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Peritoneal Carcinomatosis Risk and Long-Term Survival Following Hepatectomy for Spontaneous Hepatocellular Carcinoma Rupture: Results of a Multicenter French Study (FRENCH—AFC)

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ABSTRACT

Background. Spontaneous rupture of hepatocellular carcinoma (HCC) remains a life-threatening complication, with a reported mortality rate of between 16 and 30% and an incidence rate of approximately 3% in Europe. Survival data and risk factors after ruptured HCC are lacking, especially for peritoneal metastasis (PM).

Objectives. The aims of this study were to evaluate the pattern of recurrence and mortality after hepatectomy for ruptured HCC, and to focus on PM.

Methods. We retrospectively reviewed the files of patients admitted to 14 French surgical centers for spontaneous rupture of HCC between May 2000 and May 2012.

Results. Overall, 135 patients were included in this study. The median disease-free survival and overall survival (OS) rates were 16.1 (11.0–21.1) and 28.7 (26.0–31.5) months, respectively, and the median follow-up period was 29 months. At last follow-up, recurrences were observed in 65.1% of patients ($n = 88$). The overall rate of PM following ruptured HCC was 12% ($n = 16$). Surgical management of PM was performed for six patients, with a median OS of 36.6 months. An α -fetoprotein level

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> 30 ng/mL ($p = 0.0009$), tumor size at rupture > 70 mm ($p = 0.0009$), and vascular involvement ($p < 0.0001$) were found to be independently associated with an increased likelihood of recurrence. No risk factor for PM was observed.

Conclusion. This large-cohort French study confirmed that 12% of patients had PM after ruptured HCC. A curative approach may be an option for highly selected patients with exclusive PD because of the survival benefit it could provide.

Spontaneous tumor rupture is a rare event in Western countries, with an estimated incidence of between 2 and 3% of patients with hepatocellular carcinoma (HCC).¹ Despite recent improvements in management, mortality rates still range between 16 and 30% following a bleeding event.²

Short-term survival is conditioned by bleeding management strategy, however factors influencing long-term survival are not clear but seem to be the same as for unruptured HCC.^{3,4} In the 7th Union for International Cancer Control (UICC) classification, ruptured HCC is considered as T4 with regard to perforation of the visceral peritoneum.⁵

Following rupture, whatever the treatment modalities, the median overall survival (OS) does not exceed 9 months.⁶ In the largest clinical series, for patients with surgical resection of ruptured HCC the median OS is reported as more than 20 months;^{7,8} however, available data regarding tumor recurrence following surgical resection in the context of ruptured HCC are limited,⁹ particularly those relating to peritoneal recurrence. The fact that tumor rupture is considered a risk factor for peritoneal recurrence remains debated.^{7,9–11} Another question is whether peritoneal metastasis (PM) of HCC should be considered a palliative condition, with reported survival not exceeding 12 months. Indeed, several studies have shown that with selected patients, more aggressive therapies such as surgical resection or hyperthermic intraperitoneal chemotherapy (HIPEC) can improve prognosis.

We aimed to study the long-term prognosis following surgical resection of ruptured HCC, the risk and pattern of recurrence, and, in particular, PM in a large, retrospective, Western cohort of patients.

METHODS

Patient Selection

Data of patients managed for spontaneous rupture of HCC during the period January 2000 to May 2012 were retrospectively retrieved from the databases of 13 French

and 1 Italian tertiary care centers, all members of the FRENCH Network (French Association of Research in Digestive Surgery) or the AFC Network (French Association of Surgery).

The current study was performed with the approval of the institutional Ethics Committee Review Board (study number E2019-48). Specific written informed consent of patients was not required for this observational study.

Review of Rupture Management and Tumor Characteristics

Data collected for all patients included history of liver disease, Child–Pugh score, surgical management of ruptured HCC, tumor characteristics (size, location, tumor multiplicity, pathological analysis, and resection margins). Biological data were measured before emergency or planned surgery following rupture and included hemoglobin rate, platelet level, prothrombin time, albumin level, creatinine level, and α -fetoprotein (AFP) level.

Major liver resection was defined as resection of more than two segments.¹² Data on postoperative outcomes were also collected, and postoperative morbidity was evaluated using the Clavien–Dindo classification.¹³ Liver failure was defined using the International Study Group of Liver Surgery (ISGLS) score,¹⁴ while liver fibrosis was quantified using the METAVIR score.¹⁵

Follow-Up

Patients were followed-up every 3 months during the first year, then every 6 months until the fifth year after surgery. At each follow-up visit, an AFP level assay and a computed tomography (CT) scan were performed. Tumor recurrence was characterized by at least one of the following criteria: a typical new liver lesion present on imaging, with features of HCC with or without a rise in serum AFP; histological documentation of a new lesion; and another extrahepatic metastasis on CT scan. The date of recurrence was the earliest date at which at least one of the above criteria was met. All of the first recurrences were classified as either ‘unifocal intrahepatic recurrence’, ‘multifocal intrahepatic recurrence’, ‘exclusive peritoneal recurrence’, or ‘diffuse recurrence’ when intrahepatic lesions were associated with PM or extra-abdominal metastasis. Once a recurrence was diagnosed, patients were treated with liver resection, radiofrequency ablation, liver transplantation, transarterial chemotherapy embolization (TACE), systemic therapy, or conservative medical treatment, depending on tumor site, liver function, and the patient’s general condition.

Long-Term Survival Analysis

OS was defined as the time from liver resection to patients' death, while disease-free survival (DFS) was defined as the time of patients' survival without any sign of symptoms or HCC recurrence. Patients who died without recurrence were censored at the time of death. Postoperative deaths, defined as 90-day mortality after surgery, were excluded from the survival analysis.

Data on recurrence or death were collected during follow-up, ending in August 2015 for all patients.

Statistical Analysis

Data are expressed as median and interquartile range, with regard to small sample size. The incidence of a first relapse was estimated using methods for competing risks. The principal aim of the present cohort study was to assess the risk of HCC recurrence, especially peritoneal recurrence following rupture. The significance of site-specific prognostic factors after liver resection were assessed using the Cox model for competing risks. Approximation of survival probabilities was estimated using the Kaplan–Meier method. Statistical analysis was performed using SPSS® software version 18.0 (SPSS, Chicago, IL, USA).

RESULTS

Patient Characteristics and Surgical Management

Of the 135 patients with ruptured HCC included in this study, 27 were female and 108 were male, with a median age at rupture of 66 years (57–71). A history of liver cirrhosis was observed in 57 patients (42%). The median AFP level was 29 ng/mL (5–560). Other demographics and main biological results are detailed in Table 1.

The median size of a ruptured nodule was 76 mm (50–100). HCC was unifocal for 105 patients (78%) and subcapsular for 91 patients (67%).

Regarding the management of ruptured HCC, 39 patients (30%) had emergency liver resection. Of the 96 patients operated at distance from the bleeding event (planned liver resections), primary interventional hemostasis was achieved in 69 patients (transarterial embolization [$n = 63$, including a patient treated with TACE], surgical hemostasis [$n = 6$]), and conservative medical management (blood transfusion) in 27 patients.

Major liver resections were performed in 49 patients (36%), including 15 right hepatectomies, 12 extended right hepatectomies, 16 left hepatectomies, and 6 extended left hepatectomies. The remaining 86 patients had minor liver resections; 31 patients had non-anatomic partial resection (23%).

A total of 88 patients (65%) had postoperative complications (liver failure, $n = 33$ [Grade A: 25; Grade B/C: 8]; biliary leakage, $n = 8$; intra-abdominal collection, $n = 39$; pulmonary complications, $n = 34$; and postoperative bleeding, $n = 6$). Major complications, defined as Clavien–Dindo grade higher than II, were observed in 37 patients (27%). Ninety-day mortality was 9%, with more events following emergency liver resection, but without significant difference (15% vs. 6%; $p = 0.1$).

Pattern of Recurrence

The median follow-up period was 29 months. At last follow-up, recurrence was observed in 88 patients (65.1%) and most of the recurrences occurred during the first 2 years (91%). Distribution of the different patterns of recurrence are shown in Fig. 1. Among these 88 patients with recurrence, most had multifocal intrahepatic recurrence ($n = 37$, 42%), while a unifocal intrahepatic recurrence was observed in 17 patients (19%). Exclusive peritoneal recurrence was observed in 11 patients (13%), while the remaining 23 patients (26%) had diffuse recurrence (extra-abdominal only [$n = 16$], intrahepatic with extra-abdominal [$n = 2$], or intrahepatic with peritoneal [$n = 5$]).

In total, after hepatectomy for ruptured HCC, 12% of patients ($n = 16$) had a peritoneal recurrence (exclusive or associated intrahepatic recurrence) and the peritoneal recurrence site accounted for 18% of all recurrences.

The 5-year estimated risk of recurrence was 70% and the median DFS was 16.1 months (11.0–21.1). The median DFS for patients with a unifocal intrahepatic recurrence was significantly longer than for patients with other patterns of recurrence (21.5 vs. 10.6 months; $p = 0.047$) [Fig. 2]. In addition, the DFS rates at 1, 3, and 5 years were higher in the unifocal intrahepatic recurrence group compared with groups with other recurrence sites (64.7% vs. 45.5%, 23.5% vs. 9.1%, and 11.8% vs. 4.5%, respectively).

Overall Survival According to Recurrence Sites

The median OS of the entire cohort was 28.7 months (26.0–31.5). Patients with a unifocal intrahepatic recurrence had significantly higher OS than patients with other patterns of recurrence (49.7 vs. 21 months; $p = 0.003$) [Fig. 3]. As observed for DFS rates, the OS rates, at 1, 3, and 5 years were higher in the unifocal intrahepatic recurrence group compared with groups with other recurrence sites (94.1% vs. 86.3%, 58.8% vs. 23.8%, and 35.3% vs. 11.4%, respectively).

TABLE 1 Characteristics of the 135 included patients after liver resection for ruptured hepatocellular carcinoma

Variables	All patients [<i>n</i> = 135]
Age at rupture, years [median (range)]	66 (57–71)
Male	108 (80)
BMI [median (range)]	27 (23–29)
Known cirrhosis	57 (42)
Child A	52 (38)
Child B	5 (4)
Preoperative biological data [median (range)]	
Hemoglobin rate, g/dl	11 (10–13)
Platelet level, 10 ³ /mm ³	192 (142–302)
Prothrombin time, %	81 (70–94)
Albumin level, g/L	34 (30–38)
Creatinine level, μmol/L	80 (62–101)
α-Fetoprotein, ng/mL	29 (5–560)
Surgical management	
Scheduled liver resection	96 (70)
Emergency liver resection	39 (30)
Days between rupture and surgery [median (range)]	42 (0–61)
Major liver resection	49 (36)
Perioperative transfusion	73 (54)
Clavien Dindo grade higher than II	37 (27)
Postoperative mortality	13 (9)
Unifocal	105 (78)
Size of ruptured nodule, mm [median (range)]	76 (50–100)
Subcapsular lesion	91 (67)
R1/R2	24 (18)
Peritumoral margin [median (range)]	5 (1–10)
Peritumoral capsula	69 (51)
Satellite nodules	59 (44)
Differentiation grade-poor	24 (18)
Microvascular involvement	86 (64)
Liver fibrosis F3/F4	80 (59)
Recurrence after rupture	88 (65)

Data are expressed as *n* (%) unless otherwise specified

BMI body mass index

FIG. 1 Pattern of recurrence after ruptured hepatocellular carcinoma

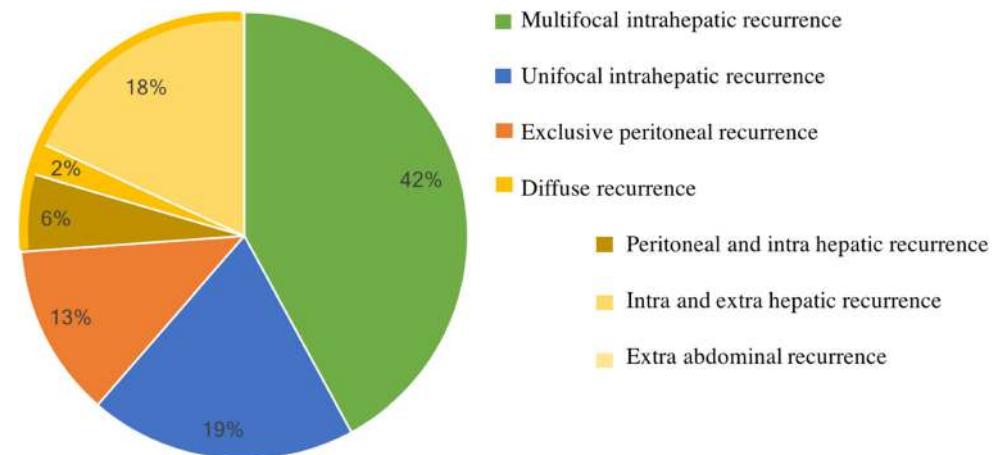
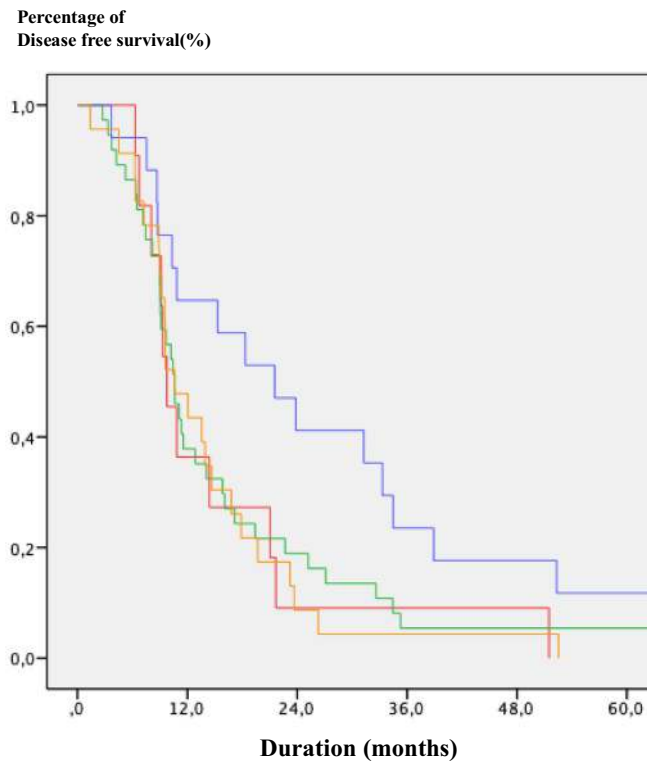


FIG. 2 Disease-free survival of patients according to the pattern of recurrence after liver resection for ruptured HCC



Type of recurrence	Overall disease free survival			
	Median (months)	1 year n(%)	3 years n (%)	5 years n (%)
Exclusive peritoneal recurrence (n = 11)	9.767	4 (36.4)	1 (9.1)	0 (0.0)
Multifocal intrahepatic recurrence (n = 37)	10.600	14 (37.8)	2 (5.4)	2 (5.4)
Unifocal intrahepatic recurrence (n = 17)	21.533	11 (64.7)	4 (23.5)	2 (11.8)
Diffuse recurrence (n = 23)	10.600	11 (47.8)	1 (4.3)	0 (0.0)
Total (n = 88)	10.8	40 (45.5)	8 (9.1)	4 (4.5)

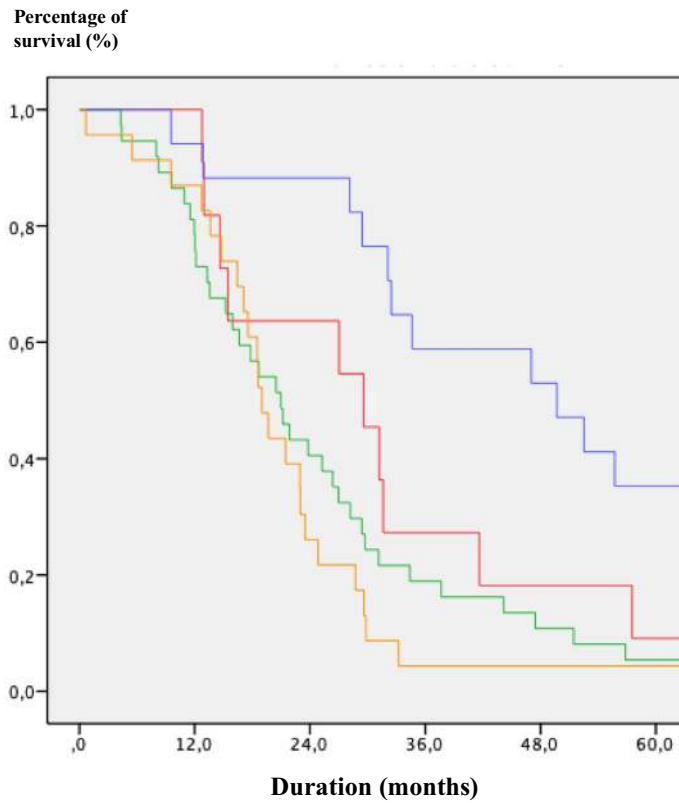
Peritoneal Metastasis (PM) Characteristics

A total of 11 patients had an exclusive peritoneal recurrence. Table 2 describes the main characteristics of these patients. The median age was 69 years (66–71.5). Four patients had cirrhosis and the median AFP level was 35 ng/mL (9–414). A major liver resection was performed in seven cases. The median tumor size was 80 mm (62.5–150), a positive resection margin was observed in four patients, and vascular involvement was present in eight cases. Surgical management of peritoneal recurrence was performed in six patients, with a median OS of 36.6 months. The remaining five patients managed with palliative therapy had a median OS of 14.6 months.

Recurrence Management for Patients without PM

Most patients with a unifocal intrahepatic recurrence were treated with curative intent (liver resection or radiofrequency ablation; $n = 14$, 83%), while multifocal intrahepatic recurrences were more frequently treated using TACE ($n = 16$, 43%) or best supportive care ($n = 14$, 38%). Patients with diffuse recurrences were mostly treated with palliative intent (Table 3).

FIG. 3 Overall survival of patients according to the pattern of recurrence after liver resection for ruptured HCC



Type of recurrence	Overall survival			
	Median (months)	1 year n (%)	3 years n (%)	5 years n (%)
Exclusive peritoneal recurrence (n = 11)	29.567	11 (100)	3 (27.3)	1 (9.1)
Multifocal intrahepatic recurrence (n = 37)	20.967	29 (78.3)	7 (19.0)	2 (5.4)
Unifocal intrahepatic recurrence (n = 17)	49.700	16 (94.1)	10 (58.8)	6 (35.3)
Diffuse recurrence (n = 23)	19.000	20 (87.0)	1 (4.3)	1 (4.3)
Total (n = 88)	23.500	76 (86.3)	21 (23.8)	10 (11.4)

Predicting Factors for Recurrence and Overall Survival

When adjusting for possible confounding variables using Cox proportional hazards modeling, several prognostic clinical, biological, and pathological factors were found to be independently associated with an increased likelihood of recurrence: an AFP level > 30 ng/mL (hazard ratio [HR] 2.681, 95% confidence interval [CI] 1.645–4.372; $p = 0.0009$), tumor size at rupture > 70 mm (HR 2.291, 95% CI 1.402–3.744; $p = 0.0009$), and vascular involvement (HR 13.256, 95% CI 3.924–44,779;

$p < 0.0001$). HCC treatment (emergency liver resection vs. planned liver resection) was not significant in univariate analysis (Table 4).

In the same way, an AFP level > 30 ng/mL (HR 4.408, 95% CI 2.479–7.840; $p < 0.0001$), R1 or R2 resection margin (HR 2.406, 95% CI 1.191–4.483; $p = 0.0057$), and tumor size > 70 mm (HR 1.910, 95% CI 1.145–3.186; $p = 0.013$) were significantly associated with poorer OS (Table 4).

No risk factors for peritoneal recurrence could be identified.

TABLE 2 Characteristics, management, and outcomes of patients with exclusive peritoneal metastasis

Patient	Age, years	Cirrhosis	AFP level (ng/mL)	Major liver resection	Emergency liver resection	Blood transfusion	Tumor size (mm)	Resection margin R1/R2	Vascular involvement	DFS (months)	Recurrence management	OS (months)
1	74	No	7	Yes	No	Yes	150	Yes	No	9.1	Surgery	31.6
2	33	No	8	Yes	No	Yes	80	No	Yes	9.8	Surgery	29.6
3	71	Yes	5690	Yes	No	No	150	Yes	Yes	8.0	BSC	15.5
4	66	Yes	35	No	No	Yes	60	No	Yes	6.3	CT	13.0
5	72	No	10	No	No	Yes	150	Yes	Yes	14.4	Surgery	31.2
6	52	No	621	No	Yes	Yes	70	No	Yes	10.8	Surgery	41.6
7	72	Yes	184	Yes	No	No	65	Yes	Yes	9.3	CT	14.6
8	66	Yes	208	Yes	Yes	No	155	No	Yes	21.0	CT	27.0
9	70	No	5	Yes	No	No	50	No	No	51.5	Surgery	57.5
10	69	No	10	No	Yes	Yes	35	No	No	21.7	Surgery	109.1
11	66	No	9000	Yes	No	No	140	No	Yes	6.7	CT	12.8

AFP α -fetoprotein, DFS disease-free survival, OS overall survival, BSC best supportive care, CT chemotherapy

TABLE 3 Recurrence management according to its different models

<i>n</i> (%)	Group 1 17 (19)	Group 2 11 (13)	Group 3 37 (42)	Group 4 23 (26)
Median DFS, months	21.5	9.7	10.6	10.6
Median OS, months	49.0	29.5	20.1	19.0
Death, <i>n</i> (%)	5 (29)	9 (82)	27 (73)	19 (83)
Treatment, <i>n</i> (%)				
Surgery or RFA	14 (83)	6 (55)	0 (0)	5 (22)
Chemotherapy	1 (5)	4 (36)	7 (19)	7 (30)
TACE	0 (0)	0 (0)	16 (43)	2 (9)
BSC	2 (12)	1 (9)	14 (38)	9 (39)

Group 1: Unifocal intrahepatic recurrence, Group 2: Exclusive peritoneal recurrence, Group 3: Multifocal intrahepatic recurrence, Group 4: Diffuse recurrence

RFA radiofrequency ablation, TACE transarterial chemoembolization, BSC best supportive care

TABLE 4 Univariate and multivariate analysis of risk factors for recurrence and overall survival after surgery

	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i> Value	HR	95% CI	<i>p</i> -Value
<i>Risk factor of recurrence after surgery</i>						
Preoperative AFP level (< 30 ng/mL vs. ≥ 30 ng/mL)	3.349	2.106–5.326	<0.0001	2.681	1.645–4.372	0.0009
Tumor size (< 70 mm vs. ≥ 70 mm)	2.792	1.781–4.379	<0.0001	2.291	1.402–3.744	0.0009
Vascular involvement						
No	Ref			Ref		0.0001
Microvascular	3.679	2.178–6.215	<0.0001	2.164	1.211–3.866	0.0092
Macrovascular	14.513	5.319–39.599	<0.0001	13.256	3.924–44.779	<0.0001
<i>Risk factor of overall survival after surgery</i>						
Preoperative AFP level (< 30 ng/mL vs. ≥ 30 ng/mL)	3.802	2.282–6.336	<0.0001	4.408	2.479–7.840	<0.0001
Resection margin (R0 vs. R1/R2)	2.512	1.470	0.0007	2.406	1.291–4.483	0.0057
Tumor size (< 70 mm vs. ≥ 70 mm)	2.221	1.680–3.574	0.0010	1.910	1.145–3.186	0.0131

HR hazard ratio, CI confidence interval, AFP α -fetoprotein

DISCUSSION

In our cohort of 135 patients, the median OS was 28.7 months, which is in line with previously published studies.⁶ The overall rate of recurrence at 5 years was 65.1%, consistent with that of published data.^{1,4} We found that 91% of the recurrences occurred during the first 2 years, without any difference according to recurrence sites. Although most recurrences were observed in the liver, 12% were found in the peritoneum, either exclusively or associated with other sites, and the peritoneal site accounted for 18% of all recurrences. In the setting of exclusive peritoneal recurrence (*n* = 11), the median OS of patients was 29.6 months. Moreover, patients operated for peritoneal recurrence had a longer median OS than non-operated patients (36.6 months vs. 14.6 months).

Ruptured HCC is the most common cause of death due to HCC, after tumor progression and liver failure.¹⁶ As with others, we found a mortality rate of 25% in the acute phase of ruptured HCC;¹¹ however, when patients had surgical resection, the reported 5-year survival was between 17 and 43%.^{6,7,17} Yang et al. found that patients with surgical resection of ruptured HCC had significantly higher rates of OS than patients without surgical resection, with 1-, 3-, and 5-year rates of 83.8%, 61%, and 50.5%, compared with 66.2%, 25.1%, and 16.8%, respectively.⁶ Even if spontaneous tumor rupture has been associated with poorer OS (HR 1.54, 95% CI 1.25–1.93) and DFS (HR 1.75, 95% CI 1.39–2.22) after partial hepatectomy for HCC, the prognosis of patients with liver resection was better than that of patients with TACE (5-year OS of 33.9 vs. 6%).

Recent studies sought to determine the accountability of the rupture event as a risk factor for poor oncological outcome.^{6,18} Four studies concluded that rupture itself was not relevant as a risk factor for recurrence or survival.^{8,16,18,19} One of the limitations of all four of these studies was the number of matched patients with ruptured HCC, which was small (between 14 and 119). In addition, patterns of recurrence were not evaluated with precision. Tanaka et al. suggested that peritoneal dissemination was more related to advanced HCC stage than to the rupture event itself.¹⁸ Conversely, Zhu et al., using a propensity score matching analysis, reported a significantly poorer survival in the group with ruptured HCC.²⁰ No previously published series have evaluated with both precision and a sufficient number of patients the recurrence pattern following ruptured HCC, except for the study of Yang et al.⁷ These authors reported peritoneal recurrences in 8.4% of patients following R0 resection, and that recurrences occurred more often in the ruptured group than in the non-ruptured group, with a risk of 32.8% compared with 5.4% ($p < 0.001$). We report an overall rate of peritoneal recurrence of 12% following liver resection. Of our 88 patients with recurrence, the rate of peritoneal recurrence and exclusive peritoneal recurrence was 18% and 13%, respectively.

Although many studies have reported higher rates of peritoneal recurrence with spontaneous rupture of HCC, this topic remains debated. Indeed, Uchiyama et al. considered that HCC fragments or cells released into the peritoneal cavity might not survive unless there were appropriate blood vessels nourishing these cells.⁹ However, in this study, as in several others, only 19 patients with ruptured HCC were analyzed, corresponding to a limited number of patients. In opposition, Zhou et al., by considering rupture as the main factor for PMs, proposed peritoneal lavage with distilled water, to reduce the soiling of cancer cells, during liver resection.¹¹ In addition, in a retrospective cohort of 141 patients, the authors reported that distilled water lavage was an independent predictor of recurrence and OS.

With regard to the rarity of PM of HCC (reported incidence of between 2 and 10%) following liver resection, there is no consensus regarding therapeutic management.^{3,10,21,22} In our study, 6 of the 11 patients with exclusive peritoneal recurrence were operated and had an OS of 36.6 months.

Better survival in the subgroup with exclusive PM could be explained by the therapeutic options available. In a palliative setting, survival of patients treated with sorafenib and/or systemic chemotherapy was between 6 and 14 months.^{23–25} In selected patients, resection of

extrahepatic metastases of HCC have yielded better survival results compared with sorafenib alone, with a median survival reaching 27 months.²⁴

Some authors have proposed surgical resection in selected patients with PM limited to a few nodules and have observed survival of more than 24 months.^{26,27} In that sense, surgical resection should be considered as an option for patients with stable liver function.^{28,29}

In addition to cytoreductive surgery (CRS) alone, some authors have discussed the interest of HIPEC. In the studies of Berger et al. and Tabrizian et al., patients who had CRS with HIPEC had better survival compared with CRS alone, but without statistical significance, possibly in view of the low number of the studied population.^{25,30} Recently, Mehta et al. reported encouraging results with CRS/HIPEC, with a median OS of 46.7 months and projected OS of 49.4% at 5 years.²²

Our study has some limitations. First, this was a retrospective study and was subject to weaknesses inherent to non-prospective studies. Second, the limited number of patients with peritoneal recurrence makes survival analysis and comparisons between types of recurrence difficult. In addition, no predictive factors for peritoneal recurrence could be highlighted.

CONCLUSION

In this large-cohort French study aiming to report recurrence patterns after hepatectomy for ruptured HCC, we show that 12% of patients had PM after ruptured HCC. As far as possible, a curative approach should be considered in these patients in view of the survival benefit it provides, i.e. median OS of > 30 months.

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