Hilar cholangiocarcinoma (HC) was first described by Altemeier and Klatskin approximately 50 years ago and comprise over 60% of all cholangiocarcinomas (1-3). It is a complex and aggressive disease with a poor prognosis.

We provide an evidence-based review of HC with a particular emphasis on the approach to management of this challenging disease. An electronic database search, including PubMed/MEDLINE, was performed using the terms hilar cholangiocarcinoma and Klatskin's tumor.

Additionally, a MESH database search was performed under the heading “Bile Duct Neoplasms” in combination with the aforementioned terms and Boolean operators AND or OR. Criteria for inclusion included English-language articles using human subjects (Figure 1).

**Incidence and epidemiology**

Cholangiocarcinoma accounts for less than 2% of all human cancer diagnoses. It is more common in Asian populations, particularly in Japan, where the incidence is about 20-30 cases per 100,000 person-years. In the United States, the incidence is about 1-2 cases per 100,000 person-years. The median age at diagnosis is 60-65 years, with a male-to-female ratio of 1.5:1.

Hilar cholangiocarcinoma (HC) is a rare disease with a poor prognosis which typically presents in the 6th decade of life. Of the 3,000 cases seen annually in the United States, less than one half of these tumors are resectable. A variety of risk factors have been associated with HC, most notably primary sclerosing cholangitis (PSC), biliary stone disease and parasitic liver disease. Patients typically present with abdominal pain, pruritus, weight loss, and jaundice. Computed topography (CT), magnetic resonance imaging (MRI), and ultrasound (US) are used to characterize biliary lesions. Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) assess local ductal extent of the tumor while allowing for therapeutic biliary drainage. MRCP has demonstrated similar efficacies to PTC and ERCP in identifying anatomic extension of tumors with less complications. Treatment consists of surgery, radiation, chemotherapy and photodynamic therapy. Biliary drainage of the future liver remnant should be performed to decrease bilirubin levels thereby facilitating future liver hypertrophy. Standard therapy consists of surgical margin-negative (R0) resection with extrahepatic bile duct resection, hepatectomy and en bloc lymphadenectomy. Local resection should not be undertaken. Lymph node invasion, tumor grade and negative margins are important prognostic indicators. In instances where curative resection is not possible, liver transplantation has demonstrated acceptable outcomes in highly selected patients. Despite the limited data, chemotherapy is indicated for patients with unresectable tumors and adequate functional status. Five-year survival after surgical resection of HC ranges from 10% to 40% however, recurrence can be as high as 50-70% even after R0 resection. Due to the complexity of this disease, a multi-disciplinary approach with multimodal treatment is recommended for this complex disease.

**Keywords:** Cholangiocarcinoma (CC); hilar; biliary neoplasm

Submitted Nov 18, 2013. Accepted for publication Dec 30, 2013.
doi: 10.3978/j.issn.2304-3881.2014.02.05
Scan to your mobile device or view this article at: http://www.thehbsn.org/article/view/3374/4195
malignancies but is the second most common primary liver tumor (4,5). Although rare in Western countries, it is more commonly seen in Asia with incidences as high as 113 per 100,000 men and 50 per 100,000 women (6). It is categorized as intrahepatic (ICC) or extrahepatic (ECC) according to the International Classification of Diseases for Oncology. There are approximately 3,000 ECC cases annually in the United States alone (5,7,8). ICC incidence has increased over the last 20 years while ECC has remained constant (9,10). However, this may be attributed to HC misclassification in the International Classification of Disease for Oncology system (8).

A variety of risk factors have been associated with HC including advanced age, male gender, cirrhosis, inflammatory bowel disease, and chronic pancreatitis (7). Parasitic liver disease (i.e., biliary ascarisis, liver flukes, and liver schistosomiasis) is an established HC risk factor along with biliary tract stone disease (4,7). The most well established risk factor for HC is primary sclerosing cholangitis (PSC). The lifetime incidence of cholangiocarcinoma (CC) in PSC patients is 6% to 36% with most patients presenting within 2.5 years of their PSC diagnosis (6,7,11). Notably, PSC involves both intra and extra hepatic bile ducts and PSC related CC is an equal risk factor for both ICC and ECC (12).

Patients commonly present with jaundice, abdominal pain and weight loss (14-16). Fatigue, pruritus, nausea, dark urine and clay colored stools are also often seen (16). Biliary stones, inflammatory bowel disease, PSC, viral hepatitis are commonly encountered co-morbidities (16,17).

Over 80% of proximal biliary obstructions are secondary to HC (18-20). The remaining 15-20% are caused by benign strictures secondary to inflammatory disease, sclerosing cholangitis, stone disease, and gallbladder cancer invading the hepatoduodenal ligament (19,21-24). Both benign and malignant biliary strictures present with similar clinical features (19-21). Moreover, bilirubin and serum tumor marker levels do not reliably distinguish malignant and benign biliary strictures (21,23). Preoperative identification of benign biliary strictures remains uncertain therefore resection remains most appropriate (19-21,23).

Serum tumor markers, specifically carcinoembryonic antigen (CEA) and CA19-9, are used for the diagnosis, treatment, and monitoring of HC with 89% sensitivity and 86% specificity when combined with other diagnostic modalities (25). Additionally, tumor marker levels are associated with tumor stage. Tumors with higher levels at presentation are more likely to be unresectable, predicting a worse overall survival (25-27).

**Presentation and diagnostic evaluation**

HC generally presents in the 6th decade of life (13-16).
radiological staging of these lesions is difficult secondary to the complexity of the hilar region, proximity to major vessels, and small tumor sizes (30). Computed topography (CT), magnetic resonance imaging (MRI), and ultrasound (US) are used to characterize suspicious biliary lesions. Initial radiographic assessment is usually transabdominal US due to its low cost and accessibility. It is sensitive for detecting biliary duct dilatation, but less sensitive in localizing the exact site of obstruction (31,32). Typically, any HC mass appears hypoechoic relative to surrounding liver parenchyma (Figure 2). US is unable to accurately determine the type of obstruction or extent of tumor involvement (33). In addition, US has relative poor sensitivity in identifying lymph node, liver, and peritoneal metastases and therefore further imaging modalities are generally needed (22,34).

CT accurately predicts HC resectability in 60-90% of cases and is the most frequently used imaging modality to assess biliary tumor resectability (35-38). CT can help differentiate between benign and malignant strictures as well as depict the level of biliary obstruction (Figure 3). Arterial and portovenous phase CT can assist in delineating vascular invasion of the corresponding hepatic hilar structures (28,39). Thinly sliced (2-5 mm) multidetector CT (MDCT) correlates well (greater than 90%) with local tumor extension when compared with operative and pathological findings (36). In one systematic review of HC imaging techniques, CT was the most well studied imaging modality and demonstrated an acceptable accuracy (>80%) in assessing ductal, portal vein and hepatic artery involvement although it was unable to accurately assess lymph node involvement (29). Moreover, peritoneal metastases are generally underestimated (28,37). Therefore, despite reported high sensitivity and specificity for HC with CT imaging, metastatic involvement and spread to contiguous organs and vascular structures remains a possibility at the time of surgery even if undetected on CT.

MRI has increasingly gained favor in assessing biliary tumors. HC appears as a hypointense signal on T1 weighted images and high signal intensity of T2 imaging (Figure 4). The tumor generally appears hypovascular in relation to adjacent hepatic parenchyma and may be characterized by irregular thickening of the bile duct wall with upstream dilation of intrahepatic bile ducts (Figure 5) (40). The combination of MRI with MRCP is about 80% accurate in predicting HC resectability (41-43). However, in a comparison of MRI combined with MRCP versus MDCT with direct cholangiography, Park and colleagues demonstrated no difference between the two groups in assessing HC resectability (44). Currently, the combination of MRCP and CT is favored over direct cholangiography. Unfortunately MRCP does not allow for invasive procedures such as biopsy, biliary drainage and stent insertion therefore direct cholangiography is still necessary in these instances.

The role of PET/CT in HC remains less clear. PET/CT has a reported specificity of over 80% to detect lymph node and distant metastases, but it seemingly does not have much utility in assessing local resectability (45-47). Case studies utilizing PET/CTs are limited and more studies are needed to further evaluate the benefit of this imaging modality in HC. Currently, PET may be useful when assessing for metastatic disease but has no clear role in helping to evaluate issues of local resectability.

**Direct cholangiography**

Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) assess local ductal extent of the tumor while allowing for therapeutic biliary drainage. The use of preoperative biliary drainage (PBD) in HC remains controversial. In Liu and colleagues systematic review comparing PBD with no PBD in resectable patients, the authors failed to note a benefit from PBD, although the lack of uniformity in the literature was a limitation of the analysis (48). Multiple retrospective reviews have shown that PBD in jaundiced HC patients decreases postoperative complications although...
Figure 3 Axial (A) and coronal (B) CT of the liver in the portal venous phase showing a large heterogeneous mass in both lobes. Axial T2 (C) and contrast enhanced portal venous phase (D) MR shows ductal dilatation resulting from the large central mass.

Figure 4 T2 (A) and contrast enhanced hepatic arterial phase (B) and portal venous phase (C) MR images of the liver demonstrate ill-defined slightly hyperintense mass on T2 with peripheral rim enhancement on the hepatic arterial phase, and central necrosis on the portal venous phase. (D) FDG PET shows increased uptake and central photopenic zone indicating necrosis.
no improvement in mortality or survival has been reported 
(14,49-52). Moreover multiple studies have shown that 
hepatic resection in jaundiced patients is associated with 
higher mortality and morbidity due to increased rates of liver 
failure and that PBD prior to hepatic resection can increase 
resectability (53-56). Kennedy and colleagues demonstrated 
improved perioperative outcomes with PBD in patients with 
future liver remnant (FLR) volume of less than 30% (57). 
Although randomized studies are needed to better address 
the potential benefits of PBD in HC, the literature indicates 
that PBD of FLR should be done routinely in jaundiced HC 
patients undergoing hepatic resection (58).

Both ERCP and PTC have similar sensitivity (75-85\%) 
and specificity (70-75\%) with regard to their ability to 
attain a tissue diagnosis; however, it is important to note 
that a negative biopsy cannot be considered definitive and an 
underlying HC should always be suspected in the right 
clinical setting regardless of the biopsy results (59-63). 
Direct comparisons have demonstrated less procedure 
related complications with PTC; however, PTC catheter 
tract recurrence may be seen in 2-5\% of patients (64,65). 
Currently both approaches provide acceptable outcomes and 
the choice of approach is generally institution dependent.

Intraductal ultrasonography has acceptable sensitivity 
when compared with histology based staging, although this 
technique is also operator dependent and its accuracy can 
 vary (38,66,67). Limited case series have demonstrated the 
feasibility of endoscopic US fine needle aspiration (FNA) 
to biopsy HC and regional lymph nodes although more 
studies are needed to understand the role of this technique 
in HC (68-71). Transperitoneal FNA of HC is associated 
with a higher rate of peritoneal metastases and should 
generally be avoided especially when curative resection is 
being considered (72).

MRCP has demonstrated similar efficacies to PTC 
and ERCP in identifying anatomic extension of tumors 
(31,60,73). Biliary staging is best assessed using MRCP 
while vascular and distant metastatic staging may be better 
assessed with either MDCT or contrast enhanced MRI (31). 
Preoperative biliary procedures such as stenting and 
percutaneous drainage induce biliary wall inflammation 
and create artifacts which hinders imaging interpretation. 
Therefore it is important for staging and assessment of 
resectability that cross-sectional imaging be obtained prior 
to biliary interventions whenever possible (32,33,41).

Staging systems

Various HC staging systems are currently used. The 
Bismuth-Corlette system provides preoperative assessment 
of local tumor spread and is used to determine the extent of 
resection (Figure 6) (74,75). It does not, however, provide 
information on vascular encasement or metastatic disease 
and is of limited prognostic value (7,76). The Memorial 
Sloan Kettering Cancer Center (MSKCC) classification 
details local tumor extent while also assessing portal vein 
involvement and hepatic lobar atrophy (Table 1). Similarly 
to the Bismuth-Corlette system, the MSKCC classification 
for HC does not account for metastatic or nodal disease 
and is most appropriate for categorizing local resectability 
(77-79).

The American Joint Committee on Cancer (AJCC) is 
the most commonly used staging system for CC (80). In 
the 7th edition of the AJCC staging system, extrhepatic 
CC was given its own independent staging that is further 
subdivided into perihilar and distal bile duct tumors. Unlike
Figure 6: The Bismuth-Corlette classification of hilar cholangiocarcinoma. Type I tumors are distal to the hepatic duct confluence (HDC) while type II neoplasms extend to and involve the HDC. Type III tumors involve the HDC and either the proximal right hepatic duct (type IIIA) or proximal left hepatic duct (type IIIB). Type IV tumors extend into the bilateral proximal hepatic ducts up to the segmental bile ducts (74).

Abbreviations: RHD, right hepatic duct; LHD, left hepatic duct; HDC, hepatic duct confluence.

Table 1: Memorial Sloan Kettering Cancer Center hilar cholangiocarcinoma classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Biliary confluence involvement</th>
<th>2nd order biliary radicle involvement</th>
<th>PV involvement</th>
<th>Hepatic lobar atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td></td>
<td>Yes</td>
<td>+/- Unilateral</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>T2</td>
<td></td>
<td>Yes</td>
<td>+/- Unilateral</td>
<td>Ipsilateral</td>
<td>+/- Ipsilateral</td>
</tr>
<tr>
<td>T3</td>
<td></td>
<td>Yes</td>
<td>Bilateral</td>
<td>Yes/no</td>
<td>Yes/no</td>
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<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>Unilateral</td>
<td>Contralateral</td>
<td>Yes/no</td>
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<td>Unilateral</td>
<td>Yes/no</td>
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<td></td>
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<td>Yes</td>
<td>+/- Unilateral</td>
<td>Bilateral</td>
<td>Yes/no</td>
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</tbody>
</table>


The Bismuth-Corlette and MSKCC staging systems, the AJCC system accounts for vascular encasement (both portal vein and hepatic artery), nodal involvement and distant metastases. It is mainly utilized as a postoperative staging system and has minimal utility in assessing resectability preoperatively. Multiple reports have demonstrated inaccuracies in survival assessment by the AJCC system that may, in part, be due to not accounting for depth of tumor invasion (81-84). In fact, retrospective case series have shown that the MSKCC staging more accurately correlates with overall survival than the AJCC system (85,86). Given the various staging systems and the difficulty in comparing HC
studies across various centers, DeOliveira and colleagues proposed a new staging strategy that accounts for tumor size, extent of disease in the biliary system, vascular involvement, lymph node involvement, distant metastases, and the volume of the putative remnant liver after resection (87).

**Pathological characteristics**

Grossly, HC is divided into three classifications; papillary, nodular and sclerosing. Both nodular and papillary subtypes typically protrude into the lumen. Sclerosing HC is diffusely infiltrating along the biliary wall with very little mucosa protuberance on gross examination (88). Sclerosing HC is the most common subtype. Papillary HC is more often resectable and is thought to have the best prognosis due to its less invasive growth pattern (88-90). Many tumors, however, have overlapping features.

Over 90% of extrahepatic epithelial bile duct tumors are adenocarcinomas. These are divided into three grades; well, moderately and poorly differentiated depending on the percentage of glands within the tumor (91,92). Direct invasion into hilar structures as well as lymphatic and perineural invasion is commonly seen. Although typically expressed on the cell membranes of benign biliary epithelium, cytoplasmic CEA and MUC1 expression is often detected in HC and is thought to play a role in the tumor's metastatic potential (88). Gene expression profiles amongst biliary tract adenocarcinomas differ depending on site of origin and can have prognostic implications. For example, cycle-dependent kinase inhibitor p27 expression was more commonly seen in HC compared with gallbladder and distal bile duct tumors and low expression has correlated with poor outcome (93). K-ras mutations are associated with a worse overall survival in bile duct cancers and are seen in higher frequency in distal bile duct tumors compared with HC (94,95).

Premalignant lesions include biliary intraepithelial neoplasia (BiIN) and intraductal papillary neoplasm of the biliary tract (IPN-B). These lesions are considered counterparts to pancreatic intraductal neoplasms (PanIN) and intraductal mucinous neoplasm of the pancreas (IPMN-P), respectively (88,91). Similarly to PanIN, BiIN progress to tubular adenocarcinoma and is graded according to the degree of atypia. BiIN-3 represents carcinoma in situ and is seen in 10-75% of extra hepatic bile duct cancers (88). Superficial spreading along the biliary epithelium is seen in approximately 10-18% of extrahepatic bile duct cancers and is associated with a better prognosis (96,97).

**Management**

**Preoperative liver optimization**

A large number of HC patients are jaundiced and hepatic resection in this setting has been associated with increased postoperative complications (54). Therefore, biliary drainage of the FLR should be performed to decrease bilirubin levels thereby facilitating future liver hypertrophy (53). If the FLR is expected to be less than 30-40%, portal vein embolization (PVE) should be considered (53,98,99). Although there are no randomized controlled clinical trials evaluating the effectiveness of PVE in HC, the implementation of PVE seems to allow for the preoperative hypertrophy of the FLR and has been associated with reduced postoperative hepatic failure and complications. Patients are generally eligible for resection 4-6 weeks after biliary drainage and PVE (53,98).

**Resection**

Criteria for unresectability include bilateral spread to secondary biliary radicals, involvement of the portal vein main trunk, bilobar involvement of hepatic arterial and/or portal venous branches, and unilateral hepatic artery involvement with evidence of extensive contralateral duct spread (100). Hepatic artery and portal vein involvement, peritoneal spread and suspicious lymph nodes on preoperative imaging are important prognostic factors of resectability (37,38,101). Despite the use of various imaging techniques to identify these features, 40-50% of surgically explored HC patients are found to have inoperable disease at the time of laparotomy (13,102). Many have advocated staging laparoscopy in order to prevent unnecessary laparotomies. In some series, staging laparoscopy was able to prevent unnecessary laparotomies in 45% of patients (102-105). The yield and accuracy of the staging laparoscopy may improve with the addition of laparoscopic US (106), however peritoneal washing and cytology provides no benefit (107). Although grade A evidence is lacking, staging laparoscopy in HC is acceptable in selected patients especially those with high CA19-9 levels or indeterminate/suspected extrahepatic disease.

Margin negative (R0) resection remains the only treatment that offers the chance at long-term survival (13-15,17,77,108-110). Surgical resection of HC can sometimes be challenging, however, due to extensive nature and central location of the tumor. Morbidity and mortality rates range from 40% to 70% and 5% to 15%, respectively (Table 2) (13-15,17,113,119). Local excision of only the extrahepatic biliary
tree should be avoided, as this approach is associated with a high likelihood of an R1 (microscopic) or R2 (macroscopic) resection, as well as worse lymph node clearance and worse survival (14,110,120-124). Major hepatectomy combined with extra hepatic bile duct resection has increased R0 resection rates as well as long term survival and should be considered standard therapy (17,77,118,120,125). In general, Bismuth-Corlette I, II, IIIa lesions typically require an extended right hepatectomy, while Bismuth-Corlette IIIb lesions require a left hepatectomy. Complete excision of the caudate lobe has also been demonstrated to improve local recurrence rates and long-term survival (100,126-128). As such, routine resection of the caudate lobe should be performed. Lymph node and perineural invasion occur early and are associated with poor survival (88,129). While lymph node dissection does not provide a survival benefit, it may help with local control and is important prognostically as the 5-year survival of patients with positive lymph node disease is 15% (130-132).

In most surgical series that include hepatic resection combined with excision of the extrahepatic biliary tree, obtaining an R0 (negative microscopic) margin is typically reported in the 60-80% range (13,14,17,113,116,120). Intraoperatively, while frozen section analysis of the margins should be obtained, it has not been shown to improve the probability of margin negative resection (20,21). Although R1 resections have shown some survival benefit compared to non-operative management, an R0 margin should always be the goal (133-135).

The routine use of vascular resection is less defined and more controversial. In one meta-analysis, portal vein resection (PVR) was associated with higher mortality rates, although this association was lost in a subgroup analysis of more experienced centers (136). Importantly, there was no difference in 5-year survival rates between the PVR cohort and the non-vein resection group, despite the fact that the PVR cohort had more advanced disease (136). Overall, PVR has demonstrated long term survival advantage in patients with advanced HC and should not be considered a contraindication to resection (120,137). Conversely, hepatic artery resection is associated with increased morbidity and mortality without an appreciable benefit in long-term survival and is not performed routinely (138,139). In 1999, Neuhaus and colleagues introduced the “no-touch” technique that calls for en bloc right trisectionectomy combined with routine PVR (140). In a recent retrospective review, Neuhaus and colleagues demonstrate a 58% 5-year survival.

<table>
<thead>
<tr>
<th>Table 2 Recent hilar cholangiocarcinoma case series</th>
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<tbody>
<tr>
<td>First author, year</td>
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<tr>
<td>Cho et al., 2012 (13)</td>
</tr>
<tr>
<td>Nuzzo et al., 2012 (14)</td>
</tr>
<tr>
<td>Cannon et al., 2012 (15)</td>
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<tr>
<td>Zheng-Rong et al., 2011 (17)</td>
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<td>Chauhan et al., 2011 (111)</td>
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<td>van Gulik et al., 2011 (112)</td>
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<td>Regimbeau et al., 2011 (113)</td>
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<td>Shimizu et al., 2010 (114)</td>
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<td>Unno et al., 2010 (115)</td>
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<td>Miyazaki et al., 2010 (116)</td>
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<tr>
<td>Lee et al., 2010 (117)</td>
</tr>
<tr>
<td>Rocha et al., 2010 (109)</td>
</tr>
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<td>Ito et al., 2008 (118)</td>
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Abbreviations: mo, month; DSS, disease specific survival; NR, not recorded; *, 5-year survival.
survival in the no touch technique cohort versus 29% 5-year survival after conventional hepatectomy (P=0.02) (141). Notably, there was no significant difference in operative mortality between the two groups. Although the results are encouraging, these reports suffer from some confounding and selection bias given the retrospective nature of the reports. As such, additional data are necessary before widespread adoption of the “no touch” technique should be adopted as the standard of care for resection of HC.

The role of minimally invasive HC resections also remains unclear. Small-scale case series and singular case reports comprise most of the literature. The available data have demonstrated the feasibility of this technique although larger studies with longer follow up are needed before this technique can be properly assessed (142-144).

Some authors have recommended operative palliation in patients who undergo a laparotomy and are then found to have unresectable disease (145). Surgical palliation in HC consists of cholecystectomy and a biliary-enteric anastomosis for biliary drainage. Although surgical biliary drainage is associated with improved patency rates, there is increased morbidity (17-51%) and mortality (6-12%) along with no difference in overall survival when surgical palliation is compared to non-operative management (146-148). The main complication seen in most series is biliary-enteric anastomotic leak (6-21%) (147). Surgical drainage is therefore not routinely recommended and palliative resections are generally not necessary if the patient has been adequately drained with biliary stenting (147,149).

In general, 5-year survival after surgical resection of HC ranges from 10% to 40% (13,14,150). Of note, even following an R0 resection, recurrence can be as high as 50-70% (151,152). Lymph node metastasis, lymphovascular invasion, positive histologic margins, and higher T stage have all been associated with worse survival and increased recurrence (13-15,111,117,153-155).

Transplantation

Over the last decade, orthotopic liver transplantation (OLT) has shown promise in the treatment of unresectable HC. Multiple early studies evaluating OLT for unresectable HC demonstrated a dismal 20-30% 5-year survival (156-158). The pioneering work from the Mayo Clinic group, however, established a successful multimodality HC OLT protocol and demonstrated a 60% five-year survival in highly selected patients (27,159). Criteria for OLT consideration include HC diagnosis by transluminal biopsy (with percutaneous biopsy being contraindicated), brush cytology, biliary stricture plus FISH polysomy, mass lesion on cross-sectional imaging or malignant—appearing stricture combined with elevated CA19-9 or FISH polysomy (160). Patients must have adequate performance status to withstand neoadjuvant therapy and liver transplantation. Exclusion criteria include patients with a mass lesion below the level of cystic duct, tumors greater than 3 cm, evidence of intrahepatic or extrahepatic metastases, or previous history of peritoneal biopsy. The treatment protocol consists of external beam radiation (40-45 Gy), transcatheater radiation (20-30 Gy) via ERCP or PTC with radiosensitizing 5-FU followed by oral capecitabine until the day of transplantation (160). Prior to transplantation, patients undergo a staging operation where lymph nodes are excised for evaluation and the abdomen is thoroughly inspected for the presence of metastatic disease. In 2009, the United Network for Organ Sharing (UNOS) recognized HC as an indication for OLT (27,161). As such, other centers have begun to use OLT increasingly for unresectable HC. In a retrospective series including 12 major US transplant centers performing UNOS approved protocol OLT for HC, Darwish Murad et al. demonstrated a 65% recurrence free survival after five years. Moreover, there was no difference in outcomes when evaluating patients transplanted at the Mayo clinic (n=131) versus all other centers (n=83) (27). Finally, when UNOS protocol adhering centers’ outcomes were compared with the results of non-protocol driven centers, protocol adherence remained strongly associated with improved recurrence free survival (27).

The three-year survival for PSC related HC is less than 20%, even after surgical resection (162,163). Moreover, CC arising in the setting of PSC typically presents at an advanced stage with multifocal disease which is not amenable to surgical resection (162). Rea and colleagues reported improved survival with OLT in PSC related HC compared to those who underwent surgical resection (164). In their 12 center multi institution analysis, Darwish Murad and colleagues showed a strong trend toward increased recurrence free survival after ten years in PSC related HC liver transplant compared to OLT in non-PSC related HC (62% vs. 51%, P=0.06) (27). Five-year survival after OLT when combined with neoadjuvant therapy in HC arising in the setting of PSC is over 70% and should therefore be considered the standard of care for this specific patient population (164). In contrast, OLT for non-PSC related HC remains more controversial. Future applications of OLT in HC should encompass stringent protocol driven...
criteria and further external validation is needed.

**Role of radiation therapy**

Studies incorporating conventional 5-FU based chemotherapy and radiation for unresectable HC have demonstrated mixed results. The data consists of small single institutional series combining various biliary tree neoplasms (i.e., gall bladder, intrahepatic and extrahepatic bile duct cancer). Prospective HC trials are limited given the tumor’s rarity, aggressiveness and late presentation. In the adjuvant setting, the goal of radiation is to provide local disease control, slow overall disease progression, and prolong survival. Local control of HC following surgery is critical because of the morbidity of local progression in the biliary tract. Chemoradiation may also help prevent or palliate symptoms associated with uncontrolled local progression in both the adjuvant and unresectable setting.

In one retrospective study, Todoroki et al. reported on 63 patients who underwent resection of Klatskin tumors between 1976 and 1999 (165). Overall 29/49 patients were treated in the adjuvant setting with intraoperative radiation therapy (IORT), external beam radiation therapy (EBRT), or a combination of IORT + EBRT. The 5-year survival was 33.9% in the adjuvant radiation arm and 13.5% in the observation arm (P<0.01). Patients who had a combination of EBRT and IORT had better survival. Locoregional failure was decreased in the group that received adjuvant radiation: 20% compared with 69%. Another study by Gerhards et al. reported on 91 patients who underwent mostly margin-positive surgical resection (86%) for HC, of which 71 received EBRT, intraluminal radiation, or a combination. The median survival for those patients who received radiation was 24 months, compared with eight months among those who were simply observed (P<0.01) (166). While retrospective, these studies suggest that adjuvant radiation therapy may improve local control and survival in patients with margin positive resections.

Historically, conventional radiation is delivered over 5-6 weeks and has been limited to approximately 54 Gy because of concern about radiation injury to organs at risk (OARs), especially surrounding bowel and stomach. With a better understanding of dose tolerances of OARs and improved conformity of treatment modalities including intensity modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT), radiation has become more widely used (167). Patients with unresectable disease treated with standard fractionated radiotherapy and/or chemotherapy have traditionally had dismal outcomes. SBRT allows for the delivery of higher doses of radiation delivered over a shorter period of time (<2 weeks) and have shown some promise with respect to local recurrence. However, distant failure remains high, underscoring a need for more effective systemic agents.

**Role of chemotherapy**

The current standard chemotherapy regimens for unresectable HC are platinum based in combination with gemcitabine. These regimens have demonstrated small improvements in survival in randomized control clinical trials as well as in small retrospective series (168-171). Despite the limited data, chemotherapy is indicated for patients with unresectable tumors and adequate functional status (172). Prospective randomized studies are needed and ongoing to fully understand its capabilities, and to optimize the regimen for specific patients, incorporating novel, targeted agents in addition to traditional cytotoxic drugs (173).

Neoadjuvant therapy in HC remains poorly characterized as well. Some studies have demonstrated encouraging outcomes, particularly in the transplant literature (27). Few prospective trials, however, have investigated its ability to downstage tumors and lead to R0 resection (174). More studies are needed and there is no indication to delay tumor resection for neoadjuvant therapy.

**Photodynamic therapy**

Photodynamic therapy (PDT) involves the intravenous administration of photosensitizing agents which accumulate within cancer cells. Light activation leads to the formation of singlet oxygen free radicals and the destruction of nearby cells. Cutaneous phototoxicity is seen in 30% of patients (175). Multiple prospective and retrospective series have demonstrated an increase in survival of 2-3 months with the addition of PDT to biliary stenting in a palliative setting (176-179). A phase II pilot study by Wiedmann et al. evaluating PDT as a neoadjuvant modality demonstrated a 1-year survival of 83% (180). Although underpowered, it did demonstrate the feasibility of this therapy and calls for future prospective studies (180).

**Conclusions**

In conclusion, HC is a rare but aggressive disease with a dismal long-term prognosis. Lymph node invasion, tumor
grade and negative margins are important prognostic indicators. R0 resection represents the only chance for long-term survival. Local resection should not be undertaken. Standard therapy consists of extrahaepatic bile duct resection, hepatectomy and en bloc lymphadenectomy. OLT has demonstrated acceptable outcomes in highly selected patients. Chemotherapy and radiation may improve overall survival although prospective randomized trials are needed. Due to the complexity of this disease, a multi-disciplinary approach with multimodal treatment is recommended.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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discussion 517-9.


133. Lee JH, Hwang DW, Lee SY, et al. The proximal margin


Cite this article as: Soares KC, Kamel I, Cosgrove DP, Herman JM, Pawlik TM. Hilar cholangiocarcinoma: diagnosis, treatment options, and management. Hepatobiliary Surg Nutr 2014;3(1):18-34. doi: 10.3978/j.issn.2304-3881.2014.02.05


