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Current principles for the surgical treatment of intrahepatic cholangiocarcinoma

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ABSTRACT

Intrahepatic cholangiocarcinoma is one of the most aggressive forms of cancer. It is usually diagnosed in advanced stages of the disease, mainly because it is asymptomatic for a long time after the onset. Consequently, intrahepatic cholangiocarcinoma still represents an important problem of diagnosis and treatment. In the multidisciplinary treatment of these patients, oncological surgery is essential, as the accuracy of resection is one of the most important prognostic factors for the long-term results of these patients. Therefore, there has been a continuing concern to improve surgical techniques, with the aim of maximizing the chances of achieving the best possible long-term survival. The purpose of this paper is to discuss the surgical standard of care in intrahepatic cholangiocarcinoma, with particular attention being paid to resection margins and lymph node dissection. For unresectable cholangiocarcinoma, locoregional therapy can be used such as transarterial chemoembolization, transarterial radioembolization, thermal ablation, radiotherapy and hepatic artery infusion pump chemotherapy.

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Introduction

Intrahepatic cholangiocarcinoma (ICC) are aggressive, rare cancers that develop from the epithelial cells of intrahepatic ducts, either from the second order bile duct or smaller branches of the biliary tree. The incidence of this pathology is increasing worldwide, with the highest incidence being in Asia, specifically North-eastern Thailand [1]. Because of the lack of specific symptoms, the diagnosis usually comes at a late stage, where surgical treatment might not be an option and the prognosis is poor [2-6]. Many factors impact prognosis of ICC, decreasing overall survival (OS) and recurrence free survival (RFS), most important ones being the resection margins and the presence of lymphatic node metastasis [7-10].

In the period January-February 2024 a literature review was comprised to assess the current status of surgical treatment for ICC. Literature on ICC was searched in available databases: Cochrane Library, PubMed, Embase, MedLine, Web of Science, Elsevier, Google Scholar. The

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literature that was reviewed, with increased interest on the surgical publications, consists mostly of studies from 2000 to December 2023, written in English. All potentially eligible articles were evaluated by two of our authors and disagreements were resolved with the participation of a third author. The review analyzes primary completed studies as well as some ongoing studies with preliminary results. Some case reports were also included.

Discussions

Patient evaluation

Preoperative evaluation is key in case selection and ensuring proper treatment. The guidelines provided by National Comprehensive Cancer Network (NCCN) contains recommendations for blood analysis, diagnosis and treatment of ICC patients [11]. Usual blood analysis also includes tumor markers such as CEA, CA 19-9 and CA 125, but also newer biomarkers [12-21] that could support diagnosis of ICCA. Patients with liver tumors suspected for malignancy should undergo computed tomography (CT) [22-24] or magnetic resonance (RMN) [25-27] of the abdomen, both with IV contrast and CT of the thorax, with or without contrast, PET -CT being also often used [28,29]. Because of the lack of symptoms, ICC diagnosis is usually established when patients do not benefit from surgical resection. Biopsy of the tumor is not required in cases where resection is planned and the imagistic evaluation and biomarkers workup suggest the diagnosis of ICC. However, biopsy is strongly recommended in unresectable cases, along with immunohistochemical analysis, before starting systemic or locoregional therapy [11]. Diagnosis test might include colonoscopy, endoscopy and mammography to rule out the presence of a primary at one of these levels and to exclude the metastatic origin of the liver lesion [11].

Imagistic diagnosis

ICC patients present often with no specific symptoms – dull, continuous pain or tenderness in the right abdomen, unexplained weight loss, cachexia, malaise, night sweats [6,30]. If the tumor develops towards the hepatic hilum, patients can present with jaundice [31,32]. Screening programs sometimes help diagnose ICC in asymptomatic patients. The lack of symptoms is one of the reasons why ICC diagnosis is usually set when patients are no longer suitable for surgical treatment [33,34].

The first imagistic procedure recommended in patients with right upper quadrant pain is transabdominal ultrasound, ICC being described as a suspect mass lesion in the liver parenchyma. Screening programs using ultrasound can help detect pre-malignant lesions or ICC at a stage where surgery is feasible, and it should be used in regions where the cases of ICC are multiplying [35]. Prospective studies on this regard have been made, more notably the studies of Sungkasubun et all. and Khuntikeo et all., both studies demonstrating that ultrasound screening for ICC is feasible and helps improve the prognosis of ICC by early detection of the tumor [35-39].

Contrast enhanced computed tomography (CE-CT) is the most used imagistic examination for characterization of a liver mass [40,41]. CE-CT can also differentiate between hepatocarcinoma (HCC) and ICC, detect distant metastasis and asses vascular invasion [24]. In advanced cases it can also asses the presence of lymph node metastasis, but specificity for this is not high [42].

Contrast – MRI is considered the reference imaging examination for both diagnostic and staging of ICC, having a higher sensitivity and specificity than CE-CT for evaluating tumor spread along bile ducts [23,25]. In selected cases, magnetic resonance cholangio-pancreatography can be used for a higher characterization of the biliary tract [23,43]. Such as in the case of CE-CT, lymph node metastasis detection has low sensitivity [43].

PET CT assesses the metabolic activity of the malignant lesion, with high sensitivity for detecting ICC. It also has a higher sensitivity then CE-CT or MRI for detecting lymph node metastasis [23,40]. Two meta-analyses have been published, with results supporting the role of routine PET scanning for better characterization of ICC: Lamarca et al. in 2019 [29] and Huang et al. in 2020 [28].

Preoperative assessment of lymph node metastasis is a challenge since the both CT and MRI have low sensitivity. Endoscopic ultrasound with fine needle aspiration (EU-FNA) could be used to determine the existence of lymph node metastasis, this representing a contraindication for curative resection or liver transplant [11]. A study published be Malikowski et al. found that lymph node metastasis detection is significantly increased by EU-FNA when compared with CT or RMN (83% vs 50%) with a lower OS when lymph node metastasis is present (353 vs 1050 days) [44].

Surgical Treatment

The surgical treatment of ICC is the only curative-intent treatment and is only recommended when R0 resection with negative microscopic margins is achievable, since incomplete resection, either R1 or R2 is associated with a lower OS and RFS [45].

Liver augmentation for future liver remnant

For patients with resectable ICC but with a future liver remnant lower than 30%, a series of augmentation strategies is available [46]. Portal vein embolization is one of the most common strategies that induces contralateral liver hypertrophy and ipsilateral atrophy [47,48]. This technique is based on interrupting the portal flow to the affected liver segments, leading to the atrophy of them and a reactive hypertrophy of the rest of the liver. With the development of radiology, percutaneous PVE is the

standard technique nowadays [49]. This procedure has its limitations, especially due to the slow growth of the future liver remnant and possible rapid progression of the ICC [49]. Multiple studies have assessed the effects of PVE, with favorable results, including a systematic review comprising 44 articles summarizing 1791 patients that underwent PVE, showing a high success rate of 99%, with mean hypertrophy rate of FLR being 37.9 [49-51].

Liver partition with portal vein ligation (ALPPS) is also being used for increasing FLR, having the advantage of inducing a faster hypertrophy of FLR [48]. This two-step surgical procedure involves ligation of the right portal vein associated with the transection of the liver parenchyma at the future resection site, followed by resection after hypertrophy has been achieved [52]. The downside of this procedure is its high morbidity and mortality, currently being recommended to be performed in high volume centers with carrefour patient selection [53]. Li et al. compared the OS of patients that underwent ALPPS with patients that received systemic chemotherapy, with results significantly in favor of the ALPPS procedure (mean survival 26.4 vs 14 months, survival rates 82.4%, 70.5% and 39.6% vs 51.2%, 21.4% and 11.3% at 1, 3 and 5 years respectively) [54].

Liver venous deprivation (LVD) is one of the other augmentation tools available, but the literature on this topic mostly comes from single center experience. It involves an association between PVE and hepatic artery embolization. It induces faster hypertrophy than PVE alone [46]. Jaundice is rare but can be present in ICC when the tumor grows towards the hepatic hilum. Preoperative drainage is not recommended [48], but it is used if palliative treatment is required [55].

Minimally invasive surgery

Minimally invasive surgery plays an important role in both staging and treatment of ICC. Laparoscopic staging, although not routinely recommended [56], can be used in patients with high CA 19-9 levels, suspicion of vascular invasion or carcinomatosis, which was not detected by preoperative evaluation [57]. Multiple studies suggest that 34-37% of unnecessary laparotomy can be avoided using laparoscopic staging [57-60]. The use of this is decreasing, since curative laparoscopic surgery is gaining ground in high volume centers. Traditionally tumors located in the segments 2-6 with a diameter under 5 cm were operated laparoscopically [59], but in the recent years major hepatectomy have been performed often, with results comparable with those of open surgery regarding oncological results (R_0 resections, quality of lymphadenectomy, RFS and OS), but associating lower hospital stay and blood loss [59-67].

Liver Transplant

Liver transplant (LT) for ICC continues to represent a contraindication in most of the transplant centers, considering the high recurrence, low tumor differentiation and possible microvascular invasion [68,69]. Current studies available in literature are insufficient to set an indication for transplant. Several studies have been published on this topic, trying to assess the benefits of LT in ICC. Sapisochin G et al. [69] published in 2016 a research based on a cohort group of patients that were transplanted for hepatocarcinoma (HCC) but on the explant were found to have ICC. These patients were split into two groups – verry early ICC (single tumor, <2cm), and advanced tumor (>2cm, multiple lesions). The recurrence risk at 1,3 and 5 years was 7%, 18% and 18% for the "verry early ICC" group and 30%, 47% and 61% for the advanced tumor group. Survival at 1,3,5 years was 93%, 84% and 65% for the verry early ICC and 79%, 50% and 45% for the advanced tumor group [69].

McMillan R et al. [70] published in 2022 the use of neoadjuvant chemotherapy followed by liver transplant in unresectable ICC. The cohort comprised 32 patients with stable disease for 6 months and no metastasis, 18 of them receiving LT. The OS at 1,3 and 5 years was 100%, 71% and 57%, with 7 cases of recurrence treated with chemotherapy. OS for patients with recurrence was still higher than for those treated with systemic chemotherapy alone [70].

In LT for ICC, most available literature comes from retrospective studies, not sufficient to set and indication for LT, although the results are promising [71]. In that regard, there are three ongoing clinical trials that evaluate this indication: NCT02878473 from University Health Network of Toronto, evaluating LT for early ICC with tumor size <2cm, positive biopsy for ICC, CA 19-9 < 100ng/ml and liver cirrhosis not feasible for resection, NCT04556214 from Oslo University, evaluating LT for non-resectable primary or recurrent ICC, without extrahepatic disease and good performance status, and NCT04195503 from University Health Network of Toronto, analyzing LT in patients with locally advanced, not resectable, with no metastasis and with positive biopsy, with stable disease under neoadjuvant chemotherapy for at least 6 month and that have a living donor available [72].

Lymphadenectomy

Lymphatic node metastasis is one of the most important prognosis factors in ICC and thus, the removal of at least 6 nodes, as the NCCN guidelines recommend, is of most importance to determine prognosis and select the proper adjuvant therapy [11]. Even so, the use of routine lymph node dissection is relatively low, and studies on this topic are conflicting [73-77]. Lymphadenectomy should include all lymph nodes from the common hepatic artery and hepatoduodenal ligament [8,78]. Patients with disease located in the right liver also cand benefit from removal of retropancreatic lymph nodes, and for the lesions of the left liver, lymphadenectomy of the lesser curvature of the stomach might provide further information about the disease spread [79-81].

Surgical resection

Surgical treatment is the only curative intent treatment, when R0 resection with negative margins can be achieved. A correct preoperative evaluation can assess resectability by considering patient's comorbidities and their tolerance for a major surgery. Only 20-30% of patients diagnosed with ICC are eligible for surgery [82].

Surgical resection aims at achieving negative margins (R0), this being considered as one of the most important prognostic factors [83-86]. In the presence of nodal metastasis, the difference between R_0 resection and positive margins resection (R_1) does not seem to influence the prognosis in terms of OS [87]. In the absence of N1 disease, the difference between R_0 and R_1 resection is significant and has been analyzed by multiple authors. In a large meta-analysis published in 2023 by Yu Shi Dai et al. [88], that comprised 11 articles with more than 3000 patients. Nine of these articles compared the 1,3- and 5-year OS between patients that had resection margins ≥ 1cm and the ones with resection margins of ≤ 1cm. For the patients that received surgery with margins over 1 cm had significantly increased OS and RFS. More so, in subgroup analysis, patients with margins ≤0.5cm had a worse prognosis than those with margins ≥0.5cm [88]. Also, in a different study, the width of the resection margin, even with negative microscopical invasion, had corelated with the median survival (15 months for ≤1mm, 36 months for 2-4mm, 57 months for 5-9mm and 64 months for over 1cm) [89]. Even in major tertiary hepatobiliary centers, the incidence of R1 resection is high (16%-23%), partially due to the fact that patients with ICC usually present at late stage when, if surgery is possible, it requires extensive resections, have large tumors or present perineural or vascular invasion [83,85-87]. The OS at 5 years of this patients that receive sometimes R1 resection is less than half of those with R0 resection [88-91].

Multifocal disease is currently classified as T2 in the AJCC 8th edition, and is estimated in current literature that almost half of the patients that are diagnosed with ICC develop multifocal disease before extrahepatic metastasis [92]. Authors have not reached a consensus on this topic, some suggesting that the hematogenous intrahepatic spread brings multifocal disease closer to M1 patients' prognosis than to those with early disease [93]. Traditionally these patients were contraindicated for surgery and were treated with systemic chemotherapy, but recently, multiple studies have been published on this subject, but the benefit of surgery over systemic chemotherapy in the event of multifocal lesions is not clear [93-95]. Stefan Buettner et al. [94] published in 2019 a study with a cohort of 1013 patients, with 185 of them having multiple lesions (ML). The patients in the ML group had associated more often LN metastasis (25.4% vs 15.5%), metastasis (15.8% vs 5.9%), usually require extensive surgery (72.4% vs 55.9%). Median OS decreased as number of tumors increased (43.2 months for 1 lesion, 21.2 months for 2 lesions and 15.3 months for ≥ 3 lesions. In the multivariant analysis, two tumors were not an independent prognosis factor [94]. Also, a study published by Linlin Yin et al. [95] evaluated the prognosis for patients with multiple lesions, that underwent primary tumor resection. The study compared a group of 580 patients that underwent surgery with a group of 429 patients treated with systemic chemotherapy. Result found that primary tumor resection greatly increases OS, with a median survival of 25 months for surgical patients and 8 months for chemotherapy patients. More so, 1-, 3- and 5-year survival was also significantly higher described in the primary tumor resection group [95].

Surgical resection in the presence of major vascular invasion, predominantly in inferior vena cava (IVC) or portal vein (PV) has been a major topic of debate in literature. Historically, the presence of vascular invasion has been considered a contraindication for surgery. As available literature presents it, approximately half of the patients with ICC have invasion in a major vessel or surrounding organ [96]. Over the past years, multiple articles have emerged presenting vascular resection of the IVC or PV as a feasible approach, even increasing the rate of R0 resection, with little to no difference in OS and RFS when compared to surgery in the absence of vascular resection [97-99].

The surgical procedure of both hepatic resection and vascular resection is challenging but vital to obtaining good short- and long-term outcome. The resection of IVC is dictated by the tumor location and extent of invasion in vena cava. In cases where IVC involvement is under 60% circumferentially and ≤ 2cm long, direct repair after resection with vascular control is feasible [100]. Prevention of lumen narrowing cand be achieved by using bovine pericardium patch [100], peritoneum [101] or a patch of left renal vein [102]. If invasion in IVC extends beyond said parameters, vascular exclusion followed by the application of a synthetic graft is necessary. A variety of synthetic grafts are available, Dacron being historically usually used, but because of the high thrombosis and stenosis rates, currently PTFE grafts such as Gore-tex have been recommended [103]. Autogenous grafts can also be used in limited resections of IVC [100]. For portal vein resection, reconstruction is usually achieved by direct anastomosis, rarely with the need of synthetic grafts [104].

To date, two major multi-center studies have been published and had analyzed both short- and long-term outcomes of patients with ICC, comparing groups of patients that underwent vascular resection with those who did not.

Reames et al. [96] published in 2017 a multi-institutional analysis comprising 1087 cases of patients that underwent resection, 128 of which needed vascular resection (21 IVC resection and 98 PV resection, 9

resection of both IVC and PV), that compared the outcomes of patients that underwent vascular resection associated with major hepatectomy and of those who had only major hepatectomy. The study shows that major vascular resection had not been associated with a decrease in either OS or RFS (RFS 14.0 vs 14.7 months in VR and no VR group, respectively, OS 33.4 vs 40.2 months). In this study major VR was not associated with higher morbidity either, assessing that VR can be safely performed in selected patients with ICC [96].

Another article, published by Conci et al. [98] in 2020, was a retrospective multi-institutional analysis of 270 patients that had major hepatectomy for ICC, of which 31 patients associated vascular resection. The patients were categorized in no vascular resection (NVR) 239 patients, portal vein resection (PVR – 15 patients) and vena cava resection (VCR – 16 patients) and R_0 resection was achieved in 73.6% for the NVR group, 73.3% for the PVR group and 68.8% for CVR group. Although OS at 5 years was lower for the VR groups (22.2% in PVR, 30.1% in CVR and 38.4% in NVR), the multi-variable analysis showed no association between VR and prognosis [98].

In the available literature, we have also found a case of laparoscopic left hepatectomy that associated hepatic artery resection and laparoscopic reconstruction, performed by our colleagues from Hospital Universitari Mutua Terrassa, Barcelona [105]. Although we do now know the follow up yet and, as a case report it has no impact statistically, it's an impressive accomplishment. Other impressive case reports came from Virgen de la Arrixaca Clinic and University, Murcia, Spain, who presented a case of extreme in situ liver surgery under total vascular exclusion with right hepatic vein and inferior vena cava grafts for a case of invasive ICC [106], and from Brian B. Whang et al. [107] who presented a case of Resection and Reconstruction of Suprahepatic IVC and Right Atrium for Invasive Intrahepatic Cholangiocarcinoma [107].

Surgical management of recurrence

Recurrence after curative intent surgery of ICC is common, occurring in approximately 65% of patients [108], and the case management varies, resection of the recurrence being uncommon. A series of factors have been found to influence recurrence such as a tumor size >5cm, lymphatic node dissemination, cirrhosis, the presence of multifocal disease, perineural and microvascular invasion. We have found only two multi-institutional studies that asses the benefit of resection for recurrent ICC. A study published by G. Spolverato et al. [108] analyzed a series of 563 patients that underwent curative intent surgical treatment for ICC. 400 patients had developed recurrence with a median RFS of 11.2 months. Of this, 210 patients received best supportive care, while 190 patients received treatment of recurrence. This treatment consisted either of chemotherapy alone (46 patients), or repeat liver-directed therapy (144 patients). Of the liver directed therapy group, 28.5% received resection of the recurrence ± ablation, 18.7% received ablation and 52.8% received intraarterial therapy. From the time of recurrence, median survival was 11.1 months (8 months in the BSC group, 16.8 for the patients who received chemotherapy only, and 18 months for the patients in the liver directed therapy group). The study concluded that the benefit of survival is small in case of resection of recurrence if compared with chemotherapy alone, and it should apply to only a small number of carefully selected patients [108]. The second multi-institutional analysis that we found has been published by Yamashita et al. [109] comprised a lot of 356 patients who received curative intent surgery for ICC. Of this lot, 214 had recurrence and 37 of them were treated with resection of recurrence. The results are similar with the results of Spolverato's study, with minimal benefits in survival for the re-resected patients [108].

Systemic Therapy

Systemic chemotherapy after curative intent resection is common and it aims to increase RFS and OS. Current standard for adjuvant therapy has become oral Capecitabine for 6 months, since the publishing of the BILCAP trial [110]. There have been other trials like the PRODIGE 12- ACCORD 18 [111] trial that has associated gemcitabine with oxaliplatin for adjuvant treatment, but it failed to prove a significant benefit. The ACTICCA-1 [112] study is ongoing and analyzes the benefits of associating gemcitabine with cisplatin. Also, the JCOG1202 study aims to evaluate the benefits of S1 chemotherapy in ICC [113].

Neoadjuvant therapy has no clear indication yet in the treatment of the ICC, in spite of the theoretical benefits associated with its use (tumor downstage, better patient selection by observing aggressive disease patterns, lowering chance of micro-metastatic disease) [114]. A series of retrospective studies have presented favorable results for its use, but the literature lacks completed prospective trials that could help set an indication for routine use [115-117].

Unresectable ICC

With less than 30% of ICC patients being eligible for curative intent surgery, various treatments have been studied for palliative treatment. This includes combination of systemic chemotherapy, and regional treatments.

Systemic palliative chemotherapy for unresectable ICC is usually done with a combination of Gemcitabine and Cisplatin [118], so far this therapy having the best results. Alternatives to this have been studied, including administration of mFOLFIRINOX, which is a combination of oxaliplatin, irinotecan and infusional fluorouracil, but results from the study of Phelip JM et al. [119] on this matter showed an inferiority of this treatment when compared to gemcitabine + cisplatin (median survival for

the mFOLFIRINOX group was 11.7 months, inferior to the survival in the gemcitabine + cisplatin – 13.8 months) [119]. One ongoing study evaluates the addition of nab – placitaxel to gemcitabine + cisplatin treatment, having so far favorable results, with a median survival or 19.2 months in the nab – placitaxel group [120].

Regional therapy used for unresectable ICC includes: radiofrequency ablation (RFA), transarterial chemo-embolization (TACE) and transarterial Yttrium-90 radioembolization (TARE).

TACE is frequently used for controlling local tumor growth in ICC, and the technique uses chemotherapeutic agents such as doxorubicin, mitomycin-C and cisplatin mixed with oil-based agents that are embolized in the arterial vessel supplying the tumor [121]. Meta-analysis data of patients with unresectable ICC that included 542 patients showed an overall survival of 15.7 months, slightly better than with systemic chemotherapy alone [122].

TARE with Yttrium-90 is a targeted therapy that releases high dose of radiation at the site of the tumor, with minimum radiation effect on surrounding tissues [123]. Studies of this procedure, including a meta-analysis reported a mean survival of approximately 15 and a half months, slightly better than palliative chemotherapy [124].

RFA aims at controlling tumor growth through thermal ablation. A needle with electrodes is inserted in the tumor, either percutaneously or surgically, which is heated to 60-100º C to induce tumor necrosis. RFA is used both in primary unresectable ICC and in recurrent ICC. Authors described that best results are present at a tumor size of under 2 cm [125].

Conclusions

ICC is one of the most aggressive cancers that, due to lack of specific symptoms, most time present with advanced or metastatic disease. For patients with resectable ICC, first treatment should be curative intent surgery, followed by adjuvant treatment with capecitabine, regardless of the negative margins' status. In the presence of macrovascular invasion of IVC or PV, surgery is feasible and short- and long-term oncological benefit does not differ from that of the patients with no macrovascular invasion. Neoadjuvant chemotherapy did not solidify its role for routine use, but prospective ongoing studies are expected to change that. For unresectable ICC, locoregional therapy can be used such as transarterial chemoembolization, transarterial radioembolization, thermal ablation, radiotherapy and hepatic artery infusion pump chemotherapy.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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