Selection of Patients for Liver Resection and Liver Transplantation

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16.1 Introduction

Complete excision of viable tumor offers the only chance for cure for hilar cholangiocarcinoma. Resection and liver transplantation have each evolved to offer significant survival advantages over non-surgical treatments. Although the two options beg comparison, currently the indications for each are different.

Although early attempts at liver transplantation for hilar cholangiocarcinoma were associated with poor cancer-related survival [1–12], more recent results with neoadjuvant chemoradiation followed by liver transplantation have shown significant improvements [13–15]. Despite the renewed interest in liver transplantation, the global limitation of organ availability and the lack of Level I data tempers its widespread use.

Resection for hilar cholangiocarcinoma, or Klatskin tumor, has also evolved. The initial poor survival rates, associated with limited duct resection [16] (see Chap. 23) have increased with bile duct and extended liver resections [17–21] performed in high-volume centers (see Chap. 18). The resection rates, documented in various series containing over 50 patients from 1990 to 2006, have ranged from 45 to 94 % (Table 16.1). In these same series, the mortality and 5-year survival rates have ranged from 0 to 15 %, and 11 to 41 %, respectively [22–24]. In this chapter, we discuss the considerations when selecting a patient for resection or liver transplantation in the setting of hilar cholangiocarcinoma.

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16.2 Populations at Risk

As development of cholangiocarcinoma is predicated on the existence of chronic inflammation, it may theoretically be possible to identify patients at increased risk of harboring the disease. While numerous conditions have been found to predispose to its development, protocol-based methods for surveillance and detection are currently employed with the intent of unearthing localized, resectable hilar disease. Other candidates include those with disease confined to the extrahepatic bile duct in which underlying biliary inflammation and impaired hepatic function would otherwise obviate extended surgical resection.

With a cancer incidence ranging from 7 to 42 % [25–29] and a cumulative neoplasia risk of 11 % within the first 10 years of diagnosis [26], patients with primary sclerosing cholangitis (PSC) can be regarded as a population specifically at risk [22, 29, 30]. There are, unfortunately, no existing features to identify those with PSC who will go on to develop cholangiocarcinoma, making PSC patients obvious candidates for surveillance protocols. It is noteworthy that a majority of patients with PSC (80 %) will also harbor a concomitant diagnosis of inflammatory bowel disease (IBD), either ulcerative colitis or Crohn's disease [31]. It is currently unknown whether patients with a non-cholestatic pattern of blood chemistries and normal radiographic findings who harbor a diagnosis of IBD are at increased risk for developing PSC and subsequent cholangiocarcinoma, but they are widely assumed to be at low risk for these disorders [32]. Certainly, the sudden manifestation of right upper quadrant pain, cholangitis, or signs of biliary obstruction in an individual with stable IBD should prompt an evaluation of the biliary tree. Similarly, the appearance of abnormal liver function tests or elevated tumor markers in a patient with Crohn's disease or ulcerative colitis merits similar investigation.

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Table 16.1 Series of over 50 patients resected for hilar cholangiocarcinoma

Authors	Liver resection (%)	Negative margin (%)	Resection (n)	Year published	5-year survival (%)
Nakeeb*	14	26	56	1996	11
Gerhards*	29	14	112	2000	NA
Launois*	32	NA	151	2000	NA
Dinant*	38	31	99	2006	27
Todoroki*	58	14	101	2000	28
Seyama*	67	64	87	2003	40
Kawarada*	75	64	65	2002	26
Klempnauer [131]	77	77	151	1997	28
Jarnagin [75]	78	78	80	2001	26
Kosuge*	50	52	65	1999	40
Jarnagin*	82	77	106	2005	NA
Neuhaus [84]	85	61	80	1999	22
Miyazaki [85]	86	71	76	1998	26
Kawasaki [133]	54	68	79	2003	30
Nimura [97]	70	100	46	1990	41
Hemming*	66	80	53	2005	35

*References found in Suggested Reading List

16.3 Diagnostics

16.3.1 Serological Testing and Imaging

Except in cases where palliation is the chief consideration, a tissue diagnosis of cholangiocarcinoma informs all subsequent decision making. Early detection of cholangiocarcinoma, however, is a formidable obstacle. Current diagnostic approaches offer suboptimal yield and must rely on a combination of serologic testing, imaging modalities, pathologic analyses, and a high index of clinical suspicion. Often times, an elevation in tumor associated markers, particularly CA 19-9, initiates further workup by clinicians to establish the presence of biliary pathology. The diagnosis of cholangiocarcinoma on the basis of this test alone is problematic, however. For example, in patents without PSC, a sensitivity of 53 % is reported at a value of 100 U/ml. This decreases to 33 % for patients with early-stage cholangiocarcinoma [33]. In these individuals, the negative predictive value ranged from 76 to 92 %. In the PSC population, sensitivity and specificity for cholangiocarcinoma detection were improved at 89 and 86 %, respectively. Increasing the threshold of concern to 129 U/ml for PSC patients improved the specificity to 98.5 %, but lowered the sensitivity to 78.6 %. In these patients, the positive predictive value was 57 % [34–36]. An elevation in CA 19-9 is also observed in the setting of cholangitis and hepatolithiasis [34], but is missing entirely in patients lacking the blood type Lewis antigen [36, 37]. For these reasons, in the absence of known risk factors or virtually diagnostic imaging studies, a diagnosis of cholangiocarcinoma should not be entertained on the basis of this tumor marker alone [34]. Conversely, additional testing should be sought if warranted by clinical suspicion despite near normal CA 19-9 levels.

An elevated CA 19-9 ordinarily precipitates further imaging of the liver and biliary tree, which should be employed with the intent of assessing tumor extent, the level of biliary obstruction, the technical feasibility of resection, and the calculation of a future liver remnant when resection is entertained [36]. While abdominal ultrasound can sometimes reveal the presence of biliary ductal dilatation, establish a diagnosis of hepatolithiasis, and provide evidence of biliary mass lesions, it can also be used in duplex mode to assess the degree to which central tumors impinge on vascular structures [22, 38, 39]. However, ultrasonographic findings have largely been supplanted by the use of cross-sectional imaging. Computed tomography (CT) is helpful in this regard and is often the first modality employed in a patient with an elevated CA 19-9 or obstructive jaundice. A typical finding is the presence of biliary ductal dilatation proximal to a blocked choledochus. Not infrequently, lobar atrophy is present from long-standing biliary obstruction or portal vein involvement on the side of tumor. However, an obvious mass is sometimes lacking on CT despite findings that would otherwise suggest neoplasia. For this reason, magnetic resonance imaging (MRI) coupled with magnetic resonance cholangiopancreatography (MRCP) is emerging as the imaging modality of choice given its ability to provide superior anatomic resolution of the intra- and extrahepatic bile ducts and adjacent vascular structures. Cholangiocarcinomas, appearing hypointense on T1-weighted images, and hyperintense on T2, can be further delineated using gadolinium contrast enhancement, which can help further define vascular encasement. Additional information can be gained with respect to invasion of adjacent liver parenchyma as well as the presence of distant and nodal metastases [22, 34, 36, 40–44]. While sensitivity and positive predictive value are roughly equivalent

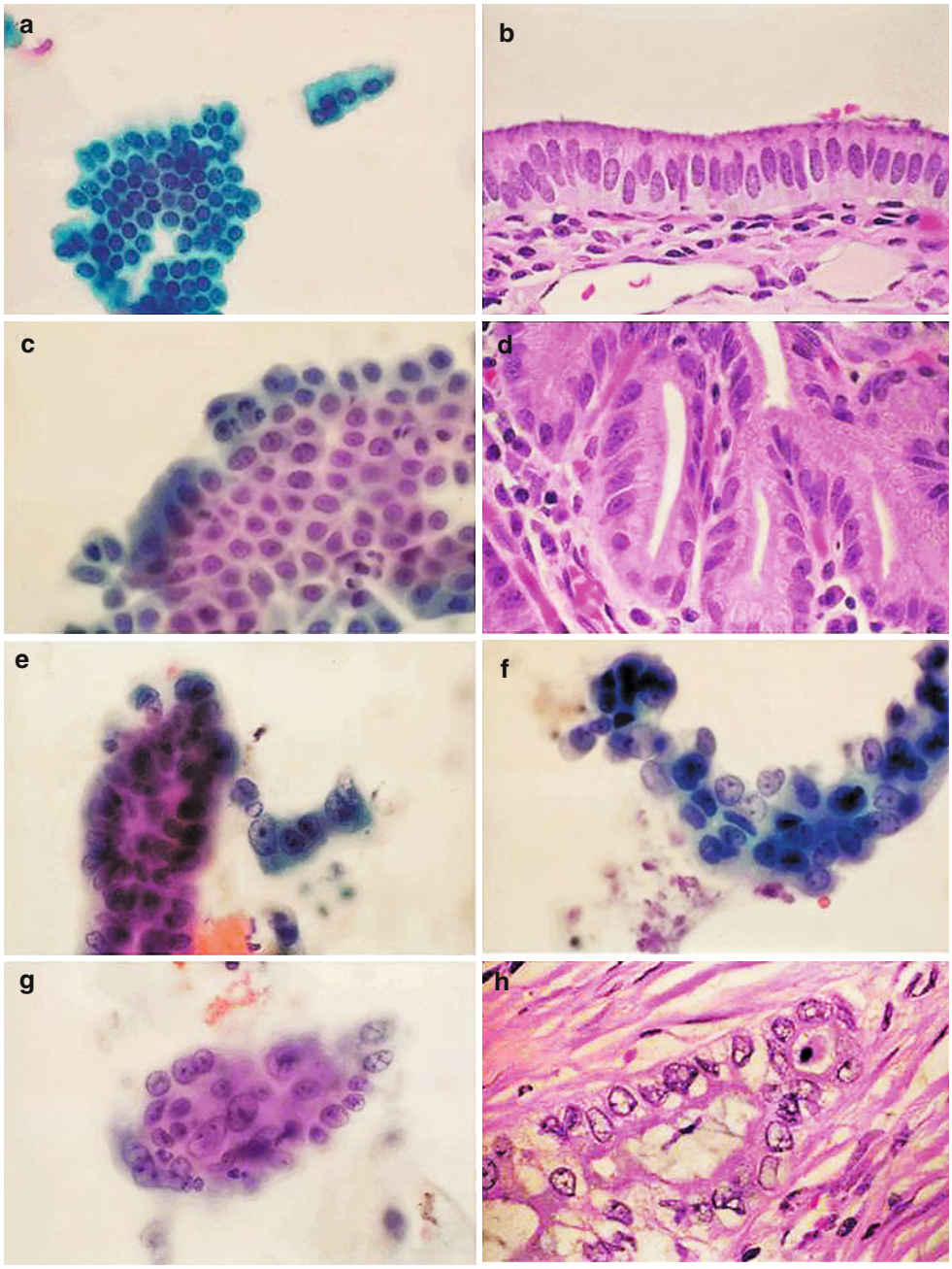

Fig. 16.1 Cytology. (**a**) Cytology of benign bile duct epithelium with sheets and strips of cells with bland round to oval nuclei (Papanicolaou). (**b**) Histology of benign bile duct epithelium with a single layer of columnar cells (H&E). (**c**) Cytology of reactive bile duct epithelium with mildly enlarged nuclei, prominent nuclei, and overlying inflammation. (**d**) Histology of reactive bile duct epithelium. (**e**–**g**) Cytology of adenocarcinoma with irregularly arranged groups of cells with increased nuclear: cytoplasmic ratio and nuclear molding, as well as increased nuclear size, anisonucleosis, and marked nuclear irregularity. (**h**) Histology of adenocarcinoma (cholangiocarcinoma) (Figure and legend reproduced with permission from Advances in Anatomic Pathology [47])

between the two modalities, comparisons in the literature have noted superior diagnostic accuracy for MRI/MRCP (92 % versus 56–84 % for CT), an improved specificity (79 % versus 33–57 %), and a higher negative predictive value (73 % versus 7–50 %) [36, 45, 46].

16.3.2 Cytologic Evaluation

Whereas imaging remains a vital component in the multimodality approach to diagnosis, pathologic evaluation is considered the gold standard. In these cases, a tissue diagnosis often hinges on cytology, which is not always confirmatory, and sometimes difficult to acquire. Diagnostic attempts via percutaneous fine needle aspiration (FNA) should be discouraged due to the theoretical risk of tumor seeding. Preferably, tissue sampling is obtained by endoscopic retrograde cholangiopancreatography (ERCP) in conjunction with over-the-wire brush sampling of a malignant-appearing stricture. Accessing the biliary tree in this manner allows for characterization of benign, atypical, suspicious, and overtly malignant-appearing epithelia (Fig. 16.1) [47]. After processing, Papanicolaou-stained slides of benign-appearing cells appear as sheet-like monolayers and orderly palisades with

Table 16.2 Diagnostic categories for biliary brush cytology

Diagnostic category	Definition	Management
Unsatisfactory	Specimen is nondiagnostic: insufficient cellular material for diagnosis, extensive artifact or specimen obscured by acellular debris	Additional attempts at biliary access required
Negative for malignancy	Benign-appearing cells in cohesive monolayers (honeycombing) and / or orderly palisades. Material is adequate for cytologic interpretation.	Additional testing unwarranted unless inconsistent with abnormal clinical or radiologic findings
Atypical indeterminate	Cells demonstrate benign, reactive changes which may manifest as nuclear enlargement, mild variation in nuclear size, and 1–2 prominent nucleoli. Occasional mitotic figures and degenerative changes may be present. Cells maintain normal tissue architecture with little crowding or overlap. Normal N/C ratio and nuclear contours are observed. Although malignancy cannot be excluded, changes are likely a function of associated ductal inflammation. This category may encompass what was previously regarded as low-grade dysplasia	Must be correlated with available clinical and radiologic data which. Timing of follow-up and repeat cytology predicated on suspicion for neoplasia
Suspicious for malignancy	Highly-dysplastic cells that display some, but not all of the features of malignancy. This may include clumping of cells with prominent nuclear crowding; irregular nuclear membranes; high N/C ratio; coarse chromatin and distinct; prominent nucleoli	Timely follow-up required. Repeat biliary access recommended in 1–3 months. May be interpreted in context of additional clinical and radiographic studies
Adenocarcinoma	Cells with unquestionable features of malignancy	No additional confirmation required

Modified from deBellis et al. [49], Henke et al. [47] and Lograno and Waxman [53]

granular chromatin and basally-oriented nucleoli. Localized infection or biliary inflammation can alter the morphology of collected material, manifesting as nuclear enlargement and increased prominence of nucleoli. Mitotic figures can also appear, as can hyperchromasia, chromatin clumping, and vacuolization of the cytoplasm. However, nuclear/cytoplasmic ratio remains unaltered, cells maintain their normal level of cohesiveness, and their nuclear appearance is otherwise unchanged [47]. Reactive changes of this type should not be confused with neoplastic transformation. Notwithstanding, some cytologic features should raise awareness of the potential for malignant progression. These include clustering of cells and crowding or overlapping of nuclei; increasing irregularity of nuclear membranes; a trend toward a more abundant nuclear: cytoplasmic ratio; coarse chromatin; and distinct, prominent nucleoli [48, 49]. Although the natural history of these lesions is currently unknown, they should be regarded with suspicion, particularly in patients with PSC or other chronic inflammatory lesions of the bile duct, where they may represent a point on a neoplastic continuum. In this setting, the theoretical risk of malignant transformation should stimulate more rigorous follow-up and encourage more frequent biliary sampling.

Although the ability to discriminate between dysplasia and overt malignancy can be difficult with cytology, features used to distinguish benign from malignant strictures include the presence of nuclear molding, chromatin clumping, and a substantially increased nuclear-cytoplasmic ratio [50]. Adenocarcinoma of the biliary tract can also harbor anisonucleosis, irregular nuclear contours/grooves, enlarged nuclei/nucleoli, and altered cell polarity, amongst other features [47]. Because of the subjective nature of cytologic interpretation and the potential for interobserver variation [49, 51, 52], we endorse the system proposed by Logrono and Waxman for the reporting of biliary cytology (Table 16.2) [53].

In reality, little may separate higher grades of dysplasia from what is clearly malignant. This, coupled with a lack of uniform interpretation of diagnostic criteria, has caused reported sensitivities for brush cytology to vary widely. With sensitivities typically ranging from 20 to 60 % [36, 54, 55], the inability to secure a diagnosis with this technique can be influenced by a variety of additional factors. As cholangiocarcinomas are tumors of the bile duct epithelium, those that fail to penetrate into the lumen (submuscosal spread) will not be sampled appropriately. Sampling error can also be encountered due to the paucicellular, desmoplastic nature of the surrounding environment in which these tumors frequently arise. The chronic inflammatory milieu common to the biliary tree in patients with PSC can introduce further ambiguity. Well-differentiated tumors such as mucinous and papillary types may also generate false negatives as these tumors are difficult to interpret on cytology. Tumors may occur at sites difficult to access, their location obviating the use of various biopsy techniques. Finally, collected material may be insufficient for analysis [36, 54]. In contrast, the diagnostic specificity of this technique has seldom been questioned, consistently approaching 100 % in most studies [54].

To improve the diagnostic yield of cytology, the use of repeat over-the wire brushings during separate procedures has been advocated in the setting of dysplasia or when cholangiocarcinoma is suspected [56–61]. Two advanced cytologic techniques have also emerged recently as important aids to diagnosis. Both techniques, fluorescent in situ hybridization (FISH) and digital image analysis (DIA), capitalize on the near-universal propensity for biliary cancer to exhibit chromosomal instability. Fluorescently-labeled DNA

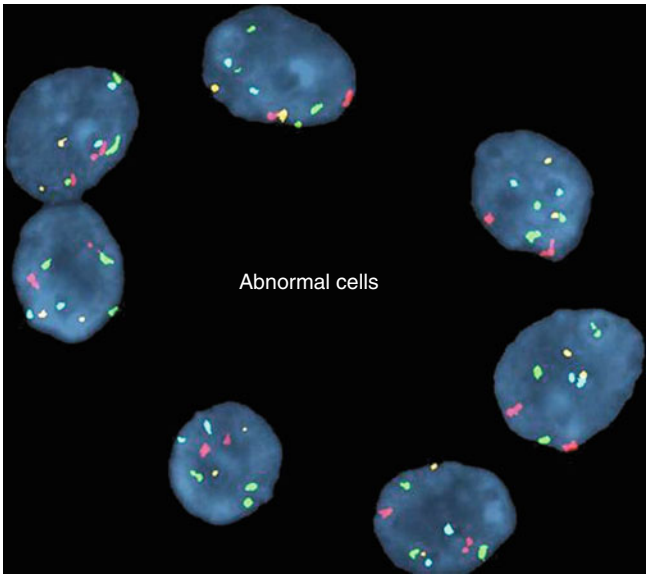

Fig. 16.2 Fluorescence in situ hybridization of biliary brushing. A representative fluorescence micrograph of biliary brushings from a patient with cholangiocarcinoma is shown here. Each colored spot represents one chromosome; therefore, two spots per color are indicative of the normal diploid state. In this example, >2 spots are seen for more than one color (indicating more than one chromosome pair is abnormal), leading to a diagnosis of polysomy (Figure reproduced with permission from the *Journal of Hepatology* [34])

probes are used in the case of FISH to detect aneuploidy or abnormalities of particular loci (gain or deletion), while DIA utilizes the stoichiometric binding properties of a cytochemical stain to quantitate nuclear DNA as a ratio of normal ploidy. Chromosomes specifically affected include 3, 7, and the 9p21 band. In this context, a finding of FISH polysomy can be equated with cytologic malignancy (Fig. 16.2). In like manner, DNA tetraploidy (DNA index >1.89) in non-PSC patients can be viewed similarly. Investigators who have examined the use of these techniques in conjunction with conventional cytology have noted an overall improvement in sensitivity without compromising specificity in patients with malignant-appearing strictures. In this population, results demonstrate that FISH has the highest sensitivity amongst those without PSC, while retaining appropriate levels of specificity. In patients with PSC, FISH retains the highest sensitivity of the three techniques. Specificity is lower, however. DIA results demonstrating aneuploidy (DNA index from 1.12 to 1.89) appear to have intermediate sensitivity and specificity compared to cytology and FISH, but its addition to PSC and non-PSC groups increases the malignant detection rate by twofold relative to cytology alone when clinical decision-making is predicated strictly on unequivocally positive cytologic results (Tables 16.3 and 16.4) [62]. As such, the inclusion of such diagnostic methodologies should be viewed as a requirement for institutions contemplating the implementation of transplant-based protocols.

16.3.3 Adjunctive Measures

Newer techniques of endoscopic retrograde cholangioscopy may facilitate direct examination of suspicious lesions and subsequent biopsy [63–67]. This method has been used extensively in the therapeutic approach to benign biliary disease. However, in the setting of cholangiocarcinoma, its utility as a screening or diagnostic tool has yet to be confirmed in a sizable cohort. With advancements in fiberoptics, it is expected that this technology will continue to evolve. The newly developed-SpyGlass Direct Visualization System™ is one such example. Cholangioscopy using this system allows for intraductal biliary imaging in all four quadrants, thereby permitting tissue sampling under direct visualization. Experience gained with its use may eventually increase the ability to discriminate benign from malignant biliary lesions.

On many occasions, a combination of methods is required when evaluating a suspicious biliary lesion. If an initial ERCP and/or cytologic diagnosis is evasive, then endoscopic ultrasound (EUS) may prove useful when examining this region. In this regard, EUS can offer greater resolution when compared to conventional cholangiography, thereby allowing the detection of a tumor mass or an infiltrating process. Vascular invasion can also be identified as can the presence of malignant-appearing lymph nodes [54]. Moreover, EUS-guided FNA of strictures, masses, and suspicious lymph nodes can supplement conventional techniques when cholangiography and/or cytology proves unremarkable. The technique frequently requires sphincterotomy and is procedurally difficult. A compilation of studies has revealed its overall cancer detection rate to be 33 % [49]. However, with some reports indicating a sensitivity closer to 100 % [61, 68, 69], the skill of the endoscopist, the experience of the cytopathologist, and the stringency of the cytologic criteria used likely inform results.

Historically, a variety of endoluminal sampling techniques have been applied to cytodiagnosis. Duodenal aspirates used in 1960's and 70's carried a high false positive rate. This technique was largely supplanted by intraductal bile aspiration cytology, the sensitivity of which ranged from 6 to 32 % across multiple studies. Despite their simplicity and low cost, these techniques should be considered inferior to contemporary cytologic methodologies [49, 54]. Neither approach should be employed routinely in surveillance protocols.

Occasionally, cytopathologic evaluation can be conducted on the material retrieved from occluded biliary stents. With diagnosis being deferred until after stent removal, the clinical utility of this sampling technique is questionable in most settings. However, in situations where frequent stent exchanges are required to maintain biliary patency, the examination of stent-adherent material may complement other sampling

Table 16.3 Sensitivity, specificity, positive predictive value, and negative predictive value of cytology, DIA, and FISH for the detection of malignancy by stricture classification

	Sensitivity (95 % CI)	Specificity (95 % CI)	PPV (95 % CI)	NPV (95 % CI)
Non-PSC patients				
Proximal				
Cytology (positive or suspicious)	9 % (0.01–0.30)	100 % (0.71–1)	100 % (0.16–1)	37 % (0.20–0.56)
Positive	4 % (0.001–0.24)	100 % (0.71–1)	100 % (–)	35 % (0.19–0.55)
Suspicious	4 % (0.001–0.24)	100 % (0.71–1)	100 % (–)	35 % (0.19–0.55)
DIA (aneuploid or tetraploid)	30 % (0.12–0.54)	90 % (0.55–1)	86 % (0.42–1)	39 % (0.20–0.61)
Tetraploid	5 % (0.001–0.25)	100 % (0.69–1)	100 % (–)	34 % (0.18–0.54)
Aneuploid	25 % (0.09–0.49)	90 % (0.55–1)	83 % (0.36–0.99)	37 % (0.19–0.59)
FISH (polysomy or trisomy)	63 % (0.38–0.84)	100 % (0.66–1)	100 % (0.73–1)	56 % (0.30–0.80)
FISH polysomy	31 % (0.12–0.56)	100 % (0.66–1)	100 % (0.54–1)	41 % (0.21–0.64)
FISH trisomy	31 % (0.12–0.56)	100 % (0.66–1)	100 % (0.54–1)	41 % (0.21–0.64)
Distal				
Cytology (positive or suspicious)	41 % (0.29–0.54)	96 % (0.86–0.99)	93 % (0.77–0.99)	54 % (0.43–0.65)
Positive	20 % (0.11–0.31)	100 % (0.93–1)	100 % (0.75–1)	47 % (0.37–0.58)
Suspicious	21 % (0.12–0.33)	96 % (0.86–0.99)	87 % (0.62–0.98)	47 % (0.37–0.57)
DIA (aneuploid or tetraploid)	49 % (0.36–0.62)	98 % (0.88–1)	97 % (0.84–1)	57 % (0.45–0.69)
Tetraploid	16 % (0.08–0.27)	100 % (0.92–1)	100 % (0.69–1)	45 % (0.35–0.56)
Aneuploid	33 % (0.22–0.46)	98 % (0.88–1)	95 % (0.77–1)	50 % (0.39–0.62)
FISH (polysomy or trisomy)	59 % (0.46–0.71)	92 % (0.80–0.98)	90 % (0.77–0.97)	63 % (0.50–0.74)
FISH polysomy	48 % (0.35–0.60)	100 % (0.93–1)	100 % (0.88–1)	59 % (0.48–0.70)
FISH trisomy	11 % (0.04–0.21)	92 % (0.80–0.98)	64 % (0.31–0.89)	44 % (0.34–0.54)
PSC patients				
Cytology (positive or suspicious)	41 % (0.18–0.67)	97 % (0.90–1)	78 % (0.40–0.97)	87 % (0.77–0.93)
Positive	18 % (0.04–0.43)	100 % (0.95–1)	100 % (0.29–1)	83 % (0.73–0.90)
Suspicious	23 % (0.07–0.50)	97 % (0.90–1)	67 % (0.22–0.96)	83 % (0.73–0.91)
DIA (aneuploid or tetraploid)	43 % (0.18–0.71)	87 % (0.76–0.94)	43 % (0.18–0.71)	87 % (0.76–0.94)
Tetraploid	14 % (0.02–0.43)	95 % (0.86–0.99)	40 % (0.05–0.85)	83 % (0.72–0.91)
Aneuploid	28 % (0.08–0.58)	92 % (0.82–0.97)	44 % (0.14–0.79)	85 % (0.74–0.92)
FISH (polysomy or trisomy 7 or 3)	70 % (0.44–0.90)	86 % (0.75–0.93)	57 % (0.34–0.78)	92 % (0.82–0.97)
FISH polysomy	47 % (0.23–0.72)	100 % (0.94–1)	100 % (0.63–1)	88 % (0.78–0.94)
FISH trisomy	23 % (0.07–0.50)	86 % (0.75–0.93)	31 % (0.09–0.61)	81 % (0.69–0.89)

Reprinted with permission from *Gastroenterology* [62]
PPV positive predictive value, *NPV* negative predictive value, *CI* confidence interval, (–) insufficient number of patients to calculate 95 % CI

methods when a lesion appears suspicious for malignancy. Pooled data indicates the overall sensitivity of stent examination to be 32 % [49].

Finally, techniques which can obtain more substantial tissue samples offer the prospect of improving diagnostic yield through the maintenance of tissue architecture, an essential component in pathologic diagnosis. The use of endoscopic forceps biopsy appears to corroborate this assertion, especially when combined with biliary brushings where in some cases it has contributed to a two-fold increase in diagnostic sensitivity [54]. Similar to EUS, the technique requires advanced endoscopic proficiency and may not be suitable for some lesions. Theoretically, an increased risk of bile duct injury is also incurred. This approach may be considered when a diagnosis is in question. Likewise, the introduction of various cutting and scraping devices, through pre-existing percutaneous transhepatic biliary drainage (PTBD) tubes, may also contribute to enhanced diagnostic yield. Two studies examining the use of the 9- French Simpson atherectomy catheter, which can obtain tissue samples 0.5–2.0 cm in length, noted sensitivities of 79 and 97 %, respectively. Specificity was retrospectively reported to be 100 %, positive predictive value 100 %, and negative predictive value 93 % [54, 70]. At the University of Utah, we have used the modern-day Silverhawk™ atherectomy catheter to similar effect.

Access to the biliary tree through pre-existing PTBD tubes can also facilitate a rendezvous approach when selective bile duct cannulation fails or a tight stricture interferes with conventional endoscopic techniques [70–73]. The rendezvous procedure combines an endoscopic technique with PTBD access to allow the antegrade passage of a guidewire through the native papilla for the purpose of establishing ERCP access. This technique can be combined with variety of biopsy and visualization techniques including EUS,

Table 16.4 Sensitivity, specificity, positive predictive value, and negative predictive value of cytology, DIA, and FISH for the detection of malignancy by stricture classification when cytology is *neither positive nor suspicious*

	Sensitivity (95 % CI)	Specificity (95 % CI)	PPV (95 % CI)	NPV (95 % CI)
Non-PSC patients				
Proximal				
DIA (tetraploid or aneuploid)	28 % (0.1–0.53)	90 % (0.55–1)	83 % (0.36–0.99)	41 % (0.21–0.64)
Tetraploid	5 % (0.001–0.27)	100 % (0.69–1)	100 % (–)	37 % (0.19–0.58)
Aneuploid	22 % (0.06–0.48)	90 % (0.55–1)	80 % (0.28–0.99)	39 % (0.20–0.61)
FISH (polysomy or trisomy 7 or 3)	59 % (0.33–0.81)	100 % (0.66–1)	100 % (0.69–1)	56 % (0.30–0.80)
FISH polysomy	23 % (0.07–0.50)	100 % (0.66–1)	100 % (0.40–1)	41 % (0.21–0.64)
FISH trisomy (7 or 3)	35 % (0.14–0.62)	100 % (0.66–1)	100 % (0.54–1)	45 % (0.23–0.68)
FISH (polysomy or trisomy) and DIA (aneuploid or tetraploid)	23 % (0.07–0.50)	100 % (0.66–1)	100 % (0.40–1)	41 % (0.21–0.64)
FISH (polysomy or trisomy) or DIA (aneuploid or tetraploid)	65 % (0.38–0.86)	89 % (0.52–1)	92 % (0.61–1)	57 % (0.29–0.82)
Distal				
DIA (aneuploid or tetraploid)	25 % (0.12–0.42)	98 % (0.87–0.99)	90 % (0.55–1)	60 % (0.48–0.72)
Tetraploid	5 % (0.007–0.19)	100 % (0.91–1)	100 % (0.16–1)	55 % (0.43–0.67)
Aneuploid	19 % (0.08–0.36)	98 % (0.87–0.99)	87 % (0.47–1)	58 % (0.46–0.70)
FISH (polysomy or trisomy 7 or 3)	35 % (0.20–0.52)	93 % (0.82–0.99)	81 % (0.54–0.96)	64 % (0.51–0.75)
FISH polysomy	22 % (0.10–0.38)	100 % (0.92–1)	100 % (0.63–1)	61 % (0.49–0.72)
FISH trisomy (7 or 3)	13 % (0.04–0.29)	93 % (0.82–0.99)	62 % (0.24–0.91)	57 % (0.45–0.69)
FISH (polysomy or trisomy) and DIA (aneuploid or tetraploid)	15 % (0.05–0.31)	98 % (0.87–1)	83 % (0.36–0.99)	58 % (0.46–0.70)
FISH (polysomy or trisomy) or DIA (aneuploid or tetraploid)	48 % (0.31–0.66)	93 % (0.80–0.98)	85 % (0.62–0.97)	68 % (0.55–0.80)
PSC patients				
DIA (aneuploid or tetraploid)	14 % (0.004–0.58)	88 % (0.77–0.95)	12 % (0.003–0.53)	90 % (0.79–0.96)
Tetraploid	0 (0–0.41)	97 % (0.88–0.99)	0 (0–0.84)	89 % (0.79–0.95)
Aneuploid	14 % (0.004–0.58)	91 % (0.81–0.97)	17 % (0.004–0.64)	90 % (0.79–0.96)
FISH (polysomy or trisomy 7 or 3)	60 % (0.26–0.88)	87 % (0.76–0.94)	43 % (0.18–0.71)	93 % (0.83–0.98)
FISH polysomy	20 % (0.02–0.56)	100 % (0.94–1)	100 % (0.16–1)	88 % (0.79–0.95)
FISH trisomy (7 or 3)	40 % (0.12–0.74)	87 % (0.76–0.94)	33 % (0.10–0.65)	90 % (0.79–0.96)
FISH (polysomy or trisomy) and DIA (aneuploid or tetraploid)	14 % (0.004–0.58)	98 % (0.91–1)	50 % (0.01–0.99)	90 % (0.80–0.96)
FISH (polysomy or trisomy) or DIA (aneuploid or tetraploid)	67 % (0.30–0.92)	75 % (0.62–0.86)	30 % (0.12–0.54)	93 % (0.82–0.99)

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PPV positive predictive value, *CI* confidence interval, *NPV* negative predictive value, (–) insufficient number of patients to calculate 95 % CI

cholangioscopy, forceps biopsy, and endoscopic brushings to improve diagnostic yield.

16.4 Liver Resection

16.4.1 Assessing Resectability

The surgeon must determine two things for resectability: (1) whether an R0 resection can be achieved and (2) the minimum amount of remnant liver volume needed to survive. Distant metastatic disease (including liver lesions not contiguous with the primary biliary tumor) and involvement of Level (L) three lymph nodes (those along the celiac artery, the superior mesenteric artery or the aortocaval groove) preclude curative resection. Otherwise, it is the extent of local disease that determines whether the cancer is resectable.

16.4.1.1 Assessing the Possibility of an R0 Resection

Hilar cholangiocarcinoma lesions are often not visible as discrete masses on imaging as the majority are of the sclerosing macroscopic subtype [74]. Obtaining tissue confirmation is therefore difficult and diagnosis is often made through a combination of factors including patient age and risk factors, signs and symptoms, CA19-9, and pattern of ductal dilatation (see Diagnostics, above) [26, 33].

The ability to resect for cure has been redefined by reports of significantly improved survival from high-volume centers describing aggressive resections of not

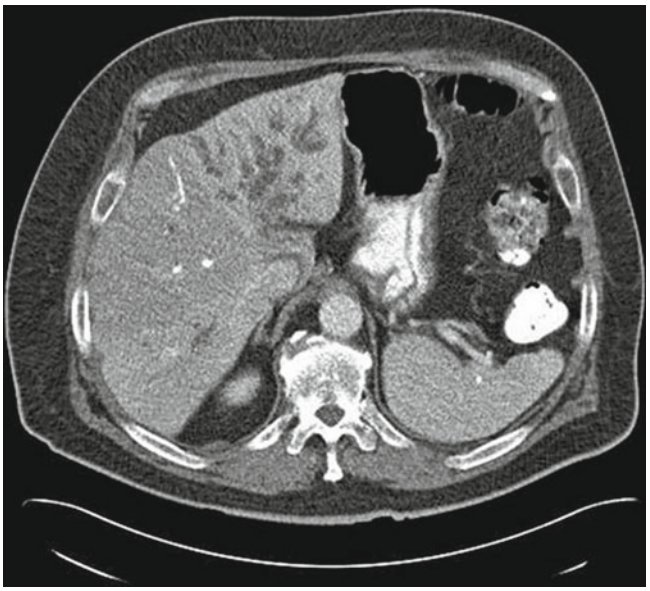

Fig. 16.3 CT scan demonstrating in a patient with hilar cholangiocarcinoma showing left-dominant biliary ductal dilatation without a common confluence suggesting involvement of the second-order biliary radicals

only the bile duct lesion, but also the ipsilateral liver and draining nodes [17–21]. Surgery is avoided if the disease in the potential remnant liver involves the second order biliary radicals, as the risk of complications from multiple biliary anastomoses (bile leaks, anastomotic strictures, residual intrahepatic disease) is greater [75, 76]. If the retropancreatic bile duct is involved, an added pancreaticoduodenectomy can offer a survival advantage [24]. In cases where a discrete mass is not visible, the longitudinal extent of disease is determined by the pattern of intrahepatic bile duct dilatation proximal to the lesion (Fig. 16.3). Circumferential involvement of portal structures [right, left, or proper hepatic artery(ies); right, left, or main portal vein(s)] may preclude resection as these vessels must be preserved to guarantee perfusion I the remnant liver. Other factors important in determining resectability include bilateral involvement in any combination of: (1) lobar atrophy, (2) tumor at second order biliary radicals, and (3) tumor at the hepatic artery or portal vein that precludes attempts at reconstruction.

The value of a given imaging modality (US, CT scan, MRI/MRCP, ERCP, EUS and PTC) [22, 34, 36, 38–44, 47, 49, 71–73] rests on its ability to demonstrate the local and regional extent of disease (see Diagnostics: Serological Testing and Imaging). Although the pattern of disease and extent may be classified by the modified Bismuth-Corlette system [17] (see Chap. 4), this system only partly answers the question of resectability as it describes only the side of the disease in relation to the bifurcation. This system is further limited by not providing information on the radial extent, vascular involvement, and longitudinal extent of the disease (i.e., involvement beyond second order biliary radicals).

Table 16.5 Proposed clinical T stage criteria for hilar cholangiocarcinoma from MSKCC [131]

Clinical Stage	Criteria
T1	Tumor involving biliary confluence ± unilateral extension to second order biliary radicals
T2	Tumor involving biliary confluence ± unilateral extension to second order biliary radicals and ipsilateral portal vein involvement ± ipsilateral hepatic lobar atrophy
T3	Tumor involving biliary confluence + bilateral extension to second order biliary radicals, unilateral extension to second order biliary radicals with contralateral portal vein involvement, unilateral extension to second order biliary radicals with contralateral hepatic lobar atrophy, or main portal vein involvement

The more useful classification system from Memorial Sloan Kettering Cancer Center (MSKCC) was created based on their experience treating 225 patients with hilar cholangiocarcinoma (Table 16.5) [75]. Unresectable local disease was defined as tumors involving (1) bilateral second order biliary radicals, (2) ipsilateral second order biliary with contralateral portal vein involvement, (3) ipsilateral second order biliary with contralateral hepatic lobar atrophy, or (4) main or bilateral portal vein involvement. Using this system, patients with stage T3 disease are considered unresectable given the inability to obtain an R0 resection while preserving a viable sector of remnant liver. MSKCC used this system to achieve resectability rates for T1, T2 and T3 tumors of 59, 31 and 0 %, respectively. Median survival after resection was similarly documented at 20, 13 and 8 months. Currently, the MSKCC classification system with pre-operative imaging is employed by most hepatobiliary surgeons to determine whether a patient is a candidate for resection.

As of this writing American Joint Committee on Cancer staging manual (AJCC 2010, Seventh Edition) [77] has incorporated the MSKCC System into the Primary Tumor (T) category to define resectable local disease (Table 16.6). Thus AJCC T4 is equivalent to the MSKCC T3 disease, both of which are unresectable. This system will likely supplant the MSKCC system as not only does it surgically stage the local disease, but it incorporates information on nodal disease, metastases, and tumor grade to predict both resectability and survival.

In planning a resection, the surgeon must decide if the lesion is left or right dominant as this initial designation will determine whether the resection will be left or right-sided. Central lesions are approached as right-dominant lesions as the right bile duct is shorter than the left and the right hepatic

Table 16.6 TNM classification of hilar cholangiocarcinomas [132]

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, super mesenteric artery, and/or celiac artery lymph nodes		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
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	Any T	N2	M0
	Any T	Any N	M1

artery is more often involved with tumor than the left. Therefore, a resection of the right liver and reconstruction to the left hepatic duct will more likely achieve a negative margin. In general, the standard operation to achieve an R0 resection for hilar cholangiocarcinoma is an extended liver resection with caudate lobectomy, extrahepatic bile duct resection to the remnant intrahepatic bile duct, portal lymphadenectomy, and hepaticojejunostomy [18, 19, 23, 78–82].

16.4.1.2 Assessing the Future Remnant Liver

The major challenge of hilar cholangiocarcinoma is its central location and proximity to the hepatic artery and portal vein. In this setting, minimal radial extension can compromise the inflow to the liver. In various series of resected Klatskin tumors, portal vein involvement has been found in 16–22 % of patients [76, 83]. In addition, its propensity to spread along the length of the bile duct and nerves that accompany the hepatic and celiac arteries, as well as its direct spread to lymph nodes (53 %) and adjacent liver parenchyma has made it difficult to achieve an R0 resection with removal of the duct alone [16]. Over the past 20 years, extended liver and bile duct resection has become the standard of care for hilar cholangiocarcinoma. This strategy facilitates negative margins despite multiple modes of spread by sacrificing the ipsilateral pedicle rather than "scraping" tumor from these pedicles, or aborting altogether. Extended liver/bile duct resections have thus increased the frequency of R0 resections, while at the same time improving recurrence-free survival [21, 75, 80, 84, 85]. In this context, studies have demonstrated improved survival in groups undergoing extended liver resection over bile duct resection alone, even when both groups had R0 duct resections [75, 84, 85]. The improvement in survival in patients undergoing extended liver resection suggests that pathologic assessment may be inaccurate when a limited specimen is submitted, and supports the concept of multiple modes of spread.

As the resection required to achieve negative tumor margins for hilar cholangiocarcinoma requires an extended hepatic lobectomy, the surgeon must confirm that the future liver remnant will be functionally adequate. A work-up for possible underlying liver disease is also needed to make this assessment. Accordingly, risk factors for intrinsic liver disease should be elicited. This could include a history of inflammatory bowel disease (PSC), intravenous drug use (hepatitis C), and either alcohol abuse or obesity (non-alcoholic steatohepatitis). Patients should be examined for signs and symptoms of cirrhosis and portal hypertension (i.e. ascites, caput medusa, splenomegaly, hepatomegaly, and

jaundice), while liver function tests, serum albumin, coagulation studies, and platelet count are used for additional screening. In general, a remnant consisting of 20–30 % of the total liver mass is sufficient to prevent liver failure following resection as long as this remaining portion is not compromised to accomplish these aims, [36, 86]. To accomplish these aims, we employ volumetric studies performed by radiologists of the total and future remnant liver volumes.

The purpose of preoperative percutaneous transhepatic cholangiocatheterization (PTC) in patients with jaundice is to: (1) delineate the extent of biliary disease, (2) drain biliary sepsis and, (3) minimize hepatocellular damage in the future remnant for maximal post-operative liver function. Because of the potential risks (tumor seeding, bleeding, and bile leaks), and the lack of benefit found by some [87], drainage has not been universally accepted. In one series of 57 patients randomized to preoperative drainage or no drainage, the peri-operative mortality was not improved with drainage (14 % versus 15 %, respectively) [88]. Still, many groups advocate pre-operative PTC for the listed reasons, citing no increase in complications, with increased resection rates [89, 90]. Our center supports the use of preoperative PTC drainage in order to improve liver function and prevent biliary sepsis and renal insufficiency. Although some centers perform a single PTC to the future liver remnant alone [91], we have found that bilateral PTCs improve anorexia while more efficiently decreasing bilirubin and rates of biliary sepsis.

As resection of 80 % or more of uninjured liver parenchyma (or 65 % of an injured liver as in case of biliary obstruction) is associated with significant morbidity including infection and hepatic insufficiency [36, 86], the ability to offer extended liver resection may be limited by liver anatomy (i.e. the size of the remnant in relation to total size). Portal vein embolization (PVE) to the side of the future specimen takes advantage of the atrophy-hypertrophy complex to induce growth of the future remnant sector over 6 weeks [92]. In addition, the absence of liver growth may suggest chronic injury that may preclude resection altogether. A number of studies document the safety and efficacy of portal vein embolization [86, 90, 92]. Nagino et al. found that in 132 patients with cholangiocarcinoma who underwent extended hepatectomy after PVE, the 5-year survival was similar to that of 136 patients with cholangiocarcinoma who underwent a less than 50 % resection of the liver without PVE (26.8 % versus 27.6 %, respectively). These authors concluded that the PVE facilitated extended liver resections with similar outcomes to patients requiring lesser resections [93]. Others have validated PVE as means of screening potential resection candidates, as they found that patients with <5 % liver growth after PVE had a higher surgical mortality as compared to patients who had >10 % liver growth (mortality 50 % versus 0, respectively) [94].

16.4.2 Intraoperative Techniques and Decision-Making

As 40–50 % of patients with Klatskin tumors undergoing surgery are found to be unresectable despite thorough pre-operative staging [21, 75], staging laparoscopy has been advocated in an attempt to decrease the morbidity of open exploration. Using this approach, the accuracy of laparoscopy (number of unresectable patients detected by laparoscopy divided by the total number of unresectable cases) for hilar cholangiocarcinoma was found to be between 42 and 53 % in some reports [95]. The addition of laparoscopic ultrasound improved the detection of unresectable tumor. In a study of 84 patients undergoing laparoscopic staging for hilar cholangiocarcinoma, the yield (number of unresectable patients detected divided by the number of patients undergoing laparoscopy) with laparoscopy alone was 24.3 % (20 of 82), but 41.5 % (35 of 82) when intraoperative ultrasound was added, for an overall accuracy of 53.1 % (35 of 66). From this, the authors concluded that staging laparoscopy could be justified in the sense that it prevented unnecessary laparotomies in 42.2 % of patients [96]. With small foci of metastatic disease not readily discernible by conventional pre-operative imaging techniques, laparoscopy is mainly useful for detecting occult, superficial liver or peritoneal metastases under 1 cm. These patients are candidates for neither resection nor transplantation. In patients without these lesions, even if unresectable due to locally advanced disease, laparoscopy only adds time and cost to the procedure as these patients will require laparotomy in order to understand the local stage. In an effort to minimize unneeded laparoscopy, Weber et al. used the MSKCC system to predict patients with occult metastases and found evidence o such for 36 % of patients with T2/T3 disease had occult metastases versus 9 % of patients with T1 disease ($P=0.02$) [95]. They concluded that staging laparoscopy should be reserved for patients with MSKCC T2/T3 disease—a criterion which our group uses.

Patients deemed resectable by pre-operative staging (up to AJCC 2010 T1–3/N0–1/M0 or Stage IIIB) undergo open exploration and possible resection (of the liver, bile duct, and lymph nodes) for hilar cholangiocarcinoma (for details see Chap. 20). In the majority of patients classifies as T1 (91 %) and T2/T3 (64 %), it is local extent of disease rather than metastases that will preclude curative resection. Thus the initial challenge at open exploration is to determine whether an R0 resection can be achieved based on visualization and palpation of (1) the nodal disease, (2) the proximal extent and laterality of the primary hilar tumor, (3) the degree of cholestasis and possible fibrosis of the liver, and (4) the freedom of remnant vascular structures from tumor. The operation is then performed in a deliberate sequence to determine these four characteristics before reaching a "point of no return" in the resection (i.e. devascularizing the ipsilateral

liver). Despite these attempts, a proportion of cases will reach this point only to learn (as the surgery progress, at the time of frozen section pathology report, or days later at final pathology) that an R0 resection was not possible.

A caudate resection is routinely added because its drainage enters near the bile duct confluence (primarily the left duct) and may be involved with tumor in 40–98 % of the time [97–100]. A number of centers have shown that in selected cases, a caudate resection may be associated with decreased local recurrence and increased 5-year survival [101]. In one series of 75 patients undergoing resection, the 5-year survival for those undergoing combined caudate lobectomy (n = 17) was significantly better than for patients who did not have a caudate lobectomy (25 % versus 5 %, respectively) [102].

Controversy remains over whether the survival advantage and prognostic information offered by nodal dissection justifies the potential morbidity incurred by the procedure. Along these lines, Kitagawa et al. found that in 110 resections for Klatskin tumors with routine L1 and L2 nodal dissections, the 5-year survival was lower for node-positive patients (30 % for node-negative, 15 % for L1 and 12 % for L2). However, these authors pointed out that when compared to patients who were not resected, patient resected with L1 nodal disease may still receive improved long term survival [103]. Other groups do not routinely dissect lymph nodes beyond the hepatoduodenal ligament as they are fatalistic about the decreased survival noted in patients with nodal disease [21, 22]. Based on these reports, and our own experience, we advocate aggressive surgical management (including lymph node dissection) for L2 disease as it may offer improved survival, particularly when there are no other curative options available.

16.5 Liver Transplantation

While surgical outcomes continue to improve, radical bile duct resection and partial hepatectomy must be capable of eliminating all gross and microscopic disease in order to achieve a disease-free resection margin (R0 resection). Leading to improved 3- and 5-year survival rates, this objective has been more readily attainable in contemporary series. However, most patients remain ineligible for resection based on well-defined oncologic principles [75]. As such, total hepatectomy and orthotopic liver transplantation (OLT) have evolved to therapeutically encompass a subset of patients with localized disease who may theoretically benefit from surgical extirpation, but who nevertheless fall outside of standard resection criteria. Despite two decades of experience in which results were less than encouraging [1–12], improved patient selection and the addition of neoadjuvant chemoradiation have re-vitalized interest in the curative potential of this approach. Recent successes in this area have been grounded in a protocol-based methodology which focuses on at-risk populations, incorporates emerging screening and surveillance techniques, retains stringent selection criteria, and makes appropriate use of scarce donor resources.

16.5.1 Screening and Surveillance Protocols

The success of current neoadjuvant protocols has been predicated on patient selection and well-defined treatment algorithms (Fig. 16.4) [11, 13–15, 104, 105]. As eligibility for transplant is restricted to stage I and II disease, early stage detection is mandatory. Unfortunately, many small tumors are asymptomatic. The goal of screening protocols should therefore be one of targeted surveillance in patients with known risk factors or high degrees of clinical suspicion. At our institution, this includes all patients with PSC or IBD who develop the sudden onset of pruritis, jaundice, rapid weight loss, or abnormalities in serum biochemistries. Patients without a mass on imaging or history of a dominant stricture undergo ERCP with brushing of the right and left hepatic ducts, main hepatic duct, and common bile duct. In those with normal cytology, patients are followed at 6-month intervals and re-brushed if they fail to improve, or if otherwise indicated. If cytology harbors evidence of cellular atypia, FISH and DIA are performed. Positive results are referred for transplant. Patients with cellular atypia or indeterminate results otherwise undergo repeat ERCP and follow-up cytology at 6–12 month intervals. The continued presence of cytologic atypia on these exams or its return after an intervening normal cytologic result should prompt the use of adjunctive diagnostic measures (forceps biopsy, cholangioscopy, EUS, etc). Resolution of atypia mandates clinical follow-up only. A patient whose cytological results are viewed as suspicious or dysplastic, in whom FISH/DIA are otherwise negative or equivocal, undergo repeat brushings within 1–3 months of their reference ERCP. Patients with overt evidence of malignancy (adenocarcinoma) are referred for additional staging to determine eligibility for transplant. Like many authors, we do not endorse routine screening of otherwise asymptomatic PSC patients due to the potential for ERCP-induced pancreatitis [34].

Using a similar approach, Wu et al. examined 119 patients with PSC over a 13 year period. In these individuals, 273 ERCPs were performed (2.3 ERCPs per patient). None of the patients with normal cytology went on to develop cholangiocarcinoma. Forty-two (35 %) were found to have abnormal reference cytologies. Of these, three tumors were found at initial evaluation. In five additional patients who originally showed evidence of atypical cells or dysplasia, cholangiocarcinoma was eventually discovered on cytology during

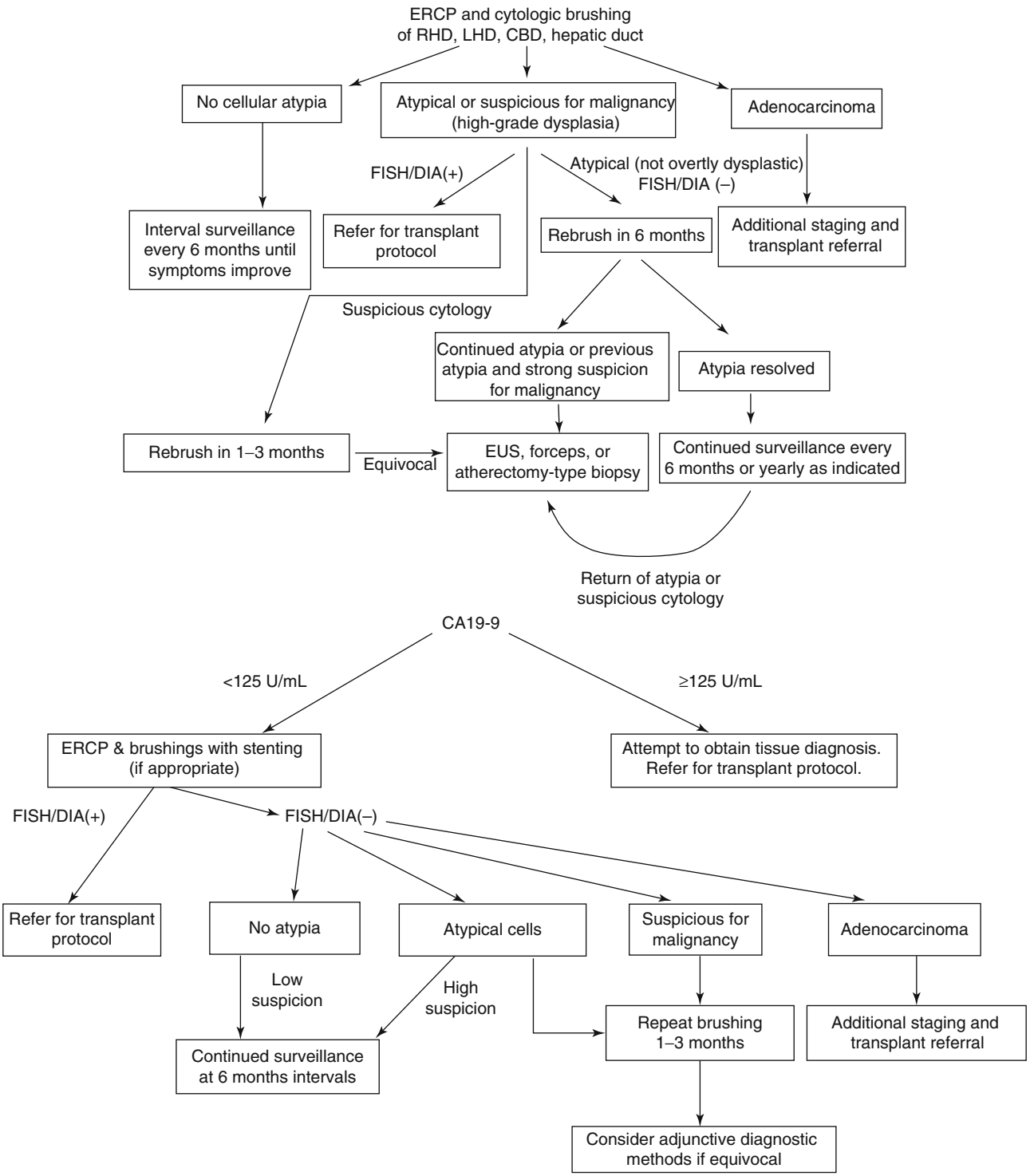

Fig. 16.4 Screening algorithm for cholangiocarcinoma. (**a**) Using ERCP and cytologic brushing as the first screening test. (**b**) Using CA 19-9 as the first screening test. *CA 19-9* Carbohydrate antigen 19-9, *ERCP* endoscopic retrograde cholangiopancreatography, *FISH* fluorescence in situ hybridization, *DIA* digital image analysis, *RHD* right hepatic duct, *LHD* left hepatic duct, *CBD* common bile duct, *EUS* endoscopic ultrasound

subsequent exams. Despite multiple ERCPs, no episodes of pancreatitis or cholangitis were reported to occur [61].

In the setting of a known dominant stricture or mass lesion, CA 19-9 levels should be examined at least semiannually. In this scenario, PSC or IBD patients with elevated CA 19-9 levels are candidates for additional staging and transplant referral [34, 106, 107]. Under these conditions, a confirmatory tissue diagnosis should be sought, but an equivocal result, particularly in the presence of a suspicious mass, does not automatically preclude transplant eligibility. Sudden clinical deterioration in a PSC patient with a high-grade stricture and equivocal CA 19-9 levels is ominous and should trigger an aggressive search for malignancy. Initial maneuvers should include conventional brush cytology, FISH/DIA, forceps biopsy, EUS, EUS-guided FNA, and an atherectomy approach and/or rendezvous procedure if first-line attempts fail. Urgent follow-up is warranted in 1–3 months if a tissue diagnosis cannot be established by a combination of these techniques.

16.5.2 Staging and Selection of Patients for Transplant

All in all, diagnosis and staging should be undertaken using a multimodality approach that includes clinical appraisal, laboratory analysis, as well as radiologic and pathologic assessment [36]. In this context, it is important to remember that an indisputable tissue diagnosis is not always possible. In these cases, diagnosis can be corroborated by a combination of radiographic and serological testing in patients deemed to be at high risk. Our selection criteria for protocol enrollment mirrors that employed by the Mayo Clinic and are demonstrated in Table 16.7. Once a diagnosis of cholangiocarcinoma has been entertained, cross-sectional imaging of the liver and hilar region should be performed, if not done already, preferably with MRI/MRCP. Those with hilar lesions should be evaluated by an experienced hepatobiliary surgeon for the purpose of determining resectability, which should take precedence over transplant referral if technically feasible. Cross-sectional imaging is also performed to establish tumor size and relationship to adjacent structures. Mass lesions below the cystic duct should negatively impact the decision to proceed with transplant. An exception to these guidelines ensues in the case of PSC patients with disease confined to the extrahepatic bile duct who otherwise do not exceed staging criteria. In these individuals, the entire biliary tree should be viewed as tissue at risk for malignant transformation. As well, many will not tolerate extensive hepatic resection as a result of intrinsic liver disease. Because of the difficulty in determining submucosal spread of tumor, its longitudinal extent along a duct does not influence suitability for transplant [108]. However, due to the negative prognostic influence of larger primary tumors, their propensity for lymphatic invasion, and their predilection to grow along neighboring bile duct walls, eligibility for protocol enrollment is predicated on a radial tumor diameter which does not exceed 3 cm on cross-sectional imaging [109–111]. Vascular encasement, per se, does not necessarily disqualify a patient. Alternatively, the failure to visualize a major branch of the portal vein on contrast-enhanced MR venography or comparable imaging study raises the specter of vascular invasion and should obviate further consideration of transplantation.

Table 16.7 Inclusion criteria for transplant protocol

Diagnosis of cholangiocarcinoma by brush cytology, endoscopic forceps biopsy, EUS-guided FNA, or atherectomy-type biopsy
Above cystic duct and unresectable by conventional surgical techniques (unless arising in setting of PSC)
CA 19-9 ≥125 U/ml with dominant stricture and/or mass on cross-sectional imaging
Stricture and FISH polysomy or FISH trisomy (7 or 3)
DIA greater than 1.89 in isolation (FISH negative, routine cytology negative)
FISH polysomy in absence of malignant stricture
Tumor unresectable by conventional techniques
Radial tumor diameter ≤3 cm
No medical contraindications to liver transplantation

Abbreviations: *CA 19-9* carbohydrate antigen 19-9, *DIA* digital image analysis, *FISH* fluorescence in-situ hybridization, *PSC* primary sclerosing cholangitis

Transplantation is not contemplated in patients with prior attempts at resection or in situations where transperitoneal biopsy has been pursued because in most cases, these practices favor peritoneal dissemination of tumor. Prior administration of chemotherapy, external beam radiation therapy, or brachytherapy is also discouraged in the absence of appropriate staging and diagnostic work-up. Patients with gallbladder cancer are excluded due to a tumor predilection to recur at distant sites [13] and due the lack of proven efficacy of chemoradiation. Transplant is similarly avoided in those harboring peripheral (non-hilar) or intra-hepatic cholangiocarcinomas (ICC) owing to rapid recurrence in these individuals [10, 108]. The largest series examining outcomes in this group was reported by the European Transplant Registry, which reported only a 29 % 5-year survival [33, 112]. Patients with combined features of ICC and hepatocellular carcinoma deserve special mention. These tumors have a propensity to infiltrate the portal venous system and share features of cholangiocarcinoma due to their predilection for regional lymph node metastasis [113, 114]. Limited data exists on the outcome after transplant. Existing series of 1–3 patients do not paint an optimistic picture despite patients remaining within Milan criteria [114–116]. As such, surgical resection with hilar lymph node dissection should be considered the most appropriate treatment for the combined variant in the absence of overt cirrhosis, with

transplant being reserved for small lesions only, or in cases of hepatic decompensation [114, 117, 118].

Extrahepatic disease is an absolute contraindication to transplantation and should merit consideration for palliative treatment. Resultantly, an aggressive search for metastatic cholangiocarcinoma is required. This can take the form of cross-sectional imaging of the chest, abdomen, or pelvis (CT or MRI) in conjunction with bone scan. More recently, the authors have incorporated ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) scanning into their staging algorithm based on reports which suggest they may offer an additional degree of sensitivity in depicting extrahepatic disease [119–123]. We have introduced this prior to neoadjuvant treatment to help exclude patients with metastatic disease who may progress while on treatment.

16.5.2.1 Role of Staging Laparotomy

A major consideration is the presence of metastatic disease in regional hepatic lymph nodes, which are found in 30–50 % of patients undergoing resection [21, 22, 75, 103]. It is expected that regional lymph node involvement contributes to local as well as distant treatment failures. All in all, patients with regional lymph node positivity do poorly in the context of transplantation [13]. As such, transplant protocols have evolved to include formal operative staging. Once neoadjuvant therapy is complete, patients undergo thorough operative staging to ascertain the presence of N2 nodal disease (celiac, periduodenal, superior mesenteric nodal basins). A formal sampling of the nodes along the common hepatic artery and hepatoduodenal ligament is thus undertaken. Evidence of gross or microscopic disease at the N2 level is a harbinger of distant recurrence and is considered a contraindication to transplant. In most cases, N1 disease (cystic and pericholedochal nodes) can be extirpated during transplant hepatectomy, but their presence portends a high risk of localized recurrence following transplant. A thorough abdominal exploration should also ensue. Specific attention is afforded to periduodenal and superior mesenteric nodal basins to rule out gross disease. The liver is inspected for the presence of intrahepatic metastases and caudate involvement. Examination of peritoneal surfaces is conducted to rule out the presence of tumoral dissemination within the coelomic cavity, a task well-suited to the laparoscope.

In regions where the interval from completion of neoadjuvant therapy to transplant is protracted (>100 days), the ideal timing for staging is a matter of debate. In these instances, it may be advantageous to delay the staging procedure until the time when transplant is imminent or during the actual transplant procedure itself (prior to hepatectomy). In the setting of nodal or extrahepatic disease, the procedure should be aborted and the donor liver re-allocated. Where living donors have been identified, the staging operation is conducted 1–3 days prior to transplant.

Table 16.8 Exclusion criteria for cholangiocarcinomas

Tumor resectable by conventional approaches
Medically unfit for transplant
Prior surgical resection or transperitoneal biopsy
Extrahepatic disease on metastatic work up
Regional lymph nodes positive for metastases on EUS or staging laparotomy
Evidence of intrahepatic spread
Prior administration of chemotherapy and /or radiation
Gallbladder cancer
Combined cholangiocarcinoma/hepatocellular carcinoma variants
Tumor size ≥3 cm on cross-sectional imaging or growth while on neoadjuvant protocol

On the whole, 20–25 % of patients are excluded due to findings wrought by the staging operation [13]. With the advent of EUS-guided FNA, regional lymph nodes can be sampled and a formal staging laparotomy avoided if nodes are positive. In a report by Gleeson et al., 70 lymph nodes in 47 patients with unresectable cholangiocarcinoma were sampled. Nine malignant nodes were detected in eight patients. In these individuals, no morphologic features predicted metastases [124]. Performed prior to neoadjuvant therapy, patients discovered using this approach are likely to have progressed during neoadjuvant treatment [108]. It is estimated that its introduction into transplant protocols prior to neoadjuvant therapy can decrease the likelihood of positive staging laparotomies by 50 % [11]. A full list of exclusion criteria can be found in Table 16.8.

16.5.2.2 Role of Positron Emission Tomography

Aside from regional lymph node infiltration, factors associated with adverse tumor biology include perineural invasion and high-grade differentiation, amongst others [104]. Unfortunately, these characteristics are not appreciated using conventional staging methodologies and are only discovered on explant. It is reasonable to assume that patient selection can further be enhanced in cases where negative prognostic indicators are known prior to transplant. In addition to its ability to foretell the existence of extrahepatic disease, PET scanning has recently been used as a tool to predict biological tumor behavior and outcome after transplantation. In a study by Kornberg et al., 13 patients with Type IV Klatskin tumors (unresectable, bilobar involvement) were examined using PET and findings correlated with histopathologic tumor characteristics and patient outcome after transplantation. Eight patients were PET-avid prior to transplant. Allograft dysfunction resulted in one patient death. All seven of the remaining PET-avid patients developed tumor recurrence. In these cases, PET-avidity was positively correlated with perineural invasion and had a positive predictive value of 89 % [125]. Conversely, all PET (−) patients were tumor-free and alive at a median of 76 months following transplant. The authors concluded that patients with non-PET-avid

cholangiocarcinoma are more likely to achieve recurrence-free long-term survival [125]. It seems defensible, as the authors suggest, that a switch from PET (−) status to one of PET-avidity during the course of neoadjuvant therapy may represent a shift in biological tumor behavior from a less aggressive to more aggressive phenotype, thereby disqualifying a patient from subsequent transplant [125]. This notion awaits prospective confirmation, however.

16.5.2.3 A Therapeutic Dilemma

Due to the difficulty in evaluating longitudinal extent of disease, evidence of malignancy below the cystic duct in a PSC patient represents a therapeutic dilemma. This is compounded by evidence which suggests that cholangiocarcinoma in PSC may be distributed widely, surfacing in multiple areas of dysplasia simultaneously [34, 61, 126]. As a consequence, up to 15 % of PSC patients have been found to have a positive distal bile duct margin at hepatectomy [11]. Surgeons must therefore be prepared for this contingency. Accordingly, it is our practice to perform pancreaticoduodenectomy in conjunction with liver transplantation in a stable recipient if the distal bile duct margin is positive by frozen section. Often times, definite confirmation will await permanent tissue fixation. In such cases, completion pancreaticoduodenectomy can be performed during the index hospitalization to effect an R0 resection. In patients with early stage disease undergoing surveillance and neoadjuvant therapy, this approach has been validated with respect to safety and efficacy. In a recent update of the Mayo series, ten concomitant pancreaticoduodenectomies have been performed since 1993. In seven cases, microscopic disease was noted at the time of hepatectomy. Five patients remained alive 1–9 years after transplantation. Two died secondary to arterial complications [11]. These results have been authenticated in a similar group of PSC patients undergoing regular surveillance. Wu and colleagues performed combined Whipple-transplant, which entailed *en bloc* total hepatectomy-pancreaticoduodenectomy in six patients [61]. All patients received combined external beam and brachytherapy. Operative time ranged from 6 to 7 h. Mean intraoperative blood loss was 3.5 units (range 0–13 units). Median post-operative length of stay was 21 days (range 16–138 days). Morbidity included two intra-abdominal infections and a pancreatic leak requiring revision. One patient developed a pancreatic duct stricture proximal to the pancreaticojejunostomy 22 months following Whipple secondary to chronic pancreatitis. There was one episode of chronic renal failure secondary to transplant immunosuppression requiring kidney transplantation 44 months following the combined procedure [61]. One patient died 55 months post-transplant from a non-tumor, unrelated cause. Upon publication, five were well at 5.7, 7.0, 8.7, 8.8, and 10.1 years following transplant. All had returned to full-time employment without evidence of tumor recurrence [61]. For patients enrolled in suitable staging and neoadjuvant protocols, these results support the concept of combining hepatectomy and pancreaticoduodenectomy, followed by orthotopic liver transplantation, in patients with early stage hilar disease. Extirpation of the entire biliary system appears to be well-tolerated and offers long-term tumor-free survival with acceptable rates of morbidity and mortality.

16.6 Resection or Transplantation for Cholangiocarcinoma?

While cholangiocarcinoma remains a surgical disease, treatment and diagnosis must be integrated using a multimodality approach to care. Along these lines, it is clear that favorable outcomes after resection or transplant are dependent on a combination of early detection, appropriate staging, and in the case of transplant, neoadjuvant chemoradiation. In arriving at a diagnosis and treatment plan, it is oftentimes necessary to assimilate information from a wide array of sources. From an institutional perspective, this mandates a full complement of interested pathologists, diagnostic radiologists, medical oncologist, interventional radiologists, endoscopists, radiation oncologists, and hepatologists. Impacting this disease at a treatable stage requires the adherence to targeted surveillance protocols. These algorithms should be developed using multidisciplinary input and may be institution-dependent. However, they should reflect the current state of knowledge regarding screening in at-risk populations. In cases where disease is resectable, recent improvements in outcomes following extended bile duct resection and partial hepatectomy have relied on strict adherence to resection criteria. Similarly, the improvement in transplant outcomes for unresectable hilar disease has been predicated on patient selection and stringent observance of staging and neoadjuvant protocols.

The decision of whether to resect or transplant should be guided by a surgeon or team experienced in performing both complex hepatobiliary resections and liver transplantation, so that bias in choosing between the two curative options is minimized. Identifying patients who should undergo liver transplantation should be the first priority. These include those with end stage liver disease (ESLD), or any one of the following: Childs-Pugh B or C functional status, cirrhosis, or portal hypertension. These individuals are not candidates for liver resection and should be considered for transplantation [75]. Patients with underlying liver disease approaching end stage or with risk factors for the development of cholangiocarcinoma (i.e., primary sclerosing cholangitis) should also be considered for transplantation due to the risk of hepatic decompensation or recurrence in the remnant liver [14].

Patients with MSKCC T3 or AJCC 2010 T4N0 lesions representing unresectable local disease should also be

considered for transplantation. However, these patients must be carefully evaluated for nodal disease, a contraindication to transplantation. It is estimated that 13 % of transplant, and 25 % of resection candidates harbor such disease [14]. The remaining group of patients with hilar cholangiocarcinoma represents the majority of individuals, all of which should be considered for curative resection [127–129]. It is rarely possible to switch strategies mid-course as the reasons that preclude resection also preclude transplantation. These reasons include: (1) discovery of nodal, liver, or distant metastases, (2) involvement of neighboring structures, or (3) failed attempt at resection which, in many cases, upstages tumor due to disruption of lymphatic drainage patterns and intraperitoneal tumor dissemination [14].

The largest study to date comparing liver transplantation to resection from the Mayo Clinic did so in a retrospective, case-controlled fashion. With the intention of preventing local recurrence and intraoperative tumor dissemination, patients in this series underwent neoadjuvant chemoradiation prior to liver transplantation. One, 3- and 5-year survival rates for transplant were 92 %, 82 %, and 82 %, versus 82 %, 48 %, and 21 % for resection. In this fashion, liver transplantation with neoadjuvant chemoradiation offered improved survival over resection ($P = 0.022$). In this study however, contrasts between the two groups are problematic and confounded by the lack of neoadjuvant therapy in the resection group, the younger age of transplant recipients, and the fact that all transplant patients R0 resection in the setting of node negative disease. With a higher rate of PSC in the transplant group, a potential selection bias can be entertained [14, 15]. However, transplantation in the setting of *de novo* cholangiocarcinoma improved survival as well. The meticulous selection process has also been implicated in the promising results observed in the Mayo series, where 38 of 71 patients entering the neoadjuvant protocol eventually underwent transplant. However, nine patients died before staging due to complications of therapy and ten additional patients were awaiting transplant at the time of the report, making this position difficult to endorse. In transplanted cases, the hepatectomy specimen failed to identify residual disease in 16 of 38 explants, perhaps inferring favorable outcomes were merely a reflection of strict inclusion criteria favoring less aggressive disease [14, 15].

These concerns are justified, but other reports tend to corroborate the Mayo data [3, 12, 15, 130–132]. Currently reported 1-, 3, and 5- year patient survival rates are 84 %, 67 %, 56 % after the start of therapy (n = 167) and 96, 83, and 72 % (n = 111) in patients undergoing transplant [11]. In examining the characteristics which predict recurrence, the Mayo group identified the following: (1) a discreet mass seen on pre-transplant imaging, (2) residual tumor >2 cm at explantation, (3) tumor grade and perineural invasion in the explanted tumor, (4) increased patient age, (5) CA 19-9 > 100 at the time of transplant (but not at enrollment), and prior cholecystectomy. Additionally, an increasing interval from enrollment to transplant (>100 days) was suggestive of a higher recurrence rate [104]. A thorough accounting of these factors is recommended when an individual's transplant candidacy is under consideration.

Despite the limitations of the Mayo series, these data are persuasive. It is not yet clear, however, whether this approach is warranted in patients with resectable disease. Lacking evidence, a transplant-based approach in this setting is difficult to defend. In the future, this may change with improvements in chemoradiotherapeutics. At the present time, however, resection should remain the primary consideration for patients presenting with hilar cholangiocarcinoma, and transplantation reserved for patients with ESLD, PSC, or locally unresectable disease.

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