



Gastric Metastasis of Primary Lung Cancer: Case Report and Systematic Review With Pooled Analysis

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Background: Gastric metastasis from lung cancer (GMLC) is a rare occurrence. The clinicopathological characteristics, outcomes, and prognostic factors remain largely elusive.

Methods: We conducted a systematic review on case reports and case series of GMLC by scanning MEDLINE, Embase, and ISI Web of Knowledge. Data involving the clinicopathological features, treatment, and outcomes were extracted and analyzed. Survival analysis was performed using Kaplan–Meier method. The Cox proportional hazards regression model was used to identify potential prognostic factors associated with survival. Furthermore, a case of metastatic gastric adenocarcinoma of pulmonary origin with epidermal growth factor receptor (EGFR) L858R+T790M mutation was also described and included.

Results: Seventy-eight records involving 114 cases (including ours) were finally included. The median age on admission was 65 years with a male predominance of 79.8%. Lung adenocarcinoma (42.1%), located in the right upper lobe (30.3%), was the most frequent primary tumor. Bleeding (36.7%) and abdominal pain (35.8%) were the two most common symptoms. Endoscopically, gastric lesions were typically presented as elevated lesions with or without volcano-like ulceration, or ulcerative lesions, mostly involving the gastric corpus. The median overall survival time and survival time after diagnosis of metastatic cancer were 11 months [95% confidence interval (CI): 7–14] and 4.5 months (95% CI: 3–9), respectively. The survival analyses revealed that surgical interventions (including lung surgery and/or abdominal surgery) and systemic therapy (including chemotherapy, radiotherapy, and/or targeted therapy) seemed to be positive prognostic factors for both overall survival and survival after diagnosis of metastatic cancer.

Conclusions: Clinicians should be alerted to the occurrence of gastric metastasis in lung cancer patients. Comprehensive evaluation and appropriate treatment for specific patients may improve the survival rate of GMLC patients.

Keywords: gastric metastasis, primary lung cancer, EGFR mutation, clinicopathological features, prognosis

INTRODUCTION

Lung cancer is a highly malignant tumor. About half of patients present metastasis at the time of diagnosis (1). The most common sites of extrapulmonary metastases are the liver, bone, brain, and adrenal glands (1). In very rare circumstances, lung cancer may metastasize to the stomach, the incidence of which has been reported to range from 0.19% to 5.1%, with a higher rate reaching 2%–14% in autopsy studies (2). Because of advances in the diagnosis and treatment of cancer, patients' survival has gradually prolonged, making the encounter with gastric metastasis more frequent. However, only limited data have been published focusing on gastric metastasis from lung cancer (GMLC), and its clinical features and treatment strategy remained poorly understood. Especially when targeted therapies including epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have been proven to induce a remarkable response in advanced non-small cell lung cancer (NSCLC) with EGFR-activating mutations (3), the effect of targeted therapies on GMLC patients has been barely reported. In the present study, we describe an unusual case of gastric metastasis from primary lung adenocarcinoma that was treated with the third-generation EGFR-TKI osimertinib and conduct a systematic review of previous case reports to study the clinical features, outcomes, and prognostic factors of this rare entity.

CASE REPORT

A 72-year-old man with a long-term smoking habit (one pack of cigarettes per day for 30 years) was referred to our hospital in April 2021 due to a 1-month history of recurrent fever and discovery of a right lung mass, which showed no change after antibiotic treatment.

His past medical history was significant for hypertension and diabetes mellitus for 5 years, and his medications were nifedipine gastrointestinal therapeutic system (GITS) 30 mg once daily, metformin 50 mg once daily, and acarbose 50 mg three times a day.

On admission, a computed tomography (CT) scan of the chest revealed an irregular mass measuring 3.5 cm × 2.7 cm in

the right upper lobe (RUL), with mediastinal mildly enlarged lymph nodes (**Figure 1A**). Additional workup using abdominal CT detected a gastric fundal mass that measured 1.9 cm (**Figure 2A**). The patient denied any abdominal symptoms. Further gastroscopy demonstrated an ulcerated tumor 2.0 cm × 2.0 cm in size located in the gastric fundus (**Figure 2C**).

A CT-guided lung mass biopsy and pathological examination revealed poorly differentiated tumor cells (**Figure 3A**). The immunohistochemical stains showed that the tumor was thyroid transcription factor-1 (TTF-1) (+), CK7 (+), p63 (±), Napsin A (focally+), Ki67 (25%+), CK20 (-), CD56 (-), CK5/6 (-), and p40 (-), which is most consistent with lung adenocarcinoma (**Figure 3B**). Meantime, a gastric mass biopsy revealed poorly differentiated carcinoma with a similar morphological feature to the tumor from the pulmonary biopsy (**Figure 3C**). The immunohistochemical profile of the gastric sample showed TTF-1 (focally+), vimentin (+), Ki67 (40%+), CK7 (-), CK20 (-), Napsin A (-), p40 (-), CEA (-), villin (-), HER2 (-), and MOC31 (-) (**Figure 3D**). Furthermore, genetic studies demonstrated the same EGFR L858R+T790M mutation in both the gastric and pulmonary lesions, while the pulmonary sample also harbored a programmed cell death ligand 1 (PD-L1) Tumor Proportion Score (TPS) of 90%. All these findings supported the metastatic gastric adenocarcinoma of pulmonary origin. Additional brain CT and bone scan identified no abnormalities. The patient was diagnosed with poorly differentiated primary lung adenocarcinoma with gastric metastases (cT2N1M1 stage IV). Hence, oral treatment with osimertinib (80 mg, once a day) was started on May 13, 2021.

After 3 months of treatment (August 2021), a follow-up chest CT scan revealed a reduction in the RUL mass (with the maximum cross section measuring 2.6 cm × 2.2 cm, **Figure 1B**). The gastric mass in the fundus exhibited complete regression in the CT scan (**Figure 2B**) and gastroscopy examination (**Figure 2D**). Meanwhile, an abdominal CT detected a nodule measuring 2.9 cm × 2.0 cm in the right adrenal gland, considered as a new metastatic lesion (**Figure 4A**). The patient's primary lesion and gastric metastatic lesion were reduced, and a new adrenal gland metastasis was observed. According to RECIST 1.1 criteria (4), the efficacy was evaluated as progressive disease (PD). However, considering the effective treatment of primary

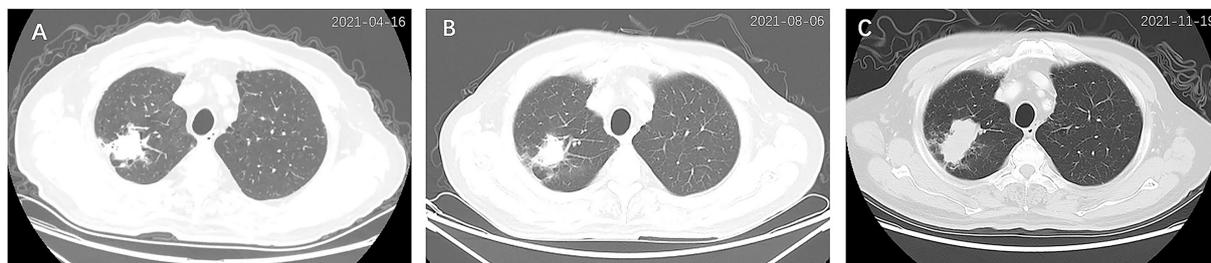


FIGURE 1 | Chest computed tomography (CT) scan of the primary lung cancer at diagnosis (**A**), 3 months after treatment (**B**), and 6 months after treatment (**C**). An irregular mass (3.5 cm × 2.7 cm) was detected in the right upper lobe (**A**), which shrunk (2.6 cm × 2.2 cm) after 3 months of treatment (**B**) but enlarged (5.2 cm × 2.6 cm) after 6 months of treatment (**C**).

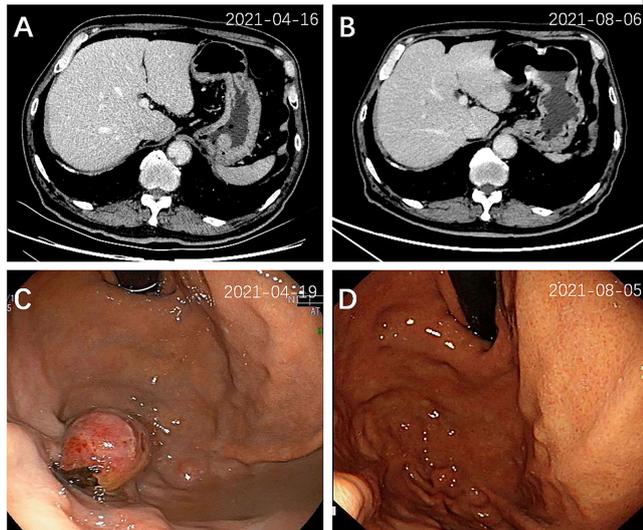


FIGURE 2 | Abdominal CT scan and endoscopic view of the gastric tumor at diagnosis (**A, C**) and 3 months after treatment (**B, D**). A mass (2.0 cm × 2.0 cm) located in the gastric fundus was detected by CT (**A**) and gastroscopy (**C**), which disappeared 3 months after treatment (**B, D**).

lesions and gastric lesions, the patient chose to continue with osimertinib treatment. Unfortunately, 6 months after the initial diagnosis, the patient showed further disease progression with the enlargement of the primary lung mass (**Figure 1C**) and multiple metastatic lesions involving the bilateral adrenal glands and abdominal cavity (**Figures 4B, C**). The patient was recommended anti-PD-1 immunotherapy, multitargeting TKI (anlotinib), or chemotherapy. After communicating with the patient and his family, the patient opted for anlotinib treatment.

At the time of writing, the patient is alive 8 months after the initial diagnosis of lung cancer.

SYSTEMATIC REVIEW

Methods

Search Strategy

A systematic review of the case reports was conducted to examine the clinical features and outcomes of GMLC. Literature search was performed by scanning MEDLINE (through PubMed), Embase, and ISI Web of Knowledge for relevant articles published until September 2021. The search terms included lung cancer-related and gastric metastasis-related index words. The specific search strategy is presented in the **Supplementary Material**. Reference lists of the relevant articles and reviews were carefully scanned to identify other eligible cases.

Study Selection

Two independent investigators (DT and JL) screened and included the relevant articles if they fulfilled all of the following criteria: 1) case reports or case series including the terms for gastric metastasis from primary lung cancer; 2) published in English or Chinese; and 3) provision of sufficient data on the demographic and/or clinicopathologic outcomes of GMLC cases. Articles were excluded if they were as follows: 1) reviews, meta-analysis, conference abstracts, or comment papers and 2) animal studies. Disparities were resolved with a third investigator (YG).

Data Extraction

Data such as title, author, publication year, age, gender, smoking habit, primary lung cancer site, pathological histology, interval time between the lung cancer diagnosis and gastric metastasis

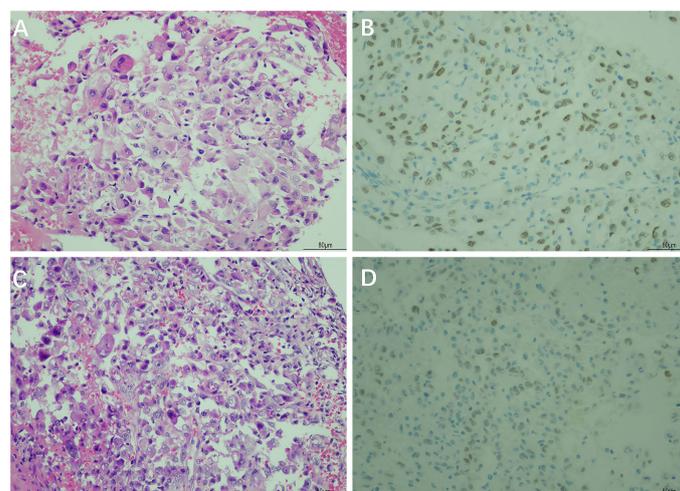


FIGURE 3 | Hematoxylin and eosin (H&E) and immunohistochemical staining of the primary lung cancer and gastric tumor biopsy. H&E staining showed poorly differentiated adenocarcinoma in the primary lung cancer tissue (**A**) and gastric tumor tissue (**C**). Immunohistochemical staining showed a positive reaction for thyroid transcription factor-1 (TTF-1) in the primary lung cancer tissue (**B**) and gastric tumor tissue (**D**) (magnification, ×200).

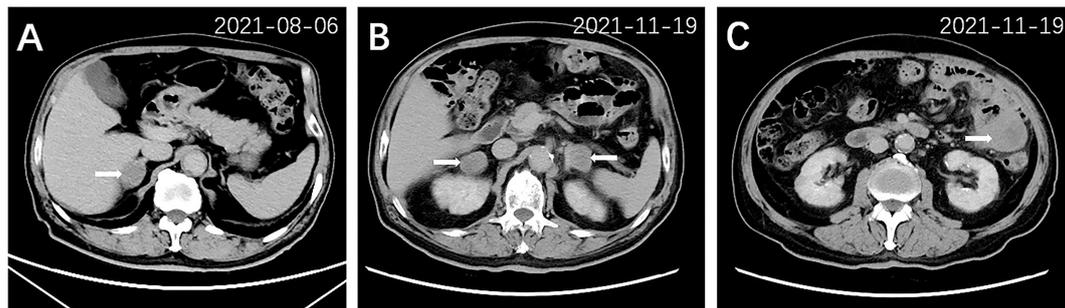


FIGURE 4 | Abdominal CT scan of other metastatic lesions 3 months after treatment (**A**) and 6 months after treatment (**B, C**). A nodule (2.9 cm × 2.0 cm) in the right adrenal gland (arrow) was detected after 3 months of treatment (**A**). Multiple metastatic lesions were shown in bilateral adrenal glands (arrow, **B**) and left lower abdominal cavity (arrow, **C**) after 6 months of treatment.

diagnosis, other metastasis site, clinical presentation, gastric tumor location, endoscopic appearance, treatment, and survival information were extracted by two investigators (JL and ZL) using a predefined form.

Statistical Analysis

Descriptive data were presented as median (interquartile range) and percentages. Overall survival (OS) was measured from the date of primary lung cancer diagnosis to the date of death. Survival after gastric metastasis was measured from the date of GMLC diagnosis to the date of death. Survival analysis was performed by Kaplan–Meier method. Univariate analysis was performed using Cox proportional hazards regression model, followed by a multivariate Cox regression analysis only including variables with a P value <0.10 during univariate analysis. Variables such as age, gender, number of metastases (solitary vs. multiple), interval (synchronous vs. metachronous), histology type, and treatment strategies were included in the univariate analysis. Synchronous metastasis is when the time interval of diagnosis between lung cancer and gastric metastasis was <1 month, while the time interval ≥ 1 month was considered as metachronous metastasis (5). Statistical analysis was performed using R software (version 4.0.3; The R Foundation for Statistical Computing, Vienna, Austria). A 2-sided $P < 0.05$ was considered statistically significant.

Results

A total of 2,078 papers were retrieved, among which 2,064 were obtained through database search (PubMed: 260; Embase: 1,357; Web of Science: 447) and 14 through manual search. After 226 duplications and 1,676 papers were excluded by title and abstract screening, 176 were screened for full text and 78 papers were finally included in this systematic review, as shown in **Figure 5**.

A total of 114 cases were recruited in the present review (113 from the literature plus our case, **Table S1**) (2, 6–84). As shown in **Table 1**, the median age was 65 years (range, 59–71 years). There were 91 men (79.8%) and 23 women (20.2%). Among 54 cases that reported smoking habits, 42 patients (77.8%) were cigarette smokers, 12 (22.2%) had never smoked. NSCLC (99 cases, 86.8%) was the main histological type of GMLC.

Adenocarcinoma (48 cases, 42.1%), squamous cell carcinoma (28 cases, 24.6%), and large cell lung cancer (12 cases, 10.5%) were the three most common histological types of NSCLC. Among 76 cases that reported the primary location of the lung cancer, gastric metastases were more commonly from the right lung (46 cases, 60.5%). Also, the most common site was the upper lobe (50%; right upper lobe: 30.3%; left upper lobe: 19.7%), followed by the lower lobe (23.7%; right lower lobe: 15.8%; left lower lobe: 7.9%) and hilum (18.4%; right hilum: 9.2%; left hilum: 9.2%).

In 107 cases that mentioned the number of metastatic sites, 28 cases (26.2%) presented as a single-site metastasis at the time of diagnosis, whereas 79 cases (73.8%) demonstrated other metastatic sites besides the stomach, with the liver, bone, brain, and adrenal gland being the four most prevalent metastatic sites. Moreover, 18 cases (16.8%) showed multiple metastases within the digestive tract, and the duodenum (11 cases, 10.3%) was the

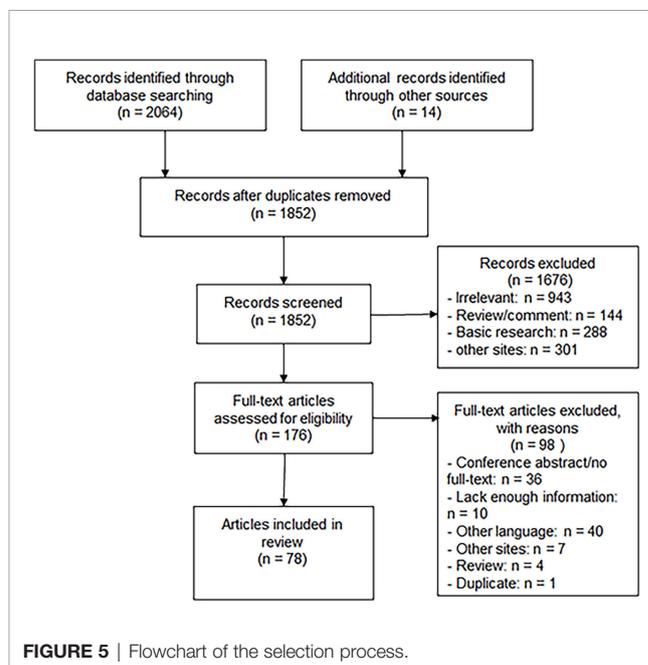


FIGURE 5 | Flowchart of the selection process.

TABLE 1 | Demographic and clinicopathologic features of GMLC.

Characteristics	Value
Age (years)	65 (59–71)
Gender	
Men	91 (79.8)
Women	23 (20.2)
Smoking	
(54 cases available)	
Smoker	42 (77.8)
Non-smoker	12 (22.2)
Histological type	
Small cell lung cancer	15 (13.2)
Adenocarcinoma	48 (42.1)
Squamous cell carcinoma	28 (24.6)
Large cell carcinoma	12 (10.5)
Pleomorphic carcinoma	6 (5.3)
Primary lung sarcoma	2 (1.8)
Non-small cell lung cancer	3 (2.6)
Primary lung location	
(76 cases available)	
Right upper lobe	23 (30.3)
Right middle lobe	2 (2.6)
Right lower lobe	12 (15.8)
Right hilum	7 (9.2)
Right lung	2 (2.6)
Left upper lobe	15 (19.7)
Left lower lobe	6 (7.9)
Left hilum	7 (9.2)
Left lung	2 (2.6)
Both lung	1 (1.3)
No. of metastasis sites	
(107 cases available)	
Solitary	28 (26.2)
Multiple	79 (73.8)
Interval	
(113 cases available)	
Synchronous	54 (47.8)
Metachronous	59 (52.2)
Interval time (m)	5 (1.6–13)
(113 cases available)	

Data presented as the number of patients (%) or median (interquartile range). GMLC, gastric metastasis from lung cancer.

main concurrent site with the stomach, followed by the colon (4 cases, 3.7%, including 1 case that showed concurrent stomach, duodenum, and colon metastases), small intestine (3 cases, 2.8%), and esophagus (1 case, 0.9%). Synchronous (54 cases, 47.8%) and metachronous (59 cases, 52.2%) metastases demonstrated similar proportions. The median time between the primary lung cancer diagnosis and gastric metastasis diagnosis was 5 months (interquartile range, 1.6–13 months).

As presented in **Table 2**, bleeding was the most common symptom on admission, which was observed in 40 cases (36.7%; 21 melena; 4 hematemesis; 1 melena and hematemesis; 14 hemorrhage), followed by abdominal pain in 39 cases (35.8%) and anemia in 11 cases (10.1%). Eleven cases showed no symptoms (10.1%), and 3 cases (2.8%) presented with acute abdomen caused by perforation. Some cases also presented with abdominal discomfort, dysphagia, nausea, vomiting, or weight loss.

Metastatic lesions were mainly located in the corpus of the stomach (56.2% in 89 cases with whom the information

TABLE 2 | Clinical and endoscopic features of gastric metastatic tumors.

Characteristics	Value
Clinical presentation	
(109 cases available)	
Bleeding	40 (36.7)
Abdominal pain	39 (35.8)
Anemia	11 (10.1)
Abdominal discomfort	5 (4.6)
Dysphagia	6 (5.5)
Nausea, vomiting	4 (3.7)
Weight loss	4 (3.7)
Perforation	3 (2.8)
Asymptomatic	11 (10.1)
Stomach location	
(89 cases available)	
Corpus	50 (56.2)
Fundus	19 (21.3)
Antrum	13 (14.6)
Cardia	7 (7.9)
Whole	6 (6.7)
Endoscopic appearance	
(85 cases available)	
Elevated lesions	50 (58.8)
Without ulcer	19 (22.4)
SMT	8 (9.4)
Mass	2 (2.4)
Polypoidal mass	6 (7.1)
Nodules	3 (3.5)
With ulcer	31 (36.5)
SMT with ulcer	13 (15.3)
(volcano-like)	
Ulcerated mass	15 (17.6)
(volcano-like)	
Ulcerated nodules	3 (3.5)
Ulcerated lesions	31 (36.5)
Ulceration	12 (14.1)
Bulging ulcerated lesion (volcano-like)	10 (11.8)
Infiltrative ulcerated lesion	9 (10.6)
Others	4 (4.7)
Linitis plastica	3 (3.5)
Erosive and atrophic gastritis	1 (1.2)

Data presented as the number of patients (%) or median (interquartile range).

SMT, submucosal tumor.

The bold value means the summarized patient numbers (bold numbers) and proportions (bold numbers in brackets) of relevant sub-items.

regarding the metastatic site in the stomach was available), followed by fundus (19 cases, 21.3%), antrum (13 cases, 14.6%), and cardia (7 cases, 7.9%). Thirteen cases had lesions in two or more parts of the stomach.

According to the endoscopic appearance of gastric metastasis that was described in 85 cases, two main types of lesions were observed: the elevated lesions with or without ulceration (50 cases, 58.8%) and ulcerated lesions (31 cases, 36.5%). Moreover, elevated lesions with volcano-like ulceration were more common than that without ulceration (36.5% vs. 22.4%). Some cases also presented with gastritis or linitis plastica-like features.

Immunohistochemical information was available in 58 cases, among which the typical immunophenotype of GMLC diagnosis was positive for TTF-1 (44, 75.9%), cytokeratin 7 (CK7, 31, 53.4%), and negative for CK20 (22, 37.9%), and caudal-related homeodomain transcription 2 (CDX2, 14, 24.1%). Other markers for diagnosis such as p63, CK5/6, CKAE1/AE3(+), and Napsin A were also reported.

As shown in **Table 3**, nearly one-third of cases underwent lung surgery (29.5%, mainly lobectomy) for primary lung cancer and abdominal surgery (31.5%, mainly partial or total gastrectomy) for gastric metastasis. Chemotherapy, radiotherapy, chemoradiotherapy, or targeted therapy were performed in 45.5% and 32.6% cases for primary lung cancer and gastric metastasis, respectively. Only supportive treatment was conducted in 25% and 35.9% of cases for primary lung cancer and gastric metastasis, respectively. The statistics were calculated based on cases with data available.

Survival information was available for 93 cases. A total of 72 cases had succumbed to disease by the end of the study, and 21 cases were alive as reported, considered as censored data. The median OS was 11 months (95% CI: 7–14), with 1- and 3-year survival rates of 41.7% and 17.9%, respectively. The median survival time after diagnosis of metastatic cancer was 4.5 months (95% CI: 3–9), with 1- and 3-year survival rates of 24.9% and 10.5%, respectively.

As for survival after diagnosis of metastatic cancer, univariate Cox analysis revealed that cases with multiple metastatic sites exhibited poorer prognosis than that with solitary gastric metastasis [unadjusted hazard ratio (HR) 2.239, 95% CI: 1.255–3.992, $P = 0.006$], while cases manifested as elevated lesions with or without ulcer in the stomach (unadjusted HR 0.385, 95% CI: 0.195–0.760, $P = 0.006$; unadjusted HR 0.352, 95% CI: 0.150–0.825, $P = 0.016$, respectively) or that underwent surgery treatment for primary lung cancer or gastric metastasis lesions (unadjusted HR 0.178, 95% CI: 0.083–0.383, $P = 0.000$; unadjusted HR 0.171, 95% CI: 0.088–0.332, $P = 0.000$, respectively) or non-surgery therapy (unadjusted HR 0.321, 95% CI: 0.171–0.604, $P = 0.000$ for lung cancer; unadjusted HR 0.223, 95% CI: 0.116–0.432, $P = 0.000$ for gastric metastasis, respectively) demonstrated better outcomes compared with cases with ulcerated lesions in the stomach or underwent only supportive treatment (**Figure 6**). As for OS, similar prognostic factors were discovered, including synchronous, multiple metastasis, ulcerated lesions, supportive treatment that indicated poorer outcome, and metachronous, solitary

metastasis, elevated lesions with or without ulcer, lung surgery, abdominal surgery and non-surgery therapy for gastric metastasis that indicated better survival prognosis (**Figure 6**).

In multivariate Cox analysis, after adjustment for prognostic factors, lung surgery for primary lung cancer, abdominal surgery, and non-surgery therapy for gastric metastasis remained prognostic factors for both OS and survival after gastric metastasis, except for synchronous metastasis that indicated a prognostic factor only for OS (**Figure 7**). Other factors were not significant.

DISCUSSION

The occurrence of GMLC is rare. The diagnosis remains challenging especially when the primary lung cancer histology is adenocarcinoma. In this study, we described a case of gastric metastasis originating from lung adenocarcinoma, which was confirmed by tissue biopsy, immunohistochemistry, and mutational analysis. As the EGFR L858R+T790M mutations were detected, the patient was treated with the third-generation EGFR-TKI osimertinib but showing rapid disease progression. To our knowledge, our patient is probably the second reported case of lung cancer with gastric involvement treated with the new-generation EGFR-TKI (8). As there is difficulty in the diagnosis and treatment of gastric metastasis patients, we further systematically analyzed 114 GMLC cases to reveal the clinical features and prognostic factors of the patients.

In the present review, GMLC is more likely to occur in the old, and male is the more susceptible gender. Adenocarcinoma is the most frequent primary histological type resulting in gastric metastasis, which is consistent with previous reports (30, 49, 85–87). However, other certain studies have shown squamous cell carcinoma to be prominent (67, 88). Thus, the dominant primary histological type remains incompletely understood.

At present, the pathway underlying gastric metastasis is not clearly elucidated; however, hematogenous and lymphatic routes are supposed to be most likely involved in GMLC (15, 29, 85, 89). The metastatic tumor cells invade the submucosal layer through blood or lymph and develop into submucosal tumors (SMTs) (30, 34, 82), which remain clinically silent unless the gastric mucosa or serosa is involved or the tumor occupies the lumen (34, 53). Thus, most patients with GMLC are asymptomatic, and detection of gastric abnormality is usually by chance during follow-up or staging procedures of primary lung cancer, like that in our patient. When symptomatic, bleeding (mainly exhibited as melena) and abdominal pain were the two most common symptoms according to our review, all of which are nonspecific and usually misinterpreted as side effects of chemotherapy or indefinite complaints (30, 67, 75). Therefore, attention needs to be paid to gastrointestinal symptoms among lung cancer patients, and endoscopic examination is recommended for further evaluation.

Endoscopically, metastatic lesions most commonly present as a solitary ulcerated lesion located in the gastric corpus (86). The typical morphological appearance has been reported as SMT-like masses with elevation and ulceration at the apex, so-called “volcano-like” lesions (90, 91). Some lesions also appear as ulcers,

TABLE 3 | Treatment and prognosis features of primary and metastatic tumors.

Characteristics	Value
Primary lung treatment	
(88 cases available)	
Lung cancer surgery	26 (29.5)
Non-surgery therapy	40 (45.5)
Supportive treatment	22 (25)
Gastric metastasis treatment	
(92 cases available)	
Abdominal surgery	29 (31.5)
Non-surgery therapy	30 (32.6)
Supportive treatment	33 (35.9)
Survival information	
(93 cases available)	
Dead	72 (77.4)
Alive	21 (22.6)
Survival after diagnosis of primary cancer, months	11 (7–14)
Survival after diagnosis of metastatic cancer, months	4.5 (3–9)

Data presented as the number of patients (%) or median (interquartile range).

polypoid nodules, or thickened walls (29). However, these endoscopic features are nonspecific, and differential diagnosis with primary lesions such as primary gastric cancer (GC) and lymphoma should be considered (14). Furthermore, about 9.4% of GMLC lesions manifested as SMTs with intact overlying mucosa, making conventional endoscopic biopsies frequently inconclusive. Endoscopic ultrasonography (EUS) is thus recommended for further evaluation. In EUS images, the metastatic tumors generally appeared as slightly hypoechoic lesions (more hyperechoic than the muscular tissue) involving the muscularis propria (fourth layer), mimicking primary subepithelial lesions such as gastrointestinal stromal tumors (GISTs), leiomyomas, and schwannomas (92, 93). EUS-guided fine-needle aspiration and biopsy (EUS-FNA/B) is currently the gold standard tissue sampling method for SMTs (92, 93). Hence, biopsies or EUS-FNA/B in conjunction with immunohistochemistry provides a reliable method to identify metastatic gastric tumors.

Several immunohistochemical markers have been reported to be useful for subclassifying tumors of different types and sites, such as TTF-1, Napsin A for lung adenocarcinoma, CDX2 for intestinal-type adenocarcinoma, and p63, CK5/6, CK34βE12/CK903 for squamous cell carcinoma (SCC) (14, 94, 95). Currently, TTF-1 is the most widely used stain for adenocarcinomas of pulmonary origin, with 61.5% sensitivity and 100% specificity in a series of 34 primary and metastatic adenocarcinomas in the lung (96). Also, different expression patterns of CK7 and CK20 are helpful for distinguishing tumor origin, with CK7+/CK20- for primary lung cancer and CK7-/CK20+ for gastrointestinal cancer (41, 62). Thus, a marker panel composed of TTF-1, CK7, CK20, and CDX-2 may be recommended to determine whether a gastric tumor was a primary or a pulmonary metastasis.

At present, there is no standard treatment protocol for GMLC patients, and treatment should be personalized

according to pathology and patients' condition. The therapeutic strategy includes surgery, chemotherapy with or without radiotherapy, targeted therapies, and supportive treatment (14).

Generally, the presence of a distant metastasis is a contraindication for surgery. High perioperative mortality and poor outcomes had been observed in surgical gastric and/or duodenal metastatic patients (49). However, our study and some other reports showed that surgery seemed to be a positive prognostic factor for GMLC patients (5, 30, 50). Accordingly, patients with solitary gastric metastasis may exhibit a survival benefit with surgical intervention (29, 50). Also, surgery may be necessary to prevent and/or control life-threatening complications such as massive hemorrhage or perforation (14, 29). Therefore, we considered surgery an option to treat gastric metastasis in properly selected patients, such as patients with unique metastatic lesions in the stomach and generally good condition, or with uncontrolled severe complications. With respect to radical surgery for isolated gastric metastasis, the optimal operating method remains to be clarified. According to our review, among 29 cases that underwent gastric surgical intervention, 5 cases received total gastrectomy, while 14 received partial or subtotal gastrectomy. The extent of gastric resection may depend on the site and size of the tumor. In selected GC patients such as early-stage and distal-third GC, subtotal gastrectomy may provide similar survival rates and better functional outcome compared to total gastrectomy (97). More recently, function-preserving gastrectomies such as proximal gastrectomy and pylorus-preserving gastrectomy have shown the advantages of preserving partial gastric physiologic functions and improving postoperative quality of life while maintaining radicality in early GC patients (98, 99). However, the impact of different surgical strategies including total gastrectomy, subtotal gastrectomy, or function-preserving

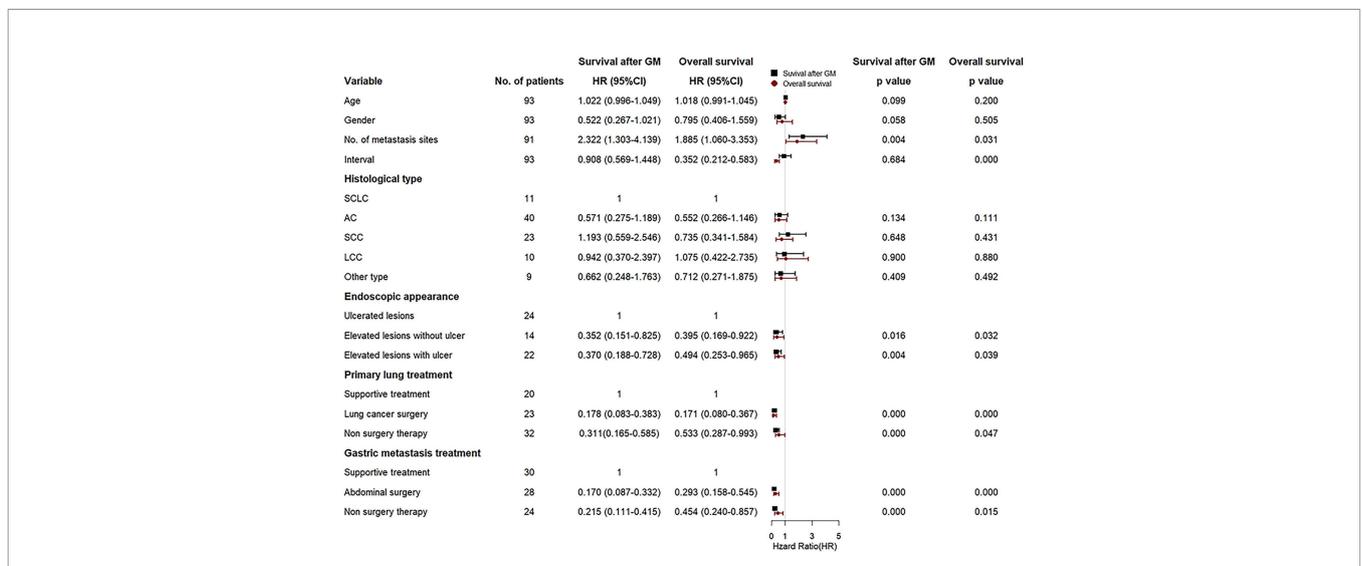


FIGURE 6 | Forest plot for the univariate Cox regression analyses of variables that may affect survival after gastric metastasis and overall survival of the gastric metastasis from lung cancer (GMLC) patient.

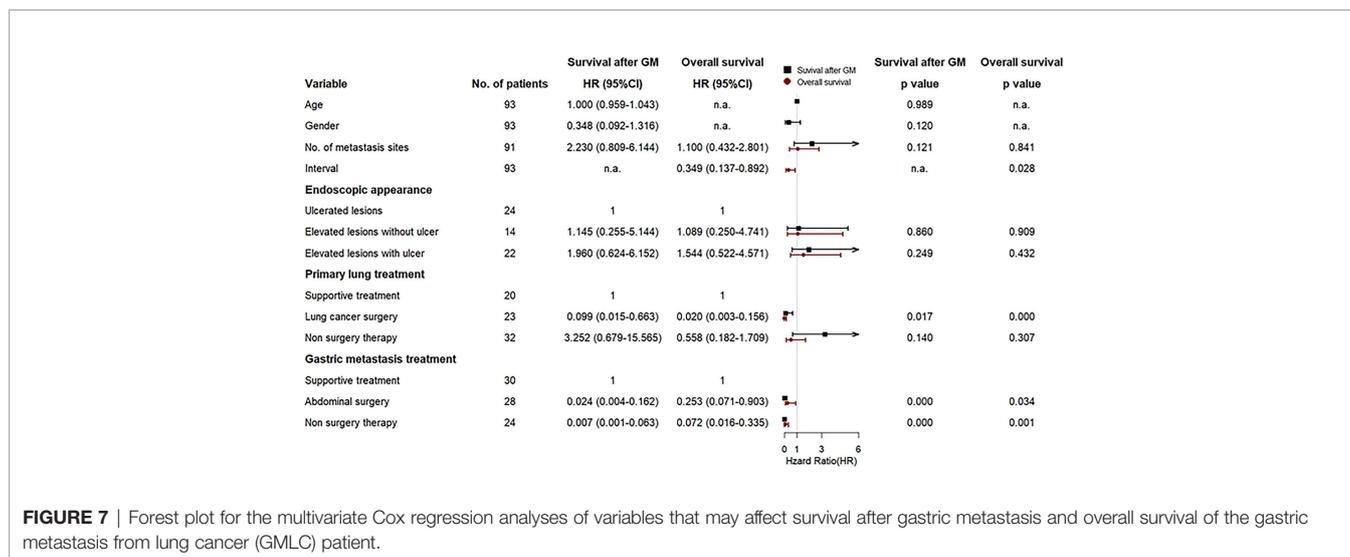


FIGURE 7 | Forest plot for the multivariate Cox regression analyses of variables that may affect survival after gastric metastasis and overall survival of the gastric metastasis from lung cancer (GMLC) patient.

gastrectomy on isolated metastatic gastric lesions still remains unclear and needs further investigation. In the present case, given the old age and generally poor condition, oral targeted therapy was prescribed other than surgery.

Currently, EGFR-TKIs represent the standard of care for advanced NSCLC patients with activating EGFR mutations, with median progression-free survival (PFS) ranging from 10 to 14.7 months (100). However, the efficacy of EGFR-TKIs on NSCLC with gastric metastasis has been barely reported. According to the present review, three cases were detected with the EGFR exon 19 deletions in gastric metastasis (24, 25, 30), which is the most common EGFR-TKI-sensitive activating mutation (101), and were treated with first-generation EGFR-TKI erlotinib. All of them tolerated the treatment well and were alive at the time of writing the reports (24, 25, 30). Our case harbored both L858R and T790M mutation at diagnosis, the latter of which is perceived as the most common resistance mutation associated with first- and second-generation EGFR-TKIs (101). At present, for NSCLC patients with T790M mutation, the third-generation EGFR-TKI osimertinib is recommended (100, 101). Also, in a randomized phase III FLAURA trial, osimertinib as first-line treatment exhibited improved PFS (18.9 months) and OS (38.6 months) compared with first-generation EGFR TKIs (median PFS of 10.2 months; median OS of 31.8 months) (102, 103). Therefore, our case was started on first-line therapy with oral osimertinib. Nevertheless, the patient experienced disease progression after 3 months of treatment, although the lesions of the lung and stomach exhibited partial response. The reason for the poor response to osimertinib in our case remains unclear. The reported potential mechanisms of resistance to osimertinib include the emergence of on-target resistance mutation such as EGFR C797S, bypass pathway activation such as MET amplification, or histologic small cell transformation (8, 100, 101, 104). Timely rebiopsies with comprehensive genomic profiling following disease

progression on osimertinib therapy may be helpful for unraveling the resistance mechanisms (8). The effective therapies after osimertinib resistance still remain elusive. Chemotherapy, immunotherapy, and antiangiogenic therapy, either alone or in combination, may be considered for further treatment (100). Also, the combination of EGFR-TKIs with other therapeutic agents such as chemotherapy or vascular endothelial growth factor (VEGF) inhibitors has emerged as a potential therapeutic approach in the first-line setting to overcome EGFR-TKI resistance (101, 104). Several clinical trials are currently exploring the role of combination approaches with osimertinib (105), which may provide critical information to inform future treatment practice.

In summary, GMLC is a rare entity with poor prognosis. Diagnosis can be challenging as for the nonspecific symptoms and heterogeneous endoscopic appearances. Histological examination with immunohistochemical staining may help to confirm the diagnosis, and genomic profiling may provide valuable information for the diagnosis and therapeutic options. Treatment should be personalized, with surgery and systemic therapy (chemotherapy, radiotherapy, and/or targeted therapy) demonstrating better survival prognosis than only supportive care. The new-generation EGFR TKI osimertinib, either alone or combined with other therapeutic agents, emerges as a promising therapeutic strategy for metastatic NSCLC patients with EGFR-activating mutations. However, more clinical evidence is needed for exploring the efficacy of osimertinib on GMLC patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YG conceived the idea and designed the study. DT collected clinical data, conducted the literature search, and analyzed the literature data. JL collected clinical data, performed the follow up, conducted the literature search, and extracted the literature data. ZL collected pathological data, and extracted the literature data. DT wrote the first version of manuscript. SZ revised the article. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2022.922016/full#supplementary-material>

Supplementary Figure 1 | Kaplan–Meier plot of the survival after gastric metastasis and overall survival curve.

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