Langenbecks Arch Surg (2017) 402:737–744
DOI 10.1007/s00423-017-1582-9

ORIGINAL ARTICLE

Treatment and outcomes of recurrent hepatocellular carcinomas

Gaëtan-Romain Joliat[1] · **Pierre Allemann**[1] · **Ismail Labgaa**[1] · **Nicolas Demartines**[1] · **Nermin Halkic**[1]

Received: 8 November 2016 / Accepted: 24 April 2017 / Published online: 11 May 2017

Abstract
Purpose Surgery is one of the best options for curative treatment of hepatocellular carcinomas (HCC). Recurrences are nevertheless common (45–75%). This study aimed to compare overall survival (OS) of patients with recurrent HCC after primary resection to OS of patients without recurrence.
Methods A retrospective review of all HCC patients operated between 1993 and 2015 was performed. Median and 5-year OS were calculated.
Results This study included 147 HCC patients. Sixty-seven patients presented a recurrence (46%). Patients with recurrence had a worse prognosis than those without recurrence (median OS 63 vs. 82 months, 5-year OS 47 vs. 54%, $p = 0.036$). First-line performed treatments were radiofrequency ablation (18, RFA), chemo-embolization (16, TACE), repeat hepatectomy (10), systemic chemotherapy (4), radioembolization (1), and alcoholization (1). Palliative care was performed in 17 patients. Median OS of patients treated by RFA, TACE, or repeat hepatectomy were similar (77, 71, and 84 months, $p = 0.735$). Patients treated with chemotherapy/palliative care had lower median OS compared to interventional treatments (20 vs. 77 months, $p < 0.0001$).
Conclusions Recurrence after surgical HCC resection is frequent and negatively impacts OS. Interventional treatments of recurrences offered improved outcomes compared to medical care. In selected patients, RFA, TACE, and repeat hepatectomy allowed similar OS as non-recurrent cases.

Keywords Hepatic surgery · Liver · Hepatocellular carcinoma · Recurrence · Oncologic treatments

Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary liver malignancy [1]. Surgical resection represents one of the best first-line treatments for selected patients. If complete resection can be performed, median survival between 50 and 70 months has been reported [2–4]. However, even after curative surgical resection with negative resection margin (R0 resection), intra- or extrahepatic HCC recurrence is frequent, ranging from 40 to 70% [5]. The presence of cirrhosis, tumor >5 cm, positive histological margins, or portal vein invasion have been shown to be risk factors for HCC recurrence [2, 6, 7].

Even though recurrences are frequent, there are no clear international and global algorithms or guidelines for the management of such recurrent lesions, but only recommendations or suggestions by some authors after comparison of one treatment to another. Recommendations are usually based on retrospective studies [8] or on studies originating from Asia where HCC incidence is higher than in Western countries [9, 10]. These recommendations mention that radiofrequency ablation (RFA), chemo-embolization (TACE), and repeat hepatectomy are feasible and safe. Some studies showed that TACE was inferior to repeat hepatectomy and that TACE should be reserved for multilobar involvement [8]. For unifocal recurrent lesion, repeat hepatectomy is usually recommended [11]. For lesion <2 cm, RFA can be an alternative as some studies showed that RFA had similar outcomes as repeat hepatectomy [12–14]. Even though several studies

This article has been presented in parts at the 103rd Annual Congress of the Swiss Society of Surgery, held in Lugano, Switzerland, 1–3 June 2016.

✉ Nicolas Demartines
demartines@chuv.ch

[1] Department of Visceral Surgery, University Hospital CHUV, Rue du Bugnon 46, 1011 Lausanne, Switzerland

have compared the different interventional methods, the real benefits of aggressive treatments in terms of overall survival (OS) are still not clear. The aim of the present study was to assess the OS of treated recurrent HCC after primary surgical resection and to compare it to the OS of non-recurrent cases.

Material and methods

Patients and data collection

From January 1, 1993 to June 30, 2015, all consecutive patients with HCC operated in the Department of Visceral Surgery at the Lausanne University Hospital CHUV (Switzerland) were included. Data on demographics, perioperative details, and postoperative outcomes were retrospectively collected from patient charts. Long-term outcomes were completed by a phone call to the general practitioners if data were missing in the hospital charts. The study was recorded in Research Registry (UIN: researchregistry930) and was approved by the local ethics committee.

Primary hepatocellular carcinoma staging and preoperative workup

The diagnosis of HCC was either based on two imaging modalities typical for HCC with elevated alpha-fetoprotein or on a positive biopsy analyzed by a senior board-certified pathologist in case of atypical images. In case of cirrhosis, the used classifications were the Child-Pugh classification and the Model for End-Stage Liver Disease (MELD) score. Before surgery, the patients benefited from blood tests (complete blood count, liver tests including bilirubin, albumin, and coagulation tests), dosage of alpha-fetoprotein, and radiological assessment with thoraco-abdominal computed tomography (CT) scanner and liver magnetic resonance imaging (MRI). Based on radiological exams, liver volumetry was calculated by the radiologists. In case of estimated remnant liver <40% and cirrhosis, an indocyanine green retention (ICGR) test at 15 min was performed to assess the liver excretion function. In case of cirrhosis, an invasive measure of the portal pressure was also performed. Once resected, the tumor was staged using the TNM classification (7th edition) of the American Joint Committee on Cancer (AJCC). A negative histological margin (R0 resection) was defined as the absence of tumor at >1 mm from the surgical margin.

Treatment strategies of primary HCC

Patients with HCC developed from cirrhosis and within Milan criteria [15] were evaluated for liver transplantation in another institution. Patients with primary HCC not candidates for liver transplantation or on the transplant waiting list ("bridge to transplantation") with a Child classification grade A or B (i.e., score < 10), a MELD score <9, a remnant liver volume >40% (>30% if no cirrhosis), an ICGR test <15% at 15 min if performed, and a portal pressure <10 mmHg were considered for surgical resection. In case of future liver remnant volume ≤40% (≤30% if no cirrhosis) of the total liver volume, a portal vein embolization of the hemi-liver containing the tumor was undertaken and a new volumetry performed 4 weeks later. All cases of HCC or suspected HCC were discussed in a weekly multidisciplinary tumor board (including radiologists, pathologists, oncologists, hepatologists, and surgeons). Major hepatectomy was defined as liver resection of ≥3 Couinaud's segments. Postoperative complications were graded according to the Clavien classification [16] and the comprehensive complication index (CCI) [17].

Follow-up

Follow-up after surgery depended on patient age and pathological results. All patients were discussed postoperatively in a multidisciplinary team tumor board. Alpha-fetoprotein levels were measured every 3 months and patients had radiological control (CT or ultrasound) 6 months after the operation. In case of suspicious images, MRI was performed.

Management algorithm for recurrent HCC

Patients with recurrence benefited from a variety of treatments: RFA, TACE, repeat hepatectomy, systemic chemotherapy, radio-embolization, alcoholization, surveillance, or combined treatments. Treatment decisions were based on the type of recurrence (intra- or extrahepatic), comorbidities, and functional liver remnant. All cases were discussed in a multidisciplinary tumor board to tailor the treatment option for each specific patient. In case of recurrence on the resection margin site, repeat hepatectomy was performed if the patient had sufficient remnant liver volume (>40% of total liver volume for cirrhotic livers and >30% of total liver volume for liver without underlying disease), was fit for surgery (ASA score ≤3 and ECOG performance status [18] ≤2), and no major hepatectomy was needed (independently of the lesion size). A recurrence on the resection margin site was defined as new appearance of tumor on the resection margin in case of R0 resection or as tumor evolution on the resection margin after resection with positive histological margin (R1 resection). If the recurrent lesions were multilobar and only intrahepatic, TACE was proposed as the first-line treatment. As second-line treatment, radio-embolization was proposed in case of contraindication to TACE (allergy to chemotherapeutic agents, renal failure, portal vein thrombosis). If TACE and radio-embolization were not possible, alcoholization was performed. If the lesion was unique, <3 cm, and in one lobe, RFA was performed. Liver transplantation was considered in case of recurrence for

patients within the Milan criteria [15], but they were not included in this analysis as liver transplantation is not performed in our hospital. In case of extrahepatic disease (lymphatic or organ metastasis), systemic chemotherapy with sorafenib (400 mg twice daily) was proposed. For recurrent cases, time to recurrence, treatment strategies and (overall and 5-year) survival were registered in a database for further analysis.

Statistical analyses

For continuous variables, a Mann-Whitney *U* test, a Kruskal-Wallis test, or a Student's *t* test were used depending on the normality of the distribution and the homogeneity of the variances. Normality was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For categorical variables, a chi-squared test was used. Survival curves were calculated using the Kaplan-Meier method, and the log-rank test was used to compare the survivals. All survivals were calculated from the primary operation date. A p value <0.05 was considered statistically significant. All statistical analyses were performed using GraphPad Prism 5.0© for Mac OS X.

Results

Patients and recurrence characteristics

During the study period, 147 patients were operated for HCC. Among these, 67 (46%) presented a recurrence. Figure 1 shows the flow chart of the recurrent HCC patients included in the study. Demographics and perioperative results of patients with recurrence are presented and compared to patients without recurrence in Table 1. The majority of patients with recurrence were men (52/67, 78%). Forty-five out of 67 HCC developed on cirrhotic livers (67%). Thirty-eight patients had Child A, and 7 Child B cirrhosis. The median MELD score was 8. Among these 45 cases, 25 had an ethylic etiology (56%), 8 a hepatitis B virus infection (18%), 6 a hepatitis C virus infection (13%), 5 a metabolic cause (11%, 4 hemochromatosis and 1 non-alcoholic steatohepatitis), and 1 was from unknown origin (2%). Among the 67 recurrent cases, overall morbidity rate after primary operation was 47% (32/67) with major complications in 19% (13/67). Demographics and surgical results of operated patients with recurrent HCC were similar to operated patients without HCC recurrence.

Table 2 presents the characteristics of recurrent HCC patients at time of recurrence. Intra-, extrahepatic recurrences, or both appeared in 57 (85%), 2 (3%), and 8 cases (12%) respectively. The median number of recurrent tumors was 2 (IQR 1–3), and the median size of recurrent tumors was 2 cm (IQR 1–3.5).

Treatments of recurrent HCC

Pretreatment decision was based on biopsy in 15 patients and on radiological images only in 52 patients. Figure 1 shows the different initial treatments of recurrent HCC. RFA was the most frequently used treatment for recurrent lesions (18/67). Twenty-six patients benefited from a combination of various treatments (RFA, TACE, repeat hepatectomy, or chemotherapy) over the years. One patient firstly treated by TACE and one firstly treated by RFA underwent afterwards an operation. On the contrary, six patients necessitated a subsequent non-surgical treatment after repeat hepatectomy (3 TACE, 1 RFA, 1 cryoablation, 1 systemic chemotherapy). Eight patients treated by RFA or TACE needed a subsequent RFA or TACE, respectively. Three patients were finally transplanted. Table 3 presents the characteristics and complications of patients with recurrence treated by RFA, TACE, or repeat hepatectomy.

Recurrence and survival

Median time to recurrence was 11 months after primary surgery. After R0 resection, the median time to recurrence was 12 months (IQR 6–12) compared to 6 months (IQR 4–6) after

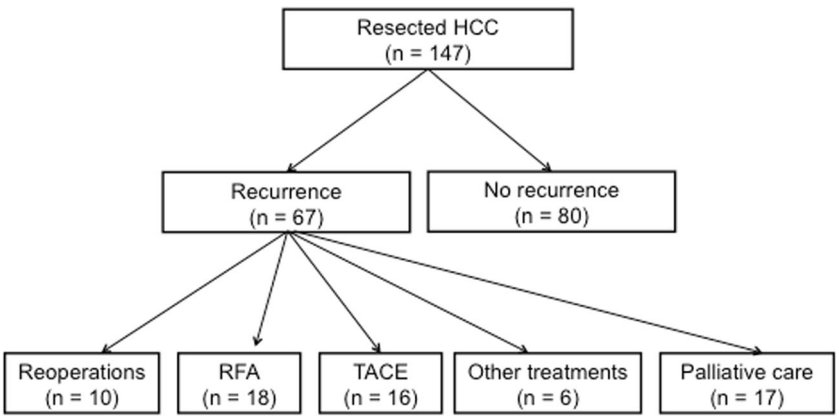

Fig. 1 Flow chart of study patients. *HCC* hepatocellular carcinomas, *RFA* radiofrequency ablation, *TACE* transarterial chemo-embolization

Table 1 Demographic characteristics and surgical results of operated hepatocellular carcinoma patients (numbers with percentage and medians with interquartile range)

	Recurrence $N = 67$	No recurrence $N = 80$	p value
Gender M/W	52 (78%)/15 (22%)	59 (74%)/21 (26%)	0.701
Median age (years)	67 (61–73)	69 (58–74)	0.335
ASA score 2/3/4	35 (52%)/31 (47%)/1 (1%)	36 (45%)/44 (55%)/0	0.344
Median body mass index (kg/m^2)	24.3 (21.5–27.4)	24.8 (22.3–27.7)	0.853
Cirrhosis	45 (67%)	48 (60%)	0.395
Ethylic	25	22	
Viral	14	20	
Metabolic	5	1	
Other etiologies	1	5	
T stage 1/2/3/4	24 (36%)/16 (24%)/22 (33%)/5 (7%)	26 (33%)/24 (30%)/24 (30%)/6 (7%)	0.870
Vascular invasion	11 (16%)	13 (16%)	1
Minor/major hepatectomy	28 (42%)/39 (58%)	39 (49%)/41 (51%)	0.412
Median number of resected segments	4 (2–4)	4 (2–4)	0.736
Median operative time (min)	209 (159–265)	223 (179–318)	0.202
Pedicular clamping yes/no	43 (64%)/24 (36%)	54 (68%)/26 (32%)	0.728
Minor/major complications	19 (28%)/13 (19%)	16 (20%)/16 (20%)	0.612
Median comprehensive complication index (CCI)	11 (0–26.2)	0 (0–32)	0.694
Postoperative mortality	0	4 (5%)	0.126
Median tumor size (cm)	6.1 (4.0–11.0)	6.0 (3.2–8.6)	0.489
Resection margin R0/R1	64 (96%)/3 (4%)	73 (91%)/7 (9%)	0.347

ASA American Society of Anesthesiologists

positive histological margins ($p = 0.070$). Among the patients who did not survive during follow-up, the median time to death was 30 months in the recurrence group. Patients with recurrence appearing less than 1 year after primary resection had worse median OS compared to patients with recurrence appearing after one year (24 vs. 60 months, $p = 0.006$).

Median and 5-year OS were lower for the recurrent cases compared to non-recurrent cases (63 vs. 82 months, $p = 0.036$ and 47 vs. 54%, $p = 0.036$) (Fig. 2).

Among the patients with recurrence, median OS of patients treated by RFA, TACE, or repeat hepatectomy were similar (77, 71, and 84 months, respectively, $p = 0.735$) (Fig. 3). Survival rates of RFA, TACE, or repeat hepatectomy adjusted to MELD scores did not show a difference either (MELD scores <11, $p = 0.829$). The 4 patients treated by systemic chemotherapy had a median OS of 24 months, and the 17 patients who had palliative care had a median OS of 20 months. Patients treated with

Table 2 Characteristics of patients at time of recurrence (numbers with percentage and medians with interquartile range)

	$N = 67$	
Child score A/B/no cirrhosis	38/7/22	57%/10%/33%
Median MELD score	8	7–10
Median creatinine level (umol/l)	84	65–103
Median albumin level (umol/l)	38	33–44
Median bilirubine level (umol/l)	10	10–16
Median INR	1	1–1.1
Median AFP level (umol/l)	13	4–286
Biopsy of recurrent lesion	15	22%
Intrahepatic/extrahepatic/intra- and extrahepatic lesion	57/2/8	85%/3%/12%
Median size of recurrent tumor (cm)	2	1–3.5
Uni-/multilobar lesion	27/40	40%/60%

MELD Model for End-Stage Liver Disease, *INR* international normalized ratio, *AFP* alpha-fetoprotein

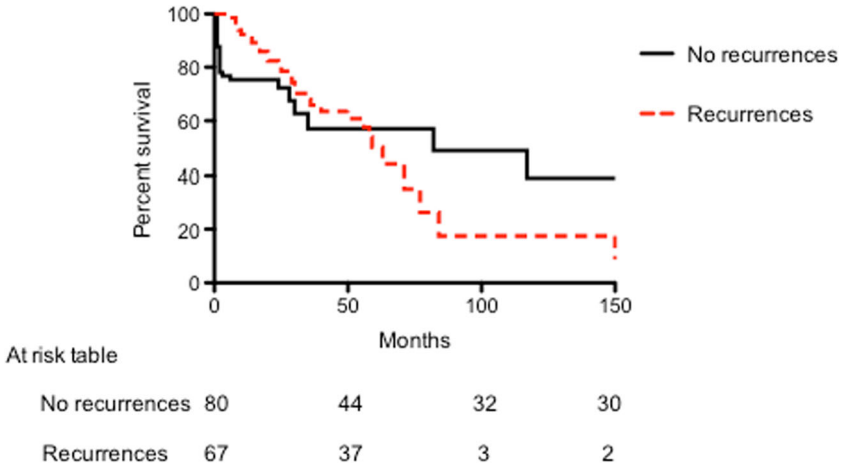

Fig. 2 Kaplan-Meier survival curves for recurrent and non-recurrent cases (log-rank test, $p = 0.036$)

chemotherapy and palliative care had lower median OS compared to interventional or surgical treatments (20 vs. 77 months, $p < 0.0001$).

Thirty-two patients were treated during the 1993–2004 period and 35 during the 2005–2015 period. There were no differences of interventional and surgical treatments between the two time periods (RFA 8 vs. 10 patients, TACE 6 vs. 10 patients, and repeat hepatectomy 6 vs. 4 patients). Median OS was 60 months during the 1993–2004 period and 61 months during the 2005–2015 period ($p = 0.159$).

Discussion

This study assessing the long-term outcomes after treatment of recurrent HCC showed that patients with recurrence had worse OS compared to non-recurrent patients. However, in selected patients who are candidates for interventional treatments (RFA, TACE) or repeat hepatectomy, similar survival as non-recurrent cases was observed.

With modern developments of interventional radiology, medical oncology, and surgery, various treatments have been proven to be effective to treat recurrence of operated HCC [19]. Patient selection is important to tailor the treatment to a particular case and multidisciplinary board decision is paramount. There are however no clear international guidelines for these situations. The present study showed that precise selection process and advanced treatments, such as RFA, TACE, and repeat hepatectomy, are valuable strategies in recurrent HCC. Several studies also showed that interventional treatments of the recurrences yield similar OS as non-recurrent cases [5, 20]. Zhang et al. found in their study the same OS between RFA, TACE, and repeat hepatectomy [19]. They additionally found that RFA and repeat hepatectomy were better for late recurrence [19]. Meniconi et al. also showed that survival was longer for patients treated by RFA, repeat hepatectomy, or transplant than by TACE [5]. This effect was not observed in the present study. The type of chemotherapy and of chemo-embolization agent, the use of lipiodol, or

Table 3 Characteristics and complications of operated patients with recurrence treated by radiofrequency (RFA), chemo-embolization (TACE), or repeat hepatectomy (numbers and medians with interquartile range)

	RFA ($N = 18$)	TACE ($N = 16$)	Repeat hepatectomy ($N = 10$)	p value
Gender M/W	13/5	14/2	8/2	0.544
Median age (years)	64 (62–68)	67 (60–72)	68 (54–75)	0.919
ASA 2/3/4	11/7/0	8/7/1	5/5/0	0.703
Median BMI (kg/m^2)	25 (22–28)	25 (22–32)	24 (21–26)	0.603
Cirrhosis	16	12	5	0.075
If cirrhosis, Child A/B	13/3	10/2	5/0	0.987
Resection margin R0/R1	18/0	15/1	9/1	0.886
Median AFP level (μmol/l)	6 (2–129)	30 (4–425)	5 (2–16,846)	0.880
Complications	4	2	5	0.093

Complications encompassed urinary retention (TACE), fever (TACE), cholangitis (repeat hepatectomy), pneumonia (2, repeat hepatectomy), wound infection (2, RFA), confusion (repeat hepatectomy), prurit (RFA), ileus (repeat hepatectomy), and ascites (RFA)

ASA American Society of Anesthesiologists, *BMI* body-mass index, *AFP* alpha-fetoprotein

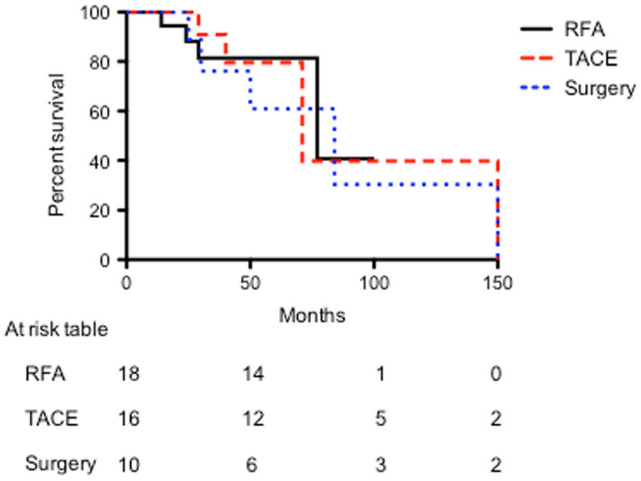

Fig. 3 Kaplan-Meier survival curves for recurrent cases treated by radiofrequency (RFA), chemo-embolization (TACE), and surgery (log-rank test, $p = 0.735$)

the numbers of TACE repetitions could explain this difference of findings.

Patients with recurrences treated by repeat hepatectomy had a median OS of 84 months, which was similar to the OS of patients without recurrence. Of course, patients in that subgroup were well selected (i.e., possibility of total resection of the lesion with negative margins, sufficient estimated remnant liver volume, good performance status). There was also in this subgroup a trend toward less cirrhosis than in the RFA and TACE subgroups (Table 3). Hou et al. found that a repeat hepatectomy for patients with recurrent HCC with microvascular invasion had a median OS of 60 months [21]. They also found that a repeat hepatectomy in recurrent cases without microvascular invasion had better prognosis [21]. A review by Lacaze et al. concluded that repeat hepatectomy and salvage liver transplantation were safe procedures and allowed good long-term survival [11]. In this study, repeat hepatectomy (only minor hepatectomy) was used for recurrent lesion on the surgical margin independently of the lesion size for patients with sufficient remnant liver volume and good general condition. Criteria to perform repeat hepatectomy in case of recurrent HCC considerably vary in the literature.

RFA showed in this cohort the same OS as TACE and repeat hepatectomy (77 vs. 71 vs. 84 months). In the literature, contradictory results are reported in heterogeneous studies, but RFA is accepted as effective in lesions <3 cm, which was the threshold to undertake RFA in this study [13]. Song et al. observed in their study similar survival results between RFA and repeat hepatectomy, corroborating the results of the present study [12]. Chen et al. similarly found in their meta-analysis comparing RFA to repeat hepatectomy that both techniques reached the same OS, and concluded that RFA should

Table 4 Summary of recent articles (retrospective and prospective studies with minimum 20 patients) published the last 3 years (2014–2016) regarding the outcomes of radiofrequency ablation (RFA), chemo-embolization (TACE), or repeat hepatectomy (RH) for recurrent hepatocellular carcinoma after primary surgical resection

Author (year)	Country	Number	Treatment	Median OS (months)	5-year OS (%)
Ali 2016 [28]	Taiwan	74/31	RFA/RH	NA	58/60
Wan 2016 [29]	China	127	TACE	18	20
Chen 2016 [30]	China	32/78	RFA/TACE	50/47	60/37
Zhang 2016 [31]	China	64	RH	11	NA
Zou 2016 [32]	China	635	RH	NA	48
Koh 2016 [33]	Hong Kong	42/60	RFA/TACE	46/42	38/31
Yong 2016 [34]	Taiwan	170	RFA	NA	51
Song 2015 [12]	Korea	178/39	RFA/RH	NA	72/84
Meniconi 2015 [5]	France	21/47/15	RFA/TACE/RH	NA	72/37/72
Tabrizian 2015 [8]	USA	62/83/68	RFA/TACE/RH	27/19/56[a]	25/9/47[a]
Yamashita 2015 [10]	Japan	146	RH	NA	61
Fukuhara 2015 [13]	Japan	72	RFA	NA	55
Hou 2015 [21]	China	130	RH	61	NA
Zu 2015 [35]	China	287	TACE	25	NA
Zhang 2015 [19]	China	23/74/25	RFA/TACE/RH	NA	64/31/74
Wang 2015 [36]	China	162/339/128	RFA/TACE/RH	NA	43/37/65
Mise 2015 [37]	Japan	289	RH	NA	61
Jin 2014 [24]	Korea	47	TACE[b]	NA	30[a]
Yamashita 2014 [38]	Japan	110	RH	74	NA
Cheng 2014 [39]	Taiwan	101	TACE	24	NA

OS overall survival, *NA* not available

[a] From time of recurrence

[b] RFA and RH were classified in a same group without distinction

be considered as first-intention treatment as it is less invasive [14]. On the contrary, a systematic review of Thomasset et al. concluded that repeat hepatectomy was the most effective treatment for recurrent HCC and that RFA was a safe and effective option for non-surgical candidates [22]. Divergently, in a meta-analysis of five non-randomized studies comparing RFA to repeat hepatectomy, Zhang et al. [23] found no differences in terms of OS with more complications in the surgery group. Finally, Jin et al. showed that TACE was better than RFA for small recurrent HCC lesions [24]. This is in contradiction with the present findings.

Embolization using chemotherapy is now used for different stages of HCC treatment (primary tumor downstaging before surgery, recurrent cases with bilobar involvement, …). In this cohort, TACE was used for recurrent multilobar lesions and had a same median OS as RFA or repeat hepatectomy (71 months). This contrasts with the recent study published by Tabrizian et al. [8], where TACE had a worse OS. A meta-analysis by Wang et al. including 12 studies showed that repeat hepatectomy in case of operated HCC recurrence had better survival than TACE [9]. The heterogeneity was nevertheless high in this meta-analysis, and included studies were of moderate or poor quality.

Salvage liver transplantation, which is also a therapeutic option in case of HCC recurrence [8] was not treated in this article, as only 3 patients finally benefited from this option. A recent study from Mount Sinai Hospital, New York City, showed that salvage transplantation had an intention-to-treat 5-year survival of 44% [8]. The role of salvage liver transplantation remains not clearly defined and should be clarified in the future [11].

In our cohort, follow-up was performed every 6 months during the first 2 years with US, CT, or MRI. As most recurrences appeared less than 1 year after primary operation, it was important to have a radiological follow-up with short time intervals to rapidly detect the recurrence. Several studies showed that recurrences appearing less than a year after the index operation have a worse prognosis due to local tumor invasiveness [20, 25, 26] and intrahepatic metastases [27]. Similar results were found in our study.

The present study has several limitations that must be addressed. Firstly, it is a retrospective cohort. This encompasses all biases inherent to such a study (missing data, charts' review). Secondly, the group of patients is also largely heterogeneous which renders the analysis complex and definitive conclusions difficult to draw. Moreover, the study period is broad and changes in treatment options have gradually appeared. Two time periods were assessed to show treatment evolution over time and to minimize this bias. There were no differences of treatment in our population between the two periods. This study brings nevertheless new data on recurrences among patients from a European population and reflects clinical day-to-day practice.

Treatment of recurrent HCC is complex, and numerous treatment improvements recently appeared (Table 4). This renders decision-making more difficult. A higher level of standardization is required. In that sense, an international consensus would probably improve the treatment outcomes worldwide.

In conclusion, recurrence is frequent after HCC resection and negatively impacts OS compared to patients without recurrence. In selected candidates, RFA, TACE, or repeat hepatectomy for HCC recurrence in operated patients offer a similar OS as patients without recurrence. RFA can be performed for unique recurrent lesions <3 cm, TACE for multilobar and intrahepatic only lesions, and repeat hepatectomy for recurrent lesions on the resection margin site in patients with good liver function and enough remnant liver.

Authors' contributions GRJ: study conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, acceptance of the final version. PA: acquisition of data, analysis and interpretation of data, critical revision of the manuscript, acceptance of the final version. IL: analysis and interpretation of data, critical revision of the manuscript, acceptance of the final version. ND: analysis and interpretation of data, critical revision of the manuscript, acceptance of the final version. NH: study conception and design, analysis and interpretation of data, critical revision of the manuscript, acceptance of the final version.

Compliance with ethical standards This retrospective study based on chart review was in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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

Source of funding This study received no particular funding.

References

1. El-Serag HB (2011) Hepatocellular carcinoma. N Engl J Med 365: 1118–1127
2. Lafaro K, Grandhi MS, Herman JM, Pawlik TM (2016) The importance of surgical margins in primary malignancies of the liver. J Surg Oncol 113:296–303
3. Sangiovanni A, Colombo M (2016) Treatment of hepatocellular carcinoma: beyond international guidelines. Liver Int 36(Suppl 1): 124–129
4. Liu H, Wang Z-G, Fu S-Y, Li A-J, Pan Z-Y, Zhou W-P et al (2016) Randomized clinical trial of chemoembolization plus radiofrequency ablation versus partial hepatectomy for hepatocellular carcinoma within the Milan criteria. Br J Surg 103:348–356
5. Meniconi RL, Komatsu S, Perdigao F, Boëlle P-Y, Soubrane O, Scatton O (2015) Recurrent hepatocellular carcinoma: a Western strategy that emphasizes the impact of pathologic profile of the first resection. Surgery 157:454–462
6. An HJ, Shin WY, Lee K-Y, Ahn S-I (2015) A comparison of the risk factors of intrahepatic recurrence, early recurrence, and multiple

recurrences after resection for single nodular hepatocellular carcinoma. Korean J Hepato-Biliary-Pancreat Surg 19:89–97
7. Hwang S, Lee Y-J, Kim K-H, Ahn C-S, Moon D-B, Ha T-Y et al (2015) The impact of tumor size on long-term survival outcomes after resection of solitary hepatocellular carcinoma: single-institution experience with 2558 patients. J Gastrointest Surg 19: 1281–1290
8. Tabrizian P, Jibara G, Shrager B, Schwartz M, Roayaie S (2015) Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. Ann Surg 261:947–955
9. Wang D-Y, Liu L, Qi X-S, Su C-P, Chen X, Liu X et al (2015) Hepatic re-resection versus transarterial chemoembolization for the treatment of recurrent hepatocellular carcinoma after initial resection: a systematic review and meta-analysis. Asian Pac J Cancer Prev 16:5573–5578
10. Yamashita Y-I, Yoshida Y, Kurihara T, Itoh S, Harimoto N, Ikegami T et al (2015) Surgical results for recurrent hepatocellular carcinoma after curative hepatectomy: repeat hepatectomy versus salvage living donor liver transplantation. Liver Transplant 21:961–968
11. Lacaze L, Scotté M (2015) Surgical treatment of intra hepatic recurrence of hepatocellular carcinoma. World J Hepatol 7:1755–1760
12. Song KD, Lim HK, Rhim H, Lee MW, Kim Y-S, Lee WJ et al (2015) Repeated hepatic resection versus radiofrequency ablation for recurrent hepatocellular carcinoma after hepatic resection: a propensity score matching study. Radiology 275:599–608
13. Fukuhara T, Aikata H, Hyogo H, Honda Y, Morio K, Morio R et al (2015) Efficacy of radiofrequency ablation for initial recurrent hepatocellular carcinoma after curative treatment: comparison with primary cases. Eur J Radiol 84:1540–1545
14. Chen X, Chen Y, Li Q, Ma D, Shen B, Peng C (2015) Radiofrequency ablation versus surgical resection for intrahepatic hepatocellular carcinoma recurrence: a meta-analysis. J Surg Res 195:166–174
15. Mazzaferro V, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R et al (2011) Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. Liver Transplant 17(Suppl 2):S44–S57
16. Dindo D, Demartines N, Clavien P-A (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213
17. Slankamenac K, Nederlof N, Pessaux P, de Jonge J, Wijnhoven BPL, Breitenstein S, et al (2014) The comprehensive complication index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. Ann Surg 260:757-762-763
18. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al (1982) Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol 5:649–655
19. Zhang X, Li C, Wen T, Yan L, Li B, Yang J et al (2015) Appropriate treatment strategies for intrahepatic recurrence after curative resection of hepatocellular carcinoma initially within the Milan criteria: according to the recurrence pattern. Eur J Gastroenterol Hepatol 27: 933–940
20. Shah SA, Cleary SP, Wei AC, Yang I, Taylor BR, Hemming AW et al (2007) Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. Surgery 141:330–339
21. Hou Y-F, Li B, Wei Y-G, Yang J-Y, Wen T-F, Xu M-Q et al (2015) Second hepatectomy improves survival in patients with microvascular invasive hepatocellular carcinoma meeting the Milan criteria. Medicine (Baltimore) 94:e2070
22. Thomasset SC, Dennison AR, Garcea G (2015) Ablation for recurrent hepatocellular carcinoma: a systematic review of clinical efficacy and prognostic factors. World J Surg 39:1150–1160
23. Zhang C, Zhang J, Li X, Li L, Li X, Zhou X (2015) Is radiofrequency ablation equal to surgical re-resection for recurrent hepatocellular carcinoma meeting the Milan criteria? A meta-analysis. J BUON 20:223–230
24. Jin Y-J, Lee J-W, Lee OH, Chung HJ, Kim YS, Lee JI et al (2014) Transarterial chemoembolization versus surgery/radiofrequency ablation for recurrent hepatocellular carcinoma with or without microvascular invasion. J Gastroenterol Hepatol 29:1056–1064
25. Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S et al (2003) Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 38:200–207
26. Shah SA, Greig PD, Gallinger S, Cattral MS, Dixon E, Kim RD et al (2006) Factors associated with early recurrence after resection for hepatocellular carcinoma and outcomes. J Am Coll Surg 202: 275–283
27. Raza A, Sood GK (2014) Hepatocellular carcinoma review: current treatment, and evidence-based medicine. World J Gastroenterol 20: 4115–4127
28. Ali MA, Li W-F, Wang J-H, Lin C-C, Chen Y-J, Lin T-L et al (2016) Impact of pathological features of primary hepatocellular carcinoma on the outcomes of intrahepatic recurrence management: single center experience from southern Taiwan. HPB 18:851–860
29. Wan X, Zhai X, Yan Z, Yang P, Li J, Wu D et al (2016) Retrospective analysis of transarterial chemoembolization and sorafenib in Chinese patients with unresectable and recurrent hepatocellular carcinoma. Oncotarget 7:83806–83816
30. Chen R, Gan Y, Ge N, Chen Y, Wang Y, Zhang B et al (2016) Transarterial chemoembolization versus radiofrequency ablation for recurrent hepatocellular carcinoma after resection within Barcelona clinic liver cancer stage 0/a: a retrospective comparative study. J Vasc Interv Radiol 27:1829–1836
31. Zhang J, Zhou Z-G, Huang Z-X, Yang K-L, Chen J-C, Chen J-B et al (2016) Prospective, single-center cohort study analyzing the efficacy of complete laparoscopic resection on recurrent hepatocellular carcinoma. Chin J Cancer 35:25
32. Zou Q, Li J, Wu D, Yan Z, Wan X, Wang K et al (2016) Nomograms for pre-operative and post-operative prediction of long-term survival of patients who underwent repeat hepatectomy for recurrent hepatocellular carcinoma. Ann Surg Oncol 23:2618–2626
33. Koh PS, Chan ACY, Cheung TT, Chok KSH, Dai WC, Poon RTP et al (2016) Efficacy of radiofrequency ablation compared with transarterial chemoembolization for the treatment of recurrent hepatocellular carcinoma: a comparative survival analysis. HPB 18: 72–78
34. Yong C-C, Tsai M-C, Lin C-C, Wang C-C, Lu S-N, Hung C-H et al (2016) Comparison of salvage living donor liver transplantation and local regional therapy for recurrent hepatocellular carcinoma. World J Surg 40:2472–2480
35. Zu Q-Q, Liu S, Zhou C-G, Yang Z-Q, Xia J-G, Zhao L-B et al (2015) Chemoembolization of recurrent hepatoma after curative resection: prognostic factors. AJR Am J Roentgenol 204:1322–1328
36. Wang K, Liu G, Li J, Yan Z, Xia Y, Wan X et al (2015) Early intrahepatic recurrence of hepatocellular carcinoma after hepatectomy treated with re-hepatectomy, ablation or chemoembolization: a prospective cohort study. Eur J Surg Oncol 41:236–242
37. Mise Y, Hasegawa K, Shindoh J, Ishizawa T, Aoki T, Sakamoto Y et al (2015) The feasibility of third or more repeat hepatectomy for recurrent hepatocellular carcinoma. Ann Surg 262:347–357
38. Yamashita Y-I, Imai D, Bekki Y, Takeishi K, Tsujita E, Ikegami T et al (2014) Surgical outcomes of anatomical resection for solitary recurrent hepatocellular carcinoma. Anticancer Res 34:4421–4426
39. Cheng Y-C, Chen T-W, Fan H-L, Yu C-Y, Chang H-C, Hsieh C-B (2014) Transarterial chemoembolization for intrahepatic multiple recurrent HCC after liver resection or transplantation. Ann Transplant 19:309–301