Original Investigation

Treatment and Prognosis for Patients With Intrahepatic Cholangiocarcinoma
Systematic Review and Meta-analysis

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IMPORTANCE Data on outcomes following surgical management of intrahepatic cholangiocarcinoma (ICC) are limited. The incidence of ICC is increasing and it has a poor prognosis. No consensus has been reached regarding the optimal treatment modalities.

OBJECTIVE To systematically review and synthesize the available evidence regarding treatment and prognosis in patients with ICC.

DATA SOURCES The PubMed database was searched for relevant articles published between January 1, 2000, and April 1, 2013.

STUDY SELECTION Only studies assessing predictors of survival or recurrence in patients undergoing curative-intent surgical treatment of ICC were included. Small series, studies reporting on mixed types of cholangiocarcinoma, or exclusively on hepatolithiasis-associated cholangiocarcinoma, and those published in a language other than English, French, German, Italian, or Greek, were excluded. Fifty-seven of 960 articles were analyzed.

DATA EXTRACTION AND SYNTHESIS Data on preoperative, intraoperative, and postoperative variables were extracted by 3 independent reviewers. Multiple studies reporting on the same population were excluded. Data were pooled using a random-effects model.

MAIN OUTCOMES AND MEASURES We hypothesized that preoperative variables and tumor characteristics affect patient survival. The outcomes of the study were overall survival and recurrence-free survival. The hypothesis was formulated before data collection.

RESULTS Fifty-seven studies (4756 patients) were included in the review. Median patient age ranged from 49 to 67 years, and 57% were male. Most patients had a solitary (69%), large (median size, 4.5-8.0 cm) tumor of the mass-forming type (86%). Approximately one-third of the patients had lymph node metastasis (34%) or vascular (38%), perineural (29%), or biliary invasion (29%). Most underwent a major hepatectomy (82%), often accompanied by lymphadenectomy (67%) and sometimes by extrahepatic bile duct resection (23%). Median and 5-year overall survival (OS) generally were approximately 28 months (range, 9-53 months) and 30% (range, 5%-56%), respectively; factors predicting shorter OS included large tumor size, multiple tumors, lymph node metastasis, and vascular invasion. Adjuvant chemotherapy or radiotherapy did not appear to be beneficial. Seven studies (2132 patients) provided data for the meta-analysis. Factors associated with shorter OS included older age (pooled hazard ratio, 1.10; 95% CI, 1.03-1.17), larger tumor size (1.09; 1.02-1.16), presence of multiple tumors (1.70; 1.43-2.02), lymph node metastasis (2.09; 1.80-2.43), vascular invasion (1.87; 1.44-2.42), and poor tumor differentiation (1.41; 1.17-1.71).

CONCLUSIONS AND RELEVANCE The prognosis of ICC is dictated mainly by tumor factors. Future research could focus on the usefulness of adjuvant treatment as well as other multidisciplinary treatment modalities.

JAMA Surg. 2014;149(6):565-574. doi:10.1001/jamasurg.2013.5137
Published online April 9, 2014.

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Although intrahepatic cholangiocarcinoma (ICC) is relatively rare, its incidence and mortality are increasing worldwide.[1,2] In the United States, the age-adjusted incidence of ICC increased from 0.32 in 1975 to 0.85 per 100 000 population in 2000 and has yet to plateau.[1,3] At the same time, long-term survival of patients with unresectable ICC is dismal, with less than 5% to 10% of the patients alive 5 years after the diagnosis.[1] The only potentially curative treatment option for patients who have resectable disease is surgery. Unfortunately, even after curative-intent surgery, the clinical outcomes of patients undergoing liver resection are disappointing, with a 5-year survival rate of 20% to 35%.[4-9] Furthermore, the role of adjuvant therapies, including systemic chemotherapy and radiotherapy, remain poorly defined and have been reported[6,7] to have only a modest therapeutic effect.

As such, the optimal treatment strategy for patients with resectable ICC has not been well characterized. Although liver resection may offer the only chance for cure, there is still debate regarding the various treatment strategies as well as the factors most associated with prognosis.[10] For instance, routine staging laparoscopy has been proposed[11] for patients with operable ICC because of concern for a high incidence of metastatic disease not detected by conventional imaging methods; however, routine use of laparoscopy at the time of surgery remains controversial. Lymphadenectomy is also not routinely performed in most Western countries despite data suggesting that lymph node status may provide considerable prognostic information.[10,11] Furthermore, the role of neoadjuvant and adjuvant treatment in patients with ICC undergoing curative-intent resection remains poorly understood. Reports on the characteristics of patients with ICC as well as predictors of recurrence and survival, are relatively scarce. Available data in the present study were largely derived from retrospective observational studies, mostly from small, single-institution series. In this context, we sought to systematically review the literature regarding treatment options, prognostic factors, and clinical outcomes of patients with ICC treated with curative intent. In addition, we performed a synthesis of the published data and a meta-analysis of these data to identify factors associated with prognosis following curative-intent surgery for ICC.

Methods

Literature Search

A systematic search of the pertinent literature was performed in April 2013. The PubMed database was queried with the search pattern *intrahepatic* and *cholangiocarcinoma* and *survival* and *surgery or surgical* for studies published on or after January 1, 2000. Studies published in English, French, German, Italian, or Greek were considered eligible. The references of relevant articles were reviewed to identify additional eligible publications.

Study Selection

Potentially eligible studies were screened for inclusion in our review. We included studies reporting on factors prognostic of survival or recurrence in patients undergoing curative-intent surgical treatment of ICC. Prognostic factors included preoperative, intraoperative, and postoperative variables. Small series assessing fewer than 20 patients, as well as studies not assessing factors prognostic of clinical outcome or not reporting results of univariate analyses, were excluded. Also excluded were studies reporting on mixed series of patients with intrahepatic and other types of cholangiocarcinoma (eg, hilar cholangiocarcinoma) as well as series of patients with exclusively hepatolithiasis-associated ICC or recurrent ICC. Conference abstracts that did not proceed to publication in peer-reviewed journals were not included in the present review.[12]

Data Extraction

Data were extracted regarding the study setting and time period as well as patients' preoperative, intraoperative, and postoperative characteristics. Preoperative variables included patient demographics (age and sex), disease characteristics (presence of concurrent hepatitis B or C infection, cirrhosis, steatohepatitis, hepatolithiasis, and primary sclerosing cholangitis as well as preoperative serum α-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen 19-9 levels), and tumor characteristics (macroscopic histologic type, differentiation, size, and number of lesions; microvascular, macrovascular, portal vein, hepatic vein, biliary, perineural, and adjacent organ invasion; and intrahepatic, extrahepatic, or lymph node metastases). Data regarding treatment included the extent of liver resection (major hepatectomy was considered the resection of 3 or more liver segments, unless otherwise defined in the original study), the concomitant resection of extrahepatic bile ducts, the surgical margins (R0 vs R1 vs R2), the performance of lymphadenectomy, and the receipt of preoperative or postoperative systemic chemotherapy, transarterial chemoembolization, or radiotherapy. We also extracted data regarding blood transfusions and postoperative complications. Finally, the clinical outcomes of the patients were recorded, including median, 3-year, and 5-year overall and recurrence-free survival as well as additional data on the recurrence sites.

When multiple studies analyzed the same population (ie, series from the same hospital), data were extracted from the larger study; if the sample size was similar, the one with the longest follow-up was assessed. To identify such studies, we assessed each study's setting (name of hospital, university affiliation, and location), and time period as well as each study's investigators.

Statistical Analysis

Summary statistics were reported as total and percentage for categorical variables and as median values and range for continuous variables, unless stated otherwise. The meta-analysis was performed with Review Manager (RevMan), version 5.2 software (Nordic Cochrane Centre, the Cochrane Collaboration, 2012). Statistical heterogeneity between studies was assessed with a χ^2 test and I^2; $P < .10$ for the χ^2 test or I^2 greater than 50% indicated significant heterogeneity. Publication bias was assessed using the Egger test by the funnel plot method.[13] Pooled hazard ratios (HRs) and 95% CIs were

calculated using each study's log(HR) and its SE log(HR); the inverse variance method and the random effects model were applied. The variance of log(HR) was calculated using the methods described by Parmar et al.[14] For studies not reporting HRs and comparing survival using the log-rank test, the log(HR) and variance were estimated using an indirect method described by Parmar et al based on the log-rank *P* value and the total number of events, provided that the effect size was not too large and the compared groups had similar sample sizes. Statistical significance was set at $P < .05$.

Results

A total of 960 studies were screened; 162 were selected for further review and 57 were included in our study.[4-8,11,15-65] Most studies originated from South Asia/Pacific (33 studies: Japan, 16; China 11; and other, 6), followed by Europe (n = 13) and the United States (n = 11). Common reasons for exclusion were the absence of specific data regarding patients with ICC (36 series had mixed populations of ICC with other types of cholangiocarcinoma or patients provided therapy with curative and palliative intent), the lack of eligible analyses of prognostic factors (n = 34), the analysis of fewer than 20 patients with ICC (n = 14), or the inclusion of the studied population in another publication without providing further eligible data (n = 16). The selection process is depicted in **Figure 1**. Of the 57 studies, 15 analyzed populations partially overlapping with those of another eligible study but provided additional eligible data.[11,52-65] The 42 index studies analyzed 4756 patients.[4-8,15-51] All studies were retrospective.

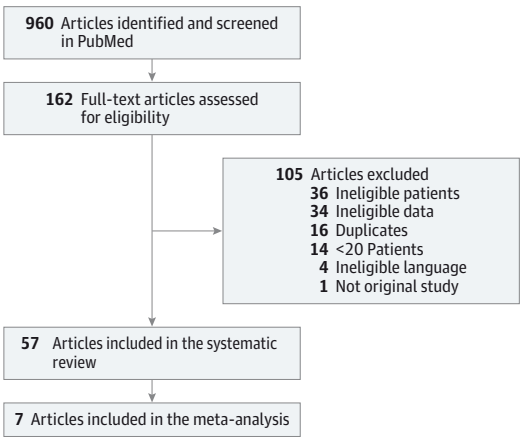
Patient and Disease Characteristics

Table 1 shows the clinicopathologic characteristics of patients included in the analyzed studies. The median age of the patients ranged from 49 to 67 years. Overall, there was a slight predominance of men (57%; range among the studies, 32%-83%). Most patients (86%; range, 24%-100%) had the mass-forming subtype of ICC. The prevalence of cirrhosis was 16% (range, 0%-35%); of hepatitis B, 15% (range, 0%-73%); and of hepatitis C, 10% (range, 0%-45%). The median size of the tumor ranged from 4.5 to 8.0 cm, and most patients (69%; range, 41%-94%) had a solitary tumor. Vascular and perineural invasion were present in 38% (range, 13%-98%) and 29% (range, 12%-55%) of the patients, respectively; biliary invasion was present in 29% of the population (range, 13%-63%). Among patients who had a lymphadenectomy, approximately one-third had lymph node metastases (34%; range, 9%-100%).

Treatment and Clinical Outcomes

Details regarding the treatment and clinical outcomes of patients are presented in Table 1. Most patients underwent a major hepatectomy (82%; range, 43%-100%), and approximately one-fourth (23%; range, 2%-59%) also had an extrahepatic bile duct resection; surgical margins were microscopically negative (R0) in most cases (74%; range, 37%-93%). Lymphadenectomy was performed in two-thirds of the patients (67%; range, 9%-100%). Postoperative administration of systemic chemotherapy, transarterial chemoembolization, or radiotherapy was described in 22 studies; 6 studies also reported the use of preoperative chemotherapy. Two studies assessed 43 patients who underwent orthotopic liver transplant.

Figure 1. Flow Diagram Depicting the Selection Process of the Reviewed Studies



No additional studies were identified during review of the references of the relevant articles.

The median follow-up period ranged from 14 to 43 months among the studies analyzed. Median, 3-year, and 5-year overall survival (OS) ranged from 9 to 53 months, 16% to 65%, and 5% to 56%, respectively. In a subset analysis of the 5 largest studies,[4-8] the median, 3-year, and 5-year OS ranged from 18 to 33 months, 32% to 47%, and 21% to 35%, respectively. With regard to recurrence, median, 3-year, and 5-year recurrence-free survival (RFS) ranged from 7 to 34 months, 6% to 47%, and 2% to 39%, respectively. The most common recurrence site was the liver; other common recurrence sites included the lymph nodes, peritoneum, and lungs, and less common sites were the bones, pleura, abdominal or chest wall, and skin.

The effect of adjuvant chemotherapy, transarterial chemoembolization, or radiotherapy was assessed in 14 studies (2289 patients). Administration of systemic chemotherapy (fluorouracil, gemcitabine, or oxaliplatin based) did not affect OS in any of the 5 studies; radiotherapy appeared to be beneficial in 1 of 2 studies, and transarterial chemoembolization seemed to prolong OS in all 3 studies that examined it; however, all 3 studies originated from the same center, although they analyzed different time periods. Four studies looking at the impact of adjuvant chemotherapy and/or radiotherapy did not detect any effect on OS or RFS.

Prognostic Factors: Systematic Review

Among the 57 studies included in the systematic review, factors reported to predict a shorter recurrence-free interval on univariate analysis included younger age (1 of 12 studies), larger tumor size (5 of 14 studies), presence of multiple tumors (10 of 14 studies) or satellite nodules (5 of 6 studies), microvascular invasion (1 of 3 studies), major vascular invasion (5 of 8

Table 1. Clinicopathologic Characteristics, Treatment, and Clinical Outcomes of Patients Assessed in the 42 Index Studies[a]

Source (Country)	No. of Patients/ Age, y/ Male Sex, %	Cirrhosis	Hepatitis B/C[b]	MF Type	Tumor Size, cm	Single Tumor	Vascular Invasion	LN Metastasis	Major Liver Resection/ EHBD	Lymphadenectomy	Postoperative CT/RT	OS, 3 y/5 y
Ariizumi et al,[24] 2011 (JP)	140/…/73	25	15/34	100	…	…	…	…	43/20	56	…/3	…/39
Uenishi et al,[40] 2008 (JP)	133/62[c]/61	…	9[d]/21[d]	50	…	…	60	47	83/17	100	…	36/29
Igami et al,[22] 2011 (JP)	61/61[c]/57	…	3/8	100	…	69	98	38	84/54	85	…	…/34
Shirabe et al,[31] 2010 (JP)	60/59/68	…	…	86	4.7[c]	…	…	43	…	47	…	47/31
Shimada et al,[45] 2007 (JP)	74/…/62	…	…	62	…	…	…	46	…/51	70	…	36/31
Nanashima et al,[34] 2009 (JP)	37/…/54	…	38	24	…	…	…	49	…	…	…	35/27
Nakagawa et al,[47] 2005 (JP)	28/…/61	…	…	61	…	79	50	…	…	68	…	…/26
Saiura et al,[35] 2011 (JP)	44/65/66	2	2/5	93	5.7	66	66	59	91/27	55	…	56/43
Nakagohri et al,[38] 2008 (JP)	56/66/70	…	…	77	…	82	…	38	79/43	38	…	42/32
Kawarada et al,[51] 2002 (JP)	37/63/41	…	22	100	…	59	…	57	85/…	100	46/11	…
Miwa et al,[46] 2006 (JP)	41/67/59	…	…	61	…	…	…	39	83/59	39	…	36/29
Murakami et al,[20] 2012 (JP)	44/…/66	…	14/18	39	4.6[c]	…	…	45	91/43	…	52/…	…
Horino et al,[19] 2012 (JP)	34/65/62	…	26	100	4.5	…	…	32	…	84	…	…/56
Wang et al,[4] 2013 (CN)	367/53/67	21	10/2	94	5.5	…	15	22	72[d]/2	100	42[d]/…	41/35
Fu et al,[48] 2004 (CN)	104/53/64[c]	35	25/…	100	…	…	…	33	…	…	37/…	17/10
Jiang et al,[8] 2011 (CN)	344/…/58	14	28/…	100	…	75	17	100[d]	…	100[d]	…/27[d]	32/21
Li et al,[33] 2009 (CN)	56/…/57	…	…	…	…	64	…	54	…	…	23/…	…
Li et al,[25] 2011 (CN)	115/64[c]/56	28	21/…	76	5.6[c]	…	77	40	65/26	…	…	27/17
Hu and Yan,[21] 2011 (CN)	20/49/70	20	25/…	…	…	45	…	45	OLT/NA	…	…	33/22
Zhang et al,[29] 2010 (CN)	40/56/60	30	73/45	…	…	…	…	28	…/3	…	3/5	33/28
Paik et al,[44] 2008 (KR)	97/…/66	18	…	74	5.0	86	…	24	93/…	…	…	52/31
Cho et al,[30] 2010 (KR)	63/61[c]/65	…	29/3	71	…	94	…	30	78/5	70	13/6	51/32
Choi et al,[32] 2009 (KR)	64/61[c]/67	…	…	61	…	…	58	27	91/…	80	…	53/40
Suh et al,[50] 2002 (KR)	69/…/83	…	…	49	…	…	…	14	48/…	…	…	…
Bunsiripaiboon et al,[28] 2010 (TH)	22/56[c]/59	…	…	…	6.1[c]	…	…	…	…	…	…	16/5
Saxena et al,[27] 2010 (AU)	40/60/53	…	8	63	6.5	…	…	28	73/…	…	35/…	48/28
Farges et al,[6] 2011 (FR)	212/63[c]/51	…	…	100	7.7[c]	41	44	37	86/18	…	30/…	43/28
Sulpice et al,[17] 2013 (FR)	87/66/78	25	3/2	100	…	…	…	18	76/…	…	12/…	47/31
Lang et al,[36] 2009 (DE)	83/62/42	…	…	…	7	57	41	34	90/…	…	17/…	38/21
Yedibela et al,[37] 2009 (DE)	45/59/62	4	2/4	100	…	73	…	13	67/…	40	42/…	…/35
Ribero et al,[5] 2012 (IT)	434/65/56	10	9/12	90	6.0	68	53	26	70/…	86	27/2	47/33
Gomez et al,[42] 2008 (UK)	27/57/33	0	0/0	…	…	85	…	41	89/…	…	38/…	16/16

(continued)

Table 1. Clinicopathologic Characteristics, Treatment, and Clinical Outcomes of Patients Assessed in the 42 Index Studies[a] (continued)

Source (Country)	No. of Patients/ Age, y/ Male Sex, %	Cirrhosis	Hepatitis B/C[b]	MF Type	Tumor Size, cm	Single Tumor	Vascular Invasion	LN Metas-tasis	Major Liver Resection/ EHBD	Lymph-adenec-tomy	Post-operative CT/RT	OS, 3 y/5 y
Robles et al,[49] 2004 (ES)	23/54[c]/61	...	...	...	...	...	26	9	OLT/NA	...	...	65/42
Tamandl et al,[39] 2008 (AT)	74/63/39	...	...	...	...	52[d]	29[d]	26[d]	72/...	...	23/...	45/28
Clark et al,[23] 2011 (US)	733/.../...	...	...	...	...	...	...	...	100/...	49	...	.../23
Fisher et al,[18] 2012 (US)	58/66/34	...	...	...	6.5	79	40	34	90/...	66	27/13	...
Ellis et al,[26] 2011 (US)	31/62[c]/32	...	...	100	6	94	...	...	90/...	...	...	40/...
Endo et al,[41] 2008 (US)	82/.../43	5	...	...	6.5	71	26	46	78/21	9	12	...
Ali et al,[16] 2013 (US)	121/60/42	...	...	...	8	...	...	28	100/12	82	...	...
Konstadoulakis et al,[43] 2008 (US)	54/62/52	0	2/2	100	...	...	13	...	94/...	19	6/...	49/25
Dhanasekaran et al,[15] 2013 (US)	53/.../55	10	...	...	...	...	...	27	...	...	40	33/19
de Jong et al,[7] 2011 (MN)	449/61/47	...	...	...	6.5	73	31	30	76/...	55	28/50[d]	44/31

Abbreviations: AT, Austria; AU, Australia; CN, China; CT, chemotherapy; DE, Germany; EHBD, extrahepatic bile duct; ellipses, not reported; ES, Spain; FR, France; IT, Italy; JP, Japan; KR, South Korea; LN, lymph node; MF, mass-forming; MN, multinational; NA, not applicable; OLT, orthotopic liver transplant; OS, overall survival; RT, radiotherapy; TH, Thailand; UK, United Kingdom; US, United States.

[a] Data are given as percentage unless otherwise indicated.

[b] Single number indicates that type of hepatitis was not specified.

[c] Denotes mean value; age and tumor size are presented as median values unless indicated otherwise.

[d] Data refer to a subpopulation of the study that was also assessed in another study by the same center.

studies), or perineural invasion (2 of 5 studies). Other factors prognostic of shorter RFS were positive surgical margin (R1 vs R0, 2 of 11 studies), lymph node metastases (11 of 15 studies), poor tumor differentiation (7 of 10 studies), history of a major hepatectomy (1 of 6 studies), administration of multiple blood transfusions (1 of 5 studies), and receipt of preoperative chemotherapy (1 of 1 study). In contrast, factors not associated with RFS included sex (12 studies), presence of concurrent chronic hepatitis infection (hepatitis B in 2 studies and hepatitis C in 1 study) or cirrhosis (2 studies), concomitant resection of extrahepatic bile ducts (4 studies), and the administration of postoperative chemotherapy (3 studies).

Factors that predicted a shorter OS on univariate analysis included age (older in 3 vs younger in 1 of 32 studies), sex (males in 4 vs females in 1 of 32 studies), larger tumor size (15 of 35 studies), presence of multiple tumors (13 of 23 studies) or satellite nodules (5 of 7 studies), any vascular invasion (13 of 19 studies), microvascular invasion (4 of 7 studies), and perineural invasion (7 of 12 studies). Other factors associated with a shorter OS included lymph node metastases (29 of 34 studies), a positive surgical margin (R1/R2 vs R0, 21 of 31 studies), poor tumor differentiation (12 of 22 studies), a major liver resection (1 of 7 studies), concomitant resection of the extrahepatic bile ducts (2 of 6 studies), presence of cirrhosis (1 of 5 studies), concurrent chronic hepatitis B (1 of 10 studies), multiple blood transfusions (2 of 6 studies), postoperative morbidity (1 of 2 studies), and administration of preoperative or postoperative chemotherapy (1 of 1 study). In contrast, administration of postoperative adjuvant chemotherapy/radiotherapy was associated with longer OS in 3 of 10 studies. The presence of concurrent chronic hepatitis C infection was not associated with OS in 3 studies. The factors analyzed in the 5 largest series (univariate and multivariate analyses) are presented in **Table 2**.[4-8]

Prognostic Factors: Meta-analysis

Seven studies[4,5,7,18,23,28,39] (2132 patients) were eligible for meta-analysis. The forest plot for all comparisons is presented in **Figure 2**. The criteria for indirect estimation of effect measures were not met for any comparison because of differences in the sample size among the compared groups or a high effect size. Men had a tendency toward shorter RFS (HR, 1.03 [95% CI, 0.999-1.06]; 458 patients) and OS (1.11 [0.97-1.26]; 1625 patients). Older age was not associated with RFS (1.02 [0.78-1.32]; 458 patients) but was associated with shorter OS (1.10 [1.03- 1.17] for each 10-year increment; 1191 patients). Larger tumor size was also not predictive of RFS (1.35 [0.78-2.33]; 458 patients); however, it was associated with shorter OS (1.09 [1.02-1.16] for each 1-cm increment; 907 patients). Other factors associated with shorter OS included the presence of multiple tumors (1.70 [1.43-2.02]; 1330 patients), lymph node metastasis (2.09 [1.80-2.43]; 1661 patients), vascular invasion (1.87 [1.44-2.42]; 1319 patients), and poor tumor differentiation (1.41 [1.17-1.71]; 561 patients). In contrast, a positive surgical margin did not affect OS (1.06 [0.49-2.32]; 583 patients) or RFS (0.89 [0.64-1.23]; 458

Table 2. Factors Prognostic of OS of Patients With ICC Treated With Curative Intent, as Reported in the Largest Published Series

Source (Country)	Study Period	No. of Patients	Prognostic Factors of Shorter OS
de Jong et al,[7] 2011 (MN [MC])	1973-2010	449	Not associated with OS: several factors (NR),[a] including biliary invasion or direct invasion of adjacent organs; univariate prognostic factors: large tumor size, multiple tumors, vascular invasion, lymph node metastasis; independent prognostic factors: multiple tumors, vascular invasion, lymph node metastasis
Ribero et al,[5] 2012 (IT [MC])	1990-2008	434	Not associated with OS: age, sex, serum CEA, tumor macroscopic type, perineural invasion, adjuvant treatment; univariate prognostic factors: high serum CA 19-9, poor tumor differentiation, lymph node metastasis, vascular invasion, large tumor size, multiple tumors, radical resection; independent prognostic factors: high serum CA 19-9, lymph node metastasis, multiple tumors
Wang et al,[4] 2013 (CN)	2002-2007	367	Not associated with OS: age, sex, hepatitis B, vascular invasion, surgical margin (<1 vs ≥1 cm), presence of intact capsule, cirrhosis, microvascular invasion; univariate prognostic factors: elevated laboratory values (serum CEA, CA 19-9, total bilirubin, albumin, GGT), blood transfusions, large tumor size, multiple tumors, lymph node metastasis, vascular invasion, direct invasion, local extrahepatic metastasis; independent prognostic factors: high serum CEA and CA 19-9, large tumor size, multiple tumors, lymph node metastasis, vascular invasion, direct invasion, local extrahepatic metastasis
Jiang et al,[8] 2011 (CN)	1998-2008	344	Not associated with OS: age, sex, hepatitis B, vascular invasion; univariate prognostic factors: low serum albumin, high serum ALP and CA 19-9, multiple tumors, large tumor size (≥10 cm), obscure tumor boundary; independent prognostic factors: multiple tumors, large tumor size, obscure tumor boundary, high serum ALP and CA 19-9
Farges et al,[6] 2011 (FR [MC])	1998-2008	212	Not associated with OS: NR; univariate prognostic factors: pathologic TNM stage, large tumor size, satellite nodules, vascular invasion, lymph node metastasis, R1 resection; independent prognostic factors: pathologic TNM stage

Abbreviations: ALP, alkaline phosphatase; CA; carbohydrate antigen; CEA, carcinoembryonic antigen; CN, China; FR, France; GGT, γ-glutamyltransferase; ICC, intrahepatic cholangiocarcinoma; IT, Italy; MC, multicenter; MN, multinational; NR, not reported; OS, overall survival.

[a] The study stated that several factors were examined and found to not affect survival. Not all factors were listed, but it was specifically mentioned that biliary invasion and direct invasion of adjacent organs did not affect OS.

patients). There was no publication bias, as evidenced in the funnel plot of all combined risk factors (**Figure 3**).

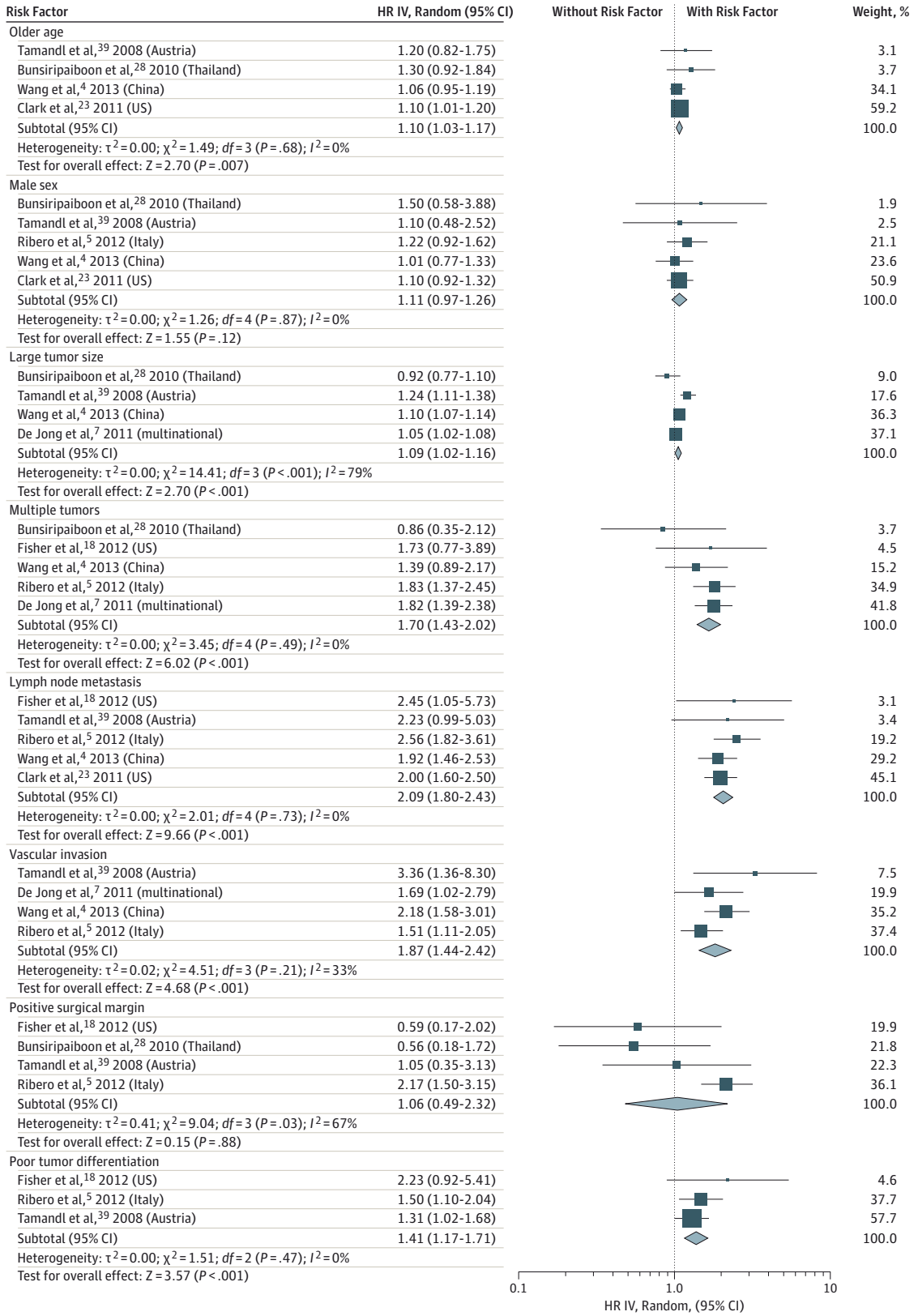
Discussion

Although the incidence of ICC continues to increase worldwide, it remains a relatively rare disease. Most institutions have limited experience with ICC, and fewer centers have an extensive surgical practice of patients with ICC. In turn, data on surgical management of ICC largely comprise small series from individual institutions. The small sample size of these cohorts may influence the ability to accurately examine the potential effect that certain factors may have on outcomes. This may explain, in part, the heterogeneity reported in the literature regarding whether certain factors are associated with long-term outcomes. In the present study, we pooled individual data from previous reports to examine a larger cohort of patients with ICC to facilitate identification of possible prognostic factors as well as to better understand the prognosis of patients with ICC. The present study is important because we amassed a large cohort of patients with ICC (N = 4756) from 42 index studies to pool the available data for systematic review. In doing so, we were able to provide a broad overview of the available literature on ICC and better define the published data on the treatment and prognosis for patients with ICC. Specifically, we found that tumor-specific factors, such as age, tumor size, tumor number, lymph node metastasis, and vascular invasion, were associated with shorter OS.

In this comprehensive systematic review, 5-year OS following curative-intent surgery rarely exceeded 30% to 35%, and median aggregate overall survival was only approximately 28 months. In the subset of data from the 5 largest studies,[4-8] the median and 5-year OS ranged from only 18 to 33 months and from 21% to 35%, respectively. These data are sobering, especially in light of the fact that surgical margins were microscopically clear (R0) in most cases (74%; range, 37%-93%). Collectively, these data strongly suggest that ICC has an aggressive natural history with a guarded prognosis despite curative-intent surgical extirpation of all measurable disease. Consistent with this, we noted that recurrence was common following surgical resection, with only 2% to 39% of patients being recurrence free at 5 years. Although the most common recurrence site was the liver, recurrent ICC can develop almost anywhere, as evidenced by the many other sites reported where ICC reappeared. Unfortunately, administration of adjuvant chemotherapy or radiotherapy did not appear to influence survival. The recent Advanced Biliary Cancer 02 trial[66] showed that response and progression-free survival were better using doublet therapy with gemcitabine and cisplatin vs gemcitabine alone among patients with inoperable biliary tract cancer. Future trials will need to investigate the role of adjuvant therapy—especially among patients at the highest risk for recurrence and death.

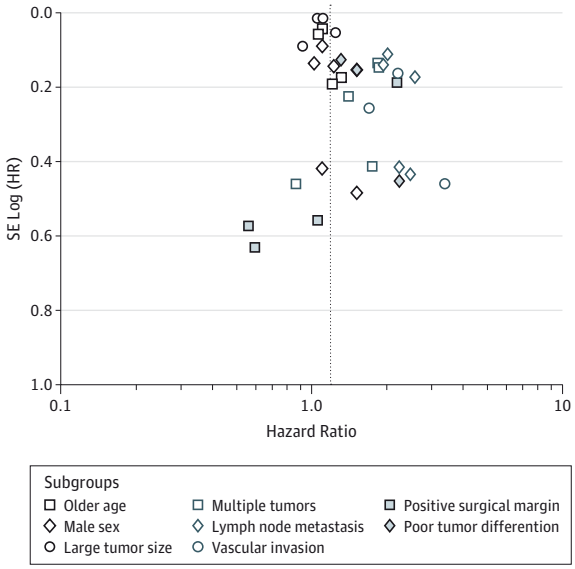
The poor prognosis following surgical resection of ICC is probably multifactorial. The prognosis may be related in part to the fact that many patients present with advanced disease. In reviewing the current literature, we noted that most patients presented with large tumors (median size, 5-8 cm),

Figure 2. Forest Plot Depicting the Hazard Ratios (HRs) of Overall Survival for the Examined Risk Factors



Vertical line indicates the no difference point between the 2 groups; square, HR; diamond, pooled HR for all studies; and horizontal lines, 95% CI. *df* Indicates degrees of freedom; IV, inverse variance; and US, United States.

Figure 3. Funnel Plot Depicting the Effect of All Risk Factors on Overall Survival



The dashed vertical line indicates the summary estimate of risk factor effect.

and approximately one-third had lymph node metastasis. In turn, each of these factors was noted to affect long-term survival (tumor size: HR, 1.09 [95% CI, 1.02-1.16] for each 1-cm increment; lymph node metastasis: 2.09 [1.80-2.43]). Although lymph node status has been strongly associated with prognosis in almost all studies,[4-8] data on tumor size have been more disparate, with some studies finding no effect of tumor size[25,36,48] and other larger studies showing that size affected survival.[4-8] Previously, the failure to identify an effect of tumor size on OS may be explained by the limited number of patients with small (eg, <5 cm) tumors included in many prior studies. By pooling data into a meta-analysis, we were able to overcome the limitation of sample size. In turn, we also were able to better define the effect of tumor-specific factors that affected recurrence and OS (Figure 2). Given these findings, future revisions to the American Joint Committee on Cancer[67] staging system may need to reconsider the impact of tumor size on prognosis as well as attribute more prognostic weight to the presence of multiple tumors.

Our findings should be interpreted in view of certain limitations. First, all studies were retrospective and therefore subject to selection bias in how patients were chosen for surgical therapy. The reviewed studies also represented a variety of clinical settings, including Asia, the United States, and Europe; therefore, treatment approaches undoubtedly varied. Data from the present study were, however, presented stratified by country. In addition, a strength of the study cohort was that it represented global trends rather than solely the experience of the United States or Europe. Although 57 studies were included in the systematic review, only 7 were included in the meta-analysis. We did not attempt to evaluate more studies to avoid potential distortion of the results, because the remaining studies did not strictly meet the statistical criteria for the data to be converted and included.[14,68]

Conclusions

The prognosis of ICC remains grave, with less than one-third of the patients who undergo curative-intent surgical treatment surviving beyond 5 years after resection. Prognosis is dictated primarily by tumor factors, such as tumor size, lymph node invasion, and vascular invasion, which underlines the necessity for earlier diagnosis. Furthermore, the high incidence of recurrence and its association with certain tumor-specific factors highlight the need for more effective adjuvant therapies. Future research should therefore target the identification of novel agents with more activity toward ICC so as to increase the goal of prolonging survival among this challenging group of patients.

ARTICLE INFORMATION

Accepted for Publication: July 30, 2013.

Published Online: April 9, 2014. doi:10.1001/jamasurg.2013.5137.

Author Contributions: Drs Mavros and Pawlik had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Mavros, Pawlik.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: All authors.
Administrative, technical, or material support: Mavros.
Study supervision: Mavros, Pawlik.

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. *Semin Liver Dis*. 2004;24(2):115-125.

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

3. 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.

4. Wang Y, Li J, Xia Y, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. *J Clin Oncol*. 2013;31(9):1188-1195.

5. Ribero D, Pinna AD, Guglielmi A, et al; Italian Intrahepatic Cholangiocarcinoma Study Group. Surgical approach for long-term survival of patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis of 434 patients. *Arch Surg*. 2012;147(12):1107-1113.

6. 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):824-830.

7. 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.

8. Jiang W, Zeng ZC, Tang ZY, et al. A prognostic scoring system based on clinical features of intrahepatic cholangiocarcinoma: the Fudan score. *Ann Oncol*. 2011;22(7):1644-1652.

9. Nathan H, Pawlik TM, Wolfgang CL, Choti MA, Cameron JL, Schulick RD. Trends in survival after surgery for cholangiocarcinoma: a 30-year population-based SEER database analysis. *J Gastrointest Surg*. 2007;11(11):1488-1497.

10. Poultsides GA, Zhu AX, Choti MA, Pawlik TM. Intrahepatic cholangiocarcinoma. *Surg Clin North Am*. 2010;90(4):817-837.

11. Weber SM, Jarnagin WR, Klimstra D, DeMatteo RP, Fong Y, Blumgart LH. Intrahepatic cholangiocarcinoma: resectability, recurrence pattern, and outcomes. *J Am Coll Surg*. 2001;193(4):384-391.

12. Rosmarakis ES, Soteriades ES, Vergidis PI, Kasiakou SK, Falagas ME. From conference abstract to full paper: differences between data presented in conferences and journals. *FASEB J*. 2005;19(7):673-680.

13. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.

14. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med*. 1998;17(24):2815-2834.

15. Dhanasekaran R, Hemming AW, Zendejas I, et al. Treatment outcomes and prognostic factors of intrahepatic cholangiocarcinoma. *Oncol Rep*. 2013;29(4):1259-1267.

16. Ali SM, Clark CJ, Zaydfudim VM, Que FG, Nagorney DM. Role of major vascular resection in patients with intrahepatic cholangiocarcinoma. *Ann Surg Oncol*. 2013;20(6):2023-2028.

17. Sulpice L, Rayar M, Boucher E, et al. Intrahepatic cholangiocarcinoma: impact of genetic hemochromatosis on outcome and overall survival after surgical resection. *J Surg Res*. 2013;180(1):56-61.

18. Fisher SB, Patel SH, Kooby DA, et al. Lymphovascular and perineural invasion as selection criteria for adjuvant therapy in intrahepatic cholangiocarcinoma: a multi-institution analysis. *HPB (Oxford)*. 2012;14(8):514-522.

19. Horino K, Beppu T, Komori H, et al. Evaluation of mass-forming intrahepatic cholangiocarcinoma with viral hepatitis. *Hepatogastroenterology*. 2012;59(116):1217-1219.

20. Murakami Y, Uemura K, Sudo T, Hashimoto Y, Nakashima A, Sueda T. Intrahepatic cholangiocarcinoma: clinicopathological differences between peripheral type and hilar type. *J Gastrointest Surg*. 2012;16(3):540-548.

21. Hu XX, Yan LN. Retrospective analysis of prognostic factors after liver transplantation for intrahepatic cholangiocarcinoma in China: a single-center experience. *Hepatogastroenterology*. 2011;58(109):1255-1259.

22. Igami T, Ebata T, Yokoyama Y, Sugawara G, Takahashi Y, Nagino M. Staging of peripheral-type intrahepatic cholangiocarcinoma: appraisal of the new TNM classification and its modifications. *World J Surg*. 2011;35(11):2501-2509.

23. Clark CJ, Wood-Wentz CM, Reid-Lombardo KM, Kendrick ML, Huebner M, Que FG. Lymphadenectomy in the staging and treatment of intrahepatic cholangiocarcinoma: a population-based study using the National Cancer Institute SEER database. *HPB (Oxford)*. 2011;13(9):612-620.

24. Ariizumi S, Kotera Y, Takahashi Y, et al. Mass-forming intrahepatic cholangiocarcinoma with marked enhancement on arterial-phase computed tomography reflects favorable surgical outcomes. *J Surg Oncol*. 2011;104(2):130-139.

25. Li YY, Li H, Lv P, et al. Prognostic value of cirrhosis for intrahepatic cholangiocarcinoma after surgical treatment. *J Gastrointest Surg*. 2011;15(4):608-613.

26. Ellis MC, Cassera MA, Vetto JT, Orloff SL, Hansen PD, Billingsley KG. Surgical treatment of intrahepatic cholangiocarcinoma: outcomes and predictive factors. *HPB (Oxford)*. 2011;13(1):59-63.

27. Saxena A, Chua TC, Sarkar A, Chu F, Morris DL. Clinicopathologic and treatment-related factors influencing recurrence and survival after hepatic resection of intrahepatic cholangiocarcinoma: a 19-year experience from an established Australian hepatobiliary unit. *J Gastrointest Surg*. 2010;14(7):1128-1138.

28. Bunsiripaiboon P, Sornmayura P, Wilasrusmee C, Lertsithichai P. The prognostic significance of microvessel density in intrahepatic cholangiocarcinoma. *J Med Assoc Thai*. 2010;93(1):66-72.

29. Zhang L, Cai JQ, Zhao JJ, et al. Impact of hepatitis B virus infection on outcome following resection for intrahepatic cholangiocarcinoma. *J Surg Oncol*. 2010;101(3):233-238.

30. Cho SY, Park SJ, Kim SH, et al. Survival analysis of intrahepatic cholangiocarcinoma after resection. *Ann Surg Oncol*. 2010;17(7):1823-1830.

31. 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.

32. 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.

33. Li FH, Chen XQ, Luo HY, et al. Prognosis of 84 intrahepatic cholangiocarcinoma patients [in Chinese]. *Ai Zheng*. 2009;28(5):528-532.

34. Nanashima A, Shibata K, Nakayama T, et al. Relationship between microvessel count and postoperative survival in patients with intrahepatic cholangiocarcinoma. *Ann Surg Oncol*. 2009;16(8):2123-2129.

35. Saiura A, Yamamoto J, Kokudo N, et al. Intrahepatic cholangiocarcinoma: analysis of 44 consecutive resected cases including 5 cases with repeat resections. *Am J Surg*. 2011;201(2):203-208.

36. 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.

37. Yedibela S, Demir R, Zhang W, Meyer T, Hohenberger W, Schönleben F. Surgical treatment of mass-forming intrahepatic cholangiocarcinoma: an 11-year Western single-center experience in 107 patients. *Ann Surg Oncol*. 2009;16(2):404-412.

38. 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.

39. 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.

40. Uenishi T, Kubo S, Yamazaki O, et al. Indications for surgical treatment of intrahepatic cholangiocarcinoma with lymph node metastases. *J Hepatobiliary Pancreat Surg*. 2008;15(4):417-422.

41. 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.

42. Gomez D, Morris-Stiff G, Toogood GJ, Lodge JP, Prasad KR. Impact of systemic inflammation on outcome following resection for intrahepatic cholangiocarcinoma. *J Surg Oncol*. 2008;97(6):513-518.

43. 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.

44. Paik KY, Jung JC, Heo JS, Choi SH, Choi DW, Kim YI. What prognostic factors are important for resected intrahepatic cholangiocarcinoma? *J Gastroenterol Hepatol*. 2008;23(5):766-770.

45. Shimada K, Sano T, Sakamoto Y, Esaki M, Kosuge T, Ojima H. Surgical outcomes of the mass-forming plus periductal infiltrating types of intrahepatic cholangiocarcinoma: a comparative study with the typical mass-forming type of intrahepatic cholangiocarcinoma. *World J Surg*. 2007;31(10):2016-2022.

46. Miwa S, Miyagawa S, Kobayashi A, et al. Predictive factors for intrahepatic cholangiocarcinoma recurrence in the liver following surgery. *J Gastroenterol*. 2006;41(9):893-900.

47. 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.

48. Fu XH, Tang ZH, Zong M, Yang GS, Yao XP, Wu MC. Clinicopathologic features, diagnosis and surgical treatment of intrahepatic cholangiocarcinoma in 104 patients. *Hepatobiliary Pancreat Dis Int*. 2004;3(2):279-283.

49. Robles R, Figueras J, Turrión VS, et al. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. *Ann Surg*. 2004;239(2):265-271.

50. Suh KS, Chang SH, Lee HJ, Roh HR, Kim SH, Lee KU. Clinical outcomes and apomucin expression of intrahepatic cholangiocarcinoma according to gross morphology. *J Am Coll Surg*. 2002;195(6):782-789.

51. 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.

52. Hyder O, Hatzaras I, Sotiropoulos GC, et al. Recurrence after operative management of intrahepatic cholangiocarcinoma. *Surgery*. 2013;153(6):811-818.

53. De Rose AM, Cucchetti A, Clemente G, et al. Prognostic significance of tumor doubling time in mass-forming type cholangiocarcinoma. *J Gastrointest Surg*. 2013;17(4):739-747.

54. Wu ZF, Zhang HB, Yang N, Zhao WC, Fu Y, Yang GS. Postoperative adjuvant transcatheter arterial chemoembolisation improves survival of

intrahepatic cholangiocarcinoma patients with poor prognostic factors: results of a large monocentric series. *Eur J Surg Oncol*. 2012;38(7):602-610.

55. Shen WF, Zhong W, Liu Q, Sui CJ, Huang YQ, Yang JM. Adjuvant transcatheter arterial chemoembolization for intrahepatic cholangiocarcinoma after curative surgery: retrospective control study. *World J Surg*. 2011;35 (9):2083-2091.

56. Zhou HB, Wang H, Li YQ, et al. Hepatitis B virus infection: a favorable prognostic factor for intrahepatic cholangiocarcinoma after resection. *World J Gastroenterol*. 2011;17(10):1292-1303.

57. Uchiyama K, Yamamoto M, Yamaue H, et al. Impact of nodal involvement on surgical outcomes of intrahepatic cholangiocarcinoma: a multicenter analysis by the Study Group for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci*. 2011;18(3): 443-452.

58. Nuzzo G, Giuliante F, Ardito F, et al. Intrahepatic cholangiocarcinoma: prognostic factors after liver resection. *Updates Surg*. 2010;62 (1):11-19.

59. Jiang W, Zeng ZC, Tang ZY, et al. Benefit of radiotherapy for 90 patients with resected intrahepatic cholangiocarcinoma and concurrent lymph node metastases. *J Cancer Res Clin Oncol*. 2010;136(9):1323-1331.

60. Tamandl D, Kaczirek K, Gruenberger B, et al. Lymph node ratio after curative surgery for intrahepatic cholangiocarcinoma. *Br J Surg*. 2009; 96(8):919-925.

61. Guglielmi A, Ruzzenente A, Campagnaro T, et al. Intrahepatic cholangiocarcinoma: prognostic factors after surgical resection. *World J Surg*. 2009; 33(6):1247-1254.

62. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg*. 2007;245(5):755-762.

63. Puhalla H, Schuell B, Pokorny H, Kornek GV, Scheithauer W, Gruenberger T. Treatment and outcome of intrahepatic cholangiocellular carcinoma. *Am J Surg*. 2005;189(2):173-177.

64. Hanazaki K, Kajikawa S, Shimozawa N, et al. Prognostic factors of intrahepatic cholangiocarcinoma after hepatic resection: univariate and multivariate analysis. *Hepatogastroenterology*. 2002;49(44):311-316.

65. 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.

66. Valle J, Wasan H, Palmer DH, et al; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362(14):1273-1281.

67. Edge S, Byrd DR, Compton CC, et al, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2011.

68. Michiels S, Piedbois P, Burdett S, Syz N, Stewart L, Pignon JP. Meta-analysis when only the median survival times are known: a comparison with individual patient data results. *Int J Technol Assess Health Care*. 2005;21(1):119-125.