

Intrahepatic cholangiocarcinoma: macroscopic type and stage classification

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Abstract

The Liver Cancer Study Group of Japan established a classification of macroscopic type and the TNM staging of intrahepatic cholangiocarcinoma (ICC). With the observation of more than 240 resected cases of ICC, three fundamental types were established. They were: (1) mass-forming (MF) type, (2) periductal-infiltrating (PI) type, and (3) intraductal growth (IG) type. The MF type forms a definite mass, located in the liver parenchyma. The PI type is defined as ICC which extends mainly longitudinally along the bile duct, often resulting in dilatation of the peripheral bile duct. The IG type proliferates toward the lumen of the bile duct papillarily or like a tumor thrombus. The TNM classification of ICC was then designed, using 136 cases of the MF type resected curatively between 1990 and 1996 at member institutes. Univariate and multivariate analyses showed: (1) tumor 2 cm or less, (2) single nodule, and (3) no vascular and serous membrane invasion as prognostic factors. T factors were defined as follows: T1 is an ICC that meets all requirements of factors (1), (2), and (3); T2 meets two of the three requirements, T3 meets one of the three requirements and T4 meets none of the three requirements. Our data did not support the idea that the hepatoduodenal lymph node is regional. The N factors were defined as N0 no lymph node metastasis; and N1, positive at any nodes. Thus, the stages of ICC were defined as stage I, T1N0M0; stage II, T2N0M0; stage III, T3N0M0; stage IVA, T4N0M0 or any TN1M0; and stage IVB, any T any NM1.

Key words Intrahepatic cholangiocarcinoma · Macroscopic type · TNM classification

Background

Although intrahepatic cholangiocarcinoma (ICC) accounts for only 5% or less of primary liver cancers¹ in recent years, with advances in diagnostic modalities, the

number of patients with ICC at an operable stage has been increasing. ICC has wide variations in clinico-pathologic features. When we surgeons construct a strategy of operation for ICC, we have to understand the clinical type of ICC. A macroscopic type classification for ICC has been desired.

A staging system for primary liver cancer was first published in 1987 by the International Union Against Cancer (UICC) in the third version of the TNM classification, which was followed, in the latest, fifth version, with minor amendments. This system of staging included both hepatocellular carcinoma (HCC) and ICC. But this system was established considering only HCC, which accounts for more than 90% of primary liver cancers. The biological behaviors of HCC and ICC are different. The oncologic natures of the two primary cancers are different. A classification for TNM staging specific to ICC has been desired, and the Liver Cancer Study Group of Japan (LCSGJ) intended to establish an ICC staging system. In 1992, the LCSGJ organized a committee to establish a macroscopic type classification and a staging system for ICC. The author played the role of chairman of the ICC committee, and here we propose classifications of macroscopic type and a staging system for ICC.

Among cholangiocarcinomas, ICC is defined as that which originates at the second branch (segmental branch) or the proximal branch of the bile duct.² Cholangioma that originates at the hepatic duct (the first branch, lobular branch of the bile duct) or at the common bile duct is defined as extrahepatic cholangiocarcinoma.

Macroscopic type of ICC

Materials and methods

The ICC committee of the LCSGJ collected 245 resected cases of ICC from the leading institutes of

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hepatic surgery in Japan for macroscopic type classification. The cases were classified according to the macroscopic shape on the largest cross-section of the operative specimen, and after long discussion and debate, three fundamental types were established.

Results

The three basic types of ICC were: (1) mass-forming (MF) type, (2) periductal-infiltrating (PI) type, and (3) intraductal growth (IG) type.² The schematic and basic forms of the three types are shown in Fig. 1. The MF type forms a definite round-shaped mass, located in the liver parenchyma, and not invading a major branch of the portal triad. The PI type is characterized by tumor that extends mainly longitudinally along the bile duct, often resulting in dilatation of the peripheral bile duct. The tumor mass itself is often not visualized by imagings. The IG type proliferates toward the lumen of the bile duct papillarily or like a tumor thrombus, occasionally involving superficial extension. This type of ICC is usually detected in a thick bile duct. "Unclassified" was added as a fourth category. When the tumor has more than one component of the three basic types, the predominant type is described first and the less dominant component follows, connected by "+", e.g., "MF + PI". Some clinical examples of the three macroscopic types are shown in Fig. 2.

Staging system for ICC

Materials and methods

In 1996, the ICC committee of the LCSGJ started work to establish a TNM classification of ICC. For this purpose, the committee collected resected cases of ICC from the member institutes of the committee. Considering the rapid advances in diagnostic imaging modalities,

the eligibility criteria of the cases for this study were as follows: (1) cases resected between 1990 and 1996, (2) resection was curable, and (3) cases without distant metastasis. A total of 173 cases eligible according to the criteria were obtained from nine institutes. Of the cases collected in this study, the number of cases of each macroscopic type were: 136, 27, and 10 for the MF type (including MF-dominant type), PI type, and IG type, respectively. In this study, for the staging system, the cases of PI and IG types of ICC were excluded because of the small number of cases. So this staging system for ICC was applied just to the MF type, tentatively.

Results

Several anatomic prognostic factors related to cancer were identified by univariate and multivariate analyses. Factors related to host (sex, age, liver function, and others) and treatment (surgical margin, extent of resection, and others) were not significant. Tumor size 2 cm or less (hazard ratio [HR], 2.39; 95% confidence interval [CI], 18.06–0.32), lymph node metastasis (HR, 2.36; 95% CI, 4.33–1.28), number of nodules, solitary or multiple (HR, 1.93; 95% CI, 3.18–1.17), serous membrane invasion (HR, 2.19; 95% CI, 3.60–1.33), portal vein invasion (HR, 1.68; 95% CI, 2.88–0.98), and hepatic vein invasion (HR, 1.18; 95% CI, 2.16–0.65) were judged to be statistically significant positive factors for predicting death. On the basis of the results above, T factors were proposed, as follows: T1 is a tumor that is (1) solitary, (2) 2 cm or less, and (3) without portal and hepatic vein and serous membrane invasion. T2 is a tumor with two of these three requirements, T3 is a tumor with one of these three requirements, and T4 is a tumor with none of these three requirements (Table 1). The TNM

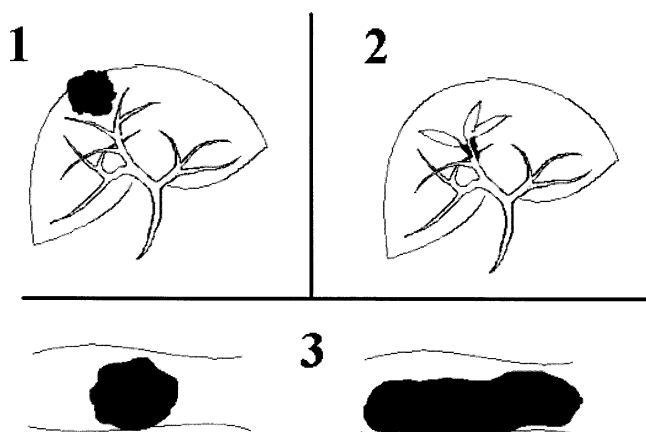


Fig. 1. Three fundamental macroscopic types of intrahepatic cholangiocarcinoma. 1, mass-forming type; 2, periductal-infiltrating type; 3, intraductal growth type

Table 1. Proposed definition of T, N, and M factors for intrahepatic cholangiocarcinoma

T Factor

- T1: meets all three requirements below.
- T2: meets two of the three requirements below.
- T3: meets one of the three requirements below.
- T4: meets none of the three requirements below.

Requirements	Description
Number of tumors	Solitary
Size of tumor	2 cm or less
Negative invasion	Portal vein, hepatic vein, serous membrane

N Factor

- N1: no metastasis to lymph node.
- N0: metastasis to any lymph nodes.

M Factor

- M0: no distant metastasis.
- M1: positive distant metastasis.

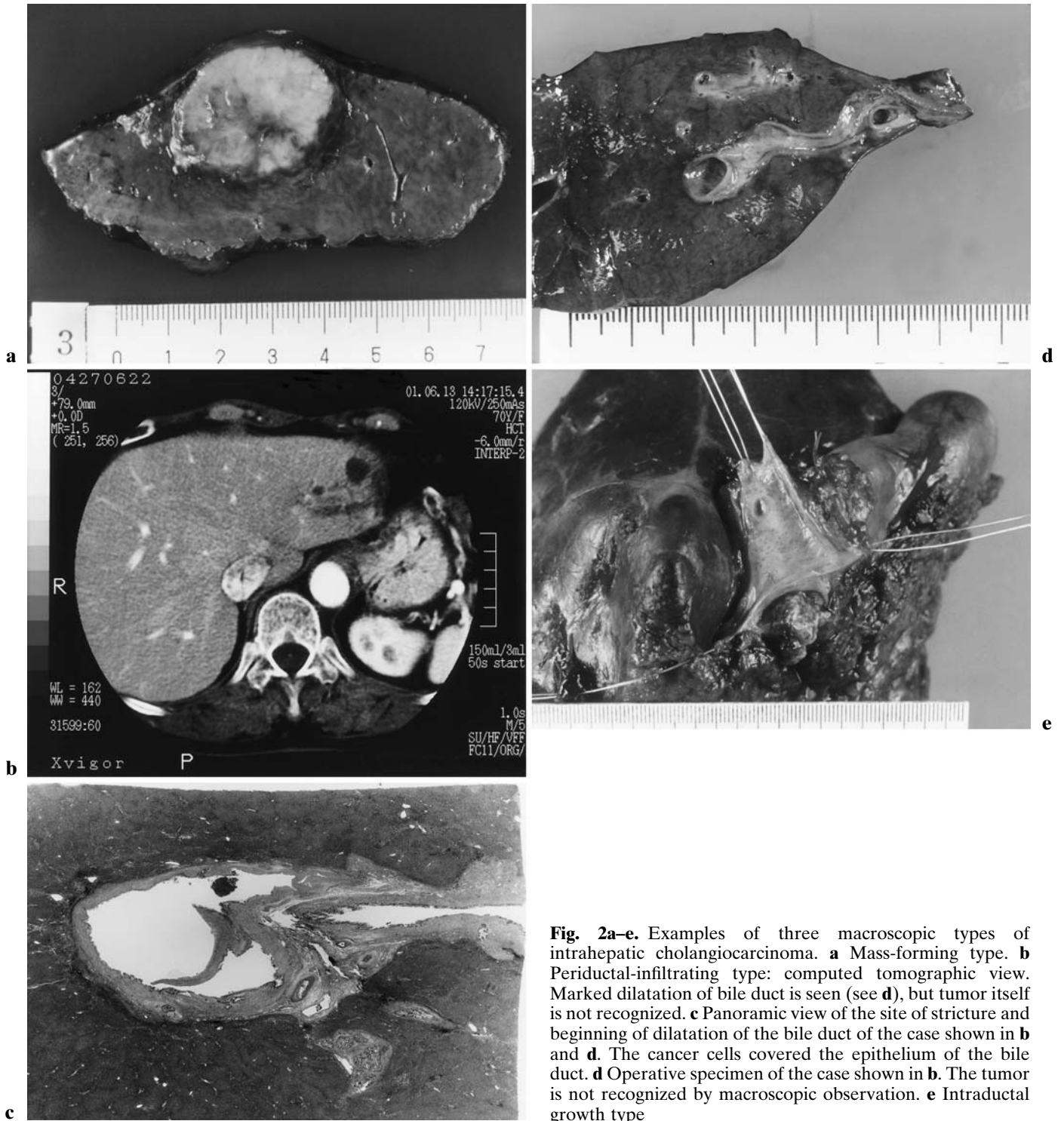


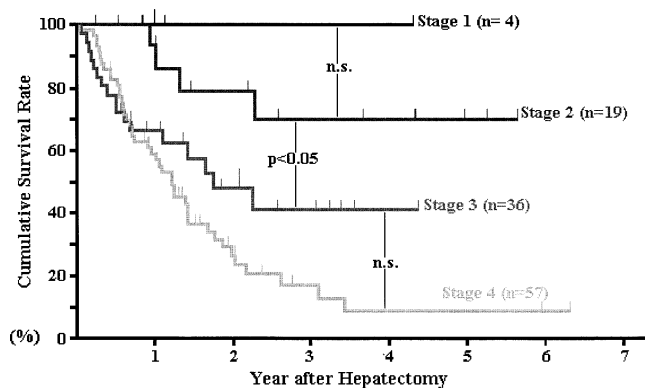
Fig. 2a-e. Examples of three macroscopic types of intrahepatic cholangiocarcinoma. **a** Mass-forming type. **b** Periductal-infiltrating type: computed tomographic view. Marked dilatation of bile duct is seen (see **d**), but tumor itself is not recognized. **c** Panoramic view of the site of stricture and beginning of dilatation of the bile duct of the case shown in **b** and **d**. The cancer cells covered the epithelium of the bile duct. **d** Operative specimen of the case shown in **b**. The tumor is not recognized by macroscopic observation. **e** Intraductal growth type

classification of the UICC defines the regional lymph nodes of the liver as those at the liver hilum and the hepatoduodenal ligament. In this study, it was suggested that lymph node metastasis is a strong prognostic factor of ICC; however, it could not be documented that regional lymph nodes as defined by the UICC were the

most frequent sites of metastasis, and the prognosis of the patients with positive regional lymph node metastasis (N1) was better than that of patients with positive distant lymph node metastasis (N2). Only the fact that any positive lymph node metastasis made the prognosis of the patient definitely worse than negative lymph

Table 2. Proposed staging system for intrahepatic cholangiocarcinoma

	T	N	M
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
State IVA	T4	N0	M0
	Or any T	N1	M0
Stage IVB	Any T	Any N	M1

**Fig. 3.** Survival rates of intrahepatic cholangiocarcinoma (ICC) according to the proposed TNM classification. *n.s.*, Not significant

node metastasis was certain. Thus, new T and N classifications were proposed, as noted in Table 1, and a new staging system was proposed, as noted in Table 2. The survival rates of ICC patients who underwent curative resection are shown in Fig. 3.

Discussion

A macroscopic type is recognized visually, not by quantitative judgment. The classification of the macroscopic type was determined rather subjectively. We expect this classification of macroscopic type to be evaluated after many clinicians have used this classification.

In the past, articles that mentioned prognostic factors of ICC treated surgically were few.³⁻⁵ The number of cases analyzed in the past articles was 30 or less, which was not enough to reach a definite conclusion. As the oncologic behaviors of the two primary cancers, HCC and ICC, are different, we anticipated that the appearance of the new staging system for ICC may be different from that for HCC. Contrary to our expectations, the classification of the TNM staging for ICC proposed here is similar to that for HCC. The difference was that serous membrane invasion was a positive prognostic factor in ICC, but not in HCC. Vascular invasion was a

positive prognostic factor in both HCC and ICC; however, we have to understand that the modes of vascular invasion of HCC and ICC are different, as HCC forms a tumor thrombus in vascular structures, whereas ICC infiltrates into the walls of vessels. With the HCC staging system, there are three types each of T2 and of T3. Most T2 types are those with solitary tumor more than 2 cm and without vascular invasion. The other two types of T2, “multiple tumors 2 cm or less and without vascular invasion” and “solitary tumor 2 cm or less with vascular invasion” were not found in our series. In regard to T3, the type with multiple tumors 2 cm or less with vascular invasion, was also not found in our series. The current TNM classification of liver cancer defines the lymph nodes at the liver hilum and at the hepatoduodenal ligament as regional lymph nodes. Nozaki et al.⁶ reported that the lymph node metastasis pattern of the UICC TNM classification, at least with respect to the regional lymph nodes, should be reconsidered. In this study, we also did not find any reason why the regional lymph nodes of primary liver cancer should be defined as the lymph nodes at the hepatoduodenal ligament.

As shown in Fig. 3, the differences in survival rates between any two neighboring stages are not always significant. The number of cases of ICC that can be collected by a single institute, especially resectable cases, has been too small to be analysed statistically. Although this was a multiinstitutional study, the number of the subjects was still not enough to obtain a statistically significant difference. But separation of the survival curves was appropriate. We are tentatively using this staging system for ICC, and in future some correction may be needed.

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