Review

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Liver resection and transplantation for intrahepatic cholangiocarcinoma

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Summary

The incidence of intrahepatic cholangiocarcinoma (iCCA) is increasing worldwide. Although several advances have been made in the past decades to better understand this complex malignancy and to develop new treatment strategies, the prognosis of iCCA remains dismal. Liver resection (LR) is the mainstay of treatment but only a minority of patients are amenable to surgery. In most cases, patients with iCCA will require a major hepatectomy for complete resection of the tumour. This may be contra-indicated or increase the surgical burden in patients with chronic liver disease and small remnant liver volume. Lymphadenectomy with a minimal harvest of 6 lymph nodes is considered adequate, as microscopic nodal metastases have been shown in more than 40% of patients. Current 5-year overall survival following LR is in the range of 25%–40%. For locally advanced disease not amenable to upfront LR, neoadjuvant locoregional therapies may be used with the aim of converting these patients to resectability or even to transplantation in well-selected cases. Recent studies have shown that liver transplantation (LT) might be a treatment option for patients with unresectable very-early iCCA (*i.e.* ≤2 cm), with survival outcomes comparable to those of hepatocellular carcinoma. In patients with unresectable, advanced tumours, confined to the liver who achieve sustained response to neoadjuvant treatment, LT may be considered an option within prospective protocols. The role of adjuvant therapies in iCCA is still under debate. Herein, we review the recent advances in the surgical treatment of iCCA and examine its correlation with locoregional therapies, adjuvant and neo-adjuvant strategies.

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Introduction

Intrahepatic cholangiocarcinoma (iCCA) arises from the intrahepatic bile ducts proximal to the second-order division. Its incidence has been rising in the last few decades.[1] Between 2003 and 2009, an annual 5.9% increase in the incidence of iCCA was reported in the United States.[2] This sustained increase throughout all ages and ethnicity strata[3] has also been seen in European countries,[4–6] paralleled by an increase in iCCA-specific mortality.[7] Negative trends in iCCA incidence and mortality could be partially explained by improved diagnosis tools, more specific classification and increases in risk factors such as chronic hepatitis, metabolic syndrome and obesity.[8] iCCA has therefore become a significant healthcare problem for hepatologists and surgeons.

Currently, the only widely accepted curative treatment for iCCA is liver resection (LR). Although the boundaries of surgical indications for iCCA have been pushed by recent advances in technique and perioperative management, even with the best care most patients with iCCA will be dead within 3 years of diagnosis. Overall, the probability of being cured by LR is 9.7%, with patients only reaching a 95% certainty of cure 9.5 years after resection.[9]

Key point

Surgical resection is the only potentially curative option for iCCA. Survival after resection ranges between 25%–40% at 5 years.

Refinements to iCCA diagnosis and better understanding of genetic profiles might lead to optimised surgical approaches, either by LR or liver transplantation (LT). Moreover, combinations of surgery with locoregional therapies and novel drugs such as checkpoint inhibitors and molecular-targeted molecules might result in opportunities to use new adjuvant and neoadjuvant treatments.

This review aims to analyze the recent advances in iCCA treatment focusing on surgical therapies and highlighting perioperative strategies to improve surgical outcomes.

Clinical diagnosis and general principles of surgical consideration of iCCA

Most patients with iCCA do not have specific symptoms and a liver mass is often discovered incidentally during evaluation for an unrelated reason. Amongst patients with symptoms, abdominal pain is the most frequently reported. Weight loss and malaise are often symptoms of more advanced disease. Early jaundice is uncommon but can occur when the tumour is located centrally within the liver and obstructs the confluence of the hepatic ducts by extrinsic compression or by directly

extending into the biliary tree. In 1 study, serum bilirubin >1.2 mg/dl was found to predict unresectable disease.[10] Consequently, unless discovered incidentally or in a screening programme, most patients present with advanced tumours: an analysis of the SEER database between 1983 and 2010 confirmed that only 15% of patients with iCCA underwent resection.[11]

Contrast-enhanced CT or MRI scans can often show characteristics suggestive of iCCA, but currently there are no accepted criteria for definitive non-invasive diagnosis based on imaging alone. On contrast-enhanced imaging, iCCA often presents as a mass with irregular borders, peripheral rim enhancement on the arterial phase and progressive filling of the central portion of the tumour on delayed phases.[12] CT and MRI scans may also demonstrate capsular retraction and obstruction of segmental biliary radicals proximal to the tumour. However, smaller tumours are less likely to demonstrate these specific features and may be difficult to distinguish from hepatocellular carcinoma (HCC), especially in the context of chronic liver diseases.

Tumour markers are of little help in the diagnostic setting. The majority of patients affected by iCCA have increased levels of CA19.9 and various cut-offs of CA19.9 serum levels (from 100 to 500 ng/ml) correlated with more advanced tumours, unresectability and poor survival.[13]

Although tissue diagnosis is recommended to establish a diagnosis of iCCA, in patients with resectable lesions suspected of having cholangiocarcinoma, in which a metastatic spread has been reasonably ruled out, a liver biopsy is generally avoided because of the risk of seeding.[14] Furthermore, even with a tissue biopsy demonstrating adenocarcinoma, uncertainties remain in distinguishing iCCA from metastases arising from the colorectum, oesophagous, stomach, pancreas and lung.[15] Currently, National Comprehensive Cancer Network (NCCN) guidelines recommend upper and lower endoscopy to rule out an occult primary in the gastrointestinal tract.[16] Likewise, distinguishing iCCA from mixed cholangiocarcinoma-HCC requires expert pathological review.

Due to the difficulties in differential diagnosis between iCCA and liver metastases, fluorodeoxyglucose positron emission tomography (FDG-PET) is also commonly used to rule out a primary tumour. Its staging role for the identification of distant metastases is less well defined, although a few small series showed that FDG-PET may detect occult metastatic spread in up to 20–30% of cases. Despite a recent meta-analysis supporting the role of FDG-PET in the assessment of distant and nodal disease in biliary tract cancers – it led to a change in management in 15% of patients – current guidelines do not recommend its routine use in the absence of radiological or clinical suspicion of metastatic disease.[17,18]

In addition to their diagnostic role, contrast-enhanced CT or MRI are essential for determining the extent of locoregional disease and metastatic spread in order to assess resectability. Both CT and MRI scans have good discriminatory ability in assessing portal and arterial invasion, with magnetic resonance cholangio-pancreatography properly defining biliary anatomy and tumour involvement. Nevertheless, digital preoperative imaging assessment of lymph node metastases remains poor. Very few studies assessed the role of FDG-PET for the evaluation of nodal status, and no recommendations can be drawn because of conflicting results.[19] Given the high prognostic impact of positive lymph nodes in patients with large tumour burden or at increased surgical risk, preoperative endoscopic ultrasound with fine needle aspiration cytology may be considered to drive clinical decisions. Lymph node metastases beyond the hepato-duodenal and gastro-hepatic ligaments are a well-established contraindication to surgical resection. Although positive lymph nodes confined to the hepatic hilum are also associated with high rates of recurrence, long-term survival in up to 15% of cases is still possible after tumour removal with locoregional lymphadenectomy; this makes resection in the presence of nodal tumour spread an individualised decision to be taken after careful risk-benefit analysis.

In patients with underlying liver disease, assessment of portal hypertension is critical as its presence is usually a contraindication to LR. In addition, size and quality of the liver remnant after resection are critical factors, as atrophy and fibrosis from biliary obstruction or steatosis and chronic damage can result in liver remnants that are unable to regenerate after surgery, leading to a high risk of post-operative liver failure. Peritoneal or distant metastases are other general contraindications to resection.

Conventional surgical aims of LR should be: complete tumour resection with free margins (*i.e.* R0 resection) and preservation of enough liver volume to avoid post-operative liver failure. As the majority of patients are referred to surgery at a locally advanced stage and/or with extrahepatic disease, only 12–40% of all patients with iCCA are candidates for surgical resection at the time of diagnosis.[1,20,21]

The multifaceted concept of resectability in iCCA

Resectability depends on 2 main variables: the location of the tumour lesion, including its relationship with intrahepatic vascular and biliary structures, and the amount and quality of the liver parenchyma remaining after tumour resection.

Concerning the topographic definition of iCCA, atypical or anatomical resections can be performed

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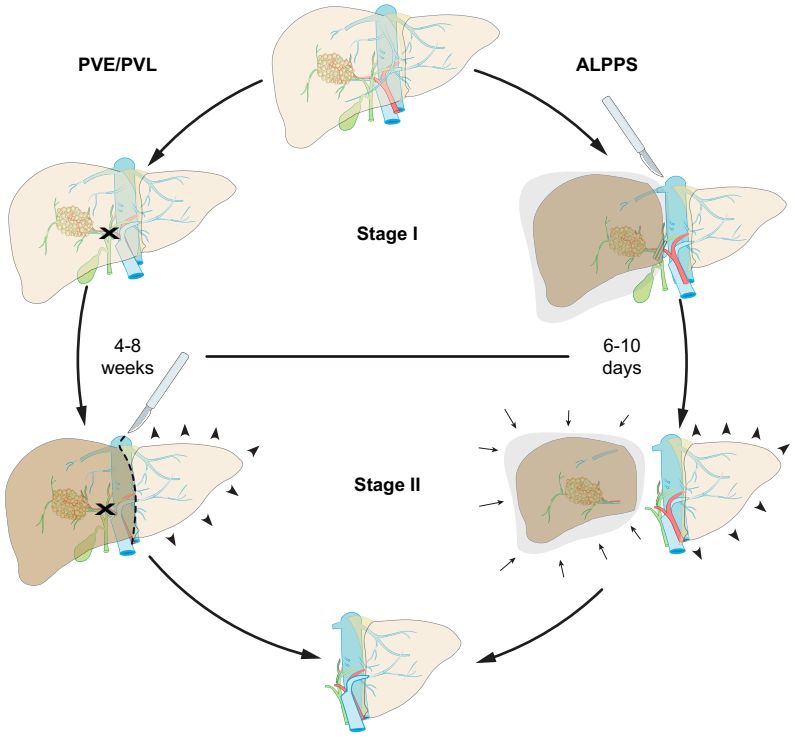

Fig. 1. Regenerative techniques for the future liver remnant to expand iCCA resectability (slow *vs.* fast techniques have various indication and outcomes; see text). ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; iCCA, intrahepatic cholangiocarcinoma; PVE, portal vein embolisation; PVL, portal vein ligation. The knife indicates the time of liver transection.

in cases of relatively small and peripheral lesions, while anatomic hepatectomies are mostly performed for large multisegmental tumours. A recent propensity-score matching analysis has demonstrated better survival and lower recurrence rates after anatomical resections.[22] Overall, due to advanced disease stage at diagnosis, most patients (70–80%) will require a major hepatectomy (*i.e.* ≥3 segments resected) to achieve complete resection. Fifty to 70% of patients with resectable iCCA undergo hemi-hepatectomy or extended hepatectomy.[20,23,24]

For centrally located lesions, the surgical planning is often complex, due to the relationship of the lesion with the first- and second-order portal and biliary branches, as well as with suprahepatic veins. In such instances – as for perihilar cholangiocarcinoma – a bilateral involvement of second-order biliary branches, a unilateral liver atrophy with contralateral biliary or vascular involvement (either portal or arterial) or a unilateral biliary involvement with contralateral vascular involvement (either portal or arterial) contraindicate LR. Additionally, these patients may present jaundice (15% of all iCCA) and need to undergo prompt endoscopic or percutaneous drainage before any treatment decision can be made. Notably, the presence of jaundice impairs liver function and, together with a consistent risk of cholangitis, worsens the surgical outcome. LR associated with biliary tree resection is indicated in tumours invading the ductal bifurcation and/or the main hepatic duct, as required in 20%–30% of hepatectomies for iCCA.[23,24] In a recent multi-institutional analysis of 128 patients who underwent major vascular resections of the inferior vena cava and portal vein (21 and 98 patients, respectively), the perioperative outcomes were comparable to those achieved in 959 cases of conventional resection, suggesting that major vascular resections and reconstructions can be considered in properly selected patients, if R0 margin can be achieved.[25,26]

Concerning the recommended future liver remnant (FLR) volume, iCCA does not differ from other indications for LR, with a threshold of 25% of liver volume to be preserved for patients with normal parenchyma. Conversely, patients with iCCA in the context of chronic liver disease will require a minimum FLR of 40% with no portal hypertension. The higher threshold in case of chronic liver diseases makes the surgical option even less likely in this subgroup, representing up to 20% of patients with iCCA.[27]

Management of the future liver remnant

In cases with an anticipated inadequate FLR, regenerative techniques may be used in order to expand resectability (Fig. 1).

- Portal vein embolisation (PVE) by preoperative radiological injection of embolic agents in the right portal system is a safe technique that enables FLR hypertrophy of around 40% in the healthy liver after a median of 4 weeks. Portal embolisation, however, is burdened by 20–30% drop-out rates due to tumour progression or insufficient regeneration. Particularly in the cirrhotic or cholestatic liver, regeneration is impaired, and levels of FLR hypertrophy as low as 9% have been reported.[28]
- In patients with very low FLR volume and those expected to have insufficient regeneration after PVE or to be at a high risk of tumour progression (possibly impairing the chances of surgical resection during the regeneration phase) an accelerated procedure called associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) may allow for faster and enhanced hypertrophy of the liver remnant (up to 70%) compared to conventional portal embolisation.[29] ALPPS, however, is limited by morbidity rates above 50% and mortality rates as high as 20%. In addition, patients affected by biliary tumours are exposed to worse perioperative outcomes with ALPPS, which may be related to previous cholestasis and/or associated severe steatosis and chronic liver damage.[30]

Staging laparoscopy

For patients who are candidates for extensive surgical procedures, at high surgical risk or with

advanced tumours (*i.e.* multifocal disease, high CA19.9 level, suspected lymph node spread or vascular invasion), exploratory laparoscopy and intraoperative ultrasound may be indicated in order to rule out peritoneal spread, distant lymph node or multifocal intrahepatic diffusion. Yields of between 27–38% have been reported for the identification of peritoneal or intrahepatic metastases that preclude resection.[17]

Multifocal disease

Multifocal iCCA is seen in nearly 50% of patients[31,32] and the role of surgery for these patients remains debatable. Patients with multifocal iCCA are at an increased risk of tumour recurrence and death after LR compared to patients with a single lesion.[20,32,33] The adverse effect is still evident even compared to patients with a single large tumour (>7 cm).[31] To account for such prognostic impact, the American Joint Committee on Cancer (AJCC) has classified multifocal tumours as T2 stage, along with single tumours with vascular invasion.[34] In these patients, LR does not seem to improve overall and recurrence-free survival compared to locoregional therapies.[35]

Death is related to intrahepatic tumour spread in the majority of cases with multifocal iCCA, so both locoregional and surgical therapies may be of help in selected patients. In this respect, International Liver Cancer Association (ILCA) guidelines support non-curative resections in patients with resectable multinodular disease or macrovascular invasion. In the future, a reasonable approach not included in the current guidelines may consider the response to locoregional therapies as a selection tool for patients with iCCA who may benefit from LR, despite initial presentation.

Role of lymphadenectomy

The role of hilar lymphadenectomy in iCCA is still under debate. Nodal metastases are found in up to 45% of patients and are known to be one of the most important prognostic factors after LR for iCCA.[36,37] NCCN and ILCA guidelines recommend lymphadenectomy with a minimum of 6 nodes harvested.[27] These recommendations are likely responsible for the increase in frequency and number of nodes removed during hepatectomy for iCCA in the last few years,[38,39] with several authors performing routine lymphadenectomy in order to achieve more precise staging of nodal status and to decrease the risk of local recurrence.[40,41] This is even more important considering the low detection rate of positive lymph nodes at imaging.[42] Contrary to the general trend, a few series have reported that routine lymphadenectomy does not directly impact on patient survival.[41,43–45]

A recent case series from 15 Western and Eastern centres showed that lymphadenectomy was performed in less than 50% of patients undergoing LR for iCCA.[39] Among patients who underwent lymphadenectomy, nearly 80% had a complete hilar lymphadenectomy performed. A median of 4 lymph nodes (IQR 4–8) were harvested and 43% of them were positive for metastatic iCCA. Interestingly, this study showed that patients who had ≥3 lymph nodes resected had better survival than those who had only 1–2 nodes removed. The AJCC staging system recently included the recommendation of a minimum of 6 lymph nodes to ensure accurate nodal staging.[34]

In cirrhotic patients, however, lymphadenectomy is associated with a complication rate of up to 71%, limiting the role of lymphadenectomy to selected cases.

Patients with positive lymph nodes may benefit from adjuvant therapies. With the advent of more effective adjuvant protocols, it is expected that precise nodal staging will become more important in the near future.

Key point

Hilar lymphadenectomy (minimum of 6 resected lymph nodes) provides prognostic information and assists in risk stratification for adjuvant trials.

Minimally invasive surgery for iCCA

Laparoscopic LR is associated with better short-term outcomes, improved pain management and shorter hospital stay,[46] but few studies assessed the role of minimally invasive surgery specifically in iCCA. A propensity-matched cohort study comparing laparoscopic to open LR showed similar outcomes between groups, with a median disease-free survival of 33 months for the laparoscopic group and 36 months for the open surgery group.[47] Similar results were also reported by other authors.[48]

Although the use of robotic technology has not been specifically evaluated for iCCA, encouraging results have been reported in a cohort of patients with different types of hepatic tumours treated by hepatectomy.[49] A recent consensus states that robotic LR is safe and has similar effectiveness to open hepatectomy in patients with hepatic malignances, although the level of evidence supporting this assertion is very low.[50]

Results of liver resection for iCCA

Even though only a minority of patients with iCCA are candidates for LR, the number of hepatectomies for iCCA is increasing worldwide.[51] This is related to technical advances in the field of hepatobiliary surgery, improved perioperative management and more focused consideration of iCCA in which sustained responses can be achieved by means of locoregional and systemic therapies. In high-volume hepatobiliary centres, surgical mortality after iCCA resection is reported to be lower than 5%.[24] Table 1 gives a literature overview of the observed outcomes after LR for iCCA.

The median overall survival after LR is reported to be 40 months, with a 5-year overall survival of 25–40%.[20,52,53] Tumour recurrence occurs in about 50–70% of patients at a median time of 26 months. A meta-analysis on curative resection for iCCA identified age (HR 1.10; 95% CI 1.03–1.17), tumour

size (HR 1.09; 95% CI 1.02–1.16), presence of multiple lesions (HR 1.70; 95% CI 1.43–2.02), lymph node metastases (HR 2.09; 95% CI 1.80–2.43), vascular invasion (HR 1.87; 95% CI 1.44–2.42) and poorly differentiated tumours (HR 1.41; 95% CI 1.17–1.71) as significant predictors of tumour recurrence and patient death.[33]

Repeated resection for treatment of intrahepatic recurrence

The liver is the most frequent site of recurrence following LR for iCCA, with exclusive intrahepatic disease found in about 60% of cases.[54,55] These finding have supported the use of repeated hepatectomy in those cases with a tendency to recur only in the liver.

In such a context, if R0 resection is achievable, patient outcomes can be improved significantly with LR. In a multicentric study, 41 repeated resections were performed among 400 recurrent cases, with a median survival of 26.1 months compared to 9.6 and 16.8 months in patients with liver-recurrent iCCA treated with intra-arterial therapy or standard chemotherapy, respectively.[56] Other studies reported a 5-year survival of 63.7% by means of resection and ablation in 103 out of 406 liver-only recurrent iCCAs. Although a clear selection bias affects retrospective studies, it should be emphasised that surgery is a viable option for recurrent iCCA with no sign of extrahepatic spread. While specific biologic markers able to single out such patients upfront are an unmet need from both the perspective of resection and transplantation, repeated surgical resection, if technically feasible, may offer competitive survival with respect to the currently available non-surgical therapies.

Role of neoadjuvant therapies from a surgical perspective

There is no evidence supporting the use of neoadjuvant systemic chemotherapy over upfront resection in patients with resectable iCCA. However, the rationale for preoperative treatment aimed at decreasing the high recurrence rates and downstaging initially unresectable disease is strong, especially considering the low resectability rates of iCCA, the high incidence of R1 resections and the significant surgical morbidity burden, often impairing the possibility of adjuvant treatments. Although randomised studies supporting neoadjuvant chemotherapy in iCCA are lacking, the use of preoperative treatments to downstage tumours is part of general practice, and positive outcomes have been reported in retrospective series of patients with iCCA, preserved liver function and no cholestasis.

In an Eastern series, 22 patients with unresectable iCCA who received neoadjuvant gemcitabine were downstaged to resection and achieved a 5-year overall survival of 45%.[57] In a Western study, 74 patients with locally advanced unresectable iCCA initially treated with chemotherapy (53% of whom were successfully converted to resection) were compared to patients with resectable iCCA who underwent surgery alone[58]: postoperative morbidity and mortality were similar, as well as median survival after surgery (24 months *vs.* 26 months, respectively: $p = 0.39$). Neoadjuvant locoregional therapies are increasingly used for iCCA, although reliable data on the efficacy of such approaches are scarce and at times disappointing.

Discouraging conversion rates to surgery have been observed in 8 out of 104 patients treated with hepatic artery infusion chemotherapy;[59] in another study, none of 12 patients prospectively treated with a combination of selective intra-arterial floxuridine with systemic cisplatin and gemcitabine became resectable.[60] Pre-surgical selective internal radiation therapy (SIRT) in iCCA has shown promising preliminary results in terms of safety and effectiveness,[61,62] even in association with chemotherapy, in the treatment of advanced iCCA.[63] In a study on 45 patients with unresectable iCCA, Yttrium^{90} (Y^{90}) SIRT combined with gemcitabine and/or platinum chemotherapy achieved an 18% rate of conversion to free-margin surgery with no significant toxicity.[62] An example of efficacy of such combination treatment is presented in Fig. 2.

Although transarterial chemoembolisation (TACE) has proven to be effective for disease control in the advanced setting, few reports are available on its role in the neoadjuvant setting. To date, TACE has conferred disappointing response rates of around 20% in patients with unresectable iCCA, which are inferior to those of intra-arterial chemotherapy and SIRT. This is possibly a consequence of the hypovascular nature of iCCA, which is characterised by extensive fibrosis and a predominantly non-arterial blood supply.[64]

External-beam radiation therapy in combination with systemic chemotherapy has also been proposed.[65] In a recent Japanese study of 15 consecutive patients, 9 were successfully downstaged to R0 resection (60%) with a 5-year overall survival of 24%.[66]

Key point

Downstaging treatments aimed at conversion of unresectable disease by means of locoregional therapies might be an option in patients with locally advanced tumours and good performance status.

Liver transplantation for iCCA

iCCA has been a contraindication for LT in most centres worldwide due to very poor initial results, with 2-year survival of around 30%.[67–69] The lack of standardised patient selection and the absence of neoadjuvant therapies likely impacted on outcomes. The landscape started to change after selection criteria were proven to be essential to improving survival in LT for early-stage HCC.[70] The excellent survival obtained in hilar cholangiocarcinoma thanks to careful patient selection and to neoadjuvant chemo-radiation protocols, together with the new oncological indications for transplant opened up by the advent of direct-acting antiviral agents for treatment of HCV

Table 1. Outcomes of liver resection for patients with intrahepatic cholangiocarcinoma: literature review.

Study	Year	Study design	n	Perioperative mortality*	Overall survival (%)			DFS (%)	Neoadjuvant treatment	Adjuvant treatment	Comments
					1-year	3-year	5-year	5-year			
Weber *et al.*[40]	2001	Retrospective single centre	33	3%	n.a.	55	31	22% (3y)	none	none	62% resectability rate
Jensen *et al.*[51]	2008	Retrospective multicentre	446	8.0%	68	n.a.	18	n.a.	n.a.	n.a.	12% resectability rate
De Jong *et al.*[20]	2011	Retrospective multicentre	449	5.7%	77	44	31	n.a.	none	none	–
Sotiropoulos *et al.*[23]	2009	Retrospective single centre	41	n.a.	90	68	44	25	none	none	Non-cirrhotic and R0 resections only
Endo *et al.*[24]	2008	Retrospective single centre	82	1.2%	n.a.	n.a.	n.a.	median 36 months	5 patients converted to resection	case-by-case basis	–
Konstadoulakis *et al.*[87]	2008	Retrospective single centre	54	2.0%	80	49	25	n.a.	none	none	–
Lang *et al.*[88]	2009	Retrospective single centre	83	7%	71	38	21	30 (in 53 R0 resections)	none	none	–
Nakagohri *et al.*[89]	2008	Retrospective single centre	56	8.9%	59	42	32	n.a.	none	none	–
Shimada *et al.*[41]	2009	Retrospective single centre	104	n.a.	n.a.	n.a.	33.7	n.a.	none	none	–
Nakagawa *et al.*[90]	2005	Retrospective single centre	44	1.9%	66.2	38.3	26.3	n.a.	none	none	–
Choi *et al.*[91]	2009	Retrospective single centre	64	n.a.	76.6	52.7	39.5	34.7 (3-year)	none	none	–
Uenishi *et al.*[92]	2008	Retrospective multicentre	133	1.5%	63	36	29	-	none	none	66% recurrence median follow-up 1.4 years
Paik *et al.*[93]	2008	Retrospective single centre	97	7.1%	74.9	51.8	31.1	2.1	none	none	–
Ohtsuka *et al.*[94]	2002	Retrospective single centre	48	n.a.	62	38	23	-	none	none	63% recurrence median follow-up 70.8 months
Kim *et al.*[43]	2015	Retrospective single centre	102 LND 113 no LND	1.0% 0%	67.7 74.3	45.5 47.8	30.0 42.5	21.7 33.4	none	yes	–
Si *et al.*[22]	2019	Retrospective single centre	319 AR 383 NAR	4.4% 4.4%	72.9 62.0	45.7 30.8	36.0 25.3	28.1 18.0	none	none	–

AR, anatomical resection; DFS, disease-free survival; LND, lymphadenectomy; n.a.: not available; NAR, non-anatomical resection.
*Defined as death within 30 days from resection.

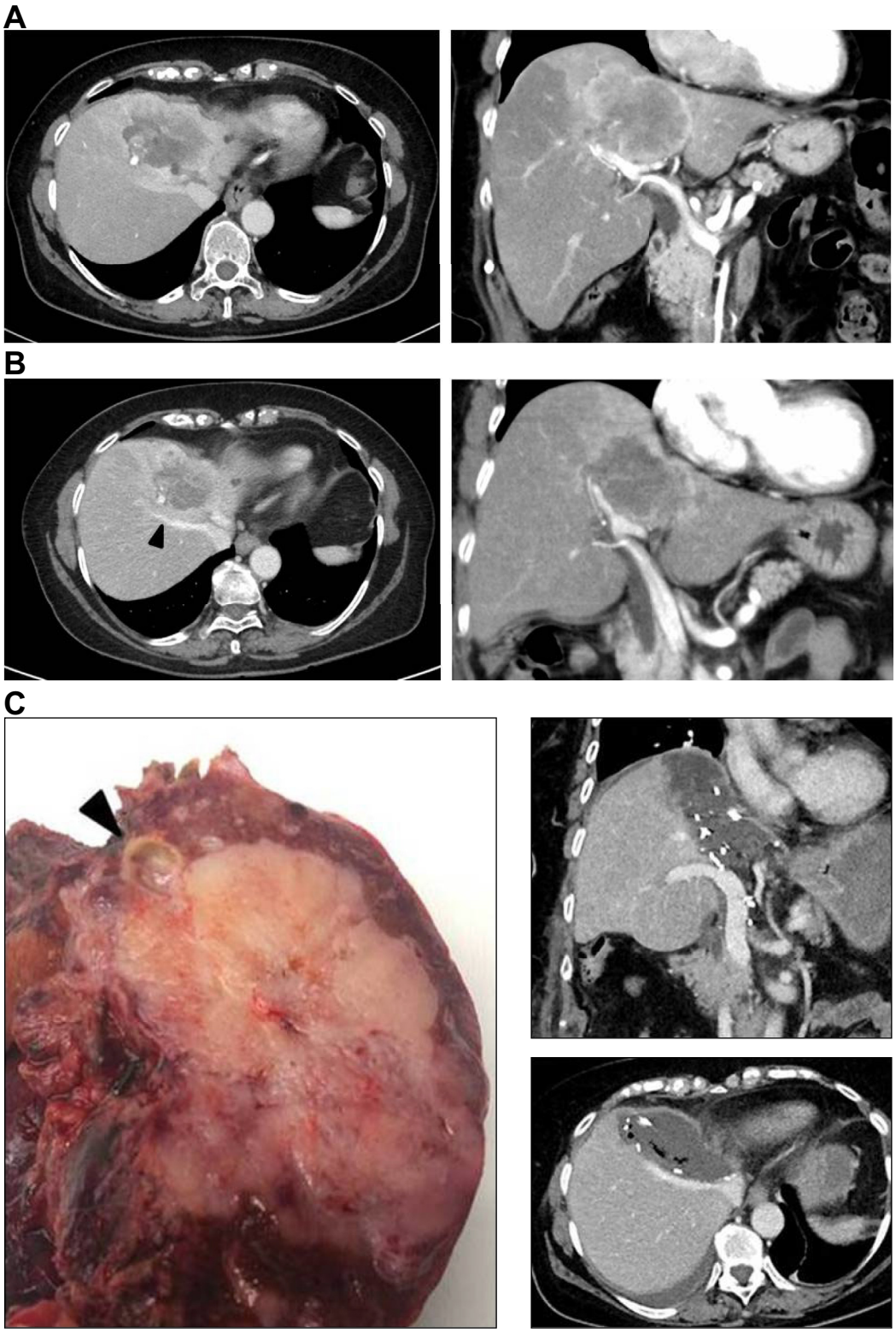

Fig. 2. Major liver resection after downstaging of iCCA. Multifocal iCCA in a 71-year-old woman presenting with epigastric pain. (A) Large multifocal iCCA: at diagnosis the main lesion of 7.5 cm infiltrates left and middle hepatic veins and is adherent to the right hepatic vein, left portal vein and the anterior branch of the right portal vein. Satellite lesions in the left liver lobe are also present. (B) Partial response to neoadjuvant therapy with enlargement of the surgical margin on the right hepatic vein (arrowhead): combination of first-line chemotherapy with gemcitabine+cisplatin and SIRT was administered and partial response was observed (*i.e.* size reduction of the main lesion with detachment from the right hepatic vein adhesion and atrophy of the right anterior sector). The patient underwent extended left hepatectomy including the right anterior sector (segments I-II-III-IV-V-VIII), with preservation of the posterior portal and biliary pedicles. Adjuvant capecitabine was administered. She is alive and well 18 months after surgery. (C) Surgical specimen and postoperative CT scan showing neoplastic thrombosis in the middle hepatic vein and the regenerated right posterior sector of the liver, left as the only functioning remnant parenchyma.

infection, further contributed to LT being considered a treatment option for selected cases of iCCA.

After 2014, several retrospective cohorts have showed satisfactory results after LT for iCCA, as summarised in Table 2. The importance of patient selection was first demonstrated in an international multicentric study enrolling patients who underwent LT with an occult iCCA found in the explant. Authors showed that patients with a single iCCA ≤2 cm (very-early iCCA) had a 5-year overall survival of 65% and a 5-year cumulative incidence of recurrence of 18%. The outcomes in the very-early iCCA group were far superior to those in patients with more advanced iCCA, who achieved a disappointing 5-year overall survival of 45% and a 5-year cumulative incidence of recurrence of 65%. These results suggest that LT might be an option for patients with very-early iCCA who are not candidates for LR (*e.g.* due to cirrhosis). As these results need to be prospectively validated, a multicentric single-arm clinical trial (NCT02878473) is underway to confirm the effectiveness of LT for very-early iCCA.

Besides the rare indication of very-early and unresectable iCCA and after exclusion of patients with positive lymph nodes or distant metastases, there remains a considerable subset of patients with liver-only disease deemed unresectable due to either local invasion of major vascular and biliary structures or to inadequate liver remnant. In such patients, the use of neoadjuvant protocols followed by LT may be a viable option, following careful patient selection based on risk stratification and tumour biology.

The effectiveness of LT for patients with locally advanced unresectable iCCA was recently addressed in a case series evaluating the use of neoadjuvant chemotherapy in select patients with favourable tumour biology.[71] The study enrolled patients with a biopsy proven iCCA >2 cm and no evidence of extrahepatic disease, vascular invasion and lymph node spread. A minimal period of 6 months with sustained response after chemotherapy with gemcitabine and cisplatin was mandatory. Out of 21 evaluated patients, 6 underwent LT and 1 was converted to LR. Adjuvant therapy with gemcitabine, capecitabine or both was recommended for patients with active iCCA in the explants, starting 4–6 weeks after LT. Despite the extensive tumour burden detected in the explanted livers (median number of 4 lesions up to 7 cm), an excellent 5-year overall survival rate of 83% with a recurrence rate of 50% at a median of 7.6 months were shown. Such results exceed those previously reported for either LR, chemotherapy or LT alone, in the absence of neoadjuvant treatments.[71]

Clearly, tumour biology and related markers are critical for proper patient selection; the role of response to neoadjuvant protocols as a surrogate of tumour aggressiveness is worth investigation. Prospective clinical trials considering survival endpoints from an intention-to-treat perspective are necessary to evaluate LT as a treatment for advanced iCCA in a modern setting, including neoadjuvant radiotherapy and SIRT in association with chemotherapy. Ideally, prospective series should be followed by randomised trials to assess the survival benefit of LT compared to optimal locoregional and systemic treatment. However, given the rarity of disease and the difficulties associated with a randomised design for transplant indications, prospective parallel studies of downstaging treatments followed by LT versus palliative treatment options may be proposed. Patient cohorts should be matched based on tumour burden and biological criteria, and the primary endpoint of such studies should be the survival benefit, defined as the difference in survival achieved by LT compared to other options.

Based on prognostic information already available, future studies should also focus on predetermined morphologic and biologic criteria for consideration of a transplant strategy. An example of such an approach that combines downstaging treatments and LT is shown in Fig. 3.

Table 3 summarises the current shared indications and contraindications to LR and LT, together with proposed approaches and future perspectives.

Key point

Retrospective studies have shown that liver transplantation may offer acceptable outcomes for patients with unresectable very-early iCCA (*i.e.* ≤2 cm).

Adjuvant therapies for iCCA

Adjuvant chemotherapy

Post-operative chemotherapy is not a standardised practice in iCCA. Given its relative rareness, few studies addressed the role of adjuvant chemotherapy exclusively in iCCA, while most chemotherapy studies still gather all types of biliary malignances. In addition, no study assessed the effectiveness of adjuvant therapy after LT for iCCA.

Overall, the available evidence is still poor. A randomised phase III trial failed to prove the superiority of gemcitabine and oxaliplatin compared to observation in patients with resected biliary cancer (HR 0.72; 95% CI 0.43–1.97).[72] The recent BILCAP trial showed that adjuvant capecitabine was associated with increased per-protocol overall survival in patients with biliary malignances, but failed to demonstrate this effect in the intention-to-treat analysis.[73] In the subgroup of 84 patients with iCCA within the BILCAP trial, 43 were treated with capecitabine while 41 belong to the observation group. At the end of 60-month follow-up, 56% of patients with iCCA were alive in the capecitabine group whereas survival in the observation group was 41%. However, such a trend did not reach statistical significance (HR 0.65; 95% CI 0.35–1.18).

A meta-analysis of retrospective cohorts showed that patients with resected iCCA who underwent adjuvant intra-arterial chemotherapy had

Key point

Combinations of neoadjuvant therapies and liver transplantation may also be an option for patients with locally advanced iCCA, but prospective studies with pre-determined selection criteria are needed.

Table 2. Outcomes of liver transplantation for patients with intrahepatic cholangiocarcinoma: literature review.

Study	Year	Study design	n	Overall survival (%)			DFS (%)	Neoadjuvant treatment	Adjuvant treatment	Comments
				1-year	3-year	5-year	5-year			
Sotiropoulos *et al.*[95]	2008	Retrospective	10	70	50	33	–	none	none	–
Vallin *et al.*[96]	2013	Retrospective Multicentre	10	80	60	24	–	none	none	–
Sapisochin *et al.*[97]	2014	Retrospective Multicentre	27	78	66	51	36	none	none	–
Facciuto *et al.*[98]	2015	Retrospective	7 iCCA 9 iCCA+HCC 16 iCCA-HCC	71	–	57	44	none	none	–
Vilchez *et al.*[99]	2016	Retrospective Multicentre	440	79	58	47	–	none	none	–
Sapisochin *et al.*[100]	2016	Retrospective Multicentre	15 single ≤2 cm 33 multiple or >2 cm	93 79	84 50	65 45	82 39	none	none	–
O'Grady *et al.*[101]	1988	Retrospective	13 iCCA	38	10	10	no	none	none	–
Yokoyama *et al.*[102]	1990	Retrospective	2	50	0	–	–	none	none	–
Meyer *et al.*[103]	2000	Retrospective Multicentre	207	72	48	23	–	none	~10% of patients	84% DFS at 25 months.
Shimoda *et al.*[104]	2001	Retrospective	16	62	39	–	35	none	none	8 patients with iCCA-HCC.
Robles *et al.*[105]	2004	Retrospective Multicentre	23	77	65	42	–	none	none	2-year DFS 35%
Ghali *et al.*[106]	2005	Retrospective Multicentre	10	–	30	–	–	none	none	1 patient with iCCA-HCC
Hong *et al.*[107]	2011	Retrospective LR *vs.* LT	LT: 25 LR: 12	–	38	32	33	9 LT no LR	16 LT and 5 LR	–
Lunsford *et al.*[71]	2018	Prospective single-arm	12 enrolled 6 underwent LT	100	83.3	83.3	50	Chemotherapy + 6-month mandatory SD	none	–

DFS, disease-free survival; HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcinoma; iCCA-HCC, mixed hepatocellular cholangiocarcinoma; LR, liver resection; LT, liver transplantation; SD, stable disease.

Key point

Adjuvant chemotherapy is recommended in high-risk patients (multifocal disease, large lesions, positive lymph nodes or R1 resection); capecitabine for 6 months has demonstrated a survival advantage over placebo.

a survival benefit (HR 0.66; 95% CI 0.55–0.79), even though the risk of bias was high (I^2 = 0.20).[74] An American Society of Clinical Oncology (ASCO) expert panel conducted a systematic review to guide decision-making for patients with resected biliary cancer and concluded that adjuvant capecitabine should be offered.[75]

Targeting molecular profile of iCCA: implication for the surgical context

As reported in other chapters of this special issue on liver cancer, novel concepts in iCCA pathology and genomics have shown important biological differences between iCCA and other types of biliary cancers.[76] Such a revolution in our understanding of iCCA biology is ongoing and likely to influence future trials specifically focused on this cancer.

Understanding gene aberrations in iCCA may provide insights on post-resection prognosis and identify potential targets for novel therapies. Nearly 40% of patients with biliary cancer have potentially targetable mutations[77] with some recurrent mutations identified in *IDH1, IDH2, FGFR1, FGFR2, FGFR3, EPHA2,* and *BAP1* genes. Of note, the mutation on *FGFR2* was found exclusively in iCCA, at reported rates of around 15%.[77] This type of genetic signature likely contributes to a more favourable biological behaviour,[76] as patients with FGFR had significantly higher overall survival (37 months *vs.* 20 months) compared to non-mutated patients.[78] In such a context, infigratinib, derazantinib and pemigatinib showed overall response rates of 19%, 21% and 36%, and disease control rates of 83%, 83% and 82%, respectively, even though progression-free survival remains around 6 months, mainly due to primary and secondary resistance.[79–81] These small molecules evaluated in phase II trials for advanced iCCA may possibly represent future alternative options in the adjuvant setting in light of preminimary data on their manageable toxicity.

The IDH1 pathway is deranged in up to 25% of patients with iCCA and a recent phase II trial with ivosidenib (AGI-120) in second-line demonstrated encouraging results.[82,83] *BRAF* is another rare targetable mutation involving 5–7% of iCCA and a trial with dabrafenib and trametinib for these patients is currently underway. The inhibition of heat-shock protein 90 has also recently been shown as an alternative target for tumours with FGFR aberrations.[84] Until now, the results of immunotherapy have been disappointing, with clinical response confined to the small subset of patients with microsatellite instability (0.5–2.5% of cases).

Although further insights on the prognostic relevance of mutations in iCCA are needed, a role for patient selection and treatment allocation also based on molecular prognostic assessment may be foreseen in the future. Molecular studies

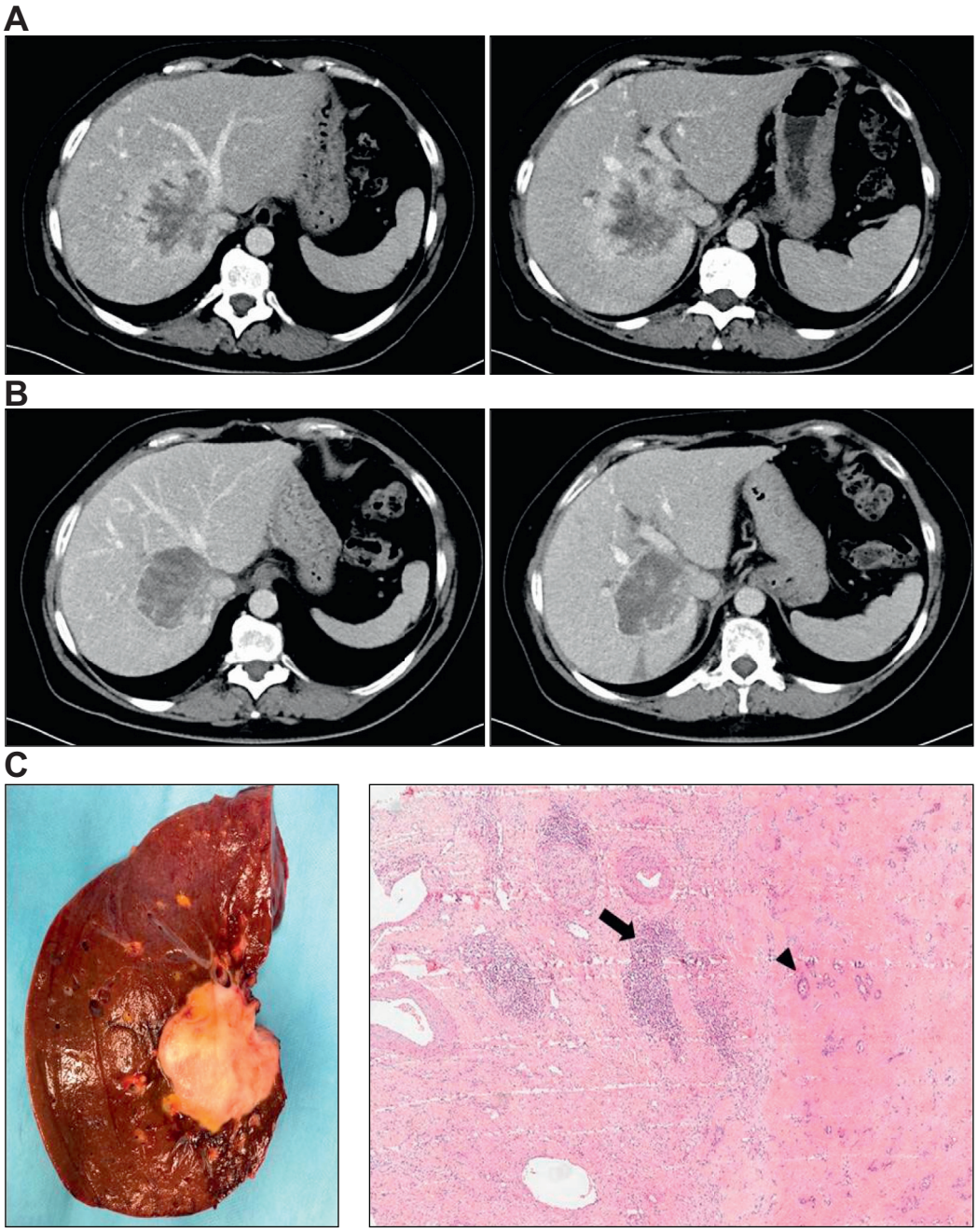

Fig. 3. Liver transplantation after sustained response to neoadjuvant combined treatment. Large, single iCCA in a 58-year-old woman with preserved liver function and metabolic syndrome. (A) Large iCCA: at diagnosis the CT scan shows tumour involving the hepato-caval confluence, with invasion of the right hepatic vein, infiltration of the inferior vena cava together with the middle and left hepatic vein common trunk. The tumour is adherent to portal bifurcation and biliary confluence. The patient underwent first-line chemotherapy with gemcitabin and cisplatin (4 courses) followed by Y^{90} radioembolisation. (B) Sustained tissue response after neoadjuvant treatment: partial response was observed with extensive necrosis of the liver lesion, remaining stable in size for 6 months. After 4 additional months, liver transplantation was performed under a prospective protocol using a graft of marginal quality. The patient is alive and free of recurrence 2 years after transplant. (C) In the explanted liver, extensive fibrosis of 70% of the tumour, necrosis and inflammatory infiltrate (arrow) were detected with residual tumour nests in its context (arrowhead), focally infiltrating the vena cava and the right hepatic vein. Middle and left hepatic veins were encased but not invaded. Portal vein thrombosis was not neoplastic.

to elucidate resistance mechanisms and trials evaluating sequential or combination treatments with other TKIs, immunotherapy or chemotherapy are also needed in order to improve outcomes. All in all, molecular characterisation of iCCA will play an important role in the context of pre- and post-surgical management of patients with iCCA.

Adjuvant radiation therapy

Few studies assessed the role of adjuvant radiation therapy for iCCA. One retrospective series showed

Table 3. Summary of indications and eligibility criteria for liver resection and liver transplantation in iCCA.

	Liver resection	Liver transplantation
Age, PS, comorbidities	Case-by-case evaluation to be balanced with resect ability criteria based on extent of liver tissue to be removed *vs.* volume and function of the liver remnant	<65 years, absence of comorbidities contraindicating LT
Histology confirmation	Recommended	Mandatory
Ca19.9	Relative contraindication for Ca19.9 >500 ng/ml in the absence of jaundice	To be defined
Tumour staging	Single resectable mass any size, if resectability is provided according to point 1 Unilateral multifocal disease	Unresectable <2 cm very-early tumour arisen in chronic liver disease/cirrhosis (*i.e.* solid data available and trial ongoing) Unresectable >2 cm lesion with sustained response to chemotherapy ± RT (experimental, within prospective protocols)
Chronic liver disease/cirrhosis/PH	Relative/absolute contraindication	No limitation regarding liver function
Macrovascular invasion	Relative contraindication (vascular reconstructions are allowed if R0 resection is achievable)	Contraindication in case of intra-/extrahepatic vascular invasion. Questionable in case of extravascular growth with encasement of major inflow/outflow tributaries (experimental)
Preoperative lymph node assessment	Recommended	Mandatory to rule out nodal disease
Multifocality*	Relative contraindication	To be defined.
Neoadjuvant treatment	Experimental	Very-early iCCA: experimental Advanced iCCA: recommended as selection tool (sustained responses may be selected for transplant consideration)
Additional procedures	PVE, ALPPS and biliary reconstructions can be added, though associated to higher morbidity/mortality	DCD, marginal grafts in pts with preserved liver function and LDLT can be proposed
Adjuvant treatment	Advisable in high-risk patients	To be defined
Future studies	- Prospective investigations on neoadjuvant "downstaging" chemotherapy ± targeted agents ± RT (EBRT *vs.* SIRT) schemes able to convert advanced liver-only tumours to resectability - Prospective randomised investigations on adjuvant CT in R1 resections and in patients at high risk of recurrence	Prospective parallel studies with matched patients cohorts (based on tumour burden and biology) to assess survival benefit of LT (± downstaging treatments) *vs.* other treatment options
Study endpoints	OS, RFS	Transplant benefit, OS (ITT), RFS and cancer-related survival

ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; DCD, donor after cardiac death; EBRT, external-beam radiotherapy; iCCA, intrahepatic cholangiocarcinoma; ITT, intention-to-treat; LDLT, living donor liver transplantation; LT, liver transplantation; PS, performance status; PVE, portal vein embolisation; OS, overall survival; RFS, recurrence-free survival; RT, radiotherapy; SIRT, selective internal radiotherapy.
*Satellite lesions (nodules <1 cm at <1 cm from the main tumour) may be considered part of the main tumour while satellite nodules at >1 cm distance from the main tumour and/or in different liver segments considered true multifocal disease.

that adjuvant radiation therapy was associated with improved survival compared to LR alone (HR 0.78; 95% CI 0.67–0.92).[85] Another report suggested that systemic chemotherapy plus radiation therapy may confer a greater benefit than chemotherapy alone in patients with resected iCCA. In a retrospective study of patients with positive margins, radiation therapy did not impact on outcomes.[86] Based on the paucity of data, the recent ASCO guidelines do not recommend radiation therapy for patients who have undergone R1 resections for iCCA.[75]

Conclusions

Hepatic resection is the only treatment able to confer long-term survival in patients with iCCA, even though the overall prognosis of resected patients remains dismal. Unfortunately, the majority of resections are offered to patients with advanced tumour stages. New strategies for tumour downstaging through neoadjuvant systemic or locoregional treatments combined with advanced surgical procedures including liver regeneration techniques and vascular reconstructions have enhanced the resectability of iCCAs.

For selected patients with exclusive liver disease, LT could be a viable option, either in early stages diagnosed in the context of chronic liver diseases or in locally advanced tumours, when neoadjuvant treatments have achieved sustained tumour response without extrahepatic tumour spread. On top of locoregional therapies and radiation therapy through intra-arterial or external-beam approaches, molecular profiling of iCCA is likely to provide improved prognostic assessment, more precise selection for surgical intervention and objective stratification of risk of recurrence to be counteracted by specifically designed adjuvant treatments.

Abbreviations

AJCC, American Joint Committee on Cancer; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; ASCO, American Society of Clinical Oncology; BAP1, BRCA1-associated protein-1; BRAF, v-raf murine sarcoma viral oncogene

homolog B1; EPHA2, erythropoietin-producing human hepatocellular receptor A2; FDG-PET, fluorodeoxyglucose positron emission tomography; FGFR, fibroblast growth factor receptor; FLR, future liver remnant; HCC, hepatocellular carcinoma; HR, hazard ratio; HSP90, heat-shock protein 90; iCCA, intrahepatic cholangiocarcinoma; IDH, Isocitrate dehydrogenase; ILCA, International Liver Cancer Association; LR, liver resection; LT, liver transplantation; NCCN, National Comprehensive Cancer Network; PVE, portal vein embolisation; SEER, Surveillance, Epidemiology, and End Results; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation; TKI, tyrosine kinase inhibitor; Y^{90}, $Yttrium^{90}$.

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Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conception and study design: V.M., S.R., G.S.; literature review and acquisition of data: A.G., M.D.D.B.; analysis and interpretation: V.M., S.R., G.S., A.G., M.D.D.B.; writing committee: V.M., A.G., S.R., M.D.D.B., G.S.

Supplementary data

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