Hepatology Snapshot:

# Surgical treatment of intrahepatic cholangiocarcinoma

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## Intrahepatic Cholangiocarcinoma: A surgical perspective

### Liver Resection (LR)

Major LR is the current mainstay for treatment for iCCA, though only 12-40% of patients referred are resectable. Overall survival at 5-years is 25-40%, and 50-70% face tumor recurrence.

### Selection

Characteristics are considered with the goal of balancing complete R0 resection and preservation of a sufficient future liver remnant (FLR).

**Metastases**
- local
- peritoneal/distant are a contraindication

**Quality of the FLR**
- atrophy and fibrosis
- cirrhosis
- steatosis

**Size of the FLR**
- 25% for normal liver
- 40% for chronic disease

**Location of tumors**
- central are complex
- portal and biliary branches
- suprahepatic veins

**Portal hypertension**
- underlying liver disease
- usually a contraindication

**Biopsy**
- differentiate from HCC
- tumoral mutations
- personalized treatment

**Endoscopy**
- exclude differential diagnosis
- not CRLM but iCCA

### Surgery

Perioperative technique is a focus for research to improve outcomes and increase resectability

**Anatomic resection**
- superior to non-anatomic
- better OS and RFS
- limited research

**PVE***
- hypertrophy of FLR
- safe procedure
- high dropout rates

*Portal vein embolization

**Lymphadenectomy**
- recommended
- at least 6 nodes for staging
- porta hepatis

**Laparoscopic LR**
- less invasive
- very controversial due to required lymphadenectomy

**Repeated LR**
- acceptable morbidity and mortality for recurrent iCCA
- Improved long-term outcomes

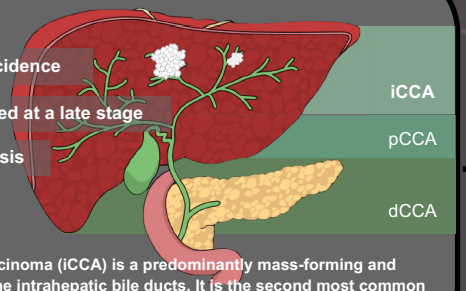
**Vascular resection**
- infiltrative with vascular enhancement
- IVC/PV resection comparable to conventional LR

**ALPPS***
- faster hypertrophy of FLR
- high morbidity/mortality
- requires high selectivity
- caution: low evidence level

*Associating liver partition and portal vein ligation

### iCCA...

- is increasing in incidence
- is usually diagnosed at a late stage
- has a poor prognosis




### What is it?

Intrahepatic cholangiocarcinoma (iCCA) is a predominantly mass-forming and lymphophilic malignancy of the intrahepatic bile ducts. It is the second most common primary liver cancer after HCC. While relatively rare, incidence of iCCA is increasing.

### Neoadjuvant therapy

+ Downstaging to LR or reducing recurrence
− No clinical trials showing benefit

**Transarterial chemoembolization**
- 20% conversion rate
- inferior to SIRT and intrarterial chemotherapy

**Hepatic artery infusion chemo**
- disappointing conversion
- combo with systemic chemo also disappointing

**Gemcitabine**
- eastern series (n = 22)
- 5-year OS = 45%

**Selective internal radiation therapy (SIRT)**
- combo with chemo
- safe and effective

**External beam radiation therapy**
- combo with systemic chemo
- 60% conversion rate
- 5-year OS = 24%

+ Downstaging to LT, response as a marker for tumor biology, LT for advanced iCCA
− No clinical trials showing benefit

**Gemcitabine and cisplatin**
- 6-month response in 33%
- 85% 5-year survival
- 50% recurrence

**Selective internal radiation therapy (SIRT)**
- to be studied in combination with chemotherapy

### Adjuvant therapy

+ Patients at high risk of recurrence (ex. + lymph node) or R1 resection
− High surgical morbidity burden

**Capecitabine**
- BILCAP trial
- increase per protocol OS
- no effect in ITT

**Gemcitabine and oxaliplatin**
- phase III trial
- no survival benefit

**Intra-arterial chemotherapy**
- meta-analysis
- survival benefit
- high risk of bias

**Radiation therapy**
- improved survival
- superior to chemo
- not for R1 resections

No studies on adjuvant therapy after LT for iCCA

### Liver Transplant (LT)

Liver transplant has become an area of interest for iCCA in recent years after which retrospective studies were conducted with more stringent selection criteria. One major study found a 5-year OS of 65% after transplantation for single tumors ≤2 cm. Advanced iCCA with neoadjuvant therapy is also considered.

**Early stage iCCA**
- good overall survival in retrospective
- being validated in clinical trial
- iCCA with low quality FLR (cirrhosis)
- ≤2 cm

**Locally advanced iCCA**
- less evidence
- acceptable outcomes with response to neoadjuvant chemotherapy

Vascular invasion
Lymph node spread
Favorable tumor biology
Extrahepatic disease

Currently not a standard therapy!

1. How can screening be improved to diagnose iCCA at an early stage?
2. What is the most effective neoadjuvant strategy to downstage locally advanced iCCA to resectability?
3. What is the most effective adjuvant strategy to reduce recurrence after LR in high risk and R1 patients?
4. How can intraoperative LR techniques be optimized and refined for patient selectivity?
5. How does LT (+ neoadjuvant) compare to other treatment strategies?
6. How can our understanding of tumor biology be improved and applied to LT selection?

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Intrahepatic cholangiocarcinoma (iCCA) is a rare malignancy of the intrahepatic bile ducts. In recent years, the incidence of iCCA has increased but it is unknown to what extent this increase can be attributed to improved classification or true escalation. From a surgical perspective, though major hepatic resection has been the most appropriate treatment option for those eligible, liver transplant has recently emerged as a second surgical option for unresectable patients. However, in order for these surgical treatments to be most effective, progress is needed at all points on the patient timeline: diagnosis, selection, neoadjuvant therapy, surgery, and adjuvant therapy. This snapshot will summarize current knowledge and future research priorities regarding surgery for iCCA.

While the prognosis of hepatocellular carcinoma (HCC) has improved with the increasing availability of surgical treatment, iCCA is still associated with much worse outcomes. iCCA is rarely diagnosed at an early stage and systemic treatment is the only mainstay at more advanced stages. As effective surgical treatment depends on early and accurate diagnoses, biopsy and molecular sequencing of iCCA are crucial, and will also be important for the development of personalized treatment plans based on molecular alterations (*e.g.* IDH1, FGFR2).[1]

Continued understanding of iCCA genetic profiles and associated tumor response could eventually inform selection for surgical treatment. Major liver resection (LR) is the only curative treatment for iCCA, though only 12-40% of patients referred are resectable.[2–4] Considering a patient for LR includes consideration of the location and spread of local tumors, the presence of peritoneal and distant metastases, the quality of the liver (presence of cirrhosis or disease), the presence of portal hypertension, the extent of lymph node involvement, and more. All are considered with respect to the difficult goal of balancing complete R0 resection with preservation of a sufficient future liver remnant (FLR).[1] Liver transplant has only been an acceptable option for iCCA since 2014 and it is limited to patients with early stage (single tumor ≤2 cm) unresectable tumors, such as those with cirrhosis.[5] Though tumor extension outside of the liver precludes transplant, some very preliminary case studies have reported transplant for locally advanced iCCA.

Neoadjuvant therapy aims to address low resectability by downstaging unresectable cases. These techniques include hepatic artery infusion chemotherapy, combined systemic and intra-arterial chemotherapy, selective internal radiation therapy, and external beam radiation.[1] Fortunately, good outcomes for neoadjuvant therapy and LR have been found in several retrospective studies but are yet to be validated prospectively. Like LR, the most effective neoadjuvant therapies/combination therapies are still an active research question, along with how response to neoadjuvant therapy can influence transplant decision-making.[1]

Even after consideration of these patient characteristics, 5-year overall survival after LR is only 25-40%, with 50-70% facing tumor recurrence.[3,6,7] This emphasizes the rationale for research beyond determining resectability, focussing on surgical approach. For instance, Si *et al.* determined that anatomic resection is associated with superior recurrence-free and overall survival compared to non-anatomic resection for iCCA and Spolverato *et al.* determined promising outcomes for repeated LR.[8,9] Due to frequent infiltration and vascular encasement of iCCA, vascular resection of the inferior vena cava or portal vein has also been studied with good outcomes in R0 resection. Most importantly, for this highly lymphophilic cancer, lymphadenectomy of a minimum of 6 nodes is suggested for staging, but further clarification on optimal number and location should be made.[10] Preliminary research has also brought up the use of techniques to induce hypertrophy of the FLR such as portal vein embolization (PVE) or associated liver partition and portal vein ligation (ALPPS). However, these are controversial techniques with low evidence levels. In the other direction, the study of laparoscopic LR for iCCA has been largely unfavorable due to the requirement for lymphadenectomy.[1] However, due to advances in this technique comparative studies are urgently needed.

After LR, adjuvant therapy has been primarily explored as a treatment for patients at high risk of recurrence such as those with R1 resection or with positive lymph nodes. Recent studies include the BILCAP trial looking at capecitabine after LR, gemcitabine and oxaliplatin trials, intra-arterial chemotherapy and radiation therapy trials. Currently adjuvant therapy with capecitabine has been adopted as standard of care by ASCO.[11] The downside of adjuvant therapies with LR for iCCA is surgical morbidity, which in many cases may preclude initiation of therapy. Though there are no studies to date on the role of adjuvant therapy after transplant for patients with iCCA, it may enable the optimization of personalized treatment in the future.[1]

Surgical treatment of iCCA has evolved and become more selective, resulting in improved outcomes after resection and, more recently, transplant. However, overall prognosis is still poor due to a combination of advanced-stage diagnosis, narrow eligibility, and limited surgical approaches. In order to move forward, improvements need to be made at each step of the iCCA patient timeline. Diagnoses made early and accurately, refined selection criteria, optimizing surgical approach, and strategizing neoadjuvant and adjuvant therapies should be the focus of future studies.

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## Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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

## Authors' contributions

Gravely A.K – conception and design. Sapisochin G – conception, design, and critical review. Vibert E – critical review.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.01.004.

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