

ORIGINAL ARTICLE

Tumoral cavitation in patients with non-small-cell lung cancer treated with antiangiogenic therapy using bevacizumab

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Abstract

Rationale and objectives: To investigate the frequency and radiographic patterns of tumoral cavitation in patients with non-small cell lung cancer (NSCLC) treated with bevacizumab, and correlate the imaging findings with the pathology, clinical characteristics and outcome. **Materials and methods:** Seventy-two patients with NSCLC treated with bevacizumab therapy were identified retrospectively. Baseline and follow-up chest computed tomography scan were reviewed to identify tumoral cavitation and subsequent filling in of cavitation. Radiographic cavitation patterns were classified into 3 groups. The clinical and outcome data were correlated with cavity formation and patterns. **Results:** Out of 72 patients, 14 patients developed cavitation after the initiation of bevacizumab therapy (19%; median time to event, 1.5 months; range 1.0–24.8 months). Three radiographic patterns of tumoral cavitation were noted: (1) development of cavity within the dominant lung tumor ($n = 8$); (2) development of non-dominant cavitory nodules ($n = 3$); and (3) development of non-dominant cavitory nodules with adjacent interstitial abnormalities ($n = 3$). Eleven patients (79%) demonstrated subsequent filling in of cavitation (the time from the cavity formation to filling in; median 3.7 months; range 1.9–22.7 months). No significant difference was observed in the clinical characteristics, including smoking history, or in the survival between patients who developed cavitation and those who did not. Smoking history demonstrated a significant difference across 3 radiographic cavitation patterns ($P = 0.006$). Hemoptysis was noted in 1 patient with cavity formation and 4 patients without, with no significant difference between the 2 groups. **Conclusion:** Tumoral cavitation occurred in 19% in patients with NSCLC treated with bevacizumab and demonstrated 3 radiographic patterns. Subsequent filling in of cavitation was noted in the majority of cases.

Keywords: Non-small cell lung cancer; antiangiogenic therapy; bevacizumab; computed tomography; tumor cavitation.

Introduction

Lung cancer remains one of the most common causes of cancer death in the United States and worldwide, accounting for over 150,000 deaths per year in the United States^[1,2]. Eighty-five percent of patients have non-small cell lung cancer (NSCLC), and conventional chemotherapy for advanced NSCLC remains marginally

effective^[1,2]. Recent advances in molecular medicine have elucidated the molecular mechanisms of lung cancer development and progression, including tumor angiogenesis, which is a fundamental step in tumor growth and metastases^[3,4]. Vascular endothelial growth factor (VEGF) is the central mediator of angiogenesis and its expression is known to correlate with new vessel formation, disease-free survival, and overall

survival in patients with NSCLC^[5–8]. Bevacizumab is a monoclonal antibody directed against VEGFA and provides a significant survival benefit in patients with NSCLC when added to the conventional chemotherapy regimen using paclitaxel and carboplatin in a phase III trial^[9]. Bevacizumab is routinely used for patients with advanced non-squamous NSCLC as one of the newer effective therapeutic options.

Patients with lung cancer treated with antiangiogenic agents including bevacizumab, commonly develop cavitation in their lung lesions^[10,11]. In 2008, Marom et al.^[10] reported development of tumoral cavitation in 17 of 124 (14%) patients with advanced lung cancer during antiangiogenic therapy, using 7 different agents including bevacizumab, vandetanib, sorafenib, erlotinib, AMG-706 (multitarget tyrosine kinase inhibitor), exherin (N-cadherin inhibitor), and squalamine (VEFG inhibitor from shark cartilage). Crabb et al.^[11] reported marked cavitation of pulmonary lesions in 8 of 33 patients (24%) treated with VEGF inhibitor, cediranib, combined with platinum-based chemotherapy, and proposed an alternative method of assessing response excluding the area of cavitation to improve response assessment. Sandler et al.^[12] evaluated clinical and radiographic risk factors for severe pulmonary hemorrhage in patients with advanced NSCLC treated with carboplatin and paclitaxel plus bevacizumab, and reported that baseline tumor cavitation may be a potential risk factor for pulmonary hemorrhage. These studies are focused on the clinical implications of tumoral cavitation, including the complication of hemoptysis, impact on response assessment, and patient outcome. The assessment of the radiographic patterns of tumoral cavitation, and the changes in the radiographic patterns during and after antiangiogenic therapy have not been described in detail. In our preliminary review of computed tomography (CT) scans of the chest in patients with advanced NSCLC treated with bevacizumab, at least 3 different radiographic patterns of tumoral cavitation were observed: (1) development of a cavity within the dominant lung tumor; (2) development of cavitation in non-dominant nodules; and (3) development of cavitation in non-dominant nodules with adjacent interstitial abnormalities. In some patients who developed tumor cavitation, the air-filled cavity was filled in from the periphery due to regrowth of solid component on follow-up scans, representing filling in of cavitation, which suggests progression of disease as previously described^[11].

The purpose of the present study was to investigate the frequency and radiographic patterns of tumor cavitation in the lung in patients with advanced NSCLC treated with bevacizumab, define the clinical course of cavitation and assess the impact on response assessment to therapy and patient outcome. We also evaluated the clinical implications, including the occurrence of hemoptysis during therapy, of cavity formation and different cavity patterns.

Patients and methods

Patients

Between February 2005 and March 2011, 101 consecutive patients with histologically or cytologically proven NSCLC who received therapy with bevacizumab at the Dana-Farber Cancer Institute were identified retrospectively using the Clinical Research Information Systems (CRIS) database, with institutional review board approval. Of 101 patients identified, 72 patients had pre-therapy chest CT prior to bevacizumab treatment, performed 2.7 weeks before the initiation of therapy on average, and at least 1 follow-up chest CT performed a minimum of 4 weeks after the initiation of bevacizumab therapy available for review. The remaining 29 patients did not have baseline and/or at least 1 follow-up CT available for review and were excluded from the present study. Therefore, the study population for the current study consisted of 72 patients (29 men and 43 women; mean age, 56 years; range, 28–73 years) with NSCLC treated with bevacizumab therapy.

Clinical data

The clinical data obtained from the CRIS database included patients' age, gender, tumor stage and histology, prospectively collected smoking history, detailed therapeutic regimen, date of therapy initiation and termination, adverse events, and progression-free and overall survival.

Chest CT examinations

Baseline chest CT scans prior to the initiation of bevacizumab therapy as well as follow-up chest CT scans were performed to assess response to therapy with bevacizumab. The standard clinical chest CT protocol at our institution utilized a 64-row multidetector CT scanner (Aquilion 64; Toshiba America Medical Systems, CA) or a 4-row multidetector CT scanner (Volume Zoom; Siemens Medical Solutions, Forchheim, Germany). Patients were scanned in the supine position from the cranial to caudal direction from the clavicles to the adrenal glands at end inspiration. During the study, 100 ml of iopromid (Ultravist 300, 300 mg iodine/ml; Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ) were injected intravenously with an automated injector (Medrad, Pittsburgh, PA) at a rate of 3 ml/s, with a scan delay of 30 s, unless medically contraindicated. Axial images (5 mm thickness) were reconstructed using standard and lung algorithms. All CT images were transferred to a Picture Archiving Communication System (PACS) for review.

Image interpretation

A board-certified thoracic radiologist with 7 years of experience (M.N.) retrospectively reviewed all available

chest CT scans for 72 patients in the study cohort, including baseline scans as well as follow-up scans during and after bevacizumab therapy to identify the presence of any tumoral cavitation in the lung, defined as the presence of air in the tumor based on visual assessment^[10]. The longest diameter of the dominant lung tumor was measured using the caliper-type measurement tool on the PACS workstation (Centricity, General Electric, Milwaukee, WI).

For the patients with cavitation, a second consensus review was performed by 2 board-certified thoracic radiologists (M.N. with 7 years of experience and H.H. with over 20 years of experience) to evaluate the radiologic patterns of cavitation. For each patient, baseline chest CT and all available chest CT studies after the initiation of bevacizumab therapy (including scans during and after the therapy) were reviewed. The details of the radiographic patterns of tumoral cavitation were evaluated on each CT scan, and the presence/absence of the following patterns was recorded at each scan: (1) development of a cavity within the dominant lung tumor; (2) development of cavitation in non-dominant nodules; and (3) development of cavitation in non-dominant nodules with adjacent interstitial abnormalities. Patients who developed both patterns 1 and 2 cavitations during the time course were grouped together into pattern 2 for the subsequent statistical analysis. Patients who developed both patterns 2 and 3 cavitations during the time course were classified in the pattern 3 group in the subsequent statistical analysis. The cavitory lesions were followed to identify the subsequent filling in on all available follow-up CT scans. Filling in was defined as the decrease in the diameter of the air-filled cavity to any extent, ranging from the smallest visually detectable decrease to complete disappearance of the cavity, due to regrowth of solid component of the tumor from the periphery of the cavity.

Review of the pathologic specimen

The pathology record was reviewed to identify patients with histologic characterization of lung cancer obtained after the initiation of bevacizumab therapy. Specimens from the lungs of patients who developed cavitation were reviewed by a thoracic pathologist (L.S., a board-certified anatomic pathologist), in conjunction with the radiologist (M.N.) for radiologic–pathologic correlation.

Statistical analysis

The demographic and clinical characteristics of patients who developed cavitation and those who did not were compared using the chi-square test or the Fisher exact test, for categorical and binary variables as appropriate. The log-rank test was used to compare overall survival or progression-free survival in the different groups. Kaplan–Meier plots were used to illustrate the difference in survival times. All statistical analyses were performed

with Statistical Analysis Software version 9.2 (SAS Institute Inc, Cary, NC). A *P* value less than 0.05 was considered statistically significant.

Results

Patients and clinical characteristics

The demographic and clinical characteristics of the 72 patients in the cohort are presented in Table 1. The anti-cancer therapeutic regimens of the 72 patients in the study cohort are shown in Table 2. In brief, 76% (55/72) of patients had stage IV disease. Adenocarcinoma was the most frequent histologic subtype of NSCLC (83%), which included 5 patients with adenocarcinoma with bronchioloalveolar features (Table 1). The remaining

Table 1 Demographic and clinical characteristics of the patients

	No. of patients without cavity	No. of patients who developed cavity	Total	<i>P</i> value
Gender				0.41
Male	22	7	29	
Female	36	7	43	
Tumor stage				0.48
IA	2	1	3	
IB	3	0	3	
IIA	0	1	1	
IIB	1	0	1	
IIIA	3	1	4	
IIIB	4	1	5	
IV	45	10	55	
Tumor histology				1.00
Adenocarcinoma	48 ^a	12 ^b	60	
Large cell carcinoma	2	0	2	
NSCLC (not otherwise specified)	8	2	10	
Radiation therapy				1.00
Prior to bevacizumab therapy	22	5	27	
Concurrent	1	0	1	
None	35	9	44	
Smoking				0.13
Never	15	4	19	
Current	15	7	22	
Former	28	3	31	
Adverse events				
Hypertension	11	5	16	0.28
Skin rash ^d	8	1	9	0.68
Proteinuria ^d	2	0	2	1.00
Hemoptysis ^d	4 ^c	1 ^c	5	1.00
Epistaxis ^d	15	3	18	1.00
Gastrointestinal bleeding ^d	1	1	2	0.36
Deep venous thrombosis or pulmonary embolism	3	1	4	1.00

^aInclude patients with bronchioalveolar cell carcinoma subtype (*n* = 4).

^bInclude patients with bronchioalveolar cell carcinoma subtype (*n* = 1).

^cAll 5 patients had grade 1 hemoptysis.

^dIn 2 patients, the status of the adverse events was unknown.

Table 2 Therapeutic regimen using bevacizumab in 72 eligible patients

Therapeutic regimen	No. of patients without cavity	No. of patients who developed cavity	Total
Bevacizumab, carboplatin and paclitaxel	40	13	53
Bevacizumab, carboplatin and pemetrexed	8	0	8
Bevacizumab and taxotere	3	0	3
Bevacizumab and pemetrexed	2	0	2
Bevacizumab and erlotinib	2	0	2
Bevacizumab, cisplatin and taxotere	1	0	1
Bevacizumab and carboplatin and gemcitabine	1	0	1
Bevacizumab, carboplatin and pemetrexed, followed by bevacizumab, carboplatin and paclitaxel	1	0	1
Bevacizumab and irinotecan	0	1	1
Total	58	14	72

17% of patients had large cell carcinoma or NSCLC not otherwise specified. None of the patients had tumors subclassified as squamous cell carcinoma, which is consistent with the treatment recommendations^[13].

Tumoral cavitation: frequency and radiographic patterns

Of the 72 patients, 14 patients (19%) developed cavitation after the initiation of bevacizumab therapy; 10 patients (14%) developed cavitation during bevacizumab therapy; and 4 patients (6%) developed cavitation after the completion of bevacizumab therapy. The median time from the beginning of cavitation in these 14 patients who developed cavitation was 1.5 months (range 1.0–24.8 months). The cavitation could occur late in their therapeutic course; 11 patients developed cavitation 6 months after the initiation of therapy. In 4 patients who developed cavitation after the completion of bevacizumab therapy, the median time from the termination of therapy to development of the cavity was 0.8 months (range 0.6–21.0 months), and 3 of 4 patients developed cavitation within 1 month after termination of bevacizumab therapy. None of these 4 patients received any other therapeutic agent between the last dose of bevacizumab therapy and the development of tumoral cavitation.

Among 14 patients who developed cavitation, 8 patients (8/14; 57%) demonstrated development of a cavity within the dominant lung tumor (pattern 1) (Fig. 1). One patient (1/14; 7%) developed cavitation in the dominant tumor and in non-dominant nodules (pattern 2). Among 5 patients with cavitation in non-dominant nodules, 3 patients subsequently showed an increase in non-dominant cavitory nodules with adjacent interstitial abnormalities (pattern 3) (Figs. 2 and 3); the remaining 2 patients showed pattern 2 (Table 3).

Eleven patients (11/14; 79%) demonstrated subsequent filling in of cavitation (the time from the cavity formation to filling in; median 3.7 months; range 1.9–22.7 months)

(Fig. 1). In all 11 patients, filling in of cavitation was noted after the termination of bevacizumab therapy, indicative of an increase in solid tumor burden, with the median time between the termination of bevacizumab therapy and filling in of cavitation being 2.8 months (range 0.7–21.5 months).

Radiologic–pathologic correlation in tumoral cavitation

Among 14 patients who developed cavitation, 3 patients had pathologic specimens available for review after the initiation of bevacizumab therapy. One patient had left upper and lower lobe wedge resections, when chest CT demonstrated cavitation in multiple non-dominant nodules involving both lungs including left upper and lower lobes (pattern 2). The subsequent CT scans of this patient demonstrated an increase in cavitory nodules with adjacent interstitial abnormalities (pattern 3). On pathology review, the left upper and lower lobes demonstrated innumerable metastatic tumor deposits ranging in size from submillimeter to 1 cm in diameter, frequently present in association with bronchovascular bundles. Focal collections of intra-alveolar foamy macrophages and interstitial lymphocytes (endogenous lipid pneumonia) were seen adjacent to the metastatic foci (Fig. 3). In some areas, air trapping was observed within the tumor or at the interface of the tumor and inflammatory infiltrates. In relatively spared areas of lung, the parenchyma was remarkable for interstitial lymphocytic infiltrates and scattered intra-alveolar macrophages, an appearance reminiscent of granuloma-poor hypersensitivity pneumonitis (Fig. 3).

Two patients had lung biopsy specimens that did not include the site of cavitation on imaging (one patient had transbronchial biopsy including only a small piece of tumor tissue, and the other had a wedge resection specimen from metastasis in the right lower lobe, but the cavitory lesion was in the left lower lobe).

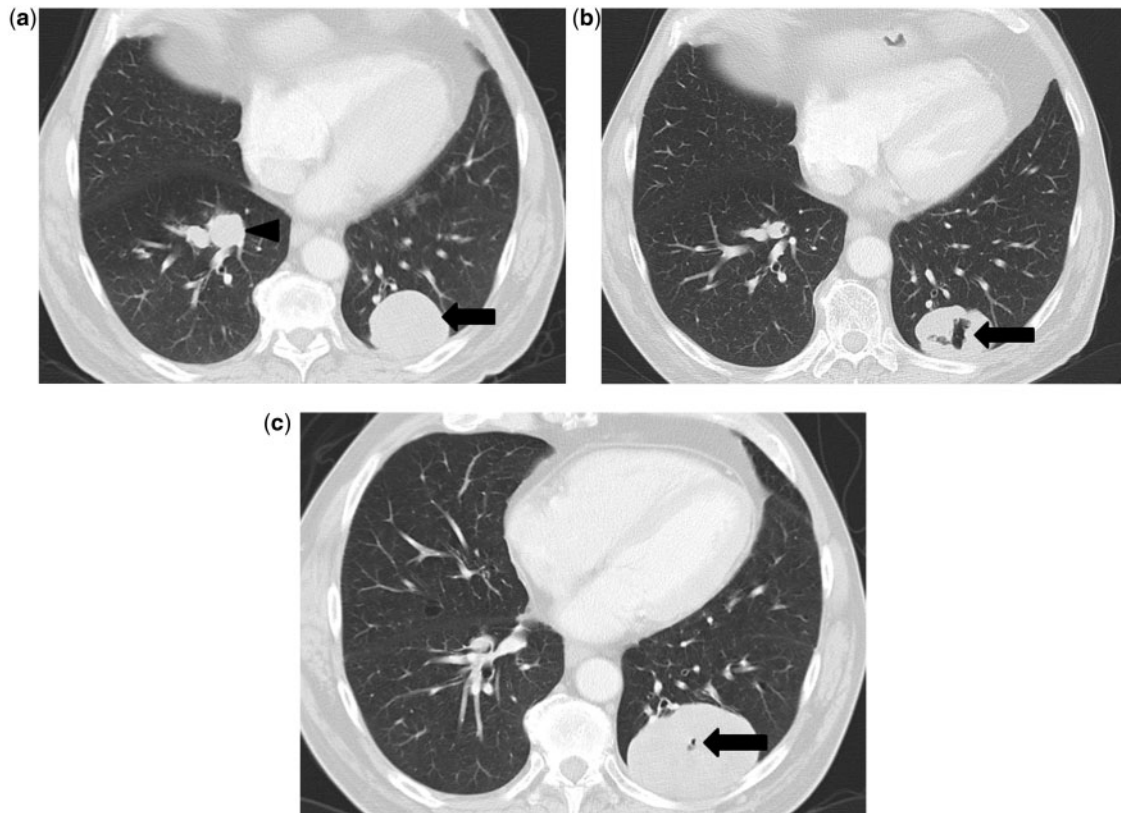


Figure 1 A 64-year-old man with stage IV adenocarcinoma of the lung treated with bevacizumab, carboplatin and paclitaxel. (a) Baseline contrast-enhanced CT of the chest prior to therapy demonstrated a solid dominant mass in the left lower lobe (arrow), without cavitation. A smaller nodule was also noted in the right lower lobe (arrowhead). (b) Follow-up CT scan at 1.5 months after the initiation of therapy demonstrated a cavity developed within the dominant mass (arrow) demonstrating pattern 1 cavitation, with decrease in size of the mass. (c) Further follow-up CT performed 16 months after the initiation of therapy demonstrated filling in of cavitation (arrow) with regrowth of the mass. The bevacizumab was completed 3 weeks prior to this CT scan.

Correlation with clinical characteristics and therapeutic regimen

Development of tumoral cavitation after initiation of bevacizumab therapy was not associated with gender ($P=0.41$), tumor stage ($P=0.48$), tumor histology ($P=1.00$), previous radiation therapy ($P=1.00$), smoking history ($P=0.13$), any comorbidity ($P\geq 0.17$) or adverse events related to bevacizumab including hypertension ($P=0.28$), skin rash ($P=0.68$), proteinuria ($P=1.00$), hemoptysis ($P=1.00$), epistaxis ($P=1.00$), gastrointestinal bleeding ($P=0.36$), deep venous thrombosis or pulmonary embolism ($P=1.00$) (Table 1). The size of the dominant lung tumor at baseline did not differ significantly between patients who developed cavitation and those who did not (median tumor size, 3.8 cm; interquartile range, 2.5–5.7 cm; for cavity group; median tumor size, 3.7 cm; range, 2.2–6.1 cm; for no cavity group; $P=0.85$).

Of 14 patients with cavitation, 13 patients (93%) were treated with the combination of bevacizumab, carboplatin and paclitaxel, and 1 patient was treated with

bevacizumab and irinotecan. However, there was no statistically significant association between the bevacizumab, carboplatin and paclitaxel regimen and the development of tumoral cavitation ($P=0.09$ for the bevacizumab, carboplatin and paclitaxel regimen versus other combination regimen) (Table 2).

When the clinical characteristics were compared among 14 patients who developed cavitation divided into the 3 groups according to the radiographic cavitation patterns, a significant difference was observed in smoking history across the groups: all 3 patients with pattern 3 cavitation were never smokers; all 8 patients with pattern 1 cavitation were current or former smokers ($P=0.006$) (Table 3). The other clinical characteristics did not show significant differences among the 3 groups ($P\geq 0.14$). Hemoptysis was noted in 5 patients in total, including 4 patients who did not develop cavitation and 1 patient who developed a cavity, without a significant difference between the 2 groups ($P=1.00$). All patients had grade 1 hemoptysis. One of 5 patients with baseline tumor cavitation had hemoptysis, however, this was not statistically significant compared with the remaining 67 patients

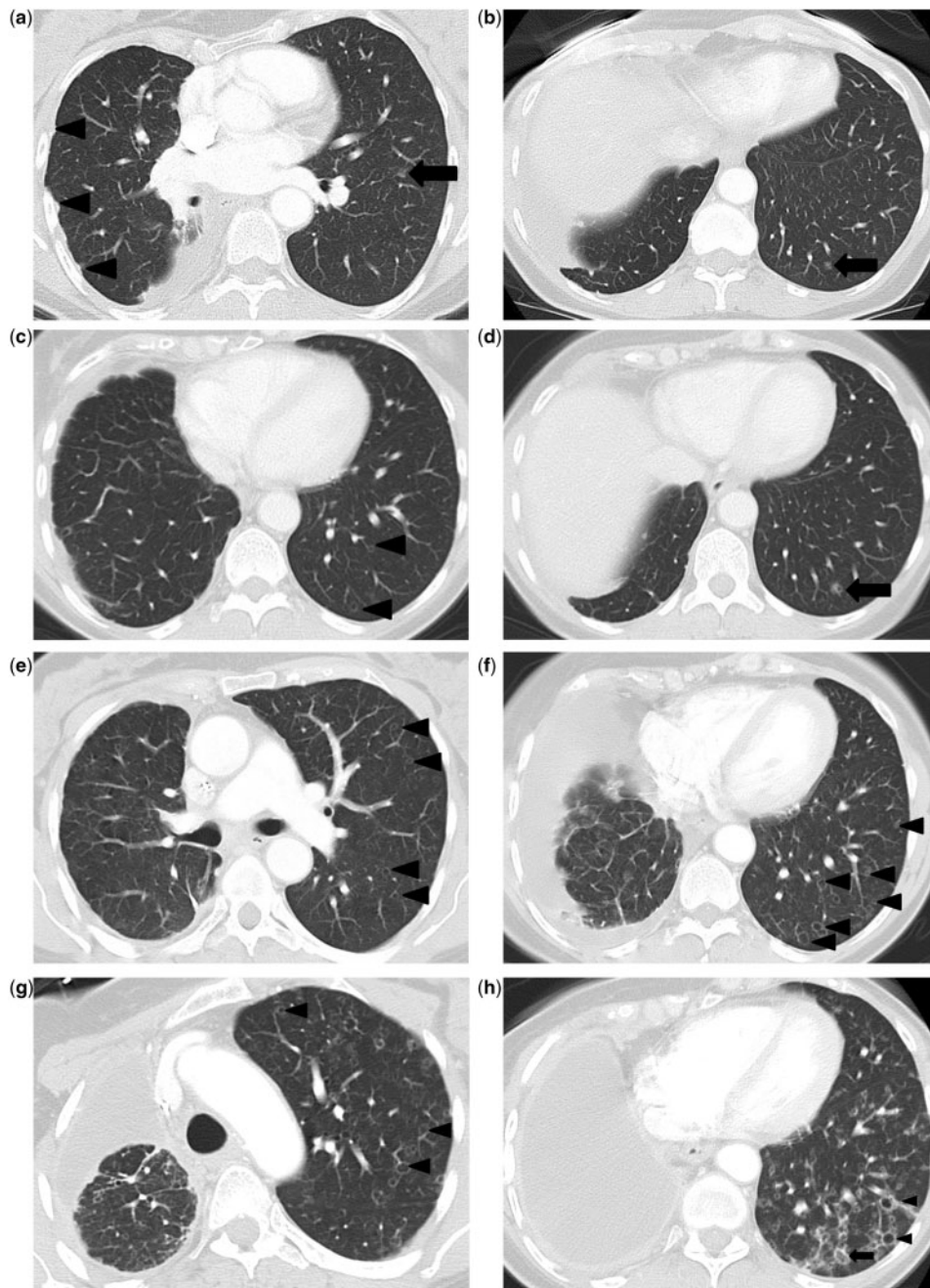


Figure 2 A 53-year-old woman with stage IA adenocarcinoma of the lung who underwent right lower lobectomy 3 years ago, presenting with histologically confirmed recurrent disease in the pleura and lung nodules. (a,b) Baseline contrast-enhanced CT of the chest prior to therapy demonstrated pleural nodularity along the right lung (arrowheads, a) and small faint nodules in the left lower lobe (arrows, a,b). Bevacizumab, carboplatin and paclitaxel therapy was initiated to treat recurrent disease. (c,d) Follow-up CT scan at 13 months of therapy demonstrated development cavitary nodules in both lungs (arrowheads, c), representing pattern 2 cavitation. In some nodules, cavitation developed within the existing solid nodules (arrow, d). The findings were thought to represent disease progression, and the bevacizumab therapy was discontinued at 14 months. The patient was then treated with pemetrexed. (e,f) While on pemetrexed therapy, the patient continued to develop cavitary nodules, which have increased in size and number. Chest CT scan 2 years since the baseline scan demonstrated multiple cavitary nodules in both lungs (arrowheads, e,f), with increase in size and number compared with the prior scans. Based on the findings, pemetrexed was discontinued and docetaxel therapy was initiated. (g,h) CT scan 4 years after the baseline scan demonstrated further increase in size and number of cavitary nodules, with faint opacities surrounding the cavitary nodules representing interstitial abnormalities (arrowheads, h) (pattern 3). Some cavities showed an elongated and tubular appearance at the peripheral and basilar lung (arrows, h). Some of the cavitary nodules are in centrilobular distribution, mimicking the appearance of Langerhans cell histiocytosis (arrowheads, g).

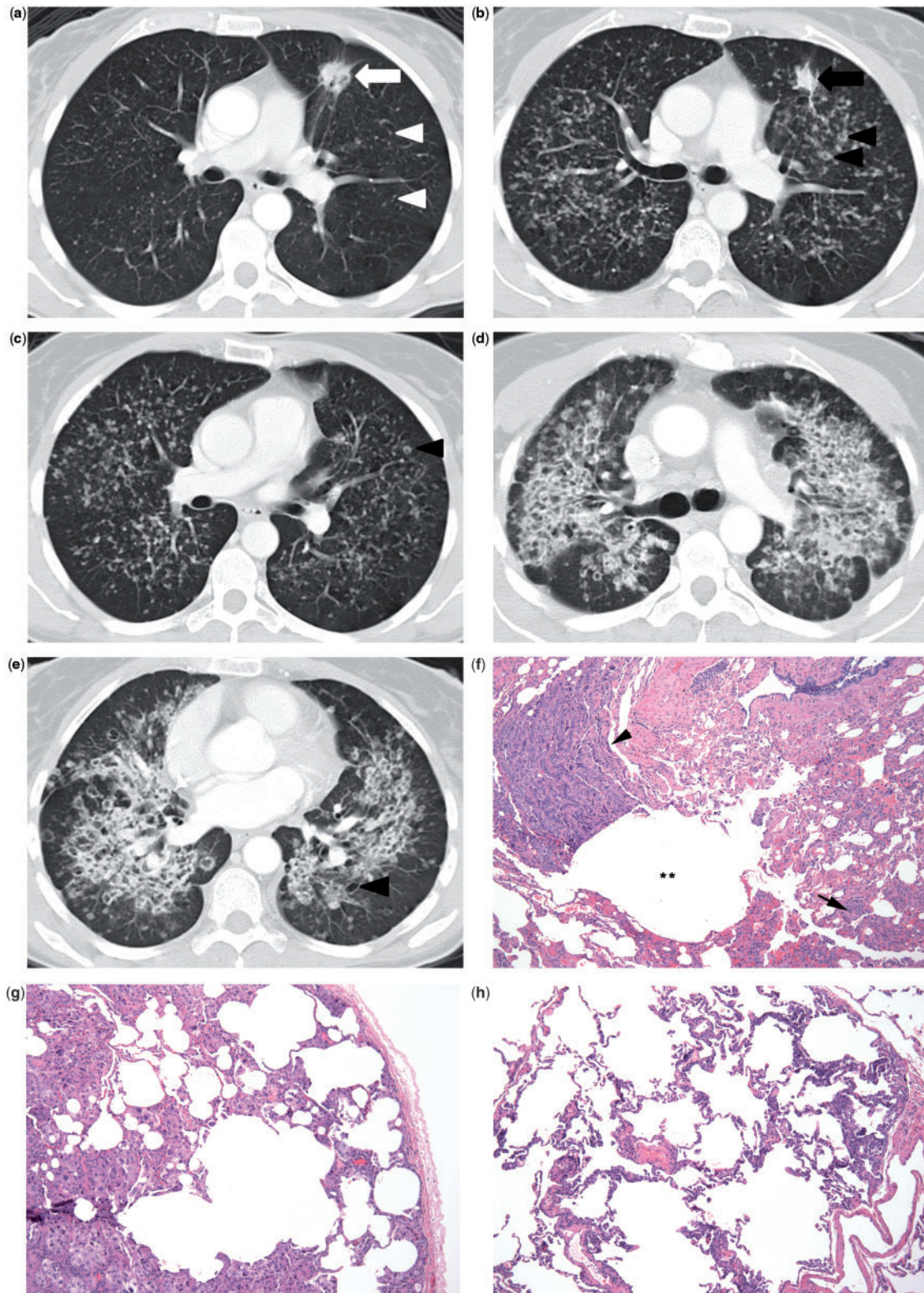


Figure 3 A 46-year-old woman with stage IV adenocarcinoma of the lung treated with bevacizumab, carboplatin and paclitaxel therapy. (a) Baseline CT scan prior to therapy demonstrated a dominant spiculated lesion in the left upper lobe with preexisting cavitation (arrow). Innumerable small metastatic nodules without cavitation were also noted in both lungs (arrowheads). Bevacizumab, carboplatin and paclitaxel therapy was started and response to therapy was noted initially with a decrease in the size of the dominant lesion as well as the metastatic nodules. However, the therapy was discontinued after 8 months due to recurrent and increased pulmonary nodules. The patient was then treated with pemetrexed. (b,c) CT scan 11 months after the baseline scan demonstrated development of cavitation within multiple

Continued

Table 3 Demographic and clinical characteristics of 14 patients who developed cavitation stratified by the radiographic cavity patterns

	No. of patients with cavity pattern 1	No. of patients with cavity pattern 2	No. of patients with cavity pattern 3	P value
Gender				0.14
Male	6	1	0	
Female	2	2	3	
Tumor stage				0.17
IA	0	0	1	
IB	0	0	0	
IIA	1	0	0	
IIB	0	0	0	
IIIA	0	0	1	
IIIB	0	1	0	
IV	7	2	1	
Tumor histology				0.69
Adenocarcinoma	7	3	2	
NSCLC (not otherwise specified)	1	0	1	
Radiation therapy				0.75
Prior to bevacizumab therapy	2	1	2	
None	6	2	1	
Smoking				0.006
Never	0	1	3	
Current or former	8	2	0	
Therapeutic regimen				0.43
Bevacizumab, carboplatin and paclitaxel	8	2	3	
Bevacizumab plus others	0	1	0	
Adverse events				
Hypertension	3	0	2	0.29
Skin rash	0	1	0	0.43
Proteinuria	0	0	0	
Hemoptysis	1	0	0	1.00
Epistaxis	1	2	0	0.29
Gastrointestinal bleeding	1	0	0	1.00
Deep venous thrombosis or pulmonary embolism	1	0	0	1.00

without baseline cavitation 4 of whom developed hemoptysis ($P=0.31$).

Correlation with survival

The progression-free survival and the overall survival did not demonstrate a statistically significant difference between patients who developed cavitation and those who did not ($P=0.49$ and 0.61 , respectively) (Fig. 4A,B). Median progression-free time was 6.0 months among patients without cavitation, and 7.0 months for patients who developed cavitation. The median time to death was 16.3 months among patients without cavitation, and 17.5 months for patients who

developed cavitation. There was no significant difference in the progression-free survival and the overall survival among the 3 groups of patients with different cavitation patterns ($P=0.54$ and 0.52 , respectively).

Discussion

The present study of 72 patients with NSCLC treated with bevacizumab therapy demonstrated that 19% (14/72) of the patients developed cavitory lesions, and that 3 radiographic patterns of tumoral cavitation were observed. Subsequent filling in of cavitation was noted in 79% (11/14) of the patients who developed cavitation.

Figure 3 Continued

lung nodules (arrowheads, b,c), demonstrating pattern 2 cavitation. The dominant lesion has decreased in size since the baseline, the preexisting cavitation at baseline is no longer present, without development of new cavitation (arrow, b). (d,e) Follow-up CT scan 17 months after the baseline scan demonstrated an increase in size and number of innumerable cavitory nodules throughout the lungs, with adjacent interstitial abnormalities (pattern 3). The cavitory nodules were seen mostly along the bronchovascular bundles and had a coalescent appearance with adjacent interstitial opacities. Some of the cavities were tubular and branching (arrowheads, d,e). (f,g,h) Left upper and lower lobe wedge resections were performed 3 weeks after the CT scan shown in (d)–(f). On pathology, metastatic tumor (arrowhead, f) is present adjacent to a terminal bronchiole and its paired arteriole (f; 100 \times magnification). Air is trapped (**, f) between the tumor and uninvolved lung, which shows atelectasis, airspace macrophages, and interstitial chronic inflammation consistent with endogenous/obstructive pneumonia (arrow, f). Metastatic tumor present in the subpleural lung shows central air trapping (g; 200 \times magnification). Lung uninvolved by tumor shows moderate lymphocyte-predominant interstitial infiltrates (h; 100 \times magnification).

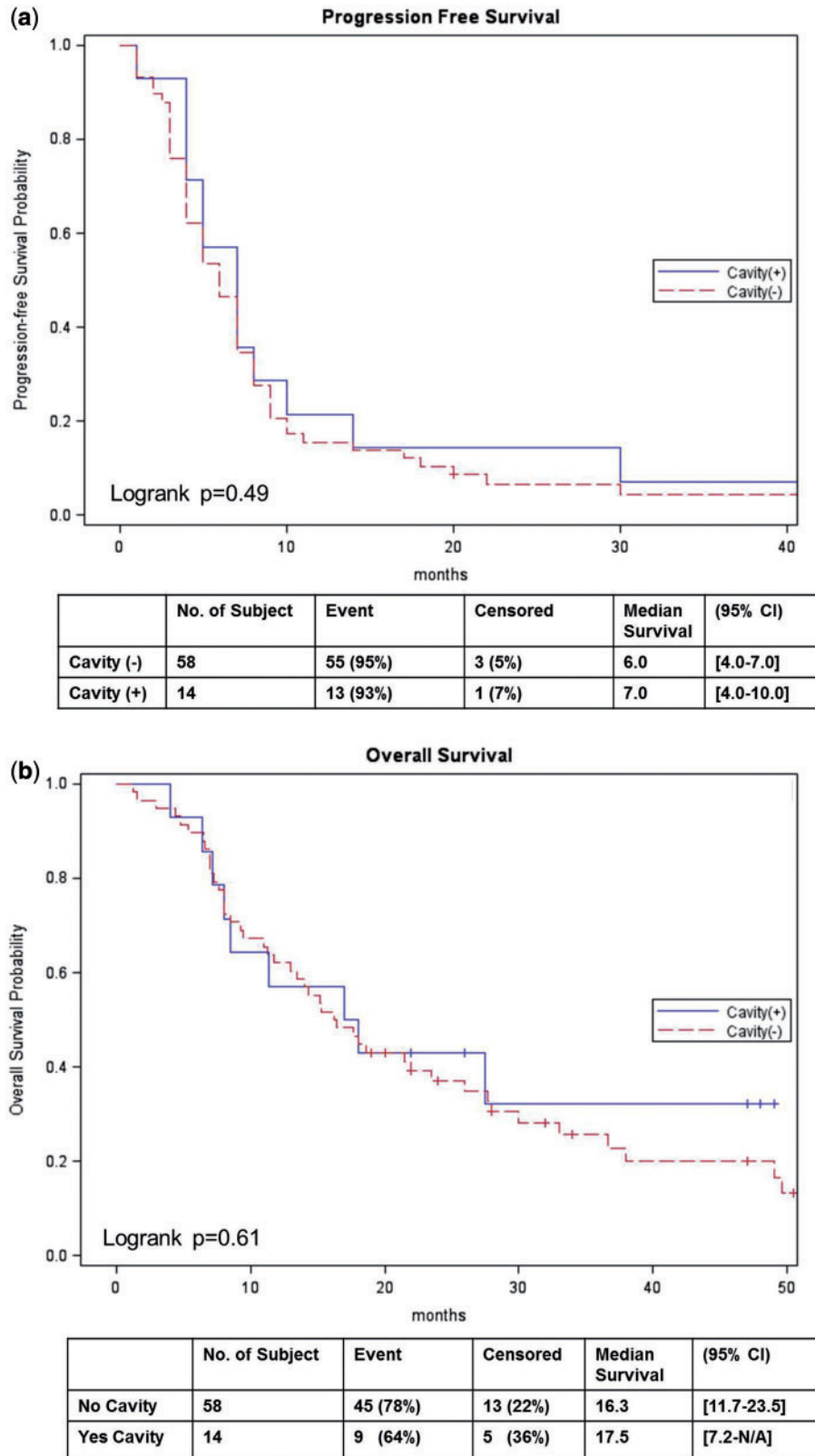


Figure 4 Progression-free survival (a) and overall survival (b) were compared between patients who developed cavitation versus those who did not.

Although the development of tumoral cavitation in NSCLC after antiangiogenic therapy has been previously described, to our knowledge, this is the first study that focuses on a cohort in which all patients received bevacizumab as an antiangiogenic agent, and describes 3 radiographic patterns of tumoral cavitation on CT.

The frequency of cavity development in our cohort (19%, 14/72 in total and 14%, 10/72 during therapy) was essentially similar to the frequency in the previous report by Marom et al.^[10] (14% during therapy for all antiangiogenic agents, 15% during therapy for the subgroup of 41 patients treated with bevacizumab). Among the different therapeutic regimens using bevacizumab, the combination of bevacizumab, carboplatin and paclitaxel had the highest frequency of cavity formation (25%, 13/53). The frequency is also similar to the data in previous reports, including the data on a small subgroup (20%, 2/10) treated with bevacizumab, carboplatin and paclitaxel in the study by Marom et al.^[10], as well as the frequency of cavitation (24%, 8/33) with cediranib (multitargeted tyrosine kinase inhibitor which inhibits VEGF receptors 1, 2, 3; platelet-derived growth factor receptor β and c-kit) reported by Crabb et al.^[11]. In the present study, although statistically not significant, there was a trend that cavity formation was most commonly noted with the combination therapy of bevacizumab, carboplatin and paclitaxel.

Among 14 patients who developed cavitation, 3 radiographic patterns were observed, including (1) development of a cavity within the dominant lung tumor; (2) development of cavitation in non-dominant nodules; and (3) development of cavitation in non-dominant nodules with adjacent interstitial abnormalities. These radiographic patterns of tumoral cavitation have not been described previously; previous reports focused on the clinical implications especially hemoptysis and impact on response assessment^[10,11]. The evolution of cavitory lesions was particularly notable in 3 patients. All started with pattern 2 cavitation and subsequently developed pattern 3 cavitation, which manifested radiographically as multiple bizarre cavitory nodules with adjacent interstitial abnormalities, an appearance mimicking pulmonary Langerhans cell histiocytosis. All patients with pattern 3 cavitation were never smokers. Radiologic interpretation of the finding was challenging, because it was unclear if the increasing bizarre cavitation represented an increase in cavitory metastasis, and therefore progression of disease; or treatment response, in which case the underlying microscopic metastatic lesions became detectable by CT due to cavitation; or drug-induced lung disease. The pathology of 1 of these patients revealed innumerable metastatic deposits adjacent to a terminal bronchiole causing air trapping. In patients treated with bevacizumab demonstrating pattern 3, in addition to cavitation of metastatic nodules, metastatic nodules along the bronchioles may be causing

bronchiolar obstruction and airway distention leading to multiple bizarre cavity formation, resulting in CT appearance mimicking Langerhans cell histiocytosis^[14].

The majority of patients (79%, 11/14) who developed cavitation showed filling in of cavity on follow-up CT scans. Notably, filling in of cavitation was observed after the completion of bevacizumab therapy in all 11 patients. This observation emphasizes the importance of incorporating tumoral cavitation and filling-in phenomena in response assessment of patients with NSCLC treated with bevacizumab therapy, even after the completion of bevacizumab therapy and during the subsequent second-line or third-line therapy.

It has been postulated that tumoral cavitation occurs through central necrosis of lesions after inhibition of angiogenesis, and is associated with response to antiangiogenic treatment^[11]. Filling in of cavitation by regrowth of solid tumor is considered to be a morphological change representing tumor progression^[11,15], as demonstrated in other solid tumors such as gastrointestinal stromal tumors treated with imatinib and metastatic renal cell carcinomas treated with antiangiogenic therapy, where enhancing tumor regrowth is noted within necrotic treated lesions^[16–19]. Since tumor progression by filling in of the cavity is not captured by the conventional RECIST-based response assessment, an alternate method of tumor measurement incorporating tumoral cavitation was first proposed in 2009, and has been shown to alter response assessment and time to progression in a minority of patients^[11]. Another criteria including the alternate method for measuring cavitory lesions has been proposed for NSCLC treated with epidermal growth factor receptor inhibitors, and demonstrated significant association of overall survival^[15]. Further prospective validation of the alternate measurement method in a larger population as well as efforts to incorporate qualitative information such as morphological changes in tumoral cavitation may be needed to establish the optimal response criteria to antiangiogenic therapy in patients with NSCLC.

There was no statistically significant difference in the demographic and clinical characteristics as well as the survival data between the patients who developed cavitation and those who did not, confirming the previously reported observations in our population treated with bevacizumab^[10,11]. There was no significant difference in the occurrence of hemoptysis between patients who developed cavitation and those who did not, as described previously^[10,12]. All 5 patients with hemoptysis had grade 1 hemoptysis, and no case of severe hemoptysis was observed in our cohort without squamous histology. In the study by Sandler et al.^[12], baseline tumor cavitation was suggested as a potential risk factor for severe pulmonary hemorrhage. In our cohort, there was no statistically significant difference in the occurrence of grade 1 hemoptysis between patients with baseline cavitation

and those without baseline cavitation. No significant difference was seen in clinical and survival data across the 3 groups of different cavitation patterns, except for the smoking history. It is not clear how the smoking history affected the radiographic patterns of tumoral cavitation.

The limitations of the present study include its retrospective design and the relatively small number of patients who developed cavitation. Given the frequency of tumoral cavitation of 19%, a larger cohort will be needed to further investigate the difference in clinical and survival data across the patient groups with different cavitation patterns. It would be ideal to have a control group of patients with NSCLC who are eligible for bevacizumab therapy but receive conventional chemotherapy without bevacizumab, in order to compare the frequency of cavitation. Lastly, we did not assess if response assessment is altered if cavitation is taken into consideration in tumor measurement. Although the altered measurement for cavitory lesions has been proposed, it has not been widely utilized in response assessment in daily practice and clinical trials, and there has been no consensus on how to measure cavitory lung lesions to best represent tumor burden.

In conclusion, the development of tumoral cavitation in patients with NSCLC treated with bevacizumab therapy was noted in 19% of patients. Tumoral cavitation demonstrated 3 radiographic patterns, and the majority of the patients (79%) demonstrated subsequent filling in of cavitation. Knowledge of tumoral cavitation associated with bevacizumab therapy and awareness of the radiographic patterns of cavitation as well as the subsequent filling-in phenomenon is important to accurately assess therapeutic response and optimize therapeutic decision making. Our observation in the present study, in combination with the further investigation in a larger population, may help to improve response assessment in patients with NSCLC treated with antiangiogenic therapy and contribute to prolongation of survival.

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