

Surgical Approach for Long-term Survival of Patients With Intrahepatic Cholangiocarcinoma

A Multi-institutional Analysis of 434 Patients

Patients **FREE**

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ABSTRACT

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Objectives To examine the outcomes of a hepatectomy for intrahepatic cholangiocarcinoma (IHC) and to clarify the prognostic impact of a lymphadenectomy and the surgical margin. Large series of patients who were surgically treated for IHC are scarce. Thus, prognostic factors and long-term survival after resection of IHC remain uncertain.

Design Prospective study of patients who were surgically treated for IHC. Clinicopathologic, operative, and long-term survival data were analyzed.

Setting Prospectively collected data of all consecutive patients with pathologically confirmed IHC who had undergone liver resection with a curative intent at 1 of 16 tertiary referral centers were entered into a multi-institutional registry.

Patients All consecutive patients who underwent a hepatectomy with a curative intent for IHC (1990-2008) were identified from a multi-institutional registry.

Results A total of 434 patients were included in the analysis. Most patients underwent a major or extended hepatectomy (70.0%) and a systematic lymphadenectomy (62.2%). The incidence of lymph node metastases (overall, 36.9%) increased with increased tumor size, with 24.4% of patients with a small IHC (diameter ≤ 3 cm) having N1 disease. Almost one-third of patients required an additional major procedure to obtain a R0 resection in 84.6% of the cases. In these patients, the median time of survival was 39 months, and the 5-year survival rate was 39.8%. Lymph node metastases (hazard ratio, 2.21; $P < .001$), multiple tumors (hazard ratio, 1.50; $P = .009$), and an elevated preoperative cancer antigen 19.9 level (hazard ratio, 1.62; $P = .006$) independently predicted an adverse prognosis. Conversely, survival was not influenced by the width of a negative resection margin ($P = .61$). The potential survival benefit of a lymphadenectomy was assessed with the therapeutic value index, which was calculated to be 5.9 points.

Conclusions Survival rates after a hepatectomy with a curative intent for IHC at tertiary referral centers exceed the survival rates reported in most study series in single institutions, which strengthens the value of an aggressive approach to radical resection. Lymph node metastases and multiple tumors are associated with decreased survival rates, but they should not be considered selection criteria that prevent other patients from undergoing a potentially curative resection. Lymphadenectomy should be considered for all patients.

Intrahepatic cholangiocarcinoma (IHC) is the second most common primary malignant neoplasm of the liver, but it remains a relatively rare disease accounting for only 4% to 14% of newly diagnosed liver tumors.^{1,4} Recently, increasing clinical interest has been focused on IHC because of the epidemiological documentation of a worldwide steady increase in the incidence of IHC and in the mortality rates associated with IHC over the last quarter century.^{1,3} In Italy, analysis of data from the Italian Association of Tumour

Registries (AIRTUM) showed a descriptive epidemiology mirroring the global trends.³ Nevertheless, the rarity of the disease and the high proportion of patients diagnosed at an advanced, unresectable stage⁵ have hindered the collection of large amounts of surgical data. Most of the available data derive from small single-institution studies reporting conflicting results in terms of overall survival.⁶⁻²⁰ Thus, the efficacy and outcomes of surgical resection of IHC are still ill-defined. In addition, the lack of effective neoadjuvant or adjuvant protocols has reinforced the traditional perception of a dismal prognosis. Therefore, assessment of the potential long-term benefits of surgical resection in a large cohort of patients is necessary to support the aggressive surgical approach often required to treat such tumors. Furthermore, controversies exist regarding optimal surgical management. Despite the data from a number of studies that have investigated the oncologic significance of lymphadenectomy,^{7-8,12-16} the evidence is still inadequate, with many Western surgeons not including locoregional lymphadenectomy as part of their routine approach to IHCs. Similarly, the issue of the appropriate surgical margin remains to be adequately addressed.^{8,19-21, 24} As such, the purpose of the present study was to examine the outcome of resection of IHC in a series of patients evaluated and treated at tertiary hepatobiliary centers. Specifically, using one of the largest series ever collected, we sought (1) to determine the expected survival rate after R0 resection; (2) to identify factors associated with poor outcome; and (3) to clarify the prognostic impact of technical factors, namely locoregional lymphadenectomy and the surgical margin width.

METHODS

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Prospectively collected data from all consecutive patients with a pathologically confirmed IHC who had undergone a liver resection with a curative intent at 1 of 16 tertiary referral centers (March 1990–December 2008) were entered into a multi-institutional registry. The registry and the present study were endorsed by the Italian Chapter of the International Hepato-Pancreato-Biliary Association. Patients with hilar cholangiocarcinoma and those with mixed IHC–hepatocellular carcinoma were considered ineligible for registration. Data collection and analysis were performed, and they conformed to the ethical standards of the Helsinki Declaration.

The preoperative workup for all patients consisted of a routine clinical evaluation, an assessment of serum laboratory tests, a colonoscopy and upper gastrointestinal endoscopy, computed tomography or magnetic resonance imaging of the abdomen, and radiography or computed tomography of the chest. A positron emission tomographic scan and a liver biopsy were performed only for selected cases. Patients were deemed to have resectable disease only if the tumor could be completely removed while preserving a sufficient functional liver remnant with adequate vascular inflow and hepatic venous outflow. Distant metastases at preoperative staging were the only formal contraindication to surgery. After hepatic resection, adjuvant chemotherapy was decided based on recommendations from each institutional multidisciplinary team meeting or from the patient's oncologist. Patients were regularly followed up every 3 to 6 months according to each institution's protocol. Follow-up data were updated on January 1, 2010.

The following clinicopathologic variables were recorded for each patient: demographics, preoperative carcinoembryonic antigen and cancer antigen 19-9 levels, details of the operation, whether or not there were postoperative complications, characteristics of tumor, and complete follow-up data including disease status and site of recurrence. All pathologic data were retrospectively reviewed to confirm the consistency of the data recorded in each prospectively collected database for the variables of interest: gross pathology (macroscopic typing was based on the Liver Cancer Study Group of Japan's classification²⁵), size and number of tumors, histological differentiation, whether or not there was vascular invasion, lymph node (LN) status, whether or not there was adjacent organ invasion, and the presence of distant metastases. For each patient, the TNM stage grouping was computed according to the criteria of the seventh edition of the *AJCC Cancer Staging Manual*.²⁶ Data on margin status and the underlying liver were also recorded. In particular, the surgical margin was classified as positive in patients with an exposed tumor along the line of transection or in those with microscopic evidence of tumor cells at the cut surface. Missing data were recorded as nonavailable. Postoperative morbidity was defined using the classification of Dindo et al.²⁷ Postoperative mortality was analyzed 90 days after surgery.

Variables are presented as absolute numbers and percentages or as median values and ranges. Statistical analyses of data were performed with appropriate nonparametric tests. Overall survival estimates were generated with the Kaplan-Meier method measuring time from the date of surgery to the date of death or last follow-up. Cox proportional hazards models were developed to test the association of relevant clinicopathologic factors with survival. All factors with a univariate $P < .100$, with the exception of those at risk of multicollinearity (specifically T stage and AJCC stage factors), were considered for independent comparison using a multivariable model. To overcome the limitations of a multivariable analysis of a data set containing missing values, a second analysis was performed using regression imputation to account for missing data.²⁸ Regression imputation was applied to a model that included only the variables selected with a

stepwise procedure; all other variables of the multivariable model were used to fill in the missing data. To assess the potential benefit of lymphadenectomy, the therapeutic value index, calculated by multiplying the frequency of LN metastasis and the 5-year survival rate of patients with LN metastasis, was computed.²⁹ Statistical significance was set at $P < .50$. The R environment version 2.13.0 (The R Foundation for Statistical Computing, Vienna, Austria) software package was used for statistical analyses.

RESULTS

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CHARACTERISTICS OF PATIENTS

In total, 434 patients were registered. There were 243 male patients (56.0%) and 191 female patients (44.0%), with a median age of 65 years (range 29-85 years). Of these 434 patients, 39 (8.9%) tested positive for serum hepatitis B surface antigen, and 53 (12.2%) tested positive for the presence of hepatitis C antibody (7 patients had a coinfection with hepatitis B virus and hepatitis C virus). Preoperatively, 195 of 325 patients (60.0%; 109 patients [25.1%] were not tested) had an elevated (ie, >37 U/mL [to convert to kilounits per liter, multiply by 1.0]) cancer antigen 19-9 level (median, 57.1 U/mL; range, 0.2-27 000 U/mL). Conversely, an increased carcinoembryonic antigen level (ie, >5 ng/mL [to convert to micrograms per liter, multiply by 1.0]) was detected only in 77 of 288 patients (26.7%; 146 patients [33.6%] were not tested) (median, 2.3 ng/mL; range, 0.1-36 000 ng/mL). Sixty patients (13.8%) presented with obstructive jaundice, 37 of whom (61.6%) underwent preoperative biliary drainage.

SURGICAL RESULTS

The type and extent of surgical procedures are detailed in [Table 1](#). During the postoperative period, 151 patients (34.8%) experienced a total of 182 adverse events. Complications were primarily related to the liver (43.9%), including hepatic dysfunction/hepatic insufficiency (16 and 22 patients, respectively) and biliary fistula (42 patients). Infectious complications (34 of 182 patients [18.7%]) were the second most common cause of morbidity, the most common being subphrenic abscess, pneumonia, and sepsis. Overall, 89 of 434 patients (20.5%) developed major (grades III-V) complications with a reoperation rate of 3.7% (16 patients). Of note, morbidity was significantly higher in patients who had undergone a biliary drainage (67.5%) ($P = .058$) compared with patients with jaundice who did not undergo biliary drainage (43.5%) and compared with patients without jaundice (31.3%) ($P < .001$). In all, 23 patients (5.3%) died postoperatively. After splitting the series into 3 groups using tertiles, the mortality rate decreased from 6.2% in the first two-thirds of patients to 3.5% in the last third of patients. However, such a decrease in mortality, which was observed in spite of a similar complexity of resections, was not statistically significant ($P = .24$). The median length of hospital stay was 12 days (range, 1-114 days) from the day of surgery. After resection, 124 patients (30.2%) received adjuvant treatments, either chemotherapy (116 patients) or radiotherapy (8 patients).

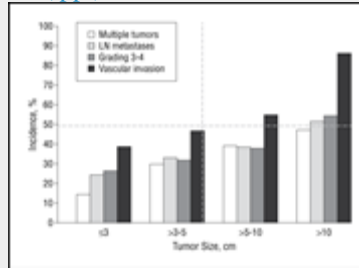
Table 1. Data on Surgical Procedures Performed for Patients Who Underwent a Hepatectomy With a Curative Intent for Intrahepatic Cholangiocarcinoma

Procedure	No. (%)
Total of operations (n = 434 patients)	133 (30.6)
Major operations	17 (3.9)
Hepatectomy	17 (3.9)
Bile duct resection	80 (18.4)
Major resection*	202 (46.7)
Right left hepatectomy	140 (32.3)
Bile duct resection	3 (0.7)
Left hepatectomy - I, II, III, or IV	88 (20.3)
Central resection†	84 (19.4)
Right hepatectomy - I, II	12 (2.8)
Right hepatectomy - III	24 (5.5)
Right hepatectomy - IV	14 (3.2)
Left hepatectomy	19 (4.4)
Large bile drainage	1 (0.2)
Bypass	45 (10.4)
Biliary fistula	107 (24.7)
Biliary stricture	119 (27.4)
Major liver preservation‡ (n = 152 procedures)	84 (20.3)
No liver resection	82 (19.4)
Partial resection	14 (3.2)
Vena ligation	4 (0.9)
Other nonresections	27 (6.3)
Bile duct resection	21 (4.8)
Biliary fistula	1 (0.2)
Biliary stricture	4 (0.9)
Other procedures	16 (3.7)

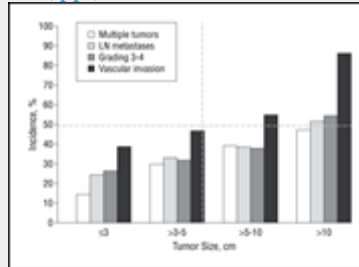
Abbreviations: I, segment I; II, segment II; III, segment III; IV, segment IV.
 *Major and extensive hepatectomy defined as resection of 3 or 4 or 5
 †Major and extensive hepatectomy, respectively.
 ‡Procedures of hepatectomy, biliary reconstruction, biliary
 bypass, and biliary fistula repair were included in group I, II, III, and IV.
 ††Reoperation for liver or biliary tract disease.

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Table 2. Pathologic Features of the Patients Who Underwent a Hepatectomy With a Curative Intent for IHC

Feature	Incidence (%)
Multiple tumors	15
LN metastases	25
Grading 3-4	25
Vascular invasion	35

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Feature	Incidence (%)
Multiple tumors	15
LN metastases	25
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Vascular invasion	35

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Feature	Incidence (%)
Multiple tumors	15
LN metastases	25
Grading 3-4	25
Vascular invasion	35

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Table 1: Summary of patient characteristics and outcomes. The table lists various clinical and demographic factors such as age, sex, tumor size, and resection type, along with their respective counts and percentages. It also includes survival statistics like median survival and 1-, 3-, and 5-year survival rates.

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Table 2: Summary of patient characteristics and outcomes. Similar to Table 1, this table provides a detailed breakdown of patient demographics, tumor characteristics, and surgical outcomes, including survival data.

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Table 3: Summary of patient characteristics and outcomes. This table continues the summary of patient data, focusing on specific prognostic factors and their impact on survival outcomes.

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On final pathologic analysis, 52 patients (12.0%) had a positive resection margin. The median width of tumor-free margin was 10 mm (range, 0.5-40 mm). Stratification for margin width was 0.5 to 9 mm (median width, 4 mm) for 133 patients (30.6%) and 1 cm or larger (median width, 15 mm) for 159 patients (36.6%). Data on margin width were unavailable for 90 patients (20.7%), and data on margin status were unavailable for 5 patients (1.2%). Overall, 67 patients (15.4%) were classified as having received an R1 resection. The causes of resections that were not radical (ie, R1 resections) were a positive resection margin (52 patients); intraoperatively discovered peritoneal implants (12 patients), albeit completely resected; positive paracaval LNs (1 patient); and IHCs in the remnant liver (2 patients). These last 2 patients for whom a 2-stage hepatectomy was initially planned eventually did not undergo the second resection because of tumor progression.

OVERALL SURVIVAL AND PROGNOSTIC FACTORS

At the time of analysis, 218 of 411 patients (53.0%) had died. After a median follow-up of 36.5 months (range, 1-181 months), overall median survival was 33 months (95% CI, 27.0-39.1 months), and the 1-, 3-, and 5-year estimates were 82.3%, 47.1%, and 32.9%, respectively. After R0 resection, corresponding survival estimates were 39 months (95% CI, 28.7-49.2 months), and the 1-, 3-, and 5-year estimates were 84.8%, 50.6% and 39.8%, respectively. The longest living survivor was alive and disease-free at 15.1 years, with 47 actual 5-year survivors (26.8% of those 175 patients with at least 5 years of follow-up). Of these patients, 31 had no evidence of disease for a minimum cure rate of 17.7%.

The univariate and multivariate predictors of overall survival are reported in [Table 3](#). On univariate analysis, an elevated preoperative cancer antigen 19-9 level, all pathologic tumor factors with the exception of

Table 3. Prevalence of Overall Survival, Intermediate and Multistage Resection*

Variable	Resection Type, %			P-value	HR (95% CI)	P-value
	TS	IS	MS			
All	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
Age	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
Sex	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
CA	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
CA stage	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
Resection	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
IS	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
MS	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs MS	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
IS vs MS	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS vs MS	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS vs MS vs CA	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS vs MS vs CA vs Resection	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS vs MS vs CA vs Resection vs Age	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS vs MS vs CA vs Resection vs Sex	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS vs MS vs CA vs Resection vs CA stage	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS vs MS vs CA vs Resection vs Age vs Sex vs CA stage	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999

Abbreviations: CA, cancer stage; HR, hazard ratio; IS, intermediate resection; MS, multistage resection; TS, tertiary resection.

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Table 3. Prevalence of Overall Survival, Intermediate and Multistage Resection*

Variable	Resection Type, %			P-value	HR (95% CI)	P-value
	TS	IS	MS			
All	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
Age	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
Sex	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
CA	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
CA stage	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
Resection	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
IS	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
MS	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs MS	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
IS vs MS	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS vs MS	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS vs MS vs CA	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS vs MS vs CA vs Resection	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS vs MS vs CA vs Resection vs Age	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS vs MS vs CA vs Resection vs Sex	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS vs MS vs CA vs Resection vs CA stage	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999
TS vs IS vs MS vs CA vs Resection vs Age vs Sex vs CA stage	52.9	52.1	52.3	> .999	1.00 (0.99-1.01)	> .999

Abbreviations: CA, cancer stage; HR, hazard ratio; IS, intermediate resection; MS, multistage resection; TS, tertiary resection.

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IMPLICATIONS FOR SURGICAL MANAGEMENT

First, as the presence of metastatic nodal disease emerged as the most powerful, independent determinant of survival, we attempted to evaluate the potential survival benefit of lymphadenectomy. The 5-year overall survival rate in patients having positive LNs was 15.9%. The therapeutic value index for the survival benefit was calculated to be 5.9 points (15.9×0.369). Notably, only 2 patients developed a clinically significant lymphorrhea.

Second, we investigated the prognostic significance of the resection margin. In particular, we tested our a priori hypothesis that all hepatectomies with negative margins (>0 mm), regardless of the margin width, should be considered radical resections. We found that the width of a negative margin has no long-term impact because survival estimates in patients with a negative margin of 0.5 to 9 mm and survival estimates in patients with a negative margin of 1 cm or larger are similar ($P = .61$) and significantly better than those in patients with a positive margin ($P < .001$). In addition, although tumor recurrence was significantly more likely to occur in patients with a positive margin (73.6% vs 53.9%; $P = .005$), in patients with a negative margin, the margin width did not predict tumor relapse or the site of recurrence (all $P > .05$).

COMMENT

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Intrahepatic cholangiocarcinoma remains a rare neoplasm despite a steady increase in the incidence of IHC and in the mortality rates associated with IHC worldwide.¹⁻³ Although liver resection is the only curative treatment, the rarity of the disease has hampered significant progress in terms of surgical approach and outcome. In addition, because effective adjuvant protocols are still lacking, the prognosis is generally perceived as unsatisfactory.^{6 15-17-19-22-30} By contrast, the present study, which analyzes one of the largest contemporary series of resected IHCs from tertiary referral centers, provides new evidence supporting the effectiveness of an aggressive surgical approach. First, adoption of a rigorous patient-selection process resulted in a formally curative (RO) resection in 84.6% of patients, a rate significantly higher than that reported in most series.^{6 20-22-30-31} The type of surgery, which entailed major or extended hepatectomies in 70% of patients and the association of additional major procedures in one-third of patients, might have contributed to this result. Interestingly, this aggressive surgical approach did not translate into a prohibitive perioperative risk. Rather, in the most recent years, the mortality rate has almost halved, a fact that likely reflects progress in surgical techniques and perioperative care. It can be hypothesized that this growing experience, by facilitating the selection of complex surgical procedures such as extended hepatectomies, may provide a chance for a cure for patients with formerly nonresectable tumors. Second, the 5-year overall survival rate of 39.8% exceeds the survival estimates reported in most single-center series.^{6 20-22-30} Although

reports based on retrospective multi-institutional cooperations have intrinsic limitations, in the present study, the collection of data from multiple centers might have reduced possible patient-selection and referral biases. Thus, the results from the data herein presented on long-term survival, both actuarial and actual, should be regarded as remarkable and repeatable.

The present study is also important because, by analyzing a cohort of more than 400 patients, it provides robust and generalizable results on the prognostic significance of various clinicopathologic factors. Such results are crucial not only for predicting a prognosis after resection but also for permitting a precise patient stratification in clinical research based on the individual risk of death. At present, however, despite promising results in terms of progression-free survival and tumor response obtained with chemotherapy for patients with unresectable biliary tract cancer,^{32,33} we believe that our findings cannot be used to routinely recommend neoadjuvant treatments for high-risk patients with resectable tumors. We found that the most important, independent determinant of survival was the presence of LN metastases and that 36.6% of patients who had their LNs evaluated had N1 disease, a percentage similar to that noted in previous reports.^{11, 16,18,22,30} Although some Western surgeons are still reluctant to routinely perform a locoregional lymphadenectomy,^{18,22,30} in aggregate, our findings argue in favor of including this procedure as a standard approach for all patients undergoing a hepatectomy for IHC. This surgical step is, in fact, essential for accurately staging as N1 the tumors in a significant proportion of patients who might be candidates for adjuvant therapies. Noteworthy is the observation that this is true also for patients with very small IHCs. We found that 24.4% patients with IHCs 3 cm in diameter or smaller have LN metastases, a percentage that progressively increases with increasing tumor size. We are aware that this incidence might be overestimated because roughly one-third of patients (27.9%) did not undergo a lymphadenectomy. Nevertheless, the prevalence of patients with N1 disease among those with IHCs 3 cm or smaller in size would have been 15% if all NX tumors had been considered NO tumors.

Beside its staging relevance, a systematic LN dissection has the theoretical potential to improve long-term survival. Yet, this is still unproven. In fact, a direct demonstration of higher survival rates in patients who had undergone a lymphadenectomy vs those who had not is impossible because, for patients who had not undergone LN dissection, the N status cannot be ascertained. Therefore, we used the concept of the therapeutic value index, which is obtained by multiplying the incidence of LN metastases by the 5-year survival rate of patients with N1 disease. This index, which provides an estimation of the survival benefit of lymphadenectomy, is based on the assumption that none of the patients who survived for 5 years after resection of LN metastases would have done so if the involved LNs had been left in situ. Although the index value determining the indication for a systematic lymphadenectomy cannot be defined, using this index, we can compare LN areas in terms of the therapeutic value of a node's dissection. Notably, our therapeutic value index (5.9) was similar to those obtained by Ueno et al²⁹ when they were evaluating the benefit of the removal of mesorectal LNs in patients with low, advanced rectal cancer. In such patients, none would argue about the appropriateness of the total mesorectal excision. Similarly, we can infer that, for patients with IHC, a routine lymphadenectomy might add a potential advantage without increasing the surgical risk. In fact, we noted that only 2 of 313 patients who had an LN dissection developed a clinically significant lymphorrhea, the sole complication that can be directly correlated with this specific, single surgical step. In addition, removal of metastatic LNs might reduce the risk of local recurrences similar to what has been reported in pancreatic cancer.³⁴ One of the limitations of our study is that we could not determine the site of LN metastases in patients with N1 disease and, thus, the most appropriate extent of a lymphadenectomy. Nevertheless, we believe that a systematic LN dissection should at least include the first echelon LNs.²⁵

The second major “technical” aspect that deserves consideration in order to define the standard surgical approach to IHC is the resection margin. In fact, the optimal margin necessary to improve survival and to reduce the risk for recurrence is still uncertain.^{8,19,21, 24} Therefore, we tested whether our definition of an optimal margin (>0 mm) was oncologically adequate. Our data indicate that, similar to colorectal liver metastases,³⁵ the status rather than the width of the margin is prognostically relevant. Therefore, any margin-negative resection should be considered a radical operation. In addition, we reported that the survival rates of patients with a positive margin (65.1% of patients lived for 1 year after surgery, 37.7% of patients lived for 3 years, and 4.7% of patients lived for 5 years), albeit significantly inferior to that of patients who had a negative-margin resection, compare favorably with the survival time of 6 to 12 months observed for patients who were managed with palliative treatments.¹ Our data, however, should be interpreted in the light of possible biases due to missing values or the absence of information on the resection technique (Kelly-clamp crush vs ultrasonic dissection).

In conclusion, hepatic resection remains the only chance of a cure for patients with IHC. Our results support an aggressive surgical approach that results in a high RO resection rate and enhanced long-term survival.

ARTICLE INFORMATION

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REFERENCES

1

Shaib YH, Davila JA, McGlynn K, El-Serag HB. Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase? *J Hepatol.* 2004;40(3):472-477

[PubMed](#) | [Link to Article](#)

2

Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. *Hepatology.* 2001;33(6):1353-1357

[PubMed](#) | [Link to Article](#)

3

Alvaro D, Crocetti E, Ferretti S, Bragazzi MC, Capocaccia R. AISF Cholangiocarcinoma committee. Descriptive epidemiology of cholangiocarcinoma in Italy. *Dig Liver Dis.* 2010;42(7):490-495

[PubMed](#) | [Link to Article](#)

4

McGlynn KA, Tarone RE, El-Serag HB. A comparison of trends in the incidence of hepatocellular carcinoma and intrahepatic cholangiocarcinoma in the United States. *Cancer Epidemiol Biomarkers Prev.* 2006;15(6):1198-1203

[PubMed](#) | [Link to Article](#)

5

Tan JC, Coburn NG, Baxter NN, Kiss A, Law CH. Surgical management of intrahepatic cholangiocarcinoma—a population-based study. *Ann Surg Oncol.* 2008;15(2):600-608

[PubMed](#) | [Link to Article](#)

6

Weimann A, Varnholt H, Schlitt HJ, et al. Retrospective analysis of prognostic factors after liver resection and transplantation for cholangiocellular carcinoma. *Br J Surg.* 2000;87(9):1182-1187

[PubMed](#) | [Link to Article](#)

7

Isa T, Kusano T, Shimoji H, Takeshima Y, Muto Y, Furukawa M. Predictive factors for long-term survival in patients with intrahepatic cholangiocarcinoma. *Am J Surg.* 2001;181(6):507-511

[PubMed](#) | [Link to Article](#)

8

Uenishi T, Hirohashi K, Kubo S, Yamamoto T, Yamazaki O, Kinoshita H. Clinicopathological factors predicting outcome after resection of mass-forming intrahepatic cholangiocarcinoma. *Br J Surg*. 2001;88(7):969-974
[PubMed](#) | [Link to Article](#)

9

Kawarada Y, Yamagiwa K, Das BC. Analysis of the relationships between clinicopathologic factors and survival time in intrahepatic cholangiocarcinoma. *Am J Surg*. 2002;183(6):679-685
[PubMed](#) | [Link to Article](#)

10

Nakagawa T, Kamiyama T, Kurauchi N, et al. Number of lymph node metastases is a significant prognostic factor in intrahepatic cholangiocarcinoma. *World J Surg*. 2005;29(6):728-733
[PubMed](#) | [Link to Article](#)

11

Nakagohri T, Kinoshita T, Konishi M, Takahashi S, Gotohda N. Surgical outcome and prognostic factors in intrahepatic cholangiocarcinoma. *World J Surg*. 2008;32(12):2675-2680
[PubMed](#) | [Link to Article](#)

12

Shimada K, Sano T, Nara S, et al. Therapeutic value of lymph node dissection during hepatectomy in patients with intrahepatic cholangiocellular carcinoma with negative lymph node involvement. *Surgery*. 2009;145(4):411-416
[PubMed](#) | [Link to Article](#)

13

Lang H, Sotiropoulos GC, Sgourakis G, et al. Operations for intrahepatic cholangiocarcinoma: single-institution experience of 158 patients. *J Am Coll Surg*. 2009;208(2):218-228
[PubMed](#) | [Link to Article](#)

14

Guglielmi A, Ruzzenente A, Campagnaro T, et al. Intrahepatic cholangiocarcinoma: prognostic factors after surgical resection. *World J Surg*. 2009;33(6):1247-1254
[PubMed](#) | [Link to Article](#)

15

Jonas S, Thelen A, Benckert C, et al. Extended liver resection for intrahepatic cholangiocarcinoma: a comparison of the prognostic accuracy of the fifth and sixth editions of the TNM classification. *Ann Surg*. 2009;249(2):303-309
[PubMed](#) | [Link to Article](#)

16

Choi SB, Kim KS, Choi JY, et al. The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node dissection with survival. *Ann Surg Oncol*. 2009;16(11):3048-3056
[PubMed](#) | [Link to Article](#)

17

Shirabe K, Mano Y, Taketomi A, et al. Clinicopathological prognostic factors after hepatectomy for patients with mass-forming type intrahepatic cholangiocarcinoma: relevance of the lymphatic invasion index. *Ann Surg Oncol*. 2010;17(7):1816-1822
[PubMed](#) | [Link to Article](#)

18

Ercolani G, Vetrone G, Grazi GL, et al. Intrahepatic cholangiocarcinoma: primary liver resection and aggressive multimodal treatment of recurrence significantly prolong survival. *Ann Surg*. 2010;252(1):107-114
[PubMed](#) | [Link to Article](#)

19

Tamandl D, Herberger B, Gruenberger B, Puhalla H, Klinger M, Gruenberger T. Influence of hepatic resection margin on recurrence and survival in intrahepatic cholangiocarcinoma. *Ann Surg Oncol.* 2008;15(10):2787-2794
[PubMed](#) | [Link to Article](#)

20

Endo I, Gonen M, Yopp AC, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg.* 2008;248(1):84-96
[PubMed](#) | [Link to Article](#)

21

Shimada K, Sano T, Sakamoto Y, Esaki M, Kosuge T, Ojima H. Clinical impact of the surgical margin status in hepatectomy for solitary mass-forming type intrahepatic cholangiocarcinoma without lymph node metastases. *J Surg Oncol.* 2007;96(2):160-165
[PubMed](#) | [Link to Article](#)

22

Farges O, Fuks D, Boleslawski E, et al. Influence of surgical margins on outcome in patients with intrahepatic cholangiocarcinoma: a multicenter study by the AFC-IHCC-2009 study group. *Ann Surg.* 2011;254(5):824-829, discussion 830
[PubMed](#) | [Link to Article](#)

23

Cho SY, Park SJ, Kim SH, et al. Survival analysis of intrahepatic cholangiocarcinoma after resection. *Ann Surg Oncol.* 2010;17(7):1823-1830
[PubMed](#) | [Link to Article](#)

24

Konstadoulakis MM, Roayaie S, Gomatos IP, et al. Fifteen-year, single-center experience with the surgical management of intrahepatic cholangiocarcinoma: operative results and long-term outcome. *Surgery.* 2008;143(3):366-374
[PubMed](#) | [Link to Article](#)

25

The Liver Cancer Study Group of Japan. Intrahepatic cholangiocarcinoma . In: The Liver Cancer Study Group of Japan, eds. *Classification of Primary Liver Cancer.* 1st English ed. Tokyo, Japan: Kanehara; 1997:6-7

26

Edge SB, Byrd DR, Compton CC, et al. Intrahepatic bile ducts. In: *AJCC Cancer Staging Manual.* 7th ed. New York, NY: Springer; 2009:201-210

27

Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240(2):205-213
[PubMed](#) | [Link to Article](#)

28

Little RJA, Rubin DB. *Statistical Analysis With Missing Data.* New York, NY: John Wiley & Sons; 1987

29

Ueno H, Mochizuki H, Hashiguchi Y, et al. Potential prognostic benefit of lateral pelvic node dissection for rectal cancer located below the peritoneal reflection. *Ann Surg.* 2007;245(1):80-87
[PubMed](#) | [Link to Article](#)

30

de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol.* 2011;29(23):3140-3145
[PubMed](#) | [Link to Article](#)

31

Nuzzo G, Giuliani F, Ardito F, et al. Intrahepatic cholangiocarcinoma: prognostic factors after liver resection. *Updates Surg.* 2010;62(1):11-19
[PubMed](#) | [Link to Article](#)

32

Gruenberger B, Schueller J, Heubrandtner U, et al. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. *Lancet Oncol.* 2010;11(12):1142-1148
[PubMed](#) | [Link to Article](#)

33

Valle J, Wasan H, Palmer DH, et al; ABC-O2 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med.* 2010;362(14):1273-1281
[PubMed](#) | [Link to Article](#)

34

Capussotti L, Massucco P, Ribero D, Viganò L, Muratore A, Calgaro M. Extended lymphadenectomy and vein resection for pancreatic head cancer: outcomes and implications for therapy. *Arch Surg.* 2003;138(12):1316-1322
[PubMed](#) | [Link to Article](#)

35

Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg.* 2005;241(5):715-722, discussion 722-724
[PubMed](#) | [Link to Article](#)