



CIGNA MEDICAL COVERAGE POLICY

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**Subject Transarterial
Chemoembolization of Liver
Tumors**

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Coverage Policy

CIGNA covers transarterial chemoembolization as medically necessary for EITHER of the following indications:

- palliative treatment for individuals with neuroendocrine tumors with hepatic metastases, when symptomatic therapy has failed to control symptoms
- unresectable primary hepatocellular carcinoma (HCC)

CIGNA does not cover transarterial chemoembolization delivered with drug-eluting beads because it is considered experimental, investigational or unproven.

CIGNA does not cover transarterial chemoembolization for the treatment/management of liver metastases from other non-neuroendocrine primaries including, but not limited to, colorectal cancer, melanoma, and breast cancer because it is considered experimental, investigational or unproven.

General Background

Hepatocellular carcinoma (HCC) is the most common form of liver cancer in adults. However, most of the time when cancer is found in the liver it did not originate from the liver, but spread to the liver from somewhere else.

This is secondary liver cancer or metastatic liver cancer. Neuroendocrine tumors usually originate in hormone-producing cells that line the small intestine or other cells of the digestive tract. When these tumors (e.g., carcinoid, islet cell/pancreatic cell) have metastasized to the liver, the liver is unable to process the substances being released by the tumors before they begin circulating throughout the body. Depending on which substances or hormones are being released, the person can have the various symptoms of carcinoid syndrome, insulinoma syndrome, Zollinger Ellison syndrome, or VIPoma syndrome. The carcinoid tumor is the most common type. Carcinoid syndrome is characterized by debilitating flushing, wheezing and diarrhea. Unfortunately, the majority of patients with neuroendocrine tumors have hepatic metastases at the time of diagnosis. Because of their slow growth and general hypervascularity, this type of metastasis is well-suited for the use of chemoembolization treatment to decrease tumor bulk and palliate symptoms.

Treatment options for primary or secondary liver cancer may include surgery, ablation, embolization, targeted therapy, radiation therapy, and chemotherapy. At the time of diagnosis, most hepatic tumors, whether primary or from metastases, are usually unresectable, and chemotherapy is generally provided only as a palliative measure. Prognosis is usually poor and depends on the degree of local tumor replacement and the extent of liver function impairment. A few patients may be candidates for liver transplantation, but the limited availability of livers for transplantation restricts the use of this approach.

Embolization / Transarterial Chemoembolization

Embolization therapy may include chemoembolization, bland embolization, or radioembolization and were developed as alternatives to conventional therapies such as systemic chemotherapy for the treatment of liver cancer. Bland embolization is the injection of an embolic agent only. Radioembolization is the injection of Yttrium-90 microspheres.

Chemoembolization (i.e., transarterial chemoembolization, transcatheter arterial chemoembolization, TACE) involves the injection of a chemotherapy agent (e.g., doxorubicin, cisplatin) combined with an emulsifying agent into the hepatic artery, immediately followed by injection of an embolic material (e.g., gelatin sponge, polyvinyl alcohol, polyacrylamide). A more recent delivery system for chemoembolization includes embolic beads pre-loaded with a chemotherapeutic agent or “drug-eluting beads” (DEB). Chemoembolization delivers a very high concentration of chemotherapy directly into the tumor, without exposing the entire body to the effects of those drugs. Secondly, because the hepatic artery supplies nearly 100% of blood supply to malignant tumors of the liver, embolization renders the tumor tissue ischemic. The procedure varies widely between centers, with different drugs (doxorubicin, mitomycin, cisplatin, and mixtures), embolic agents, doses, and schedules used. Response rates vary and evidence of a survival benefit, particularly at three years, is low.

Chemoembolization is not recommended in cases where severe liver or kidney dysfunction, abnormal blood clotting or a blockage of the bile ducts. Depending on the number and type of tumors, chemoembolization may be used as the sole treatment or may be combined with other treatment options such as surgery, chemotherapy, and radiation therapy or radiofrequency ablation. Side effects of chemoembolization such as abdominal pain, nausea, vomiting, and fever (i.e., post-embolization syndrome) are common. General patient selection criteria for chemoembolization include unresectable or inoperable HCC, and unresectable carcinoid and islet cell tumor (pancreatic cell tumor) metastases to the liver. Procedure-related complications are rare but may be life threatening and include liver failure, hepatic abscess, cholecystitis, renal failure, and carcinoid crisis.

Food and Drug Administration (FDA)

Approvals for chemotherapeutic and embolic agents used in chemoembolization are not specific for use in chemoembolization. Chemotherapeutic agents may be approved for numerous oncologic indications. Several embolic beads are FDA-approved for “embolization of hypervascular tumors and arteriovenous malformations” (e.g., LC Bead™ and Bead Block™ [Biocompatibles UK Ltd., Farnham, Surrey, UK]; EmboSphere, EmboGold, and QuadraSphere [BioSphere Medical, Inc., Rockland, MA, USA]; Contour SE Microspheres [Boston Scientific Corporation, Natick, MA, USA]). Drug-eluting chemoembolic beads (e.g., DC Bead™, PRECISION Bead, PARAGON Bead [Biocompatibles UK Ltd, Farnham, Surrey, UK]) are not FDA-approved but their ingredients may be FDA-approved on a stand-alone basis.

Literature Review

Neuroendocrine Tumors With Hepatic Metastases

Neuroendocrine tumors (NETs) with hepatic metastasis are uncommon in the general population, yet are a common indication for chemoembolization. Although the existing literature consists mainly of small retrospective

reports, studies support the use of chemoembolization as palliative therapy (Dong, et al., 2010; Liapi, et al., 2008; Ho, et al., 2007; Ruutinen, et al., 2007; Gupta, et al., 2005). Dong et al. (2010) retrospectively analyzed 123 patients with unresectable NETs with hepatic metastases. An average of seven cycles of chemoembolization was administered. There were no technical delivery failures and no >grade 2 treatment toxicities. Mean survival for the entire cohort was 5.47 years. Overall 3-, 5- and 10-year survivals were 59, 36, and 20%. The authors noted baseline low serum albumin levels, high prothrombin time and old age are variables identifying patients at risk of poorer survival. The authors stated overall patient survival in this cohort was comparable to previous observations.

Hepatocellular Carcinoma (HCC)

Studies in the published, peer-reviewed scientific literature demonstrate a significant survival benefit with the use of chemoembolization compared with supportive care only or when added as an additional therapy (Biselli, et al., 2005; Yuen, et al., 2003; Lo, et al., 2002; Llovet, et al., 2002; Koda et al., 2001). A survival benefit of chemoembolization over symptomatic treatment or systematic chemotherapy was demonstrated in a meta-analysis of randomized controlled trials; however, overall survival at 3 years remained low (<30%) for intermediate HCC patients (Llovet, et al., 2003).

Chemoembolization has become a standard treatment in order for a liver transplantation candidate to receive higher priority on the waiting list. The United Network for Organ Sharing (UNOS) policy on liver transplantation candidates with HCC notes that under certain circumstances individuals with unresectable tumors who have received chemoembolization may qualify for additional MELD score points, allowing them higher priority on the liver transplant waiting list (UNOS, 2010). Studies in the peer-reviewed scientific literature support the use of chemoembolization for down-staging patients with advanced HCC to allow eligibility for liver transplant, although studies remain mixed regarding what if any long-term survival advantage is gained (Lewandowski, et al., 2009; Chapman, et al 2008; Alba, et al., 2008; Heckman, et al., 2008; Decaens, et al., 2005; Graziadei, et al., 2003).

HCC/Drug-eluting Beads (DEB): Evidence in the peer-reviewed published scientific literature evaluating chemoembolization delivered with embolic beads pre-loaded with a chemotherapeutic agent consists of small retrospective and prospective studies with mixed results; therefore, DEB chemoembolization delivery remains unproven. Preliminary evidence of DEB delivery in patients with unresectable HCC with Child-Pugh class A or B looks promising; however, large prospective, long-term studies are needed.

Dhanasekaran et al. (2010) retrospectively reported on 71 consecutive patients who received chemoembolization with DEB or conventional chemoembolization as sole therapy. A total of 45 (63.4%) received therapy with DEB (group A) and 26 (36.6%) underwent conventional chemoembolization (group B). The two groups were similar with respect to age, gender, race, Child–Pugh class, Okuda class, mean model end-stage liver disease (MELD) score, mean tumor size, and tumor burden. Median survival times from the diagnosis of HCC in those treated with DEB and conventional chemoembolization were 610 and 284 days ($p=0.03$). Median survival from the time of first transcatheter therapy in those treated with DEB and conventional chemoembolization were 403 and 114 days ($p=0.01$). In Child–Pugh classes A and B, survival from the first transcatheter therapy in patients treated with DEB and conventional chemoembolization were 641 and 323 days ($p=0.002$). There were no significant differences in median survival of patients in Child–Pugh class C when treated with either therapy ($p=0.33$). Grade 5 clinical toxicity- and procedure-related death (30 days) due to liver failure was experienced by 6.6% (3/45) of patients treated with DEB and 7.8% (2/26) of the patients treated with conventional chemoembolization. The patients who experienced liver failure after treatment with DEB all belonged to Child–Pugh class C. The authors note a limitation of the study is its retrospective design, which allows for the possibility for selection bias.

In a prospective randomized trial, Malagari et al. (2010) compared DEB chemoembolization (group A; $n=41$) with bland embolization (group B; $n=43$). Patients were randomized for tumor diameter. It should be noted that enrolled were patients unsuitable for curative treatments, with potentially resectable lesions but at high risk for surgery. All patients were Child A or B. Follow-up was 12 months. Stable disease at 12 months remained statistically higher in the DEB chemoembolization group ($p=0.006$). Progression of disease at 12 months developed in 48.6% in the DEB chemoembolization group and 78.4% in the bland group. The correlation showed that patients treated with DEB chemoembolization were less likely to present progression of disease compared to patients treated with bland embolization ($p=0.014$). However, there is no difference in survival within one year between the two groups. A limitation of this study is the short follow-up period.

Scartozzi et al. (2010) retrospectively evaluated 150 consecutive patients, 87 traditional chemoembolization and 63 DEB chemoembolization. All groups of patients showed similar clinical characteristics according to all staging systems used. In the group of patients treated with chemoembolization only, 50 (61%) underwent traditional chemoembolization, while 32 (39%) received DEB chemoembolization with microspheres. Median overall survival was 46 months for patients undergoing traditional chemoembolization and 19 months for those who were treated with DEB chemoembolization ($p < 0.0001$). Time to progression was 30 months versus 16 months for patients receiving either traditional chemoembolization or DEB chemoembolization respectively ($p = 0.003$). These results were confirmed also among the subgroup of patients who received exclusive traditional chemoembolization or DEB chemoembolization as the only treatment approach. The toxicity profiles were not statistically different between the groups of patients treated with traditional chemoembolization or DEB chemoembolization. A limitation of the study is its retrospective design.

Lammer et al. (2009) conducted a prospective, randomized trial, comparing conventional chemoembolization delivery ($n = 108$) with chemoembolization delivery with embolic beads pre-loaded with doxorubicin, DEB chemoembolization ($n = 93$). Doxorubicin was used in both groups. The primary endpoint was tumor response at 6 months. Results showed no statistically significant difference between treatments for 'treatment-related severe adverse events within 30 days of a procedure'. The DEB chemoembolization group showed higher rates of complete response, objective response, and disease control compared with the conventional chemoembolization group (27% vs. 22%, 52% vs. 44%, and 63% vs. 52%, respectively). These differences were not statistically significant. With regard to the systemic side effects of doxorubicin (alopecia, skin discoloration, mucositis, and marrow suppression), post hoc analyses established a significant benefit ($p = 0.012$) in favor of DC Bead over conventional chemoembolization. DC Bead was associated with improved tolerability, with a significant reduction in serious liver toxicity ($p < 0.001$) and a significantly lower rate of doxorubicin-related side effects ($p = 0.0001$). The authors noted that a limitation of this study was that the number of patients required to show statistically significant superiority was underestimated due to the higher response rate of conventional chemoembolization (44%) compared with the original assumption (35%); therefore statistical superiority in objective response rates of DEB chemoembolization compared to conventional chemoembolization could not be demonstrated.

Several small prospective, observational studies support the use of DEB chemoembolization. Reyes et al. (2009) evaluated 20 patients and demonstrated overall survival rates at one and two years were 65% and 55%, respectively; with a median overall survival was 26 months. Poon et al. (2007) ($n = 30$) reported a partial response rate and the complete response rate of 50% and 0%, respectively. The first human trial was a prospective observational trial conducted by Varela et al. (2007). A total of 27 patients underwent DEB chemoembolization and 13 of those underwent repeat blood analysis. The primary endpoints were safety and efficacy. At six months, the rate of objective responses was 66.6%; 26% presented a complete response (disappearance of the enhancement of all the measurable lesions) and 41% a partial response (>50% decrease of enhanced lesions from baseline). Varela et al. also reported the use of DEB chemoembolization sharply decreased the passage of drug to the systemic circulation. Up to 150 mg of doxorubicin was injected, exceeding the common schedule, and the peak concentration and the area under the curve (AUC) were significantly lower than those of conventional chemoembolization. 1- and 2-year survival was 92.5% and 88.9%, respectively. The authors reported DEB chemoembolization reduced the drug-related side effects, maintaining the same therapeutic efficacy as reported historically with conventional chemoembolization. Limitations of these studies include small sample size and a lack of direct comparison with conventional chemoembolization delivery.

HCC/Comparison With Radioembolization: Lewandowski et al. (2009) retrospectively evaluated the results from unresectable HCC patients who had undergone either chemoembolization ($n = 43$) or transarterial radioembolization with Yttrium-90 microspheres (Y90, $n = 43$). The median follow-up was 51.9 months for chemoembolization and 34.1 months for Y90. Both chemoembolization and Y90 resulted in a statistically significant reduction in tumor size from baseline. Y90 resulted in a significantly increased percentage of patients who were successfully downstaged (58%) compared with chemoembolization (31%). The trend favoring Y90 for downstaging was maintained for all lesion sizes. Event-free survival was significantly greater for Y90 than chemoembolization (17.7 vs. 7.1 months). Kooby et al. (2009) noted the outcomes from a retrospective chart review of unresectable HCC patients treated with either chemoembolization ($n = 44$) or radioembolization ($n = 27$). No significant differences (i.e., toxicity, efficacy) were seen between the two types of embolization methods. Survival at one year from therapy was 16% for patients treated with radioembolization and 20% for patients treated with chemoembolization. Limitations of these studies include small sample size and lack of direct

comparison. Future randomized controlled trials will aid in determining if there is a survival advantage to one type of embolization therapy over another.

Hepatic Metastases from Non-neuroendocrine Primary Sites

There is insufficient evidence in the published, peer-reviewed scientific literature demonstrating the effectiveness of chemoembolization for the treatment of liver metastases from any other primary site, including, but not limited to, colorectal cancer, ocular melanoma, or breast cancer. There is a paucity of studies and evidence consists primarily of retrospective studies with small sample sizes. Additional studies can help clarify and validate the role of chemoembolization for hepatic metastases from non-neuroendocrine primary sites.

Colorectal: Albert et al. (2011) retrospectively evaluated 121 patients with metastatic colorectal carcinoma. Indication for treatment was most commonly failure of systemic chemotherapy to control unresectable liver-dominant disease. Median survival was 33 months from diagnosis of the primary colon cancer, 27 months from development of liver metastases, and 9 months from chemoembolization. The authors commented these results suggested “a possible improvement over reported survival times for systemic therapies alone.” From primary diagnosis, including patients with synchronous metastases, 1-, 2-, and 5-year survival was 94%, 74%, and 13%, respectively. From time of diagnosis of liver metastases, survival at 1, 2, and 5 years was 85%, 55%, and 6%, respectively. Survival was significantly better when chemoembolization was performed after first- or second-line systemic therapy (11-12 months) than after third- to fifth-line therapies (six months) ($p=0.03$). A limitation of this study was its retrospective design.

Vogl et al. (2009) prospectively evaluated 463 patients with unresectable liver metastases of colorectal cancer that had previously not responded to systemic chemotherapy. The indication for chemoembolization of liver metastases in patients with colorectal cancer was primarily palliative. Results demonstrated a median survival time from the start of chemoembolization of 14 months. Hong et al. (2009) conducted a retrospective records review of patients who underwent either ($n=21$) or radioembolization ($n=15$) for palliation. Similar results were seen with a median survival of 7.7 months for the chemoembolization group and 6.9 months for the radioembolization group. Tellez et al. (1998) retrospectively reported on 30 patients with previously treated metastatic colorectal cancer to the liver who underwent chemoembolization. Median survival for all 30 patients was 8.6 months following initiation of chemo-embolization. Sanz-Altamira et al. (1997) reported a median survival from date of first chemoembolization of ten months in a retrospective review of 40 patients.

Colorectal/Drug-eluting Beads: Martin et al. (2010) conducted a prospective, observational trial including 55 patients with liver dominant metastatic colon cancer. After failing other therapies, these patients underwent DEB chemoembolization with irinotecan DEBs. Median follow-up for this patient cohort was 18 months. In an evaluation of 99 separate treatments, adverse events occurred in 28% ($n=28$ treatments), with a majority of adverse events being nausea, vomiting, and liver dysfunction. There were no deaths at 30 days post-procedure. The 12-month response rates were 40%, with 15% ($n=8$) showing complete response and 25% ($n = 14$) showing partial response. Overall survival in these patients was 19 months, with progression-free survival of 11 months.

Melanoma: Gupta et al. (2009) retrospectively reported on 105 patients with uveal (ocular) melanoma metastatic to the liver who underwent chemoembolization, noting a median overall survival and progression-free survival of 6.7 and 3.8 months, respectively. Kamat et al. (2008) reported on the use of embolization and chemoembolization in 48 patients with metastatic neuroendocrine tumors, melanomas, or gastrointestinal stromal tumors (GISTs) with >75% liver involvement by metastatic disease. Median overall survival and progression-free survival were 9.3 and 4.9 months, respectively. Patients with neuroendocrine tumors ($n=38$) had a significantly longer median overall survival (17.9 months) than patients with melanomas ($n=17$ [11 ocular, 6 cutaneous], 2.4 months) and GISTs ($n=5$, 2.3 months). Limitations of this study include the lack of separate embolization and chemoembolization data, and its retrospective design.

Schuster et al (2010) retrospectively reported on 25 patients who underwent chemoembolization after treatment failure of systemic therapy. Eleven patients had additional extra-hepatic metastatic sites (skin, lung, bone, and kidney). Results included no grade IV toxicity or catheter-associated complications. The median progression-free survival (PFS) was 3 months. Median overall survival (OS) was 5 months. The 1-year survival rate was 15%. The benefit of chemoembolization in pre-treated patients was more obvious in patients with lactate dehydrogenase (LDH) below two times the upper limit of normal (ULN). Survival was significantly longer in patients with pretreatment LDH \leq two times ULN versus $\geq 2 \times$ ULN (11 versus 5 months; $p=0.012$). The authors

commented that the low toxicity and high rate of responses and stabilizations, especially in patients with LDH below 2×ULN, are the basis for future randomized trials comparing chemoembolization with intravenous chemotherapy in first-line treatment of patients with metastatic uveal melanoma, in whom the liver is the predominant site of metastases.

Sharma et al. (2008) conducted a retrospective review to assess the outcomes of hepatic arterial chemoembolization for metastasis of stage 4 melanoma. Twenty patients, (17 with ocular melanoma and three with cutaneous melanoma) with liver metastasis of ocular or cutaneous melanoma were treated with chemoembolization and included in the study. Outcome measures included overall survival and progression free survival. Mean and median overall survival was 334 ± 71 and 271 days, respectively. Thirteen of the 20 patients had progression of the disease. Mean and median progression free survival times for these patients was 231 ± 42 and 185 days, respectively.

Other: There is a paucity of studies in the peer-reviewed scientific literature addressing chemoembolization for hepatic metastases from other non-neuroendocrine primary sites, including but not limited to breast cancer.

Professional Societies/Organizations

National Comprehensive Cancer Network® (NCCN®): The NCCN Practice Guideline™ for Hepatobiliary Cancers (v.2.2010) supports the use of transcatheter arterial chemoembolization, noting its survival benefit versus supportive care. The NCCN notes general patient selection criteria for arterial embolization therapy (chemoembolization, bland embolization, radioembolization) includes unresectable/inoperable HCC disease with tumors not amenable to ablation therapy only, and the absence of extrahepatic disease. Recommend tumor lesions > 5 centimeters (cm) can be treated with embolic approaches, tumors 3-5 cm can be considered for combination ablation and embolization. Chemoembolization is not recommend and/or contraindicated in main portal vein thrombosis, liver function classified, according to the Child Pugh Classification system, 'Child-Pugh C', and total bilirubin level > 3 mg/mL as they are significant predictors of poor prognosis in patients treated with chemoembolization. The NCCN cited Lammer et al. (2009), stating that comparable effectiveness was shown between doxorubicin-eluting embolic beads and conventional chemoembolization with doxorubicin although the toxicity was significantly decreased with the DEB approach.

The NCCN Practice Guideline™ for Neuroendocrine Tumors (v.2.2010) recommends chemoembolization among other treatments for unresectable liver metastases from carcinoid or islet cell tumors (pancreatic cell tumors).

The NCCN Practice Guideline™ for Occult Primary (v.2.2011) recommends chemoembolization among other locoregional therapeutic options for unresectable localized liver lesions (either localized adenocarcinoma or carcinoma not otherwise specified).

American College of Radiology (ACR): The ACR Appropriateness Criteria® for Hepatic Malignancy (2007) supports chemoembolization for neuroendocrine tumors with hepatic metastases and HCC. Regarding colorectal cancer metastases to the liver, the ACR notes that arterial therapies such as chemoembolization have been studied with limited results (Sanz-Altamira PM, 1997; Tellez C, 1998). The ACR Appropriateness Criteria® for Rectal Cancer - Metastatic Disease at Presentation (2010), states that chemoembolization and other local therapies can be considered for palliation of symptoms.

Society of Interventional Radiology (SIR): The SIR Position Statement on Chemoembolization of Hepatic Malignancies states that chemoembolization is a safe, proven, and effective technique for the treatment of a number of malignancies, including HCC, neuroendocrine tumors, ocular melanoma, cholangiocarcinoma, and sarcoma. It has a palliative role for patients with colon carcinoma. It may be useful with patients who have hepatic-dominant metastatic disease from other primary malignancies. The benefit of chemoembolization for these individuals should be evaluated on a case-by-case basis (Brown, et al 2006).

Summary

Evidence in the published, peer-reviewed scientific literature demonstrates that transarterial chemoembolization is effective as a palliative treatment of neuroendocrine tumors (e.g., carcinoid tumors, pancreatic islet cell tumors) with hepatic metastases, when symptomatic therapy has failed. Additionally, chemoembolization provides a significant survival benefit for the treatment of unresectable primary hepatocellular carcinoma (HCC) when compared with supportive care only or when added as an additional therapy. Although there is little peer-

reviewed, scientific literature regarding the effects of chemoembolization used in the preoperative setting, it has become a standard treatment for those patients awaiting a liver transplant.

The evidence in the published, peer-reviewed literature does not support chemoembolization delivered with drug-eluting beads or the use chemoembolization in the treatment of liver metastases from non-neuroendocrine primaries, including, but not limited to, colorectal cancer, melanoma, and breast cancer.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary when used to report transarterial chemoembolization for liver tumors:

CPT ^{®*} Codes	Description
37204	Transcatheter occlusion or embolization (e.g., for tumor destruction, to achieve hemostasis, to occlude a vascular malformation), percutaneous, any method, non-central nervous system, non-head or neck

ICD-9-CM Diagnosis Codes	Description
155.0	Malignant neoplasm of liver, primary
157.4	Malignant neoplasm of islets of Langerhans
197.7	Secondary malignant neoplasm of liver
209.00-209.36	Neuroendocrine tumors
230.8	Carcinoma in situ of liver and biliary system
259.2	Carcinoid syndrome

Experimental/Investigational/Unproven:

ICD-9-CM Diagnosis Codes	Description
153.0-153.9	Malignant neoplasm of colon
172.0-172.9	Malignant melanoma of skin
174.0-174.9	Malignant neoplasm of female breast
175.0-175.9	Malignant neoplasm of male breast
190.0	Malignant neoplasm of eyeball except conjunctiva, cornea, retina, and choroid
190.6	Malignant neoplasm of choroid
	All other codes

***Current Procedural Terminology (CPT[®]) © 2010 American Medical Association: Chicago, IL.**

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	2/15/2008	0282	Transcatheter Arterial Chemoembolization (TACE) of Liver Tumors

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