Surgical Management of Intra-Hepatic Cholangiocarcinoma

Kimberly M. Brown and David A. Geller

Contents

Abstract

Intra-hepatic cholangiocarcinoma (ICC) arises from the biliary epithelium of secondary bile ducts or beyond. Many patients present with advanced, often unresectable disease due to vague or absent symptoms. Staging is based on tumor number, vascular invasion, extra-hepatic spread, lymph node involvement, and distant metastatic disease. When feasible, complete surgical resection offers the best hope of long-term survival, and may be approached via open or minimally invasive techniques depending on tumor location and surgeon expertise. Extended hepatic resection, vascular resection, and/or biliary-enteric reconstruction may be required for complete tumor resection. Mortality rates in most modern surgical series are 1–5 %. Five-year overall survival following resection ranges from 17 to 44 %. The role of liver transplant is limited to select centers with clinical trials including rigorous neoadjuvant therapy. The role of adjuvant therapy is still being explored as newer, potentially more effective systemic agents are developed.

1 Introduction

Cholangiocarcinoma is the second most common primary liver cancer after hepatocellular carcinoma (HCC). It arises from the epithelial lining of bile ducts and is anatomically categorized as intra-hepatic or extra-hepatic. Intra-hepatic cholangiocarcinoma (ICC) originates from the secondary or more peripheral bile ducts and does not involve the hepatic duct confluence. Some series in the literature refer to them as peripheral cholangiocarcinomas. These tumors are the least common, representing 5–10 % of cholangiocarcinomas, compared with tumors arising in the peri-hilar extra-hepatic duct (50–60 %) or distal bile duct (20–25 %) [1]. The majority of patients have no identifiable risk factor for ICC, which contributes to the problem of developing an effective screening process. Risk factors that have been

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associated with ICC relate to chronic inflammation within the bile ducts and include primary sclerosing cholangitis (PSC), choledochal cyst, chronic bile duct stones, exposure to Thorotrast contrast agent, smoking, liver fluke infestation, and chronic typhoid carriers [1–4]. Approximately 6,000 new cases of cholangiocarcinoma are diagnosed in the United States each year; the incidence of ICC in the US and worldwide has been increasing, along with the mortality rate [5–7]. The reasons for these increases are a subject of debate. Some authors argue it is influenced by recent changes in the classification system [6], while others point to hepatitis C as an emerging risk factor for cholangiocarcinoma [8].

Patients with ICC present more often with abdominal pain, constitutional symptoms, or an incidental mass, and less commonly with jaundice, as compared with extrahepatic cholangiocarcinoma [9, 10]. Historically, staging systems for cholangiocarcinoma were derived from data on HCC patients [11], but in the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) 7th edition staging manual, a unique staging system for ICC was introduced, based on an analysis of SEER data performed by Nathan et al. [12, 13]. Prognostic variables for T classification include vascular invasion, multiple tumors, extra-hepatic extension, and periductal infiltration (Table 1). Noteworthy is that tumor size, which had been a factor in the prior AJCC staging system, was not associated with survival and is not included in the updated edition. The AJCC 7th edition TNM staging correlated well with survival (Fig. 1). This staging system was subsequently found to accurately discriminate outcomes in patients who underwent resection for ICC in a multi-institution European study [14] and was also validated in an international multi-institutional analysis [15].

In addition to TNM staging, macroscopic histologic subtypes of ICC have been associated with prognosis. The main subtypes identified are mass-forming, periductal-infiltrating, and intraductal, although tumors may also have features of more than one subtype, such as mass-forming plus periductal-infiltrating (Fig. 2). These subtypes have different biological behaviors and are associated with different outcomes in Japanese studies [16, 17]. Mass-forming is the most common subtype in Western series, and independent influence on prognosis has not been established in this population [15].

Surgery is the only modality associated with long-term survival; unfortunately, the majority of patients are unresectable at the time of presentation, either due to local invasion or distant metastasis [18, 19]. The remainder of this chapter will address the preoperative preparation, intraoperative technical and decision-making considerations for resection, and postoperative outcomes. The role of adjuvant therapy and liver transplantation will also be discussed.

Table 1 Staging classification for ICC (adapted from AJCC 7th edition cancer staging manual)

Classification	Description
T1	Solitary tumor without vascular invasion[a]
T2a	Solitary tumor with vascular invasion[a]
T2b	Multiple tumors, with or without vascular invasion[a]
T3	Tumor perforating visceral peritoneum or involving local extra-hepatic structures by direct invasion
T4	Tumor with periductal invasion[b]
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis[c]
M0	No distant metastasis
M1	Distant metastasis
Stage groupings	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
Stage IVA	T4 N0 M0, Any T N1 M0
Stage IVB	Any T Any N M1

[a] Includes major vascular invasion (portal vein or hepatic vein) and microvascular invasion
[b] Includes tumors with periductal-infiltrating or mixed mass-forming and periductal-infiltrating growth pattern
[c] Nodal involvement of the celiac, periaortic or caval lymph nodes is considered to be distant metastasis (M1)

2 Preoperative Considerations

ICC is commonly identified on ultrasound or cross-sectional imaging, which may be performed for symptoms such as abdominal pain, or for an unrelated indication. Once a liver mass has been identified, an appropriate workup to evaluate for other potential diagnoses such as metastasis should be undertaken. History and physical examination, blood work including hepatitis panel, CA-19-9, CEA, and AFP, and upper and lower endoscopy can help narrow the differential diagnosis. Imaging for preoperative planning is accomplished with contrast-enhanced helical computed tomography (CT) or magnetic resonance imaging (MRI). The goal is to evaluate the local extent of disease to determine resectability and to identify metastatic disease that would preclude resection. A CT of the chest should also be included in the preoperative evaluation to rule out pulmonary metastases.

The definition of a resectable liver tumor in a medically fit candidate is determined by tumor size, number, and location. For ICC, resectability is defined as being able to completely excise a tumor with negative margins, with at least two contiguous segments of liver remaining, and with adequate arterial and portal venous inflow, hepatic venous

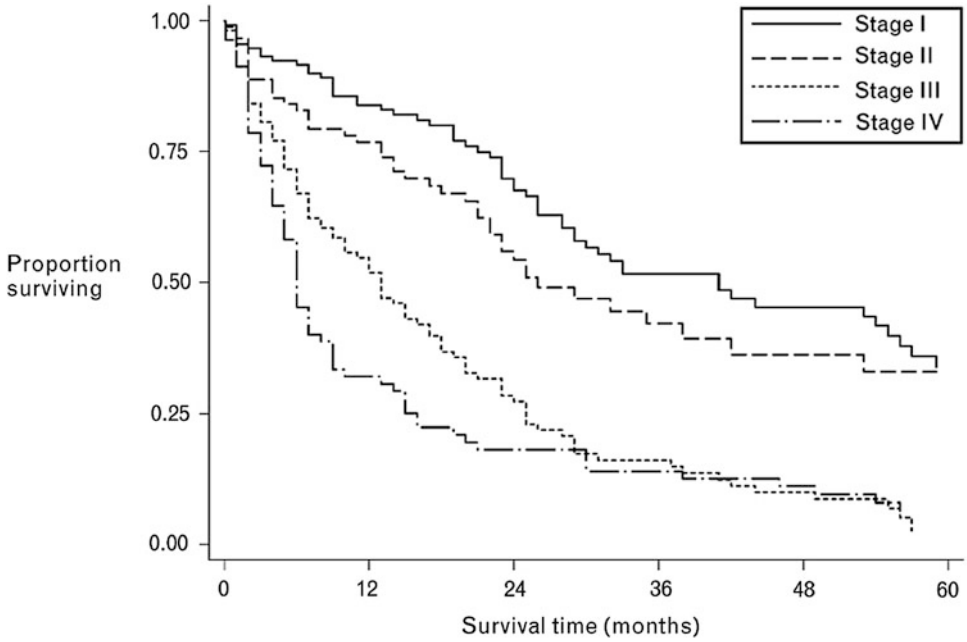

Fig. 1 Kaplan–Meier survival curve for ICC, stratified by AJCC 7th edition stage (with permission, from Ref [13])

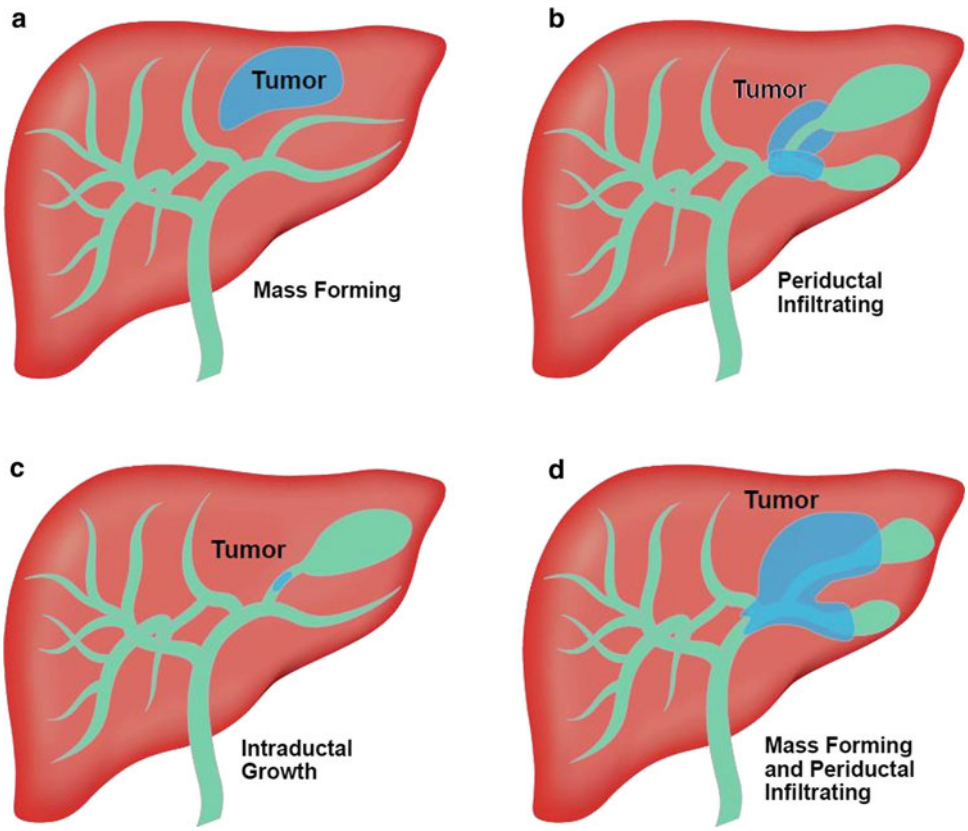

Fig. 2 Macroscopic subtypes of ICC

outflow, and biliary drainage. The amount of sufficient parenchymal future liver remnant required ranges from 20 to 40 %, depending on the health of the background liver [20]. The presence of multiple intra-hepatic tumors and/or grossly involved lymph nodes beyond the porta hepatis influence the likelihood of recurrence and should be considered when determining if a patient will benefit from resection. In addition, there should be no extra-hepatic metastatic disease [1]. ICC is associated with advanced stage at presentation, and thus, a significant number of patients will not be candidates for resection. In one series of 238 patients diagnosed with ICC over a 16-year period, 128

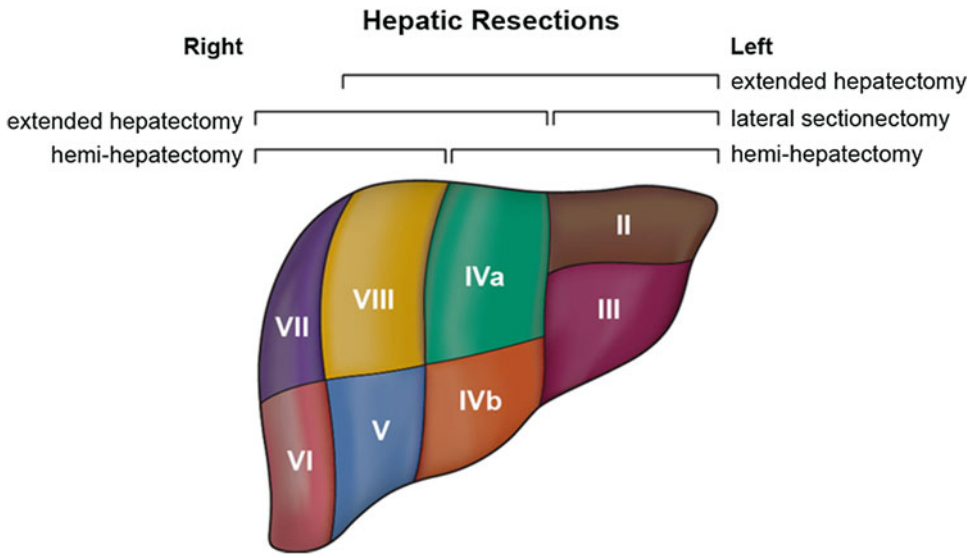

Fig. 3 Anatomic basis for liver resection procedures, according to Brisbane terminology

patients (54 %) were initially unresectable, based on the presence of multiple tumors (70), locally advanced intrahepatic disease (37), or metastatic disease (32); 20 patients had more than one indication for unresectability [19].

Hepatic resections are described in terms of the anatomic segments removed. Couinaud [21] defined the hepatic segments based on internal vascular anatomy (Fig. 3). The main portal vein divides into a left and right branch, supplying each hemi-liver. The right portal vein branches into anterior and posterior sections, which supply segments 5/8 and 6/7, respectively. The left portal vein divides into lateral and medial sections, supplying segments 2/3 and 4a/4b, respectively. In 2000, the International Hepato-Pancreato-Biliary Association (IHPBA) published a standardized terminology for liver resections at the World Congress of the IHPBA in Brisbane, Australia, referred to as the Brisbane terminology of liver anatomy and resections, which follows internal vascular anatomic terms [22].

In surgical series of ICC patients, a hemi-hepatectomy is required in 20–70 % of cases to resect the tumor, while extended resections (>4 Couinaud segments) are required in up to 60 % of cases. In 5–25 % of cases, tumor clearance can be accomplished by removal of less than a hemi-liver (segmentectomy, bisegmentectomy, or non-anatomic resection) [10, 15, 19, 23–29]. The utility of subjecting patients to extended resections has been studied; one series of 27 patients undergoing at least an extended hepatectomy demonstrated overall 1- and 3-year survivals of 69 and 55 %, which is in the range of published series for ICC. In patients achieving a complete margin-negative resection (R0), the median survival was 46 months, with 1- and 3-year survivals of 94 and 82 %, respectively [30]. Thus, the need for an extended resection should not deter operative planning in experienced hands. The appearance of grossly involved regional lymph nodes on preoperative imaging portends a poor prognosis; however, nodal involvement outside of the regional lymph node basin is considered metastatic disease and a contra-indication to exploration [19].

3 Preoperative Portal Venous Embolization

Postoperative liver failure is a potential complication of hepatic resection for any indication. Risk factors for postoperative liver failure include the ratio of the size of the future liver remnant (FLR) to the total estimated liver volume, and the degree of liver dysfunction, which may be a result of cholestasis, chemotherapy, non-alcoholic steatohepatitis (NASH), or fibrosis/cirrhosis. There are varying criteria for determining a safe FLR; some authors advocate for no less than 40 % FLR in a healthy liver [31], while others use 20–25 % FLR as a cutoff in normal liver [20, 32, 33].

Portal vein embolization (PVE) is a process of inducing compensatory hypertrophy in the FLR preoperatively by interrupting portal venous flow to the portion of the liver that will be resected. First introduced in 1990 for patients with biliary tract cancers, the rationale for PVE prior to surgery is to reduce the risk of complications including postoperative liver failure in patients with marginal FLR by increasing the FLR before resection [34]. The technique is performed by accessing the portal vein on the tumor-bearing side of the liver, usually by a percutaneous trans-hepatic or trans-ileocolic route, and delivering embolic microcoils, and polyvinyl particles, and/or alcohol to the segments of liver that will be resected [35].

In one series of 240 patients undergoing PVE before planned resection for biliary tract cancers, the future liver remnant increased significantly from 33 ± 8 % to 43 ± 8 %. Among patients who ultimately underwent

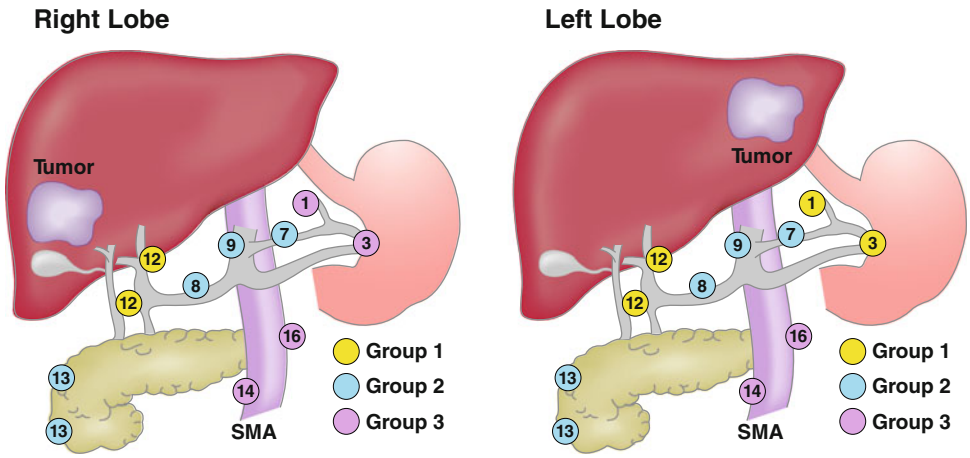

Fig. 4 Patterns of lymphatic spread for *left-sided* and *right-sided* hepatic tumors

resection, the degree of hypertrophy was not different between those who died in the perioperative period ($n = 17$) and those who did not ($n = 176$), but the function of the FLR, as measured by indocyanine green clearance, was significantly worse in non-survivors [36]. This series was recently updated and now includes 353 patients with cholangiocarcinoma and 141 patients with gallbladder cancer [31]. The operative mortality was 6.5 %, and 5-year survival of patients with cholangiocarcinoma (mostly hilar) was 39 %, which is comparable with other published studies. The number of patients with ICC in PVE studies is very low [37, 38], which is likely a reflection of the higher incidence of hilar tumors and the less frequent need for extensive resections in ICC compared with hilar cholangiocarcinoma.

There is evidence to suggest that PVE stimulates tumor growth in an animal model of colorectal cancer liver metastases [39]. The oncologic impact of this is unknown, but an emerging strategy that may address this concern is the addition of intra-arterial therapy (IAT) in a sequential fashion with PVE [40]. This approach has not been shown to cause more hypertrophy than PVE alone, but more tumor necrosis was seen. The role for combined preoperative IAT and PVE remains to be defined.

4 Operative Considerations

4.1 Laparoscopic Staging

Staging laparoscopy with or without laparoscopic ultrasonography at the time of planned surgical resection for hepatobiliary-pancreatic malignancy was originally introduced to spare patients with occult metastatic disease, a non-therapeutic laparotomy [41]. In 62 patients explored for ICC without laparoscopy, metastatic disease was identified in 14 (23 %), suggesting that laparoscopy could benefit up to 1 in 4 ICC patients [42]. Early studies of laparoscopy in mixed hepatobiliary-pancreatic tumors found that laparoscopy identified unresectable disease in up to 46 % of patients [41, 43, 44]. One small study of 11 patients with ICC found that occult metastatic disease was detected at laparoscopy in four patients, for a yield of 36 %. An additional two patients were found to be unresectable at laparotomy, making the sensitivity 67 % (4/6) [45]. A larger review of 53 ICC patients, of whom 22 underwent staging laparoscopy, reported unresectable disease in six of 22 (27 %). Peritoneal metastases (4) and intra-hepatic metastases (2) were the findings precluding resection. At laparotomy, five additional patients had metastatic disease identified in celiac lymph nodes, making the sensitivity of laparoscopy 6/11 or 55 % [28].

As cross-sectional imaging has improved, the efficacy and cost-effectiveness of diagnostic laparoscopy in liver tumors have come into question [46, 47]. This is particularly true for cholangiocarcinoma, which tends to invade locally, such that the determination of resectability may be made only after dissection of biliary or vascular structures, compared with tumors such as gallbladder carcinoma, which demonstrate earlier peritoneal dissemination. Data specific to the utility of laparoscopy in patients with ICC remain sparse.

Studies reporting resectability at laparotomy offer rates of 62–83 %, which varies in part by the era of study, the use of laparoscopy, and the approach to tumors with lymph node or vascular involvement [9, 10, 19, 24, 26, 28].

4.2 Lymphadenectomy

The lymphatic drainage for liver tumors has been described, based on tumor location within the liver (Fig. 4). Left-sided tumors tend to spread toward the gastro-hepatic ligament to the lesser curve and cardia of the stomach, while right-sided tumors drain to the hepatoduodenal ligament [48]. However, left-sided ICC has been shown to follow "right-sided" drainage patterns in half of cases subjected to systematic

lymphadenectomy [49]. The incidence of lymph node metastasis in published series of ICC ranges from 16 to 81 %; the higher rates reflect the tendency in many Western centers to perform lymphadenectomy only when suspicious lymph nodes are encountered [9, 10, 15, 19, 23, 24, 26, 29, 50]. In centers where lymphadenectomy is routinely performed, the incidence is 20–50 % [42, 49, 50].

Lymph node metastases are associated with poor prognosis in numerous studies [9, 10, 15, 26, 28]; thus, lymphadenectomy may help select patients for adjuvant therapy. However, routine lymphadenectomy has not been performed in many large Western series [15, 19, 24, 28, 51], with the rationale that routine lymphadenectomy has not been shown to influence survival [52].

4.3 Vascular Resection

Cholangiocarcinoma tends to display locally aggressive growth, which may involve major vascular structures such as the inferior vena cava (IVC) or the main or contra-lateral portal vein. Some form of vascular resection is required in 9–14 % of resections for ICC in large series [19, 23–28]. The impact of major vascular resection on outcomes for ICC patients was studied in a single institution review [23]. In a series of 121 patients, 14 underwent vascular resection. Of the vascular resection group, three of 12 patients with lymph nodes removed had lymph node metastases, and R0 resection was achieved in 86 %. There was no difference in overall survival at 1, 3, or 5 years between patients with (85, 56, 44 %) and without (85, 45, 23 %) vascular resection. Median overall survival was 32 versus 49 months, which was not statistically different. Thus, there is evidence that vascular resection is feasible and should be performed if necessary to achieve complete tumor excision, as outcomes are comparable in experienced hands.

4.4 Minimally Invasive Approach

Minimally invasive liver resections have been performed in over 3,000 patients worldwide for a variety of benign and malignant indications [53]. In the largest review of laparoscopic liver cases, <13 % of malignant cases were for the indication of ICC; overall morbidity and mortality for minimally invasive resection in all patients were 10.5 and 0.3 % [54]. The benefits of a laparoscopic approach, when technically feasible and performed by appropriately trained and experienced surgeons, include shorter length of stay, less pain medication requirements, less blood loss, quicker resumption of oral intake, with equivalent rates of complications [55]. While operating room costs may be higher in a laparoscopic procedure compared with a matched open procedure, the total hospital costs are equivalent or reduced [55, 56].

Peripherally located tumors are most amenable to a laparoscopic approach; the ideal candidate would have no tumor near the planned transection plane. Vascular resections and extra-hepatic bile duct resections are more technically demanding in the minimally invasive setting, and most experienced surgeons would approach those tumors in an open fashion. The use of robotic assistance facilitates the more complex dissection and suturing required in extended hepatectomies, and has been employed in a variety of benign and malignant tumors, including ICC [57, 58]. Preliminary evidence demonstrates feasibility from a technologic and oncologic perspective, and the role of robotic-assisted minimally invasive hepatectomy continues to be explored [59].

4.5 Transplant in ICC

As ICC frequently presents at an advanced stage that precludes complete resection, total hepatectomy with orthotopic liver transplant (OLT) has been explored as a potential solution to this clinical problem. Reports on early experience with OLT for cholangiocarcinoma include a review of 54 patients with ICC who underwent resection (34) or OLT (20) at the University of Pittsburgh Medical Center [60]. OLT was performed for unresectable disease in 12 patients and concurrent advanced cirrhosis in 8. Overall survival at 1, 3, and 5 years for resection was 60, 37, and 31 %, which was similar to survival after OLT (70, 29 and 18 %), and comparable with the authors' outcomes for OLT in patients with HCC [61].

While these authors concluded that the comparable survival outcomes support the application of transplant to ICC, subsequent reports documented high rates of tumor recurrence in patients undergoing OLT for ICC and questioned the appropriateness of transplant in patients with ICC. Using data from the Cincinnati tumor registry, Meyer et al. [62] reported a 51 % rate of tumor recurrence in 207 patients transplanted for cholangiocarcinoma or mixed HCC-cholangiocarcinoma, including both peri-hilar and intra-hepatic tumors. The median time to recurrence was 9.7 months (range <1–64 months), and the median time between recurrence and death was 2 months (range <1–53 months). These data, and other studies with similar findings [63–66], led to a general consensus that cholangiocarcinoma should

Table 2 Perioperative outcomes in surgical series of ICC

First author	Year	N	Resectability (%)	LN pos (%)	R0 (%)	Mortality (%)	Morbidity (%)
Madariaga	1998	34	–	18	71	14	32
Weber	2001	33	62	15	88	3	19
Nakagawa	2005	44	83	47	75	5.7	–
DeOliveira	2007	44	66	30	45	4.5	35
Paik	2007	97	64	24	93	0	–
Shimada	2007	76	n/a	16	67	1	–
Endo	2008	77	70	16	85	1.2	38
Konstadoulakis	2008	54	75	82	78	7	11
Gugliemi	2009	62	–	18	90	–	–
Lang	2009	83	52	33	64	7.1	44
Nathan	2009	598	–	21	–	–	–
Shen	2009	429	–	20	74	1.2	6
de Jong	2011	449	–	17	81	–	–
Ali	2012	121	–	28	96	1	43

not be considered an appropriate indication for liver transplant outside of clinical trials focusing on neoadjuvant and/or adjuvant therapy to improve outcomes.

For ICC, investigators at UCLA have developed a protocol using preoperative radiation—either external beam or short-course stereotactic body radiation therapy (SBRT)—followed by 5-FU-based chemotherapy until the time of transplant [67]. In a review of 40 patients (26 intra-hepatic, 13 hilar), the 5-year recurrence-free survival was 29 %, with a median time to recurrence of 11 months. Multivariate analysis identified seven pathologic and treatment factors independently associated with prognosis: multi-focal disease, perineural invasion, infiltrative subtype, lymphovascular invasion, hilar location, history of PSC, and use of adjuvant and/or neoadjuvant therapy. A scoring system based on these risk factors was created, and the lowest-risk patients' 5-year recurrence-free survival was 78 %, compared with 19 % for intermediate risk and 0 for high risk.

In another study, the same group compared OLT to radical bile duct resection and partial hepatectomy in 57 patients (37 with intra-hepatic tumors and 20 hilar) [68]. Twenty-five patients with ICC underwent OLT, and 12 underwent resection. The overall 5-year survival for all ICC patients was 34 %. 3- and 5-year recurrence-free survival for all patients was 39 and 6 % for OLT compared with 33 % and 0 ($p = 0.05$). For intra-hepatic tumors, the improved survival with OLT was not statistically significant. On multivariate analysis, resection versus OLT, hilar versus intra-hepatic location, perineural invasion and multifocal tumors were factors associated with diminished survival. However, given the global shortage of organ donors, most transplant centers consider ICC a contraindication for OLT, and should only be performed in the setting of a clinical trial or protocol.

4.6 Perioperative Outcomes

Over the past several decades, the rates of postoperative death and complications following hepatic resection have decreased, such that most modern series from high-volume centers report less than 3 % mortality [69–72]. One review of 30-day outcomes of hepatectomies from the National Surgical Quality Improvement Project (NSQIP) database found a 30-day mortality of 2.5 % and morbidity of 19.6 % [73]. Improvements in surgical and anesthetic techniques, better patient selection, and innovations in hemostatic equipment are thought to contribute to these trends. Unfortunately, there is significant disparity in outcomes between high-volume and low-volume institutions performing hepatectomy, with lower mortality at high-volume centers (5.8 vs. 8.9 % in low-volume centers) [74].

In series of ICC patients, surgical mortality ranges from 1 to 14 % [9, 19, 23–25, 27–29, 50], and when reported, the most common causes for mortality are liver failure, sepsis, and cardiac events [19, 24, 27–29]. Several authors anecdotally note an association between extended liver resections, extra-hepatic bile duct resections and/or vascular resections and reconstructions with mortality, but this has not been formally demonstrated.

There is significant variability in how surgical complications are defined and reported; thus, the observed incidences of complications for resection of ICC have a wide range from 6 to 43 % [9, 19, 23–25, 27–29, 50]. The more common complications include intra-abdominal abscess, transient hepatic failure, infections (wound infections, pneumonia or sepsis), other pulmonary complications (pleural effusions or symptomatic atelectasis, ARDS), bile leak, and cholangitis [9, 19, 24, 27–29, 50]. Perioperative outcomes in recent series are summarized in Table 2.

Table 3 Factors influencing survival after resection of ICC

First author	Year	R0 resection	LN+	Tumor size	Multiple tumors	Vascular invasion
Madariaga	1998	Yes-OS	No	No	Yes	No
Weber	2001	Yes	No	Yes-DFS	No	Yes-OS
Nakagawa	2005	Yes-OS	Yes-OS	No	Yes-OS	No
DeOliveira	2007	Yes	Yes	No	No	No
Paik	2007	Yes-DFS	Yes-DFS	Yes-DFS	Yes-DFS	No
Endo	2008	No	Yes-RFS	Yes	Yes-RFS	No
Lang	2009	Yes	No	No	No	No
Nathan	2009	n/a	Yes	No	Yes	Yes
Shen	2009	Yes-OS	Yes-OS	Yes-OS	No	No
de Jong	2011	Yes-OS	Yes-OS	No	Yes	Yes
Farges	2011	Yes-OS in N0 pts	No	No	Yes-OS	No

OS overall survival; *DFS* disease-free survival; *RFS* recurrence-free survival

The goal of surgical resection of ICC is the complete removal of all gross and microscopic disease (R0 resection). This was achieved in 45–96 % of attempted curative resections [9, 10, 15, 19, 23, 24, 26–28, 50, 75]. Many studies have found R0 resection to be associated with more favorable outcomes [9, 10, 15, 25–28, 75]. In one recent multi-institutional review of 449 patients with resected ICC, the influence of resection margins on overall survival was significant only in patients with node-negative disease; those with positive lymph nodes had no other factors independently associated with survival [15]. This relationship was also seen in a European multi-institutional study of 212 patients undergoing resection for ICC; patients with N0 disease demonstrated resection margin to be associated with survival, but node-positive patients did not have additional factors influencing survival [75].

While the practice of routine lymphadenectomy is variable, there is consistency across centers that lymph node involvement with ICC is a poor prognostic factor [9, 10, 15, 19, 26, 27]. However, in the absence of more effective treatment, surgical resection with lymphadenectomy is still advocated for patients with ICC and regional nodal disease [18]. Tumor size [10, 19, 27, 28], multiple tumors [10, 15, 19, 25, 26, 75], and vascular invasion [12, 15, 28] have also been associated with survival. Factors associated with survival in modern series are summarized in Table 3. Median overall survival following resection ranges from 12.4 to 52.9 months [9, 10, 15, 23, 25, 27, 28, 50]. Some series report overall survival for a cohort that contains unresected or R2 patients [27]. Overall survival at one year ranges from 51 to 85 %, 3 years 22–66 %, and 5 years 17–44 % [9, 10, 15, 23–28, 50]. Survival outcomes are summarized in Table 4.

5 Adjuvant Therapy

Given the overall poor prognosis of ICC, even following a potentially curative resection, multimodality therapy is an attractive strategy to improve outcomes. The study of adjuvant and/or neoadjuvant therapy in ICC is limited by the relative rarity of ICC compared with other tumors such as HCC. However, studies of systemic therapy in unresectable cholangiocarcinoma may offer some insights.

For many years, 5-FU-based regimens were the only option for biliary tract cancers, with little efficacy [76, 77]. Single-agent gemcitabine was subsequently investigated in small studies of advanced biliary tract cancer, after promising results in pancreatic cancers [78–80]. Most recently, multi-agent gemcitabine-based regimens have been studied in phase II and phase III trials. One of the largest such studies enrolled 410 patients with unresectable biliary tract cancers, including 241 cholangiocarcinomas, which were not stratified by anatomic tumor location. Patients were randomized to receive gemcitabine (1,000 mg/m^2) on days 1, 8 and 15 of a 4-week cycle, or cisplatin (25 mg/m^2) and gemcitabine (1,000 mg/m^2) on days 1 and 8 of a 3-week cycle. Overall survival in the cisplatin–gemcitabine group was significantly longer at 11.7 months, compared with 8.1 months in the gemcitabine-only group, and progression-free survival was also significantly improved in the cisplatin–gemcitabine group, at 8.0 versus 5.0 months [81].

It is not clear whether these modest but promising results will be applicable in the patients undergoing resection. In a retrospective review, Glazer et al. analyzed 157 patients with biliary tract cancer, 54 of whom had ICC. These patients were treated with a variety of adjuvant and/or neoadjuvant treatments (gemcitabine/platinum based or

Table 4 Median and overall survival after resection for ICC

First author	Year	N	Median survival (mos)	1-year OS (%)	3-year OS (%)	5-year OS (%)
Madariaga	1998	34	19	67	40	35
Weber	2001	33	37		55	31
Nakagawa	2005	44	22	66	38	26
DeOliveira	2007	44	28			40
Paik	2007	97	53	75	52	31
Endo	2008	77	36 (DSS)			
Konstadoulakis	2008	54		80	49	25
Gugliemi	2009	62	41		55	26
Lang	2009	83	26	71	38	21
Nathan	2009	598	21		31	18
Shen	2009	429	12	51	22	17
de Jong	2011	449	27	78	44	31
Ali	2012	121	43	85	66	44

OS overall survival; *DSS* disease-specific survival

5-FU neoadjuvant regimens, 5-FU or capecitabine-based adjuvant regimens). On univariate analysis, chemotherapy was associated with diminished survival, but on multivariate analysis, neither adjuvant nor neo-adjuvant treatment had any impact on survival [82].

6 Conclusions

ICC is increasing in incidence for unclear reasons, but perhaps related to hepatitis C as a risk factor. Over 50 % of patients are unresectable at presentation, most often due to locally advanced disease. Staging laparoscopy may spare some patients a non-therapeutic laparotomy, but will not identify all patients with locally advanced, unresectable disease. Surgical resection is the only possibility for long-term survival, and extended resection and/or vascular resection with reconstruction should be undertaken by an experienced team if needed to achieve complete tumor clearance. Effective neo-adjuvant or adjuvant treatments have not been demonstrated, but this remains the subject of ongoing investigation.

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