

## Late Pulmonary Metastasis of a Rectal Cancer Resected 20 Years after Low Anterior Resection

Kenji Takahashi, MD,<sup>1</sup> Genichiro Ishii, MD,<sup>2</sup> Mitsuyo Nishimura, MD,<sup>1</sup> Junji Yoshida, MD,<sup>1</sup> Tomoyuki Hishida, MD,<sup>1</sup> Youichi Naitoh, MD,<sup>1</sup> Shigehiro Kitamura, MD,<sup>3</sup> and Kanji Nagai, MD<sup>1</sup>

**A 54-year-old man underwent a low anterior resection for rectal cancer in July 1986. A right pulmonary tumor was pointed out in March 2006 by screening a chest X-ray. Because pulmonary metastasis from colorectal cancer was suspected by transbronchial biopsy, a colonofiberscopy was performed. However, no primary tumor was found. Furthermore, positron emission tomography (PET) revealed no other positive lesion. This tumor was resected in April 2006, and the pathological findings, including immunohistochemical findings, were similar to those of the previously resected rectal cancer. This tumor was therefore diagnosed to be pulmonary metastasis from rectal cancer resected 20 years ago based on a comparison of primary and pulmonary tumors using immunohistochemical examination. This shows that pulmonary metastasis from colorectal cancer is possible even 20 years after the initial operation. (Ann Thorac Cardiovasc Surg 2008; 14: 386–389)**

**Key words:** pulmonary metastasis, rectal cancer, disease-free interval, metastasectomy

### Introduction

Colon cancer frequently metastasizes to the lung. Surgery for resectable pulmonary metastases from colorectal cancer is generally accepted and is curative in most cases. There are some reports that the disease-free interval (DFI) is the predictor of survival after thoracotomy.<sup>1,2)</sup> We recently treated a patient of pulmonary metastasis from rectal cancer with an extremely long DFI. Pulmonary metastasectomy was performed

almost 20 years after the initial operation, and a similarity between primary and metastatic tumors was clearly demonstrated by immunohistochemical examination. To the best of our knowledge, the time interval between initial surgery and pulmonary metastasectomy is the longest as a case report.

### Case Report

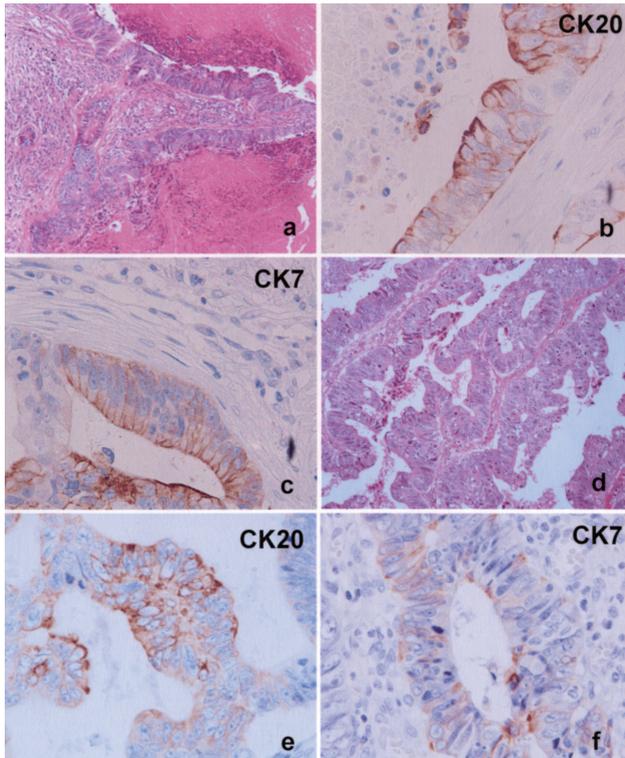
A 54-year-old man underwent a low anterior resection for rectal cancer in July 1986. The disease was histopathologically diagnosed as moderately differentiated adenocarcinoma that had invaded the subserosa (Fig. 1d). Focal involvement of lymphatic vessels and venous invasion was seen, but there was no lymph node metastasis. In March 2006, an abnormal shadow was pointed out on a screening chest X-ray (Fig. 2), and the patient was referred to our institution. Computed tomography (CT) revealed a large tumor in the right middle lobe with enlargement of hilar lymph nodes (Fig. 3), and serum carcinoembryonic antigen (CEA) was elevated to

*From <sup>1</sup>Department of Thoracic Oncology, National Cancer Center Hospital East; <sup>2</sup>Pathology Division, National Cancer Center Research Center for Innovative Oncology, Kashiwa; and <sup>3</sup>Pathology Division, Social Insurance Central Hospital, Tokyo, Japan*

Received October 16, 2007; accepted for publication November 22, 2007

Address reprint requests to Kenji Takahashi, MD: Department of Thoracic Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan.

©2008 The Editorial Committee of *Annals of Thoracic and Cardiovascular Surgery*. All rights reserved.



**Fig. 1.** Microscopic findings, including immunohistochemical examinations of the pulmonary tumor (a–c), are similar to the previously resected rectal cancer (d–f).

**a,d:** The tumor cells in hematoxylin and eosin-stained tissue sections (magnification of photographs,  $\times 100$ ).

**b,e:** The immunohistochemical staining with cytokeratin 20 and both tumors are positive (magnification of photographs:  $\times 400$ ).

**c,f:** The immunohistochemical staining with cytokeratin 7 and both tumors are positive (magnification of photographs:  $\times 400$ ).

CK, cytokeratin.

212 ng/ml. We performed a bronchofiberscopy, and this tumor was diagnosed as moderately differentiated adenocarcinoma consisting of high columnar tumor cells by transbronchial biopsy. We suspected pulmonary metastasis from colorectal cancer, so colonofiberscopy was performed. However, no primary tumor was found. Furthermore, positron emission tomography (PET) revealed no other positive lesions except for the lung tumor and the hilar lymph nodes. This tumor was therefore diagnosed as pulmonary metastasis from rectal cancer resected 20 years previously or primary lung cancer. A right middle lobectomy and lymph node dissection was performed in April 2006.

Macroscopically, the tumor was  $5.5 \times 5.0 \times 3.0$  cm in



**Fig. 2.** Chest X-ray showing a mass shadow in the right middle lung field.



**Fig. 3.** Computed tomography scan of the chest showing a large tumor in the right middle lobe and enlargement of hilar lymph nodes.

size and with extensive necrosis. Microscopically, it consisted of moderately differentiated adenocarcinoma with high columnar cells and extensive necrosis (Fig.

**Table 1. Recent published series of disease-free intervals of pulmonary metastases from colorectal cancer**

Authors	Publication year	No. of patients	Disease-free interval (months)	
			Median	Range
Sakamoto et al. <sup>10)</sup>	2001	47	33	1–260
Headrick et al. <sup>3)</sup>	2001	58	38.4	0–102
Rena et al. <sup>1)</sup>	2002	80	37.5	0–167
Saito et al. <sup>9)</sup>	2002	165	28.4	0–111
Vogelsang et al. <sup>14)</sup>	2004	75	30	0–178
Shiono et al. <sup>13)</sup>	2005	89	24.3	ND
Koga et al. <sup>6)</sup>	2006	58	25	0–76
Yedibela et al. <sup>2)</sup>	2006	153	29	2–114
Lee al. <sup>7)</sup>	2007	59	20	0.9–69.9

ND, not described.

1a). No regions contained components having the usual pulmonary adenocarcinoma histology, including lepidic growth and features of clear cytoplasm. Twenty-seven lymph nodes were examined, and three were metastatic. Immunohistochemical examinations showed tumor cells to be positive for cytokeratin (CK) 20 (Fig. 1b) and CK7 (Fig. 1c), and negative for thyroid transcription factor (TTF)-1. The rectal tumor resected 20 years before the lobectomy was also positive for CK20 (Fig. 1e) and CK7 (Fig. 1f), so we diagnosed this lung tumor as metastasis from rectal cancer resected 20 years ago.

The postoperative course was uneventful, and the patient was discharged on postoperative day 7. The serum CEA level normalized after operation. One year after the operation, however, serum CEA was re-elevated to 66 ng/ml, and recurrence in mediastinal lymph nodes was detected by chest CT. The patient rejected chemotherapy and continued follow-up 14 months after the operation.

## Discussion

The lung is among the most common sites of distant metastases from colorectal cancer. Until now, there has been no curative chemotherapeutic treatment for these metastases. So when possible, surgical resection has been accepted as appropriate therapy. Prognostic factors after thoracotomy were discussed by many authors. Rena et al. and Yedibela et al. reported long DFI as one of the important prognostic factors after thoracotomy.<sup>1,2)</sup> On the other hand, there are some papers stating that DFI does not influence survival after thoracotomy.<sup>3–11)</sup> Besides DFI, prethoracotomy serum CEA level, hilar and/or mediastinal lymph node metastasis, number of

pulmonary metastases, tumor size, and the patient's age are proposed as candidate prognostic factors.<sup>1–10,12–15)</sup> Among them, many papers reported that the presence of hilar and/or mediastinal lymph node metastasis and elevated prethoracotomy serum CEA level are poor prognostic factors. The DFI of the present case was almost 20 years (237 months). As shown in Table 1, reported median DFI ranges 20–38.4 months. Sakamoto et al. reported 47 patients with pulmonary metastases from colorectal cancer and DFI ranges 1–260 months.<sup>10)</sup> To the best of our knowledge, 260 months is the longest DFI, and the present case is the next longest. As a case report, this is the longest one. Kamiyoshihara et al. reported 6 patients with various types of cancer with DFI greater than 10 years and concluded that early death could occur regardless of long DFI.<sup>16)</sup> The present case exhibited lymph node metastases, and prethoracotomy serum CEA was elevated. These observations suggest poor prognosis, and in fact recurrence at the mediastinal lymph node was seen.

A comparison of primary and pulmonary tumors using immunohistochemical examination will be helpful in the diagnosis of pulmonary tumors with extremely long DFIs. In this case, it was difficult to determine whether it was pulmonary metastasis from rectal cancer or primary lung adenocarcinoma with enteric differentiation. Inamura et al. reported the histological characteristics of pulmonary adenocarcinoma with enteric differentiation.<sup>17)</sup> In that paper, they described that all the pulmonary adenocarcinomas with enteric differentiation more or less contained components having a usual pulmonary adenocarcinoma histology, including lepidic growth and features of clear cytoplasm, whereas metastases from colorectal cancer were largely monotonous in histology. The present case

had no region containing usual pulmonary adenocarcinoma. Furthermore, both rectal and pulmonary tumors were positive for CK7 and CK20. Well/moderately differentiated adenocarcinomas in the large intestine showing CK7<sup>+</sup>/CK20<sup>+</sup> immunophenotype account for less than 10% of cases.<sup>18)</sup> In the present case, this rare immunophenotype was seen in both the primary and lung tumors. From the above results, we diagnosed this lung tumor as pulmonary metastasis.

In conclusion, pulmonary metastasis from colorectal cancer is possible 20 years after the initial operation. Thus if the histology of a pulmonary tumor resembles colorectal cancer without colorectal tumor presence, we must review the past history carefully, even going back 20 years.

### Acknowledgment

The authors thank Professor J. Patrick Barron of the International Medical Communications Center of Tokyo Medical University for reviewing this manuscript.

### References

1. Rena O, Casadio C, Viano F, Cristofori R, Ruffini E, et al. Pulmonary resection for metastases from colorectal cancer: factors influencing prognosis. Twenty-year experience. *Eur J Cardiothorac Surg* 2002; **21**: 906–12.
2. Yedibela S, Klein P, Feuchter K, Hoffmann M, Meyer T, et al. Surgical management of pulmonary metastases from colorectal cancer in 153 patients. *Ann Surg Oncol* 2006; **13**: 1538–44.
3. Headrick JR, Miller DL, Nagorney DM, Allen MS, Deschamps C, et al. Surgical treatment of hepatic and pulmonary metastases from colon cancer. *Ann Thorac Surg* 2001; **71**: 975–80.
4. Iizasa T, Suzuki M, Yoshida S, Motohashi S, Yasufuku K, et al. Prediction of prognosis and surgical indications for pulmonary metastasectomy from colorectal cancer. *Ann Thorac Surg* 2006; **82**: 254–60.
5. Inoue M, Kotake Y, Nakagawa K, Fujiwara K, Fukuhara K, et al. Surgery for pulmonary metastases from colorectal carcinoma. *Ann Thorac Surg* 2000; **70**: 380–3.
6. Koga R, Yamamoto J, Saiura A, Yamaguchi T, Hata E, et al. Surgical resection of pulmonary metastases from colorectal cancer: Four favourable prognostic factors. *Jpn J Clin Oncol* 2006; **36**: 643–8.
7. Lee WS, Yun SH, Chun HK, Lee WY, Yun HR, et al. Pulmonary resection for metastases from colorectal cancer: prognostic factors and survival. *Int J Colorectal Dis* 2007; **22**: 699–704.
8. Okumura S, Kondo H, Tsuboi M, Nakayama H, Asamura H, et al. Pulmonary resection for metastatic colorectal cancer: experiences with 159 patients. *J Thorac Cardiovasc Surg* 1996; **112**: 867–74.
9. Saito Y, Omiya H, Kohno K, Kobayashi T, Itoi K, et al. Pulmonary metastasectomy for 165 patients with colorectal carcinoma: A prognostic assessment. *J Thorac Cardiovasc Surg* 2002; **124**: 1007–13.
10. Sakamoto T, Tsubota N, Iwanaga K, Yuki T, Matsuoka H, et al. Pulmonary resection for metastases from colorectal cancer. *Chest* 2001; **119**: 1069–72.
11. Takahashi S, Nagai K, Saito N, Konishi M, Nakagohri T, et al. Multiple resections for hepatic and pulmonary metastases of colorectal carcinoma. *Jpn J Clin Oncol* 2007; **37**: 186–92.
12. Shiono S, Ishii G, Nagai K, Murata Y, Tsuta K, et al. Immunohistochemical prognostic factors in resected colorectal lung metastases using tissue microarray analysis. *Eur J Surg Oncol* 2006; **32**: 308–9.
13. Shiono S, Ishii G, Nagai K, Yoshida J, Nishimura M, et al. Histopathologic prognostic factors in resected colorectal lung metastases. *Ann Thorac Surg* 2005; **79**: 278–83.
14. Vogelsang H, Haas S, Hierholzer C, Berger U, Siewert JR, et al. Factors influencing survival after resection of pulmonary metastases from colorectal cancer. *Br J Surg* 2004; **91**: 1066–71.
15. Zink S, Kayser G, Gabius HJ, Kayser K. Survival, disease-free interval, and associated tumor features in patients with colon/rectal carcinomas and their resected intra-pulmonary metastases. *Eur J Cardiothorac Surg* 2001; **19**: 908–13.
16. Kamiyoshihara M, Hirai T, Kawashima O, Morishita Y. Resection of pulmonary metastases in six patients with disease-free interval greater than 10 years. *Ann Thorac Surg* 1998; **66**: 231–3.
17. Inamura K, Satoh Y, Okumura S, Nakagawa K, Tsuchiya E, et al. Pulmonary adenocarcinomas with enteric differentiation: histologic and immunohistochemical characteristics compared with metastatic colorectal cancers and usual pulmonary adenocarcinomas. *Am J Surg Pathol* 2005; **29**: 660–5.
18. Kende AI, Carr NJ, Sobin LH. Expression of cytokeratins 7 and 20 in carcinomas of the gastrointestinal tract. *Histopathology* 2003; **42**: 137–40.