

# Gastrointestinal metastasis of primary lung cancer: An analysis of 366 cases

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**Abstract.** The gastrointestinal (GI) tract is not a common site of metastasis in primary lung cancer. The aim of the present study was to reveal the clinical and prognostic characteristics of gastrointestinal metastases of lung cancer (GMLC). Information on 366 cases of GMLC was collected and factors that affect severe GI complications were analyzed. Univariate and multivariate survival analyses were performed using the Cox proportional hazards model. Of the cases analyzed, the small intestine (59.6%) and colorectum (25.6%) were the two organs where lung cancer was most likely to metastasize in the GI tract. Squamous cell carcinoma (28.5%), adenocarcinoma (27.6%) and large cell carcinoma (20.9%) were the three most common histological types. However, compared with the histological distributions of primary lung cancer, patients with large cell carcinoma exhibited the highest elevated risk of GMLC [relative risk (RR), 4.07;  $P < 0.001$ ] and those with adenocarcinoma exhibited the lowest risk (RR, 0.58;  $P < 0.001$ ). Differences in organ involvement and in histological type led to varying GI complications. It was also indicated that chemotherapy was associated with a decreased risk of hemorrhage ( $P = 0.006$ ), but there was no reduction in the risk of hemorrhage associated with perforation and obstruction ( $P > 0.05$ ). The median overall survival time of GMLC patients was 2.8 months (range, 0-108 months). The survival analyses revealed that perforation and extra-GI metastasis were negative prognostic factors but abdominal surgery was identified a

positive prognostic factor. In conclusion, the histological distribution of GMLC differed from that of primary lung cancer. Sufficient and careful patient evaluation, targeted surgeries and systemic therapies for specific patients are able to increase patient survival rate and improve the quality of life.

## Introduction

As a common cancer and the leading cause of cancer-associated mortality, lung cancer has always been universally associated with poor patient prognosis (1). The incidence and mortality rates of lung cancer occupy the first or second position in malignant tumors in China and the United States (2,3). Until 2015, the 5-year total survival rate for lung cancer was  $\leq 20\%$  in developed and developing countries (4). Between 40 and 50% of patients present with distant metastases upon diagnosis with lung cancer have a poor 5-year survival rate of  $< 5\%$  (1). Small cell lung cancer accounts for only 10% of lung cancer but non-small cell lung cancer accounts for  $\sim 90\%$ , including squamous cell carcinoma, adenocarcinoma, large cell carcinoma, adenosquamous carcinoma and sarcomatoid carcinoma (4).

As demonstrated in autopsy studies, lung cancer metastases may be identified in every organ system (4). However, the gastrointestinal (GI) tract is not a common site of metastasis for primary lung cancer when compared with other sites, including bone, brain, liver and adrenal glands (5). Gastrointestinal metastases of lung cancer (GMLC) was caused by hematogenous spread and occurred at the end-stage of lung cancer. The incidence of GMLC was  $< 2\%$  in clinical studies, which was much lower compared with its prevalence identified during autopsies (5-8). In previous studies, GMLC was described primarily in case reports. Systemic survival analyses and association between clinicopathological factors, therapeutic factors and GI complications were seldom discussed. The present study reviewed  $> 130$  studies from the last 50 years and analyzed 366 cases of GMLC to reveal its clinical and prognostic characteristics by univariate and multivariate survival analyses.

## Patients and methods

**Patients.** A total of 33 cases of GMLC from 32 Chinese articles (9-40) and 3 cases from the School of Medicine, Second

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**Key words:** gastrointestinal neoplasm, lung cancer, metastasis, complication, prognosis

Affiliated Hospital of Zhejiang University (Hangzhou, China). The 3 cases were presented to the hospital between 2008 and 2015 were collected in the present study. The Chinese literature was obtained from the VIP Journal Integration Platform (Chongqing, China; <http://lib.cqvip.com/>) published between 1993 and 2013. A total of 95 articles (5,841-133) from the PubMed database from 1961 to 2013 were reviewed, and 330 cases of GMLC were included. In all 366 cases of GMLC assessed, demographic and clinicopathological information was recorded and reviewed, including ethnicity, sex, age, pathology, initial lung cancer stage and therapy, interval between lung cancer diagnosis and identification of GMLC, clinical presentation, location, diameter and number of gross metastases, other metastatic site locations at the time of GMLC, GI surgeries, survival information and immunohistochemical information.

**Disease classification.** The histological classification of primary lung cancer was performed according to the 2004 World Health Organization classification system of lung tumors (134). The Tumor-Node-Metastasis staging was performed according to the 7th edition of the 2010 American Joint Committee on Cancer Staging manual (135). The histological distribution data of primary lung cancer was acquired from the International Lung Cancer Consortium (136).

**Statistical analysis.**  $\chi^2$  test and Fisher's exact test were used to compare the incidence rates of different groups. Overall survival (OS) time was measured from the date of GMLC diagnosis to the date of mortality. This end point was computed using the Kaplan-Meier product limit method and the groups were compared using the log-rank test. Univariate and multivariate analyses of OS time were performed using Cox proportional hazards model. Only the variables with  $P < 0.25$  in the univariate analysis were included in the multivariate analysis model and, the backward sequencing method was used (137). The variables in the univariate and multivariate analyses included region (Asia vs. The Americas vs. Europe), histological type of lung cancer (squamous cell carcinoma vs. adenocarcinoma vs. large cell carcinoma vs. small cell lung cancer vs. adenosquamous carcinoma vs. sarcomatoid carcinoma), time (synchronous vs. metachronous), number (solitary vs. multiple), the organ where metastasis has been identified (esophagus vs. stomach vs. small intestine vs. colorectum vs. multiple organs), extra-GI metastasis (yes vs. no), perforation (yes vs. no), surgery of primary lung cancer (yes vs. no) and abdominal surgery (yes vs. no). Metastasis was considered synchronous if the interval of diagnosis between lung cancer and GI metastasis was  $< 1$  month. Metastasis was considered metachronous if the interval was  $> 1$  month.  $P < 0.05$  (two-sided) was considered statistically significant. The statistical analyses were performed using SPSS Statistics software (version 19.0; IBM Corp., Armonk, NY, USA).

## Results

**Patient and tumor characteristics.** As presented in Table I, the majority of the patients were from Asia (62.3%) and  $> 80\%$  of them were male. The three countries with the greatest

number of patients analyzed were Japan (139 cases), China (65 cases) and the United States (64 cases). The median age was 63 years (range, 31-92 years). The small intestine was the most frequently involved organ (59.6%) in the GI tract, and the colorectum ranked second (25.6%). Of the small intestine cases of GMLC, where the site of metastasis was specific, the majority of cases (63.4%) occurred in the jejunum. GI perforation (42.0%), hemorrhage (24.6%) and obstruction (20.4%) were the three most common complications. Synchronous and metachronous metastases were similarly probable (46.2% vs. 53.8%). The median time of metachronous patients from primary cancer diagnosis to GI metastasis was 6 months (range, 1-108 months). Solitary GMLCs were present in an increased number of patients compared with multiple metastases (69.4% vs. 30.6%). Furthermore, extra-GI metastases were present in the majority of patients (70.5%). The liver, brain, bone and adrenal gland were the four most prevalent sites of metastasis (data not shown), which was expected. In total,  $\sim 1/3$  of the patients (33.3%) underwent surgical resection to remove the primary cancer and surgeries were performed in the GI tract in 75.8% of patients. Partial gastrectomy and enterectomy were the main types of abdominal resections performed (86.5%). These statistics are based solely upon cases where data was available.

Squamous cell carcinoma (28.5%), adenocarcinoma (27.6%) and large cell carcinoma (20.9%) were the three most common histological types of GMLC. When the histological distributions between GMLC and primary lung cancer were compared, it was observed that there was an increased frequency of GMLC of large cell carcinoma, small cell lung cancer and squamous cell carcinoma compared with GMLC of adenocarcinoma and other types of cancer ( $P < 0.01$ ; Table II).

**Complications.** The association between involved organs, histological type and GI complications is presented in Table III. Perforation of the small intestine (63.7%) occurred more frequently compared with perforation of stomach and colorectum ( $P < 0.001$ ). The organs at risk of hemorrhage, from most to least common, were the stomach, colorectum and small intestine ( $P < 0.05$  in comparisons between two organs). No obstruction occurred in all 36 patients with gastric metastasis, and the incidence of obstruction was much lower compared with colorectum ( $P = 0.003$ ) or small intestine ( $P = 0.003$ ). In all the histological types of lung cancer analyzed, sarcomatoid carcinoma exhibited the lowest likelihood of perforation and the greatest likelihood of hemorrhage ( $P < 0.05$ ). The risks of perforation of squamous cell carcinoma and small cell lung cancer were increased compared with the risks associated with adenocarcinoma ( $P < 0.05$ ). The risks of hemorrhage of squamous cell carcinoma and small cell lung cancer were lower compared with the risks for large cell carcinoma ( $P < 0.05$ ). No statistically significant difference was observed between two other organs or histological types ( $P > 0.05$ ). No significant association was identified between histological type and GI obstruction ( $P > 0.05$ ).

The association between GI complications and chemotherapy is indicated in Table IV. In total,  $\sim 1/4$  (26.5%, 97/366) of the cases analyzed contained patient data of chemotherapy. Hemorrhage was more common in patients with GMLC who received no chemotherapy ( $P = 0.006$ ). There was no significant

Table I. Patient, tumor and treatment characteristics of 366 cases of gastrointestinal metastases of lung cancer.

A, Demographic factors

Characteristics	Patients, n	Percentage
Region		
Asia	228	62.3
America	67	18.3
Europe	71	19.4
Sex (not reported in 114 cases)		
Male	208	82.5
Female	44	17.5
Age, years (not reported in 13 cases)		
≤54	54	15.3
55-64	133	37.7
65-74	116	32.9
≥75	50	14.2

B, Tumor factors

Characteristics	Patients, n	Percentage
Involved organ (not reported in 10 cases)		
Esophagus	1	0.3
Stomach	40	11.2
Small intestine <sup>a</sup>	212	59.6
Colorectum <sup>b</sup>	91	25.6
Multiple organs	12	3.4
Complications (not reported in 9 cases)		
Perforation	150	42.0
Hemorrhage	88	24.6
Obstruction	73	20.4
Histological type (not reported in 22 cases)		
Small cell lung cancer	46	13.4
Squamous cell carcinoma	98	28.5
Adenocarcinoma	95	27.6
Large cell carcinoma	72	20.9
Sarcomatoid carcinoma	15	4.4
Adenosquamous carcinoma	5	1.5
Other types	13	3.8
Synchronous or metachronous metastasis (not reported in 208 cases)		
Synchronous	73	46.2
Metachronous	85	53.8
Number of GI metastasis (not reported in 268 cases)		
Solitary	68	69.4
Multiple	30	30.6
Extra-GI metastasis (not reported in 220 cases)		
No	43	29.5
Yes	103	70.5

Table I. Continued.

C, Treatment factors

Treatment	Patients, n	Percentage
Lung cancer surgery (not reported in 234 cases)		
No	88	66.7
Yes	44	33.3
Abdominal surgery (not reported in 180 cases)		
No	45	24.2
Yes <sup>c</sup>	141	75.8

<sup>a</sup>Metastasis in the small intestine: Duodenum, 19 cases; jejunum, 104 cases; ileum, 41 cases; not otherwise specified, 60 cases. <sup>b</sup>Metastasis in the colorectum: Appendix and ileocecus, 10 cases; colon, 78 cases; rectum, 5 cases. <sup>c</sup>Abdominal surgery: Partial gastrectomy and enterectomy, 122 cases; gastrointestinal fistula, bypass surgery and repair of the perforation, 7 cases; not otherwise specified, 12 cases.

difference in the risks of perforation and obstruction between patients who had received and had not received chemotherapy ( $P>0.05$ ).

**Immunohistochemical analysis.** In total, there were 35 cases for which immunohistochemical data were available. Information from this limited number of cases illustrated that a typical immunohistochemical staining of GMLC was positive for thyroid transcription factor-1 (TTF-1; 84.4%, 27/32) and cytokeratin 7 (CK7, 96.6%, 28/29), but negative for CK20 (96.6%, 28/29) and caudal-related homeodomain transcription 2 (CDX2, 100%, 23/23).

**Survival estimates.** Survival rate data was available for 268 of the 366 patients studied. A total of 246 patients had succumbed to disease by the end of the duration of the study, and the data of the other 22 patients were censored data. The median OS time was 2.8 months (range, 0-108 months, Fig. 1A). Univariate Cox analysis (Table V) revealed that patients from the Americas exhibited poorer prognoses compared with patients from Asia ( $P<0.001$ ). It was also indicated that the survival rates for patients with small cell lung cancer and sarcomatoid carcinoma were increased compared with patients with squamous cell carcinoma (unadjusted hazard ratios (HRs), 0.62 ( $P=0.03$ ) and 0.34 ( $P=0.005$ ), respectively). The other prognostic factors, which indicate a poor survival outcome, included synchronous metastasis, perforation of GMLC, extra-GI metastasis and lack of abdominal surgery ( $P<0.05$ ). Patients with multiple metastases exhibited marginal poorer prognoses compared with patients with solitary metastases ( $P=0.06$ ). There were no statistical significance between overall survival rate and other factors, (sex, age, organs of GI metastasis, and surgery on the primary lung cancer) ( $P>0.05$ ).

In multivariate analysis, following adjustment for prognostic factors, the region where the patients were from,

Table II. Comparison of the histological distributions between gastrointestinal metastases of lung cancer and primary lung cancer.

Histological type	GMLC, %	Primary lung cancer, % <sup>a</sup>	$\chi^2$ -value	P-value	RR (95% CI)
Small cell lung cancer	13.37	9.28	6.61	0.01	1.44 (1.10-1.90)
Squamous cell carcinoma	28.49	20.48	13.08	<0.001	1.39 (1.17-1.65)
Adenocarcinoma	27.62	47.34	52.31	<0.001	0.58 (0.49-0.69)
Large cell carcinoma	20.93	5.15	158.81	<0.001	4.07 (3.27-5.06)
Other types	9.59	17.76	15.43	<0.001	0.54 (0.39-0.75)

<sup>a</sup>Data from the International Lung Cancer Consortium (133). GMLC, gastrointestinal metastases of lung cancer; RR, relative risk; 95% CI, 95% confidence interval.

Table III. Association between GI complications, organ and histological types of gastrointestinal metastases of lung cancer.

Organ <sup>a</sup> /histological type <sup>b</sup>	Perforation, n (%)		Hemorrhage, n (%)		Obstruction, n (%)		Total
	Yes	No	Yes	No	Yes	No	
Esophagus	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	1
Stomach	5 (13.9)	31 (86.1)	19 (52.8)	17 (47.2)	0 (0.0)	36 (100.0)	36
Small intestine	135 (63.7)	77 (36.3)	33 (15.6)	179 (84.4)	43 (20.3)	169 (79.7)	212
Colorectum	10 (11.5)	77 (88.5)	28 (32.2)	59 (67.8)	18 (20.7)	69 (79.3)	87
Multiple organs	0 (0.0)	12 (100.0)	7 (58.3)	5 (41.7)	4 (33.3)	8 (66.7)	12
Unreported organ	0 (0.0)	9 (100.0)	1 (11.1)	8 (88.9)	8 (88.9)	1 (11.1)	9
Squamous cell carcinoma	49 (50.5)	48 (49.5)	20 (20.6)	77 (79.4)	20 (20.6)	77 (79.4)	97
Adenocarcinoma	33 (35.5)	60 (64.5)	23 (24.7)	70 (75.3)	16 (17.2)	77 (82.8)	93
Large cell carcinoma	26 (36.6)	45 (63.4)	26 (36.6)	45 (63.4)	18 (25.4)	53 (74.6)	71
Small cell lung cancer	24 (53.3)	21 (46.7)	8 (17.8)	37 (82.2)	6 (13.3)	39 (86.7)	45
Adenosquamous carcinoma	3 (60.0)	2 (40.0)	0 (0.0)	5 (100.0)	2 (40.0)	3 (60.0)	5
Sarcomatoid carcinoma	0 (0.0)	15 (100.0)	8 (53.3)	7 (46.7)	5 (33.3)	10 (66.7)	15
Other types or unreported	15 (48.4)	16 (51.6)	3 (9.7)	28 (90.3)	6 (19.4)	25 (80.6)	31
Total	150 (42.0)	207 (58.0)	88 (24.6)	269 (75.4)	73 (20.4)	284 (79.6)	357 <sup>c</sup>

<sup>a</sup>Perforation of the small intestine was more likely to occur compared with perforation of the stomach and colorectum ( $P<0.001$ ). The prevalence of hemorrhage descended in order of the stomach, colorectum and small intestine ( $P<0.05$ ). Obstruction of the stomach was much less than that of other organs ( $P=0.003$ ). <sup>b</sup>Perforation of SARC was the least in all the types ( $P<0.05$ ). Perforations of squamous cell carcinoma and small cell lung cancer were more likely compared with adenocarcinoma ( $P<0.05$ ). Hemorrhage of sarcomatoid carcinoma was more likely to happen compared with hemorrhage of squamous cell carcinoma ( $P=0.016$ ), adenocarcinoma ( $P=0.049$ ) and small cell lung cancer ( $P=0.018$ ). Hemorrhage of large cell carcinoma was more likely to happen compared with hemorrhage of squamous cell carcinoma ( $P=0.022$ ) and small cell lung cancer ( $P=0.030$ ). No significant association was identified between histological type and gastrointestinal obstruction ( $P>0.05$ ). <sup>c</sup>The complications in 9 cases were not reported.

histological type, GI perforation, extra-GI metastasis and abdominal surgery remained prognostic factors for survival rate. Other factors were not significant (Table V; Fig. 1B-D).

## Discussion

As the digestive tract remains a rare site of metastasis of primary lung cancer, GMLC was previously described primarily in case reports (8). The clinical incidence of GMLC was <2% in patients with primary lung cancer and >10% in autopsy-associated studies (5-8). The majority of GMLC cases occurred at the end-stage of lung cancer, and misdiagnosis and missed diagnosis occurred frequently (138). In the present study, the sex and age of the patients with GMLC was similar

with cases reported in previous studies with small sample sizes (7,8). In the present study, the majority of the patients were elderly men.

The intestines, particularly the small intestine, were the main organs involved in GMLC, owing to their abundant blood supply. There were certain patients that presented with metastases in multiple GI organs, due to the lethality of the first involved organ and the involvement of additional GI organs. On account of the significant difference between the GMLC incidences from clinical and autopsy-associated studies, the majority of the patients with GMLC were subclinical with minimal or no symptoms. The symptoms of GMLC always appeared alongside clinical complications, including GI perforation, hemorrhage and obstruction. The incidence of severe



Table IV. Association between gastrointestinal complications and chemotherapy.

Complications	Chemotherapy, n (%)		P-value
	Yes	No	
Perforation			0.405
Yes	7 (19.4)	8 (13.1)	
No	29 (80.6)	53 (86.9)	
Hemorrhage			0.006 <sup>a</sup>
Yes	7 (19.4)	29 (47.5)	
No	29 (80.6)	32 (52.5)	
Obstruction			0.448
Yes	7 (19.4)	16 (26.2)	
No	29 (80.6)	45 (73.8)	
Total <sup>b</sup>	36	61	

<sup>a</sup>Hemorrhages were less likely in patients who had received chemotherapy compared with patients who have not received chemotherapy (P=0.006). <sup>b</sup>Available data, 97 cases.

complications differed between organs due to differences in individual anatomical structures of the organs. Previous studies (129,132,139) reported that the incidence of perforation in the small intestine was markedly increased compared with the incidence in the colorectum. The present study indicated similar findings. The probability and quantity of hemorrhage may depend on the incubation time of GMLC and the inner diameter of the involved organ. Metastases are able to grow for a longer period of time in the large gastric cavity, leading to more bleeding in the stomach compared with other organs. In the present study, no obstruction was identified in the stomach, and it was hypothesized that this may be associated with the wider inner diameter of the stomach compared with other GI organs.

In the present study, >3/4 of GMLC cases analyzed were squamous cell carcinoma, adenocarcinoma and large cell carcinoma. The high incidence of squamous cell carcinoma and adenocarcinoma was due to their high prevalence in primary lung cancer. The highest risk of GI metastasis was identified in large cell carcinoma, whereas the lowest risk of all the major histological types of GI metastasis was identified in adenocarcinoma. This finding is partly consistent with the autopsy data from Antler *et al* (6). On the other hand, different histological types of lung cancer exhibit different GI complications. A previous study on metastasis in the small intestine indicated that large cell carcinoma is associated with the greatest likelihood of perforation, whereas adenocarcinoma is most closely associated with the lowest rate of perforation in all the histological types (69). The present study partly confirmed this result and suggested that sarcomatoid carcinoma was associated with a lower rate of perforation and a greater rate of hemorrhages of the GI tract (Table III). This may be due to the relatively compact structure of sarcomatoid carcinoma with its differentiation of connective tissues. A number of previous studies (112,140) have suggested that GI perforation may be caused by chemotherapy, but other studies (106,141) indicated

that GI perforation is brought about mainly by ischemia and necrosis of metastases, obstruction and high pressure in the GI cavity. In the present study, in which only a quarter of the total studies contained data on GI perforation, patients with or without chemotherapy experience statistically similar incidences of perforation and obstruction. The risk of hemorrhage may be decreased by chemotherapy, which may lead to tumor atrophy and ischemia.

The diagnosis of GMLC is not easy owing to its non-specific symptoms, although its complications are well known. When patients with lung cancer complain of potential GMLC symptoms (abdominal pain, nausea, vomiting, anemia, hematochezia, melena, constipation or other changes in bowel habits), particularly those that cannot be explained by primary lung cancer or undergoing chemotherapy or radiotherapy treatment, GMLC should be considered. As part of systemic metastases, GMLC is caused by hematogenous dissemination (8). In previous studies (88,141), 42.9-100.0% of the patients with GMLC had extra-GI metastasis, and this ratio was 70.5% in the present study. Therefore, it is necessary for patients with GMLC to undergo sufficient evaluations prior to initiation of treatment (142). On the other hand, it was reported that GMLC was more common in patients with metastases in adrenal glands, kidneys and celiac lymph nodes compared with in patients with other type of metastases (5). However, this finding was not supported by the data in the present study.

Laboratory examination, endoscopy, gastroenterography, computed tomography (CT) and positron-emission tomography (PET)-CT may aid the diagnosis of GMLC (120). In a study by Kim *et al* (141) on the signs of GMLC in CT, it was reported that positive signs could be identified in 93% of patients, including localized GI wall thickening, the presence of a mass in the GI cavity, regional glandular enlargement, indigitation and perforation. PET-CT was able to assist the detection of subclinical GMLC and systemic evaluation of extra-GI metastases (133,143,144). Pathology was a critical factor in diagnosis. The pathology of primary lung cancer should be reviewed and compared with that of GMLC. In the present study, in the majority of cases of GMLC considered, there was positive immunohistochemical staining for thyroid transcription factor 1 and cytokeratin-7 but negative staining for CK20 and CDX2, which was consistent with a previous study (8).

As the end-stage of lung cancer, GMLC was always associated with a poor prognosis (69). In the present study, the median OS time was 2.8 months and 53.4% of the patients succumbed to disease within 3 months of diagnosis of GMLC. Only 9.0% (24/268) of patients were reported to survive for >1 year and 2 patients (0.7%) with large cell carcinoma survived >7 years. Patients in the dataset analyzed by the present study generally exhibited longer overall survival times compared with patients assessed by Garwood *et al* (69). The patients that Garwood *et al* (69) studied are part of the present dataset. All patients in the study by Garwood *et al* (69) exhibited perforation of the small intestine, which appears to be associated with shorter OS (based on comparisons between the results of the present study and Garwood *et al*) (69). In the present study, there were five factors, including region, histological type, GI perforation, extra-GI metastasis and surgical resection, which formed the final components included in the multivariate Cox

Table V. Univariate and multivariate Cox regression analyses of variables that may affect overall survival of patients with gastrointestinal metastases of lung cancer.

A, Univariate analysis			
Variable	Overall survival		P-value
	HR	95% CI	
Demographic factors			
Region			
Asia	1.00		
America	3.27	2.32-4.59	<0.001
Europe	1.27	0.92-1.76	0.148
Sex			
Male	1.00		
Female	0.81	0.53-1.25	0.351
Age, years			
≤54	1.00		
55-64	0.86	0.60-1.25	0.430
65-74	0.96	0.66-1.42	0.849
≥75	1.27	0.78-2.07	0.339
Histological type			
Squamous cell carcinoma	1.00		
Adenocarcinoma	0.78	0.55-1.10	0.150
Large cell carcinoma	0.75	0.52-1.08	0.123
Small cell lung cancer	0.62	0.41-0.96	0.031
Adenosquamous carcinoma	2.01	0.73-5.56	0.177
Sarcomatoid carcinoma	0.34	0.16-0.72	0.005
Time of GI metastasis			
Synchronous	1.00		
Metachronous	0.62	0.43-0.90	0.011
Number of GI metastasis			
Solitary	1.00		
Multiple	1.64	0.98-2.76	0.064
GI metastasis organ			
Esophagus <sup>a</sup>	N/A		
Stomach	1.00		
Small intestine	1.19	0.82-1.73	0.367
Colorectal	0.78	0.48-1.28	0.321
Multiple organs	0.95	0.44-2.05	0.886
Perforation			
No	1.00		
Yes	2.13	1.61-2.78	<0.001
Extra-GI metastasis			
No	1.00		
Yes	2.94	1.85-4.76	<0.001
Treatment factors			
Surgical resection of the primary cancer			
No	1.00		
Yes	0.68	0.43-1.04	0.078
Abdominal surgery			
No	1.00		
Yes	0.53	0.35-0.78	0.001

Table V. Continued.

B, Multivariate analysis

Variable	Overall survival		P-value
	Adjusted HR	95% CI	
Demographic factors			
Region			
Asia	1.00		
America	3.91	2.41-6.34	<0.001
Tumor factors			
Histological type			
Squamous cell carcinoma	1.00		
Adenosquamous carcinoma	5.57	1.84-16.83	0.002
Perforation			
No	1.00		
Yes	2.00	1.26-3.17	0.003
Extra-GI metastasis			
No	1.00		
Yes	1.92	1.12-3.29	0.018
Treatment factors			
Surgical resection			
No	1.00		
Yes	0.47	0.28-0.81	0.006
Other factors			NS

<sup>a</sup>Esophageal metastasis in 1 case. HR, hazard ratio; CI, confidence interval; GI, gastrointestinal; NS, not significant.

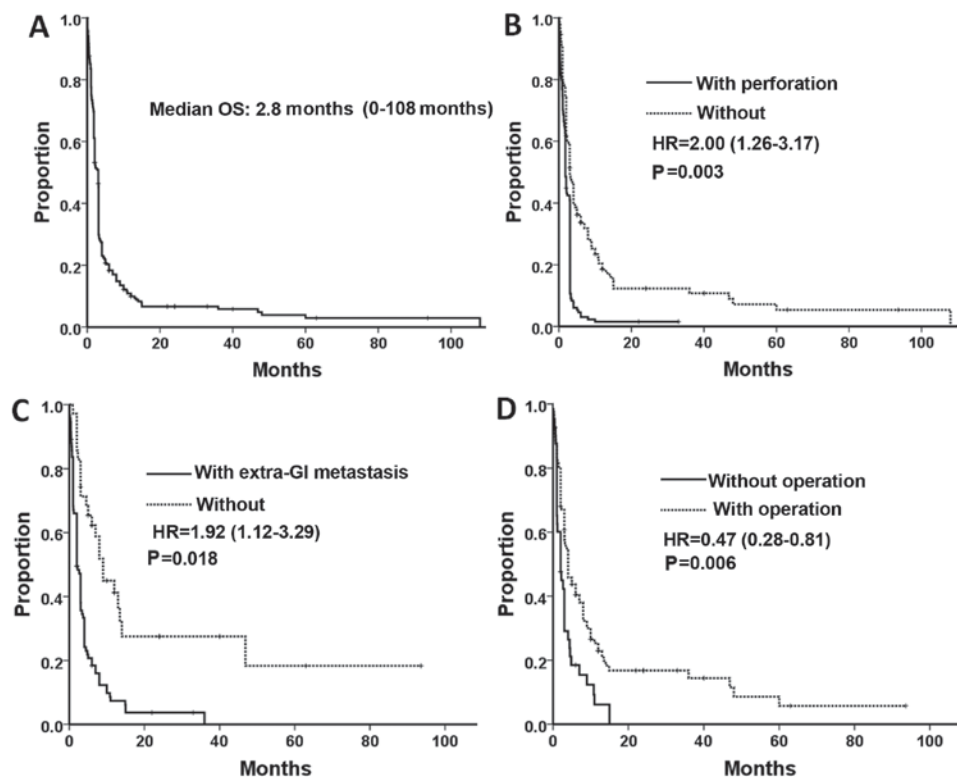


Figure 1. (A) OS of patients with gastrointestinal metastases of lung cancer. Variables affecting OS in multivariate Cox regression analysis: (B) Perforation, (C) extra-GI metastasis and (D) abdominal surgery. GI, gastrointestinal; HR, hazard ration; OS, overall survival.

model. Although it was indicated that the survival times for Asian patients were longer compared with American patients, region was not a useful factor in determining survival times as American studies assessed in the present study were undertaken on average ~20 years earlier compared with the studies from Asia. With an adjusted hazard ratio of 5.57 ( $P=0.002$ ), it was indicated that patients with adenosquamous carcinoma had a significantly poorer prognosis compared with patients with squamous cell carcinoma based on multivariate Cox analysis. However, only four cases of adenosquamous carcinoma were available in the present survival analysis, so this result is of limited value. Perforation of GMLC and extra-GI metastasis were indicated to be negative prognostic factors, but abdominal surgery appeared to be a positive prognostic factor. However, the selective bias of the patients, particularly in treatment choice, must be considered in the present retrospective study. The patients with less severe general conditions were more likely to undergo surgery than those in critical conditions.

The present study revealed that, due to the increasing incidence of lung cancer, as well as the ability of modern medicine to prolong the life of lung cancer patients, GMLC is no longer rare. On the basis of the assessment performed in the present study, the histological distribution of GMLC was different from that of primary lung cancer. Early detection, diagnosis and treatment are central to improving patient prognosis. Sufficient and careful evaluations, targeted surgeries and systemic therapies for specific patients following discussion between multi-disciplinary teams of medics are able to improve the survival rate and quality of life of patients (138,145). The main purpose of surgery is to relieve symptoms while causing the least trauma possible to the patient. Data from the present study revealed that >30% of the patients had multiple metastases in their GI tract, therefore careful investigations during the surgery are required to avoid subclinical metastases being missed.

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