Title: Cryosurgical Ablation of Primary or Metastatic Liver Tumors

DESCRIPTION
Cryosurgical ablation involves freezing of target tissues, most often by inserting into the tumor a probe through which coolant is circulated. Cryosurgical ablation can be performed as an open surgical technique or percutaneously or laparoscopically, typically with ultrasound (US) guidance.

Hepatic tumors can arise either as primary liver cancer or by metastasis to the liver from other tissues. Local therapy for hepatic metastasis is indicated only when there is no extrahepatic disease, which rarely occurs for patients with primary cancers other than colorectal carcinoma or certain neuroendocrine malignancies. At present, surgical resection with tumor-free margins or liver transplantation represent the only treatments with curative potential. For liver metastases from colorectal cancer, post-surgical adjuvant chemotherapy has been reported to decrease recurrence rates and prolong time to recurrence. However, most hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size, number of lesions, or underlying liver reserve.
Combined systemic and hepatic arterial chemotherapy may increase disease-free intervals for patients with hepatic metastases from colorectal cancer but apparently is not beneficial for those with unresectable hepatocellular carcinoma.

Various locoregional therapies for unresectable liver tumors are being studied: cryosurgical ablation (CSA) (cryosurgery), radiofrequency ablation (RFA), laser ablation, transhepatic artery embolization/ chemoembolization, microwave coagulation, and percutaneous ethanol injection. Ablation occurs in tissue that has been frozen by at least 3 mechanisms: 1) formation of ice crystals within cells, thereby disrupting membranes and interrupting cellular metabolism among other processes; 2) coagulation of blood, thereby interrupting blood flow to the tissue in turn causing ischemia and cell death; and 3) induction of apoptosis (cell death).

Recent studies report experience with cryosurgical and other ablative methods used in combination with subtotal resection and/or procedures such as TACE (transarterial chemoembolization).

**POLICY**

A. Cryosurgical ablation of primary hepatocellular carcinoma (HCC) may be considered **medically necessary** as a primary treatment of HCC for patients when all tumor foci can be adequately treated.

B. Cryosurgical ablation of primary hepatocellular carcinoma (HCC) is considered **medically necessary** as a bridge to transplant, where the intent is to prevent further tumor growth and to maintain a patient’s candidacy for liver transplant.

C. Cryosurgical ablation of primary hepatocellular carcinoma (HCC) is considered **investigational** when not all sites of tumor foci can be adequately treated.

D. Cryosurgical ablation may be considered **medically necessary** as a primary treatment of hepatic metastases from colorectal cancer in the absence of extrahepatic metastatic disease when all tumor foci can be adequately treated.

E. Cryosurgical ablation may be considered **medically necessary** as treatment of hepatic metastases from neuroendocrine tumors in patients with symptomatic disease.

F. Cryosurgical ablation for hepatic metastasis is considered **experimental / investigational:**
   1. for hepatic metastases from colorectal cancer or neuroendocrine tumors that do not meet the criteria above; and
   2. for hepatic metastases from other types of cancer with the exception of colorectal cancer or neuroendocrine tumors.
Rationale
The policy was initially developed following a 2000 TEC Assessment that found insufficient data to permit conclusions regarding the effect of cryosurgery on health outcomes of patients with unresectable hepatocellular carcinoma (HCC), cholangiocarcinoma, or liver metastases. (1) The policy has been updated on a regular basis with literature searches of the MEDLINE database. The most recent search was conducted for the period of October 2011 through October 2012. The findings of the literature searches are summarized below.

Four patient groups have been treated with hepatic cryosurgery: those with primary HCC, liver metastases from colorectal cancer, neuroendocrine tumors metastatic to the liver, and liver metastases from other non-colorectal cancers.

Hepatocellular carcinoma (HCC)
Authors of a 2009 Cochrane review of cryotherapy for HCC reported finding 2 prospective cohort studies and 2 retrospective studies in their literature search but no randomized controlled trials (RCTs) or quasi-randomized, controlled trials. (2) Only one study could be considered for the assessment of benefit. In that study, (3) results were stratified according to both the type of hepatic malignancy (primary or secondary) and the intervention group (percutaneous cryotherapy or percutaneous radiofrequency ablation [RFA]). Sixty-four patients were treated based on random availability of probes; 31 patients received cryotherapy and 33 received RF. Of all patients treated, 26 (84%) of 31 who had cryotherapy and 24 (73%) of 33 who had RF developed a local recurrence, all within 1 year. The distribution of primary cancers was not specified. Among the HCC patients, rates of initial tumor ablation were similar after cryosurgery or RFA (65% and 76%, respectively), but local recurrences were more frequent after cryosurgery (38%) than after RFA (17%). Survival at 1 year did not differ by ablative technique (cryosurgery, 66%; RFA, 61%). The study did not include controls managed with an established alternative. Authors of the Cochrane review concluded that there is no evidence to recommend or refute cryotherapy in the treatment of patients with HCC and that randomized, clinical trials may be useful.

In 2011, Yang and colleagues reported on a series of 300 patients treated between 2003 and 2006 with percutaneous argon-helium cryoablation for hepatocellular carcinoma. (4) Complete tumor ablation occurred in 185 tumors in 135 patients with mean tumor diameter of 5.6 ± 0.8 cm, while 223 tumors in 165 patients with a mean tumor diameter of 7.2 ± 2.8 cm were incompletely ablated (p=0.0001). Serious complications occurred in 19 patients (6.3%) and included liver hemorrhage in 5 patients, cryoshock syndrome in 6 patients, gastric bleeding in 4 patients, liver abscess in 1 patient and intestinal fistula in 1 patient. Liver failure resulted in the death of 2 patients. Patients with incomplete ablation received additional treatment with transarterial catheter embolization or a multikinase inhibitor (sorafenib). During the median follow-up of 36.7 months (range 6-63 months), local tumor recurrence was 31%. Larger tumors and tumor location were significantly related to tumor recurrence (p=0.029 and 0.037, respectively). Overall survival was 80% at 1 year, 45% at 2 years, and 32% at 3 years.

Clavien et al. (5) treated 15 patients with cirrhosis and a single liver lesion (biopsy-proved HCC or suspicious mass on imaging) using open cryosurgery after transhepatic arterial chemoembolization. In all patients, cryosurgery was offered because the tumor was “unresectable or surgical resection was not thought to be feasible because of tumor location or...
size, or patient comorbidity.” Actuarial survival rate of these patients after cryosurgery was 79% at 5 years. The study did not include a control group.

In a 2009 study, Zhou and colleagues divided 124 patients with primary nonresectable HCC into early, middle, and advanced stage groups by Barcelona Clinic Liver Cancer staging classification. (6) After argon-helium cryoablation, serum level of alpha-fetoprotein was reduced in 76 (82.6%), and 205 (92.3%) of 222 tumor lesions were diminished or unchanged. Median survival time was 31.35 months in the early stage, 17.4 months in the middle stage, and 6.8 months in the late stage groups. As of April 2008, 14 patients survived and 110 had died. To determine risk factors that predict metastasis and recurrence Wang et al. studied a series of 156 patients with hepatitis B (HBV)-related HCC and tumors smaller than 5 cm in diameter who underwent curative cryoablation. (7) One-, 2-, and 3-year overall survival rates were 92%, 82%, and 64%, respectively, and 1-, 2-, and 3-year recurrence-free survival (RFS) rates were 72%, 56%, and 43%, respectively. The multivariate analysis showed that Child-Pugh class and expression of vascular endothelial growth factor (VEGF) in HCC tissues could be used as independent prognostic factors for overall survival. The expression of VEGF in HCC tissues and HBV basal core promoter mutations were independent prognostic factors for RFS.

In a nonrandomized comparative study, Xu and colleagues evaluated outcomes of cryosurgery alone and transcatheter arterial chemoembolization (TACE) followed by cryosurgery in 420 patients with nonresectable HCC. (8) Patients in the sequential TACE-cryosurgery group tended to have larger tumors and a greater number of tumors than patients in the cryoablation alone group. Tumors larger than 10 cm were seen only in the sequential group. During mean follow-up of 42 months (range: 24–70), the local recurrence rate at the ablated area was 17% for all patients, 11% in the sequential group, and 23% in the cryosurgery alone group (p=0.001). One- and 2-year survival rates were similar in both treatment groups (p=0.69); however, 5-year survival rates were 39% in the sequential group and 23% in the cryosurgery alone group (p=0.001). Eighteen patients with large HCC (i.e., larger than 5 cm) survived for more than 5 years after sequential TACE-cryosurgery, while no patient with large HCC and cryosurgery alone survived more than 5 years. The incidence of hepatic bleeding was higher in the cryosurgery alone group. The authors conclude that precryosurgical TACE may increase the efficacy of cryoablation and reduce adverse effects.

Neuroendocrine cancer liver metastases
Neuroendocrine tumors are relatively slow-growing malignancies (mean survival times of 5–10 years) that commonly metastasize to the liver. As with other cancers, the most successful treatment of hepatic metastasis is resection with tumor-free margins, but treatment benefits for a slow-growing tumor must be weighed against the morbidity and mortality of major surgery. (9) The intent of cryosurgery in these cases is to minimize or eliminate symptoms caused by liver metastases while avoiding the complications of open surgery.

A 2009 Cochrane review evaluated the benefits and harms of liver resection versus other treatments in patients with resectable liver metastases from gastro-entero-pancreatic neuroendocrine tumors. (10) Trials comparing liver resection (alone or in combination with RFA or cryoablution) versus other interventions (chemotherapy, hormonetherapy, or immunotherapy) and studies comparing liver resection and thermal ablation (RFA or cryoablution) were sought. Authors of the Cochrane review reported finding neither an RCT suitable for review nor any quasi-randomized, cohort, or case-control studies “that could inform meaningfully.” No analysis
was performed, and the authors refer to only RFA in their discussion, noting that RF is not suitable for large tumors (i.e., larger than 5-6 cm) and that neuroendocrine liver metastases are frequently larger than that. The authors conclude that further randomized trials comparing surgical resection and RFA in selected patients may be appropriate.

In 2012, Saxena and colleagues reported on a retrospective review of 40 patients treated with cryoablation and surgical resection for hepatic metastases from neuroendocrine cancer. (11) The median period of follow-up was 61 months with a range of 1 to 162 months. One death occurred within 30 days of treatment. No other complications were reported. Median survival was 95 months, and the rate of survival was 92%, 73%, 61% and 40% at 1-, 3-, 5-, and 10-year survival, respectively.

In 2001, Chung and colleagues reported on outcomes of for hepatic metastases from neuroendocrine cancer. (12) This study used cytoreduction (resection, cryosurgery, RFA, or a combination) and adjuvant therapy (octreotide, chemotherapy, radiation, interferon alfa) in 31 patients with neuroendocrine metastases to the liver and “progressive symptoms refractory to conventional therapy.” Following treatment, symptoms were eliminated in 87% of patients; median symptom-free interval was 60 months with octreotide and 16 months with alternatives. Since outcomes were not reported separately for different cytoreductive techniques, it was not possible to compare the benefits of cryosurgery with those of other cytoreductive approaches or octreotide alone.

Liver metastases from other cancers including colorectal cancer
In 2011, Pathak and colleagues reported on a systematic review of ablative therapies for colorectal liver metastases. (13) Included in the review were 26 nonrandomized studies on cryoablation. The authors reported local recurrence rates in the studies reviewed ranged from 12-39%. Survival rates ranged from 46-92% at 1 year, 8-60% at 3 years, and 0-44% at 5 years. Mean survival rates at 1, 3, and 5 years were 84%, 37% and 17%, respectively. Major complications ranged from 7% to 66%. Cryoshock was indicated to be of major concern.

A 2008 Cochrane review was undertaken to compare outcomes of resection of colorectal cancer liver metastases to no intervention or other modalities of intervention, including RFA and cryosurgery. (14) Only RCTs reporting on patients who had curative surgery for adenocarcinoma of the colon or rectum and who had been diagnosed with liver metastases and who were eligible for liver resection were considered. Only one randomized trial was identified, a 1997 study from the Ukraine comparing surgical resection and cryosurgery in 123 subjects, 82 of whom had liver metastases from primary colorectal cancers and the remainder who had metastases from other primary tumors. (15) Survival outcomes were not provided by type of cryogenic procedure or primary tumor site. The authors of the Cochrane review conclude that local ablative therapies are probably useful but that they need to be further evaluated in a RCT.
In a 2002 review of the literature, Sotsky and Ravikumar (16) summarized the results of 27 studies reporting outcomes of cryosurgery in more than 1,000 patients. In studies with only patients with colorectal cancer, outcomes diverged markedly (median survival ranged from 18 to greater than 33 months), liver recurrences were frequent (20–50%), and significant procedure-related complications were common. (17) While the review's authors asserted that cryosurgery is an established procedure, the data reported in the studies cited in the review appear inconclusive, since baseline characteristics of study populations were heterogeneous, and published outcomes were variable and inconsistently reported.

In 2012, Ng and colleagues reported on a retrospective review of 293 patients treated between 1990 and 2009 for colorectal liver metastases with cryoablation with or without surgical resection. (18)

Perioperative death occurred in 10 patients (3%) and included liver abscess sepsis in 4 patients, cardiac events unrelated to treatment in 3 patients, and one case each of dilated cardiomyopathy, cerebrovascular event, and multiorgan failure. Median follow-up was 28 months (range 0.1 to 220 months). Overall survival was 87%, 41.8%, 24.2%, and 13.3% at 1, 3, 5, and 10 years, respectively.

A Phase I comparison of single versus dual cryoprobe configurations in 15 patients given multiple treatments (25 single-probe and 14 dual-probe) did not report long-term outcomes or health benefits. (19) Three studies administered cryosurgery as a planned or incidental adjunct to surgery in patients with hepatic tumors. (20-22) Two of these were retrospective studies (20, 22), and all 3 pooled results across patients with heterogeneous disease characteristics (e.g., tumors of varied numbers and location). A prospective study (21) did not adequately describe criteria used to select patients for cryosurgery. Another report was a “retrospective review of prospectively collected data” on 172 patients treated with cryosurgery with (n=157) or without (n=25) post-procedure 5-fluorouracil or 5-fluorodeoxyuridine as hepatic arterial chemotherapy (HAC), and with (n=80) or without (n=92) resection (23). The authors concluded that the results of cryosurgery in their study (25% survival at 5 years) are encouraging but may partly reflect the effects of HAC, completeness (or, rather, incompleteness) of cryosurgery in some patient groups, and patient selection.

Niu and colleagues reported on an analysis of data collected prospectively for patients who underwent hepatic resection for metastatic colorectal cancer with or without cryoablation from 1990 to 2006. (24) A decision about resectability was determined at the time of surgery. Patients who had resections and cryoablation were more likely to have bilobar disease (85% vs. 27%, respectively) and to have 6 or more lesions (35% vs. 3%, respectively). In addition, 73% of this combined treatment group received HAC compared to 32% in the resection-only group. Median follow-up was 25 months (range: 1–124 months). The 30-day perioperative mortality was 3.1%. For the resection group, the median survival was 34 months, with 1-, 3- and 5-year survival values of 88%, 47%, and 32%, respectively. The median survival for the resection/cryotherapy group was 29 months, with 1-, 3- and 5-year survival values of 84%, 43%, and 24%, respectively (p=0.206). The overall recurrence rates were 66% for resection only, but 78% for resection/cryotherapy. Five factors were independently associated with an improved survival: absence of extrahepatic disease at diagnosis, well- or moderately differentiated colorectal cancer, largest lesion size being 4 cm or less, a postoperative carcinoembryonic antigen (CEA) of 5 ng/mL or less, and absence of liver recurrence. While the recurrence rates between groups were
not different in this study, it is not clear how representative the patients who had resection/cryotherapy are of the total potential patients. The comparability of the 2 groups is uncertain, especially given the differential use of HAC. In this study, a direct comparison was not made to chemotherapy. Finally, the 16-year duration of the study raises concerns about inter-current changes that could have had an impact on the results.

Seifert et al. reported on a series of patients with colorectal liver metastases that were treated from 1996–2002. (25) In this series, 168 patients underwent resection and 55 had cryosurgical ablation (CSA) (in 25 of these patients, it was combined with resection.) Twenty-nine percent (16 of 55) of the ablation group had prior liver resection compared with only 5% in the resection group. Twenty percent of both groups had extrahepatic disease at the time of surgery. With a median follow-up of 23 months, median and 5-year survival rates following resection and cryotherapy were comparable, with 29 months and 29 months and 23% and 26%, respectively. However, the median disease-free survival (DFS) times and 5-year DFS rates following resection were superior at 10 months and 19%, respectively, for resection compared with 6 months and 12%, respectively for cryotherapy. Overall recurrence was 61% in the resection group and 76% in the cryotherapy group, and liver recurrence was 45% and 71%, respectively. Limitations of this study include the small sample size, limited follow-up, and noncomparability of the groups.

Ruers and colleagues reported on a consecutive series of 201 colorectal cancer patients, without extrahepatic disease, treated between 1995 and 2004 and who underwent laparotomy for surgical treatment of liver metastases. (26) These patients were prospectively followed up for survival and quality of life. At laparotomy, 3 groups were identified: patients in whom radical resection of metastases proved feasible, patients in whom resection was not feasible and received local ablative therapy (with or without resection), and patients in whom resection or local ablation was not feasible for technical reasons and who received systemic chemotherapy. The study reported that patients in the chemotherapy and local ablation groups were comparable for all prognostic variables tested. For the local ablation group, OS at 2 and 5 years was 56% and 27%, respectively (median: 31 months; n=45), for the chemotherapy group 51% and 15%, respectively (median: 26 months; n=39; p=0.252). After resection, these figures were 83% and 51%, respectively (median: 61 months; n=117; p<0.001). The median DFS after local ablation was 9 months. The authors concluded that although overall survival (OS) of local ablation versus chemotherapy did not reach statistical significance, the median DFS of 9 months suggested a beneficial effect of local tumor ablation. However, given the heterogeneity of the groups in this study, it is very difficult to compare outcomes among the groups. In addition, this study used both cryotherapy and RF for local ablation, and results are reported for the combined group.

In a relatively small study, Joosten et al. reported on 58 patients with unresectable colorectal liver metastases where CSA or RFAs were performed in patients not eligible for resection. (27) Median follow-up was 26 and 25 months for CSA and RFA, respectively. One- and 2-year survival rates were 76% and 61% for CSA and 93% and 75% for RFA, respectively. In a lesion-based analysis, the local recurrence rate was 9% after CSA and 6% after RFA. Complication rates were 30% and 11% after CSA and RFA, respectively (p=0.052). While the small size of this study makes drawing conclusions difficult, it does raise questions about the relative efficacy of both techniques.

Kornprat and colleagues reported on thermoablation combined with resection in the treatment of hepatic metastasis from colorectal cancer. (28) In this series, from January 1, 1998, to December
31, 2003, 665 patients with colorectal metastases underwent hepatic resection. Of these, 39 (5.9%) had additional intraoperative thermoablatfive procedures (19 RFA, 20 CSA). The total morbidity rate was 41% (16 of 39). No RFA-related complications occurred; however, 3 patients developed an abscess at cryoablation sites. The median DFS was 12.3 months (range: 8.4–16.2 months). Overall, the local in situ recurrence rate according to number of ablated tumors was 14% for RFA and 12% for CSA. Tumor size correlated directly with recurrence (p=0.02) in RFA-treated lesions. In the comment section of this paper, the authors indicate that an ongoing controversy is whether resection of extensive disease combined with chemotherapy is better than either treatment alone.

Xu et al. reported on a series of 326 patients with nonresectable hepatic colorectal metastases treated with 526 percutaneous cryosurgery procedures. (29) At 3 months post-treatment, CEA levels decreased to normal range in 197 (77.5%) of patients who had elevated markers before cryosurgery. Among 280 patients who had computed tomography (CT) follow-up, cryotreated lesions showed complete response in 41 patients (14.6%), partial response in 115 (41.1%), stable disease in 68 (24.3%), and progressive disease in 56 (20%). During median follow-up of 32 months (range: 7–61 months), the recurrence rate was 47.2%. The recurrence rate at the cryotreated site was 6.4% for all cases. During median follow-up of 36 months, the median survival of all patients was 29 months (3–62 months). OS was 78%, 62%, 41%, 34%, and 23% at 1, 2, 3, 4, and 5 years, respectively, after treatment. Patients with tumor size smaller than 3 cm, tumor in right lobe of liver, CEA levels less than 100 ng/dL and post-cryosurgery TACE had higher survival rates.

**Procedure-related complications**

Cryosurgery is not a benign procedure. Treatment-related deaths occur in approximately 2% of study populations and are most often caused by cryoshock, liver failure, hemorrhage, pneumonia/sepsis, and acute myocardial infarction. (30) Clinically significant nonfatal complication rates in the reviewed studies ranged from zero to 83% and were generally due to the same causes as treatment-related deaths. The likelihood of complications arising from cryosurgery may be predicted, in part, by the extent of the procedure, (31) but much of the treatment-related morbidity and mortality reflect the generally poor health status of patients with advanced hepatic disease.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received from 2 physician specialty societies and 3 academic medical centers while this policy was under review in 2008. While the various Physician Specialty Societies and Academic Medical Centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the Physician Specialty Societies or Academic Medical Centers, unless otherwise noted. All reviewers supported use of cryosurgical ablation for liver tumors and, in general, cited the studies reviewed above in the policy rationale. Some reviewers viewed this as one of several ablative techniques that could be used in these patients.

**Ongoing Clinical Trials**

A search of online site ClinicalTrials.gov in November 2012 identified no clinical trials on cryoablation for liver tumors.
Summary
Cryosurgical ablation involves the freezing of target tissues, most often by inserting into the tumor a probe through which coolant is circulated. Cryosurgical ablation can be performed as an open surgical technique or percutaneously or laparoscopically, typically with ultrasound (US) guidance.

Most patients in published series were candidates for cryosurgery because of unresectable disease, due either to large number of metastases, inaccessible location (e.g., near large vessels), or insufficient hepatic reserve to support resection. However, some of the studies included patients with resectable tumors, as well as patients with unresectable tumors. Furthermore some studies pooled results for mixed series of patients with liver metastases from various non-colorectal cancers (e.g., breast, sarcoma, ovarian, testicular, pancreatic, esophageal, head and neck) despite the differing characteristics and prognoses of these malignancies. Few controlled studies were found and those had methodological weaknesses including lack of randomization and noncomparable groups. Therefore, published outcomes of cryosurgery are inconclusive. The recent literature provides little new information on cryosurgical techniques, and interest appears to be concentrated on radiofrequency ablation. Thus, cryoablation for primary or metastatic liver tumors is investigational.

Practice Guidelines and Position Statements
The National Comprehensive Cancer Network (NCCN) indicates that ablative techniques may be used in the treatment of certain hepatic tumors. The guideline on hepatobiliary cancer includes cryoablation in a list of ablative techniques; however, the literature cited in the guideline reports on only radiofrequency ablation and ethanol ablation. (32) The NCCN neuroendocrine guidelines indicate cryotherapy is an option for unresectable liver metastases. (33) The guideline on treatment of metastatic hepatic lesions for colon cancer indicates that ablative techniques may be considered alone or in conjunction with resection. (34) However, cryoablation is not listed anywhere in the guideline. The potential role of chemotherapy in converting unresectable to resectable hepatic lesions is also discussed.

CODING
The following codes for treatment and procedures applicable to this policy 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. 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.

CPT/HCPCS
47371 Laparoscopy, surgical, ablation of 1 or more liver tumor(s); cryosurgical
47381 Ablation, open, 1 or more liver tumor(s); cryosurgical
76940 Ultrasound guidance for, and monitoring of, parenchymal tissue ablation

DIAGNOSIS
155.0 Malignant neoplasm of liver and intrahepatic bile ducts; Liver, primary
155.2 Malignant neoplasm of liver and intrahepatic bile ducts; Liver, not specified as primary or secondary
197.7  Secondary malignant neoplasm of respiratory and digestive systems; Liver, specified as secondary
209.72 Secondary neuroendocrine tumors; Secondary neuroendocrine tumor of liver

**ICD-10 DIAGNOSIS (Effective October 1, 2014)**
- C22.0  Liver cell carcinoma
- C22.2  Hepatoblastoma
- C22.3  Angiosarcoma of liver
- C22.4  Other sarcomas of liver
- C22.7  Other specified carcinomas of liver
- C22.8  Malignant neoplasm of liver, primary, unspecified as to type
- C22.9  Malignant neoplasm of liver, not specified as primary or secondary
- C78.7  Secondary malignant neoplasm of liver and intrahepatic bile duct
- C7B.02  Secondary carcinoid tumors of liver

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**REFERENCES**