

review

# Current management of intrahepatic cholangiocarcinoma: from resection to palliative treatments

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**Background.** Intrahepatic cholangiocarcinoma (ICC) is the second most common liver primary tumour after hepatocellular carcinoma and represents 20% of all the cholangiocarcinomas. Its incidence is increasing and mortality rates are rising. Surgical resection is the only option to cure the disease, despite the high recurrence rates reported to be up to 80%. Intrahepatic recurrences may be still treated with curative intent in a small percentage of the patients. Unfortunately, due to lack of specific symptoms, most patients are diagnosed in a late stage of disease and often unsuitable for resection. Liver transplantation for ICC is still controversial. After the first published poor results, improving outcomes have been reported in highly selected cases, including locally advanced ICC treated with neoadjuvant chemotherapy, when successful in controlling tumour progression. Thus, liver transplantation should be considered a possible option within study protocols. When surgical management is not possible, palliative treatments include chemotherapy, radiotherapy and loco-regional treatments such as radiofrequency ablation, trans-arterial chemoembolization or radioembolization.

**Conclusions.** This update on the management of ICC focusses on surgical treatments. Known and potential prognostic factors are highlighted in order to assist in treatment selection.

Key words: intrahepatic cholangiocarcinoma; liver resection; liver transplantation

## Introduction

### Epidemiology

Cholangiocarcinoma is a rare tumour originating from the biliary epithelium. It can arise from the distal biliary tract, at the hepatic hilum or from intrahepatic ducts, beyond second-order biliary ducts. The classification based on the site of origin identifies three entities requiring different treatments and prognoses.<sup>1</sup>

With an incidence of 0.85 per 100,000 worldwide<sup>2</sup>, intrahepatic cholangiocarcinoma (ICC) represents up to 20% of all the cholangiocarcino-

mas. It is the second primary liver tumour following hepatocellular carcinoma (HCC)<sup>1</sup> accounting for 5-30% of all primary liver malignancies.<sup>3,4</sup> Although reports in literature are scarce, its incidence has been rising all over the world in the last three decades.<sup>1,5</sup> Such increase may be associated with a greater prevalence of risk factors but also to improvements in diagnostic tools.<sup>6</sup> Intrahepatic cholangiocarcinoma is a highly invasive tumour, it is frequently multifocal and it is scarcely responsive to treatments. Thus, its mortality rate is about 0.69 per 100,000 and it is increasing along with tumour incidence.<sup>2</sup>

Well-known risk factors include liver disease and chronic inflammation including cirrhosis, hepatitis B (mostly in Asian countries) and C (mostly in the Western countries), primary sclerosing cholangitis (PSC), biliary tract cysts, intrahepatic biliary stones, toxins, infection with hepatobiliary flukes (frequently in East Asia), metabolic syndrome and obesity.<sup>1,7,8</sup>

## Presentation and diagnosis

Intrahepatic cholangiocarcinoma is often clinically silent and there are no specific symptoms in the early stages. Diagnosis is therefore incidental in at least 20-25% of the patients.<sup>1</sup> Symptoms include abdominal pain and, in more advanced cases, weight loss, malaise and asthenia.<sup>1</sup> Jaundice is rarely present (about 15% of the cases) and it can be caused by both external compression and infiltration of the hepatic hilum.<sup>7</sup>

Macroscopically, ICC may present as a mass-forming tumour, with periductal or intraductal growth, or with a combination of these patterns.<sup>9</sup> The mass-forming pattern is the most frequent and it spreads mostly via portal system. Instead, the periductal forms grow mostly through lymphatic vessels.<sup>10</sup> Microscopically, it is composed of bile duct cells with stromal fibrosis and collagen fibres.<sup>1</sup>

Diagnosis can be difficult, clinical suspicion and laboratory exams need to be confirmed by radiologic findings.<sup>11</sup> Laboratory investigations comprehend serum tumour markers including CA19-9 and CEA. The CA 19-9 sensitivity is 62% and its specificity is 63%.<sup>10</sup>

However, tumour markers may be elevated also in presence of tumours different from ICC or in case of benign conditions including cholangitis or cholestasis.<sup>6</sup> Therefore, they are not sensitive enough to be utilised for screening purposes.

Recently, some effort has been placed in the proteomic evaluation of organic fluids and in searching products of cancer cells (including cytokines, enzymes and growth factors) trying to find better biomarkers.<sup>12</sup> Potential serum, urinary and biliary biomarkers have been investigated over the years. Serum markers include trypsinogen-2, IL-6, MUC5AC, cytocheratin-19 fragment (CYFRA 21-1) and progranulin while some of the biliary biomarkers are insulin-like growth factor 1 (IGF1) and microRNA-laden vesicles. However, none of these is currently used in clinical practice.<sup>1,12</sup>

The Ultrasound Sonography (US) is the first imaging test that usually identifies an abdominal mass, but its sensitivity and specificity are opera-

tor-dependent. Tumour markers may improve significantly the sensitivity of US. Furthermore, the colour Doppler mode may show portal venous and parenchymal involvement.<sup>13</sup>

Unlike HCC, there are no specific radiological patterns for an imaging-based diagnosis.<sup>3</sup> On Computed Tomography (CT), ICC presents as a predominantly hypodense mass with irregular margins, with a peripheral rim enhancement in the arterial phase. Contrast uptake is progressive on the venous and late phases.<sup>3</sup> The hyper-enhancing pattern on delayed phase reflects stromal fibrosis of interstitial space. Therefore, hyper-attenuating ICCs are more aggressive. Other characteristics of advanced tumours include bile ducts thickening and dilatation, retraction of liver capsule, enlarged regional lymph nodes, vascular invasion and distant metastases.<sup>13</sup>

On contrast-enhanced Magnetic Resonance Imaging (MRI), the ICC is a hypo-intense lesion on T1-weighted images and hyper-intense on T2-weighted images. Central hypo-intensity, on delayed pictures, reflects the presence of fibrosis.<sup>13</sup> The contrast medium uptake in MRI is similar to CT scan. The typical HCC “wash-in and wash-out” pattern is never present, even in case of small tumours.<sup>1,10</sup> The MRI with cholangiopancreatography (MRCP) is the gold standard in the imaging of the biliary tree without the need of invasive techniques (i.e. percutaneous transhepatic cholangiography). The MRI is a powerful tool to evaluate tumour extent and resectability with an accuracy of up to 95%.<sup>13</sup>

However, both CT scan and MRI have low specificity and the diagnosis of small or rare forms of tumour, including mixed HCC-ICC or in presence of PSC, may be difficult by imaging only.<sup>10,14</sup>

Positron emission tomography with 18-fluorodeoxyglucose (FDG-PET) scan is not recommended as a routine staging exam.<sup>14</sup> However, it could be a great tool to discover occult primary tumours, distant or nodal metastasis with a sensitivity and specificity of about 40-55% and 80-87%, respectively.<sup>13</sup> Furthermore, a modification in patient management has been reported in up to 15% of the cases after diagnosis of nodal involvement with FDG-PET.<sup>14,15</sup>

The role of biopsy is still controversial when diagnostic doubt persists after imaging techniques. When a nodule is suitable for resection, most authors suggest that liver biopsy should not be performed because of the risk of seeding.<sup>7,11</sup> Anyway, there is no strong evidence supporting this risk.<sup>1</sup> Moreover, histological analysis on biopsy is not al-

ways able to differentiate a primary from a secondary adenocarcinoma.<sup>16</sup> On the contrary, since distant nodal metastases are a contraindication to liver resection, a biopsy of suspect distant lymph nodes should be performed via endoscopic ultrasound (EUS) with fine-needle aspiration, eventually.<sup>17</sup>

## Treatment and prognosis

When technically feasible, surgical resection is the best treatment that can be offered to the patients. In the great majority of them, a major hepatectomy will be necessary to achieve a R0 resection. Nevertheless, reported 5-years survival rates range from 22% and 45%,<sup>5,11,18</sup> mostly due to high recurrence rates (up to 80%).<sup>19-21</sup> Unfortunately, 60 to 88% of the patients with ICC have unresectable tumours due to a late diagnosis.<sup>22,23</sup>

Indications for liver transplantation (LT) for ICC are still controversial. Outcomes of liver transplantation have been changed over the years. In the '90s, a 5-year survival rate of less than 25% was reported.<sup>24-26</sup> Recent papers reported an acceptable 5-years overall survival rate, up to 83%, in highly selected patients.<sup>5,27</sup>

The most important prognostic factors after resection include: tumor-related features (e.g. size and number, vascular and nodal involvement, perineural and periductal invasion and tumour biology)<sup>17</sup>, margin status<sup>2</sup>, and time-to-recurrence.<sup>21</sup>

Palliative treatments include chemotherapy, radiation therapy or locoregional therapies but all these strategies provide only a modest improvement in prognosis with a median survival inferior to 1 year<sup>5,23,28</sup> and a 5-years survival of less than 10%.<sup>29</sup>

The focus of this paper is on surgical management of ICC with an assessment of prognostic factors for recurrence, which may assist to better select the appropriate treatment for each patient. A brief overview of palliative treatments is also provided.

## Surgical management

### Surgical resection

Currently, surgical resection is the only accepted treatment for potential cure.<sup>1</sup> Due to the improvements in surgical techniques and advances in perioperative care, surgical indications have been extended in recent years. However, only a minority of patients, 12-40%, are resectable at the time of diagnosis.<sup>11,30</sup>

Surgery aims to achieve complete resection of the tumour with adequate free margins, and, at the

same time, leaving a sufficient functional liver remnant. The assessment of resectability is associated with a variety of factors including tumour location and extension, liver function and underlying liver disease and, last but not least, performance status.

In case of involvement of major vascular structures or of first- and second-order biliary branches, a liver resection should be carefully assessed and planned.

Up to half of patients have multifocal disease at presentation.<sup>31</sup> Resection of multifocal ICC is controversial since it usually requires a more demolitive liver resection and it is associated with poorer survival rates. However, multifocality itself should not prevent surgery according to current published evidence.<sup>18,31,32</sup>

On the other hand, distant metastases are a contraindication to surgery. Similarly, metastases of distant lymph nodes are considered a reason for unresectability.<sup>17</sup> In case of suspected infiltration of regional lymph nodes, surgical resection should be assessed carefully given that lymph nodes positivity is one of the most important factors linked to poor prognosis.<sup>29</sup> In 10-20% of the patients, locally advanced tumours may be downstaged and reconsidered for liver resection after neoadjuvant treatments including chemotherapy (based on gemcitabine, cisplatin and paclitaxel) and locoregional procedures.<sup>32</sup> Conversion rate varies between 0% and 53% and up to half of the patients present with stabilized disease.<sup>32</sup>

In presence of cirrhosis, portal pressure should be assessed since clinically significant portal hypertension, defined as an hepatic vein pressure gradient (HVPG)  $\geq 10$  mmHg<sup>33</sup>, is a relative contraindication to major resections.<sup>17,20</sup> Further tests to reduce at a minimum the risk of postoperative liver failure include liver function tests, calculation of future liver remnant volume, and evaluation of the presence of fibrosis.<sup>17</sup>

Small tumours or peripherally located lesions can be treated with an atypical or anatomical minor resection. However, in most cases (70-80%), the lesion is multisegmental and a major hepatectomy may be needed.<sup>19</sup> Similarly to HCC, anatomical resections of ICC seem to have better outcomes in terms of survival and recurrence when compared with non-anatomical resections.<sup>34</sup>

A biliary resection and reconstruction is required in about 20-30% of the cases.<sup>19</sup> The necessity of a vascular reconstruction to achieve an R0 resection should not prevent surgery in selected patients. Reames *et al.*, in a multicentric analysis evaluating a total of 1087 patients, reported similar

results between patients requiring a caval or portal resection and those who did not.<sup>35</sup>

In case of a predicted small future liver remnant, portal vein embolization can be performed prior to surgery. Liver hypertrophy develops in approximately 40% of patients within 4 weeks. However, 20-30% of these patients will never undergo resection because of tumour progression or inadequate future liver remnant hypertrophy.<sup>17</sup>

The use of ALPPS (Associating Liver Partition and Portal vein ligation for Staged hepatectomy) has been reported for ICC. Liver hypertrophy is achieved faster when compared with PVE and the rate of achievement of second stage is higher with ALPPS compared to other staged procedures, but the cost in terms of morbidity and mortality is significant.<sup>36</sup>

Similarly to other cancers, lymphadenectomy has an undisputed role in staging the disease correctly.<sup>37</sup> For this purpose, a minimum of 6 lymph nodes are required as suggested in the 8th edition of the American Joint Committee on Cancer (AJCC) manual.<sup>38</sup> However, the impact of lymphadenectomy has been previously questioned and only about 50% of patients have been reported to receive a lymphadenectomy.<sup>39</sup> In particular, the therapeutic role of lymphadenectomy is debated although several more recent papers reported a survival benefit.<sup>39</sup> A complete lymphadenectomy is routinely performed by some authors to try to reduce local recurrence but in the subgroup of cirrhotic patients the related high morbidity rates may exceed the benefits.<sup>17</sup>

Minimally invasive surgery for ICC is feasible and safe in selected cases, with the advantages of laparoscopic and robotic techniques and similar oncological outcomes to open surgery.<sup>40,41</sup>

Adjuvant therapy is not fully standardized yet due to the rarity of this disease. However, chemotherapy should be offered to patients with positive nodes at histology though it seems to offer only partial control on lymph node metastatic disease.

Post-operative mortality is less than 5% in high-volume centres.<sup>1</sup> Five-years OS rates after curative surgery range between 22 and 45%. Median survival is reported to be 40 months.<sup>5,11,21,42</sup> Recurrence rates are still very high, ranging from 53% to 80%.<sup>5,21</sup> The reported 1-, 3-, and 5-year disease-free survival is 44%, 18%, and 11%, respectively.<sup>18</sup> The great majority of patients experience disease recurrence within 2 years<sup>5</sup> with a median time to recurrence ranging from 9 to 26 months.<sup>43</sup> However, recurrence has been reported up to 9.5 years after liver resection.<sup>18</sup>

Despite improvements in pre- and intra-operative imaging<sup>21,44</sup>, local tumour control may result incomplete, possibly due to unidentified small metastatic lesions at surgery.<sup>5,21</sup> Common extrahepatic sites of recurrence include lungs, abdominal lymph nodes and peritoneum.<sup>21</sup>

In case of intrahepatic only recurrence, further treatments with curative intent may still be possible if an R0 treatment is achievable by surgical resection or radiofrequency ablation.<sup>2,21</sup> However, disease recurrence is the major cause of death in these patients with a disease-specific mortality rate of about 90%.<sup>21</sup>

## Liver transplantation

Currently, ICC is a controversial indication for LT.<sup>5,27</sup> The main reasons of such controversy include the shortage of deceased donor organs, the potential of tumour progression whilst waiting for LT after chemotherapy, the high recurrence rates of ICC and the fact that immunosuppression may facilitate recurrence.

Papers from the '90s reported a poor prognosis after liver transplant for ICC with 5-years survival rates of 10-25%.<sup>24,25,45</sup> Furthermore, in most LTs ICC was an incidental diagnosis on the resected specimen, thus patients had not received preoperative adjuvant treatments.<sup>26</sup>

Recently, Sapisochin *et al.* retrospectively looked at 48 patients transplanted for presumed HCC or decompensated cirrhosis but diagnosed as ICC at post-transplant pathology.<sup>27</sup> Fifteen had very early ICC (<2 cm) and 33 had advanced ICC (>2 cm or multifocal). The 5-years OS rate was 65% and 45% for very early and advanced ICC, respectively. Tumour recurrence occurred in 13% of the very early group and in 54.5% of the advanced group, being the main cause of death of the latter. Therefore, LT could be a possible treatment only for cirrhotic patients with very early ICC.<sup>27</sup>

However, the role of neoadjuvant chemotherapy has remained unclear for a long time. Good results in terms of survival (5-years OS rate up to 76%) have been reported in highly selected patients with hilar cholangiocarcinoma who received LT after neoadjuvant chemotherapy or chemo-radiotherapy with good disease control.<sup>46-48</sup> These results encouraged further studies.

In their well-designed prospective case-series, Lunsford *et al.* reported a 1-, 3- and 5-years overall survival rate of 100%, 83.3% and 83.3%, respectively. One-, 3- and 5-years recurrence-free survival was 50% with a median time of recurrence of 7.6 months.

**TABLE 1.** A comparison between the prognostic factors of the three main recognized staging systems (the Liver Cancer Study Group of Japan [LCSGJ]<sup>9</sup>, the National Cancer Center of Japan [NCCJ]<sup>53</sup>, and the American Joint Committee on Cancer [AJCC, 8<sup>th</sup> edition<sup>38</sup>], Wang *et al.*<sup>49</sup> and Hyder *et al.*<sup>43</sup> nomograms

	Tumor diameter	Number of lesion	Extent of disease	Nodal Invasion	Vascular invasion	Metastatic disease	Other prognostic factors
LCSGJ <sup>9</sup>	Cut-off: 2 cm	Yes	Invasion of the serosa	Yes	Yes	Yes	
NCCJ <sup>53</sup>		Yes		Yes	Yes		Symptoms
AJCC <sup>38</sup>	Cut-off: 5 cm		Yes	Yes	Yes	Yes	
Wang <i>et al.</i> <sup>49</sup>	Yes	Yes		Yes	Yes	Yes	CEA CA19.9
Hyder <i>et al.</i> <sup>43</sup>	Yes	Yes		Yes	Yes		Age Cirrhosis

CA19.9= Carbohydrate Antigen 19.9; CEA = Carcinoembryonic Antigen

Inclusion criteria included: the presence of a locally advanced ICC (> 2 cm or multifocal, confirmed with biopsy or cytology), deemed unresectable after the evaluation of the multidisciplinary team; absence of distant metastasis or major vascular structures involvement; absence of tumour progression after a minimum of 6 months of neoadjuvant chemotherapy or radio-chemotherapy (gemcitabine-based regimens). Prior to proceeding to LT, sampling and frozen section of the hepatic hilum lymph nodes was performed to exclude malignancy.<sup>5</sup>

Despite promising results, the main issue with this paper was related to the highly selected patients and such good prognosis could be a consequence of the indolent behaviour of the disease. Responsiveness to chemotherapy for at least 6 months is a “test of time” and excludes patients with aggressive disease from transplantation. Furthermore, this paper included a small sample size (six patients in 8 years received LT) and the short median follow-up of 36 months.

Further prospective clinical trials taking into account tumour morphology and biology are still needed to draft definite conclusions.

### Prognostic factors for recurrence

There are many recognized prognostic factors related to the tumour and to liver resection as well as the previous history of PSC.

Tumour-related factors include size and number, vascular and nodal involvement, perineural and periductal invasion and tumour biology.<sup>17</sup> Serum biomarkers have a controversial role in prognosis establishment.<sup>49</sup>

Most authors recognize tumour size as a prognostic factor for recurrence.<sup>42</sup> Different cut-offs have been reported: 2-3 cm<sup>27</sup>, 5 cm<sup>18,19</sup> or 8 cm.<sup>50</sup> In

particular, Sapisochin *et al.* stratified the patients into three groups according to tumour size: smaller than 2 cm, between 2 and 3 cm, larger than 3 cm. They found a 5-years OS of 80%, 61% and 42%, respectively.<sup>27</sup> However, some other authors found alternative factors with a stronger prediction potential after resection<sup>10</sup> or LT including not receiving neoadjuvant therapies.<sup>51</sup>

Since multifocality and vascular invasion have a prognostic impact, the American Joint Committee on Cancer (AJCC) classifies both multifocal and single tumours in presence of vascular invasion as T2.<sup>38</sup> Furthermore, multifocality has been reported to significantly correlate with tumour size and differentiation, nodal metastasis and vascular infiltration. Satellitosis seems to confer a worse prognosis when compared with bilateral tumour location although this result may suffer from a selection bias of the patients.<sup>31</sup>

On the contrary, the previously cited paper of Lunsford reported that both volume and number of lesions do not impact on recurrence after LT.<sup>5</sup> However, these different findings may suffer from bias related to the small sample group evaluated.

Node metastasis is an important prognostic factor. Lymph nodes positivity resulted in about 45% of resections and even N0 patients may harbour nodal micrometastases in about 10-20% of the cases.<sup>52</sup>

There are three main recognized staging systems: the Liver Cancer Study Group of Japan (LCSGJ)<sup>9</sup>, the American Joint Committee on Cancer (AJCC), 8<sup>th</sup> edition<sup>38</sup> and the National Cancer Center of Japan (NCCJ)<sup>53,54</sup> (Table 1).

Principal prognostic factors for LCSGJ are tumour diameter with a cut-off of 2 cm, number of lesions, vascular infiltration and invasion of the serosa.<sup>9</sup>



The AJCC, 8<sup>th</sup> edition<sup>38</sup>, applied a cut-off of 5 cm to divide T1 into T1a and T1b.

The NCCJ, Okabayashi and Nathan system<sup>53,54</sup>, do not consider tumour diameter as an independent prognostic factor while presence of symptoms, nodal invasion, lesion number and vascular invasion have a prognostic impact. These three systems displayed lack of accuracy in predicting prognosis<sup>10</sup>, thus several nomograms have been proposed to predict survival.<sup>43,49</sup> Spolverato *et al.* developed a model to specifically predict cure rate and time necessary to define the patient cured. This cure model included tumour number, size and differentiation, vascular and periductal invasion, nodal positivity and it is easily accessible on internet.<sup>18</sup> Similar results have been previously published.<sup>43,49</sup>

Tumour biology is another fundamental aspect. Grading has been reported to be significantly related with tumour recurrence.<sup>27,29</sup> A high grade of diversity in ICC molecular profile has been reported.<sup>1</sup> Several genetic modifications, epigenetic alterations, gene fusions products (including FGFR2 gene fusion), hormone influences (including evaluation of tumour estrogen sensitivity) and growth factors effects have been assessed and are still under continuous evaluation.<sup>1</sup> The whole-genome analysis helped in understanding two potential altered pathways related with ICC development: activation of the inflammatory response pathway and cellular proliferation pathway, the latter being related with a worse prognosis.<sup>1,55</sup> However, a complete knowledge at the cellular level together with the microenvironment in which tumours develop is far from being achieved.<sup>1</sup> This effort may widen the perspectives in different aspects of tumour management: diagnosis (with the discovery of new circulating biomarkers), treatment allocation (including personalized targeted therapies) and prognosis prediction. For example, while KRAS mutation has been found in patients experiencing recurrence, FGFR gene fusion seems related with an indolent disease.<sup>5,56</sup> Obviously, patients with indolent tumours will have a better prognosis despite the treatments received and they will benefit more from each treatment. The previously reported absence of disease progression during chemotherapy is strictly related with tumour biology.<sup>2,5</sup>

The most important prognostic factor after surgical resection is the state of the margins. Tumour-free margins are related with a significantly better prognosis when compared with infiltrated margins.<sup>2,57</sup>

Finally, time-to-recurrence after surgery with a curative intent has been reported to be itself a

prognostic factor.<sup>21</sup> Using a cut-off of 24 months, Zhang *et al.* showed a significantly worse prognosis for patients experiencing early recurrence when compared with those with late recurrence (median OS of 10 and 18 months, respectively).<sup>21</sup> Although recurrence was mainly in the liver, the frequency of extrahepatic localization was higher in the early recurrence group.<sup>21</sup> Furthermore, they found that the size and number of tumours, vascular invasion, presence of satellitosis or surgical margins of less than 1 cm were all associated with the early recurrence pattern at univariate analysis. On the contrary, adjuvant treatments and presence of cirrhosis resulted significantly linked to late recurrence.<sup>21</sup> Interestingly, when further treatments with a curative intent were possible, OS rates resulted similar between the two groups.<sup>21</sup>

Further studies are needed to evaluate with greater detail potential prognostic factors and their weight.

## Palliative treatments

Unfortunately, a great majority of the patients present with unresectable disease due to major vascular or bile duct involvement, metastasis or huge burden of disease leading to a potential insufficient future liver remnant.<sup>11</sup> The 5-years survival rate of these patients is less than 10%.<sup>29</sup>

Although ICC tends to develop chemoresistance, systemic therapy is the main treatment in the subset of palliative cures. Chemotherapy could be considered to treat patients with macroscopic residual tumour after surgery, locally advanced or metastatic unresectable tumours or recurrent ICCs. The National Comprehensive Cancer Network guidelines recommend gemcitabine/cisplatin therapy as first-line treatment.<sup>37</sup> In alternative, fluoropyrimidine-based or other gemcitabine-based chemotherapy regimens could be considered.<sup>37</sup> However, the optimal second-line therapy is still controversial.<sup>58</sup> The role of targeted therapy is still under evaluation.<sup>1</sup> Furthermore, a better understanding of the mechanisms that are behind chemoresistance may widen and improve treatment options.

The addition of radiation to chemotherapy is associated with better outcomes in terms of disease-free and overall survival.<sup>59,60</sup> On the contrary, the role of radiotherapy alone for ICC is controversial. Different approaches of radiotherapy are available such as external beam irradiation, brachytherapy with iridium-192, stereotactic body radiotherapy and proton beam irradiation.<sup>59</sup> Technical advances

now allow a selective delivery of radiation to the lesion, sparing adjacent tissue. To date there are no randomized trials comparing new techniques with the more conventional ones.

While distant metastasis is a less frequent cause of death, many of these patients die of liver failure caused by tumour-related vascular involvement or biliary obstruction. It is thus important to try to achieve local control of the tumour to improve quality of life.<sup>32</sup> There are no randomized data showing a single optimal local treatment, so a tailored therapy is required. The choice of the best locoregional treatment must consider factors related to the patient (comorbidity, liver function, previous treatments) and to the tumour, such as size, vascularity and its involvement of bile ducts, blood vessels, bowel and chest wall.<sup>32</sup>

Data concerning the use of transarterial embolization therapies for ICC are scarce. These treatments include transarterial chemoembolization (TACE), bland embolization, chemoinfusion (TACI) and radioembolization (TARE, known also as selective internal radiation therapy, SIRT). These therapies are indicated in case of hypervascular lesions and in absence of complete portal vein thrombosis<sup>61</sup> with the exception of TARE that can be used in cases of neoplastic thrombosis. Unfortunately, ICC is typically hypovascular and characterized by fibrous content.<sup>62</sup>

In a retrospective multi-institutional analysis evaluating 198 patients with ICC, partial/complete response or stability of disease was found in 26% and 62% of patients, respectively. Median OS was 13.2 months. Outcomes did not differ on the type of intra-arterial treatment.<sup>63</sup> These results were confirmed by Yang who performed a systematic review including 926 patients.<sup>64</sup> Mean complete radiological response was 10% while partial radiological response was 22.2%. One third of patients suffered from acute toxicity, 30-day mortality was less than 1% and median OS was 13 months. These data showed that transarterial embolization therapies could be safely and effectively used in unresectable cholangiocarcinoma, conferring a survival benefit.<sup>64</sup>

Percutaneous ablation techniques such as radiofrequency or microwave ablation are effective for small lesions (4-5 cm), not located close to major bile ducts or blood vessels or on the liver surface.<sup>65</sup> Irreversible electroporation is a new ablation technique with similar results for small lesions but with no limitations in terms of distance from bile ducts and vessels.<sup>61</sup>

Photodynamic therapy is another palliative treatment that may have a small beneficial effect on survival.<sup>66</sup>

## Conclusions

Intrahepatic cholangiocarcinoma is a rare tumour but with an increasing incidence over the years. Unfortunately, mortality rates are rising consensually despite improvements in surgical techniques and perioperative care. When technically feasible and patients are fit, surgical resection is the best option that can be offered. However, survival rates are still discouraging and recurrence rates are high. Liver transplantation may be considered in highly selected patients including those with a very early tumour and cirrhosis or in locally advanced unresectable ICC but stable after neoadjuvant therapy. Unfortunately, the majority of patients present with unresectable disease. Palliative treatments may confer an improvement in survival. However, we should aim at an improved stratification of patients using the known prognostic factors and, hopefully, at a better understanding of biologic cancer profiling. This stratification, together with standardization and improvements in neoadjuvant and adjuvant therapies, may allow a better allocation of treatments and, possibly, an expansion of the indications for surgery in a subset of patients.

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