Radiologic Management of Hepatic Malignancy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol.* 2012;56(4):908-943.	Review/Other-Tx	N/A	EASL–EORTC Clinical Practice Guidelines on the management of HCC.	N/A	4
2. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology.* 2011;53(3):1020-1022.	Review/Other-Tx	N/A	An update of the AASLD practice guidelines on the management of HCC which published in 2005.	N/A	4
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.	Observational-Tx	48 patients	To evaluate the role of OLT in the treatment of patients with cirrhosis and HCC.	Median follow-up 26 months. The overall mortality rate was 17%. After 4 years, the actuarial survival rate was 75% and the rate of recurrence-free survival was 83%. HCC recurred in 4 patients (8%). The OS and recurrence-free survival rates at 4 years among the 35 patients (73% of the total) who met the predetermined criteria for the selection of small HCC at pathological review of the explanted liver were 85% and 92%, respectively, whereas the rates in the 13 patients (27%) whose tumors exceeded these limits were 50% and 59%, respectively (P=0.01 for OS; P=0.002 for recurrence-free survival). In this group of 48 patients with early-stage tumors, tumor-node-metastasis status, the number of tumors, the serum AFP concentration, and treatment received before transplantation, and 10 other variables were not significantly correlated with survival. Liver transplantation is an effective treatment for small, unresectable HCC in patients with cirrhosis.	2

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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.	Observational-Tx	321 patients	To report the effectiveness of limited hepatic resection for cirrhotic patients with HCC.	Anatomic resection did not influence overall and recurrence-free survival rates after hepatic resection. In the liver damage A group (n=215), both 5-year overall and recurrence-free survival rates in the anatomic resection group were considerably better than those in the limited resection group (87% vs 76%, P=0.02, and 63% vs 35%, P<0.01, respectively). In the liver damage B group (n=106), both 5-year overall and recurrence-free survival rates in the anatomic resection group were substantially worse than those in the limited resection group (48% vs 72%, P<0.01, and 28% vs 43%, P=0.01, respectively). The results of multivariate analysis revealed that anatomic resection was a notably poor factor in promoting recurrence-free survival in patients with liver damage B.	2
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.	Review/Other-Tx	N/A	To review results of published clinical trials of systemic therapy and immunotherapy that has impacted the present treatment of HCC.	With recent progress in the elucidation of HCC molecular pathways, targeted agents show promise. The multikinase inhibitor sorafenib has provided survival benefit in patients with advanced HCC and well-preserved liver function. Sunitinib, bevacizumab, epidermal growth factor receptor inhibitors, and mammalian target of rapamycin inhibitors have shown activity in small patient cohorts. Immunotherapy appears to be a promising approach that can result in the regression of bulky, invasive cancer in some patients.	4
6. Feng M, Ben-Josef E. Radiation therapy for hepatocellular carcinoma. *Semin Radiat Oncol.* 2011;21(4):271-277.	Review/Other-Tx	N/A	To review role of radiation therapy in the treatment of HCC.	With today's highly conformal techniques, high doses can be delivered via conventional fractionation or SBRT with a low risk of toxicity in patients with intact liver function. Patients with compromised liver function should be treated more cautiously. Because of a high likelihood of progressive disease outside of the treated volumes, combination therapy with TACE or systemic agents should be further explored.	4

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7. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359(4):378-390.	Experimental-Tx	602 patients	To evaluate the effectiveness of sorafenib in advanced HCC.	Median OS was 10.7 months in the sorafenib group and 7.9 months in the placebo group (HR in the sorafenib group, 0.69; 95% CI, 0.55 to 0.87; $P<0.001$). There was no significant difference between the 2 groups in the median time to symptomatic progression (4.1 months vs 4.9 months, respectively, $P=0.77$). The median time to radiologic progression was 5.5 months in the sorafenib group and 2.8 months in the placebo group ($P<0.001$). 7 patients in the sorafenib group (2%) and 2 patients in the placebo group (1%) had a partial response; no patients had a complete response. Diarrhea, weight loss, hand-foot skin reaction, and hypophosphatemia were more frequent in the sorafenib group. In patients with advanced HCC, median survival and the time to radiologic progression were nearly 3 months longer for patients treated with sorafenib than for those given placebo.	1
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.	Meta-analysis	8 studies	To evaluate the evidence, comparing RFA, PEI and PAI using meta-analytical techniques.	8 studies were identified: RFA vs PEI (n=5), PAI vs PEI (n=2) and RFA vs PAI vs PEI (n=1) including 1,035 patients with 9 comparisons. RFA was superior to PEI for survival (OR 0.52; 95% CI, 0.35–0.78; $P=0.001$), complete necrosis of tumor and LC. For tumors 2 cm RFA was not significantly better than PEI. PAI did not differ significantly from PEI for survival (OR 0.55; 95% CI, 0.23–1.33; $P=0.18$), and LC but required less sessions. PAI had similar outcomes, except LC, to RFA in the direct and indirect comparison.	M

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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.	Meta-analysis	652 patients; 4 randomized trials	To identify survival benefit of any percutaneous ablation therapy as compared with PEI in the treatment of patients with unresectable HCC.	A meta-analysis of the 4 randomized controlled trials demonstrated a significant improvement in 3-year survival favoring RFA over PEI (OR 0.477, 95% CI, 0.340–0.670; $P<0.001$). Heterogeneity among the 4 trials was not significant (Q = 4.586; $P=0.205$). Egger's test revealed that the publication bias was not significant ($P=0.647$). However, the number of patients included in the analysis was insufficient for a robust meta-analysis of initial tumor response. The definition of local tumor progression or major complication was not unified among the trials included in the meta-analysis. RFA demonstrated significantly improved 3-year survival status for patients with HCC, when compared to PEI.	M
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.	Meta-analysis	701 patients; 5 randomized controlled trials	To review the available evidence comparing RFA to PEI for small HCC.	The OS was significantly higher in patients treated with RFA than in those treated with PEI (risk differences 0.116, 95% CI, 0.173/0.060; heterogeneity not present). LR rate is significantly higher in patients treated with PEI than in those treated with RFA. In the RFA group the 1, 2, and 3 years cancer-free survival rates were significantly better than in the PEI-treated patients (respectively: risk differences 0.098, 95% CI, 0.006/0.189; heterogeneity $P=0.57$; risk differences 0.187, 95% CI, 0.082/0.293; heterogeneity $P=0.98$; risk differences 0.210, 95% CI, 0.095/0.325; heterogeneity $P=0.78$). A small number of adverse events were reported in the 2 treatments. RFA is superior to PEI in the treatment of small HCC with respect to OS, 1, 2, and 3 years survival rates, 1, 2, and 3 cancer-free survival rates, and tumor response. RFA shows a significantly smaller risk of LR.	M

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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.	Review/Other-Tx	N/A	To evaluate the presently available data for microwave coagulation therapy and assess the level of evidence to support its clinical use.	Although randomized controlled trials comparing RFA and microwave coagulation therapy for hepatic ablation are lacking, our review (based on level 2 data) supports that microwave coagulation therapy may be optimal when larger necrosis zones and/or ablation of multiple lesions are the objectives. The data support that the potential procedural advantage(s) noted for ablation of CRHM and HCC >3 cm, is not supported for HCC <3 cm; moreover microwave coagulation therapy shares with all other ablation modalities a high rate of locoregional recurrence in HCC; likely due to the multicentricity of this disease process.	4
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.	Review/Other-Tx	N/A	To review the current state of microwave ablation including technical and clinical considerations.	Microwave ablation is an extremely promising heat-based thermal ablation modality that has particular applicability in treating hepatic malignancies. Microwaves can generate very high temperatures in very short time periods, potentially leading to improved treatment efficiency and larger ablation zones. As the available technology continues to improve, microwave ablation is emerging as a valuable alternative to RFA in the treatment of hepatic malignancies.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Meta-analysis	7 clinical studies with 700 participants	Meta-analysis was performed to evaluate the efficacy and safety of DEB-TACE and conventional TACE treatments for patients with unresectable HCC.	Significantly better objective tumor response was found following DEB-TACE over conventional TACE (OR=1.92, 95% CI, [1.34, 2.77]; *P*=0.0004) with relative risk difference of 0.15 [0.07, 0.24] (*P*=0.0003). 1-year, 2-year survival rates were statistically significant higher in DEB-TACE group compared with conventional TACE group (Peto OR, 95% CI: 0.64 [0.46, 0.89], *P*=0.007; 0.61 [0.47, 0.80], *P*=0.0003; respectively). Peto OR of 6-month and 3-year survival were 0.72 [0.46, 1.14] (*P*=0.16) and 0.77 [0.55, 1.06] (*P*=0.11) respectively; showing no difference statistically. The authors could still find tendency that favors DEB-TACE group. Adverse side effects were similar in both groups and post-embolization syndrome existed most commonly.	M
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.	Observational-Tx	206 patients	To perform a prospective, intention-to-treat clinical trial to determine the long-term survival rates of patients with hepatic cirrhosis and early-stage HCC in whom percutaneous image-guided RFA was used as the sole first-line anticancer treatment.	OS rates were 97% at 1 year, 67% at 3 years, and 41% at 5 years. Median survival was 49 months. In the 187 patients treated with RFA, OS rates were 97% at 1 year, 71% at 3 years, and 48% at 5 years. Median survival was 57 months. The difference between the 2 survival curves was not statistically significant (*P*=.5094). Survival of patients treated with RFA was dependent on Child class (*P*=.0006) and tumor multiplicity (*P*=.0133). Patients who had Child class A cirrhosis with solitary HCC (n=116) had 1-, 3-, and 5-year survival rates of 100%, 89% and 61%; median survival was 65 months. The 1-, 3-, and 5-year recurrence rates were 14%, 49%, and 81% for the emergence of new tumors and 4%, 10%, and 10% for local tumor progression. RFA is an effective first-line treatment for cirrhotic patients with early-stage HCC who were excluded from surgery.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	235 consecutive patients	To assess RFA as a first-line therapeutic option in the treatment of HCC.	The overall 5-year survival rate was 76% for operable patients. Factors associated with OS were prothrombin activity (HR = 0.97, 0.96–0.98; $P<0.0001$) and serum levels of AFP (HR = 1.02, 1.02–1.02; $P<0.0001$), and factors associated with tumor recurrence were multinodular forms (HR = 2.34; 1.52–3.6; $P=0.0001$) and serum AFP levels (HR=1.015, 1.014–1.016; $P=0.015$). Tumor size was associated with LR but not with overall and tumor-free survival. RFA is a safe and effective first-line treatment of HCC up to 5 cm in diameter, especially for patients with a single tumor, a low serum AFP level, and well-preserved liver function.	2
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.	Observational-Tx	194 patients	To prospectively evaluate survival rates in patients with early-stage, unresectable HCC treated with RFA.	Median follow-up 34.8 months. Percutaneous and open intraoperative RFA was performed in 140 (72%) and 54 (28%) patients, respectively. The median diameter of tumors treated with RFA was 3.3 cm. Disease recurred in 103 (53%) of 194 patients, including 69 (49%) of 140 patients treated percutaneously and 34 (63%) of 54 treated with open RFA (not significant). LR developed in 9 patients (4.6%). Most recurrence was intrahepatic. The overall complication rate was 12%. OS rates at 1, 3, and 5 years for all 194 patients were 84.5%, 68.1%, and 55.4%, respectively. Treatment with RFA can produce significant long-term survival rates for cirrhotic patients with early-stage, unresectable HCC. RFA can be performed in these patients with relatively low complication rates. Confirmation of these results in randomized trials should be considered.	1

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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.	Meta-analysis	7 randomized-controlled trials	A meta-analysis of randomized-controlled trials was performed to provide greater clarity on whether RFA plus TACE was more effective than RFA alone for HCC.	Meta-analysis showed that RFA plus TACE significantly improved the survival rates of patients with HCC at 1 and 3 years (for the 1-survival rate, fixed-effects OR=2.71, 95% CI 1.65–4.43, $P<0.0001$; for the 3-survival rate, fixed-effects OR=2.27, 95% CI 1.57–3.27, $P<0.0001$) compared with RFA alone. There was no difference in terms of major complications (fixed-effects OR=1.26, 95% CI 0.33–4.77, $P=0.73$). Subgroup analyses by tumor size showed that RFA plus TACE significantly improved the survival rates at 1, 3, and 5 years compared with RFA alone in patients with HCC larger than 3 cm; however, there was no advantage of TACE plus RFA over RFA alone for patients with HCC >3 cm. The quality of evidence was high for the 1-year survival rate, the 3-year survival rate, and major complications. No evidence of publication bias was observed.	M
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.	Experimental-Tx	180 total patients: 90 received percutaneous local ablative therapy; 90 received surgical resection	Randomized trial to compare the results of percutaneous local ablative therapy with surgical resection in the treatment of solitary and small HCC.	The 1-, 2-, 3-, and 4-year OS rates after percutaneous local ablative therapy and surgery were 95.8%, 82.1%, 71.4%, 67.9% and 93.3%, 82.3%, 73.4%, 64.0%, respectively. The corresponding DFS rates were 85.9%, 69.3%, 64.1%, 46.4% and 86.6%, 76.8%, 69%, 51.6%, respectively. Statistically, there was no difference between these 2 treatments. Percutaneous local ablative therapy was as effective as surgical resection in the treatment of solitary and small HCC. Percutaneous local ablative therapy had the advantage over surgical resection in being less invasive.	1

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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.	Observational-Tx	218 patients	To assess the response and complications rates after RFA of very early HCC in cirrhosis compared to results achieved with resection.	After a median follow-up of 31 months, sustained complete response was observed in 216 patients (97.2%). In the remaining 6, PEI, selective intra-arterial chemoembolization, or resection were used as salvage therapy. Perioperative mortality, major complication, and 5-year survival rates were 0%, 1.8%, and 68.5%, respectively. Conclusion: Compared with resection, RFA is less invasive and associated with lower complication rate and lower costs. RFA is also just as effective for ensuring local control of stage T1 HCC, and it is associated with similar survival rates (as recently demonstrated by 2 randomized trials). These data indicate that RFA can be considered the treatment of choice for patients with single HCC ≤2.0 cm, even when surgical resection is possible. Other approaches can be used as salvage therapy for the few cases in which RFA is unsuccessful or unfeasible.	2

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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.	Observational-Tx	277 patients with 382 treatment-naive HCCs	To report 10-year outcomes of treating HCCs by combination therapy of chemoembolization and RFA.	Tumor enhancement disappeared after 466 RFA sessions in all tumors, resulting in a complete response rate of 100% (277/277) based on modified Response Evaluation Criteria In Solid Tumors. Local tumor progression developed in 15 patients (5.4%; 15/277) during the mean follow-up of 44.9 months +/- 29.1 (range, 6.0–134.4 months). OS and recurrence-free survival rates were 56.3% (95% CI, 52.5%–60.2%) and 22.5% (95% CI, 19.3%–25.6%) at 5 years and 23.5% (95% CI, 17.7%–29.2%) and 9.3% (95% CI, 6.3%–12.4%) at 10 years. The Child-Pugh class was the only significant prognostic factor detected in both the univariate (P<.001) and the multivariate analyses (HR, 3.8; 95% CI, 2.5–5.6; P<.001). The 5-year and 10-year OS rates were 66.4% (95% CI, 62.0%–70.8%) and 30.6% (95% CI, 23.3%–37.9%) in 210 Child-Pugh class A patients. In addition to the Child-Pugh class, the maximum tumor diameter (≤3 cm vs >3 cm) and the tumor number (single vs multiple) were significant independent factors affecting recurrence-free survival. No death was related to the combination therapy. The major complication rate was 3.2% (15/466).	2

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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.	Observational-Tx	145 patients	To compare retrospectively the effects of percutaneous RFA with those of hepatic resection in the treatment of HCC measuring 2 cm or smaller.	One death was considered to be related to treatment after surgical resection. Major complications occurred significantly more often in the surgical resection group (38/74 patients) than in the RFA group (14/71 patients) (*P*=.009). The 1-, 3-, and 5-year OS rates were 98.5%, 87.7%, and 71.9%, respectively, with RFA and 90.5%, 70.9%, and 62.1% with surgical resection (*P*=.048). The corresponding recurrence-free survival rates were 76.4%, 65.2%, and 59.8% with RFA and 75.6%, 56.1%, and 51.3% with surgical resection (*P*=.548). At subgroup analysis of patients with central HCC, 1-, 3-, and 5-year OS rates were 96.6%, 93.0%, and 79.9% with RFA and 92.0%, 71.6%, and 61.5% with surgical resection (*P*=.020). The corresponding recurrence-free survival rates were 86.5%, 74.0%, and 67.0% with RFA and 68.0%, 40.0%, and 40.0% with surgical resection (*P*=.033). For patients with peripheral HCC, 1-, 3-, and 5-year OS rates were 97.3%, 83.3%, and 65.1% with RFA and 87.8%, 68.4%, and 62.9% with surgical resection (*P*=.464). The corresponding recurrence-free survival rates were 68.7%, 59.2%, and 54.9% with RFA and 82.9%, 66.6%, and 52.9% with surgical resection (*P*=.351).	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	110 patients	To compare survival outcomes after hepatic resection and RFA in early-stage HCC at a Western hepatobiliary centre.	Patients who underwent hepatic resection had larger tumors, a longer length of stay and a higher rate of postoperative complications. After a median follow-up of 29 months, there were no significant differences between the treatment groups in 1-, 3- and 5-year OS [RFA group: 86%, 50%, 35%, respectively; hepatic resection group: 88%, 68%, 47%, respectively (P= 0.222)] or DFS [RFA group: 68%, 42%, 28%, respectively; hepatic resection group: 66%, 42%, 34%, respectively (P= 0.823)]. The 58 patients who underwent RFA demonstrated ablation success on follow-up CT at 3 months. Of these, 96.5% of patients showed sustained ablation success over the entire follow-up period. In a subgroup analysis of patients with tumors measuring 2–5 cm, no differences in OS or DFS emerged between the hepatic resection and RFA groups. Similarly, no significant differences in outcomes in patients with Child-Pugh class A cirrhosis were seen between the RFA and hepatic resection groups.	2
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.	Experimental-Tx	168 patients	To compare the efficacy of RFA with surgical resection in the treatment of small HCC.	The 1-, 2-, and 3-year survival rates for the surgical resection and RFA groups were 96.0%, 87.6%, 74.8% and 93.1%, 83.1%, 67.2%, respectively. The corresponding recurrence-free survival rates for the 2 groups were 90.6%, 76.7%, 61.1% and 86.2%, 66.6%, 49.6%, respectively. There were no statistically significant differences between the 2 groups in OS rate (P=0.342) or recurrence-free survival rate (P=0.122). Multivariate analysis demonstrated that the independent risk factors associated with survival were multiple occurrences of tumors at different hepatic locations (relative risk of 2.696; 95% CI: 1.189–6.117; P=0.018) and preoperative indocyanine green retention rate at 15 min (relative risk of 3.853; 95% CI: 1.647–9.015; P=0.002).	1

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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.	Experimental-Tx	230 patients	To compare the long-term outcomes of surgical resection and RFA for the treatment of small HCC.	The 1-, 2-, 3-, 4- and 5-year OS rates for the RFA group and the surgical resection group were 86.96%, 76.52%, 69.57%, 66.09%, 54.78% and 98.26%, 96.52%, 92.17%, 82.60%, 75.65%, respectively. The corresponding recurrence-free survival rates for the 2 groups were 81.74%, 59.13%, 46.08%, 33.91%, 28.69% and 85.22%, 73.92%, 60.87%, 54.78%, 51.30%, respectively. OS and recurrence-free survival were significantly lower in the RFA group than in the surgical resection group (P=0.001 and P=0.017). The 1-, 2-, 3-, 4-, and 5-year overall recurrence rates were 16.52%, 38.26%, 49.57%, 59.13%, and 63.48% for the RFA group and 12.17%, 22.60%, 33.91%, 39.13%, and 41.74% for the surgical resection group. The overall recurrence was higher in the RFA group than in the surgical resection group (P=0.024).	1
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.	Review/Other-Tx	N/A	To review the current status of RFA in the management of HCC.	The evidence in the medical literature showed RFA was more effective than other local ablative therapies, and supported its use in the treatment of unresectable small HCC, recurrent small HCC, and as bridging therapy before liver transplantation, and as a primary treatment in competition with partial hepatectomy for resectable small HCC.	4

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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.	Observational-Tx	170 patients: RFA (n= 77) and No Treatment groups (n= 93)	To measure the effect of RFA on time to drop-off in HCC-listed patients.	The primary effectiveness of RFA was 83% (complete radiographic response). RFA was associated with a longer median wait time to transplant (9.5 vs 5 months). Tumor-specific drop-off events were equivalent between RFA (21%) and No Treatment (12%) groups (P=0.11). Controlling for wait time, there was no difference in overall (P=0.56) or tumor-specific drop-off (P=0.94). Furthermore, there were no differences in 5-year OS or tumor-free survivals from list date or transplant. Using multivariate analysis, the likelihood of receiving a transplant and patient survivals were associated with tumor characteristics (AFP, tumor number and size) and not with bridge therapy or waiting time.	2
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.	Observational-Tx	60 patients	To evaluate the safety and efficacy of SBRT for the treatment of primary HCC.	The median follow-up time was 27 months, and the median tumor diameter was 3.2 cm. The 2-year LC, PFS, and OS were 90%, 48%, and 67%, respectively, with median TTP of 47.8 months. Subsequently, 23 patients underwent transplant, with a median time to transplant of 7 months. There were no ≥Grade 3 nonhematologic toxicities. 13% of patients experienced an increase in hematologic/hepatic dysfunction >1 grade, and 20% experienced progression in Child-Turcotte-Pugh class within 3 months of treatment.	2
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.	Observational-Tx	10 patients	To report the safety and efficacy of SBRT, the explant pathology findings and survival of patients treated with SBRT as a bridge to transplantation for HCC.	At 5 years, the OS rate and the DFS rate were both 100%. Overall, 4 of the 10 patients (40%) experienced acute toxicity. Most toxicities were grade 1, and they included nausea, fatigue, and abdominal discomfort. One patient had grade 2 nausea/vomiting. Explant pathology revealed no viable tumor in 3 of the 11 tumors for a complete response rate of 27%. The remaining 8 tumors decreased or remained stable in size.	3

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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.	Observational-Tx	102 patients	To describe outcomes of prospective trials of SBRT for HCC.	A total of 102 patients were evaluable (Trial 1, 2004 to 2007: n = 50; Trial 2, 2007 to 2010: n = 52). Underlying liver disease was hepatitis B in 38% of patients, hepatitis C in 38%, alcohol related in 25%, other in 14%, and none in 7%. 52% received prior therapies (no prior sorafenib). TNM stage was III in 66%, and 61% had multiple lesions. Median gross tumor volume was 117.0 mL (range, 1.3 to 1,913.4 mL). Tumor vascular thrombosis was present in 55%, and extrahepatic disease was present in 12%. Local control at 1-year was 87% (95% CI, 78% to 93%). SBRT dose (HR = 0.96; *P*=.02) and being in Trial 2 (HR = 0.38; *P*=.03) were associated with local control at 1-year on univariate analysis. Toxicity ≥ grade 3 was seen in 30% of patients. In 7 patients (2 with tumor vascular thrombosis progressive disease), death was possibly related to treatment (1.1 to 7.7 months after SBRT). Median OS was 17.0 months (95% CI, 10.4 to 21.3 months), for which only tumor vascular thrombosis (HR = 2.47; *P*=.01) and being in Trial 2 (HR = 0.49; *P*=.01) were significant on multivariate analysis.	1
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.	Review/Other-Tx	N/A	An overview on the palliative, combined, neoadjuvant, bridging, and symptomatic indications of TACE in patients with HCC.	Palliatively, TACE is performed to control symptoms and prolong survival in HCC patients; in some indications TACE allows a local tumor control of 18%–63%. For combined indications, excellent results were achieved by combined therapies, such as PEI/TACE, RFA/TACE, and laser-induced thermotherapy/TACE. As a neoadjuvant therapy prior to liver resection TACE showed 70% tumor control. Though debatable, TACE still plays a role as a bridging tool before liver transplantation. Symptomatic indication of TACE in ruptured HCC showed 83%–100% control of bleeding but survival was poor. TACE represents an important therapeutic tool against HCC in general in addition to its special role in cases of unresectable HCC.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
31. Zangan SM, Patel J. Chemoembolization for hepatocellular carcinoma. *Semin Roentgenol.* 2011;46(2):105-114.	Review/Other-Tx	N/A	To examine role of chemoembolization in patients with HCC.	Chemoembolization is an effective treatment for patients with unresectable HCC. It is considered the standard of care of intermediate stage HCC.	4
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.	Review/Other-Tx	108 citations	Results of an extensive literature review on the treatment of unresectable HCC with TACE were combined with atuhors' clinical experience to identify factors that may predict survival after TACE.	Although TACE is 1 of the most widely used methods of treating unresectable HCC, the lack of standardization in treatment methodology and patient selection makes it difficult to draw any firm conclusions from study data.	4
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.	Observational-Tx	32 consecutive patients	To determine whether TACE can be performed safely in patients with HCC and portal vein thrombosis and to correlate relevant variables with survival.	Median OS was 9.5 months (range, 3–50 months). Child-Pugh numerical disease stage was the prognostic factor most strongly related to survival. The 30-day mortality rate was zero and there was no evidence of TACE-related hepatic infarction or acute liver failure. The 6-, 9-, 12-, and 18-month survival rates were 60%, 47%, 25%, and 12.5%, respectively. Portal vein thrombosis should not be considered a contraindication to TACE. Compared with historical control subjects who received traditional forms of treatment, the patients in the present study had extended survival. However, prospective randomized trials are necessary to show this conclusively and to show which subgroups benefit.	2
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.	Review/Other-Tx	15 patients	To examine use of Y-90 glass microspheres (TheraSphere) for the treatment of unresectable HCC in patients with portal vein thrombosis. This study presents hepatic toxicity results after unilobar and bilobar intra-arterial administration of Y-90- microS in patients with unresectable HCC who had known portal vein thrombosis without evidence of cavernous transformation.	Y-90- microS treatment was well tolerated and appears to be safe to use in patients with compromised portal venous flow in 1 or both first order and related segmental portal venous branches and no evidence of cavernous transformation. In patients who did not exhibit disease progression, there appeared to be no clinically significant change in bilirubin.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. Barone M, Ettorre GC, Ladisa R, et al. Transcatheter arterial chemoembolization (TACE) in treatment of hepatocellular carcinoma. *Hepatogastroenterology.* 2003;50(49):183-187.	Observational-Tx	193 total consecutive patients: 110 treated; 83 controls	To evaluate the efficacy of segmental transcatheter arterial chemoembolization in amelioring patient survival and to determine which patients might really benefit from this treatment.	Median survival significantly longer with TACE (26 vs 10 months). Multivariate analysis demonstrated longer survival with TACE, Child Class A, low AFP, and tumor diameter <3 cm. Transcatheter arterial chemoembolization significantly ameliorates survival in patients with HCC. However, the presence of large tumors producing high AFP levels in patients with advanced Child class should discourage treatment.	1
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.	Experimental-Tx	79 total patients: 40 chemoembolization; 39 controls	Randomized trial to assess the efficacy of transarterial Lipiodol chemoembolization in patients with unresectable HCC.	Chemoembolization resulted in a marked tumor response, and the actuarial survival was significantly better in the chemoembolization group (1 year, 57%; 2 years, 31%; 3 years, 26%) than in the control group (1 year, 32%; 2 years, 11%; 3 years, 3%; *P*=.002). When adjustments for baseline variables that were prognostic on univariate analysis were made with a multivariate Cox model, the survival benefit of chemoembolization remained significant (relative risk of death, 0.49; 95% CI, 0.29-0.81; *P*=.006). Although death from liver failure was more frequent in patients who received chemoembolization, the liver functions of the survivors were not significantly different. In conclusion, in Asian patients with unresectable HCC, transarterial Lipiodol chemoembolization significantly improves survival and is an effective form of treatment.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	903 patients assessed; 112 patients included	Randomized controlled trial to assess the survival benefits of regularly repeated arterial embolization (gelatin sponge) or chemoembolization (gelatin sponge plus doxorubicin) compared with conservative treatment.	25/37 patient's assigned embolization. 21/40 assigned chemoembolization, and 25/35 assigned conservative treatment died. Survival probabilities at 1 year and 2 years were 75% and 50% for embolization; 82% and 63% for chemoembolization, and 63% and 27% for control (chemoembolization vs control P=0.009). Chemoembolization induced objective responses sustained for at least 6 months in 35% (14) of cases, and was associated with a significantly lower rate of portal-vein invasion than conservative treatment. Treatment allocation was the only variable independently related to survival (OR 0.45 [95% CI, 0.25–0.81], P=0.02). Chemoembolization improved survival of stringently selected patients with unresectable HCC.	1
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.	Observational-Tx	322 patients	Retrospective study to determine the survival of patients with HCC treated with a standardized method of transcatheter arterial embolization with small embolic particles intended to impart terminal vessel blockade, and to evaluate prognostic factors that impact OS.	The median survival time was 21 months, with 1-, 2-, and 3-year OS rates of 66%, 46%, and 33%, respectively. In patients without extrahepatic disease or portal vein involvement by tumor, the overall 1-, 2-, and 3-year survival rates increased to 84%, 66%, and 51%, respectively. Okuda stage, extrahepatic disease, diffuse disease (≥5 tumors), and tumor size were independent predictors of survival on multivariate analysis. There were 90 complications (11.9%) in 75 patients, including 8 deaths (2.5%), within 30 days of embolization. Hepatic arterial embolization with small particles to cause terminal vessel blockade is an effective treatment method for patients with unresectable HCC. These data support the hypothesis that particles alone may be the critical component of catheter-directed embolotherapy.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	25 TAE patients matched in a 1:2 ratio with TACE patients	A retrospective, matched case-control study of patients undergoing TAE and TACE while awaiting transplantation was performed. Equivalency between treatments was hypothesized.	The mean adjusted MELD scores at transplantation and waiting times were not significantly different between the TAE and TACE patients (MELD scores: 26 +/- 3 vs 24 +/- 3 points, *P*=0.12; waiting times: 13 +/- 8 vs 11 +/- 10 months, *P*=0.43). TAE patients (16%) were less likely than TACE patients (40%) to require 2 procedures (*P*=0.04). Explant tumors were completely necrotic for 36% of the TAE patients and for 26% of the TACE patients. The 3-year OS rates were 78% for the TAE patients and 74% for the TACE patients (*P*=0.66), and the 3-year recurrence-free survival rates were 72% for the TAE patients and 68% for the TACE patients (*P*=0.67). On an intention-to-treat basis, there was no significant risk of wait-list dropout associated with TAE or TACE (*P*=0.83).	2
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.	Review/Other-Tx	9 randomized control trials	To evaluate whether specific patient characteristics and/or radiological transarterial techniques result in better outcomes.	Anticancer drugs were used as sole agent in 75% of cases (double 15% and triple 6%): doxorubicin (36%), cisplatin (31%), epirubicin (12%), mitoxantrone (8%), mitomycin (8%), and SMANCS (5%). Embolizing agents used were: gelatin sponge particles (71%), polyvinyl alcohol particles (8%), degradable starch microspheres (4%), and embospheres (4%). Sessions per patient were 2.5 +/- 1.5 (interval: 2 months). Objective response was 40 +/- 20%; survival rates at 1, 2, 3, and 5 years were: 62 +/- 20%, 42 +/- 17%, 30 +/- 15%, and 19 +/- 16%, respectively, and survival time was 18 +/- 9.5 months. The post-TACE complications were: acute liver failure, 7.5% (range 0%–49%); acute renal failure, 1.8% (0%–13%); encephalopathy, 1.8% (0%–16%); ascites, 8.3% (0%–52%); upper gastrointestinal bleeding; 3% (0%–22%); and hepatic or splenic abscess, 1.3% (0%–2.5%). Treatment-related mortality was 2.4% (0%–9.5%), mainly due to acute liver failure.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	202 patients referred for transplant	To evaluate outcomes of downstaging patients with advanced (American liver tumor study group stage III/IV) HCC with TACE to allow eligibility for OLT.	18/76 (23.7%) patients had adequate downstaging to qualify for OLT under the Milan criteria. By Response Evaluation Criteria in Solid Tumors, 27/76 (35.5%) patients had a partial response, 22/76 (29%) had stable disease, and 27/76 (35.5%) had progressive disease. 17/76 (22.4%) patients who met other qualifications underwent OLT after successful downstaging (13/38 stage III; 4/38 stage IV). Explant review demonstrated 28 identifiable tumors in which post-TACE necrosis was greater than 90% in 21 (75%). At a median of 19.6 months (range 3.6-104.7), 16/17 (94.1%) patients who underwent OLT are alive. Selected patients with stage III/IV HCC can be downstaged to Milan criteria with TACE. Importantly, patients who are successfully downstaged and transplanted have excellent midterm DFS and OS, similar to stage II HCC.	2
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.	Review/Other-Tx	3,927 patients: 1,293 underwent neoadjuvant TACE; 18 studies; 3 randomized trials; 15 observational trials	To identify published studies of TACE administered preoperatively as a neoadjuvant treatment for resectable HCC.	The median DFS in the TACE and non-TACE group ranged from 10 to 46 and 8 to 52 months. 67% of studies reporting similar DFS between groups despite higher extent of tumor necrosis from the resected specimens indicating a higher rate of pathological response (partial TACE 27%–72% vs non-TACE 23%–52%). Complete TACE 0%–28% vs non-TACE 0%), with no difference in surgical morbidity and mortality outcome. No conclusion could be drawn with respect to OS. Both randomized and non-randomized trials suggest the use of TACE preoperatively as a neoadjuvant treatment in resectable HCC is a safe and efficacious procedure with high rates of pathological responses. However, it does not appear to improve DFS.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	123 total patients: 50 patients received therapy (20 TACE, 16 Y-90,13 RFA, 3 resections); 73 patients transplanted without therapy	To examine locoregional therapies and their effect on survival compared with transplantation alone.	Median list time was 28 days (range 2–260 days) in group I, and 24 days (range 1–380 days) in group II. Median time from therapy to OLT was 3.8 months (range 9 days to 68 months). 12 patients (24%) were successfully downstaged (8 TACE, 2 Y-90, 2 RFA/resection). Overall 1-, 3-, and 5-year survival were 81%, 74%, and 74%, respectively. Survival was not statistically significantly different between the 2 groups (P=0.53). The 12 patients downstaged did not have a significant difference in survival as compared with the patients who received therapy but did not respond or the patients who were transplanted without therapy (P=0.76). Report addresses locoregional therapy for HCC as a bridge to transplant. There was no statistical difference in OS between patients treated and those not treated prior to transplant. Locoregional therapy is a safe tool for patients on the transplant list, does not impact survival, and can downstage selected patients to allow life-saving liver transplantation.	2
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.	Review/Other-Tx	N/A	To assess the impact of TACE as a neoadjuvant therapy prior to OLT for HCC.	There is currently no convincing evidence that TACE allows to expand the current selection criteria for OLT, nor that TACE decreases dropout rates on the waiting list (grade C). However, TACE does not increase the risk for postoperative complications (grade C). There is insufficient evidence that TACE offers any benefit when used prior to OLT, neither for early nor for advanced HCC. Well-designed randomized controlled trials are needed to define the role of TACE in OLT patients.	4
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.	Review/Other-Tx	N/A	To review HCC locoregional therapies for patients in the waiting list.	With a persistent scarcity of organ donors, neo-adjuvant treatments can help identify patients with different probabilities of cancer progression, and consequently balance the priority of HCC and non-HCC candidates through revised additional scores for HCC.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	206 patients	To retrospectively analyze the risk of progression of HCC (death or progression outside United Network of Organ Sharing stage T2) in a consecutive cohort of prospectively followed patients that presented within the Milan criteria.	Progression occurred in 84 patients, and 8 patients died. Risk factors for the time to disease progression (death or progression beyond T2) were analyzed in 170 patients with a complete data set. Risk factors with the strongest relationship to progression included tumor diameter and tumor persistence/recurrence after local therapy (HRs of 1.51 and 2.75, respectively, when transplanted patients were censored at the time of transplantation and HRs of 1.53 and 3.66, respectively, when transplantation was counted as an event; $P \leq 0.0001$). To evaluate the current MELD exception, we compared the expected progression rate with our observed progression rate in 133 stage T2 patients. The current policy resulted in a large overestimation of the progression rate for T2 HCC and an unsatisfactory performance [Harrell's concordance index (C index) = 0.60, transplant censored; C index = 0.55, transplant as progression]. Risk factors for progression that were identified by univariate analysis were considered for multivariate analysis. With these risk factors and the patients' natural MELD scores, an adjusted model applicable to organ allocation was generated, and this decreased the discrepancy between the expected and observed progression rates (C index = 0.66, transplant censored; C index = 0.69, transplant as progression).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	54 patients	To analyze drop-out rates on the waiting list for patients with HCC.	Between January 1994 and August 2001, 54 patients with HCC were listed for liver transplantation. Patients underwent chemoembolization prior to liver transplantation, and were assessed every 3 months for disease progression until LT. Two patients were stage T1, 45 patients were stage T2, and 7 patients were stage T3 at time of first chemoembolization. Median time was 211 days (range 28–1,099 days) for patients that were eventually transplanted. 8 patients were removed from the list. Cumulative probability of drop out on the waiting list, assessed by Kaplan-Meier analysis, was 15% and 25% at 6 and 12 months, respectively. There were no significant differences in age, gender, initial tumor stage, or serum AFP levels in those who eventually underwent liver transplantation vs those who dropped out.	4
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.	Observational-Tx	71 consecutive patients: Group A - 45 received therapy with drug eluting beads; Group B - 26 underwent chemoembolization	To explore long-term survival benefits of TACE and chemoembolization with doxorubicin drug eluting beads for unresectable HCC.	Median survival from diagnosis of HCC in groups A and B were 610 (351–868) and 284 days (4–563; P=0.03), respectively. In Okuda stage I, survival in groups A and B were 501 (421–528) and 354 days (148–560, P=0.02). In Child-Pugh classes A and B, survival in groups A and B were 641 (471–810) and 323 days (161–485, P=0.002). Median survival in patients with Cancer of Liver Italian Program score ≤3 in groups A and B were 469 (358-581) and 373 days (195–551, P=0.03). NCI CTCAEv3 Grade 5 clinical toxicity was similar. Transcatheter therapy with drug eluting beads offers a survival advantage over conventional chemoembolization for patients with unresectable HCC.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	212 patients	To compare conventional TACE with TACE with drug-eluting bead for the treatment of cirrhotic patients with HCC.	The primary endpoint was tumor response (EASL) at 6 months following independent, blinded review of MRI studies. The drug-eluting bead group showed higher rates of complete response, objective response, and disease control compared with the conventional TACE group (27% vs 22%, 52% vs 44%, and 63% vs 52%, respectively). The hypothesis of superiority was not met (one-sided P=0.11). However, patients with Child-Pugh B, ECOG 1, bilobar disease, and recurrent disease showed a significant increase in objective response (P=0.038) compared to conventional TACE. Drug-eluting bead was associated with improved tolerability, with a significant reduction in serious liver toxicity (P<0.001) and a significantly lower rate of doxorubicin-related side effects (P=0.0001). TACE with drug-eluting bead and doxorubicin is safe and effective in the treatment of HCC and offers a benefit to patients with more advanced disease.	1
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.	Meta-analysis	7 clinical studies with 700 participants	To evaluate the efficacy and safety of the 2 treatments for patients with unresectable HCC.	Significantly better objective tumor response was found following DEB-TACE over conventional TACE (OR=1.92, 95%CI [1.34, 2.77]; P=0.0004) with relative risk difference of 0.15 [0.07, 0.24] (P=0.0003). 1-year, 2-year survival rates were statistically significant higher in DEB-TACE group compared with conventional TACE group (Peto OR, 95% CI: 0.64 [0.46, 0.89], P=0.007; 0.61 [0.47, 0.80], P=0.0003; respectively). Peto OR of 6-month and 3-year survival were 0.72 [0.46, 1.14] (P=0.16) and 0.77 [0.55, 1.06] (P=0.11) respectively; showing no difference statistically. But we could still find tendency that favors DEB-TACE group. Adverse side effects were similar in both groups and post-embolization syndrome existed most commonly.	M

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	N/A	To compare current conventional TACE to the drug eluting beads loaded with doxorubicin device in the treatment of HCC.	The drug eluting beads loaded with doxorubicin are an effective therapy with a favorable pharmacokinetic profile with significantly less systemic doxorubicin exposure when compared to conventional TACE. The drug eluting beads loaded with doxorubicin had a significant (P<0.05) advantage in objective response in the more advanced patients (defined as Child-Pugh B, ECOG 1, recurrent disease and bilobar disease; P=0.038) and overall disease control in the more advanced patients (P=0.026). The drug eluting beads loaded with doxorubicin was also found to have a highly significant (P<0.01) advantage in the reduction of doxorubicin associated side effects (P=0.0001) in all patients.	4
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.	Observational-Tx	291 patients	To assess clinical outcomes of patients treated with intra-arterial Y-90 microspheres.	A total of 526 treatments were administered (mean, 1.8; range, 1–5). Toxicities included fatigue (57%), pain (23%), and nausea/vomiting (20%); 19% exhibited grade 3/4 bilirubin toxicity. The 30-day mortality rate was 3%. Response rates were 42% and 57% based on WHO and EASL criteria, respectively. The overall TTP was 7.9 months (95% CI, 6–10.3). Survival times differed between patients with Child-Pugh A and B disease (A, 17.2 months; B, 7.7 months; P=.002). Patients with Child-Pugh B disease who had portal vein thrombosis survived 5.6 months (95% CI, 4.5–6.7). Baseline age; sex; performance status; presence of portal hypertension; tumor distribution; levels of bilirubin, albumin, and AFP; and WHO/EASL response rate predicted survival.	2
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.	Review/Other-Tx	N/A	Review biological lessons, current challenges, and clinical perspectives of Yttrium 90 radioembolization for the treatment of HCC.	N/A	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	691 patients	To evaluate the therapeutic equivalence in survival for hepatic arterial chemoembolization and Y-90 microsphere treatments in unresectable HCC.	OS was slightly better in the Y-90 group compared with the TACE group (median survival, 11.5 months vs 8.5 months). However, the selection criteria indicated a small but significant bias toward milder disease in the Y-90 group. By using stratification into a 3-tier model with patients dichotomized according to bilirubin levels <1.5 mg/dL, the absence of portal vein thrombosis, and low AFP plasma levels (<25 U/dL), an analysis of survival in clinical subgroups indicated that the 2 treatments resulted in similar survival. In addition, patients who had portal vein thrombosis or high AFP levels also had similar survival in both treatment groups. Given the current evidence of therapeutic equivalence in survival, Y-90 and TACE appeared to be equivalent regional therapies for patients with unresectable, nonmetastatic HCC.	2
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.	Observational-Tx	71 patients: 44 chemoembolization; 27 radioembolization	To compare the effectiveness and toxicity of transcatheter arterial chemoembolization and Y-90-labeled microspheres in patients with unresectable HCC.	Progressive disease at 3 months was observed in 16 (36%) of the 44 patients treated with chemoembolization and 9 (33%) of the 27 patients treated with radioembolization (*P*=not statistically significant). The median OS was similar for both groups (6 months with chemoembolization vs 6 months with radioembolization, *P*=.7). Grade 3 or higher toxicity was observed in 24/71 patients (34%). Tumor multifocality, vascular invasion, and hepatitis C seropositivity were independently associated with worse survival, whereas method of treatment was not. In this single-center study, preliminary evidence suggests that chemoembolization and radioembolization provided similar effectiveness and toxicity in patients with unresectable HCC.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	73 patients	To compare retrospectively the safety and efficacy of Y-90 radioembolization with the safety and efficacy of chemoembolization in patients with unresectable HCC.	This study included 73 patients with HCC who underwent index embolization with radioembolization (n = 38; 52.1%) or chemoembolization (n = 35; 47.9%). The 2 patient populations were similar in terms of demographics, etiology of cirrhosis, functional status, tumor characteristics, Child-Pugh class, previous liver-directed therapy, and number of patients with bilirubin > 2.0 mg/dL. There was no significant difference in survival between the radioembolization (median 8.0 months) and chemoembolization (median 10.3 months) cohorts (*P*=.33). Postembolization syndrome was significantly more severe in patients who underwent chemoembolization, which led to increased total hospitalization rates in these patients. The rates of other complications and rehospitalization were similar between groups. Increased age, Child-Pugh class B, hepatitis seropositivity, bilobar tumor distribution, tumor vascular invasion, and presence of extrahepatic metastases were associated with reduced patient survival.	2
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.	Observational-Tx	61 TARE group; 55 TACE group	To compare the outcomes and safety of TARE vs TACE in patients with unresectable HCC	Complete tumor response was more common after TARE (12%) than after TACE (4%) (*P*=0.17). When complete response was combined with partial response and stable disease, there was no difference between TARE and TACE. Median survival did not differ between the 2 groups (15.0 months for TARE and 14.4 months for TACE; *P*=0.47). 2-year survival rates were 30% for TARE and 24% for TACE. TARE patients received fewer treatments (*P*<0.001). 59 (97%) TARE patients received outpatient treatment. In contrast, 53 (98%) TACE patients were hospitalized for ≥1 day (*P*<0.001). Compared with TACE, TARE was more likely to induce fatigue (*P*=0.003) but less likely to cause fever (*P*=0.02).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	463 patients	A comparative effectiveness analysis between Y-90 and chemoembolization was performed in patients with HCC.	Abdominal pain and increased transaminase activity were more frequent following chemoembolization ($P<.05$). There was a trend that patients treated with radioembolization had a higher response rate than with chemoembolization (49% vs 36%, respectively, $P=.104$). Although TTP was longer following radioembolization than chemoembolization (13.3 months vs 8.4 months, respectively, $P=.046$), median survival times were not statistically different (20.5 months vs 17.4 months, respectively, $P=.232$). Among patients with intermediate-stage disease, survival was similar between groups that received chemoembolization (17.5 months) and radioembolization (17.2 months, $P=.42$).	2
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.	Observational-Tx	150 patients	To present the clinical data of 35 patients with T3 unresectable HCC that were treated with Y-90 with the specific intent of downstaging to resection, RFA candidate, United Network for Organ Sharing (UNOS) stage T2 or liver transplantation.	19/34 patients (56%) were successfully downstaged from T3 to T2 following treatment. 11/34 (32%) patients treated were downstaged to target lesions measuring ≤3.0 cm. 23/35 (66%) were downstaged to either T2 status, lesion <3.0 cm (RFA candidate), or resection. 17/34 (50%) had an objective tumor response by WHO criteria. 8 patients (23%) were successfully downstaged and underwent OLT following treatment. 1, 2, and 3-year survival was 84%, 54%, and 27%, respectively. Median survival by Kaplan-Meier analysis for the entire cohort was 800 days. These data suggest that intra-arterial Y-90 microspheres can be used as a bridge to transplantation, surgical resection, or RFA.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	86 total patients: 43 TACE; 43 TARE Y-90	To compare the downstaging efficacy of TACE vs transarterial radioembolization.	Median tumor size was similar (TACE: 5.7 cm, TARE-Y-90: 5.6 cm). Partial response rates favored TARE-Y-90 vs TACE (61% vs 37%). Downstaging to UNOS T2 was achieved in 31% of TACE and 58% of TARE-Y-90 patients. TTP according to UNOS criteria was similar for both groups (18.2 months for TACE vs 33.3 months for TARE-Y-90, *P*=0.098). Event-free survival was significantly greater for TARE-Y-90 than TACE (17.7 vs 7.1 months, *P*= 0.0017). OS favored TARE-Y-90 compared to TACE (censored 35.7/18.7 months; *P*=0.18; uncensored 41.6/19.2 months; *P*=0.008). In conclusion, TARE-Y-90 appears to outperform TACE for downstaging HCC from UNOS T3 to T2.	2
61. Liapi E, Geschwind JF. Intra-arterial therapies for hepatocellular carcinoma: where do we stand? *Ann Surg Oncol.* 2010;17(5):1234-1246.	Review/Other-Tx	N/A	To review intra-arterial therapies for unresectable HCC.	The levels of evidence for treatment recommendations in oncology provide a common framework to understand the current status of intra-arterial therapies for HCC. Here we use an evidence-based approach to critically review and comprehend the current role and future potential of intra-arterial therapies in unresectable HCC.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	26 patients	To evaluate tumor response and safety of concurrent bevacizumab and TACE in patients with unresectable HCC.	Median follow-up was 6 months (range 1.4–34). Patients received <1–3 cycles of TACE with bevacizumab. On follow-up imaging (n=23), index lesions had a mean decrease in size of 13% (P<0.0005). Using RECIST, 8 (35%) achieved partial response, 15 (65%) had stable disease. Targeted tumors demonstrated mean decrease in contrast enhancement of 69% (P<0.0005). By EASL criteria, 14 (60%) patients had complete or partial response, and 9 (39%) had stable disease. The disease control rate was 100% by either criteria while undergoing treatment. Median OS was 13.5 months with 10 patients still alive. 15 (58%) patient's experienced grade 3/4 toxicities possibly related to either therapy. 10 (38%) patient's toxicities resolved; the 30-day mortality rate was 4%. Combination therapy with TACE and bevacizumab is reasonably well tolerated in unresectable HCC patients, with 100% disease control rate by imaging criteria and median OS of 13.5 months. These results support the general concept of combining TACE with an antiangiogenic agent.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	115 stage IIIA HCC patients	To evaluate if hepatectomy combining with adjuvant TACE for stage IIIA HCC result in better long-term survival outcome when compared with hepatectomy alone.	There were no significant differences in the morbidity and in-hospital mortality between the 2 arms of patients. The most significant toxicities associated with adjuvant TACE were nausea/vomiting (54.4%) and transient hepatic toxicity (elevation of aminotransferase, 52.6%). Although there was no significant difference in the rate of recurrence between the 2 arms (50/57 vs 56/58, *P*=0.094), hepatectomy with adjuvant TACE arm seemed to have more proportion of single lesion of recurrent HCC (chi (2) = 3.719, *P*=0.054) and more proportion of potential curative therapy for recurrence (chi (2) = 4.456, *P*=0.035). Until the time of censor, 92 patients had died. The 1-, 3-, and 5-year OS rates and median OS for hepatectomy with adjuvant TACE arm were 80.7%, 33.3%, 22.8% and 23.0 months, respectively. The corresponding OS rates and median OS for hepatectomy alone arm were 56.5%, 19.4%, 17.5% and 14.0 months, respectively. The difference was significant (stratified log-rank test, *P*=0.048). The 1-, 3-, and 5-year DFS rates and median DFS for hepatectomy with adjuvant TACE arm were 29.7, 9.3, 9.3% and 6.0 months, respectively; correspondingly, for hepatectomy alone arm were 14.0%, 3.5%, 1.7% and 4.0 months, respectively (stratified log-rank test, *P*=0.004). For stage IIIA HCC, hepatectomy with adjuvant TACE efficaciously and safely improved survival outcomes when compared with hepatectomy alone.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	355 patients	To compare the TTP and OS in patients with advanced-stage HCC who are undergoing sorafenib treatment combined with TACE vs sorafenib monotherapy.	In the combined and monotherapy groups, respectively, 64.6% and 49.2% of patients had vascular invasion, 87.8% and 91.1% had extrahepatic metastasis, and 54.3% and 47.1% had both. During follow-up (median duration, 5.5 months), the median TTP and OS in the combined group were longer than those in the monotherapy group (TTP: 2.5 months vs 2.1 months, respectively, *P*=.008; OS: 8.9 months vs 5.9 months, *P*=.009). At univariate and subsequent multivariate analyses, additional TACE was an independent predictor of favorable TTP and OS (adjusted HR: 0.74 and 0.57, respectively; *P*<.05 for both), consistent with the outcomes of inverse probability of treatment weighting. In the propensity score-matched cohort (96 pairs), the median TTP in the combined group was significantly longer than that in the monotherapy group (2.7 months vs 2.1 months, respectively; *P*=.011), but median OS was not (9.1 months vs 6.7 months, *P*=.21).	2
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.	Observational-Tx	50 patients	To evaluate the safety and efficacy of concurrent conventional TACE and sorafenib in patients with unresectable HCC.	50 patients were treated and followed from July 2009 to May 2011. All patients were in Barcelona Clinic Liver Cancer (BCLC) stage B (82%) or C (18%). The median time of follow-up was 14.9 months and a median of 1 TACE session was given (range, 1–4). The median dose intensity of sorafenib was 68.7% (range, 37.3–100) of 800 mg daily. The most common reasons for dose reduction were hand-foot syndrome and thrombocytopenia. 30 patients completed the study and 17 patients discontinued sorafenib due to disease progression. The overall median TTP was 7.1 months (95% CI, 4.8–7.5 months): 7.3 months in BCLC stage B; 5.0 months in BCLC stage C. The 6-month PFS rate was 52% (95% CI, 37.3–66.1).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	35 patients	To evaluate safety and efficacy of combined DEB-TACE and sorafenib in patients with advanced HCC.	DEB-TACE in combination with sorafenib was successfully administered in 35 patients: mean age, 63 years; Child's A, 89%; Barcelona Clinic Liver Cancer stage C, 64%; Eastern Cooperative Oncology Group performance status of 0 and 1, 46% and 54%, respectively; and mean index tumor size, 7.7 cm (SD, +/- 4.2 cm). Patients underwent 128 cycles of therapy (sorafenib plus DEB-TACE, 60 cycles; sorafenib alone, 68 cycles). Median number of cycles per patient was 2 (range, 1 to 5 cycles); median number of days treated with sorafenib was 71 (range, 4 to 620 days). The most common toxicities during cycle 1 were fatigue (94%), anorexia (67%), alterations in liver enzymes (64%), and dermatologic adverse effects (48%). Although most patients experienced at least one grade 3 to 4 toxicity, most toxicities were minor (grade 1 to 2, 83% v grade 3 to 4, 17%). Toxicity during cycle 2 was decreased. Over the course of the study, there were 40 sorafenib dose interruptions and 25 sorafenib dose reductions. Sorafenib plus DEB-TACE was associated with a disease control rate of 95% (Response Evaluation Criteria in Solid Tumors Group)/100% (European Association for the Study of the Liver [EASL]), with an objective response of 58% (EASL).	1
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.	Review/Other-Tx	N/A	To examine the currently available and emerging technologies for diagnosis and treatment of this group of diseases.	Biliary tract cancers (gallbladder cancer, intra- and extra-hepatic cholangiocarcinoma, and selected periampullary cancers) accounted for 12,760 new cases of cancer in the USA in 2010. These tumors have a dismal prognosis with most patients presenting with advanced disease. Early, accurate diagnosis is essential, both for potential cure where possible and for optimal palliative therapy in all others.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
68. Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation.* 2000;69(8):1633-1637.	Review/Other-Tx	207 patients	To review results in patients who underwent liver transplantation for otherwise unresectable cholangiocarcinoma or cholangiohepatoma.	The 1, 2, and 5-year survival estimates using life table analysis were 72%, 48%, and 23%. 51% of patients had recurrence of their tumors after transplantation and 84% of recurrences occurred within 2 years of transplantation. Survival after recurrence was rarely more than 1 year. 47% of recurrences occurred in the allograft and 30% in the lungs. Tumor recurrence, and evidence of tumor spread at the time of surgery, were negative prognostic variables. There were no positive prognostic variables. Patients with incidentally found cholangiocarcinomas did not have improved survival over patients with known or suspected tumors. A small number of patients survived for more than 5 years without recurrence. However, this group had no variable in common that would aid in the selection of similar patients in the future.	4
69. Rosen CB, Heimbach JK, Gores GJ. Liver transplantation for cholangiocarcinoma. *Transpl Int.* 2010;23(7):692-697.	Review/Other-Tx	N/A	To review results of liver transplantation with and without neoadjuvant therapy and discuss the current role of liver transplantation in the treatment of hilar cholangiocarcinoma.	Hilar cholangiocarcinoma – once a contraindication for transplantation has re-emerged as an indication for liver transplantation when combined with effective preoperative neoadjuvant therapy.	4
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.	Experimental-Tx	410 patients	To conduct a randomized trial to compare cisplatin plus gemcitabine with gemcitabine alone.	After a median follow-up of 8.2 months and 327 deaths, the median OS was 11.7 months among the 204 patients in the cisplatin-gemcitabine group and 8.1 months among the 206 patients in the gemcitabine group (HR, 0.64; 95% CI, 0.52 to 0.80; $P<0.001$). The median PFS was 8.0 months in the cisplatin-gemcitabine group and 5.0 months in the gemcitabine-only group ($P<0.001$). In addition, the rate of tumor control among patients in the cisplatin-gemcitabine group was significantly increased (81.4% vs 71.8%, $P=0.049$). Adverse events were similar in the 2 groups, with the exception of more neutropenia in the cisplatin-gemcitabine group; the number of neutropenia-associated infections was similar in the 2 groups.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	13 patients	To present the results of percutaneous RFA in patients with unresectable primary ICC.	Technical effectiveness of RFA was achieved for 15 of the 17 tumors (88%), all <5 cm in diameter. Treatment failure occurred in 2 patients with large tumors (7 and 8 cm). After the 17 RFA sessions, 1 major complication (6%), a liver abscess, occurred 1 month later. During follow-up (median, 19.5 months; range, 3.3–82.1 months), 9 patients died and 4 remain alive. Median local PFS and OS periods were 32.2 and 38.5 months, respectively. The 1-, 3-, and 5-year survival rates were 85%, 51%, and 15%, respectively.	2
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.	Observational-Tx	18 patients	To evaluate the treatment efficacy and OS of percutaneous ultrasound-guided thermal ablation by means of microwave ablation or RFA for ICC.	Complete ablation was achieved in 23 (92.0%, 23/25) nodules (diameter, 0.7–4.3 cm; mean, 2.5 +/- 0.9 cm) and incomplete ablation was found in 2 (8.0%, 2/25) larger tumors (6.4 and 6.9 cm in diameter). No death associated with the treatment was found. The major complication rate was 5.5% (1/18). The follow-up periods ranged from 1.3 to 86.2 months (mean, 20.5 +/- 26.3 months; median, 8.7 months). OS rates for all patients at 6, 12, 36 and 60 months were 66.7%, 36.3%, 30.3% and 30.3%, respectively. By univariate analysis, the patient source (primary or recurrent case) was found to be a significant prognostic factor for OS rates (P=0.001). The patient source (P=0.001) and the number of nodules (P=0.038) were found to be significant prognostic factors for recurrence-free survival. OS rates for the primary ICC at 6, 12, 36 and 60 months were 87.5%, 75.0%, 62.5% and 62.5%, respectively.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	33 patients	A retrospective analysis to establish which factors influenced TTP and OS.	34 treatments were administered to 33 patients without major complications. By RECIST, 12 patients had a partial response, 17 had stable disease, and 5 had progressive disease after 3 months. The median OS was 22 months post-treatment and 43.7 months post-diagnosis. Median TTP was 9.8 months. Survival and TTP were significantly prolonged in patients with ECOG 0 (vs ECOG 1 or 2; median OS: 29.4, 10, and 5.1 months; TTP: 17.5, 6.9, and 2.4 months), tumor burden ≤25% (OS: 26.7 vs 6 months; TTP: 17.5 vs 2.3 months), or tumor response (partial response or SD vs PD; OS: 35.5, 17.7 vs 5.7 months; TTP: 31.9, 9.8 vs 2.5 months), respectively (P<0.001).	2
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.	Observational-Tx	46 patients	To present data on safety, antitumoral response, and survival following Y-90 radioembolization for patients with unresectable ICC.	92 treatments were performed, with a mean of 2 per patient. Fatigue and transient abdominal pain occurred in 25 patients (54%) and 13 patients (28%), respectively. Treatment-related gastroduodenal ulcer developed in 1 patient (2%). WHO imaging findings included partial response (n = 11; 25%), stable disease (n = 33; 73%), and progressive disease (n = 1; 2%). EASL imaging findings included partial/complete response (n = 33; 73%) and stable disease (n = 12; 27%). Survival varied based on presence of multifocal (5.7 months vs 14.6 months), infiltrative (6.1 months vs 15.6 months), and bilobar disease (10.9 months vs 11.7 months). Disease was converted to resectable status in 5 patients, who successfully underwent curative resection.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	25 patients	To present data on the safety and efficacy of a novel treatment option, Y-90 radioembolization for unresectable ICC.	No patient was lost to follow-up. The median follow-up was 8.1 (range, 0.4–56) months and the median survival after Y-90 radioembolization was 9.3 months. 2 patients died within 1 month of treatment; the median follow-up for the remaining 23 was 8.9 (range, 1.5–56) months. 2 factors were associated with an improved survival: peripheral tumor type (vs infiltrative, P=.004) and ECOG performance status of 0 (vs 1 and 2, P<.001). On imaging follow-up of 23 patients, a partial response to treatment was observed in 6 patients (24%), stable disease in 11 patients (48%), and progressive disease in 5 patients (20%). The most common clinical toxicities were fatigue (64%) and self-limiting abdominal pain (40%). 2 patients (8%) each developed grade III bilirubin and albumin toxicity. One patient (4%) developed grade III alkaline phosphatase toxicity.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	115 patients	To evaluate the effectiveness of TACE with 4 chemotherapeutic protocols in terms of local tumor control and survival of patients with unresectable cholangiocarcinoma and to identify the prognostic factors governing treatment success.	In the single-center study, 115 patients (mean ages = 60.4 years) with unresectable cholangiocarcinoma were repeatedly treated with TACE. In total, 819 chemoembolization sessions were performed in 4 week intervals with a mean of 7.1 (range, 3–30) sessions per patient. The chemotherapeutic used was mitomycin C only in 20.9% of patients, gemcitabine only in 7%, mitomycin C with gemcitabine in 47% and combination of gemcitabine, mitomycin C and cisplatin in 25.1%. Local tumor response was evaluated by MRI according to RECIST. Survival data were calculated according to the Kaplan-Meier method. Prognostic factors for patient's survival were evaluated using log-rank-test. The local tumor controls were: partial response 8.7%, stable disease 57.4% and progressive disease 33.9% of patients. The median and mean survival times from the start of TACE were 13 and 20.8 months. Survival rate from the start of TACE was 52% after 1-year, 29% after 2-years and 10% after 3-years. Initial tumor response, high tumor vascularity and Child-Pugh class A were statistically significant factors for patient's survival. No statistically significant difference between patients treated with different chemotherapy protocols was noted.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	3 trials; 67 patients	To evaluate the feasibility, safety, and efficacy of conventional TACE with mitomycin-C and of DEB-TACE, and to retrospectively compare them with chemotherapy with oxaliplatin and gemcitabine.	DEB-TACE resulted in PFS of 3.9 months and OS of 11.7 months, compared with a PFS of 1.8 months and OS of 5.7 months, respectively, in patients treated with conventional TACE, and a PFS of 6.2 months and OS of 11.0 months, respectively, in patients treated with oxaliplatin and gemcitabine. The medium follow-up of patients treated with DEB-TACE was 12 months; 2 months after treatment, 13 patients (50%) had progressive disease, 11 patients (42%) had stable disease, and 1 patient had a partial response and became eligible for secondary liver resection. Local tumor control was achieved in 66% of patients; 4% had a partial response, 62% had stable disease, and 27% progressive disease. Common Toxicity Criteria grade III or IV toxicities for DEB-TACE were abdominal pain (n=7), hepatic abscess (n=1), pleural empyema due to biliary leakage (n=1), and 1 death due to cholangitis with hepatic failure in a patient with liver cirrhosis. No hematological side-effects were observed. Almost every patient experienced a 'postembolization syndrome' with low-grade fever, nausea, and abdominal pain for up to 2 weeks.	1
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.	Review/Other-Tx	20 articles	To evaluate the comparative effectiveness of hepatic artery based therapies -hepatic arterial infusion, TACE, DEB-TACE, and Y-90 radioembolization for unresectable ICC.	A total of 20 articles (of 793, n = 657 patients) were selected for data extraction. Highest median OS was observed for hepatic arterial infusion (22.8, 95% CI, 9.8–35.8) months vs Y-90 (13.9, 9.5–18.3) months vs TACE (12.4, 10.9–13.9) months vs DEB-TACE (12.3, 11–13.5) months. Response to therapy (complete and partial) was highest for hepatic arterial infusion (56.9%, 95% CI, 41.0–72.8) vs Y90 (27.4%, 17.4–37.5) vs TACE (17.3%, 6.8–27.8). The grade III/IV toxicity (Events per patient) was highest for hepatic arterial infusion (0.35, 95% CI, 0.22–0.48) vs TACE (0.26, 0.21–0.32) vs DEB-TACE (0.32, 0.17–0.48).	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	N/A	Review of the standards of practice of NETs management.	NETs are rare and represent a diverse collection of malignancies that occur in many organ systems throughout the body, including the gastrointestinal and respiratory tracts. Unfortunately, the majority of patients with NETs have hepatic metastases at the time of diagnosis.	4
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.	Review/Other-Tx	N/A	Guidelines compiled by a multidisciplinary group for the clinical committees of the British Society of Gastroenterology, the Society for Endocrinology, the Association of Surgeons of Great Britain and Ireland, as well as its Surgical Specialty Associations, and the United Kingdom Neuroendocrine Tumor Group (UKNET) to identify and inform the key decisions to be made in the management of GEP NETs, including carcinoid tumors.	For detecting the primary tumor, a multimodality approach is best and may include CT, MRI, SSRS, EUS, endoscopy, DSA, and venous sampling (grade B/C). For assessing secondaries, SSRS is the most sensitive modality (grade B).When a primary has been resected, SSRS may be indicated for follow-up (grade D). The overall 5-year survival for pancreatic NETs is 50%–80%, with insulinoma and gastrinoma having up to 94% 5-year survival, although clearly there is large variation depending on the stage at presentation and whether curative surgery is possible.	4
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.	Experimental-Tx	85 patients	A randomized, placebo controlled study in patients with metastatic midgut NETs was performed to demonstrate that octreotide LAR prolongs time to tumor progression and long-term survival.	Median time to tumor progression in the octreotide LAR and placebo groups was 14.3 and 6 months, respectively (HR = 0.34; 95% CI, 0.20 to 0.59; *P*=.000072). After 6 months of treatment, stable disease was observed in 66.7% of patients in the octreotide LAR group and 37.2% of patients in the placebo group. Functionally active and inactive tumors responded similarly. The most favorable effect was observed in patients with low hepatic tumor load and resected primary tumor. 7 and 9 deaths were observed in the octreotide LAR and placebo groups, respectively. The HR for OS was 0.81 (95% CI, 0.30 to 2.18).	1
82. Wolin EM. The expanding role of somatostatin analogs in the management of neuroendocrine tumors. *Gastrointest Cancer Res.* 2012;5(5):161-168.	Review/Other-Tx	N/A	A review article on the expanding role of somatostatin analogs in the management of NETs.	Somatostatin analogues represent the cornerstone of therapy for patients with NETs.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	15 studies; 481 patients	To review 35 years of experience regarding the clinical application and efficacy of somatostatin analogues.	In a review of 15 studies including 481 patients, the slow-release formulations Sandostatin LAR and Somatuline SR/Autogel achieved symptomatic relief in 74.2% (61.9%–92.8%) and 67.5% (40.0%–100%), biochemical response in 51.4% (31.5%–100%) and 39.0% (17.9%–58%), and tumor response in 69.8% (47.0%–87.5%) and 64.4% (48.0%–87.0%) respectively. Novel SST analogues like SOM230 (pasireotide) that exhibit pan SST receptor activity and analogues with high affinity to specific somatostatin receptor subtypes may further advance the field, but efficacy studies are lacking.	4
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.	Observational-Tx	48 patients	To determine the effect of 3 major treatment modalities including medical therapy, hepatic artery embolization, and surgical resection, ablation, or both in patients with liver-only neuroendocrine metastases, with the hypothesis that surgical treatment is associated with improvement in survival.	No difference was noted in the percentage of liver involved with tumor between the 3 groups. An association of improved survival was noted in patients treated surgically, with a 3-year survival of 83% for patients treated by surgical resection, compared with 31% in patients treated with medical therapy or embolization (P=.01). No difference in palliation of symptoms was noted among the 3 treatment groups (P=.2). In patients with liver-only neuroendocrine metastases, surgical therapy using resection, ablation, or both is associated with improved survival.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	170 consecutive patients	To determine outcomes of surgery for neuroendocrine metastases in the liver.	The postoperative complication rate was 14%, and 2 patients died (1.2%). Operation controlled symptoms in 104/108 patients, but the recurrence rate at 5 years was 59%. Operation decreased 5-hydroxyindoleacetic acid levels considerably, and no patient experienced carcinoid heart disease postoperatively. Recurrence rate was 84% at 5 years. OS was 61% and 35% at 5 and 10 years, respectively, with no difference between carcinoid and islet cell tumors. Hepatic resection for metastatic NETs is safe and achieves symptom control in most patients. Debulking extends survival, although recurrence is expected. Hepatic resection is justified by its effects on survival and quality of life.	2
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.	Observational-Tx	19 patients	To assess patient outcomes after liver transplantation for hepatic metastases from GEP.	Mean follow-up of 22 months with a range of 0 to 84 months. Overall estimated 1-year survival for 17 patients included in the treatment protocol (mean follow-up, 15 months) was 87% with an estimated 1-year recurrence-free rate (conditional on survival) of 77%. 3/11 patients with pancreatic islet cell GEP developed disease recurrence, whereas all 8 patients with carcinoid GEP remain free of disease. Analysis of the Ki67 proliferation index in 18 patients did not differentiate those with recurrence from those without disease recurrence. In conclusion, liver transplantation for patients with hepatic metastases from GEP is a viable therapeutic option in highly selected patients.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	N/A	To review the management of advanced NETs with hepatic metastasis.	Although biotherapy is currently the most efficient treatment to achieve palliation, conventional chemotherapy may have some utility in undifferentiated or highly proliferating neuroendocrine carcinomas and pancreatic NETs. Hepatic metastases, depending on size, location, and number may be amenable to surgical resection or RFA. If surgery is not feasible, embolization either alone (bland), in combination with chemotherapeutic agents, or using radioactive microspheres can be used. Peptide receptor targeted radiotherapy using radiolabeled octapeptide analogs (Yttrium or Lutetium-octreotide) may lead to reduction in tumor size, but in most circumstances has a tumor stabilizing effect. A variety of antiangiogenesis and growth factor-targeted agents have been evaluated, but to date, the results have failed to meet our expectations.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	N/A	Guidelines for the treatment of neuroendocrine GEP tumors.	Surgery is the primary treatment for localized tumors and might be curative, giving 5-year survival rates of 80%–100%. Cytotoxic treatment has been the standard for advanced neuroendocrine pancreatic tumors, but is of limited value for the treatment of low proliferating neuroendocrine GEP tumors (response rates 30%–50% compared with <10. Biological treatment, such as somatostatin analogues and α interferons has proved effective in control of associated clinical syndromes related to hormone production and release (carcinoid syndrome, gastrinoma, glucagonoma, etc.) in up to 60% of patients. Their use in non-functioning tumors is still not widely accepted [IV, B]. Tumor-targeted radioactive treatment is an option in the selected group of patients with tumors that present a high grade of uptake of [111In] pentaoctreotide (octreoscan) scintigraphy. Biological treatments with a promising prospect include sunitinib, everolimus and bevacizumab when associated with capecitabine and oxaliplatin. These treatments should be applied only in the setting of clinical trials.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	171 patients	A phase 3, randomized, double-blind, placebo-controlled trial was performed to assess the efficacy and safety of continuous daily administration of sunitinib at a dose of 37.5 mg per day in patients with advanced pancreatic NETs.	The study was discontinued early, after the independent data and safety monitoring committee observed more serious adverse events and deaths in the placebo group as well as a difference in PFS favoring sunitinib. Median PFS was 11.4 months in the sunitinib group as compared with 5.5 months in the placebo group (HR for progression or death, 0.42; 95% CI, 0.26 to 0.66; $P<0.001$). A Cox proportional-hazards analysis of PFS according to baseline characteristics favored sunitinib in all subgroups studied. The objective response rate was 9.3% in the sunitinib group vs 0% in the placebo group. At the data cutoff point, 9 deaths were reported in the sunitinib group (10%) vs 21 deaths in the placebo group (25%) (HR for death, 0.41; 95% CI, 0.19 to 0.89; $P=0.02$). The most frequent adverse events in the sunitinib group were diarrhea, nausea, vomiting, asthenia, and fatigue.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
90. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):514-523.	Experimental-Tx	410 patients	To evaluate everolimus, an oral inhibitor of mammalian target of rapamycin, in a prospective, randomized, phase 3 study.	The median PFS was 11.0 months with everolimus as compared with 4.6 months with placebo (HR for disease progression or death from any cause with everolimus, 0.35; 95% CI, 0.27 to 0.45; $P<0.001$), representing a 65% reduction in the estimated risk of progression or death. Estimates of the proportion of patients who were alive and progression-free at 18 months were 34% (95% CI, 26 to 43) with everolimus as compared with 9% (95% CI, 4 to 16) with placebo. Drug-related adverse events were mostly grade 1 or 2 and included stomatitis (in 64% of patients in the everolimus group vs 17% in the placebo group), rash (49% vs 10%), diarrhea (34% vs 10%), fatigue (31% vs 14%), and infections (23% vs 6%), which were primarily upper respiratory. Grade 3 or 4 events that were more frequent with everolimus than with placebo included anemia (6% vs 0%) and hyperglycemia (5% vs 2%). The median exposure to everolimus was longer than exposure to placebo by a factor of 2.3 (38 weeks vs 16 weeks).	1
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.	Observational-Tx	25 patients: 189 tumors	To assess image-guided thermal ablation in the treatment of neuroendocrine liver metastases.	Imaging follow-up was available in 19 patients at a median of 21 months (range, 4–75 months). There was a complete response in 6 patients, a partial response in 7, and stable disease in 1; hence, tumor load was controlled in 14/19 patients (74%). Relief of hormone-related symptoms was achieved in 9/14 patients (69%). The median survival period from the diagnosis of liver metastases was 53 months. One patient with end-stage cardiac disease died after a carcinoid crisis. There were 8 (12%) complications: 5 local and 3 distant, 4 major and 4 minor. As a minimally invasive, readily repeatable procedure that can be used to ablate small tumors, preferably before patients become severely symptomatic, RFA can provide effective control of liver tumor volume in most patients over many years.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	N/A	To review the role of ablative techniques in the treatment of neuroendocrine cancer metastatic to the liver.	Image-guided ablation, as either an adjunct to surgery or a primary treatment modality, can be used to treat neuroendocrine cancer metastatic to the liver. Image-guided ablative techniques, including RFA, alcohol injection, and cryoablation, can be used in selected patients to debulk hepatic tumors and improve patient symptoms. Although long-term follow-up data are not available, the surgical literature indicates that significant ablative debulking may improve patient survival. In this review, we discuss metastatic neuroendocrine disease and its treatment options, especially image-guided ablative techniques.	4
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.	Observational-Tx	63 total patients	To analyze the use of laparoscopic RFA for the treatment of neuroendocrine hepatic metastases.	Mean hospital stay was 1.1 days. Perioperative morbidity was 5%, with no 30-day mortality. 57% of patients exhibited symptoms. One week postoperatively, 92% of these reported at least partial symptom relief, and 70% had significant or complete relief. Duration of symptom control was 11 +/- 2.3 months. CT follow-up demonstrated 6.3% local tumor recurrence. Median survival times were 11.0 years postdiagnosis of primary tumor, 5.5 years postdiagnosis of neuroendocrine hepatic metastases, and 3.9 years post-1st RFA. Survival for patients undergoing repeat ablation sessions was not significantly lower. This study represents the largest series of neuroendocrine hepatic metastases treated by RFA. In this group of patients with aggressive NET metastases and limited treatment options, RFA provides effective local control with prompt symptomatic improvement.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	N/A	To provide a practical clinical guideline for indication, technical aspects, protocol guideline and strategies for the interventional treatment of liver metastases from NETs and focusing on the results of various protocols of management.	TACE has been associated with symptomatic response rates of 60%–95%, biologic response of 50%–90%, morphological response of 33%–80%, symptomatic response of 20–80 months, and a 5-year survival of between 50% and 65%. PFS was also between 18 and 24 months. In the TAE group, symptomatic response was similar to the TACE group, morphological response was 32% and 82%, survival was between 18 and 88 months with a survival rate of 40%–67%, and biologic response was between 50% and 69%. RFA, either percutaneous or during surgery, has been associated with symptomatic response of 71%–95% for a mean duration of 8–10 months, biologic response of 65%, and mean survival periods of 1.6 years after ablation. The mean survival following surgical resection for operable cases is 4.26 years +/- SD: 1.1. The interventional protocols for the management of liver metastases from NETs: for oligonodular liver metastatic deposits, local resection or RFA and/or laser-induced thermotherapy is recommended, while in multinodular diseases with higher tumor load, TACE or TAE is recommended.	4

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	123 patients: 69 carcinoid tumors; 54 islet cell tumors	To determine prognostic variables that influence survival and response for carcinoid and islet cell tumors.	Patients who had carcinoid tumors had a higher response rate (66.7% vs 35.2%; *P*=0.0001) and had longer PFS (22.7 months vs 16.1 months; *P*=0.046) and OS (33.8 months vs 23.2 months; *P*=0.012) compared with patients who had islet cell carcinomas. Patients with carcinoid tumors, multivariate analysis identified male gender as the only independent risk factor for poor survival (*P*=0.05). Octreotide was predictive marginally for PFS (*P*=0.06). Patients who were treated with hepatic arterial embolization had a higher response rate than patients who were treated with chemoembolization (*P*=0.004). For patients with islet cell carcinoma, an intact primary tumor, ≥75% liver involvement, and extrahepatic metastases were associated with reduced OS in the univariate analysis; the presence of bone metastases was the only risk factor (*P*=0.031) in the multivariate analysis. Patients treated with chemoembolization had a prolonged OS (31.5 months vs 18.2 months) and improved response (50% vs 25%) than those who were treated with hepatic arterial embolization, although the differences did not reach statistical significance. Patients with carcinoid tumors had better outcomes than patients with islet cell carcinomas. Addition of intra-arterial chemotherapy to hepatic arterial embolization did not improve the outcome of patients with carcinoid tumors, but it seemed to benefit patients with islet cell carcinomas. In patients who had carcinoid tumors, male gender predicted a poor outcome, and a trend toward prolonged PFS was observed in patients who received concomitant octreotide carcinomas.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
96. Pitt SC, Knuth J, Keily JM, et al. Hepatic neuroendocrine metastases: chemo- or bland embolization? *J Gastrointest Surg.* 2008;12(11):1951-1960.	Observational-Tx	100 patients: 49 hepatic artery chemoembolization; 51 bland embolization	Retrospective review to evaluate whether patients with hepatic neuroendocrine metastases, hepatic artery chemoembolization would result in better symptom improvement and survival compared to bland embolization.	The percentage of patients experiencing morbidity, 30-day mortality, and symptom improvement were similar between the 2 groups (hepatic artery chemoembolization vs bland embolization: 2.4% vs 6.6%; 0.8% vs 1.8%; and 88% vs 83%, respectively). No differences in the median OS were observed between hepatic artery chemoembolization and bland embolization from the time of the first embolization procedure (25.5 vs 25.7 months, P=0.79). Multivariate analysis revealed that resection of the primary tumor predicted survival (73.8 vs 19.4 months, P<0.04). These data suggest that morbidity, mortality, symptom improvement, and OS are similar in patients with hepatic neuroendocrine metastases managed by chemoembolization or bland hepatic artery embolization.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	67 total patients: 23 received bland embolization with polyvinyl administration; 44 received chemoembolization with cisplatin	To assess the toxicity and efficacy of chemoembolization and bland embolization in patients with NET metastases to the liver.	The mortality rate at 30 days was 1.4%. Toxicities of grade 3 or worse in severity occurred after 25% of chemoembolization procedures and 22% of bland embolization procedures (OR, 1.2; 95% CI, 0.4–4.0). Rates of freedom from progression at 1, 2, and 3 years were 49%, 49%, and 35% after chemoembolization and 0%, 0%, and 0% after bland embolization (log-rank test, *P*=.16). Among the subgroup with carcinoid tumors, the proportions without progression were 65%, 65%, and 52% after chemoembolization and 0%, 0%, and 0% after bland embolization (log-rank test, *P*=.08). Patients treated with chemoembolization and bland embolization experienced symptomatic relief for means of 15 and 7.5 months, respectively (*P*=.14). Survival rates at 1, 3, and 5 years after therapy were 86%, 67%, and 50%, respectively, after chemoembolization and 68%, 46%, and 33%, respectively, after bland embolization (log-rank test, *P*=.18). Chemoembolization was not associated with a higher degree of toxicity than bland embolization. Chemoembolization demonstrated trends toward improvement in TTP, symptom control, and survival. Based on these results, a multicenter prospective randomized trial is warranted.	2
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.	Observational-Tx	13 patients	To evaluate safety in an interim analysis of DEB-TACE in 13 patients with hepatic metastases from NETs as part of a phase II trial.	DEB-TACE was successfully performed in all 13 patients. At 1 month follow-up, there was a mean 12% decrease in tumor size (*P*<0.0003) and a 56% decrease in tumor enhancement (*P*<0.0001). By EASL criteria, the targeted lesion objective response rate was 78%. Grade 3 to 4 toxicities were fatigue (23%), increased alanine amino transferase (15%), hyperglycemia (15%), and abdominal pain (8%). 7 patients developed bilomas (54%); all of these patients had multiple small (<4 cm) lesions. Subsequently, 4 underwent percutaneous drainage, 3 for abscess formation and 1 for symptoms related to mass effect.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	208 patients (n = 120 in the NET-group); n = 88 in the HCC-group)	To describe and compare liver/biliary injuries encountered with TACE in tumors developed in HCC and non-cirrhotic (endocrine tumors (NETs)) livers.	A liver/biliary injury followed 17.2% (82/476) of sessions in 30.8% (64/208) of patients. The occurrence of liver/biliary injury was associated with DEB-TACE (OR=6.63; $P<0.001$) irrespectively of the tumor type. Biloma/parenchymal infarct was strongly associated with both DEB-TACE (OR=9.78; $P=0.002$) and NETs (OR: 8.13; $P=0.04$). Biloma/liver infarcts were managed conservatively but were associated with an increase in serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatases, and gamma glutamyl transpeptidase ($P=0.005$, $P=0.005$, $P=0.012$, and $P=0.006$, respectively).	2
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.	Observational-Tx	148 total patients from 10 institutions	To review the use of Y-90-microspheres to treat unresectable liver metastases originating from a variety of NETs.	There were no acute or delayed toxicity of Common Terminology Criteria for Adverse Events v3.0 grade 3 in 67% of patients, with fatigue (6.5%) the most common side effect. Imaging response was stable in 22.7%, partial response in 60.5%, complete in 2.7% and progressive disease in 4.9%. No radiation liver failure occurred. The median survival is 70 months. Radioembolization with Y-90-microspheres to the whole liver, or lobe with single or multiple fractions are safe and produce high response rates, even with extensive tumor replacement of normal liver and/or heavy pretreatment. The acute and delayed toxicity was very low without a treatment related grade 4 acute event or radiation induced liver disease in this modest-sized cohort. The significant objective response suggests that further investigation of this approach is warranted.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	34 total patients	To prospectively assess the safety and efficacy of treatment with Y-90 microspheres for patients with unresectable neuroendocrine liver metastases.	The mean (+/-standard error) follow-up was 35.2 +/- 3.2 months. The site of the primary NET was the bronchus in 1 patient, the medullary thyroid in 2 patients, gastrointestinal in 15 patients, the pancreas in 8 patients, and of unknown origin in 8 patients. The tumors were classified as vipoma (1 tumor), somatostatinoma (1 tumor), glucagonoma (2 tumors), large cell (3 tumors), carcinoid (25 tumors), and of unknown origin (2 tumors). Complications after Y-90 radioembolization included abdominal pain, which was mild to severe; nausea and fever; and lethargy that lasted from 1 week to 1 month. 2 patients developed biopsy-proven radiation gastritis, 1 patient developed a duodenal ulcer, and there was 1 early death from liver dysfunction and pneumonia. Subjective changes from recorded baseline hormone symptoms were reported every 3 months. Symptomatic responses were observed in 18/33 patients (55%) at 3 months and in 16/32 patients (50%) at 6 months. Radiologic liver responses were observed in 50% of patients and included 6 (18%) complete responses and 11 (32%) partial responses, and the mean OS was 29.4 +/- 3.4 months). In patients who had evaluable chromogranin A marker levels, there was a fall in chromogranin A marker levels after Y-90 radioembolization in 19 patients (26%) at 1 month, in 19 patients (41%) at 3 months, in 15 patients (43%) at 6 months, in 11 patients (42%) at 12 months, in 8 patients (38%) at 24 months, and in 3 patients (46%) at 30 months.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	16 total patients: 7 patients treated with TACE; 9 with Y-90	To compare efficacy and safety of transcatheter treatment with Y-90 vs TACE in patients with unresectable and chemorefractory NET hepatic metastases.	Median (95% CI) survival in patients treated with TACE and Y-90 from the first transcatheter therapy were 675 days (318-1,031) and 518 days (444-591, *P*=0.79). The survival rates at 1, 2 and 3 years in patients treated with TACE and Y-90 were 71%, 29%, 14% and 89%, 39%, 19%. Progressive disease by RECIST criteria was found in 28.5% (2/7) and 11.1% (1/9) of patients treated with TACE and Y-90, respectively. No procedure related mortality or hepatic failure was reported in patients treated with either modality. CTACE grade 4 clinical toxicity (contrast nepropathy) was reported in 1 patient treated with TACE and in none of the patients treated with Y-90. No CTCAE grade 3 clinical toxicity was reported in either group. Palliative treatment for unresectable hepatic metastases of NETs with radioembolization is safe and feasible. Efficacy of radioembolization appears similar to TACE.	1
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.	Review/Other-Tx	N/A	To review guidelines for the management of patients with liver and other distant metastases.	N/A	4
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.	Review/Other-Tx	N/A	To present the final clinical statements and proposals for future research for management of patients with neuroendocrine liver metastases.	N/A	4
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.	Review/Other-Tx	N/A	To develop state-of-the-art recommendations for neuroendocrine tumors management.	18 publications were reviewed. These comprised 11 reports on TAE or TACE and 7 on radioembolization. 4 questions posed to the panel were answered and recommendations offered.	4

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106. Primrose JN. Surgery for colorectal liver metastases. *Br J Cancer.* 2010;102(9):1313-1318.	Review/Other-Tx	N/A	To review the surgery of colorective livers metastases.	It has long been known that liver surgery can cure metastatic CRC although in only a small proportion of the population with the disease. However, with better understanding of the natural history of the condition and advances in technique, more patients can have safe, potentially curative surgery. The multidiscipline management of patients with effective chemotherapy has led to more patients benefiting from surgery after reducing the size of the metastases and allowing operation on patients who were previously inoperable. Chemotherapy also improves at least the medium-term outcome in those who are operable at the outset. Minimally invasive techniques have been developed so that major hepatectomy may be accomplished in up to half of such cases with a very short hospital stay and limited interference with quality of life. Lastly, using portal vein embolization to cause hypertrophy of the future liver remnant and on occasions combining it with staged liver resection allows potentially curative surgery on patients who previously could not have survived resection. These developments have led to more patients being cured of advanced CRC.	4
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.	Review/Other-Tx	N/A	To describe all currently available oncological and surgical options to convert patients with technical unresectable liver metastases to a resectable situation.	Hepatic resection of colorectal liver metastases after downstaging by chemotherapy provides the only chance of long-term survival for patients with initially unresectable disease.	4

Radiologic Management of Hepatic Malignancy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	127 patients	A retrospective study to compare outcomes of patients undergoing at least the first stage of two-stage resection with those of selected nonsurgically treated patients responding to modern chemotherapy.	65 patients underwent the first stage of two-stage resection; 62 patients fulfilled the inclusion criteria for the medical group. Two-stage resection patients had a mean of 6.7 +/- 3.4 colorectal liver metastases with mean size of 4.5 +/- 3.1 cm. Nonsurgical patients had a mean of 5.9 +/- 2.9 colorectal liver metastases with mean size of 5.4 +/- 3.4 cm (not significant). 47 two-stage resection patients (72%) completed the second stage. Progression between stages was the main cause of noncompletion of the second stage (61%). After 50 months median follow-up, the 5-year survival rate was 51% in the two-stage resection group and 15% in the medical group (*P*=.005). In patients who underwent two-stage resection, noncompletion of two-stage resection and major postoperative complications were independently associated with worse survival.	2
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.	Review/Other-Tx	N/A	To present various current strategies for the use of portal vein embolization in patients with metastatic liver cancer.	As a result of more potent, more prolonged, and more diverse chemotherapies, and also extended indications for liver resection of the metastases associated with RFA, different indications and types of portal vein embolization will increase in the near future. The quantitative (volumetric) assessment of the future remnant liver will become more refined and more accurate, as will its quantitative (functional) assessment.	4
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.	Review/Other-Tx	N/A	To review the rationale and existing literature on portal vein embolization, including the mechanisms of liver regeneration, the pathophysiology of portal vein embolization, the imaging techniques used to measure liver volumes and estimate functional hepatic reserve, and the technical aspects of portal vein embolization, including approaches and embolic agents used.	Portal vein embolization is gaining acceptance in the preoperative management of patients selected for major hepatic resection. Portal vein embolization redirects portal blood flow to the intended liver remnant to induce hypertrophy of the nondiseased portion of the liver and thereby reduce complications and shorten hospital stays after resection.	4

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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.	Review/Other-Tx	N/A	To review technique, indications, clinical results, and future prospects of RFA in the therapeutic management of metastatic CRC patients.	Solitary tumors <2.5 cm have the longest survival. Overall 47% survival at 3 years. RFA technology is undergoing continuous improvement, and its clinical application has been successfully expanded to the treatment of colorectal metastases to the lung. Randomized trials comparing RFA with either surgical resection or chemotherapy protocols, however, are still missing.	4
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.	Review/Other-Tx	30 articles from literature search and 99 patients from database of patients undergoing laparoscopic RFA	A systematic review of published literature was performed, identifying studies involving patients with colorectal liver metastases treated with RFA or resection.	The base-case analysis (60-year-old man) demonstrated a mean +/- SD quality-adjusted life expectancy of 5.67 +/- 0.71 years and a 5-year survival of 38.2% following resection. Based on current literature, the mean +/- SD quality-adjusted life expectancy for RFA was 3.61 +/- 0.49 years, with a 5-year survival of 27.2%. Sensitivity analyses demonstrated that RFA becomes the preferred strategy if the median DFS reaches 1.42 years. When limited to patients from our institution with resectable lesions, the quality-adjusted life expectancy for RFA improved to a mean +/- SD of 5.72 +/- 0.50 years.	4
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.	Observational-Tx	138 intrahepatic tumors of 90 patients	To present results from more than 10 years of clinical experience and evaluate long-term outcome and efficacy of single-dose radiosurgical treatment.	Median OS of all patients was 24.3 months. Local PFS was 87%, 70% and 59% after 6, 12 and 18 months, respectively. Median time to local progression was 25.5 months. Patients with a single lesion and no further metastases at time of RT had a favorable median PFS of 43.1 months according to the Kaplan-Meier estimator. The type of tumor showed a statistical significant influence on local PFS, with a better prognosis for breast cancer histology than for colorectal carcinoma in uni- and multivariate analysis (P=0.05). Multivariate analysis revealed no influence of planning target volume, patient age and radiation dose on local PFS. Treatment was well tolerated with no severe adverse events.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	55 patients	To evaluate the efficacy of hepatic arterial sulfonate hydrogel microsphere (drug-eluting beads), irinotecan preloaded therapy in metastatic CRC refractory to systemic chemotherapy.	The median number of drug-eluting bead, irinotecan treatments was 2 (range 1–5), median treatment dose was 100 mg (range 100–200 mg), with total hepatic treatment of 200 mg (range 200–650 mg), with 86% of treatments performed as lobar infusion and 30% of patients treated with concurrent simultaneous chemotherapy. Adverse events occurred in 28% of patients with median grade of 2 (range 1–3) with no deaths at 30 days post procedure. Response rates were 66% at 6 months and 75% at 12 months. OS in these patients was 19 months, with PFS of 11 months.	2
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.	Review/Other-Tx	N/A	To outline the rationale for combining radioembolization with the cytotoxic and molecularly targeted agents licensed for the systemic treatment of CRC.	Clinical trials of radioembolization used with concomitant radiosensitizing chemotherapy have shown promising results in patients with metastatic CRC. Several reports suggest that radioembolization is associated with significant downsizing of liver metastases to permit subsequent surgical resection.	4
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.	Review/Other-Tx	N/A	To review data on chemoembolization and radioembolization for metastatic disease to the liver.	Transarterial locoregional therapies, such as chemoembolization and radioembolization, have been widely investigated during the past decade for the treatment of hepatic metastatic disease and have generated encouraging outcomes in term of survival, response, and quality of life. Moreover, these options are applicable in many clinical scenarios, because they are less limited by tumor characteristics. Currently, a large number of trials are investigating the combination of locoregional and systemic therapies, and the results are expected to benefit the treating physicians and patients alike.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
117. Ammori JB, Kemeny NE. Regional hepatic chemotherapies in treatment of colorectal cancer metastases to the liver. *Semin Oncol.* 2010;37(2):139-148.	Review/Other-Tx	N/A	To assess regional hepatic chemotherapies in the treatment of CRC metastases to the liver.	Chemotherapy can be delivered in high concentration to the liver with minimal systemic toxicity. Hepatic artery infusional chemotherapy both alone and in combination with systemic chemotherapy in the treatment of isolated hepatic metastases from CRC has resulted in high response rates and increased resection rates for previously unresectable liver disease. Regional chemotherapy can also be used as adjuvant treatment after complete resection of liver metastases to reduce hepatic recurrences. The combination of hepatic artery infusional therapy with modern systemic chemotherapy has a role in the palliative, adjuvant, and neoadjuvant settings.	4
118. Kulaylat MN, Gibbs JF. Regional treatment of colorectal liver metastasis. *J Surg Oncol.* 2010;101(8):693-698.	Review/Other-Tx	N/A	To review regional treatment of colorectal liver metastasis.	Compared to systemic chemotherapy, intraarterial administration of tumoricidal agents with or without systemic chemotherapy in the treatment of nonresectable metastatic colorectal cancer is associated with superior response rate. The time-to-hepatic progression is also increased but the effect on overall survival is variable. When combined with other treatment modalities the number of patients who benefit from the treatment increases. In a subgroup of patients with resectable disease, hepatic artery infusion of chemotherapy as adjuvant therapy may be beneficial. Progression of the disease, hepatic and systemic toxicity, and complexity of the surgical aspects of the treatment limit the routine use of this treatment modality.	4

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.
- M = Meta-analysis

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

AFP = Alpha-fetoprotein
CI = Confidence interval
CRC = Colorectal cancer
CT = Computed tomography
DEB-TACE = Doxorubicin-eluting bead transarterial chemoembolization
DFS = Disease-free survival
DSA = Digital-subtraction angiography
EUS = Endoscopic ultrasound
GEP = Gastroenteropancreatic
HCC = Hepatocellular carcinoma
HR = Hazard ratio
ICC = Intrahepatic cholangiocarcinoma
LR = Local recurrence
MELD = Model for End-Stage Liver Disease
MRI = Magnetic resonance imaging
NET = Neuroendocrine tumor
OLT = Orthotopic liver transplant
OR = Odds ratio
OS = Overall survival
PAI = Percutaneous acetic acid injection
PEI = Percutaneous ethanol injection
PET = Positron emission tomography
PFS = Progression-free survival
RFA = Radiofrequency ablation
ROC = Receiver-operator characteristic
SBRT = Stereotactic body radiotherapy
SD = Standard deviation
SSRS = Somatostatin receptor scintigraphy
TACE = Transarterial chemoembolization
TAE = Transarterial embolization
TARE-Y-90 = Transarterial radioembolization with Yttrium-90 microspheres
TTP = Time-to-progression
Y-90 = Yttrium-90