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Indications for Palliative Reduction Surgery for Hepatocellular Carcinoma with Multiple Intrahepatic Metastases

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ABSTRACT

We evaluated the efficacy of and the indications for palliative reduction surgery as a procedure to improve the prognosis of hepatocellular carcinoma (HCC) patients with multiple intrahepatic metastases. From January 1986 to October 1997, 25 HCC patients with multiple intrahepatic metastases who underwent necessary palliative reduction surgery due to advanced disease, were participated in the study. The 1-, 3-, 5-year survival rates of 25 patients with reduction surgery were 54.7%, 29.9%, 22.4%, respectively. Moreover, the 1-, 3-, 5-year survival rates of patients with some postoperative supplemental treatment were 68.8%, 41.2% and 30.9%, respectively. All 6 patients who had been alive for more than 3 years had had primary tumors with diametric sizes of approximately 5 cm and had undergone, at most, one segmentectomy. These patients received postoperative supplemental treatments. The indication for palliative reduction surgery for HCC patients with multiple intrahepatic metastases was patients with a relatively small primary tumor (around 5 cm) which could be removed by one segmentectomy or less.

Key words: *Hepatocellular carcinoma, Hepatectomy, Intrahepatic matastasis*

Hepatocellular carcinoma (HCC) is one of the commonest malignancies throughout the world, especially in East Asian countries. Recent advances in diagnostic modalities have made it possible to detect HCC at an early stage and have therefore improved the prognosis of HCC patients[12]. However, it is impossible for most patients to undergo curative hepatic resection on account of multiple intrahepatic metastases, invasion into major hepatic vasculatures and/or poor hepatic functional reserve. In Japan although the proportion of HCC patients with resectable tumors has been gradually increasing in the last quarter of this century, the number is still low, at approximately 20%[16]. For advanced HCC patients, some nonsurgical treatments have been performed. However, the effect of these treatments on prolongation of their lives is equivocal[2]. The poor prognosis of HCC is mainly the result of tumor spread to the entire liver via the portal system[9]. It has been considered that the majority of HCC patients with multiple intrahepatic metastases had no indication for hepatic resection. Furthermore, there have been few investigations on the indications for palliative reduction surgery for patients with advanced HCC[19,20]. Since 1986, we have employed palliative reduction surgery as a modality for improvement of the prognosis of HCC patients with multiple intrahepatic metastases. In the present study, we evaluate the efficacy of and indication for these procedures.

PATIENTS AND METHODS

From January 1986 to October 1997, 339 HCC patients underwent hepatic resection at Hiroshima University Hospital, Hiroshima, Japan. Out of that number, twenty-five patients with multiple intrahepatic metastases who underwent palliative reduction surgery out of necessity due to advanced disease were included in this study. Palliative reduction surgery was indicated for patients with multiple intrahepatic metastases who had a primary tumor to be safely resected within their hepatic functional reserves. Patients who had well-differentiated cancer nodules within their multiple nodules, as verified by surgical

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and/or biopsy specimens, were excluded from this study. The patients and their tumors are characterised as follows: 23 males and 2 females with a mean age of 59.6 years (range: 49 to 71). Although positivity of serum hepatitis B surface antigen (HBs Ag) was 12.0%, that of hepatitis C virus (HCV) antibody was 84.2%. Thus, the frequency of HCV infections predominated over hepatitis B virus (HBV) infections in this study. With respect to associated liver disease, chronic hepatitis and liver cirrhosis were found in 9 and 16 patients, respectively. Therefore, 6 patients had grade A, 15 had grade B and 4 had grade C liver dysfunction according to Child-Pugh grading[15]. The mean size in diameter of the primary tumors was 7.1 cm (range: 3.0–27.0 cm). The number of tumors was between 3 and 5 in 11 patients, between 6 and 9 in 7 patients, and 10 or more in 7 patients. There were only 4 patients with multiple tumors limited to one lobe and 21 patients with tumors in bilateral lobes. Sixteen of 25 (64.0%) patients had vascular invasion (portal vein and/or hepatic vein tumor thrombi). According to UICC tumor staging[5], 4 patients had stage III-A, and 21 patients had stage IV-A tumors. Histological grades of resected primary tumors according to Edmondson and Steiner's classification[1] were II in 14 patients, and III in 11 patients (Table 1).

Table 1. Characteristics of patients and their tumors

No. of patients	25
Gender: M/F	23/2
Age: Mean± SD, (range)	59.6±5.7 (49–71)
Posivility of HBs Ag (%)	3/25 (12.0)
*Posivility of HCVAb (%)	16/19 (84.2)
Associated liver disease: CH/LC	9/16
Serum albumin levels (g/dl)	3.3±0.4
ICG-retention at 15min (%)	23.9±11.9
Child-Pugh grading: A/B/C	6/15/4
Size of primary tumor	
Mean±SD (cm)	7.1±5.4
Median (cm)	5.0
No.of tumors 3–5	11
6–9	7
≥10	7
Grade of intrahepatic metastasis	
Unilobar/Bilobar	4/21
Vascular invasion (%)	16/25 (64.0)
#Stage: III-A/IV-A	4/21
##Histological grade of primary tumor	
II/III	14/11

* In six patients, HCV Ab were not examined

\# According to the International Union Against Cancer (UICC) macroscopic staging

Edmondson and Steiner's classification

HBs Ag, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody

CH, chronic hepatitis; LC, liver cirrhosis; ICG, indocyanine green

Table 2. Pre- and intra-operative treatments

Preoperative treatment	
L-TAI/TACE/PEIT/ not performed	17/3/1/5
Type of hepatic resection	
subsegmentectomy or less:	12
one segmentectomy:	7
lobectomy or more:	6
No. of resected tumors	
1/2–3/4≤	9/11/5
Operative EIT for residual tumors	
performed/not performed	13/12
Operative MCT for residual tumors	
performed/not performed	4/21

L-TAI, lipiodol-transcatheter arterial infusion; TACE, transcatheter arterial chemoembolization; EIT, ethanol injection therapy; MCT, microwave coagulation therapy

In 20 out of 25 patients, several kinds of treatments were performed preoperatively and in one out of 20 treated patients, both transcatheter arterial chemolipiodolization with lipiodol (L-TAI) and percutaneous ethanol injection therapy (PEIT) was performed. All patients underwent hepatic resections for the purpose of mass reduction. Twelve patients received, at most, a subsegmentectomy, 7 received one segmentectomy, and 6 received at least a lobectomy. Intraoperative ethanol injection therapy (EIT) in 13 patients and microwave coagulation therapy (MCT) in 4 patients was performed for intrahepatic residual tumors (Table 2).

Several kinds of treatment alone, or in combination, were performed postoperatively for supplemental therapies in 16 patients. However, in 9 patients no postoperative treatment was performed on account of postoperative serious complications and/or poor hepatic functional reserve (Table 3).

Out of 25 patients, 11 patients died in less than 1 year (poor prognosis group); on the other hand, 6 patients survived for more than 3 years after hepatic resection (good prognosis group). In order to clarify the indication for reduction surgery, comparison between the two groups was made with respect to clinicopathological factors and perioperative treatment.

All the data were collected and analysed retrospectively. Data were expressed as mean ±SD, and statistical analyses were performed using Student's t-test or χ^2 test. Cumulative survival rates and curves were calculated by Kaplan-Meier's method from the time of surgery until November 30,1997. P-values of less than 0.05 were considered statistically significant.

RESULTS

The 1-, 3-, 5-year cumulative survival rates in 25 patients with reduction surgery were 54.7%, 29.9%, 22.4%, respectively, and their mean survival was 19 months (Fig.1). One patient died

Table 3. Postoperative treatments

		No. of patients	Anti-cancer drug used
None		9	
L-TAI	alone	5	Cisplatin,4'-epi-doxorubicin,5/FU
	+TAI	3	
	+PEIT	1	
	+radiation	1	
	+re-hepatectomy+systemic chemotherapy	1	
	+PEIT+chemotherapy via PV	1	
TAI	alone	1	Doxorubicin, 5-FU
	+MCT	1	
Systemic chemotherapy		2	Cisplatin

L-TAI, lipiodol-transcatheter arterial infusion; TAI, transcatheter arterial infusion;
PEIT, percuraneous ethanol injection therapy; PV, portal vein; MCT, microwave coagulation therapy

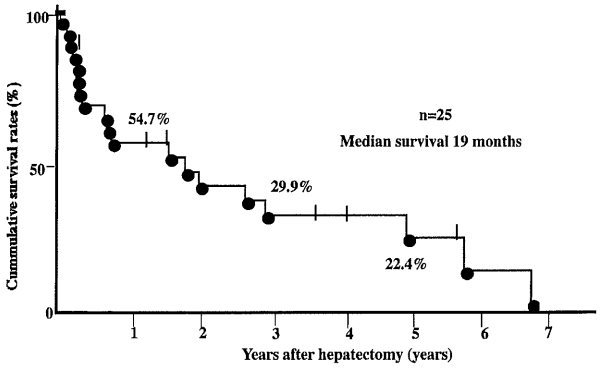

Fig. 1. Cumulative survival curve of all patients (n=25) who performed reduction surgery for HCC with intrahepatic metastase.
The 1-, 3-, 5-year survival rates were 54.7%, 29.9%, 22.4%, respectively. Mean survival was 19 months.

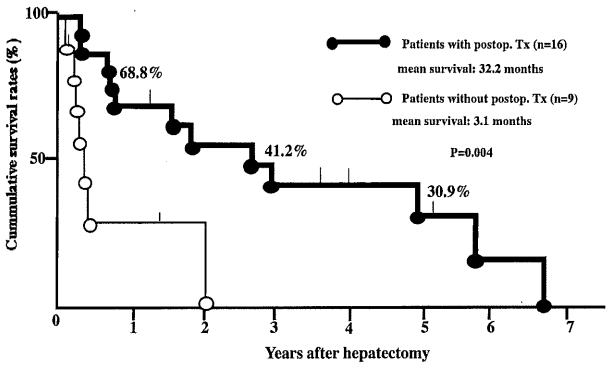

Fig. 2. Survival curves of patients with or without postoperative treatments.
There was significant difference between the two groups (P=0.004). Mean survival with or without postoperative treatments were 32.2 months and 3.1 months, respectively.

within 1 month after hepatic resection due to multiple organ failure resulting from postoperative bleeding; the operative mortality rate was 4.0%. The 1-, 3-, 5-year survival rates in patients who received some postoperative supplemental treatment were 68.8%, 41.2% and 30.9%, respectively, and mean survival in these patients was 32.2 months. However, 1-, 3-year survival rates in patients who could not undergo any postoperative supplemental treatments were 27.8% and 0%, respectively, and their mean survival was only 3.1 months. There was a significant difference between the groups (p=0.004) (Fig. 2).

The good prognosis group had vascular invasion significantly (p=0.036) less frequently than the poor prognosis group. Six of 11 patients in the poor prognosis group were unable to receive the postoperative supplemental treatment which all patients in the good prognosis group received, for residual tumors. There was a significant difference between the groups (p=0.026). The resected primary tumors in the good prognosis group were relatively smaller than those in the poor prognosis group, although there was no significant difference (p=0.069). Moreover, no patient in the good prognosis group underwent even a lobectomy for resection of the primary tumor. With respect to other clinicopathological and treatment factors, there were no differences between the two groups (Table 4). Six patients who were alive for more than 3 years after surgery are listed in Table 5. All patients had had primary tumors with diametric sizes of approximately 5 cm and had undergone at most one segmentectomy. These patients were able to receive postoperative supplemental treatments by transcatheter arterial chemotherapy and/or chemolipiodolization. Furthermore, only one had vascular invasion.

DISCUSSION

Recent advances in preoperative estimation for hepatic functional reserve[10], surgical technique[8] have improved the outcome of hepatic resection which is generally accepted as the first choice of treatment for HCC. However, most HCC patients have intrahepatic multiple tumors which are inoperable and therefore must be treated mainly by

Table 4. Prognostic factors

Factors	Poor prognosis group (n=11)	Good prognosis group (n=6)	p value
Age (y.o.)	59.4±6.4	60.7±4.5	0.668
Sex (M/F)	11/0	4/2	0.042
ICG-retention at 15min (%)	20.9±14.1	24.5±9.1	0.576
Child-Pugh grading (A/B/C)	2/6/3	3/3/0	0.225
Associated liver disease (CH/LC)	3/8	3/3	0.349
Tumor size of primary tumor (cm)	9.6±7.0	3.9±1.1	0.069
Number of tumors (≤5/>5)	6/5	1/5	0.129
Vasculat invasion: vp–/+	2/9	5/1	0.036
vv–/+	8/3	5/1	0.622
# Macroscopic staging (III/IV)	1/10	2/4	0.210
## Histological grading (II/III)	5/6	3/3	0.858
Type of hepatic resection ~ one segmentectomy/lobectomy~	7/4	6/9	0.091
Preoperative treatment (performed/nor performed)	9/2	3/3	0.169
Supplemental operative EIT or MCT (performed/nor performed)	4/7	4/2	0.232
Postoperative treatment (performed/nor performed)	5/6	6/0	0.025

According to the International Union Against Cancer (UICC) macroscopic standing
Edmondson and Steiner's classification
ICG, indocyanine green; CH, chronic hepatitis; LC, liver cirrhosis;
vp, portal vein invasion; vv, hepatic vein invasion; EIT, ethanol injection therapy
MCT, microwave coagulation therapy

Table 5. Patients who survived for more than 3 years after reduction surgery

Case	Age	Gender	Child-Pugh grading	Associated liver disease	Size of primary tumor (cm)	No. of tumors	vp	vv	Type of hepativ resection	Postperative treatment	Prognosis (months)
1	62	F	B	LC	4.0	10	3	1	one segmentectomy	L-TAI, Chemo-therapy	81 dead
2	54	M	B	CH	3.8	6	0	0	partial resection	L-TAI	70 dead
3	59	M	B	LC	5.8	6	0	0	partial resection	L-TAI and TAI	67 alive
3	68	F	A	LC	3.0	3	0	0	partial resection	TAI	59 dead
5	60	M	A	CH	3.0	10<	0	0	partial resection	TAI	49 alive
6	61	M	A	CH	3.8	7	0	0	subsegmentectomy	L-TAI	44 alive

vp, portal vein invasion; vv, hepatic vein invasion; LC, liver cirrhosis; CH, chronic hepatitis;
L-TAI, lipodol-transcatheter arterial infusion; PV, portal vein; TAI, transcatheter arterial infusion

nonsurgical modalities such as transcatheter arterial chemoembolization (TACE) or transcatheter arterial infusion chemotherapy with or without lipiodolization[6] (L-TAI or TAI). TACE is a form of targetting chemotherapy that employs a combination of anticancer drug and lipiodol, and arterial embolization with small gelform particles. Yamada et al[18] reported that the use of TACE for 1,061 inoperative HCC patients resulted in 1-, 2-, 3-, 4- and 5-year survival rates of 51%, 28%, 13%, 8%, and 6%, respectively. Our patients who underwent reduction surgery had better prognosis than those in this TACE series. However, it is impossible to compare our results with this large TACE series simply because the patients' background in this TACE study is not clear, especially with regard to spread of intrahepatic metastases.

Urata et al[17] reported 205 unresectable HCC patients who were treated by lipiodolization. The 1-, 2-, 3-, 4-, and 5-year survival rates were 55.6%, 31.7%, 16.3%, 8.7%, and 2.9%, respectively. They demonstrated that median survival of patients with intrahepatic metastases, numbers ranging from 3 to 9 and 10 or more, were 513 days and 276 days, respectively; one of the important prognostic factors was the number of intrahepatic metastases. However, in our results, the median survival was 19 months and 2 of 7 patients with 10 or more intrahepatic metastases survived for 49 and 81 months, respectively; thus the number of tumors was not a significant prognostic factor.

There have been few investigations on the indica-

tions for palliative reduction surgery for patients with advanced HCC. Yamamoto et al[20] have demonstrated the efficacy of tumor mass reduction surgery and subsequent multidisciplinary treatments including immunotherapy for stage IV HCC patients. It was demonstrated that 2-year survival rates in stage IV-A and IV-B were 49% and 19%, respectively, and 6 survivors for more than 2 years had no vascular invasion and distant metastases. Additionally, some of the long-lived survivors were given postoperative immunotherapy. Nevertheless, 42% of their patients with intrahepatic multiple tumors contained well-differentiated multicentric HCC.

Multiple tumors of HCC within the liver can result from two causes: 1) the result of the growth of synchronous and multicentric tumors of independent origin from the primary tumor, 2) via metastatic spread from the primary tumor via portal system. Although the rules for objective identification of intrahepatic multiple HCCs as unicentric or multicentric are still not standardized[4,11], morphologic criteria for multicentric HCCs have been proposed and defined as follows: "adenomatous hyperplasia (AH) containing cancerous foci", "well-differentiated HCC", and "well-differentiated HCC containing moderately or poorly differentiated cancerous tissues" considered to have originated and proliferated in situ. When these conditions are met, the case is evaluated as HCC of synchronous multicentric origin[7]. Compared to that of patients with metastatic HCC, the prognosis of the patients with multicentric HCCs was better despite a bilobular distribution, if appropriate local therapy, especially resection, was undertaken for each tumor[20]. Therefore, when evaluating the prognosis of patients with multiple HCCs, it is necessary to distinguish intrahepatic metastases from multicentric occurrences as best as possible. In this study, patients who had well-differentiated cancer nodules within their multiple nodules, confirmed by surgical and/or biopsy specimens, were excluded.

Yamamoto et al[19] proposed a remnant tumor index (RTI) as an important factor that influenced the prognosis of advanced HCC patients who underwent palliative reduction surgery. The RTI was calculated on the basis of the size and number of estimated residual tumors after palliative reduction surgery. It was demonstrated that survival rates in patients whose RTI were less than 5.0 were significantly better than those in patients with an RTI of greater than 5.0. Palliative reduction surgery was indicated for patients with an RTI of less than 5.0 and with no extrahepatic metastasis. However, in our study 4 of 6 survivors for more than 3 years and 2 of 3 survivors for more than 5 years had an RTI of greater than 5.0.

Although it is clear that both reduction hepatectomy for primary tumor and postoperative L-TAI for residual tumors play a central role in improving the prognosis of HCC patients with intrahepatic metastases, it is evident also that intraoperative supplemental treatments should be performed for intrahepatic residual tumors. Ozawa et al[13] reported 16 patients with bilobular disease who had the primary tumor resected and the remaining smaller nodules either resected, enucleated or injected with absolute alcohol under intraoperative ultrasound guidance. We performed ethanol injection therapy and/or MCT for residual tumors as often as possible if the residual tumor number was small. Both procedures were feasible and MCT was effective, especially on relatively large tumors[21]. Therefore, recently in our institute, MCT has been adopted mainly as an intraoperative supplemental therapy for residual tumors, although ethanol injection therapy is more feasible and safer than MCT, if residual tumors are located near the major glissons.

We recognize the significance and efficacy of reduction surgery for multiple intrahepatic metastases as follows: 1) it is possible to prevent new metastases from the primary tumor with microscopic and macroscopic portal vein tumor thrombi, 2) it is possible to target the anticancer drug with lipiodol to the metastatic foci once the main tumor, where it would otherwise concentrate, is removed. Higuchi et al[3] reported 84 resections after TAE. The necrosis rate (>95%) was 70% (35 of 50) in small HCCs (<3cm), and only 44% (15 of 34) in HCCs larger than 3 cm; for small HCCs, residual viable cancer usually appeared in the extracapsular zone, whereas it was found in the interior of nonsmall HCCs. This report supports our strategy for treatment of advanced HCC with multiple intrahepatic metastases for which it is impossible to perform curative hepatic resection.

With respect to liver transplantation for advanced HCC, Pichlmayr et al[14] demonstrated that 1-, 3- and 5-year survival rates in patients with stage III or IV HCC were 37.0%, 22.2%, 22.2% and 47.0%, 19.0%, 14.0%, respectively. From these data, they concluded that stage III and IV HCC should be contraindications for liver transplantation alone.

The present study has clarified the significant factors for better prognosis. These are relatively small primary tumors which could be removed by one segmentectomy or less, and no tumor thrombi. However, the longest-lived survivor in this study was a patient with tumor thrombi in the main portal trunk. Therefore, patients with a portal tumor thrombi never have the contraindication for reduction surgery if the size of the primary tumors to be resected is not so large and can be removed with one segmentectomy or less. The 3- and 5-year survival rates and mean survival in patients with postoperative treatments were 41.3%, 30.9%, and 32.2 months, respectively. Such favorable results demonstrate that multidisciplinary treatment

after hepatic resection had a major influence on the outcome of these patients. In other words, it is most important to preserve adequate hepatic function for toleration of subsequent supplemental treatments.

In conclusion, the indication for palliative reduction surgery for HCC patients with multiple intrahepatic metastases was patients with relatively small primary tumors which could be removed by one segmentectomy or less.

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