Radiological Findings and Surgical Outcomes of Pulmonary Metastases Originating from Biliary Tract Carcinoma

Short title: LUNG METASTASIS FROM BILIARY CARCINOMA

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Abstract

Purpose: Metastasis to the lungs arising from biliary tract carcinoma (BTC) is extremely rare, and the patient characteristics and prognosis are not well known. We aimed to identify the imaging findings of pulmonary metastasis originating from BTC and the eligible indications for surgical treatment.

Methods: Fifteen patients who underwent pulmonary resection for metastases originating from BTC were retrospectively analyzed.

Results: The primary sites included cholangiocarcinoma (n = 12) and gallbladder carcinoma (n = 3), and all cases were histologically diagnosed as well to moderately differentiated adenocarcinomas. The median disease-free interval between resection for the primary site and the detection of pulmonary metastasis was 30 months (range, 0 to 144 months). Nine patients had a single lesion, and six had multiple lesions. As features of pulmonary lesions on thin-section computed tomography (CT), many appeared as solid nodules with smooth margins, whereas six lesions were concomitant with spiculation or pleural indentation, three with air bronchogram or ground glass attenuation, and one with intra-tumoral cavity, and six cases with solitary pulmonary lesion were diagnosed as primary lung cancer before metastasectomy. The 3-year survival rate in the 11 patients who underwent complete metastasectomy was 45%. A disease-free interval of more than 3 years ($p = 0.03$) and single lesion ($p < 0.01$) were significant prognostic factors.

Conclusions: The CT findings of pulmonary metastases from BTCs sometimes resemble the characteristic findings of primary lung cancer. A long disease-free interval and single lesion are therefore considered to be good surgical indicators.

Introduction

Biliary tract carcinoma (BTC) is characterized by the presence of aggressive adenocarcinoma, and its treatment for a cure remains the most difficult challenge for hepatobiliary surgeons [1, 2]. The recurrence rate following complete resection remains high, being reported to be more than 50% [3-5]. The liver is the most frequent site of distant relapse, followed by the peritoneal region, lymph nodes, bone, and lung [6, 7]. ￥Resectable pulmonary metastasis originating from BTC has been rarely encountered, and the prognosis after pulmonary metastasectomy has only been investigated in a very small number of cases [8, 9]. However, most thoracic surgeons do not recognize the imaging findings of lung metastatic lesions and the prognostic factors after pulmonary metastasectomy.

Therefore, we aimed to clarify the clinical features of pulmonary metastases originating from BTC and to determine the indications for surgical treatment.

Methods

Study design

From January 2006, 15 patients who underwent pulmonary resection for metastases from BTC in our hospital were reviewed for this study after obtaining institutional review board approval (2014-0295). Two patients had undergone lung resection twice for metachronous pulmonary metastases, and the initial metastasectomies were included in this study. Patients who underwent incomplete resection or exploratory thoracotomy for pulmonary metastases were not excluded, as this study focused mainly on the radiological features of pulmonary metastasis from BTC.

The medical records of all patients were reviewed for demographic information, stage, and the treatment of primary cancer. All patients underwent complete resection for primary cancer, and pulmonary metastases were detected on postoperative follow-up computed tomography (CT) (n = 14) or preoperative CT (n = 1) for staging of the primary tumor. All lesions of lungs were less than 3 cm in maximum diameter, and no biopsies were performed before pulmonary metastasectomy. Our strategy for pulmonary metastasectomy originating from BTC was as follows: patient must have (1) indicated for pulmonary resection, (2) controlled disease at the primary site, (3) no other extrapulmonary metastases, and (4) all pulmonary metastases completely resectable. Thin-section CT was performed routinely before pulmonary metastasectomy, and two

thoracic surgeons (K.K and T.T) reviewed the findings in this study. Assessments of the CT findings of pulmonary metastasis mainly focused on whether or not spicula, pleural indentation, air bronchogram, ground-glass attenuation, and/or intra-tumoral cavity were present in the lesion (Figure 1).

Six cases with solitary pulmonary lesions were clinically diagnosed as primary lung cancer before metastasectomy, and two of them underwent lobectomy with systematic lymph node dissection because a definitive diagnosis of pulmonary metastasis from BTC could not be achieved from the frozen section.

Pathological findings

The pathological examination was generally performed using hematoxylin and eosin (H&E) staining of the lung tumors, with findings compared with those of previously resected BTC lesions. In addition, immunohistochemical studies using cytokeratin 7 and 20 (CK7 / 20), caudal-related homeoprotein 2 (CDX2), thyroid transcription factor 1 (TTF-1), and carbohydrate antigen 19-9 (CA19-9) were performed in order to confirm the diagnosis, if necessary (Figure 2).

The tumor stage was based on the classification of biliary tract cancers established by the Japanese Society of Hepato-Biliary-Pancreatic Surgery [10].

Statistical analyses

To elucidate the potential prognostic factors for pulmonary metastasectomy, the disease-free interval from the surgery of primary BTC, the number and laterality of the lung metastases, the preoperative serum level of CA19-9, and perioperative chemotherapy were recorded for the analysis.

The overall survival was calculated from the date of pulmonary metastasectomy to the date of last follow-up, or death. The survival curves were estimated according to the Kaplan–Meier method, and differences in the survival were assessed using the log-rank test. A p value < 0.05 was considered to be significant. The data were analyzed using the SPSS 24.0 software program (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

From October 2006, 15 patients were enrolled in this study (10 males and 5 females; mean age at the time of pulmonary metastasectomy of 69 years). The primary sites were cholangiocarcinoma (n = 12) and gallbladder carcinoma (n = 3). The median interval between resection for BTC and the detection of pulmonary metastasis was 30 months (range, 0 to 144 months). Nine patients had a single lesion, and six had multiple lesions on chest CT (Table 1). The serum levels of CA19-9 were measured in all cases prior to pulmonary metastasectomy, and those in 3 cases were shown to be elevated (40-109 U/ml).

CT findings

The average size of the lung lesions in the 15 cases was 15 mm, with a range of 5 to 21 mm. Figure 1 shows the typical features of the lung lesions on thin-section CT. Many of them appeared as solid nodules with smooth margins (Fig. 1A), and six were concomitant with spiculation or pleural indentation, three with air bronchogram interiorly or ground-glass attenuation around, and one with intra-tumoral cavity. Eight of all 15 cases had pulmonary lesions in the outer third of the individual lobes. Based on the radiological findings, six cases with solitary pulmonary lesions were diagnosed with primary lung

cancer before undergoing metastasectomy (Table 2).

Operative procedures

The cases of multiple lesions were considered to be metastases arising from BTC and were treated with pulmonary resection without pathological confirmation. In contrast, four single lesions were pathologically diagnosed as metastatic carcinoma originating from BTC during the operation using frozen sections. The remaining single lesion was diagnosed as metastatic carcinoma derived from BTC after the operation based on permanent sections using H&E and immunohistochemical staining. For complete resection of the pulmonary metastases, surgical procedures of lobectomy (n = 4), segmentectomy (n = 1), and wedge resection (n = 10) with an adequate surgical margin were employed. Four cases were judged as incomplete resection: three cases with pleural dissemination or malignant effusion and one case with numerous metastases that were unable to be detected on preoperative CT. All other patients had microscopically negative surgical margins.

Pathological findings

All cases were histologically diagnosed as well to moderately differentiated adenocarcinomas, and the pathological appearance on H&E staining of the lung tumors

was comparable to that of the previously resected BTC lesions in all cases except one, which was morphologically diagnosed as metastatic carcinoma arising from BTC. In addition, immunohistochemical studies were performed in the four cases with a single lesion in order to confirm the diagnosis precisely. All of these tumors were negative for TTF-1 and positive for CA19-9 (Figure 2).

Outcomes and prognostic factors

Excluding 4 cases with incomplete resection, 11 cases were analyzed for the outcomes and prognostic factors. Adjuvant chemotherapy was administered in only one patient using gemcitabine (Case 6). The median survival time after resection of the lung metastases was 34 months (range, 2 to 79 months), and the 3-year survival rate was 45% (Figure 3). Four patients with a single metastasis are currently alive without disease, although all patients with multiple metastases died within 2 years after undergoing metastasectomy (Figure 4). Two patients underwent metastasectomies twice for a single lesion with intervals of 33 and 36 months (Cases 5 and 6, respectively). Figure 5 shows the survival curves according to the disease-free interval of ≥36 months after the surgery for primary BTC. There was a significant difference in the survival between the 2 groups ($p = 0.03$). Other factors, like the patient's gender, primary site, stage of the primary cancer, and perioperative chemotherapy, were not shown to be significant prognostic

factors.

Discussion

BTC is characterized by the presence of aggressive adenocarcinoma, clinically classified into gallbladder carcinoma as well as distal, perihilar, and intrahepatic cholangiocarcinoma, and the only curative treatment is surgical resection [1]. However, the recurrence rates following complete resection of BTC remains high at 50% to 80% [2-6]. Pulmonary metastasis of BTC has been reported very rarely, and surgical treatment is typically not performed in such cases. According to the clinical guidelines for the management of biliary tract cancers published in 2015, BTCs with metastases to the lung are considered contraindicated for surgical resection [11]. Therefore, most hepatobiliary surgeons would not consult thoracic surgeons regarding indications for pulmonary metastasectomy of BTC.

In the literature, Saxena et al. found that systemic dissemination of BTC to multiple sites occurs in 24% of cases of recurrent disease [12]. In their series, recurrent disease was treated aggressively whenever possible; however, resection of metastatic pulmonary lesions was feasible in only three patients, and all other patients received palliative treatment with cytotoxic chemotherapy or best supportive care. In a report of 44 patients with intrahepatic cholangiocarcinoma, recurrence occurred in 57% of the operative cases, with a median period of 23 months before recurrence and an initial site of recurrence of solitary pulmonary metastasis occurring in only 1 case (2.3%) [4]. The previous findings

suggest that recurrent BTC tends to become a systemic disease in the early phase.

When pulmonary lesions are detected in patients with a history of treatment for malignancy, the distinction between a new primary lung tumor and pulmonary metastasis has important prognostic and therapeutic implications, particularly in association with the increasing application of pulmonary metastasectomy [13, 14]. However, the clinical difficulty of distinguishing between solitary pulmonary metastasis of BTC and primary lung cancer may have a significant effect on the method of surgical resection. We assumed that the CT findings of pulmonary metastasis originating from BTCs would show a solid nodule with smooth margins, similar to those of colorectal carcinomas. However, some of the metastases presented as lung lesions concomitant with spiculation, pleural indentation, and/or surrounding ground-glass attenuation, which are the characteristic CT findings in primary lung adenocarcinomas. Indeed, six cases with solitary pulmonary lesions were diagnosed as primary lung cancer before metastasectomy. At present, there are no criteria by which solitary metastases may be definitively distinguished from primary lung cancer based on the findings of chest roentgenograms and/or CT, with a few exceptions, [15-17]. On the other hand, there were 2036 operative cases for primary lung cancer that were treated during the same time period, and only 6 (0.3%) patients had a history of surgery for BTC. The very rare occurrence of second primary lung cancer was suggested because of the rather poor prognosis of patients with BTC. Therefore, we

should determine the diagnosis of solitary pulmonary nodules in patients with a history of BTC based on the clinical course and decide on treatment with the goal of minimizing any possibility of making a misdiagnosis of primary lung cancer or pulmonary metastasis from BTC.

The pathological differentiation between primary lung cancer and pulmonary metastasis from BTC was also the crucial point. In the present study, the pathological differential diagnosis was usually made morphologically according to the findings of H&E staining, while immunohistochemical studies using CA19-9, TTF-1, CK7 / 20, and CDX2 were performed in order to confirm the diagnosis, which was a method similar to that used by Robinson and coworkers [8]. Park and colleagues also reported that negative staining for TTF-1 indicates that adenocarcinoma lesions did not arise from the lungs, while positive staining for CK20 and weak or negative staining for CK7 suggest adenocarcinoma of biliary tract origin [18]. In addition, they reported the need to limit the use of multiple-marker phenotypes due to the lack of sensitivity and that the most predictive phenotype for BTC was expressed in only 28.4% of the cases. Recently, genetic studies such as epidermal growth factor receptor (EGFR) mutation in lung cancer were performed in various cancers in practice, however, few genetic alterations were detected in BTC [19]. Hence, physicians should generally make a diagnosis of metastatic disease using the clinical data and radiographs, as well as comparing former excisional BTC

specimens together.

Despite the relatively short follow-up period, the present findings suggest that surgical resection of single pulmonary metastasis arising from BTC is effective. However, the prognosis of patients with multiple metastases appears to be poor. The only curative treatment for BTC at present is surgical treatment, and the use of chemotherapy is limited to patients with unresectable lesions and recurrence after resection [11]. Furthermore, there are no suggestions regarding the treatment of choice for pulmonary metastasis arising from BTC. Although the surgical indication is not conclusive, due to the very small number of patients enrolled in our study, the current results suggest that patients with single metastasis to the lungs originating from BTC are good candidates for surgical treatment.

In conclusion, the CT findings of single metastasis of BTC resemble the findings characteristic of primary lung cancer, making it difficult to determine whether a nodule is a primary cancer or a metastatic lesion. In addition, a short disease-free period after primary resection and multiple pulmonary lesions were found to be poor prognostic factors in this study.

Acknowledgments and Disclosures.

The authors declare no conflicts of interest in association with this study.

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Figure legends

Figure 1: The chest CT appearance of single pulmonary metastases arising from biliary tract carcinoma resembling primary lung cancer. The findings of the metastases included (A) a solid nodule with a smooth margin, (B) an irregular border with spiculation or pleural indention, (C) air bronchogram or ground-glass attenuation , and (D) intra-tumoral cavity.

Figure 2: Histological appearance of the lung tumor, comparable with that of the primary biliary tract carcinoma (hematoxylin and eosin staining, original magnification ×400) in Case 2; (A) biliary tract carcinoma; (B) lung tumor. The lung tumor originating from the biliary tract carcinoma showed positive staining for cytokeratin 20 (C) and negative staining for thyroid transcription factor 1 (D).

Figure 3: The survival curves for the patients who underwent pulmonary resection for metastases originating from biliary tract carcinoma. The median survival time after complete resection of lung metastasis in 11 patients was 34 months, and the 3- and 5-year survival rates were 45% and 30%, respectively.

Figure 4: The survival curves for the patients who underwent pulmonary resection for metastases originating from biliary tract carcinoma according to the number of lung metastases (single vs. multiple). A significant difference in the survival was seen between the 2 groups ($p < 0.01$).

Figure 5: The survival curves for the patients who underwent pulmonary resection for metastases originating from biliary tract carcinoma according to the disease-free interval after the surgery for primary BTC (<36 months vs. ≥36 months). A significant difference in the survival was seen between the 2 groups ($p = 0.03$).

Table 1. Characteristics of the patients with primary biliary tract carcinoma

No.	Age/ Sex	Primary site	Stage	DFI (months)	Size (mm)	Num.	Laterality	Procedure	Comp.	Survival (months)
1	73M	PCC	IIIA	145	21	1	Uni.	Wedge	No	36/DOD
2	81M	PCC	IIB	83	17	1	Uni.	Wedge	Yes	79/NED
3	78M	PCC	IIIB	83	13	1	Uni.	Lobe.	Yes	27/NED
4	78F	PCC	IB	70	8	1	Uni.	Wedge	Yes	20/NED
5	71F	DCC	IIIB	44	15	1	Uni.	Lobe.	Yes	69/NED
6	64M	PCC	IIA	25	18	1	Uni.	Lobe.	Yes	44/DOD
7	48F	PCC	IIIB	0	10	1	Uni.	Wedge	No	13/DOD
8	76M	PCC	IVA	35	20	2	Uni.	Wedge	Yes	2/NED
9	68M	PCC	IIIA	30	15	2	Uni.	Seg.	Yes	15/DOD
10	71M	PCC	IVA	18	15	2	Uni.	Wedge	Yes	13/DOD
11	73F	PCC	IIIA	54	11	4	Bi.	Wedge	Yes	18/DOD
12	45M	DCC	IIIA	20	5	14	Bi.	Wedge	No	35/DOD
13	69M	PCC	IIA	22	11	1	Uni.	Wedge	Yes	34/DOD
14	72F	GB	IIIA	3	20	1	Uni.	Wedge	No	1/AWD
15	75M	GB	IIB	26	10	5	Bi.	Lobe.	Yes	17/DOD

DFI: disease-free interval, Comp.: completeness of resection, PCC: perihilar

cholangiocarcinoma, DCC: distal cholangiocarcinoma, GB: gallbladder carcinoma, Uni.: unilateral, Bi.: bilateral, Lobe.: lobectomy, Seg.: segmentectomy, DOD: dead of disease, NED: no evidence of disease, AWD: alive with disease

Table 2. CT Findings of Pulmonary Metastasis from Biliary Tract Carcinoma

Factors	Cholangiocarcinoma (n = 12)	Gallbladder ca. (n = 3)	Total
CT findings			
Well defined	5	2	7
Spiculation/PL	5	1	6
Air bronchogram/GGA	3	0	3
Intra-tumoral cavity	0	1	1
Suspicious of primary lung cancer	5	1	6

PL: pleural indentation, GGA: ground glass attenuation, CT: computed tomography