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Spread through Air Spaces (STAS) in Solitary Pulmonary Metastases from Colorectal Cancer (CRC)

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Abstract

Background Spread through air spaces (STAS) is a recently described route of tumor invasion associated with poor prognosis in primary lung cancer. Aim of this study was to investigate the presence of STAS and to assess its prognostic significance in patients undergoing pulmonary metastasectomy (PM) for solitary metastases from colorectal cancer (CRC).

Materials and Methods All 49 CRC patients (30 male and 19 female, median age 66 years) who underwent PM between January 2008 and December 2015 were retrospectively analyzed.

Results STAS was identified in 26.5% ($n = 13$) of resected specimens. Location of pulmonary lesions (central vs. peripheral) was assessed based on the available computed tomography imaging ($n = 47$, 96%). STAS was detected in all five patients with central metastases (100%) versus 7 of 42 (17%) with peripheral metastases ($p = 0.0001$). Locoregional recurrence occurred in STAS-positive patients ($n = 4$ of 13 vs. $n = 0$ of 36), all STAS-negative patients remained recurrence-free ($p = 0.003$). Median number of alveoli with STAS involvement was four (range from 2 to 9). There was statistically positive relationship between the number of alveoli invaded with STAS and locoregional recurrence of metastases ($p = 0.0001$). The presence of STAS is not a factor affecting the 5-year overall survival rate ($p = 0.6651$).

Conclusion We identified STAS as a frequent finding in resected CRC lung metastases and found insignificant association with outcome.

Keywords
- metastases/ metastasectomy
- lung cancer
- diagnosis
- histology

Introduction

The lung is the second most common site of colorectal cancer (CRC) metastases, and colorectal metastases are the most common indication for pulmonary metastasectomy (PM).[1] Many retrospective studies demonstrated that PM can lead to improved disease control and prolonged survival in carefully selected patients. The reported post-PM 5-year survival rate is approximately 50%, which is significantly better than that predicted for metastatic CRC and indicates that resection provides a survival benefit.[2] Surgery is the standard treatment for patients with isolated lung metastases,[3] but local

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recurrence within the surgical margin following a limited surgical approach is a known problem, with relatively high incidence.[4,5] One of the most important factors determining the occurrence of local recurrence in the surgical margin in patients with pulmonary CRC metastases is the number of aerogenic spreads with floating cancer cell clusters,[4,5] which was later named "spread through air spaces (STAS)" in primary lung cancer.[6] STAS has been recognized as a new pattern of invasion in lung adenocarcinoma and its role in worsening prognosis and increasing the likelihood of recurrence was postulated.[7] In published studies, the classification and definition of STAS varies in terms of distance from the main tumor and morphologic features.[8] The aim of this study is to further investigate the prevalence and prognostic significance of STAS in lung metastases from CRC.

Patients and Methods

All patients who underwent anatomical (lobectomy/segmentectomy) and nonanatomical (wedge) pulmonary resection with curative intent for solitary pulmonary metastases from CRC (SPM-CRC) at our single institution between 2008 and 2015 were retrospectively analyzed. Selection criteria for surgery were as follows: stable primary tumor site, intent of complete (R0) resection, and cardiorespiratory fitness. Stable tumor site meant either the absence of a primary tumor, for example, after resection or definitive radiochemotherapy applied, or the absence of primary tumor progression according to standard oncological follow-up criteria at the time the indication for PM was made. All metastatic lesions were evaluated by a senior pathologist to ensure complete (R0) resection.

Preoperative patient characteristics are outlined in ►**Table 1**.

Table 1 Patient characteristics after PM for solitary colorectal metastasis

Characteristics	Number of patients	%
Total	49	
Gender		
Male	30	61.2
Female	19	38.8
Primary tumor site		
Colon	14	28.6
Rectum	35	71.4
Synchronous metastases		
No	45	91.8
Yes	4	8.2
Extrapulmonary metastases		
No	34	69.4
Yes	15	30.6
Location of pulmonary metastasis in CT		
Central	5	10.2
Peripheral	42	85.7
Missing	2	4.1
Presence of STAS		
No	36	73.5
Yes	13	26.5
Surgical technique		
Open	41	83.7
VATS	8	16.3
Type of pulmonary resection		
Anatomical resection	24	49.0
Wedge resection	25	51.0
Adjuvant therapy for primary tumor		
No	11	22.4
Yes	38	77.6
Induction therapy prior to PM		
No	43	87.8
Yes	6	12.2

Abbreviations: CT, computed tomography; PM, pulmonary metastasectomy; STAS, spread through air spaces; VATS, video-assisted thoracic surgery.

Pathological Analysis

The histopathology slides of resected SPM-CRC were reassessed by an experienced pathologist blinded to the patients' clinical data ►**Fig. 1**. The different diagnostic criteria for STAS in the various studies may have contributed to numerous discrepancies in the pathological identification of STAS. Onozato et al[9,10] used the term "tumor island" to refer to isolated, large collections of tumor cells within alveolar spaces without well-defined configuration.[8] Warth et al[11] classified tumor cells as STAS when there is no direct connection of the cells to the main tumor mass. Warth et al[11] have also categorized STAS according to their distance from the primary tumor as limited when the solid cell nests are no more than 3 alveoli away from the primary tumor and as extensive when they are more than 3 alveoli away.

In our study, STAS was defined morphologically as the presence of tumor cells without direct connection to the main tumor mass. To reduce the risk of including artificially dissected cells during metastasis resection or grossing, an accumulation of more than five tumor cells in the alveolar space was considered STAS.[5,11] However, we identify isolated large cluster of tumor cells "Tumor Island" as a subtype of STAS. In regards to the distance parameter, STAS was located in intra-alveolar spaces within 0.5 mm of the main tumor margin. If the alveoli are collapsed (atelectatic), for example, we considered STAS from the third alveolar space from the main tumor as a method to measure the distance. Slides were digitized and reevaluated using a virtual microscope.

Analysis of Computed Tomography Images and Locoregional Recurrence

The central versus peripheral location of pulmonary metastases was assessed on preoperative chest computed tomography (CT) and defined according to the American College of

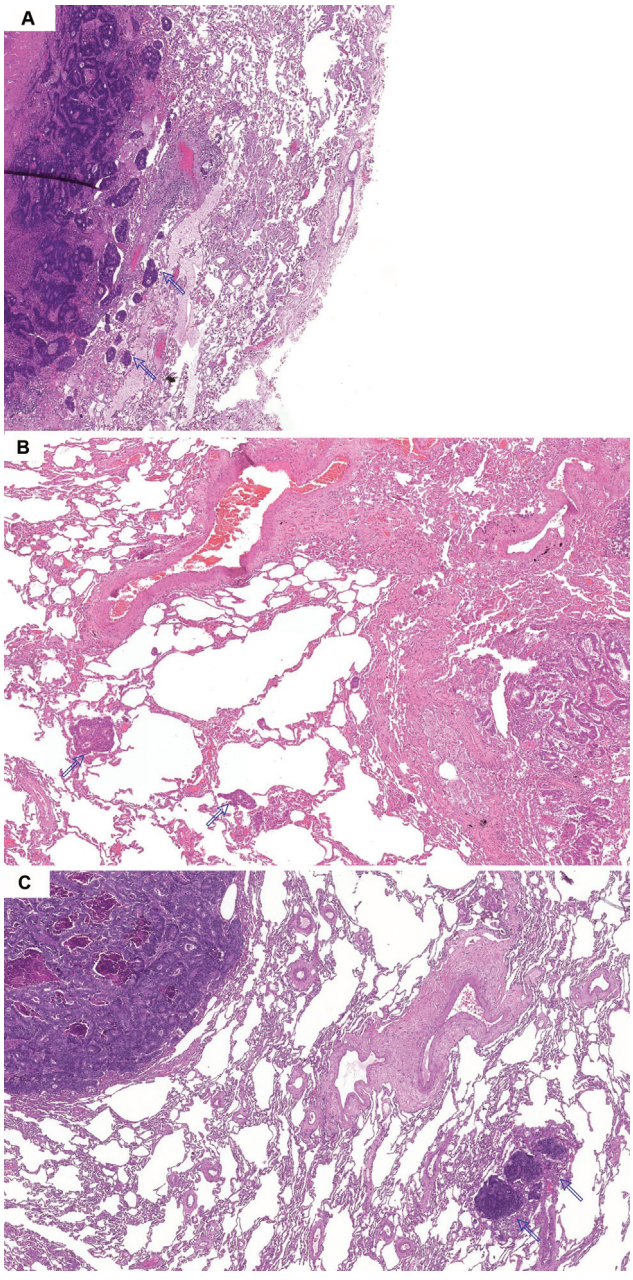

Fig. 1 (**A**–**C**) Spread through air spaces (STAS) cluster (as indicated by the arrowheads) detected in the air spaces of the lung parenchyma beyond the margin of the main tumor. (**C**) Noted a reactive response in the intra-alveolar space with an isolated tumor island (presence of lymphocytes and fibroblasts).

Chest Physicians (ACCP), National Comprehensive Cancer Network (NCCN), and European Society of Thoracic Surgery (ESTS) guidelines. The ACCP defines central lesions as those located in the inner third of the hemithorax, whereas the NCCN and ESTS define central lesions as those located in the inner two-thirds of the hemithorax.[12] In this study, we decided to apply the NCCN and ESTS definition of central lesion. Postoperative chest CT images were reviewed for locoregional recurrence. Recurrence was classified either as locoregional, or as tumor evidence within the same segment/lobe or ipsilateral side of the original metastatic lesion. All lesions radiologically suspected for recurrence were qualified for resection. ►**Fig. 2** demonstrates the thirds concept of hemithorax.

Statistical Analysis

Categorical variables including gender, location of STAS, and other specified factors, were assessed using the chi-square test to analyze the relationship between STAS and locoregional recurrence of metastases. The significance of differences between the two groups (locoregional recurrence and number of the tumor-surrounding alveoli affected by STAS) was assessed using the Mann–Whitney test.

The effect of age, disease-free interval (DFI), and size of pulmonary metastasis on the risk of STAS was assessed using three logistic regression models in which the dependent variable was the presence of STAS and the independent variables were, in turn, age, DFI, and size of pulmonary metastasis. The results were grouped with the mean and standard deviation of each factor in relation to the presence of STAS, the odds ratio of the presence of STAS with a 1-year change, a 1-month change in DFI, and a 1-cm change in metastasis size, and the p-value of the test probability to assess the significance of the effect of each factor on the presence of STAS. The odds ratio values of STAS for the comparison groups of a given factor (together with the 95% confidence interval) were calculated. For both univariable and multivariable analysis, a probability value (p) of less than 0.05 was considered statistically significant. STATISTICA 10.0 (StatSoft, Tulsa, Oklahoma, United States) software was used for statistical analysis.

Results

Forty-nine patients (30 men and 19 women) were included in the study. The presence of STAS was confirmed in 26.5% ($n = 13$) patients. STAS was detected in 14.3% (2 of 14) patients with colon carcinoma compared with 31.4% (11 of 35) patients with rectal carcinoma. Although there was a clear difference between these site-dependent frequencies, it was not statistically significant for STAS ($p = 0.2195$). The majority of patients (83.7%, $n = 41$) underwent open surgery, 16.3% ($n = 8$) of patients underwent video-assisted thoracic surgical resections, with no statistical significance for STAS ($p = 0.325$). Twenty-five patients (49%) underwent wedge resection, while anatomical resections were performed in 51% ($n = 24$) of patients including segmentectomy ($n = 13$), lobectomy ($n = 10$), and bilobectomy ($n = 1$). There was no correlation between STAS and extent of resection (anatomical vs. wedge, $p = 0.376$). Resections of metastatic lesions were performed using staplers and cautery. Laser resections were not performed in the presented group. Systematic lymph node dissection was not performed routinely. The association between STAS and clinical characteristics of patients after resection of pulmonary metastases was evaluated and summarized in ►**Table 2**.

Clinical-Pathological Findings and Locoregional Recurrence

The median length of follow-up was 95 months (range 50–163 months). The median size of the resected lesion was 1.4 cm

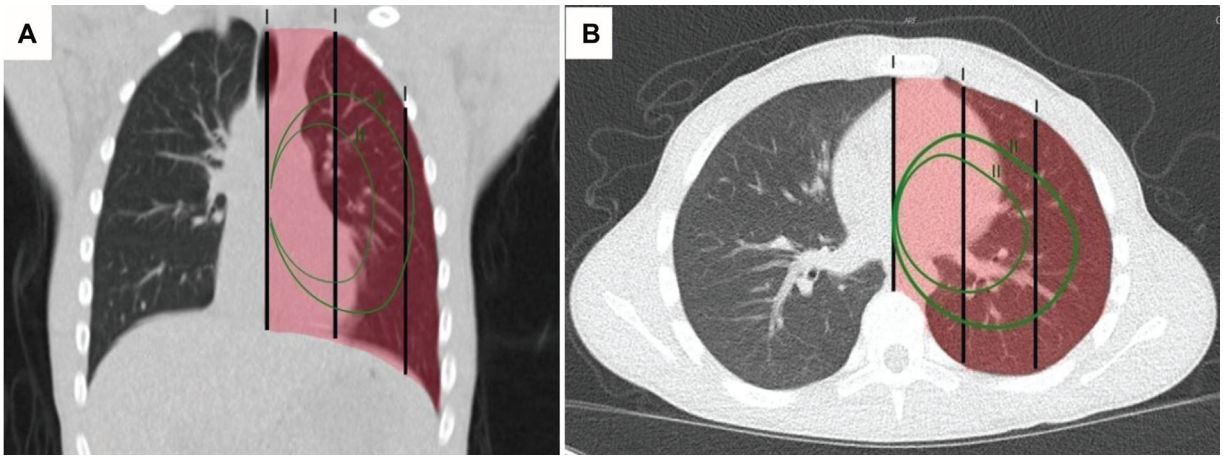

Fig. 2 (A) The (I) lines represent the thirds of the hemithorax that are straight lines on a coronal computed tomography (CT) image of the thorax parallel to the chest wall. (B) The (II) lines also represent the thirds of the hemithorax seen on an axial CT image of the thorax as eccentric circles emanating from the hilum.

(range 0.6–4.5 cm). The median number of the STAS-involved alveoli was 4 (range 1–9). There was a statistically significant association between the number of tumor-surrounding alveoli invaded by STAS and locoregional recurrence of metastases ($p = 0.0001$ ►**Table 4**). ►**Table 3** demonstrates associations between STAS and other factors.

Ninety-six percent ($n = 47$) of preoperative CT images were available for analysis of the location of metastases (central vs. peripheral). There were 10.2% ($n = 5$) centrally versus 85.7% ($n = 42$) peripherally located lesions (►**Table 1**). We found that all 5 patients with central metastases were STAS positive compared with 17% ($n = 7$ of 42) peripheral metastases ($p = 0.0001$, ►**Table 2**).

All STAS-negative patients remained recurrence-free. In 30.7% of STAS-positive patients ($n = 4$ of 13) there was radiological suspicion of locoregional recurrence. All 4 patients with a suspected lesion underwent pulmonary resection, which confirmed the locoregional recurrence. The presence of STAS was therefore significantly associated with locoregional recurrence ($p = 0.003$). Five-year overall survival rates in 13 STAS-positive patients were not significantly different compared with 36 STAS-negative patients ($p = 0.6651$, ►**Fig. 3**).

Discussion

Previous studies reported the incidence of pulmonary metastases of 5.6% in rectal carcinoma and 3.7% in colon carcinoma, almost 5% of CRC patients had synchronous lung metastases.[13,14] In other reviews, the incidence of CRC lung metastases ranged from 5 to 15%, including metachronous metastases.[13,15] Although controversial according to many authors, so-called curative-intent surgery remains the first-line treatment worldwide for CRC lung metastases.[13,16] Several retrospective studies have concluded that PM provides long-term survival benefits, but this has not been supported by the results of randomized trials. A challenge to the curative intent concept of pulmonary metastatic CRC is the recurrence of metastases; numerous retrospective studies have investigated this topic.

Previous studies have shown recurrence of CRC lung metastases in 50% of patients after PM; multiple recurrence prognosticators have been identified: DFI, carcinoembryonic antigen, number of lesions, and thoracic lymph node involvement.[17] STAS is being investigated as one of these prognostic factors.

Some studies described STAS as a mode of neoplastic spread that pulmonary metastases may adopt.[4,5] In 2015, STAS was defined as one or more pathological micropapillary clusters, solid nests, or single tumor cells extending beyond the tumor edge into the air spaces of the surrounding lung parenchyma and detaching from the main tumor.[15] The latest 2021 World Health Organization Classification of Thoracic Tumours recognizes STAS as a histological feature of prognostic significance in adenocarcinoma of the lung.[18] In our study of 49 patients with solitary CRC lung metastases, we identified STAS in 26.5% ($n = 13$) of patients. There was a close association between STAS and the central location of lung metastases on CT images ($p = 0.0001$). In our study, we aimed to distinguish STAS from artifacts occurred during surgical resection. Several studies reported relapse within the resection margin after pulmonary wedge resection for pulmonary CRC metastases.[4,5] We hypothesize that due to the distant presence of STAS beyond the margin of pulmonary metastatic lesion, local recurrence may be more extensive than recurrence only within the surgical resection margin. Nevertheless, all 5 patients with centrally located metastases underwent anatomical resection. Of the 42 patients with peripheral metastases, 19 underwent anatomical resection and 23 underwent wedge resection. Therefore, it is very unlikely that the central lesions had insufficient resection margin.

In our study, STAS was strongly associated with locoregional recurrence and the number of STAS-positive alveoli was a significant factor in determining local recurrence ($p = 0.0001$). Histological examination showed no association between STAS and the size of lung metastases ($p = 0.908$).

Table 2 Relationship between STAS and clinical characteristics of patients after PM

Variables	STAS-positive number	%	OR (95% CI)	*p*-Value
Gender			2.67 (0.63–11.35)	0.175
Male	10 ($n=30$)	33.3		
Female	3 ($n=19$)	15.8		
Primary tumor site			2.75 (0.52–14.44)	0.219
Colon	2 ($n=14$)	14.3		
Rectum	11 ($n=35$)	31.4		
Synchronous metastasis			0.92 (0.09–9.69)	0.942
No	12 ($n=45$)	26.7		
Yes	1 ($n=4$)	25.0		
Extrapulmonary metastasis			0.60 (0.14–2.60)	0.491
No	10 ($n=34$)	29.4		
Yes	3 ($n=15$)	20.0		
Location of pulmonary metastasis in CT			52.07 (2.59–1046.1)	0.0001
Central	5 ($n=5$)	100		
Peripheral	7 ($n=42$)	17		
Surgery technique			2.90 (0.32–26.16)	0.325
Open	12 ($n=41$)	29.3		
VATS	1 ($n=8$)	12.5		
Type of PM			1.79 (0.49–6.53)	0.376
Anatomical resection	5 ($n=24$)	20.8		
Wedge resection	8 ($n=25$)	32.0		
Adjuvant therapy for primary tumor			0.95 (0.21–4.31)	0.949
No	3 ($n=11$)	27.3		
Yes	10 ($n=38$)	26.3		
Induction therapy			1.45 (0.23–9.07)	0.687
No	11 ($n=43$)	25.6		
Yes	2 ($n=6$)	33.3		

Abbreviations: CI, confidence interval; CT, computed tomography; OR, odds ratio; PM, pulmonary metastasectomy; STAS, spread through air spaces; VATS, video-assisted thoracic surgery.

Table 3 Correlation between STAS and age, size of metastases, and DFI

Variable	Presence of STAS				OR (95% CI)	*p*-Value
	No		Yes			
	Mean	SD	Mean	SD		
Age (y)	65.3	11.7	60.2	10.0	0.962 (0.910–1.017)	0.1742
Size of pulmonary metastasis (cm)	1.76	1.01	1.72	1.16	0.964 (0.517–1.799)	0.9089
DFI (mo)	28.8	20.9	37.7	34.0	1.014 (0.989–1.039)	0.2755

Abbreviations: CI, confidence interval; DFI, disease-free interval; OR, odds ratio; SD, standard deviation; STAS, spread through air spaces.

Table 4 Correlation between number of STAS clusters and locoregional recurrence of metastasis

	Locoregional recurrence of metastases						
	No ($n=45$)			Yes ($n=4$)			
	Mean	Median	SD	Mean	Median	SD	*p*-Value
No. of STAS clusters	0.23	0	0.84	4.00	3.5	1.41	0.0001

Abbreviations: SD, standard deviation; STAS, spread through air spaces.

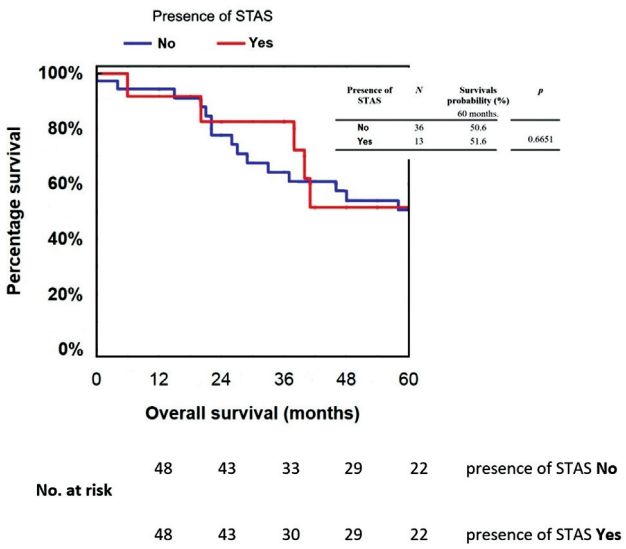

Fig. 3 Five-year survival rate in spread through air spaces (STAS)-positive versus STAS-negative patients with solitary colorectal lung metastasis.

As most lung tissue consists of air spaces, the likelihood of tissue fragments being displaced and trapped in these spaces during surgery is much higher. The spread of benign or malignant tissue fragments in airspaces may be caused by mechanical stresses at the tissue level as an artifactual effect. This artifact occurs in tumors with poor cohesiveness and fewer intercellular adhesions, which is responsible for the worsened prognosis.[19] On the other hand, we suggest that the tumor microenvironment (TME) may be responsible for the origin of STAS. TME is often associated with tumorigenesis, as it indicates the involvement of tumor cells in surrounding stromal cells, which affects tumor progression. Interestingly, nonmalignant cells in the TME play an important role in all phases of carcinogenesis.[8,20]

Importantly for the surgeons, this study did not demonstrate statistical significance between anatomical versus wedge resection in terms of the presence of STAS, nor differences in post-PM overall survival between patients with and without STAS. We believe that the decision between anatomical and wedge resection should not be made solely on the basis on the STAS presence to avoid local recurrence, as metastatic disease may also relapse despite anatomical resection. The incidence of intrathoracic lymph node involvement at the time of PM is higher in CRC compared with other epithelial pathologies, ranging from 12 to 44%. Intrathoracic lymph node involvement has been found to be a negative survival prognosticator for pulmonary metastatic CRC.[21,22] However, mediastinal lymph node dissection is not routinely performed during PM.[13]

The limitation of our study is the small size of the presented cohort. However, the broad definition and different diagnostic criteria for STAS in previous studies may lead to different analyses, for example, in our study, we identified the isolated, tumor island as a subtype of STAS. Another limitation is the single-institution retrospective design, for this reason, our analysis should rather be considered as a hypothesis-generating case series study.

Conclusion

Through this study, we were able to investigate the presence of STAS in solitary CRC lung metastases and its prognostic significance by associating it with other clinicopathological factors. Our most important finding is the significant association between centrally located CRC metastases and the presence of STAS.

Conflict of Interest

None declared.

Acknowledgment

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References

1 Treasure T, Milošević M, Fiorentino F, Macbeth F. Pulmonary metastasectomy: what is the practice and where is the evidence for effectiveness? Thorax 2014;69(10):946–949
2 Nelson DB, Tayob N, Mitchell KG, et al. Surgical margins and risk of local recurrence after wedge resection of colorectal pulmonary metastases. J Thorac Cardiovasc Surg 2019;157(04):1648–1655
3 Pfannschmidt J, Dienemann H, Hoffmann H. Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series. Ann Thorac Surg 2007;84(01):324–338
4 Shiono S, Ishii G, Nagai K, et al. Predictive factors for local recurrence of resected colorectal lung metastases. Ann Thorac Surg 2005;80(03):1040–1045
5 Takeda-Miyata N, Konishi E, Tanaka T, et al. Prognostic significance of spread through air spaces in pulmonary metastases from colorectal cancer. Lung Cancer 2020;149:61–67
6 Kadota K, Nitadori J-I, Sima CS, et al. Tumor spread through air spaces is an important pattern of invasion and impacts the frequency and location of recurrences after limited resection for small stage I lung adenocarcinomas. J Thorac Oncol 2015;10(05):806–814
7 Travis WD, Brambilla E, Nicholson AG, et al; WHO Panel. The 2015 World Health Organization Classification of Lung Tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015;10(09):1243–1260
8 Toki MI, Harrington K, Syrigos KN. The role of spread through air spaces (STAS) in lung adenocarcinoma prognosis and therapeutic decision making. Lung Cancer 2020;146:127–133
9 Onozato ML, Kovach AE, Yeap BY, et al. Tumor islands in resected early-stage lung adenocarcinomas are associated with unique clinicopathologic and molecular characteristics and worse prognosis. Am J Surg Pathol 2013;37(02):287–294
10 Onozato ML, Klepeis VE, Yagi Y, Mino-Kenudson M. A role of three-dimensional (3D) reconstruction in the classification of lung adenocarcinoma. Stud Health Technol Inform 2012; 179:250–256
11 Warth A, Muley T, Kossakowski CA, et al. Prognostic impact of intra-alveolar tumor spread in pulmonary adenocarcinoma. Am J Surg Pathol 2015;39(06):793–801
12 Casal RF, Vial MR, Miller R, et al. What exactly is a centrally located lung tumor? Results of an online survey. Ann Am Thorac Soc 2017; 14(01):118–123

13 Handy JR, Bremner RM, Crocenzi TS, et al. Expert consensus document on pulmonary metastasectomy. Ann Thorac Surg 2019;107(02):631–649
14 Qiu M, Hu J, Yang D, Cosgrove DP, Xu R. Pattern of distant metastases in colorectal cancer: a SEER based study. Oncotarget 2015;6(36):38658–38666
15 Tan KK, Lopes GdeL Jr, Sim R. How uncommon are isolated lung metastases in colorectal cancer? A review from database of 754 patients over 4 years. J Gastrointest Surg 2009;13(04): 642–648
16 Hou Z, Zhang H, Gui L, Wang W, Zhao S. Video-assisted thoracoscopic surgery versus open resection of lung metastases from colorectal cancer. Int J Clin Exp Med 2015;8(08):13571–13577
17 Hwang MR, Park JW, Kim DY, et al. Early intrapulmonary recurrence after pulmonary metastasectomy related to colorectal cancer. Ann Thorac Surg 2010;90(02):398–404
18 Tsao MS, Nicholson AG, Maleszewski JJ, Marx A, Travis WD. Introduction to 2021 WHO Classification of Thoracic Tumors. J Thorac Oncol 2022;17(01):e1–e4
19 Blaauwgeers H, Flieder D, Warth A, et al. A Prospective study of loose tissue fragments in non-small cell lung cancer resection specimens: an alternative view to "spread through air spaces". Am J Surg Pathol 2017;41(09):1226–1230
20 Arneth B. Tumor microenvironment. Medicina (Kaunas) 2019;56 (01):E15
21 Pfannschmidt J, Klode J, Muley T, Dienemann H, Hoffmann H. Nodal involvement at the time of pulmonary metastasectomy: experiences in 245 patients. Ann Thorac Surg 2006;81(02):448–454
22 Ercan S, Nichols FC III, Trastek VF, et al. Prognostic significance of lymph node metastasis found during pulmonary metastasectomy for extrapulmonary carcinoma. Ann Thorac Surg 2004;77(05): 1786–1791