

Effectiveness of repeat hepatic resection for patients with recurrent intrahepatic cholangiocarcinoma: Factors associated with long-term outcomes

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Background. Tumor recurrence after liver resection for intrahepatic cholangiocarcinoma is common. The effective treatment for recurrent intrahepatic cholangiocarcinoma remains to be established. This study evaluated the short- and long-term prognoses of patients after repeat hepatic resection for recurrent intrahepatic cholangiocarcinoma.

Methods. Data for 72 patients who underwent R0 repeat hepatic resection for recurrent intrahepatic cholangiocarcinoma at the Eastern Hepatobiliary Surgery Hospital between 2005 and 2013 were analyzed. Tumor re-recurrence, recurrence-to-death survival, and overall survival were calculated and compared using the Kaplan-Meier method and the log-rank test. Independent risk factors were identified by Cox regression analysis.

Results. Operative morbidity and mortality rates were 18.1% and 1.4%, respectively. The 1-, 2-, and 3-year re-recurrence rates were 53.2%, 80.2%, and 92.6%, respectively, and the corresponding recurrence-to-death survival was 82.9%, 53.0%, and 35.3%, respectively. The 1-, 3-, and 5-year overall survival was 97.2%, 67.0%, and 41.9%, respectively. Patients with a time to recurrence of >1 year from the initial hepatectomy achieved higher 1-, 2-, and 3-year recurrence-to-death survival than patients with a time to recurrence of ≤1 year (92.5%, 61.7%, and 46.6% vs 70.4%, 42.2%, and 23.0%, $P = .022$). Multivariate analysis identified that recurrent tumor >3 cm (hazard ratio: 2.346; 95% confidence interval: 1.288–4.274), multiple recurrent nodules (2.304; 1.049–5.059), cirrhosis (3.165; 1.543–6.491), and a time to recurrence of ≤1 year (1.872; 1.055–3.324) were independent risk factors of recurrence-to-death survival.

Conclusion. Repeat hepatic resection for recurrent intrahepatic cholangiocarcinoma was safe and produced long-term survival outcomes in selected patients based on prognostic stratification with the presence of the independent risk factors of recurrence-to-death survival. (Surgery 2016;■:■-■.)

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INTRAHEPATIC CHOLANGIOCARCINOMA (ICC) is the second most common primary hepatic malignancy,

with its global incidence increasing significantly.^{1,2} Operative resection is the only established

Supported by the State Key Project on Infectious Diseases of China (2012ZX10002-016 to FS), the Natural Science Foundation of Shanghai (12ZR1439700 to JL), and the Medical Guiding Project of Shanghai (201346801 to JL). AS and JL contributed equally to this work.

No potential conflicts of interest were disclosed.

Accepted for publication October 18, 2016.

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0039-6060/\$ - see front matter

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<http://dx.doi.org/10.1016/j.surg.2016.10.024>

treatment to achieve possible cure for ICC patients.^{3,4} Unfortunately, only about 20%–40% of potentially operable patients are offered operative resection.³ In addition, the 5-year survival after operative resection has been considered dismal due to the high incidence of tumor recurrence, which has been reported to be up to 50%–60% of patients with a median disease-free survival being 26 months.^{3,5–9} Although the liver is the most common site of tumor recurrence (eg, 50%–60%), metastasis in lymph nodes or the peritoneum is not uncommon (eg, 20%–25%).^{3,7–9}

The management of recurrent ICC (RICC) is still a challenge. Although the role of repeat hepatectomy for recurrent hepatocellular carcinoma (HCC) has been well documented, only a few studies reported the procedure in RICC patients, and the majority of the previous studies only reported one or several cases treated with reoperation (Supplementary Table I).^{10–28} The results of a multi-institutional study showed that the re-resection yielded better prognoses than systemic chemotherapy and best supportive care.²⁴

A study from our institution reported 32 RICC patients undergoing repeat liver resection and suggested the survival benefits in patients with recurrence >3 cm, but the exact effectiveness of this procedure has not been well demonstrated due to limited sample size.²⁵ Spolverato et al²⁸ showed that the combination of repeat liver resection and ablation might prolong patients' survival in 41 RICC patients. Overall, evidence supporting the effectiveness of this procedure in RICC is still insufficient.²⁹ On the other hand, the increased understanding of risk factors of ICC recurrence and improved postoperative monitoring with modern imaging studies permit diagnosis of RICC at an early stage when repeat resection is still technically possible.

In this study, we evaluated the short- and long-term prognoses of patients who were treated with repeat hepatic resection for RICC based on the data of the currently largest series.

PATIENTS AND METHODS

Patients and operative intervention. Between September 2005 and December 2013, 342 patients underwent liver resection for pathologically proven ICC at the Department of Hepatic Surgery IV and II of the Eastern Hepatobiliary Surgery Hospital (EHBH); 304 patients received an R0 resection, and of these, 210 patients developed RICC during the follow-up period. Among 133 patients who had only intrahepatic RICC, repeat hepatic resection was considered as first-line treatment in 60 patients,

and another 73 patients were treated with nonoperative multimodality options, which included percutaneous radiofrequency ablation (PRFA, $n = 20$), transarterial chemoembolization (TACE, $n = 13$), chemotherapy ($n = 9$), radiotherapy ($n = 7$), traditional Chinese medicine ($n = 3$), and a combination of nonoperative procedures with varied patterns ($n = 21$).

In addition, 25 patients with intrahepatic and resectable RICC who underwent initial operations in other hospitals were admitted in our departments and also indicated for re-resection during this period. The data of these 85 candidates of re-resection for RICC were prospectively collected and retrospectively reviewed. This study was approved by the Institutional Ethics Committee of the EHBH. Informed consent was obtained from all patients before re-resection for their data to be used for research.

Patients were routinely investigated with liver and renal function tests, hepatitis B surface antigen (HBsAg), hepatitis C virus antibody, and serum levels of carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), and alpha-fetoprotein (AFP). Preoperative imaging studies included plain radiography or noncontrast computed tomography (CT) of chest, abdominal ultrasonography, and contrast-enhanced CT and/or magnetic resonance imaging (MRI) of abdomen. Positron emission tomography (PET) was used in patients with uncertainty of diagnosis of recurrence or with suspected distant metastasis.

The operative indications of repeat hepatic resection for RICC was similar to those of the initial operative as reported previously.³⁰ Briefly, re-operation was considered for patients with good general performance and liver functional reserve, technically resectable recurrent lesion(s), sufficient estimated volume of future liver remnant (FLR), but without distant metastasis and extensive nodal metastasis. In addition, an R0 resection, defined as the complete removal of macroscopic tumor nodule(s) with a microscopic tumor-free operative margin, for the primary tumor was generally required in deciding the use of re-resection in patients with RICC.

In repeat hepatic resection, intraoperative ultrasonography was routinely used to detect additional nodules that were not revealed by preoperative imaging studies. The range of hepatectomy was decided by the surgeons based on the size and location of the recurrent tumors and degree of cirrhosis, with an intention of complete removal of macroscopic tumors and retaining sufficient volume of FLR. Regional lymph nodes

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