http://dx.doi.org/10.1016/j.hpb.2017.08.025 HPB

ORIGINAL ARTICLE

The prognostic value of portal vein and hepatic artery involvement in patients with perihilar cholangiocarcinoma

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Abstract

Background: Although several classifications of perihilar cholangiocarcinoma (PHC) include vascular involvement, its prognostic value has not been investigated. Our aim was to assess the prognostic value of unilateral and main/bilateral involvement of the portal vein (PV) and hepatic artery (HA) on imaging in patients with PHC.

Methods: All patients with PHC between 2002 and 2014 were included regardless of stage or management. Vascular involvement was defined as apparent tumor contact of at least 180° to the PV or HA on imaging. Kaplan–Meier method with log-rank test was used to compare overall survival (OS) between groups. Cox regression was used for multivariable analysis.

Results: In total, 674 patients were included with a median OS of 12.2 (95% CI 10.6–13.7) months. Patients with unilateral PV involvement had a median OS of 13.3 (11.0–15.7) months, compared with 14.7 (11.7–17.6) in patients without PV involvement ($p = 0.12$). Patients with main/bilateral PV involvement had an inferior median OS of 8.0 (5.4–10.7, $p < 0.001$) months.

Median OS for patients with unilateral HA involvement was 10.6 (9.3–12.0) months compared with 16.9 (13.2–20.5) in patients without HA involvement ($p < 0.001$). Patients with main/bilateral HA involvement had an inferior median OS of 6.9 (3.3–10.5, $p < 0.001$). Independent poor prognostic factors included unilateral and main/bilateral HA involvement, but not PV involvement.

Conclusion: Both unilateral and main HA involvement are independent poor prognostic factors for OS in patients presenting with PHC, whereas PV involvement is not.

Received 13 June 2017; accepted 29 August 2017

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Introduction

Perihilar cholangiocarcinoma (PHC) is the most common bile duct cancer and arises at or near the confluence of the right and left main bile duct. The annual incidence in Western countries is about 2 per 100,000.[1] Patients usually present with obstructive jaundice, abdominal pain, and weight loss.[2] Surgical resection is the only potentially curative option for patients with PHC, resulting in a median overall survival (OS) of about 40 months.[3] Unfortunately, only about 20% of all patients are eligible for a curative-intent surgical resection because the majority of patients has metastatic or locally advanced disease at presentation or during explorative laparotomy.[4–6]

Staging and resectability are determined primarily using computed tomography (CT) and magnetic resonance imaging (MRI). Most staging systems consider vascular involvement of the tumor to determine prognosis and resectability. Apparent vascular involvement on imaging is typically defined as tumor contact of at least 180°.[7] Actual involvement on pathological

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Please cite this article in press as: van Vugt JLA, et al., The prognostic value of portal vein and hepatic artery involvement in patients with perihilar cholangiocarcinoma, HPB (2017), http://dx.doi.org/10.1016/j.hpb.2017.08.025

examination is only evaluated in patients who undergo an en-bloc resection of the tumor and (branches of) the portal vein (PV) or hepatic artery (HA). The American Joint Committee on Cancer (AJCC) staging system has a prominent role for unilateral PV or HA involvement (i.e. stage T3) and main PV or HA involvement (i.e. stage T4).[8] The DeOliveira/Clavien classification also requires detailed assessment of both unilateral and main HA and PV involvement.[7] The Mayo Clinic staging system considered any tumor contact with the PV or HA a poor prognostic factor.[9] The Blumgart staging system was developed to predict resectability based on unilateral and main PV involvement of the tumor in addition to biliary extent and hepatic atrophy.[4]

Differences between the staging systems demonstrate disagreement about which aspect of vascular involvement is most important: PV or HA involvement, and unilateral or main/bilateral involvement. The prognostic value of unilateral and main PV or HA involvement has not been evaluated in a large group of PHC patients. The aim of this study was to investigate the prognostic value of unilateral and main/bilateral involvement of the PV and HA on imaging in patients with PHC, regardless of subsequent treatment.

Methods

Study population and data acquisition

All consecutive patients with suspected PHC between 2002 and 2014 in the Erasmus MC University Medical Center, Rotterdam, the Netherlands and the Academic Medical Center (AMC), Amsterdam, the Netherlands, were identified through a systematic search in all medical files, discharge letters, reports of multidisciplinary hepatopancreatobiliary team meetings, and operative and pathology reports. All PHC care in our region is centralized and all patients are being referred to one of the specialized centers according to a national protocol. All patients referred for curative-intent surgery, palliative treatment, or best supportive care were included.

PHC was defined as a mass or malignant-appearing stricture at or near the biliary confluence, arising between the origin of the cystic duct and the segmental bile ducts.[10] If no histopathological evidence was obtained, the multidisciplinary hepatopancreatobiliary team determined the diagnosis based on clinical, radiological, endoscopic and laboratory findings, and follow-up. Patients with hilar-invasive intrahepatic cholangiocarcinoma, gallbladder carcinoma, cystic duct carcinoma, and distal cholangiocarcinoma were excluded, as well as patients who had no imaging available for review. We also excluded patients who underwent treatment (e.g., resection or chemotherapy) prior to referral or who visited our centers for a single biliary drainage without further follow-up at our centers.

Demographics (e.g., age, gender), clinical parameters (e.g., cholangitis), and laboratory results (e.g., bilirubin and carbohydrate antigen (CA) 19.9 levels) were collected from medical records. Cholangitis was defined by the presence of fever, abdominal complaints, or leukocytosis requiring biliary drainage.[11–13]

Experienced abdominal radiologists revised imaging (i.e. contrast-enhanced CT and/or MRI or MRI with cholangiopancreatography (MRCP)) performed at the time of first presentation. Parameters assessed on imaging were radial diameter of the tumor, biliary extent of the tumor (Bismuth-Corlette classification),[14] clinical AJCC staging (7th edition), presence of lymph node and distant metastases, lobar atrophy, and vascular involvement. The clinical AJCC (7th edition) stages I and II were pooled, because T1 (stage I) and T2 (stage II) cannot be distinguished on imaging.[8] Suspicious lymph nodes were defined as nodes larger than 1 cm in short-axis diameter, with central necrosis, an irregular border, or hyperattenuation compared to portal phase liver parenchyma. Nodes along the cystic duct, common bile duct, hepatic artery and portal vein were classified as N1; involvement of periaortic, pericaval, superior mesenteric artery, and celiac nodes as N2, according to the AJCC staging (7th edition).[8] Vascular involvement was defined as apparent tumor contact of at least 180° to the PV or HA. It was classified separately for PV and HA as main, bilateral, or unilateral involvement.[8,15,16] Vascular involvement was mainly assessed on contrast-enhanced CT imaging. MRI was only used in the few patients with unavailable contrast-enhanced CT.

The Institutional Review Boards of both centers approved the study and the need for informed consent was waived.

Diagnostic work-up and treatment algorithm

The diagnostic work-up and treatment algorithm were performed as previously described and were comparable between the two centers.[29] In short, diagnostic work-up included contrast-enhanced CT and/or MRI/MRCP. Metastatic disease was defined, according to the AJCC staging (7th edition), as the presence of distant metastases or lymph node metastases beyond the hepatoduodenal ligament (N2).[8] Locally advanced disease was defined as invasion of surrounding organs or vascular or biliary involvement that precluded an R0 resection.[9]

Exploratory laparotomy was rarely performed in patients with stage IVb disease (i.e. N2 or M1) or with main/bilateral HA involvement on imaging. Patients did not receive adjuvant chemotherapy in compliance with Dutch guidelines.[17–19] Palliative systemic chemotherapy (gemcitabine with or without cisplatin) was considered for patients with locally advanced or metastatic disease. Patients who did not receive chemotherapy, received best supportive care. Liver transplantation was only performed in highly selected patients based on a nationwide protocol since 2014.[20,21]

Statistical analyses

All statistical analyses were performed using SPSS for Windows (IBM Corp., Armonk, NY, USA), version 22. Continuous data

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