

## Patterns of Distribution of Hepatic Nodules (Single, Satellites or Multifocal) in Intrahepatic Cholangiocarcinoma: Prognostic Impact After Surgery

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### ABSTRACT

**Objective.** We aimed to compare the clinicopathological features and survival after surgery of patients with intrahepatic cholangiocarcinoma (ICC) according to the patterns of distribution of hepatic nodules.

**Methods.** A retrospective analysis of a multi-institutional series of 259 patients with resected ICC was carried out. Patients were further classified according to the pattern of distribution of hepatic nodules: single tumors (type I), single tumors with satellites in the same liver segment (type II), or multifocal tumors (type III).

**Results.** Overall, 64.5% of patients had type I, 21.9% had type II, and 13.5% had type III. The 5-year overall survival rate was 49.4, 34.2, and 9.9% for types I, II, and III, respectively ( $p < 0.001$ ). A multivariate survival analysis identified the following independent prognostic factors: pattern types II and III ( $p = 0.001$  and  $p = 0.001$ , respectively), size  $\geq 50$  mm ( $p = 0.021$ ), lymph node (LN) metastases ( $p = 0.005$ ), and R1 resections ( $p = 0.019$ ). We stratified survival for each type of pattern according to the other prognostic factors identified in the multivariate

analysis. N0 and R0 patients with type II and III tumors had encouraging long-term results. Conversely, patients with LN metastases and R1 resections had poor prognosis, particularly patients with type III tumors.

**Conclusion.** ICC has distinct patterns of distribution with different prognoses that should be considered when making therapeutic decisions. Patients with type III tumors had a significantly worse prognosis, and the benefits of upfront surgery should be carefully evaluated.

Intrahepatic cholangiocarcinoma (ICC) is an aggressive neoplasm that arises from the epithelium of the intrahepatic bile ducts,<sup>1</sup> accounting for 10–15% of all primary liver malignancies.<sup>2,3</sup> The incidence of ICC has increased during the last few decades, likely due to both an escalation in the prevalence of viral and chronic hepatitis and improved clinical-pathological knowledge of the disease.<sup>4–6</sup> The treatment of patients with ICC often represents a challenging issue for hepato-pancreatico-biliary (HPB) surgeons and radical surgery remains the only chance for long-term survival.<sup>7,8</sup> The prognosis of patients with ICC after surgery has improved in the last few decades, with an overall 5-year survival rate ranging from 25 to 40%.<sup>9–11</sup> Tumor size, lymph node (LN) metastasis, vascular invasion, radicality of surgery, and the presence of multiple nodules are the main clinicopathological factors that have a prognostic role after surgery.<sup>5,9,10,12</sup> Some authors consider the presence of multifocal tumors a contraindication to liver resection;<sup>13</sup> however, the presence of multiple nodules varies in surgical series, ranging from 20 to 32%,<sup>6,14</sup> but the data show that different definitions and terminology

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have been used, including terms such as ‘satellite nodules’, ‘multifocal tumor’, and ‘intrahepatic metastases’. For these reasons, differentiation between ‘multiple nodules’, which may correspond to a multifocal carcinogenesis or to nodules that spread from the primary tumor, remains debatable. Moreover, in the recently released 8th edition of the American Joint Committee on Cancer (AJCC) staging system, ICC patients with vascular invasion or multiple nodules are both considered to be in the same T2 category, without any further classification.<sup>15</sup> A recent radiological study, based on computed tomography (CT) scans, identified and proposed three different patterns of ICC at the time of presentation, according to the distribution of hepatic nodules (single tumor, single with satellites, and multifocal tumors), and each had a progressively worse prognosis, regardless of the type of treatment.<sup>16</sup>

The current multi-institutional study aimed to compare the clinical-pathological characteristics and to evaluate the long-term outcomes of patients who underwent surgery for ICC according to the pattern of distribution of hepatic nodules.

## PATIENTS AND METHODS

### *Patients*

From January 1995 to December 2015, a total of 282 consecutive patients who underwent surgery for ICC at three hepatobiliary Italian tertiary referral centers (the Division of General and Hepatobiliary Surgery, G.B. Rossi Hospital, University of Verona, Verona; the Division of Hepatobiliary and General Surgery, Humanitas Clinical and Research Center, Humanitas University, Rozzano and Milan; and the Department of General and Emergency Surgery and Organ Transplantation, S. Orsola-Malpighi Hospital, University of Bologna, Bologna) were considered for this study. Of these patients, 13 did not undergo resection (exploratory or palliative surgery) due to advanced disease. The remaining 269 patients underwent resection, of whom 10 (3.7%) had a residual macroscopic tumor after surgery (R2 resection) and were therefore excluded. Moreover, a total of eight patients who were classified as having pM1 disease were also excluded—six patients who had non-regional LN metastases (the celiac artery, the superior mesenteric artery, and/or the periaortic LN) and two patients with a resectable hepatic lesion and a single peritoneal nodule of carcinomatosis. Thus, the remaining 251 patients who underwent curative resection were enrolled in this study. The distribution of hepatic nodules was collected based on preoperative imaging and pathological evaluation. The pattern of distribution of hepatic nodules for the analysis was defined according to

the final pathological evaluation. Patients were further classified as follows: single tumor (type I), single tumor with satellite nodules in the same Couinaud liver segment (type II), and multifocal scattered tumors in different Couinaud liver segments (type III).<sup>16</sup> A serum cancer antigen (CA) 19-9 level > 55 U/mL was considered abnormally high.

Clinical data were retrieved from each center’s prospectively collected database, pathological data in each institution were retrospectively reviewed according to the proposed classification, and the analysis was performed retrospectively. Data collection and analysis were performed according to the institutional guidelines and conformed to the ethical standards of the World Medical Association (Declaration of Helsinki). The study was approved by each local ethical committee, and signed consent was obtained from all subjects.

To analyse the prognostic role of the association of the pattern of distribution of hepatic nodules with other prognostic factors, a subgroup analysis was performed that stratified each pattern of distribution according to the main prognostic factors identified by the multivariate analysis.

### *Statistical Analysis*

Numerical variables were summarized using the mean and standard deviation, or the median and interquartile range (IQR), as appropriate. Student’s *t* test, and the Chi square and Fisher tests were used to compare means and proportions, respectively, between independent groups. CA19-9 levels were compared between groups using the non-parametric Kruskal–Wallis test and non-parametric Mann–Whitney *U* test.

Overall survival (OS) was calculated from the date of surgery to the date of death from any cause or last follow-up, whichever came first. The median follow-up period for surviving patients was 38.6 months. Eight patients with 90-day postoperative mortality were excluded from the survival analysis. The OS curves were estimated according to the Kaplan–Meier method and were compared using the log-rank test. Multivariable Cox modeling was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs), adjusting for potential confounders, and the pattern of distribution was considered a categorical variable. Differences were considered statistically significant at *p* values ≤ 0.05.

**RESULTS**

*Patient Characteristics*

Clinical and pathological characteristics of the study population are summarized in Table 1.

*Comparison of Clinical and Pathological Characteristics According to the Pattern of Distribution of Hepatic Nodules*

Comparison of the clinical and pathological characteristics according to the different patterns of distribution are summarized in Table 2. Compared with patients with type I tumors, patients with type II and III tumors had significantly larger tumors ( $p = 0.019$  and  $p = 0.007$ , respectively), a greater number of nodules ( $p < 0.001$  and  $p < 0.001$ , respectively) and a higher serum CA19-9 level ( $p = 0.035$  and  $p = 0.018$ , respectively). Preoperative chemotherapy was performed in eight (4.9%) patients with type I, eight (14.5%) patients with type II, and five (14.7%) patients with type III (type I vs. type II,  $p = 0.024$  and type I vs. type III  $p = 0.037$ , respectively). In 30 (54.5%) patients with type II and six (17.6%) patients with type III, preoperative imaging identified only one lesion ( $p < 0.001$ ), and the diagnosis of multiple nodules (satellites or multifocal lesions) was made based on pathology. The sensitivity and accuracy of preoperative imaging in identifying the correct pattern, using pathology as the reference, were 45.5 and 88.1% for type II, and 82.3 and 97.6% for type III. The rate of LN metastases increased according to the pattern of distribution, from 21.6% ( $n = 35$ ) in patients with single tumors, to 34.5% ( $n = 19$ ) in patients with satellites, and to 35.2% ( $n = 12$ ) in patients with multifocal tumors, but the differences were not statistically significant. The rate of R0 resection significantly decreased from 76.5% in type I, to 74.5% in type II, and to 52.9% in type III.

*Prognostic Factors for Overall Survival*

The 5-year OS rate and median OS of the entire cohort were 40.6% and 45.9 months, respectively. Table 3 shows the univariate and multivariate analysis of the prognostic factors for OS.

Based on univariate analysis, sex (male), CA19-9 level ( $\geq 55$  U/mL), tumor size ( $\geq 50$  mm), LN metastases, vascular invasion, radicality of surgery (R1), and pattern of distribution of hepatic nodules were identified as prognostic factors for OS. The 5-year OS rate was 49.4% in patients with single tumors (type I), 34.2% in patients with satellites (type II), and 9.9% in patients with multifocal tumors (type III) [ $p < 0.001$ ; Fig. 1]; however, only one

**TABLE 1** Clinical and pathological characteristics of 251 patients with intrahepatic cholangiocarcinoma

Characteristics	Values
Age, years [median (IQR)]	68.0 (59.0–73.0)
Male sex	126 (50.2)
Size, mm [median (IQR)]	57 (3–80)
Number of nodules [median (IQR)]	1 (1–2)
CA19-9, U/mL [median (IQR)]	48 (15–163)
Pattern of distribution of nodules based on preoperative imaging	
Preoperative type I—single	198 (78.9)
Preoperative type II—single with satellites	25 (10.0)
Preoperative type III—multifocal	28 (11.1)
Pattern of distribution of nodules	
Type I—single	162 (64.5)
Type II—single with satellites	55 (21.9)
Type III—multifocal	34 (13.5)
Preoperative chemotherapy	21 (8.4)
Type of surgery	
Major hepatectomy	150 (59.8)
Minor hepatectomy	101 (40.2)
Biliary confluence resection	18 (7.2)
AJCC 8th edition pT stage	
T1a	46 (18.3)
T1b	19 (7.6)
T2	116 (46.2)
T3	56 (22.3)
T4	14 (5.6)
AJCC 8th edition pN stage	
N0	120 (47.8)
N1	66 (26.3)
NX	65 (25.9)
AJCC 8th edition stage	
IA/IB	16 (6.4)/10 (4.0)
II	57 (22.7)
III A/IIIB	27 (10.8)/76 (30.3)
NA	65 (25.9)
Vascular invasion	91 (36.3)
Biliary invasion	27 (10.8)
Histologic grading	
G1–2	160 (63.7)
G3–4	91 (36.3)
Radicality	
R0	183 (72.9)
R1	68 (27.1)
Postoperative mortality	8 (3.2)
Postoperative chemotherapy	100 (41.2)

Data are expressed as  $n$  (%) unless otherwise specified  
*IQR* interquartile range, *AJCC* American Joint Committee on Cancer

**TABLE 2** Comparison of clinical and pathological characteristics according to the pattern of distribution of hepatic nodules in patients with intrahepatic cholangiocarcinoma

Characteristics	Single tumor (type I) [n = 162]	Single tumor with satellites (type II) [n = 55]	Multifocal (type III) [n = 34]	p value <sup>a</sup>	p value <sup>b</sup>	p value <sup>c</sup>
Age, years [median (IQR)]	67.5 (59.7–72.0)	69.0 (59.0–74.0)	67.0 (55.8–77.0)	0.252	0.880	0.500
Male sex	84 (51.9)	29 (52.7)	13 (38.2)	0.518	0.104	0.198
Size, mm [median (IQR)]	50.0 (30.0–70.0)	70.0 (44.0–90.0)	70.0 (48.2–95.0)	0.019	0.007	0.544
Number of nodules [median (IQR)]	1	3 (2–3)	4 (3–6)	< 0.001	< 0.001	0.002
CA19-9, U/mL [median (IQR)]	29.5 (12.0–119.2)	64.5 (20.0–146.8)	78.0 (20.5–647.5)	0.035	0.018	0.087
Preoperative chemotherapy	8 (4.9)	8 (14.5)	5 (14.7)	0.024	0.037	0.606
Single tumor at preoperative imaging	162 (100.0)	30 (54.5)	6 (17.6)	< 0.001	< 0.001	< 0.001
Multiple tumor at preoperative imaging	0 (0.0)	25 (45.5)	28 (82.4)			
Major hepatectomy	91 (56.2)	34 (61.8)	25 (73.5)	0.284	0.083	0.183
AJCC 8th edition pT stage				< 0.001	< 0.001	0.066
T1a	46 (28.4)	0 (0.0)	0 (0.0)			
T1b	19 (11.7)	0 (0.0)	0 (0.0)			
T2	60 (37.0)	31 (56.4)	25 (73.5)			
T3	30 (18.5)	17 (30.9)	9 (26.5)			
T4	7 (4.3)	7 (12.7)	0 (0.0)			
AJCC 8th edition pN stage				0.099	0.224	0.588
N0	80 (49.4)	26 (47.3)	13 (38.2)			
N1	35 (21.6)	19 (34.5)	12 (35.3)			
NX	47 (29.0)	10 (18.2)	9 (26.5)			
AJCC 8th edition stage				0.001	0.212	0.468
IA/IB	16 (9.9)/10 (6.2)	0 (0.0)/0 (0.0)	0 (0.0)/0 (0.0)			
II	31 (19.1)	17 (29.8)	9 (26.5)			
IIIA/IIIB	18 (11.1)/41 (25.3)	4 (6.9)/24 (41.4)	5 (14.7)/11 (32.4)			
NA	46 (28.4)	10 (18.2)	9 (26.5)			
Vascular invasion	54 (33.3)	24 (43.6)	13 (38.2)	0.113	0.359	0.391
Biliary invasion	18 (11.1)	4 (7.3)	5 (14.7)	0.298	0.366	0.219
Histologic grading G3–4	57 (35.2)	18 (32.7)	16 (47.1)	0.437	0.135	0.130
Radicality				0.447	0.006	0.032
R0	124 (76.5)	41 (74.5)	18 (52.9)			
R1	38 (23.5)	14 (25.5)	16 (47.1)			
Postoperative chemotherapy	57 (36.1)	25 (47.2)	18 (56.3)	0.102	0.028	0.279
Postoperative mortality	3 (1.9)	3 (5.5)	2 (5.9)	0.172	0.208	0.637

Data are expressed as n (%) unless otherwise specified

IQR interquartile range, AJCC American Joint Committee on Cancer, NA not available

<sup>a</sup>Type I versus type II

<sup>b</sup>Type I versus type III

<sup>c</sup>Type II versus type III

patient in the type III group survived more than 3 years (patient alive at 66.8 months). Based on multivariate analysis, a tumor size  $\geq 50$  mm (HR 2.539, 95% CI 1.150–5.606,  $p = 0.021$ ), presence of LN metastases (HR

2.482, 95% CI 1.323–4.653,  $p = 0.005$ ), and radicality of surgery (HR 2.101, 95% CI 1.129–3.910,  $p = 0.019$ ) were confirmed to be the main prognostic factors for OS, but the pattern of distribution of hepatic nodules was the strongest

**TABLE 3** Univariate and multivariate analysis of the clinical and pathological factors for overall survival

Characteristics	5-year OS (%)	<i>p</i> value	HR	95% CI	<i>p</i> value
Age, years					
< 70	43.6	0.133			
≥ 70	34.9				
Sex					
Male	32.8	0.002	1.646	0.864–3.133	0.130
Female	48.8				
CA19-9, U/mL					
< 55	51.7	< 0.001	1.650	0.836–3.255	0.149
≥ 55	28.9				
Pattern of distribution					
Type I	49.4	< 0.001	–		
Type II	34.2		3.101	1.552–6.197	0.001
Type III	9.9		4.064	1.825–9.049	0.001
Size, mm					
< 50	53.5	0.019	2.539	1.150–5.606	0.021
≥ 50	32.0				
Lymph node metastases					
No	53.0	< 0.001	2.482	1.323–4.653	0.005
Yes	20.0				
Vascular invasion					
No	45.1	0.017	1.150	0.601–2.200	0.674
Yes	32.9				
Biliary invasion					
No	38.5	0.436			
Yes	43.7				
Histologic grading					
G1–2	44.8	0.154			
G3–4	31.2				
Radicality					
R0	41.8	0.047	2.101	1.129–3.910	0.019
R1	34.0				
Postoperative chemotherapy					
No	39.6	0.553			
Yes	45.8				

OS overall survival, HR hazard ratio, CI confidence interval

prognostic factor (type II: HR 3.101, 95% CI 1.552–6.197, *p* = 0.001; type III: HR 4.064, 95% CI 1.825–9.049, *p* = 0.001).

The 5-year OS rate according to the preoperative imaging-based pattern of distribution of hepatic nodules was 47.9% in patients with single tumors (preoperative type I), 21.7% in patients with satellites (preoperative type II), and 0.0% in patients with multifocal tumors (preoperative type III) [*p* < 0.001; electronic supplementary Figure 1].

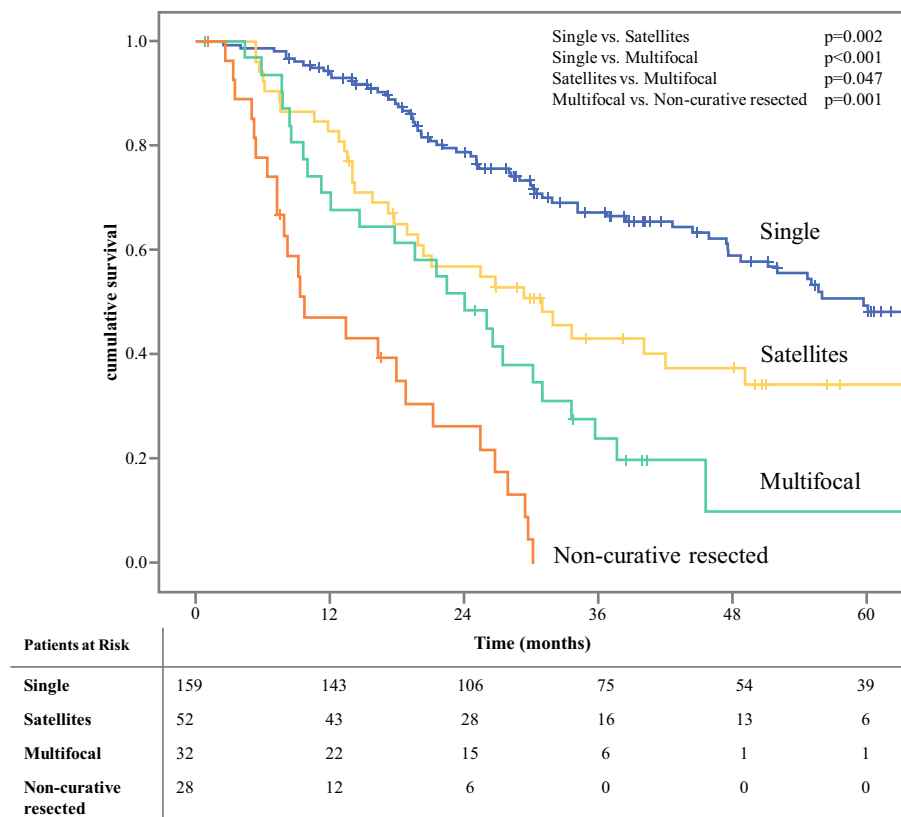
The 5-year recurrence-free survival rate was 37.1% in patients with single tumors (type I), 16.7% in patients with satellites (type II), and 0% in patients with multifocal

tumors (type III) [*p* < 0.001; electronic supplementary Table 1]. Univariate and multivariate analysis of the prognostic factors for recurrence-free survival are shown in electronic supplementary Table 1.

*Prognostic Impact of the Association of the Pattern of Distribution of Hepatic Nodules and Other Prognostic Factors*

Figure 2 shows the survival curves of patients with a single tumor (type I, 2A), single tumors with satellites (type II, 2B), and multifocal tumors (type III, 2C) stratified by the other prognostic factors identified in the multivariate

**FIG. 1** Overall survival according to the pattern of distribution of hepatic nodules. Survival curves of patients with macroscopic residual tumor after surgery (R2 resection), classified as M1, or explorative or palliative surgery, known as *non-curative resected* ( $n = 28$ ), are shown



analysis, including the size of the tumor, LN status, and the radicality of surgery.

The size ( $\geq$  or  $<$  50 mm) of the main hepatic lesion seems to have a prognostic role in patients with type I tumors, but not in patients with type II and III tumors ( $p = 0.048$ ,  $p = 0.457$ , and  $p = 0.930$ , respectively). Conversely, patients without LN metastases and those who underwent R0 resection had better long-term survival in both the patients with satellites ( $p = 0.049$  and  $p = 0.047$ , respectively) and patients with multifocal tumors groups ( $p = 0.001$  and  $p = 0.048$ , respectively). Patients with LN metastases and R1 resection had very poor prognosis in association with multifocal tumors (type III).

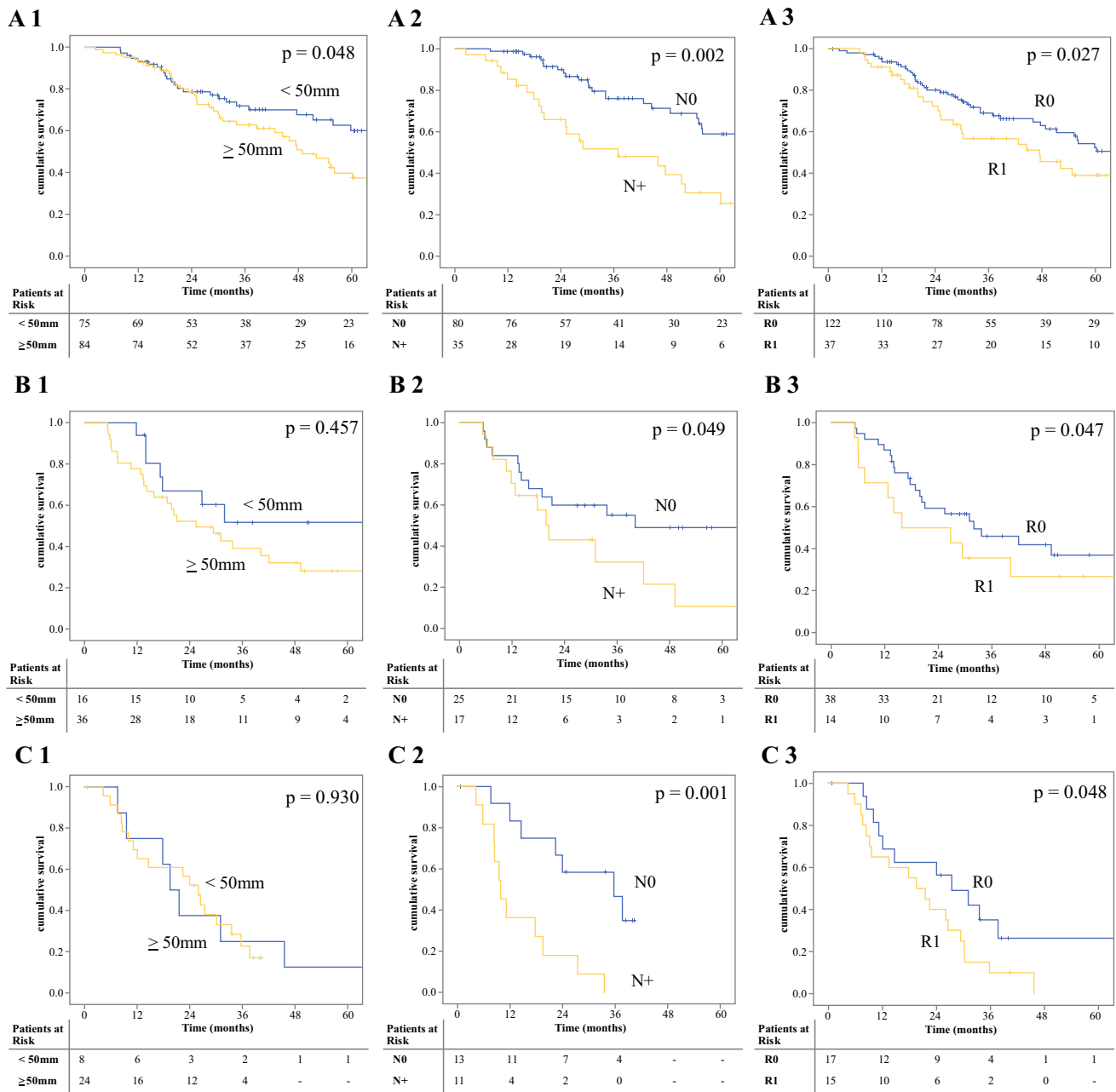
## DISCUSSION

Improvements in surgical techniques and perioperative care have enhanced the feasibility and safety of liver resection, with satisfactory long-term results in patients with ICC.<sup>8,17,18</sup>

The current study represents a large surgical series that focuses on this topic and specifically analyses the clinical, pathological, and prognostic impact of the different patterns of distribution of hepatic lesions in patients who underwent surgery for ICC.

Of the 251 patients included in the study, 21.9% ( $n = 55$ ) had a type II pattern (single tumor with satellite nodules) and 13.5% ( $n = 34$ ) had a type III pattern (multifocal tumors). A recent study based on an international multi-institutional cohort of over 1100 patients reported the presence of satellite nodules and intrahepatic metastasis in 22 and 7% of patients, respectively, even in the absence of a clear definition of multiple nodules. Moreover, the authors considered both satellite nodules and intrahepatic metastases to be multifocal tumors in the survival analysis.<sup>19</sup>

A radiological study by Baheti et al. defined and proposed three different patterns of ICC according to the distribution of hepatic nodules (single tumor, single with satellites, and multifocal tumors) identified, at the time of presentation, on CT scans, which had different impacts on survival.<sup>16</sup> However, preoperative imaging may have underestimated the real presence and distribution of multiple nodules. In our series, patients with satellite nodules (type II) or multifocal tumors (type III) appeared to have a single nodule on preoperative imaging in 54.5 and 17.6% of cases, respectively, leading the surgeon into an unexpected and critical decision-making situation during surgery. In case of intraoperative discovery of lesions that were not detected at preoperative imaging, the presence of other prognostic factors, such as the presence of LN



**FIG. 2** Overall survival according to the type I (a), II (b), and III (c) pattern of distribution of hepatic nodules stratified by the other prognostic factors identified at multivariable analysis: **a1, b1, c1** size (< 50 or ≥ 50 mm); **a2, b2, c2** lymph node status (N0 or N+); **a3, b3, c3** radicality of surgery (R0 or R1 resection)

metastases, may guide the therapeutic choice, therefore the hepatic pedicle LN sampling with frozen section pathological analysis could be suggested prior to aggressive surgery.

In our study, patients with satellite nodules (type II) and multifocal tumors (type III) had some differences in their clinical characteristics (see Table 2). These aspects suggest different biological behaviors of single tumors with satellite nodules compared with multifocal tumors. This

hypothesis is also supported by the survival results (Fig. 1). In multivariate analysis, the pattern of distribution of hepatic nodules was the strongest predictor of OS.

Therefore, the prognosis in patients with multifocal tumors seems to be poor after surgical resection. Nevertheless, some long-term survivors exist in this subgroup of patients.

Uenishi et al. analyzed the prognostic impact of LN metastases in patients with single or multifocal ICC in a surgical series of 133 patients. The study reported no

survivors at 3 years following surgery when the multifocal appearance of the hepatic lesions was associated with LN metastases. However, in patients without LN metastases, the 5-year survival rates were 54 and 26% in patients with single and multifocal tumors, respectively. According to these results, the authors concluded that surgery alone cannot prolong survival in patients with both LN metastases and multifocal tumors.<sup>20</sup>

We performed a similar subgroup analysis in our multi-institutional series. Patients with LN metastases and R1 resection had poor prognosis, particularly if associated with multifocal tumors (type III). Conversely, the long-term survival of patients with satellite nodules (type II) and multifocal tumors (type III) improves in the absence of other prognostic factors (N0 and R0 resection).

According to these results, surgery alone should not be recommended in patients with multifocal tumors (type III) when LN metastases are present and when R0 resection could not be achieved. A recent study of 116 patients with multifocal ICC comparing the survival outcomes of patients who underwent surgery with patients submitted to intra-arterial therapy (TACE and hepatic arterial infusion pump) shows promising results for non-surgical treatment.<sup>13</sup>

The retrospective nature of the current study should be considered a limitation that resulted in selection bias of patients who underwent surgery based on tumor characteristics and the hepatic distribution of lesions. Moreover, due to the low incidence and resectability rate of ICC, the multi-institutional design over a long period of time should also be considered a limitation of this study. External validation and further study are needed to confirm our results.

## CONCLUSIONS

ICC has distinct patterns of distribution with peculiar clinical characteristics and different prognoses that should be considered when making therapeutic decisions. The prognosis of patients with multifocal tumors (type III) is significantly worse than the prognosis of patients with other patterns of nodule distribution. More efforts should be made to identify type III patients who may benefit from upfront surgery. In the remaining patients, multimodal treatments should be explored.

**CONFLICT OF INTEREST** Simone Conci, Andrea Ruzzenente, Luca Viganò, Giorgio Ercolani, Andrea Fontana, Fabio Bagante, Francesca Bertuzzo, Andrea Dore, Antonio Daniele Pinna, Guido Torzilli, Calogero Iacono and Alfredo Guglielmi have no conflict of interest to declare.

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