# Surgical Approach for Long-term Survival of Patients With Intrahepatic Cholangiocarcinoma A Multi-institutional Analysis of 434 Patients FREE

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*Arch Surg*. 2012;147(12):1107-1113. doi:10.1001/archsurg.2012.1962.

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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 stage[5] 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

ABSTRACT | METHODS | RESULTS | COMMENT | ARTICLE INFORMATION |REFERENCES

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 classification[25]), 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



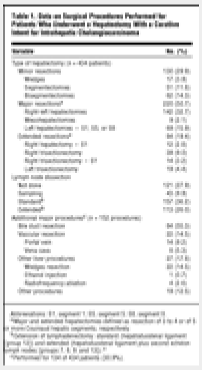
### CHARACTERISTICS OF PATIENTS

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



| Variable | No. (%) |
|---|---|
| Type of hepatectomy (n = 434 patients) | |
| Minor resections | [illegible] |
| Wedges | [illegible] |
| Segmentectomies | [illegible] |
| Bisegmentectomies | [illegible] |
| Major resections | [illegible] |
| Right-left hepatectomies | [illegible] |
| Mesohepatectomies | [illegible] |
| Left hepatectomies + S1, S5, or S8 | [illegible] |
| Extended resections | [illegible] |
| Right hepatectomy + S1 | [illegible] |
| Right trisectionectomy | [illegible] |
| Right trisectionectomy + S1 | [illegible] |
| Left trisectionectomy | [illegible] |
| Lymph node dissection | |
| Not done | [illegible] |
| Sampling | [illegible] |
| Standard | [illegible] |
| Extended | [illegible] |
| Additional major procedures (n = [illegible] procedures) | |
| Bile duct resection | [illegible] |
| Vascular resection | [illegible] |
| Portal vein | [illegible] |
| Vena cava | [illegible] |
| Other liver procedures | [illegible] |
| Wedges resection | [illegible] |
| Ethanol injection | [illegible] |
| Radiofrequency ablation | [illegible] |
| Other procedures | [illegible] |

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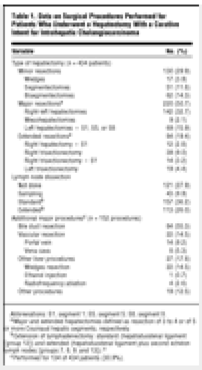

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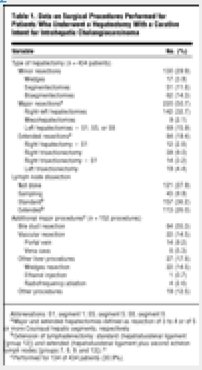

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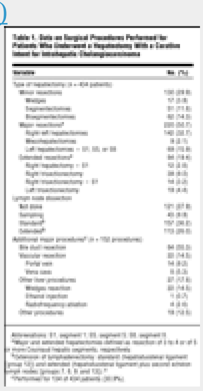

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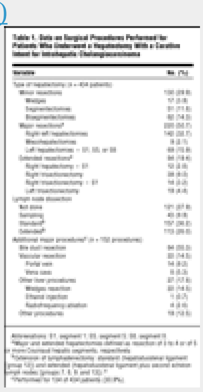

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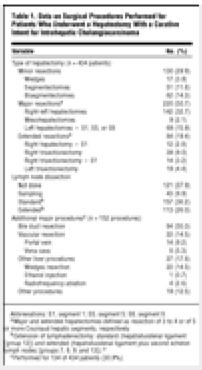

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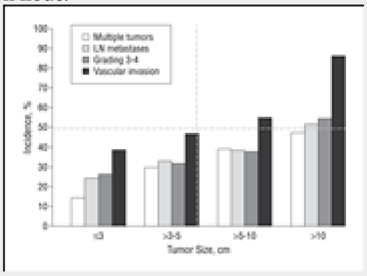
**PATHOLOGIC FINDINGS**

The descriptive pathologic characteristics of the study cohort are detailed in Table 2. The overall incidence of LN metastases was 36.9% in patients who had undergone some form of LN dissection. As tumor size increased, the incidence of nodal involvement increased (≤3 cm, 24.4% of patients; 3.1-5 cm, 32.8% of patients; 5.1-10 cm, 38.6% of patients; and ≥10 cm, 51.6% of patients [*P* = .012]). Similarly, the incidence of multiple tumors, vascular invasion, and poorly undifferentiated tumors increased with tumor size (all*P* < .005) (Figure).

**Figure.** Relation between tumor size and other pathologic parameters of 434 patients who underwent a hepatectomy with a curative intent for intrahepatic cholangiocarcinoma. LN indicates lymph node.

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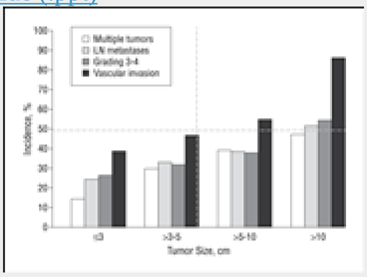


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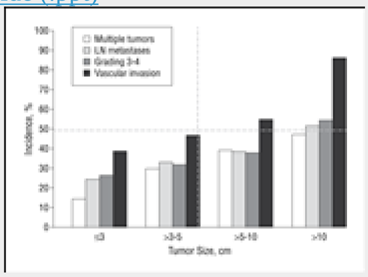


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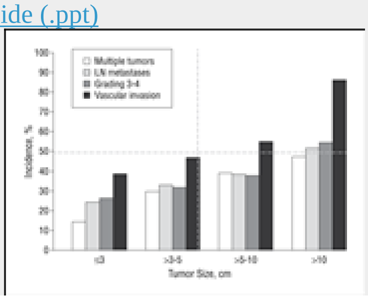

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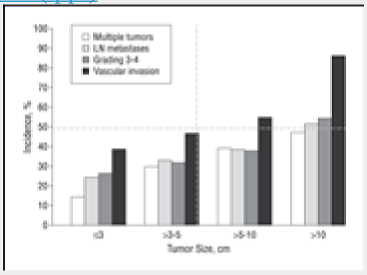


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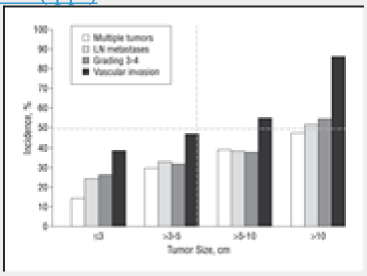


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Table 2. Pathologic Features of the Patients Who Underwent a Hepatectomy With a Curative Intent for IHC

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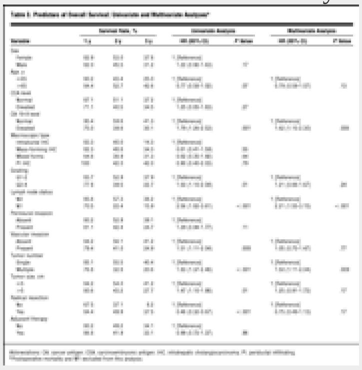
On final pathologic analysis, 52 patients (12.0%) had a positive resection margin. The median width of tumor-free margin was 10 mm (range, 0.5-40 mm). Stratification for margin width was 0.5 to 9 mm (median width, 4 mm) for 133 patients (30.6%) and 1 cm or larger (median width,15 mm) for 159 patients (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 macroscopic typing and perineural invasion, and the radicality of resection proved to correlate with survival. On multivariate analysis, only LN metastases (hazard ratio, 2.21 [95% CI, 1.55-3.15]; $P = .005$), multiple tumors (hazard ratio, 1.50 [95% CI, 1.11-2.04]; $P < .001$), and an elevated preoperative cancer antigen 19-9 level (hazard ratio, 1.62 [95% CI, 1.15-2.30]; $P = .006$) remained independent predictors of poor survival. Similar results were obtained in the second set of analyses using regression imputation to account for missing data. The corresponding hazard ratios were 2.01 (95% CI, 1.49-2.72) for LN metastases ($P < .001$), 1.57 (95% CI, 1.16-2.10) for multiple tumors ($P = .004$), and 1.60 (95% CI, 1.16-2.21) for an elevated preoperative cancer antigen 19-9 level ($P = .004$).

Table 3. Predictors of Overall Survival: Univariate and Multivariate Analyses[a]



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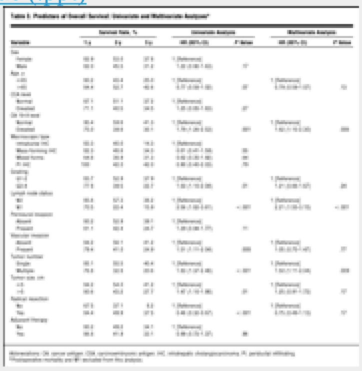

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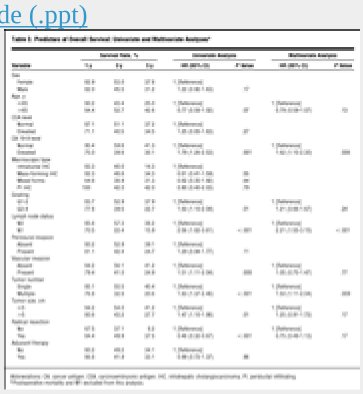

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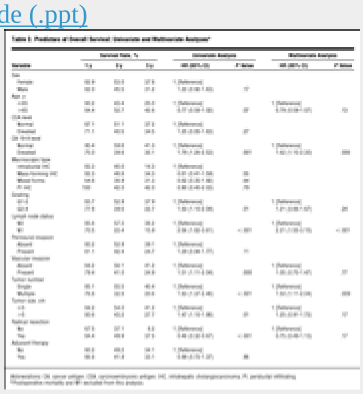

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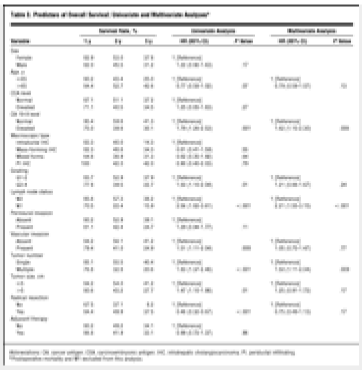

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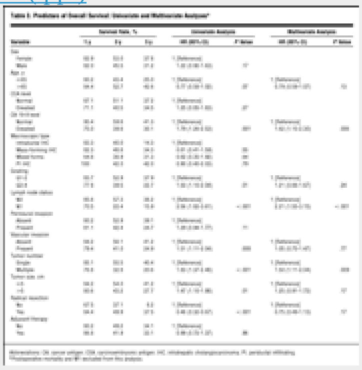

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#### IMPLICATIONS FOR SURGICAL MANAGEMENT

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

ABSTRACT | METHODS | RESULTS | COMMENT | ARTICLE INFORMATION |REFERENCES

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 (R0) 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 N0 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 al[29] 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 R0 resection rate and enhanced long-term survival.

# ARTICLE INFORMATION

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**Accepted for Publication:** June 18, 2012.
**Published Online:** August 20, 2012. doi:10.1001 /archsurg.2012.1962
**Author Contributions:** *Study concept and design*: Ribero, Ponti, Nuzzo, Giulini, Calise, Gerunda, Torzilli, and Capussotti. *Acquisition of data*: Ribero, Pinna, Guglielmi, Nuzzo, Aldrighetti, Calise, Amisano, Berloco, Torzilli, and Capussotti. *Analysis and interpretation of data*: Ribero, Pinna, Ponti, Calise, Gerunda, Tomatis, Amisano, and Capussotti. *Drafting of the manuscript*: Ribero and Tomatis. *Critical revision of the manuscript for important intellectual content*: Pinna, Guglielmi, Ponti, Nuzzo, Giulini, Aldrighetti, Calise, Gerunda, Amisano, Berloco, Torzilli, and Capussotti. *Statistical analysis*: Ribero, Ponti, Tomatis, Amisano, and Capussotti. *Study supervision*: Pinna, Guglielmi, Nuzzo, Giulini, Aldrighetti, Calise, Gerunda, Torzilli, and Capussotti.
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**Financial Disclosure:** None reported.

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