Original paper

Safety of Hepatectomy Accompanying Combined Resection of Other Organs

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Short title: Hepatectomy with multiorgan resection

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Abstract

Background/Aims: The present study analyzed postoperative outcomes for patients who underwent hepatectomy accompanied by resection of other organs, to clarify operative safety.

Methodology: We examined perioperative parameters in 95 patients who underwent hepatectomy and other organ resections (colorectal resection, n=46; gastrectomy or duodenectomy, n=13; splenectomy, n=17; resection of diaphragm, n=9; pulmonary resection, n=4; others, n=6).

Results: Prevalence of chronic liver dysfunction (100%) or of hepatocellular carcinoma (HCC) (100%) was significantly higher in patients who underwent splenectomy than in other groups (17% and 21%, respectively; p<0.01). Extent of hepatectomy, operating time, blood loss did not differ significantly between groups. Frequency of blood transfusion use was highest in patients who underwent splenectomy (p<0.01). Postoperative complications tended to be more frequent among patients who underwent splenectomy, but this difference was not significant. Wound infection tended to be more frequent among patients who underwent colorectal resection, but not significantly (p=0.11). Hepatectomy-associated complications in patients who underwent splenectomy most often appeared in the form of uncontrolled ascites (p<0.01), with hospital deaths rarely observed and hospital stay not significantly different between groups.

Conclusion: Good postoperative outcomes in multi-organ resections with hepatectomy were observed by careful perioperative management based on adequate indications for hepatectomy.

KEY WORDS: Hepatic resection; Combined resection; Safety; Patient outcome

INTRODUCTION

The incidence of postoperative hepatic failure has markedly decreased in recent years following the introduction of adequate preoperative evaluation of hepatic function and estimation of resected liver volume, as well as improvements in perioperative management (1, 2). In case of hepatectomy for patients with malignancy or concomitant diseases, hepatectomy combined with resection of other organs is often necessary, including tissues such as diaphragm, lung, adrenal gland, and spleen (3-9). Surgeons may carefully decide the operative indications for simultaneous multi-organ resections and may select patients with better functional organ reserve, including liver functions. This is because combined resection may provide greater surgical stress in patients, which would lead to postoperative complications or poor outcomes. However, to the best of our knowledge, indications and operative safety regarding hepatectomy with combined resection of other organs has not been fully evaluated (10).

The present study analyzed postoperative survival in 95 patients who underwent hepatic resections accompanied by simultaneous resection of other organs, and examined surgical records and patient outcomes to clarify operative safety.

METHODOLOGY

Patients

A total of 108 consecutive patients undergoing hepatic resection accompanied by combined resection of other surrounding organs other than the gallbladder in the Division of Surgical Oncology at Nagasaki University Hospital (NUH) between 1990 and January 2011 were retrieved from the NUH database. Thirteen patients who underwent hepatectomy with pancreaticoduodenectomy for biliary carcinomas were excluded from the present study, as operative strategies were different and these data from our institute have already been reported (11, 12). Combined resection of adjacent major vessels was also excluded in this study (12-14). The remaining 95 patients (65 men, 30 women) were enrolled for the present analysis. Mean patient age at the time of surgery was 61.8 ± 12.5 years (range, 29-85 years). Chronic hepatitis was present in 30 patients (22%), including cirrhosis in 16 patients, while the liver was normal in 65 patients. Child-Pugh classification was B in 3 patients (3%) and A in 92 patients. Diseases included hepatocellular carcinoma (HCC) in 32 patients (34%). intrahepatic cholangiocarcinoma (ICC) in 7 (7%), metastatic liver tumor in 54 (57%), gastric carcinoma in one, and diaphragmatic tumor in one. Hepatectomy included hemi-hepatectomy or greater (n=29), sectionectomy (n=20), segmentectomy (n=4) and partial resection (n=42). Radical hepatectomy was performed to remove hepatic tumor without leaving any residual tumor. All hepatic tumors were completely resected without macroscopic exposure of the amputated section to the remaining liver.

All study protocols were approved by the Human Ethics Review Board of our institution. Informed consent for data collection was obtained from each patient during this period. Anesthetic and patient data were retrieved from the NUH database. No financial support was received for this study and the authors have no conflicts of interest to disclose.

Operative indications and evaluated parameters

For hepatectomy, the volume of liver to be resected was estimated according to the indocyanine green retention rate at 15 min (ICGR15) using Takasaki's formula (15). Furthermore, acceptable hepatic function for hepatectomy was limited to ICGR15 <40%, Child-Pugh classification A or B, and total bilirubin level <2 mg/dL. The expected liver volume for resection, excluding the tumor, was measured by computed tomography (CT) volumetry (16). Our protocol of indications for hepatectomy was not influenced by indications for resection of other organs. In cases of pulmonary resection, forced expiratory volume in 1 s (FEV1.0) >1 L was considered necessary by our indications.

We examined preoperative clinical parameters, operative procedures, surgical records, postoperative morbidity and mortality and hospital stay in the 95 patients.

Statistical analysis

All continuous data are expressed as mean \pm standard deviation. Data for different groups were compared using one-way analysis of variance and examined by Student's *t*-test. A two-tailed P value <0.05 was considered significant. Linear regression formula was calculated using correlated parameters. PASW Statistics for Windows version 18.0.0 software (SPSS, an IBM Company, Chicago, IL) was used for all statistical analyses.

RESULTS

Among the 95 patients in the present study, colorectal resection was performed in 46, gastrectomy in 11, splenectomy including Hassab's procedure (17) (n=5) in 17, resection of the diaphragm in 9, pulmonary resection in 4, resection of the adrenal gland in 3, resection of the duodenum in two, costal resection in one, and right nephrectomy in two.

Demographics of patients who underwent hepatectomy with combined resection of other various organs are shown in Table 1. Age and gender did not differ significantly between groups of colorectal resections, gastric or duodenal resections, splenectomy, resections of diaphragm or lung, and other resections. Prevalence of chronic hepatitis and cirrhosis was significantly more frequent (100%) among patients who underwent splenectomy than among other groups (17%, 13/78; p<0.001). In patients who underwent colorectal resection, colectomy was performed in 74%. Prevalence of HCC was significantly more frequent among patients who underwent splenectomy (100%) than among other groups (21%, 16/78; p<0.001). In patients who underwent splenectomy (100%) than among other groups (21%, 16/78; p<0.001). In patients who underwent colorectal resection, only one patient (2%) had HCC with chronic hepatitis. Child-Pugh A was the predominant class in all groups. However, total bilirubin level and ICGR15 were highest and prothrombin activity and platelet count were lowest among patients who underwent splenectomy in comparison with other groups. Liver functional parameters tended to be the best in patients who underwent colorectal resection in comparison with other groups. Prevalence of chief operators among surgeons with various levels of experience did not differ significantly between groups.

Application of the median incision was significantly more frequent in colorectal or gastroduodenal resections than in other groups (p<0.05). Extent of hepatectomy was not significantly different between groups, but laparoscopic partial resection of the liver was applied more often in patients who underwent colorectal resections than in other groups. Although operating time did not differ significantly between groups, blood loss was the lowest

in patients who underwent colorectal resections. On the other hand, red cell blood transfusion was most frequently used in patients who underwent splenectomy (p<0.01). Postoperative complications tended to be the highest in patients who underwent splenectomy, but this difference was not significant. Wound infection tended to occur most frequently in patients who underwent colorectal resection, but again this difference was not significant. Hepatectomy-associated complications in patients who underwent splenectomy most often appeared in the form of uncontrolled ascites (p<0.01). Hospital death was observed in two patients (2%), who had undergone gastrectomy and rib resection. Hospital stay did not differ significantly between groups.

Case presentation

Case 1

A 54-year old man presented with invasive HCC and splenomegaly. The patient showed hypersplenism and the ICGR15 was 8.9%. Examination of abdominal images revealed a 7-cm diameter macroscopically invasive HCC and tumor thrombus spreading from the main tumor to the portal trunk (Fig. 1A, B). Gastroscopy showed the gastric varices. Intraoperative portal pressure was high (22 cmH₂O), so we first performed splenectomy and dissection of the marginal vessels of the upper stomach ("Hassab's operation") followed by right hepatectomy with thrombectomy of the tumor thrombus. Operating time was 8 h 18 min and blood loss was 2960 ml. Transfusion of 5 units of red cells was required. Long-term ascites lasting more than 1 month despite use of diuretics was observed, but the patient did not experience hepatic failure and was discharged 43 days postoperatively. The gastric varix disappeared and thrombocytopenia improved. The tumor was 6.5 cm in diameter and portal vein tumor thrombus was viable (Fig. 1C). Histological examination revealed poorly differentiated HCC with liver cirrhosis

Case 2

A 68-year-old man had undergone thymectomy for malignant thymoma and combined partial resection of the right lung 10 months earlier. He developed tumor recurrences on the right diaphragm invading into the right lower lung and in the posterior sector of the liver (Fig. 2A, B). ICGR15 was 15%. Under an oblique thoraco-abdominal incision along the 7th intercostal space, resection of the lower lung and right diaphragm was performed (Fig. 2C), followed by right posterior sectionectomy of the liver at the same time. The large deficit in the right diaphragm was fixed using an artificial patch graft with GORE-TEX[®] Soft Tissue Patch (W.L. Gore & Associates, NY) (Fig. 2D). Operating time was 9 h 45 min and blood loss was 1700 ml. Transfusion of 2 units of red cells was required. Pleural effusion was observed, but the patient was discharged at 17 days postoperatively. No hepatic failure or other hepatectomy-associated complications were observed. Histological examination showed metastasis of the malignant thymoma in the lung, diaphragm and liver.

Case 3

An 82-year old man with non-viral chronic hepatitis presented with a 4-cm diameter HCC in the right liver, splenomegaly and metastasis of HCC in the right adrenal gland (Fig. 3A). Furthermore, the patient showed concomitant early-stage esophageal and gastric carcinomas. Hypersplenism was evident and the platelet count was 70,000/mm³. Preoperative portal vein embolization increased portal pressure from 23 to 32 cmH₂O. Before hepatectomy, ICGR15 was 14%, but platelet count was still around 60,000/mm³. Intraoperatively, portal pressure decreased to 14 cmH₂O and we first performed the splenectomy. Portal pressure then decreased further to 9 cmH₂O. Subsequently, right hepatectomy and resection of the right adrenal gland were performed (Fig. 3B, C). Operating time was 6 h 45 min and blood loss was 1260 ml. Only

platelet blood transfusion for low platelet count was required. The patient was discharged 15 days postoperatively without any postoperative complications, by which time the platelet count had improved to 170,000/mm³. Histological examination showed well-differentiated HCC with liver cirrhosis and metastasis to the adrenal gland. The patient underwent endoscopic submucosal dissection for the remnant esophageal and gastric carcinomas 35 days after hepatectomy.

DISCUSSION

Recently, even major hepatectomy has been safely performed by adequate preoperative evaluation of functional liver reserve and improvement of postoperative management (1, 2). In some situations, simultaneous or combined resections of other organs are needed accompanying hepatectomy (3-10). In such situations, increased surgical stress is anticipated preoperatively and decisions on concomitant multi-organ resection may be discussed from perspectives of patient condition or organ function (10). The present series collected 95 patients underwent multi-organ resection with hepatectomy, excluding who hepato-pancreaticoduodenectomy (HPD) or combined resection with surrounding major vessels of the liver. This was because HPD was inevitably performed for resection of biliary disease using a careful strategy and combined resection of major vessels might be part of hepatectomy (12-14). The indications for simultaneous multi-organ resection in the present cases might not be always accepted by each physician or institute. Our aim in this study was to clarify whether simultaneous resection with these various diseases was acceptable.

In cases of colorectal carcinoma with simultaneous liver metastasis, we attempted to perform simultaneous resection of the colorectum and liver in accordance with our policy. Major hepatectomy was also selected when liver function was well preserved. Previous reports have shown that simultaneous resection might be controversial (18-23). As the possibility of occult liver metastasis exists, "the wait-and-see policy" was proposed as an alternative (22). However, existence of occult liver metastasis cannot be predicted using any current parameters and chemotherapy remains possible for hepatic recurrence after hepatectomy at any stage. Ueno et al. recently reported that delayed hepatectomy in patients with liver metastasis from colorectal carcinoma did not provide any survival benefit and, furthermore, liver metastases invaded major vessels during chemotherapy after resection of the primary colorectal carcinomas in some cases (23). The chance for hepatectomy may be lost in some cases with

liver metastasis. Our previous results have shown no significant difference in survival between patients with simultaneous and metachronous liver metastasis (24). The present indication for simultaneous hepatectomy with colorectal resection at our institute is a case with <4 liver metastases, while we select systemic chemotherapy such as FOLFOX6 or hepatic arterial infusion chemotherapy after resection of primary tumors showing \geq 4 liver metastases (25, 26). In colorectal carcinoma, most cases showed good liver function, so the opportunity for hepatectomy was seen more often with fellowship and resident surgeons in our series in accordance with our educational policy (27), resulting in better patient outcomes in comparison with other groups. The safety of simultaneous hepatectomy was thus able to be confirmed.

Hepatectomy with gastrectomy or duodenectomy was not frequent, supporting previous reports (8, 28, 29). Many patients showed direct invasion of liver malignancy to the adjacent stomach or duodenum, so limited resection of these organs was selected. En bloc resection might be significant_use according to a previous study (8). In cases of gastric carcinoma, simultaneous hepatectomy for liver metastasis must not be selected because of poor prognosis (30). In patients with metachronous liver metastasis, operative indications would be carefully considerable with various preoperative examinations (29). In cases of double primary cancers in the liver and stomach, we applied the same operative indications for each organ. Our results showed relatively good patient outcomes, which might show the safety of resection in both organs.

Patients with HCC frequently show chronic hepatitis or cirrhosis, because of the origin of carcinogenesis in HCC (31). In such cases, liver function is often decreased and splenomegaly with hypersplenism and portal hypertension would be more common than in other groups, as reported previously (32). The present results also showed hepatic dysfunction. As shown in Cases 1 and 3, platelet count often decreased to less than 90,000/mm3 and this might indicate a risk of intraoperative blood loss or hepatic failure (33). In our series, splenectomy was

performed first and hepatectomy was subsequently used to reduce the risk of bleeding due to portal hypertension and low platelet count. Our results showed no cases with uncontrolled bleeding during hepatectomy, even in right hepatectomy as in Case 2. In other cases showing gastric varices with portal hypertension, Hassab's operation was performed first, followed by hepatectomy as in Case 1 (17). In cases with F-2 grade esophageal varices and the red color sign (34), preoperative endoscopic treatment as endoscopic varicose vein ligation or ethanol injection sclerotherapy was selected and hepatectomy was performed after 1 month, on confirmation of the disappearance or improvement of varices. Reflecting preoperative hepatic dysfunction, long-term ascites were frequently observed in our series, but no mortality was encountered. In patients such as the case presentations, liver function was almost completely preserved. Careful preoperative examination of functional liver reserve is thus more necessary in cases of anatomical resection than in single hepatectomy (32). Careful examination and perioperative management allow simultaneous resection of the liver and spleen.

Simultaneous hepatectomy with resection of the diaphragm has been seen in cases of direct invasion of liver malignancy (3), with most cases able to undergo direct closure of the deficit in the diaphragm, which did not result in respiratory dysfunction. In cases of hepatectomy for liver tumor located in the posterior sector or segment 8, we preferred a thoracoabdominal approach (35, 36), allowing a smaller skin incision and easy approach to the liver tumor. Access to the diaphragm and right thoracic space using an oblique or J-shaped incision is easy (36). On the other hand, as previously reported, thoracotomy might carry a risk of postoperative complications (37), and the present study showed a higher incidence of hepatectomy-associated complications and increased blood loss. Thoracotomy itself is not a major risk factor for postoperative outcomes according to our previous study (36), but simultaneous resection of lung or diaphragm with hepatectomy might lead to such complications. Postoperative respiratory complications other than pleural effusion were rare

and thoracic drainage tubes could be removed within a couple of days at present. In Case 3, operative risk was thought to be high despite good liver function, because the lower lung, whole right diaphragm and part of the chest wall had to be resected along with posterior sectionectomy. However, postoperative course was actually uneventful with the exception of the inevitable pleural effusion. In Case 3, respiratory rehabilitation was fully performed for 2 weeks preoperatively to avoid respiratory failure. We still consider that simultaneous resection of the lung and liver should be carefully selected based on liver and respiratory functions and general condition (4, 5). In cases with simultaneous lesions in the left lung or thorax, pulmonary resection is performed first, followed by hepatectomy after 1-2 months according to our policy.

Other simultaneous multi-organ resections with hepatectomy included right nephrectomy and resection of the right adrenal gland. The adrenal gland sometimes shows metastases from liver tumors, as in Case 3 (6, 7). Hemi-side resection of the kidney or adrenal gland might not cause severe complications when function of the contralateral organ remains preserved. As a result, hepatic status was stable preoperatively and postoperative outcomes were good in our cases. Simultaneous resection of the kidney or adrenal gland on one side might thus be safely performed. However, cases requiring resection of the left kidney or left adrenal gland need a more extended skin incision, although we encountered only one case (left lateral sectionectomy with resection of the left adrenal gland). In Case 3, the right adrenal gland was simultaneously resected, but no abnormal laboratory data were obtained. As previously reported, adrenal gland resection on one side seems safe without severe complications (6, 7).

In conclusion, we have demonstrated multi-organ resection accompanying minor or major hepatectomy. The present results show good postoperative outcomes with resection of other organs following careful pre- and perioperative management based on our usual indications for hepatectomy. Good outcomes can be obtained in cases with multi-organ resection including hepatectomy using the present strategy.

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FIGURE LEGENDS

FIGURE 1 Case 1 showed invasive HCC in the right liver (A; arrow) with portal vein tumor thrombus (PVTT) in the main portal trunk (B; dotted arrow). The spleen was enlarged and gastric varices were also present. The resected specimen showed invasive HCC with PVTT and liver cirrhosis. Spleen weight was 780 g (C).

FIGURE 2 Case 2 showed metastatic malignant thymoma in the right diaphragm invading into the right lower lung (A and C; arrow) and in the right posterior sector of the liver (B). Using a thoraco-abdominal incisional approach, both metastases were resected simultaneously and a large deficit in the diaphragm was covered by the artificial patch (D; thick arrow). The cut surface of the liver was isolated in the abdomen (dotted arrow).

FIGURE 3 Case 3 showed a 4-cm HCC (arrow) in the right liver with hypersplenism and metastasis in the right adrenal gland (dotted arrow) (A). Splenectomy was first performed (B), followed by right hepatectomy (arrowhead) and combined resection of the right adrenal gland (thick arrow) (C).

TABLE 1 Demographics in patients who underwent hepatectomy accompanied with other organs

	Colorectal	Gastric or	Splenectomy	Diaphragm or	Others	Р			
	resection (n=46)	duodenal	(n=17)	lung (n=13)	(n=6)				
	resection (n=13)								
Age (years)	59±14	67±6	61±11	64±13	69±12				
Gender									
Male/Female	29/17	9/4	12/5	11/2	4/2	0.69			
Background liver									
Normal/Chronic hepatitis/Cirrhosis	45/1/0	9/3/1	0/4/13	8/5/0	3/3/0	< 0.001			
Diseases of other organs									
Colon carcinoma/Rectal carcinoma	34/12								
Gastric carcinoma		3							
Hypersplenism			17						
Lung carcinoma/Thymoma/Diaphragmatic tumor				1/1/1					
Liver diseases									
MLC/HCC/ICC/GBC	44/1/1/0	3/6/3/1	0/17/0/0	4/5/1/0	1/4/1/0	< 0.001			
Child-Pugh classification									
A/BC	46/0	12/1	15/2	13/0	6/0	0.12			
Liver functional parameter									
Total bilirubin (mg/dl)	$0.9{\pm}0.5$	0.9±0.3	$1.4{\pm}0.6^{\dagger}$	0.8 ± 0.6	0.8 ± 0.4				
Prothrombin activity (%)	96±15	92±11	$83{\pm}14^{\dagger}$	96±8	85±14				
Platelet count (/mm ³)	29±13	18±5	7±3 [*]	29±12	17±6				
Indocyanine green retention rate at 15 min (%)	7.5±5.2	14.9 ± 10.0	21.0±11.4*	9.0±3.8	9.7±7.3				
Surgeons									
Chief/Fellow/Resident	28/16/2	7/5/1	11/3/3	10/1/2	6/0/0	0.18			
Incision									
Median/Transverse/J-shape/Oblique/Laparoscopic	23/0/20/2/1	7/1/5/0/0	0/6/11/0/0	0/0/6/7/0	1/0/5/0/1	0.003			
Extent of hepatectomy			-						
Partial resection/Segmentectomy/Hemihepatectomy	8* /13/25	5/3/5	7/3/7	4/3/6	1*/1/4	0.67			

Type of resection for other organs						
(Colectomy)Partial/Colonic/Anterior/Hartmann/APR	1/24/17/1/3					
(Gastrectomy or dudenectomy) Partial/Distal/Total		8/3/2				
(Splenectomy) Simple splenectomy/Hassab's operation [#]			12/5			
(Thorax) Lung/Thymus/Rib/Diaphragm				4/1/2/11		
(Others) Kidney/Adrenal gland					2/4	
Surgical records						
Operating time (min)	417±128	400±174	460±125	510±172	586±173	
Blood loss (ml)	$684 \pm 560^{\$}$	1203±1182	1694 ± 844	1808 ± 1095	1195±435	
Transfusion (No/Yes)	36/10	10/3	5/12 \$	9/4	3/3	0.005
Postoperative complication						
No/Yes	30/16	7/6	6/11	5/8	2/4	0.11
Systemic and wound infection	6	2	3	4	1	
Ileus	1					
Stasis		2				
Leakage at colonic anastomosis	1	1				
Others	3	1	1	1	3	
Hepatectomy-associated complication						
No/Yes	42/4	11/2	7/10	7/6	6/0	< 0.001
Hepatic failure	0	2	1	2		
Intraabdominal infection	2	1		3		
Uncontrolled ascites	3	0	9	6		
Bile leakage	1	0	0	2		
Hospital death						
No/Yes	46/0	12/1	17/0	12/1	6/0	0.23
Hospital stay (days)	22±15	39±22	26±9	31±25	28±12	

MLC, metastatic liver carcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

*Laparoscopic partial resection in one patient.

Dissection of marginal blood vessels around the upper stomach with splenectomy

\$ Platelet transfusion was included.

† p<0.05 vs. colorectal resection; %p<0.01 vs. colorectal resection or diaphragm-lung resection;

§ p<0.01 vs. diaphragm-lung resection or splenectomy

Fig 1









