Healthy Blue

Clinical UM Guideline

Subject:	Locoregional and Surgical Techniques for Treating Primary and Metastatic Liver Malignancies		
Guideline #:	CG-SURG-78	**Publish Date:**	04/15/2020
Status:	Revised	**Last Review Date:**	02/20/2020

Description

This document addresses surgical excision and locoregional therapies to treat primary or metastatic cancer of the liver. Treatment focuses on excising tumors or inducing tumor necrosis and can be used as a curative or palliative therapy, as a bridge to liver transplantation or in those who may become eligible for liver transplantation with treatment. Locoregional therapies both ablative and arterially directed therapies:

- Ablative Therapy
  - Cryosurgical ablation, or cryotherapy
  - Microwave ablation (MWA)
  - Percutaneous ethanol injection (PEI)
  - Radiofrequency ablation (RFA)
- Arterially directed therapy
  - Transcatheter arterial chemoembolization (TACE)
  - Transcatheter arterial embolization (TAE)
  - Selective internal radiation therapy (SIRT); also known as transarterial radioembolization (TARE)

Note: For related topics, please see the following:

- CG-SURG-61 Cryosurgical or Radiofrequency Ablation to Treat Solid Tumors Outside the Liver
- RAD.00059 Catheter-based Embolization Procedures for Malignant Lesions Outside the Liver
- SURG.00126 Irreversible Electroporation
- TRANS.00008 Liver Transplantation

Clinical Indications

Medically Necessary:

I. ***Primary Hepatic Carcinoma***

A. Surgical excision* of primary hepatobiliary carcinoma (including but not limited to hepatocellular carcinoma and cholangiocarcinoma) is considered **medically necessary** when **all** of the following criteria are met:

1. Complete excision of the carcinoma is anticipated; **and**
2. Two contiguous hepatic segments are preserved; **and**
3. At least 20% of the total estimated liver volume is anticipated to be preserved; **and**

4. Extrahepatic disease, if present, has been or will be resected.

B. Local ablative techniques* (specifically, percutaneous ethanol injection [PEI], radiofrequency [RFA], cryosurgical, or microwave ablation) are considered **medically necessary** in individuals with hepatocellular carcinoma who meet **all** of the following criteria:
1. The individual must be a poor candidate for surgical resection or unwilling to undergo surgical resection; **and**
2. The presence of 3 lesions or less, as documented by MRI or computerized tomography (CT) scan; **and**
3. Each lesion measures no more than 5 cm in diameter; **and**
4. No evidence of extra-hepatic disease; **and**
5. All foci of disease are amenable to ablative therapy; **and**
6. If a repeat procedure, at least 6 months have elapsed since the prior surgical resection or ablation.

C. Transcatheter arterial chemoembolization (TACE), transcatheter arterial embolization (TAE) is considered **medically necessary** for **either** of the following indications:
1. Primary treatment for surgically unresectable primary hepatocellular carcinoma (HCC) when **all** of the following criteria are met:
   a. Preserved liver function defined as Childs-Turcotte-Pugh Class A or B; **and**
   b. Three or fewer encapsulated nodules, and each nodule is less than or equal to 5 centimeters in diameter; **and**
   c. No evidence of extra-hepatic metastases; **and**
   d. No evidence of severe renal function impairment; **and**
   e. No evidence of portal vein occlusion.
2. Palliative treatment of specific liver-related symptoms due to tumor bulk (for example, pain) from a primary hepatic tumor.

D. SIRT/TARE is considered **medically necessary** for **either** of the following conditions:
1. Palliative treatment for individuals with specific liver-related symptoms due to tumor bulk (for example, pain) from a primary hepatic tumor, **or**
2. Primary treatment of surgically unresectable primary hepatocellular carcinoma when all of the following criteria are met:
   a. Preserved liver function defined as Childs-Turcotte-Pugh Class A or B; **and**
   b. Three or fewer encapsulated nodules and each nodule is less than or equal to 5 centimeters in diameter; **and**
   c. No evidence of extra-hepatic metastases; **and**
   d. No evidence of severe renal function impairment; **and**
   e. No evidence of portal vein occlusion.

II. ***Metastatic Tumors to the Liver***

A. Surgical excision* of liver *metastases* from colorectal cancer or functioning neuroendocrine tumors is considered **medically necessary** when **all** of the following criteria are met:
   1. Complete excision of the carcinoma is anticipated; **and**
   2. Two contiguous hepatic segments are preserved; **and**
   3. At least 20% of the total estimated liver volume is anticipated to be preserved; **and**
   4. Extrahepatic disease, if present, has been or will be resected; **and**
   5. If a repeat procedure, at least 6 months have elapsed since the prior surgical resection or ablation.

B. Surgical excision* of liver *metastases* from other solid tumors is considered **medically necessary** when **all** of the following criteria are met:
   1. The presence of 3 lesions or less, as documented by MRI or computerized tomography (CT) scan; **and**
   2. Each lesion measures no more than 5 centimeters (cm) in diameter; **and**
   3. Complete excision of the carcinoma is anticipated; **and**
   4. Two contiguous hepatic segments are preserved; **and**
   5. At least 20% of the total estimated liver volume is anticipated to be preserved; **and**
   6. Extrahepatic disease, if present, has been or will be resected; **and**
   7. If a repeat procedure, at least 6 months have elapsed since the prior surgical resection or ablation.

C. Local ablative techniques* (specifically, percutaneous ethanol injection [PEI], radiofrequency [RFA], cryosurgical, or microwave ablation) are considered **medically necessary** in individuals with liver metastases from colorectal cancer or functioning neuroendocrine tumors who meet **all** of the following criteria:
   1. The individual must be a poor candidate for surgical resection or unwilling to undergo surgical resection; **and**
   2. The presence of 3 lesions or less, as documented by MRI or computerized tomography (CT) scan; **and**
   3. Each lesion measures no more than 5 cm in diameter; **and**
   4. No evidence of extra-hepatic disease; **and**
   5. All foci of disease are amenable to ablative therapy; **and**
   6. If a repeat procedure, at least 6 months have elapsed since the prior surgical resection or ablation.

D. TACE or TAE is considered **medically necessary** for **any** of the following indications:
   1. Treatment for individuals with liver-only metastasis from uveal (ocular) melanoma; **or**
   2. Palliative treatment for individuals with neuroendocrine tumors (for example, carcinoid tumors, pancreatic islet cell tumors, parathyroid, pituitary angiomas) with hepatic metastases when systemic therapy has failed to control symptoms such as carcinoid syndrome (for example, debilitating flushing, wheezing, and diarrhea); **or**
   3. Palliative treatment for individuals with symptoms from non-carcinoid neuroendocrine tumors with hepatic metastases (for example, hypoglycemia, severe diabetes, Zollinger-Ellison Syndrome); **or**

4. Palliative treatment for individuals with specific liver-related symptoms due to tumor bulk (for example, pain) from any metastatic hepatic tumor.

E. SIRT/TARE therapy is considered **medically necessary** as palliative treatment for individuals with **any** of the following:
1. Neuroendocrine tumors (for example, carcinoid tumors, pancreatic islet cell tumors, parathyroid adenomas, pituitary adenomas) with hepatic metastases, when systemic therapy has failed to control symptoms such as carcinoid syndrome (for example, debilitating flushing, wheezing, and diarrhea); **or**
2. Symptoms from non-carcinoid neuroendocrine tumors with hepatic metastases (for example, hypoglycemia, severe diabetes, Zollinger-Ellison Syndrome); **or**
3. Specific liver-related symptoms due to tumor bulk (for example, pain) from any metastatic hepatic tumor.

*__Note:__ When surgical excision and local ablative techniques are used together, the criteria for each technique should be considered.

III. ***Bridge to Liver Transplantation***

A. SIRT/TARE, TACE, TAE, PEI, RFA, or microwave ablation is considered **medically necessary** as a bridge to liver transplantation, when **all** of the following criteria are met:
1. Preserved liver function defined as Childs-Turcotte-Pugh Class A or B; **and**
2. Three or fewer encapsulated nodules and each nodule is less than or equal to 5 centimeters in diameter; **and**
3. No evidence of extra-hepatic metastases; **and**
4. No evidence of severe renal function impairment; **and**
5. No evidence of portal vein occlusion.

IV. ***Hepatocellular Carcinoma in Individuals Who May Become Eligible for Liver Transplantation***

PEI, RFA, TACE, TAE, or SIRT/TARE is considered **medically necessary** for the treatment of an individual when **both** of the following criteria are met**:**

A. May become eligible for liver transplantation except that the hepatic lesion(s) size is greater than 5 centimeters in maximal diameter; **and**

B. It can be reasonably expected that treatment will result in tumor size reduction to less than or equal to 5 centimeters in maximal diameter.

Not Medically Necessary:

SIRT/TARE is considered **not medically necessary** when the above criteria are not met.
TACE or TAE is considered **not medically necessary** when the above criteria are not met.

Surgical excision of liver tumors is considered **not medically necessary** when the above criteria are not met.

Ablation by radiofrequency ablation, cryosurgical ablation, microwave ablation, or percutaneous ethanol injection of hepatocellular carcinoma or metastatic lesions of the liver is considered **not medically necessary** when the above criteria are not met.

Ablation by radiofrequency ablation, cryosurgical ablation, microwave ablation, or percutaneous ethanol injection of metastatic lesions of the liver from tumor primaries other than colorectal or neuroendocrine cancer is considered **not medically necessary.**

TACE utilizing chemotherapy-loaded microspheres (that is, drug-loaded microspheres, drug-eluting beads) is considered **not medically necessary** for all liver-related indications, including but not limited to, palliative treatment of hepatic metastases from neuroendocrine tumors or unresectable hepatocellular carcinoma, as primary treatment for surgically unresectable primary hepatocellular carcinoma, as a bridge to liver transplantation, or for liver metastasis from other primary tumors.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Surgical Excision

CPT

47120	Hepatectomy, resection of liver; partial lobectomy
47122	Hepatectomy, resection of liver; trisegmentectomy
47125	Hepatectomy, resection of liver; total left lobectomy
47130	Hepatectomy, resection of liver; total right lobectomy

ICD-10 Procedure

0FB00ZZ-0FB04ZZ	Excision of liver [by approach; includes codes 0FB00ZZ, 0FB03ZZ, 0FB04ZZ]
0FB10ZZ-0FB14ZZ	Excision of right lobe liver [by approach; includes codes 0FB10ZZ, 0FB13ZZ, 0FB14ZZ]
0FB20ZZ-0FB24ZZ	Excision of left lobe liver [by approach; includes codes 0FB20ZZ, 0FB23ZZ, 0FB24ZZ]
0FT10ZZ-0FT14ZZ	Resection of right lobe liver [by approach; includes codes 0FT10ZZ, 0FT14ZZ]
0FT20ZZ-0FT24ZZ	Resection of left lobe liver [by approach; includes codes 0FT20ZZ, 0FT24ZZ]

ICD-10 Diagnosis

C00.0-C96.9	Malignant neoplasms
D01.5	Carcinoma in situ of liver, gallbladder and bile ducts

E34.0	Carcinoid syndrome

Ablative Techniques

CPT	
47370	Laparoscopy, surgical, ablation of 1 or more liver tumor(s); radiofrequency
47371	Laparoscopy, surgical, ablation of 1 or more liver tumor(s); cryosurgical
47380	Ablation, open, of 1 or more liver tumor(s); radiofrequency
47381	Ablation, open, of 1 or more liver tumor(s); cryosurgical
47382	Ablation, 1 or more liver tumor(s), percutaneous, radiofrequency
47383	Ablation, 1 or more liver tumor(s), percutaneous, cryoablation
47399	Unlisted procedure, liver [when specified as microwave ablation or percutaneous ethanol injection]

ICD-10 Procedure	
0F500ZZ-0F504ZZ	Destruction of liver [by approach; includes codes 0F500ZZ, 0F503ZZ, 0F504ZZ]
0F510ZZ-0F514ZZ	Destruction of right lobe liver [by approach; includes codes 0F510ZZ, 0F513ZZ, 0F514ZZ]
0F520ZZ-0F524ZZ	Destruction of left lobe liver [by approach; includes codes 0F520ZZ, 0F523ZZ, 0F524ZZ]

ICD-10 Diagnosis	
C18.0-C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0-C21.8	Malignant neoplasm of anus and anal canal
C22.0-C22.9	Malignant neoplasm of liver and intrahepatic bile ducts
C25.4	Malignant neoplasm of endocrine pancreas
C73	Malignant neoplasm of thyroid gland
C74.00-C74.92	Malignant neoplasm of adrenal gland
C75.0-C75.9	Malignant neoplasm of other endocrine glands and related structures
C7A.00-C7A.8	Malignant neuroendocrine tumors
C7B.00-C7B.8	Secondary neuroendocrine tumors
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
D01.5	Carcinoma in situ of liver, gallbladder and bile ducts
E34.0	Carcinoid syndrome

Ablative Techniques for Bridge to Liver Transplant

CPT	
47370	Laparoscopy, surgical, ablation of 1 or more liver tumor(s); radiofrequency
47380	Ablation, open, of 1 or more liver tumor(s); radiofrequency

47382	Ablation, 1 or more liver tumor(s), percutaneous, radiofrequency
47399	Unlisted procedure, liver [when specified as microwave ablation or percutaneous ethanol injection]

ICD-10 Procedure

	For the following when specified as PEI, RFA or microwave ablation:
0F500ZZ-0F504ZZ	Destruction of liver [by approach; includes codes 0F500ZZ, 0F503ZZ, 0F504ZZ]
0F510ZZ-0F514ZZ	Destruction of right lobe liver [by approach; includes codes 0F510ZZ, 0F513ZZ, 0F514ZZ]
0F520ZZ-0F524ZZ	Destruction of left lobe liver [by approach; includes codes 0F520ZZ, 0F523ZZ, 0F524ZZ]

ICD-10 Diagnosis

C22.0-C22.9	Malignant neoplasm of liver and intrahepatic bile ducts
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
D01.5	Carcinoma in situ of liver, gallbladder and bile ducts
Z76.82	Awaiting organ transplant status

TACE or TAE

CPT

37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction [when specified as TAE, or TACE not using drug-loaded microspheres or drug-eluting beads] Note: the procedure using drug-loaded microspheres or drug-eluting beads is considered not medically necessary.

ICD-10 Procedure

04L33ZZ	Occlusion of hepatic artery, percutaneous approach [when specified as TAE, or TACE not using drug-loaded microspheres or drug-eluting beads] Note: the procedure using drug-loaded microspheres or drug-eluting beads is considered not medically necessary.

ICD-10 Diagnosis

	For the diagnosis codes listed below or for a metastatic liver tumor from any primary tumor site when criteria are met:
C22.0-C22.9	Malignant neoplasm of liver and intrahepatic bile ducts
C25.4	Malignant neoplasm of endocrine pancreas
C69.30-C69.32	Malignant neoplasm of choroid
C69.40-C69.42	Malignant neoplasm of ciliary body
C73	Malignant neoplasm of thyroid

C74.00-C74.92	Malignant neoplasm of adrenal gland
C75.0-C75.9	Malignant neoplasm of other endocrine glands and related structures
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C7A.00-C7A.8	Malignant neuroendocrine tumors
C7B.02	Secondary carcinoid tumors of liver
D01.5	Carcinoma in situ of liver, gallbladder and bile ducts
E16.0-E16.2	Drug-induced, other and unspecified hypoglycemia
E16.4	Increased secretion of gastrin (Zollinger-Ellison syndrome)
E34.0	Carcinoid syndrome
Z76.82	Awaiting organ transplant status

SIRT/TARE

CPT

37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction [when specified as radioembolization using yttrium-90 microspheres]
79445	Radiopharmaceutical therapy, by intra-arterial particulate administration [when specified as transcatheter tumor destruction procedure using yttrium-90 microspheres]

HCPCS

C2616	Brachytherapy source, nonstranded, yttrium-90, per source [when specified as yttrium-90 microspheres]
S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres

ICD-10 Procedure

3E053HZ	Introduction of radioactive substance into peripheral artery, percutaneous approach [when specified as SIRT/TARE using yttrium-90 microspheres]

ICD-10 Diagnosis

	For the diagnosis codes listed below for treatment of primary liver tumors:
C22.0-C22.9	Malignant neoplasm of liver and intrahepatic bile ducts
D01.5	Carcinoma in situ of liver, gallbladder and bile ducts
Z76.82	Awaiting organ transplant status
	For the following diagnosis code ranges for palliation of liver metastases:
C00.0-C80.2	Malignant neoplasms
E16.0-E16.2	Drug-induced, other and unspecified hypoglycemia
E16.4	Increased secretion of gastrin (Zollinger-Ellison syndrome)
E34.0	Carcinoid syndrome

Note: All other diagnoses are considered not medically necessary when criteria are not met.

Discussion/General Information

Description and Prevalence of Disease

According to the American Cancer Institute (ACS), there will be an estimated 42,810 new cases of primary liver cancer and intrahepatic bile duct cancer diagnosed in the United States (U.S.) in 2020 and approximately 30,160 deaths associated with the disease. Since 1980, the incidence of hepatic cancer has more than tripled and the increasing incidence attributed to high rates of hepatitis C (HCV), nonalcoholic fatty liver disease (NAFLD), and metabolic syndrome (Heimbach, 2017).

Primary hepatobiliary carcinoma pertains to malignancies arising from the liver, bile ducts and/or gallbladder, known as intrahepatic and extrahepatic cholangiocarcinoma. Hepatic carcinoma can arise either as primary liver cancer or by metastasis to the liver from other tissue origins. Malignancies of the liver are comprised primarily of adenocarcinomas classified by hepatocellular and cholangiocarcinoma cell types (National Cancer Institute [NCI], 2019). Hepatocellular carcinoma is the most common form of hepatic malignancies and makes up 90% of the cases. Gallbladder cancer is the most common type of biliary tract malignancies. Cholangiocarcinoma occurs throughout the biliary tree (NCCN, 2019).

Neuroendocrine tumors may also involve the liver, where hormone production can cause systemic symptoms. The most common neuroendocrine tumor is the carcinoid tumor where excessive hormone production is associated with the carcinoid syndrome, characterized by debilitating flushing, wheezing and diarrhea. Pancreatic endocrine tumors that produce gastrin, insulin or other pancreatic hormones are unusual types of neuroendocrine tumors. Pancreatic endocrine (i.e., islet cell) tumors differ from the more common pancreatic epithelial tumors that arise from the exocrine portion of the pancreas. Surgical resection is typically not possible for neuroendocrine tumors, and treatment tends to focus on palliation of specific systemic symptoms.

Melanoma of the uveal tract (iris, ciliary body, and choroid), also known as ocular melanoma (OM), though rare, is the most common primary intraocular malignancy in adults. Uveal melanomas can arise in the anterior (iris) or the posterior (ciliary body or choroid) uveal tract. Extraocular extension, recurrence, and metastasis are associated with an extremely poor prognosis, and short-term survival (Gragoudas, 1991). The most frequent sites of metastasis are the liver, lungs, skin/soft tissue and bones (NCCN, V1.2019).

Liver metastases can develop from any type of cancer, but metastases from colorectal cancer (CRC) are the most common. Metastases develop in approximately 50-60% of those diagnosed with CRC and 80-90% of those individuals present with unresectable metastatic liver disease. Important prognostic factors for survival include site and extent of primary tumor, hepatic tumor burden, and performance status.

After the initial workup, individuals with primary hepatobiliary carcinoma are stratified into one of four categories consisting of:

- Potentially resectable or transplantable (adequate performance status or comorbidities)
- Unresectable
- Local disease only, but inoperable based on inadequate performance or comorbidities
- Metastatic disease

There is no universal staging system utilized by all facilities within the US. In addition, the potential presence of an underlying liver disease complicates the treatment of HCC (NCCN, V4.2019). More than 80% of the individuals diagnosed with HCC are found to have pre-existing cirrhosis (Marrero, 2018).

Surgical resection

The National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology® for HCC (V4.2019) lists the following with Category 2A recommendations in the Principles of Surgery section:

- Hepatic resection is indicated as a potentially curative option in the following circumstances:
  - Adequate liver function (generally Child-Pugh Class A without portal hypertension, but small series show feasibility of limited resections in patients with mild portal hypertension
  - Solitary mass without major vascular invasion
  - Adequate future liver remnant (FLR) (at least 20% without cirrhosis and at least 30%-40% with Child-Pugh Class A cirrhosis, adequate vascular and biliary inflow/outflow)
- Hepatic resection is controversial in the following circumstances, but can be considered:
  - Limited and resectable multifocal disease
  - Major vascular invasion

The 2018 AASLD Practice Guidelines on the diagnosis, staging and management of HCC notes that surgical resection remains the treatment of choice for resectable T1 or T2 HCC. While surgical resection is ideally performed when cirrhosis is not present, resection is still favored in the absence of clinically significant portal hypertension. For individuals with a single lesion 5 cm or less, or 3 or less tumors which are 3 cm or less that can be completely resected and who is non-cirrhotic or has cirrhosis but still has well preserved liver function, normal bilirubin and hepatic vein pressure gradient less than 10 mmHg, the survival rate is nearly 70% at 5 years (Marrero, 2018; NCCN, V4.2019). However, other factors, such as the number and location of tumors also impact the effectiveness of available therapies. Surgical resection of isolated primary and metastatic tumors continues to be the gold standard for curative intent of colorectal and neuroendocrine carcinomas as well as hepatocellular carcinoma (Berber, 2005; Bleicher, 2003; Bruix, 2010; Feng, 2013; Fong, 1999; Lermite, 2005; Lesurtel, 2015; Solmi, 2006).

In a consensus statement by the Society of Surgical Oncology, American Hepato-Pancreato-Biliary Association and the Society for Surgery of the Ailmentary Tract regarding the selection of individuals for resection of hepatic colorectal metastases (Charnsangavej, 2006), the authors concluded that individuals with primary colorectal tumors presenting with synchronous resectable liver metastases should be considered for aggressive curative-intent therapy when appropriate. The authors noted a "paradigm shift" in the definition of resectability noting 20% of the total liver volume "appears to be the minimum safe volume that can be left following extended resection in patients with normal underlying liver." The consensus was:

> Feasibility of hepatic resection should also be based on three criteria related to the remaining liver following resection: (1) the ability to preserve two contiguous hepatic segments, (2) preservation of adequate vascular inflow and outflow as well as biliary drainage, and (3) the ability to preserve adequate future liver remnant (greater than 20% in a healthy liver).

The authors reported extrahepatic disease is considered a relative contraindication that requires careful selection when considering liver resection.

The American Society of Clinical Oncology (ASCO) convened a panel to systematically review of the literature and develop clinical practice guidelines for the radiofrequency treatment of hepatic metastases from colorectal carcinoma (Wong, 2009). The reviewers located no published randomized controlled trials and the data from 46 unique data sets were extracted from single-arm, retrospective and prospective studies. The panel was unable to provide specific clinical practice guidelines, but was able to perform a review of the clinical evidence. Wong and colleagues reported there were a large number of studies demonstrating long-term survival with hepatic resection for approximately 40% of individuals with resectable colorectal hepatic metastases (CRHM). In selected studies, median survival after resection is greater than 40 months and the studies with long-term follow-up have 10-year survival rates of 20%. The panel determined the data demonstrated "extrahepatic disease predicts poor [disease-free survival] DFS and OS after hepatic resection."

Ruiz and associates (2018) evaluated the long-term survival outcomes of 139 consecutive women who underwent hepatectomy for breast cancer liver metastases (BCLM). The characteristics of those women who survived more than 5 years were compared to those who survived less than 5 years. A mean of 2 tumors were resected in the group which survived 5 or more years while a mean of 3 tumors was resected in the group which survived less than 5 years. While tumor size was not included as a predictive factor, the authors noted that tumor size is a well-documented predictor in overall survival.

Adam and colleagues (2006) reported the results of a retrospective study of 1452 individuals with noncolorectal nonendocrine liver metastases (NCNELM), all of whom received hepatic resection. The most frequent primary sources for the liver metastases were 32% breast, 16% gastrointestinal and 14% urologic. The overall 5-year and 10-year survival rates for all individuals were 36% and 23%, respectively. The median overall survival was 35 months. The median recurrence-free survival was 11 months, and 5 and 10 year recurrence-free survival was 14% and 10%, respectively. Major complications occurred at a rate of 21.5% with a 60-day mortality rate of 2.3%. Although the study data appeared to be encouraging, there was no analysis of how many other individuals with such metastases were refused or otherwise did not receive surgery, or the criteria used in making the decision to operate. Thus, while such a descriptive study showed that longer-term survival may be possible in some individuals and the authors assessed multivariate factors affecting survival, there was no comparison of variables between the surgical group and those with similar disease who never received surgery.

Uggeri and associates (2015) evaluated the outcomes of hepatic resection of liver metastases from non-colorectal, non-neuroendocrine, and non-sarcoma (NCNNNS) primary malignancies. A total of 30 case series were included in the meta-analysis. While the meta-analysis included a heterogeneous group of liver metastases, the authors

identified several prognostic factors including primary site and histological subtype, surgical margin status, type of the intervention performed and time of metastasis appearance. In addition, the authors noted a worse prognosis when the number of metastases was greater than 3-4 and the size was greater than 5-6 cm. While the role of surgery in the treatment of liver metastases from colorectum or neuroendocrine tumors has been defined, due to the discrepant characteristics of affected individuals, the difficulty in their selection and the lack of high volume series, there is not a clearly defined surgical role in the treatment of NCNNNS liver metastases. The authors noted:

> There is a paucity of data in medical literature. In fact, studies either had small number of patients likely due to the relative rarity and the lack of centralization in high volume centers, or they investigated diseases from primary tumors with different prognoses, including metastasis from cancer of the colorectum, neuroendocrine tissues, and sarcoma.

Metastases to the liver are common in breast cancer and are associated with a poor prognosis. The NCCN Breast Cancer CPG (2019) recommends systemic treatment for stage IV disease. The CPG does note that surgery "may be indicated for localized clinical scenarios". The NCCN Kidney Cancer clinical guideline practice (2019) recommends nephrectomy and surgical metastasectomy for surgical candidates with resectable primary renal cell carcinoma (RCC) and a solitary metastatic site (that is, lung, bone or brain). Recommendations for routine hepatic metastasectomy in the NCCN CPGs are limited to colorectal cancer, neuroendocrine cancers and solitary or small number of resectable in-transit cutaneous melanoma metastasis.

Ablative Techniques

Local ablative therapy for hepatic metastasis is generally indicated when there is no extrahepatic disease, which rarely occurs for individuals with primary cancers other than colorectal carcinoma or certain neuroendocrine malignancies. Currently, surgical resection with adequate margins or liver transplantation is considered the treatments of choice. However, many individuals are not candidates for surgical resection due to the location or number of lesions, inadequate liver reserve or comorbid conditions. Ablative therapy (cryosurgical, RFA, MWA and PEI) is an option these individuals. Common complications of ablative therapies include abscess formation, infection, hemorrhage and injury to adjacent anatomical organs. There have also been reports of mortalities associated with the ablative procedures.

Cryosurgery, also called cryotherapy or cryosurgical ablation, is the use of extreme cold produced by liquid nitrogen (or argon gas) to destroy abnormal tissue. Cryosurgical ablation is performed by inserting a hollow instrument called a cryoprobe into the lesion followed by circulation of coolant such as liquid nitrogen or argon gas through the hollow probe. The physician utilizes imaging procedures such as ultrasound or MRI to guide the cryoprobe to the tumor location and monitor the freezing process. The monitoring process is important so freezing of the cells is limited to the tumor and its immediate area, limiting the amount of damage to nearby healthy tissue. During a cryosurgical procedure, a ball of ice crystals forms around the probe, freezing nearby cells and killing them. The dead tissue is then naturally absorbed by the body. Cryosurgical ablation may also be performed in conjunction with surgical resection of other lesions or hepatic artery infusion. Cryosurgery does have side effects; however, they may be less severe than those associated with conventional surgery or radiation therapy. In rare cases, cryosurgery may interact adversely with certain types of chemotherapy.

RFA involves inserting an electrode into the center of the tumor with the delivery of alternating current with the intent to destroy tumor cells. Protein denaturation and coagulation is the ultimate cause of cell death. The procedure kills cells (cancerous and normal) by applying a heat-generating rapidly alternating current through probes inserted into the tumor. The effective volume of RFA depends on the frequency and duration of applied current, local tissue characteristics, and probe configuration (for example, single versus multiple tips). RFA can be performed as an open surgical procedure, laparoscopically, or percutaneously with ultrasound or computed tomography (CT) guidance. NCCN (V4.2019) notes that although individuals with HCC should first be considered for surgical curative therapy, RFA may be considered a potential curative therapy in select individuals who are not surgical candidates.

MWA is a thermal ablative technique. Probes are percutaneously inserted into the tumor delivering microwave energy into the tumor and heating it to high temperatures and killing cancerous cells. One purported advantage of MWA over RFA is the ability to achieve higher temperatures and obtain a larger ablation zone (Abdelaziz, 2015; Veltri, 2015). For this reason, MWA has generated some interest as a potential therapy for larger lesions although the evidence does not currently support that use.

Percutaneous ethanol injection uses the injection of ethanol directly into tumor tissue, where it destroys the tumor tissue due to its dehydrative and protein degenerative effects. The relative hypervascularity of HCC ensures good penetration of the tumor with minimal spillover of ethanol into normal liver tissue.

The NCCN CPG for HCC (V4.2019) states the following with Category 2A recommendations in the Principles of Locoregional Therapy- Ablation section:

- Locoregional therapy should be considered in patients who are not candidates for surgical curative treatments, or as a part of a strategy to bridge patients for other curative therapies.
- All tumors should be amenable to ablation such that the tumor and, in the case of thermal ablation, a margin of normal tissue is treated. A margin is not expected following percutaneous ethanol injection.
- Tumors should be in a location accessible for percutaneous/laparoscopic/open approaches for ablation. Caution should be exercised when ablating lesions near major vessels, major bile ducts, diaphragm and other intra-abdominal organs.
- Ablation alone may be curative in treating tumors ≤ 3 cm. In well-selected patients with small properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review.

The AASLD practice guideline (Marrero, 2018) for HCC notes that ablation is the best treatment option for individuals with early stage HCC who are not suitable for resection or liver transplantation. The modalities to achieve destruction of the malignant cells include RFA, microwave, PEI, and cryotherapy. The most effective treatment is generally dependent size and location of lesions. RFA has been shown to be more effective than PEI in lesions between 2 and 4 cm. However, in cases in which RFA is contraindicated, (for example, near to the main biliary tree, abdominal organs, or heart) PEI could be an acceptable option.

In a position statement for the Society of Interventional Radiology (SIR), Gervais and colleagues (2009) noted "HCCs 5 cm or less in diameter have a higher probability of having complete ablation compared to those greater than 5 cm in diameter." The authors also noted superior results with tumors smaller than 3 cm, acceptable (intermediate) results with tumors 3 to 5 cm, and "fairly dismal results for tumors larger than 5 cm."

Feng and colleagues (2015) conducted a meta-analysis to compare percutaneous RFA and surgical resection as treatments of small hepatocellular carcinoma (HCC). A total of 15,482 individuals from 3 randomized controlled trials (RCTs) and 20 retrospective studies were included in the efficacy and safety analysis. There were 7524 individuals treated with surgical resection of the liver, and 7958 treated with RFA. At 1, 3 and 5 years, surgical resection had higher overall survival (OS) and recurrence-free rates compared to RFA. OS at 1 year was odds ratio (OR) 0.71 (95% confidence interval [CI], 0.52-0.96); at 3 years OR 0.62 (95% CI, 0.49-0.78) and at 5 years OR 0.55 (95% CI, 0.47-0.66). The surgical resection recurrence-free survival rate at 1 year was OR 0.58 (95% CI, 0.45-0.76); 3 years OR 0.52 (95% CI, 0.40-0.68) and 5 years OR 0.50 (95% CI, 0.34-0.76). There was no difference in mortality between the two groups (OR 0.80; 95% CI, 0.30-2.15). The RFA group had a significantly lower morbidity rate compared to the surgical resection group (OR 0.37; 95% CI, 0.24-0.58).

In the ASCO clinical practice guideline, Wong and colleagues (2009) noted 5-year survival rates for RFA of colorectal hepatic metastases varied between 14% to 55% and the local tumor recurrence rates varied between 3.6% and 60%. The panel concluded:

> There are no compelling data to guide use of RFA in patients with viable extrahepatic disease. Extrahepatic disease is a poor prognostic indicator for patients, predicting decreased disease-free survival (DFS) and overall survival (OS) compared with patients without extrahepatic disease.

The ASCO panel noted the use of palliative RFA when curative treatment was not feasible. However, there were no data to determine the effectiveness of this application. Therefore, the panel recommended future randomized controlled trials to study comparative effectiveness, safety and efficacy.

Lencioni and colleagues (2003) published a randomized comparison of RFA and PEI in 102 individuals with hepatocellular cancer. Tumors were fully ablated in 91% of the participants treated with RFA and 85% of the individuals treated with PEI; however, an average of 5.4 sessions were required for PEI versus 1.1 for RFA. Additionally, there was a significant difference in the local recurrence-free survival rate at 1 year of 83% and 62% at 2 years for the PEI group. In comparison, the RFA group had a local recurrence-free survival rate at 1 year of 96% and 95% at 2 years. The overall 2-year survival was similar in both groups. Additional nonrandomized comparative studies reporting survival data also support the equivalency of these two options (Ikeda, 2001; Livraghi, 1999).

In a study of 153 enrolled individuals with newly diagnosed HCC, Morimoto and colleagues (2007) described two cohorts of participants. A total of 110 individuals received RFA ablation while 43 participants received PEI. Of those, 102 participants had single HCC tumors and 51 participants had two or three HCC nodules with a maximum diameter of 5 cm or less. The overall survival at 3 years was 75% and 59% at 5 years. No local tumor growth at 6

months following initial treatment was reported in 125 (82%) individuals. Twenty-eight (18%) participants had residual tumor and were retreated. There was no significant difference in successful initial treatment outcomes between the treatment modalities; 90 (82%) of the 110 individuals treated with RFA, and 35 (81%) of 43 individuals treated with PEI, had no residual tumor by contrast enhanced computerized tomography (CT) at 6 months. Median follow-up of 34 months revealed 58 (53%) of 110 individuals treated with RFA and 25 (58%) of 43 individuals treated with PEI had tumor recurrence. Twenty-three participants died and 3 participants were lost to follow-up. Tumor size was one of the pre-treatment factors associated with survival. Overall, the significant predictor of survival was the response to initial treatment.

Taniguchi and colleagues (2008) reported long-term study results of 31 individuals with HCC lesions less than or equal to 15 mm treated with PEI. Overall survival rate at 3, 5, 7 and 10 years was 74.1%, 49.9%, 27.2% and 14.5%, respectively. A subset analysis noted a significant correlation between hepatic function and survival. Individuals with Child-Pugh class A had a higher survival rate compared with Child-Pugh class B (p=0.011).

Other studies also report on the effects of tumor size and quantity and the impact on the results. Results from PEI on necrosis rates in HCC had a correlation to the tumor size. HCC smaller than 2 cm resulted in 90%-100% necrosis rates, while tumors between 2 cm to 3 cm had a 70% necrosis rate and tumors between 3 cm to 5 cm resulted in 50% necrosis (Bruix, 2005). Lermite and colleagues (2006) reported the significant risk factor that resulted in local recurrence was tumor size greater than 3 cm. In a study by Luo (2005), a lower complete necrosis rate of 23% was reported in a group with tumors larger than 3 cm versus 92.2% in a group with tumors ranging from 1-3 cm. Overall survival was also significant between the groups with an advantage in individuals with smaller tumors less than 3 cm with a 5 year survival of 33.3% compared to 0.4% in the group with tumors larger than 3 cm.

In a RCT involving 285 individuals with HCC, the use of PEI treatment was compared to RFA. There were no statistically significant differences between the treatment modalities in the 1, 2, 3, 4 and 5 year survival rates of 95%, 83%, 78%, 70% and 68%, respectively in the PEI cohort, and in the RFA group 95%, 90%, 83%, 73% and 70%, respectively (Giorgio, 2011).

RFA is considered the most effective treatment of early stage (3 or less nodules each 3cm or smaller), unresectable, not transplantable HCC. The current RFA devices are capable of producing a lesion of 5cm or more in one session. This is sufficient to allow for the full ablation of a 3cm tumor with adequate margins (Peng, 2013; Tovoli, 2016). Ablation of larger tumors was more technically challenging as overlapping fields were required to ensure adequate ablation. Radiographic studies present challenges when used to accurately determine the defining margins for overlap. Recent smaller, prospective or retrospective studies have shown some promising results in the treatment of larger lesions with locoregional therapies such as MWA or RFA (Abdelaziz, 2015; Dai, 2015; Veltri, 2015). However, at this time, the use of ablative therapies (that is, RFA, PEI, microwave ablation or cryosurgery) have not been shown in studies to be clinically appropriate in the treatment of more than 3 liver lesions or tumors larger than 5 cm.

Treatment of neuroendocrine cancers is primarily palliative in nature, to reduce levels of functioning hormones, which may result in significant morbidity. One study reported that radiofrequency ablation resulted in successful treatment of 63% of individuals with functioning neuroendocrine tumors (Henn, 2003).

Neuroendocrine tumors with a high incidence of distant metastases frequently involve the liver (Bacchetti, 2013). There is considerable literature regarding the use of ablative techniques, which support an increase in survival times when compared to conservative treatment in select individuals (Adam, 2002; Bacchetti, 2013; Saxena, 2012). Overall, the studies do not appear to support that a specific ablative technique is superior. While RFA appears to be the most common modality used in this country, the choice of ablative technique is often based on individual physician and institution experience and preference. Locally ablative techniques are frequently used with resective surgery.

Retrospective studies and case series using a locally ablative technique to treat liver metastases from primaries other than colorectal and neuroendocrine tumors generally report the feasibility of the procedure and suggest improved progression-free survival (Bleicher, 2003; Fairhurst, 2016; Kümler, 2015; Seidensticker, 2015; Xiao, 2018).). However, because of the limited data and heterogeneous clinical presentations, optimal selection criteria have not been identified and uniformly adopted. Various authors noted prospective trials are needed to confirm the results. Recommendations for routine local ablation of hepatic metastases are included in the NCCN clinical practice guidelines (2018) for colorectal cancer and neuroendocrine cancers. However, the treatments are not recommended for other metastatic tumors to the liver.

Zhang and colleagues (2008) reported on a retrospective study of 160 individuals treated with microwave ablation of liver tumors. Specific diagnoses included primary hepatic cancer (i.e., hepatoma/hepatocellular carcinoma [HCC]) in 97 individuals, and metastatic cancer to the liver from other primary sites in 63 individuals. A mean number of 2.2 microwave applications were performed per person. A second microwave treatment for recurrent disease was performed on eight individuals, and two individuals required a third treatment. A total of 86 individuals were followed for more than 1 year and 96% of individuals treated for primary liver cancer were alive after 1 year versus 82.1% of individuals treated for metastases ($p=0.022$). One-year OS was 91.8%. Alfa-fetoprotein (AFP) levels in 25 individuals with primary liver cancer decreased from 104.2 ± 22.5 ng/ml to 24.6 ± 3.6 ng/ml ($p<0.05$) after microwave ablation. There were no operative deaths, and complications were medically managed. Fever was reported in 76.3% of individuals, and was managed with indomethacin. Increased transaminases occurred in 80% (128/160) of individuals, and resolved within a day or two without special treatment in individuals without pre-existing ascites. Pleural effusions were noted in 14 individuals with only 1 individual requiring a chest tube for drainage. The authors concluded microwave ablation therapy was safe and effective for liver tumors. In addition, specialty consensus opinion suggests microwave ablation therapy may be used for primary and secondary liver carcinomas.

In a retrospective review of 110 individuals, Shady and colleagues (2018) compared the local tumor progression free survival (LTPFS) in individuals who underwent either radiofrequency ablation (RFA) or microwave ablation (MWA) to treat colorectal liver metastases. A total of 62 individuals with 85 tumors underwent RFA in 72 sessions, and 48 individuals with 60 tumors underwent microwave ablation in 52 sessions. The median tumor size was 1.8 cm and 1.7 cm in the RFA and microwave ablation groups respectively. Complete ablation or no evidence of

residual disease on the first post-ablation contrast enhanced CT (6 weeks), was used as the basis for monitoring for local tumor progression. Complete ablation was reported in 93% (79/85) of the RFA group and 97% (58/60) of the MWA group. The LTPFS rate for RFA versus MWA at 12 month was 69% versus 75%, at 18 months 66% versus 66%, and at 24 months 61% versus 60% respectively. An ablation margin of 5 mm or less was a predictor of shorter LTPFS in both groups while the presence of peri-vascular tumors was a predictor of LTPFS in only the RFA group. The authors noted that while the heat sink effect is a limitation of RFA, MWA might be relatively resistant to the heat sink effect. There were no differences in complication rates between the two modalities.

TACE and TAE

Arterial embolization therapy, including TACE and TAE, in the treatment of HCC is based on selective catheter-based infusion of particles targeted to the arterial branch of the hepatic artery feeding the portion of the liver in which the tumor is located. TACE has been investigated to treat resectable, unresectable, and recurrent HCC, as a bridge to liver transplantation, and to treat liver metastases, most commonly from colorectal cancer. TACE of the liver is a proposed alternative to conventional systemic or intra-arterial chemotherapy, and to various nonsurgical ablative techniques, to treat resectable and nonresectable tumors. The rationale for TACE is that infusions of viscous material containing one or more antineoplastic agents may exert synergistic effects: cytotoxicity from the chemotherapy that is potentiated by anoxia in the infarcted region. The liver is especially amenable to such an approach, given its distinct lobular anatomy, the existence of two independent blood supplies, and the ability of healthy hepatic tissue to grow and thus compensate for tissue mass lost during TACE. Another rationale is that TACE delivers effective local doses, while possibly minimizing systemic toxicities associated with oral or intravenous chemotherapy.

TACE procedures require hospitalization for placement of the hepatic artery catheter and workup to establish eligibility for TACE. Prior to the procedure, the patency of the portal vein is demonstrated to ensure an adequate post-treatment hepatic blood supply. With the individual under local anesthesia and mild sedation, a superselective catheter is inserted via the femoral artery and threaded into the hepatic artery. Angiography is then performed to delineate the hepatic vasculature, followed by injection of the embolic chemotherapy mixture. Chemotherapeutic agents delivered with TACE include doxorubicin (the single agent that is most widely used), epirubicin, mitomycin C, or cisplatin, either alone or in combination, mixed with a viscous embolic material (for example, lipiodol). After infusion of this viscous chemotherapeutic agent, embolization of the arterial blood supply to the tumor is completed using embolic agents, including but not limited to, gelatin sponge particles, polyvinyl alcohol particles (PVA), or hydrophilic, polyacrylamide microporous beads, known as microspheres. Typically, only one lobe of the liver is treated during a single session, with subsequent embolization procedures scheduled from 5 days to 6 weeks later. In addition, since the embolized vessel recanalizes, TACE can be repeated as many times as necessary. Repeat x-rays are taken to confirm that the tumor has been optimally treated. The procedure is usually performed by an interventional radiologist.

TAE is carried out during selective hepatic arterial catheterization through the arteries supplying a tumor and involves the infusion of lipiodol (without a chemotherapeutic agent) followed by embolization using any of the embolic agents (for example, gelatin sponge cubes) as during TACE procedures. Advocates of this catheter-based

therapy state that TAE may be equally effective as TACE for palliative treatment of primary liver cancer (Brown, 1998).

The most common adverse event associated with TACE or TAE is post-embolization syndrome which consists of fever, abdominal pain, nausea, vomiting, leukocytosis, and an increase in liver enzymes lasting for a few hours to a few days. This syndrome, which has widely variable manifestations, is usually self-limited and experienced after 80% to 90% of the procedures. The syndrome is treated symptomatically and decreases in severity with subsequent procedures in most individuals. The chemotherapeutic and embolizing agents may also cause acute portal vein thrombosis, acute cholecystitis, biliary tract necrosis, pancreatitis, gastric erosions, or ulcers if they are inadvertently injected into these organs. Infection of the necrotic tumor presenting as liver abscess can also occur. Hepatic insufficiency and liver failure (a major treatment-related complication that may result in morbidity), can develop after TACE in individuals with borderline liver function before treatment (Lau, 2008). Studies have consistently reported that the toxicity of TACE after treatment in individuals with HCC in a standardized oncology protocol setting results in considerably lower toxicity rates than those reported after treatment with currently used systemic chemotherapeutic agents (Buijs, 2008; Llovet, 2002b;). Reported rates of TACE and TAE treatment-associated mortality for both are usually less than 5%.

The NCCN CPG for HCC (V4.2019) states the following with Category 2A recommendations in the Principles of Locoregional Therapy- Arterially directed therapies section:

- Locoregional therapy should be considered in patients who are not candidates for surgical curative treatments, or as a part of a strategy to bridge patients for other curative therapies.
- Lesions 3 to 5 cm may be treated to prolong survival using arterially directed therapies, or with combination of an arterially directed therapy and ablation as long as tumor location is accessible for ablation.
- All tumors irrespective of location may be amenable to arterially directed therapies provided that the arterial blood supply to the tumor maybe isolated without excessive non-target treatment.
- Unresectable/inoperable lesions > 5cm should be considered for treatment using arterially directed or systemic therapy.
- Arterially directed therapies include transarterial bland embolization (TAE) chemoembolization (transarterial chemoembolization [TACE] and TACE with drug-eluting beads [DEB-TACE]) and radioembolization with yttrium-90 microspheres.
- All arterially directed therapies are relatively contraindicated in patients with bilirubin >3 mg/dL unless segmental injections can be performed.
- Arterially directed therapies in highly selected patients have been shown to be safe in the presence of limited tumor invasion of the portal vein.
- The angiographic endpoint of embolization may be chosen by the treating physician.

RCTs in the peer-reviewed literature have focused on the impact of embolization procedures as palliation of noncurable HCC. According to Liapi and Geschwind (2007), TACE is currently considered the mainstay of therapy for unresectable HCC. In two prospective RCTs (Llovet, 2002b; Lo, 2002), TACE was shown to prolong survival

significantly in select individuals with HCC with preserved liver function and adequate performance status. In a meta-analysis of pooled data of seven RCTs assessing TAE/TACE as a primary treatment of unresectable HCC in comparison to an untreated control arm, Llovet and Bruix (2003) found a considerable 2-year survival benefit associated with TACE compared with control (p=0.017). Ideal candidates for TACE include individuals with preserved liver function and asymptomatic multinodular tumors without vascular invasion or extrahepatic spread not suitable for radical treatments (Llovet, 2004). Additional criteria include individuals with 3 or fewer encapsulated nodules, each < 5 centimeters (cm) in diameter, absence of extra-hepatic metastases, no evidence of severe renal function impairment, and no evidence of altered portal blood flow (for example, portal vein thrombosis) (Bruix, 2005; Bruix 2011; Lau, 2006; Molinari, 2006). The evidence suggests that individuals who do not meet these criteria do not respond adequately to TACE and receive little or no benefit from the treatment. This is confirmed in a retrospective study by Maluccio and colleagues (2008), where predictors of poor prognosis following TAE for HCC were tumor size ≥ 5 cm, 5 or more tumors, and extrahepatic disease; portal vein occlusion was not found to be an independent predictor of survival. Overall survival (OS) rates observed at 1, 2, and 3 years were 66%, 46%, and 33%, respectively; survival rates increased to 84%, 66%, and 51%, respectively, when only the subgroup of individuals without extrahepatic spread or portal vein involvement by tumor were considered.

Takayasu and colleagues (2006) reported results from an 8-year prospective cohort study of 8510 individuals with unresectable HCC who underwent initial treatment with TACE using emulsion of lipiodol and anticancer agents followed by gelatin sponge particles. The mean follow-up period was 34 months. The OS rates by TACE at 1, 3, 5 and 7 years were 82%, 47%, 26%, and 16%, respectively. Multivariate analyses showed significant differences (p=0.0001) in degree of liver damage, alpha-fetoprotein value, maximum tumor size, number of lesions, and portal vein invasion. TACE-related mortality rate after the initial therapy was 0.5%. The authors concluded that TACE was a safe, therapeutic modality for unresectable HCC, with a 5-year survival rate of 26% and a 0.5% mortality rate.

A Cochrane review (Oliveri, 2011) included 9 trials with 645 participants comparing treatment with TACE (n=6 trials) or TAE (n=3 trials) to control for unresectable HCC. Seven trials had low risk of selection bias, but all had other risks of bias. Three trials were stopped early due to interim inspections and one trial due to slow accrual. Meta-analysis of trials with low risk of selection bias showed that TACE or TAE versus control does not significantly increase survival (Hazard ratio [HR] 0.88; 95% confidence interval [CI], 0.71 to 1.10). Two trials with low risk of selection bias, no early stopping, and no co-intervention did not establish a significant effect of TACE or TAE on OS (HR 1.22; 95% CI, 0.82 to 1.83; p=0.33). Trial sequential analysis confirmed the absence of evidence for a beneficial effect of TACE or TAE on survival, indicating the need for future randomization of up to 383 additional participants in adequately powered and bias-protected clinical trials. Despite the lack of firm evidence to support or refute the use of TACE or TAE for unresectable HCC, the NCCN CPGs for hepatobiliary cancers (V1.2018) include a category 2A recommendation and uniform consensus for TACE and TAE as standard locoregional treatment for individuals with unresectable HCC.

TACE has been studied for other indications including large HCC, preoperative shrinkage of resectable HCC, and for tumor types other than HCC and neuroendocrine tumors. Cheng and colleagues (2005a) evaluated the value and limitations of postoperative TACE in preventing recurrence of HCC. In this retrospective study, the authors compared the recurrence rates for a group of 987 individuals with HCC treated with TACE compared to a control

group of 643 postoperative individuals with HCC who did not receive TACE. The 6-, 12-, and 18-month recurrence rates for the TACE group compared to the non-TACE group were 22.2% versus 61.6%, 78.0% versus 74.7% and 88.6% versus 80.1%. There were also significant differences between the recurrence rates of the 2 groups at 6 months ($p<0.0001$). The authors concluded that TACE had a good effect in preventing recurrence of HCC at 6 months, but the rate of recurrence was less satisfactory in a longer period. The data reported in this trial did not demonstrate that TACE resulted in a significant advantage in quality of life or length of survival for these conditions.

Chua and colleagues (2009) conducted a systematic review of neoadjuvant TACE for resectable HCC, evaluating 18 studies including 3 RCTs and 15 observational studies. The review comprised 3927 individuals, of whom 1293 underwent neoadjuvant TACE. The conclusions were that TACE could be used safely and resulted in high rates of pathologic responses but did not appear to improve disease-free survival in the TACE group. No conclusions could be drawn with respect to OS differences between the TACE and non-TACE groups due to the heterogeneity of the results across studies.

Zhou and colleagues (2013) reported on a meta-analysis of 21 studies evaluating preoperative TACE including 4 RCTs and 17 nonrandomized studies with a total of 3210 participants. Preoperative TACE was given to 1431 individuals with the remaining 1779 serving as controls. The 5-year disease-free survival for preoperative TACE in 18 studies ranged from 7% to 57% and 8% to 49% in the controls. In 16 studies, the 5-year OS for preoperative TACE was 15% to 63% and 19% to 63% in the controls. In the pooled analyses, there were no significant improvements with preoperative TACE versus controls in the 5-year disease-free (32% vs. 30%, $p=0.17$) and OS (40% vs. 45%, $p=0.37$). Intra-and extra-hepatic recurrence were also not significantly different in the pooled analyses (51% vs. 54% and 13% vs. 10%; $p=0.19$, respectively).

For individuals with hepatic metastasis from neuroendocrine tumors, data in the medical literature confirms that catheter-based arterial embolization procedures, with or without chemotherapy, have a role in the palliative care of individuals with various neuroendocrine tumor symptoms such as carcinoid syndrome (for example, severe flushing, wheezing, and diarrhea), Zollinger-Ellison syndrome, hypoglycemia, severe diabetes, and other neuroendocrine-related manifestations (Christante, 2008, Gupta, 2003; Hur, 2013; Maluccio, 2006; Roche, 2003; Ruutiainen, 2007). The treatment has been shown to be useful in diminishing the effect of these symptoms on the individual, consequently producing significant improvements in the quality of life for individuals with neuroendocrine tumors. TACE or TAE is also known to improve pain and control symptoms attributable to the effect of tumor bulk associated with either primary or metastatic liver disease through shrinkage of tumor size.

The NCCN CPG for neuroendocrine tumors of the gastrointestinal tract and/or distant metastases (V1.2019) includes a recommendation to consider hepatic-directed therapy for hepatic-predominant disease including arterial embolization and TACE for individuals with locoregional unresectable disease and/or distant (liver) metastases (symptomatic, clinically significant tumor burden, or clinically significant progressive disease) (2A recommendation).

For individuals with liver metastases from colorectal cancer who do not qualify for surgical resection, systemic chemotherapy is considered the first-line treatment. However, more than 60% of individuals experience treatment

failures and disease progression. For the large proportion of those in whom second- and third-line medical treatment has failed, other palliative therapies to control disease progression and symptoms have been studied, including TACE. The early studies of TACE for metastatic colorectal cancer consist of small numbers of participants with variable results across studies due to variation in participant selection criteria and treatment regimens (Salman, 2002; Sanz-Altamira, 1997; Tellez, 1998).

Vogl and colleagues (2009) evaluated tumor control and survival in individuals with unresectable liver metastases of colorectal origin that did not respond to systemic chemotherapy and were treated with TACE. Participants were treated at 4-week intervals, with a total of 2,441 TACE procedures performed (mean, 5.3 sessions per participant), using 1 of 3 local chemotherapy protocols. Local tumor control was PR in 68 participants (14.7%), stable disease in 223 participants (48.2%), and progressive disease in 172 participants (37.1%). Median survival from the start of TACE treatments was 14 months. The 1- and 2-year survival rates after TACE were 62% and 28%, respectively. No difference in survival was observed between the 3 different local chemotherapy protocols.

A Cochrane review (Riemsma, 2013) concluded that in individuals with colorectal liver metastases, no significant survival benefit or benefit on extrahepatic recurrence was found when comparing TACE to palliative care. "At present, transarterial (chemo) embolisation cannot be recommended outside randomised clinical trials."

The NCCN CPGs for colon cancer (V2.2020) and rectal cancer (V2.2019) address a number of non-surgical liver-directed therapies for the treatment of unresectable metastatic disease. The NCCN states that arterially directed catheter therapy is an option for a highly selective group of individuals with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.

TACE with Drug-Loaded Microspheres or Drug-Eluting Beads (DEBs)

The development of DEBs or injectable microspheres loaded with chemotherapy is being considered as a drug delivery system for intraarterial treatment of hepatic lesions during TACE. In the setting of locoregional hepatic intraarterial infusion, TACE-administered DEBs are precisely delivered with a controlled and sustained release, as well as high intratumoral concentration for a sufficient time without damaging the surrounding hepatic tissue and microcirculation (Kettenbach, 2008). Randomized studies are currently underway to determine the additional value of this technique over other established methods of TACE. To date, the U.S. Food and Drug Administration (FDA) has not cleared TACE-administered DEBs or microspheres loaded with chemotherapeutic agents for sale or distribution in the United States. However, the FDA has stand-alone approvals for chemotherapeutic and embolic agents used with TACE that are not specifically approved as combination therapy when administered during TACE. Specific chemotherapeutic agents may be approved for a number of oncologic indications and several embolic beads are FDA-approved for "embolization of hypervascular tumors and arteriovenous malformations" (FDA, 2014). Several brands of DEBs include, but are not limited to, DC Bead™, DEBDOX™-loaded with doxorubicin, and DEBIRI™ - loaded with irinotecan (Boston Scientific, Marlborough, MA) and HepaSphere™ Microspheres (Merit Medical, Inc., South Jordan, UT)- loaded with doxorubicin. A number of studies evaluating the use of DEBs to treat colorectal cancer on unresectable HCC have been completed. These studies are limited by several factors, including small size, lack of standardized treatment within the groups, lack of a control group and

high drop-out rates (Grosso, 2008; Lee, 2017; Martin, 2009; Martin, 2015; Poggi, 2008; Poon, 2007; Reyes, 2009; Varela, 2007).

Richardson and colleagues (2013) systematically reviewed an RCT and five observational studies (n=235) on the use of TACE with irinotecan-DEBs for the treatment of unresectable colorectal liver metastasis. Survival times ranged from a median of 15.2 months to 25 months. The most common adverse event was postembolization syndrome (abdominal pain, nausea, and vomiting) followed by hypertension. In the RCT in this review (Fiorentini, 2012), 74 participants were randomly allocated to TACE with irinotecan-DEBs (n=36) or systemic irinotecan, fluorouracil and leucovorin (FOLFIRI) (n=38). The OS in the irinotecan-DEBs group was significantly longer with a median OS of 22 months (95% CI, 21-23 months) compared to 15 months (95% CI, 12-18 months) for the FOLFIRI chemotherapy group (p=0.031). Progression-free survival was 7 months in the irinotecan-DEBs group compared to 4 months in the FOLFIRI group; and, the difference between groups was statistically significant (p=0.006, long-rank). Extrahepatic progression occurred in all participants by the end of the study, at a median time of 13 months in the irinotecan-DEBs group compared to 9 months in the FOLFIRI group; however, a statistically significant difference between groups was not observed (p=0.064, log-rank).

For HCC, the Society of Interventional Radiology's Quality Improvement Guidelines for Transarterial Chemoembolization and Embolization of Hepatic Malignancy (Gaba, 2017) states that drug-eluting transarterial chemoembolization is "associated with favorable pharmacokinetics and reduced systemic drug and may improve drug delivery compared with conventional transarterial chemoembolization."

A number of studies have compared of TACE therapy with DEBs to TACE or TAE in the treatment of unresectable HCC. Although these studies suggest that there might be a survival benefit associated with the use of DEBs, they fail to report conclusive evidence to support that TACE with DEBs resulted in statistically significant improved objective response rates or survival benefits when compared to TACE or TAE alone (Dhanasekaran, 2010; Lammer, 2010 RCT; Malagari, 2010). In addition, a number of meta-analysis and systematic reviews compare the safety and efficacy of conventional TACE to DEB-TACE in the treatment of unresectable HCC and have concluded that the evidence in inconclusive regarding the clinical effectiveness of DEB therapy as conventional TACE or TAE therapy (Facciorusso, 2016a; Hui, 2015; Katsanos, 2017; Xie, 2015).

SIRT/TARE

SIRT, also known as TARE, relies on targeted delivery of small beads (microspheres) impregnated with radioactive 90Y to cure or palliate unresectable hepatic tumors by improving loco-regional control. The rationale for SIRT is based on the following: (1) the liver parenchyma is sensitive to radiation; (2) the hepatic circulation is uniquely organized, whereby tumors greater than 0.5 cm rely on the hepatic artery for blood supply while normal liver is primarily perfused via the portal vein; and (3) 90Y is a pure beta emitter with a relatively limited effective range and short half-life that helps focus the radiation and minimize its spread. Candidates for SIRT are examined by liver angiography and technetium (99mTm) lung scan to rule out aberrant hepatic vasculature or significant lung shunting that would permit diffusion of injected microspheres.

Currently, two commercial forms of 90Y microspheres are available: TheraSpheres™ (Boston Scientific, Marlborough, MA) are glass beads bound to 90Y, and SIR-Sphere® (Sirtex Medical Inc., Lake Forest, IL), in which 90Y is bound to resin beads. Non-commercial forms are used mostly outside the U.S. While the commercial products use the same radioisotope (90Y) and have the same target dose (100 Gy), they differ in microsphere size profile, base material (i.e., glass versus resin, respectively) and size of commercially available doses. These physical characteristics of the active and inactive ingredients affect the flow of microspheres during injection, their retention at the tumor site, spread outside the therapeutic target region, and dosimetry calculations. Note also that the U.S. FDA granted PMA of SIR-Sphere, for use in combination with 5-floxuridine (5-FUDR) chemotherapy by adjuvant hepatic artery chemotherapy (IHAC), to treat unresectable hepatic metastases from CRC cancer. In contrast, TheraSpheres is approved is indicated for use as monotherapy to treat or as a neoadjuvant therapy to transplantation or surgery in individuals with unresectable hepatocellular cancer (HCC). In addition, therapy is also indicated when there is partial or branch portal vein thrombosis/occlusion in those with HCC. For these reasons, results obtained with one product do not necessarily apply to other commercial (or non-commercial) products. The uses of both technologies are additionally regulated by the U.S. Nuclear Regulatory Commission (NRC).

The FDA labeling for TheraSpheres (2014) and Sir-Spheres (2019) state that the following tests are recommended before treatment:

- A hepatic angiogram should be performed to establish arterial anatomy of the liver;
- A nuclear medicine break-through scan (intrahepatic technetium MAA Scan or Tc-99 MAA) to evaluate hepatic flow to gastrointestinal tract and/or pulmonary shunting. If a port has been inserted, this test can be performed through the port;
- Serologic tests of liver function should be performed to determine the extent of liver function/damage;

Appropriate imaging studies are recommended to determine the extent of disease. These may include chest x-ray, CT scan of chest and abdomen, abdominal ultrasound and a bone scan.

In 2009, Salem and colleagues published the findings of a large prospective case series. This study included 291 participants with unresectable HCC. Using World Health Organization (WHO) and European Association for the Study of the Liver (EASL) guidelines, response rates were reported to be 42% and 57% respectively. Survival times differed significantly between individuals with Child-Pugh A and Child-Pugh B classifications, with the former surviving a mean of 17.2 months and the latter 7.7 months. Furthermore, individuals with Child-Pugh B class disease with portal vein thrombosis (PVT) survived a mean of only 5.6 months. Similar findings regarding the impact of PVT on SIRT outcomes were reported by Woodall (2009). A smaller, retrospective case-series (n=195) assessed long-term survival in individuals with HCC and PVT and found that within this population the most significant predictors of survival included albumin, bilirubin, ascites, tumor < 5 cm, ECOG status and the degree of PVT (Abouchaleh, 2018).

Vente and colleagues (2009) conducted a meta-analysis of the literature addressing SIRT for unresectable liver metastases. The authors included all forms of SIRT, including SIR-Spheres and TheraSpheres, analyzing 30 articles that included 1217 subjects. For individuals with colorectal cancer (CRC) metastases, a total of 19 eligible studies, which included 792 subjects, were included in the analysis. Of these, 195 had received SIRT as a first-line

treatment and 486 received SIRT as salvage therapy. There was a significant difference in response when used for first-line therapy versus salvage, with the response rates reported as 91% and 79% respectively (p=0.07). The median survival time varied between 6.7 to 17 months, irrespective of microsphere type, chemotherapy regimen, disease stage, or salvage versus first-line therapy. Median survival from time of diagnosis ranged from 10.8 to 29.4 months. For individuals with HCC, the authors included 14 studies in their analysis. These studies included 425 subjects who underwent SIRT therapy. Of these studies, only 12 reported on tumor response, leaving 318 subjects. The authors noted that treatment with resin microspheres (e.g., SIR-Spheres) was associated with a significantly higher response rate when compared to glass microspheres (e.g., TheraSpheres) (89% versus 78%, p=0.02). Median survival was reported in only seven studies. Median survival from time of SIRT treatment varied between 7.1 to 21 months. Median survival from time of diagnosis or recurrence was reported to be between 9.4 to 24 months.

Six meta-analyses have been published comparing the safety and efficacy of TACE compared to SIRT in the treatment of unresectable HCC (Facciorusso, 2016; Katsanos, 2017; Lobo, 2016; Ludwig, 2017; Yang, 2018; and Zhang, 2015). The published literature chosen for inclusion in the analyses varied on SIRT's utility as primary versus salvage treatment and on outcomes of interest, some of which included tumor response, survival and quality of life measures. Other variations between studies included subjects with PVT or minimal extra-hepatic disease while others excluded for any evidence of PVT or extra-hepatic disease. Three of the six meta-analyses concluded that outcomes, including survival, appear comparable or better when comparing SIRT to TACE for unresectable HCC, and SIRT resulted in fewer complications and less hospitalization when compared to TACE. Zhang (2015), reported that only three of the eight studies chosen for inclusion in their analysis reported on OS but among them, SIRT was found to have a statistically significant survival advantage over TACE (HR=0.74, 95% CI, 0.61-0.90; p=0.002). Although OS appeared to be improved in those who received SIRT versus TACE, Zhang (2015) also reported that no beneficial effect was seen in SIRT recipients in the outcomes of complications (other than abdominal pain), tumor response or over-all tumor control. Yang (2018) conducted their analysis by reviewing data from nine observational studies and 1 moderate bias-risk RCT. Although 1-year survival rates were comparable, 2-year OS favored SIRT with marginal significance (p=0.3). Ludwig (2017) similarly found a survival benefit with SIRT but no significant difference in tumor response. Katsanos (2017) conducted a very large analysis with 55 RCTs (n=5763) and conversely concluded that "Chemoembolization [e.g. TACE] combined with external radiotherapy or local liver ablation may significantly improve tumour response and patient survival rates over embolization monotherapies [e.g SIRT]," but included the caveat that evidence is of low to moderate quality due to clinical diversity of studies. The contradictory findings amongst and within the meta-analyses does not provide a high-level of evidence in support of the safety and efficacy of SIRT relative to TACE in individuals with unresectable HCC.

Ragnoni (2016) conducted a systematic review and meta-analyses to evaluate the efficacy and safety of SIRT in intermediate-advanced HCC, with 21 studies included in the analysis. Only three comparative studies were identified (SIRT versus TACE or sorafenib), two of which were RCTs, the rest were observational cohorts; all were deemed to be of low to medium methodological quality. Authors concluded that evidence supporting the use of SIRT in HCC is largely based on retrospective and cohort studies and that SIRT appears to be a valid treatment option for intermediate-advanced stage HCC.

In 2017, a manufacturer-sponsored, open-label, phase 3, randomized controlled clinical trial was conducted comparing the safety and efficacy of SIRT with sorafenib (Nexavar®; Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ) in locally advanced and inoperable HCC (Vilgrain, 2017). Eligible participants were at least 18 years of age, had an ECOG status of 0-1, previous treatment with TACE, and a Child-Pugh liver function class of A or B. A total of 406 participants were randomized to one of the two treatment groups; SIRT (n=184) or sorafenib (n=222). After a median follow-up of approximately 28 months, OS was 8.0 months in the SIRT group and 9.9 months in the sorafenib group (HR=1.15, 95% CI, 0.94-1.41; p=0.18). Reporting of adverse events did not significantly differ between study arms and 19 treatment-related deaths occurred in the SIRT group compared to only 12 in the sorafenib group. In this industry-sponsored, phase 3 trial, SIRT did not demonstrate superior safety or efficacy over sorafenib in the treatment of unresectable HCC.

Bridge to Liver Transplantation

As the incidence of HCC continues to rise and availability of donor organs remains low, the waiting time for potentially curative therapy with orthotopic liver transplantation (OLT) increases. Heckman (2008) noted the incidence of disease progression while listed for transplant was 10-23%. Various technologies have been explored to maintain transplant eligibility by controlling disease progression, of which transcatheter arterial chemoembolization (TACE) and RFA were the most frequently studied. A "bridge" to liver transplant involves ablative techniques to minimize and control disease progression to allow individuals with limited HCC to remain eligible on the OLT waitlist. The goal of bridging is to prevent drop-off from the waiting list and to improve post-transplant survival (DuBay, 2011).

The current Organ Procurement and Transplantation Network (OPTN) and United Network for Organ Sharing (UNOS) allocation policy (2019) provides incentives to use loco-regional therapies to downsize tumors to T2 status and to prevent progression while on the transplant wait list. In addition, the OPTN/UNOS policy implicitly recognizes the role of loco-regional therapy in the pre-transplant setting. These indications are in part related to the current OPTN/UNOS liver allocation scoring system referred to as the Model for End-Stage Liver Disease (MELD), for adults ages 12 and older, and the Pediatric End-stage Liver Disease (PELD) scoring system for candidates younger than 12 years of age. The MELD score is a continuous disease severity scale incorporating serum bilirubin, prothrombin time (for example, international normalized ratio-INR), and serum creatinine into an equation, producing a number ranging from 6 (less ill) to 40 (gravely ill). The MELD score estimates how urgently the individual needs a liver transplant within the next 3 months. PELD is similar to MELD but uses additional factors to recognize the specific growth and development needs of children. PELD scores may also range higher or lower than the range of MELD scores. The PELD scoring system includes measures of serum bilirubin, INR, albumin, growth failure, and whether the child is less than 1 year old. Candidates that meet the staging and imaging criteria specified in the OPTN/UNOS Allocation of Livers and Liver-Intestines Policy, Candidates with Hepatocellular Carcinoma (HCC) sections 9.3.G.iv-v may receive extra priority on the "Waiting List." A candidate with an HCC tumor that is stage T2 may be registered at a MELD/PELD score equivalent to a 15% risk of candidate death within 3 months if additional criteria are also met. OPTN/UNOS defines Stage T2 lesions as:

- One lesion greater than or equal to 2 cm and less than or equal to 5 cm; or,
- Two or three lesions each greater than or equal to 1 cm and less than or equal to 3 cm in size.

The largest dimension of each tumor is used to report the size of HCC lesions. Nodules less than 1 cm are indeterminate and cannot be considered for additional priority. Past loco-regional treatment for HCC (OPTN Class 5 [T2] lesion or biopsy proven prior to ablation) are eligible for automatic priority.

The NCCN clinical practice guideline in Oncology for hepatocellular carcinoma (2019) states:

> Bridge therapy is used to decrease tumor progression and the dropout rate from the liver transplant list…It is considered for patients who meet the transplant criteria. It is considered for patients who meet the transplant criteria… A number of studies have investigated the role of locoregional therapies as a bridge to liver transplantation in patients on a waiting list. These studies included RFA, transarterial embolization (TAE), chemoembolization, TACE, TACE with drug-eluting beads (DEB-TACE), transarterial radioembolization (TARE) with yttrium-90 microspheres, conformal radiation therapy (RT) and sorafenib as "bridge" therapies.

The AASLD (Gervais, 2011) lists the following recommendations:

> Local ablation is safe and effective therapy for patients who cannot undergo resection, or as a bridge to transplantation. Alcohol injection and radiofrequency are equally effective for tumors <2 cm. However, the necrotic effect of radiofrequency ablation is more predictable in all tumor sizes and in addition its efficacy is clearly superior to that of alcohol injection in larger tumors.

The use of locally ablative techniques such as percutaneous ethanol injection, radiofrequency or microwave ablation may be used as a bridge technique to OLT.

Nicolini and colleagues (2013) reported on a retrospective analysis of individuals with HCC who met the Milan criteria and were treated with TACE or DEB-TACE prior to liver transplant. DEB-TACE was associated with a trend towards higher response rates, that is, ≥ 90% necrosis (44.7% versus 32.0%; p=0.2834) and higher 3-year relapse-free survival rates after liver transplant (87.4% versus 61.5%; p=0.0493) compared to TACE.

Limitations of these studies include small sample sizes and heterogeneous study populations; however, the NCCN CPG for hepatobiliary cancer (V4.2019) states, "Nevertheless, the use of bridge therapy in this setting is increasing, and it is administered at some NCCN Member Institutions."

The Society of Interventional Radiology's *Quality Improvement Guidelines for Transarterial Chemoembolization and Embolization of Hepatic Malignancy* (Gaba, 2017) states that TACE may be indicated as a bridge to liver transplantation for individuals with liver-dominant hepatic malignancies.

In 2009, Lewandowski and colleagues published the results of a nonrandomized controlled study that compared TACE (n=43) to SIRT with Theraspheres (n=43) as a method of downstaging subjects with T3 HCC as a bridge to transplantation. The authors reported that successful downstaging to T2 was observed in 31% (11/35) of TACE subjects and 58% (25/42) of SIRT subjects (p=0.023). This trend was noted in all lesion sizes. The median time to

UNOS downstaging was not reached in the TACE group, but was reported as 3.1 months in the SIRT group (p=0.027). There was no significant difference in the number of subjects downstaged to resection, but 8 TACE and 18 SIRT subjects were downstaged to RFA treatment. The median WHO time to progressive disease was 19.6 months in the TACE group vs. 48.6 months in the SIRT group (p=0.008). The 1-year progression rates according to EASL criteria were 4% in the TACE group and 8% in the SIRT group (p=0.01). Using the UNOS criteria, time to progression (TTP) was 18.2 months for the TACE group and 33.3 months in the SIRT group. For TACE, OS without censoring to radical therapies (for example, transplantation/resection) at 1, 2 and 3 years was 75%, 42% and 19%, and 81%, 69% and 59%, respectively, for the SIRT group (p=0.008). When censored to radical therapies, OS at 1, 2 and 3 years was 73%, 28% and 19% for the TACE group and 77%, 59% and 45%, respectively, for the SIRT group (p=0.18). A total of 2 out of 11 of the TACE subjects had relapsed following transplantation with a 1-year relapse-free survival of 73%, 2 out of the 9 SIRT subjects relapsed following transplantation with a 1-year relapse-free survival of 89%. This difference was not found to be statistically significant.

A systematic review conducted by Braat and colleagues (2016) included 43 original studies and case reports (including the two described in detail above) evaluating SIRT as a therapy option for bridge to liver transplant. Authors caution that although SIRT has shown promise as a tool for down-staging to liver transplant, more research is warranted in quantifying dose-response relationships to mitigate both the potential for insufficient tumor response (if an inadequate amount of radiation is delivered) and the potential for liver failure (from damage to non-tumorous parenchyma if radiation quantities exceed the balance of efficacy and overall benefit).

Yamashiki and colleagues (2005) reported on 288 individuals given various ablative therapies; the dropout rate due to tumor progression at 1 and 3 years was 6.25% and 23%, respectively. Tumors > 3 cm affected the dropout rate due to tumor progression.

Cheng and colleagues (2005b) studied 29 individuals with hepatitis-related cirrhosis and unresectable HCC who received pre-liver transplantation TAE (group A: 19 of 29) or underwent liver transplantation without prior TAE (group B: 10 of 29). The individuals in the pre-liver transplantation TAE group (A) were further subdivided according to the Milan criteria into group A1 (12 of 19) who met the criteria and group A2 (7 of 19) who did not. The primary outcome measure was actuarial survival rate. In the explanted liver, CT images correlated well with pathological specimens, showing that TAE induced massive tumor necrosis (> 85%) in 63% of individuals in group A; all 7 individuals in group A2 exhibited tumor downgrading that met Milan criteria. The overall 5-year actuarial survival rate was 80.6%. The TAE group had a better survival (84% at 5 years) than the non-TAE group, (75% at 4 years). The 3-year survival of group A2 (83%) was also higher than that of group A1 (79%). Tumor necrosis > 85% was associated with survival of 100% at 3 years, which was significantly better than the others who showed < 85% tumor necrosis (57.1% at 3 years) or who did not have TAE (75% at 3 years). The authors concluded that TAE may be considered an effective treatment for HCC before liver transplantation and help in further reducing the dropout rate from transplant wait lists for individuals with HCC.

Obed and colleagues (2007) systematically reviewed the outcome of individuals who underwent TACE for HCC and subsequently OLT, irrespective of tumor size when no tumor progression was observed. Records, imaging studies, and pathology of 84 individuals with HCC were reviewed. Ten individuals received no treatment, 67 individuals had TACE and 35 were listed for OLT. Tumor progression was monitored by ultrasound and alpha-

fetoprotein (AFP) level every 6 weeks. Fifteen individuals showed signs of tumor progression without transplantation. The remaining 20 individuals underwent OLT. Further records of 7 individuals with HCC seen in histological examination after OLT were included. The authors reported that the individuals after TACE without tumor progression underwent transplantation and had a median survival of 92.3 months. Individuals who did not qualify for liver transplantation or had signs of tumor progression had a median survival of 8.4 months. The individuals without treatment had a median survival of 3.8 months. Independent of International Union Against Cancer (UICC) stages, the individuals without tumor progression and subsequent OLT had longer median survival. No significant difference was seen in the OLT treated individuals if they did not fulfill the Milan criteria. The authors concluded that the selection of individuals for OLT based on tumor progression results in good survival, citing the evaluation of individuals with HCC should be based not only on tumor size and number of foci but also on tumor progression and growth behavior under therapy.

Hepatocellular Carcinoma in Individuals Who May Become Eligible for Liver Transplantation

Downstaging therapy is defined as treatment used to reduce the tumor burden in individuals without distant metastasis, but do have more advanced HCC whose tumor characteristics are beyond the accepted transplant criteria (NCCN, 2019).

Yao and colleagues (2005a) reported on a case series of 30 individuals with HCC who underwent a variety of locoregional therapies including TACE, specifically to downstage tumors to meet the University of California at San Francisco (UCSF) transplant criteria. Eligibility for locoregional therapy seeking to downstage individuals included either 1 nodule between 5 cm and 8 cm in diameter; 2 or 3 nodules with at least 1 between 3 cm and 5 cm in diameter, with the sum of diameters no > 8 cm; or 4 or 5 nodules all ≤ 3 cm, with sum of diameters < 8 cm. Among the 30 individuals, 21 (70%) met the criteria for locoregional therapy and 16 of these were successfully downstaged and underwent transplantation. No tumors recurred at a median follow-up of 16 months. The authors concluded that downstaging can be successfully achieved in most individuals, but that data regarding tumor recurrence requires longer follow-up.

Chapman and colleagues (2008) evaluated outcomes of downstaging individuals with TACE to allow eligibility for OLT. A total of 76 individuals with stage 3/4 HCC were potential transplant candidates if downstaging was achieved by TACE. OLT was considered based on follow-up imaging findings. Individuals were tracked who were successfully downstaged within the Milan criteria, tumor response using Response Evaluation Criteria in Solid Tumors (RECIST) criteria, findings at explant, and outcomes after transplant. A total of 18 of 76 (23.7%) individuals had adequate downstaging to qualify for OLT under the Milan criteria. By RECIST, 27 of 76 (35.5%) individuals had a partial response (PR), 22 of 76 (29%) had stable disease, and 27 of 76 (35.5%) had progressive disease. A total of 17 of 76 (22.4%) individuals who met other qualifications underwent OLT after successful downstaging (13 of 38 stage 3; 4 of 38 stage 4). Explant review demonstrated 28 identifiable tumors in which post-TACE necrosis was > 90% in 21 (75%). At a median of 19.6 months (range 3.6-104.7), 16 of 17 (94.1%) individuals who underwent OLT were still alive. One individual expired 11 months after OLT secondary to medical comorbidities and 1 individual with recurrent HCC subsequently underwent resection of a pulmonary metastasis and was still alive at 63.6 months from OLT. The authors proposed that select individuals with stage 3/4 HCC can be successfully downstaged to Milan criteria with TACE and those transplanted had midterm disease-free and OS,

similar to stage 2 HCC. The treatment strategy proposed in this study is limited in drawing conclusions as the data was evaluated retrospectively from a case series of individuals. In addition, only 22% of the stage 3/4 HCC individuals who received TACE went on to OLT, eliminating many individuals with progressive disease.

Heckman and colleagues (2008) studied the effect of locoregional therapy on survival utilizing TACE, yttrium-90Y, RFA, or resection prior to OLT for HCC. A retrospective review of a prospectively collected database included groups consisting of 50 individuals that received therapy (20 TACE; 16: yttrium-90Y; 13 RFA, 3 resections) in Group I and 73 individuals in the transplanted without therapy (Group II). Median wait 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). A total of 12 individuals (24%) were successfully downstaged with 8 of these 12 receiving TACE. Survival was not statistically significantly different between the 2 groups (p=0.53). The 12 individuals who were downstaged did not have a significant difference in survival as compared with those who received therapy but did not respond or the individuals who were transplanted without therapy (p=0.76). This review suggests that locoregional therapy, particularly TACE, is a safe tool for individuals on the transplant list, does not impact survival, and can downstage selected individuals to allow for OLT.

The NCCN CPG for hepatobiliary cancers (V4.2019), principles of surgery, includes the following recommendation:

> Patients meeting the UNOS criteria [(single lesion ≤5 cm, or 2 or 3 lesions ≤3cm]…) should be considered for transplantation (cadaveric or living donation). More controversial are those patients whose tumor characteristics are marginally outside of the UNOS guidelines and may be considered at some institutions for transplantation. Furthermore, patients with tumor characteristics beyond Milan criteria that are downstaged to within criteria can also be considered for transplantation.

The 2019 OPTN and UNOS allocation policy (2019) notes that lesions which are eligible for downstaging protocols must meet one of the following criteria:

1. One lesion greater than 5 cm and less than or equal to 8 cm
2. Two or three lesions that meet all of the following:
   - at least one lesion greater than 3 cm
   - each lesion less than or equal to 5 cm, and
   - a total diameter of all lesions less than or equal to 8 cm
3. Four or five lesions each less than 3 cm, and a total diameter of all lesions less than or equal to 8 cm

For individuals who have meet the downstaging criteria and subsequently undergo local-regional therapy, any residual therapy must meet the definition for T2 lesions in order to be eligible for a standardized MELD or PELD exception.

The Society of Interventional Radiology's Quality Improvement Guidelines for Transarterial Chemoembolization and Embolization of Hepatic Malignancy (Gaba, 2017) states that TACE may be indicated as a downstage to liver transplantation for individuals with liver-dominant hepatic malignancies.

Definitions

Ablation: The destruction of a body part or tissue or its function, which may be achieved by surgery, hormones, drugs, radiofrequency, heat, or other methods.

Bridge Therapy: Therapy considered for those who meet transplant criteria, used slow tumor progression in order to decease the liver transplantation dropout rate.

Childs-Turcotte-Pugh (CTP): A scoring system for severity of liver disease and likelihood of survival based on the presence of: degenerative disease of the brain (encephalopathy), the escape or accumulation of fluid in the abdominal cavity (ascites), laboratory measures of various substances in the blood (see table below), and the presence of other co-existing diseases; after calculating the CTP score using a table similar to the one below, candidates can be classified into 1 of 3 categories:

- Childs A (5-6 points): 10 year survival 80-90%
- Childs B (7-9 points): 5 year survival 60-80%
- Childs C (10-15 points): 2 year survival less than 50%

Variable	1 Point	2 Points	3 Points
Encephalopathy	None	Moderate	Severe
Ascites	None	Mild	Moderate
Albumin (mg/dL)	Greater than 3/5	2.8-3.5	Less than 2.8
Prothombin time (International Normalized ratio) prolonged	Less than 4	4-6	Greater than 6
Bilirubin (mg/dL) Primary biliary cirrhosis Cirrhosis/primary Primary sclerosing cholangitis	1-4	4-10	Greater than 10
All other diseases	Less than 2	1-3	Greater than 3

Cancer of the Liver Italian Program (CLIP): A tumor classification system from Italy that includes scoring for 8 clinical parameters for HCC, combining the Child-Turcotte-Pugh scoring system with tumor criteria including tumor morphology, portal invasion, and alpha fetoprotein levels.

Cholangiocarcinoma: A type of cancer developing in cells that line the bile ducts in the liver.

Encapsulated nodules: Any group of abnormal cells confined to a specific area, surrounded by a covering of specialized cells called a capsule.

Extra-hepatic disease: Cancer that is located outside of the liver.

Hepatic metastases: Cancer that has spread from its original location to the liver.

Metastasis: The spread of cancer from one part of the body (the origin of the cancer) to another part of the body. A metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.

Neuroendocrine tumor: Tumors arising from cells that produce hormones that can cause systemic symptoms such as flushing or wheezing. Examples of neuroendocrine tumors include, but are not limited to carcinoid tumors, islet cell tumors, medullary thyroid carcinoma, and pheochromocytoma.

Palliative treatment: Treatment given for relief of symptoms and pain rather than effecting a cure.

Primary hepatocellular cancer: A cancer that originates within liver cells.

Unresectable: Refers to a tumor that cannot safely be removed surgically due to size or location.

References

Peer Reviewed Publications:

1. Abdelaziz AO, Nabeel MM, Elbaz TM, et al. Microwave ablation versus transarterial chemoembolization in large hepatocellular carcinoma: prospective analysis. Scand J Gastroenterol. 2015; 50(4):479-484.
2. Abouchaleh N, Gabr A, Ali R, et al. 90Y Radioembolization for locally advanced hepatocellular carcinoma with portal vein thrombosis: Long-term outcomes in a 185-patient cohort. J Nucl Med. 2018; 59(7):1042-1048.
3. Adam R, Chiche L, Aloia T, et al. Hepatic resection for noncolorectal nonendocrine liver metastases: analysis of 1452 patients and development of a prognostic model. Ann Surg. 2006; 244(4):524-535.
4. Adam R, Hagopian EJ, Linhares M, et al. A comparison of percutaneous cryosurgery and percutaneous radiofrequency for unresectable hepatic malignancies. Arch Surg. 2002; 137(2):1332-1339.
5. Al-Adra DP, Gill RS, Axford SJ, et al. Treatment of unresectable intrahepatic cholangiocarcinoma with yttrium-90 radioembolization: a systematic review and pooled analysis. Eur J Surg Oncol. 2015; 41(1):120-127.
6. Albert M, Kiefer MV, Sun W, et al. Chemoembolization of colorectal liver metastases with cisplatin, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol. Cancer. 2011; 117(2):343-352.
7. Ali R, Riaz A, Gabr A, et al. Clinical outcomes of Y90 radioembolization for recurrent hepatocellular carcinoma following curative resection. Eur J Nucl Med Mol Imaging. 2017; 44(13):2195-2202.
8. Aliberti C, Fiorentini G, Muzzio PC, et al. Trans-arterial chemoembolization of metastatic colorectal carcinoma to the liver adopting DC Bead®, drug-eluting bead loaded with irinotecan: results of a phase II clinical study. Anticancer Res. 2011; 31(12):4581-4587.
9. Artinyan A, Nelson R, Soriano P, et al. Treatment response to transcatheter arterial embolization and chemoembolization in primary and metastatic tumors of the liver. HPB (Oxford). 2008; 10(6):396-404.
10. Bacchetti S, Bertozzi S, Londero AP, et al. Surgical treatment and survival in patients with liver metastases from neuroendocrine tumors: a meta-analysis of observational studies. Int J Hepatol. 2013; 2013:235040.
11. Baltatzis M, Siriwardena AK. Liver resection for colorectal hepatic metastases after systemic chemotherapy and selective internal radiation therapy with Yttrium-90 microspheres: a systematic review. Dig Surg. 2019; 36(4):273-280.

12. Bangash AK, Atassi B, Kaklamani V, et al. 90Y radioembolization of metastatic breast cancer to the liver: toxicity, imaging response, survival. J Vasc Interv Radiol. 2007; 18(5):621-628.
13. Bedikian AY, Legha SS, Mavligit G, et al. Treatment of uveal melanoma metastatic to the liver: a review of the M. D. Anderson Cancer Center experience and prognostic factors. Cancer. 1995; 76(9):1665-1670.
14. Benson AB 3rd, Geschwind JF, Mulcahy MF, et al. Radioembolisation for liver metastases: results from a prospective 151 patient multi-institutional phase II study. Eur J Cancer. 2013; 49(15):3122-3130.
15. Berber E, Felsher N, Siperstein AE. Laparoscopic radiofrequency ablation of neuroendocrine liver metastasis. World J Surg. 2002; 26(8):985-990.
16. Berber E, Pelley R, Siperstein AE. Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: a prospective study. J Clin Oncol. 2005; 23(7):1358-1364.
17. Berber E, Siperstein AE. Laparoscopic radiofrequency ablation of neuroendocrine liver metastases. Problems in General Surgery. 2003; 20(3):134-142.
18. Bergenfeldt M, Jensen BV, Skjoldbye B, Nielsen D. Liver resection and local ablation of breast cancer liver metastases – a systematic review. Eur J Surg Oncol. 2011; 37(7):549-557.
19. Bester L, Meteling B, Pocock N, et al. Radioembolization versus standard care of hepatic metastases: comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. J Vasc Interv Radiol. 2012; 23(1):96-105.
20. 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.
21. Bleicher RF, Allegra DP, Nora DT, et al. Radiofrequency ablation in 447 complex unresectable liver tumors: lessons learned. Ann Surg Oncol. 2003; 10(1):52-58.
22. 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.
23. Bouchard-Fortier A, Lapointe R, Perreault P, et al. Transcatheter arterial chemoembolization of hepatocellular carcinoma as a bridge to liver transplantation: a retrospective study. Int J Hepatol. 2011; 2011:974514.
24. Braat MN, Samim M, van den Bosch MA, Lam MG. The role of (90)Y-radioembolization in downstaging primary and secondary hepatic malignancies: a systematic review. Clin Transl Imaging. 2016; 4:283-295.
25. Brown DB, Chapman WC, Cook RD, et al. Chemoembolization of HCC: patient status at presentation and outcome over 15 years at a single center. AJR Am J Roentgenol. 2008; 190(3):608-615.
26. Brown KT, Do RK, Gonen M, et al. Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. J Clin Oncol. 2016; 34(17):2046-2053.
27. Brown KT, Nevins AB, Getrajdman GI, et al. Particle embolization for hepatocellular carcinoma. J Vasc Interv Radiol. 1998; 9(5):822-828.
28. Buijs M, Vossen JA, Frangakis C, et al. Nonresectable hepatocellular carcinoma: long-term toxicity in patients treated with transarterial chemoembolization--single-center experience. Radiology. 2008; 249(1):346-354.
29. Camma C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology. 2002; 224(1):47-54.
30. Cao CQ, Yan TD, Bester L, et al. Radioembolization with yttrium microspheres for neuroendocrine tumour liver metastases. Br J Surg. 2010; 97(4):537-543.

31. Cao X, He N, Sun J, et al. Hepatic radioembolization with Yttrium-90 glass microspheres for treatment of primary liver cancer. Chin Med J. (Engl) 1999; 112(5):430-432.
32. Cassera MA, Hammill CW, Ujiki MB, et al. Surgical management of breast cancer liver metastases. HPB (Oxford). 2011; 13(4):272-278.
33. 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.
34. Charalampoudis P, Mantas D, Sotiropoulos GC, et al. Surgery for liver metastases from breast cancer. Future Oncol. 2015; 11(10):1519-1530.
35. Cheng BQ, Jia CQ, Liu CT, et al. Chemoembolization combined with radiofrequency ablation for patients with hepatocellular carcinoma larger than 3 cm: a randomized controlled trial. JAMA. 2008; 299(14):1669-1677.
36. Cheng HY, Wang X, Chen D, et al. The value and limitation of transcatheter arterial chemoembolization in preventing recurrence of resected hepatocellular carcinoma. World J Gastroenterol. 2005a; 11(23):3644-3646.
37. Cheng YF, Huang TL, Chen TY, et al. Impact of pre-operative transarterial embolization on the treatment of hepatocellular carcinoma with liver transplantation. World J Gastroenterol. 2005b; 11(10):1433-1438.
38. Christante D, Pommier S, Givi B, Pommier R. Hepatic artery chemoinfusion with chemoembolization for neuroendocrine cancer with progressive hepatic metastases despite octreotide therapy. Surgery. 2008; 144(6):885-893; discussion 893-894.
39. Cho YK, Rhim H, Noh S. Radiofrequency ablation versus surgical resection as primary treatment of hepatocellular carcinoma meeting the Milan criteria: a systematic review. J Gastroenterol Hepatol. 2011; 26(9):1354-1360.
40. Chua TC, Liauw W, Saxena A et al. Systematic review of neoadjuvant transarterial chemoembolization for resectable hepatocellular carcinoma. Liver Transpl. 2009; 30(2):166-174.
41. Cianni R, Urigo C, Notarianni E, et al. Radioembolisation using yttrium 90 (Y-90) in patients affected by unresectable hepatic metastases. Radiol Med. 2010; 115(4):619-633.
42. Dai WC, Cheung TT, Chok KS, et al. Radiofrequency ablation versus transarterial chemoembolization for unresectable solitary hepatocellular carcinomas sized 5-8 cm. HPB (Oxford). 2015; 17(3):226-231.
43. Derek E, Matsuoka L, Alexopoulos S, et al. Combined surgical resection and radiofrequency ablation as treatment for metastatic ocular melanoma. Surg Today. 2013; 43(4):367-371.
44. Devcic Z, Rosenberg J, Braat AJ, et al. The efficacy of hepatic 90Y resin radioembolization for metastatic neuroendocrine tumors: a meta-analysis. J Nucl Med. 2014; 55(9):1404-1410.
45. Dhanasekaran R, Kooby DA, Staley CA, et al. Comparison of conventional transarterial chemoembolization (TACE) and chemoembolization with doxorubicin drug eluting beads (DEB) for unresectable hepatocellular carcinoma (HCC). J Surg Oncol. 2010; 101(6):476-480.
46. Do Minh D, Chapiro J, Gorodetski B, et al. Intra-arterial therapy of neuroendocrine tumour liver metastases: comparing conventional TACE, drug-eluting beads TACE and yttrium-90 radioembolisation as treatment options using a propensity score analysis model. Eur Radiol. 2017; 27(12):4995-5005.
47. DuBay D, Sandroussi C, Kachura JR, et al. Radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. HPB (Oxford). 2011; 13(1):24-32.
48. Dunfee BL, Riaz A, Lewandowski RJ, et al. Yttrium-90 radioembolization for liver malignancies: prognostic factors associated with survival. J Vasc Interv Radiol. 2010; 21(1):90-95.
49. El Fouly A, Ertle J, El Dorry A, et al. In intermediate stage hepatocellular carcinoma: radioembolization with yttrium 90 or chemoembolization? Liver Int. 2015; 35(2):627-635.

50. Facciorusso A, Di Maso M, Muscatiello N. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: meta-analysis. Dig Liver Dis. 2016a; 48(6):571-577.
51. Facciorusso A, Mariani L, Sposito C, et al. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma. J Gastroenterol Hepatol. 2016b; 31(3):645-653.
52. Facciorusso A, Serviddio G, Muscatiello N. Transarterial radioembolization vs chemoembolization for hepatocarcinoma patients: a systematic review and meta-analysis. World J Hepatol. 2016; 8(18):770-778.
53. Fairhurst K, Leopardi L, Satyadas T, Maddern G. The safety and effectiveness of liver resection for breast cancer liver metastases: A systematic review. Breast. 2016; 30:175-184.
54. Fegrachi S, Besselink MG, van Santvoort HC, et al. Radiofrequency ablation for unresectable locally advanced pancreatic cancer: a systematic review. HPB (Oxford). 2014; 16(2):119-123.
55. 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.
56. Feng Q, Chi Y, Liu Y, et al. Efficacy and safety of percutaneous radiofrequency ablation versus surgical resection for small hepatocellular carcinoma: a meta-analysis of 23 studies. J Cancer Res Clin Oncol. 2015; 141(1):1-9.
57. Fiorentini G, Aliberti C, Tilli M, et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. Anticancer Res. 2012; 32(4):1387-1395.
58. Fiorentini G, Aliberti C, Turrisi G, et al. Intraarterial hepatic chemoembolization of liver metastases from colorectal cancer adopting irinotecan-eluting beads: results of a phase II clinical study. In Vivo. 2007; 21(6):1085-1091.
59. Fisher RA, Maluf D, Cotterell AH, et al. Non-resective ablative therapy for hepatocellular carcinoma: effectiveness measured by intention-to-treat and dropout from liver transplant waiting list. Clin Transplant. 2004; 18(5):502-512.
60. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999; 230(3):309-321.
61. Garin E, Rolland Y, Edeline J, et al. Personalized dosimetry with intensification using 90Y-loaded glass microsphere radioembolization induces prolonged overall survival in hepatocellular carcinoma patients with portal vein thrombosis. J Nucl Med. 2015; 56(3):339-346.
62. Georgiades CS, Ramsey DE, Solomon S, et al. New non-surgical therapies in the treatment of hepatocellular carcinomas. Tech Vasc Intervent Radiol. 2001; 4(3):193-199.
63. Giorgio A, Di Sarno A, De Stefano G, et al. Percutaneous radiofrequency ablation of hepatocellular carcinoma compared to percutaneous ethanol injection in treatment of cirrhotic patients: an Italian randomized controlled trial. Anticancer Res. 2011; 31(6):2291-2295.
64. Giroux MF, Baum RA, Soulen MC. Chemoembolization of liver metastasis from breast carcinoma. J Vasc Interv Radiol. 2004; 15(3):289-291.
65. Golfieri R, Giampalma E, Renzulli M, et al.; PRECISION Italia Study Group. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer. 2014; 111(2):255-264.
66. Gomez D, Malik HZ, Al-Mukthar A, et al. Hepatic resection for metastatic gastrointestinal and pancreatic neuroendocrine tumours: outcome and prognostic predictors. HPB (Oxford). 2007; 9(5):345-351.

67. Gragoudas ES, Egan KM, Seddon JM, et al. Survival of patients with metastases from uveal melanoma. Ophthalmology. 1991; 98(3):383-389, discussion 390.
68. Gramenzi A, Golfieri R, Mosconi C, et al. Yttrium-90 radioembolization vs sorafenib for intermediate-locally advanced hepatocellular carcinoma: a cohort study with propensity score analysis. Liver Int. 2015; 35(3):1036-1047.
69. Gray B, Van Hazel G, Hope M, et al. Randomized trial of SIR-Spheres® plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol. 2001; 12(12):1711-1720.
70. Graziadei IW, Sandmueller H, Waldenberger P, et al. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. Liver Transpl. 2003; 9(6):557-563.
71. Grosso M, Vignali C, Quaretti P, et al. Transarterial chemoembolization for hepatocellular carcinoma with drug-eluting microspheres: preliminary results from an Italian multicentre study. Cardiovasc Intervent Radiol. 2008; 31(6):1141-1149.
72. Gulec SA, Pennington K, Wheeler J, et al. Yttrium-90 microsphere-selective internal radiation therapy with chemotherapy (chemo-SIRT) for colorectal cancer liver metastases: an in vivo double-arm-controlled phase II trial. Am J Clin Oncol. 2013; 36(5):455-460.
73. Gupta S, Yao JC, Ahrar K, et al. Hepatic artery embolization and chemoembolization for treatment of patients with metastatic carcinoid tumors: the M.D. Anderson experience. Cancer J. 2003; 9(4):261-267.
74. Hayashi PH, Ludkowski M, Forman LM, et al. Hepatic artery chemoembolization for hepatocellular carcinoma in patients listed for liver transplantation. Am J Transplant. 2004; 4(5):782-787.
75. Heckman J, Devera M, Marsh J, et al. Bridging locoregional therapy for hepatocellular carcinoma prior to liver transplantation. Ann Surg Oncol. 2008; 15(11):3169-3177.
76. Hendlisz A, Van den Eynde M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol. 2010; 28(23):3687-3694.
77. Henn AR, Levine EA, McNulty W, Zagoria RJ. Percutaneous radiofrequency ablation of hepatic metastases for symptomatic relief of neuroendocrine syndromes. AJR Am J Roentgenol. 2003; 181(4):1005-1010.
78. Herba MJ, Thirlwell MP. Radioembolization for hepatic metastases. Semin Oncol. 2002; 29(2):152-159.
79. Ho S, Lau WY, Leung TW, et al. Internal radiation therapy for patients with primary or metastatic hepatic cancer. Cancer. 1998; 83(9):1894-1907.
80. Hong K, McBride JD, Georgiades CS, et al. Salvage therapy for liver-dominant colorectal metastatic adenocarcinoma: comparison between transcatheter arterial chemoembolization versus yttrium-90 radioembolization. J Vasc Interv Radiol. 2009; 20(3):360-367.
81. Hui Y, Ruihua T, Jing L, et al. Meta-Analysis of doxorubicin-eluting beads via transcatheter arterial chemoembolization in the treatment of unresectable hepatocellular carcinoma. Hepatogastroenterology. 2015; 62(140):1002-1006.
82. Huppert PE, Fierlbeck G, Pereira P et al. Transarterial chemoembolization of liver metastases in patients with uveal melanoma. Eur J Radiol. 2010; 74(3):e38-e44.
83. Hur S, Chung JW, Kim HC, et al. Survival outcomes and prognostic factors of transcatheter arterial chemoembolization for hepatic neuroendocrine metastases. J Vasc Interv Radiol. 2013; 24(7):947-956.

84. Jakobs TF, Hoffmann RT, Fischer T, et al. Radioembolization in patients with hepatic metastases from breast cancer. J Vasc Interv Radiol. 2008; 19(5):683-690.
85. Jia Z, Wang W. Yttrium-90 radioembolization for unresectable metastatic neuroendocrine liver tumor: A systematic review. Eur J Radiol. 2018; 100:23-29.
86. Kallini JR, Gabr A, Thorlund K et al. Comparison of the adverse event profile of TheraSphere(®) with SIR-Spheres(®) for the treatment of unresectable hepatocellular carcinoma: a systematic review. Cardiovasc Intervent Radiol. 2017; 40(7):1033-1043.
87. Katsanos K, Kitrou P, Spiliopoulos S, et al. Comparative effectiveness of different transarterial embolization therapies alone or in combination with local ablative or adjuvant systemic treatments for unresectable hepatocellular carcinoma: A network meta-analysis of randomized controlled trials. PLoS One. 2017. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5608206/pdf/pone.0184597.pdf. Accessed on January 24, 2020.
88. Kemeny MM, Adak S, Gray B, et al. Combined-modality treatment for resectable colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy – an intergroup study. J Clin Oncol. 2002; 20(6):1499-1505.
89. 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.
90. Kettenbach J, Stadler A, Katzler IV, et al. Drug-loaded microspheres for the treatment of liver cancer: review of current results. Cardiovasc Intervent Radiol. 2008; 31(3):468-476.
91. Kiefer MV, Albert M, McNally M, et al. Chemoembolization of intrahepatic cholangiocarcinoma with cisplatinum, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol: a 2-center study. Cancer. 2011; 117(7):1498-1505.
92. Kim DY, Park BJ, Kim YH, Radioembolization with yttrium-90 resin microspheres in hepatocellular carcinoma: a multicenter prospective study. Am J Clin Oncol. 2015; 38(5):495-501.
93. Kim JH, Yoon HK, Sung KB, et al. Transcatheter arterial chemoembolization or chemoinfusion for unresectable intrahepatic cholangiocarcinoma: clinical efficacy and factors influencing outcomes. Cancer. 2008; 113(7):1614-1622.
94. King J, Quinn R, Glenn DM, et al. Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. Cancer. 2008; 113(5):921-929.
95. Kivelä T, Eskelin S, Kujala E. Metastatic uveal melanoma. Int Ophthalmol Clin. 2006; 46(1):133-149.
96. Kloeckner R, Weinmann A, Prinz F, et al. Conventional transarterial chemoembolization versus drug-eluting bead transarterial chemoembolization for the treatment of hepatocellular carcinoma. BMC Cancer. 2015; 15:465.
97. Knüppel M, Kubicka S, Vogel A, et al. Combination of conservative and interventional therapy strategies for intra- and extrahepatic cholangiocellular carcinoma: a retrospective survival analysis. Gastroenterol Res Pract. 2012; 2012:190708.
98. Kolligs FT, Bilbao JI, Jakobs T, et al. Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. Liver Int. 2015; 35(6):1715-1721.
99. Kuei A, Saab S, Cho SK, et al. Effects of yttrium-90 selective internal radiation therapy on non-conventional liver tumors. World J Gastroenterol. 2015; 21(27):8271-8283.

100. 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.
101. Kümler I, Parner VK, Tuxen MK, et al. Clinical outcome of percutaneous RF-ablation of non-operable patients with liver metastasis from breast cancer. Radiol Med. 2015; 120(6):536-541.
102. Kwok PC, Leung KC, Cheung MT, et al. Survival benefit of radioembolization for inoperable hepatocellular carcinoma using yttrium-90 microspheres. J Gastroenterol Hepatol. 2014; 29(11):1897-1904.
103. Ikeda M, Okada S, Ueno H, et al. Radiofrequency ablation and percutaneous ethanol injection in patients with small hepatocellular carcinoma: a comparative study. Jpn J Clin Oncol. 2001; 31(7):322-326.
104. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of HCC: results of the PRECISION V study. Cardiovasc Intervent Radiol. 2010; 33(1):41-52.
105. 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.
106. Lau WY, Lai EC. Hepatocellular carcinoma: current management and recent advances. Hepatobiliary Pancreat Dis Int. 2008; 7(3):237-257.
107. Lau WY, Yu SC, Lai EC, Leung TW. Transarterial chemoembolization for hepatocellular carcinoma. J Am Coll Surg. 2006; 202(1):155-168.
108. Lee M, Chung JW, Lee KH, et al. Korean multicenter registry of transcatheter arterial chemoembolization with drug-eluting embolic agents for nodular hepatocellular carcinomas: six-month outcome analysis. J Vasc Interv Radiol. 2017; 28(4):502-512.
109. Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radiofrequency thermal ablation versus percutaneous ethanol injection. Radiology. 2003; 228(1):235-240.
110. Lermite E, Lebigot J, Oberti F, et al. Radiofrequency thermal ablation of liver carcinoma. Prospective study of 82 lesions. Gastroenterol Clin Biol. 2006; 30(1):130-135.
111. Lesurtel M, Nagorney DM, Mazzaferro V, et al. When should a liver resection be performed in patients with liver metastases from neuroendocrine tumours? A systematic review with practice recommendations. HPB (Oxford). 2015; 17(1):17-22.
112. 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.
113. Lewandowski RJ, Memon K, Mulcahy MF, et al. Twelve-year experience of radioembolization for colorectal hepatic metastases in 214 patients: survival by era and chemotherapy. Eur J Nucl Med Mol Imaging. 2014; 41(10):1861-1869.
114. Li XP, Meng ZQ, Guo WJ, Li J. Treatment for liver metastases from breast cancer: results and prognostic factors. World J Gastroenterol. 2005; 11(24):3782-3787.
115. Li L, Zhang J, Liu X, et al. Clinical outcomes of radiofrequency ablation and surgical resection for small hepatocellular carcinoma: a meta-analysis. J Gastroenterol Hepatol. 2012; 27(1):51-58.
116. Liapi E, Geschwind JF. Transcatheter and ablative therapeutic approaches for solid malignancies. J Clin Oncol. 2007; 25(8):978-986.

117. Lim L, Gibbs P, Yip D, et al. Prospective study of treatment with selective internal radiation therapy spheres in patients with unresectable primary or secondary hepatic malignancies. Intern Med J. 2005; 35(4):222-227.
118. Liu H, Wang ZG, Fu SY, et al. Randomized clinical trial of chemoembolization plus radiofrequency ablation versus partial hepatectomy for hepatocellular carcinoma within the Milan criteria. Br J Surg. 2016; 103(4):348-356.
119. Livraghi T, Goldberg SN, Lazzaroni S, et al. Hepatocellular carcinoma: radio-frequency ablation of medium and large lesions. Radiology. 2000; 214(3):761-768.
120. Livraghi T, Goldberg SN, Lazzaroni S, et al. Small hepatocellular carcinoma: treatment with radiofrequency ablation versus ethanol injection. Radiology. 1999; 210(3):655-661.
121. Llovet JM. Evidence-based medicine in the treatment of hepatocellular cancer. J Gastroenterol Hepatol. 2002a; 17 Suppl 3:S428-S433.
122. Llovet JM, Bruix J. Systemic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology. 2003; 37(2):429-442.
123. Llovet JM, Di Bisceglie AM, Bruix J, et al. Panel of Experts in HCC-Design Clinical Trials. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008; 100(10):698-711.
124. Llovet JM, Fuster J, Bruix J. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. Liver Transpl. 2004; 10(2 Suppl 1):S115-S120.
125. Llovet JM, Real ML, Montaña X, et al. Arterial embolization or chemoembolization versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. Lancet. 2002b; 359(9319):1734-1739.
126. Lo C, Ngan H, Tso W, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 2002; 35(5):1164-1171.
127. Lobo L, Yakoub D, Picado O, et al. Unresectable hepatocellular carcinoma: radioembolization versus chemoembolization: a systematic review and meta-analysis. Cardiovasc Intervent Radiol. 2016; 39(11):1580-1588.
128. Lu DS, Yu NC, Raman SS, et al. Radiofrequency ablation of hepatocellular carcinoma: treatment success as defined by histologic examination of the explanted liver. Radiology. 2005; 234(3):954-960.
129. Ludwig JM, Zhang D, Xing M, Kim HS. Meta-analysis: adjusted indirect comparison of drug-eluting bead transarterial chemoembolization versus (90)Y-radioembolization for hepatocellular carcinoma. Eur Radiol. 2017; 27(5):2031-2041.
130. Majno P, Giostra E, Mentha G. Management of hepatocellular carcinoma on the waiting list before liver transplantation: time for controlled trials? Liver Transpl. 2007; 13(11 Suppl 2):S27-S35.
131. Malagari K, Pomoni M, Kelekis A, et al. Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland embolization with Bead Block for hepatocellular carcinoma. Cardiovasc Intervent Radiol. 2010; 33(3):541-551.
132. Malagari K, Pomoni M, Spyridopoulos TN, et al. Safety profile of sequential transcatheter chemoembolization with DC Bead: results of 237 hepatocellular carcinoma (HCC) patients. Cardiovasc Intervent Radiol. 2011; 34:774-785.
133. 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.
134. Maluccio MA, Covey AM, Schubert J, et al. Treatment of metastatic sarcoma to the liver with bland embolization. Cancer. 2006; 107(7):1617-1623.

135. 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.
136. Martin RC, Howard J, Tomalty D, et al. Toxicity of irinotecan-eluting beads in the treatment of hepatic malignancies: results of a multi-institutional registry. Cardiovasc Intervent Radiol. 2010; 33(5):960-966.
137. 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.
138. Martin RC, Robbins K, Tomalty D, et al. Transarterial chemoembolisation (TACE) using irinotecan-loaded beads for the treatment of unresectable metastases to the liver in patients with colorectal cancer: an interim report. World J Surg Oncol. 2009; 7:80.
139. Martin RC, Scoggins CR, McMasters KM. Safety and efficacy of microwave ablation of hepatic tumors: a prospective review of a 5-year experience. Ann Surg Oncol. 2010; 17(1):171-178.
140. Martin RC 2nd, Scoggins CR, Schreeder M, et al. Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis. Cancer. 2015; 121(20):3649-3658.
141. Mavligit GM, Charnsangavej C, Carrasco CH, et al. Regression of ocular melanoma metastatic to the liver after hepatic arterial chemoembolization with cisplatin and polyvinyl sponge. JAMA. 1988; 260(7):974-976.
142. 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.
143. McDevitt JL, Alian A, Kapoor B, et al. Single-center comparison of overall survival and toxicities in patients with infiltrative hepatocellular carcinoma treated with Yttrium-90 radioembolization or drug-eluting embolic transarterial chemoembolization. J Vasc Interv Radiol. 2017; 28(10):1371-1377.
144. Meloni MF, Andreano A, Laeseke PF, et al. Breast cancer liver metastases: US-guided percutaneous radiofrequency ablation--intermediate and long-term survival rates. Radiology. 2009; 253(3):861-869.
145. Merli M, Nicolini G, Gentilli F, et al. Predictive factors of outcome after liver transplantation in patients with cirrhosis and hepatocellular carcinoma. Transplant Proc. 2005; 37(6):2535-2540.
146. Meta-Analysis Group in Cancer. Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. J Natl Cancer Inst. 1996; 88(5):252-258.
147. Molinari M, Kachura JR, Dixon E, et al. Transarterial chemoembolisation for advanced hepatocellular carcinoma: results from a North American Cancer Centre. Clin Oncol (R Coll Radiol). 2006; 18(9):684-692.
148. 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.
149. Morimoto M, Numata K, Sugimori K, et al. Successful initial ablation therapy contributes to survival in patients with hepatocellular carcinoma. World J Gastroenterol. 2007; 13(7):1003-1009.
150. Moroz P, Anderson JE, Van Hazel G, et al. Effect of selective internal radiation therapy and hepatic arterial chemotherapy on normal liver volume and spleen volume. J Surg Oncol. 2001; 78(4):248-252.
151. Mulcahy MF, Lewandowski RJ, Ibrahim SM, et al. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. Cancer. 2009; 115(9):1849-1858.
152. Mulier S, Ni Y, Jamart J, et al. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. Ann Surg. 2005; 242(2):158-171.

153. Nace GW, Steel JL, Amesur N, et al. Yttrium-90 radioembolization for colorectal cancer liver metastases: a single institution experience. Int J Surg Oncol. 2011; 2011:571261.
154. Nicolini D, Svegliati-Baroni G, et al. Doxorubicin-eluting bead vs conventional transcatheter arterial chemoembolization for hepatocellular carcinoma before liver transplantation. World J Gastroenterol. 2013; 19(34):5622-5632.
155. Obed A, Behan A, Pullmann K, et al. Patients without hepatocellular carcinoma progression after transarterial chemoembolization benefit from liver transplantation. World J Gastroenterol. 2007; 13(5):761-767.
156. Park SY, Kim JH, Yoon HJ, et al. Transarterial chemoembolization versus supportive therapy in the palliative treatment of unresectable intrahepatic cholangiocarcinoma. Clin Radiol. 2011; 66(4):322-328.
157. Patel K, Sullivan K, Berd D, et al. Chemoembolization of the hepatic artery with BCNU for metastatic uveal melanoma: results of a phase II study. Melanoma Res. 2005; (4):297-304.
158. Pawlik TM, Reyes DK, Cosgrove D, et al. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. J Clin Oncol. 2011; 29(30):3960-3977. Erratum in: J Clin Oncol. 2011; 29(34):4596-4598.
159. Pawlik T, Schulick RD, Choti M. Expanding criteria for resectability of colorectal liver metastases. Oncologist. 2008; 13(1):51-64.
160. Peng ZW, Liu FR, Ye S, et al. Radiofrequency ablation versus open hepatic resection for elderly patients (> 65 years) with very early or early hepatocellular carcinoma. Cancer. 2013; 119(21):3812-3820.
161. Peng ZW, Zhang YJ, Chen MS, et al. Radiofrequency ablation as first-line treatment for small solitary hepatocellular carcinoma: long-term results. Eur J Surg Oncol. 2010; 36(11):1054-1060.
162. Peng ZW, Zhang YJ, Liang HH, et al. Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: a prospective randomized trial. Radiology. 2010; 262(2):689-700.
163. Petrelli F, Coinu A, Cabiddu M, et al. Hepatic resection for gastric cancer liver metastases: a systematic review and meta-analysis. J Surg Oncol. 2015; 111(8):1021-1027.
164. Petruzzi NJ, Frangos AJ, Fenkel JM, et al. Single-center comparison of three chemoembolization regimens for hepatocellular carcinoma. J Vasc Interv Radiol. 2013; 24(2):266-273.
165. Poggi G, Quaretti P, Minoia C, et al. Transhepatic arterial chemoembolization with oxaliplatin-eluting microspheres (OEM-TACE) for unresectable hepatic tumors. Anticancer Res. 2008; 28(6B):3835-3842.
166. Poon RT, Tso WK, Pang RW, et al. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. Clin Gastroenterol Hepatol. 2007; 5(9):1100-1108.
167. Prajapati HJ, Dhanasekaran R, El-Rayes BF, et al. Safety and efficacy of doxorubicin drug-eluting bead transarterial chemoembolization in patients with advanced hepatocellular carcinoma. J Vasc Interv Radiol. 2013; 24(3):307-315.
168. Pulitanò C, Bodingbauer M, Aldrighetti L, et al. Liver resection for colorectal metastases in presence of extrahepatic disease: results from an international multi-institutional analysis. Ann Surg Oncol. 2011; 18(5):1380-1388.
169. Ramsey DE, Geschwind JF. New interventions for liver tumors. Semin Roentgenol. 2002; 37(4):303-311.
170. Ramsey DE, Kernagis LY, Soulen MC, Geschwind JF. Chemoembolization of hepatocellular carcinoma. J Vasc Interv Radiol. 2002; 13(Pt 2):S211-S221.
171. Ravaioli M, Grazi GL, Piscaglia F, et al. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. Am J Transplant. 2008; 8(12):2547-2557.

172. Reyes DK, Vossen JA, Kamel IR, et al. Single-center phase II trial of transarterial chemoembolization with drug-eluting beads for patients with unresectable hepatocellular carcinoma: initial experience in the United States. Cancer J. 2009; 15(6):526-532.
173. Rhee TK, Lewandowski RJ, Liu DM, et al. 90Y Radioembolization for metastatic neuroendocrine liver tumors: preliminary results from a multi-institutional experience. Ann Surg. 2008; 247(6):1029-1035.
174. Richardson AJ, Laurence JM, Lam VW. Transarterial chemoembolization with irinotecan beads in the treatment of colorectal liver metastases: systematic review. J Vasc Interv Radiol. 2013; 24(8):1209-1217.
175. Roayaie S, Frischer J, Emre SH, et al. Long-term results with multimodal adjuvant therapy and liver transplantation for the treatment of hepatocellular carcinomas larger than 5 centimeters. Ann Surg. 2002; 235(4):533-539.
176. Roche A, Girish BV, de Baere T, et al. Trans-catheter arterial chemoembolization as first-line treatment for hepatic metastases from endocrine tumors. Eur Radiol. 2003; 13(1):136-140.
177. Rognoni C, Ciani O, Sommariva S, et al. Trans-arterial radioembolization in intermediate-advanced hepatocellular carcinoma: systematic review and meta-analyses. Oncotarget. 2016; 7(44):72343-72355.
178. Ruiz A, Sebagh M, Wicherts DA, et al. Long-term survival and cure model following liver resection for breast cancer metastases. Breast Cancer Res Treat. 2018; 170(1):89-100.
179. 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.
180. Sacco R, Bargellini I, Bertini M, et al. Conventional versus doxorubicin-eluting bead transarterial chemoembolization for hepatocellular carcinoma. J Vasc Interv Radiol. 2011; 22(11):1545-1552.
181. Sadick M, Haas S, Loehr M, et al. Application of DC beads in hepatocellular carcinoma: clinical and radiological results of a drug delivery device for transcatheter superselective arterial embolization. Onkologie. 2010; 33(1-2):31-37.
182. 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.
183. 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.
184. Sangro B, Carpanese L, Cianni R, et al.; European Network on Radioembolization with Yttrium-90 Resin Microspheres (ENRY). Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology. 2011; 54(3):868-878.
185. Sangro B, Martínez-Urbistondo D, Bester L, et al. Prevention and treatment of complications of selective internal radiation therapy: Expert guidance and systematic review. Hepatology. 2017; 66(3):969-982.
186. Salman HS, Cynamon J, Jagust M, et al. Randomized phase II trial of embolization therapy versus chemoembolization therapy in previously treated patients with colorectal carcinoma metastatic to the liver. Clin Colorectal Cancer. 2002; 2(3):173-179.
187. Sanz-Altamira PM, Spence LD, Huberman MS, et al. Selective chemoembolization in the management of hepatic metastases in refractory colorectal carcinoma: a phase II trial. Dis Colon Rectum. 1997; 40(7):770-775.

188. Sarmiento JM, Heywood G, Rubin J, et al. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg. 2003; 197(1):29-37.
189. Sato KT, Lewandowski RJ, Mulcahy MF, et al. Unresectable chemorefractory liver metastases: radioembolization with 90Y microspheres--safety, efficacy, and survival. Radiology, 2008; 247(2):507-515.
190. Saxena A, Bester L, Shan L, et al. A systematic review on the safety and efficacy of yttrium-90 radioembolization for unresectable, chemorefractory colorectal cancer liver metastases. J Cancer Res Clin Oncol. 2014; 140(4):537-547.
191. Saxena A, Chua TC, Bester L, et al. Factors predicting response and survival after yttrium-90 radioembolization of unresectable neuroendocrine tumor liver metastases: a critical appraisal of 48 cases. Ann Surg. 2010; 251(5):910-916.
192. Saxena A, Chua TC, Chu F, et al. Optimizing the surgical effort in patients with advanced neuroendocrine neoplasm hepatic metastases: a critical analysis of 40 patients treated by hepatic resection and cryoablation. Am J Clin Oncol. 2012; 35(5):439-445.
193. Saxena A, Chua TC, Chu RC, et al. Impact of treatment modality and number of lesions on recurrence and survival outcomes after treatment of colorectal cancer liver metastases. J Gastrointest Oncol. 2014; 5(1):46-56.
194. Saxena A, Meteling B, Kapoor J, et al. Yttrium-90 radioembolization is a safe and effective treatment for unresectable hepatocellular carcinoma: a single centre experience of 45 consecutive patients. Int J Surg. 2014; 12(12):1403-1408.
195. Sauer P, Kraus TW, Schemmer P, et al. Liver transplantation for hepatocellular carcinoma: is there evidence for expanding the selection criteria? Transplantation. 2005; 80(1 Suppl):S105-S108.
196. Seidensticker M, Garlipp B, Scholz S, et al. Locally ablative treatment of breast cancer liver metastases: identification of factors influencing survival (the Mammary Cancer Microtherapy and Interventional Approaches (MAMMA MIA) study). BMC Cancer. 2015; 15:517.
197. Shady W, Petre EN, Do KG, et al. Percutaneous microwave versus radiofrequency ablation of colorectal liver metastases: ablation with clear margins (A0) provides the best Local tumor control. J Vasc Interv Radiol. 2018; 29(2):268-275
198. Siperstein AE, Berber E. Cryoablation, percutaneous alcohol injection, and radiofrequency ablation for treatment of neuroendocrine liver metastases. World J Surg. 2001; 25(6):693-696.
199. Solmi L, Nigro G, Roda E. Therapeutic effectiveness of echo-guided percutaneous radiofrequency ablation therapy with a LeVeen needle elect rode in hepatocellular carcinoma. World J Gastroenterol. 2006; 12(7):1098-1104.
200. Song do S, Choi JY, Yoo SH, et al. DC Bead transarterial chemoembolization is effective in hepatocellular carcinoma refractory to conventional transarteral chemoembolization: a pilot study. Gut Liver. 2013; 7(1):89-95.
201. Song JE, Jung KS, Kim DY, et al. Transarterial radioembolization versus concurrent chemoradiation therapy for locally advanced hepatocellular carcinoma: A Propensity Score Matching Analysis. Int J Radiat Oncol Biol Phys. 2017; 99(2):396-406.
202. Song MJ, Chun HJ, Song do S, et al. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. J Hepatol. 2012; 57(6):1244-1250.
203. Steel J, Baum A, Carr B. Quality of life in patients diagnosed with primary hepatocellular carcinoma: hepatic arterial infusion of cisplatin versus 90-yttrium microspheres (Therasphere) Psycho-oncology. 2004; 13(2):73-79.

204. Stippel DL, Brochhagen HG, Arenja M, et al. Variability of size and shape of necrosis induced by radiofrequency ablation in human livers: a volumetric evaluation. Ann Surg Oncol. 2004; 11(4):420-425.
205. Takayasu K, Arii S, Ikai I, et al. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology. 2006; 131(2):461-469.
206. Takemura N, Saiura A, Koga R, et al. Long-term results of hepatic resection for non-colorectal, non-neuroendocrine liver metastasis. Hepatogastroenterology. 201; 60(127):1705-1712.
207. Taniguchi M, Kim SR, Imoto S, et al. Long-term outcome of percutaneous ethanol injection therapy for minimum-sized hepatocellular carcinoma. World J Gastroenterol. 2008; 14(13):1997-2002.
208. Tateishi R, Shiina S, Teratani, et al. Percutaneous radiofrequency ablation for hepatocellular carcinoma: an analysis of 1000 cases. Cancer. 2005; 103(6):1201-1209.
209. Tellez C, Benson AB III, Lyster MT, et al. Phase II trial of chemoembolization for the treatment of metastatic colorectal carcinoma to the liver and review of the literature. Cancer. 1998; 82(7):1250-1259.
210. Tian JH, Xu BX, Zhang JM, et al. Ultrasound-guided internal radiotherapy using yttrium-90-glass microspheres for liver malignancy. J Nucl Med. 1996; 37(6):958-963.
211. Tovoli F, Negrini G, Bolondi L. Comparative analysis of current guidelines for the treatment of hepatocellular carcinoma. Hepat Oncol. 2016; 3(2):119-136.
212. Trinchet JC, Ganne-Carrie N, Beaugrand M. Review article: intra-arterial treatments in patients with hepatocellular carcinoma. Aliment Pharmacol Ther. 2003; 17(Suppl 2):111-118.
213. Uggeri F, Pinotti E, Sandini M, et al. Prognostic Factors Affecting Long-Term Survival after Resection for Noncolorectal, Nonneuroendocrine, and Nonsarcoma Liver Metastases. Gastroenterol Res Pract. 2017; 2017:5184146.
214. Uggeri F, Ronchi PA, Goffredo P, et al. Metastatic liver disease from non-colorectal, non-neuroendocrine, non-sarcoma cancers: a systematic review. World J Surg Oncol. 2015; 13:191.
215. Van Hazel G, Pavlakis N, Goldstein D, et al. Treatment of fluorouracil-refractory patients with liver metastases from colorectal cancer by using Yttrium-90 resin microspheres plus concomitant systemic irinotecan chemotherapy. J Clin Oncol. 2009; 27(25):4089-4095.
216. van Malenstein H, Maleux G, Vandecaveye V, et al. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. Onkologie. 2011; 34(7):368-376.
217. Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol. 2007; 46(3):474-481.
218. Veltri A, Gazzera C, Calandri M, et al. Percutaneous treatment of hepatocellular carcinoma exceeding 3 cm: combined therapy or microwave ablation? Preliminary results. Radiol Med. 2015; 120(12):1177-1183.
219. Vente MA, Wondergem M, van der Tweel I, et al. Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis. Eur Radiol. 2009; 19(4):951-959.
220. Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2017; 18(12):1624-1636.
221. Virani S, Michaelson JS, Hutter MM, et al. Morbidity and mortality after liver resection: results of the patient safety in surgery study. J Am Coll Surg. 2007; 204(6):1284-1292.
222. Vogl TJ, Gruber T, Balzer JO, et al. Repeated transarterial chemoembolization in the treatment of liver metastases of colorectal cancer: prospective study. Radiology. 2009; 250(1):281-289.

223. Vogl TJ, Lammer J, Lencioni R, et al. Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with PRECISION TACE with drug-eluting beads: results from the PRECISION V randomized trial. AJR Am J Roentgenol. 2011; 197(4):W562-W570.
224. Vogl TJ, Naguib NN, Lehnert T, et al. Initial experience with repetitive transarterial chemoembolization (TACE) as a third line treatment of ovarian cancer metastasis to the liver: indications, outcomes and role in patient's management. Gynecol Oncol. 2012; 124(2):225-229.
225. Vogl TJ, Naguib NN, Nour-Eldin NE, et al. Transarterial chemoembolization (TACE) with mitomycin C and gemcitabine for liver metastases in breast cancer. Eur Radiol. 2010; 20(1):173-180.
226. Vouche M, Habib A, Ward TJ, et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: multicenter radiology-pathology correlation and survival of radiation segmentectomy. Hepatology. 2014; 60(1):192-201.
227. Wasan HS, Gibbs P, Sharma NK, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol. 2017; 18(9):1159-1171.
228. Woodall EC, Scoggins CR, Ellis SF, et al. Is selective internal radioembolization safe and effective for patients with inoperable hepatocellular carcinoma and venous thrombosis? J Am Coll Surg. 2009; 208(3):375-382.
229. Xiao YB, Zhang B, Wu YL. Radiofrequency ablation versus hepatic resection for breast cancer liver metastasis: a systematic review and meta-analysis. J Zhejiang Univ Sci B. 2018; 19(11):829-843.
230. Xie ZB, Wang XB, Peng YC, et al. Systematic review comparing the safety and efficacy of conventional and drug-eluting bead transarterial chemoembolization for inoperable hepatocellular carcinoma. Hepatol Res. 2015; 45(2):190-200.
231. Yamakado K, Nakatsuka A, Takaki H, et al. Early-stage hepatocellular carcinoma: radiofrequency ablation combined with chemoembolization versus hepatectomy. Radiology. 2008; 247(1):260-266.
232. Yamashiki N, Tateishi R, Yoshida H, et al. Ablation therapy in containing extension of hepatocellular carcinoma: a simulative analysis of dropout from the waiting list for liver transplantation. Liver Transpl. 2005; 11(5):508-514.
233. Yang Y, Si T. Yttrium-90 transarterial radioembolization versus conventional transarterial chemoembolization for patients with hepatocellular carcinoma: a systematic review and meta-analysis. Cancer Biol Med. 2018; 15(3):299-310.
234. Yao FY, Bass NM, Nikolai B, et al. A follow-up analysis of the pattern and predictors of dropout from the waiting list for liver transplantation in patients with hepatocellular carcinoma: implications for the current organ allocation policy. Liver Transpl. 2003; 9(7):684-692.
235. Yao FY, Hirose R, LaBerge JM, et al. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. Liver Transpl. 2005a; 11(12):1505-1514.
236. Yao FY, Kerlan RK Jr, Hirose R, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. Hepatology. 2008; 48(3):819-827
237. Yao FY, Kinkhabwala M, LaBerge JM, et al. The impact of pre-operative locoregional therapy on outcome after liver transplantation for hepatocellular carcinoma. Am J Transplant. 2005b; 5(4 Pt 1):795-804.
238. Young JY, Rhee TK, Atassi B, et al. Radiation dose limits and liver toxicities resulting from multiple yttrium-90 radioembolization treatments for hepatocellular carcinoma. J Vasc Interv Radiol. 2007; 18(11):1375-1382.

239. Yun BL, Lee JM, Baek JH, et al. Radiofrequency ablation for treating liver metastases from a non-colorectal origin. Korean J Radiol. 2011; 12(5):579-587.
240. Zacharias AJ, Jayakrishnan TT, Rajeev R, et al. Comparative effectiveness of hepatic artery based therapies for unresectable colorectal liver metastases: a meta-analysis. PLoS One. 2015; 10(10):e0139940.
241. Zhang X, Chen B, Hu S, et al. Microwave ablation with cooled-tip electrode for liver cancer: an analysis of 160 cases. Hepatogastroenterology. 2008; 55(88):2184-2187.
242. Zhang CS, Zhang JL, Li XH, et al. Is radiofrequency ablation equal to surgical re-resection for recurrent hepatocellular carcinoma meeting the Milan criteria? A meta-analysis. J BUON. 2015; 20(1):223-230.
243. Zhong JH, Rodríguez AC, Ke Y, et al. Hepatic resection as a safe and effective treatment for hepatocellular carcinoma involving a single large tumor, multiple tumors, or macrovascular invasion. Medicine (Baltimore). 2015; 94(3):e396.
244. Zhang Y, Li Y, Ji H, et al. Transarterial Y90 radioembolization versus chemoembolization for patients with hepatocellular carcinoma: A meta-analysis. Biosci Trends. 2015; 9(5):289-298.
245. Zhou Y, Zhang X, Wu L, et al. Meta-analysis: preoperative transcatheter arterial chemoembolization does not improve prognosis of patient with resectable hepatocellular carcinoma. BMC Gastroenterol. 2013; 13:51.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Abdel-Rahman OM, Elsayed Z. Yttrium-90 microsphere radioembolisation for unresectable hepatocellular carcinoma. Cochrane Database Syst Rev. 2016;(2):CD011313.
2. American College of Gastroenterology. ACG Clinical Guideline: The Diagnosis and Management of Focal Liver Lesions (2014). Available at: https://journals.lww.com/ajg/Fulltext/2014/09000/ACG_Clinical_Guideline__The_Diagnosis_and.7.aspx#pdf-link . Accessed on January 26, 2020.
3. American College of Radiology. ACR Appropriateness Criteria®. Radiologic Management of Hepatic Malignancy. Last review date 2015. Available at: https://acsearch.acr.org/list. Accessed on January 26, 2020.
4. American College of Radiology (ACR), American Brachytherapy Society (ABS), American College of Nuclear Medicine (ACNM), American Society for Radiation Oncology (ASTRO), Society of Interventional Radiology (SIR), and Society of Nuclear Medicine and Molecular Imaging (SNMMI). ACR–ABS–ACNM–ASTRO–SIR–SNMMI Practice parameter for selective Internal Radiation Therapy (SIRT) or Radioembolization for Treatment of Liver Malignancies. Revised 2019. Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/RMBD.pdf. Accessed on January 27, 2020.
5. Bala MM, Riemsma RP, Wolff R, Kleijnen J. Cryotherapy for liver metastases. Cochrane Database Syst Rev. 2013;(6):CD009058.
6. Bala MM, Riemsma RP, Wolff R, Kleijnen J. Microwave coagulation for liver metastases. Cochrane Database Syst Rev. 2013;(10):CD010163.
7. Brown DB, Geschwind JF, Soulen M, et al. Society of Interventional Radiology (SIR) position statement on chemoembolization of hepatic malignancies. J Vasc Interv Radiol. 2006; 17(2):217-223.
8. Brown DB, Nikolic B, Covey AM, et al. Society of Interventional Radiology Standards of Practice Committee. Quality improvement guidelines for transhepatic arterial chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancy. J Vasc Interv Radiol. 2012; 23(3):287-294.
9. Bruix J, Sherman M. American Association for the Study of Liver Disease (AASLD) Practice Guideline: Management of hepatocellular carcinoma. Hepatology. 2005; 42(5):1208-1235.

10. Bruix J, Sherman M. American Association for the Study of Liver Disease (AASLD) Practice Guideline: Management of hepatocellular carcinoma: an update. Hepatology. 2011; 53(3):1020-1058.
11. Charnsangavej C, Clary B, Fong, Y, et al. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol. 2006; 13(10):1261-1268.
12. Cirocchi R, Trastulli S, Boselli C, et al. Radiofrequency ablation in the treatment of liver metastases from colorectal cancer. Cochrane Database Syst Rev. 2012;(6):CD006317.
13. Fedorowicz Z, Lodge M, Al-Asfoor A, Carter B. Resection versus no intervention or other surgical interventions for colorectal cancer liver metastases. Cochrane Database Syst Rev. 2008;(2):CD006039.
14. Gaba RC, Lokken P, Hickey RM, et al. Society of Interventional Radiology. Quality improvement guidelines for transarterial chemoembolization and embolization of hepatic malignancy. 2017; (9):1210-1223.
15. Gervais DA, Goldberg SN, Brown DB, et al. Society of Interventional Radiology position statement on percutaneous radiofrequency ablation for the treatment of liver tumors. J Vasc Interv Radiol. 2009; 20(7 Suppl):S342-S347.
16. Gurusamy KS, Ramamoorthy R, Sharma D, Davidson BR. Liver resection versus other treatments for neuroendocrine tumours in patients with resectable liver metastases. Cochrane Database Syst Rev. 2009;(2):CD007060.
17. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018; 67(1):358-380. Available at: https://www.aasld.org/publications/practice-guidelines. Accessed on January 27, 2020.
18. Kulik L, Heimbach JK, Zaiem F, et al. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. Hepatology. 2018; 67(1):381-400. Available at: https://www.aasld.org/sites/default/files/2019-06/Kulik_Therapies%20for%20HCC%20Patients%20Awaiting%20LT%20et_al-2018-Hepatology-bookmarked.pdf. Accessed on January 27, 2020.
19. Kutlu OC, Chan JA, Aloia TA, et al. Comparative effectiveness of first-line radiofrequency ablation versus surgical resection and transplantation for patients with early hepatocellular carcinoma. Cancer. 2017; 123(10):1817-1827
20. National Cancer Institute (NCI). Adult Primary Liver Cancer Treatment (PDQ®). Last modified October 3, 2019. Available at: https://www.cancer.gov/publications/pdq/information-summaries. Accessed on January 27, 2020.
21. National Comprehensive Cancer Network® (NCCN) Practice Guidelines in Oncology™. © 2020 National Comprehensive Cancer Network, Inc. For additional information, visit the NCCN website: http://www.nccn.org. Accessed on January 26, 2020.
    - Breast Cancer (V.2.2020). Revised January 15, 2020.
    - Cervical Cancer (V.1.2020). Revised January 14, 2020.
    - Colon Cancer (V.2.2020). Revised December 19, 2019.
    - Cutaneous Melanoma (V.1.2020) Revised December 19, 2019.
    - Hepatobiliary Cancer (V.4.2019). Revised December 20, 2019.
    - Neuroendocrine and Adrenal Tumors (V.1.2019). Revised March 5, 2019.
    - Occult Primary (Cancer of Unknown Primary [CUP]. (V2.2019). Revised January 23, 2019.
    - Rectal Cancer (V.2.2019). Revised May 15, 2019.

- Soft Tissue Sarcoma (V.2.2019). Revised February 4, 2019.
- Uveal Melanoma (V1.2019) Revised June 14, 2019.

22. Oliveri RS, Wetterslev J, Gluud C. Transarterial (chemo) embolisation for unresectable hepatocellular carcinoma. Cochrane Database Syst Rev. 2011;(3):CD004787.
23. Organ Procurement and Transplantation Network. United Network for Organ Sharing (UNOS). Policy: 9 Allocation of Livers and Liver-Intestines. Effective January 9, 2020. Available at: http://optn.transplant.hrsa.gov/governance/policies/. Accessed on January 24, 2020.
24. Riemsma RP, Bala MM, Wolff R, Kleijnen J. Electro-coagulation for liver metastases. Cochrane Database Syst Rev. 2013;(5):CD009497.
25. Riemsma RP, Bala MM, Wolff R, Kleijnen J. Percutaneous ethanol injection for liver metastases. Cochrane Database Syst Rev. 2013;(5):CD008717.
26. Riemsma RP, Bala MM, Wolff R, Kleijnen J. Transarterial (chemo)embolization versus no intervention or placebo intervention for liver metastases. Cochrane Database Syst Rev. 2013;(4):CD009498.
27. SIR-Spheres Product Information [PI] Label. Woburn, MA. Sirtex Medical Inc., December 19, 2019. Available at: https://www.sirtex.com/media/169247/ssl-us-14-sir-spheres-microspheres-ifu-us.pdf. Accessed on January 27, 2020.
28. TheraSphere. PI Label. Surrey, UK. Biocompatibles UJNK Ltd. 2014. Available at: https://btgplc.com/BTG/media/TheraSphere-Documents/PDF/TheraSphere-Package-Insert_USA_Rev-14.pdf . Accessed on January 27, 2020.
29. Townsend A, Price T, Karapetis C. Selective internal radiation therapy for liver metastases from colorectal cancer. Cochrane Database Syst Rev. 2009;(4):CD007045.
30. Weis S, Franke A, Berg T, et al. Percutaneous ethanol injection or percutaneous acetic acid injection for early hepatocellular carcinoma. Cochrane Database Sys Rev. 2015;(1):CD006745.
31. Weis S, Franke A, Mössner J, et al. Radiofrequency (thermal) ablation versus no intervention or other interventions for hepatocellular carcinoma. Cochrane Database Sys Rev. 2013;(12):CD003046.
32. Wong SL, Mangu PB, Choti MA, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol. 2010; 28(3):493-508.
33. United States Nuclear Regulatory Commission (U.S. NRC). Microsphere Brachytherapy Sources and Devices. Licensing Guidance: ThereSphere® and SIR-Spheres® Yttrium-90 Microspheres. Revised November 8, 2019. Available at: https://www.nrc.gov/docs/ML1920/ML19204A272.pdf. Accessed on January 23, 2020.

Websites for Additional Information

1. American Cancer Society. Available at: www.cancer.org. Accessed on January 26, 2020.
2. National Cancer Institute. Cancer topics Available at: http://www.cancer.gov/cancertopics. Accessed on January 26, 2020.
   - Adult Primary Liver Cancer (PDQ®): Treatment. Last updated October 3, 2019.
   - Childhood Liver Cancer Treatment (PDQ). Last updated October 8, 2019.
   - Colon Cancer Treatment (PDQ). Last updated January 22, 2020.
   - Intraocular (Eye) Melanoma Treatment (PDQ). Last updated December 17, 2019.

- Pancreatic Neuroendocrine Tumors (Islet Cell Tumors) Treatment (PDQ). Last updated January 2, 2020.
- Rectal Cancer Treatment (PDQ). Last updated January 29, 2019.

3. Ocular Melanoma Foundation. About Ocular Melanoma. Available at: http://www.ocularmelanoma.org/about-om. Accessed on January 26, 2020.
4. U.S. National Institutes of Health (NIH). Clinical trials. Available at: https://clinicaltrials.gov/ct2/search. Accessed on January 26, 2020.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Revised	02/20/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised term SIRT to SIRT/TARE within all clinical indications statements.

		Reordered clinical indications statements without change in intents. Revised Description, Discussion, Definitions and References sections.
Revised	08/22/2019	MPTAC review. Moved content of CG-SURG-80 Transcatheter Arterial Chemoembolization (TACE) and Transcatheter Arterial Embolization (TAE) for Treating Primary or Metastatic Liver Tumors and CG-THER-RAD-04 Selective Internal Radiation Therapy (SIRT) of Primary or Metastatic Liver Tumors into document. Revised title from Locally Ablative Techniques for Treating Primary and Metastatic Liver Malignancies to Locoregional and Surgical Techniques for Treating Primary and Metastatic Liver Malignancies. Added Percutaneous Ethanol Injection (PEI) and Radiofrequency Ablation (RFA) as medically necessary procedures in those who may become eligible for liver transplantation. Updated Description, Discussion, References, Websites for Additional Information and Index sections.
Reviewed	03/21/2019	MPTAC review.
Reviewed	03/20/2019	Hematology/Oncology Subcommittee review. Updated Discussion and References sections.
New	05/03/2018	MPTAC review.
New	05/02/2018	Hematology/Oncology Subcommittee review. Initial document development. Moved content of SURG.00065 Locally Ablative Techniques for Treating Primary and Metastatic Liver Malignancies to new clinical utilization management guideline document with the same title.