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Does the margin width influence recurrence rate in liver surgery for hepatocellular carcinoma smaller than 5 cm?

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Abstract. – OBJECTIVE: Liver surgery is considered a curative treatment for hepatocellular carcinoma (HCC) but the importance of resection margin width remains controversial. The aim of this study is to clarify the role of 5-10 mm surgical margin width on post-operative recurrence and overall survival after resection.

PATIENTS AND METHODS: We analyzed recurrence rate and overall survival rate of 72 patients who underwent curative hepatic resection for HCC smaller than 5 cm with 5-10 mm surgical margin width between January 2005 and December 2014.

RESULTS: The mean follow-up period was 36 months. Among the seventy-two patients, thirty-one (31/72; 43%) developed recurrence but only eleven (11/31; 15.3%) along the resection margin. The disease-free survival was 77.2%, 50%, 41.4% at 1, 3 and 5 years respectively, and the overall survival was 89.9%, 78.8%, 60% at 1, 3 and 5 years respectively.

CONCLUSIONS: 5-10 mm surgical resection margin for HCC smaller than 5 cm seems to be safe as a wider surgical margin because does not increase the risk of marginal recurrence and does not decrease overall survival rate. Further prospective and randomized studies are required to definitively clarify the importance of surgical margin width in hepatic resection for HCC.

Key Words:
Hepatocellular carcinoma, Resection margin, Liver surgery, Recurrence rate.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor worldwide[1-3]. Incidence and prevalence are higher in Asia and Africa but are increasing in developed countries[4]. In the United States HCC is responsible of 6.0 deaths per 100,000 people per year[5]. Nowadays surgical resection has become – together with liver transplantation – a safe and potentially curative option, with a low death rate[6-11]. Despite the improvement of surgical techniques and perioperative management which allowed surgeons to reach a 5-year survival rate of 31-59% in different series, the recurrence rate is still very high and the long-term survival is unsatisfactory[12-14]. Many risks factors for HCC recurrence after surgery have been evaluated. Resection margin was also considered for its importance on long-term survival and disease-free survival, but its influence is still unclear[13]. Although some studies[16-22] have demonstrated that a margin of less than 10 mm was a risk factor for recurrence, other authors did not find a correlation between the surgical margin width and long-term prognosis. These contradictory results have led to a not uniform surgical approach to HCC. The aim of this study is to investigate the influence of a 5-10 mm wide resection margin on post-hepatectomy local recurrence rate, recurrence-free survival rate and overall survival rate.

Patients and Methods

Between January 2005 and December 2014, 166 patients with hepatocellular carcinoma were treated at the Surgical Oncology Unit, University Hospital of Messina. During this research period approach to patient, therapeutic choice, surgical technique and postoperative follow-up were substantially the same. Our study population was re-

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ferred to surgery according to the management plan discussed and defined for each patient during the weekly multidisciplinary meeting held by surgeons and hepatologists at our University Hospital. Among the recruited cases, we excluded seventy-five patients who, accordingly to their remnant liver, co-morbidities, and high operative risk, were treated with loco-regional ablation therapies (Radiofrequency, microwave ablation or Percutaneous Ethanol Injection). Moreover, among patients who underwent liver surgery, we excluded nineteen patients with tumors size ≥ 5 cm who were treated with anatomical resection. Therefore, seventy-two patients were the subjects of our investigation (Figure 1). Patients demographics are shown in Table I, post-operative morbidity and resection margin status in Table II, disease-free survival (DFS) and overall survival (OS) rates in Figure 2 and 3. Patients with hepatoviral infection were defined as those positive for hepatitis C virus antibody or hepatitis B virus surface antigen. Tumor size and number of lesions were confirmed during surgery by intraoperative ultrasonography. The surgical approach, open or laparoscopic, was established accordingly to patients co-morbidity and tumor localization. The operations were performed under general anesthesia using a right subcostal incision and ultrasonic dissector for liver transection in the laparotomy group, and with four trocars incisions in the laparoscopic group; the width of the margin was defined as the shortest distance between the transection plane and the edge of the tumor. By this definition, we left a 5-10 mm surgical margin in both laparotomic and laparoscopic group. We did not observe perioperative deaths. Early complications occurred in 17/72 (23.6%) patients during hospital stays (pleural effusion, surgical wound infection, and intra-abdominal collection) (Table II).

Postoperative Follow-up

All the patients in this study were followed-up for at least 12 months at the time of the analysis. All patients underwent regular follow-up care and were monitored for recurrence by tumor markers, ultrasonography and CT-scan or magnetic resonance imaging (MRI). During the first

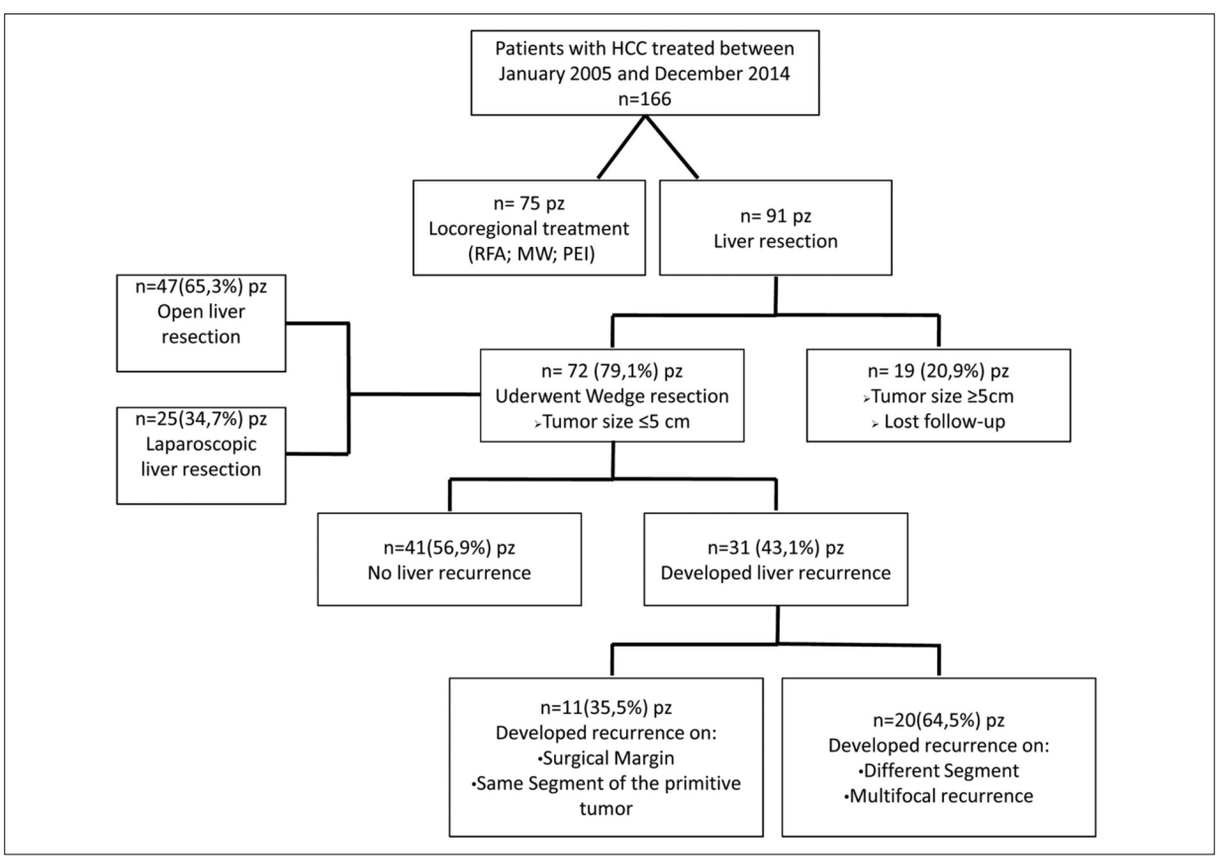

Figure 1. Flow chart of the study.

Table I. Clinicopathologic data.

Characteristic	n	%
Age (years)		
≤ 65	21	29.1
> 65	51	70.9
Mean	68.44	
Median	62	
Gender		
Male	46	63.8
Female	26	36.2
Child-Pugh Score		
A5	38	52.8
A6	26	36.1
B7	8	11.1
Etiology		
HBV	20	27.8
HCV	35	48.6
Alcol	14	19.4
Others	3	4.2
Cirrhosis		
Yes	66	91.6
No	6	8.4
Tumor number		
1	53	73.6
> 1	19	26.4
Tumor size		
≤ 25 mm	40	55.5
> 25 mm	32	45.5
Mean	28.57	
Median	21.5	
Lymph node metastasis		
No	72	100
Yes	0	
Surgical technique		
Open resection	47	65.3
Laparoscopic resection	25	34.7

Table II. Operative procedures performed.

Operative procedure	n
Laparotomy liver resection (with associated RF)	47 (14)
Laparoscopic liver resection (with associated RF)	25 (3)
Segment treated	
Right liver (S5-S6-S7-S8)	32
Left liver (S2-S3-S4)	40
Morbidity	17
Pleural effusion	5
Surgical wound infection	8
Intra-abdominal Collection	3
Biliary Fistula	1

RF: radiofrequency ablation; S: segment, defined by the Couinaud's nomenclature.

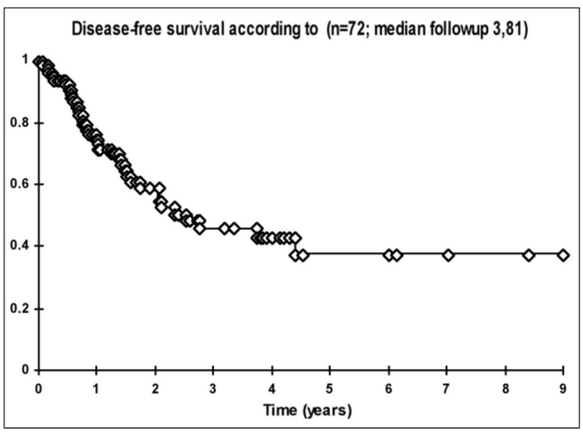

Figure 2. Disease-free survival.

year following the surgery, we measured out serum levels of alpha-fetoprotein every month and performed an ultrasonography or CT-scan every 6 months. After 1 year we followed patients by ultrasound scan every 6 months. When there was a suspect of intrahepatic recurrence, patients underwent an extra CT scan or MRI and, if necessary, percutaneous needle biopsy. The site and pattern of intrahepatic recurrence were determined following Poon et al[16] classification: Type I – Marginal recurrence; Type II – Recurrence at an adjacent segment; Type III – Recurrence at distal segment; Type IV – Multisegmental recurrence.

Statistical Analysis

Survival time was calculated from the time of liver resection to last follow-up or death of the patient. We concentrated our interest in cumulative recurrence-free survival and overall survival

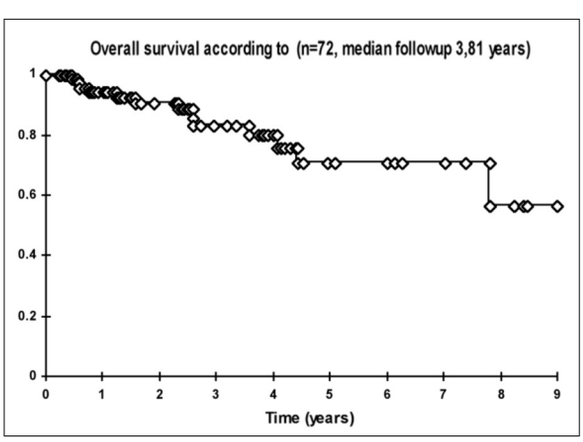

Figure 3. Overall survival.

rates after surgery which were analyzed using the Kaplan-Meier method. Disease-free survival rate was identified as the time between hepatectomy and the first diagnosis of a recurrence. We considered only the appearance of the first recurrence also in those patients who, after firstly tumor recurrence, underwent potentially curative treatments and developed a second recurrence.

Results

Among 72 patients, with a mean follow-up period of 36 months (range, 3-120 months), 31/72 (43%) experienced recurrence: 11/31 (15.3%) had recurrence along surgical margin or in the same segment of the primitive tumor; others 20/31 (27.7%) developed recurrence in a different hepatic segment compared to the primitive lesion or presented multifocal disease (Figure 1). According to the Poon et al[16] classification, we identified number 7, 6, 10 and 8 patients with recurrence type I, II, III and IV respectively (Table III). The mean time to recurrence was 23.8 months (range, 2-84 months) but 13/31 (42%) patients relapsed in the first year after surgery. The disease-free survival (DFS) rate at 1, 3 and 5 years was 77.2%, 50%, 41.4% respectively (Figure 2). The overall survival (OS) rate at 1, 3 and 5 years was 89.9%, 78.8%, 60%, respectively (Figure 3). Our results are similar to those present in literature[23-25]. These results led us to confirm that, in spite of improvement of surgical techniques and perioperative procedures, and regardless to the width of the surgical margin, the recurrence rate for HCC is still very high. About one out of two patients who underwent surgery (43%) develops recurrence approximately within three years after resection- and, further, that overall survival rate is still low at 5 years after surgery (60%).

Table III. Poon classification.

Recurrence type	Number of patients (%)
Type I	7 (23%)
Type II	6 (19%)
Type III	10 (32%)
Type IV	8 (26%)

Discussion

Resection with disease-free margin is the premise for radical excision of malignant tumors. Unfortunately, this consideration is not totally applicable to the liver disease for many reasons. Firstly, patients with HCC have 5-years intrahepatic recurrence rate of 75-100% after resection, are cirrhotic due to viral infection and, accordingly, the treatment strategy must strike a balance between resecting the tumor and saving liver function[26]. Therefore, even if there are a lot of studies that have compared anatomic versus non-anatomic liver resection and most of them have demonstrated a survival advantage among patients undergoing anatomic resection, this approach is feasible only in few patients[27-29]. Secondly, HCC for its ability to invade the portal vein system tends to develop recurrences anywhere in the remnant liver[26,30-32]; and also in cirrhotic patients, intrahepatic recurrence can arise from multicentric carcinogenesis in the remnant liver. The most important risk factors for postoperative recurrence, in patients who underwent surgical resection for HCC, were widely analyzed in literature and can be categorized in tumor, host, and surgical-related risk factors[16]. Tumor risk factors are tumor size, satellite nodules and vascular invasion, but there are also others that are 'biologic factors' as mutation of p53 gene[33], androgen receptor[34], telomerase[35] that are closely associated with invasiveness and growth of HCC. Host factors are related to liver disease and its function; patients with HBV or HCV hepatitis in the absence of antiviral therapy seems to have a higher risk of recurrence[35,36]. For the surgical factors, while perioperative transfusion[37] and extent of resection – anatomic versus non-anatomic[30] – have been widely examined and represent independent risk factors for recurrence, the significance of resection margin and its width is still controversial. To date, many authors tried to investigate the width of surgical margin which could predict and avoid recurrence in HCC, but there is not accordance and is still an unresolved issue. Poon et al[16] stated that the only effect of a wide resection margin seems to be the prevention of marginal recurrence, although in cirrhotic patients with reduced liver function, they strongly recommended that sparing functional liver parenchyma should take priority over a wide resection margin. They valued that, in most patients, intrahepatic metastasis are already present beyond 1 or 2 cm from surgical margin, so a wider resection cannot prevent recurrence. Lee et al[23] reported that there is a weak association be-

tween liver resection with wider surgical margin (≥10 mm) and disease-free survival or overall survival rates. They affirmed that in long-term follow-up resection margin is not an important risk factor compared with others as extent of resection, blood loss and transfusion or albumin, that are steadily and certainly associated with both DFS and OS rates[21,23,24,38]. Furthermore, they found that a wider surgical margin implied major blood transfusions and a higher in-hospital mortality rate[24]. Sasaki et al[25] demonstrated that -despite in their analysis wider resection margin group does not have a clearly improvement in overall survival or local recurrence rate compared with a narrow margin group- for tumors larger than 30 mm the long-term prognosis was importantly influenced and improved from a ≥ 3 mm width of surgical margin. Shi et al[26] reported – in patients with HCC < 2 cm – a survival benefit related to a wider resection margin. They, comparing results between a narrow (1 cm) and a wide (2 cm) resection margin groups, found that incidence of multiple recurrences was higher in the narrow margin group and also that wide margin group had a better survival after tumor recurrence. Chau et al[40] affirmed that a < 1 cm surgical margin hepatectomy for HCC is related to tumor recurrence. They recommend to enlarge the resection margin to reduce the probability of a marginal recurrence. Among these contradictory results, our purpose was to evaluate the influence of 5-10 mm resection margin in post-operative outcomes of patients who underwent hepatic resection for HCC. Our findings, confirming literature data for overall survival and recurrence rates[23-25], demonstrated that a narrow surgical margin does not increase risk of disease recurrence – probably according to the hypothesis that liver recurrence are often determined by tumor microsatellites, microscopic venous thrombi or multicentric tumors – while allows to preserve functional liver parenchyma in patients with limited liver function reserve. Consequently, we can affirm that a 5-10 mm resection margin is a valid choice for those patients – with an HCC smaller than 5 cm – who cannot undergo anatomic liver resection for their poor residual liver function.

Conclusions

5-10 mm surgical resection margin width for HCC smaller than 5 cm seems to be safe as a wider surgical margin because does not increase the risk of marginal recurrence and does not decrease overall survival rate. Further prospective and randomized studies are required to definitively clarify the importance of surgical margin width in hepatic resection for HCC.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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