBIRI has additionally been explored as a neoadjuvant therapy: PARAGON II demonstrated that a single treatment of DEBIRI was comparable to systemic neoadjuvant chemotherapy in terms of tumor response and overall survival[48]. Interestingly, one study on DEBIRI examined outcomes stratified by left-sided or right-sided primary colorectal cancer and found that left-sided colorectal cancer was associated with median OS of 33 mo, while median survival in right-sided colorectal cancer was only 17 mo[49].

TARE in CRLM

Transarterial radioembolic therapy with yttrium-90 has shown a survival benefit in unresectable CRLM. The MORE trial, a retrospective study of 606 patients with unresectable CRLM refractory to one or more lines of chemotherapy, demonstrated that treatment with TARE resulted in median OS of 10 mo[50]. SIRFLOX, a phase III trial, was designed to compare standard systemic chemotherapy (FOLFOX +/- bevacizumab) with systemic chemotherapy plus TARE. Results from this trial showed that the addition of TARE was associated with comparable survival, longer progression free survival, and better tumor response rates in the liver[51]. Further, adding TARE to systemic chemotherapy is associated with less viable tumor tissue after treatment and greater gains in resectability of primarily unresectable tumors than systemic chemotherapy alone[13,52]. Differences in outcomes between right and left-sided colorectal cancers have been demonstrated in TARE. Of note, TARE added to first-line FOLFOX was associated with a 4.9 mo increase in median OS compared to chemotherapy alone, a difference that was not seen in patients with left-sided primary tumors[53]. Further phase III trials are currently underway to assess the benefit of adjunctive TARE with second-line chemotherapy in CRLM[54].

Ablation in CRLM

Ablation has been long studied in CRLM and demonstrates comparable outcomes to resection when used for small tumors (< 3 cm) with appropriate margins (> 5 mm)[37]. Phase II trials on unresectable colorectal liver metastases revealed that the addition of RFA to systemic chemotherapy increased OS at eight years to 35.9% from 8.9% with chemotherapy alone, with a median OS of 45.6 mo[55]. Recent work has demonstrated the non-inferiority of RFA and MWA for treatment of small resectable liver metastasis[56-58]. These results led to the ongoing COLLISON trial, a random-

mized, controlled phase III trial comparing overall survival in RFA *vs* surgery in resectable CRLM < 3 cm. Initial discussion suggests there may be a particular role for radiofrequency ablation in small but deep-seated tumors, which would require major hepatectomy using traditional surgical approaches[45]. If shown to be non-inferior, there would be many benefits to adopting a minimally invasive approach like ablation, including decreased morbidity and mortality, length of hospital stay and recovery time. Regarding MWA, recent metaanalyses suggest superiority over RFA for resectable CRLM: MWA was found to have similar adverse effect profile and may be associated with increased overall and disease-free survival[59].

Future directions

The five-year survival rate for CRLM has been increasing in recent decades, in part due to locoregional approaches that have enabled downstaging and curative resection in previously unresectable patients. With the recent therapeutic options like DEBIRI and the further development of ablative therapies such as MWA, which can be combined with various chemotherapy regimens, these outcomes will hopefully continue to improve. Other therapies currently under investigation include new ablative techniques like irreversible electroporation[45], for which a phase II trial is currently underway (NCT02082782)[60]. While the role for interventional liver-directed techniques continue to expand, additional research is needed regarding the application of these therapies in an adjuvant setting to improve the multidisciplinary care of CRLM and reduce recurrence rates.

NEUROENDOCRINE TUMORS

Introduction to neuroendocrine tumors with liver metastasis

Neuroendocrine tumors (NETs) are a diverse group of neoplasms that arise from neuroendocrine cells in various parts of the body. They are primarily classified by histology and are generally separated into two groups: indolent, well-differentiated tumors, and more aggressive, poorly differentiated carcinomas. NETs can also secrete hormone peptides, resulting in systemic syndromes. The liver is the most common site of metastasis and the majority of patients with metastatic NETs have neuroendocrine liver metastasis (NELM). Treatment options include surgery, locoregional therapies, chemotherapy, somatostatin analogs, and liver transplant in select patients. After failure of somatostatin analogs, resection is the preferred method of treatment in liver-predominant disease, but curative resection is only possible in 10%-25% of patients and recurrence occurs in 50%-95% of patients[61,62]. Ablation can be used as curative therapy and for downstaging of previously unresectable disease. In patients who are not surgical candidates, typically due to bilobar multifocal disease, locoregional therapies including TAE, TACE, and TARE are the preferred approach for tumor control and management of carcinoid symptoms[62]. Even in the absence of complete disease eradication, locoregional therapies can achieve complete remission of symptoms due to hormone peptide secretion.

TAE and TACE in NELM

TAE and TACE are the preferred therapies for well-differentiated, unresectable, liver-dominant NELM with symptoms that are refractory to medical therapy[19]. In a direct comparison, TAE and TACE were associated with similar outcomes, but TAE was associated with fewer adverse effects than TACE[63]. Dermine *et al*[61] pooled the results of 25 retrospective studies (1986-2017) that examined TACE in NELM and found a progression-free survival (PFS) of 18.5 mo with median OS of 34.5 mo. Measures of response rate were variable, but overall the morphological response rate was 49%, with an additional 27% showing tumor stabilization[61]. In a more recent retrospective study, 197 patients with NELM treated with TACE demonstrated a 96% response by RECIST criteria with a median OS of 35.9 mo and PFS of 15.9 mo[14]. In a comparison between c-TACE with cisplatin, mitomycin C and doxorubicin and DEB-TACE with doxorubicin, c-TACE was associated with higher symptomatic response (47% *vs* 30%) but a higher rate of post-embolization and LFT elevations[64]. Currently, there is an ongoing prospective randomized trial comparing TAE, c-TACE, and DEB-TACE which recently closed its DEB-TACE arm based on initial safety data[65].

TARE in NELM

One analysis which pooled 15 retrospective studies of NELM treated with TARE from

2008 to 2016 found a median symptom response of 89.5% (range: 55-100%), median response rate of 51% (range: 12%-73%) by RECIST criteria, PFS of 10 mo (range: 9-11 mo), and median OS of 28.5 mo (range: 14-70 mo)[61]. The largest study to date included 148 patients with NELM who were treated with TARE and demonstrated a response rate of 70% with a median OS of 70 mo[66]. More recent studies include a retrospective study of 30 patients with NELM who were treated with TARE for a median OS for 39 mo[67]. In one retrospective study, 51 patients with NELM were treated with TARE and demonstrated 83% response by RECIST with median OS of 50.1 mo and PFS of 19.9 mo[14]. A randomized controlled pilot study of 11 patients compared TAE to TARE and found similar response rates by RECIST criteria at 6 mo [68]. A recent multi-institutional analysis found that both TACE and TARE were safe and effective liver-directed therapies for unresectable NELM. Although TACE demonstrated improved short-term disease control and response rates, both resulted in comparable long term outcomes[14].

Ablation in NELM

Ablation can be used alone or in conjunction with surgical resection. When used in conjunction with resection, it can both widen the candidates for resection and provide debulking in bilobar disease. Retrospective study of 16 patients who had a median of 23 liver metastases each were treated with resection and RFA and achieved a 3-year OS of 86 percent[69]. Another retrospective study of 40 patients treated with resection and RFA achieved PFS of 22 mo and median OS of 95 mo[70]. These findings are supported by a third retrospective study of 94 patients who underwent resection with intraoperative ablation, achieving a 5-year OS of 80% and 10-year OS of 59%[71]. Indeed, a recent population-based study found that 30% of patients undergoing resection of NELM also had concomitant ablation with no increase in perioperative morbidity[72]. In some cases, RFA may be as effective as surgical resection; a prospective study of 89 patients with NELM who were treated with RFA alone demonstrated symptom relief in 97% of patients, with a PFS of 16 mo and median OS of 72 mo. Further, the 5-year survival rate of 57% in this study is comparable to the 5-year survival rate of 61% seen in surgical resection[73]. MWA with or without concomitant resection has also been studied for NELM. In a phase II trial of 11 patients, complete ablation, defined as lack of enhancement on triple phase CT, was achieved in 90% of patients at 5 years[74].

Future directions

In addition to locoregional approaches, advances in the molecular understanding of neuroendocrine tumors has led to growing interest in the use of small molecule inhibitors for the treatment of neuroendocrine tumors. Sunitinib, a tyrosine kinase inhibitor, and everolimus, an mTOR inhibitor, have already been approved for use in neuroendocrine tumors[62,75]. An exciting new therapy for neuroendocrine tumors is peptide receptor radionucleotide therapy (PRRT), in which radionucleotides bound to SSA are delivered directly to somatostatin receptor positive tumors[76,77]. In fact, a phase 2 study of TARE with holmium-166 following PRRT is currently underway[78]. Additional research combining locoregional approaches with new therapeutics is needed to explore the benefits in the setting of liver-predominant disease.

BREAST CANCER

Introduction to breast cancer with liver metastasis

Breast cancer is a leading cause of mortality worldwide. Roughly 1 in 5 women with breast cancer will develop metastatic disease to the liver[12,79]. Breast cancer with liver metastasis (BCLM) typically occurs late in the disease course and is associated with a worse prognosis than metastasis to other sites like brain or bone. With treatment, median OS in BCLM is 14 mo[80]. For metastatic disease, systemic therapy remains the standard of care. For patients with isolated BCLM who respond to systemic chemotherapy, surgical resection can be offered[81]. However, recurrence rates even in highly selected patients remain high and the vast majority of patients harbor unresectable disease[12]. Given these limitations, local options like TAE, TACE, and TARE have been used for palliation and to enhance locoregional control.

TACE for BCLM

TACE is a palliative option for BCLM and has shown benefit as an adjunct to systemic

chemotherapy in retrospective studies. Li *et al*[82,83] compared DEB-TACE plus systemic chemotherapy with systemic chemotherapy alone in 47 patients, which demonstrated a median OS of 28 mo, the highest to date for TACE. This is consistent with more recent work by Duan *et al*[84] in 44 patients with liver-only metastatic disease, which demonstrated improved response rates (59.1% *vs* 34.9% by RECIST criteria) and improved survival at 1, 2, and 3 years. In the largest study to date, Vogl *et al*[85] demonstrated a median OS of 25-mo in 208 patients treated with c-TACE and systemic chemotherapy. More recently, a pilot study of DEB-TACE demonstrated disease control and median OS of 17 mo in 23 patients with chemo-resistant disease, though the treatment protocol was associated with adverse effects[86].

TARE for BCLM

TARE is an alternative palliative treatment with promising response rates in chemo resistant BCLM. A study of 81 patients with unresectable liver metastases demonstrated a median OS of 8 mo and a 61% response rate by PERCIST criteria[87]. Most recently, Deipolyi *et al*[88] demonstrated a response rate of 75% at 3-5 mo (PERCIST) and median OS of 15 mo. A recent review of 47 patients who received either TARE or TACE found that TARE was significantly better tolerated and demonstrated a trend toward improved survival. In this study, TARE was associated with a median OS of 13 mo and 3-month disease control in 47% of patients by mRECIST criteria[79].

Ablation for BCLM

For small isolated metastases, ablative therapy may be associated with similar survival outcomes with fewer adverse events compared to surgical resection[12,83]. Recent studies demonstrate median OS ranging from 30 to 70 mo[83]. One retrospective study of 69 patients with BCLM demonstrated PFS of 24 mo, with median OS of one-, two-, three- and five-year survival rates of 81.8, 50.1, 25.3 and 11.0%, respectively[89]. A more recent retrospective study of 33 patients with oligometastatic breast cancer demonstrated a median OS of 70 mo. Subgroup analysis of 14 patients with hepatic metastasis revealed PFS of 9 mo, which improved to 13 mo in patients who were able to achieve ablation of all metastatic disease in the liver[90]. Prognostic factors associated with improved tumor control and PFS across multiple trials include tumor size, estrogen receptor positivity, and 5-10 mm ablation margins.

Ablation is an appropriate therapy for tumor control of isolated liver metastases and reduces the need for time on systemic chemotherapy. Prospective randomized trials comparing systemic therapy alone to systemic therapy with ablation are needed to determine whether ablation offers a survival benefit as an adjunctive therapy. Further, given that ablation is associated with similar overall survival and decreased morbidity and mortality compared to resection, prospective randomized trials are needed to compare the two approaches to determine the appropriate standard of care.

Future directions

In addition to recent advances in locoregional strategies, new immunotherapies, pembrolizumab and atezolizumab, have been recently FDA-approved to treat metastatic breast cancer[91,92]. Additionally, the FDA recently approved the use of poly(ADP-ribose) polymerase (PARP) inhibitors olaparib and talazoparib in metastatic breast cancer[93,94]. There is growing interest in the synergistic effects of PARP inhibitors combined with radiotherapy, and additional studies are needed to determine outcomes in BCLM[95]. Future studies comparing combination strategies of immunotherapy, PARP inhibitors, and locoregional therapies like ablation and TARE are needed, as they may be able to demonstrate improved outcomes BCLM and strengthen the multidisciplinary care of BCLM.

LUNG CANCER

Introduction to lung cancer with liver metastasis

Lung cancer is the leading cause of cancer death worldwide and metastatic disease is associated with a 5-year survival rate of 4%. Liver metastasis in particular is associated with a worse prognosis compared to metastasis to the brain or bone and is most common in small cell lung carcinoma[96]. In this setting, treatment consists of palliative systemic chemotherapy. However, the 2018 TMN staging criteria distinguish between single and multiple extra thoracic metastasis, suggesting that a more aggressive approach to limited metastatic disease may improve outcomes. Data on

surgical resection is limited to a handful of case reports, which describe benefit in select patients[97-99].

Locoregional therapies for lung cancer with liver metastasis

The benefit of local therapies like TACE, TARE, and ablation are not well characterized for lung cancer with liver metastasis. Regarding TACE, review of a prospective multi-institutional registry containing 13 patients with liver metastasis who were treated with DEB-TACE using either doxorubicin or irinotecan revealed a response rate of 50% at 12 mo and a median OS of 14 mo[100]. Data on TARE is limited to nine patients discussed in two case reports and one retrospective review and demonstrate its potential as salvage therapy in chemo-refractory disease[101]. Regarding ablation, one retrospective review contained four patients with solitary liver metastasis from a primary non-small cell lung cancer who were treated with MWA. Treatment was well tolerated, but subgroup analysis on response rate and overall survival was not performed[102]. Despite the lack of prospective data, local therapies may provide benefit as adjunctive treatment in select patients with oligometastatic disease.

UVEAL MELANOMA

Introduction to uveal melanoma with liver metastasis

Uveal melanoma is the most common primary malignant intraocular tumor in adults. Nearly half of patients will develop metastatic disease, and of those, over 90% will have primary metastasis to the liver. While surgical resection remains the standard of care when feasible, less than 10% of patients will be candidates for surgical resection [10]. Additionally, metastatic uveal melanoma is generally unresponsive to systemic chemotherapy. Without treatment, prognosis for metastatic disease is poor, with median survival of less than nine months[10]. As no medical therapies have yet been shown to prolong survival, there are currently no FDA-approved therapies for metastatic disease. Notably, the major advances in metastatic cutaneous melanoma using immunotherapy have not yet been replicated in metastatic uveal melanoma. Therapeutic approaches under investigation include systemic immunotherapy with checkpoint inhibitors nivolumab and ipilimumab as well as a number of locoregional approaches including ablation, radio- and chemoembolization, and intrahepatic perfusion. The rarity of metastatic uveal melanoma presents a challenge for study design, and many studies comprise cohorts of 20 to 50 patients with wide ranges in outcome measurements between studies.

Locoregional therapies for uveal melanoma with liver metastasis

Recent work by Höppener *et al*[103] provides a meta-analysis of locoregional approaches in uveal melanoma with metastasis to the liver. The vast majority of studies are retrospective cohort studies and outcomes examined include tumor control, progression free survival, and overall survival. In 19 studies of TACE median OS was 6 mo (range 5 to 28). Cisplatin was the most common chemotherapeutic used, and others included doxorubicin, mitomycin-c, fotemustine, and irinotecan. Of these, two studies compared TACE to systemic chemotherapy and found no difference in overall survival[104,105]. Thirteen studies of SIRT with ⁹⁰Y demonstrated a median OS of 11 mo (range 4-26) and included a recent phase II trial showing median survival of 10 mo [10]. Six studies of ablation (predominantly RFA) demonstrated median OS of 19 mo (range: 11-46) and included a recent phase Ib/II trial that combined RFA with ipilimumab to little clinical effect[106]. Fourteen studies examined intrahepatic perfusion of melphalan, a unique approach which involves the introduction of melphalan *via* the hepatic arteries paired with IVC bypass with melphalan filtration to prevent systemic circulation of chemotherapy. This approach demonstrated a median OS of 11 mo (range 5-27). While comparable in terms of overall survival, unique adverse events have been reported using this approach due to the cardiovascular and coagulopathic risks of bypass.

Future directions

Given the lack of a standard of care for metastatic uveal melanoma, many other approaches are being developed alongside locoregional therapies. In addition to the locoregional approaches above, hepatic artery infusion with fotemustine has shown potential benefit in uveal melanoma with liver metastasis[107]. Seventeen studies of hepatic artery infusion with fotemustine had a median OS of 13 mo (range 3-21). In the

last ten years, the development of immune checkpoint inhibitor therapies including ipilimumab, nivolumab and pembrolizumab have transformed outcomes for malignant melanoma[108]. While these results have not yet been replicated in uveal melanoma, trials of combination therapy have shown some potential benefit[109]. Other experimental agents for uveal metastatic melanoma include tumor infiltrating lymphocytes[110], epigenetic therapies[111-113], and tebentafusp, a bispecific fusion protein that targets CD3+ and T-cell receptors[114]. Additional research is needed regarding the application of these therapies in a neoadjuvant or adjuvant setting to improve the multidisciplinary care of metastatic uveal melanoma.

CHOLANGIOCARCINOMA

Introduction to intrahepatic cholangiocarcinoma

Cholangiocarcinoma is a rare malignancy of the biliary system that is occurring with increasing incidence and can be anatomically divided into intrahepatic, perihilar, and extrahepatic types. Given the aggressive and asymptomatic course of early disease, late presentation is common. While the current standard of therapy is resection, recurrence is seen in 60% of patients[115,116]. Further, about 75% of patients are not candidates for resection at time of presentation due to tumor size, location, multifocality, or distant metastatic disease[117]. In the case of unresectable disease, the current standard of care is systemic platinum-based chemotherapy plus gemcitabine, which confers a median OS 11.7 mo based on the results of the ABC-02 trial[118]. In the decade since this trial, studies have shown benefits associated with locoregional therapies in the treatment of intrahepatic cholangiocarcinoma (IHC), including improved overall survival and successful downstaging to surgical intervention[119].

TACE in IHC

With regard to trans-arterial chemoembolization, both c-TACE and DEB-TACE have been investigated in patients with IHC. Park *et al*[120] demonstrated improved OS in patients treated with c-TACE *vs* supportive care, and meta-analysis of 542 patients with IHC treated with c-TACE reveals a median OS of 13.4 mo after treatment[121]. In a study of 24 patients, DEB-TACE was associated with median OS of 17.5 mo[122], and studies of combination DEB-TACE with systemic chemotherapy have demonstrated higher median overall survival than treatment with chemotherapy alone[123,124]. In a three-way comparison of systemic chemotherapy, c-TACE, and DEB-TACE in patients with IHC, DEB-TACE was associated with greater OS than c-TACE, and similar OS to systemic chemotherapy[125]. The ongoing CTILC study (NCT03317483) investigating DEB-TACE in various liver cancers includes 37 patients with IHC[126].

TARE in IHC

Radioembolization with ⁹⁰Y plus first-line chemotherapy has been shown to increase overall survival and successfully downstage patients to surgical resection. A recent single-center retrospective study of 85 patients showed median OS of 21 mo from time of diagnosis and median OS of 12 mo after treatment[127]. These findings were further supported by a multicenter retrospective study of 115 patients showing median OS from diagnosis of 29 mo with median OS after treatment of 11 mo[128]. Within the last year, Edeline *et al*[129] published the results of a phase 2 trial of ⁹⁰Y with first-line chemotherapy in 41 patients with a response rate of 40%, median OS of 22 mo, and successful downstaging of over 20% of trial participants. Given the significant improvement in overall survival compared to the current standard of care, a phase 3 trial is ongoing[129].

Ablation in IHC

Ablation is an option in select patients who are poor surgical candidates and have early-stage IHC (< 5 cm)[130]. Given these criteria, few patients are candidates and available study sizes are small. Recent metanalysis of 10 studies with a total of 206 patients showed median OS for patients treated with RFA ranged from 8.7 to 52.4 mo [131]. Preliminary research suggests that MWA confer a survival benefit *vs* RFA in tumors less than 3cm[132]. Given the invasive nature of the disease, multiple authors recommend wide ablation margins[133-135]. No studies have specifically investigated the role of cryoablation or irreversible electroporation for IHC[136].

Future directions in IHC

Given the importance of chemotherapy in the treatment of IHC, ongoing trials of DEB-TACE represent an exciting area of research. Additionally, the development of targeted therapies for IHC is an area of active research and may eventually be used in conjunction with locoregional approaches to improve outcomes. Currently, phase III trials of the isocitrate dehydrogenase 1 (IDH-1) inhibitor ivosidenib and fibroblast growth factor receptor (FGFR) inhibitors are ongoing[117]. Finally, there are promising results from studies of hepatic artery infusion with floxuridine (FUDR-HAI) combined with first-line chemotherapy[137-140]. While the role of interventional liver-directed therapies continues to expand, it remains to be seen how new targeted approaches can be combined with locoregional strategies to improve multidisciplinary care of IHC.

SARCOMA

Introduction to sarcoma with liver metastasis

Sarcomas are a diverse set of tumors that arise from mesenchymal cells in various parts of the body. These mesenchymal cells can differentiate into a variety of tissues including muscle, adipose, cartilage, nerve, and vascular tissue. Prognosis is related to tumor type — gastrointestinal stromal tumors, for example, are associated with better prognosis, while leiomyosarcomas, which are notoriously resistant to systemic chemotherapies are associated with poor prognosis[141]. In all types, the feared complication is hematogenous metastasis, which is considered incurable and associated with median survival of 12 to 19 mo. In metastatic disease, palliative chemotherapy is the standard of care, despite the fact that only 10-25% of metastatic sarcomas respond to systemic chemotherapy[142]. There is growing interest in more aggressive local treatment, especially for oligometastatic disease. While complete surgical resection is preferred, many patients are not surgical candidates. In unresectable, recurrent or chemo-resistant disease, local therapies like TAE, TACE, and ablation are associated with increased tumor response and overall survival.

TAE in sarcoma with liver metastasis

Two studies of TAE demonstrated improved response rate and overall survival in patients with unresectable, chemoresistant sarcoma with liver metastasis (SLM). The first was a retrospective study of patients with hepatic metastasis that was either incompletely resectable or had failed other therapies. Treatment response was defined as greater than 25% reduction in tumor size or greater than 50% necrosis and achieved response in 9 of 15 patients. OS was 62%, 41%, and 29% at 1-, 2-, and 3 years respectively[143]. The second study examined TAE in 11 patients with GIST that had metastasized to the liver in patients who had either been treated with first line imatinib alone or first-line imatinib followed by and second line sunitinib. In the first group, median survival was 15 mo and PFS was 3.8 mo. In the second group, TAE achieved a median OS of 24 mo and PFS of 3.4 mo. Response rate was 46% overall by mRECIST criteria[144]. GIST tumor type and radiographic response were both associated with prolonged survival. These results represent improvement in both response rate and overall survival compared to treatment with second- or third-line chemotherapy.

TACE in SLM

Three retrospective studies examine the use of TACE in sarcomas with liver metastasis. The earliest, in 1995, used cisplatin beads with vinblastine arterial infusion in 14 patients with gastrointestinal leiomyosarcoma with prior resection. However, local therapy with cisplatin and vinblastine induced > 50% reduction in tumor size in 70% of patients with median PFS of 12 mo[145]. These findings are supported by a retrospective review of 16 patients, most with leiomyosarcoma, which demonstrated tumor control or response in 83% of patients and a median OS of 20 mo after treatment with cisplatin, doxorubicin, and mitomycin-C[146]. Most recently, a retrospective study of 30 patients treated with c-TACE using doxorubicin, cisplatin, and mitomycin-C demonstrated a response of 48% by mRECIST criteria, PFS of 6.3 mo, and median OS of 21 mo[142]. These studies reveal that TACE is an appealing option, particularly in the treatment of leiomyosarcomas, which are highly resistant to systemic chemotherapy.

Ablation in SLM

Ablation for SLM has been examined in three retrospective studies. The first included 66 patients with SLM who were treated with either surgical resection, RFA, or combination therapy. Of the 18 patients who underwent surgical resection with RFA and 13 patients who underwent RFA alone, PFS was 7.4 mo and median OS was 33.2 mo [147]. The second retrospective study comprised 13 patients with GIST with liver metastasis and 12 patients with other sarcoma subtypes with liver metastasis. Of the patients with GIST, 85% showed tumor response with a single treatment of RFA, and non-responders were treated with a second round of RFA, achieving total response. Patients with GIST demonstrated PFS of 28 mo. In other tumor types with liver metastasis, response was observed in 71% of patients, with PFS of 7 mo [148]. Most recently, data from a large retrospective study of 281 patients with metastatic sarcoma support the use of RFA in non-resectable metastatic disease [149]. In addition to these retrospective studies, there are a number of recent case reports on RFA in SLM [150-152]. Ablation is generally well-tolerated and is associated with greatly improved tumor response, progression free, and overall survival in patients, particularly in patients with unresectable or chemo resistant SLM. Further, RFA and surgery can be used in conjunction in many sarcoma subtypes to maximize outcomes.

Future directions

Given the diversity of sarcomas, there is ongoing research into a number of small molecule inhibitors for specific sarcoma subtypes [153]. For metastatic sarcoma in general, preliminary research demonstrates promising outcomes with tivozanib, a VEGF inhibitor [154], and a new chemotherapeutic, eribulin, which has demonstrated benefit in combination with dacarbazine [155]. Additional studies exploring the use of these therapies in conjunction with DEB-TACE would elucidate the role for these therapies in liver-predominant disease.

CONCLUSION

Metastatic disease to the liver is the most common malignant liver condition and a major cause of cancer-related morbidity and mortality. Surgical resection and systemic chemotherapy remain the standard of care in most types of metastatic liver disease, but there is an expanding role for locoregional therapies in liver metastasis with various aims including curative intent, tumor control, downstaging to resection, symptom control, and palliation. TAE, which can be combined with chemotherapy and/or radiotherapy, has the potential to improve tumor response rates and disease-free and overall survival in select patients. Ablative procedures using high frequency alternating currents or microwaves represent comparable alternatives to resection and can even achieve curative results in selected patients. Combined with advances in immunotherapy and targeted therapies, advances in locoregional approaches are providing more robust, multidisciplinary treatment options for metastatic liver disease.

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