Local Therapies for Hepatic Metastases

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Abstract

The liver is one of the most common sites for metastatic disease, and optimal management of hepatic metastases often requires a multidisciplinary approach. Most commonly, liver metastases are derived from a colorectal or neuroendocrine primary tumor. Liver resection with curative intent is standard for resectable cases, but unfortunately most patients are not initially resectable because of the size, location, and/or extent of disease; inadequate remnant liver volume; or comorbidities. For patients with liver-limited or liver-dominant colorectal liver metastases (CRLM), the current challenges are to use different locoregional treatments to convert some borderline unresectable cases to resectable, and improve local control and overall survival. Although neuroendocrine liver metastases (NELM) may behave in a relatively indolent manner from an oncologic perspective, significant morbidity may be caused by excess hormone production when compared with metastatic liver disease from other primaries, and liver-directed treatment may be beneficial in reducing symptoms and perhaps extending survival. In the multidisciplinary management of patients with liver metastases, local therapies are especially important. Local approaches may be complementary (ie, portal vein embolization) or an alternative (ie, ablation, hepatic arterial infusion, selective radioembolization, and stereotactic body radiotherapy) to surgical resection. This article evaluates the available evidence on current regional strategies for managing patients with liver metastases, with an emphasis on CRLM and NELM, highlighting the clinical usefulness and limitations of each modality. (JNCCN 2013;11:153–160)

Traditionally, local therapy for hepatic metastases has been largely reserved for patients with colorectal liver metastases (CRLM) or, less often, neuroendocrine liver metastases (NELM). Colorectal cancer is one of the most common types of cancer in the West, and approximately 35% to 55% of patients develop hepatic metastases during the course of their disease.1 Although primary neuroendocrine tumors (NET) are much less common, the liver is the most common site of metastatic disease, with 40% to 75% of patients with NET having liver involvement at some point.2 Although local therapy of hepatic metastases from other primary tumor subtypes has been advocated,3 the published evidence is scarce, and treatment recommendations should be made in a multidisciplinary setting.

The potential types of local therapy for hepatic metastases continue to evolve. Although surgical resection remains the cornerstone of local therapy for liver metastases, other therapeutic modalities are increasingly being used. Local therapies to treat hepatic metastases include the use of concentrated energy (eg, radiofrequency or microwave ablation), the delivery of chemotherapy (eg, transarterial chemoembolization [TACE] or drug-eluting beads), and the use of radiotherapy to the liver (eg, yttrium 90 [Y-90], conformal external beam, or stereotactic body radiation therapy [SBRT]). This article reviews local treatment strategies for managing hepatic metastases, with a particular emphasis on the treatment of CRLM and NELM.

Surgical Resection

Improvements in patient selection, preoperative risk factor modification, operative technique, and perioperative management have led to improved mortality in high-volume centers4 and population-based reports. Additionally, the development of targeted biologic agents
and their integration with cytotoxic chemotherapy regimens has led to the potential to downsize some tumors that were previously considered inoperable.\(^5\)

Hepatic resection is generally accepted as the most effective therapy for patients with CRLM, and is therefore considered the standard first-line approach for resectable disease. Five-year overall survival exceeding 50% has been reported in contemporary series after hepatic resection of CRLM with curative intent. A median survival approaching, and even exceeding, 5 years after resection of CRLM is likely secondary to better perioperative outcomes and better patient selection, but mostly to more effective perioperative systemic chemotherapy. When assessing resectability of CRLM, the surgeon must consider whether the entire tumor can be resected with clear margins (R0) while leaving an adequately functional future liver remnant (FLR). In this paradigm, determining resectability is based on whether all of the disease can be removed while leaving an adequate-size future liver remnant with good function. Even patients with advanced intrahepatic disease may be candidates for resection if all CRLMs can be resected and 2 contiguous liver segments with an adequate volume and adequate vascular supply and biliary drainage can be preserved.

The adequacy of the FLR depends on the degree of underlying liver disease, because typically a larger FLR is needed in the presence of underlying parenchymal injury. In general, to avoid an increased risk of liver insufficiency, the target FLR should be approximately 20% to 30% in patients with normal liver, 30% to 40% in those with moderate liver disease, and 40% to 50% in those with fibrosis/well-compensated cirrhosis.\(^6\) Liver volumetrics can be obtained via preoperative cross-sectional imaging; if the FLR volume is inadequate, preoperative portal vein embolization (PVE) can be used in an attempt to induce hypertrophy of the FLR, thereby increasing its volume and function preoperatively.\(^6\) PVE is generally well tolerated, and patients who undergo resection after PVE can have long-term outcomes comparable to those of patients who underwent resection without the need for PVE.\(^7\)

The primary goal of surgical resection is to obtain an R0 (microscopically negative) surgical margin, although the actual width of the negative margin has been shown not to impact local recurrence or overall survival.\(^8\) Several factors have been associated with prognosis after resection; the Clinical Risk Score (eg, Fong score) proposed a prognostic system based on node-positive primary, disease-free interval from primary to metastases of less than 12 months, more than 1 hepatic tumor, largest hepatic tumor greater than 5 cm, and carcinoembryonic antigen greater than 200 ng/mL.\(^9\) More recent studies, however, have questioned the performance of the Clinical Risk Score and other prognostic scoring systems and have noted that these scoring systems are only fair to moderate in predicting long-term outcome.\(^10\) Therefore, although these factors may have prognostic implications, they should not be used to make categorical decisions regarding resectability.

For patients with synchronous disease (eg, primary colorectal cancer and liver metastases presenting concurrently), the optimal sequence of operations may differ based on the clinical situation and the surgeon’s expertise. In general, simultaneous resection of the primary and the CRLM has not been reported to be associated with an increase in perioperative morbidity or mortality. A simultaneous approach is therefore favored in many cases; however, when resection of the CRLM requires a major hepatectomy, perisurgical morbidity and mortality may be higher with a simultaneous approach, and therefore a sequential approach should be considered.

In a subset of patients with multifocal bilobar CRLM, complete extirpation of all liver disease may not be feasible with a single hepatectomy, even with the use of preoperative chemotherapy and PVE. In these situations, a 2-stage hepatectomy may be considered.\(^11\) In general, a 2-stage approach involves an initial minor hepatectomy to remove the CRLM from one hemiliver (typically the left liver). The right portal vein is either ligated at the initial surgery or a PVE is undertaken postoperatively. After a period to allow for hypertrophy of the FLR, a second-stage hepatectomy is performed, which typically involves a more major hepatectomy (eg, right hepatectomy). Data suggest that this 2-staged approach is safe and, among patients who were able to complete both stages, resulted in a long-term survival comparable to that of patients who underwent a planned single-stage hepatectomy.\(^11\)

After surgical resection of CRLM, up to two-thirds of patients will experience a recurrence within 5 years. The overall pattern of recurrence usually involves the liver in approximately two-thirds of pa-
tients, with one-third having liver-only recurrence; approximately half of the patients will also experience recurrence at an extrahepatic site. In the subset of patients with liver-only recurrence, repeat hepatectomy can be considered. Data from a large multicenter study showed that repeat resection is safe and can provide long-term survival in a subset of well-selected patients.

The other secondary disease of the liver that is commonly treated with liver resection is NELM. Although the optimal management of NELM remains controversial, hepatic resection has been advocated to achieve symptomatic benefit and to improve long-term survival. Resection of NELM has been associated with favorable long-term outcomes, with a reported median overall survival of 81 to 125 months and 5-year overall survival of 60% to 75%. However, even after complete resection of all NELM disease in the liver, recurrence is common. In fact, median and 5-year progression-free survival rates are reported to be only 15 to 25 months and 0% to 15%, respectively. The almost universal recurrence that is seen after resection of NELM is probably from the high incidence of occult disease within the liver at the time of surgery. Furthermore, until recently, effective systemic agents have not been available to treat NELM. More recently, prospective data have shown a benefit of certain targeted agents, including octreotide, everolimus, and sunitinib, in the treatment of advanced metastatic neuroendocrine tumors.

Many patients with NELM initially present with extensive liver metastases, and complete surgical resection is often not possible. Among patients with significant paraneoplastic symptoms, debulking of the liver disease can be considered a way to help to alleviate the hormonal symptoms. Because in this group of patients the main goal is palliation, surgical debulking should only be considered for patients with significant symptoms. Data from the authors’ own group noted that surgery held marginal benefit for patients who underwent an R2 debulking for asymptomatic disease, calling into question the usefulness of hepatic resection in this setting.

Although most of the oncologic community agrees that resection of noncolorectal, nonneuroendocrine liver metastases is not warranted in most patients, a small subset of patients may benefit from this therapy. The primary tumor site is an important prognostic factor, with resection of breast cancer liver metastases conferring a better prognosis compared with the very poor prognosis of patients undergoing hepatic resection of metastases derived from melanoma or squamous cell cancer. The primary histology of the specific hepatic metastases must therefore be weighed heavily before considering liver resection of noncolorectal, nonneuroendocrine liver metastases. Other factors that must be considered include disease burden (size of liver lesions, number of lesions), the disease-free interval between the primary tumor diagnosis and the liver metastases, and the presence of extrahepatic disease. This is a very heterogeneous group of patients; although most patients will not benefit from surgical resection, a select few who are treated in a multidisciplinary manner may yield a benefit.

### Ablative Techniques

#### Radiofrequency Ablation

Radiofrequency ablation (RFA) is an option for patients with secondary liver malignancies who cannot undergo resection because of comorbidities, location of metastatic lesions, or an inadequate liver remnant volume. It may be performed during open surgery, laparoscopically, or percutaneously, either alone or with concomitant hepatic resection or other procedures. Ultrasound or another imaging modality is used to guide placement of the electrodes into the metastatic site. Energy is delivered with high-frequency alternating radiofrequency current. The energy increases the temperature in the target lesion and the surrounding tissue, promoting protein denaturation, tissue coagulation, and desiccation as the tumor dissolves.

Data on the efficacy of RFA for CRLM is fairly heterogeneous (Table 1). Although some studies have reported local recurrence rates around 10%, others have noted local recurrence rates as high as 40% to 50%. Although many retrospective cohorts have shown RFA to be inferior to resection in terms of recurrence and overall survival, these data are difficult to interpret because the treated groups are very different with regard to underlying tumor biology. Local recurrence after RFA does appear, however, to be higher than after resection. Recurrence after RFA is highly dependent on tumor size, and lesions larger than 6 cm are usually not considered suitable for RFA. Moreover, recurrence may be influ-
enced by both physician factors (laparoscopic vs. open approach; experience) and tumor factors (tumor size, nonsubcapsular location, distance from larger hepatic vasculature).

In general, RFA should not replace resection as the preferred approach to treating patients with completely resectable disease. RFA remains, however, an option for patients with poor performance status, a modality to combine with resection, and a means to treat unresectable liver metastases.

Ablation has also been an important tool in the armamentarium to treat NELM. Although data on the use of RFA for NELM are more scarce than those available for CRLM, RFA for NELM has been shown to be useful for NELM with acceptable morbidity, especially in patients who are not operative candidates (ie, unresectable or significant comorbidities) and whose symptoms are refractory to medical management.

Survival after RFA of NELM has been associated with tumor number, tumor size, presence of symptomatic disease, and extrahepatic disease.

Microwave Ablation
Microwave ablation (MWA) represents the newest generation of thermal ablation techniques. Compared with RFA, MWA may allow for the easier creation of larger ablation zones and less heat-sink effect. Although data on WMA are still limited compared with those on RFA, several studies have reported that MWA is feasible and safe both when used alone and when combined with partial hepatectomy. Additionally, various reports have noted that MWA is as efficacious as—or perhaps in some instances, better than—RFA in treating hepatic lesions. MWA has been reported to be associated with a procedure-related mortality rate ranging from 0.2% to 5.1%, with a major morbidity occurring in 2.6% to 10.2% of patients.

In patients with extensive disease, larger lesions can sometimes be resected, whereas smaller lesions can be targeted with ablation. Ablation can also be considered salvage therapy after surgical resection for local recurrences or in patients with an isolated intrahepatic recurrence who are not candidates for repeat hepatectomy. Although the survival of patients undergoing ablative therapies alone compared with those undergoing resection is difficult to interpret because of significant differences between the groups in terms of comorbidities and cancer-specific factors, resection should remain the gold standard for resectable disease given its low morbidity and well-established association with long-term survival.

Regional Arterial Therapy and Radiotherapy
TACE/Intra-Arterial Therapy
TACE involves the selective catheterization of the hepatic artery followed by the introduction of a chemotherapeutic agent often in conjunction with a drug carrier (eg, embolic agent, lipiodol, drug-eluting beads). The proposed therapeutic efficacy of this treatment results from the combined occlusion of the arterial network, resulting in ischemia and necrosis of the tumor, together with localization of the chemotherapeutic agent to induce an antineoplastic effect. Traditionally, TACE has been used for hepatocellular carcinoma and has not been used in treating patients with CRLM. More recently, intra-arterial therapy...
for CRLM has gained renewed interest with the use of irinotecan drug-eluting beads (DEBIRIs). Several studies have reported that treatment of CRLM with DEBIRIs resulted in control of disease in most patients, with some even becoming operable after treatment (3%–20%). In a phase III randomized study to investigate DEBIRIs, 74 patients for whom at least 2 lines of chemotherapy failed were randomized to either 2 courses of DEBIRI or 8 courses of systemic FOLFIRI (irinotecan, 5-FU, and leucovorin) at 2-week intervals; the DEBIRI group had significantly longer overall and progression-free survivals, and a higher quality of life.

The role of intra-arterial therapy for NELM is more defined. Several studies have shown that intra-arterial therapy can help treat extensive intrahepatic disease and lead to cytodestruction of the disease and, in turn, hormone-related symptoms. In one multi-institutional analysis, when compared with intra-arterial therapy, surgery was not found to provide a benefit to patients with asymptomatic disease who had extensive liver disease (Figure 1). Therefore, for patients with extensive bilateral NELM, intra-arterial therapy seems to be preferred over resection as a means to control the disease, especially among patients who are asymptomatic and in whom surgical debulking would not even provide a palliative benefit. Despite the use of intra-arterial therapy for patients with advanced NELM, disease progression remains a problem, with some patients developing extrahepatic progression. As noted, recent data suggested a role for new systemic targeted agents, such as octreotide, everolimus, and sunitinib, in the treatment of these patients. Intra-arterial therapy should therefore be considered when treating patients with advanced NELM, either alone or as part of a treatment algorithm that includes targeted systemic agents.

**Hepatic Artery Infusions**

Hepatic artery infusions (HAIs) permit delivery of high concentrations of chemotherapy directly to the tumor via a catheter and implantable pump. Floxuridine (FUDR), which is converted to 5-FU in the liver, is the preferred agent because of its short half-life, 95% first-pass extraction rate, up to 400-fold estimated increase in tumor exposure, and low rate of systemic toxicity. The rationale for using HAI chemotherapy to treat patients with liver-only disease is based on the theory that regional chemotherapy can treat tumor cells with high doses of chemotherapy and minimal systemic toxicity. HAI has been compared with systemic chemotherapy in a meta-analysis of 10 randomized trials involving 1277 patients with unresectable CRLM. Although the findings of the meta-analysis were limited by heterogeneity of the different studies included, the authors concluded that HAI was associated with a higher intrahepatic response rate but no significant survival advantage compared with systemic chemotherapy alone.

Recent studies in patients with resectable CRLM have shown that adjuvant HAI and systemic chemotherapy can improve hepatic disease-free survival, but whether HAI confers an improvement in overall survival is considerably less clear. Largely because of the lack of definitive evidence showing an improvement in overall survival, and some logistical issues in managing the HAI pump once placed, HAI therapy for CRLM has not been widely embraced by the oncologic community. For patients with isolated unresectable but potentially “convertible” CRLM, HAI and systemic therapy seems to be associated with a higher response than chemotherapy alone, and this
approach may need to be reconsidered in this group of patients.

Studies documenting the use of HAI for patients with NELM are limited to small case series and reports. Currently, HAI has not been shown to have a benefit, and the use of HAI for NELM has largely been superseded by intra-arterial chemotherapy or Y-90 therapy.

**Selective Internal Radiation Therapy**

Selective internal radiation therapy (SIRT), or radioembolization, delivers Y-90 microspheres via a catheter in the hepatic artery to treat intra-hepatic disease (Table 2). SIRT takes advantage of the fact that the blood supply for much of the normal liver parenchyma arrives through the portal circulation, whereas tumors are preferentially fed by the arterial system. Glass- or resin-based microspheres tagged with Y-90 are delivered typically in a lobar fashion and preferentially distribute into the tumoral and peritumoral vasculature, thereby delivering a high radiation dose (>100 Gy). Because Y-90 is a beta emitter, the effect is relatively selective and mostly affects the metastatic sites while sparing normal liver parenchyma. The 2 currently available Y-90 products include SIR-spheres and TheraSphere. SIR-spheres deliver a higher dose per treatment and are more embolic. In contrast, the TheraSphere product delivers a higher specific radioactivity dose per microsphere, allowing for a smaller dose per treatment, and is not as embolic. Both products have been shown to be well-tolerated.

The role of SIRT in treating CRLM remains not well defined. Nonrandomized trials of SIRT, both given in combination with chemotherapy and alone, have shown significant activity and response rates when given in first-line treatment of CRLM and in the treatment of chemotherapy-refractory disease. However, as a recent systematic review noted, there is no evidence showing that the addition of SIRT to systemic or regional chemotherapy improves progression-free or overall survival. Only one trial has been published to date comparing SIRT plus systemic chemotherapy versus systemic chemotherapy alone in patients with CRLM. In this study, a significant difference was seen in progression-free and overall survivals, but some methodologic limitations and the heterogeneity of the treatment techniques make interpretation of this study difficult.

In the future, larger, prospective clinical trials will help better define the benefit of SIRT. Specifically, the EPOCH trial is a randomized phase III trial of second-line Y-90 with or without FOLFOX (oxaliplatin, 5-FU, and leucovorin) or FOLFIRI in patients with liver metastases from colorectal cancer.

In a separate initiative, the SIRFLOX study is an international study designed to evaluate whether FOLFOX chemotherapy in combination with SIRT is more effective than chemotherapy alone. The SIRFLOX study is unique in that it is the first time that combination SIRT and chemotherapy will be assessed as first-line therapy for unresectable CRLM as part of a randomized controlled trial.

Limited evidence exists on the use of SIRT in NELM. To date, studies using SIRT Y-90 therapy have shown promising results. Several studies have shown a complete or partial response ranging from 50% to 63.2%, with a median survival ranging from 28 to 70 months. Y-90 treatment seems to be a safe and potentially effective option for patients with otherwise diffuse intrahepatic disease, especially those with symptoms that are treatment-refractory.

### Table 2 Summarized Results of Yttrium 90 Treatment in Patients With Liver Metastases

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Tumor Design</th>
<th>Response (SD)</th>
<th>TTP (mo)</th>
<th>Median Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhee et al</td>
<td>42</td>
<td>NET RCT</td>
<td>51.7 (41.4%)</td>
<td>NA</td>
<td>25</td>
</tr>
<tr>
<td>Kennedy et al</td>
<td>148</td>
<td>NET RS</td>
<td>63.5 (22.7%)</td>
<td>NA</td>
<td>70</td>
</tr>
<tr>
<td>Kalinowski et al</td>
<td>9</td>
<td>NET PS</td>
<td>67 (33%)</td>
<td>11.1</td>
<td>&gt;36</td>
</tr>
<tr>
<td>Hendlisz et al</td>
<td>44</td>
<td>CRLM RCT</td>
<td>10 (76%)</td>
<td>2.1 vs. 4.5</td>
<td>7.3 vs. 10</td>
</tr>
<tr>
<td>Nace et al</td>
<td>51</td>
<td>CRLM RS</td>
<td>12.9 (64.5%)</td>
<td>NA</td>
<td>10.2</td>
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<tr>
<td>Martin et al</td>
<td>24</td>
<td>CRLM RS</td>
<td>NA</td>
<td>3.9</td>
<td>8.9</td>
</tr>
<tr>
<td>Kucuk et al</td>
<td>78</td>
<td>Mixed RS</td>
<td>55</td>
<td>NA</td>
<td>25.6</td>
</tr>
</tbody>
</table>

Abbreviations: CRLM, colorectal liver metastases; NA, not applicable; NET, neuroendocrine tumor; PS, prospective study; RCT, randomized controlled trial; RS, retrospective study; SD, stable disease; TTP, time to progression.
Local Therapies for Hepatic Metastases

Long-term control of unresectable NELMs with Y-90 microspheres may therefore be possible; however, the potential benefit of Y-90 therapy on long-term survival must be considered in light of the presence and extent of extrahepatic disease. Current data remain inconclusive regarding the exact role of Y-90 because of limited sample size. Therefore, although Y-90 seems promising, with a high reported radiologic response and symptom control, further investigations are needed.

SBRT

SBRT involves the use of highly ablative radiation doses that are delivered directly and accurately to the metastases in a limited number of fractions, with sharp dose gradients surrounding the target, minimizing radiation to uninvolved normal liver. One benefit of SBRT is its noninvasive nature. Although radiation therapy of the liver was traditionally believed to be associated with a high risk of radiation-induced liver disease, newer technology has minimized the dose to the normal liver and other normal organs while maximizing tumor control. SBRT has been assessed in a few series of patients with CRLM. Factors associated with better local control included the dose per fraction and the total radiation dose. Overall survival after SBRT is associated with, unsurprisingly, the presence of extrahepatic disease and the histology of the primary tumor. Importantly, most studies of SBRT for liver metastases are limited by small case numbers, methodologic limitations, heterogeneity of tumor types, and the radiation doses delivered. Although SBRT may be considered in the treatment algorithm of patients with liver metastases, it should be performed in a multidisciplinary setting after other treatment options have been explored.

Conclusions

A multidisciplinary approach is important for coordinating care of patients with liver metastases. For patients with resectable CRLM or NELM, complete surgical resection is the cornerstone of management. The role of resection for patients with noncolorectal, nonneuroendocrine liver metastases is more controversial and warrants a comprehensive multidisciplinary plan. Other locoregional treatment options, such as ablation, intra-arterial therapy, and radiotherapy, are increasingly being used to treat patients with liver metastases. The application of any one of these therapies demands an individualized approach that is tailored to the clinical situation, location and burden of disease, and the local expertise of the treating team.

References


