Downstaging followed by resection plays a role in improving prognosis of unresectable hepatocellular carcinoma

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BACKGROUND: **Curable outcome of unresectable hepatocellular carcinoma (HCC) was seldom encountered in the past. This study was designed to assess the role of downstaging followed by resection (downstaging-resection) in the improvement of prognosis of unresectable HCC.**

METHODS: **During the period of 1958-2003, a total of 1085 patients were verified surgically to be unresectable. Of these patients, 139 received downstaging-resection, with a rate of 84.2% for coexisting cirrhosis and a median tumor diameter of 11.1 cm. Resection of the right lobe, hepatic hilum and bilateral cancer accounted for 97.8% of the patients. Downstaging including hepatic artery ligation (HAL)+hepatic artery chemo-infusion (HAI) was performed in 65.5% of the patients, HAL+HAI+radiotherapy/radioimmunotherapy in 29.5%, and HAL or HAI alone in 5.0%. Retrospective analysis was made of the survival of patients with unresectable HCC, downstaging-resection rate and treatment pattern.**

RESULTS: **In the 139 patients with downstaging-resection, the median interval between the first and second operation was 7.2 months and the 5-year survival rate calculated from the first operation was 48.7%. In the 1085 patients with unresectable HCC, their 5-year survival was 0% in the period of 1958-1973, 11.5% in the period of 1974-1988 and 19.3% in the period of 1989-2003. These figures were correlated with the increasing downstaging-resection rate from 0%, 9.0% to 15.6%, and the increasing percentage of triple or double combination treatment from 32.2%, 60.4% to 69.7%. The 5-year survival in triple treatment group was 24.9%, double treatment 15.2%, and single treatment only 10.9%, which was also correlated with the downstaging-resection rate of 34.6%, 16.2% and 1.8% respectively.**

CONCLUSIONS: **Downstaging-resection plays a role in improving prognosis of unresectable HCC. Triple and double treatments provide a higher downstaging-resection rate and may result in better prognosis.**

(*Hepatobiliary Pancreat Dis Int 2004; 3: 495-498*)

KEY WORDS: **hepatocellular carcinoma; downstaging; cytoreduction; resection; multimodality treatment**

Introduction

In hepatocellular carcinoma (HCC) surgery, small HCC resection plays an important role in improving the outcome of resectable HCC. At the Liver Cancer Institute of Fudan University, Shanghai, the 10-year survival rate of patients with small HCC after resection ($n=1000$) was doubled that of patients with large HCC after resection ($n=1366$), being 46.3% versus 29.2%.[1] Moreover, downstaging followed by resection (downstaging-resection, or cytoreduction and sequential resection) plays a role in improving prognosis of patients with unresectable HCC. In clinical practice, large unresectable HCC still dominates in patients, for whom downstaging-resection is a new approach to surgery. With the progress of regional cancer therapy and multimodality treatment, localized unresectable large HCCs have been feasible converted to resectable small HCCs. Unfortunately, most of the conversions in the past were done for hepatoblastomas, and only few delt with HCC.[2-4] At our institution, studies on this subject have started since the early 1980s.[5-8] In this study, 1085 patients with surgically verified unresectable HCC including downstaging-resection in 139 patients were analyzed retrospectively. Transcatheter arterial chemoembolization (TACE) as a non-surgical approach for downstaging of unresectable HCC and TACE followed by resection have also been practised at our institution,[9,10] but their results are not summarized in this paper because some of the patients were not initially unresectable.

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Methods

In 1085 patients with surgically verified unresectable HCC from 1958 to 2003, 139 (12.8%) received downstaging-resection after reduction of tumor size.

In the 139 patients, aged from 24 to 75 years (median 47), the male to female ratio was 4.6∶1. Serum hepatitis B surface antigen (HBsAg) was detected in 110 patients (79.1%). The level of serum alpha fetoprotein (AFP) was abnormal in 100 patients (71.9%). During the first operation, coexisted cirrhosis was found in 117 patients (84.2%). The median diameter of HCC was 11.1 cm. Right lobe cancer was found in 112 patients (80.6%), hepatic hilum cancer in 7 (5.0%), left lobe cancer in 3 (2.2%), and bilateral cancer in 17 (12.2%).

Therapy for downstaging of the 139 patients included hepatic artery ligation (HAL) + hepatic arterial chemo-infusion (HAI) (91 patients, 65.5%), HAL + HAI + radioimmunotherapy/radiotherapy (41, 29.5%), and HAL or HAI alone (7, 5.0%).

HAL and/or HAI was performed by inserting a catheter with implanted injection port through the right gastric epiploic artery to the proper, right or left hepatic artery according to the location of the tumor. The accuracy of catheterization should be verified by injection of methylene blue. HAL was done to occlude the arterial blood flow to the HCC-affected liver section, and HAL + HAI to occlude the arterial blood supply but maintain the patency of the inserted catheter. Chemotherapeutic agents commonly used were cisplatin, adriamycin (or epirubicin), 5-fluorouracil or fluorodeoxyuridine, and mitomycin C. Hepatic artery embolization was done by injecting lipiodol. Limited resection was employed for downstaging-resection.

In all cases of unresectable HCC (n=1085), survival and downstaging-resection rate were compared between the periods of 1958-1973, 1974-1988 and 1989-2003. The relations of downstaging-resection rate to treatment groups were also analysed. The survival rate was calculated by the life table method.

Results

Outcome of patients receiving downstaging-resection

The median interval between the first and second operation was 7.2 months (1-22 months). The 1-, 3- and 5-year survival rates of the 139 patients calculated from the first operation was 90.4%, 64.5% and 48.7% respectively. By the year 2003, 43 patients survived for more than 5 years, and 16 of them survived for more than 10 years. Their median survival was 58 months.

Table 1. Survival of unresectable HCC with relation to treatment pattern and downstaging-resection rate (%)

Items	1958-1973	1974-1988	1989-2003
No. of patients (n)	59	323	703
5-year survival (%)	0	11.5	19.3
Triple or double combination (%)	32.2(19/59)	60.4(195/323)	69.7(490/703)
Downstaging-resection (%)	0(0/59)	9.0(29/323)	15.6(110/703)

Table 2. Survival of unresectable HCC with relation to different treatment groups and their downstaging-resection rate (%)

Items	5-year survival	Downstaging-resection
Triple combination	24.9	34.6(142/410)
Double combination	15.2	16.2(91/562)
Single modality	10.9	1.8(7/379)

The relation of survival of 1085 patients with unresectable HCC in different periods to downstaging-resection rate and treatment modality

In the 1085 patients with surgically verified unresectable HCC, the 5-year survival was 0% in the period of 1958-1973 (n=59), 11.5% in 1974-1988 (n=323) and 19.3% in 1989-2003 (n=703) respectively. These rates were related to the increasing number of downstaging-resection rate from 0%, 9.0% to 15.6% respectively, and were also correlated to the increasing number of patients using triple or double modality combination treatment from 32.2%, 60.4% to 69.7%, respectively (Table 1).

The survival of patients with unresectable HCC was related to different treatment groups and their downstaging-resection rate. The 5-year survival rate of patients with unresectable HCC receiving triple combination treatment and double combination treatment was 24.9% and 15.2% respectively, whereas it was only 10.9% in patients with single modality treatment. These different outcomes of patients with unresectable HCC were correlated with the downstaging-resection rates of different treatment groups (34.6%, 16.2% and 1.8% respectively, Table 2).

Discussion

The role of downstaging-resection in the improvement of prognosis of patients with unresectable HCC

Surgical resection remains the best treatment for HCC, and small HCC resection has markedly improved the outcome after resection. Resection of large HCC may still provide an opportunity of long-term survival, but the outcome of patients with unresectable HCC is extremely poor. In our institution, however, it has been

much improved with a 5-year survival rate of 0% in 1958-1973, 11.5% in 1974-1988 and 19.3% in 1989-2003 respectively. These encouraging results were closely related to the increasing downstaging-resection rates from 0%, 9.0% to 15.6% and the increasing percentages of triple or double combination treatment from 32.2%, 60.4% to 69.7%. The 5-year survival in the triple treatment group was 24.9%, in the double treatment group 15.2%, and in the single treatment group only 10.9% which was also correlated with their downstaging-resection rates (34.6%, 16.2% and 1.8% respectively). In our 139 patients with downstaging-resection, the 5-year survival rate was 48.7%, which was higher than that of patients with large HCC resection (37.1%, n=1366).[1] Therefore, downstaging-resection has provided a hope for part of patients with unresectable HCC and improved the overall prognosis of patients with unresectable HCC. In the recent literature, downstaging-resection has been considered after intra-arterial chemotherapy,[11] systemic chemoimmunotherapy[12] and radiofrequency ablation.[13]

Approaches for downstaging of unresectable HCC

There are two approaches for conversion of large HCC into small HCC, namely surgical approach and non-surgical approach. In surgical approach, hepatic artery ligation (HAL) plus cannulation (HAI) with perfusion of chemotherapy or radioimmunotherapy is one of the effective combinations. Other regional therapies such as intraoperative cryosurgery, radiofrequency or microwave ablation can also be used. In non-surgical approach, transcatheter arterial chemoembolization (TACE) is commonly used. External radiotherapy will add weight to both of the approaches for effective downstaging.

In our institution, we have found that triple or double combination treatment with hepatic artery ligation (HAL), hepatic artery cannulation with infusion (HAI), radioimmunotherapy, fractionated regional radiotherapy and biotherapy may provide more effective downstaging as compared with single treatment.[14-18] In this study, this conclusion was confirmed. In recent reports, approaches for downstaging of unresectable HCC included intra-arterial chemotherapy,[11,19] radiofrequency ablation[13] and systemic chemoimmunotherapy[12] and ^{131}I-lipiodol treatment.[20]

HCC resection after downstaging

Histopathologic study[6] showed residual cancer cells in 69.7% of the surgical specimens resected after multiple combination treatment, hence, sequential resection is needed for a curative outcome. TACE is commonly used for downstaging as a nonsurgical approach; unfortunately incomplete necrosis is found in the majority of TACE treated HCCs. Majno et al[21] reported that downstaging or total necrosis of the tumor induced by TACE occurred in 62% of the cases. Huang et al[22] also mentioned that only a small proportion of tumors showed complete necrosis after TACE treatment. Because the residual tumor cells after TACE may have more aggressive behavior, sequential liver resection is preferred when it is feasible.

We conclude that downstaging followed by resection plays a role in the improvement of prognosis of patients with surgically verified unresectable HCC. Triple and double treatments provide a higher downstaging-resection rate, which results in better prognosis. The search for more effective cytoreductive therapies is a principal issue for downstaging-resection. In recent years, many regional cancer therapies have been developed and the better combination of those therapies needs further study. Biotherapy such as interferon alpha is used to enhance the response of chemotherapy,[23] and to prevent metastasis and recurrence of HCC after resection.[24]

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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Received July 19, 2004
Accepted after revision August 16, 2004