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Original Paper

Intrahepatic Cholangiocarcinoma - the Impact of Pathological Characteristics on the Long-Term Outcome after Resection

Zenaida Emilia Ionel[1], T. Dumitrașcu[1], V. Brașoveanu[1], I. Lupescu[2], R. Anghel[3], V. Herlea[4], M. Ionescu[1], I. Popescu[1]

[1]"Dan Setlacec" Center of General Surgery and Liver Transplantation, Fundeni Clinical Institute, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2]Department of Radiology, Fundeni Clinical Institute, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[3]"Alexandru Trestioreanu" Oncological Institute, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[4]Department of Pathology, Fundeni Clinical Institute, Bucharest, Romania

REZUMAT

Colangiocarcinomul intrahepatic - impactul caracteristicilor histopatologice în supraviețuirea pe termen lung după rezecție

Introducere: Scopul acestui studiu retrospectiv este de a identifica factori de prognostic cu valoare în supraviețuirea pe termen lung la un lot de pacienți operați pentru colangiocarcimom intrahepatic (ICC).

Material și metodă: In Centrul de Chirurgie Generală și Transplant Hepatic "Dan Setlacec al Institutului Clinic Fundeni, între 1995 și 2012, la 104 pacienți diagnosticați cu ICC s-a practicat rezecția hepatică cu viză curativă. Au fost analizate retrospectiv procedurile chirurgicale, evoluția postoperatorie, rezultatele examenului histopatologic și s-a urmărit identificarea unor factori de prognostic pentru supraviețuirea pe termen lung a acestor pacienți. Macroscopic tumorile au fost clasificate conform recomandărilor Grupului de Studiu al Cancerului Hepatic din Japonia (LCSGJ), iar clasificarea pTNM a fost făcută conform prevederilor 7th AJCC/UICC din 2010.

Rezultate: Rezecția radicală R0 a fost obținută la 86 de pacienți (82.6%). Rezecții hepatice majore au fost practicate la 74 de pacienți (71.1%). Rezecții de duct biliar extrahepatic au fost efectuate la 17 pacienți (16.3%). Au fost identificate următoarele forme macroscopice: nodulară (MF) la 58 de pacienți (55.7%), intraductală (IG) la 8 pacienți (7.6%), periductal-infiltrativă (PI) la 7 pacienți (6.3%) și mixtă (MF + PI) la 31 de pacienți (29.8%). Supraviețuirea mediană pentru întregul lot a fost de 17.9 luni (2-126.5 luni). Supraviețuirea

Corresponding author: Irinel Popescu, MD, PhD, FACS, FEBS
Professor of Surgery, Director Center of General Surgery and Liver Transplantation
Fundeni Clinical Institute
Sos. Fundeni, no. 258, sector 2, Bucharest, Romania
e-mail: irinel.popescu220@gmail.com

în grupul de pacienți cu rezecție R0 pentru tumori unice fără invazia seroasei, a fost de 38% la 5 ani. Supraviețuirea s-a corelat semnificativ statistic cu forma macroscopică, cu o mediană de 61.8 luni (35-117 luni) pentru tipul IG, 19.9 luni (39-126.5 luni) pentru MF, 8.8 luni (3-12 luni) pentru PI și 7.5 luni (2-110 luni) pentru MF + PI. In analiza univariată, aspectul macroscopic, radicalitatea rezecției, dimensiunea marginilor de rezecție, invazia seroasei, tumorile multiple, stadializarea pT și stadializarea TNM au avut semnificație statistică pentru supraviețuire. In analiza multivariată marginile de rezecție cuprinse între 1 și 4 mm (HR=2.1-9.2), au fost identificate drept factor de prognostic negativ individual cu rol în supraviețuire. Tipul macroscopic MF + PI a fost în mod semnificativ asociat cu factori de prognostic negativ precum invazia de duct biliar extrahepatic, invazia seroasei, margini de rezecție sub 5 mm, tumori multiple, limfonoduli pozitivi și stadiu avansat.
Concluzii: Rezecția radicală R0 este singurul tratament care poate prelungi supraviețuirea pacienților cu ICC. Rezultatele cele mai bune au fost înregistrate în cazul pacienților la care s-a obținut rezecția R0, cu margine de peste 5 mm, pentru tumori de tip MF sau IG, solitare, fără invazia seroasei. Cei mai importanți factori de prognostic negativ pentru supraviețuire sunt tipul macroscopic MF + PI, rezecțiile cu margini sub 5 mm, tumorile multiple, invazia seroasei și stadiul IVB.

Cuvinte cheie: colangiocarcinom intrahepatic, aspect macroscopic, rezecție R0, dimensiuni margini de rezecție, tumori multiple, invazie seroasă, stadiu avansat

ABSTRACT

Background: The purpose of this retrospective study is to identify prognostic factors relevant for survival in a group of resected patients with intrahepatic cholangiocarcinoma (ICC).
Methods: A number of 104 patients diagnosed with ICC underwent hepatic resection with curative purpose within the Center of General Surgery and Liver Transplantation, ”Dan Setlacec”, Fundeni Clinical Institute, between 1995 and 2012. Surgical procedures, postoperative evolution, histopathological results have been analyzed and groups of patients with long time survival were identified. The tumors have been macroscopically classified according to the recommendations of the Liver Cancer Study Group of Japan (LCSGJ) and pTNM classification was done according to the 2010 7th Edition AJCC/UICC
Results: Curative resection (R0) was achieved in 86 patients (82.6%). Major hepatic resection was performed on 74 patients (71.1%). Extrahepatic bile duct resection was performed on 17 patients (16.3%). The following macroscopic gross type were identified: mass forming (MF) in 58 patients (55.7%), intraductal growth (IG) in 8 patients (7.6%), periductal-infiltrating (PI) in 7 patients (6.3%) and mixed (MF + PI) in 31 patients (29.8%). Median survival for the entire group was 17.9 months (2-126 months). Survival for the subgroup with R0 resection for single tumor without serosal invasion was 38% at 5 years. Statistically, survival significantly correlated with the macroscopic type, with a median of 61.8 months (35-117 months) for IG type, 19.9 months (39-126 months) for MF type, 8.8 months (3-12 months) for PI type and 7.5 months (2-110 months) for MF + PI. At univariate analysis, macroscopic aspect, radicality of resection, dimension of resection margins, serosal invasion, multiple tumors, pT and TNM staging were statistically significant for survival. In multivariate analysis, resection margins between 1-4 mm (HR=2.1-9.2) were independent poor prognostic factors. MF + PI macroscopic type was significantly associated with negative prognostic factors, such as extrahepatic bile duct invasion, serosal invasion, resection margins under 5 mm, multiple tumors, positive lymph nodes and advanced stage.
Conclusions: Radical resection R0 is the only treatment that can extend the survival rate in ICC patients. Best results were obtained in solitary tumors, without serosal invasion, in patients underwent R0 resection, with over 5 mm resection margins for MF or IG type. The most important factors for negative prognosis were MF + PI macroscopic tumor type, resections with margins under 5 mm, multiple tumors, serosal invasion and stage IVB.

Key words: Intrahepatic cholangiocarcinoma, macroscopic gross type, R0 resection, the width of margins, multiple tumors, serosal invasion, advanced stage

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is the second as frequency primary liver cancer after hepatocellular carcinoma (HCC), arising from the biliary epithelium of the second branch (segmental branch) or the proximal branch of bile duct (1,2). Recent reports suggest that the incidence of ICC varies considerably according to geographical location, and accounts for about 5-30% of primary liver cancers, with an increasing incidence during the past years all over the world (3-6). Radical resection (R0) remains the only potential curative treatment, but the resectability rate is still low because of late diagnosis. In general, prognosis is poor, with a reported rate of 5-year survival, usually below 20 to 40% for patients with potentially curative resection (7).

However, the recent progress in anesthesiology and intensive care, the development of more effective surgical techniques in hepatobiliary surgery, and the advent of new devices for parenchymal transsection made more applicable aggressive surgical approaches for ICC, improving the resectability rate in the last two decades (8,9).

Surgical resection showed best results in patients with single lesion, negative lymph nodes, and absence of gross biliary infiltration, with a 5-year survival rate of 42% (10-12). However, even in patients with advanced-stage tumors, surgery can improve long-term survival compared to other therapeutic strategies (10).

The prognostic significance of a gross appearance (macroscopic classification proposed by the LCSG in 1997) has been confirmed in several clinical trials in the literature from Eastern countries (13-15) and in one single study from western countries on 52 patients (10).

Other prognostic factors that have been recently investigated in several surgical series are the R0 surgical margin, the margin width, intrahepatic metastases, vascular invasion, positive lymph node metastases. It was proved that they do indeed influence survival rate (10,15-19)

The purpose of this study was to identify prognostic factors for survival in a group of patients operated for ICC.

PATIENTS AND METHODS

Between 1995 and 2012, a total number of 104 consecutive patients with ICC underwent surgical resection at "Dan Setlacec" Center of General Surgery and Liver Transplantation, Fundeni, Bucharest.

All patients underwent complete physical examination and provided clinical history.

Preoperative blood tests included liver and renal function tests, tumor marker tests, and complete blood count tests. Preoperative imaging workup included abdominal ultrasound, chest x-ray film, upper endoscopy, colonoscopy, abdominal computed tomography (CT) and/or magnetic resonance imaging (MRI) in all cases.

In four patients with initially unresectable ICC, in order to induce compensatory hypertrophy of the estimated remnant liver and to decrease the risk of postoperative liver failure, portal branch ligation was performed as a first step of a planned "two stage" hepatectomy.

In order to assess the resectability, to identify the presence of satellite lesions, the adequate transsection plane and the relationship between tumors and vascular liver anatomy, intraoperative ultrasound was routinely used. The type of procedure was defined according to the Brisbane 2000 Terminology of Liver Anatomy and Resections. (20). Major hepatectomy was defined as resection of 3 or more Couinaud segments. Extended hepatectomy was defined as resection of 5 or more Couinaud segments.

Lymph node dissection was performed in only 49 patients. Picking the lymph nodes along hepatoduodenal ligament was performed in 34 patients. In 12 patients complete lymph node dissection was performed along and beyond the regional nodes. In 55 patients, the lymph nodes were staging based on the preoperative imaging and operative finding. We now advocate routine lymphadenectomy during hepatectomy.

Surgical morbidity was defined according to the classification proposed by Dindo et al. (21). Surgical mortality was defined as death occurring within 1 month after surgery.

Curative resection was defined as negative resection margin at histopathological definitive examination.

The gross type of tumor on the surface cut was categorized into the following: mass forming (MF), periductal infiltrating (PI), intraductal growth (IG) and mass forming combined with periductal infiltrative (MF + PI), according to the Liver Cancer Study

Group of Japan (22).

Tumor stage was defined according to the 7-th edition, 2010, of pathological tumor node metastasis (pTNM) classification proposed by the American Joint Committee of Cancer / International Union Against Cancer (AJCC/UICC) (23). T4 was definite as pure PI type and MF + PI type with more predominant (55-65%) PI type.

Satellite lesions were definte as one or more lesions in the same segment Couinaud within 1 cm from primary tumor. Intrahepatic metastases was definite the lesions from other segment Couinaud/ over 1 cm from primary tumor. Satellite lesions and intrahepatic metastases were definite as multiple tumors.

The resection margin greater than 10 mm was definite as wide margin (WM >10 mm), the margin between 5 and 9 mm was definite close margin (CM 5-9 mm) and the margin between 1 and 4 mm was definite close margin (CM 1-4 mm). The width of margins (mm) were obtained from pathological exam combined in the most of cases with intra-operative frozen-section examination on the resection margin.

To identify the relevant prognostic factors for survival after surgical resection for ICC, the following 11 pathological characteristics and surgical procedure were analyzed by univariate and multivariate analyses: radicality of resection (R0), the tumor margins status (CM 1-4 mm, CM 5-9 mm, and WM >10 mm), serosal invasion, macroscopic type, multiple tumors, macroscopic vascular invasion, lymph nodes metastases, histologic grading, extrahepatic bile duct resection, pTstage, TNM stage.

After resection, all patients underwent regular follow-up for 1 month after operation and every 3-6 months after. Follow-up in this study ended September, 5th, 2013.

Statistical calculation was performed using Graph Pad Prism version 5. (Trial) for Windows, 2007. Variables to be entered into the multivariate analysis were selected on basis of the results of univariate analysis ($p < 0.1$).

RESULTS

Clinicopathologichal characteristics of the patients and types of liver resection

There were 53 (51%) females and 51 (49%) males, with a median age of 59 years (range 21-78 years). Patient characteristics and the type of surgical procedures performed are presented in Table 1. A curative resection was achieved in 86 patients (82.6%). Extrahepatic bile duct resection was performed in 17 patients (16.3%), when the tumor invaded the biliary confluence. Vascular resections and reconstructions were performed in 9 patients (8.6%): portal vein in 5 patients (55.6%), inferior vena cava in 3 patients (33.3%), hepatic artery in 1 patient (11.1%).

Table 1. Characteristics of the patients with ICC and types of surgical procedure

Characteristics	No
Sex	
Male	53 (51%)
Female	51 (49%)
Extension of liver resection	
Major	74 (71.1%)
Minor	30 (28.9%)
Vascular resection with reconstruction	
No	95 (91.3%)
Yes	9 (8.7%)
Resection of extrahepatic bile duct	
No	87 (83.7%)
Yes	17 (16.3%)
Caudate lobe resection	
No	79 (76%)
Yes	25 (24%
Adjacent organs resection	
Diaphragm	4 (3.8%)
Colon	1 (1%)
Adrenal gland	1 (1%)

The median size of the primary tumor was 8 cm (range 2-25 cm). Satellite lesions were present in 34 patients (32.6%). The median number of satellite lesions was 4 (range 2-11). Intrahepatic metastases were detected in 11 patients (10.5%). The median number of intrahepatic metastases was 3 (range 1-9).

Postoperative outcome

The morbidity rate was 36.53% (38/104) (Dindo-Clavien grade I in 15 patients, II in 1, IIIa in 2, IIIb in 7, IVa in 2, IVb in 2 and V in 9).

The most frequent complications observed were biliary fistula in 18 patients (47.3%), liver failure in 7 patients (18.4%), perihepatic abscess in 5 patients (13.1%).

Nine postoperative deaths (8.6%) occurred during the hospital stays. The mortality rates decreased over time. Thus, between August 1995 and January 2003, the mortality rate was 14.2% (3/21). The mortality rate between January 2003 to July 2012 was 7.2% (6/83).

The median follow-up was 63.1 months (range 2-126.5 months). 86 patients died during follow-up. The 1-,3- and 5-year actuarial survival rates in 95 patients (except for the nine hospital-stay deaths) were 64.2%, 30.8% and 19.9%, respectively, and the median survival of these patients was 17.6 months.

Among the 11 factors considered at univariate analysis, 7 were significantly related to survival: positive resection margin (R1), CM 1-4 mm, the macroscopic gross type of tumor, multiple tumors, serosal invasion, (T3), TNM (IVB) (Table 2).

Patients with R0 resection had a 5-year survival rate of 23.3% compared to 0% in patients with R1 resection, and 18 of these patients (R0) are alive at the end of the follow-up (9 patients are alive and tumor-free, one of them is disease-free after repeated resection for tumor reccurence, and 9 patients are alive with reccurence). Also, patients with CM 1-4 mm had a significantly shorter median survival compared to those with WM>10 mm (CM 1-4 mm: 11 months; CM 5-9 mm: 19.9 months; WM>10 mm: 47.2 months).

Table 2. Univariate analysis of factors related to survival

Factors	No	1-year	3-year	5-year	Median (months)	P value
Resection of extrahepatic bile duct						
No	87	65.0	20.0	0.0	12.0	
Yes	17	40.0	30.2	17.7	17.7	0.7446
R0/R1						
R1	18	14.2	0.0	0.0	6.8	<0.0001
R0	86	70.3	36.1	23.3	19.9	
Surgical margin (mm)						
1-4	38	36.3	7.2	7.2	11.0	
5-9	17	88.2	0.0	0.0	19.9	
>10	31	90.3	67.7	47.9	47.2	<0.0001
Serosal invasion						
No	66	77.7	38.2	25.8	19.9	
Yes	38	27.5	6.8	6.8	6.6	<0.0001
Macroscopic type						
MF	58	81.1	31.1	17.3	19.9	
PI	7	17.0	0.0	0.0	8.8	
MF+PI	31	25.0	12.5	12.5	7.5	
IG	8	87.5	75.0	37.5	61.8	0.0016
Multiple tumors						
Yes	45	50.0	10.9	10.9	14.2	
No	59	70.9	42.7	26.4	26.9	0.0027
Lymph node metastases						
No	78	69.0	24.7	18.2	19.6	
Yes	26	41.6	14.2	14.2	10.6	0.0978
Macroscopic vascular invasion						
No	90	65.4	31.2	20.1	17.6	
Yes	14	45.0	18.8	18.8	12.0	0.6128
Histologic grading						
G1	32	50.0	30.3	17.3	15.2	
G2	53	70.8	26.0	21.7	18.7	
G3	19	52.9	17.6	17.6	16.8	0.7077
T stage (TNM)						
T1	34	82.8	56.4	33.1	36.4	
T2a	3	0.0	0.0	0.0	0.0	
T2b	25	33.3	0.0	0.0	15.3	
T3	25	26.3	15.7	7.8	7.4	
T4	17	46.6	20.0	20.0	12.0	0.0048
TNM stage						
I	28	82.1	56.0	27.7	37.0	
II	22	71.4	14.2	7.1	17.6	
III	14	25.0	25.0	0.0	0.0	
IVa	31	46.6	21.8	18.9	12.5	
IVb	9	12.6	0.0	0.0	6.0	<0.0001

Table 3. Multivariate analysis of factors related to survival

Factor	Coefficient	Hazard ratio	p
CM 1-4 mm	2.1	9.2	0.0008
Serosal invasion	-	-	0.1007
Multiple tumors	-	-	0.9115
Stage IVB AJCC 7	-	-	0.2660
Macroscopic gross type (MF + PI)	-	-	0.7201

CM = close margin between 1-4 mm

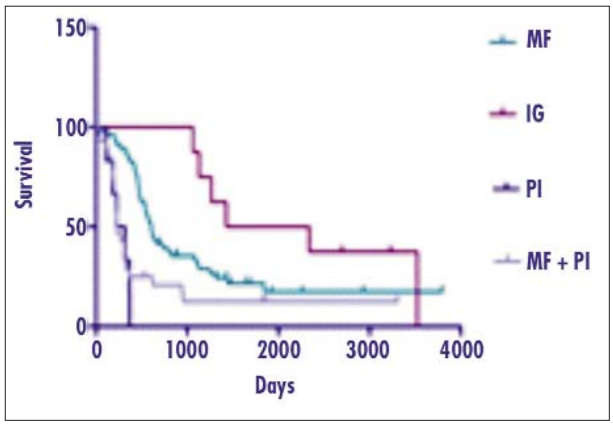

Figure 1. Survival curves according to the macroscopic type: MF= mass- forming type; IG= intraductal type; PI= periductal infiltrating type; MF + PI= mass-forming plus periductal infiltrating type

Multivariate analysis using the Cox proportional hazards model identified close margin CM 1-4 mm, as an independent factor, being significantly related to survival with hazard ratio of 2.1-9.2 (**Table 3**).

Correlation between macroscopic type and survival

In our series, the MF type was present in 58 patients (55.8%), MF + PI in 31 (29.8%), IG in 8 (7.7%) and PI type in 7 patients (6.7%).

Several histological factors were significantly related to the MF + PI type: positive margins in 32.2.% (10/31) patients, CM 1-4 mm in 41.9% (13/31), lymph node metastasis in 38.8% (12/31), serosal invasion in 54.9% (17/31), multiple tumors in 54.9% (17/31), T4 in 32.2% (10/31), IVA stage in 54.9% (17/31), IVB stage in 16.1% (5/31) and extrahepatic bile duct resection in 32.2% (10/31). PI tumors also they had a poor prognosis but the analysis in only 7 patients although statistically significant, does not provide relevant results in a series of 104 patients (**Table 4**)

Kaplan-Meier survival analysis identified that survival was significantly related to the gross type, with median survivals of 61.8 months for patients with IG type, 19.9 months for MF, 8.8 months for the PI, and 7.5 months for MF + PI (p= 0.0016: MF vs. MF + PI) (**Table 2, Fig. 1**).

DISCUSSION

Intrahepatic cholangiocarcinoma is a malignant tumor developed from the intrahepatic bile ducts and the second most primary malignancy of the liver. Its incidence increases steadily over the last three decades all over the world (4,6).

The prognostic factors after surgical resection for intrahepatic cholangiocarcinoma were reported in several series, but the majority, from single institutions, have studied a limited number of cases, mainly because at the time of diagnosis, patients with ICC are frequently staged beyond the limits of surgical therapy. Surgical resection has been shown to provide a chance for cure in patients with ICC, but the resectability rate is still low, varying between 19% and 74% in reports from different centers (10, 24-28).

Although surgical technique and perioperative management improved, major or extended liver resections still has significant rates of morbidity and mortality. Previous series have reported a mortality rate lower than 5%, but the morbidity rate still remains high, varying between 20% and 50% (10, 24,25,29-32).

Thus, in our series, the morbidity and mortality rates were 36.5% and 8.6%, respectively. However, our relatively acceptable morbidity and mortality exceeded other reports. This facts can be related to a high percent of major hepatic resections, in 71% (74/104) of patients, and due to the complex procedures performed. Also, due to the progress in anesthesia and intensive care, and a more adequate operative technique, perioperative mortality has decreased in our series from 14.2% to 7.2% in the last ten years. A similar situation was reported in five previous studies (24,26-28,33)

However, the prognosis for patients with ICC after surgical resection still remains poor. The 5-year overall survival rate has varied from 11.8% to 39.5%, and it does not exceed 50% in most of the surgical series with at least 50 resected patients with an intention of cure (R0 and R1) reported between 2000 to 2014 (19,28,33-46).

In this study, the median survival time was 17.6

Table 4. Relation between the tumor macroscopic type with the type of surgery and the histologic characteristics

Tumor gross type (no)	IG (8)	MF (58)	MF + PI (31)	PI (7)	P value
Resection of extrahepatic bile duct					
No	0	0	21 (67.8%)	0	
Yes	0	0	10 (32.2%)	7 (100%)	0.0001
R1/R0					
R1	0	6 (10.3%)	10 (32.2%)	2 (28.6%)	
R0	8 (100%)	52 (89.7%)	21 (67.8%)	5 (71.4%)	0.0184
Surgical margin (mm)					
1-4	1 (12.5%)	19 (32.8%)	13 (41.9%)	5 (71.4%)	
5-9	0	14 (24.1%)	3 (9.8%)	0	
>10	7 (87.5%)	19 (32.8%)	5 (16.1%)	0	0.1325
Serosal invasion					
No	7 (87.5%)	44 (75.9%)	14 (45.1%)	1 (14.2%)	
Yes	1 (12.5%)	14 (24.1%)	17 (54.9%)	6 (85.8%)	0.0052
Multiple tumors					
No	7 (87.5%)	34 (58.7%)	14 (45.1%)	4 (57.1%)	0.2679
Yes	1 (12.5%)	24 (41.3%)	17 (54.9%)	3 (42.9%)	
Lymph node metastases					
No	7 (87.5%)	49 (84.4%)	19 (61.2%)	3 (42.9%)	
Yes	1 (12.5%)	9 (15.6%)	12 (38.8%)	4 (57.1%)	0.0191
Macroscopic vascular invasion					
No	7 (87.5%)	52 (89.7%)	26 (83.9%)	5 (71.4%)	
Yes	1 (12.5%)	6 (10.3%)	5 (16.1%)	2 (28.6%)	0.5050
Histologic grading					
G1	5 (62.5%)	13 (22.4%)	11 (35.5%)	3 (42.9%)	
G2	3 (37.5%)	35 (60.4%)	13 (41.9%)	2 (28.6%)	
G3	0	10 (17.2%)	7 (22.6%)	2 (28.5%)	0.1204
T stage (TNM)					
T1	6 (75%)	26 (44.9%)	2 (6.5%)	0	
T2a	0	2 (3.4%)	1 (3.2%)	0	
T2b	1 (12.5%)	16 (27.6%)	8 (25.9%)	0	
T3	1 (12.5%)	14 (24.1%)	10 (32.2%)	0	
T4	0	0	10 (32.2%)	7 (100%)	0.0001
TNM stage					
I	5 (62.5%)	21 (36.2%)	2 (6.4%)	0	
II	1 (12.5%)	17 (29.4%)	4 (12.9%)	0	
III	1 (12.5%)	10 (17.2%)	3 (9.7%)	0	
IVa	1 (12.5%)	6 (10.3%)	17 (54.9%)	7 (100%)	
IVb	0	4 (6.9%)	5 (16.1%)	0	0.0021

months, and the 1-, 3-, and 5-year survival rates of 64.2%, 30.8% and 19.9% respectively, compared to those reported by Weimann et al, Ohtsuka et al, Jonas et al. (34, 35,41). Our relatively low 5-year survival rate achieved can be related to a high frequency of tumors in advanced stage. In the sub-group of patients who underwent R0 resection for a single ICC without involvement of serosa, the 5-year survival rate was 38%, similar to the maxim of 5-year survival reported by majority of series with at least 50 patients resected with a curative intent (R0, R1), between 2000-2014 (19,28,33-46).

The most important prognostic factors after surgical resection for ICC reported in the literature are radical resection (R0), lymph node invasion, multiple tumors and vascular invasion. In the present study neither lymph node invasion, multifocality or vascular invasion, have no impact in survival.

The rate of radical resection (R0) varies in different studies from 30% to 86% (10,13,15,17,18, 30,38,42,49,50). Several studies have demonstrated that a positive ICC resection margin is closely associated with a poor prognosis (7,33,37,38,47, 50,51). Some authors have demonstrated that R0 resection is the only therapy that can achieve cure and improve survival rate in these patients. Guglielmi et al. reported a 5-year survival of 20% for a group of 52 patients with ICC; survival was 23% in R0 resection

group and 0 in R+ resection group (10). Morimoto et al. reported a 5-year survival of 32.4% for a group of 51 patients with ICC; survival was 40.8% in R0 resection group and 0 in R+ resection group (18). We achieve a curative R0 resection in 83% of patients with a 5-year survival of 23.3% compared to R1 resection in 17% of patients where 5-year survival was 0. In our series, liver resection was performed with curative intent in every patient. However, in 18 patients (17.3%), microscopic residual tumors were detected at the cutting margin (in 9 patients). Isolated peritoneal implants albeit completely in four patients (3.8%) and positive paracaval lymph nodes in 5 patients (4.8%), were classified as R1 resections.

The width of tumor margins was investigated in several studies and some authors have reported different results. Recently, Farges et al. showed that in patients who underwent curative resection for ICC without lymph node metastases, median survival was closely associated with margin width (≤ 1 mm: 15 months; 2–4 mm: 36 months; 5–9 mm: 57 months; and >10 mm: 64 months) and a margin > 5 mm was an independent predictor of survival (52). Cho et al. reported that every effort should be made to gain a wide resection margin to improve survival, since they found that a narrow resection margin (≤1 cm) was associated with significantly reduced survival after surgery (53). In opposite, Ribero et al. and Tamandl et al. did not found a relationship between resection margin width and recurrence or survival after surgery (39,47). In our series, the median survival was closely associated with margin width (CM 1-4 mm: 11 months; CM 5–9 mm: 19.9 months; WM >10 mm: 47.2 months), and CM 1-4 mm was an individual negative prognostic factor in multivariate analyses.

Serosal invasion - which is a distinctive feature of the LCSGJ system - was rarely mentioned in the pathological reports. Uenishi et al., in a retrospective study that analyzed sixty-three patients resected for MF type of ICC, found that serosal invasion alone has no impact on survival (54). However, the significance of serosal invasion for survival is still unclear, some previous studies reporting different results. Okabayashi et al. reported that serosal invasion was not associated with poor prognosis (48), while Ohtsuka et al. reported that serosal invasion was a negative prognostic factor in univariate analysis, but not in multivariate analysis (19). In our study, the 1-,3-,5-year survival rate was 77.7%, 38.2%, respectively 25.8% for patients without serosal invasion, in contrast to 27.5%, 6.8%, respectively 6.8% for patients with serosal invasion ($p<0.0001$).

The presence of multiple tumors is an important prognostic factor for ICC. De Jong et al., in a multicentric study on 449 patients, analyzed different prognostic factors related to survival and confirmed that the presence of multiple tumors has impact on survival with a median survival of 36 months for patients with a single lesion compared to 19 months for patients with multiple lesions ($p<0.001$) (55). Moreover, Harrison et al. reported for a group of 32 patients that the presence of satellite lesions was a negative prognostic factor ($p<0.05$) (11). In our series, the 1-,3-,5-year survival rate among patients with a single lesion was 70.9%, 42.7%, respectively 26.4% compared to 50%, 10.9%, respectively 10.9% for patients with multiple lesions ($p= 0.0027$).

Macroscopic vascular invasion is another important prognostic factor for ICC. Uenishi et al., Okabayashi et al., Choi et al., and other authors found macroscopic vascular invasion to be a negative prognostic factor according to univariate analysis (38,42,48). Okabayashi et al., reported a 1-,3-,5-year survival rate of 53%, 0%, respectively 0% for patients with major vascular involvement compared to 68%, 56.7%, respectively 42.5% for patients without vascular involvement (48). Also, Inoue et al., Yamasaki et al., and Nathan et al. did not found macroscopic vascular invasion as independent prognostic factor (33,56,57).

Lymph node metastasis is one of the most important prognostic factor in patients who undergo hepatic resection for ICC. The prevalence of lymph node metastases detected, varies between 25-50% (10,38,42,48,58). Guglielmi et al., found the presence of lymph node metastases as a independent prognostic factor according to multivariate analysis (10).The value of lymph node dissection for ICC is still controversial although was found to be an negative prognostic factor in several studies with a 5-year survival rate of 0% to 9% (10,38,42,48). Our series suggested that there is no difference in survival rates between the patients with positive lymph nodes and the patients with negative lymph nodes.

The 7th edition of AJCC/UICC and LCSGJ staging systems are characterized by a stricter definition of stage IV as a metastatic stage. The proportion of stage IV patients in the LCSGJ classification was 47% (59). According to this new edition, in a recent study, Farges et al. found that 6% of 522 patients operated with curative intent were stage IV, and none of whom survived 2 years after

surgery (16). In our series, the proportion of stage IV patients was 38.4%. Herein, the subgroup of IVA stage patients (21 positive regional lymph nodes) had a 1-,3-,5 year survival rate of 46.6%, 21.8%, respectively 18.9% and a median survival of 12.5 months, compared to 71.4%, 14.2%, respectively 7.1% and a median survival of 17.6 months for II stage patients (p=0.2752). However, the outcome for IVB patients with distant lymph nodes metastases or single peritoneal implants was quite poor with a 1-year survival rate of 12.6%.

In our series, the most significant prognostic factors after surgical resection of ICC identified at univariate analysis were the presence of positive resection margins (R1), the width of margin: CM 1-4 mm, multiple tumors, serosal invasion, T stage (T3), TNM stage (IVB) and the gross type of tumor (MF + PI). Further multivariate analysis identified that CM 1-4 mm is an independent predictor to survival (HR= 2.1-9.2).

Previous studies have reported that macroscopic types are associated with their biological behaviors and neoplastic diffusion suggested that characteristics of invasion were influenced by the site of origin (13,60). The gross type of tumor is related to R0 resection rate. In a series reported by Yamamoto et al., the curative resection rate was significantly lower in patients with MI + PI type than in those with either MF or IG (13). Hirohashi et al., have showed that overall survival rates in patients with MF + PI tumors were significantly wrose than in those with MF types, because the resection margins in 85.7% of patients with MF + PI tumors were positive (50,61). Other authors have confirmed that macroscopic type of tumor is related to radicality of resection (10,17,18, 50,54,61). The multifocality of tumor that significantly related to MF + PI type were reported by Hirohashi in 42.8% (6/14) of cases and by Nakagama in 33.3% (3/9) (50,61). Shirabe et al., have reported that serosal invasion was statistically significant prognostic factor for poor outcome related to MF type only in univariate analyse on 60 cases (62).Yamamoto et al. reported a significantly higher rate (11/15) of lymph node metastases related to MF + PI than that in patients with IG type (2/10) (13).

Isaji et al. and Hirohashi et al. have reported that postoperative survival in patients with MF + PI type of ICC were shorter than in patients with MF type tumors (15,61). Shimada et al. reported a 5-year survival of 39.8 % for the MF type and 0% for MF + PI type (63). In 2009, Guglielmi et al. reported the first study in Western countries that confirms the relation between various histologic prognostic factors and the gross type, with a 5- year survival rate of 29 % for MF type and 0% for MF + PI type (10).

Our study on 104 patients resected for ICC is the second in Western countries that confirms the relation between histological prognostic factors and the macroscopic type and also confirm that macroscopic type is related to survival, with a median survival of 61.8 months for IG type, 19.9 months for MF type, 8.8 months for PI type and 7.5 months for MF + PI type. Our series also confirms that MF + PI type is associated with an aggressive biological behavior and poor outcome, the only R0 resection for an MF or IG type achieving a long time survival.

CONCLUSION

Only R0 surgical resection in cases of ICC significantly increase survival rate and provides the chance for a cure. We confirm the prognostic significance for macroscopic gross type of ICC in Western countries. The best results were achieved in patients underwent R0 resection for a solitary MF or IG type, with margins over 5 mm, without serosal invasion.

Important prognostic factors related to poor survival are MF + PI macroscopic tumor type, resections with margins under 5 mm, multiple tumors, serosal invasion, and stage IVB. These patients have a poor prognosis after operation and should receive additional treatment such as adjuvant chemotherapy.

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