Intrahepatic Cholangiocarcinoma

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Intrahepatic cholangiocarcinoma (ICC) is a rare, aggressive cancer of the biliary tract. It often presents with locally advanced or metastatic disease, but for patients with early-stage disease, surgical resection with negative margins and portahepatis lymphadenectomy is the standard of care.

Keywords: intrahepatic cholangiocarcinoma ; biliary tract cancers

1. Introduction

Intrahepatic cholangiocarcinoma (ICC) is a rare aggressive cancer of the biliary tract. It is the second most common primary hepatic malignancy and is occurring with increasing incidence in the United States [1][2]. The last decade has seen several advances in the diagnosis, staging, and management of ICC. The 7th edition of the American Joint Committee on Cancer (AJCC) Staging Manual introduced a distinct staging system for ICC, and the 8th edition provided further refinement of this staging system, leading to more accurate stratification of prognosis [3]. An improved understanding of the genetic underpinnings of ICC has led to identification of new molecular biomarkers and increased opportunities for targeted therapies [4][5]. Refinement of liver-directed therapies have expanded treatment options for patients with locally advanced disease and improved local control [6][7][8]. New randomized controlled trials have clarified the role of adjuvant therapy for biliary tract cancers [9][10][11]. Despite improvements in prognostication and targeted treatment options, overall survival (OS) among patients with ICC remains low with 5-year overall survival of less than 10% [12][13][14]. This is partly related to the fact that the majority of patients with ICC present with either metastatic, or locally advanced, unresectable disease, and effective systemic therapy options are still lacking.

2. Diagnostic Imaging of ICC

A variety of imaging techniques are used for the diagnosis and evaluation of ICC. There are three described morphologic sub-types of ICC including mass-forming, periductal-infiltrating, and intraductal-growth subtypes, with the mass-forming type being the most common type of ICC. Morphologic subtype impacts diagnostic sensitivity and specificity of diagnostic imaging modalities [15].

Ultrasound is often the first imaging modality used to evaluate patients with obstructive jaundice or abdominal pain and can rule out choledocholithiasis and identify cholangiocarcinoma. Contrast-enhanced ultrasound can help to distinguish ICC from hepatocellular carcinoma (HCC) with 64.1% sensitivity, 97.4% specificity, and 73.6% accuracy; peripheral rim-like enhancement and quick contrast washout has high efficiency to distinguish ICC from HCC [16]. Mass-forming ICC appears as homogeneous masses with intermediate to increased echogenicity and a peripheral hypoechoic halo. On contrast enhanced ultrasound, mass-forming ICC may mimic HCC with early enhancement and washout [15].

Multiphase contrast-enhanced CT with arterial, portal venous, and delayed phases can be used to identify and characterize liver masses and demonstrate prognostic features including vascular encasement, nodal involvement, and metastatic disease. On triple-phase CT, in the arterial and portal venous phases, ICC remains hypoattenuating with or without rim enhancement relative to liver parenchyma, with enhancement in the delayed phase and gradual centripetal enhancement on dynamic studies [17]. Furthermore, the portal venous phase accentuates the presence of fibrous stroma, a distinguishing feature of ICC [15]. Degree of enhancement on delayed phases helps to distinguish mass-forming ICC from HCC and has prognostic value [18]. Additionally, CT techniques can be used to calculate liver volume and assist in individualizing plans for resection. Shortcomings of CT include exposure to ionizing radiation and more limited ability to detect tumor tracking along bile ducts and reduced sensitivity to detect lymph node involvement compared with MRI [19].

MRI evaluation of ICC should include magnestic resonance cholangiopancreatography (MRCP), conventional T1- and T2-weighted images, diffusion weighted images, and multiphase contrast-enhanced sequences in arterial, portal venous and delayed phases [15]. On MRI mass-forming ICC demonstrates intensity on T2-weighted imaging and low signal intensity

on T1-weighted imaging. On contrast-enhanced MRI, ICC exhibit peripheral rim enhancement with centripetal or progressive enhancement [17]. Several features can be used to distinguish ICC from HCC on MRI with a lobulated shape, rim enhancement in the arterial phase, and a target appearance with a peripheral hyperenhancing rim on diffusion-weighted imaging favoring ICC, while intralesional fat, diffuse hyperintensity on T1-weighted images, nodule-in-nodule appearance, and capsular appearance during portal venous or transitional phase favor HCC [17]. Gadoxetic acid-enhanced MRI can lead to more effective discrimination between ICC and HCC [20].

Moreover, 18F-Fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) coupled with CT can also be used to identify and evaluate liver cholangiocarcinoma, with higher sensitivity and specificity for ICC (>90%) compared with extrahepatic cholangiocarcinoma. All morphologic types of ICC are FDG-avid on PET-CT, which may improve nodal staging over MRI and preoperative standardized uptake value may be an independent risk factor for recurrence after resection [21][22].

3. Perioperative Therapies

3.1. Adjuvant Therapy

Patients with ICC who undergo curative-intent resection still have a high incidence of recurrence; therefore, adjuvant therapy should be considered [23]. In particular, patients with a high tumor burden are at particularly high risk of recurrence and may be in need of postresection therapy [24]. Several recent trials have helped to clarify the role of adjuvant therapy for patients with ICC. The PRODIGE 12-ACCORD 18 trial was a multicenter, open-label, phase III trial that randomized patients to adjuvant chemotherapy with gemcitabine/oxaliplatin (GEMOX) versus observation following R0/1 resection for biliary tract cancers (BTC) including ICC (43%). The trial demonstrated no difference in health-related quality-of-life, relapse-free survival or OS [11]. The investigators concluded that, while the regimen was well tolerated, there was no benefit to adjuvant GEMOX among patients with resected BTCs [11]. The BILCAP trial was a randomized, controlled, multicenter, phase III study in which patients with R0/R1 resected cholangiocarcinoma or muscle-invasive gallbladder cancers were randomized to oral capecitabine or observation. Of note, only 84 of the 447 (19%) of the patients included in the trial had intrahepatic cholangiocarcinoma. Although the study did not meet its primary end point of improving OS in the intention-to-treat analysis, capecitabine was associated with improved OS in the prespecified sensitivity and perprotocol analyses (53 months versus 36 months, p = 0.028) [9]. Based on the results of BILCAP trial, adjuvant therapy after resection of ICC should be considered, but further studies are still needed to clarify its' role. The ACTICCA-1 trial is a randomized, multidisciplinary, multinational phase III trial in which patients with biliary tract cancers (BTCs) were randomized to gemcitabine and cisplatin versus observation; this study is ongoing [10]. The JCOG1202, ASCOT trial is an open-label, multicenter, randomized phase III trial randomizing patients with resected BTCs to S-1 therapy versus observation and is also ongoing [25].

3.2. Neoadjuvant Therapy

While debated, there is a sound rationale for the delivery of neoadjuvant chemotherapy in ICC. Preoperative chemotherapy may help downstage locally advanced tumors, improve margin negative resection, increase receipt of systemic therapy, prioritize the early systemic treatment of potential micrometastatic disease, as well as enhance patient selection for major surgery and facilitate in vivo test of chemotherapy effectiveness [26]. While no prospective randomized controlled trials of neoadjuvant chemotherapy have been conducted for patients with BTCs, increasing retrospective data highlight its utility to treat a subset of patients with locally advanced disease [27]. A single-center study included 74 patients with locally advanced ICC, 53% (N = 39) of whom underwent secondary resection after a median of six cycles of chemotherapy using various chemotherapeutic regimens and locoregional approaches. These patients were compared to a group of patients who underwent upfront resection. The secondary resection group patients were younger, had more advanced disease and more commonly had lymphadenopathy and vascular invasion. The authors found no difference in postoperative morbidity, mortality or median survival (24.1 versus 25.7 months, p = 0.391) between groups. The authors concluded that neoadjuvant chemotherapy may be an effective downstaging option for patients with locally advanced ICC [28]. Neoadjuvant chemotherapy regimens usually include gemcitabine and cisplatin, based on the ABC-02 trial, which demonstrated the improved efficacy of combination therapy over gemcitabine alone [29]. Locoregional approaches have been successfully used both for palliative treatment and for downstaging of ICC prior to resection including transarterial chemoembolization, combination of Yttrium-90 radioembolization and systemic chemotherapy, and selective internal radiation therapy with or without chemotherapy [7][30][31][32]. Downstaging locally advanced ICC prior to LT has also been reported [33].

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