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Gastrointestinal metastases from primary lung cancer

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ABSTRACT

The aim of this study was to evaluate gastrointestinal metastases from primary lung cancer confirmed by autopsy. We identified and examined patients with a diagnosis of primary lung cancer over 33 years. We also reviewed patients with gastrointestinal metastases including the stomach, small bowel, and large bowel. This study comprised 470 patients with lung cancer. We detected 56 (11.9%) cases with gastrointestinal metastases. There were 12 (30%) cases with gastrointestinal metastases among 40 cases with large cell carcinoma. The histological type of large cell carcinoma led to a significantly higher rate of gastrointestinal metastases compared with that of non-large cell carcinoma ($P = 0.004$, odds ratio 3.524). Life threatening gastrointestinal metastases occurred in 12 cases and five occurred in large cell carcinoma. Gastrointestinal metastases from primary lung cancer may occur in the clinical course and result in life threatening gastrointestinal metastases, particularly if patients have the histological type of large cell carcinoma.

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1. Introduction

Lung cancer is the most frequent cause of cancer death in the world.¹ Approximately one half of patients with lung cancer have metastatic disease at the time of initial diagnosis. Lung cancer usually spreads from the lungs to lymph nodes, lungs, liver, adrenal glands, brain, and bone.^{2,3} Metastases to the gastrointestinal tract from lung cancer are not uncommon.^{4–11} Physicians should be aware of gastrointestinal tract metastases as the incidence of lung cancer increases, and patients with lung cancer now live longer due to recent improvement in treatment. The aim of this study was to evaluate the frequency of metastases to the gastrointestinal tract (stomach, small bowel, and large bowel) from primary lung cancer confirmed by autopsy at a single institution. In addition, we tried to identify factors that predicted gastrointestinal metastases.

2. Patients and methods

We identified and examined all autopsy reports of patients with a diagnosis of primary lung cancer at the Pathology Section, Graduate School of Medical Science, Kanazawa University over 33 years (from 1972 to 2004). All available reports and some slides were carefully studied and re-examined. We investigated patient information such as age at autopsy, gender, histological type, smoking history, primary site of the tumour, primary tumour size at autopsy, stage at autopsy, and metastatic sites. We classified the histological types according to the World Health Organisation guidelines including the following histological grading: small cell carcinoma, adenocarcinoma, squamous cell carcinoma, adenosquamous cell carcinoma, large cell carcinoma, and others including unclassified types. If patients had more than double primary lung cancer, we adopted the pathological type that caused

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Table 1 – Gastrointestinal metastases from primary lung cancer according to histological types

Histological types	Cases	Cases with metastases	Multiple metastases	Stomach	Small intestine	Large intestine
Small	101	10 (9.9%)	4 (4.0%)	3 (3.0%)	7 (6.9%)	5 (5.0%)
Adeno	191	25 (13.1%)	11 (5.8%)	12 (6.3%)	15 (7.9%)	10 (5.2%)
Squamous	123	8 (6.5%)	7 (5.7%)	5 (4.1%)	6 (4.9%)	5 (4.1%)
Adenosquamous	12	1 (8.3%)	1 (8.3%)	0 (0%)	1 (8.3%)	1 (8.3%)
Large	40	12 (30.0%)	6 (15.0%)	4 (10.0%)	9 (22.5%)	2 (5.0%)
Others	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	470	56 (11.9%)	29 (6.2%)	24 (5.1%)	38 (8.1%)	21 (4.5%)

death. We also reviewed patients with gastrointestinal metastases including stomach, small bowel, and large bowel. We excluded direct invasion from abdominal lymph nodes and from abdominal dissemination. We estimated patients with direct mucous metastases to the gastrointestinal tract. Furthermore, we compared patients to those without gastrointestinal metastases.

We evaluated continuous variants by Student's t-test for comparison of the two groups, and nominal data by the chi-squared test or Fisher's exact test, as appropriate. We considered *P* values less than 0.05 as significant. To identify which independent factors had a significant influence on gastrointestinal metastases, we used the logistic regression modelling technique.

3. Results

There were 525 autopsy cases with a diagnosis of lung cancer. Of those, three underwent local autopsy, 21 were free of tumours because of treatment (surgery, radiotherapy, and chemotherapy), and 31 showed pathological stages of I to IIIA. The remaining 470 cases showed pathological stages of IIIB and IV that caused death. So, this study comprised 470 patients with lung cancer who were autopsied over a period of 33 years. Table 1 shows gastrointestinal metastases according to histological types. We detected 56 (11.9%) cases with gastrointestinal metastases. Multiple metastases occurred in 6.2%. We detected metastases to the stomach in 5.1%, small intestine in 8.1%, and large intestine in 4.5%. There were 12 (30%) cases with gastrointestinal metastases among 40 cases with large cell carcinoma. Table 2 shows gastrointestinal

metastases from primary lung cancer according to other metastatic sites. There were 44 (22.6%) cases with gastrointestinal metastases among 195 cases with adrenal gland metastases, and 34 (29.1%) cases with gastrointestinal metastases among

Table 3 – Characteristics between the two groups

Characteristics	Metastases (n = 56)	Non-metastases (n = 414)	P-value
Age, mean SD	63.9 ± 10.5	67.3 ± 10.9	0.028
Gender			0.531
Male	46 (82.1%)	325 (78.5%)	
Female	10 (17.9%)	89 (21.5%)	
Smoking history			0.293
Smoker	42 (75.0%)	267 (64.5%)	
Non-smoker	10 (17.9%)	109 (26.3)	
Unknown	4 (7.1%)	38 (9.2%)	
Histologic type			0.004
Small	10 (17.9%)	91 (22.0%)	
Adeno	25 (44.6%)	166 (40.1%)	
Squamous	8 (14.3%)	115 (27.8%)	
Adenosquamous	1 (1.8%)	11 (2.7%)	
Large	12 (21.4%)	28 (6.8%)	
Others	0 (0%)	3 (0.7%)	
Primary site (left or right)			0.218
Left	30 (53.6%)	174 (42.0%)	
Right	26 (46.4%)	236 (57.0%)	
Unclassified	0 (0%)	4 (1.0%)	
Primary sites (central or peripheral)			0.608
Central	18 (32.1%)	155 (37.4%)	
Peripheral	35 (62.5%)	245 (59.2%)	
Unclassified	3 (5.4%)	14 (3.4%)	
Primary site lobe			0.291
Upper and middle	31 (55.4%)	184 (44.4%)	
Lower	20 (35.7%)	177 (42.8%)	
Unclassified	5 (8.9%)	53 (12.8%)	
Primary tumour size (cm)			0.073
3.0 or less	14 (25.0%)	102 (24.6%)	
3.1–6.0	10 (17.9%)	119 (28.7%)	
6.1–10.0	13 (23.2%)	82 (19.8%)	
More than 10.0	4 (7.1%)	52 (12.6%)	
Unclassified	15 (26.8%)	59 (14.3%)	

Table 2 – Gastrointestinal metastases from primary lung cancer according to other metastatic sites

Metastatic sites	Cases	Case with gastrointestinal metastases
Stage IIIB and IV	470	56 (11.9%)
Stage IV	438	56 (12.8%)
Lung	296	41 (13.9%)
Liver	227	43 (18.9%)
Adrenal gland	195	44 (22.6%)
Kidney	117	34 (29.1%)
Abdominal lymph node	194	48 (24.7%)

Table 4 – Factors that predict gastrointestinal metastases logistic regression analysis

Factors	P-value	Odds ratio	95% CI
Gender			
Male/female	0.485	1.301	0.622–2.723
Histology			
Large/non-large	0.001	3.524	1.642–7.564
Location			
Left/right	0.140	1.539	0.868–2.729
Location			
Peripheral/central	0.838	1.067	0.572–1.989

117 cases with kidney metastases. Table 3 shows characteristics between cases with and without gastrointestinal metastases. Although there were no significant differences between the two groups in gender, smoking history, primary site of the tumour, primary tumour size at autopsy, there were significant differences in the mean age at autopsy ($P = 0.028$) and histological types ($P = 0.004$). Although gastrointestinal metastases occurred in 30% of large cell carcinoma cases, in other histological types the rate of occurrence was about 10%. So, in multi-variant analysis, we adopted large cell carcinoma versus non-large cell carcinoma. Logistic regression analysis (Table 4) shows that the histological type of large cell carcinoma predicts a significantly higher rate of gastrointestinal metastases than non-large cell carcinoma ($P = 0.004$, odds ratio 3.524). Life threatening gastrointestinal metastases occurred in 12 cases (2.6%) and five occurred with large cell carcinoma (Table 5). Perforation occurred in four cases, bleeding from the tumour in four, ileus in two, and acute appendicitis in two.

4. Discussion

In this study, we detected gastrointestinal metastases in 11.9% of patients with lung cancer who had been autopsied. We detected metastases to the stomach in 5.1%, small intestine in 8.1%, and large intestine in 4.5%. In past reports, gastrointestinal metastasis from lung cancer at autopsy was

not rare. Stenbygaard et al. reported small bowel metastases in 10 (4.6%) out of 218 patients with non-small cell lung cancer who were autopsied.¹² McNeill et al. reported small bowel metastases in 46 (10.7%) and large bowel metastases in 24 (5.7%) out of 431 patients with lung cancer who were autopsied.¹³ In other reports, gastrointestinal metastases (stomach, small intestine, and large intestine) from lung cancer at autopsy occurred in 7.3–12.2%.^{14–17}

McNeil et al. reported that all patients with small bowel metastases had at least one other site of metastatic disease, with an average of 4.8 sites.¹³ Stenbygaard et al. reported that gastrointestinal metastases are usually a part of otherwise widespread metastatic disease.¹² Our study also showed that gastrointestinal metastases occurred in more than 20% of cases who had adrenal gland, kidney, and abdominal lymph node metastases. It does not seem to be justified to examine for metastases to the gastrointestinal tract in the pre-treatment work up. However, physicians should take a gastrointestinal metastases work up into consideration if patients with lung cancer have metastases to abdominal organs.

Our study showed that the histological type of large cell carcinoma in lung cancer was significantly associated with gastrointestinal metastases. Large cell carcinoma accounted for 30% of gastrointestinal metastases. In multivariate analysis, large cell carcinoma predicted a significant 3.5-fold increase in the rate of gastrointestinal metastases compared with other histological types. Past autopsy studies also showed that large cell carcinoma led to gastrointestinal metastases more frequently than the other histological types.^{13–16} Large cell carcinoma may lead to a poorer prognosis and metastasise to many organs. Physicians should take gastrointestinal metastases into consideration if patients with lung cancer have large cell carcinoma.

Most patients with gastrointestinal metastases have no specific symptoms. Physicians do not suspect gastrointestinal metastases unless the patient has symptoms referable to this system. The route by which lung cancer metastasises to the gastrointestinal tract is not well described; however, haematogenous and lymphatic routes are thought to be the most likely. Tumours replace all or part of the bowel wall, resulting in various symptoms.^{4,6,9,13} In past reports, physicians have emphasised the importance of perforation of the small intestine.

Table 5 – Cases with life threatening metastases

	Age, gender	Histological type	Organs causing symptoms	Symptoms caused by metastases
1	58, male	Small	Appendix	Acute appendicitis
2	63, male	Squamous	Jejunum	Perforation and peritonitis
3	51, female	Large	Jejunum	Bleeding from the tumour
4	76, male	Squamous	Jejunum	Perforation
5	80, male	Large	Duodenum	Bleeding from the tumour
6	67, male	Large	Large intestine	Ileus
7	71, male	Squamous	Jejunum	Bleeding from the tumour
8	56, male	Adeno	Appendix	Acute appendicitis
9	72, male	Large	Duodenum	Bleeding from the tumour
10	77, male	Large	Duodenum	Ileus and intussusception
11	73, male	Squamous	Jejunum	Perforation and peritonitis
12	76, female	Adenosquamous	Jejunum	Perforation and peritonitis

tine. Physicians speculated that the chemotherapy-induced necrosis of the metastatic tumour might have led to the gastrointestinal tract perforation.^{18–20} However, many cases with gastrointestinal tract perforation occur without chemotherapy. An obstructing tumour may lead to increased intra-luminal pressure and perforation, or tumour embolisation may lead to gastrointestinal tract ischemia and perforation.¹⁹

In our study, bleeding from the tumour, ileus, and acute appendicitis were important in life threatening gastrointestinal metastases as well as perforation. Large cell carcinoma accounted for five of 12 cases of life threatening gastrointestinal metastases. In past reports, physicians have emphasised the importance of large cell carcinoma leading to perforation.^{4,8,9} Large cell carcinomas may be more significant as life threatening gastrointestinal metastases than other histological types. Although widespread metastases occur in the terminal stage of lung cancer, physicians should recognise that gastrointestinal metastases may occur in the clinical course and result in perforation, obstruction, bleeding, and acute appendicitis, particularly if patients have the histological type of large cell carcinoma.

In conclusion, metastases to the gastrointestinal tract from lung cancer are not uncommon. Gastrointestinal metastases may occur over the clinical course and result in life threatening gastrointestinal metastases, particularly if patients have the histological type of large cell carcinoma.

Conflict of interest statement

None declared.

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