CDX2 as a useful marker of colorectal adenocarcinoma metastases to lung in pre-operative biopsy specimens

SHIGEBUMI TANAKA[1], KANA SAITO[1,2], TOMOKAZU ITO[1], KOHEI TAJIMA[3], AKIRA MOGI[3], YOSHINORI SHITARA[4], TAKAAKI SANO[2] and HIROYUKI KUWANO[1]

Departments of [1]General Surgical Science, [2]Tumor Pathology, Gunma Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511; [3]Department of Surgery, Fujioka General Hospital, 942-1 Fujioka, Fujioka, Gunma 375-8503; [4]Department of Surgery, Isesaki General Hospital, 12-1 Tsunatorihoncho, Isesaki, Gunma 372-0821, Japan

Abstract. Although distinguishing metastatic colorectal adenocarcinoma from primary lung adenocarcinoma is often difficult, pre- or intra-operative identification is very important, as the resection areas for each diagnosis differ substantially. CDX2, a recently cloned homeobox gene, represents a highly specific and sensitive marker of colorectal adenocarcinoma. We evaluated CDX2 expression using pre- and intra-operative biopsy specimens. The study examined 50 consecutive colorectal adenocarcinoma metastases to the lung, including 20 biopsy specimens and 66 resected specimens, and 21 primary lung adenocarcinomas. All specimens were immunohistochemically stained for CDX2, cytokeratin (CK) 7, CK20 and thyroid transcription factor (TTF)-1, and scored in a semi-quantitative manner. Mean staining score in biopsy specimens was significantly higher for CDX2 than for CK20. Sensitivities for CDX2 and CK7$^-$/20$^+$ in biopsy specimens were 95.0 and 65.0%, respectively. If CDX2 immunostaining had not been performed, 8 biopsy specimens (40%), and 20 resected specimens (30.3%) might have been diagnosed as equivocal cases either as primary lung cancer or metastatic colorectal cancer, using other markers. These results suggest that positive CDX2 staining represents a highly sensitive and specific marker of metastatic colorectal carcinoma in both biopsy and resected specimens, and is superior to staining for the CK7$^-$/20$^+$ phenotype.

Introduction

The lung is one of most frequent target organs for metastatic tumors. Colorectal carcinoma often metastasizes to the lung

as a solitary nodule. Differential diagnosis between metastatic adenocarcinoma of colorectal origin and primary lung adenocarcinoma using imaging techniques such as chest computed tomography (CT) is thus often difficult in patients with a history of colorectal cancer. However, this differentiation is crucial for therapeutic and prognostic purposes (1). Particularly in cases with operative indications, pre- or intra-operative identification is very important, as the resection areas differ substantially between the diagnoses. If the tumor is a solitary metastatic colorectal carcinoma to the lung, partial lung resection is feasible (2). Conversely, primary lung carcinoma requires lobectomy with dissection of regional lymph nodes (3,4).

Immunohistochemical markers have an important role in the differential diagnosis between primary and metastatic lung lesions (5). Immunohistochemical analyses for the expression of cytokeratin (CK) 7 and CK20 and thyroid transcription factor (TTF)-1 have become routine in many laboratories (6). CK7$^-$/20$^+$ and TTF-1$^-$ patterns are known to be typical of colorectal adenocarcinoma (7,8). Conversely, CK7$^+$/20$^-$ and TTF-1$^+$ patterns are typical of primary lung adenocarcinoma.

CDX2 is a recently cloned homeobox gene related to the *Drosophila* Caudal gene, and encodes a transcription factor that plays an important role in pattern formation in the developing embryo and induction of intestine-specific genes (9). Werling and colleagues (10) reported that immunohistochemical examination for CDX2 in resected specimens offered a useful marker of colorectal metastases in lung. Although several reports have identified CDX in almost all cases of colorectal carcinoma metastasis to the lung, these studies have only analyzed resected specimen, not pre- or intra-operative biopsy specimens. Since pre-operative diagnosis is clinically more important, the present study immunohistochemically evaluated biopsy specimens for CDX2 as a potential marker of metastatic colorectal adenocarcinoma to the lung.

Materials and methods

Materials. Subjects comprised 50 consecutive patients (66 resected specimens) with colorectal adenocarcinoma metastases to the lung who presented to Department of General Surgical
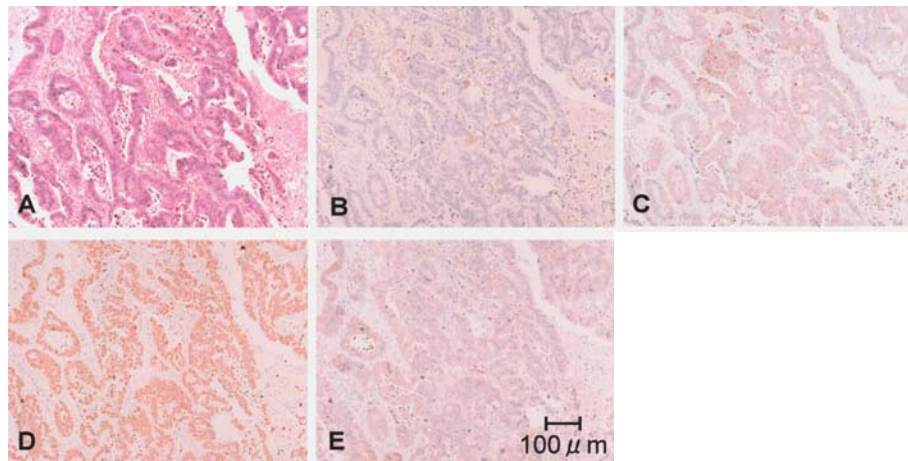

Figure 1. Immunostaining of a typical case with metastatic colorectal adenocarcinoma to the lung using resected specimen (x200). (A) Hematoxylin and eosin; (B) CK7 loss of cytoplasmic expression; (C) CK20 positive cytoplasmic expression; (D) CDX2 positive nuclear expression; (D) TTF-1 loss of cytoplasmic expression.

Science, Gunma University Hospital, Fujioka General Hospital or Isesaki General Hospital between February 1994 and September 2006. Pre-operative and intra-operative biopsy was performed in 26 patients, respectively. As pre- or intra-operative pathological diagnosis failed to distinguish metastatic from primary adenocarcinoma of the lung in 3 cases, lobectomy with dissection of regional lymph nodes was performed. Twenty-one primary lung adenocarcinomas, diagnosed by lung biopsy pre-operatively, were used as controls. Among the primary lung adenocarcinomas, no mucinous bronchioloalveolar carcinoma (BAC), one non-mucinous BAC, 9 mixed type adenocarcinomas with non-mucinous BAC and 3 mixed type adenocarcinomas without BAC were included in this study. All specimens were evaluated after receiving approval from the institutional review board and written informed consent from the patient.

Immunohistochemical analysis. Sections (4-μm) from paraffin-embedded tissue blocks of biopsies and resected specimens were stained. Immunohistochemical examination proceeded according to standard avidin-biotin-peroxidase complex methods using monoclonal antibodies against CDX2, CK7, CK20 and TTF-1. The primary antibodies used were: CDX2 (CDX2-88) from Biogenex, San Ramon CA, USA, CK7 (clone OV-TL 12/30) and CK20 (clone Ks20.8), both from Dako Cytomation, Glostrup, Denmark, and TTF-1 (clone 8G7G3/1), from Neomarkers, Fremont, CA, USA. Antigen retrieval was performed for the primary antibodies as follows: overnight incubation in 0.1 M citric acid pH 7.2 at room temperature for CK20, 8 min of protease digestion for CK 7; and microwave for 8 min in citrate buffer at pH 6.0 for CDX2 and in 1 mM EDTA at pH 8.0 for TTF-1. All slides were counterstained using hematoxylin and eosin (H&E) and coverslips were applied prior to microscopic evaluation.

Microscopic evaluation. Two observers (K.S. and T.S.) blinded to previous histopathological diagnoses assessed the immuno-staining. Tumors were scored in a semi-quantitative manner according to the criteria of Yatabe *et al* (11). Signal intensity exceeding a moderate level was considered positive and populations of positive cells were scored as: 0, no signal in
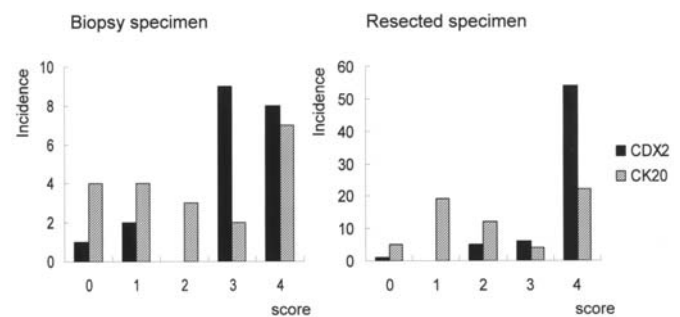

Figure 2. Staining score distribution for metastatic colorectal cancer in biopsy and resected specimens are shown. Staining score range for CDX2 was mainly 3-4. Staining score range for CK20 was 0-4.

any tumor cell; 1, positive signals of any intensity in <25% of sampled tumor area; 2, 26-50%; 3, 51-75%; and 4, ≥76%. For CDX2, only nuclear staining was considered positive. In evaluation of sensitivity and specificity, CDX2$^+$, CK7$^-$/20$^+$ and TTF-1$^-$ patterns were considered as patterns of metastatic colorectal carcinoma to the lung.

Statistical analysis. Data are expressed as mean ± SD. Associations between variables were assessed using the χ^2 or Fisher's exact test when appropriate. Values of $p < 0.05$ were considered statistically significant.

Results

A total of biopsy specimens from 26 patients with metastatic colorectal cancer were investigated. Biopsy specimens were obtained from 7 patients by transbroncheal lung biopsy (TBLB), from 9 patients by CT-guided needle biopsy (CTNB), and from 10 patients by intra-operative biopsy. Malignancy was diagnosed in 20 specimens. The remaining 6 specimens were considered inadequate for diagnosis of malignancy, because no cluster of malignant tumors was recognized in slides of those specimens from paraffin-embedded tissue blocks of biopsies. Therefore, 20 specimens (5 by TBLB, 5 by CTNB, and 10 by intra-operative biopsy) were used for

A. Metastatic colorectal carcinoma to the lung

Biopsy specimen

Resected specimen

B. Primary lung adenocarcinoma
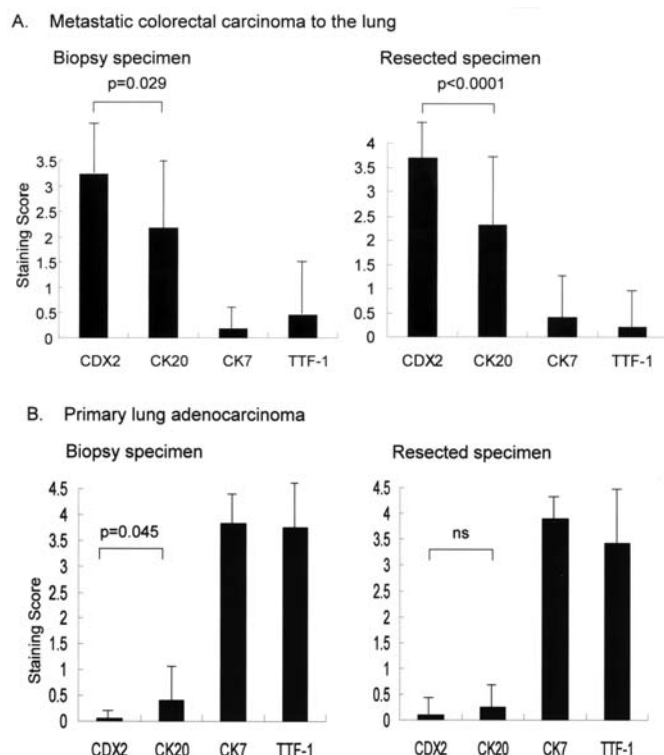
Biopsy specimen

Resected specimen

Figure 3. Mean staining score of metastatic colorectal adenocarcinoma (A) and primary lung adenocarcinoma (B). Among the patients with metastatic colorectal adenocarcinoma, the mean staining score was significantly higher for CDX2 than for CK20 in biopsy specimens (p=0.029), and in resected specimens (p<0.0001). Among the patients with primary lung adenocarcinoma, mean staining score was significantly higher for CK7 than for CDX2 (p=0.045) in biopsy specimen.

this study as biopsy specimens. A total of 47 resected specimens from the 38 patients were investigated.

Immunohistochemically, nuclear expression was noted for CDX2, and cytoplasmic expression for CK7, CK20 and TTF-1. A typical case with metastatic colorectal adenocarcinoma is demonstrated in Fig. 1. Staining score distributions for metastatic colorectal cancer in biopsy and resected specimens are shown in Fig. 2. Among colorectal

cancer patients, staining score range for CDX2 was 2-4, except for one biopsy specimen. In contrast, staining score for CK20 was 0-4. Mean staining scores for CDX2 and CK20 were 3.4 ± 1.1, 1.3 ± 1.0, respectively, and mean staining score was significantly higher for CDX2 than for CK20 in biopsy specimens (p<0.01). Mean staining score was also significantly higher for CDX2 than for CK20 in resected specimens (p<0.001; Fig. 3A). Among primary lung cancer patients, mean staining score for CDX2 and CK20 were low, and there was no difference between them (Fig. 3B).

Among the 20 primary lung cancer patients, only one resected specimen was positive for CDX2 and CK20 expression in which the staining score was 1 each. The pathological type of the tumor was mixed adenocarcinoma with acinar, non-mucinous BAC and papillae.

An interesting case is demonstrated in Fig. 4. The patient was a 46-year-old man who underwent surgical resection for sigmoid colon cancer 4 years earlier. Chest radiography revealed a 2.7-cm tumor in the right upper lobe. Two biopsy specimens were obtained by bronchoscopy. One was considered inadequate for diagnosis of malignancy, as no malignant cells were recognized in the H&E specimen. Based on the other specimen, the pathological diagnosis was adenocarcinoma, probably metastatic, as morphological findings resembled the original resected specimen of sigmoid carcinoma. Using the paraffin-embedded block of former one, which was inadequate for diagnosis of malignancy, CDX2 staining revealed a small mass of cells with diffuse nuclear staining. Re-evaluation using H&E staining diagnosed these stained cells as adenocarcinoma. No staining of this mass was recognized using other markers.

Metastatic colorectal adenocarcinoma in biopsy specimen showed positive staining for CDX2, TTF-1, CK7 and CK20 in 19 (95.0%), 4 (20.0%), 3 (15.0%) and 16 (80.0%) of 20 cases, respectively; metastatic colorectal adenocarcinomas in resected specimen were positive in 65 (98.5%), 7 (10.6%), 15 (22.7%), and 62 (93.9%) of 66 cases, respectively. Primary lung adenocarcinomas in biopsy specimen showed positive staining for CDX2, TTF-1, CK7 and CK20 in 1 (4.8%), 20 (95.2%), 21 (100%), 5 (23.8%), respectively; primary lung
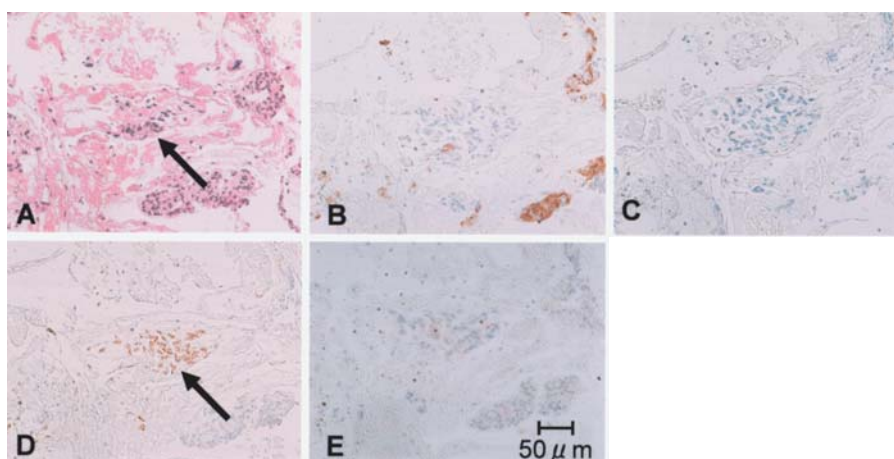

Figure 4. Immunohistochemical study in a biopsy specimen of metastatic colorectal carcinoma which was considered inadequate for diagnosis of malignancy. (A) H&E, tumor cells (arrowhead) were recognized after re-evaluation in the same place of CDX2 positive cells. (B) CK7 loss of expression; (C) CK20 loss of expression; (D) CDX2 positive nuclear expression (arrowhead); (E) TTF-1 loss of expression.

Table I. Sensitivity and specificity of each marker.

	CDX2	CK7⁻/20⁺	P-value
Biopsy (n=20)			
Sensitivity	95.0	65.0	0.0234
Specificity	95.2	76.2	NS
PPV	95	72.2	NS
NPV	95.2	69.6	0.0481

	CDX2	CK7⁻/20⁺	P-value
Resected specimen (n=66)			
Sensitivity	98.5	72.3	0.0002
Specificity	90.5	76.2	NS
PPV	97.0	91.1	NS
NPV	95.0	51.6	0.0015

PPV, positive predict value. NPV, negative predict value. NS, not significant.

adenocarcinomas in resected specimen were positive in 2 (9.5%), 20 (95.2%), 21 (100%) and 5 (23.8%) of 21 cases, respectively.

Sensitivity and specificity for CDX2 expression, and CK7⁻/20⁺ phenotype are demonstrated in Table I. Sensitivity was significantly higher for CDX2 expression than for CK7⁻/20⁺ phenotype in both biopsy and in resected specimens. There were no significant differences in specificities of these markers in biopsy or in resected specimens. There were no significant differences in positive predictive

values of CDX2 and CK7⁻/20⁺ either in the biopsy or in the resected specimen. Negative predictive value of CDX2 was significantly higher (p<0.001) than that of CK7⁻/20⁺ in both the biopsy and in the resected specimens.

Table II shows frequency of each pattern of four markers. Among the metastatic colorectal cancers, CK7⁻/CK20⁺/TTF-1⁻ phenotype, only one combination as metastatic colorectal cancer, was recognized in 12 out of 20 biopsy specimens and in 46 out of 66 resected specimens. If CDX2 immunostaining had not been performed, 8 biopsy specimens (40%), and 20 resected specimens (30.3%) might have been misdiagnosed as non-colorectal cancer or diagnosed as equivocal case. Likewise, among the 21 primary lung cancers, CK7⁺/CK20⁻/TTF-1⁺ phenotype, as primary lung cancer, was recognized in 15 biopsy specimens and in 16 resected specimens. Without CDX2 immunostaining, 8 biopsy (40.0%) and 20 resected specimens (30.3%) would have been diagnosed as equivocal cases either as primary lung cancer or metastatic colorectal cancer.

Discussion

The present study assessed the potential of CDX2 immuno-histochemical staining as a significant marker of colorectal metastases in the lung, using both biopsy and resected specimens.

Pulmonary resection is the most effective treatment for metastatic carcinoma to the lung, as no other effective treatment for this disorder has yet been established (12). Indications for pulmonary metastasectomy have basically followed the criteria of Thomford *et al* (13) reported in 1965: i) the patient must be a good candidate for surgical intervention; ii) primary malignancy must be controlled; iii) evidence of metastatic disease elsewhere must be absent; and iv) radiographic evidence of pulmonary metastasis must be limited to one lung. With the development of anesthetic and surgical

Table II. Distribution of each phenotype for four markers.

	Metastatic colorectal cancer			Primary lung cancer	
	Biopsy (20)	Resection (66)		Biopsy (21)	Resection (21)
CDX2⁺					
CK20⁺/CK7⁻/TTF-1⁻	11	45	**CK20⁺/CK7⁻/TTF-1⁻**	0	0
CK20⁺/CK7⁻/TTF-1⁺	1	2	CK20⁺/CK7⁺/TTF-1⁺	1	2
CK20⁺/CK7⁺/TTF-1⁻	2	10			
CK20⁺/CK7⁺/TTF-1⁺	1	4			
CK20⁻/CK7⁻/TTF-1⁻	3	3			
CK20⁻/CK7⁻/TTF-1⁺	1	0			
CK20⁻/CK7⁺/TTF-1⁻	0	1			
CDX2⁻					
CK20⁺/CK7⁻/TTF-1⁻	1	1	CK20⁻/CK7⁺/TTF-1⁺	15	16
			CK20⁺/CK7⁺/TTF-1⁺	5	3

Typical phenotype for colorectal cancer shown in bold.

techniques, indications have been extended. For example, synchronous bilateral metastasectomy is now possible (14,15). Generally, wedge resection is the standard technique for metastasectomy. Lobectomy should be selected in cases where the tumor is located centrally or is too large for wedge resection. The necessity of mediastinal lymph node dissection remains controversial (16). Pulmonary metastasis often occurs as multiple lesions and/or recurrences, and repeat pulmonary resection for isolated recurrent colorectal metastases to the lung yields results comparable to those after first pulmonary resection in terms of operative mortality and survival in the absence of hilar/mediastinal lymph node or extrathoracic involvement (17). The volume of resected lung should be minimized to preserve lung function. This is a key reason why pre-operative differentiation between metastatic colorectal adenocarcinoma and primary lung adenocarcinoma requires attention.

CDX2 is expressed specifically in colonic and small intestinal mucosa and has been implicated in disorders involving abnormal intestinal differentiation and neoplasia (18). Among malignant tumors, CDX2 is expressed in colorectal adenocarcinoma, gastric adenocarcinoma, ovarian mucinous carcinoma, transitional carcinoma, pancreatic duct carcinoma and biliary duct carcinoma (10,19,20). Several reports have already compared immunohistochemical analysis for CDX2, TTF-1 and CK7/20 between metastatic colorectal carcinoma and primary lung adenocarcinoma (5,11). These reports identified CDX2 as a sensitive and specific marker of metastatic colorectal carcinoma, findings supported by the present results.

Although various reports have described CDX2 expression in resected specimen, few have examined biopsy specimens. To our knowledge, this is the first study investigating the usefulness of CDX2 in separating metastatic colorectal carcinoma to the lung from primary lung adenocarcinoma using not only resected specimens but also lung biopsy specimens. Tot (6) demonstrated the CK7$^-$/20$^+$ immunophenotype as more specific in predicting the colorectal origin of liver metastasis than CDX2 expression for liver biopsy specimens. In that report, the CK7$^-$/20$^+$ pattern showed a specificity of 98.7% in predicting colorectal primary colorectal localization, which was superior to that of CDX2 expression. In contrast, our results found CDX2 expression to be higher than that of the CK7$^-$/20$^+$ phenotype. Moreover, mean staining score for biopsy specimens of metastatic colorectal adenocarcinoma was significantly higher for CDX2 than for the CK7$^-$/20$^+$ phenotype. These differences in results might be attributable to differences in the metastasized organs.

In the present study, the mean staining score in biopsy specimens was significantly higher for CDX2 than for CK20, and also significantly higher for CDX2 than for CK20 in resected specimens. These results are very important for pathological diagnosis, especially for biopsy specimens, because larger number of staining cells were helpful for diagnosis with small mass of cancer cells such as in biopsy specimen. Furthermore, nuclear expression presented in CDX2 is easier for evaluation than cytoplasmic expression presented in CK20, because cytoplasmic expression is often undistinguishable from non-specific staining of cytoplasm (21).

In this study, only one biopsy specimen of metastatic colorectal carcinoma was negative for CDX2 expression. This specimen was collected by bronchoscopy, and showed faint staining for CDX2 in 75% of tumor cells. This finding is not within the criteria in which signal intensity exceeding moderate was considered positive. The staining score for CK20 in this case was 3. In all other biopsy specimens of metastatic colorectal carcinoma, however, CDX2 demonstrated staining scores exceeding moderate intensity, as in resected specimens. Sensitivity was lower in biopsy specimen than in resected specimens for CK7$^+$/20$^-$. CDX2 provided high sensitivity even with small biopsy specimens obtained by transbroncheal or percutaneous approaches.

Among the metastatic colorectal carcinomas, pre- or intra-operative diagnosis failed to distinguish metastatic from primary adenocarcinoma of the lung in three cases. As a result, lobectomy with dissection of regional lymph nodes was performed. Retrospectively, partial lung resection was feasible in those three cases, as the tumors were metastatic colorectal cancer, located peripherally and were small enough for partial lung resection. Furthermore, expression of CDX2 was positive in both biopsy and resected specimens in those cases. Lobectomy could have been avoided if CDX2 immunostaining had been performed. As indicated in Table II, it is noteworthy that 40.0% of biopsy specimen in metastatic colorectal cancer might receive incorrect diagnosis, if CDX2 immunostaining is not available. Futile lobectomy could be performed instead of partial resection for these cases.

CDX2 expression for BAC in primary lung carcinoma remains controversial. Saad *et al* (5) evaluated CDX2 and CK7/20 immunostaining for 30 mucinous and 32 non-mucinous BACs of the lung, and 30 colorectal adenocarcinomas metastatic to the lung. Mucinous BACs showed positive staining for CDX2, TTF-1, CK7 and CK20 in 0, 17, 100 and 60%, respectively, while non-mucinous BACs were positive in 0, 94, 100 and 0%, respectively. Rossi *et al* (22) reported similar results in mucinous BAC, with positive rates for CDX2, TTF-1, CK7 and CK20 of 0, 30, 100 and 90%, respectively. These results suggest CDX2 as a sensitive and specific marker for distinguishing colorectal adenocarcinoma from BAC. Conversely, Franchi *et al* (23) demonstrated uniform expression of CDX2 in most ethmoid sinus adenocarcinomas, which were also positive for CK20 and goblet cell morphology. Some reports have demonstrated that various neuroendocrine carcinomas and lung adenocarcinomas, particularly those with goblet cell morphology, express CDX2 and CD20 (11,24). The differential diagnosis should thus be integrated with other findings. Fortunately, mucinous and non-mucinous BACs are often distinguishable from metastatic colorectal adenocarcinoma using clinicopathological and radiographic findings (25,26). The typical radiographic appearance of BAC is ground glass opacity, clearly different from the coin lesion of metastatic colorectal cancer. In the present study, 2 out of 21 resected specimens of lung cancer patients showed positive expression for CDX2 in which the staining score was 1. In fact, it was easy to distinguish morphologically from metastatic colorectal cancer in these cases. CK7/20 immunostaining was not useful in these cases, because expression of CK20 as well as CDX2 was positive.

Our ongoing plan is to establish intra-operative distinguishable diagnosis using CDX2 expression. Approaching small pulmonary lesions located near the mediastinum or on the diaphragm by CT-guided percutaneous needle biopsy or transbronchial biopsy is difficult. Thoracoscopic lung biopsy is feasible and intra-operative diagnosis is necessary in such cases. Establishment of a quick evaluation for CDX2 could prove helpful for intra-operative diagnosis, and could avoid futile lobectomy.

In conclusion, CDX2 expression represents a highly sensitive and specific marker of metastatic colorectal carcinoma in both biopsy and resected specimens, and is superior to use of the CK7$^-$/20$^+$ phenotype.

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