Complete Summary

GUIDELINE TITLE

Hepatic malignancy.

BIBLIOGRAPHIC SOURCE(S)

Brown DB, Bakal CW, Weintraub JL, Bass JC, Dickey KW, Gemery JM, Klyde DP, Millward SF, Patel AA, Salem R, Selby JB Jr, Silberzweig JE, Expert Panel on Interventional Radiology. Hepatic malignancy. [online publication]. Reston (VA): American College of Radiology (ACR); 2007. 7 p. [40 references]

GUIDELINE STATUS

This is the current release of the guideline.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Hepatic malignancy

GUIDELINE CATEGORY

Diagnosis
Evaluation
Treatment

CLINICAL SPECIALTY

Family Practice
Gastroenterology
Internal Medicine
Oncology
Radiology
Surgery

INTENDED USERS

Health Plans
Hospitals
Managed Care Organizations
Physicians
Utilization Management

GUIDELINE OBJECTIVE(S)

To evaluate the appropriateness of interventional radiologic (ablative and endovascular) procedures/treatments for hepatic malignancy

TARGET POPULATION

Patients with hepatic malignancies: hepatocellular carcinoma, neuroendocrine tumors, colorectal metastases to the liver

INTERVENTIONS AND PRACTICES CONSIDERED

1. Transplantation
2. Resection
3. Thermal ablation
    - Percutaneous
    - Intraoperative
4. Arterial chemoembolization
5. Arterial radioembolization
6. External beam radiation
7. Systemic chemotherapy
8. Arterial therapy combined with ablation
9. Arterial embolization
10. Systemic chemotherapy
11. Chemical ablation
12. Long-acting octreotide

MAJOR OUTCOMES CONSIDERED

Utility of interventional radiologic (ablative and endovascular) procedures/treatments for hepatic malignancy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developer performed literature searches of peer-reviewed medical journals and the major applicable articles were identified and collected.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Not Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

One or two topic leaders within a panel assume the responsibility of developing an evidence table for each clinical condition, based on analysis of the current literature. These tables serve as a basis for developing a narrative specific to each clinical condition.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Since data available from existing scientific studies are usually insufficient for meta-analysis, broad-based consensus techniques are needed for reaching agreement in the formulation of the appropriateness criteria. The American College of Radiology (ACR) Appropriateness Criteria panels use a modified Delphi technique to arrive at consensus. Serial surveys are conducted by distributing questionnaires to consolidate expert opinions within each panel. These questionnaires are distributed to the participants along with the evidence table and narrative as developed by the topic leader(s). Questionnaires are completed

by participants in their own professional setting without influence of the other members. Voting is conducted using a scoring system from 1-9, indicating the least to the most appropriate imaging examination or therapeutic procedure. The survey results are collected, tabulated in anonymous fashion, and redistributed after each round. A maximum of three rounds is conducted and opinions are unified to the highest degree possible. Eighty percent agreement is considered a consensus. This modified Delphi technique enables individual, unbiased expression, is economical, easy to understand, and relatively simple to conduct.

If consensus cannot be reached by the Delphi technique, the panel is convened and group consensus techniques are utilized. The strengths and weaknesses of each test or procedure are discussed and consensus reached whenever possible. If "No consensus" appears in the rating column, reasons for this decision are added to the comment sections.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

ACR Appropriateness Criteria®

Summary of Recommendations

- 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.

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

Treatment/Procedure	Appropriateness 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	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Variant 2: Hepatocellular carcinoma: Solitary tumor 5 cm.

Treatment/Procedure	Appropriateness Rating	Comments
Transplantation	9	
Resection	8	
Arterial chemoembolization	7	
Arterial therapy combined with ablation	7	
Arterial embolization	6	

Treatment/Procedure	Appropriateness Rating	Comments
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	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

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

Treatment/Procedure	Appropriateness 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 below.

Treatment/Procedure	Appropriateness Rating	Comments
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **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	Appropriateness 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	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

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

Treatment/Procedure	Appropriateness 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	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Variant 6: Solitary colorectal liver metastasis

Treatment/Procedure	Appropriateness 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	

Treatment/Procedure	Appropriateness Rating	Comments
External beam radiation	1	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

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. 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. 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. 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. 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. 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. 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. One of these studies had two separate treatment arms: chemoembolization and "bland" embolization (i.e., treatment with particulate embolization alone). 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.

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.

For patients with hormonally active disease, most oncologists will initially attempt to control symptoms with depot octreotide injections. 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%. Transplantation is uncommonly performed for neuroendocrine metastases. Systemic chemotherapy has a limited role, with benefit more commonly for islet cell than carcinoid tumors. 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.

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. 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. 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. 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. 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. Larger tumors may be treated with a combination of ablation and arterial embolization or chemoembolization.

Arterial therapies such as chemoembolization have been studied with limited results. 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%. Determination of the effect of Y90 on survival rates is evolving.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are based on analysis of the current literature and expert panel consensus.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Selection of appropriate interventional radiologic (ablative and endovascular) procedures/treatments for hepatic malignancy

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

An American College of Radiology (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

exams 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 U.S. Food and Drug Administration (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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Brown DB, Bakal CW, Weintraub JL, Bass JC, Dickey KW, Gemery JM, Klyde DP, Millward SF, Patel AA, Salem R, Selby JB Jr, Silberzweig JE, Expert Panel on Interventional Radiology. Hepatic malignancy. [online publication]. Reston (VA): American College of Radiology (ACR); 2007. 7 p. [40 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007 Jan

GUIDELINE DEVELOPER(S)

American College of Radiology - Medical Specialty Society

SOURCE(S) OF FUNDING

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

GUIDELINE COMMITTEE

Committee on Appropriateness Criteria, Expert Panel on Interventional Radiology

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: Daniel B. Brown, MD; Curtis W. Bakal, MD; Joshua L. Weintraub, MD; James C. Bass, MD; Kevin W. Dickey, MD; John M. Gemery, MD; David P. Klyde, MD; Steven F. Millward, MD; Aalpen A. Patel, MD; Riad Salem, MD; John B. Selby, Jr., MD; James E. Silberzweig, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

ACR Appropriateness Criteria® *Anytime*, *Anywhere*™ (PDA application). Available from the ACR Web site.

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- ACR Appropriateness Criteria®. Background and development. Reston (VA): American College of Radiology; 2 p. Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

PATIENT RESOURCES

None available

NGC STATUS

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