Review

New Insights into Surgical Management of Intrahepatic Chol-Angiocarcinoma in the Era of “Transplant Oncology”

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Abstract: Intrahepatic cholangiocarcinoma (iCCA) represents the second most frequent type of primary liver neoplasm. The diagnosis and treatment of patients with iCCA involves many challenges. To date, surgical resection with negative margins is the main curative option, achieving an acceptable long-term survival. Despite enabling a considerable improvement in the outcome, iCCA recurrence after surgery is still common. Tumor extension and the histological subtype, as well as vascular and lymph node involvements, are key factors used to define the prognosis. In this narrative review, we aimed to discuss the potential benefits of using different surgical strategies in the field of iCCA, including vascular resection, the mini-invasive approach, liver transplantation, the mechanism used to enable future liver remnant augmentation, and lymph node dissection. We also discussed the new protocols developed in the field of systemic treatment, including immunotherapy and molecular targeted therapy. Recent advancements in the diagnosis, surgical treatment, and understanding of tumor biology have changed the landscape in terms of treatment options. Creating a multidisciplinary tumor board is essential to achieving the best patient outcomes. Further investigational trials are required with the intent of tailoring the treatments and establishing the right patient population who would benefit from the use of new therapeutics algorithms.

Keywords: cholangiocarcinoma; liver transplantation; intrahepatic cholangiocarcinoma; hepatic surgery

1. Introduction

Intrahepatic cholangiocarcinoma (iCCA) is the second most common liver tumor, and its worldwide mortality rate is rising due to the increasing penetration of risk factors. Improvements in surveillance and diagnosis have widened iCCA incidence, particularly in male patients older than 70 years old [1,2].

No risk factors are recognizable in approximately 60–70% of iCCA cases, but certain agents have been associated with an increased likelihood of developing the disease. High-risk categories could be considered to include patients affected by congenital or chronic hepatic disease, namely biliary cysts, liver flukes (Opisthorchiidae as Clonorchis and Opisthorchis, as well as Fasciolidae as Fasciola), viral or alcoholic hepatitis, metabolic-associated fatty liver disease (MAFLD), and cirrhosis. Environmental toxins are also being recognized as risk factors, such as asbestos and vinyl chloride exposure, nitrosamine-contaminated food assumption, and dioxins [2].

A multifactorial biological process including inflammatory signals also plays a crucial role in the tumor invasion process [3]. Symptoms may vary from person to person, and some individuals may not experience any signs in the early stages of the disease.
Jaundice represents the first clinical presentation in 10–15% of iCCA cases; biliary obstruction is often related to tumor growth in the biliary tree or lymph node compression in the hilum. Several non-specific symptoms or signs could be related to the disease, such as frequent abdominal pain or discomfort in the upper right side of the abdomen, significant and unintentional weight loss without an apparent cause, fatigue, pruritus, loss of appetite, fever and chills, nausea, and vomiting [4].

2. Diagnosis and Staging

Diagnosing iCCA can be challenging, and it often requires a combination of imaging, blood tests, and, sometimes, a biopsy.

Radiological staging is based on a CT-scan or MRI (magnetic resonance imaging). CT-scans are used to detect the tumor local extension, the lymph nodes’ involvement, and the distant metastasis.

MRI outperforms CT-scans in terms of defining liver staging and the number of lesions. In patients presenting with clinical biliary obstruction, a combination of MRI and magnetic resonance cholangiopancreatography (MRI+MRCP) is the radiological technique of choice.

A fluorodeoxyglucose positron emission tomography (FDG-PET) procedure is strongly recommended to identify lymph node metastasis if it is not apparent on standard CT-scans or MRI imaging during the staging assessment [2].

Tumor biomarkers used in clinical practice do not show high specificity and sensitivity during the diagnosis; for example, carcino-embryonic antigen (CEA) has low sensitivity in iCCA patients [5]. An increased level of carbohydrate antigen (CA) 19–9 is not specific to malignancy and is also present in cholestatic conditions. Notably, a population with negative Lewis A antigen does not halt CA 19–9 [6].

In resectable disease, performing percutaneous biopsy for diagnostic confirmation is not mandatory.

Histological diagnosis is required in advanced disease to schedule systemic therapy or locoregional treatments.

For the specimens, immunohistochemical evaluation is required to confirm the diagnosis of iCCA and its subtypes, as well as to distinguish it from metastatic liver tumors.

New tumor biomarkers emerged in the diagnostic assessment and the choice of tailored therapies [7]. The introduction of liquid biopsy into the diagnostic panel allowed us to better define the disease genetic profile by making use of new sequencing technologies to perform next-generation sequencing [8].

Isocitrate dehydrogenase (IDH1/IDH2) are two genetic markers characterized by high rates of mutations in iCCA. The prognostic role played by IDH is still unclear, but a recent trial based on an IDH inhibitor (ivosidenib) showed improved progression-free survival [9].

Fibroblast growth factor receptor 2 (FGFR2) fusion is another genomic mutation that emerged as a marker of target therapies with promising results in phase-two studies involving FGFR2 inhibitors, such as infigratinib, pemigatinib, and TAS-120 [7].

The potential of other genetic targets, which are already well studied in other malignancies, such as KRAS, B-RAF, and HeR2/neu, have attracted significant interest and experienced advances in the last few years, but further investigations are needed to determine their effective roles in diagnosing iCCA [7].

3. Prognosis

Only 35% of iCCA patients are eligible for surgical resection when the diagnosis is confirmed. If a patient is a candidate for surgical resection, the specific procedure performed will depend on the tumor’s location and the extent of liver tissue that needs to be removed [10].

A five-year survival rate of 20–35% can be reached in patients when R0 resection is performed.
The prognosis is strongly influenced by the tumor grade and dimensions, vascular infiltration, and local lymph nodes’ involvement [11].

During surgery, absolute contraindications are represented by extrahepatic/peritoneal localization, distant lymph node metastases, multifocal and bilobar liver disease, and cirrhosis with or without portal hypertension. The severity of hepatopathy must carefully evaluated to avoid inadequate liver remnant.

Recently, well-selected patients with relative contraindications, such as vascular involvement, limited multifocal disease, or liver recurrence, have been evaluated for surgery thanks to emerging surgical strategies and neoadjuvant and adjuvant therapies [12].

A high rate of recurrence is reported for this disease (ranging from 40 to 60%) [13,14]. Careful evaluation of the performance status and comorbidities are pivotal to ensure the selection of patients eligible for surgery with the intent of minimizing peri-operative complications [15,16].

Employing multidisciplinary teams involving medical oncologists, surgeons, radiologists, and other specialists is essential to provide the best possible care to affected patients.

In this review, we will review recent trends in iCCA surgical management, with particular regard given to new protocols, including liver transplantation (Figure 1).

Figure 1. Overview of the treatment strategies used in the management of cholangiocarcinoma.

4. Surgical Management

In the last few decades, the outcomes of iCCA in patients who underwent resection have been improved. New technologies adopted in hepatic surgery, the implementation of peri-operative assessments, and new algorithms, including locoregional treatments and neoadjuvant protocols, have supported surgeons in the management of this disease.

Hepatic resection is recommended in cases of single iCCA, as it achieves the free resection margin (R0) and ensures the preservation of the future liver remnant (FLR) [7]. FLR will be at least 25–30% of the liver size in patients with healthy parenchyma, as well as at least 40% in pathological livers affected by steatosis, fibrosis, cirrhosis, or previous chemotherapy [2–12].

The R0 margin is one the most notable factors affecting both disease free-survival (DFS) and overall survival (OS) [17,18]. Moreover, a recent meta-analysis, which included 11 articles and 3007 patients, identified a R0 margin >1 cm as the distance that positively impacts the survival benefit [19]. In case of lymph node metastases, the R0 margin is not associated with prognosis improvement [20], as is also true in cases of stage II or III.
disease, as categorized based on the guidelines of the American Joint Committee on Cancer (AJCC) [18].

Morbidity after surgical resection is an important pitfall of “high risk surgery”, like iCCA.

The peri-operative, 30-day, and 90-day mortality rate was 5.9%, 4.6%, and 6.1%, respectively. The overall major complications rate was 22.2%. In the minor resection, the 90-day mortality was 3.1%, and the major complication rate was 11.3%. In the major resection, the 90-day mortality was 7.4%, and the major complication rate was 38.8% [21].

Post-operative major complications ≥3, according to the Clavien–Dindo classification, are independent unfavorable factors affecting outcomes in patients with a low tumor burden score (TBS), a new score including the number and size of the lesions, and N0 status, as reported in a recent international multi-center study [22].

iCCA’s morphological and biological features at tumor presentation have also been associated with the outcome after curative surgery. A high value of TBS, high CA 19–9 levels, and a high neutrophil-to-lymphocyte ratio (NLR) are predictors of unfavorable evolution in this setting [23,24].

Multifocal presentation is considered to be an oncological contraindication to surgery due its negative impact on the iCCA outcome. The data in the literature are conflicting in this field.

A SEER (surveillance epidemiology and end results) database analysis of 580 patients demonstrated that the five-year OS of resected patients (n = 151) with multifocal iCCA is higher than that of the non-resection group (14% vs. 0%, p < 0.001) [25].

In contrast, a meta-analysis conducted by Mavros et al. [26] reported no advantages associated with using surgical management rather than chemotherapy to treat multifocal disease in terms of the long-term outcome.

Moreover, a large study comparing patients treated via hepatic arterial infusion pump (HAIP) floxuridine versus resection found no advantage associated with performing surgery in terms of OS and a significantly higher mortality in the first 30 days after the procedure (6.2% for the resection group (95% CI, 0.0−2.1%) vs. 0.8% for the HAIP group (95% CI, 2.3−9.7%), p = 0.0)) [27].

Vascular infiltration is another factor that negatively affects the prognosis, but more favorable OS was recognized when vascular involvement was compared to multifocal disease or peri-neural invasion [28].

Vascular resection is considered in select cases of cholangiocarcinoma when the tumor is deemed to be unresectable based on conventional criteria due to vascular involvement.

In the case of resection of major vessels or an inferior cava vein, complex surgery is necessary: in selected cases, the total vascular exclusion and ex situ hypothermic perfusion of the liver are required to perform resection, followed by vascular reconstructions. To date, the probable outcome of iCCA cases involving vascular and other adjacent structures is still poor; nevertheless, in the era of new adjuvant protocols being used to treat locally advanced disease, combined strategies, including vascular and/or biliary reconstruction and the resection of other organs, could be justified to achieve R0 curative resection [29].

The role played by staging laparoscopy is still a debated issue. The American Hepato-Pancreato-Biliary Association’s [30,31] guidelines recommend only performing preliminary laparoscopic exploration in selected “high-risk” patients (i.e., high Ca 19–9, suspected vascular invasion, and multifocal disease).

As previously discussed, recurrence ranges from 43 to 66%. Recent retrospective experiences reported a favorable role played by the repeat surgery in hepatic recurrence when performed with the intent of controlling the disease [32,33].

Laurenzi et al. [32] reported 18 repeated hepatic resections, identifying a median OS of 21 months after the second resection and 1-, 3-, and 5-year survival of 87%, 41%, and 29%, respectively. The median DFS was 18 months (1-, 3-, and 5-year DFS of 75%, 27%, and 17%, respectively).
Promising results in the field of systemic and radiological therapies could improve patient outcomes in the recurrence scenario.

5. Anatomical vs. Non-Anatomical Liver Resection

Anatomical resection is typically considered to be the standard of care for treating resectable hepatocellular carcinoma (HCC).

Similarly, anatomic liver resection should be preferred in cases of iCCA in which the future liver remnant is sufficient. Hence, as reported in two recent large Chinese studies [34,35], this approach showed advantages in terms of OS and DFS, as well as no differences in the post-operative complications rate, compared to non-anatomical resection.

Moreover, non-anatomical resection is considered to be an independent prognostic marker of worse outcome.

One study reported a non-inferiority of non-anatomical resection in terms of OS and DFS [36], showing similar median survival for both surgical approaches (1-, 3-, and 5-year OS were 70.2%, 22.9%, and 22.9% and 71.1%, 51.7%, and 51.7%, respectively, \( p = 0.229 \); 1-, 3-, and 5-year DFS were 53.2%, 19.2%, and 19.2% and 58.6%, 41.0%, and 41.0%, respectively, \( p = 0.370 \)).

6. Lymphadenectomy

Lymph node metastases are detected in more than 50% of the patients at the time of surgery. In case of positive lymph nodes status, the five-year OS drops to 0–20% [37,38]. Evidence of lymphadenectomy at the diagnostic workup, positive CEA, and CA 19-9 are all prognostic markers of pathological N1 status [39].

The “8th American Joint Committee on Cancer Staging Manual, (AJCC)” [40] recommended performing a regional lymphadenectomy of at least six lymph nodes to achieve complete staging. “Standard lymphadenectomy” includes porta hepatis, station 8 (common hepatic artery), and station 12 (hepatoduodenal ligament) dissection.

Regional lymphadenectomy at the hilar, inferior phrenic, and gastro-hepatic levels should be performed in cases of left-side lesions, whereas hilar, peri-duodenal, and peri-pancreatic nodes should be dissected in cases of right-side lesions.

The presence of at least one positive lymph node is considered indicative of N1 disease (stage IIIB). Celiac-, peri-aortic-, and peri-caval-positive nodes are considered distant metastatic disease [41].

Comparable outcomes between cases with no lymph node involvement and those with one or two positive nodes were shown in a study by Zhang et al. [42], whereas three or more positive nodes were found to be detrimental to the disease’s prognosis.

The benefit of adequate lymphadenectomy (at least six retrieved lymph nodes) in terms of improving the outcome is still a subject of ongoing debate and research for pre-operative N0 (cN0) patients [43,44].

A recent meta-analysis published by Zhou et al. [45] showed no significant improvement in oncological outcomes when standard lymphadenectomy was performed.

In contrast, a French/Japanese multi-center experience that included 192 cN0 stage patients, standard lymph node dissection seems to be associated with more favorable prognosis [46] compared to the no dissection group.

A recent Italian multi-center study by Sposito et al. [47] showed that standard lymphadenectomy improves correct staging, survival, and DFS in patients with cN0 and cN1 status.

Moreover, in patients with high suspicious of N1, harvesting at least four lymph nodes could improve the prognosis, as reported in a large Eastern multi-center experience [48]. Standard lymphadenectomy seems to have therapeutic effect when iCCA is close the hilum, whereas no benefit was displayed in peripheral iCCA [49].

In a study conducted by Vitale et al. [50], the authors built a propensity score to match 826 patients who underwent surgical resection, and OS in patients who underwent lymph nodes dissection (defined as the retrieval of >3 LNs) was comparable to that of patients who
experienced resection without lymphadenectomy (22 vs. 25 months, \( p = 0.6563 \)). A survival benefit has only been found via simulation analysis including young male patients (less than 60 years old) and in cases of tumors with diameters larger than 5 cm.

In terms of post-operative complications, Zhou et al. [44] reported significantly higher morbidity in patients who underwent lymphadenectomy, even if the patients received more extensive surgery, in this group. The high rate of complications was particularly prevalent in cirrhotic patients, as reported by Bagante et al. [51], suggesting that doctors were cautious when making the decision to perform lymphadenectomy in this category of patients.

7. Inadequate Future Liver Remnant

Portal vein embolization (PVE), associating liver partition and portal vein ligation (ALPPS), and liver venous deprivation (LVD) are used in patient who need extended resection to ensure an adequate FLR and avoid a post-operative liver failure.

PVE, which is a gold standard hypertrophy strategy used to treat CCA patients, is an easy and safe procedure with a low morbidity and mortality. Despite this fact, the success of this technique is limited by the slow growth of FRL and high rate of inadequate liver regeneration and tumor progression [52].

To obviate this issue, ALPPS was used as a surgical strategy to quickly induce liver hypertrophy. The main limitation of ALPPS is the high rate of 90-day mortality and morbidity. For this reason, after initial enthusiasm, the popularity of this approach has slightly declined in the last few years [53].

Despite this issue, several studies showed acceptable outcome after the ALPPS procedure compared to those of palliative care. A multi-institutional analysis of 102 patients showed an improved one- and three-OS (82.4% and 70.5% vs. 51.2% and 21.4%, \( p < 0.01 \)) in patients who underwent ALPPS compared to those who underwent chemotherapy alone. The complications rate remains high: the overall morbidity was 25.1% after the first stage and 76.8% after the second stage. Post-hepatectomy liver failure (PHLF) was reported in 10.8% and 34.9% of cases after each stage, with a 90-days overall mortality of 21.2% [54].

The study of Serenari et al. [53] showed that the completion of stage 1 of ALPPS is protective in terms of the 90-day mortality rate.

A retrospective single-center experience conducted in Germany confirmed the improved outcomes of patients undergoing ALPPS, resulting in a median OS of 4.2 years if lymph nodes were negative. N1 patients did not survive after one year of follow-up [55].

LVD is an emerging strategy that includes simultaneous PVE and hepatic vein embolization in the same hemiliver. LVD showed a higher degree of hypertrophy than PVE and a better safety profile than ALPPS. This technique showed advantageous functional and volumetric results in HCC and CRLM patients, as well as and emerging advantages in the field of CCA [56,57].

Better selection of candidates, the utilization of mini-invasive surgery, and the implementation of pre-operative workup to assess the risk of post-operative major complications could improve the results of ALPPS in the iCCA scenario.

8. Role Played by Liver Transplantation in Treating iCCA

Liver transplantation (LT) is the treatment of choice in cases of acute hepatic failure or hepatic cirrhosis due to viral hepatitis, alcohol, and metabolic diseases. Historically, hepatocellular carcinoma (HCC) has been the most common oncological indication in the field of LT. iCCA has been associated with contraindication worldwide due to poor outcome, with reported five-year survival ranging between 10 and 18% [58] in the pioneering era of transplants.

Transplant oncology has attracted renewed interest in the last few years thanks to advances in the diagnosis and treatment protocols used to cure colorectal liver metastasis, neuroendocrine metastases, Klatskin tumors, and iCCA [59] (Table 1).
The first retrospective study based on the histology of cirrhotic livers was published in Spain by Sapisochin et al. [60]. Of the twenty-nine iCCA cases diagnosed via pathology examination, height was a “very early” indicator of iCCA up to a maximum 2-centimeter diameter. “Very early” iCCA showed similar outcomes to HCC, with an acceptable 5-year OS of 73% and a low recurrence rate. The lesions of more than 2 cm showed significantly higher rates of recurrence. Other factors related to poor prognosis were microvascular invasion and a poor degree of differentiation.

Another study conducted by a group at Mount Sinai Hospital [61] examined explant specimens, which were present in 32 cases of iCCA and had similar outcomes to those of HCC when the tumor met the “Milan Criteria in”. A five-year survival of 78% and a recurrence rate of 10% were reported. Outside of the Milan Criteria, iCCA patients did not have a statistically significant lower 5-year survival than HCC patients (48% for iCCA vs. 53% for HCC, \( p = 0.12 \)).

In contrast, Lee et al. [62], in a retrospective analysis that compared 12 “very early” iCCA patients and 319 patients with HCC within the Milan criteria, reported worse OS (1-year OS 63.6% vs. 90.0%; 5-year OS 63.6% vs. 70.3%; log-rank, \( p = 0.25 \)) and a higher incidence of recurrence (33.3% vs. 11.0%).

The role played by LT was also explored in patients with locally advanced disease: the first protocol combined neoadjuvant chemotherapy and LT and was described by Lunsford et al. [63] in a case series of 12 patients. This experience, based on gemcitabine–cisplatin or gemcitabine–capecitabine schedules, showed promising results: after an observational period of at least six months to exclude progression disease, six patients underwent LT, achieving an acceptable one-year OS rate of 100% and three- and five-year OS rates of 83.3%. Recurrence was shown in three patients after a median time of 7.6 months.

An Italian experience published by Gruttadauria et al. [64] regarding two cases of combined treatment with selective internal radiation therapy (SIRT) and LT reported no recurrence after 19 and 2 months of follow-up, respectively.

A recent propensity score-matched analysis published by Huang et al. [65] showed that patients with very early-stage tumors (tumor size ≤2 cm) and cirrhosis, as well as patients with locally advanced tumors (AJCC stage I and II) previously treated via chemotherapy, had better five-year survival rates than patients treated via liver resection (43.8% and 61.7% in the transplant group, respectively, \( p = 0.01 \)). In this series, LT for iCCA showed inferior outcomes compared to LT for HCC (HR: 2.14, \( p < 0.001 \)).

These preliminary experiences highlight the importance of considering LT in the context of multimodal treatment when upfront resection is not indicated (e.g., due to cirrhosis) or in locally advanced disease.

9. Minimally Invasive Surgery

The minimally invasive approach has also been increasingly utilized in the last years in the field of cholangiocarcinoma, despite this method being a demanding surgery.
Several recent studies analyzed the impacts of laparoscopic surgery on the short-term and oncological outcomes of iCCA [66–69].

A meta-analysis conducted by Aliseda et al. [70] reported interesting data related to laparoscopic resection for iCCA compared to open resection.

The authors showed significantly lower blood loss (mean difference: $-161.47 \text{ mL}$ \ ([95% CI $-237.26$ to $-85.69 \text{ mL}$]; $p = 0.0001$)), risk of transfusions (OR = 0.42 \ ([95% CI 0.26–0.69]; $p = 0.0006$]), length of hospital stay (95% CI $-4.98$ to $-1.34$ days; $p = 0.0007$), and risk of major complications (OR = 0.60 \ ([95% CI 0.39–0.93]; $p = 0.023$)). A non-significant reduction in the overall complication rate was reported (OR = 0.80 \ ([95% CI 0.45–1.42]; $p = 0.44$)). No difference was shown in terms of obtaining the R0 margin (OR = 1.10 \ ([95% CI 0.58–2.10]; $p = 0.762$)) and the performance of lymphadenectomy (OR = 0.52 \ ([95% CI 0.27–1.01]; $p = 0.054$)), despite one study reporting the lymph node dissection rate being significantly lower (OR = 0.44, 95%CI = 0.23–0.82, $p = 0.01$).

The number of harvested lymph nodes was higher in patients who underwent the laparoscopic approach than those who underwent the open approach.

In terms of oncological outcomes (both OS and DFS), laparoscopic surgery showed a reduced risk of death ([HR] = 0.795 \ ([95% confidence interval [CI]: 0.638–0.992]; $p = 0.041$]) and better OS rates in the laparoscopic group (1-, 3-, and 5-year OS rates of 87.4%, 64.0%, and 44.6%, vs. 87.4%, 51.8% and 37.8% in the open resection group) (log-rank $p = 0.04$).

In contrast, in a recent multicentric international experience conducted by Brustia et al. [71], after PSM, in patients with complete N status, a non-significant difference in terms of OS (92%, 75%, and 63% in the laparoscopic group vs. 92%, 58%, and 49% in the open group, respectively, $p = 0.0043$) and DFS (74%, 44%, and 44% for laparoscopic group vs. 66%, 39%, and 39% for open group, respectively, $p = 0.47$) were detected between laparoscopic and open surgery.

In an Italian high volume-center cohort [72] that included 446 resections (179 laparoscopic resection), data regarding OS (44 months vs. 41 months, respectively, $p = 0.212$) and DFS ($p = 0.120$) were comparable between the two approaches used.

Few experiences report on robotic resections used to treat iCCA.

Magistri et al. [73] described a case series of two robotic right hepatectomies with an excellent outcome.

A large cohort studied in USA included 72 patients who underwent robotic resection, showing a gain in terms of hospital stay (5.8 ± 4.6 days) compared to patients who underwent open resection [74]. Minor resection was performed on 36 patients (54.5%), and major hepatectomy was performed on 30 patients (30.3%). The conversion rate was of 8.3% (six patients).

Robotic surgery improves adequate lymphadenectomy compared to laparoscopic surgery, as reported in the study by Ratti et al. [75], including 13 iCCA cases; whereas the number of harvested nodes was comparable (10 vs. 9), the OS rate of patients who experienced the dissection of at least six lymph nodes was significantly different between two groups (96% vs. 86.6%, $p = 0.043$). The same advantages have been identified when robotic resection was compared to open resection (96% in the robotic group vs. 79.6% in the open group, $p = 0.032$).

### 10. Neoadjuvant Therapy

Current guidelines do not recommend neoadjuvant therapy (NT) in patients with resectable iCCA. Conversely, in locally advanced disease, NT strategies are applied.

A recent meta-analysis that included five studies and 2412 patients [76] explored the role played by NT in iCCA compared to upfront surgery. In the study, the post-resection complication rate did not differ between two groups. The R0 rate was significantly lower in NT group; the explanation for this finding could be that patients who underwent NT were more likely to have advanced disease. Despite this issue, the NT group had a better five-year OS, showing the lesser impact on the prognosis of R1 when NT was administered. The benefit in terms of OS was only shown in patients with
advanced iCCA (stage II and III), whereas in stage 1 iCCA, no difference was detected compared to upfront surgery. No advantages in terms of DFS have been shown for NT patients at all stages.

Combined treatment, including trans arterial chemoembolization (TACE) or trans arterial radioembolization with yttrium-90, and chemotherapy showed acceptable results in terms of disease downstaging [77].

A recent meta-analysis conducted by Shartz et al. reported an 11% rate of downstaging to resectable disease in patients treated via yttrium-90 ($^{90}$Y) radioembolization [78].

Several incoming trials, including target therapies that use immunotherapy, are being developed to better define the neoadjuvant protocols in iCCA.

11. Systemic Treatments in Advanced Disease

As previously reported, only 15% of patients are resectable after being diagnosed with iCCA. Unresectable patients classically receive systemic treatments with cisplatin and gemcitabine for the first line. In second-line treatment, the phase-three ABC-06 trial showed better results in terms of survival when using 5-fluorouracil with oxaliplatin (mFOLFOX) rather than the best supportive care [79]. Recently, another phase-two trial (NIFTY trial) reported significant improved progression-free survival in patients treated with liposomal irinotecan and fluorouracil and leucovorin compared to the 5-fluorouracil and leucovorin alone protocol (7.1 vs. 1.4 months; $p = 0.0019$) [80].

Immunotherapy has shown promise as a potential treatment option for advanced iCCA. In the phase-three TOPAZ-1 trial, durvalumab (a human monoclonal antibody to programmed cell death ligand 1 (PD-L1)) and gemcitabine and cisplatin enhanced overall survival compared to treatment with placebo (24.9 vs. 10.4 after two years) [81].

Same results are shown in KEYNOTE-966 trial using pembrolizumab (a selective humanized IgG4 kappa monoclonal antibody that inhibits the programmed death-1 (PD-1)), vs. placebo [82].

In patients in whom first-line therapy failed, the use of regorafenib (an oral small-molecule multi-kinase inhibitor) is considered, as reported in a phase-two study, with a median progression-free survival (PFS) rate of 15.6 weeks (90% CI = 12.9–24.7) and a median OS of 31.8 weeks (90% CI = 13.3–74.3). The survival rate was 40% at 12 months and 32% at 18 months [83].

As previously reported, new molecular targeted therapies for use against FGFR2 fusions/rearrangements and IDH1 mutations (e.g., pemigatinib, ivosidenib) have emerged in the last few years with encouraging results [84].

12. Conclusions

Surgery remains the best curative option in patients affected by iCCA despite limited rate of radical resection at the time of diagnosis. Advances in peri-operative management, neoadjuvant chemotherapy protocols and vascular resections could offer more chances of cure in well selected patients.

The renewed interest in transplant oncology considered new perspectives for the liver transplantation in cirrhotic patients with small lesions and locally advanced iCCA. Clinical trials are essential to expand transplant indication and improve prognosis.

Minimally invasive surgery, including laparoscopic and robotic approaches, could be challenging but offer several potential benefits compared to traditional open surgery, namely improved peri-operative outcomes and oncological outcomes comparable to those of open surgery.

For advanced disease, ongoing research into treatment options, including immunotherapy and targeted therapies, are exploring its potential use to combat iCCA.

A multidisciplinary and comprehensive assessment of the pathology and performance statuses of the patient are pivotal to selecting the best strategy for the treatment of iCCA.
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