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Intrahepatic Cholangiocarcinoma

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Cholangiocarcinoma is a rare malignancy that arises from epithelial cells of the biliary system. Its desmoplastic histology and the heterogeneity of its presentation have contributed to its poor prognosis, with limited therapeutic options previously available. However, recent advances using locoregional therapy may expand the treatment arsenal used to manage this resistant malignancy. Although surgical resection has previously been reserved for relatively few patients because of inadequate hepatic reserve, portal vein embolization can induce contralateral hepatic lobe hypertrophy to increase the number of patients eligible for resection. For unresectable cases, both transarterial chemoembolization and yttrium-90 radioembolization have shown effectiveness in controlling tumor growth and prolonging survival.
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Background

It is believed that the incidence of cholangiocarcinoma is increasing throughout the world, especially in the United States, owing to the prevalence of chronic hepatitis C.[1] However, these data may be confounded by the fact that detection is more prevalent in the current era of widespread cross-sectional imaging, especially in light of recent changes in liver tumor classification systems.[2] Multiple predisposing factors for cholangiocarcinoma have been identified, such as chronic biliary inflammation (ie, primary sclerosing cholangitis, biliary stones, choledochol cysts, and parasitic infections), heavy alcohol use, viral hepatitis, and nonalcoholic fatty liver disease. However, the correlation of these predisposing factors to cholangiocarcinoma is far weaker compared with etiologies for hepatocellular carcinoma. Most cases of cholangiocarcinoma are found incidentally without any known predisposing factors. In these cases, malignancy is detected on imaging that is often performed for other reasons.

Although several different classifications for cholangiocarcinoma have been proposed, the most commonly accepted one is to divide this malignancy into cases of intrahepatic cholangiocarcinoma (ICC) and cases of ductal cholangiocarcinoma. The ductal type, which includes hilar cholangiocarcinoma, is far more common, representing 90% of all cholangiocarcinoma cases.[3] Ductal cholangiocarcinoma often has a different clinical presentation compared with ICC, consisting of biliary obstruction. ICC, which constitutes the remaining 10% of cholangiocarcinoma cases, involves the formation of a mass within the liver parenchyma, which likely arises initially from small intrahepatic bile ducts. There is often overlap in appearance with hepatocellular carcinoma, or the masses may grow in a linear fashion along bile ducts. The management of the 2 cholangiocarcinoma subtypes is divergent, with ablation and artery-directed therapy offered only for ICC. The remainder of this discussion focuses on the management of ICC.

Diagnosis

Imaging of patients with ICC consists of multiphase magnetic resonance (MR) imaging or computed tomography (CT) imaging with intravenous contrast. Unlike hepatocellular carcinoma, which typically demonstrates washout of contrast on delayed imaging, there is progressive enhancement of tumor over time in cases of ICC.[4] This is possibly due to the tumor's fibrotic nature, which gradually retains contrast. Segmental biliary dilatation is often associated with the mass, which may help differentiate it from liver metastases. Other imaging characteristics include a thin rim of contrast enhancement on

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arterial and venous phase contrast-enhanced CT, and T1 hypointensity and T2 hyperintensity on MR imaging. However, there is often an overlapping appearance in images for hepatocellular carcinoma and ICC, so biopsy may be required for definitive diagnosis. The similarity in imaging appearance between the 2 primary hepatic malignancies may actually mask the true incidence of ICC.

Biopsy in cases of ICC demonstrates features of an adenocarcinoma phenotype. CA19-9 or CEA levels may be elevated, but these factors are not highly sensitive or specific for cholangiocarcinoma.[5,6] Finally, some patients may present with a mixed-type tumor consisting of both cholangiocarcinoma and hepatocellular carcinoma. This could have implications for prognosis and may help determine the appropriate treatment. Although specific imaging features may suggest a mixed-type tumor (ie, irregular shape and biliary dilatation),[7] these characteristics are not definitive for diagnosis; a biopsy is needed for confirmation.

Prognosis

Because there is often no significant predisposing etiology (such as in hepatocellular carcinoma), diagnosis of ICC often occurs when the disease is at an advanced stage and patients are symptomatic.[8,9] At this presentation, prognosis is usually poor with relatively few treatment options. The overall 3- and 5-year survival rates for ICC are 31% and 18%, respectively.[10] Prognostic factors include the number of tumors, presence of vascular invasion, and extent of lymph node metastases.[10]

Surgery

Only a minority of patients with ICC are candidates for surgical resection. Even when negative surgical margins (R0) are achieved, the 5-year overall survival rate is only 30%.[11] Despite these modest results with respect to survival, surgical resection is still recommended for patients who are candidates. Candidacy for surgical resection is often institution dependent and largely depends on the functional reserve of the potential future liver remnant. Vascular invasion and extrahepatic disease are considered relative contraindications to surgical resection. Positive tumor margins (R1), multifocal tumors, lymph node metastases, advanced liver disease, vascular invasion, and portal hypertension are associated with limited outcomes after resection.[3,12,13] If positive margins (R1) at the time of surgical resection are found, then clinicians should consider further therapy (ie, re-resection and adjuvant chemotherapy). Local tumor recurrence rates vary but have been reported to be as high as 93% in patients with advanced disease who undergo surgical resection.[12]

Portal Vein Embolization

In general, a future liver remnant of 20%-25% is recommended after surgery, although higher volumes are needed for patients with compromised liver function. Percutaneous portal vein embolization can induce contralateral lobe hypertrophy and can therefore reduce the risks of postoperative liver insufficiency and increase the number of patients who may be eligible for surgical resection. Portal vein embolization has been used for both primary liver cancer and metastatic liver disease. Although the data on portal vein embolization for ICC are limited, an acceptable safety margin and low rates of postresection complications have been reported.[14] One of the major disadvantages of portal vein embolization is the time required to induce hypertrophy, which can be more than 1 month. This delay before surgery may allow for interval tumor growth, which could theoretically worsen prognosis or exclude patients from surgical resection.

Portal vein embolization is typically performed as an outpatient procedure, with the patient under moderate sedation. In most cases, a right portal vein embolization is needed (Fig. 1). Left portal vein embolization is rarely performed because a left trisegmentectomy typically results in a future liver remnant of greater than 30%. An ipsilateral approach is preferred, as one traverses the same hepatic parenchyma that would eventually be resected. Therefore, any vascular or tissue complications that occur from accessing the portal vein would likely not be permanent. Portal vein access is obtained under US guidance using the Seldinger technique, with eventual placement of a vascular sheath. After access into the portal vein is obtained, a variety of embolic agents can be used, including particle embolization, coils, and liquid adhesives (ie, n-butyl cyanoacrylate or Onyx).[15] Interestingly, postembolization syndrome is uncommon compared with the incidence observed in transarterial embolization. If an extended right hepatectomy is planned (resection of the right hepatic lobe plus segment IV), then embolization of the segment IV branch of the portal vein should also be performed.[16] At the conclusion of the procedure, embolization of the hepatic tract should be performed.

Hypertrophy starts immediately and is often seen on imaging 1 month after the procedure. The degree of hypertrophy varies significantly based on different published studies. Recently, multiple studies have compared the hypertrophy seen with portal vein embolization to that seen with yttrium-90 (^{90}Y) radioembolization. Portal vein embolization tends to induce more significant contralateral hypertrophy at an early time point compared with radioembolization.[17]

Complications include issues at the access site such as hematoma and pneumothorax. Portal vein thrombosis can also occur; therefore, the ipsilateral approach is favored so as not to compromise the future liver remnant.[18] Finally, the largest concern is the wait time needed for hypertrophy, during which time the tumor remains untreated. In several series, nonoperative rates were as high as 25% after an initial intent for surgical resection.[14] In these cases, artery-based therapy becomes far more challenging, as the right hepatic lobe becomes dependent on arterial inflow for perfusion.