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Treatment of tumour recurrence after resection of hepatocellular carcinoma. Analysis of 97 consecutive patients

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Abstract

Objective: To evaluate the long-term results of aggressive treatment of HCC recurrence.
Methods: Two hundred and nine consecutive patients underwent hepatic resection for HCC in our hospital. Tumour recurrence was diagnosed in 97 (51%) of the 190 patients with curative resection. Sixteen underwent hepatic resection: two right hepatectomies, one three-segmentectomy, one left hepatectomy, five two-segmentectomies, six segmental resections and one subsegmentectomy. Two patients with metastasis in the spine were submitted to a vertebral body resection. Twenty-five patients were treated with percutaneous ethanol injection or intra-arterial chemoembolization. Fifty-four patients with a poor performance status and liver function or multiple extra hepatic recurrences did not receive any treatment.
Results: There were no operative deaths. The postoperative mortality rate was 5.5% (one patient). The cumulative overall survival after the second resection was respectively 89%, 46% and 31% at 1, 3 and 5 years. There was a significant difference in survival between patients treated with repeat resection and those submitted to a non-surgical or conservative treatment ($p < 0.0001$). There were no differences in operative deaths, postoperative mortality and morbidity between the first and second hepatic resection.
Conclusions: Aggressive management with combined resection or loco regional therapy for intrahepatic recurrence and resection of isolated extra-hepatic recurrence may offer long-term survival in selected patients. Second liver resection for recurrence of HCC can be safely performed.

Keywords: Hepatocellular carcinoma; Recurrence; Treatment

Introduction

The treatment of choice for hepatocellular carcinoma (HCC) is surgical resection. Unfortunately, long-term results of HCC resection have been disappointing because the rate of postoperative HCC recurrence is high. The majority of patients develop intrahepatic recurrence and a smaller proportion develop both intrahepatic and extrahepatic or very rarely only extrahepatic recurrences.[1–7] This high recurrence rate might be due to inadequate resection of the original tumour, occult intrahepatic metastases and/or the persistence of multicentric hepatocarcinogenesis foci in the remnant liver. Recurrence caused by inadequate resection or intrahepatic metastases could be prevented by anatomical resection on the basis of vascular anatomy, prevention of intraoperative bleeding or blood transfusion, and by obtaining a fair surgical margin (>10 mm). Although there is some indication that adjuvant radioactive intra-arterial infusion might decrease the rate of recurrence due to multicentric hepatocarcinogenesis, this has not yet been confirmed.

Aggressive treatment of HCC recurrence after liver resection increases patients' survival.[6–8] Re-resection of intrahepatic recurrence or isolated extrahepatic recurrence may be effective in prolonging survival.[4,6–12] Most frequently, patients are not suitable for surgery because of the multifocality and location of the tumours and/or the degree of cirrhosis. In these patients, new lesions can be treated by

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transarterial chemoembolization (TACE), or by local percutaneous tumour destruction with ethanol injection (PEI) or percutaneous thermal ablation (radiofrequency).

The purpose of this study was to analyse the results of the aggressive treatment of HCC recurrence after resection of HCC in a series of 97 consecutive patients.

Patients and methods

Between June 1984 and March 2004, 209 patients underwent hepatic resection for HCC in the Surgical Department of Antoine-Béclère Hospital. One hundred and ninety resections were curative (the type of resection in these 190 patients is indicated in Table 1). Patients were followed up with serum αFP measurement and ultrasonography in the first month after hepatectomy and every 4 months thereafter. Suspected intrahepatic recurrence was confirmed using a computerized tomography (CT) scan and/or hepatic angiography and/or percutaneous biopsy. A chest radiograph or CT scan was used to detect any concurrent extrahepatic recurrence.

Tumour recurrence was diagnosed in 97 patients (51%) of the 190 patients with curative resection, 88 of whom were men (91%) and 9 women (9%). The mean age of the patients with recurrence was 60.3 ± 10.8 years (range 17–83 years). The stage of chronic liver disease at the time of recurrence was classified according to the Child–Pugh score:[13] it was A in 90 (92.8%) and B in 7 (7.2%). Recurrence was discovered by ultrasonography during surveillance in 95 patients and by α-fetoprotein (αFP) increase in two. Recurrence was confirmed by tumour biopsy in 39 of them. In other patients it presented typical features in the CT scan and/or an increase in blood αFP above 100 ng/ml.

Recurrence occurred only in the liver in 76 patients (78.4%), in the liver and other organs in 19 patients (19.6%) and only in another organ in two patients (2%). In only nine of the patients with liver recurrence (9.5%) was it located near the hepatic stump. In all other patients it occurred far from the hepatic stump: multifocal in 58 and uninodular (or less than three nodules) in 28. Metastases in the lung/pleura, lung/adrenal gland, lymph node, bone and skin were respectively 11 (6%), 1 (0.5%), 3 (1.6%), 5 (2.6%), and 1 (0.5%).

Table 1
Type of hepatectomy in 190 patients having undergone curative resection of hepatocellular carcinoma between June 1984 and March 2004

Type of resection	Number of patients ($n = 190$)
Extended right hepatectomy	15
Extended left hepatectomy	6
Right hepatectomy	29
Left hepatectomy	12
Central hepatectomy	4
Left lateral lobectomy	18
Combined segmentectomy	25
Segmentectomy	47
Subsegmentectomy	34

Repeat liver resection was considered the treatment of choice for resectable recurrent tumours in the liver. Determination of resectability was based on the number and site of the tumours, their pathological features, any concurrent extrahepatic recurrence, size of liver remnant, liver function, and general status of the patients. Among the 28 patients with fewer than three recurrent nodules, 16 (57.2%) underwent hepatic resection. The type of repeat resection was dependent on the size, number and location of liver recurrence, the type of the first liver resection and liver function. Three patients underwent major liver resection (two right hepatectomies and one left hepatectomy) and 13 patients underwent either segmental resection of one (six patients), two (five patients) or three segments (one patient) or subsegmentectomy (one patient). In addition, two patients with spinal metastases underwent a vertebral body resection.

Eleven patients with a single nodular recurrence and an atrophied liver remnant and/or poor liver function, and 14 patients with multiple diffuse lesions and good hepatic function were treated respectively by PEI ($n = 11$) or TACE ($n = 14$).

Fifty-four patients with a poor performance status and liver function or multiple extrahepatic recurrences did not receive any oncological treatment.

Statistical analysis

Results were expressed as mean (SD) and median (range). To compare characteristics among groups, the Student's t or chi-square tests for nominal variables were used. Overall and disease-free survivals were determined in patients with curative first and second resections after exclusion of patients' postoperative mortality. To compare characteristics among groups chi-square or Kruskal–Wallis tests were used. Disease-free survival was evaluated in the group of patients who were discharged from the hospital from the date of surgery to the time of recurrence. Cumulative analysis of overall and disease-free survivals was calculated by the Kaplan–Meier method, and statistical comparisons were based on the log-rank test. All analyses were performed using Stat View software (version 5.1) for Macintosh computer (Apple Computer, Inc., Cupertino, CA) and statistical significance was considered when p values were ≤ 0.05.

Results

Characteristics of patients with tumour recurrence undergoing surgical or non-surgical treatment or conservative treatment

Table 2 summarizes the clinical and pathological features of the 97 patients with HCC recurrence after hepatic

Table 2
Pretherapeutic characteristics of patients with hepatocellular carcinoma recurrence treated by repeat resection, non-surgical treatment or conservative treatments

Variables	Repeat resection ($n = 16$)	Non-surgical treatment ($n = 25$)	Conservative treatment ($n = 54$)	p
Age (years)	61.3 ± 7.9	62.3 ± 8.7	58.3 ± 12.3	ns
Sex (male/female)	14/2	21/4	51/3	ns
Child–Pugh score B/A	1/15	1/24	4/50	ns
Cirrhosis present/absent	15/1	10/15	50/4	0.001
First resection major/minor	2/14	10/15	19/35	ns
Hepatic recurrence				
Nodular	7	11	14	
2–3 nodules	9	3	10	
>3 nodules	0	11	30	0.002
Extrahepatic recurrence	0	11	1	ns
Portal invasion (yes/no)	1/15	2/23	7/47	ns
Tumour differentiation (well/moderate + poor)	9/7	10/15	21/33	ns

resection There were significantly more cirrhotic (94%) than non-cirrhotic patients (6%, $p < 0.001$) and significantly more patients with three nodules or less in the group of patients with re-resection ($p < 0.002$) than in the other two groups. None of the patients submitted to surgical treatment had more than three nodules. Two patients with spinal metastases without hepatic recurrence had vertebral body resection.

Mortality and morbidity of the patients undergoing repeat liver resection and non-surgical treatment

There were no operative deaths during repeat resection. Postoperative mortality was 6% (one patient) (Table 3). There were postoperative complications in five patients (28%) (Table 3): ascites in three, lung infection in one and encephalopathy in one. There were no statistically significant differences in postoperative mortality and morbidity between the first and second hepatic resection (Table 3).

Table 3
Operative mortality and postoperative mortality and morbidity after first (209 patients) and second (16 patients) hepatic resections

	First hepatic resection ($n = 209$)	Second hepatic resection ($n = 16$)	p
Operative mortality (%)	0 (0)	0 (0)	ns
Postoperative mortality (%)	16 (7.7)	1 (6)	ns
Postoperative morbidity %	70 (34)	5 (28)	ns

One patient (4%) died from hepatic necrosis after TACE. Three other patients (12%) developed complications: ascites in two and variceal bleeding in one. There was no mortality and no complications in the 11 patients treated by PEI.

Survival of patients with hepatic recurrence after resection of HCC

Cumulative overall survival of the 97 patients with recurrent HCC from the time of resection was respectively 83%, 44%, and 22% at 1, 3, and 5 years The mean (SD) and median overall survival was respectively 30.3 (23.7) months and 27 months (range 2–108). Cumulative disease-free survival was respectively 55.3%, 18%, and 4.3% at 1, 3, and 5 years The mean (SD) and median disease-free survival were 15.9 (17) months and 12 months (range 1–100).

After HCC recurrence, the cumulative 1-, 3-, and 5-year overall survival from the time of recurrence was respectively 54%, 21.3% and 5% (Fig. 1) and the mean (SD) and median disease-free survival were 15.8 (17.4) months and 12 months (range 0–100).

Following repeat resection of tumour recurrence, the cumulative overall 1-, 3- and 5-year survival was respectively 89%, 46% and 31% (Fig. 2) and the mean (SD) and median survival were 49 (10) months and 27 months (range 8–100).

Following non-surgical treatment of tumour recurrence, the cumulative overall 1-, 3-, and 5-year survival was respectively 58%, 27% and 0% (Fig. 2) and the mean (SD) and median survival were respectively 19 (3) months and15 months (range 1–48).

In patients receiving non-specific treatment of HCC recurrence, the cumulative overall 1-, 3-, and 5-year survival was respectively 30.2%, 9.7% and 0% (Fig. 2) and the

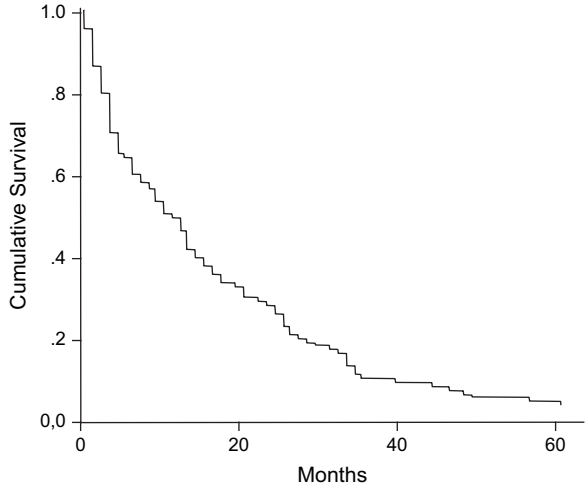

Figure 1. Overall cumulative survival rate after diagnostic and treatment of 97 patients with hepatocellular carcinoma recurrence.

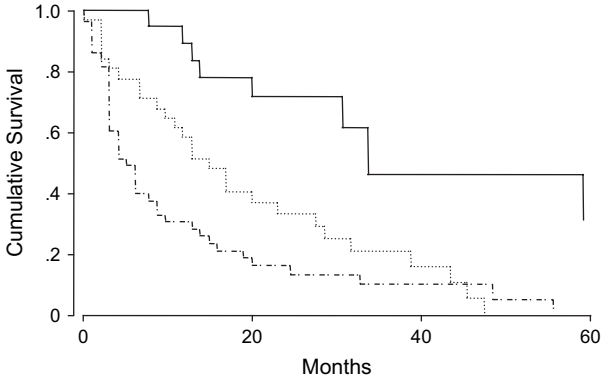

Figure 2. Overall survival from the time recurrence of patients with surgical treatment ($n = 18$; continuous line), non-surgical treatment ($n = 25$, dotted/continuous line) and conservative treatment ($n = 54$, dotted line). The difference between the cumulative survival of patients with surgical treatment and those having a non-surgical or a conservative treatment is significant ($p < 0.0001$). The difference between patients having non-surgical treatment and those having conservative treatment is significant ($p < 0.025$).

mean (SD) and median survival were 12 (2) months and 5 months (range 0–58).

Cumulative survival after tumour recurrence was significantly better in patients with repeat resection than in those having non-surgical or conservative treatment ($p < 0.0001$) (Fig. 2). Furthermore, survival was significantly better ($p < 0.025$) in patients having non-surgical treatment than in those with conservative treatment. Median survival was significantly higher in patients with repeat liver resection than in those with non-surgical treatment ($p < 0.001$) or those without specific treatment ($p < 0.001$).

Recurrence and disease-free survival of the patients undergoing repeat liver resection

Fourteen patients (87.5%) had another recurrence after repeat liver resection. It was located within the liver in 12 (86%) and outside in 2 (14%). Disease-free survival after second liver resection was respectively 40%, 13%, and 10.5% at 1, 3, and 5 years. Three of them (21.4%) had a third liver resection (three segmentectomies) with no operative mortality or morbidity. The mean (SD) and median survival after a third liver resection was 12 (8) months and 11 months (range 1–24). Two other patients with liver recurrence after repeat liver resection had intra-arterial chemoembolization and one had PEI. The mean (SD) and median survival of these patients was 6 (7.1) months and 6 months (range 4–21).

Treatment of extrahepatic metastases after HCC resection

Two patients with metastasis in the lumbar spine survived 3 and 13 months after a vertebral body resection. One developed a secondary recurrence in the liver and the other in the lung.

Discussion

There have been few reports on the results of the treatment of HCC recurrence after resection.[4,6–12,14,15] Our study emphasizes several important points: first, an aggressive policy with surgical or non-surgical treatments improved survival in patients with HCC recurrence; second, re-resection of recurrent HCC whenever possible offered the best chances of cure; and finally, re-resection could be performed safely even in patients with cirrhosis.

Recurrence of HCC after resection

A high recurrence rate (ranging from 50% to 60%) remains the major drawback after resection of HCC.[1–7,16,17] and is responsible for low long-term survival. In our series the intrahepatic recurrence rate was 51% after curative resection of a HCC. In 81% of our patients the major cause of late deaths was malignant cachexia resulting from tumour recurrence. Our study confirms that HCC recurrence most often takes place in the liver and is mainly located far from the liver stump. This high recurrence rate after liver resection may result either from the growth of occult carcinomatous foci in the liver remnant, from the ongoing carcinogenic process associated with chronic liver disease or from an inadequate margin.

Prevention of HCC after resection

It is difficult to decrease this high recurrence rate: previous studies on postoperative adjuvant chemotherapy after hepatic resection for HCC have equally failed to demonstrate a reduction,[18] and this has been confirmed at our centre (unpublished data). However, studies of hepatic arterial administration of I^{131} radiolabelled oil (lipiocis)[19–21] have shown promising results in reducing the HCC recurrence rate. Other approaches such as interferon-alpha therapy after resection of hepatitis C virus-related HCC[22,23] and immunotherapeutic strategies with activation of an HCC-specific response[24–27] are still under evaluation, although these new adjuvant therapies require further evaluation by more randomized studies. We are now engaged in a French multicentric trial in adjuvant therapy with lipiocis following HCC resection. In the initial group of 190 patients with a curative resection, 53 (28%) were within Milan criteria and could have been treated by liver transplantation rather than liver resection. Whether or not liver transplantation should be offered as the primary treatment for small hepatocellular carcinoma or should be reserved as salvage treatment in case of recurrence is still being debated.[17,28,29] It is worth noting that four of the patients undergoing repeat resection for recurrence also had Milan criteria for transplantation.

Treatment of hepatic recurrence

Life expectancy of patients with intrahepatic HCC recurrence after resection is grim.[7] In the present series the 3-year survival rate of patients with recurrence and no treatment was 8%. Our results suggest that an aggressive management strategy using multiple modalities improve survival. The best results were observed in patients in whom re-resection of recurrent HCC could be performed with 3- and 5-year survivals of 50% and 30%. Three patients survived for more than 5 years. Re-resection is technically more demanding than primary resection because of hypertrophy of the residual liver, modifications in anatomical landmarks and post-operative adhesions. It is particularly troublesome in cirrhotic patients in whom the risk of bleeding is augmented. However, in the present study, as in others,[6–8,12] resection could be safely performed even in cirrhotic patients with operative mortality and morbidity comparable to those of a first resection. It should be noted that the favourable results of re-resection might partly be due to a selection of patients with only one or a few recurrent nodules and a well preserved liver function.[15] Therefore in this group of patients re-resection should be considered whenever possible.

Only 19% of all patients with recurrence were suitable for repeat surgery in the present series. Amongst the remaining patients, 54 could not receive any treatment because they presented with multiple disseminated nodules or with a single or a few nodules but a poor liver function and/or portal vein invasion or an atrophic liver remnant. Twenty-five patients (26%) with multiple nodules and/or contra indications for surgery were treated by TACE or PEI. One patient died after TACE and 12% developed complications associated with the procedure. Survival was not as good as that following re-resection but still better than that of patients with conservative treatment, with a 20.7% 3-year survival. Both treatments can be combined. Our results suggest that whenever resection is not indicated, the non-surgical treatment that should be used is TACE in patients with multifocal recurrence, or local treatments such as PEI or RF thermal ablation in those with single recurrent nodules. PEI or RF can be complementary to surgery.[8,27,28] This encourages an aggressive therapeutic policy, whether surgical or non-surgical, in patients with HCC recurrence after hepatic resection.

Treatment of extrahepatic recurrence

Treatment of extrahepatic recurrence after resection of HCC is more controversial, not only because it is less common than intrahepatic recurrence, but also because a distant metastasis from HCC is often considered a contraindication for active treatment. Two of our patients were submitted to a vertebral body resection of a metastasis of HCC in the spine with survival of more than 1 year in one. A few previous reports suggested that resection of an isolated metastasis in the lung,[11,12,14] adrenal gland,[30] peritoneal cavity,[31] and abdominal wall[32] may result in long-term survival in selected patients. A recent study demonstrated that resection of an isolated extrahepatic recurrence might offer long-term survival.[8] Furthermore, like other studies, our results clearly show that surgical treatment of recurrence of HCC can be done safely, just as with the first resection of primary HCC.

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