American College of Radiology
ACR Appropriateness Criteria®

Clinical Condition: **Hepatic Malignancy**

Variant 1: **Hepatocellular carcinoma: Solitary tumor <3 cm.**

Treatment/Procedure	Rating	Comments
Transplantation	9	
Resection	8	
Percutaneous thermal ablation	7	
Arterial chemoembolization	6	
Intraoperative thermal ablation	6	
Percutaneous chemical ablation	5	
Arterial embolization	5	
Arterial radioembolization	5	
External beam radiation	1	
Systemic chemotherapy	1	
Rating Scale: 1=Least appropriate, 9=Most appropriate		

Variant 2: **Hepatocellular carcinoma: Solitary tumor 5 cm.**

Treatment/Procedure	Rating	Comments
Transplantation	9	
Resection	8	
Arterial chemoembolization	7	
Arterial therapy combined with ablation	7	
Arterial embolization	6	
Arterial radioembolization	6	
Thermal ablation	5	
Intraoperative thermal ablation	4	
Systemic chemotherapy	3	Especially in portal vein thrombosis.
Chemical ablation	2	
External beam radiation	1	
Rating Scale: 1=Least appropriate, 9=Most appropriate		

Clinical Condition: **Hepatic Malignancy**

Variant 3: **Hepatocellular carcinoma: More than one tumor, at least one of the tumors >5 cm.**

Treatment/Procedure	Rating	Comments
Arterial chemoembolization	8	
Arterial embolization	7	
Arterial radioembolization	7	
Arterial therapy combined with ablation	6	Depends on location of tumors.
Resection	3	Depends on location of tumors and status of liver.
Intraoperative thermal ablation	3	
Thermal ablation	3	
Transplantation	2	
Chemical ablation	2	
External beam radiation	1	
Systemic chemotherapy	No consensus	The expert panel recognizes this is a promising therapy. See text.
Rating Scale: 1=Least appropriate, 9=Most appropriate		

Variant 4: **Metastatic liver disease: Multifocal metastatic neuroendocrine tumor (includes carcinoid tumors as well as islet cell tumors of the pancreas).**

Treatment/Procedure	Rating	Comments
Long-acting octreotide	9	
Arterial chemoembolization	8	
Arterial embolization	8	
Arterial radioembolization	6	Very limited published evidence.
Arterial therapy combined with thermal ablation	4	
Resection	3	Resection appropriate in limited number of patients.
Intraoperative thermal ablation	3	
Systemic chemotherapy	3	
Thermal ablation	3	
Transplantation	2	
External beam radiation	1	
Chemical ablation	1	
Rating Scale: 1=Least appropriate, 9=Most appropriate		

Clinical Condition: **Hepatic Malignancy**

Variant 5: **Metastatic liver disease: Multifocal colorectal carcinoma (liver dominant or isolated), ≥5 cm tumors.**

Treatment/Procedure	Rating	Comments
Systemic chemotherapy	9	
Resection	7	If resection is anatomically feasible.
Arterial chemoembolization	3	
Arterial embolization	3	
Arterial radioembolization	3	Pending further data.
Intraoperative thermal ablation	2	
Thermal ablation	2	
Transplantation	1	
External beam radiation	1	
Chemical ablation	1	
Rating Scale: 1=Least appropriate, 9=Most appropriate		

Variant 6: **Solitary colorectal liver metastasis.**

Treatment/Procedure	Rating	Comments
Resection	9	
Systemic chemotherapy	9	Appropriate alone and with resection.
Thermal ablation	6	If not a surgical candidate.
Intraoperative thermal ablation	4	
Arterial chemoembolization	3	
Arterial embolization	3	
Arterial radioembolization	3	
Chemical ablation	2	
Transplantation	1	
External beam radiation	1	
Rating Scale: 1=Least appropriate, 9=Most appropriate		

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Summary of Literature Review

Management of hepatic malignancy remains a challenging problem. For primary and many metastatic processes, traditional therapies such as resection, systemic chemotherapy, or external beam radiation therapy are unavailable or ineffective. A number of novel techniques have been developed by interventional radiologists to treat patients with hepatic malignancy. These treatment methods include direct tumor ablation via chemical or thermal means and endovascular techniques such as embolization, chemoembolization, and radioembolization with Yttrium-90 (Y90). The relative role of these treatments in management of various disease processes is reviewed below.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the index tumor around which the discipline of interventional oncology is based. The only cure for HCC is liver transplantation [1]. Unfortunately, the number of patients awaiting transplant far outstrips the number of available organs. Patients younger than 65 with limited tumor burden (described at many centers as one tumor measuring 5 cm or less or up to three tumors all measuring less than 3 cm) should undergo evaluation for transplantation. Patients with adequate hepatic reserve may undergo resection if obtaining a margin does not leave too small a remnant [2]. Chemotherapy and external beam radiation have traditionally been ineffective in treating these tumors. Recently, results of a double-blinded randomized study of Sorafenib versus placebo in patients with HCC, which is powered for survival, have been reported. This trial demonstrated a statistically significant improvement in survival of 10.7 versus 7.9 months in favor of Sorafenib [3]. The panel will await the publication of this data before making a final recommendation. Since most patients are not candidates for surgery, and in light of the ineffectiveness of other treatments, newer therapies were developed in the 1980s and 1990s.

Ablative therapies are broken into two groups: chemical and thermal. Chemical ablation is typically performed with absolute alcohol, while thermal ablation most commonly refers to radiofrequency ablation (RFA) or cryoablation [4-8]. Ablative therapies are effective at treating small HCCs. Ablative therapies can be performed either percutaneously or surgically, using open or laparoscopic methods. Since most patients with HCC are poor surgical candidates, this option may not be the most appropriate. As tumor number and/or size (>3 cm) increases, the operator may want to focus on arterial-based therapies as a supplement [9,10]. A variety of endovascular techniques have been described to treat hepatocellular carcinoma. These include chemoembolization, embolization, and radioembolization.

Chemoembolization for HCC was initially controversial, as early randomized trials did not demonstrate clinical benefit [3,11,12]. However, these trials had significant flaws in design. More recent trials have demonstrated a significant survival benefit with use of chemoembolization for HCC versus no treatment [13-15]. One of these studies had two separate treatment arms: chemoembolization and "bland" embolization (ie, treatment with particulate embolization alone) [15]. When chemoembolization reached statistical significance versus no treatment, the study was stopped. Bland embolization had not yet reached statistical significance but outcomes in this group were much closer to the chemoembolization group than to the no-treatment group.

Radioembolization with beta-emitting Y90 beads is emerging as another treatment option for patients with HCC. Initial outcomes with this new agent are similar to those described with chemoembolization and embolization [16-18].

Neuroendocrine Tumors

Neuroendocrine tumors include carcinoid tumors which arise from the small bowel, appendix, lung, bronchi, and pancreas, as well as pancreatic islet cell malignancies with related hormonal symptoms from glucagon, vasoactive intestinal peptide, insulin, and gastrin secretion. Carcinoid tumors are much more common than islet cell tumors. Management of these tumors is complex and varies depending on the aggressiveness of the intrahepatic process and the presence or absence of related hormonal syndromes [19].

For patients with hormonally active disease, most oncologists will initially attempt to control symptoms

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with depot octreotide injections [20]. Resection of hepatic metastases can be performed in appropriate cases. In carefully selected patients, 5-year survival rates can approach 70%, although the symptom recurrence rate within 5 years is 84% [21,22]. Transplantation is uncommonly performed for neuroendocrine metastases [23]. Systemic chemotherapy has a limited role, with benefit more commonly for islet cell than carcinoid tumors [24-27]. Although thermal or chemical ablation is feasible in certain cases, most patients present with multiple bilobar metastases, making ablation a suboptimal option for the majority of patients [28].

Many patients with neuroendocrine tumors present with bilateral hepatic metastases and limited treatment options. Arterial therapies play a significant role in management since these tumors receive most of their supply from the hepatic arteries. Embolization and chemoembolization have been shown to decrease hormonal symptoms and contribute to median survival as long as 80 months [29-31]. There has been preliminary research into use of Y90 in this patient population, with ancecdotally promising results.

Colorectal Cancer Metastases to the Liver

The gold standard in management of colon cancer metastatic to the liver is resection [32,33]. Unfortunately, most of these patients are not candidates for surgery due to either disease bulk or the presence of extrahepatic metastases. This group of patients should be treated with systemic chemotherapy [34,35]. A subgroup of patients with liver metastases will progress after chemotherapy options are exhausted or toxicity from systemic therapy limits chemotherapy options. These patients are potential candidates for palliative ablative or arterial interventions.

Thermal ablation is accepted as preferable to chemical ablation for treating colorectal metastases [36]. As with HCC, ablation should be reserved for patients with a limited number of smaller tumors. Local recurrence is significantly higher when colorectal metastases larger than 2.5 cm are treated and when more than one tumor is present at the time of ablation [37]. Larger tumors may be treated with a combination of ablation and arterial embolization or chemoembolization [7].

Arterial therapies such as chemoembolization have been studied with limited results [37,38]. Patients without extrahepatic disease survive longer than those with extrahepatic disease following chemoembolization. Use of Y90 for liver-dominant colorectal metastases is expanding, with early response rates reported to be as high as 79% [39]. Determination of the effect of Y90 on survival rates is evolving [40].

Summary

- Use of percutaneous ablative techniques vs. arterial methods will vary from institution to institution depending on operator expertise.
- Thermal ablation or chemical ablation alone does poorly in treating tumors more than 3 cm in diameter. Combining thermal and arterial treatments may be better than arterial treatments alone, but this issue has not been formally studied.
- Systemic chemotherapy is often temporarily effective for noncarcinoid islet cell tumors.
- Resection may be indicated for dominant expansile tumors.
- Radioembolization may be as effective as chemoembolization or embolization, but there is limited literature available to date.

Supporting Document(s)

- ACR Appropriateness Criteria® Overview
- Evidence table under review

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