American College of Radiology
ACR Appropriateness Criteria®

Clinical Condition: **Radiologic Management of Hepatic Malignancy**

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

Treatment/Procedure	Rating	Comments
Systemic chemotherapy	3	
Resection	8	
Transplantation	9	
Chemical ablation	5	
Thermal ablation	8	
Stereotactic body radiotherapy (SBRT)	5	
Transarterial embolization (TAE)	5	
Transarterial chemoembolization (TACE)	5	
Selective internal radiation therapy (SIRT)	5	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

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

Treatment/Procedure	Rating	Comments
Systemic chemotherapy	3	
Resection	8	
Transplantation	9	
Chemical ablation	3	The tumor is too large for chemical ablation. This procedure can be used instead of or in addition to thermal ablation, depending on the tumor location.
Thermal ablation	5	
Stereotactic body radiotherapy (SBRT)	4	
Transarterial embolization (TAE)	6	
Transarterial chemoembolization (TACE)	7	This procedure refers to either conventional TACE or DEB-TACE.
Selective internal radiation therapy (SIRT)	7	This procedure is especially applicable in portal vein thrombosis or extensive bilobar disease.
Transarterial chemoembolization (TACE) combined with thermal ablation	7	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Radiologic Management of Hepatic Malignancy**

Variant 3: **Hepatocellular carcinoma: More than 1 tumor, at least 1 of them >5 cm.**

Treatment/Procedure	Rating	Comments
Systemic chemotherapy	6	Consider this procedure for patients not amenable to other localized therapies.
Resection	5	Consider resection following neoadjuvant TAE or TACE in the noncirrhotic patient.
Transplantation	1	
Chemical ablation	2	
Thermal ablation	3	This procedure depends on local expertise.
Stereotactic body radiotherapy (SBRT)	3	
Transarterial embolization (TAE)	7	
Transarterial chemoembolization (TACE)	8	This procedure refers to either conventional TACE or DEB-TACE.
Selective internal radiation therapy (SIRT)	8	
Transarterial chemoembolization (TACE) combined with thermal ablation	6	Early evidence is promising. More data are needed.
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Variant 4: **Intrahepatic cholangiocarcinoma: 4 cm in diameter, no evidence of biliary obstruction.**

Treatment/Procedure	Rating	Comments
Systemic chemotherapy	8	
Resection	8	
Transplantation	5	
Chemical ablation	3	
Thermal ablation	5	
Stereotactic body radiotherapy (SBRT)	4	
Transarterial embolization (TAE)	4	
Transarterial chemoembolization (TACE)	5	
Selective internal radiation therapy (SIRT)	5	
Transarterial chemoembolization (TACE) combined with thermal ablation	5	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Radiologic Management of Hepatic Malignancy**

Variant 5: **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	
Systemic chemotherapy	3	
Resection	3	
Transplantation	2	
Chemical ablation	1	
Thermal ablation	3	
Stereotactic body radiotherapy (SBRT)	2	
Transarterial embolization (TAE)	7	
Transarterial chemoembolization (TACE)	8	DEB-TACE potentially carries a higher risk of biloma formation.
Selective internal radiation therapy (SIRT)	8	
Transarterial chemoembolization (TACE) combined with thermal ablation	5	Early evidence is promising. More data are needed.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 6: **Metastatic liver disease: Multifocal colorectal carcinoma (liver dominant or isolated).**

Treatment/Procedure	Rating	Comments
Systemic chemotherapy	9	
Resection	6	
Transplantation	1	
Chemical ablation	1	
Thermal ablation	2	
Stereotactic body radiotherapy (SBRT)	2	
Hepatic arterial chemotherapy infusion	5	
Transarterial embolization (TAE)	6	
Transarterial chemoembolization (TACE)	6	
Selective internal radiation therapy (SIRT)	7	
Transarterial chemoembolization (TACE) combined with thermal ablation	5	This procedure depends on the tumor burden.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Radiologic Management of Hepatic Malignancy**

Variant 7: **Solitary colorectal liver metastasis.**

Treatment/Procedure	Rating	Comments
Systemic chemotherapy	9	This procedure is appropriate alone and with resection.
Resection	9	
Transplantation	1	
Chemical ablation	2	
Thermal ablation	8	This procedure is recommended if the tumor is <3–5 cm. Use of this procedure depends on local expertise.
Stereotactic body radiotherapy (SBRT)	5	
Hepatic arterial chemotherapy infusion	4	
Transarterial embolization (TAE)	5	
Transarterial chemoembolization (TACE)	6	This procedure may be especially useful for downstaging patients for more definitive therapies. Conventional TACE is not as well established for this indication, but DEB-TACE with irinotecan shows early promise and is being investigated further.
Selective internal radiation therapy (SIRT)	6	This procedure is often used after failure of 1 or more lines of systemic therapy. However, prospective studies are pending which may show a benefit to moving SIRT earlier in the treatment algorithm.
Transarterial chemoembolization (TACE) combined with thermal ablation	6	Early evidence is promising. More data are needed. This procedure may be especially useful for downstaging patients for more definitive therapies.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

RADIOLOGIC MANAGEMENT OF HEPATIC MALIGNANCY

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Summary of Literature Review

Introduction/Background

Management of hepatic malignancy remains a challenging problem. Depending on the clinical scenario, traditional therapies such as resection, systemic chemotherapy, and external beam radiation are either unavailable or ineffective. To help fill this void, a number of techniques have been developed by interventional radiologists to treat hepatic malignancy. These treatments include direct tumor ablation via chemical or thermal means and endovascular techniques such as embolization, chemoembolization, and radioembolization with yttrium-90 (Y90). The role of these treatments in the management of primary and secondary hepatic malignancy is reviewed below.

Discussion by Variant

Variants 1–3: Primary hepatic malignancy; hepatocellular carcinoma

Despite marked advances in interventional oncology over the past decade, the preferred first-line treatment for hepatocellular carcinoma (HCC) remains liver transplantation when proper indications are met [1,2]. Unfortunately, the number of patients awaiting transplant far outstrips the number of available organs. Patients younger than age 65 with a limited tumor burden (conventionally defined by the Milan criteria as 1 tumor measuring ≤5 cm or up to 3 tumors all measuring <3 cm) should undergo evaluation for transplantation [3]. Resection also offers acceptable long-term survival in suitable patients, often defined as those with low-volume tumor burden, well-preserved liver function, and no significant portal hypertension [4].

Systemic therapy [5] and radiation therapy [6] have traditionally been ineffective in treating HCC. Marginal therapeutic improvement has been accomplished in recent years with the development of sorafenib, a multikinase inhibitor. A double-blinded randomized study of sorafenib versus placebo in patients with HCC demonstrated a statistically significant difference in median overall survival: 10.7 months for those taking sorafenib compared to 7.9 months for those taking placebo [7]. Nevertheless, since many patients are not candidates for surgery and in light of the relative ineffectiveness of other treatments, percutaneous therapies often play a central role in the management of HCC. These therapies can be categorized as either ablative or transarterial techniques.

Ablative therapies are typically divided into 2 groups: chemical and thermal. Chemical ablation is accomplished by injection of a tumoricidal agent, typically absolute alcohol, directly into the tumor under imaging guidance. Thermal ablation commonly refers to radiofrequency ablation (RFA), but other techniques include cryoablation and microwave ablation. Ablative therapies can be performed either percutaneously or surgically, using open or laparoscopic methods. RFA has been shown to be a more effective ablative therapy than percutaneous ethanol injection (PEI) for treating HCC [8]. However, PEI may still have a legitimate role for treating tumors adjacent to critical structures that would be at higher risk of injury with RFA [9,10]. Microwave ablation has also shown promise for this indication [11]. There is also theoretical justification to suggest microwave ablation may carry certain advantages when compared to RFA. These potential advantages include a decreased susceptibility to heat sink from adjacent large vessels, increased ability to supply thermal energy through desiccated tissue, and the

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potential to create larger ablation zones in a shorter period of time [12]. Justification for the use of cryotherapy in treating HCC is currently not as well supported [13].

Ablative therapies are typically most effective at treating small HCCs (≤3 cm in diameter) [14-16]. As tumor diameter increases above 3 cm, treatment results improve when ablation is combined with chemoembolization rather than being used as a stand-alone treatment [17]. Additionally, although ablative therapies have traditionally been viewed as only palliative, recent research has demonstrated their potential to offer equivalent opportunities for overall survival relative to surgical resection in certain clinical scenarios [18-24]. Ablative therapies are also now commonly used as a neoadjuvant therapy intended to "downstage" or bridge patients to transplant or resection. In this role, ablative therapies have been found to effectively decrease the dropout rate for liver transplant, but published evidence is inconclusive as to whether this effectively improves patient survival [25,26]. Recently, stereotactic body radiation therapy (SBRT) has emerged as a potential alternative to percutaneous ablative techniques for all of the above indications [27-29].

As tumor number and/or size increases, transarterial therapy is more commonly indicated [30]. A variety of endovascular techniques have been developed to treat HCC. These include transarterial embolization (TAE) with embolic particles alone, transarterial chemoembolization (TACE), and selective internal radiation therapy (SIRT). Exclusion criteria for these techniques often focus on the extent of underlying liver disease and tumor burden [31,32]. Surprisingly, given the theoretical risk of rendering the liver globally ischemic, hepatic arterial embolization techniques tend to be well tolerated even in the setting of portal vein thrombosis [33,34].

Several trials have demonstrated a significant survival benefit with the use of TACE for HCC compared to best supportive care [35-37]. There is limited evidence that TAE may have similar efficacy as TACE; however, in practice TACE appears to be typically favored by most operators [38-40]. TACE has also been studied as a neoadjuvant therapy to transplantation or resection. As with RFA, recent studies suggest TACE may control tumor progression, thereby decreasing transplant list dropout rates. However, the survival benefit of this technique is still debated despite present data suggesting a positive impact of bridging treatments on both tumor recurrence and patient/graft survival following transplantation [41-47]. Recently, TACE has been further refined through the development of drug-eluting beads as the embolic agent. Several studies have suggested that this agent may be more efficacious with less systemic toxicity than the established conventional TACE technique of direct infusion of chemotherapeutic agents emulsified in ethiodized oil, followed by bland embolization [48-51].

SIRT with beta-emitting Y90 beads is another widely accepted treatment option for patients with HCC [52,53]. Outcomes with this new agent are similar to those described with TACE and TAE, with the possible advantage of less patient discomfort and toxicity [54-58]. SIRT has also shown the ability to effectively downstage patients for potential transplant or resection [59,60]. Potential disadvantages to SIRT compared to TACE and TAE include the need for more extensive arteriography for treatment planning as well as additional logistical hurdles and cost involving dose planning.

Therapeutic regimens using different combinations of ablative techniques, transarterial techniques, systemic therapy, and surgical treatments are also commonly utilized, given the theoretical benefits of a multifaceted treatment regimen compared to monotherapy [61-66].

Variant 4: Intrahepatic cholangiocarcinoma: 4 cm in diameter, no evidence of biliary obstruction

Cholangiocarcinoma is an epithelial cancer of the biliary duct system. Resection is the only commonly accepted potentially curative treatment modality; however, in most cases the tumor is not resectable at the time of diagnosis [67]. Unlike with hepatocellular carcinoma, transplantation is not widely considered a reasonable option due to poor results from prior studies [68]. Nevertheless, the Mayo Clinic has demonstrated a survival advantage in a select subset of patients with small (<3 cm) hilar cholangiocarcinoma in the setting of underlying primary sclerosing cholangitis when combined with neoadjuvant chemoradiation. These results have not yet been shown to be generalizable to other centers [69].

Systemic therapy with combination gemcitabine and cisplatin has been shown to increase survival. Nevertheless, the impact of chemotherapy on survival remains modest, with median overall survival being approximately 11.7 months [70]. After gemcitabine/cisplatin therapy, there is essentially no known effective chemotherapy. The poor response of cholangiocarcinoma to current systemic therapy highlights the need for the development of more effective liver-directed therapy.

Several small studies have been published in recent years which demonstrate the potential for increased survival both with ablative therapies as well as transarterial therapies. With respect to thermal ablation, there is evidence that both microwave and RFA are potentially effective therapeutic modalities, particularly for tumors with a diameter <5 cm [71,72]. Likewise, survival benefit has also been demonstrated through the use of transarterial therapies such as radioembolization and chemoembolization [73-76]. There is limited evidence that drug-eluting bead chemoembolization may be more effective than conventional chemoembolization for this indication [77]. As with other types of hepatic malignancy, hepatic arterial chemoinfusion (HAI) has also been shown in small series to improve overall survival. However, the applicability of this technique is hindered by cost, potential complications, and other logistical hurdles [78].

Variant 5: Metastatic liver disease: Multifocal metastatic neuroendocrine tumor (includes carcinoid tumors as well as islet cell tumors of the pancreas)

Neuroendocrine tumors include carcinoid tumors that 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. These tumors tend to follow a relatively indolent course and often become symptomatic only when the liver is involved with extensive metastatic disease. Consequently, many patients initially present with widespread liver involvement. Management of these tumors focuses on controlling tumor growth as well as managing symptoms related to tumor bulk and hormonal syndromes [79].

For patients with hormonally active disease, treatment typically focuses initially on controlling symptoms with medical therapy in the form of somatostatin analogs [80]. Some studies suggest somatostatin analogs may have an antiproliferative effect as well, thereby prolonging progression-free survival [81,82]. However, a significant percentage of patients either receive no clinical benefit from somatostatin analogs or become refractory to their therapeutic benefits over time [83].

With respect to managing tumor burden, resection of hepatic metastases can be beneficial in appropriate cases. In properly selected patients, resection confers a survival advantage over other treatment modalities [84,85]. Transplantation is uncommonly performed for neuroendocrine metastases [86]. Systemic therapy also has a limited role [87,88]. However, emerging data suggest that in certain subsets of neuroendocrine cancer, particularly pancreatic neuroendocrine tumors, systemic therapy options provide improved progression-free survival [89,90].

As with resection, thermal or chemical ablation may be feasible in certain cases; however, most patients present with multiple bilobar metastases, making ablation a suboptimal option for most patients [91]. Image-guided ablation, however, can still play a meaningful role as an adjunctive intraoperative therapy or as an alternative treatment for poor surgical candidates [92-94].

Due to the limited effectiveness or applicability of medical therapy and surgical/ablative techniques, arterial therapies often play a significant role in management. TAE and TACE have been shown to decrease hormonal symptoms and improve survival. Debate remains over which method of embolization is most effective, with some published studies arguing that bland hepatic artery embolization (TAE) produces essentially equivalent results as chemoembolization (TACE) [95-97]. As with treatment for other primary and secondary hepatic malignancies, there is also interest in treating metastatic neuroendocrine tumors with drug-eluting bead chemoembolization (DEB-TACE). This interest, however, has waned as there appears to be a higher rate of biloma formation when using DEB-TACE in this clinical setting [98,99]. There has also been increasing research into the use of SIRT in this patient population, with small studies suggesting therapeutic equivalency with more traditional arterial embolization techniques [100-102]. This finding was also reiterated in recent consensus guidelines from the European Neuroendocrine Tumor Society, in which it was found that insufficient evidence exists to determine which modality is superior with respect to treatment response and overall survival [103]. Moreover, recently published findings from a multidisciplinary expert working group suggest that, when compared with TAE and TACE, radioembolization patients experience fewer side effects from treatment and require fewer overall treatments [104,105].

Variants 6 and 7: Secondary hepatic malignancy; colorectal cancer, metastases to the liver

The gold standard in management of colon cancer metastatic to the liver remains resection [106]. Unfortunately, most patients are not candidates for surgery due to either disease bulk or the presence of extrahepatic metastases [107]. However, preoperative portal vein embolization can potentially increase the number of candidates for surgical resection [108-110]. Patients who are not eligible for resection may be potential candidates for palliative ablative or arterial interventions.

Ablation is most successful in patients with a limited number of smaller tumors [111]. Larger tumors can be treated with a combination of ablation and TAE or TACE. As with HCC, recent data have suggested that for properly selected patients, ablative techniques may approach equivalency with resection with respect to survival [112]. As with primary hepatic malignancy, early experience with SBRT also shows a potential role for this therapy for the treatment of liver metastases [113].

Arterial therapies such as TACE and SIRT, either as monotherapy or in combination with other therapeutic regimens, have also shown survival benefit [114,115]. As with HCC and metastatic neuroendocrine tumors, there continues to be a need for further research comparing the effectiveness of various locoregional treatment options as well as their use in conjunction with other treatments, including systemic therapy [116].

Primarily due to the development of more effective systemic therapy agents, HAI therapy has also been shown to be potentially beneficial for unresectable disease as well as in a neoadjuvant role [117]. However, this technique remains relatively unpopular due to the added cost and complexity of arterial pump placement as well as concerns over liver toxicity [118].

Summary of Recommendations

- Management of primary and secondary hepatic malignancy remains a complex issue due to the multitude of treatment options. For this reason, a multidisciplinary approach offers the best hope for optimal treatment with respect to any individual patient.
- Resection and transplantation remain the best options for cure in properly selected patients for primary malignancy as well as secondary malignancy in some limited scenarios; however, the role of RFA and potentially SBRT as primary treatment options are worthy of future research.
- SIRT is likely as effective as TACE or TAE for both primary and secondary hepatic malignancy and is often better tolerated.
- The choice between percutaneous ablative techniques and arterial methods will vary from institution to institution depending on operator expertise.
- Combining ablative and arterial treatments may yield better outcomes than arterial treatments alone.
- Due to the development and refinement of a wide range of therapies, particularly for secondary hepatic malignancies, protocols focusing on the proper combination and sequence of treatments may benefit from reexamination.

Summary of Evidence

Of the 118 references cited in the *ACR Appropriateness Criteria® Radiologic Management of Hepatic Malignancy* document, all of them are categorized as therapeutic references including 20 well designed studies, 45 good quality studies, and 3 quality studies that may have design limitations. There are 44 references that may not be useful as primary evidence. There are 6 references that are meta-analysis studies.

The 118 references cited in the *ACR Appropriateness Criteria® Radiologic Management of Hepatic Malignancy* document were published from 1996-2015

While there are references that report on studies with design limitations, 65 well designed or good quality studies provide good evidence.

Supporting Documents

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

References

1. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol.* 2012;56(4):908-943.
2. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology.* 2011;53(3):1020-1022.
3. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med.* 1996;334(11):693-699.

4. Yamashita Y, Taketomi A, Itoh S, et al. Longterm favorable results of limited hepatic resections for patients with hepatocellular carcinoma: 20 years of experience. *J Am Coll Surg.* 2007;205(1):19-26.
5. Giglia JL, Antonia SJ, Berk LB, Bruno S, Dessureault S, Finkelstein SE. Systemic therapy for advanced hepatocellular carcinoma: past, present, and future. *Cancer Control.* 2010;17(2):120-129.
6. Feng M, Ben-Josef E. Radiation therapy for hepatocellular carcinoma. *Semin Radiat Oncol.* 2011;21(4):271-277.
7. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359(4):378-390.
8. Germani G, Pleguezuelo M, Gurusamy K, Meyer T, Isgro G, Burroughs AK. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocelullar carcinoma: a meta-analysis. *J Hepatol.* 2010;52(3):380-388.
9. Cho YK, Kim JK, Kim MY, Rhim H, Han JK. Systematic review of randomized trials for hepatocellular carcinoma treated with percutaneous ablation therapies. *Hepatology.* 2009;49(2):453-459.
10. Orlando A, Leandro G, Olivo M, Andriulli A, Cottone M. Radiofrequency thermal ablation vs. percutaneous ethanol injection for small hepatocellular carcinoma in cirrhosis: meta-analysis of randomized controlled trials. *Am J Gastroenterol.* 2009;104(2):514-524.
11. Boutros C, Somasundar P, Garrean S, Saied A, Espat NJ. Microwave coagulation therapy for hepatic tumors: review of the literature and critical analysis. *Surg Oncol.* 2010;19(1):e22-32.
12. Lubner MG, Brace CL, Ziemlewicz TJ, Hinshaw JL, Lee FT, Jr. Microwave ablation of hepatic malignancy. *Semin Intervent Radiol.* 2013;30(1):56-66.
13. Huang YZ, Zhou SC, Zhou H, Tong M. Radiofrequency ablation versus cryosurgery ablation for hepatocellular carcinoma: a meta-analysis. *Hepatogastroenterology.* 2013;60(125):1131-1135.
14. Lencioni R, Cioni D, Crocetti L, et al. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. *Radiology.* 2005;234(3):961-967.
15. N'Kontchou G, Mahamoudi A, Aout M, et al. Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. *Hepatology.* 2009;50(5):1475-1483.
16. Raut CP, Izzo F, Marra P, et al. Significant long-term survival after radiofrequency ablation of unresectable hepatocellular carcinoma in patients with cirrhosis. *Ann Surg Oncol.* 2005;12(8):616-628.
17. Lu Z, Wen F, Guo Q, Liang H, Mao X, Sun H. Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: a meta-analysis of randomized-controlled trials. *Eur J Gastroenterol Hepatol.* 2013;25(2):187-194.
18. Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg.* 2006;243(3):321-328.
19. Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? *Hepatology.* 2008;47(1):82-89.
20. Fujimori M, Takaki H, Nakatsuka A, et al. Survival with up to 10-year follow-up after combination therapy of chemoembolization and radiofrequency ablation for the treatment of hepatocellular carcinoma: single-center experience. *J Vasc Interv Radiol.* 2013;24(5):655-666.
21. Peng ZW, Lin XJ, Zhang YJ, et al. Radiofrequency ablation versus hepatic resection for the treatment of hepatocellular carcinomas 2 cm or smaller: a retrospective comparative study. *Radiology.* 2012;262(3):1022-1033.
22. Tohme S, Geller DA, Cardinal JS, et al. Radiofrequency ablation compared to resection in early-stage hepatocellular carcinoma. *HPB (Oxford).* 2013;15(3):210-217.
23. Feng K, Yan J, Li X, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J Hepatol.* 2012;57(4):794-802.
24. Huang J, Yan L, Cheng Z, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg.* 2010;252(6):903-912.
25. Lau WY, Lai EC. The current role of radiofrequency ablation in the management of hepatocellular carcinoma: a systematic review. *Ann Surg.* 2009;249(1):20-25.
26. DuBay DA, Sandroussi C, Kachura JR, et al. Radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. *HPB (Oxford).* 2011;13(1):24-32.

27. Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys.* 2011;81(4):e447-453.
28. O'Connor JK, Trotter J, Davis GL, Dempster J, Klintmalm GB, Goldstein RM. Long-term outcomes of stereotactic body radiation therapy in the treatment of hepatocellular cancer as a bridge to transplantation. *Liver Transpl.* 2012;18(8):949-954.
29. Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol.* 2013;31(13):1631-1639.
30. Vogl TJ, Naguib NN, Nour-Eldin NE, et al. Review on transarterial chemoembolization in hepatocellular carcinoma: palliative, combined, neoadjuvant, bridging, and symptomatic indications. *Eur J Radiol.* 2009;72(3):505-516.
31. Zangan SM, Patel J. Chemoembolization for hepatocellular carcinoma. *Semin Roentgenol.* 2011;46(2):105-114.
32. Raoul JL, Sangro B, Forner A, et al. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. *Cancer Treat Rev.* 2011;37(3):212-220.
33. Georgiades CS, Hong K, D'Angelo M, Geschwind JF. Safety and efficacy of transarterial chemoembolization in patients with unresectable hepatocellular carcinoma and portal vein thrombosis. *J Vasc Interv Radiol.* 2005;16(12):1653-1659.
34. Salem R, Lewandowski R, Roberts C, et al. Use of Yttrium-90 glass microspheres (TheraSphere) for the treatment of unresectable hepatocellular carcinoma in patients with portal vein thrombosis. *J Vasc Interv Radiol.* 2004;15(4):335-345.
35. Barone M, Ettorre GC, Ladisa R, et al. Transcatheter arterial chemoembolization (TACE) in treatment of hepatocellular carcinoma. *Hepatogastroenterology.* 2003;50(49):183-187.
36. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology.* 2002;35(5):1164-1171.
37. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet.* 2002;359(9319):1734-1739.
38. Maluccio MA, Covey AM, Porat LB, et al. Transcatheter arterial embolization with only particles for the treatment of unresectable hepatocellular carcinoma. *J Vasc Interv Radiol.* 2008;19(6):862-869.
39. Kluger MD, Halazun KJ, Barroso RT, et al. Bland embolization versus chemoembolization of hepatocellular carcinoma before transplantation. *Liver Transpl.* 2014;20(5):536-543.
40. Marelli L, Stigliano R, Triantos C, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. *Cardiovasc Intervent Radiol.* 2007;30(1):6-25.
41. Chapman WC, Majella Doyle MB, Stuart JE, et al. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. *Ann Surg.* 2008;248(4):617-625.
42. Chua TC, Liauw W, Saxena A, et al. Systematic review of neoadjuvant transarterial chemoembolization for resectable hepatocellular carcinoma. *Liver Int.* 2010;30(2):166-174.
43. Heckman JT, Devera MB, Marsh JW, et al. Bridging locoregional therapy for hepatocellular carcinoma prior to liver transplantation. *Ann Surg Oncol.* 2008;15(11):3169-3177.
44. Lesurtel M, Mullhaupt B, Pestalozzi BC, Pfammatter T, Clavien PA. Transarterial chemoembolization as a bridge to liver transplantation for hepatocellular carcinoma: an evidence-based analysis. *Am J Transplant.* 2006;6(11):2644-2650.
45. Cescon M, Cucchetti A, Ravaioli M, Pinna AD. Hepatocellular carcinoma locoregional therapies for patients in the waiting list. Impact on transplantability and recurrence rate. *J Hepatol.* 2013;58(3):609-618.
46. De Giorgio M, Vezzoli S, Cohen E, et al. Prediction of progression-free survival in patients presenting with hepatocellular carcinoma within the Milan criteria. *Liver Transpl.* 2010;16(4):503-512.
47. Maddala YK, Stadheim L, Andrews JC, et al. Drop-out rates of patients with hepatocellular cancer listed for liver transplantation: outcome with chemoembolization. *Liver Transpl.* 2004;10(3):449-455.
48. Dhanasekaran R, Kooby DA, Staley CA, Kauh JS, Khanna V, Kim HS. Comparison of conventional transarterial chemoembolization (TACE) and chemoembolization with doxorubicin drug eluting beads (DEB) for unresectable hepatocelluar carcinoma (HCC). *J Surg Oncol.* 2010;101(6):476-480.

49. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol.* 2010;33(1):41-52.
50. Huang K, Zhou Q, Wang R, Cheng D, Ma Y. Doxorubicin-eluting Bead versus Conventional Transarterial Chemoembolization for the Treatment of HCC: a Meta-Analysis. *J Gastroenterol Hepatol.* 2013.
51. Martin R, Geller D, Espat J, et al. Safety and efficacy of trans arterial chemoembolization with drug-eluting beads in hepatocellular cancer: a systematic review. *Hepatogastroenterology.* 2012;59(113):255-260.
52. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology.* 2010;138(1):52-64.
53. Salem R, Mazzaferro V, Sangro B. Yttrium 90 radioembolization for the treatment of hepatocellular carcinoma: biological lessons, current challenges, and clinical perspectives. *Hepatology.* 2013;58(6):2188-2197.
54. Carr BI, Kondragunta V, Buch SC, Branch RA. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. *Cancer.* 2010;116(5):1305-1314.
55. Kooby DA, Egnatashvili V, Srinivasan S, et al. Comparison of yttrium-90 radioembolization and transcatheter arterial chemoembolization for the treatment of unresectable hepatocellular carcinoma. *J Vasc Interv Radiol.* 2010;21(2):224-230.
56. Lance C, McLennan G, Obuchowski N, et al. Comparative analysis of the safety and efficacy of transcatheter arterial chemoembolization and yttrium-90 radioembolization in patients with unresectable hepatocellular carcinoma. *J Vasc Interv Radiol.* 2011;22(12):1697-1705.
57. Moreno-Luna LE, Yang JD, Sanchez W, et al. Efficacy and safety of transarterial radioembolization versus chemoembolization in patients with hepatocellular carcinoma. *Cardiovasc Intervent Radiol.* 2013;36(3):714-723.
58. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology.* 2011;140(2):497-507 e492.
59. Kulik LM, Atassi B, van Holsbeeck L, et al. Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. *J Surg Oncol.* 2006;94(7):572-586.
60. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. *Am J Transplant.* 2009;9(8):1920-1928.
61. Liapi E, Geschwind JF. Intra-arterial therapies for hepatocellular carcinoma: where do we stand? *Ann Surg Oncol.* 2010;17(5):1234-1246.
62. Reyes DK, Vossen JA, Kamel IR, et al. Phase II trial of bevacizumab combined with transarterial chemoembolization (TACE) for hepatocellular carcinoma: Initial experience at two institutions. Paper presented at: ASCO 2010 Gastrointestinal Cancers Symposium 2010; Orlando, FL.
63. Zhong C, Guo RP, Li JQ, et al. A randomized controlled trial of hepatectomy with adjuvant transcatheter arterial chemoembolization versus hepatectomy alone for Stage III A hepatocellular carcinoma. *J Cancer Res Clin Oncol.* 2009;135(10):1437-1445.
64. Choi GH, Shim JH, Kim MJ, et al. Sorafenib alone versus sorafenib combined with transarterial chemoembolization for advanced-stage hepatocellular carcinoma: results of propensity score analyses. *Radiology.* 2013;269(2):603-611.
65. Park JW, Koh YH, Kim HB, et al. Phase II study of concurrent transarterial chemoembolization and sorafenib in patients with unresectable hepatocellular carcinoma. *J Hepatol.* 2012;56(6):1336-1342.
66. Pawlik TM, Reyes DK, Cosgrove D, Kamel IR, Bhagat N, Geschwind JF. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. *J Clin Oncol.* 2011;29(30):3960-3967.
67. Marsh Rde W, Alonzo M, Bajaj S, et al. Comprehensive review of the diagnosis and treatment of biliary tract cancer 2012. Part I: diagnosis-clinical staging and pathology. *J Surg Oncol.* 2012;106(3):332-338.

68. Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation.* 2000;69(8):1633-1637.
69. Rosen CB, Heimbach JK, Gores GJ. Liver transplantation for cholangiocarcinoma. *Transpl Int.* 2010;23(7):692-697.
70. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med.* 2010;362(14):1273-1281.
71. Kim JH, Won HJ, Shin YM, Kim KA, Kim PN. Radiofrequency ablation for the treatment of primary intrahepatic cholangiocarcinoma. *AJR Am J Roentgenol.* 2011;196(2):W205-209.
72. Xu HX, Wang Y, Lu MD, Liu LN. Percutaneous ultrasound-guided thermal ablation for intrahepatic cholangiocarcinoma. *Br J Radiol.* 2012;85(1016):1078-1084.
73. Hoffmann RT, Paprottka PM, Schon A, et al. Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: factors associated with prolonged survival. *Cardiovasc Intervent Radiol.* 2012;35(1):105-116.
74. Mouli S, Memon K, Baker T, et al. Yttrium-90 radioembolization for intrahepatic cholangiocarcinoma: safety, response, and survival analysis. *J Vasc Interv Radiol.* 2013;24(8):1227-1234.
75. Saxena A, Bester L, Chua TC, Chu FC, Morris DL. Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. *Ann Surg Oncol.* 2010;17(2):484-491.
76. Vogl TJ, Naguib NN, Nour-Eldin NE, et al. Transarterial chemoembolization in the treatment of patients with unresectable cholangiocarcinoma: Results and prognostic factors governing treatment success. *Int J Cancer.* 2012;131(3):733-740.
77. Kuhlmann JB, Euringer W, Spangenberg HC, et al. Treatment of unresectable cholangiocarcinoma: conventional transarterial chemoembolization compared with drug eluting bead-transarterial chemoembolization and systemic chemotherapy. *Eur J Gastroenterol Hepatol.* 2012;24(4):437-443.
78. Boehm LM, Jayakrishnan TT, Miura JT, et al. Comparative effectiveness of hepatic artery based therapies for unresectable intrahepatic cholangiocarcinoma. *J Surg Oncol.* 2015;111(2):213-220.
79. Madoff DC, Gupta S, Ahrar K, Murthy R, Yao JC. Update on the management of neuroendocrine hepatic metastases. *J Vasc Interv Radiol.* 2006;17(8):1235-1249; quiz 1250.
80. Ramage JK, Davies AH, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. *Gut.* 2005;54 Suppl 4:iv1-16.
81. Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol.* 2009;27(28):4656-4663.
82. Wolin EM. The expanding role of somatostatin analogs in the management of neuroendocrine tumors. *Gastrointest Cancer Res.* 2012;5(5):161-168.
83. Modlin IM, Pavel M, Kidd M, Gustafsson BI. Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. *Aliment Pharmacol Ther.* 2010;31(2):169-188.
84. Musunuru S, Chen H, Rajpal S, et al. Metastatic neuroendocrine hepatic tumors: resection improves survival. *Arch Surg.* 2006;141(10):1000-1004; discussion 1005.
85. Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *J Am Coll Surg.* 2003;197(1):29-37.
86. van Vilsteren FG, Baskin-Bey ES, Nagorney DM, et al. Liver transplantation for gastroenteropancreatic neuroendocrine cancers: Defining selection criteria to improve survival. *Liver Transpl.* 2006;12(3):448-456.
87. Khasraw M, Gill A, Harrington T, Pavlakis N, Modlin I. Management of advanced neuroendocrine tumors with hepatic metastasis. *J Clin Gastroenterol.* 2009;43(9):838-847.
88. Oberg K, Jelic S. Neuroendocrine gastroenteropancreatic tumors: ESMO clinical recommendation for diagnosis, treatment and follow-up. *Ann Oncol.* 2009;20 Suppl 4:150-153.
89. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):501-513.
90. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):514-523.

91. Gillams A, Cassoni A, Conway G, Lees W. Radiofrequency ablation of neuroendocrine liver metastases: the Middlesex experience. *Abdom Imaging.* 2005;30(4):435-441.
92. Atwell TD, Charboneau JW, Que FG, et al. Treatment of neuroendocrine cancer metastatic to the liver: the role of ablative techniques. *Cardiovasc Intervent Radiol.* 2005;28(4):409-421.
93. Mazzaglia PJ, Berber E, Milas M, Siperstein AE. Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10-year experience evaluating predictors of survival. *Surgery.* 2007;142(1):10-19.
94. Vogl TJ, Naguib NN, Zangos S, Eichler K, Hedayati A, Nour-Eldin NE. Liver metastases of neuroendocrine carcinomas: interventional treatment via transarterial embolization, chemoembolization and thermal ablation. *Eur J Radiol.* 2009;72(3):517-528.
95. Gupta S, Johnson MM, Murthy R, et al. Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rates and survival. *Cancer.* 2005;104(8):1590-1602.
96. Pitt SC, Knuth J, Keily JM, et al. Hepatic neuroendocrine metastases: chemo- or bland embolization? *J Gastrointest Surg.* 2008;12(11):1951-1960.
97. Ruutiainen AT, Soulen MC, Tuite CM, et al. Chemoembolization and bland embolization of neuroendocrine tumor metastases to the liver. *J Vasc Interv Radiol.* 2007;18(7):847-855.
98. Bhagat N, Reyes DK, Lin M, et al. Phase II study of chemoembolization with drug-eluting beads in patients with hepatic neuroendocrine metastases: high incidence of biliary injury. *Cardiovasc Intervent Radiol.* 2013;36(2):449-459.
99. Guiu B, Deschamps F, Aho S, et al. Liver/biliary injuries following chemoembolisation of endocrine tumours and hepatocellular carcinoma: lipiodol vs. drug-eluting beads. *J Hepatol.* 2012;56(3):609-617.
100. Kennedy AS, Dezarn WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. *Am J Clin Oncol.* 2008;31(3):271-279.
101. King J, Quinn R, Glenn DM, et al. Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. *Cancer.* 2008;113(5):921-929.
102. Dhanasekaran R, Kooby D, Staley C, et al. Radioembolization vs. chemoembolization for unresectable neuroendocrine tumor hepatic metastases. *Society of Nuclear Medicine Annual Meeting Abstracts.* 2009;50(Supplement 2):159.
103. Pavel M, Baudin E, Couvelard A, et al. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology.* 2012;95(2):157-176.
104. Frilling A, Modlin IM, Kidd M, et al. Recommendations for management of patients with neuroendocrine liver metastases. *Lancet Oncol.* 2014;15(1):e8-21.
105. Kennedy A, Bester L, Salem R, Sharma RA, Parks RW, Ruszniewski P. Role of hepatic intra-arterial therapies in metastatic neuroendocrine tumours (NET): guidelines from the NET-Liver-Metastases Consensus Conference. *HPB (Oxford).* 2015;17(1):29-37.
106. Primrose JN. Surgery for colorectal liver metastases. *Br J Cancer.* 2010;102(9):1313-1318.
107. Wicherts DA, de Haas RJ, Adam R. Bringing unresectable liver disease to resection with curative intent. *Eur J Surg Oncol.* 2007;33 Suppl 2:S42-51.
108. Brouquet A, Abdalla EK, Kopetz S, et al. High survival rate after two-stage resection of advanced colorectal liver metastases: response-based selection and complete resection define outcome. *J Clin Oncol.* 2011;29(8):1083-1090.
109. Elias D, Goere D, Kohneh-Sahrhi N, de Baere T. Strategies for resection using portal vein embolization: metastatic liver cancer. *Semin Intervent Radiol.* 2008;25(2):123-131.
110. Madoff DC, Abdalla EK, Vauthey JN. Portal vein embolization in preparation for major hepatic resection: evolution of a new standard of care. *J Vasc Interv Radiol.* 2005;16(6):779-790.
111. Lencioni R, Crocetti L, Cioni D, Della Pina C, Bartolozzi C. Percutaneous radiofrequency ablation of hepatic colorectal metastases: technique, indications, results, and new promises. *Invest Radiol.* 2004;39(11):689-697.
112. Khajanchee YS, Hammill CW, Cassera MA, Wolf RF, Hansen PD. Hepatic resection vs minimally invasive radiofrequency ablation for the treatment of colorectal liver metastases: a Markov analysis. *Arch Surg.* 2011;146(12):1416-1423.

113. Habermehl D, Herfarth KK, Bermejo JL, et al. Single-dose radiosurgical treatment for hepatic metastases - therapeutic outcome of 138 treated lesions from a single institution. *Radiat Oncol.* 2013;8(1):175.
114. Martin RC, Joshi J, Robbins K, et al. Hepatic intra-arterial injection of drug-eluting bead, irinotecan (DEBIRI) in unresectable colorectal liver metastases refractory to systemic chemotherapy: results of multi-institutional study. *Ann Surg Oncol.* 2011;18(1):192-198.
115. Nicolay NH, Berry DP, Sharma RA. Liver metastases from colorectal cancer: radioembolization with systemic therapy. *Nat Rev Clin Oncol.* 2009;6(12):687-697.
116. Memon K, Lewandowski RJ, Riaz A, Salem R. Chemoembolization and radioembolization for metastatic disease to the liver: available data and future studies. *Curr Treat Options Oncol.* 2012;13(3):403-415.
117. Ammori JB, Kemeny NE. Regional hepatic chemotherapies in treatment of colorectal cancer metastases to the liver. *Semin Oncol.* 2010;37(2):139-148.
118. Kulaylat MN, Gibbs JF. Regional treatment of colorectal liver metastasis. *J Surg Oncol.* 2010;101(8):693-698.