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ORIGINAL ARTICLE

Surgical outcomes of pulmonary metastasis from hepatopancreatobiliary carcinomas: a comparison with pulmonary metastasis from colorectal carcinomas

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Abstract

Objectives Surgical indications for pulmonary metastasis from hepatopancreatobiliary (HPB) carcinomas remain controversial.

Methods Between 2000 and 2015, 25 patients with pulmonary metastasis from HPB carcinomas and 145 with that from colorectal carcinomas underwent metastasectomies in our institution. The primary diseases were hepatocellular carcinoma (HCC) in 8 patients, pancreatic carcinoma (PC) in 12 and biliary tract carcinoma (BTC) in 5. All patients had a sufficient pulmonary reserve, controlled primary disease and no evidence of other metastatic disease. Perioperative factors were investigated retrospectively to analyze the overall survival (OS), pulmonary metastasis-free survival (PmFS) after pulmonary metastasectomy and disease-free interval between surgery for primary disease and the development of pulmonary metastasis (DFI).

Results Complete resection was performed in all patients with lobectomy in 3, segmentectomy in 5 and partial resection in 17. The respective 1-, 2- and 5-year OS rates after metastasectomy were 82.6%, 69.8% and 69.8% in HPB patients and 98.3%, 92.4% and 78.0% in colorectal carcinoma patients ($p=0.351$). The 2-year PmFS of HPB patients was 80.0%, versus 60.6% for colorectal carcinoma patients ($p=0.265$). The DFI was 41.4 months for HPB patients and 34.5 months for colorectal carcinoma patients ($p=0.273$).

Conclusions Metastasectomy for pulmonary metastasis from HPB may be performed in carefully selected patients.

Keywords Surgery · Pulmonary metastasis · Hepatopancreatobiliary carcinomas

Introduction

Hepatopancreatobiliary (HPB) carcinomas have an extremely poor prognosis because of their highly aggressive malignant nature. In most cases, multiple metastases to other organs are also present when pulmonary metastasis is detected. Despite recent developments in surgical techniques, interventional therapy and chemotherapy, the long-term outcomes remain unfavorable because of the high incidence of recurrence, even after complete surgical resection. Among patients with HPB carcinomas, the lung is a major site of the first recurrence, and some patients have only a solitary lung metastasis [1, 2].

Several recent reports have described an improved prognosis in patients with distant metastasis from HPB carcinomas in light of improvements in chemotherapy and molecular-targeted therapy [3–6]. However, as there are still few opportunities for aggressive surgical treatment of pulmonary metastasis from HPB carcinomas, the benefits of local therapy remain controversial, and the surgical indications of pulmonary metastasis from HPB carcinomas are unclear.

In contrast to the situation with HPB carcinomas, surgery for pulmonary metastasis from colorectal carcinoma has been widely accepted and has obtained a general consensus. The Japanese Society for Cancer of the Colon and Rectum (JSCCR) reported in 2016 that pulmonary metastasectomy should be considered if the metastatic

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lung tumor is resectable [7]. The 5-year survival rates after primary colorectal surgery in patients who underwent resection for pulmonary recurrence were reportedly better than in those without resection [8, 9]. This surgical option is, therefore, now recognized as a curative treatment strategy for select patients with colorectal cancer with lung metastases.

This study was performed to elucidate the surgical outcomes of pulmonary metastasectomy from HPB carcinomas and compare the surgical outcomes of pulmonary metastasis from HPB carcinomas with those from colorectal carcinomas.

Materials and methods

Patients

A thoracic surgery clinical database was reviewed in order to identify 25 patients with pulmonary metastasis from HPB carcinomas and 145 with that from colorectal carcinomas who underwent metastasectomy between 2000 and 2015 at our institution. The primary diseases were hepatocellular carcinoma (HCC) in 8 patients, pancreatic carcinoma (PC) in 12 and biliary tract carcinoma (BTC) in 5 patients. All patients had a sufficient pulmonary reserve. The primary site and other potentially metastatic organs were evaluated by computed tomography (CT) and fluorodeoxyglucose-positron emission tomography (PET)/CT.

The selection criteria for pulmonary resection were as follows: no evidence of uncontrollable HPB disease, no evidence of metastatic disease at another site, and CT findings demonstrating the feasibility of complete resection regardless of the number of lesions. Tumors in the bilateral thorax were not considered a contraindication. During follow-up after metastasectomy, second or further metastasectomies were considered if additional lung metastases developed. If uncontrolled liver disease or unresectable multiple lung metastases were found, chemotherapy was performed. The multidisciplinary team of our institution, which included thoracic surgeons, HPB surgeons, medical oncologists and radiation oncologists who evaluated each patient, made final decisions regarding any surgical interventions.

A retrospective chart review was performed, and various perioperative factors were investigated to analyze the overall survival (OS), pulmonary metastasis-free survival (PmFS) after pulmonary metastasectomy and disease-free interval between surgery for primary disease and the development of pulmonary metastasis (DFI).

The ethics committee at Chiba University accepted this study (No. 2220), and written informed consent was waived due to the retrospective nature of this chart review.

Statistical analyses

Statistical analyses for categorical factors were performed using Fisher's exact tests. The OS was defined from the date of metastasectomy to the date of last contact or death. OS curves were plotted using the Kaplan–Meier method with log-rank test. Univariate Cox proportional hazard regression was used to assess the association between the clinical characteristics and the OS rates. All statistical analyses were performed using the statistical software program "R" (Ver 3.5.1 [10]).

Results

The patient characteristics are listed in Table 1. The average ages of the HPB group and colorectal group were 65.2 years (range 36–80) and 65.7 years (range 31–88). Analyses of the clinical characteristics showed no significant difference between the two groups.

Perioperative chemotherapies for pulmonary metastasis in the HPB patients were applied to 1 HCC (12.5%), 9 PC (75.0%) and 3 BTC (60.0%) patients. Complete resection was performed in all patients, and the types of surgery included lobectomy in 3 (12.0%), segmentectomy in 5 (20.0%) and partial resection in 17 (68.0%) patients. During the clinical course after metastasectomy, 2 HCC (25.0%), 9 PC (75.0%) and 3 BTC (60.0%) patients received chemotherapy. Liver metastasis was found in one PC patient who received chemotherapy and one BTC patient who underwent hepatectomy.

The 1-, 2- and 5-year OS rates of HPB patients after metastasectomy were 82.6%, 69.8% and 69.8%, respectively, whereas those of colorectal carcinoma patients were 98.3%, 92.4% and 78.0%, respectively, with no significant difference noted between the 2 groups ($p = 0.351$) (Fig. 1A). The survival curves for the subgroups of HPB patients were comparable (Fig. 1B).

The 2-year PmFS of HPB patients was 80.0%, versus 60.6% for colorectal carcinoma patients, with no significant difference recognized ($p = 0.265$) (Fig. 2a). The PmFS curves for the subgroups of HPB patients were comparable (Fig. 2b).

The DFI was 41.4 months for the HPB patients and 34.5 months for the colorectal carcinoma patients ($p = 0.203$), with similar values noted among the HPB subgroups (Fig. 3).

Of the 7 subjects (HCC, $n = 3$; PC, $n = 2$; BTC, $n = 2$) who survived for at least 5 years after pulmonary surgery, 4 survived with pulmonary recurrence after pulmonary surgery. No patients died during the perioperative period.

Table 1 Patient characteristics at pulmonary metastasectomy in the hepatopancreatobiliary and colorectal groups

	HCC ($n=8$)	PC ($n=12$)	BTC ($n=5$)	HPB All ($n=25$)	Colorectal ($n=145$)	p value
Age, years						0.832
Mean (range)	65.6 (49–74)	65.3 (36–80)	64.4 (57–79)	65.2 (36–80)	65.7 (31–88)	
Sex						0.663
Male	5	5	3	13 (52.0)	84 (57.9)	
Female	3	7	2	12 (48.0)	61 (42.1)	
Side						0.362
Right	6	5	3	14 (56.0)	62 (42.8)	
Left	2	6	2	10 (40.0)	64 (44.1)	
Bilateral	0	1	0	1 (4.0)	19 (13.1)	
Operation						0.241
Partial resection	7	7	3	17 (68.0)	66 (45.5)	
Segmentectomy	1	3	1	5(20.0)	40 (27.6)	
Lobectomy	0	2	1	3 (15.0)	36 (24.8)	
Pneumonectomy	0	0	0	0 (0.0)	3 (2.1)	
Number of metastases						0.493
1	6	6	3	15 (60.0)	97 (66.9)	
2	2	2	1	3 (12.0)	24 (16.6)	
3	0	3	0	5 (20.0)	17 (11.7)	
4	0	1	1	2 (8.0)	7 (4.8)	
Maximum size of metastases (cm)						0.320
Mean (range)	12.0 (9–15)	21.3 (7–67)	15.8 (12–21)	17.2 (7–67)	20.1 (5–90)	
0–1.0	2	1	0	3 (12.0)	34 (23.5)	
> 1.0–2.0	6	7	4	17 (68.0)	65 (44.8)	
> 2.0–3.0	0	2	1	3 (12.0)	20 (13.8)	
> 3.0	0	2	0	2 (8.0)	26 (17.9)	
Chemotherapy for HPB carcinomas						–
Perioperative	1	9	3	13 (52.0)	–	
Recurrence	2	9	3	14 (56.0)	–	

HCC hepatocellular carcinoma, *PC* pancreatic carcinoma, *BTC* biliary tract carcinoma, *HPB* hepatopancreatobiliary

Discussion

HPB carcinomas show unfavorable prognoses due to their highly aggressive behavior. HCC is known to have a high recurrence rate after liver resection, and extrahepatic recurrences are not uncommon, with a reported incidence rate of 13.5% [11]. Common sites of extrahepatic recurrence include the lungs, bones and brains [12]. In PC, even under optimum clinical trial conditions, the median survival of resected patients after adjuvant therapy was found to range from 20.1 to 28.0 months [13]. PC is one of the most common causes of cancer-related death among both males and females. For BTC, the 5-year cumulative survival rates have been reported to range from 22 to 40%, although the long-term survival rates for BTC are thought to be improving [14].

Data from the International Registry of Lung Metastases, which accrued 5206 cases, reported a median survival of 35 months and 5-year survival of 36%, with the primary tumor type, DFI and number of lesions being prognostic factors for the survival [15]. Several reports have found that the surgical outcome of pulmonary metastasectomy did not differ markedly between video-assisted thoracoscopic surgery (VATS)-based procedures and those involving open thoracotomy, regardless of the type of primary tumor involved.

The purpose of pulmonary metastasectomy is to achieve a cure or lengthen the survival by removing all known remaining cancer. Pulmonary metastasectomy has been a well-recognized surgical option for select patients with lung metastases of stage IV solid tumors, such as colorectal carcinoma, sarcoma, renal cell carcinoma, melanoma and others. As already demonstrated in the literature, the completeness of surgery after pulmonary metastasectomy is the most important prognostic factor in terms of the survival. Regarding the indications for surgical resection of metastatic tumors in the lung, as already mentioned, patients were selected based on the Thomford criteria [16]. In our series, all cases were selected based on the following criteria established

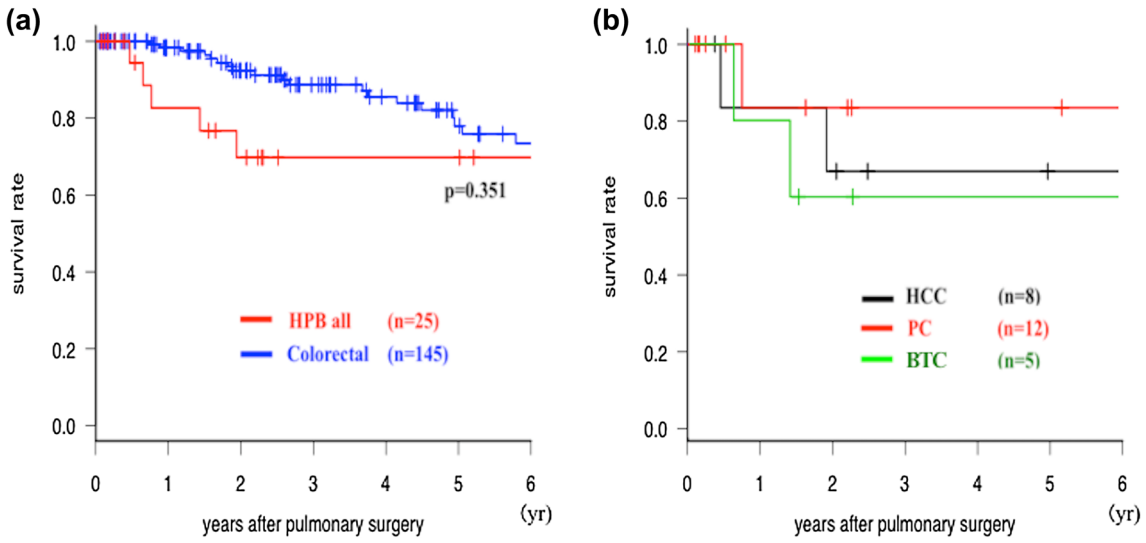

Fig. 1 The overall survival after surgery for pulmonary metastasis. **a** Hepatopancreatobiliary all group versus colorectal group. **b** Subgroups of the hepatopancreatobiliary group. *HPB* hepatopancreatobiliary, *HCC* hepatocellular carcinoma, *PC* pancreatic carcinoma, *BTC* biliary tract carcinoma

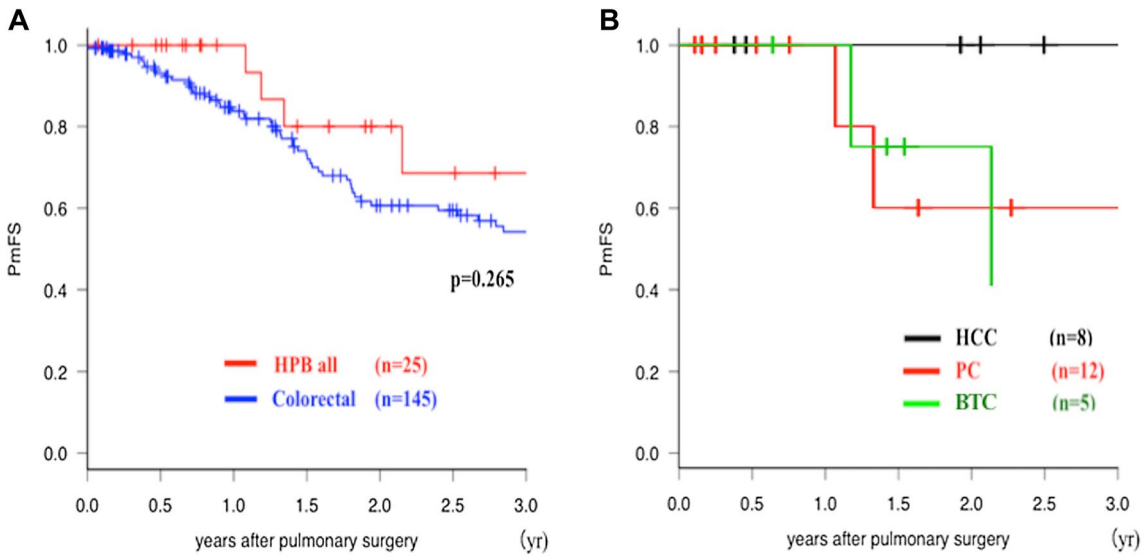

Fig. 2 The pulmonary metastasis-free survival after pulmonary metastasectomy. **a** Hepatopancreatobiliary all group versus colorectal group. **b** Subgroups of the hepatopancreatobiliary group. *HPB* hepatopancreatobiliary, *HCC* hepatocellular carcinoma, *PC* pancreatic carcinoma, *BTC* biliary tract carcinoma

by our multidisciplinary team: no evidence of uncontrollable intrahepatic disease, no evidence of metastatic disease at another site and CT findings suggesting the feasibility of complete resection, regardless of the number of lesions. Careful patient selection by these criteria might have contributed to the relatively good prognosis in our cases.

The efficacy of chemotherapy for these tumors is improving dramatically, consequently resulting in better survival outcomes. For example, sorafenib (oral multikinase inhibitor of vascular endothelial growth factor receptor, platelet-derived growth factor receptor and Raf) prolonged the median survival and the time to progression in cases of advanced HCC by nearly three months [3]. For PC, gemcitabine (GEM) + S-1 [5] and GEM + nab-paclitaxel [6] for pancreatic adenocarcinomas improved the OS, progression-free survival and response rate. In BTC, patients treated with cisplatin + gemcitabine lived an average of 3.6 months longer than those treated with gemcitabine alone [4].

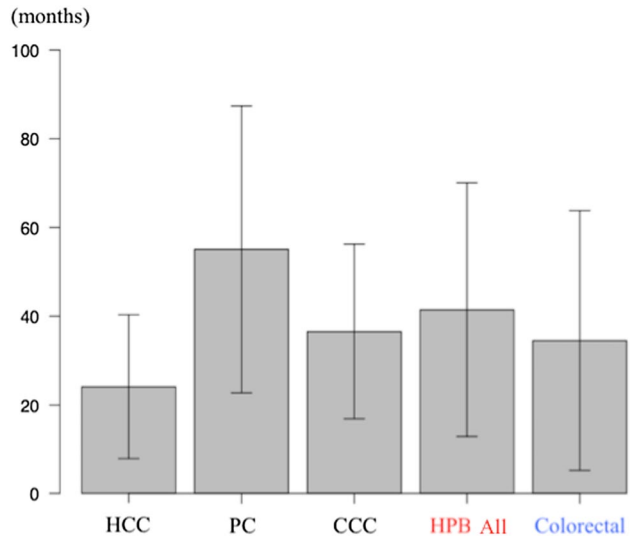

Fig. 3 The disease-free interval between surgery for the primary site and the detection of pulmonary metastasis. *HCC* hepatocellular carcinoma, *PC* pancreatic carcinoma, *BTC* biliary tract carcinoma, *HPB* hepatopancreatobiliary

The OS after recurrence is expected to improve as new therapeutic drugs are developed, and the indications for surgery to treat pulmonary metastases of HPB carcinoma may be expanded in the near future. Thus, the clinical significance of pulmonary metastasectomy, including repeated metastasectomy, must be reevaluated with consideration of possible improvements in the survival outcome. The National Comprehensive Cancer Network Clinical Practice Guidelines for Pancreatic Adenocarcinoma (Version 2, 2017) suggest that pulmonary metastasectomy may be effective in patients with isolated lung metastases after resection of localized pancreatic adenocarcinoma [13]. However, it was noted that more data would be needed before recommendations could be made regarding the management of pulmonary metastases of pancreatic cancers.

Very few data are available regarding the outcomes of pulmonary metastasis from HPB carcinomas. Our analysis showed similar surgical outcomes in terms of the 1-, 2- and 5-year OS, 2-year PmFS and DFI compared to previous studies [17–24] (Table 2). Although the PmFS after pulmonary metastasectomy in HCC patients was superior to that in PC and BTC patients, the survival rate of HCC patients was worse than that of PC patients. This may be due to biological characteristics. The following clinical factors strongly predicted a favorable prognosis: the DFI, number of metastases, serum AFP level and history of recurrence in HCC [18–20] and the serum CA 19-9 level in PC [23]. However, no significant difference in the OS, PmFS or DFI according to such clinical features was noted in the present study.

In colorectal carcinoma, a number of previous studies have shown that pulmonary metastasectomy is associated with a prolonged survival and the possibly of a complete cure. The 5-year survival rate after pulmonary metastasectomy for colorectal cancer metastasis was historically reported to be 30–40% in retrospective studies [9]; however, the survival profile has improved in recent years (now ≥ 50% at 5 years), possibly due to advances made in radiologic examinations for discriminating extrathoracic metastases as well as developments in systemic chemotherapy regimens [25]. Prognostic factors that have been identified

Table 2 The overall survival, pulmonary metastasis-free survival and disease-free interval of pulmonary metastasis for hepatopancreatobiliary all, hepatocellular carcinoma and pancreatic carcinoma in the present and previous studies

	n	1-year OS (%)	2-year OS (%)	5-year OS (%)	2-year PmFS (%)	DFI (mean) (month)
HPB All						
Oyama [17]	18	88	73	73	–	50.8
Our series	25	82.6	69.8	69.8	80.0	41.4
HCC						
Nakagawa [18]	25	80	–	36	–	16.3
Kawamura [19]	61	69.8	–	32.2	–	28.7
Kow [11]	30	92	55	55	–	12
Mizuguchi [20]	19	89	–	48	–	–
Takahashi [21]	93	–	–	41.4	–	17.0
Our series	8	83.3	69.8	69.8	100	24.1
PC						
Arnaoutakis [22]	9	100	100	15	–	34
Kitasato [24]	20	100	90	50	–	49.3
Robinson [23]	29	–	–	47		24
Our series	12	83.3	83.3	83.3	60	55.1

OS overall survival, *PmFS* pulmonary metastasis-free survival, *DFI* disease-free interval, *HPB* hepatopancreatobiliary, *HCC* hepatocellular carcinoma, *PC* pancreatic carcinoma

include the tumor number, tumor size, serum carcinoembryonic antigen (CEA) level, lymph node involvement and completeness of resection [26]. Thus, the efficacy of surgery for pulmonary metastasis from colorectal carcinoma has been widely accepted and has obtained a general consensus. We observed no significant difference in the OS or PmFS between the HPB and colorectal groups, although patients in the HPB group tended to be strictly selected in terms of the discrimination of extrathoracic metastasis as well as the general patient status. To our knowledge, this is the first report comparing the surgical outcomes of pulmonary metastasis from HPB with those of pulmonary metastasis from colorectal carcinoma. Our findings will be useful for selecting candidates for clinical trials in the future.

This study is associated with some limitations. First, this was a single-institution retrospective study. Second, the longer-term survival could not be evaluated for all patients, as this was a retrospective study. Finally, the number of patients in this study was quite small. As such, multicenter, prospective clinical trials involving sufficient numbers of patients are necessary to clarify the true indications of pulmonary metastasectomy for patients with HPB carcinomas. The accumulation of more cases and longer-term follow-up data will be needed in order to draw any definitive conclusions or establish recommendations.

In conclusion, the findings from the present study suggest that resection of lung metastases from HPB as well as colorectal carcinoma in well-selected patients has the potential to achieve a long-term survival and might be a suitable choice of treatment. Multicenter prospective clinical trials involving sufficient numbers of patients are warranted to elucidate the significance of surgical treatment for patients with pulmonary metastases from HPB carcinomas.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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