Locoregional Management Pathways for Liver Cancer

A practical approach to treating tumors in the liver caused by primary liver cancer, colorectal cancer, and neuroendocrine tumors.

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A range of options are now available to treat both primary and secondary hepatic malignancies, and many treatments are performed by the interventional radiologist, often in conjunction with surgical or medical therapy. Significant debate exists as to the best treatment option for each malignancy, and consideration must be given to the initial presentation, hepatic reserve, and optimization of sequencing to maximize therapeutic efficacy. This article shares our approach to treating liver tumors that arise from primary liver cancer, colorectal cancer, and neuroendocrine tumors (NETs).

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) constitutes approximately 85% to 90% of all liver cancers. The Barcelona Clinic Liver Cancer (BCLC) staging system continues to be the most widely used staging and treatment algorithm. Locoregional options in this staging system include ablation and transarterial chemoembolization (TACE). However, the BCLC staging system is often thought to be overly conservative with treatment, particularly in patients with advanced-stage disease in which only sorafenib or best supportive care are recommended.

Recent evidence suggests a wider range of treatment options both in early and advanced disease, as seen in the recently released Hong Kong staging system.[1] Although the Hong Kong staging system suggests that surgical resection should play a larger role in treatment, it may not be feasible in the Western population, which has higher rates of cirrhosis and portal hypertension. However, locoregional treatments such as ablation and embolization could similarly play a larger role in the Western population. Hence, these therapies should be stratified based on tumor burden and distribution.

Before initiating locoregional therapy, several options should be considered, including the goals of therapy for an individual patient and the possibilities of surgical or medical management. In general, inclusion criteria for interventional options include adequate underlying liver function (Child-Pugh class A or B). Patients should be sufficiently ambulatory in the daytime (Eastern Cooperative Oncology Group [ECOG] score, 0–2). Tumor burden can then be stratified into four categories:

1. Localized (single tumor or tumors confined to one segment): ablation, segmental yttrium-90 (Y-90) radioembolization, segmental chemoembolization
2. Multifocal unilobar: radioembolization, chemoembolization
3. Multifocal bilobar: chemoembolization, radioembolization
4. Vascular invasion: radioembolization

For HCC confined to a single segment, the gold-standard treatment is surgical resection or a liver transplant for patients with tumors within Milan criteria. If the patient is not a surgical candidate, which may be due to a constellation of reasons including portal hypertension, liver dysfunction, small future remnant liver volume, comorbidities, or patient preference, then percutaneous ablation is a viable option for tumors < 3 cm. However, many tumors are not technically amenable to ablation, most often due to proximity to critical structures, which are sensitive to thermal damage. In these cases, selective chemoembolization or Y-90 radioembolization should be considered. When done selectively (ie, catheterization of feeding vessels instead of lobar treatment), toxicity is minimized and tumor response rates have been promising.[2,3] Several studies have shown higher complete response rates with segmental radioembolization, with local tumor progression rates equivalent to surgical resection and ablation.

For multifocal disease, TACE is the current recommended treatment; however, growing evidence supports the use of radioembolization as well. Multiple trials of both chemoembolization and radioembolization have demonstrated survival times in excess of 12 months. Preserved quality of life is seen in patients undergoing these therapies, even those who show mildly diminished performance status (ECOG score, 1–2).[4] Radioembolization has the advantage of a longer time to progression compared to chemoembolization; however, no study has demonstrated a significant difference in overall survival rates. Some patients with unilobar multifocal disease may be candidates for surgical resection if their future liver remnant volume is adequate. In this scenario, lobar radioembolization can potentially result in hypertrophy of the contralateral lobe while allowing for a longer time to progression and facilitating eventual surgical resection.[5]

Portal vein tumor thrombus is a manifestation of advanced HCC and portends a poor prognosis. These patients are not considered transplant candidates, and surgical resection is generally not recommended. The results of ablation for localized HCC with vascular invasion are limited, and no large series have shown significant benefit. Similarly, chemoembolization can likely be safely performed in the setting of segment portal vein thrombus, but its efficacy in this setting is unproven. The only Western series of chemoembolization for patients with portal vein tumor thrombus showed a disappointing overall survival rate of < 6 months.[6] In contrast, radioembolization has shown promising efficacy results in this setting. Due to its nonembolic nature, the lack of hepatic ischemia from radioembolization results in tolerable rates of toxicity. In the advanced-stage setting, recent trials comparing radioembolization to sorafenib did not show a survival advantage for locoregional therapy. However, the tolerability of radioembolization compared to sorafenib was significantly better.[7] Due to the particles' distal penetration into the tumor thrombus itself, it is likely that improved response rates can be achieved with segmental or multisegmental infusions and a higher delivered dose.

HEPATIC METASTASES FROM COLORECTAL CANCER

Up to 50% of all patients with initial colorectal cancer diagnoses will already have liver metastases. Surgical resection remains the gold standard of therapy for solitary tumors; however, the majority of patients are not eligible for surgery. Current guidelines from the National Comprehensive Cancer Network (NCCN) recommend systemic chemotherapy with or without biologic agents for nonresectable colorectal liver metastases (metastatic colorectal cancer [mCRC]). Typically, these consist of first-line therapy with either 5-fluorouracil (5-FU) and oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) with or without bevacizumab, with second-line therapy consisting of the other combination (ie, oxaliplatin changed to irinotecan). However, systemic chemotherapy can occasionally be associated with significant toxicities and is not always tolerated by patients, with up to one-third of patients dropping out of treatment due to side effects. As a result, locoregional therapies have gained interest in multiple scenarios.

Percutaneous thermal ablation is a viable option with similar overall survival rates as surgery and decreased complication rates for a defined number of lesions that are technically amenable to ablation. When used as part of an aggressive regimen that may include surgical resection, ablation has resulted in superior long-term overall survival compared to systemic chemotherapy (8-year survival, 36% vs 9%).[8]

Arterial embolization is either performed with irinotecan drug-eluting bead chemoembolization or Y-90 radioembolization. Guidelines suggest using smaller particles for chemoembolization, typically delivered in a sequential lobar fashion.[9] In treatment-naive patients, irinotecan chemoembolization has resulted in improved objective response rates and liver progression-free survival when added to systemic chemotherapy, but an improvement in overall progression-free survival was not seen.[10] In the salvage setting, the only study comparing chemoembolization alone versus chemotherapy alone demonstrated improved overall survival with chemoembolization.[11] Irinotecan drug-eluting bead chemoembolization can be associated with significant short-term toxicity, specifically intense abdominal pain during and immediately after administration, thus an aggressive pre- and postprocedural pain management regimen is encouraged. Due to the poor short-term tolerability of chemoembolization, Y-90 radioembolization has largely been favored for treating mCRC. Although there are concerns of liver toxicity and gastrointestinal ulceration with radioembolization, it is well tolerated overall with minimal morbidity when performed by experienced operators and with appropriate patient selection.

The use of radioembolization in the first-line setting has recently been studied. In three prospective

TABLE 1. CONSIDERATIONS FOR RADIOEMBOLIZATION VERSUS BLAND EMBOLIZATION TO TREAT NEUROENDOCRINE TUMORS	
Factors Favoring Radioembolization	**Factors Favoring Bland Embolization**
• Selective or segmental treatment • High tumor burden of the treated area • First-time treatment • Portal vein thrombus • Sphincter of Oddi dysfunction • Operator experience	• Lobar treatment with a low tumor burden • Previous lobar liver-directed therapy • Underlying liver dysfunction or signs of fibrosis • Arterial anatomy or lung shunt fraction not safely amenable to radioembolization

randomized trials including a total of 1,103 patients, radioembolization was added to first-line systemic chemotherapy in the treatment arm and compared with first-line chemotherapy alone in the control arm.[12] Although patients in the radioembolization arm showed improved rates of objective tumor response and liver-specific progression, it did not result in an improvement in overall survival. Furthermore, significant toxicities were higher in the radioembolization group (74% vs 66%; *P* = .009). Therefore, radioembolization should not be considered as standard-of-care therapy for newly diagnosed hepatic metastases, except in unusual circumstances. For the purposes of downstaging to surgical resection, radioembolization may be useful in achieving objective tumor response and causing contralateral lobar hypertrophy, thereby facilitating safe and effective surgical resection.[13]

Use of radioembolization in the salvage setting for CRC metastases has been shown to prolong survival. Two retrospective, matched cohort studies demonstrated a 5-month survival advantage in the salvage setting compared to further salvage chemotherapy or best supportive care.[14,15]

In summary, ablation should be considered at any time point, assuming that it is technically feasible to treat all visible disease. Arterial embolization in the form of radioembolization or chemoembolization should not be offered in the first-line setting, except in atypical circumstances. It is currently unknown whether liver-directed therapy is beneficial in the second-line setting. However, it should be considered in the salvage setting, assuming that patients have preserved performance status, normal underlying liver function, and liver-dominant disease. In the salvage or chemorefractory setting, radioembolization has a category 2A recommendation by the NCCN, which is the same designation as systemic chemotherapy. In the setting of arterial anatomy that is not technically amenable to radioembolization or has excessively high lung shunting, chemoembolization would be a preferable salvage option instead of radioembolization.

NEUROENDOCRINE TUMOR METASTASES

NETs primarily metastasize to the liver, and if they are "functional," patients generally present clinically with hormone-induced symptoms such as flushing and diarrhea. Surgical resection remains the mainstay of curative treatment for lesions within one lobe or within two adjacent segments, with percutaneous ablation as a viable alternative if surgery is contraindicated. Most patients are not candidates for ablation or surgical resection, as patients with metastatic NETs usually present with multifocal disease. Because of this, ablation is more often useful as an intraoperative adjunct to treat satellite lesions that are outside the confines of a simple resection. For diffuse disease, systemic chemotherapy combined with a somatostatin analog or peptide receptor radionuclide therapy can be effective for high-grade tumors.[16] Transarterial therapy is a feasible option for low- and medium-grade hepatic tumors that are not symptomatically controlled by somatostatin. Although multiple criteria differentiate tumor aggressiveness, arterial embolization can safely and effectively be performed in any NET grade or origin. Bland embolization, chemoembolization, and Y-90 radioembolization have all shown excellent efficacy in controlling symptoms and achieving reasonable tumor response rates without significant differences in overall survival.[17] However, most studies have very heterogeneous populations, with inherent institutional selection biases with regard to patient selection.

The treatment choice then becomes highly operator and institution dependent. Despite personal preferences, multiple factors can be considered to determine the type of therapy (Table 1). Factors to consider include operator expertise, patient preferences, potential toxicities, previous treatment history, arterial anatomy, and tumor burden.

When comparing chemoembolization and bland embolization, a paucity of data show superior tumor control, improved toxicity, or prolonged survival with chemoembolization. Bland embolization has lower systemic toxicity and potentially better preservation of arterial vasculature for future treatments. Therefore, bland embolization is generally preferred over chemoembolization in most settings for the treatment of neuroendocrine metastases.

Although no proven survival benefit has been shown with radioembolization compared with bland embolization, radioembolization has numerous advantages, making it a preferable option in specific scenarios. It is associated with lower rates of systemic toxicity such as postembolization syndrome and carcinoid crisis. Because it is a minimally embolic therapy with a smaller particle size, arterial vasculature remains preserved, allowing for future treatments, if necessary, in addition to outpatient-based treatments. This is especially pertinent to the NET patient, who may require numerous treatments over several years. In the setting of previous biliary intervention contributing to sphincter of Oddi disruption, such as a Whipple procedure commonly performed for pancreatic head tumors, there is a higher risk of biloma and abscess formation after embolization. In these cases, radioembolization is a more suitable treatment choice due to its minimally embolic effect.[18] Radioembolization would also be preferred in the setting of portal vein thrombus, thereby preserving arterial flow to the normal liver parenchyma.

Several scenarios may shift consideration toward bland embolization as opposed to radioembolization, such as:

- If a high lung shunt fraction would result in excessive pulmonary dosing, radioembolization should be avoided.
- Hepatic arterial anatomy might not be suitable for radioembolization due to high risk of nontarget particle deposition.
- In patients with compromised liver function or early signs of hepatic fibrosis from previous radioembolization, bland embolization would be a safer alternative.
- In patients who have diffuse disease necessitating lobar treatment with a low overall tumor burden, radioembolization may result in excessive particle deposition in the normal underlying hepatic parenchyma. In these cases, bland embolization should be considered.

Regardless of therapy, the survival rate is very promising, with average survival in many cohorts exceeding 5 years. When treating a patient with metastatic NETs, one must keep average survival rates in mind and preserve both hepatic function for the long term and arterial vasculature to allow for repeat treatments.

CONCLUSION

Multiple treatment strategies are now available to the interventional radiologist for the treatment of both primary and secondary liver malignancy. The ideal choice of therapy continues to evolve as outcomes become refined. Knowledge of potential benefits and pitfalls of each treatment strategy should allow the operator to tailor the therapy for each patient. ■

1. Yau T, Tang VY, Yao TJ, et al. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology. 2014;146:1691-1700.e3.
2. Miyayama S, Matsui O. Superselective conventional transarterial chemoembolization for hepatocellular carcinoma: rationale, technique, and outcome. J Vasc Interv Radiol. 2016;27:1269-1278.
3. Padia SA, Johnson GE, Horton KJ, let al. Segmental yttrium-90 radioembolization versus segmental chemoembolization for localized hepatocellular carcinoma: results of a single-center, retrospective, propensity score-matched study. J Vasc Interv Radiol. 2017;28:777-785.e1.
4. Salem R, Gordon AC, Mouli S, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology. 2016;151:1155-1163.e2.
5. Lewandowski RJ, Donahue L, Chokechanachaisakul A, et al. (90) Y radiation lobectomy: Outcomes following surgical resection in patients with hepatic tumors and small future liver remnant volumes. J Surg Oncol. 2016;114:99-105.
6. Gorodetski B, Chapiro J, Schernthaner R, et al. Advanced-stage hepatocellular carcinoma with portal vein thrombosis: conventional versus drug-eluting beads transcatheter arterial chemoembolization. Eur Radiol. 2017;27:526-535.
7. Vilgrain V, Abdel-Rehim M, Sibert A, et al. Radioembolisation with yttrium-90 microspheres versus sorafenib for treatment of advanced hepatocellular carcinoma (SARAH): study protocol for a randomised controlled trial. Trials. 2014;15:474.
8. Ruers T, Van Coevorden F, Punt CJ, et al. Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. J Natl Cancer Inst. 2017;109.
9. Lencioni R, Aliberti C, de Baere T, et al. Transarterial treatment of colorectal cancer liver metastases with irinotecan-loaded drug-eluting beads: technical recommendations. J Vasc Interv Radiol. 2014;25:365-369.
10. Martin RC, Scoggins CR, Schreeder M, et al. Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis. Cancer. 2015;121:3649-3658.
11. Fiorentini G, Aliberti C, Tilli M, et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. Anticancer Res. 2012;32:1387-1395.
12. Virdee PS, Moschandreas J, Gebski V, et al. Protocol for combined analysis of FOXFIRE, SIRFLOX, and FOXFIRE-Global randomized phase III trials of chemotherapy +/- selective internal radiation therapy as first-line treatment for patients with metastatic colorectal cancer. JMIR Res Protoc. 2017;6:e43.
13. Garlipp B, de Baere T, Damm R, et al. Left-liver hypertrophy after therapeutic right-liver radioembolization is substantial but less than after portal vein embolization. Hepatology. 2014;59:1864-1873.
14. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc Intervent Radiol. 2012;35:1066-1073.
15. Bester L, Meteling B, Pocock N, et al. Radioembolization versus standard care of hepatic metastases: comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. J Vasc Interv Radiol. 2012;23:96-105.
16. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of (177)lu-dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376:125-135.
17. Chen JX, Rose S, White SB, et al. Embolotherapy for neuroendocrine tumor liver metastases: prognostic factors for hepatic progression-free survival and overall survival. Cardiovasc Intervent Radiol. 2017;40:69-80.
18. Cholapranee A, van Houten D, Deitrick G, et al. Risk of liver abscess formation in patients with prior biliary intervention following yttrium-90 radioembolization. Cardiovasc Intervent Radiol. 2015;38:397-400.

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