Staging Systems

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4.1 Introduction

Originally described by Altmeier [1] and Klatskin [2], hilar cholangiocarcinoma is an adenocarcinoma of the extrahepatic biliary tree arising from the main left or right hepatic ducts or their confluence. Along with distal bile duct cancer and intrahepatic cholangiocarcinoma, they comprise the spectrum of bile duct cancers that arise from the biliary epithelium. However, unlike those tumors, which can be usually be removed, respectively, with pancreaticoduodenectomy or liver resection alone, the surgical approach to hilar cholangiocarcinoma often combines bile duct resection with concomitant hepatectomy and/or portal vein resection due to the infiltrative nature of the disease. Therefore, a complete, margin-negative resection can be difficult to achieve.

While curative resection remains the only treatment modality associated with prolonged survival, the majority of patients present with disease not amenable to surgical correction. Over the last several decades, improvements in operative techniques and cross-sectional imaging, a better understanding of tumor biology, and the advent of perioperative interventions such as portal vein embolization and biliary decompression of the liver remnant have been adopted in order to maximize resectability and reduce morbidity associated with a major hepatectomy and bile duct resection. Furthermore, caudate resection has been adopted when the left hepatic duct is involved by tumor given it is the origin of the caudate bile ducts. Despite these advances, the 5-year survival rate following curative resection for hilar cholangiocarcinoma remains in the range of 20–40 % [3].

Therefore, accurate staging of this disease to guide therapy and properly select patients who would benefit from surgical extirpation, while sparing potential morbidity in those patients with advanced disease is of utmost importance. Several systems have been developed to distinguish the extent of disease from an anatomic, pathologic and clinical perspective; however, no uniform, universally accepted standard has been embraced. The purpose of this chapter is to examine the historical basis and current applications of the available staging systems and their role in the management of patients with hilar cholangiocarcinoma.

4.2 Anatomic Staging Systems (Bismuth-Corlette)

Given the significant challenges in the surgical removal of hilar cholangiocarcinoma and the lack of a common terminology for the description of these tumors, a preoperative classification system was initially described by Bismuth and Corlette from the Hospital Paul Brousse in Paris [4]. It is a simple system that attempts to stratify the location of the tumor and its longitudinal extent along the biliary ductal system for the purpose of determining extent of resection. Originally described in 1975 and modified in 1992, it is depicted in Fig. 4.1 as a progression of cholangiocarcinoma from the distal extrahepatic portion of the duct up to the hilus and into the secondary biliary radicles. A type I tumor involves the common hepatic and/or bile duct below the confluence and is sometimes referred to as middle CBD cancer or perihilar cholangiocarcinoma depending on its location with regards to the cystic duct of the gallbladder. Some authors argue this type of tumor can be managed with resection of the extrahepatic ductal system and regional lymphadenectomy without the need for hepatic resection provided the surgical margins are negative by frozen section. Bismuth-Corlette type II lesions are sometimes considered the true Klatskin tumors as they involve the confluence of the right and left hepatic ducts without involvement of the intrahepatic ductal system. Depending on the tumor encroachment, resection of the common hepatic duct and regional lymph

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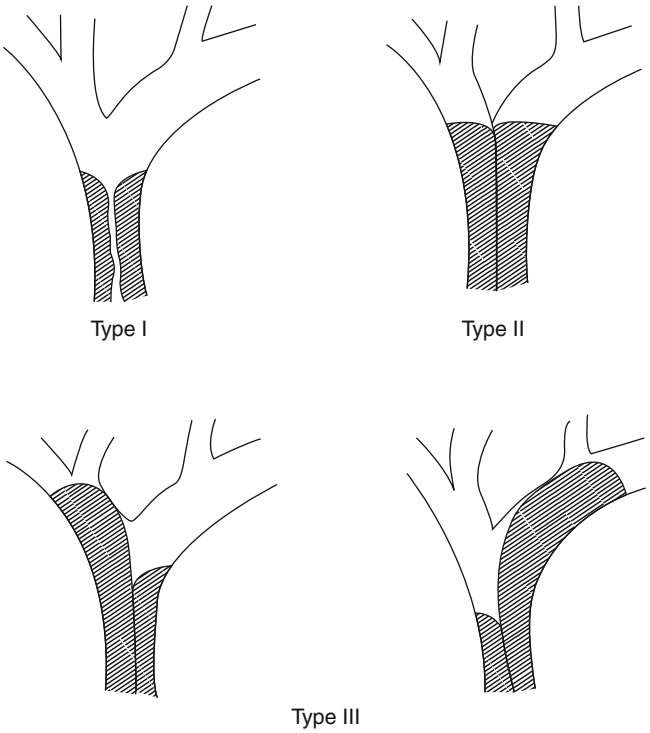

Fig. 4.1 Bismuth-Corlette classification for carcinoma of the hilus. Type I, non-obstructed primary confluence; Type II, obstruction limited to primary confluence; Type III, primary confluence with extension to the right or left secondary confluence (With permission from Bismuth and Corlette [4])

nodes along with a right or left hepatectomy may be warranted. For technical purposes, the longer extrahepatic course and therefore accessibility of the left hepatic duct can be exploited to facilitate bilioenteric reconstruction following resection. In this case, a right hepatectomy should be performed to ensure negative margins. However, if the tumor extends into the left hepatic duct, then a left hepatectomy should be performed, along with caudate lobectomy, for the same reason. This is certainly the case with Bismuth-Corlette type III tumors whereby IIIa tumors involve the confluence along with the right secondary biliary ducts while IIIb tumors involve the left secondary bile ducts. Hepatectomy is universally mandated in these cases in order to achieve complete tumor clearance. Type IV tumors, which by definition extend to involve the bilateral secondary biliary radicles, were traditionally considered unresectable, and patients with this extent of disease are typically referred for palliative treatments or liver transplantation. In addition, patients with multicentric tumors are considered Bismuth-Corlette type IV.

In response to the extension of tumor beyond the traditional Bismuth-Corlette borders, Starzl and others proposed a modification to this classification system, whereby type IIIa+ tumors would include tumors that penetrated both the anterior and posterior sectoral ducts and type IIIb+ in which the tumor extended into the segment 4, 3 and 2 ducts [5]. In addition, he proposed type IVa tumors where the right-sided component extended to the second bifurcation and type IVb which involved the segment 4, 3, 2 ducts. Lastly, type V would comprise the combination of type IVa and IVb.

Pitt and others from Johns Hopkins developed an expanded system that classifies the entire spectrum of cholangiocarcinoma from the intrahepatic ducts down to the ampulla of Vater including the gallbladder using nine stages [6]. Of 196 perihilar tumors comprising the Bismuth types in this series, 106 were resected with a median survival of 19 months and 5-year survival of 11 % [7]. Of note, they did not report a difference in survival for the 15 patients who had a hepatectomy as part of their procedure.

The French group spearheaded by Bismuth, evaluated 136 consecutive patients between 1960 and 1990 with hilar cholangiocarcinoma [8]. With the assistance of preoperative ultrasound, computed tomography, mesenteric angiography, intraoperative ultrasound and cholangiography, 23 of these patients were considered suitable for resection. There were three type I, three type II, 16 type III (9IIa, 7IIIb), and four type IV tumors. In this early series, only nine patients had negative margins with a 50 % 3-year survival. Local excision was performed in eight cases but only those with type I tumors had a margin and recurrence-free resection. In 2 of the 3 type II lesions, where local excision of the bile duct only was performed, both patients developed early recurrence. Conversely, 4 of 7 patients with type III lesions who had a concomitant hepatectomy along with bile duct resection had R0 resections and were disease-free. The authors concluded that some type II tumors may require caudate and/or segment 4 resection if a significant portion of the left hepatic duct is involved. In addition, they also suggested that resection in combination with liver transplantation should be considered for type IV lesions.

A similar study over the same period examined 94 patients with hilar cholangiocarcinoma stratified by Bismuth-Corlette stage [9]. Of the 40 patients that underwent resection, the majority presented with type III disease (62.5 %) followed by type IV (15 %) while type I and type II disease were seen in 12.5 and 10 % of patients respectively. Twenty-five patients had a concomitant hepatectomy along with bile duct resection while 4 of them required liver transplantation (all type IV). The overall resectability rate was 49 % and was dependent on the Bismuth-Corlette type with higher types (III, IV) requiring liver resection. In addition, tumors with bilateral vascular invasion were treated with primary hepatectomy, and reconstruction of contralateral vascular supply. Determining resectability was facilitated by the posterior approach to the hepatic hilus used to separate the remnant inflow structures proximal to the tumor at the biliary confluence in those tumors without hepatic parenchymal invasion and contained in the Glissonian sheath. The mean survival according to tumor location was 31 months for type I, 58 months for type II, 25 months for type III and 22 months for type IV lesions.

Another large report of 95 patients resected for hilar cholangiocarcinoma demonstrated an R0 resection rate of 43 %

for type I/II, 63 % type IIIa, 59 % of type IIIb and 72 % of type IV tumors likely due to the fact that the early stage tumors (I, II) only had hilar bile duct resections [10]. This translated into no 5 year survivors in the type I, II patients, with 48, 40, and 34 % 5 year survivors in type IIIa, IIIb, IV patients.

More recent updates, mainly from Asia, have challenged the traditional paradigm of resectability in advanced hilar tumors. The largest series from Nagoya describes 428 patients diagnosed between 2000 and 2008, of which 298 were resected [11]. They comprised 15 type I tumors (5 %), 21 type II (7 %), 120 type III (40 %), 142 type IV tumors (48 %). The surgical strategy was right hepatectomy for type I, II and IIIA lesions, standard or extended left hepatectomy for type IIIB lesions, and extended right or extended left hepatectomy or central hepatectomy for type IV lesions. With a majority of patients undergoing >50 % of their liver resected due to liberal use of portal vein embolization and aggressive resection of the portal vein (37 %) and hepatic artery (18 %), the authors achieved a 52 % 5 year survival rate for patients with R0, N0, M0 disease. However, there was no mention of whether the Bismuth-Corlette stage correlated with resectability or outcome. Meanwhile, other contemporary reports from Japan have failed to demonstrate a relationship between Bismuth-Corlette classification and survival [12–14].

Although this system simplifies the anatomical location of hilar cholangiocarcinoma, there are several considerations that are not evaluated. For example, the known variability of biliary tree can affect the Bismuth-Corlette classification. Some of the most common variations include a trifurcation at the biliary confluence of the right anterior and posterior sectoral ducts along with the left hepatic duct. Others include the drainage of either the right anterior or right posterior duct directly into the left hepatic duct. These anatomical considerations must be taken into account because they may render type IV tumors resectable. Another potential conflicting factor is the presence of a papillary tumor which may have a long intraductal mucosal component that is underestimated by standard imaging techniques. This is usually not the case with infiltrative tumors whose submucosal extent can be visualized as enhancement of the ductal wall. In summary, while the Bismuth-Corlette classification can be used as a common terminology to determine the likely extent of resection along anatomic borders of the biliary duct system, it has not served as a preoperative stating system in order to determine resectability or survival following resection.

4.3 Pathologic Staging Systems (AJCC, JSBS)

One of the major drawbacks of the Bismuth-Corlette classification however, is that it does not account for the radial extension of tumor away from the biliary ductal system into adjacent hepatic parenchyma, vascular structures and perihilar soft tissues. The American Joint Commission on Cancer (AJCC) developed a pathologic staging system which accounts for both the lateral spread of cancer as well as the presence of lymph node and distant metastases (Fig. 4.2). This tumor, node, metastases model (TNM) has been applied to several disease sites in the hope of stratifying patients to different survival categories based on the invasiveness or biology of the tumor.

Prior to the current 7th edition, the AJCC system separated the primary lesion into 4 T stages of which T1 was tumor confined to the bile duct wall and T2 was tumor

Anatomic stage/Prognostic groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a–b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1–3	N1	M0
Stage IVA	T4	N0–1	M0
Stage IVB	AnyT	N2	M0
	AnyT	Any N	M1

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)
N2	Metastasis to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes

Distant metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Fig. 4.2 American Joint Commission on Cancer 7th Edition TNM staging for Perihilar Bile ducts (With permission from AJCC)

beyond the bile duct wall [15]. This is followed by T3 lesions that involve the liver, gallbladder or pancreas or the ipsilateral portal vein or hepatic artery. A T4 lesion was one that extended to the main portal trunk or its left and right branches simultaneously, the common hepatic artery or other adjacent structures such as the colon, stomach, duodenum or abdominal wall. This system created some ambiguity with regard to the definition of "beyond" the bile duct wall. This was further complicated by the 5th edition, which had split T1 lesions into T1a (invading the subepithelial connective tissue) and T1b (invading the fibromuscular tissue) from T2 lesions which were described as those within the perifibromuscular connective tissue of the bile duct [16]. Histologically, the outer muscular layer of the bile duct is variable along its length [17]. While a continuous layer may be found in the distal CBD, intermittent muscle fibers are found along the middle portion of the duct with little or no muscle seen in its proximal portion. Therefore the distinction between a T1 and T2 tumor may be difficult in a densely inflamed bile duct tumor. Furthermore, the correct identification of a T3 lesion is highly dependent on its longitudinal location on the bile duct. For example, a T3 lesion in the middle duct is likely to be more advanced than a T3 lesion in the hilus or distal duct, which is in close proximity to their respective adjacent structures (i.e., the liver and pancreas). However, the separation of T3 lesions into two separate categories of visceral and vascular invasion updated in the 6th edition was noted to improve survival prediction [18].

A better system to separate depth of penetration between T1 and T2 lesions has been proposed by Hong et al. [19]. His group of four experienced pathologists examined 222 bile duct specimens with the operative definition of T1 as tumors confined to the outermost layer of muscle and fibrous tissue and T2 as tumors in the adipose tissue beyond the bile duct while preserving the T3 and T4 nomenclatures. They found that there was a statistically significant difference in survival between patients with T1 and T2 tumors; however, there was no difference in survival between T2 and T3 tumors and therefore no difference between Stages Ib and IIa in the 6th edition. This was likely due to the discrepancy in T staging depending on the location of the tumor whereby proximal and distal tumors were overstaged while middle tumors were understaged. They did note however, that patients with papillary and nodular tumors had an improved outcome than those with infiltrative growth patterns. In an attempt to standardize the T staging of extrahepatic bile duct tumors, the same authors examined the absolute depth of invasion measured in centimeters in the 222 patient cohort and stratified tumors into those with <5 mm of invasion, 5–12 mm of invasion and >12 mm of invasion based on censored local regression and recursive partitioning [20]. Using this technique, they noted a statistically significant decrease in survival as depth of invasion increased between groups. This difference remained significant on multivariate analysis.

Due to these observations, the T staging criteria were amended for the 7th Edition so that T1 are defined to be tumors confined to the bile duct with extension to the muscle layer or fibrous tissue while T2 are separated into T2a which are tumors that invade beyond the bile duct wall into surrounding adipose tissue and T2b which are tumors that invade adjacent hepatic parenchyma. Another important change in the 7th Edition was the separation of perihilar and distal bile duct cancer into separate staging categories. Perihilar carcinomas were defined as extrahepatic bile duct tumors arising anywhere proximal to the cystic duct up to the right and/or left hepatic ducts. Middle bile duct tumors, which are rare, are assigned depending on the type of resection needed for clearance: perihilar group if they required a hilar and hepatic resection or distal group if they required a pancreaticoduodenectomy. This separation allows for the proper staging with regard to invasion of adjacent structures such as the liver and pancreas. The other amendment to the T staging was the adjustment of T3 to unilateral vascular invasion only as this has been demonstrated to have a worse prognosis than hepatic parenchymal involvement which had been included in T3 lesions according to the 6th edition [21]. Lastly, T4 lesions, which are characterized by bilateral vascular invasion, bilateral secondary biliary radical involvement or the combination of unilateral vascular invasion with contralateral secondary biliary radical involvement have been upstaged to Stage IVa disease and differentiated from Stage IVb (distal nodal or metastatic disease) reflecting their low resectability rates while preserving the possibility for neoadjuvant chemotherapy and liver transplantation in that cohort of patients [22].

It is well known that the presence of lymph node metastases is directly correlated with increasing T stage. Overall, positive lymph nodes are found in 30–50 % of cases [23]. Often, the hilar and periductal nodes within the porta hepatis are involved primarily, but extension to periaortic, pericaval, celiac and superior mesenteric nodal basins can occur in advanced cases. In a study of 110 patients with hilar cholangiocarcinoma and 2,652 resected lymph nodes, 47 patients contained lymph node metastases (42.7 %). Out of 382 dissected lymph nodes 14 % contained metastases with the pericholedochal nodes involved most frequently (20.1 %) followed by periportal (15.4 %), common hepatic (15 %), paraaortic (14 %) and posterior pancreaticoduodenal (12.5 %) [24]. The authors found that the presence of nodal metastases was significantly higher in patients with pT3 disease than those with pT2 disease (64.7 % vs. 33.3 %, $P<0.005$) using the AJCC/UICC 5th Edition staging system.

Paraaortic nodal metastases translated to a worse outcome with 3 and 5 year survival rates of 12.3 and 12.3 % compared to patients with no lymph node metastases (55.4 and 30.5 %) or limited to regional nodal involvement (31.8 and 14.7 %). Of note, there were few patients who had isolated paraaortic lymph node involvement alone without positive regional nodes suggesting a progression of disease along existing lymphatic channels. In fact, lymphatic dye staining studies have demonstrated a distinct pathway from pericholedochal nodes to the posterior pancreatic, retroportal, common hepatic and paraaortic nodes [25, 26]. Therefore, in the current 7th Edition the N category has been edited to reflect this finding properly with N1 disease being regional (i.e. periportal) node involvement while presence of tumor in distant mesenteric or aortocaval nodes categorized as N2. Accordingly, N1 has been upstaged from Stage IIb to Stage IIIb while N2 disease is now considered Stage IVb even in the absence of widely metastatic disease reflecting its poor prognosis.

Much like other gastrointestinal tumors, lymph node involvement is also a major prognostic factor for overall and disease-specific survival. However, unlike gastric [27], pancreatic [28] and colon [29] carcinoma where specific guidelines for number of harvested lymph nodes for accurate staging of disease have been established, there are no such recommendations for hilar cholangiocarcinoma. The 6th Edition of the AJCC staging system defined the absence (N0) or presence (N1) of regional nodal disease based on the analysis of three lymph nodes despite minimal support from published studies. In fact, a large epidemiological study using the SEER database have suggested a minimum lymph node harvest of ten nodes for proper stage assignment [30]. From their cohort of 20,068 patients with extrahepatic bile duct cancers including gallbladder and ampullary cancers, those with node-negative tumors who had >10 lymph nodes in their specimen had the highest median survival of 36 months. Although a projection model using linear regression comparing the impact of increasing lymph node count on survival failed to show a statistically significant improvement ($P = 0.0742$), the authors concluded that the presence of at least ten negative lymph nodes were predictive of improved survival. Interestingly, this number was consistent among N0 and N1 disease in all anatomic sites except for ampullary cancers.

In response to this observation and the fact that the SEER data was contaminated with gallbladder cancer patients, our group embarked on a study to examine the importance of adequate lymph node assessment in extrahepatic bile duct cancers. Out of a cohort of 247 patients with cholangiocarcinoma, 144 with hilar cholangiocarcinoma were identified and noted to have a median total lymph node count (TLNC) of 3 with a range of 0–16 [31]. Multivariate analysis revealed that lymph node metastasis was an independent prognostic factor for DSS. Additionally, in patients who underwent R0, N0 resection, DSS was higher in those with higher TLNC. Using maximal chi-square analysis, the optimal lymph node harvest for hilar cholangiocarcinoma in our population was determined to be seven. In the 97 patients who had an R0 resection (with concomitant hepatectomy) and found to be node-negative based on a TLNC greater than seven, the 5 year DSS was significantly higher than those whose TLNC was below that number (85 % vs. 48 %). Another study from Japan examined the incidence of lymph node metastases in 209 cases of extrahepatic bile duct cancers excluding intrahepatic and periampullary tumors. The authors found a significant survival cutoff point in patients with at least five lymph nodes examined between those with 1–4 positive nodes and five or greater nodes positive for metastases [32]. They proposed the AJCC nodal classification should be amended to N0 (no regional node metastases), N1 (1–4 regional node metastases) and N2 (five or more regional node metastases). These observations likely reflect more accurate staging of patients with advanced disease as opposed to a therapeutic effect of lymphadenectomy. Although no randomized, controlled trials of lymphadenectomy specifically in cholangiocarcinoma have been performed, data from trials including periampullary tumors do not support the role of extended lymphadenectomy in bile duct tumors [33]. Besides overall number and number of negative lymph nodes, other groups have focused on the ratio of positive lymph nodes to the total number harvested [34]. This lymph node ratio (LNR) has been examined in other pancreatobiliary malignancies and found to have prognostic capabilities. Recently, Oshiro et al. found that a LNR ≥ 0.2 was an independent predictive factor of survival in multivariate analysis and supported the notion of more aggressive tumor biology [35].

Although the AJCC classification is most commonly used internationally, a separate pathologic staging system has been established by the Japanese Society of Biliary Surgery (JSBS) in 1981 and subsequently revised to its current 5th edition in 2003 (Fig. 4.3). In this system, the T classification is carefully separated into categories of invasion based on histologic landmarks such as mucosa, serosa and subserosa as well as depth of invasion into adjacent structures such as the liver or pancreas which stratified into less than 5 mm, between 5 and 20 mm and greater than 20 mm. Vascular invasion is distinguished between portal and hepatic arterial, with each type having three depths (adventitial, tunica medial, and tunica intimal with stenosis or obstruction) numbered 1–3 respectively. The type of tumor growth is also separated into papillary, nodular, flat types each with their own subcategories of expanding and infiltrating patterns. In addition, nodal metastases are numbered according to

$_{P}T$classification	
$_{P}T$	Contents
$_{P}T1$	m, fm, hinf0, panc0, pv0, a0
$_{P}T2$	ss, hinf1, panc1, pv0 ,a0
$_{P}T3$	se, hinf2, panc2 , pv1, a1
$_{P}T4$	si, hinf3, panc3 , pv2, pv3, a2, a3

Lymph node grouping			
Lymph node (site number)	Group		
	Hilar and proximal	Middle	Distal
Infrapyloric LN (6)	pN3	pN3	pN3
LN around the common hepatic artery (8)	pN2	pN2	pN2
LN at the splenic hilum (10)	pN3	pN3	pN3
LN along the splenic artery (11)	pN3	pN3	pN3
LN at the hepatic hilum (12h)	pN1	pN2	pN2
LN along the hepatic artery (12a)	pN1	pN2	pN2
Periportal LN (12p)	pN1	pN2	pN2
Pericholedochal LN (12b)	pN1	pN1	pN1
LN around the cystic duct (12c)	pN1	pN1	pN1
Posterior superior pancreatoduodental LN (13a)	pN2	pN2	pN2
Posterior inferior pancreatoduodental LN (13b)	pN3	pN3	pN3
LN along the superior mesenteric artery (14)	pN3	pN3	pN2
Para-aortic LN (16)	pN3	pN3	pN3
Anterior superior pancreatoduodenal LN (17a)	pN3	pN3	pN3
Anterior inferior pancreatoduodenal LN (17b)	pN3	pN3	pN3

Stage grouping	H(–) and P(–) and M(–)				H(+) and/or P(+) and/or
	pN0	pN1	pN2	pN3	M(+) and any N
pT1	I	II	III	IVa	IVb
pT2	II	III	III	IVa	IVb
pT3	III	III	IVa	IVb	IVb
pT4	IVa	IVa	IVb	IVb	IVb

m invasion limited to the mucosa, *fm* invasion limited to the fibromuscular layer, *ss* invasion limited to the subserosa, *se* invasion of serosal surface, *si* invasion beyond the serosa and invasion of other organs or structures, *hinf0* no direct invasion of the liver, or direct invasion limited to the fibromuscular layer of intrahepatic bile ducts, *hinf1* direct invasion of fibromuscular layer of intrahepatic ducts and/or liver parenchyma which invasion is not more than 5 mm in depth, *hinf2* direct invasion of liver parenchyma, which invasion is 5 mm or more but not more than 20 mm in depth, *hinf3* direct invasion of liver parenchyma, which invasion is 20 mm or more in depth, *panc0* no invasion of the fibromuscular layer of the inferior bile duct, *panc1* invasion of the fibromuscular layer of the inferior bile duct and/or pancreatic parenchyma of which invasion is not more than 5 mm in depth, *panc2* invasion of the pancreatic parenchyma of which invasion is 5 mm or more but not more than 20 mm in depth, *panc3* invasion of the pancreatic parenchyma of which invasion is 20 mm or more in depth, *pv0* no invasion of portal vein, *pv1* invasion of the adventita, *pv2* invasion of the media, *pv3* invasion of the intima, *a0* no invasion of hepatic arteries, *a1* invasion of the adventita, *a2* invasion of the media, *a3* invasion of the intima, *LN* lymph node, *H(–)* no liver metastasis, *H(+)* liver metastasis, *P(–)* no peritoneal metastasis, *P(+)* peritoneal metastasis, *M(–)* no distant metastasis, *M(+)* distant metastasis

Fig. 4.3 Japanese Society for Biliary Surgery Classification for Cholangiocarcinoma (With permission from Langebecks Archives of Surgery)

location of the node and classified according to location the primary tumor (hilar, middle or distal) in order to more accurately stage the extent of disease. For example, a lymph node at the hepatic hilus (#12 h) is considered N1 for a hilar tumor but N2 for a middle or distal duct tumor. Conversely, a lymph node along the superior mesenteric artery (#14) is considered

N2 for a distal tumor but N3 for a hilar or middle duct tumor. Although the JSBS system permits a very detailed description of tumor extent, there are no studies that report a correlation between JSBS stage assignment and either resectability or outcome. Recently, this system was compared to the AJCC/UICC TNM classification and it was found to provide improved survival stratification of patients according to stage [36]. However outside of Japan, it has not been applied extensively due to its inherent complexity and lack of validation.

Besides depth of invasion, presence and location of nodal and distant metastases, the AJCC recognized that certain stage-independent factors contribute to survival in these patients. Probably, the most well-established is the ability to achieve an R0 resection which is the major contributor to outcome. Additionally, tumor grade and lobar atrophy are features associated with poorer survival. Recently, papillary morphology has been demonstrated to carry a more favorable prognosis than nodular sclerosing tumors [37]. The 7th Edition of the AJCC recommended these factors be incorporated into the reporting of staging information of patients with hilar cholangiocarcinoma.

4.4 Preoperative Clinical Staging Systems (Gazzaniga, Blumgart)

Despite the anatomic and pathologic descriptions of the Bismuth-Corlette and AJCC staging systems, neither classification is associated with ability to determine resectability of the tumor which is the only proven modality for long-term survival. The propensity of hilar cholangiocarcinoma to spread longitudinally along the duct up to 2 cm beyond the location of the primary mass may underestimate the extent of disease on radiographic studies. It is possible that complete tumor clearance may not be appreciated even on palpation during operation highlighting the need for frozen section analysis of the margins. In addition, the presence of vascular invasion suggested on preoperative imaging may be technically difficult to assess intraoperatively given the lateral spread of tumor away from the bile duct to the portal vessels directly beneath it.

Therefore it is important for a clinical staging system to accurately predict resectability, need for hepatectomy and survival following R0 resection. Gazzaniga and colleagues first proposed a system accounting for the extrabiliary growth of tumor into surrounding vasculature in 1985 [38] (Fig. 4.4). The stages were divided into four categories where stage 1 was disease confined to the biliary confluence, stage 2 was disease that extended from the biliary confluence to secondary biliary ducts or vascular structures in the same lobe, stage 3 was disease that extended from the biliary confluence to secondary biliary ducts and/or vascular

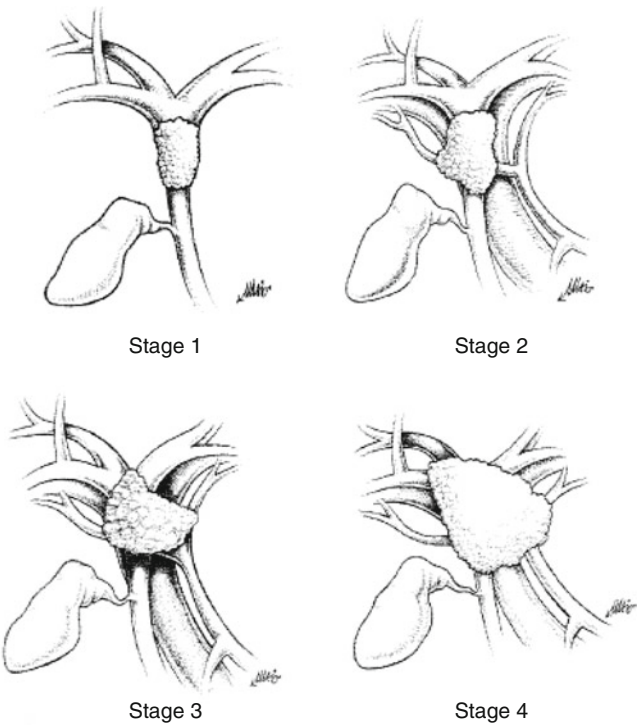

Fig. 4.4 Gazzaniga classification. Stage 1: hilar neoplasm with no extrabiliary involvement. Stage 2: hilar neoplasm with extrabiliary development concerning structures belonging to a single hepatic lobe and/or endobiliary diffusion in second-order branches of a single lobe. Stage 3: hilar neoplasm with endobiliary and/or extrabiliary diffusion to a single lobe, associated with infiltration due to the proximity of the contralateral lobe vascular structures, limited to the first-order branches. Stage 4: hilar neoplasm with large endo- and extrabiliary diffusion

structures in the same lobe and infiltration to the contralateral vascular structures while stage 4 was diffuse disease involving the entire porta hepatis. They proposed a treatment algorithm whereby stages 1–3 could undergo potentially curative resection by bile duct resection and caudate lobectomy for stage 1, a similar operation plus hemihepatectomy for stage 2, and the operation in stage 2 in addition to a vascular resection and reconstruction for stage 3 while surgical palliation would be reserved for stage 4. Using this system, the authors found a 43.5 % resectability rate for stage 1 tumors, 45.6 % for stage 2 tumors and 10.9 % for stage 3 tumors; however, the authors did not report the survival of patients according to stage [39].

At Memorial Sloan-Kettering, we have developed a preoperative clinical staging system for hilar cholangiocarcinoma using factors characterizing local tumor extent regardless of nodal or metastatic disease. In order to evaluate a patient for curative resection, tumor longitudinal growth along the biliary tree must be taken into account in conjunction with its radial growth into adjacent vascular structures as the combination will influence resectability. This is because ipsilateral involvement of vessels and bile ducts can be amenable to resection, whereas contralateral involvement

Table 4.1 Blumgart preoperative T staging system

Stage	Criteria
T1	Tumor involving biliary confluence ± unilateral extension to second-order biliary radicles
T2	Tumor involving biliary confluence ± unilateral extension to second-order biliary radicles **and** *ipsilateral* portal vein involvement ± *ipsilateral* hepatic atrophy
T3	Tumor involving biliary confluence + bilateral extension to second-order biliary radicles; **or** unilateral extension to second-order biliary radicles with *contralateral* portal vein involvement; **or** unilateral extension to second-order biliary radicles with *contralateral* hepatic lobar atrophy; **or** main or bilateral portal venous involvement

cannot be managed surgically. Lastly, lobar atrophy caused by long-standing biliary obstruction or by lack of portal blood flow has been a crucial determinant of resectability and subsequent therapy. First proposed in 1998 as four separate T stages, it was amended in 2001 to the current 3 T stages that include biliary extent, vascular involvement and lobar atrophy of the tumor (Table 4.1). These criteria are evaluated preoperatively using non-invasive, cross-sectional or ultrasound imaging with rare need for direct cholangiography through endoscopic or percutaneous approaches or angiography/portography for staging.

Using the original classification system, 90 patients with hilar cholangiocarcinoma were evaluated between 1991 and 1997 and 48 % of patients deemed T1 were resectable compared to 0 of T4 patients [40]. In addition, 58 % of T1 patients required concomitant hepatectomy for gross tumor clearance compared to 100 % of T2 and T3 tumors. Although the T-staging system does not account for N or M status, 39 % of T1 had evidence of metastatic disease compared to 53 % of those with T3 tumors. This translated into improved median survival of T1 patients compared to T3 tumors and although there was no difference between T3 and T4 tumors, there were no 5 year survivors in the T4 group.

In an updated series of patients, this Blumgart classification system was used to stratify 225 patients with hilar cholangiocarcinoma into 3 T categories including the previous 90 patients that had been staged [41]. Of the 219 that had complete staging information available, 87 were T1, 95 were T2, and 37 were T3 tumors. On logistic regression, increasing T stage significantly reduced the resectability rate and likelihood of R0 resection. While 33 (65 %) T1 patients required hepatectomy with two (4 %) portal vein resections, all T2 patients underwent liver resection with seven (24 %) requiring portal vein resection. Furthermore, distal and N2 nodal metastatic disease was significantly associated with increasing T-stage. Using Cox regression with T stage as a categorical covariate and T1 as a reference, median survival was reduced significantly as T stage increased (20 months for T1, 13 months for T2, 8 months for T3). In order to compare outcome data, 187 patients were staged using the AJCC system. Unlike the Blumgart T staging system, AJCC tumor stage did not correlate with resectability, likelihood of R0 resection and did not predict survival. In fact, 46 out of 80 patients who underwent resection and seven out of nine 5 year survivors were classified as AJCC Stage IV tumors.

The most contemporary series of 118 patients from Memorial Sloan-Kettering with hilar cholangiocarcinoma from 2001 to 2008 were staged by the updated preoperative classification [42]. Forty eight patients had primary tumor involvement of the biliary confluence but without unilateral extension into second-order biliary radicles, portal vein involvement or lobar atrophy and therefore T1 tumors. Forty one patients had T2 tumors due to ipsilateral lobar atrophy or portal vein involvement (n = 31 for both). There were 29 patients with T3 tumors, 10 due to main portal vein involvement, 7 due to extension to unilateral second-order biliary radicles and contralateral lobar atrophy, 9 due to extension to unilateral second-order biliary radicles and contralateral portal vein involvement, 2 due to extension to bilateral second-order biliary radicles, and 1 due to tumor encasing the contralateral hepatic artery. Using this system, resectability and feasibility of R0 resection decreased progressively with increasing stage (T1 to T3). Furthermore, the presence of metastatic disease precluding resection correlated with increasing T stage (T1 to T3).

The Blumgart system has also been evaluated by other groups. Hemming et al. evaluated 87 consecutive patients with resected hilar cholangiocarcinoma and retrospectively staged them simultaneously with the Bismuth-Corlette and Blumgart classifications [43]. There was no correlation between resectability and Bismuth-Corlette stage while 84 % of Blumgart T1 lesions were resectable followed by 55 % of Blumgart T2 lesions and 0 of Blumgart T3 lesions. The authors also highlighted the importance of the lobar atrophy/hypertrophy complex in determining survival following resection. However, on their univariate analysis, no staging system was predictive of survival due to a statistical lack of sufficient numbers for analysis. This phenomenon was suggested in another single institution report of 69 patients from the University of Wisconsin where the correlation between Blumgart T stage and resectability had a p-value of 0.06 [44]. Another underpowered study of 42 patients failed to demonstrate prognostic capability of any staging system [45].

Recently, a novel staging system has been proposed by Blechacz et al. [46]. Recognizing the fact that an optimal staging system is required in order to properly evaluate patients in clinical trials, they maintain that such a system would take into the account not only the stage of the tumor but also the physiological consequences of biliary and vascular obstruction as well as the performance status of the patient and effectiveness of available therapies. In their system, tumor stage would include size of the lesion, vascular encasement, lobar atrophy and extent of extrahepatic disease. The authors

suggest that the primary tumors should be separated into those that can be visualized on imaging and those that are radiographically occult. In addition, lesions should be stratified according to size greater or less than 3 cm. They also propose the presence of vascular encasement and subsequent lobar atrophy represent long-standing events that have a high likelihood of harboring regional micrometastases. Lastly, given recent evidence that the timing of the resolution of jaundice following biliary stenting leading to recovery of liver functional status, this variable is included in this proposed staging system [47]. This system is currently being validated.

Conclusion

In summary, there are currently several staging systems available in the management of hilar cholangiocarcinoma. Unlike other disease sites, most patients with perihilar malignancies have locoregional and/or distant spread which may be radiographically occult and prevent surgical intervention. Therefore, while pathologic staging of the specimen can provide definitive confirmation of extent of disease, decisions on therapy are often based on clinical judgment and/or intraoperative evaluation in unresectable cases. The Bismuth-Corlette system provides a good introduction to the level of biliary involvement by tumor and allows surgeons to standardize an operative plan. However, the growth pattern of hilar cholangiocarcinoma is such that local vascular (portal and arterial) as well as parenchymal atrophy from longstanding obstruction can adversely affect the potential for surgical resection. Given that long-term survival is dependent not only on tumor characteristics but also the ability to achieve a margin-negative curative resection, better preoperative staging is needed. The Blumgart system provides a more comprehensive framework to base preoperative decisions by predicting not only resectability, but also the likelihood of R0 resection and subsequent survival. However, the ideal system would incorporate this information along with status of regional or distant disease so that all patients could be stratified for clinical trials to test novel therapies for this aggressive malignancy.

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