CURRENT TREND

Clinical presentation and management of intrahepatic cholangiocarcinoma

Présentation clinique et prise en charge des cholangiocarcinomes intrahépatiques

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In both the International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC), intrahepatic cholangiocarcinoma (IHCC) are considered as primary intrahepatic liver tumors, along with hepatocellular carcinoma (HCC). This differentiates them from malignancies of the biliary confluence (Klatskin tumors) that are stratified as extrahepatic tumors along with malignancies of the gallbladder and of the common bile duct. The definition of IHCC (primary tumor of the intrahepatic bile ducts) implies that it encompasses all malignancies developed from the intrahepatic bile ducts, starting from the second order branches and up to the Hering ducts.

This heterogeneity of origins readily explains that the clinical presentation and management of this tumor are quite variable depending on whether the tumor originates from the end-order peripheral branches or from the juxtahepatic branches (Fig. 1A and B). The former is likely to be more frequent than the latter, at least in part because as bile structures divide, their number increases. However, the proportion of each is still ill-defined as mass forming type IHCC may behave as hilar malignancies as a result of their location in the vicinity of the biliary confluence (Fig. 1C) or centrifugal extension along the glissonian pedicles (Fig. 1D).

Two words of caution should be given on the source of informations available in the medical literature that will be used in this chapter. First, the figures that will be presented relate, as a rule, to patients who have been operated for an IHCC and not to the general population of IHCC. As a matter of fact, virtually all series or registries of IHCC-patients are surgical series. They have the advantage of focusing on patients with pathologically proven tumors but the disadvantage of dealing with a subgroup of patients (those referred to surgeons for resection) that probably account for less than 20% of all patients with IHCC. Second, most data originate from single surgical centers and usually include a limited number of patients (around 50) gathered over a fairly large period of time (typically 10–20 years). The few exceptions are in particular the Surveillance, Epidemiology and End Results Program (SEER) that collects information from...
Figure 1. Heterogeneity of the morphological presentation of IHCC. The two extreme situations depending on the origin of the tumor are the mass forming type that originates from the end division of the intrahepatic bile ducts (A) and the periducal infiltrating type that originates from the proximal segmental or sectional bile ducts and resembles a Klatskin tumor (B). Some mass forming type IHCC may however behave as hilar tumor either when they develop from small bile ducts but in liver segments adjacent to the biliary confluence (C) or when they extend along the glissonian pedicles (D).

approximately 25% of the population of the United States [1], a Japanese registry of liver tumors which is declarative and likely not comprehensive [2] and a recent French multi-institutional survey of operated patients at the initiative of the French Association of Surgery [3].

Frequency

A specific chapter of this monography being dedicated to the epidemiology of IHCC, we will only attempt to highlight here how this tumor compares to extrahepatic bile duct tumors on one side and to HCC (the other and predominant intrahepatic primary tumor) on the other side.

IHCC in relation to other bile duct malignancies

It has been widely assumed in the past, in particular in surgical series, that IHCC account for a very small proportion (approximately 10%) of all bile duct malignancies [4]. This view is challenged worldwide by more recent epidemiological database and in particular the latest edition (published in 2007) of "Cancer incidence in five continents" that covers the period 1998–2002 [5]. In France for example, the incidence of IHCC in 11 regional registries ranged between 0.5 and 1.3 per 10⁵ for men and between 0.2 and 0.9 per 10⁵ for women whereas the respective incidences of all extrahepatic bile duct malignancies ranged between 0.6–1.3 and 0.7–2.3 per 10⁵. Caution in interpreting these data are given in the first chapter of this monography but according to these figures, IHCC are almost as frequent as all extrahepatic bile ducts in men and only twice less frequent in women. The same holds true in most other countries, except in those where the incidence of gallbladder cancers is particularly high (in particular Chile, Peru and Korea).

IHCC in relation to primary liver malignancies

It has recently been estimated that in France IHCC is 15 times less frequent than HCC [6]. This figure is in between that observed in the Unites States (eight times) [7] and that reported in Japan where the prevalence of HCC is particularly high (23 times) [2]. These variations are indeed more influenced by the numerator (i.e. the incidence of HCC which is highly variable in different areas of the world) than by the denominator (i.e. the incidence of IHCC which is fairly constant, except in South East Asia where distomatosis is endemic). Interestingly, in the French analysis (performed in nine administrative regions accounting for one tenth of the population) there were (unexplained) geographical variations and the ratio actually also ranged between 8 and 22.

Further evaluations are warranted as these studies, although published recently, refer to patients registered 10 years ago whereas the incidence of IHCC is considered to have increased since then.

Circumstances of diagnosis

Age and gender

The peak incidence of IHCC occurs between the age of 55 and 75 years and this tumor is extremely rare before the age of 45 (~10% of the patients). Although the sex-ratio may fluctuate slightly around 1 in different areas of the world (0.9 in the Western world and 1.5 in Asia) this may simply
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for IHCC. Expectedly much lower[8]. Altogether, these data suggest that the course of the disease might be more indolent than previously thought and explains that this tumor is usually discovered at an advanced stage.

Although IHCC by definition exclude tumors located within the biliary confluence or first order branches (left or right bile duct), jaundice is present in 10 to 15% of the patients[12,14,15]. It may result from the protrusion or migration of tumor material within the bile duct lumen, or compression of the common bile duct by metastatic lymph nodes. However, the most frequent cause of bile duct obstruction is compression of the bile duct confluence by tumors located in the liver segments adjacent to the biliary confluence (segment 4 and 1) or carcinomatous infiltrating extension along the glissonian sheet of segmental or sectional bile ducts (Fig. 1C and D).

Liver function tests are not specific. Gamma Glutamyl Transferase levels at least are always above the normal upper range although this increase might be slight. This feature is however common to any space occupying lesion of the liver (except angioma).

Associated conditions

As detailed in the first chapter, classical risk factors for IHCC observed in the Western world and Japan (as opposed to South Eastern Asia and in particular Thailand, where it is clearly related to parasitic infections) include primary sclerosing cholangitis (PSC), intrahepatic lithiasis, and malformations of the bile ducts (such as an anomalous junction of the biliary-pancreatic ducts or Caroli’s disease). In fact, an analysis of surgical series reveals that these risk factors are exceptionally found. As an example, out of the 2743 patients included in Western and Japanese series or surgically treated patients, PSC was present in approximately 1%, intrahepatic lithiasis in 3%, and biliary malformations in less than 1% [3]. These figures might of course somewhat underestimate the reality as the patients from these surgical series might not have been screened comprehensively. They however underline that although there is a clinical rationale for searching these risk factors, they are unlikely to be found.

On the other hand, cirrhosis (as well as more broadly hepatitis B and C viral infections) is observed in 8% of the patients[3]. This incidence is much higher than the general population, but much less than what is observed for HCC. Altogether, these results indicate that most patients with an IHCC have currently no identified cause of their tumor.

Methods of diagnosis

Tumor markers are of little help in the diagnosis of IHCC because of their lack of sensitivity, as well as specificity. The most widely used are the CEA and CA19-9 but neither has in fact been very extensively studied. Overall, CEA levels are above 20 ng/ml and above 100 in 15% and 5% of the patients respectively[2]. CA19-9 levels are between 100 and 1000 U/ml in 25% of the patients and above 1000 in a further 30% but these values have not been stratified for the serum bilirubin level. AFP levels are below 200 ng/ml in 95% of the patients[2] as compared to 73% of patients with HCC.

With a little of experience, the diagnosis of most IHCC is usually fairly obvious on imaging studies (CT-scan and/or MRI). It typically presents as a liver tumor that has three distinctive features (see previous chapter):

- firstly, it is fibrotic and therefore enhances at the delayed phase of the injection and is associated with a retraction of the capsule and an encasement of the vascular and biliary structures;
- secondly, it is frequently associated with satellite nodules that predominate at the periphery of the tumor;
- thirdly, enlarged lymph nodes in the hepatic pedicle (in particular at its right inferior part) or above the junction of the common and proper hepatic arteries are frequent.

The main differential diagnosis is colorectal liver metastases (and to a lesser extent, liver metastases of breast cancer). Depending on the context, there are two options to confirm the diagnosis which are both invasive. The first is to perform a colonoscopy to rule out a colon cancer. The second is to perform a biopsy of the tumor (and of the adjacent liver) with immunostaining for cytokeratins (CK) 7 and 20. IHCC are CK7+ CK20− whereas colorectal metastases are CK7− CK20+.

Staging of IHCC

As previously indicated, IHCC are considered by the World Health Organization (WHO) as intrahepatic liver malignancies along with HCC. HCC being more frequent than IHCC and the diagnosis of IHCC having been rather unreliable until the end of the 1980s, staging systems have been developed based on the clinical, pathological and therapeutic characteristics of HCC. There are in fact two types of staging systems, a medical and a surgical one, neither of which is adapted to IHCC.

"Medical staging systems" are designed for all patients with the aim to predict spontaneous survival, stratify patients for clinical trials or help rationalize treatment
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Table 1: Staging systems of primary liver tumors. UICC and LCSGJ were designed for hepatocellular carcinoma. The staging advocated by Nathan et al. [18] was more specifically designed for intrahepatic cholangiocarcinoma.

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0: absent; +: present; —: either absent or present; VI: vascular invasion; UL: unilobar; BL: bilobar; (a): invasion of the main vascular branches; (b): invasion of adjacent organs or ruptured tumor; UICC: International Union Against Cancer; LCSGJ: Liver Cancer Study Group of Japan.

options. Examples of these include the Okuda staging, the Cancer of the Liver Italian Program (CLIP), the Barcelona Clinic Liver Cancer staging, the Japan Integrated Staging Score (JIS), the Chinese University Prognostic Index, or the French Score [16]. None have been tested in patients with IHCC. They are anyway unlikely to be very accurate as they all rely to some extent on the severity of the underlying liver disease, which is not a prominent feature of IHCC.

“Surgical staging systems” are constructed from — and specifically designed for — operable patients. The most widely used have been developed by the AJCC/UICC and by the Liver Cancer Study Group of Japan (LCSGJ). Of note is that, unlike medical staging, they do not include parameters of liver function (Table 1). Both the AJCC and LCSGJ grading of the “T” have good discriminating ability in HCC patients (i.e. T1 patients fare better than T2 patients who fare better than T3 and so on) [17]. In contrast, discrimination is poor when this staging is applied to patients with IHCC [18]. The same holds true for the overall “stage” of the tumor that integrates both the “T” and the “N” status [10,19,20]. Reasons for this relate to specific features that IHCC have in comparison with HCC and examples are given below:

- T staging: the T1 stage of HCC includes single tumors less than 2 cm without vascular invasion. This defines early stage HCC which is an excellent indication for all potentially curative treatments including ablation, resection and transplantation. Following curative resection, the survival is 70% at five years; beyond five years, this survival is mainly impacted by the presence of an underlying liver disease which favors the development of de novo (as opposed to local) recurrence [17]. As a result of screening policies, T1 HCC account for approximately one third of HCC [2].

In contrast, mass-forming type IHCC less than 2 cm are almost exceptional. They were actually never observed in a surgical series of 60 patients reported from Tokyo [21] and accounted for 2% of the 195 resected patients from Berlin [20]. Higher figures up to 5% or 10% have been reported in recent French [3] or Japanese [2] surveys but it is likely that some of these small tumors corresponded to the periductal infiltrating or the intraductal growth variants of IHCC rather than to the classical mass-forming type (for a comprehensive description of these morphological subtypes, the reader is invited to refer to the previous chapter).

- N staging: another example of the difference between the two tumors is the incidence of lymph node extension. In surgical series of HCC patients, the incidence of positive lymph nodes (N+) ranges between 5% (when an underlying liver disease is present) and 10% (for HCC developed within normal livers) [22].

In contrast, the proportion of positive lymph nodes is 40% in surgical series of IHCC [22]. This high propensity for lymphatic extension has two consequences. The first one is that the N status is likely to overweight some of the...
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‘‘T’’ characteristics of IHCC (a ‘‘small’’ tumor which is N− will have a poorer prognosis than a ‘‘large’’ tumor which is N−). The second consequence, which is even more problematic, is that accurate surgical staging of IHCC requires that all surgically treated patients undergo lymph node dissection. This is still not the case whereas the accuracy of imaging studies to predict lymph node invasion is low [23]. Hence, although some have considered patients who did not have lymph node dissection as being N−, these patients in fact have a prognosis intermediate between the true N+ and the true N− [3] suggesting that some of them were in fact N+.

More recently, there have been attempts to design surgical staging systems specific for IHCC both in the East [21,24] and the West [18] (Table 1). Although they still need cross-validation, it is interesting to underline that size has virtually disappeared from these classifications to evaluate the ‘‘T’’ (tumor) staging in favor of tumor number or extension to adjacent organs. Tumor size is indeed currently a poor predictor of survival following resection of IHCC or more precisely did not to turn out in most series to be an independent variable by multivariate analysis [10,12,15,20,24,25] in contrast to what has been repeatedly observed for HCC.

Treatment options

Tumor resection is currently the only effective treatment of IHCC. As for other liver tumors, there is no randomized controlled trial to support this statement. However, the 3-year survival is virtually nil without resections whereas it is usually 40 to 50% in patients whose tumors have been removed [2,10,11,13,26,27]. In fact, there is little alternative to surgery in the treatment of IHCC, in contrast to that of HCC for which liver transplantation, percutaneous ablation, transarterial chemoembolisation are validated treatment options. We will first see why these alternatives to surgery have a very limited place in the management of IHCC. The consequence is that treatment decision is fairly simple being either surgical resection or palliation. Systemic chemotherapy, although promising, has not proven yet to be effective.

Alternatives to surgery

Radiofrequency ablation has recently been estimated to be used as frequently (or slightly more frequently) than resection in the treatment of HCC in France1. There are in contrast two main reasons why it is exceptionally indicated and performed for IHCC. The first is anatomical and relates to the usually large diameter of IHCC at the time of diagnosis. Any tumor larger than 3 cm is unlikely to be efficiently destroyed by currently available devices. Besides, the frequent proximity between IHCC and Glissonian pedicles both limits the efficacy of ablation (through the so-called cooling effect) and increases the risk of biliary complications. The second is the usual absence of a severe underlying liver disease. The risk of post-hepatectomy decompensation of the underlying liver disease was the main rational for the development of ablation for HCC. In contrast, the incidence of underlying cirrhosis is much less in IHCC and the justification to use a less aggressive treatment than surgical resection is therefore limited. In the Japanese registry, this treatment was performed in 2% of IHCC patients as compared to 31% of HCC patients [2]. Besides, when performed, incomplete response to ablation was twice more frequent in the former than in the latter (36% vs. 18%). The only circumstance when ablation has been successfully used for IHCC is single and small hepatic recurrence following resection. This situation is however so rare that this indication is more theoretical than realistic.

Transarterial chemoembolisation (TACE) which is widely used and increasingly effective for HCC is, as a rule, neither indicated for IHCC. Being mainly fibrotic, this tumor is not hypervascular at the arterial phase of the injection and there is therefore no blush to help identify the feeding artery. Besides, TACE is less likely to induce tumor necrosis of non-hypervascular tumors, which is the case of IHCC. Finally, although Child-Pugh C cirrhosis (which is a formal contraindication to TACE) is rare in patients with IHCC, significant portal or biliary involvement by the tumor is more frequent and may represent a relative or absolute contraindication. In the latest edition of the Liver Cancer Study Group of Japan [2], chemoembolisation was actually performed in only 4% of the patients and the morphological response was either minor or absent in two thirds of them. There are however some IHCC that are at least partly hypervascular and could benefit from TACE as a palliative treatment [28]. Encouraging results have also been recently reported using doxorubine-eluting beads [29] or Yttrium-90 microspheres [30]. There is no report on the use of Iodine-131 for IHCC.

Liver transplantation has been infrequently used to treat IHCC and it is extremely difficult to have a clear idea on its results. One reason is that patients with IHCC are usually grouped with patients with hilar cholangiocarcinoma in liver transplant series. In a recent French national survey, IHCC accounted for 30% of all patients transplanted for a cholangiocarcinoma while 70% had been transplanted for a Klatskin tumor [31]. All cholangiocarcinoma patients (peripheral and hilar) themselves account for less than 1% of all liver transplants in the North American and European liver transplant registries. The 5-year survival following transplantation is usually around 30% and in the recent French survey, survival curves of patients with hilar and peripheral cholangiocarcinoma were almost exactly the same. This survival figure is considered much too low by the transplant community in a context of graft shortage to justify this indication. There are however two exceptions when transplantation achieves good results. The first is transplantation for very small IHCC that are incidentally discovered on the resected specimen or have been mistaken for a T1 HCC. However, as indicated previously, this situation is exceptional as only approximately 5% of IHCC measure less than 2 cm in diameter. Besides, it is unsure if liver transplantation offers better outcome than resection in this setting even when there is an underlying cirrhosis. The second is transplantation for Klatskin tumours, and by extrapolation of small IHCC developed from second order biliary branches.

provided that this transplantation is preceded by a very aggressive regimen of radio and chemotherapy [32]. Such a treatment however requires very strict oncologic criteria and preparation and proves very difficult to implement. It is in fact still unsure whether it is the transplant itself or the neoadjuvant radiochemotherapy which is the mainstay of treatment. As the tumor and the hilar area are being almost completely destroyed by the radiotherapy, the rationale for transplantation is of course to remove potential residual tumors but also to prevent the middle- or long-term complications of radiation injury.

Systemic chemotherapy

Non-targeted systemic therapies of IHCC has until recently been considered to be relatively ineffective. The problem however is that the number of studies is limited, most of which are phase II, tend to mix up a variety of biliary locations that do not have the same spontaneous survival (i.e. intrahepatic, gallbladder, extrahepatic) and are occasion- ally discordant. Hence, no standard palliative chemotherapy has been defined. The current national recommendations (published in 2007) is abstention for patients in poor general condition and a regimen based on cisplatin, gemcitabine or oxaliplatine for patients with a good performance status [33]. These schedules may yield a response rate between 10 and 20%. At the latest ASCO meeting (2009), encouraging results were reported using a combination of gemcitabine and cisplatin (over gemcitabine alone). Nevertheless, there is a relative chemoresistance of IHCC that may relate to the expression of multidrug resistance genes as well as up-regulation of anti-apoptotic bcl-2 proteins. These could be overcome by the new-targeted therapies.

Targeted therapies have not been as extensively studied in the management of IHCC as of HCC. There are however a number of experimental or functional evidences that these treatments might be effective. These include in particular over expression of VEGF in IHCC [34]. However, the priority for the industry up to now was HCC rather than IHCC because of its higher frequency. Potential treatments include EGFR inhibitors (cetuximab, erlotinib, and gefitinib), Raf-kinase inhibitors (sorafenib), Her-2—directed inhibitors (trastuzumab and lapatinib), and vascular endothelial growth factor—directed inhibition (sorafenib and bevacizumab) that are currently under investigation. At the latest ASCO meeting (2009), encouraging results were also reported using a combination of cetuximab and GEMOX (over GEMOX alone, and irrespective of Kras mutation) and the final version of the publications are awaited.

Surgical resection

Since tumor resection is currently the first-line treatment of IHCC, it is important that physicians be aware of its efficacy and limits that have four specificities compared to other indications of liver surgery:

- the efficacy of surgery for IHCC is usually assessed in terms of patient survival up to five years after surgery. There are little data on survival beyond five years or on disease-free survival rates. In fact, the latter has not been considered a very necessary end-point as the vast majority of the deaths are related to recurrence and as very few recurrences are amenable to repeat surgery. According to the series published over the past decade in the international medical literature, the 1-, 3- and 5-year survival rates following resection of IHCC are 67% (IC: 63—71), 38% (IC: 34—42) and 27% (IC: 23—31) (reviewed in [3]). These figures are very much the same in different areas of the world (Fig. 2). Accordingly the prognosis of resected IHCC is a little less than that of other liver malignancies. The 5- and 10-year survival of all HCC treated by hepatic resection (liver transplantation excluded) is for example 53% and 28% in the Japanese registry [2]. Corresponding figures for colorectal liver metastases are 42% and 26% in an international registry [35]. It is of course possible that these differences witness selection bias towards the most suitable patients, as there are other treatments than surgery for HCC and colorectal metastases, whereas surgery is the main or only treatment of IHCC. Nevertheless, there is general agreement amongst surgeons that there is a place for improved patient selection and neoadjuvant or adjuvant treatments;
- the second specificity of surgery for IHCC is the fairly high risk associated with the procedure. Although postoperative mortality is highly variable between centers, it is hardly ever nil whereas some groups have rightfully publicized 0% mortality rates for HCC-patients despite the presence of an underlying liver disease [36]. When pooling data from different geographical areas, it turns out to be exactly the same (6%) in the Western world (United States and Europe), in Japan, in Corea, and in France [3]. This figure is again somewhat higher than that of liver resection on normal livers (actual figures for colorectal metastasis or HCC without underlying liver disease are around 1—2%) and comparable to that of liver resections on cirrhotic livers (the majority of resections for HCC). The main complications are liver failure and sepsis. As a matter of fact, hepatectomy for IHCC usually consists in a major hepatectomy removing more than three liver segments in 75—80% of the patients (and actually removing more than four segments in 50 to 60%). Besides, a significant number of patients have an associated removal of segment 1 (30 to 50%), of the common bile duct (20 to 40%) or of vascular structures (10 to 20%) to achieve complete resection (Fig. 1). In other words, the extent of surgery for IHCC is occasionally the same as that for hilar cholangiocarcinoma which is the indication for elective liver surgery associated with the highest morbi-mortality;
- the third specificity is that both the resectability and curability rates of IHCC are somewhat less than for other malignancies. In approximately 20 to 30% of patients operated for an IHCC, incidental liver metastases or peritoneal deposits that have been missed by preoperative imaging and contraindicate resection will be discovered. The prognosis of these patients is dismal with no 3-year survivors. Besides, among resected patients, approximately 25% will have an R1 or R2 resection. Survival following an R2 resection is usually comparable to, and occasionally worse [10,20] than that of non-resected patients. Median survival following an R1 resection is in most series less than 12 months and the 3-year survival is nil. However, prolonged survival has also occasionally been reported but it is still unclear why. Some patients might have had a particular type or location of their tumor (intraductal growth
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Figure 2. Survival following surgical resection of IHCC in different geographical area. Data are expressed as the median [25–75 CI] survival published in clinical series published over the past 10 years. In case of multiple publications, only the most relevant was retained (reproduced from reference [3] with permission).

- type and/or juxtahilar location) or have benefitted from adjuvant chemotherapy;
- the fourth specificity is that there is little or no evidence that the prognosis of IHCC following liver resection has clearly improved over the past 10 years, in contrast to what has been reported for other liver malignancies such as HCC or colorectal liver metastases [12,20] and it may be useful to understand why.

For HCC, the 5-year survival has increased from 30% to 50–60%. The main reasons are better patient selection and preparation (portal vein embolisation to test the ability of the liver to regenerate), improved oncolgic surgical technique (anterior approach to avoid mobilization of the tumor), refined definition of the optimal surgical margins (anatomical resection with 2 cm margins) and active treatment of recurrence. For colorectal liver metastases the 5-year survival has increased similarly. The main reasons are the more liberal use of highly effective adjuvant or neoadjuvant chemotherapies and again active treatments of recurrences.

As a rule, none of these features has developed to a comparable level for IHCC. There are limited informations on the location and kinetics of recurrence (although they account for the majority of postoperative deaths). Confusing data have been reported on their risk factors. There is currently evidence that the efficacy of chemotherapy is improving but not yet to the extent that it can be advocated in the neoadjuvant setting. Finally, there is a general belief amongst surgeons that recurrences following resection are not amenable to repeat resection although most are located within the liver.

Current management and areas of improvement

Overall results of management

As previously indicated, most data on IHCC arise from specialized hepatobiliary units that do not reflect overall practice. However, over the past five years, a broader view has been available through national registries. These include the SEER Program of the National Cancer Institute in the United States that covers 25% of the US population [37,38] and the Francim registry in France that covers 11% of the French population [8]. Both are fairly concordant in showing that:
- the median survival of all patients with IHCC (treated and untreated) is seven months and the 5-year survival is 5% or less;
- surgery is the only effective treatment but is performed in only 10 to 20% of the patients;
- the adjusted odds ratio for receiving surgery may vary from 1 to 3 between regions [38].

A first area of improvement is therefore the earlier diagnosis of this tumor and its evaluation by dedicated teams.

Selection of patients for surgery

Evaluation of risk factors for recurrence is the cornerstone of patients’ selection for surgery. Somewhat conflicting results have however been reported in the literature and the validity of the results are further hampered by the discordance between the limited number of patients and the high number of variables evaluated. Nevertheless, the presence of satellite nodules or of positive lymph nodes are determinants and when both conditions are present, survival is so low that surgery might not be justified. Selection criteria however need to be validated and refined.

Development of chemotherapy

The efficacy of surgery, although obvious, has its limits considering the high rate of R1 resections and of recurrence. Further improvement will require more active use of chemotherapy, either as neoadjuvant or adjuvant treatments. These have been delayed for a number of reasons but in the future, inclusion of patients into randomized controlled trials should be encouraged.

Conclusions

IHCC is the second most frequent primary liver tumor and is increasingly recognized because of both a better identification of this entity and a rising incidence. The diagnosis should be suspected in either male or female patients in his or her 60s, with no or minimal symptoms, and a fibrotic liver mass. Surgery is currently the only effective treatment and may yield a 5-year survival of 40% provided that the resection is curative (R0). Unfortunately, this occurs in as few as 20% of the patients due to delayed diagnosis or technical difficulties to achieve safe margins. Improvement in prognosis may require a higher index of suspicion, an earlier referral to specialized surgeons and the development of innovative chemotherapy regimens. Considering that chemotherapy for IHCC is behind the times compared to HCC or colo-rectal liver metastases, it should (ideally) not be used outside clinical trials.
Conflict of interest statement

Authors declare that there is no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three (3) years of beginning the work submitted that could inappropriately influence (bias) this work.

References


