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Local and Systemic Therapies for Liver Metastases

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Abstract

Liver metastases are accountable for a high mortality and morbidity in patients with metastatic diseases. The majority of liver metastases are derived from colorectal, gastric and neuroendocrine primary tumors. Resection is the only potentially curative approach to selected colorectal liver metastases (CRLM) and neuroendocrine liver metastases (NELM). Improvements in systemic therapies and operative technologies have succeeded in converting some borderline unresectable cases to resectable, resulting in a more favorable overall survival. For unresectable CRLM or NELM because of the size, location or comorbidities, other locoregional treatments including ablation, intra-atrial therapy and stereotactic body radiotherapy can serve as an alternative with proved efficacy and safety. Evidences on locoregional strategies for non-colorectal, non-neuroendocrine liver metastases (NCNELM) are scarce and warrant large randomized controlled trials for verification. Resection has been indicated as a curative attempt for highly selected gastric liver metastases in Eastern centers. Systemic therapy remains the cornerstone for metastatic diseases. The optimal management of liver metastases requires a multidisciplinary team to form an individualized therapeutic approach. This article evaluates current evidences on the management of liver metastases, with an emphasis on liver-directed local treatment.

Introduction

The liver is one of the most common sites for metastatic diseases. The majority of liver metastases are derived from gastrointestinal neoplasms based on the filter role of the portal circulation. Colorectal liver metastases (CRLM) afflict 35% to 60% of the patients with colorectal cancer (CRC), representing the leading type of liver metastases [1-3]. Neuroendocrine tumors (NET) also present a high affinity to the liver and the liver metastases of NET (NELM) affect approximately 40% to 75% of the patients during the disease course [4]. Non-colorectal, non-neuroendocrine liver metastases (NCNELM) derived from a heterogeneous group of primary tumors are always associated with a more disseminated status and a poorer prognosis. Although chemotherapy and molecular targeted therapy remain the cornerstone for metastatic diseases, surgical resection serves as a potentially curative approach to selected patients with CRLM and NELM [2,5]. On the other hand, resections of NCNELM have still been undefined. Recently, improved molecular understanding of the primary tumors and the development of targeted therapies as well as immunotherapy have not only gained better overall survival (OS) but also provided more chances for local therapies of hepatic metastases. Meanwhile, the advancement in the operative technologies has succeeded in expanding resectability standard. Besides surgical resection, other local therapies including ablative therapy, intra-atrial therapy (IAT) and the use of radiotherapy to the liver have also evolved. Herein, we briefly explored recent advances in the treatment of liver metastases with an emphasis on the local therapies.

Surgical Resection

Surgical resection remains the only potentially curative option for patients with resectable CRLM. The 5-year OS rate for patients undergoing hepatic resection has exceeded 50% [6,7]. Regardless of the number, the size, and the distribution of metastases in the liver, CRLM are deemed as resectable when RO margins (microscopic negative) can be obtained with adequate functional future liver remnant (FLR) [8]. If the initial target FLR of 30% to 50% dependent on the degree of underlying liver disease can't be achieved, preoperative portal vein embolization (PVE) or two-stage hepatectomy can be adopted to induce hypertrophy of the FLR [7,9]. More recently, associating liver partition with portal vein ligation for staged hepatectomy (ALLPPS) has been advocated to achieve a more favorable oncological outcome in patients with advanced CRLM load [10,11]. The presence of synchronous resectable porta-hepatis node or extra hepatic metastases like resectable pulmonary metastases are no longer deemed as contradictions to tumor resections in highly selected patients [12,13]. On the other hand, for solitary small CRLM(≤ 30 mm in size) , parenchymal-sparing hepatectomy has been recommended as it didn't increase recurrence

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Table 1: Five-year Overall Survival After Resection in Patients with NCNELM.

Studies	Patients	Years	Primary site	5-y OS rate	Negative prognostic factors
Adam et al.[39]	1452	2006	Breast (32%), Gastrointestinal (16%), Urological (14%)	36%	Higher age (>60), Histology (melanoma or squamous), Short disease free interval (<12 months), Extrahepatic disease, R2 resection, Major hepatectomy
Groeschl et al.[40]	420	2007	Breast (27%), Sarcoma (23%), Urological (22%)	31%	Lymphovascular invasion Large metastases (>5 cm)
Lendoire, et al.[41]	106	2008	Urogenital (37.7%), Sarcomas (21.7%), Breast (17.9%)	19%	Non-curative resection Synchronous liver metastases
Rourke et al.[42]	102	2012	Genitourinary (31.4%), Gastrointestinal (26.5%), Melanoma (20%)	27%	Large metastases (>5 cm), Presence of extrahepatic nodal disease
Takemura et al.[43]	145	2013	Gastrointestinal (55%), Breast (21%), genitourinary (8%)	41%	Postoperative complication
Slotta et al.[44]	101	2014	Gastrointestinal (33%), Breast (24%) Genitourinary (17%)	30%	Gastrointestinal primary
Hoffmann et al.[45]	150	2015	Breast (28%), urological (13%), melanoma (10%)	42%	Histology (melanoma or squamous), Short disease free interval (<2 years)

in the liver remnant but more importantly improved 5-year survival in case of recurrence (salvageability) [14]. However, approximately 80-90% of patients have unresectable CRLM at initial diagnosis [15,16]. For those with liver-limited unresectable lesions because of involvement of critical structures, an attempt to downsize CRLM via chemotherapy alone or in combination with epidermal growth factor receptor (EGFR) inhibitors has successfully converted some responders from unresectable to resectable status [17-19]. Compared to chemotherapy alone, the addition of EGFR inhibitors cetuximab or panitumumab significantly increased the response rate and the RO resection rate in CRLM patients with wild-type *KRAS*. Due to the risk of developing liver steatohepatitis and sinusoidal liver injury associated with modern chemotherapy, the neoadjuvant period is limited to 2 to 3 months [20]. For a small percent of patients who have a complete radiological response to neo-adjuvant systemic treatment, surgical resection of the disappearing CRLM, if accessible, has still been recommended [21,22]. In fact, local residual disease at the site of the disappearing CRLM could still be found in 11-67% of patients at laparotomy and in 80% of the resected specimens microscopically, resulting in recurrences in more than 19% of patients under conservative management [23-26]. For patients presenting with synchronous CRLM, resection of the primary tumor and CRLM can be performed in a simultaneous or staged approach [27,28]. The usual practice of the staged practice is to resect the primary tumor followed by chemotherapy and delayed hepatic resection. A new liver-first approach to prevent liver disease progression in patients with advanced CRLM has been suggested by recent studies, which resulted in a comparable morbidity and mortality to the traditional strategy [6,29,30]. Repeated resections for successively recurrent CRLM have been verified to continue to provide survival benefit [31].

Hepatic resection represents the mainstay of treatment for patients with grade 1 or grade 2 NELM whereas grade 3 carcinoma is candidate for systemic treatment [32]. The 5-year OS rate of patients with NELM after resection has exceeded 60%, indicating a prolonged survival compared to those with conservative management [33,34]. Selected patients with primarily unresectable NELM might be amendable to conversion therapy via PVE or radiation lobectomy with ^{90}Y-radiolabeled microspheres [35,36]. Despite the apparent benefit of surgical resection in NELM, the majority of patients develop intrahepatic recurrence during the disease course, partly resulting from an underestimation of the true extent of disease burden on preoperative imaging [37]. As it is unlikely to render durable disease control, repeated surgery should be undertaken only in a selected group of patients [33]. Unlike CRLM with surgical resection for a curative intent, debulking of NELM that required resecting at least 90% of the tumor burden was warranted to help alleviate significant paraneoplastic symptoms and prolong overall survival [38].

The benefit of surgical resection for NCNELM remains controversial. Recent retrospective studies have justified hepatic resection of NCNELM with the reported 5-year OS rate ranged from 19% to 42% (Table 1) [39-45]. The significant difference in OS was partly attributed to the great variety of the origin of the primary tumor. Histologically, resection of NCNELM derived from breast cancers and stromal tumors provided far more benefit than those from melanoma and squamous tumors. Other negative prognostic factors included shorter disease-free interval between the primary tumor diagnosis and NCNELM, positive resection margin, poor response to chemotherapy or hormone therapy, the presence of extrahepatic diseases and large liver disease extent (Table 1). Notably, although current treatment protocols in Western centers do not recommend patients with gastric carcinoma to receive surgical resection of hepatic metastases, patients with a small number of hepatic metastases and no other non-curative factor have been indicated for hepatectomy in the East [46,47]. Despite the fact that patients with hepatic metastases from gastric carcinoma are liable to develop multiple nodules distributed to both hepatic lobes as well as outside of the liver, the median 5-year survival rate of highly-selected patients following resection reached 27% according to a recent meta-analysis of retrospective studies [48]. The survival benefit needs to be further demonstrated by prospective randomized controlled trials [49]. Nonetheless, both intrahepatic and extrahepatic recurrences are common for patients with gastric carcinoma, indicating far worse prognosis than those with CRLM. Considering the complexity of NCNELM and lack of well-established treatment paradigm, surgical resection should generally be reserved for patients with liver-limited lesion and more importantly relatively favorable tumor biology.

Ablative Therapy

Ablative techniques including radiofrequency ablation (RFA) or microwave ablation (MWA) are parenchymal-sparing treatment for hepatic malignancies, especially effective for small lesions (preferably≤3cm) [50,51]. RFA can be performed during open surgery, laparoscopically or percutaneously with robust evidences of efficacy and safety [52]. MWA represents a relatively new generation of ablative techniques, taking its advantage over RFA in making larger ablation zones and less heat-sink effect. For patients with unresectable liver metastases because of comorbidities, location or inadequate FLR, ablation can be tried alone or in combination with

Table 2: FDA-approved Targeted Agents for Solid Cancer Treatment.

Cancer type	Targeted agents	Indication enrichment
Colorectal cancer	Cetuximab,Pantitumumab, Bevacizumab, Ramucirumab Regorafenib	KRAS/BRAF wide type None
Gastric adenocarcinoma	Trastuzumab, Ramucirumab	HER2/neu overexpressing None
Gastrointestinal stromal tumor	Imatinib, Regorafenib, Suntinib	None
Pancreatic cancer	Erlotiinib	None
Pancreatic neuroendocrine cancer	Suntinib	None
Breast cancer	Lapatinib, Trastuzumb, Palbocicilib	HER2 overexpressing HER2 negative, ER postivie
Melanoma	Dabrafenib, Trametinib, Vemurafenib	BRAF V600E or V600K mutation
Non-small cell lung cancer	Afatinib, Erlotinib, Gefitinib Crizontinib, Certinib Ramucirumab	EGFR exon 19 deletion or exon 21 (L858R) mutations ALK-positive None
Medullary thyroid cancer	Cabozantinib, Vandetanib	None
Differentiated thyroid cancer	Lenvatinib	None
Renal cell carcinoma	Axitinib, Pazopanib,Sorafenib, Suntinib,Bevacizumab	None
Soft tissue sarcoma	Pazopanib	None

resection. The concomitant ablation and resection approach taking advantage of destroying small tumors via frictional heating and resecting large ones resulted in a 5-year OS rate of approximately 37% to 80% in patients with extensive CRLM [53-56]. In one retrospective study, patients with even poorer prognosis and higher risk factors who underwent RFA plus resection achieved comparable 5-year OS rate (56%) to those (49%) who had resection alone [56]. On the other hand, the reported 5-year OS rate of patients who received ablation alone including those with initially resectable CRLM was merely 28% [57,58]. Another study, however, revealed comparable 5-year OS rate (51.9% vs. 53%) between ablation and resection for patients with CRLM whereas RFA therapy induced significantly more recurrences [59]. As such, current evidences don't support the use of ablative therapy over resection in patients with potentially resectable CRLM. For patients with unresectable NELM, ablative technique can also serve as an effective anti-tumor treatment. Symptom relief was achieved in more than 90% of the patients and the 5-year OS rate exceeded 57% when RFA was applied alone or as an adjunct to resection [60]. Data on the use of ablation for NCNELM are scarce. A few retrospective studies presented the efficacy and safety of RFA performed on patients with breast cancer liver metastases [61,62]. In general, ablative therapy remains as an adjunct to resection, a salvage therapy for post-operation recurrences and an option for patients with unresectable lesions in terms of comorbidities and cancer-specific factors.

Regional Arterial Therapy

While systemic chemotherapy remains the first-line therapy for liver dominant colorectal metastases, recent studies have suggested a survival advantage for transarterial chemoembolization (TACE) using drug-eluting bead irinotecan (DEBIRI) in such patients [63,64]. DEBIRI therapy functions through mechanical occlusion of the feeding artery and direct delivery of high concentrations of irinotecan to the metastatic lesions without systemic exposure, thus exerting minimal side effects to the subjects. Not only can it serve as salvage therapy for patients who have failed multiple lines of chemotherapy, but also can deliver superior response when utilized in combination with FOLFOX chemotherapy. Another promising alternative is radioembolization that transfers Y-90 microspheres to the tumoral and peritumoral vasculature and delivers a high radiation dose (>100Gy) to CRLM [65]. Considering its nature of short-ranged beta radiation, radioembolization is also referred to as selective internal radiation therapy (SIRT). According to the recent SIRFLOX study, an addition of SIRT to FOLFOX-based chemotherapy significantly delayed disease progression in the liver [66]. Nevertheless, the combination therapy did not improve progression-free survival at any site due to increased incidence of progression in the lungs. Thereby, it remains uncertain whether improved control of CRLM delivered by addition of SIRT can translate to improve OS, the result of which is proposed to publish in 2017. Conventional TACE, on the other hand, remains a palliative therapy for patients with CRLM refractory to systemic chemotherapy [67].

NLEM are classically hypervascular lesions with the majority of blood supply derived from the hepatic artery, making them more eligible for intra-arterial therapy. It has been illustrated that IAT yielded improved radiological, biological and symptomatic response for patients with extensive NELM [68,69]. Regardless of the variety of the angiographic procedures, transarterial embolization (TAE) showed comparable efficacy to TACE in NELM [70]. And increasing evidences supported the use of radioembolization in NELM with the median OS reaching approximately 35 months [71-73]. The therapeutic effect of IAT on NCNELM has not been well established, although there are some studies supporting its application as palliative strategy for patient's refractory to chemotherapy [73, 74].

Stereotactic Body Radiation Therapy

External beam radiation therapy for treatment of hepatic metastases has long been frustrated by low tolerance of the normal liver parenchyma. Stereotactic body radiation therapy (SBRT) involves a direct and accurate delivery of highly ablative radiation doses to one or more discrete lesions, representing a new safe and effective strategy for liver metastases. When SBRT was applied to CRLM, 2-year local control rate of the lesions≤3cm was 100% [75]. The median OS of patients with CRLM≤6cm ranged from 20.5 to 29.2 months among studies with heterogeneous enrollment [75,76]. A recent study demonstrated a long-term survival benefit for patients with oligometastases after SBRT [77]. Meanwhile, the study identified

a breast cancer history, a longer distant metastasis-free interval and a longer time from metastatic diagnosis to the end of SBRT as positive predictors of OS.

Systemic Therapy

Chemotherapy remains the cornerstone for patients with stage IV cancers. Besides the advent of new cytotoxic agents, the past decades have witnessed great improvements in targeted therapy and immunotherapy. Improved understanding of molecular profiling of tumors and novel technologies for identification of genetic alterations in patient tissue have led to a massive expansion of targeted agents (Table 2) [78]. Cetuximab or panitumumab targeting EGFR, or bevacizumab targeting vascular endothelial growth factor (VEGF) in combination with cytotoxic chemotherapy is considered as equivalent choice in the first-line, RAS wild-type, metastatic CRC [79,80]. VEGFR-2 monoclonal antibody ramucirumab in addition to FOLFIRI or irinotecan has demonstrated to be effective in the second-line setting [81]. Furthermore, multi-kinase inhibitor regorafenib serves as an additional line of therapy for patients with metastatic CRC refractory to all standard therapy [82]. For patients with HER2-positive gastric cancer, trastuzumab has been recommended to add to first-line chemotherapy to gain survival benefit [83]. Similar to metastatic CRC, ramucirumab alone or in combination with paclitaxel can be opted as second-line therapy for metastatic gastric cancer [84,85]. Although targeted therapy alone or in combination with conventional chemotherapy result in prolonged patient survival and improved disease control, resistance problem remains as tumor progresses. Recently, more attention has been attracted to immunotherapy, especially immune checkpoint inhibitors in solid tumors and chimeric antigen receptor (CAR)-modified T cell (CAR-T) therapy in hematologic malignancies. Ipilimumab is the only FDA-approved agent targeting cytotoxic lymphocyte–associated protein 4 (CTLA), demonstrating a significantly improved survival in patients with metastatic melanoma [86]. When ipilimumab fails in advanced melanoma, anti-programmed-death-receptor-1 (PD-1) treatment with pembrolizumab or nivolumab has been suggested [87,88]. More recently, nivolumab has also been approved for its use in NSCLC [89]. Treatments with checkpoint inhibitors in other tumors are still under clinical trials.

Conclusion

Regarding the complexity of treatment paradigm of liver metastases, optimal decision-making relies on a multidisciplinary team involving surgical, medical, interventional and radiation oncologists. While systemic therapy remains the cornerstone of management, complete surgical resection should given priority for resectable CRLM or NELM. The role of resection for NENLM is still controversial and warrants randomized controlled trials for verification. Other locoregional treatments including ablation, IAT and radiotherapy have also presented efficacy and safety in liver metastases, each with specific tumor-related requirements. Individualized approach for each patient demands an integrated consideration of the biology, location as well as disease burden of the liver metastases.

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