Clinical parameters predicting survival duration after hepatectomy for intrahepatic cholangiocarcinoma

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BACKGROUND: Currently, the most effective treatment for intrahepatic cholangiocarcinoma (ICC) is complete hepatic tumour excision.
OBJECTIVE: To identify the clinical parameters associated with survival duration for ICC patients following hepatectomy, and to construct a mathematical model for predicting survival duration.
METHODS: Demographic data and clinical variables for 102 patients diagnosed with ICC, who underwent exploratory laparotomy at a single centre from July 1998 to December 2000 and were followed for an average of 24 months, were collected in 2011. Patients were randomly assigned into training (n=76) and validation (n=26) groups. Univariate and multivariate analyses were performed to identify factors associated with posthepatectomy survival duration.
RESULTS: Univariate analysis revealed that more than three lymph node metastases, a serum carbohydrate antigen 19-9 level >37 U/mL, stage IVa tumours, and intra- or perihepatic metastases were significantly associated with decreased survival duration. Curative resection was significantly associated with increased survival duration. A mathematical model incorporating parameters of age, sex, metastatic lymph node number, curative surgery, carbohydrate antigen 19-9 concentration, alpha-fetoprotein concentration, hepatitis B, TNM stage and tumour differentiation was constructed for predicting survival duration. For a survival duration of less than one year, the model exhibited 93.8% sensitivity, 92.3% total accuracy and a positive predictive value of 93.8%; for a survival duration of one to three years, the corresponding values were 80.0%, 69.2% and 57.1%, repsectively.
CONCLUSIONS: The mathematical model presented in the current report should prove to be useful in the clinical setting for predicting the extent to which curative resection affects the survival of ICC patients, and for selecting optimal postoperative treatment strategies.

Key Words: *Intrahepatic cholangiocarcinoma; Mathematical model; Prognosis; Survival duration prediction*

Les paramètres cliniques prédisant la durée de survie après une hépatectomie consécutive à un cholangiocarcinome intrahépatique

HISTORIQUE : Le traitement le plus efficace contre un cholangiocarcinome intrahépatique (CCI) consiste à procéder à une excision complète de la tumeur hépatique.
OBJECTIF : Déterminer les paramètres cliniques associés à la durée de survie des patients atteints d'un CCI après une hépatectomie et construire un modèle mathématique pour prédire la durée de survie.
MÉTHODOLOGIE : En 2011, les chercheurs ont colligé les données démographiques et les variables cliniques de 102 patients ayant un diagnostic de CCI qui avaient subi une laparotomie exploratoire à un seul centre entre juillet 1998 et décembre 2000 et qui ont été suivis pendant une moyenne de 24 mois. Les patients ont été répartis au hasard entre un groupe de formation (n=76) et un groupe de validation (n=26). Des analyses univariées et multivariées ont permis d'établir les facteurs associés à la durée de survie après l'hépatectomie.
RÉSULTATS : L'analyse univariée a révélé que plus de trois métastases des ganglions lymphatiques, un taux d'antigène carbohydrate 19-9 sérique supérieur à 37 U/mL, des tumeurs de phase IVa et des métastases intrahépatiques ou périhépatiques s'associaient de manière significative à une durée de survie réduite. Quant à la résection curative, elles'associait de manière significative à une durée de survie accrue. Un modèle mathématique intégrant les paramètres de l'âge, du sexe, du nombre de ganglions lymphatiques métastatiques, de la chirurgie curative, de la concentration d'antigènes carbohydrates 19-9, de la concentration d'alpha-fœtoprotéines, d'hépatite B, de classification TNM et de différenciation tumorale a été construit pour prédire la durée de survie. En cas de durée de survie de moins d'un an, le modèle affichait une sensibilité de 93,8 %, une exactitude totale de 92,3 % et une valeur prédictive positive de 93,8 %. En cas de durée de survie de un à trois ans, les valeurs correspondantes s'élevaient à 80,0 %, 69,2 % et 57,1 %, respectivement.
CONCLUSIONS : Le modèle mathématique présenté dans le présent rapport devrait se révéler utile en milieu clinique pour prédire la mesure selon laquelle une résection curative influe sur la survie des patients atteints d'un CCI et pour sélectionner les stratégies thérapeutiques postopératoires optimales.

Intrahepatic or peripheral cholangiocarcinoma (ICC), a primary adenocarcinoma of the liver originating from the peripheral biliary epithelium, is the second most common primary liver cancer after hepatocellular carcinoma (1). ICC accounts for approximately 10% of primary liver malignancies, with a rapidly increasing incidence and mortality being reported in recent years (2-4). The prognosis for patients with ICC is usually poor, with advanced tumours often observed due to the absence of early symptomatology. The median survival duration is less than six to nine months after diagnosis (5).

Presently, complete hepatic tumour excision is considered to be the most effective treatment for ICC (6-8). Although tumour resection has been shown to increase the probability of long-term survival for patients with ICC, the prognosis after surgery remains unsatisfactory due to early and frequent systemic spread of disease, and advanced tumour stage at the time of diagnosis (5,8-15). In fact, a retrospective analysis by Suzuki et al (11) showed that the rate of lymph node (LN) metastasis ranges from 14% to 58%, and that the rate of intrahepatic or satellite metastasis ranges from 26% to 58% in patients with ICC who had undergone surgical treatment. Even if surgical resection with complete dissection of LNs is achieved, postoperative survival is poor whenever multiple tumours, LN metastasis and/or vascular invasion occur; long-term survival of patients with these characteristics is rarely reported (6). Radiation and chemotherapy are alternative options for the treatment of ICC; however, neither has been demonstrated to be more efficacious than surgery for increasing long-term survival (5,16).

Variables correlated with poor survival in patients with ICC have been identified in several previous reports. These variables include the presence of multiple tumours, extrahepatic bile duct involvement,

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intrahepatic metastasis, metastasis to multiple LNs, disease stage, *Union Internationale Contre le Cancer* (UICC) pT, pN and pM factors, high serum carbohydrate antigen (CA) 19-9 level, histological type, positive histological margin, vascular invasion and the extent to which the tumour is susceptible to complete removal (ie, curative resection) (8,9,12,17). The seventh edition of *The American Joint Committee on Cancer Staging Manual* provides approaches to predict survival for patients with ICC. To date, however, no predictive mathematical survival model that accounts for various risk factors has been provided. Therefore, the present retrospective study was undertaken to the assess risk factors for survival in patients with ICC who underwent hepatectomy, and to use such assessments in constructing a mathematical model for predicting survival.

METHODS

Subjects

The records of patients diagnosed with ICC from July 1998 to December 2000 who underwent exploratory laparotomy at the Eastern Hepatobiliary Surgery Hospital (Shanghai, People's Republic of China) were examined retrospectively in 2011. ICC was defined as cholangiocarcinoma arising from a segmental duct or from a more peripheral duct. Patients with hilar cholangiocarcinoma (Klatskin tumours) or mixed hepato/cholangiocellular carcinoma were excluded from analysis.

Surgical procedures

Surgical procedures included curative resection, noncurative resection and exploratory surgery without resection. Resection was considered to be curative when all detectable regional and invasive tumours were completely removed and confirmed by imaging examination. Areas of tumour dissection included the hepatic portal vein, hepatoduodenal ligament and LNs surrounding the pancreatic head. The margin of liver tumour resection was ≥1 cm. Resection was considered to be noncurative when tumours were incompletely or partially removed due to adhesion to organs, involvement of major blood vessels or ongoing invasion, and when either partial clearing or no clearing of LNs was observed. Resection was not performed when very late stage or diffuse disease was revealed by exploratory surgery, indicating that attempts to remove the tumour(s) were not appropriate. The type of hepatectomy performed depended on both the tumour location and the mode of extension. Approximately 10 surgeons affiliated with the Eastern Hepatobiliary Surgery Hospital, with titles of Associate Professor, Associate Chief Physician or higher, were involved in the performance of these hepatectomies.

Assessments

To identify significant prognostic factors, pathological examinations were performed for all resected specimens by a single pathologist as described previously (18). All specimens were cut into serial slices 5 μm thick, fixed in 10% formalin and subsequently embedded in paraffin. Paraffin-embedded tissues were stained with hematoxylin and eosin, periodic acid-Schiff and Alcian blue. The following parameters were assessed: LN metastasis, number of LNs with metastases, intrahepatic metastasis, vascular invasion, tumour size, degree of histological differentiation, resection margin status and liver cirrhosis. Tumours were staged (tumour, node, metastasis [TNM] I, II, IIIa, IIIb or IVa) according to the classification system of the UICC (fifth edition).

The concentrations of serum factors including CA 19-9, α-fetoprotein (AFP), α-L-fucosidase, carcinoembryonic antigen, γ-glutamyl transferase, alkaline phosphatase, total bilirubin and albumin were measured. Patient demographics and case history details (including postoperative survival duration) were recorded.

Statistical analysis

Continuous variables are presented as medians and interquartile ranges, whereas categorical variables are expressed as counts and percentages. To establish a predictive model of survival duration, all patients were randomly assigned to a training or validation group (3:1 ratio) using the random number generator provided with SPSS version 15.0 software (IBM Corporation, USA). Statistical comparisons between the training and validation groups were performed to confirm that no significant differences existed between the two randomly allocated groups. Continuous variables were compared using the Mann-Whitney U test, whereas categorical variables were compared using the χ^2 test or, when expected values of 20% of cells were less than 5, using Fisher's exact test. Univariate linear regression analysis was performed to identify factors that correlated with survival duration in the training group. Factors with $P<0.1$ in this analysis were then entered into a multiple linear regression model. After a stepwise selective procedure, certain factors were eliminated from the backward multiple linear regression model. Thereafter, multiple linear regression analysis was performed to predict the duration of patient survival in the validation group. Additionally, due to their demographic importance, age and sex were included in the multiple linear regression analysis regardless of whether $P<0.1$ was obtained for these variables in the univariate analysis. Actual and predicted survival durations for the validation group were classified as either ≤1 or >1 year. The accuracy, sensitivity, specificity and positive predictive value of the constructed model were calculated, and $P<0.05$ was considered to be statistically significant. All assessments were two sided and performed using SPSS software.

RESULTS

Demographics and clinical characteristics

A total of 102 patients (72 [71%] men and 30 [29%] women) ranging in age from 25 to 78 years, were included in the present study. It was the same cohort previously used to identify histopathological prognostic factors after hepatectomy for ICC (18). All patients were proven to have ICC either by pathological examination of surgical specimens or, in the case of 'nonsurgical' patients (ie, those who did not undergo resection after exploratory surgery), by using pathological examination of biopsy specimens. In both the training and validation groups, no significant association between hepatitis B and surgical curability was observed. The demographic and clinical characteristics of patients in both groups are presented in Table 1. No significant differences between the training and validation groups were observed. Slightly less than one-third of patients had no symptoms, whereas more than one-half experienced epigastric pain or distension. Approximately 7%, 12% and 43% of patients had a history of schistosomiasis, hepatic calculus and hepatitis B, respectively. With respect to TNM staging, 35.3% of patients had tumours that were classified at or above stage IIIa. All survivors were followed for at least one month, with the median follow-up duration being slightly longer than one year. The overall one-, three- and five-year survival rates after hepatectomy were 57%, 26% and 17%, respectively.

Survival duration

Univariate analysis: Table 2 summarizes the univariate analysis findings regarding survival duration for the 76 patients randomly assigned to the training group. Metastatic LN number, CA 19-9 concentration, surgical curability, schistosomiasis, hepatitis B, TNM stage, albumin concentration, γ-glutamyl transferase concentration, carcinoembryonic antigen concentration, and intra- and perihepatic metastasis were significantly correlated with survival duration (all $P<0.05$). Specifically, patients who had more than three LN metastases, serum CA 19-9 concentrations >37 U/mL, stage IVa tumours, or intra- or perihepatic metastases had significantly shorter survival durations. In contrast, survival duration was significantly increased in patients who underwent curative resection.

Multivariate analysis: The results of the multiple stepwise regression analysis are shown in Table 3. Increased survival duration was found to correlate significantly with the presence of well-differentiated tumours ($P=0.002$) and with curative surgery ($P=0.007$). Moreover, patients with serum CA 19-9 concentrations ≥37 U/mL, TNM stage above III,

TABLE 1
Characteristics of patients who underwent hepatectomy for treatment of intrahepatic cholangiocarcinoma (n=102)

Variable	Total (n=102)	Training group (n=76)	Validation group (n=26)	P*
Age, years, median (interquartile range)	52.0 (43.0–62.3)	51.0 (40.0–60.0)	52.0 (43.0–63.8)	0.575
Follow-up duration, months, median (interquartile range)	14.5 (7.0–35.3)	15.5 (7.8–36.8)	14.5 (9.0–36.0)	0.716
Male sex	72 (70.6)	53 (69.7)	19 (73.1)	0.747
Symptoms				0.604
None	32 (31.4)	24 (31.6)	8 (30.8)	
Hepatomegaly	2 (2.0)	2 (2.6)	0 (0.0)	
Epigastric pain or distention	58 (56.9)	41 (53.9)	17 (65.4)	
Jaundice	4 (3.9)	4 (5.3)	0 (0.0)	
Weight loss	3 (2.9)	3 (3.9)	0 (0.0)	
Fever	3 (2.9)	2 (2.6)	1 (3.8)	
History of schistosomiasis	7 (6.9)	5 (6.6)	2 (7.7)	1.000
History of hepatic calculus	12 (11.8)	9 (11.8)	3 (11.5)	1.000
History of hepatitis B	44 (43.1)	34 (44.7)	10 (38.5)	0.650
Tumour stage (TNM)				0.456
I	24 (23.5)	17 (22.4)	7 (26.9)	
II	42 (41.2)	32 (42.1)	10 (38.5)	
III	30 (29.4)	24(31.6)	6 (23.1)	
IV	6 (5.9)	3(3.9)	3 (11.5)	
Surgical procedures				0.439
Noncurative resection†	37 (36.3)	30 (39.5)	7 (26.9)	
Curative resection‡	57 (55.9)	41 (53.9)	16 (61.5)	
Exploratory only§	8 (7.8)	5 (6.6)	3 (11.5)	

*Data presented as n (%) unless otherwise indicated. *Calculated using the Mann-Whitney U test for continuous variables, and by either the χ^2 or Fisher's exact test for categorical variables; †Tumours were not completely removed and perihepatic lymph nodes were either partially cleared or were not cleared; ‡All tumours were removed and perihepatic lymph nodes were cleared broadly; §Resection was not recommended to the patient because of diffused tumours or late stage of the disease. TNM Tumour, node, metastasis*

and AFP values of 20 ng/mL to 400 ng/mL had shorter survival durations compared with those with CA 19-9 concentrations ≤37 U/mL (P<0.05), TNM stage I (P<0.001) and AFP concentrations <20 ng/mL (P=0.002). It should be noted that the positive correlations of hepatitis B and of perihepatic metastasis with survival duration observed in the univariate analysis were not observed in the multivariate analysis. In addition, metastatic LN number was found to correlate negatively with survival duration in the multivariate analysis; the presence of one or more tumours was associated with longer survival duration compared with the absence of tumours (P=0.021).

Model for predicting survival

The parameters chosen for inclusion in the equation for predicting survival following hepatectomy were age, sex, metastatic LN number, curative surgery, CA 19-9 concentration, AFP concentration, hepatitis B, TNM stage and tumour differentiation. Age, sex and CA 19-9 concentration were included in the model regardless of their statistical significance, whereas other variables were included because they were found to be significant. The established model is as follows:

Predicted log (survival duration [years]) = 1.26 – 0.06 × (age between 41 and 65 years) – 0.26 × (age greater than 65 years) + 0.14 × (male sex) + 0.33 × (one or two LNs) – 0.03 × [more than three LNs) – 0.23 × (CA19-9 ≥37 U/mL) + 0.66 × (presence of strong differentiation) – 0.01 × (poor differentiation) + 0.24 × (curative surgery) + 0.23 × (explored surgical curability) + 0.13 × (hepatitis B – 0.17 [TNM stage II] – 0.51 × [TNM stage at III or above) – 0.40 × (AFP concentration between 20-400 pg/mL) – 0.05 × (AFP concentration >400 pg/mL).

In this model, all variables were categorical and each received a value of '1' when exhibited by the patient.

The findings summarizing the accuracy of this predictive model are shown in Tables 4 and 5. For predicting survival duration longer than one year, the sensitivity, specificity, overall accuracy and positive predicted values were 93.8%, 90.0%, 92.3% and 93.8%, respectively (Table 4). However, the sensitivity, specificity, overall accuracy and positive predictive values for predicting survival duration between one and three years were each considerably reduced (Table 5).

The predicted survival time based on the model described above, and the real survival time for all patients who died (n=89) are shown in Figure 1. Regression analysis revealed that predicted survival (months) = 0.47 × actual survival months + 8.2 (γ=0.62; P<0.0001) for these patients. The predicted survival among patients who survived no longer than 24 months (n=60) was closer to the actual survival time; for this group, predicted survival (months) = 0.92 × survival months + 3.75 (γ=0.63; P<0.001). These findings indicate that prediction was better when the survival time was no longer than two years.

DISCUSSION

In the present study, we retrospectively analyzed the records of patients who underwent hepatectomy for the treatment of ICC to assess factors associated with survival duration. These factors were then incorporated into a mathematical model for predicting survival duration.

The factors included in the equation to predict survival duration were age, sex, metastatic LN number, curative surgery, CA 19-9 concentration, AFP concentration, hepatitis B, TNM stage and tumour differentiation. Use of this equation should, therefore, permit clinicians to make a prognosis based on preoperative (eg, laboratory tests, patient-related circumstances) and intraoperative tumour characteristics. Although similar to TNM staging, mathematical modelling is more specific because each factor is given its own clear weight. Of particular importance is the capability of this formula to predict the extent to which curative hepatectomy affects survival duration. As shown in the present report, use of this model revealed that surgical curability positively and substantially contributes to survival, and indicates that management of ICC should include curative hepatectomy if possible. This mathematical model may also be helpful for evaluating the efficacy of new treatments. For example, should survival duration following the use of updated operative techniques, or new postoperative chemotherapies or radiation treatments prove to be longer than

TABLE 2
Summary of the univariate linear regression analysis findings regarding survival duration of patients in the training group who underwent hepatectomy for treatment of intrahepatic cholangiocarcinoma* (n=76)

Variable	Beta	SE	95% CI	P
Age, years				
<40	Ref	–	–	–
41–65	0.08	0.14	–0.19 to 0.36	0.552
>65	–0.05	0.18	–0.42 to 0.31	0.774
Sex				
Female	Ref	–	–	–
Male	0.11	0.12	–0.12 to 0.35	0.337
Metastatic lymph nodes, n				
0	Ref	–	–	–
1–2	–0.03	0.17	–0.37 to 0.31	0.869
≥3	–0.38	0.14	–0.66 to –0.09	0.011†
CA 19-9 U/mL				
<37	Ref	–	–	–
≥37	–0.40	010	–0.60 to –0.21	<0.001†
Differentiation				
Well	0.49	0.28	–0.07 to 1.04	0.083
Moderate	Ref	–	–	–
Poor	0.12	0.11	–0.10 to 0.33	0.291
Positive lymph node	–0.24	0.12	–0.48 to 0.01	0.051
Intrahepatic metastasis	–0.26	0.11	–0.47 to –0.05	0.018†
Perihepatic metastasis	–0.35	0.14	–0.64 to –0.07	0.016†
Surgical procedures				
Noncurative resection‡	Ref	–	–	–
Curative resection§	0.42	0.10	0.22 to 0.62	<0.001†
Exploratory only¶	–0.07	0.20	–0.48 to 0.33	0.723
Tumour size, cm				
<3	Ref	–	–	–
3–5	–0.20	0.24	–0.67 to 0.27	0.400
5–10	–0.46	0.26	–0.97 to 0.05	0.076
Schistosomiasis	–0.51	0.21	–0.93 to –0.09	0.018†
Hepatic calculus	–0.17	0.17	–0.50 to 0.16	0.305
HBsAg positive	0.24	0.11	0.29 to 0.45	0.026†
Hepatic cirrhosis	0.07	0.11	–0.14 to 0.29	0.495
Tumour stage TNM				
I	Ref	–	–	–
II	–0.34	0.12	–0.57 to –0.11	0.004†
III+IV	–0.72	0.12	–0.96 to –0.49	<0.001†
Total bilirubin, µmol/L				
<20	Ref	–	–	–
≥20	–0.32	0.18	–0.69 to –0.04	0.084
Albumin, g/L				
≥34	Ref	–	–	–
<34	0.32	0.18	–0.04 to 0.69	0.031†
GGT, U/L				
<50	Ref	–	–	–
≥50	–0.25	0.11	–0.47 to –0.03	0.028†
ALP, U/L				
<140	Ref	–	–	–
≥140	–0.10	0.11	–0.33 to 0.12	0.177
AFU, U/L				
<10.2	Ref	–	–	–
≥10.2	0.07	0.13	–0.2 to 0.36	0.624
CEA, ng/mL				
<10	Ref	–	–	–
≥10	–0.36	0.14	–0.63 to –0.09	0.011†
AFP, ng/mL				
<20	Ref	–	–	–
20–400	–0.26	0.15	–0.56 to 0.05	0.097
>400	0.14	0.18	–0.20 to 0.49	0.413
Type of tumour growth				
Normal	Ref	–	–	–
Infiltration	0.02	0.12	–0.26 to 0.23	0.895
Multifocus	0.08	0.15	–0.22 to 0.38	0.594

**Determined using linear regression analysis. Log transformation was applied to the survival period; †Statistically significant survival duration (ie, P<0.05); ‡Tumours were not completely removed and perihepatic lymph nodes were either partially cleared or were not cleared; §All tumours were removed and perihepatic lymph nodes were cleared broadly; ¶Resection was not recommended to the patient because of diffused tumours or late stage of the disease. AFP Alpha-fetoprotein; AFU Arbitrary fluorescence units; ALP Alkaline phosphatase; CA Carbohydrate cell surface antigen; CEA Carcinoembryonic antigen; GGT Gamma-glutamyl transferase; HBsAg Hepatitis B surface antigen; Ref Reference; TNM Tumour, node, metastasis*

TABLE 3
Summary of the multivariate analysis findings regarding survival duration for patients in the training group who underwent hepatectomy for treatment of intrahepatic cholangiocarcinoma* (n=76)

	Beta	SE	95% CI	P
Age, years				
<40	Ref	–	–	–
41–65	–0.06	0.11	–0.28 to 0.15	0.573
>65	–0.26	0.15	–0.55 to 0.04	0.084
Sex				
Female	Ref	–	–	–
Male	0.14	0.08	–0.03 to 0.30	0.115
Metastatic lymph nodes, n				
0	Ref	–	–	–
1–2	0.33	0.14	0.05 to 0.61	0.021†
≥3	–0.03	0.14	–0.31 to 0.26	0.856
CA 19-9, U/mL				
<37	Ref	–	–	–
≥37	–0.23	0.09	–0.40 to –0.05	0.012†
Differentiation				
Well	0.66	0.20	0.25 to 1.07	0.002†
Moderate	Ref	–	–	–
Poor	0.01	0.08	–0.16 to 0.16	0.995
Surgical procedures				
Noncurative resection‡	Ref	–	–	–
Curative resection§	0.24	0.08	0.07 to 0.40	0.007†
Exploratory only¶	0.23	0.17	–0.12 to 0.58	0.189
Hepatitis B				
No	Ref	–	–	–
Yes	0.13	0.09	–0.04 to 0.31	0.126
TNM stage				
I	Ref	–	–	–
II	–0.17	0.11	–0.38 to 0.05	0.124
III+IV	–0.51	0.13	–0.78 to –0.24	<0.001†
Alpha fetoprotein, ng/mL				
<20	Ref	–	–	–
20–400	–0.40	0.12	–0.64 to –0.16	0.002†
>400	–0.05	0.14	–0.33 to 0.23	0.710

**Multiple stepwise regression was used. Log transformation was applied to survival duration; †Statistically significant survival duration (ie, P<0.05); ‡Tumours were not completely removed and perihepatic lymph nodes were either partially cleared or were not cleared; §All tumours were removed and perihepatic lymph nodes were cleared broadly; ¶Resection was not recommended to the patient because of diffused tumours or late stage of the disease. CA Carbohydrate cell surface antigen; Ref Reference: TNM Tumour, node, metastasis*

TABLE 4
Accuracy of predicting a survival duration of longer than one year for subjects in the validation group (n=26)

	Actual survival duration, years	
Predicted result, years	≤1 (n=10)	>1 (n=16)
≤1	9	1
>1	1	15
Sensitivity, %	93.8	–
Specificity, %	90.0	–
Total accuracy, %	92.3	–
Positive predictive value, %	93.8	–

TABLE 5
Accuracy of predicting survival duration of between one and three year(s) for subjects in the validation group (n=26)

	Actual survival duration, years	
Predicted result (years)	<1 or >3 (n=15)	1–3 (n=11)
<1 or >3	10	2
1-3	6	8
Sensitivity, %	80.0	–
Specificity, %	62.5	–
Total accuracy, %	69.2	–
Positive predictive value, %	57.1	–

initially calculated, such techniques or treatments can be considered to be effective or improved. In some cases, good survival prediction may result in patients receiving more effective hospice care.

The presence of intrahepatic metastasis is reported to represent an important factor affecting the prognosis of patients with ICC (11,13,14,19,20). For example, Suzuki et al (11) found that none of the six patients with intrahepatic metastasis in their study survived beyond 14 months. Furthermore Endo et al (19), who evaluated approximately 300 patients with ICC, observed that those with multiple hepatic tumours demonstrated significantly poorer rates of disease-free survival. In agreement with these findings, the univariate analysis performed in the present study showed that intrahepatic metastasis is significantly associated with decreased survival of patients with ICC.

Regional LN metastasis is another factor reported to be significantly associated with poor outcome in several ICC-related studies (8,10,13,14,21). Nakagawa et al (17) concluded that prognosis and survival were related not only to the presence of extrahepatic LN metastasis, but also to the number of LN metastases. While some authors have suggested that LN dissection is necessary to prolong survival in patients with ICC (8,10,17), others have argued that this procedure does not appear to markedly influence long-term survival (13,14,22). In agreement with the latter observations, the multivariate analysis performed in the present study suggests that the number of LN metastases does not significantly influence survival. The difference between these findings and those of other studies (8,10,17) may reflect differences in tumour stages and/or in the ability to perform radical surgery.

It should be noted that reports of patients surviving more than six years (6,7,23) or even up to seven years (24) after LN dissection, without tumour recurrence have been published. Okami et al (25) used advanced molecular techniques to demonstrate the presence of extrahepatic LN micrometastases in patients with bile duct tumours that cannot be detected by traditional pathological examinations, suggesting that extensive lymphadenectomy would be of benefit in such patients. Clearly, some patients with extrahepatic LN metastases can obtain the same benefit from surgical treatment after lymphadenectomy as can those without such metastases.

The present study has several limitations that should be noted, the most obvious of which is the relatively short follow-up duration (mean of 22 months). It is necessary to ascertain whether the findings presented are relevant for longer follow-up durations. It is also acknowledged that the sample size was relatively small for a study of this nature. Accordingly, the decreased predictive accuracy of the model for longer survival durations may have been a consequence of inadequate sample size. Larger scale studies of longer duration are, therefore, planned to confirm the findings presented in the current report.

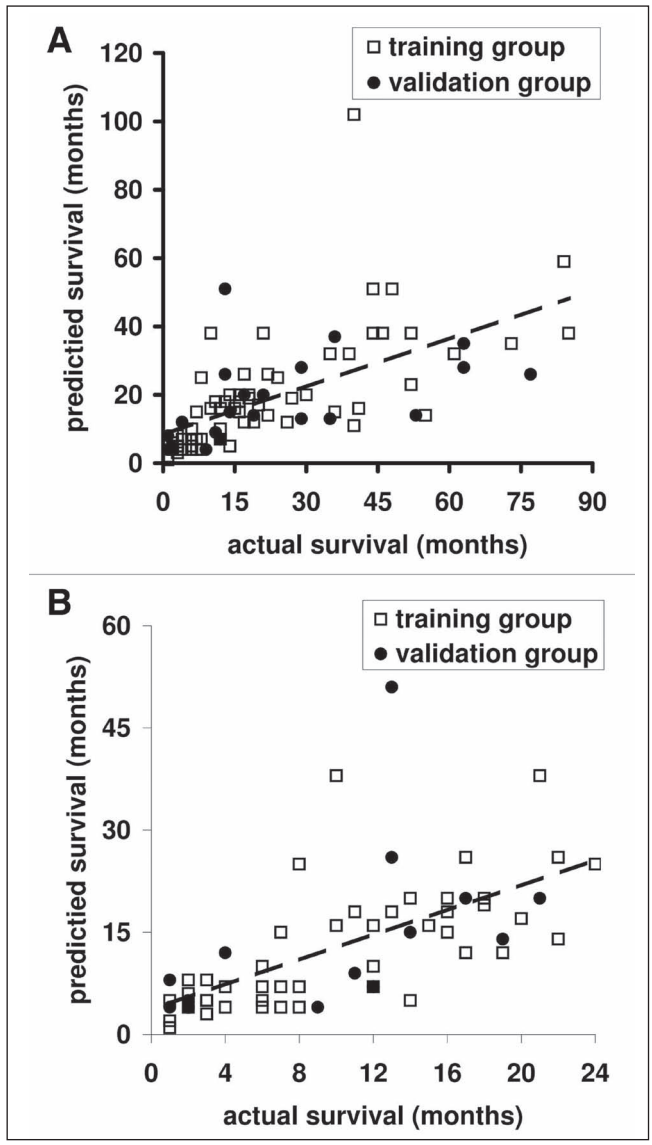

Figure 1) *Comparison of predicted survival time with actual survival time. Predictions were made for patients who died during follow-up including 65 patients in the training group and 24 patients in the validation group* (**A**)*. The plot of predicted survival time against real survival time reveals that predictive survival = 0.47 × actual survival time + 8.24 (γ=0.62; P<0.001). However, for patients with a survival time of no more than two years* (**B**) *(n=60), predicted survival = 0.92 × actual survival time + 3.75 (γ=0.63; P<0.001)*

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