

**American College of Radiology
ACR Appropriateness Criteria®
Management of Liver Cancer**

Variant 1: Hepatocellular cancer: Solitary tumor less than 3 cm, cirrhotic.

| Procedure | Appropriateness Category |
|----------------------------------|--------------------------|
| Liver transplantation | Usually Appropriate |
| Percutaneous ablation liver | Usually Appropriate |
| Surgical liver resection | Usually Appropriate |
| Combination locoregional therapy | May Be Appropriate |
| External beam radiation therapy | May Be Appropriate |
| Transarterial chemoembolization | May Be Appropriate |
| Transarterial radioembolization | May Be Appropriate |
| Bland transarterial embolization | May Be Appropriate |
| Systemic therapies | Usually Not Appropriate |

Variant 2: Hepatocellular cancer: Solitary tumor 3 to 5 cm, cirrhotic.

| Procedure | Appropriateness Category |
|----------------------------------|--------------------------|
| Liver transplantation | Usually Appropriate |
| Combination locoregional therapy | Usually Appropriate |
| Surgical liver resection | Usually Appropriate |
| Transarterial chemoembolization | Usually Appropriate |
| Transarterial radioembolization | Usually Appropriate |
| Bland transarterial embolization | May Be Appropriate |
| External beam radiation therapy | May Be Appropriate |
| Percutaneous ablation liver | May Be Appropriate |
| Systemic therapies | Usually Not Appropriate |

Variant 3: **Hepatocellular cancer: Multifocal, bilobar disease, at least 1 tumor greater than 5 cm, cirrhotic.**

| Procedure | Appropriateness Category |
|----------------------------------|--------------------------|
| Transarterial chemoembolization | Usually Appropriate |
| Transarterial radioembolization | Usually Appropriate |
| Bland transarterial embolization | Usually Appropriate |
| Systemic therapies | Usually Appropriate |
| Combination locoregional therapy | May Be Appropriate |
| External beam radiation therapy | May Be Appropriate |
| Percutaneous ablation liver | Usually Not Appropriate |
| Surgical liver resection | Usually Not Appropriate |
| Liver transplantation | Usually Not Appropriate |

Variant 4: **Hepatocellular cancer: Solitary or multifocal disease with vascular invasion, cirrhotic.**

| Procedure | Appropriateness Category |
|----------------------------------|--------------------------|
| Systemic therapies | Usually Appropriate |
| Transarterial radioembolization | Usually Appropriate |
| Transarterial chemoembolization | May Be Appropriate |
| Bland transarterial embolization | May Be Appropriate |
| Combination locoregional therapy | May Be Appropriate |
| External beam radiation therapy | May Be Appropriate |
| Percutaneous ablation liver | Usually Not Appropriate |
| Surgical liver resection | Usually Not Appropriate |
| Liver transplantation | Usually Not Appropriate |

Variant 5: **Intrahepatic cholangiocarcinoma: Peripheral hepatic lobar cholangiocarcinoma, less than 3 cm; no biliary ductal dilatation, macroscopic vascular invasion, regional lymphadenopathy, or distant metastases.**

| Procedure | Appropriateness Category |
|----------------------------------|--------------------------|
| Surgical liver resection | Usually Appropriate |
| Percutaneous ablation liver | Usually Appropriate |
| Liver transplantation | May Be Appropriate |
| Systemic therapies | May Be Appropriate |
| Transarterial radioembolization | May Be Appropriate |
| External beam radiation therapy | May Be Appropriate |
| Transarterial chemoembolization | May Be Appropriate |
| Bland transarterial embolization | Usually Not Appropriate |

Variant 6:**Ductal cholangiocarcinoma: Hilar cholangiocarcinoma, greater than 3 cm with poorly defined margins, vascular invasion, and periportal lymphadenopathy.**

| Procedure | Appropriateness Category |
|----------------------------------|--------------------------|
| Systemic therapies | Usually Appropriate |
| Transarterial radioembolization | May Be Appropriate |
| External beam radiation therapy | May Be Appropriate |
| Bland transarterial embolization | Usually Not Appropriate |
| Transarterial chemoembolization | Usually Not Appropriate |
| Percutaneous ablation liver | Usually Not Appropriate |
| Surgical liver resection | Usually Not Appropriate |
| Liver transplantation | Usually Not Appropriate |

Variant 7:**Metastatic liver disease: Multifocal metastatic neuroendocrine tumor (includes carcinoid tumors as well as islet cell tumors of the pancreas).**

| Procedure | Appropriateness Category |
|---------------------------------------|--------------------------|
| Long-acting somatostatin analogs | Usually Appropriate |
| Bland transarterial embolization | Usually Appropriate |
| Peptide receptor radionuclide therapy | Usually Appropriate |
| Transarterial chemoembolization | Usually Appropriate |
| Transarterial radioembolization | Usually Appropriate |
| Systemic therapies | May Be Appropriate |
| External beam radiation therapy | May Be Appropriate |
| Percutaneous ablation liver | May Be Appropriate |
| Surgical liver resection | May Be Appropriate |
| Combination locoregional therapy | Usually Not Appropriate |
| Liver transplantation | Usually Not Appropriate |

Variant 8: Metastatic liver disease: Solitary colorectal liver metastasis.

| Procedure | Appropriateness Category |
|--|--------------------------|
| Systemic therapies | Usually Appropriate |
| Surgical liver resection | Usually Appropriate |
| Percutaneous ablation liver | Usually Appropriate |
| Combination locoregional therapy | May Be Appropriate |
| External beam radiation therapy | May Be Appropriate |
| Transarterial chemoembolization | May Be Appropriate |
| Transarterial radioembolization | May Be Appropriate |
| Bland transarterial embolization | Usually Not Appropriate |
| Hepatic arterial chemotherapy infusion | Usually Not Appropriate |
| Liver transplantation | Usually Not Appropriate |

Variant 9: Metastatic liver disease: Multifocal bilobar colorectal carcinoma (liver dominant or isolated).

| Procedure | Appropriateness Category |
|--|-----------------------------------|
| Systemic therapies | Usually Appropriate |
| Hepatic arterial chemotherapy infusion | May Be Appropriate |
| Transarterial chemoembolization | May Be Appropriate |
| Transarterial radioembolization | May Be Appropriate |
| Bland transarterial embolization | May Be Appropriate (Disagreement) |
| Combination locoregional therapy | May Be Appropriate |
| Percutaneous ablation liver | May Be Appropriate |
| Surgical liver resection | May Be Appropriate |
| External beam radiation therapy | Usually Not Appropriate |
| Liver transplantation | Usually Not Appropriate |

MANAGEMENT OF LIVER CANCER

Expert Panel on Interventional Radiology: Erica M. Knavel Koepsel, MD^a; Amanda R. Smolock, MD, PhD^b; Jason W. Pinchot, MD^c; Charles Y. Kim, MD^d; Osmanuddin Ahmed, MD^e; Murthy R.K. Chamarthy, MD^f; Elizabeth M. Hecht, MD^g; Gloria L. Hwang, MD^h; David E. Kaplan, MD, MScⁱ; Join Y. Luh, MD^j; Jorge A. Marrero, MD, MS^k; Eric J. Monroe, MD^l; George A. Poultsides, MD, MS^m; Matthew J. Scheidt, MDⁿ; Eric J. Hohenwalter, MD.^o

Summary of Literature Review

Introduction/Background

The treatment and management of hepatic malignancies can be complex because it encompasses a variety of primary and metastatic malignancies and an assortment of local and systemic treatment options. Knowing when to use each of these treatments is critical to ensure the most appropriate care for patients. Interventional radiologists have a key role to play in the delivery of a variety of liver-directed treatments including percutaneous ablation, transarterial embolization (TAE) with bland embolic particles alone, transarterial chemoembolization (TACE) with injection of a chemotherapeutic emulsion, and transarterial radioembolization (TARE). Based on 9 clinical variants, the appropriateness of each treatment is described in this document.

Discussion of Treatments by Variant

Variant 1: Hepatocellular cancer: Solitary tumor less than 3 cm, cirrhotic.

Systemic Therapies

There is no evidence to support the use of systemic agents in very early-stage hepatocellular carcinoma (HCC).

Surgical Liver Resection

For patients with early-stage disease, treatment should be completed with curative intent in the absence of extrahepatic metastatic disease or portal vein invasion [1,2]. Patients with early-stage localized cancer with good liver function should be considered for resection [3]. Surgical resection provides a treatment pathway with comparable long-term survival to transplantation in patients without significant underlying liver disease and low-volume disease [4-6]. Patients with Child-Turcotte-Pugh (CTP) Class A cirrhosis without evidence of portal hypertension are generally appropriate candidates for resection [7]. Patients with CTP Class B and CTP Class C cirrhosis are at higher risk for decompensation and have a less favorable 5-year survival rate, making them poor resection candidates. However, they could be considered for transplantation [7,8]. The tumor location and invasion of hepatic vasculature can also limit resectability.

Liver Transplantation

For patients with 1 tumor measuring ≤ 5 cm or 3 tumors measuring < 3 cm (ie, patients falling within the “Milan criteria”), treatment should be completed with curative intent in the absence of extrahepatic metastatic disease or portal vein invasion [2,9]. Transplant patients with limited tumor burden, as defined by the Milan criteria, have been found to have equivalent survival outcomes compared with patients who have received transplants for non-HCC indications [7]. Liver transplantation confers the best long-term survival for patients with HCC who meet the Milan criteria but can be hindered by donor organ availability [1,10-12]. For patients with more advanced liver disease, who are not surgical resection candidates, transplantation may be an excellent option to treat both their underlying liver disease and their HCC.

Percutaneous Ablation Liver

Ablative therapies include thermal (radiofrequency ablation [RFA], microwave ablation [MWA], and cryoablation) and nonthermal (percutaneous ethanol injection) modalities. Currently, thermal techniques are more commonly

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performed because of superior control and efficacy [13,14]. These techniques can be performed percutaneously or surgically (open or laparoscopic). Thermal ablative techniques are an effective treatment for tumors <3 cm in diameter with good local control rates, which have been demonstrated to be similar to resection [15-21]. RFA and MWA are the most commonly used thermal techniques. MWA may have potential advantages over RFA, based on the clinical situation, because it is less susceptible to heat-sink, creates larger ablation zones in a shorter period of time, and is less susceptible to the effects of tissue impedance [9].

External Beam Radiation Therapy

Stereotactic body radiotherapy (SBRT) is generally reserved for unresectable disease [22]. However, there is some evidence to suggest the use of SBRT as a first-line therapy for HCC tumors <6 cm in diameter [22-24]. Several studies have found 1-year local control rates between 75% and 100%, with acceptable toxicity rates with lesions up to 6 to 7 cm in diameter [24-26]. There are some studies showing improved local control and mixed results for overall survival for early-stage HCC treated with SBRT compared to RFA, although they are limited by sample size and varying methodologies [27-31]. SBRT has been used to downstage or bridge patients to transplant or resection [32-35]. Unfortunately, there are limited long-term prospective data regarding SBRT for HCC [22].

Bland Transarterial Embolization

Transarterial techniques are generally unnecessary with solitary tumors <3 cm and are reserved for unresectable disease [36].

Transarterial Chemoembolization

Transarterial techniques are generally unnecessary with solitary tumors <3 cm and are reserved for unresectable disease [36]. However, TACE has been used as an adjuvant procedure before ablation using the injected lipiodol as a target for tumors with ill-defined borders or those which are difficult to see with CT or ultrasound (US) [37,38].

Transarterial Radioembolization

TARE with Yttrium-90 is a transarterial therapy that is an option for patients with multifocal HCC. Yttrium-90 emits damaging beta particles, which locally causes radiation-induced cell death, without causing vascular occlusion [39,40]. TARE has gained support for its use as an alternative to focal therapy for patients with low-volume disease with results similar to other curative intent treatment strategies, such as ablation. TARE is administered at a higher dose to targeted liver segments (usually <2), maximizing the lethal effects and minimizing damage to unaffected parenchyma [41-44].

TARE has been used to downstage or bridge patients to transplant or resection [3,32,35,36,45-47]. Initial studies seemed to favor TARE for downstaging, but a recent study demonstrated similar posttreatment outcomes [32,45,48]. In general, TARE and other transarterial techniques are unnecessary with solitary tumors <3 cm and are reserved for unresectable disease, but additional applications have been developed.

Combination Locoregional Therapy

Combination locoregional therapies (ablation plus TACE or TAE) can be used to improve tumoricidal effects and increase the size of the ablation by reducing the heat-sink effect but are usually indicated for intermediate size lesions >3 to 4 cm, or those lesions with poorly defined margins [9,49-55]. Combination therapy can also be advantageous for poorly visible tumors on US or CT, and preablation TACE can aid in localizing and targeting the tumor for ablation [38].

Variant 2: Hepatocellular cancer: Solitary tumor 3 to 5 cm, cirrhotic.

Systemic Therapies

There is no evidence to support the use of systemic agents in early-stage HCC.

Surgical Liver Resection

For patients with 1 tumor measuring ≤ 5 cm, treatment should be completed with curative intent in the absence of extrahepatic metastatic disease or vascular invasion [1,2]. The patient's underlying liver disease, the location of the tumor, and the presence of vascular invasion may exclude them from these surgical approaches [56]. Patients with CTP Class A cirrhosis without evidence of portal hypertension are generally appropriate candidates for resection [7]. Patients with CTP Class B and CTP Class C cirrhosis are at higher risk for decompensation and less favorable 5-year survival, making them poor resection candidates, but they could be considered for transplantation [7,8].

Liver Transplantation

Solitary tumors between 3 and 5 cm still meet the Milan criteria for liver transplantation, and long-term survival in patients with solitary tumors has been shown to be 70% after 5 years [1,57]. Liver transplantation confers the best long-term survival for patients with HCC who meet the Milan criteria but can be hindered by donor organ availability [1,10-12]. For patients with more advanced liver disease who are not surgical resection candidates, transplantation may be an excellent option for treating both their underlying liver disease and their HCC.

Percutaneous Ablation Liver

Ablation therapies can still be used in this scenario but are commonly combined with TACE or TAE to improve tumoricidal effects and increase the size of the ablation for intermediate size lesions >3 cm in diameter [49-55]. MWA, which is less susceptible to heat-sink and tissue impedance, has shown effectiveness as a monotherapy for tumors >3 cm in diameter [58,59].

External Beam Radiation Therapy

Unfortunately, there is limited long-term prospective data regarding SBRT for HCC, and it is usually reserved for unresectable disease [22]. However, there is some evidence to suggest including SBRT as a first-line therapy for HCC <6 cm in diameter [22-24]. Several studies have found 1-year local control rates between 75% and 100% with acceptable toxicity rates with lesions up to 6 to 7 cm in diameter [24-26]. There are some studies showing improved local control and mixed results for overall survival for early-stage HCC treated with SBRT compared with RFA, although they are limited by sample size and varying methodologies [27-31]. SBRT has been used to downstage or bridge patients to transplant or resection [32-35].

Bland Transarterial Embolization

There is variable evidence in the literature regarding the superiority of TACE, drug-eluting beads (DEB)-TACE, or bland TAE, with limited evidence that TAE is similar in effectiveness to TACE or DEB-TACE [60-63]. However, DEB-TACE may have less systemic toxicity compared with TACE [64-67].

Transarterial Chemoembolization

For patients with acceptable liver function and unresectable disease, TACE has shown a survival advantage compared with supportive care in several small randomized controlled studies [68,69]. However, there have been additional conflicting studies that have failed to demonstrate a survival advantage compared with conservative management [70-72]. These studies are also small in size and use variable TACE techniques and chemotherapeutics. There is variable evidence in the literature regarding the superiority of TACE, DEB-TACE, or TAE, with limited evidence that TAE is similar in effectiveness to TACE/DEB-TACE [60-63]. However, DEB-TACE may have less systemic toxicity [64-66,73]. TACE has also been used to control tumor progression for those awaiting transplant or as adjuvant treatment before resection [74-80].

Transarterial Radioembolization

TARE has gained support for its use as an alternative to focal therapy for patients with low-volume disease, with results similar to other curative intent treatment strategies, such as ablation. TARE is administered at a higher dose to targeted liver segments (usually <2), maximizing the lethal effects and minimizing damage to unaffected parenchyma [41-44].

TARE has been used to downstage or bridge patients to transplant or resection [3,32,45-47,81]. Initial studies comparing TACE versus TARE for downstaging seemed to favor TARE, but a recent larger study demonstrated similar posttreatment outcomes [32,45,48]. TARE as a bridging therapy may be especially important if the time on a wait list is >6 months [82].

Combination Locoregional Therapy

Combination locoregional therapies (ablation plus TACE or TAE) can be used to improve tumoricidal effects and increase the size of the ablation by reducing the heat-sink effect but are usually indicated for intermediate size lesions >3 to 4 cm or those lesions with poorly defined margins [9,49-55]. Several studies have shown improved overall survival with combination therapy of MWA and TACE for the treatment of HCC (>5 cm in diameter) compared with patients who underwent TACE alone or MWA alone [83,84].

Variant 3: Hepatocellular cancer: Multifocal, bilobar disease, at least 1 tumor greater than 5 cm, cirrhotic.

Systemic Therapies

Systemic therapies can be an option for patients with more advanced multifocal disease. Treatment with sorafenib, a tyrosine kinase inhibitor (TKI), has shown a statistically significant increase in median overall survival compared

with placebo (2-3 months over placebo) [85,86]. However, recently, atezolizumab and bevacizumab given to patients with Child-Pugh A and Eastern Cooperative Oncology Group (ECOG) 0 or 1 in combination resulted in better overall and progression-free survival than sorafenib alone (overall survival at 12 months, 67.2% in combination group compared with 54.6% in sorafenib alone group) [87].

Regorafenib is an additional TKI, which has been approved for patients previously treated with sorafenib. It has shown improved overall survival compared with placebo (10.6 versus 7.8 months) [88]. Lenvatinib is a vascular endothelial growth factor inhibitor, approved for first-line treatment of unresectable HCC. The REFLECT trial demonstrated noninferiority to sorafenib with improved overall survival (13.6 months versus 12.3 months). Nivolumab and pembrolizumab, PD-1 immune checkpoint inhibitors, and cabozantinib, an inhibitor of multiple tyrosine kinases, are additional developing treatments for HCC with promising findings on overall survival and disease progression [89-91].

Surgical Liver Resection

Curative therapy with surgical resection is not a first-line therapy for multifocal HCC. Adjuvant ablation, SBRT, TAE, TACE, or Yttrium-90 could potentially be used to downstage to resection [3,32,33,35,36,45-47,54,75,81,92-97].

Liver Transplantation

Liver transplantation for multifocal HCC outside of the Milan criteria is not a first-line treatment strategy. Adjuvant ablation, SBRT, TAE, TACE, or Yttrium-90 could potentially be used to downstage to transplant [3,32,33,35,36,45-47,54,75,81,92-97].

Percutaneous Ablation Liver

In the setting of multifocal HCC, ablation may serve an adjunctive role to other locoregional and systemic treatments. In this setting, it would not be considered for curative intent or as initial therapy.

External Beam Radiation Therapy

SBRT can be used for inoperable HCC. Several studies have found 1-year local control rates between 75% and 100%, with acceptable toxicity rates with lesions up to 6 to 7 cm in diameter [22,24-26]. SBRT has been used to downstage or bridge patients to transplant or resection [32-35]. Unfortunately, there are limited long-term prospective data regarding SBRT for HCC [22]. Feasibility of SBRT will depend on number of lesions and lesion location, but unfortunately, there is a lack of literature to define a strict cutoff for treatment candidates [98]. SBRT may also play a role in palliation of symptomatic lesions and can also be used as salvage therapy post-TAE or TACE [99].

Bland Transarterial Embolization

There is variable evidence in the literature regarding the superiority of TACE, DEB-TACE, or TAE, with limited evidence that TAE is similar in effectiveness to TACE or DEB-TACE [60-63]. However, DEB-TACE may have less systemic toxicity compared with TACE [64-67]. Severe underlying liver dysfunction and tumor burden limits the use of these techniques. TACE or TAE could also be used for selective embolization of multiple lesions if technically feasible [100,101].

Transarterial Chemoembolization

For patients with acceptable liver function and unresectable disease, TACE has shown a survival advantage compared with supportive care in several small randomized controlled studies [68,69]. However, there have been additional conflicting studies that have failed to demonstrate a survival advantage compared with conservative management [70-72]. These studies are also small in size and use variable TACE techniques and chemotherapeutics. There is variable evidence in the literature regarding the superiority of TACE, DEB-TACE, or TAE, with limited evidence that TAE is similar in effectiveness to TACE or DEB-TACE [60-63]. However, DEB-TACE may have less systemic toxicity [64-67]. Severe underlying liver dysfunction and tumor burden limits the use of these techniques. TACE could also be used for selective embolization of multiple lesions if technically feasible [100,101].

Transarterial Radioembolization

This treatment can be used to treat an entire hepatic lobe if there is extensive multifocal disease but can also be administered to a segment at high dose to minimize normal parenchyma injury and maximize radiation deposition within the lesion [41-44,47]. Studies comparing TARE and TACE have shown similar survival rates and complication rates with potentially less postprocedural pain and toxicity with TARE [102-108]. TARE traditionally requires a planning angiogram, calculation of hepatopulmonary shunting, and dose calculation before treatment,

which has required 2 separate visits to complete, but some high-volume centers have demonstrated the feasibility of same-day and single-session treatments [109,110]. TARE has been used to downstage or bridge patients to transplant or resection [3,32,35,36,45-47].

Combination Locoregional Therapy

Combination locoregional therapies could be used with palliative intent or to downstage patients in this setting. Several studies have shown improved overall survival with combination therapy of MWA and TACE for the treatment of HCC (>5 cm in diameter) compared with patients who underwent TACE alone or MWA alone [83,84].

Variant 4: Hepatocellular cancer: Solitary or multifocal disease with vascular invasion, cirrhotic.

Systemic Therapies

Systemic therapies can be an option for patients with advanced-stage disease. Treatment with sorafenib, a TKI, showed a statistically significant increase in median overall survival compared with placebo (2-3 months over placebo) [85,86]. However, recently, atezolizumab and bevacizumab given to patients with Child-Pugh A and ECOG 0 or 1 in combination resulted in better overall and progression-free survival than sorafenib alone (overall survival at 12 months, 67.2% in combination group compared with 54.6% in sorafenib alone group) [87]. Regorafenib is an additional TKI, which has been approved for patients previously treated with sorafenib. It has shown improved overall survival compared with placebo (10.6 versus 7.8 months) [88]. Lenvatinib is a vascular endothelial growth factor inhibitor approved for first-line treatment of unresectable HCC. The REFLECT trial demonstrated noninferiority to sorafenib with improved overall survival (13.6 months versus 12.3 months). Nivolumab and pembrolizumab, PD-1 immune checkpoint inhibitors, and cabozantinib, an inhibitor of multiple tyrosine kinases, are additional developing treatments for HCC with promising findings on overall survival and disease progression [89-91].

Surgical Liver Resection

Patients with solitary or multifocal disease with vascular invasion would not be candidates for resection. However, a retrospective study showing improved overall survival with hepatic resection compared with TACE for patients with intermediate- and advanced-stage disease has suggested expanding the surgical criteria, as long as the patient's preoperative liver function and postoperative liver remnant are appropriate for surgery [111].

Liver Transplantation

Patients with solitary or multifocal disease with vascular invasion would not be candidates for transplantation. Patients with macrovascular invasion are at increased risk for HCC recurrence and decreased survival [112,113].

Percutaneous Ablation Liver

Patients with solitary or multifocal disease with vascular invasion would not be candidates for ablation.

External Beam Radiation Therapy

SBRT can be used as palliative therapy for inoperable HCC. Several studies have found 1-year local control rates between 75% and 100%, with acceptable toxicity rates with lesions up to 6 to 7 cm in diameter [24-26]. Feasibility of SBRT will depend on the number of lesions and lesion location; unfortunately, there is a lack of literature to define a strict cutoff for treatment candidates [98]. SBRT may also play a role in palliation of symptomatic lesions and can also be used as salvage therapy post-TAE or TACE [99].

Bland Transarterial Embolization

Generally, TAE or TACE is not ideal in cases of macroscopic portal vein invasion given that occlusive embolization of the hepatic artery could increase the risk of liver failure [114]. However, there have been some recent studies showing a survival benefit of TACE over conservative therapy when portal vein thrombus is present; however, this benefit, although still statistically significant, was less pronounced in patients with advanced vascular invasion [115,116].

Transarterial Chemoembolization

Generally, TAE or TACE is not ideal in cases of macroscopic portal vein invasion given that occlusive embolization of the hepatic artery could increase the risk of liver failure [114]. However, there have been some recent studies showing a survival benefit of TACE over conservative therapy when portal vein thrombus is present; however, this benefit, although still statistically significant, was less pronounced in patients with advanced vascular invasion [115,116].

Transarterial Radioembolization

TARE has been used for patients with advanced disease, even safely with portal vein thrombosis, to prolong survival. Underlying liver function, performance status, and/or hepatopulmonary shunting can limit the use of this technique [81]. Patients with multifocal disease usually require staged lobar treatment, which can increase the risk for radiation-induced liver disease. Studies comparing TARE and TACE have shown similar survival rates and complication rates with potentially less postprocedural pain and toxicity with TARE [46,102-106,108]. TARE traditionally requires a planning angiogram, calculation of hepatopulmonary shunting, and dose calculation before treatment, which has required 2 separate visits to complete, but some high-volume centers have demonstrated feasibility of same-day and single-session treatments [109,110].

Combination Locoregional Therapy

Limited evidence is available regarding combination therapy for patients with vascular invasion. One study using a combination of SBRT and TACE showed an improved survival benefit over systemic therapy alone for macroscopic vascular invasion [117].

Variant 5: Intrahepatic cholangiocarcinoma: Peripheral hepatic lobar cholangiocarcinoma, less than 3 cm; no biliary ductal dilatation, macroscopic vascular invasion, regional lymphadenopathy, or distant metastases.

Systemic Therapies

The efficacy of chemotherapy regimens for the treatment of intrahepatic cholangiocarcinoma is usually poor. With that in mind, systemic chemotherapy is generally reserved for unresectable intrahepatic cholangiocarcinoma. A combined analysis of the ABC-02 and BT22 trials in recent years [118,119] has led to widespread adoption of gemcitabine plus cisplatin as the standard palliative regimen for locally advanced or metastatic intrahepatic cholangiocarcinoma.

Surgical Liver Resection

Currently, surgical resection is the only curative treatment option and the only treatment that can provide a chance at long-term survival [120]. Unfortunately, at the time of diagnosis, many patients have locally advanced or metastatic disease, with only 15% to 30% of patients presenting with resectable disease [121]. The goals of surgical resection are to obtain a microscopically negative margin while maintaining an adequate future liver remnant. Still, 5-year survival remains poor.

Liver Transplantation

Liver transplantation is only considered in select patients because recurrence rates, and survival data have been poor for this population [121]. A review of the Cincinnati Transplant Tumor Registry demonstrated a 5-year survival rate of 28%. This study also reported a 51% recurrence rate after transplantation with a median time to recurrence of 9.7 months [122].

Percutaneous Ablation Liver

Heat-based thermal ablation modalities have also shown a treatment advantage for tumors <5 cm in diameter [123]. Ablation can be used for small (<3 cm in diameter) and intermediate (3-5 cm in diameter) intrahepatic cholangiocarcinomas, which are inoperable, with a median overall survival ranging from 33 to 38.5 months [123-125]. A meta-analysis of RFA performed for intrahepatic cholangiocarcinoma found a survival benefit for this treatment in patients who are not surgical candidates [126].

External Beam Radiation Therapy

There is currently no evidence for the use of radiotherapy alone for intrahepatic cholangiocarcinoma. Radiotherapy has been used in conjunction with systemic chemotherapy.

Bland Transarterial Embolization

The use of TAE is supported for more advanced intrahepatic cholangiocarcinoma.

Transarterial Chemoembolization

The use of TACE is supported for more advanced intrahepatic cholangiocarcinoma.

Transarterial Radioembolization

An early study of radioembolization at a single center demonstrated improved survival in patients with peripheral cholangiocarcinoma [127].

Variant 6: Ductal cholangiocarcinoma: Hilar cholangiocarcinoma, greater than 3 cm with poorly defined margins, vascular invasion, and periportal lymphadenopathy.

Systemic Therapies

Limited systemic chemotherapy options are available currently. Systemic chemotherapy with gemcitabine and cisplatin remains the standard of care for patients with advanced disease. Gemcitabine plus cisplatin compared with gemcitabine alone was associated with improved survival for patients with advanced biliary tract cancer in a randomized controlled phase III trial. In this trial, patients treated with gemcitabine plus cisplatin lived on average 3.6 months longer and did not have an increase in adverse events [119].

Surgical Liver Resection

Surgical resection is not a treatment option in this scenario.

Liver Transplantation

Liver transplantation is not a treatment option for advanced cholangiocarcinoma.

Percutaneous Ablation Liver

Ablation therapy has a limited role in the treatment of advanced and central ductal cholangiocarcinoma.

External Beam Radiation Therapy

Radiotherapy alone has not been used for this scenario and has only been used in conjunction with systemic chemotherapy. Postoperative adjuvant chemoradiation may reduce local recurrence and improve overall survival, particularly in high-risk patients. Definitive chemoradiation along with biliary stenting in the nonoperative setting may confer a small survival benefit [128].

Bland Transarterial Embolization

Bland embolization has been studied less than chemoembolization but could be considered in patients with inoperable disease [129].

Transarterial Chemoembolization

TACE has been demonstrated to prolong survival in patients with unresectable disease (9.1-30 months median survival after procedure) [130]. There is no consensus in the literature in regard to the superiority of DEB-TACE or TACE.

Transarterial Radioembolization

TARE may be beneficial for unresectable intrahepatic cholangiocarcinoma after failed first-line chemotherapy, with a disease control rate reported at 81.8% [131]. TARE has shown a survival benefit in multiple studies in patients with unresectable intrahepatic cholangiocarcinoma [132].

Variant 7: Metastatic liver disease: Multifocal metastatic neuroendocrine tumor (includes carcinoid tumors as well as islet cell tumors of the pancreas).

Neuroendocrine cancers include carcinoid tumors, with the primary tumor located most commonly in the gastrointestinal tract and lungs, as well as pancreatic islet cell malignancies. These tumors can secrete a variety of hormones (glucagon, vasoactive intestinal peptide, insulin, and gastrin) causing related symptoms. Patients usually become symptomatic once the disease has metastasized to the liver, thus presenting with more advanced disease. Treatment of neuroendocrine cancers has focused on symptom management and controlling disease progression.

Long-Acting Somatostatin Analogs

A majority of neuroendocrine tumors express somatostatin receptors. Somatostatin analogs, like octreotide, have been a steadfast part of the treatment regimen for symptomatic neuroendocrine cancers to control symptoms but may have limited effect on overall survival [133,134]. Over time, decreased effectiveness of somatostatin analogs limits symptomatic control.

Systemic Therapies

Chemotherapeutic agents (eg, streptozocin, 5-fluorouracil, doxorubicin, capecitabine) or molecularly targeted agents (eg, everolimus, sunitinib) are not commonly used as initial treatment but can be used for patients with rapidly progressive disease, rapidly progressive symptoms, or failure of initial therapy [135-139]. Alpha interferon has also been used as a systemic treatment, but its adverse effects have limited its use [135].

Surgical Liver Resection

Surgical resection, when feasible, can reduce symptoms by cytoreduction. It has also been shown to improve survival [140-143]. If complete resection is not possible, removal of 90% of the disease is thought to be necessary to achieve symptom control. However, this can be difficult to accomplish if the disease is diffuse [144].

Liver Transplantation

Liver transplant has been performed and can confer a survival benefit for patients with advanced, diffuse disease, but it is unfortunately fraught with high recurrence rates of 31% to 56% [145].

Percutaneous Ablation Liver

Thermal ablation, like surgical resection, can help with cytoreduction and is less invasive than surgery [135]. Ablation can be an important treatment option for patients who are not surgical candidates, in combination with surgery performed intraoperatively, or in the treatment of recurrences for those patients who have already undergone surgery [135].

External Beam Radiation Therapy

SBRT (an advanced technique of hypofractionated external beam radiation therapy that delivers ablative doses of radiation) can be performed based on liver tolerance [146]. If the liver is diffusely involved or constraints cannot be met, external beam radiation therapy via 3-D conformational radiation or intensity modulated radiation therapy can be performed [147]. Whole-liver radiation is an effective palliative intervention [148].

Bland Transarterial Embolization

Transarterial therapies are an important treatment strategy for multifocal liver dominant metastatic neuroendocrine tumors. TAE, TACE, DEB-TACE, and TARE have all shown efficacy for overall survival, tumor growth reduction, and symptom control, without clear superiority of one transarterial therapy over the others [132,133,149-156].

Transarterial Chemoembolization

Transarterial therapies are an important treatment strategy for multifocal liver dominant metastatic neuroendocrine tumors. TAE, TACE, DEB-TACE, and TARE have all shown efficacy for overall survival, tumor growth reduction, and symptom control, without clear superiority of one transarterial therapy over the others [132,133,149-156]. However, embolization with DEB-TACE has been associated with an increased risk of biloma formation [152,157].

Transarterial Radioembolization

Transarterial therapies are an important treatment strategy for multifocal liver dominant metastatic neuroendocrine tumors. TAE, TACE, DEB-TACE, and TARE have all shown efficacy for overall survival, tumor growth reduction, and symptom control, without clear superiority of one transarterial therapy over the others [132,133,149-156]. Patients treated with TARE can have fewer side effects following treatment, but one study found that overall survival may be worse than with TAE or TACE [158]. TARE may also be associated with long-term liver toxicity with lobar and bilobar treatment [159].

Combination Locoregional Therapy

No high-quality evidence exists for the use of combination locoregional therapy for the treatment of metastatic neuroendocrine tumors.

Peptide Receptor Radionuclide Therapy

Yttrium-90 (beta-emitter)–and lutetium-177 (beta and gamma-emitter)–labeled somatostatin analogs selectively bind to somatostatin receptors, which are internalized and cause radiation-induced cell death known as PRRT [160]. PRRT has shown to have an effect on disease control with decreased tumor size, increased progression-free survival, and improvement in overall survival compared with octreotide long-acting repeatable [160-162]. PRRT treatment can be expensive and may or may not be covered by insurance.

Variant 8: Metastatic liver disease: Solitary colorectal liver metastasis.

Systemic Therapies

Systemic therapies are first-line therapies for metastatic colorectal cancer. Therapy options are increasing in number and are becoming more selective based on known biomarkers [163]. Fluorouracil forms the basis of multiple combination therapies, including with irinotecan (FOLFIRI), oxaliplatin (FOLFOX), or capecitabine (CAPOX or XELOX), resulting in similar outcomes [164]. Recently, triple therapy with fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI) has shown superiority over FOLFIRI [165-167]. Additionally, the above regimens have also been combined with biologic agents, with some studies demonstrating survival benefits [164,168].

Surgical Liver Resection

Surgical resection remains the best chance for potential cure and has the best overall survival for patients with metastatic colorectal cancer. However, very few patients (<20%) with colorectal liver cancer have metastases that are resectable at the time of diagnosis [169,170]. Resectability is generally considered with limited metastatic disease: up to 5 tumors with adequate intervening nontumor liver parenchyma. Portal vein embolization is an adjunctive procedure before surgery used to hypertrophy the future liver remnant to ensure adequate liver function following resection [171].

Liver Transplantation

The use of liver transplantation is limited because of the high risk of disease recurrence [172].

Percutaneous Ablation Liver

Thermal ablation (RFA and MWA) is an ideal treatment option for carefully selected patients with results similar to resection [173-175]. Ablation of a limited number of smaller tumors (<3 cm) with an ablation margin >5 mm confers the best chance for local tumor control [176]. With less morbidity compared to resection, ablation can be a good option for poor surgical candidates [175].

External Beam Radiation Therapy

SBRT is a treatment proposed as an additional local therapy option in place of percutaneous thermal ablation. A single retrospective study suggested an advantage of SBRT over MWA for local disease control particularly for metastases >3 cm in diameter, but this study was performed on a lesion-by-lesion basis without accounting for additional clinical factors in a retrospective review of a small number of cases [177].

Hepatic Arterial Chemotherapy Infusion

Hepatic arterial chemotherapy infusion is not conventionally used for solitary disease.

Bland Transarterial Embolization

TAE may serve an adjunctive role to surgery for resectable colorectal liver metastasis.

Transarterial Chemoembolization

Chemoembolization may serve a role in improving surgical outcomes for resectable colorectal hepatic metastasis [178].

Transarterial Radioembolization

TARE should be reserved for the treatment of multifocal disease that has failed other therapies.

Combination Locoregional Therapy

Larger lesions (3-5 cm in diameter) can be treated with a combination of TACE/TAE and ablation with excellent local tumor control and survival benefit [179].

Variant 9: Metastatic liver disease: Multifocal bilobar colorectal carcinoma (liver dominant or isolated).

Systemic Therapies

Systemic therapy is vital first-line therapy for multifocal metastatic colorectal cancer. Fluorouracil can be combined with irinotecan (FOLFIRI), oxaliplatin (FOLFOX), or capecitabine (CAPOX or XELOX), resulting in similar outcomes [164]. Recently, FOLFOXIRI has shown superiority over FOLFIRI [165-167]. Additionally, these regimens have also been combined with biologic agents, with some studies demonstrating survival benefits [164,168]. Systemic therapies have also been used for downstaging to resection [169], and one study showed bevacizumab plus FOLFOXIRI may outperform bevacizumab plus modified FOLFOX in terms of resectability rate in initially unresectable disease. Other chemotherapy regimens such as FOLFOX or FOLFOXIRI plus cetuximab have also been shown to convert some unresectable metastatic disease to resectability [180].

Surgical Liver Resection

Feasibility of surgical resection is based on volume of disease and conventionally limited to <5 hepatic metastases with adequate remnant nontumor liver. FOLFOX and FOLFOXIRI plus cetuximab may promote resectability of initially unresectable disease [180].

Liver Transplantation

Liver transplantation has a limited role for multifocal colorectal liver metastases because of a risk of recurrence in this volume of disease.

Percutaneous Ablation Liver

A phase II clinical trial (CLOCC study) demonstrated a survival benefit for early aggressive local treatment of unresectable colorectal liver metastases using RFA with or without surgical resection in conjunction with systemic therapy compared to systemic therapy alone. In this study, the median overall survival was higher for the combined treatment arm at 45.6 months compared with 40.5 months for the systemic treatment group, and the median progression-free survival was significantly longer at 16.8 months in the combined group compared with 9.9 months for systemic treatment alone [181].

External Beam Radiation Therapy

The conventional role for radiotherapy in unresectable colorectal liver metastases has been limited to palliation for tumor burden and related pain. Early data on the use of SBRT for disease control in this setting suggest a possible role, but data are continuing to emerge [182].

Hepatic Arterial Chemotherapy Infusion

Hepatic arterial chemotherapy infusion has been used for treatment of unresectable disease [183-185]. Hepatic arterial chemotherapy infusion along with systemic therapy can convert some disease into resectable disease, possibly improving survival [186]. Direct arterial administration can result in an increased drug concentration within the liver but can be limited by procedural complexity and liver toxicity [183]. This therapy has conventionally involved surgical implantation, but a clinical trial in Japan demonstrated the ability to safely perform image-guided hepatic arterial infusion [187].

Bland Transarterial Embolization

TAE can be used for unresectable colorectal liver metastases. This can be combined with other techniques such as ablation.

Transarterial Chemoembolization

TACE, in addition to TAE, is a treatment option for unresectable disease providing a survival benefit without data demonstrating superiority of one over the other [68,69]. DEBIRI chemoembolization may show a survival benefit on par with systemic chemotherapy for unresectable colorectal liver metastases [188]. Chemoembolization can provide local disease control and may be of the most benefit earlier in therapy after 0 to 2 lines of systemic chemotherapy as opposed to salvage therapy following several failed lines of systemic chemotherapy [189].

Transarterial Radioembolization

TARE provides no additional survival benefit when added to systemic chemotherapy as first-line therapy [190,191]. However, subgroup analysis from 2 randomized controlled trials did identify a survival benefit of TARE plus systemic chemotherapy for colorectal liver metastases from right-sided colon primary tumors compared with left-sided primaries (22 versus 17.1 months) [192]. TARE has, however, been shown to be associated with a survival benefit for patients with colorectal liver metastases that have failed multiple prior systemic chemotherapy options [193,194]. Therefore, this therapy should be reserved as salvage therapy in the treatment of chemo-refractory colorectal liver metastases.

Combination Locoregional Therapy

The strategy of combining transarterial therapies with ablation to enhance therapeutic effect can also be used in multifocal colorectal liver metastases. One prospective study demonstrated good control of tumor treated with combination chemoembolization and RFA [179].

Summary of Recommendations

- **Variation 1:** Liver transplantation or percutaneous ablation liver or surgical liver resection is usually appropriate for hepatocellular cancer in which the solitary tumor is <3 cm in a patient with cirrhosis. These procedures are comparable alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
- **Variation 2:** Liver transplantation or combination locoregional therapy or surgical liver resection or TACE or TARE is usually appropriate for hepatocellular cancer in which the solitary tumor is 3 to 5 cm in a patient with cirrhosis. These procedures are comparable alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
- **Variation 3:** TACE or TARE or bland TAE or systemic therapies are usually appropriate for hepatocellular cancer that is multifocal and bilobar with at least 1 tumor >5 cm in a patient with cirrhosis. These procedures

are comparable alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient’s care).

- **Variante 4:** Systemic therapies or TARE is usually appropriate for hepatocellular cancer that is solitary or multifocal disease with vascular invasion in a cirrhotic patient. These procedures are comparable alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient’s care).
- **Variante 5:** Surgical liver resection or percutaneous liver ablation is usually appropriate for peripheral intrahepatic lobar cholangiocarcinoma that is <3 cm with no biliary ductal dilatation, macroscopic vascular invasion, regional lymphadenopathy, or distant metastases. These procedures are comparable alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient’s care).
- **Variante 6:** Systemic therapies are usually appropriate for hilar ductal cholangiocarcinoma that is >3 cm with poorly defined margins, vascular invasion, and periportal lymphadenopathy.
- **Variante 7:** Long-acting somatostatin analogs or bland TAE or peptide receptor radionuclide therapy or TACE or TARE is usually appropriate for multifocal metastatic neuroendocrine tumor to the liver, including carcinoid tumors as well as islet cell tumors of the pancreas. These procedures are comparable alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient’s care).
- **Variante 8:** Systemic therapies or surgical liver resection or percutaneous ablation liver is usually appropriate for solitary colorectal liver metastasis. These procedures are comparable alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient’s care).
- **Variante 9:** Systemic therapies are usually appropriate for multifocal bilobar colorectal carcinoma where the liver is dominant or isolated. Bland TAE may be appropriate for this clinical scenario, but the experts could not agree on the exact appropriateness category.

Supporting Documents

The evidence table, literature search, and appendix for this topic are available at <https://acsearch.acr.org/list>. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

Appropriateness Category Names and Definitions

| Appropriateness Category Name | Appropriateness Rating | Appropriateness Category Definition |
|-----------------------------------|------------------------|--|
| Usually Appropriate | 7, 8, or 9 | The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients. |
| May Be Appropriate | 4, 5, or 6 | The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal. |
| May Be Appropriate (Disagreement) | 5 | The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel’s recommendation. “May be appropriate” is the rating category and a rating of 5 is assigned. |
| Usually Not Appropriate | 1, 2, or 3 | The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable. |

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.