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ORIGINAL ARTICLE

Prognostic Impact of Tumor Multinodularity in Intrahepatic Cholangiocarcinoma

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Abstract

Background The prognostic value of tumor multinodularity in intrahepatic cholangiocarcinoma (ICC) remains debated. We aimed to evaluate the impact of tumor multinodularity according to the presence and distribution of multiples ICC's nodules.

Methods A retrospective review of a prospectively maintained database of patients undergoing resection for ICC from January 1995 to September 2017 was performed. Prognostic factors for survival were assessed by multivariate Cox analysis. Tumoral nodules were defined according to their number (single and multiple) and localization (satellites and contralateral).

Results Out of 120 selected patients, 64 (53%) had single and 56 (47%) had multiple lesions. Multiple lesions included tumors with satellites ($n = 40$; 71.5%) and tumors with contralateral lesions ($n = 16$; 28.5%). Patients with multiple tumors had significantly larger mean main lesion size ($p = 0.02$), required a higher rate of perioperative transfusion ($p = 0.04$), had a greater rate of lymph node involvement ($p < 0.0001$), vascular invasion ($p = 0.04$), and poor differentiation ($p = 0.04$) than single tumors. Patients with single tumors experienced a 5-year survival significantly longer (40%) than patients with multiple tumors (14%; $p = 0.004$). Patients having tumors with satellites had inferior median overall survival and 5-year survival rates (20 months, 7%) compared with patients with contralateral tumors (33.6 months, 29%) ($p = 0.09$). Multivariable analysis identified tumor multinodularity, morbidity, tumor size < 5 cm, poor differentiation, and lymph node involvement as independent prognostic factors for overall survival.

Conclusions Tumor multinodularity represents an independent risk factor for survival in ICCs and identifies a category of patients in need of more effective perioperative treatment.

Keywords Intrahepatic cholangiocarcinoma · Satellites · Intrahepatic metastases · Surgery · Prognosis

Introduction

Intrahepatic cholangiocarcinoma (ICC) represents the second most common malignant primary liver tumor and has shown an alarming increase in incidence over the last two decades.[1,2] Because of late diagnoses, ICCs frequently present with large and/or multiple tumors and/or with regional adenopathy.[1] Until the sixth edition of the American Joint Committee on Cancer (AJCC), ICC staging was based on prognostic factors determined for HCC. This was changed in 2010 in the seventh edition of the AJCC and further modified in the eighth edition.[3] Among the different prognostic factors, tumor multinodularity has been characterized by a debate about its prognostic value in ICC. Some authors identified multiple tumors as a negative prognostic factor[4–9] and questioned the role of surgery in case of tumor multinodularity.[1,7] Others did not confirm this value and reported good oncological outcomes even in the presence of multiple tumors.[10–13] In clinical practice, some authors do not even differentiate between peritumoral and distant tumoral nodules and consider both as either multifocal disease or even as intrahepatic metastases.[12,14–17] Multiple ICCs are merged into the T2

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category regardless if unilateral or bilateral nodules are present.[3] The reasons for these discrepancies are multifactorial and include several parameters: (1) the limited sample size of some studies, (2) lack of differentiation in cases of multinodularity between peritumoral and distant nodules, and (3) the fact that multinodularity in ICCs is frequently associated with other poor prognostic factors, which could have introduced a selection bias.[6,10] The best patient management with multinodular ICCs still remains a subject of debate as does the role of adjuvant, neoadjuvant and interventional radiology treatment.[7,18,19] Therefore, in the present study, we aimed to evaluate the prognostic impact of multinodularity and multiple tumor nodules localization in patients with resected ICCs.

Methods

Data Selection

This was a retrospective cohort study conducted at the Hepato-Pancreato-Biliary Surgery and Liver Transplantation Center of the University of Strasbourg, France. Data from all patients undergoing surgery for ICC between January 1, 1995, and September 30, 2017, that were collected prospectively were then retrospectively analyzed. In the present study, inclusion criteria included consecutive patients undergoing radical (R0/R1) resection for ICC with available data regarding surgical characteristics, pathology, and survival. Exclusion criteria included postoperative death within the first 90 days ($n = 15$), histological diagnosis of hepato-cholangiocarcinoma ($n = 3$), and resection after neoadjuvant chemotherapy ($n = 8$). This was done to evaluate the real prognostic weight of tumoral multinodularity after resection of ICC.

Data Collection, Patient Management, and Study Definitions

Collected data included demographics, surgical details, and pathological ICC information. Surgical variables included operating time, transfusion requirements, and postoperative complications, which were graded according Dindo-Clavien classification with grades 3 and 4 indicating major morbidity.[20] Liver-specific complications included liver failure (50–50 criteria),[21] and biliary fistula as defined elsewhere.[22] Major hepatectomy was defined as resection of > 3 contiguous liver segments according to Couinaud's classification. All patients underwent surgery using the open approach, and regional lymphadenectomy has been systematically included since 2003. Lymphadenectomy included the hepatic pedicle, retroduodenopancreatic area, common hepatic artery, celiac trunk, and interaorticocaval area as an en bloc procedure.[11] The extent of definitive resection was dictated by the surgical findings, and preoperative right portal vein embolization was systematically used in patients undergoing major hepatectomy with a future liver remnant volume < 30%.[23] Radiofrequency ablation was used in combination with resection in patients with multiple tumoral nodules as indicated. Resection of major vascular vessels (inferior vena cava, portal vein, hepatic arteries) and resection of nearby organs (right colon, duodenum, common bile duct) was performed according to the local disease extent. Resection margins were labeled as R0 when they were > 1 mm. In this study, tumors were divided into three categories according to tumor nodularity pattern. Unique tumor nodule was considered as single tumor (S) independently of size; tumor with satellites (Sa) included patients who had one main tumor nodule with one or more peritumoral nodules in the same liver lobe. Contralateral distant (C) tumoral nodules consisted of patients having a tumor nodule(s) in one liver lobe with contralateral liver lesions (Fig. 1). Overall survival (OS) was defined as the length of time from surgery to the patient's death or last follow-up. Disease-free survival (DFS) was defined as the length of time from operation to recurrence. Outpatient follow-up was regularly obtained. The date of the last follow-up was December 31, 2017.

Statistical Analysis

Results for continuous data were expressed as mean ± standard deviation or median and range as appropriate, whereas categorical variables were presented as numbers and percentages. Differences between groups were assessed by chi-square or Fisher's exact test for categorical variables as appropriate. In cases of continuous variables, the Wilcoxon rank sum test or the Student t test were used as appropriate. Survival curves were estimated by the Kaplan-Meier method; differences were assessed by the log-rank test. Multivariable analysis was performed using the Cox proportional hazards model with a stepwise approach including variables reaching $p \leq 0.15$ in the univariate analysis. The level of significance was set at 0.05. Two-sided p values were computed. Statistical analysis was carried out by the SAS software (release 9.4, SAS Institute, Cary, NC).

Results

Overall Population

During the study period, 146 consecutive patients underwent surgical resection for ICC at our institution. Among those, 120 met our inclusion criteria and composed the study population. The median age was 64 years (median 64 years, range 27–86). A major hepatectomy was performed in 94 (78.3%) patients prepared by preoperative right portal vein embolization in 13 patients. Lymphadenectomy was performed in 112 (93.3%) patients, vascular resection in 21 (17.5%), and combined

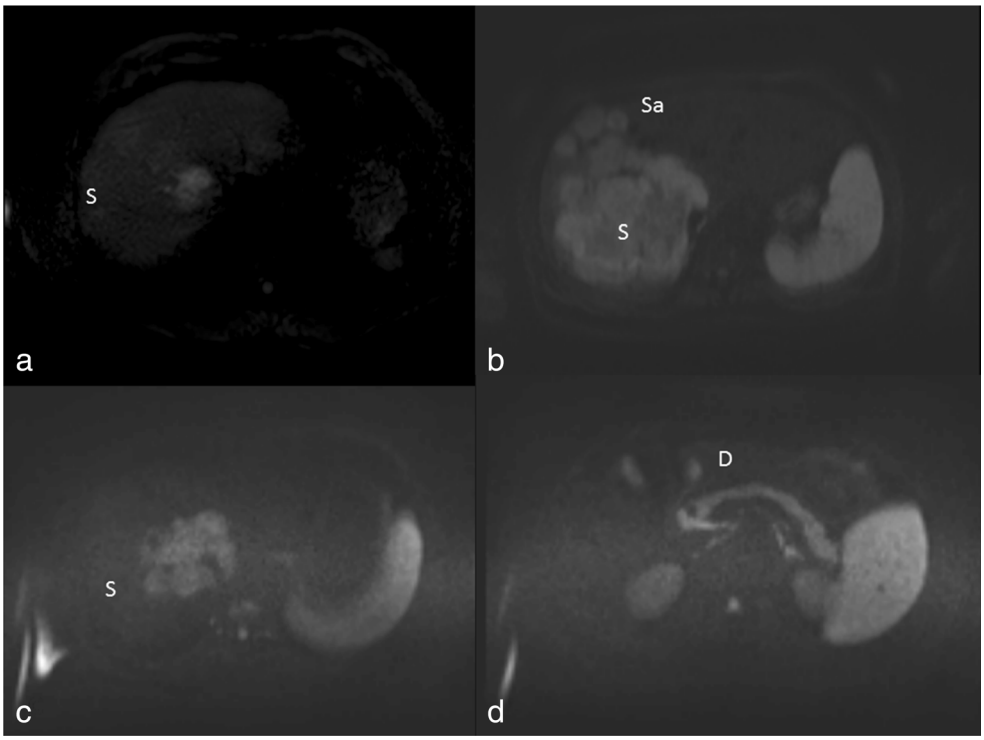

Fig. 1 Diffusion-weighted magnetic resonance images showing (A) a single (S) intrahepatic cholangiocarcinoma (ICC), (B) an ICC with satellite (Sa) nodules, and (C, D) an ICC with contralateral distant (D) nodules

radiofrequency ablation in four patients (3.3%). The morbidity rate was 37.5% with a major morbidity rate of 31.1% (14/45). The rate of tumor with LN+ was 37 (45%). The majority of tumor lesions had a diameter > 5 cm (73.3%). Some degree of liver parenchyma steatosis was present in 33% of the patients. Tumor size > 5 cm was more frequently associated with LN+ (47% versus 27%; $p = 0.08$), tumor multinodularity (51% versus 34%; $p = 0.14$), microvascular invasion (36% versus 12%; $p = 0.01$), and macrovascular invasion (16% versus 3.1%; $p = 0.06$).

The rate of R0 resection was 86% ($n = 103$). Overall, 24 patients received postoperative adjuvant chemotherapy. They were most exclusively randomized into the national prospective study PRODIGE 12-ACCORD 18 phase 3 trial or were those operated on before the year 2000 with poor histologic prognostic factors. At the time of the last follow-up, 88 patients had died, and the median overall survival was 27.80 months (95% CI 22.7–34.13 months) with 1-, 3-, 5-, and 10-year survival rates of 83%, 40%, 28%, and 14%, respectively. The median 1-, 3-, and 5-year DFS for the entire cohort was 8.62 months with 37%, 10%, and 5%, respectively.

Impact of Tumor Multinodularity on Perioperative, Pathology, and Long-Term Outcomes

According to tumor multinodularity, 64 (53%) patients had single liver tumors, and 56 had multiple tumors (47%). Patients with multiple tumors had significantly larger mean lesion sizes (87 ± 43 versus 71 ± 37 mm; $p = 0.02$) and were more frequently LN+ (62% versus 22.8%; $p < 0.0001$) rather than single tumors. Perioperatively, the presence of tumor multinodularity was not associated with any differences in the rate of major or extended liver resections (Table 1). Resection of multiple tumors was characterized, however, by a higher transfusion rate ($p = 0.004$). Multiple tumors were also associated with a greater rate of lymph node (LN+) involvement ($p = < 0.0001$), vascular invasion ($p = 0.04$), and poor differentiation ($p = 0.04$) than seen in single tumors. For patients with single tumors, the median overall survival was 36.6 months (95% CI 26.6–63.6 months) with 1-, 3-, 5-, and 10-year survival rates of 93%, 50%, 40%, and 17%, respectively. Patients with multiple tumors had a median overall survival of 21.0 months (95% CI 14.5–30.1 months) with 1-, 3-, 5-, and 10-year survival rates of 72%, 28%, 14%, and 9%, respectively. Patients with a single tumor experienced a significantly longer median OS compared with multiple tumors (36.5 months versus 21.08 months; $p = 0.004$) (Fig. 2). Patients with multiple tumors also experienced early (< 12 months after surgery) recurrence more frequently when compared with patients with single nodules (66% versus 46%; $p = 0.10$). However, the rates of isolated liver recurrence were similar between patients with single and multiple tumors (22% versus 13%; $p = 0.29$).

Impact of Multiple Tumor Localization on Perioperative, Pathology, and Long-Term Outcomes

The group of multiple tumors included 40 (71.4%) patients with peritumoral satellites and 16 (28.5%) having distant

Table 1 Comparison of demographics, operative outcomes, and pathology according to tumor nodularity

	Single (64)	Multiples (56)	*p*
Normal CA19-9	32 (51%)	21 (37%)	0.14
Major hepatectomy	48 (75%)	46 (82%)	0.38
Vascular resection	11 (17.1%)	10 (17.8%)	1.00
Bile duct resection	14 (22%)	15 (26%)	0.66
Transfusion	13 (23.2%)	26 (50.9%)	0.04
Morbidity	16 (25%)	19 (34%)	0.31
N1	13 (22.81%)	32 (62.7%)	< 0.0001
Tumor size (mean, mm)	87 ± 43	71 ± 37	0.02
Size > 5 cm	21 (32.8%)	11 (19.6%)	0.14
G3	9 (14%)	17 (30.3%)	0.04
Macrovascular invasion	4 (6.2%)	11 (19.6%)	0.04
Microvascular invasion	16 (25%)	20 (35.7%)	0.23
Perineural invasion	9 (14%)	15 (26%)	0.10
R0	56 (87.5%)	47 (83.9%)	0.60
Median survival (months)	36.5	21.08	0.004
Five-year survival	40%	14%	0.004

contralateral tumor nodules. Tumors presenting with satellites were associated with a statistically significant higher rate of LN+ (76%; $p < 0.0001$), higher microvascular invasion rate (27%; $p = 0.001$), greater percentage of poor differentiation (32%; $p = 0.08$), perineural invasion (32%; $p = 0.06$), and higher number of > 2 tumors (65%; $p = 0.07$) (Table 2).

Patients with single tumors had greater median OS and 5-year survival rates (36.5 months; 40%) compared with patients with satellites (20 months, 7%; $p = 0.0004$) but were comparable to patients with contralateral tumors (33.6 months, 29%; $p = 0.59$) (Fig. 3). There was a trend toward longer DFS in patients with single nodules (12.8 months) compared with satellites and contralateral (7.5 and 7.9 months, respectively), but it did not reach statistical significance ($p = 0.30$). Patients with satellites and contralateral nodules had similar early recurrence rates (65 versus 70%; $p = 0.25$).

Prognostic Factors for Overall Survival for the Entire Cohort

Univariate and multivariable analyses of risk factors for survival are shown in Table 3. Multivariable analysis identified morbidity (HR 2.18; 95% CI 1.30–3.65; $p = 0.003$), tumor size < 5 cm (HR 0.44; 95% CI 0.24–0.80; $p = 0.007$), poor differentiation (HR 2.38; 95% CI 1.41–4.02; $p = 0.001$), LN+ (HR 1.66; 95% CI 1.21–2.82; $p = 0.001$), and tumor multinodularity (HR 1.61; 95% CI 1.02–2.54; $p = 0.03$) as independent prognostic factors for overall survival.

Discussion

The present study demonstrated the negative prognostic value of tumor multinodularity in ICC. Patients presenting with

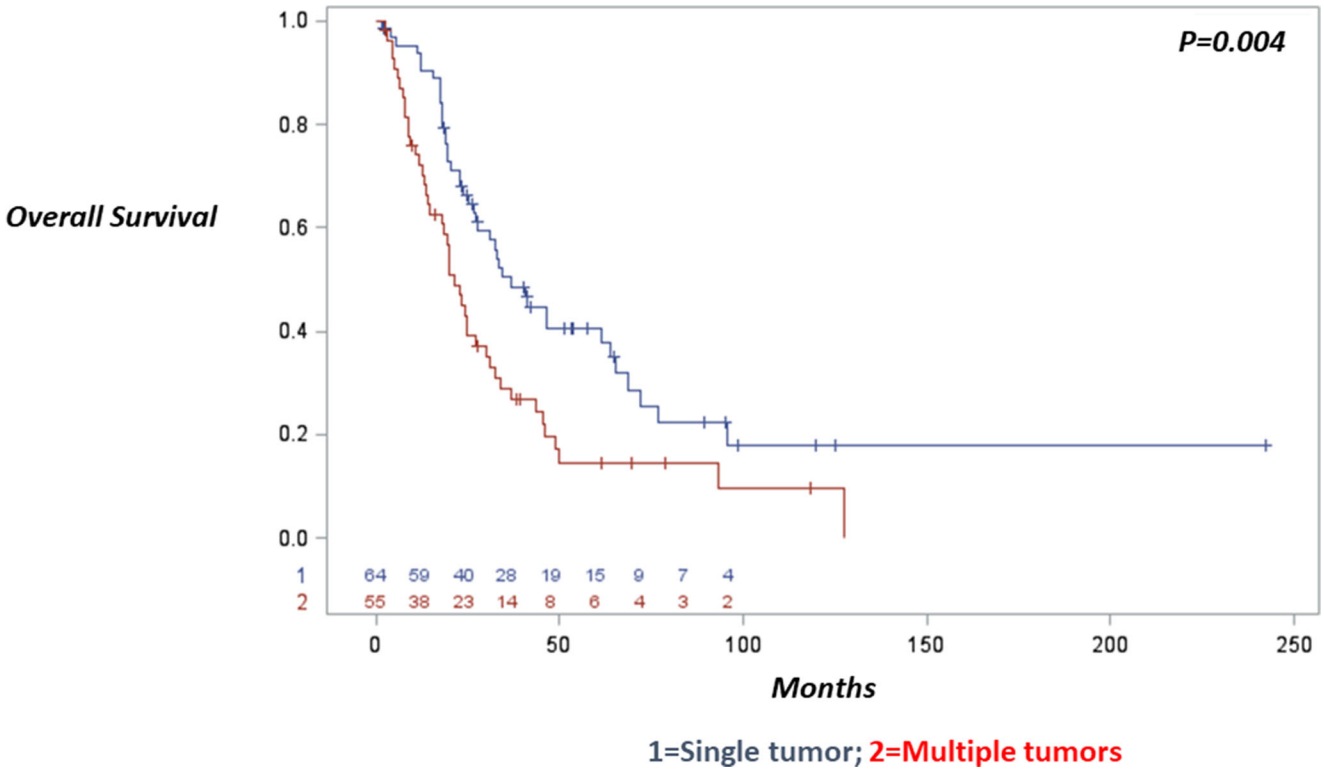

Fig. 2 Kaplan-Meyer estimates of overall survival of patients with single and multiple ICC tumor nodules

Table 2 Comparison of demographics, operative outcomes, and pathology according to tumor localization

	Single (64)	Satellites (40)	Contralateral (16)	*p* Single vs satellites	*p* Single vs contralateral	*p* Satellites vs contralateral
Normal CA19-9	32 (51.6%)	14 (35%)	7 (43.7%)	0.10	0.77	0.55
Major Hepatectomy	48	35	11	0.14	0.75	0.12
Vascular Resection	11 (17.1%)	7 (17.7%)	3 (18.7%)	1.00	1.00	1.00
Bile duct Resection	14 (21.8%)	13 (32%)	2 (12.5%)	0.50	0.25	0.18
Transfusion	13 (26%)	19 (61%)	7 (50%)	0.006	0.10	0.76
Morbidity	12 (24%)	14 (47%)	4 (25%)	0.37	0.75	1.00
N1	13 (23%)	28 (76%)	4 (28.5%)	< 0.0001	0.72	0.003
Taille > 5 cm	43 (67%)	32 (80%)	13 (81%)	0.18	0.36	1.00
G3	9 (14%)	13 (32%)	4 (25%)	0.04	0.28	0.75
> 2 nodules	–	26 (65%)	6 (37.5%)			0.07
Macrovascular invasion	4 (6%)	11 (27%)	0 (0%)	0.004	0.57	0.02
Microvascular invasion	16 (25%)	13 (32.5%)	7 (43.7%)	0.50	0.21	0.53
Perineural invasion	9 (14.2%)	13 (32.5%)	2 (13%)	0.04	1.00	0.19
R0	56 (87%)	34 (85%)	13 (81%)	0.21	0.68	0.70
Median Survival (months)	36.5	20	33.6	0.0004	0.58	0.09
Five-year Survival	40%	7%	29%	0.0004	0.58	0.09

multiple tumors were characterized by a decrease in OS and DFS and a trend toward earlier recurrence. Satellite nodules, more than contralateral nodules, negatively impacted the survival of patients with ICC, identifying a subgroup of patients with a reduced survival in need of more effective perioperative treatment.

Tumor multinodularity is common in ICC; in the present study, 47% of the patients had multiple tumors with 10% of the patients having contralateral tumor nodules. In three recent multicentric studies, the rate of multinodular tumors ranged from 18 to 44%.[6,10,24] The differences between rates are probably due to the heterogeneity of the population selected for surgery in those multicentric settings but are in accordance with a previous study.[24]

Tumor multinodularity is associated with other poor prognostic factors in ICCs.[25] In the current study, tumor multinodularity was associated with an increase in LN+ rate, perineural, and vascular invasion, factors that most likely

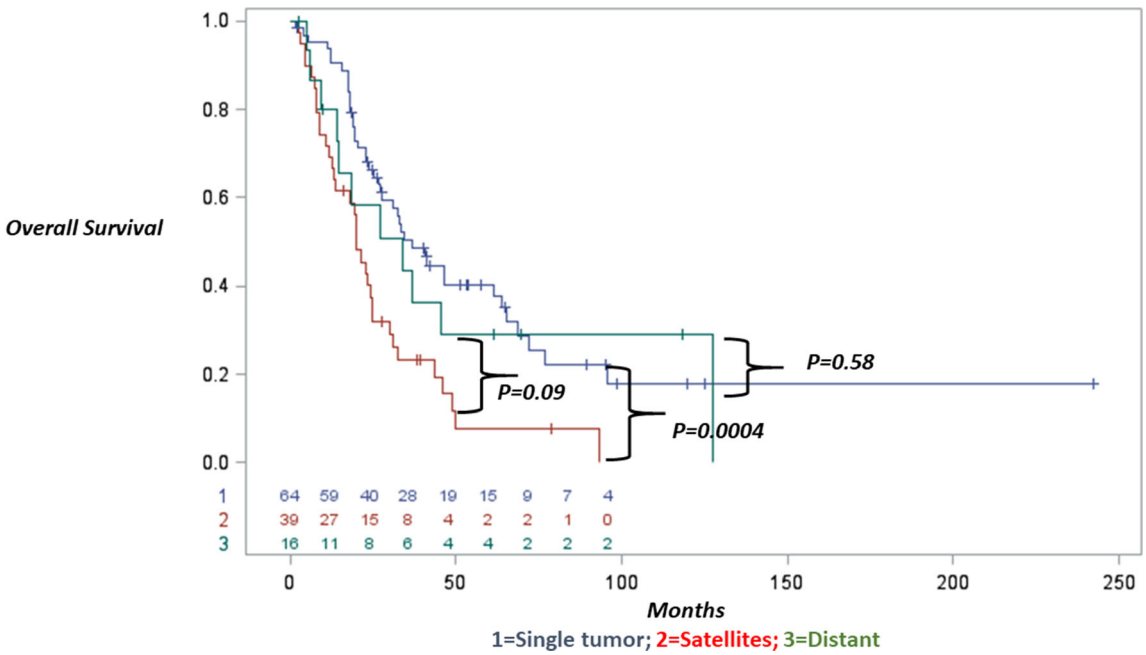

Fig. 3 Kaplan-Meyer estimates of overall survival of patients with single, satellites, and contralateral ICC tumor nodules

Table 3 Univariate and multivariable Cox regression analysis of overall survival (OS) in relation to clinicopathologic features

Characteristics			Univariate analysis			Multivariable analysis		
	5-year OS log-rank	Median OS (months)	HR	95% CI	*p*	HR	95% CI	*p*
Age								
> 70 vs	14%	27.2						
< 70 years	32%	30.9	1.34	(0.83–2.16)	0.22			
CA19–9								
< 36 ng/ml	38%	43.5						
> 36 ng/ml	21%	23.6	1.63	(1.05–2.52)	0.02			
Cirrhosis								
Yes	27%	24.8						
No	30%	30.1	1.50	(0.65–3.47)	0.19			
PVE						–	–	–
Yes	22%	23.2						
No	28%	27.8	1.35	(0.70–2.73)	0.36			
Vascular resection								
Yes	22%	26.6	1.19	(0.68–2.05)	0.53	–	–	–
No	29%	30.9						
Bile duct resection								
Yes	19%	19.6						
No	31%	30.1	1.36	(0.84–2.20)	0.20	–	–	–
Transfusion								
Yes	16%	26.6						
No	31%	30.9	1.33	(0.84–2.12)	0.21			
Major Morbidity								
Yes	23%	12.3	2.00	(1.25–3.21)	0.003	2.18	(1.30–3.65)	0.003
No	28%	31.1						
Major Hepatectomy								
Yes	27%	24.4						
No	33%	36.6	1.24	(0.73–2.10)	0.41			
Nodularity								
Single	40%	36.5						
Satellites	8%	20.0						
Contralateral	29%	33.6						
Multiples	14%	21.08	1.83	(1.20–2.80)	0.004	1.61	(1.02–2.54)	0.03
Tumor size								
< 5 cm	42%	46				0.44	(0.24–0.80)	0.007
≥ 5	23%	23.2	1.85	(1.10–3.10)	0.01			
Poor differentiation								
Yes	15%	17.5						
No	31%	32.3	1.93	(1.16–3.19)	0.01	2.38	(1.41–4.02)	0.001
Lymph node invasion								
N1	16%	20.0						
N0	38%	41.3	2.16	(1.37–2.41)	0.0009	1.66	(1.21–2.82)	0.001
Perineural invasion								
Yes	16%	22.7	1.56	(0.93–2.62)	0.08	–	–	–
No	31%	31.1						
Microvascular invasion								
Yes	19%	19.9	1.43	(0.90–2.27)	0.12	–	–	–

Table 3 (continued)

Characteristics			Univariate analysis			Multivariable analysis		
	5-year OS log-rank	Median OS (months)	HR	95% CI	*p*	HR	95% CI	*p*
No	31%	32.2						
Macrovascular invasion								
Yes	0%	12.9						
No	31%	32.2	2.95	(1.60–5.44)	0.0005	–	–	–
R0								
Yes	28%	30.9						
No	25%	19.9	1.13	(0.61–2.09)	0.69			
Adjuvant treatment								
Yes	18%	25.3						
No	30%	27.8	0.74	(0.44–1.24)	0.25			

further contributed to the poor prognosis of patients with multiple tumors. Tumor multinodularity was associated with the highest rate of lymph node metastases (62%) confirming similar findings of two previous studies.[6,10]

In patients with multiple ICCs, the exact impact of tumor location (satellite versus contralateral) remains poorly explored.[9] Some authors consider multiple tumors as intrahepatic metastases independent of their location.[12,14,17] One of the principal aim of the current study was to determine the precise impact of tumor location on survival. We found that patients with satellites were characterized by the lowest survival rate. This can be explained by several factors.

First, peritumoral satellites could be the consequence of tumoral vascular permeation and being a form of highly aggressive ICCs. This could be partially explained by the higher rate of lymph node involvement, poor tumoral differentiation, perineural infiltration, and macrovascular invasion which we observed in ICC with satellites. Second, patients with satellites nodules presented the largest tumor burden with more than 70% of patients having > 2 nodules. This could confirm the data by Spolverato et al. who reported that the absolute number of tumor nodules > 3 was an independent prognostic factor.[10]

On the contrary, contralateral lesions could be expression of a multifocal disease which could explain the better survival rate of these tumors observed in the present study. Alternatively, the good survival rates observed in patients with contralateral tumoral nodules could be the result of a selection bias with only patients with few nodules being operated.

Our survival rates in patients with tumors with satellites and contralateral tumors are different from those of the recent study by Conci et al.[9] who reported the lowest survival rates in patients with distant nodules. This is more likely observed because of (1) their different classification used for defining satellites nodules (i.e., based on the segmental distribution) and (2) their higher number of tumoral nodules observed in patients with distant tumoral nodules.

Our study further confirms the validity of the TNM classification which did not consider contralateral nodules as distant metastases and not preclude surgery in these cases. We believe that the number of multiple nodules, their localization, the presence of other negative prognostic factors (lymph node involvement and/or macrovascular invasion), the performance status of patients, and the potential morbidity related to the extent of the hepatectomy should be considered when selecting patients for surgery.

The safety of ICC surgical resection remains a major concern, and the mortality rate after resection approached 10% in this and other studies.[12,14] This was probably due to the extent of liver resection (80% of major and extended resections), the rate of major associated procedures, and the presence of an underlying diseased parenchyma.[14] In the current study, surgical resection of multinodular tumors was associated with both higher major morbidity and transfusion rates. This should be considered when selecting patients for surgery by balancing the risks and benefits of surgery in the context of such disease.

The occurrence of major morbidity was also identified as independent risk factors for OS. This was in accordance with two previous larger multicentric studies,[26,27] which found that major morbidity negatively impacted the OS of patients with ICC. The occurrence of major morbidity could have lowered immune response of patients with ICC favoring earlier recurrence and death.[26,27] This should be considered when selecting patients for adjuvant therapy.

The best management of patients with multinodular ICC remains a subject of debate. The use of neoadjuvant and adjuvant therapies in this context remains to be evaluated.

Le Roy et al. reported stable and partial responses in 45% and 24% of patients, respectively, who were treated with neoadjuvant chemotherapy for locally advanced ICCs with a rate

of conversion to resectability of > 50%.[12] However, the use of neoadjuvant chemotherapy did not modify the rate or the number of multifocal tumors when compared with patients resected without neoadjuvant chemotherapy (46% versus 37%; $p = 0.36$; 2.3 versus 1.9; $p = 0.59$).

Recently, Sur et al. reported a clear survival benefit for adjuvant treatment only in a subgroup of patients with LN+ or positive margin; this study, however, lacked details about tumor multinodularity.[28] In the current study, it was difficult to evaluate the role of adjuvant chemotherapy because this procedure was utilized for only 20% of cases in the presence of poor prognostic factors. The prospective study PRODIGE 12-ACCORD 18 phase 3 trial failed to demonstrate a significant difference in recurrence-free survival between patients undergoing adjuvant treatment by GEMOX or those undergoing surveillance after biliary cancer radical resection.[28] However, in this study, different types of biliary tract cancer were analyzed together. Since the prognosis of patients with multinodular tumors appears particularly poor after upfront surgical resection (14% at 5 years) in the current study, the exact role of GEMOX-based neoadjuvant chemotherapy in ICCs deserves further comparison in a well-designed multicentric prospective study.

The present study presents several limitations that deserve discussion: first, its retrospective nature and the small sample size with subgroup analysis which could have introduced bias; second, the tertiary referral center setting with a trend toward more complex cases treated and a trend toward reduced morbidity which limits the generalizability of the results; third, the definition used for the multiples nodules localization which is different from previous studies and deserve further evaluation; and finally, the scarce, sporadic, and heterogeneous use of adjuvant treatments, which made it difficult to adequately evaluate its value in patients with multi-nodular tumors.

Conclusions

The present study from a specialized unit in hepato-biliary surgery provides further evidence on the negative prognostic value of tumor multinodularity in ICCs. We have confirmed the decreased survival associated with multiple ICCs, especially in the presence of satellite nodules after surgery adding this factor to other well-recognized poor prognostic factors for ICC. Further research should be done to evaluate the role of neoadjuvant and adjuvant chemotherapy in patients with tumor multinodularity.

Authors' Contributions Substantial contributions to the conception or design of the work: PA, IJ, AL, FF, OA, and PB.

Acquisition, analysis, or interpretation of data for the work: PA, IJ, AL, FF, CO, OA, and PB.

Drafting the work or revising it critically for important intellectual content: PA and PB.

Final approval of the version to be published: PA, IJ, AL, FF, CO, OA, and PB.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: PA, IJ, AL, FF, CO, OA and PB.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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