Original Article

Tumor cavitation in patients with non-small-cell lung cancer receiving anti-angiogenic therapy with apatinib

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Background: Cavities have been reported in approximately 20% of lung cancer after anti-angiogenesis treatments. However, the effect of which on treatment outcomes remains unclear. This study sought to investigate the incidence and radiographic patterns of tumor cavitation in patients with non-small cell lung cancer (NSCLC) treated with apatinib, and its associations with patients' clinical characteristics and outcomes.

Methods: A total of 300 patients with NSCLC treated with apatinib were retrospectively identified. Baseline and follow-up chest computed tomography scans were reviewed to identify tumor cavitation, and the subsequent filling-in of the cavitation. A multivariate logistic regression analysis was conducted to identify the factors associated with tumor cavitation. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test.

Results: Of the 300 patients, 51 (17.0%) developed lung cavitation after initiating apatinib therapy. The results of the multivariate analysis showed that apatinib combination therapy (*vs.* apatinib monotherapy, odds ratio: 0.593, 95% confidence interval: 0.412–0.854, P=0.005) was significantly associated with tumor cavitation. Patients with tumor cavitation had significantly longer progression-free survival (PFS) than those without cavitation (8.2 *vs.* 5.2 months, P<0.01). Of the patients, 18 had cavity filling after progression, while 13 had persistent cavities after progression. The corresponding median PFS times were 11.9 and 3.2 months in patients with filled and persistent cavities after disease progression, respectively (P<0.001).

Conclusions: Tumor cavitation occurred in 17% of the NSCLC patients treated with apatinib and was associated with better PFS. Patients who had cavities filled after progression had a better prognosis than those with persistent cavities.

Keywords: Tumor cavitation; non-small cell lung cancer (NSCLC); anti-angiogenic therapy

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Introduction

A lung cavity is a gas-filled space that is characterized by a transparent or low attenuation area in pulmonary nodules, masses, or a consolidation (1). Cavities have been frequently reported in lung cancer, particularly after treatment with angiogenesis inhibitors (2-7). Approximately 16–24% of non-small cell lung cancer (NSCLC) patients develop cavities after taking anti-angiogenic drugs (2-7).

The effect of tumor cavitation on treatment outcomes

in NSCLC has been previously reported with conflicting results (8,9). These conflicting findings may be related to heterogeneity of the study design, including different tumor histology, disease staging, and treatment modalities. In lung cancer patients receiving apatinib treatment, the development of cavitation was found to be beneficial irrespective of whether they had primary or metastatic diseases (8). However, in other studies of NSCLC patients, no clear association was observed between clinical response and tumor cavitation (9,10).

The relationship between the development of lung cavitation and anti-angiogenic therapy is crucial to avoid severe adverse events and guide clinical treatment. Currently, according to the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v.1.1), tumor cavitation is not included in the response assessment, but it is often considered a sign of effective treatment. In this study, we primarily focused on the incidence and patterns of lung cavitation during apatinib treatment and its effect on treatment outcomes. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-465/rc).

Highlight box

Key findings

- Tumor cavitation was observed in 17% of patients with non-small cell lung cancer (NSCLC) who received apatinib therapy, and this phenomenon was significantly correlated with improved progression-free survival (PFS).
- Patients who had cavities filled after progression demonstrated a more favorable prognosis compared to those with persistent cavitation.

What is known and what is new?

- Cavities have been frequently reported in lung cancer after anti-angiogenic treatments, and the effect of which on treatment outcomes in NSCLC has been previously reported with conflicting results.
- Our research showed tumour cavities related to better prognoses. Two patterns of disease progression of tumor cavities were observed in our research, which led to different prognoses.

What is the implication, and what should change now?

- The correlation between pulmonary cavitation development and anti-angiogenic therapy is pivotal for the prevention of severe adverse events and for the formulation of clinical management strategies.

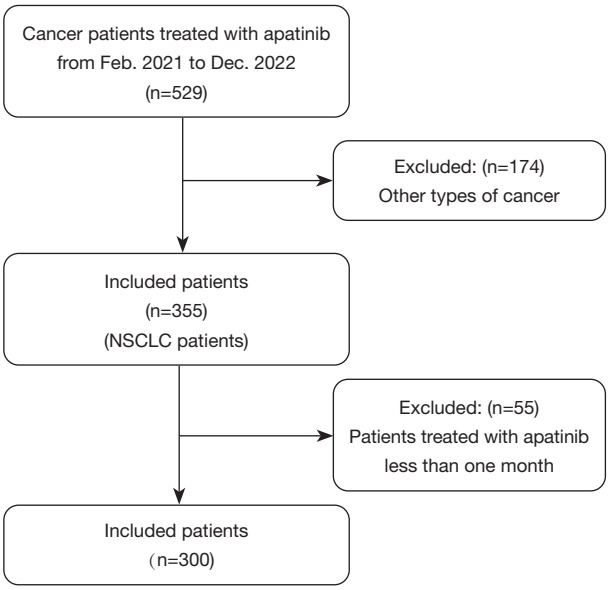

Figure 1 Study flow diagram. NSCLC, non-small cell lung cancer.

Methods

Study design and patients

This was a single-center retrospective study of NSCLC patients treated with apatinib at the Thoracic Inner Department I, Hubei Cancer Hospital, between February 2021 and December 2022. Among 529 cancer patients who received apatinib, 355 had NSCLC without baseline tumor cavity, and of those 355 NSCLC patients, 300 who had received at least 1 month of apatinib treatment were ultimately included in the analysis (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Hubei Cancer Hospital (No. LLHBCH2024YN-001) and individual consent for this retrospective analysis was waived.

Procedures and imaging analysis

Patients were administered oral apatinib (250 mg, once daily) alone or in combination with chemotherapy, and/or targeted therapy, and/or immunotherapy, until disease progression, intolerable toxicity, or death. Brain magnetic resonance imaging (MRI) and single-photon emission

computed tomography (CT) whole-body bone scans were performed at the baseline and then as clinically indicated. The initial tumor response was evaluated 4 weeks after the start of apatinib treatment as per the RECIST v1.1. CT scans of the neck, chest, and abdomen were performed at the baseline, and then every 8 weeks until disease progression. Thoracic radiologist assessed cavitary change on (initial) or follow-up chest CT. Tumor cavity was defined as the emergence of an air-filled cavity of ≥10% in at least one lung tumor lesion. Progression-free survival (PFS) was defined as the time from the initial apatinib treatment to disease progression or death from any cause.

Statistical analysis

The continuous variables were expressed as the mean ± standard deviation (SD), and were compared between the cavitation and non-cavitation groups. The categorical variables were expressed as the frequency and percentage and were compared using the χ^2 test. A multivariate logistic regression analysis was performed to identify any potential factors associated with tumor cavitation. The Kaplan-Meier method was used to estimate PFS, and the corresponding 95% confidence interval (CI) was calculated using the Brookmeyer-Crowley method. All the statistical analyses were performed with SPSS and Stata. A two-sided P value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 300 patients were included in the analysis in this study. No patient had baseline pulmonary cavitation. Of the 300 patients, 51 (17%) developed pulmonary cavitation during apatinib treatment. The baseline patient characteristics are shown in *Table 1*. The median age was 60 (range, 48–72) years in patients without pulmonary cavitation and 57 (range, 49–65) years in those with pulmonary cavitation. All the patients who developed lung cavitation had a histological type of non-squamous cell carcinoma. Among the 249 patients in the non-cavitation group, 74 (29.7%) received apatinib monotherapy, and 175 (70.3%) received apatinib combination therapy. In the cavitation group of 51 patients, 27 (52.9%) received apatinib monotherapy, and 24 (47.1%) received combined therapy. The main adverse clinical outcomes included hypertension (13.2% *vs.* 15.7%, non-cavity group *vs.* cavity group, P=0.38) and hemoptysis (2.4% *vs.* 3.9%, P=0.19). The median time for the occurrence of hypertension was 2 weeks.

Interestingly, none of the 14 patients with epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) mutations in the cavitation group received tyrosine kinase inhibitors (TKIs). Conversely, 18 of the 100 patients harboring driver mutations in the non-cavitation group received TKIs in combination with apatinib. One possible explanation is that the patients with concurrent *EGFR* mutations might have already experienced TKI failure during frontline treatment, as EGFR TKIs are considered a first-line treatment for NSCLC patients with *EGFR*-sensitive mutations.

Factors associated with pulmonary cavitation

The incidence rate of pulmonary cavitation was 17.0%, with a median time to occurrence of 1.76 (range, 0.48–2.32) months. The results of the multivariate logistic regression analysis showed that apatinib combination therapy was significantly associated with tumor cavitation [vs. apatinib monotherapy, odds ratio (OR): 0.593, 95% CI: 0.412–0.854, P=0.005], while other factors, such as age, driver mutation, and tumor histology, were not significantly associated with tumor cavitation (*Table 2*).

Clinical outcomes

The median PFS time was 8.21 (95% CI: 7.61–11.98) months in patients with pulmonary cavitation, which was significantly longer than that in patients without pulmonary cavitation (median: 5.18 months, 95% CI: 4.54–7.87) (*Figure 2*).

Among the 51 patients who developed tumor cavitation, 31 had disease progression, including 18 with filled cavities after progression (pattern 1) and 13 with persistent cavities after progression (pattern 2) (*Figure 3*). In patients with cavity filling, progression was defined as an increase in solid components in the central area of the cavity, leading to cavity filling. Among those with persistent cavities, there were two types of disease progression, which were defined as either an increase in solid components surrounding the cavity, or the appearance of new metastatic lesions, while the cavities remained present.

There were no significant differences in the clinical characteristics and treatment patterns between the patients with filled and persistent cavities. The median PFS was

Table 1 Characteristics of the 300 patients enrolled in this study

Characteristics	Non-cavitation (n=249)	Cavitation (n=51)	P value
Mean age ± standard deviation, years	60.3±12.3	57.0±8.4	0.42
Sex, n (%)			0.12
Male	153 (61.4)	30 (58.8)	
Female	96 (38.6)	21 (41.2)	
TNM stage, n (%)			0.008
I	0	0	
II	0	0	
III	32 (12.9)	8 (15.7)	
IV	217 (87.1)	43 (84.3)	
Histology, n (%)			<0.001
Adenocarcinoma	157 (63.0)	47 (92.2)	
Squamous carcinoma	40 (16.1)	0	
Other	52 (20.9)	4 (7.8)	
Driver mutations, n (%)			0.21
Wide type	149 (59.8)	37 (72.5)	
EGFR 19 del	49 (19.7)	5 (9.8)	
EGFR 21 L858R	42 (16.9)	4 (7.9)	
ALK	3 (1.2)	5 (9.8)	
Others	6 (2.4)	0	
Apatinib treatment line, n (%)			0.02
First line	0	0	
Second line	31 (12.4)	11 (21.6)	
Above second line	218 (87.6)	40 (78.4)	
Apatinib treatment, n (%)			0.02
Monotherapy	74 (29.7)	27 (52.9)	
Combination therapy	175 (70.3)	24 (47.1)	
Chemotherapy	83 (33.3)	17 (33.3)	
Immunotherapy	52 (20.9)	0	
Chemotherapy plus immunotherapy	22 (8.8)	7 (13.7)	
Tyrosine kinase inhibitors	18 (7.2)	0	
Duration of apatinib treatment (range), months	8 (1.4–15.9)	5 (1.0–11)	<0.001
Hypertension (TRAEs), n (%)			0.38
Yes	29 (13.2)	8 (15.7)	
No	220 (86.8)	43 (84.3)	
Hemoptysis (TRAEs), n (%)			0.19
Yes	6 (2.4)	2 (3.9)	
No	243 (97.6)	49 (96.1)	

TNM, tumor node metastasis; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TRAE, treatment-related adverse event.

Table 2 Multivariate logistic regression analysis of the factors associated with pulmonary cavitation

Characteristics	Odds ratio	95% CI	P value
Age	0.988	0.974–1.002	0.09
Sex			<0.001
Male	0.438	0.304–0.63	
Female	2.285	1.587–3.29	
Histology			0.46
Adenocarcinoma	0.871	0.602–1.26	
Squamous carcinoma	1.148	0.793–1.662	
Driver mutations			0.16
EGFR	0.765	0.528–1.109	
ALK	1.307	0.902–1.896	
Apatinib treatment patterns			0.005
Monotherapy	1.686	1.171–2.429	
Combination therapy	0.593	0.412–0.854	

CI, confidence interval; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

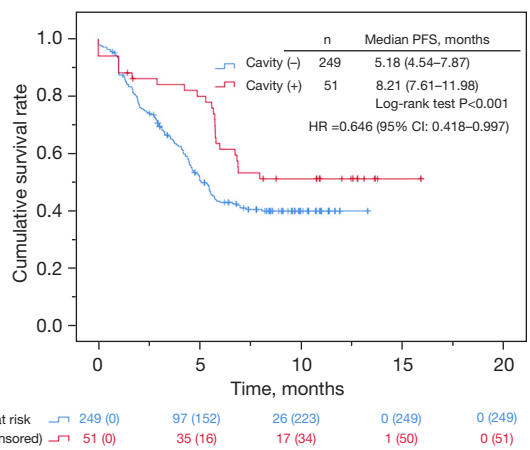

Figure 2 Progression-free survival of patients with and without pulmonary cavitation. PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

11.93 (95% CI: 10.31–13.44) months in patients with filled cavities, and 3.19 (95% CI: 1.65–4.74) months in those with persistent cavities (P<0.001) (*Figure 4*).

Among the 51 patients with cavities, 24 patients received apatinib combination therapy, including 17 in combination with chemotherapy, and 7 in combination with chemotherapy and immunotherapy. The median PFS was 11.13 (95% CI: 9.04–13.21) months for the 24 patients receiving combination therapy and 7.56 (95% CI: 5.49–9.63) months for the 27 patients receiving apatinib monotherapy (P=0.04) (*Figure 5*). However, there was no significant difference in PFS in terms of the different combined treatment modes (P=0.09) and the presence or absence of *EGFR* mutations (P=0.70) in patients with tumor cavitation.

Case presentation

A 53-year-old woman underwent right middle lobe resection on September 18, 2018, and was pathologically diagnosed with right lung adenocarcinoma (pT4N0M0, stage IIIA). The patient tested negative for *EGFR*, *ALK*, and *ROS-1* mutations and had a PD-L1 expression of 0 (Dako Link 48; 22C3: TPS =0). Postoperatively, she received six cycles of chemotherapy with pemetrexed and nedaplatin. On July 11, 2019, multiple lung metastases were detected by chest CT scan. The patient then received several lines of treatment, including chemotherapy and an immune checkpoint inhibitor; however, her disease kept expanding until she started oral anlotinib (an orally administered multi-targeting TKI) targeted therapy on November 14, 2019. In 2020 March, she complained of coughing and hemoptysis, and a chest CT scan showed disease progression. Her PFS was 4 months at that

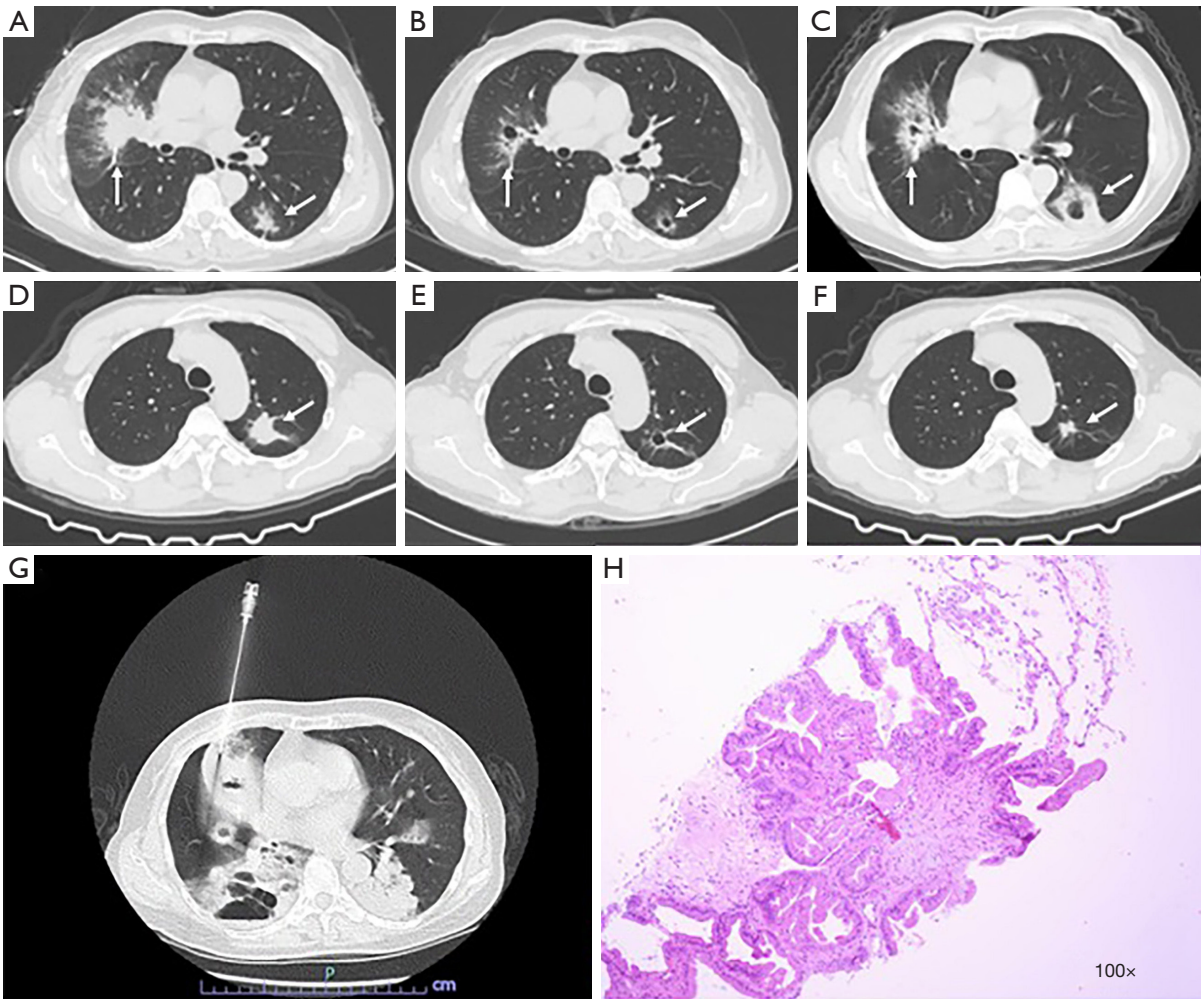

Figure 3 A 53-year-old woman with stage IIIA adenocarcinoma of the lung underwent right middle lobectomy some 3 years ago, and presented with recurrent disease in the left lower lobe and right upper lobe. (A) Baseline contrast-enhanced CT of the chest prior to apatinib therapy. Arrows point to the pulmonary lesions. (B) Follow-up CT at 1.5 months after the therapy demonstrated that cavities had developed in the metastatic masses (arrows). (C) Further follow-up CT performed at 6 months demonstrated progression around the cavities, and that the cavities remained (arrows). A 61-year-old man with stage IV adenocarcinoma of the lung was treated with apatinib and camrelizumab. (D) Baseline contrast-enhanced CT of the chest demonstrated a solid dominant mass in the left upper lobe (arrow). (E) Follow-up CT at 1.5 months after the therapy demonstrated that a cavity had developed in the dominant mass (arrow). (F) Further follow-up CT performed at 6 months demonstrated cavity filling (arrow) with regrowth of the mass. (G) Needle biopsy of the cavity wall; and (H) hematoxylin-eosin staining of the biopsy sample showing adenocarcinoma. CT, computed tomography.

time, and she had not yet developed lung cavities. On July 7, 2021, she underwent treatment with pemetrexed combined with triplimab and apatinib and cavities appeared 1 month later. In October 2021, the patient showed slow progression, as the cavities persisted but with the thickening of the cavity walls, new metastatic lesions gradually appeared. A needle biopsy of the cavity wall revealed adenocarcinoma (*Figure 3G,3H*).

Discussion

NSCLC accounts for approximately 85% of all lung cancers, with over half of the cases diagnosed at an advanced stage (11). Chemotherapy reaches a plateau in the overall

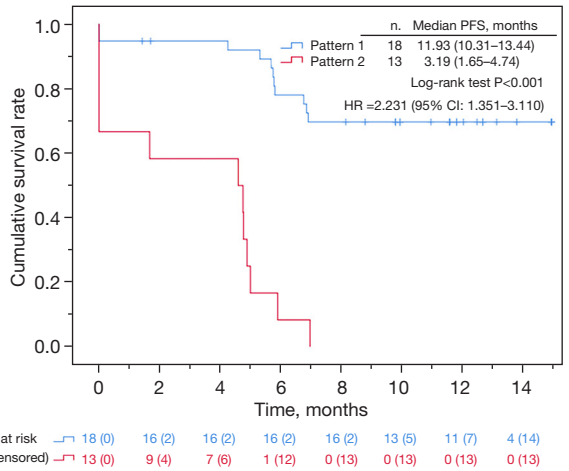

Figure 4 Progression-free survival of patients with filled or persistent cavities after progression. Pattern 1: with filled cavities; pattern 2: with persistent cavities. PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

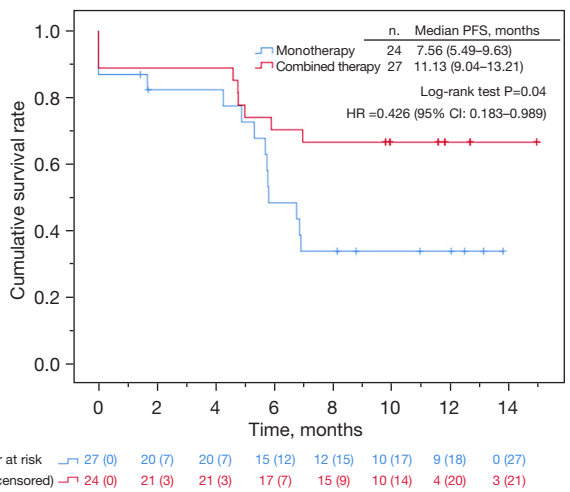

Figure 5 Progression-free survival was compared between patients receiving apatinib monotherapy and combined therapy. PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

survival (OS) curve at around 10 months. Hence, in the past decade, new targeted approaches, including anti-angiogenic therapy, have been developed to prolong the survival of NSCLC patients. Tumor angiogenesis is critical for cancer pathogenesis, providing not only oxygen to the tumor but also an important pathway for cancer cell metastasis and dissemination (12-14). Targeted anti-angiogenic agents targeting vascular endothelial growth factor (VEGF) or its receptors (VEGFRs) can normalize the pathological tumor vasculature, modulate the tumor microenvironment, and inhibit neoangiogenesis. Receptor tyrosine kinase (RTK) inhibitors, including anti-angiogenic agents (e.g., bevacizumab and apatinib), have shown significant efficacy as targeted anti-cancer agents (15-17). Apatinib is an oral RTK that targets VEGFR-2, RET, platelet-derived growth factor receptor-beta, c-Src, and stem cell factor receptor (c-Kit) (18). It has been approved for the late-line treatment of local advanced or metastatic gastric adenocarcinoma, gastric-esophageal junction adenocarcinoma, and hepatocellular carcinoma. Apatinib has also been used in combination with chemotherapy or immunotherapy in NSCLC (19,20).

In a previous study of 72 NSCLC patients treated with bevacizumab, 14 (19%) patients developed tumor cavitation, but no differences were observed in terms of either PFS or OS between those with and without tumor cavitation (2). Marom *et al.* found that tumor cavitation induced by anti-angiogenesis agents occurred in 16% of 108 NSCLC patients (3). Crabb *et al.* observed that 24% (8/33) of patients developed cavitation after anti-angiogenic therapy and platinum-based chemotherapy (9). In our study, 51 (17.0%) patients developed lung cavitation when treated with apatinib monotherapy or combination therapy. Lung cavitation was clearly associated with apatinib treatment, as it occurred in a short period, less than 12 weeks, according to the prior imaging. We also observed a significantly higher proportion of adenocarcinoma patients with cavities (63.0% *vs.* 92.2%, P<0.001). However, since we would like to analyze the prognosis of patients with/without cavities, rather than the prognosis of different pathological types, we included patients of different pathological types in the K-M analysis.

Patients receiving combination therapy with apatinib and chemotherapy, TKIs, or immunotherapy have a higher likelihood of developing lung cavitation. One possible explanation is that combination therapy enhances the anti-vascular effects of apatinib, leading to tumor cell necrosis and cavity formation. Additionally, among the patients who developed cavities, those who received combination therapy also had longer PFS.

This study also observed two growth patterns of tumor cavities that may be associated with survival outcomes: cavity filling (pattern 1), and maintenance (pattern 2). Among the 39 patients with tumor progression, in 18 patients (pattern 1), the tumor grew inward into the cavity,

while in 13 patients, the tumor expanded outward from the cavity (pattern 2). The median PFS was significantly longer in the patients with filled cavities than in those with persistent cavities (11.93 *vs.* 3.19 months, P<0.001). Patients with filled cavities might have had better PFS because the patients with persistent cavities included a subset of patients who had experienced new metastatic lesions.

The mechanism underlying tumor cavitation remains unclear. A previous study indicated that anti-angiogenic drugs affect the blood vessel structure and function of tumors, resulting in damage to endothelial cells and the increased permeability of vascular walls (8). Moreover, research has shown that anti-angiogenic therapy affects the immune environment of tumors and subsequently affects tumor growth and progression (21). Anti-angiogenic therapy can participate in immune responses, stimulating the release of cytokines, and enhancing the sensitivity to immune checkpoint inhibitors, thus decreasing tumor volume and the likelihood of cavity formation (8,22-25). It has also been observed that autophagy has a significant role in the mechanisms of immune resistance (26). Further, disturbances in key autophagy molecules, such as Rubicon, can contribute to the process of cavitation (27).

In a previous case, three negative bronchoscopies and numerous blood and sputum cultures ruled out tuberculosis, opportunistic infection, parasitic infestation, and other potential causes of cavitation (2). In the present case, a needle biopsy of the cavity wall revealed the presence of adenocarcinoma without apparent bacterial or viral infections or the infiltration of inflammatory cells. One explanation is that the effective treatment received by this patient led to massive tumor cell necrosis in the center of the tumor, resulting in cavity formation. After disease progression, the inhibitory effect on blood vessels, especially in the central region of the tumor, might have caused the tumor to expand outward.

Our study had certain limitations. First, we are unable to explain why patients with tumor growth inward into the cavity after progression exhibited a better prognosis. Second, we did not conduct relevant cell experiments to confirm the signaling pathway through which apatinib may cause cavity formation.

Conclusions

Our study showed that patients who developed cavitation after apatinib treatment had longer PFS. Among the patients with tumor cavitation, those who had cavity filling and had no emergence of new lesions had a better prognosis. The results of the multivariate analysis revealed that among the clinical features examined, only apatinib combination therapy was significantly associated with the development of cavitation. The underlying mechanism of cavity formation still requires further investigation.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-465/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-465/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-465/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-465/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Hubei Cancer Hospital (No. LLHBCH2024YN-001) and individual consent for this retrospective analysis was waived.

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