REVIEW

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Clinical Diagnosis and Staging of Intrahepatic Cholangiocarcinoma

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ABSTRACT

Intrahepatic cholangiocarcinomas are the second most common primary liver malignancies with an increasing incidence over the past decades. Due to a lack of early symptoms and their aggressive oncobiological behavior, the diagnostic approach is challenging and the outcome remains unsatisfactory with a poor prognosis. Thus, a consistent staging system for a comparison between different therapeutic approaches is needed, but independent predictors for worse survival are still controversial. Currently, four different staging systems are primarily used, which differ in the way they determine the ‚T' category. Furthermore, different nomograms and prognostic models have been recently proposed and may be helpful in providing additional information for predicting the prognosis and therefore be helpful in approaching an adequate treatment strategy. This review will discuss the diagnostic approach to intrahepatic cholangiocarcinoma as well as compare and contrast the most current staging systems and prognostic models.

Key words: Intrahepatic cholangiocarcinoma – staging systems – nomograms – liver neoplasms – biliary tract cancer

Abbreviations: AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase; ALD: Alcoholic liver disease; CA: Carbohydrate-antigen; CEA: Carcinoembryonic antigen; EGD: Esophagogastroduodenoscopy; ERCP: Endoscopic retrograde cholangiopancreatography; EUS-FNA: Endoscopic ultrasound-guided fine-needle aspiration; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; ICC: Intrahepatic cholangiocarcinoma; INR: International normalized ratio; LCSGJ: Liver Cancer Study Group of Japan; LNM: Lymph node metastases; MRCP: magnetic resonance cholangiopancreatography; NAFLD: Non-alcoholic fatty liver disease; PA: Pre-albumin; PSC: Primary sclerosing cholangitis.

INTRODUCTION

The intrahepatic cholangiocarcinoma (ICC) is a tumor that arises from the endothelial cells of second-order branches or more peripheral branches of the biliary tree. Due to different oncobiologic behavior compared with hepatocellular carcinoma (HCC), ICC has to be regarded as a distinct malignant entity. Therefore, a different way of approaching an adequate treatment strategy as well as its own staging system is required [1-6]. Subtypes of ICCs can further be distinguished according to a mass-forming, periductal-infiltrating and intraductal-growth pattern, whereby the mass-forming type is by far the most common (79–86%) [1, 4, 5, 7-9]. A rare subtype of the ICC is the combined hepatocellular–cholangiocellular carcinoma [3].

Intrahepatic cholangiocarcinomas are the second most common primary liver malignancies, behind only HCCs, with a prevalence of 3% of all gastrointestinal malignancies worldwide [4, 10, 11]. The incidence varies depending on the geographic location, showing predominance in Thailand with 80 cases per 100,000 population (for comparison: 1.7 per 100,000 in the USA) [5, 10, 11].

For a reason unknown, the incidence of ICC has drastically increased over the past decades, while extrahepatic cholangiocarcinoma incidence is decreasing. It may be partly due to a change in the International Classification of Diseases (ICD). An attribution of improved diagnostic methods and tumor detection seems to be unlikely, since there is no change in the proportion of early tumor stages. It may rather be related to a simultaneously increasing rate of certain risk factors [3-

7, 10, 11], the distribution of which also varies depending on the geographic location [9]. While in Western countries the main factors are primary sclerosing cholangitis (PSC) and fibropolycystic liver disease, in East-Asian countries, hepatitis B virus (HBV) appears to be the dominant etiology for ICC [3, 5, 6, 10, 12]. Recently, some studies have suggested an impact of non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD) and hepatitis C and B, as well as metabolic syndrome in developing ICC. Other established and associated risk factors are listed in Table I [3, 5-7, 10-14].

Only in a small number of cases can a specific factor be identified [3, 12], which is why there is no chance for a targeted surveillance in a population with predisposing conditions. Diagnosis of ICCs in an early stage is challenging because of anatomic location and growth patterns as well as the lack of specific symptoms [1, 5, 10]. Most ICCs are diagnosed by chance or from arising symptoms in advanced stage disease [10].

The only potential curative treatment option for this rare cancer is a partial hepatectomy, limited to early stages. Despite improved surgical and perioperative management, the prognosis remains unsatisfactory with high rates of recurrence. Three- and 5-year overall survival rates for all patients are 30% and 18%, respectively [1, 4, 15, 16]. In addition, there is no consensus regarding a staging system and prognostic factors, which makes it even harder to compare different treatment strategies.

CLINICAL PRESENTATION AND DIAGNOSIS

The silent clinical character and unspecific presentation of ICCs means that a thorough diagnostic investigation including clinical and radiologic examination, and serologic assessment is required. As mentioned above, ICCs mostly present mass-forming growth patterns. Thus, a broad range of different mass-forming liver lesions have to be considered during the differential diagnosis. Most important differential diagnosis includes HCC and metastases from other primary cancer sites. The diagnosis of an ICC remains a diagnosis of exclusion, requiring an accurate diagnostic approach.

Signs and symptoms

The clinical presentation is mostly nonspecific and, compared with extrahepatic cholangiocarcinomas, a presentation with obstructive jaundice is rarely seen. Patients with an early stage disease are usually asymptomatic. Weight loss, abdominal pain, and general malaise are more frequently reported, while jaundice and cholangitis do not manifest until the hilar infiltration [1, 2, 7, 17]. Less common symptoms that may occur in advanced stages are hepatomegaly, night sweats, and ascites, especially when the cancer arises from peripheral, small bile ducts. However, in general, the disease remains silent until an advanced stage. Thus, it is not surprising that ICCs diagnosed incidentally occur in 12–30% of cases and are asymptomatic in up to 30–73% of all diagnosed cases [2, 18-21]. This nonspecific and aggressive behaviour leads to a reported unresectability at presentation in half of all patients [20, 22].

Serologic tests

Laboratory tests are only suitable to a limited extent, mainly because of the nonspecific findings in patients with ICC. Several elevated laboratory parameter may be suggestive, but not diagnostic for an ICC. Serum bilirubin is mostly normal or slightly elevated, and serum aminotransferases and the international normalized ratio (INR) tend to be elevated in advanced stages due to hepatocellular damage [2, 23]. Elevated levels of alkaline phosphatase (ALP), pre-albumin (PA), carbohydrate-antigen (CA) 19-9 and carcinoembryonic antigen (CEA) may be helpful in approaching a diagnosis, but cannot be used as screening test for surveillance. Elevated, they are independent prognostic markers associated with worse prognosis [2, 6, 11, 24, 25].

The diagnostic utility of CA 19-9 and CEA is limited due to their low sensitivity (50–63% and 15–68%, respectively). In addition, CA 19-9 can be significantly elevated in other malignancies and in inflammatory and infectious conditions [1, 2, 5, 7, 14, 26]. A study revealed a specificity for biliary malignancies of only 42% in patients with cholangitis and cholestasis using a cut off value of >37 U/mL [26]. By increasing the value to >300 U/mL, an acceptable specificity of 87% was reached, but at the expense of a low sensitivity (40%) [2, 26]. Furthermore, 5–10% of the population shows a Lewis-negative blood-group phenotype. Since the expression of CA19-9 requires the Lewis-blood group antigen, the marker will not be elevated regardless of the tumor burden [2]. In all patients presenting a solid liver lesion, alpha-fetoprotein (AFP) should be assessed. Increased levels are more likely in patients with HCC than with ICC, but can also be found in rare cases of combined hepatocellular and cholangiocarcinoma [2, 7].

Thus, tumor markers by themselves are mostly inconclusive and have to be seen in the diagnostic context. However, if assessed critically, they may be useful for a differential diagnosis, especially in relation to HCCs, and can be useful in early detection of recurrence after therapy [2].

Table I. Associated risk factors for cholangiocarcinoma

Microbiologic	Inflammatory	Congenital	Other
Opistorchis viverrini	PSC	Caroli's disease	NAFLD
Clonorchis sinensis	Hepatolithiasis	Congenital hepatic fibrosis	Obesity
HBV	Crohn's disease	Choledochal cyst	Smoking
HCV	Colitis ulcerosa	Bile duct adenomas	Type II diabetes
HIV	Biliary cirrhosis	Biliary papilomatosis	Alcohol abuse
			Chemical noxes

HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; NAFLD: non-alcoholic fatty liver disease; PSC: primary sclerosing cholangitis.

Imaging assessment

Imaging studies are very important for the diagnosis of ICCs as well as for planning management strategies, especially when evaluating a currative resectability. The enhancement characteristics may vary depending on the different subtypes, and the assessment is even more challenging in patients with a cirrhotic liver [10].

Ultrasonography is the usual modality of choice, which is used for a first impression in patients with unclear abdominal complaints. The mass-forming subtype usually appears as a homogeneous, hypoechoic lesion, while the periductal-infiltrating subtype presents as a small mass-like lesion or as a diffuse biliary tract thickening [8, 17, 27]. However, ultrasound is limited because of nonspecific findings and, therefore, it is not capable of differentiating ICCs from HCCs or metastases [28, 29]. Ultrasound alone cannot be recommended for a diagnosis or for surveillance [5, 30], and if a suspect lesion is detected by ultrasonography, further cross-sectional imaging is required for confirmation.

Dynamic computer tomography (CT) and magnetic resonance imaging (MRI) have been shown to be of equal value regarding the detection of satellite lesions as well as in the distinction between ICCs and HCCs for lesions >2 cm. In the detection of arterial and portal vein infiltration, CT proved to be a useful modality and superior to MRI, for which the value in detecting lymph node metastases is limited due to low sensitivity (54%) [5, 8, 31, 32].

The mass-forming subtype appears in CT scans as a hypodense lesion with irregular margins. In most cases, a rim-like enhancement in the arterial phase is shown followed by a progressive hyperattenuation in the portal venous phase. The typically maximum enhancement during the delayed phase is in contrast to the features of HCC, and may help to distinguish between ICC and HCC. An HCC presents with rapid early enhancement followed by a washout on the delayed phase, whereas an ICC may present with central diffuse hypoenhancement due to fibrotic remodeling, capsular retraction caused by liver atrophy (21–36% of all cases), dilated bile ducts distal to the mass, or satellite nodules [1, 8, 10, 17, 27, 33-35]. The periductal-infiltrating subtype appears similar to the mass-forming type, except for the periductal location. This subtype is characterized by diffuse periductal thickening and may present with peripheral bile duct dilatation [10, 27, 36]. The intraductal subtype usually presents with diffuse ductal dilatation and an intraductal polypoid lesion may also be seen [8, 10, 27, 36].

On MRI scans, ICCs appear hypointense on T1-weighted images and heterogeneously hyperintense in T2-weighted images with a central hypointensity due to fibrotic remodeling and necrosis in mass-forming subtypes. The contrast-enhanced MRI is characterized by peripheral enhancement followed by progressive centripetal filling and contrast pooling on delayed images. Periductal-infiltrating subtypes appear with an enhanced ductal dilation, while the intraductal subtype can occur with different features [7, 8, 17]. In addition, MRI with cholangiopancreatography (MRCP) may be helpful in evaluating the intra- and extrahepatic bile ducts, as well as vascular structures [2, 17].

The diagnostic value of positron emission tomography (PET)-CT remains controversial. While this type of imaging has a sensitivity of about 85–94% in detecting mass-forming ICCs with a size >1 cm, the sensitivity in other subtypes is poor (18%) [5, 7, 10, 17]. Some studies suggest a limitation in patients with inflammatory or infectious conditions, and the sensitivity of regional lymph node detection remains poor (13–38%) [5, 7]. Thus, the performance of PET-CT in relation to CT and MRI has been questioned. However, some studies revealed that PET-CT was able to detect occult metastases in 20–30% of all patients, which have not been identified by CT or MRI, leading to treatment modification in 17–30% of all cases [8, 17, 37-39].

Radiographic imaging may be useful in approaching an accurate diagnosis, especially when different modalities are combined. However, it remains particularly inconclusive in patients with a cirrhotic liver or small mass-forming tumors, which may mimic HCCs [2, 7, 11].

Additional assessment

Considering that secondary metastases are more common than ICCs, a thorough evaluation to rule out other primary malignancies is required. This should include assessment of cross-sectional imaging of the chest, abdomen, and pelvis, as well as an esophagogastroduodenoscopy (EGD) and colonoscopy to exclude a primary tumor in the lungs, colon, rectum, esophagus, or stomach. Furthermore, a gynecologic evaluation and a mammography to assess breast cancer should be performed [7, 10].

Depending on the clinical setting, a liver biopsy may be needed, the decision of which should be based on evaluation of whether the benefit of the histopathologic findings outweighs the disadvantages and risks. The most common techniques for approaching a sample of the suspect lesion is either performing a brush cytology during an endoscopic retrograde cholangiopancreatography (ERCP) or an endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). Brush cytology is quick, simple, and safe to use, which are advantageous attributes, while the EUS-FNA can lead to seeding of the biopsy canal with malignant cells. However, compared with the sensitivity of EUS-FNA (up to 83%), the sensitivity for brush cytology has been described as unsatisfactorily low (30–60%) [40-42]. Recently, in the course of improved brush design and cytologic protocols, an increased sensitivity of 74% for brush cytology was described in a small group of patients [41, 43, 44].

Adenocarcinoma is the most common histologic finding in ICCs and can be difficult to distinguish from metastatic adenocarcinomas. However, the accuracy may be improved by immunohistochemical evaluation. Negative findings in TTF1 (lung), CDX2 (colon), DPC4 (pancreas), and positive findings in AE1/AE3, CK7, and CK20 (biliary epithelium) suggest an ICC diagnosis [1, 17]. Considering potential complications such as tumor spread and hemorrhage, a liver biopsy is neither recommended nor required in noncirrhotic patients undergoing a curative resection [1, 2]. However, patients not fulfilling the limitations for a partial hepatectomy, and therefore in need of systemic radio- or chemotherapy, require a liver biopsy. Due to the differences in the oncobiologic features,

systemic therapy and further management differs between HCCs and ICCs [1, 17].

STAGING SYSTEMS AND PROGNOSTIC MODELS

Considering the rarity and increasing mortality of ICCs, a consensus and universally applicable staging system would be essential in improving the treatment and poor outcome. Unfortunately, there is currently no consensus regarding a staging system for ICC. Independent prognostic factors are still considered controversial, and different staging systems as well as prognostic models have been proposed. Therefore, comparison of clinical trials and treatment strategies of different centers is still difficult to do, and the selection of an appropriate treatment strategy due to a variety of statements and recommendations is demanding. Historically, ICCs were staged the same as HCCs, but in the course of understanding their different clinicopathologic features, the need for a distinct staging system was realized. Currently, there are four main staging systems for ICCs, two Eastern and two Western; the characteristics for each are described in Table II.

Okabayashi et al. proposed their ICC staging classification based on a small group of 60 patients with a mass-forming subtype [19]. Noteworthy, 33% of all patients showed evidence of a HBV or HCV infection. Using their identified, independent, negative prognostic factors, 'T' was classified according to the tumor number and the presence of hepatic or portal vein invasion. Tumor number was found to have a greater impact on the survival than vein invasion, whereas the presence of both was found to be unrelated to survival. Additionally, a close relationship was found between vascular invasion and abnormal levels of liver enzymes. Presence of hepatic regional lymph node metastasis was defined as N1 and distant metastasis as M1, although patients with distant metastases were excluded from the study. Another significant factor in the multivariate analysis of overall survival was the presentation of a symptomatic tumor boundary, although this was not incorporated in the staging system. Tumor size failed to show a significant impact, which is most likely due to the small sample size (only three patients in the smallest tumor size category). Taking all mentioned TNM-factors into account, patients were stratified in different staging groups (stage I–IV) (Table III) [18].

In 2002, the Liver Cancer Study Group of Japan (LCSGJ) proposed a classification based on 136 patients with mass-forming ICCs [9]. In agreement to the published staging system of Okabayashi et al., they identified tumor number, portal or hepatic vein invasion, and regional lymph node metastasis as significant prognostic factors. The N and M factors were defined as per the Okabayashi's staging system. However, in contrast, the LCSGJ also found that serous membrane invasion and tumor size with a threshold of 2 cm were significant independent predictors. The T factor was classified based on three requirements: no vein or serous membrane invasion, tumor size ≤2 cm, and solitary tumor (Table III). After evaluating the different factors, the patients were stratified in stages I–IV (Table III). Although the difference between the survival rate of stage II and III was shown to be significant, the staging system failed to show any significant differences between stages I and II, as well as between stages III and IV [9]. Furthermore, the T stages failed to provide any differences in

Table II. Characteristics of the different staging systems

	Okabayashi	LCSGJ	Nathan	AJCC/UICC 7th
Number of patients	60	136	598	598
Years	1981-1999	1990-1996	1988-2004	NM
Race	Japanese	Japanese	Western	Western
Subtypes	Mass-forming	Mass-forming	All	All
Prognostic factors (worse survival)				
Tumor size	No	>2 cm	No	No
Tumor number	≥2	≥2	≥2	≥2
Vascular invasion	Yes	Yes	Yes	Yes
Visceral peritoneum invasion	No	Yes	NM	Yes
Symptomatic tumor	Yes	NM	NM	NM
Lymph node metastases	Yes	Yes	Yes	Yes
CEA preoperative	>5 ng/mL*	NM	NM	NM
ALP preoperative	>300 IU/mL*	NM	NM	NM
CA 19-9 preoperative	No	NM	NM	Yes
R1 resection	No	No	NM	Yes
Periductal growth pattern	NM	NM	NM	Yes
PSC	No	NM	NM	Yes

NM: Not mentioned in the original publication; yes: significant prognostic factor; no: no significant impact on survival; *only significant prognostic factor in univariate analysis.
ALP: alkaline phosphatase; CA: carbohydrate antigen; CEA: carcinoembryonic antigen; LCSGJ: Liver Cancer Study Group of Japan; PSC: primary sclerosing cholangitis;

Table III. Different classifications

	AJCC/UICC 7th	Nathan	LCSGJ	Okabayashi
T1	Solitary tumor, V0	Solitary tumor, V0	Meets 3 of 3 requirements*	Solitary tumor, V0
T2		Solitary tumor V1 or multiple tumor V0-1	Meets 2 of 3 requirements*	Solitary tumor, V1
T2a	Solitary tumor, V1			
T2b	Multiple tumors, V0-1			
T3	Invasion visceral peritoneum	Extrahepatic extension	Meets 1 of 3 requirements*	Multiple tumors, V0-1
T4	Periductal invasion		Meets 0 of 3 requirements	
Stage				
I	T1N0M0	sT1N0M0	T1N0M0	Solitary tumor V0
II	T2N0M0	sT2N0M0	T2N0M0	Solitary tumor V1
		sT3N0M0		
III	T3N0M0	sT1-3N1M0	T3N0M0	
IIIA				Multiple tumors, V0-1
IIIB				Any tumor, N1
IV		sT1-4N0-1M1		Any tumor, M1
IVA	T1-4N0M0		T4N0M0	
	T1-4N1M0		T1-4N1M0	
IVB	T1-4N0-1M1		T1-4N0-1M1	

LCSGJ: Liver Cancer Study Group of Japan; V1: Venous invasion; *requirements: tumor size ≤ 2cm, solitary tumor, no invasion (serosa, vein).

survival between the T categories, although this was improved by omitting serous membrane invasion [1, 5, 45, 46].

Nathan et al. proposed the first staging system to use data from Western patients with all subtypes of ICC [45]. As mentioned in the previous staging systems, regional lymph node metastasis, venous invasion, and tumor number were found to be independent predictors for worse survival. The impact of venous invasion and tumor number was similar, with no synergistic effect or interaction between them. In addition, patients with metastatic disease in three or more lymph nodes had a significantly worse outcome, which was already suggested by Japanese data [45, 47]. However, N1 was defined as the presence of at least one positive regional lymph node and M1 as the presence of a distant metastasis. The main difference to the proposed staging system of Okabayashi et al. was that patients with a solitary tumor and vascular invasion were not separated from patients with multiple tumors (Table III). Furthermore, in contrast to the staging system of LCSGJ, tumor size was omitted from Nathan et al.'s new staging system. In this study, tumor size had no impact on survival, neither with a threshold of 2 cm nor with a threshold of 5 cm. To compare the discriminative capabilities of the three staging systems, the c-indices were calculated. The T classification system of Nathan et al. was comparable to the system of Okabayashi (c=0.61 vs. c=0.59), and significantly better than the LCSGJ classification (c=0.51), whereby the stage groupings were comparable [45]. The study was performed using the database from the Surveillance, Epidemiology, and End Results (SEER) Program. This database provides access to a large population, but is also limited in the collected components. For instance, no differentiation of the subtypes was recorded. Therefore, a statement regarding other predictors is critical, considering that some significant factors may not be recorded [45].

Based on the findings of Nathan et al., the AJCC proposed the 7th edition of the staging manual, which is the first edition specifically based only on ICC patients using the SEER database. According to the previously mentioned staging systems, vascular invasion, regional lymph node metastasis, and tumor number were identified as independent prognostic factors. Besides vascular invasion and tumor number, periductal invasion and invasion of the visceral peritoneum were found to be significant predictors and, therefore, were included in the T classification. The invasion of the visceral peritoneum was already mentioned by the LCSGJ classification, whereas periductal invasion or periductal growth pattern were not mentioned in any of the previous staging systems. By adapting the proposal of Nathan et al., tumor size was omitted from the new staging system. Elevated CA19-9 levels and underlying PSC were also identified as other predictive factors. Additionally, they proposed a new macroscopic classification system, which differs slightly from the established classification by the LCSGJ; the three proposed subtypes are mass-forming, periductal-infiltrating, and a mixed form of both subtypes [48, 49].

In 2010, the AFC-IHCC-2009 study group published an evaluation and comparison of these four staging systems in a cohort of 163 patients with resectable, mass-forming ICCs [49]. The study revealed that the AJCC 7th edition staging system was the only classification to achieve significant discrimination between the different stages [49]. However, a Japanese group found poor stratification between stages II and III, and Doussot et al. revealed a worse outcome for stage II than for stage III

[16, 24]. One cause of this might be the underestimation of the effect of multiple tumors. The presence of multiple tumors is determined by T2b and, therefore, in the absence of lymph node metastases, is classified as stage II. However, the impact of intrahepatic metastasis or satellite lesions might be greater than the impact of visceral peritoneum invasion (T3) on the survival [14, 24].

Prognostic models and nomograms are tools that are used for the prediction of long-term survival for individual patients. The evaluated prognostic factors are partly overlapping with factors incorporated into staging systems, partly different. There are currently four different nomograms and prognostic scores (Table IV). The Fudan score was one of the first proposed prognostic scores [25]. It is only based on preoperatively available factors and therefore can be applied to nonsurgical patients. The included prognostic factors (ALP and CA19-9 levels, and tumor number, boundary, and size) were transformed into binary variables, of which each counts as one point when fulfilled. Patients were stratified into four risk groups according to score (higher scores = worse survival rate) [24, 25]. Afterwards, the prognostic validity was assessed in 74 nonsurgical patients and was found to be superior to the AJCC 7th edition staging system. Tumor size was an independent predictor with a threshold of 10 cm. However, an important limitation of this score was the highly subjective assessment of the tumor boundary in cross-sectional imaging [50].

The prognostic nomogram proposed by Wang et al. [4] is based on linear, continuous variables (preoperative CEA and CA19-9 levels, and tumor size) as well as on dichotomous variables (vascular invasion, direct invasion and local extrahepatic metastasis, lymph node metastasis, and tumor number [1, 2–3, and >3 nodules]). Every factor is weighted with a different impact, which results in a different number of points (e.g. lymph node metastasis = 40 points; vascular invasion = 27.5 points). In agreement with the Fudan score, tumor size was identified as a significant predictor for a worse survival rate. The prognostic validity, which was assessed using the c-index in 84 patients who underwent surgical resection, was significantly higher for the Wang nomogram (c=0.75) than the AJCC 7th edition (c=0.60), Nathan (0.60), LCSGJ (c=0.63), and Okabayashi (c=0.63) staging systems. However, 52.4% of the validation group had a background of HBV infection, which is much higher than in Western cohorts [4, 13, 24].

Hyder et al. [13] proposed the first score based on a multiethnic population with data from Asia, Europe, and the USA. In contrast to the Wang nomogram, age and tumor size were seen as nonlinear predictive factors, whereas the effect of tumor size was linear below a cut-off value of 7 cm. Number of tumors was transformed into a binary variable; nodal status, vascular invasion, and liver cirrhosis were seen as categorical variables, even though liver cirrhosis was not proven to be a significant prognostic factor. Similar to the Wang score, the factors were weighted based on their presumed impact on overall survival. The prognostic validity of the Hyder nomogram was found to be superior (c=0.69) to the AJCC 7th edition (c=0.59) staging system. In addition, the earlier statement of this group [45] regarding the impact of tumor size on the outcome was revised. Furthermore, it was found that the significant impact of tumor size plateaued behind the threshold [13].

The most recent prognostic staging system to be proposed was published by Zhou et al. in 2015 [6]. Similar to the Fudan score, the significantly independent predictors for overall survival (vascular invasion, regional lymph node metastasis, local extrahepatic metastasis, tumor number, level of prealbumin, and CA19-9 as well as CEA) were transformed into binary variables. According to the total risk score (0–7 points), patients were stratified into four groups. In contrast to the other prognostic models, tumor size (≥5 cm) was found not to be a significant predictor in the multivariate analysis. The predictive accuracy of this scoring system was shown to be superior to that of the AJCC 7th edition staging system,

Table IV. Characteristics of the different prognostic models

	Fudan 2011	Wang 2012	Hyder 2014	Zhou 2015
Population	Chinese	Chinese	Multiethnic	Chinese
Number of patients	344	367	514	370 + 115
Binary variables	Yes			Yes
Tumor number	≥2	Yes	Yes	≥2
Vascular invasion		Yes	Yes	Yes
Lymph node metastasis		Yes	Yes	Yes
Tumor size	≥10	Yes	Yes	
CA 19-9 ug/L	>37	Yes		>39
CEA ug/L		Yes		>10
Direct invasion/metastasis		Yes		Yes
ALP U/L	>147			
Tumor boundary	Obscure			
Age			Yes	
Liver cirrhosis			Yes	
Prealbumin mg/L				≥ 170

ALP: alkaline phosphatase; CA: carbohydrate-antigen; CEA: carcinoembryonic antigen

considering that 49.1% of patients had a background of HBV infection [6].

Doussot et al. [24] compared and evaluated the prognostic validity of the Wang and Hyder nomograms, the Fudan score, and AJCC 7th edition staging system using a Western study population. Wang's nomogram demonstrated the highest survival prediction accuracy (c=0.72) when compared with Hyder (c=0.66), the AJCC 7th edition (c=0.63), and the Fudan score (c=0.55) [24]. The survival prediction of the Fudan score was inadequate [24]; however, it is a simple score, which can also be applied to patients with unresectable tumors. The Wang nomogram had the best overall prognostic accuracy, even though it was developed using an Eastern population [24]. The only disadvantage might be a difficult clinical application because of the requirement for assessing many variables, such as portal lymph node dissection and preoperative tumor markers [24].

Even though tumor markers are not incorporated in any of the current staging systems, many studies confirmed the independent association of CEA and CA19-9 with a worse survival rate [4, 6, 24, 25, 50]. Adachi et al. and Nakagawe et al. found C19-9 to be an independent predictor for regional lymph node metastases (LNM) [47, 51].

Lymph node metastasis was found to be a strong independent predictor, and was therefore included in all staging systems and most nomograms. Patients with LNM had an extremely poor outcome, regardless of a performed lymph node dissection [4, 6, 9, 10, 13, 16, 19, 45, 48, 52]. However, the current staging systems only assess the presence or absence of LNM, although some studies suggest that there might be a further important impact regarding the number of affected lymph nodes [45, 48, 52, 53].

Venous invasion as well as number of tumors were also found to be independent factors in many different multivariate analyses and were therefore included in all staging systems and most nomograms [4, 6, 9, 13, 16, 19, 45, 48, 54-56]. A synergistic effect of multiple tumors and venous invasion on the survival, however, is considered controversial [16, 45].

Additional controversial factors with respect to their impact on the overall survival include serous membrane invasion, periductal growth pattern and, in particular, tumor size. Although serous membrane invasion is incorporated in the LCSGJ and AJCC 7th edition staging systems, various studies could not confirm a significant impact on the overall survival in multivariate analysis. Uenishi et al. even proposed to omit this variable from the LCSGJ staging system, and other studies revealed an improved stratification between different stages when omitting serous membrane invasion [1, 5, 9, 16, 45-49, 55-57]. Periductal growth pattern was only incorporated in the AJCC 7th edition staging system, whereas several studies showed no significant association with a worse survival rate after resection [16, 48, 49, 54, 57]. Igami et al. even suggested an elimination of this variable as a T stage determinant [57].

Tumor size remains one of the most controversial variables. The LCSGJ staging system is the only staging system that takes tumor size into account, but it is also incorporated in the Fudan, Wang, and Hyder scoring systems. The impact of tumor size was mostly evaluated with a certain threshold, but Hyder et al. revealed a more nuanced, nonlinear effect [13]. DeOliveira et al. found no impact on survival, whereas several other studies suggested tumor size to be an independent predictive factor [1, 17, 21, 22, 53, 58].

CONCLUSION

Intrahepatic cholangiocarcinoma is a rare and aggressive malignancy with an increasing incidence. The diagnosis remains a challenge due to a lack of early symptoms and nonspecific findings. Nomograms may be useful as complementary tools to staging systems for making treatment management decisions, whereby surgical resection is still the only curative treatment. Staging systems mainly distinguish in the determination of the 'T' category, but none of them demonstrated a satisfactory stratification for all of the different stages.

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