



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Percutaneous Ethanol Injection (PEI) for Liver Cancer

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- Transarterial Chemoembolization of Liver Tumors

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Coverage Policy

CIGNA covers percutaneous ethanol injection (PEI) as medically necessary for the treatment of unresectable hepatocellular liver cancer when radiofrequency ablation (RFA) is either contraindicated or not available.

General Background

Liver cancer, also known as hepatocellular carcinoma (HCC), is the fifth most common cancer globally. Liver cancer incidence has been linked to the prevalence of chronic hepatitis B virus, and can also develop as a result of the hepatitis C virus, cirrhosis, alcohol abuse, or aflatoxin B1 exposure (National Cancer Institute [NCI], 2009). In patients with underlying liver disease, the biological marker (alpha-fetoprotein [AFP]) and/or alkaline phosphatase, is a prognostic indicator, as patients who are AFP-negative have a significantly longer median survival time than patients who are AFP-positive. Other prognostic indicators include: performance status, liver function, the presence or absence of cirrhosis, and the severity of any cirrhosis. Staging systems for liver cancer include the Child-Pugh Classification, The MELD (Model for End Stage Liver Disease), used for patients age 12 and older, and the PELD (Pediatric End Stage Liver Disease) Model which is used for pediatric patients under the age of 12.

The natural course of the disease and the median survival of patients are dependent on the stage of the disease at the time of diagnosis, with median survival ranging from 1–69 months. The staging system is clinically most important for the appropriate choice of the therapeutic strategy for individual patients. Once diagnosed, curative treatments for liver cancer include surgical resection or liver transplantation; these treatments are only appropriate for a small group of patients. Surgical resection is recommended only in the setting of preserved liver function. Study results suggest that selected patients for selected patients with early HCC, surgical resection is associated with a five-year overall survival rate of approximately 70%. Candidates for transplantation must meet the criteria set forth by the United Network for Organ Sharing (UNOS) (National Comprehensive Cancer Network Guidelines™ [NCCN Guidelines™], 2010). When hepatic resection or transplant is not a treatment option, alternative treatment interventions include radiofrequency ablation (RFA), transarterial embolization (TAE), transarterial chemoembolization (TACE), cryoablation and percutaneous ethanol injection (PEI).

Percutaneous Ethanol Injection (PEI)

PEI involves the injecting of pure alcohol (i.e., ethanol) through the skin via ultrasonic or computerized tomographic (CT) guidance into the tumor bed. The alcohol induces tumor destruction by drawing water out of the tumor cells (dehydrating them) and denaturing the structure of the cellular proteins. This procedure can be done under local anesthetic and on an outpatient basis. PEI has been used as an alternative to liver resection when an individual has a single localized mass less than 5 cm in diameter or several small tumors measuring 3–4 cm in diameter. Patients are typically not candidates if they have evidence of extrahepatic metastases. Tumor response rates to PEI have been reported to be 90–100% in HCCs smaller than 2 cm in diameter, 70% in HCCs of 3 cm in diameter, and 50% in HCCs of 5 cm in diameter (Blum, 2005). The most common side effect of PEI therapy is leakage of alcohol onto the surface of the liver and into the abdominal cavity, causing pain and fever. PEI is a simple technique with a low rate of major complications.

Literature Review

Several meta-analyses have compared the safety and effectiveness of PEI to that of RFA for the treatment of HCC. An analysis of randomized clinical trials and quasi-randomized studies (n=8 trials; 1035 patients) by Germani et al. (2010) compared local ablation therapies. Study results from five comparative trials of RFA and PEI indicated that RFA was superior for outcomes of survival (p=0.001), complete necrosis of tumor and local recurrence. For tumors ≤2 cm, outcome benefits comparing RFA and PEI were found to be similar.

Bouza et al. (2009) analyzed data from six randomized controlled trials (RCTs) involving patients with unresectable HCC treated by RFA (n=396) and PEI (n=391). The survival rate showed a significant benefit for RFA over PEI at one, two, three and four years (i.e., 62%, 51% respectively). A higher rate of total complications after treatment with RFA (19.2%) was reported than with PEI (10.5%).

A meta-analysis of five RCTs (n=701) by Orlando et al. (2009) found overall survival to be significantly higher in HCC patients with cirrhosis after treatment with RFA versus PEI. It was noted that PEI should be reserved for cases in which RFA is not technically able to be performed, such as with pericholecystic and subcapsular lesions or lesions near the hilum (Orlando, et al., 2009).

While study results suggest that RFA for the treatment of unresectable HCC demonstrates improved survival rates compared to PEI, there is evidence in the published, peer-reviewed scientific literature in to support the safety and effectiveness of PEI for small HCC. A three-armed RCT (n=157) by Lin et al. (2004) found that PEI delivered conventionally (single injection) or at a higher dose (multiple sites, simultaneous injections) was equivalent to RFA in the treatment of patients with HCC lesions measuring 3–5 cm in diameter. Systematic reviews (Cho, et al., 2009; Lopez, et al., 2006; Galandi and Antes, 2004) and uncontrolled studies (Ebara, et al., 2005; Sung, et al., 2006) have reported overall survival rates ranging from 70%–85% at three years and 40%–60% at five years. Early randomized and uncontrolled studies have reported similar survival rates among PEI and resection patients (Huang, et al., 2005; Gournay, et al., 2002). However, both Wakai et al. (2006) and Cho et al. (2007) reported improved one-, three- and five-year overall survival rates for patients who had hepatectomy (e.g., 94.8%, 76.5% and 65.6%, respectively) versus PEI (e.g., 95.7%, 73.5% and 49.3% respectively).

Professional Societies/Organizations

According to the NCCN guidelines for Hepatobiliary Cancers, all HCC patients should be evaluated for potential curative therapies (i.e., resection, transplantation). Locoregional therapy including ablation (i.e., PEI, RFA,

cryoablation, microwave ablation) and transarterial embolization may be appropriate for patients who are not candidates for curative treatments. Tumors that are ≤ 3 cm are optimally treated with ablation, while those between 3–5 cm may be treated with a combination of embolization and ablation as long as tumor location is favorable (NCCN, 2011).

The National Cancer Institute (NCI) states that patients whose tumors are localized but unresectable due to location in the liver, concomitant medical considerations (e.g., cirrhosis), or even limited bilateral tumors, may be candidates for PEI, RFA, chemoembolization, or cryosurgery for cancers smaller than 5 cm. Treatment options for patients with recurrent HCC may include the use of transarterial oily chemoembolization (TOCE), PEI therapy, chemotherapy, or liver transplantation if re-resection is not an option (NCI, 2010).

The American Association for the Study of Liver Diseases (AASLD) recommends local ablation is safe and effective therapy for patients who cannot undergo resection, or as a bridge to transplantation. The AASLD further states that alcohol injection and radiofrequency are equally effective for tumors <2 cm. However, the necrotic effect of radiofrequency is more predictable in all tumor sizes and in addition, its efficacy is clearly superior to that of alcohol injection in larger tumors (Bruix, et al 2005).

The British Society of Gastroenterology (BSG) care guidelines for the diagnosis and treatment of HCC state that nonsurgical therapy should only be used on HCC patients who are not candidates for surgery. According to the guidelines, PEI has been shown to produce necrosis of small HCCs. The BSG notes that PEI is best suited to peripheral lesions, less than 3 cm in diameter. Although PEI has not been subjected to randomized controlled trials, several large studies have shown complete response rates of 75% in lesions ≤ 3 cm, with five-year survival rates of 35–75% (Ryder, 2003).

Summary

Evidence in the published, peer-reviewed scientific literature in the form of uncontrolled studies and limited RCTs indicates that percutaneous ethanol injection (PEI) is a safe and effective alternative for the treatment of hepatocellular carcinoma (HCC) that is unresectable, small in lesion size and localized. This procedure is one of several minimally invasive standard treatment options available to patients with unresectable, localized primary liver cancer.

Coding/Billing Information

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

Covered when medically necessary and used to report surgical ablation of hepatocellular liver cancer by percutaneous ethanol injection.

CPT ^{®*} Codes	Description
47399	Unlisted procedure, liver

ICD-9-CM Diagnosis Codes	Description
155.0	Malignant neoplasm of the liver, primary, hepatocellular

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

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	5/15/2008	0364	Percutaneous Ethanol Injection (PEI) for Liver Cancer

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