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ORIGINAL ARTICLE

Retrospective Study

Indeterminate pulmonary nodules in colorectal cancer

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Abstract

AIM: To investigate the clinicopathologic parameters of pulmonary metastasis in colorectal cancer (CRC) patients after lung operation of indeterminate pulmonary nodules (IPNs).

METHODS: From a prospective database of CRC patients, 40 cases that underwent lung operation between November 2008 and December 2012 for suspicious metastatic pulmonary nodules on chest computed tomography (CT) were enrolled. The decision to perform a lung operation was made if the patient met the following criteria: (1) completely resected or resectable primary CRC; (2) completely resectable IPNs; (3) controlled or controllable extrapulmonary metastasis; and (4) adequate general condition and pulmonary function to tolerate pulmonary operation. Lung operation was performed by a thoracic surgeon without CT-guided biopsy for pathologic confirmation.

RESULTS: A total of 40 cases of lung resection was performed in 29 patients. Five patients underwent repeated lung resection. The final pathology result showed metastasis from the CRC in 30 cases (75%) and benign pathology in 10 cases (25%). The primary tumor site was the rectum in 26/30 (86.6%) cases with pulmonary metastasis, but only 3/10 (30%) cases in the benign group had a primary rectal cancer (P = 0.001). Positron emission tomography (PET)-CT was performed for 22/30 (73.4%) patients in the lung metastasis group and for 6/10 (60.0%) patients in the benign group. PET-CT revealed hot uptake of ^{18}fluorine 2-fluoro-2-deoxy-*D*-glucose with all IPNs in both groups. The group with pulmonary metastasis had a higher incidence of primary rectal cancer (P = 0.001), a more advanced tumor stage (P = 0.011), and more frequent lymphatic invasion of tumor cells (P = 0.005). Six cases with previous liver metastasectomy were present in the lung metastasis group. Serum carcinoembryonic antigen levels before lung operation were not elevated in any of the patients.

CONCLUSION: The stage and location of the primary tumor and tumor cell infiltration of lymphatics provide useful indicators for deciding on lung resection of IPNs in CRC.

Key words: Colorectal neoplasm; Lung neoplasm; Indeterminate pulmonary nodule; Lung metastasis;

Chest computed tomography

Core tip: This study demonstrated that 25% of indeterminate pulmonary nodules are benign lesions, even though metastasis was suspected after chest computed tomography or positron emission tomography before surgical pulmonary resection. More importantly, we demonstrated that useful indicators for deciding on lung resection of indeterminate pulmonary nodules in colorectal cancer were the primary tumor stage, location of the primary tumor, and tumor cell infiltration of lymphatics.

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INTRODUCTION

In colorectal cancer (CRC) patients, an evaluation for pulmonary metastasis is important for accurate initial staging and decision making regarding follow-up treatment. Many radiologic evaluations, including chest X-ray in the past to chest computed tomography (CT) and positron emission tomography (PET)-CT, are performed for preoperative or postoperative surveillance[1-3]. This clinical process has been described in the National Comprehensive Cancer Network (NCCN) guidelines[4]. If indeterminate pulmonary nodules (IPNs) suspicious of metastasis are found in chest CT, deciding on the next step can be challenging. The decision is complicated by several factors, including radiologic uncertainty, the small size of IPNs, and reluctance of the patient to undergo another operation. Targeting the small-sized IPNs preoperatively for lung operation is not easy, and preoperative percutaneous biopsy for pathologic confirmation is risky due to the possibility of tumor cell contamination in the biopsy tract. Therefore, the aim of this study was to identify the clinicopathologic parameters of CRC lung metastasis after the resection of suspicious pulmonary metastatic nodules.

MATERIALS AND METHODS

From a prospective database of CRC patients in our center, this study included 40 cases that underwent lung operation between November 2008 and December 2012 for IPNs on chest CT in which metastasis was suspected. Three other cases, in which the diagnosis of primary lung cancer was confirmed after CRC operations, were excluded from this analysis.

For IPNs on chest CT, short-term follow-up chest CT or PET-CT was performed. When radiologic findings of the chest CT favored a diagnosis of metastasis by an experienced radiologist (Yi JG), lung operation was considered for suspicious IPNs. The radiologic features used for pulmonary metastasis were as follows: peripheral and parenchymal rather than subpleural location, and features of lobulated, speculated, and ill-defined borders in nodules[5].

The decision to perform lung operation was made if the patient met the following criteria: (1) completely resected or resectable primary CRC; (2) completely resectable IPNs; (3) controlled or controllable extra-pulmonary metastasis; and (4) adequate general condition and pulmonary function to tolerate pulmonary operation. Lung operation was performed by a thoracic surgeon without CT-guided biopsy for pathologic confirmation.

Based on the pathology results of resected IPNs, the patients were subdivided into metastatic and benign groups for comparison of clinical characteristics and histopathologic parameters of the primary CRC.

Statistical analysis

Data analysis was performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, United States). Summary statistics in the two groups were compared using χ^2 and two-sample *t* tests with Welch's correction and Fisher's exact test. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 40 CRC cases comprised of 26 men and 14 women (median age = 59.1 years, range: 45-69 years) were included in this study. Pulmonary metastasis from CRC was confirmed in 30 cases (75%), and the other 10 cases (25%) had benign lesions. The 40 cases were divided into a pulmonary metastasis group and a benign group according to the pathology results.

Patient's characteristics for both groups are shown in Table 1. There was no statistically significant difference in age at primary CRC diagnosis, gender ratio, age at lung operation, or disease-free interval, which is the period between primary CRC operation and lung operation.

The pathologic features are presented in Table 2. Significantly more metastatic cases than benign cases had the rectum as the primary tumor site ($P = 0.001$), though the size of the primary tumor was similar in the two groups. The patients in the pulmonary metastasis group had more advanced T stage and more positive lymph node involvement than those in the benign group (Ps < 0.05). Therefore, the proportion of tumor-node-metastasis stage Ⅲ or Ⅳ patients was higher in the pulmonary metastasis group than in the benign group ($P = 0.011$).

Table 1 Patient characteristics

Characteristic	Lung metastasis (*n* = 30)	Benign (*n* = 10)	*P* value
Gender, male:female	21:9	5:5	0.220
Mean age at diagnosis of CRC, yr	57.6 ± 9.3	60.1 ± 11.6	0.520
Mean age at pulmonary resection, yr	60.6 ± 8.2	61.9 ± 10.7	0.158
Previous hepatic resection for metastasis, *n*	6	0	0.026
Disease free interval, mo (range)	29.5 (0-104)	16.2 (9-42)	0.078
Timing of thoracotomy, *n*			0.067
Synchronous	4	0	
Metachronous	26	10	
> 5 yr after primary CRC surgery	2	2	

Disease free interval = the period between primary CRC operation and lung operation. CRC: Colorectal cancer.

Table 2 Pathologic features of primary colorectal cancer *n* (%)

Feature	Lung metastasis (*n* = 30)	Benign (*n* = 10)	*P* value
Primary tumor site			0.001
Colon	4 (13.3)	7 (70.0)	
Rectum	26 (86.6)	3 (30.0)	
Primary tumor size, cm	5.2 ± 1.5	5.7 ± 2.9	0.505
T stage			0.015
Tis	0	1 (10.0)	
T1	0	1 (10.0)	
T2	1 (3.3)	0	
T3	28 (93.3)	5 (50.0)	
T4	1 (3.3)	3 (30.0)	
N stage			0.001
N0	5 (16.6)	8 (80.0)	
N1	17 (26.6)	2 (20.0)	
N2	8 (26.6)	0	
TNM stage			0.011
0	0	1 (10.0)	
Ⅰ	1 (3.3)	1 (10.0)	
Ⅱ	3 (10.0)	5 (50.0)	
Ⅲ	16 (53.4)	2 (20.0)	
Ⅳ	10 (33.3)	1 (10.0)	
Metastatic LN (*n*)	33 ± 23	22 ± 9	0.034
LN ratio[1]	0.171 ± 0.155	0.031 ± 0.072	0.009
Histologic differentiation			0.195
WD	0	1 (10.0)	
MD	26 (86.6)	8 (80.0)	
PD	3 (10.0)	0	
Mucinous	1 (3.3)	1 (10.0)	
Lymphatic invasion	22 (73.3)	2 (20.0)	0.005
Vascular invasion	4 (13.3)	1 (10.0)	0.633
Perineural invasion	5 (16.6)	1 (10.0)	0.526
Adjuvant chemotherapy	23 (76.7)	3 (30.0)	0.048

[1]Involved LN (*n*)/total LN (*n*). LN: Lymph node; MD: Moderately differentiated; PD: Poorly differentiated; TNM: Tumor-node-metastasis; WD: Well differentiated.

The types of lung operation, numbers and bilaterality of IPNs are presented in Table 3. All IPNs were located in the periphery of the lung and resected by wedge resection. The mean size of IPNs was similar between the two groups (11.8 mm, $P = 0.881$). Pre-thoracotomy serum carcinoembryonic antigen (CEA) level was not elevated in either group. PET-CT was performed for 22/30 (73.4%) patients in the lung metastasis group and for 6/10 (60.0%) patients in the benign group, which revealed the hot uptake of ^{18}fluorine 2-fluoro-2-deoxy-*D*-glucose (FDG) with all IPNs in both groups. There was no thoracotomy-related mortality or complications, such as persistent air leak, pneumonia, postoperative bleeding, chylothorax, and empyema.

Table 3 Characteristics of lung lesions *n* (%)

Characteristic	Lung metastasis (*n* = 30)	Benign (*n* = 10)	*P* value
Type of lung operation			
VATS	25 (83.3)	9 (90.0)	0.526
Open	5 (16.6)	1 (10.0)	
Lung operation-related complications	0	0	
Number of lung nodules			
1	18 (60.0)	6 (60.0)	0.547
2	10 (33.3)	2 (20.0)	
3	2 (6.6)	2 (20.0)	
Size of lung nodules (mm)	11.8 ± 7.5	11.8 ± 7.0	0.881
Bilaterality			
Unilateral	27 (90.0)	10 (100)	0.411
Bilateral	3 (10.0)	0	
Pre-thoracotomy serum CEA elevation	0	0	
Pre-thoracotomy serum CA19-9 elevation	0	0	

CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; VATS: Video-assisted thoracoscopic surgery.

In the benign group, histopathologic examination of IPNs revealed chronic granulomatous inflammation in three cases, tuberculosis in two cases, pleural fibrosis in two cases, anthracofibrotic nodules in two cases, and aspergillosis in one case. The patient profile for the benign group is shown in Table 4.

In the lung metastasis group, repeated pulmonary resection was performed in five cases; it was performed five, four, and three times in three separate cases, and twice in two cases.

DISCUSSION

Of the CRC patients who underwent lung operation for suspicious IPNs in our study, only 75% had pulmonary metastasis from CRC. Despite a more advanced tumor-node-metastasis stage for patients in the pulmonary metastasis group, their pre-thoracotomy serum CEA levels were not elevated.

The lung is the second most common metastatic organ for CRC, and pulmonary metastasis has been detected in 10%-22% of all CRC patients[3,6]. It is known that pulmonary metastasis from CRC is more common in patients with rectal cancer than in those with colon cancer[3]. The reason for this occurrence is that the venous blood stream of the rectum, from the middle and inferior rectal veins, is connected to systemic circulation *via* the internal iliac vein rather than the portal vein[3]. Similarly, in our data, the

Table 4 Clinicopathologic features of patients with benign lung nodules

Case No.	Sex/age	Primary tumor location	Primary operation	TNM stage	Interval to lung OP (mo)	PET	Histology of pulmonary lesions
1	M/70	HF	RHC	0	4	+	Tuberculosis
2	F/35	TC	T-C	Ⅱ	23	+	Tuberculosis
3	M/66	RS	LAR	Ⅱ	60	-	Chronic granulomatous inflammation
4	F/58	HF	RHC	Ⅱ	60	+	Chronic granulomatous inflammation
5	M/70	SC	AR	Ⅲ	88	-	Chronic granulomatous inflammation
6	M/51	SC	AR	Ⅰ	29	-	Pleural fibrosis and fatty metaplasia
7	F/69	AC	RHC	Ⅱ	3	+	Pleural fibrosis and fatty metaplasia
8	M/53	RS	AR	Ⅲ	34	-	Anthracofibrotic nodule
9	F/58	AC	RHC	Ⅳ	26	+	Anthracofibrotic nodule
10	F/71	TC	T-C	Ⅱ	8	+	Aspergillosis

AC: Ascending colon; AR: Anterior resection; F: Female; HF: Hepatic flexure colon; LAR: Low anterior resection; M: Male; OP: Operation; PET: Positron emission tomography; RHC: Right hemicolectomy; RS: Rectosigmoid colon; SC: Sigmoid colon; T-C: Transverse colectomy; TC: Transverse colon; TNM: Tumor-node-metastasis.

incidence of pulmonary metastasis was higher with rectal cancer than with colon cancer.

Serum CEA is a well-known tumor marker for CRC, and metastasis or recurrence of CRC can be detected by an increase in the serum CEA level before the detection of radiologic changes[4]. In this regard, NCCN guidelines recommend a regular assessment of CEA for surveillance of CRC[4]. For pulmonary metastasis of CRC, the serum CEA level is considered a prognostic factor, and the elevation of pre-thoracotomy CEA level is considered a poor prognostic factor[7,8]. However, Iida *et al*[8] reported identifying small pulmonary metastatic nodules prior to the elevation of serum CEA level. The report also stated that the serum CEA level was normal in 52% of CRC patients with pulmonary metastasis. Our data showed similar results, as all cases had normal pre-thoracotomy serum CEA levels, even the pulmonary metastasis group. This finding indicates that the serum CEA level may be ineffective for early detection of pulmonary metastasis after curative primary CRC operation.

Chest CT is a useful tool for identifying lung nodules, with > 70% sensitivity for detecting suspicious pulmonary metastatic nodules from CRC[3,9,10]. However, confirmation of pulmonary metastasis is difficult. Biopsy is the most accurate diagnostic tool for pathologic confirmation of IPNs. However, it is too difficult or occasionally risky to perform in most cases, especially for small lesions. Hence, physicians usually decide whether or not to perform surgery based on the radiologic findings of lung nodules, which are located in peripheral areas 80%-90% of the time and have features with lobulated, speculated, and ill defined borders[5].

PET-CT can be useful as an alternative modality for detecting metastasis[2,11,12]. PET-CT is a relatively accurate, non-invasive modality for detecting metastasis or the recurrence of CRC, and has a higher sensitivity than conventional CT in detecting extra-hepatic metastasis[2,11,13]. However, PET-CT has some limitations. First, this modality cannot clearly discriminate a metastatic lesion from an inflammatory lesion, because the uptake of FDG also increases with inflammation[13]. In our study, PET-CT was performed in 6/10 cases with benign lung nodules, and FDG uptake was seen in all six of them. Secondly, the accuracy of PET-CT for detecting small lung nodules is not satisfactory[13]. It has been reported that the failure rate of PET-CT for detecting subcentimeter lung nodules was nearly 50%[11,14]. Bamba *et al*[1] reported that PET-CT is reliable when the size of the lung nodules is > 9 mm. In addition, the accuracy of PET-CT for detecting lung metastasis varies[1], and its sensitivity and specificity are about 57% and 99%, respectively[1]. Considering that the accuracy of PET-CT for detecting liver metastasis of CRC is usually about 90%[2,13,15,16], its accuracy with detecting pulmonary metastasis is inferior compared to hepatic metastasis.

From the many studies of pulmonary metastasis in CRC patients, patients with diagnoses based on radiologic findings were reviewed[3,17-20]. That is, pathologic confirmation of pulmonary metastasis was not obtained in all cases. However, our study included only patients with suspicious IPNs who received surgical treatment and pathologic confirmation was obtained.

It has already been reported in many studies that complete surgical resection of pulmonary metastasis in CRC patients is useful for prolonging survival[3,6,8,9,17,18,20-26]. The five-year survival rate after complete resection for pulmonary metastasis is reportedly 25%-50%[21,23]. However, complete resection of pulmonary metastasis is possible only in 10% patients with pulmonary metastasis[3,10]. Consequently, when resectable and suspicious IPNs in small numbers are detected on chest CT in CRC patients, surgery is highly recommended. But the decision for resection of suspicious IPNs is usually not easy and is affected by many other factors, including uncertainty of imaging studies, lack of elevated tumor

markers, as already mentioned, as well as reluctance of the patient to undergo another operation. Our study is therefore meaningful for identifying differences in the characteristics of metastatic lung nodules in CRC from those of benign lesions after resection of IPNs, in spite of the small number of cases.

Of the pathologically confirmed IPNs in our study, the incidence of metastatic lung nodules was more common than benign pulmonary nodules. However, it is important to note that as many as 10 cases (25% of all cases) had benign nodules, identified using a highly reliable radiologic imaging modality, such as chest CT and PET-CT. Metastatic lung nodules were associated with a more advanced primary tumor stage including a higher T stage, greater lymph node involvement, and lymphatic invasion of tumor cells. Furthermore, the incidence of pulmonary metastasis was higher in patients with rectal cancer than with colon cancer. Also, the serum CEA level was not elevated in all cases in the pulmonary metastasis group.

In conclusion, radiologic characteristics of suspicious IPNs in CRC provided limited assistance for predicting metastasis. Therefore, consideration of the primary tumor stage, location of the primary tumor and tumor cell infiltration of lymphatics might be more beneficial for deciding on lung operation for suspicious IPNs.

COMMENTS

Background

In colorectal cancer (CRC) patients, an evaluation for pulmonary metastasis is important for accurate initial staging and decision making regarding follow-up treatment. If indeterminate pulmonary nodules (IPNs) suspicious of metastasis are found by chest computed tomography (CT), deciding on the next step can be challenging. The decision is complicated by several factors including radiologic uncertainty, the small size of IPNs, and reluctance of the patient to undergo another operation.

Research frontiers

This study demonstrates that consideration of the primary tumor stage, location of the primary tumor, and tumor cell infiltration of lymphatics are useful indicators for deciding on lung resection of IPNs in CRC.

Innovations and breakthroughs

Many reports concerning pulmonary metastasis in CRC enrolled the patients with suspicious pulmonary nodules determined radiologically. This study is focused on the patients with pathologically confirmed pulmonary nodules after lung resection for the IPNs, in which pulmonary metastasis was radiologically suspicious in CRC patients.

Applications

By consideration of the primary tumor stage, location of the primary tumor, and tumor cell infiltration of lymphatics, lung operation of IPNs in CRC is decided more accurately, and this is helpful for individulized tailored therapy in CRC patients.

Terminology

IPN in this study is a metastasis suspicious lesion, which is found on chest CT, not confirmed pathologically.

Peer-review

Radiologic characteristics of suspicious IPNs in CRC provided limited assistance for predicting metastasis. Consideration of the primary tumor stage, location of the primary tumor, and tumor cell infiltration of lymphatics might be more beneficial for deciding on lung operation for suspicious IPNs.

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