# The Impact of Surgical Treatment and Poor Prognostic Factors for Patients with Intrahepatic Cholangiocarcinoma: Retrospective Analysis of 60 Patients

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**Abstract.** *Background: Intrahepatic cholangiocarcinoma (ICC) is a primary adenocarcinoma of the liver arising from the intrahepatic bile duct. Hepatectomy with extensive lymph node dissection is the standard treatment for ICC. Patients and Methods: Sixty patients with ICC who underwent hepatectomy in our institution between 1986 and 2005 were investigated to determine prognostic factors and to evaluate the impact of surgical treatment for ICC using univariate and multivariate analyses. Results: The overall survival rate of the R0 resection group (n=43) was significantly higher than that of the R1/2 group (n=17). However, in patients with lymph node metastasis (n=24), R0 resection had no survival impact. According to multivariate analysis, the independent factors of poor prognosis were: the presence of lymph node metastasis, lymphatic invasion, poor differentiation and R1/2 resection. Conclusion: R0 resection can provide prolonged survival for patients with ICC. Patients with lymph node metastasis, lymphatic invasion, or poorly differentiated ICC have poor prognosis after operation and additional treatment, such as adjuvant chemotherapy, is recommended.*

Intrahepatic cholangiocarcinoma (ICC), also referred to as peripheral cholangiocarcinoma, is a primary liver cancer arising in the intrahepatic bile ducts. ICC is the second most common primary hepatic tumor after hepatocellular carcinoma, comprising 5% to 15% of all hepatic tumors (1, 2). Early symptoms are uncommon and many patients therefore tend to present with large, often unresectable tumors. The outcomes for patients with ICC have been poor, with a 3-year survival rate ranging from 15% to 40% after resection (3-6). It has always been a challenge to successfully treat this disease, which has such a dismal prognosis. Hepatic resection is the only curative treatment modality (7-10), but no standard chemotherapeutic regimens or other effective treatment modalities have yet been established.

The natural history of unresected ICC shows a median survival rate of under one year and the median survival rate after a palliative (R2) resection is under 3 months (11, 12). These data indicate that only a curative resection can prolong survival, thus providing some hope of cure. Most previous reports have emphasized the importance of major hepatic resection. Yamamoto *et al*. suggest that anatomic and extensive hepatectomy is the optimal procedure for mass-forming ICC and that hepatectomy with extrahepatic bile duct excision and hilar lymph node resection is therefore the rational procedure for infiltrating ICC (13). Nevertheless, the one-year survival rate of patients with nodal metastasis who undergo lymph node dissection is reported to be 0% (3, 14). Thus, these data indicate almost the same survival rate as that seen with non-curative resection. An important question remains: can extensive lymph node dissection prolong survival in ICC patients with lymph node metastasis?

The following factors have been reported to affect the prognosis of patients with ICC after surgical treatment: macroscopic classification (13), lymph node metastasis (2, 3, 15), vascular invasion (6, 10), a high serum carbohydrate antigen (CA) 19-9 level (16) and a positive surgical margin (4, 10). To date, however, studies involving more than 50 patients who underwent surgical treatment in a single institution over an acceptable period have been very rare (15, 17). The aim of the present

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retrospective study was to identify factors of poor prognosis among various clinicopathological features of ICC and to examine the impact of surgical treatment, including R0 resection and extended lymph node dissection, for patients with ICC in order to determine a more effective surgical strategy.

## Patients and Methods

*Patients*. Sixty patients who underwent hepatic resection for ICC in the Department of Surgery II, Kyushu University Hospital, between January 1986 and December 2005 were entered into this trial. ICC was defined as malignancy arising from the intrahepatic bile ducts; perihilar (Klatskin) tumors were excluded. Hepatic resections with lymph node dissection [D(+)]were performed on 25 patients (42%). Lymph node dissections were performed in patients with at least Group 2 ICC according to the Classification of Primary Liver Cancer by the Liver Cancer Study Group of Japan (18). Thirty-five patients (58%) underwent hepatic resection only without lymph node dissection [D(–)]. The D(–) group also included patients who underwent lymph node sampling. After discharge, all patients were examined every month for recurrence by ultrasonography and underwent testing for tumor markers such carcinoembryonic antigen (CEA) and CA19-9, while every 3 months, dynamic computed tomography was carried out (14). The median follow-up period after surgery in this series was 37 months.

*Data analysis*. The survival curves were generated by the Kaplan-Meier method and compared by the log-rank test. To evaluate the survival impact of surgical treatment [R0 or D(+)] against node-positive patients (n=24), the same methods were applied. To evaluate factors of poor prognosis after surgical treatment, multivariate analysis with the Cox proportional hazard model was performed using a variable-selection method involving the backward-elimination procedure. A value of $p<0.05$ was set as the cutoff for elimination. To identify the relevant prognostic factors after surgical treatment for ICC, the following 17 clinical, surgical and tumor-related variables were analyzed in accordance with the findings of previous reports (2, 5, 10, 14, 15-17): age (older *vs*. younger than 60 years); Child-Pugh class (A *vs*. B); preoperative CEA (greater *vs*. less than 2.5 ng/mL); preoperative CA19-9 (greater *vs*. less than 100 IU/l); tumor size (larger *vs*. smaller than 50 mm); lymph node metastasis (n; yes or no); lymphatic invasion (ly; yes or no); vascular invasion (yes or no); intrahepatic metastasis (yes or no); tumor cell differentiation (well or moderate *vs*. poor); tumor-node-metastasis (TNM) stage according to the latest edition of the International Union Against Cancer (UICC) TNM classification (I or II *vs*. III) (19); duration of surgery (more *vs*. less than 480 minutes); surgical blood loss (more *vs*. less than 1500 ml); lymph node dissection (yes or no); intra-operative blood cell transfusion (yes or no); surgical margin (greater *vs*. smaller than 5 mm); and remnant tumor (R0 or R1/2).

Continuous variables were expressed as means±S.E. and compared using Student's *t*-test. Categorical variables were compared using either the $\chi^2$ test or Fisher's exact test, as appropriate. All analyses were performed with Statview 5.0 software (Abacus Concepts, Berkeley, CA, USA). *P*-values of less than 0.05 were considered to indicate statistical significance.

Table I. *Background characteristics, surgical outcomes and tumor-related factors*.

| Variables | ICC n=60 |
|---|---|
| Background characteristics | |
| Age (years) | 60±1 |
| Male:Female | 41:19 |
| Hepatitis B infection: yes:no | 9:51 |
| Hepatitis C infection: yes:no | 8:52 |
| ICG R15 (%) | 10.7±0.8 |
| Child-Pugh: A:B | 49:11 |
| Surgical outcomes | |
| Major hepatectomy*: Minor hepatectomy | 39:21 |
| Surgical time (min) | 457±24 |
| Surgical blood loss (g) | 1,505±210 |
| Transfusion: yes:no | 28:32 |
| Resected volume (g) | 408±36 |
| Surgical margin > 5 mm: yes:no | 22:38 |
| D(+): D(–) | 25:35 |
| R0:R1:R2 | 43:8:9 |
| Complications (%) | 18 (30%) |
| Hospital stay (days) | 42±11 |
| Tumor-related factors | |
| Tumor size (cm) | 4.6±0.3 |
| Well:Mod:Poor | 13:14:33 |
| Vascular invasion: yes:no | 22:38 |
| Lymphatic invasion: yes:no | 28:32 |
| Lymph node metastasis: yes:no | 24:36 |
| Stage I/II/IIIA/IIIB/IIIC | 17:12:6:1:24 |
| CEA (ng/ml) | 5.7±2.2 |
| CA19-9 (mAU/l) | 1,697±1241 |

ICG R15, indocyanine green retention rate at 15 minutes; Well, well-differentiated ICC; Mod, moderately-differentiated ICC; Poor, poorly-differentiated ICC; CEA, carcinoembryonic antigen; CA19-9; carbohydrate antigen 19-9. *Major hepatectomy indicates lobectomy or greater.

## Results

*Patient characteristics*. The background characteristics, surgical outcomes and tumor-related factors of the present series of patients are shown in Table I. Hepatitis B or C infection was a complication in 17 patients (28%) and liver function was relatively well maintained in all patients [mean indocyanine green retention rate at 15 minutes (ICG15R), 10.7±0.8% ; Child-Pugh A patients, 49 cases (82%)]. Major hepatectomies (lobectomy or more) were performed in 39 patients (65%) and lymph node dissection was performed in 25 patients (42%). Seventeen patients (28%) underwent non-curative operations (R1 or R2). Mean tumor size was relatively large at up to 4.6±0.3 cm, and 24 patients (40%) were complicated by lymph node metastasis. According to the sixth edition of UICC stage grouping (19), 17, 12, 6, 1 and 24 patients in our series had Stage I, II, IIIA, IIIB and IIIC disease, respectively.

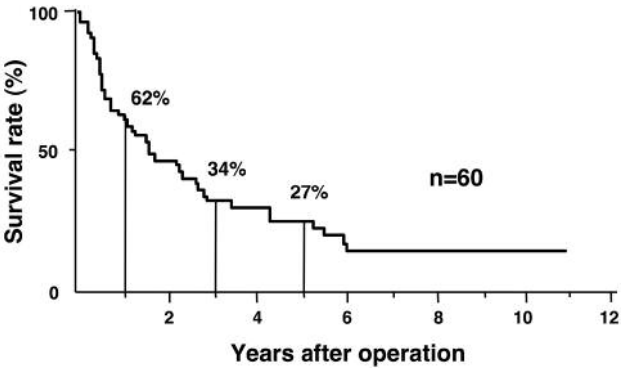



Figure 1. *Overall survival curves after operation in all 60 patients. Survival rates were 62% at 1 year, 34% at 3 years and 27% at 5 years.*

Table II. *Reasons for R1 or R2 operation.*

| R1 operations: 8 cases | |
|---|---|
| Indication | No. of cases |
| Microscopically involved bile duct stump | 4 |
| Microscopically involved liver stump | 3 |
| Positive for irrigation cytology | 1 |
| **R2 operations: 9 cases** | |
| Indication | No. of cases |
| Remnant of n(+) beyond group 3* | 5 |
| Ablation of intrahepatic metastasis | 4 |

*Grouping of regional lymph nodes according to the Classification of Primary Liver Cancer by the Liver Cancer Study Group of Japan (18).

*The impact of surgical treatment for patients with ICC*. The overall survival of the present 60 patients who underwent surgical resection of ICC is illustrated in Figure 1. Survival rates were 62% at 1 year, 34% at 3 years and 27% at 5 years. The overall survival rate of the R0 resection group (n=43) was significantly higher than that of the R1/2 group (n=17; Figure 2A). The overall 5-year survival rate of the R0 group was 58%, but no patient survived over 24 months in the R1/2 group.

The main indications for R1 or R2 resection are summarized in Table II. The indication for R1 operation was the microscopic involvement of surgical stumps, either a bile duct stump (4 cases; 7%), or a liver stump (3 cases; 5%). There were two primary indications for R2 operation: remnant lymph node metastasis (5 cases; 8%) and tumor ablations (4 cases; 7%). The overall and recurrence-free survival curves of the D(+) and D(–) groups were similar, indicating that no survival impact of lymph node dissection can be recognized for patients with ICC.

The overall survival curves for all patients and for n(+) patients (24 patients; 40%) according to R0 or R1/2 operation are shown in Figure 2B. The postoperative results were similar in the 2 groups, suggesting that extended lymph node dissection does not provide any extra benefit for node-positive ICC patients.

*Factors of poor prognosis evaluated by multivariate analysis and survival curves*. The results of multivariate analysis with the Cox proportional hazards model using a variable-selection method involving the backward-elimination procedure among the variables listed in the Patients and Methods section above are summarized in Table III. The independent factors of poor prognosis in overall survival were found to be the following: the presence of lymph node metastasis (hazard ratio, HR 28.3), lymphatic invasion (HR 8.5), poor differentiation (HR 8.3) and R1/2 resection (HR 6.4). In recurrence-free survival, the independent factors of poor prognosis were lymph node metastasis (HR 2.8) and lymphatic invasion (HR 2.7).

Table III. *Multivariate analysis to determine poor prognostic factors.*

| Variable | Hazard ratio | 95% Confidence interval | *p*-value |
|---|---|---|---|
| Overall survival | | | |
| n(+) | 28.3 | 5.4-148.0 | <0.01 |
| ly(+) | 8.5 | 2.3-30.5 | 0.01 |
| Poorly diff. | 8.3 | 2.4-29.2 | 0.01 |
| R1/2 | 6.4 | 1.4-28.7 | 0.01 |
| Recurrence-free survival | | | |
| n(+) | 2.8 | 1.1-7.6 | 0.03 |
| ly(+) | 2.7 | 1.1-6.7 | 0.03 |

ly(+), Presence of lymphatic invasion; n(+), presence of lymph node metastasis; Poorly diff., poorly differentiated ICC.

The overall survival curves according to the status of lymph node metastasis (n) and lymphatic invasion (ly) are illustrated in Figure 3A and B, respectively. The overall 5-year survival rate of the n(–) group was 72%, but only 1 patient (4%) survived over 36 months in the n(+) group. The overall 5-year survival rates were 57% in the ly(–) group and 27% in the ly (+) group. The recurrence-free survival rates according to the status of lymph node metastasis and lymphatic invasion are illustrated in Figure 4A and B, respectively. The recurrence-free 5-year survival rates were 64% in the n(–) group, but only 1 patient (4%) survived over 36 months recurrence-free in the n(+) group. The recurrence-free 5-year survival rates were 76% in the ly(–) group and 19% in the ly(+) group.

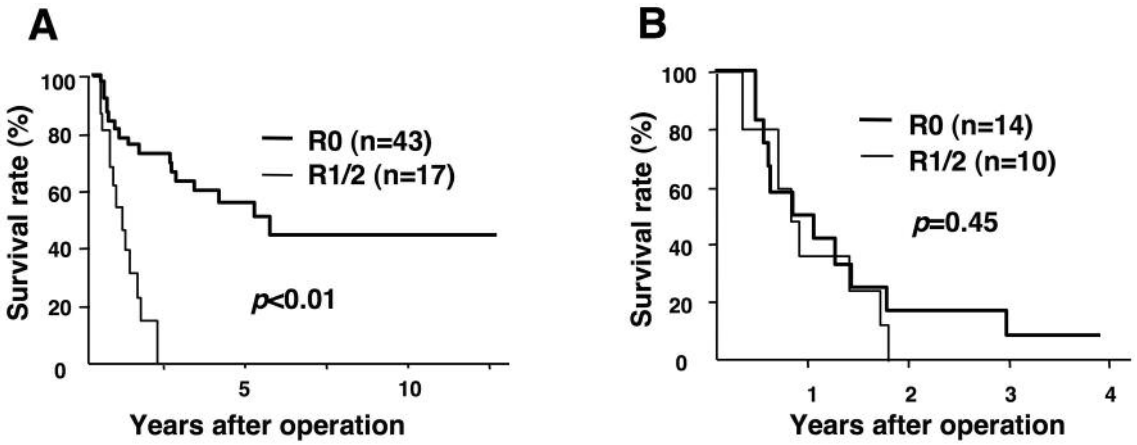



Figure 2. *Overall survival curves according to R0 or R1/2 operation in all patients (A) and in n(+) patients (B). The overall 5-year survival rate of the R0 group was 58%, but no patient survived over 24 months in the R1/2 group. The postoperative results were similar in the 2 groups in n(+) patients.*

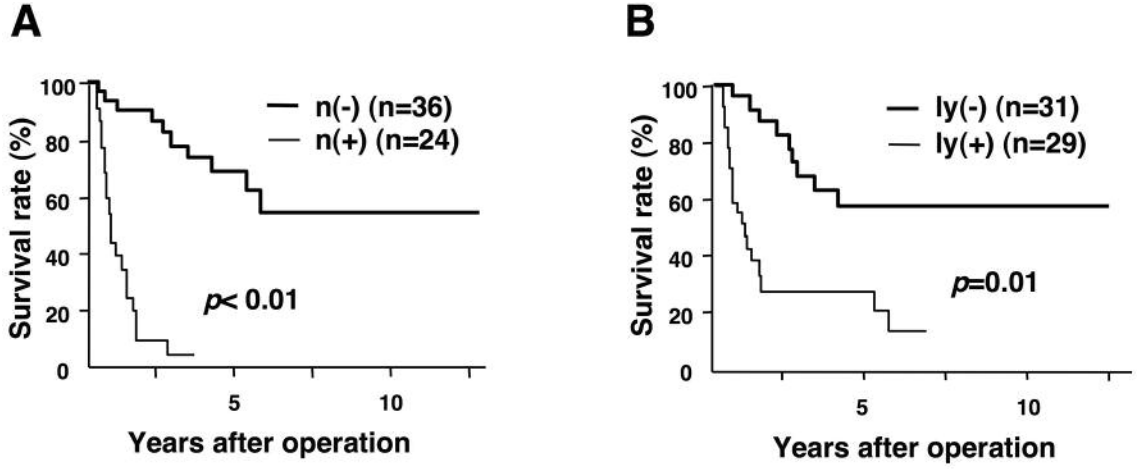



Figure 3. *Overall survival curves according to n (A) and ly (B). The overall 5-year survival rate of the n(–) group was 72%, but one patient (4%) survived over 36 months in the n(+) group. The overall 5-year survival rates were 57% in the ly(–) group and 27% in the ly(+) group.*

## Discussion

The prognosis after aggressive resection for ICC remains unsatisfactory, with a 5-year survival rate reported to be approximately 25% (2, 7, 16), which was similar to the results obtained in the present series (27%). Surgical resection has been shown to provide a greater chance of long-term survival for patients with ICC (2, 16, 20-22). This is also consistent with the present series of patients, whose 5-year survival reached 58% when the R0 operation was completed. In our present series, the independent factors indicating a poor prognosis were found to be the following: the presence of lymph node metastasis (HR 28.3), lymphatic invasion (HR 8.5), poor differentiation (HR 8.3), and R1/2 resection (HR 6.4).

Most previous series have shown that one of the strongest prognostic factors is lymph node metastasis (2, 3, 6, 15, 23-26): almost patients with lymph node metastasis could not survive for more than 3 years after operation. Inoue *et al*. (26) insist that lymph node metastasis in the mass-forming type (18) of ICC is a sign of non-curable disseminated disease and that hepatectomy is therefore contraindicated if lymph node metastasis is observed at the time of sampling. In the present series, the strongest indicator of a poor prognosis was lymph node metastasis (HR 28.3); no positive survival impact of surgical treatment such as R0 or D(+) operation was recognized in node-positive patients. The present results demonstrate that aggressive surgical resection for ICC patients with lymph node metastasis is likely to have little survival impact.

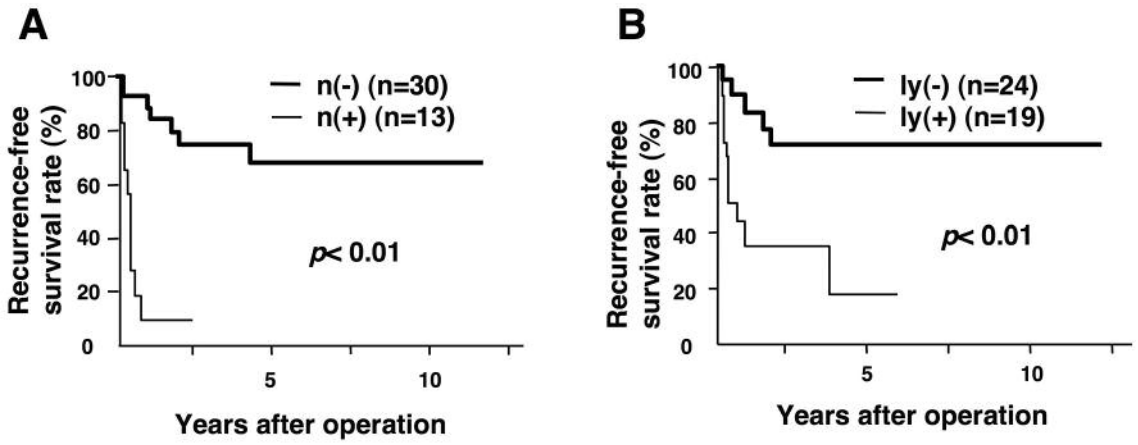
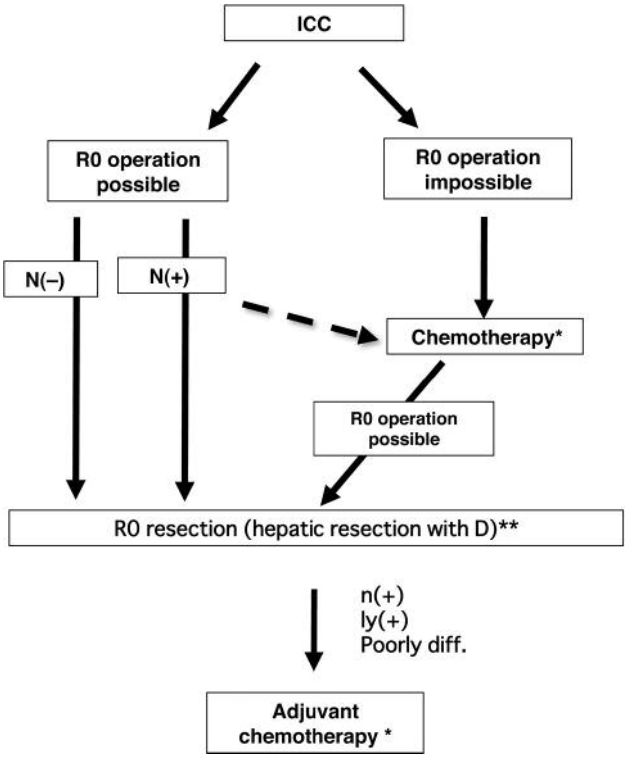



Figure 4. *Recurrence-free survival according to n (A) and ly (B) status. The recurrence-free 5-year survival rates were 64% in the n(–) group, but 1 patient (4%) survived over 36 months recurrence-free. The recurrence-free 5-year survival rates were 76% in the ly(–) group and 19% in the ly(+) group.*

Ohtsuka *et al*. (16) reported that lymph node metastasis was not identified as a significant prognostic factor in patients who underwent lymph node dissection. Murakami *et al*. (27), Yamamoto *et al*. (28) and Weber *et al*. (29) reported long-term (more than 5 years) survivors with lymph node metastasis. In our series, there was only 1 patient (2%) with lymph node metastasis who underwent lymph node dissection and lived for more than 3 years after the resection (30). These results suggest that although lymph node metastasis may generally be associated with an unfavorable prognosis, long-term survival might be expected following adequate curative resection (R0 resection), including lymph node dissection, in patients with nodal metastasis. Therefore, we cannot agree that surgical treatments for ICC patients with lymph node metastasis is contraindicated and instead recommend the development of adjuvant or neoadjuvant chemotherapy.

The clinical effectiveness of gemcitabine (31, 32) and gemcitabine-based chemotherapies (33, 34) has been reported in recent phase II trials. We also previously demonstrated the clinical effectiveness and favorable toxicity profile of gemcitabine combined with 5-fluorouracil and cisplatin (GFP) in patients with advanced biliary tree cancer in a pilot study (35); the good clinical results of GFP chemotherapy for patients with advanced biliary tree cancer were consistent in over 25 patients (data not shown). The use of a gemcitabine-based chemotherapy such as GFP as an adjuvant or neoadjuvant treatment could improve the surgical results of patients with ICC, especially those of patients complicated with lymph node metastasis.

Figure 5. *Treatment strategy for patients with ICC.*




*Gemcitabine-based chemotherapy such as GFP. **If the R0 operation is possible, lymph node dissection is not always performed.

Some authors have reported that tumor involvement of the resection margin is an independent factor associated with poor prognosis in patients with ICC (4, 10, 16, 36, 37). Non-curative operations for ICC with histologically involved resection margins have represented 15-40% of operations performed with curative intent in previous reports (21, 23, 24, 37, 38). In the present series, the indications for R1 resection were a microscopically involved bile duct (4

cases), liver stump (3 cases), and positivity for irrigation cytology (1 case). Resection margin status is difficult to confirm macroscopically during an operation and clear margins are difficult to achieve. Intraoperative frozen-section examination of the margin should be performed to confirm the absence of cancer cells. In addition, ablation of intrahepatic metastasis of ICC is not believed to be effective based on the present results. Therefore, to maintain sufficient surgical margins by wide liver resection to complete the R0 operation, portal vein embolization before extended hepatectomy should be considered (39, 40).

Our present treatment strategy for patients with ICC is summarized in Firgure 5. The most important consideration in the treatment of ICC should be the potential success of the R0 operation (10). If R0 operation is possible, extended lymph node dissection need not always be performed. For ICC patients with lymph node metastasis diagnosed by preoperative imaging, one possible treatment choice should be a neoadjuvant gemcitabine-based chemotherapy such as GFP. If at least one of the three independent indicators of poor prognosis in our series [n(+), ly(+) or poor differentiation] is pathologically diagnosed, adjuvant chemotherapy should be included in the treatment strategy.

In conclusion, R0 resection can provide prolonged survival for patients with ICC, but extended lymph node dissection does not appear to improve survival, especially in node-positive patients. Patients with lymph node metastasis, lymphatic invasion or poorly-differentiated ICC have a poor prognosis after operation and should receive additional treatment such as adjuvant chemotherapy.

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