# Lymphatic drainage of lung cancer follows an intersegmental pathway within the visceral pleura

Alex Fourdrain[1,2], Julien Epailly[1], Chloé Blanchard[1], Olivier Georges[1], Jonathan Meynier[3], Pascal Berna[1]

[1]Department of Thoracic Surgery, Amiens University Hospital, Amiens, France

[2]Research Unit SSPC (Simplification des Soins des Patients chirurgicaux Complexes), Amiens University Hospital, Amiens, France

[3]Department of Biostatistics, Clinical Research and Innovation Directorate, Amiens University Hospital, Amiens, France

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Corresponding author:

Alex Fourdrain, MD

Department of Thoracic Surgery, Amiens University Hospital, F-80054 Amiens, France

Phone: +33-322-087-328 Fax: +33-322-455-657

E-mail: fourdrain.alex@chu-amiens.fr

## Highlights

- Lung cancers are known to be highly lymphophilic tumors

- Lymphatic drainage of the lung follows both a peribronchial and a visceral pleura pathway

- Lymphatic drainage of lung cancer in the visceral pleura largely follows an intersegmental pathway

- Peripheral location of the tumor is a risk factor for intersegmental visceral pleura lymphatic drainage

Abstract

Objectives: Lung cancer tumors are known to be highly lymphophilic. There are two different pattern of lymphatic drainage of the lung: one peribronchial lymphatic pathway, and another one within the visceral pleura which appears to be more intersegmental than the peribronchial pathway. We aimed to assess the prevalence of an intersegmental pathway in the lymphatic drainage of lung tumors within the visceral pleura and determine potential influential factors.

Methods: In this prospective study, we included all patients for whom a major pulmonary resection (lobar) was indicated and performed for suspected or proven lung cancer. An immediate ex-vivo evaluation of the surgical specimen after resection was conducted by trans-pleural injection of blue dye within the tumor. The pathways followed by the lymphatic vessels under the visceral pleura were assessed to define the occurrence of an intersegmental pathway, which was defined by the presence of blue dye within the lymphatic vessel crossing to a neighboring pulmonary segment, distinct from the tumorous segment.

Results: Fifty-three patients met the inclusion criteria and were assessed over a three-year period. Lymphatic drainage within the visceral pleura followed an intersegmental pathway in 35 of 53 patients (66%). When the lymphatic drainage of the tumor was intersegmental, it drained in a single other segment in 21/35 cases and two or more in 14/35 cases. Logistic regression with multivariate analysis showed a peripheral location of the tumor to be a risk factor for the intersegmental pathway of visceral pleura lymphatic drainage (OR = 0.87 [079-0.95], p = 0.003).

Conclusion: These results confirm that lymphatic drainage of lung cancer in the visceral pleura appears to largely follow an intersegmental pathway, especially when the tumor is peripheral, close to the visceral pleura.

Keywords: lung cancer, lymphatic drainage, visceral pleura, lobectomy, segmentectomy

## Introduction

The standard treatment for early-stage lung cancer is surgery, consisting of an anatomical pulmonary resection with systematic lymph-node dissection. Generally, a lobar surgical resection is performed, although the possibility of a segmentectomy is also possible for stage I non-small cell lung cancer (NSCLC), especially for peripheral tumors < 2 cm [1,2]. The problem lies in the higher rate of local recurrence in patients treated by sublobar than lobar resection [1]. There are several hypotheses for such recurrence, including the role of incomplete lymphadenectomy [3] and the spread of the tumor through the air space (STAS) [4], although no clear physiopathology has been associated with local recurrence.

Lung cancer tumors are known to be highly lymphophilic, particularly in NSCLC. It has been largely described that lymphatic drainage in the lungs occurs through parenchymal lymphatic vessels toward the hilar and mediastinal lymph nodes [5] and eventually directly into the mediastinal lymph nodes [6]. This lymphatic drainage follows a well-characterized peribronchial pathway [7,8], which is generally segmental, although some authors have reported rare cases of intersegmental drainage of the lung lymphatics through the same peribronchial pathway [9]. Recently, we extensively assessed lymphatic drainage of the lungs through a visceral pleura pathway and determined that intersegmental lymphatic drainage is much more common for the visceral pleural pathway than the peribronchial pathway [10]. The objective of the current study was to evaluate the practical aspects of lung cancer lymphatic drainage in the visceral pleura by immediate ex-vivo assessment of surgical specimens after resection for NSCLC to evaluate the occurrence of intersegmental lymphatic drainage of lung segments and potential influential factors.

## Materials and Methods

### Study Design

We performed a prospective non-interventional study over a three-year period (between June 2016 and February 2019) under the approval of a regional ethics review board (ID-RCB: 2016-A00036-45), which was granted on March 22, 2016. Every patient was informed and had given their signed written consent to participate in the study prior to surgery. Patient characteristics, including anatomical and clinical data, were collected perioperatively and registered in a dedicated institutional database.

### Patient selection

We included all patients > 18 years of age for whom a major pulmonary resection (lobar) was indicated and performed for suspected or proven lung cancer. Exclusion criteria were a proven preoperative benign histology, an intraoperative decision of sub-lobar resection, and all factors that could compromise the evaluation of pleural lymphatic drainage, including prior lung surgery on the same operated side, intraoperative adhesiolysis, with injured visceral pleura, and surgery requiring intraoperative wedge resection with frozen section examination.

### Specimen examination

After the surgeon completed the lobectomy, including systematic hilar and mediastinal lymph node dissection, the specimen was removed and then evaluated on a back table by another dedicated and trained surgeon. The procedure was adapted from our previous cadaveric study [10] and consisted of rewarming the specimen, if needed (in water at 40°C), and performing a transpleural injection of the tumor with 5 ml of a triphenylmethane blue dye solution (Blue Patent V Sodium 2.5%, Guerbet, France). The pathways followed by the lymphatic vessels under the visceral pleura were assessed to define the occurrence of intersegmental drainage. An intersegmental pathway for lymphatic drainage in the visceral pleura was defined by the presence of blue dye within the lymphatic vessel crossing to a neighboring pulmonary segment, distinct from the segment in which the tumor was located. The intersegmental plan was defined by ex-vivo inspection and specimen palpation. When in doubt with the exact location of the intersegmental plan, identification of the exact boundary between segments was enhanced using selective bronchial insufflation.

## Statistical analysis

Dichotomous/categorical patient characteristics are expressed as the frequency (percentage) and continuous patient characteristics as the mean and standard deviation. Intergroup differences were evaluated by logistic regression with univariate (threshold $p < 0.20$) and multivariate analysis. As a descriptive study, the protocol estimated the number of cases to include to be at least 20 patients to match the preliminary study, which was raised in order to perform a multivariate analysis. Statistical analysis was performed by a dedicated biostatistician using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

## Results

### Patients

In this prospective study, 62 patients matched the inclusion criteria and 53 were enrolled after the exclusion of nine patients. Among the nine excluded patients, seven were excluded because of intraoperative adhesiolysis, compromising the assessment of lymphatic drainage of the visceral pleura, and two because of an unplanned intraoperative wedge resection required for frozen section examination. The population of the study consisted mostly on early stage lung cancer (n = 34/53, 64.2%, stage cI), with a predominance of adenocarcinoma (n = 32/53, 64.2%). The characteristics of the included patients, including preoperative and intraoperative data and postoperative outcomes, are summarized in Table 1.

### Tumor lymphatic drainage in the visceral pleura

All the samples of the 53 patients were assessed following transpleural injection of the dye within the tumor. Lymphatic drainage in the visceral pleura appeared to follow an intersegmental pathway for 35 of the 53 (66%) patients (Figure 1, Table 2). Lymphatic drainage of the tumor in the visceral pleural tended to be more frequent in the lower than upper lobes, without reaching statistical significance (Table 2, Figure 2). When the lymphatic drainage of the tumor in the visceral pleural was intersegmental, it drained to a single other segment in 21/35 cases and two or more segments in 14/35 cases (Table 2). Histological examination was performed and confirmed that injected vessels were visceral pleura lymphatic vessels (Figure 3). Regarding lymphadenectomy, a mean number of 15.4 (+/-8) lymph nodes were harvested per patient, including at least 3 hilar or intrapulmonary stations in 34/53 patients (64.2%), and at least 3 mediastinal stations in 49 patients (92.5%). According to IASLC guidelines [11], an uncertain resection status was retained in 22/53 patients (41.6%). Detailed data regarding lymphadenectomy and uncertain resection are displayed in table 3.

### Risk factors for intersegmental lymphatic drainage of the visceral pleura

The patients were divided into two groups based on the tumor lymphatic drainage of the visceral pleura: an intersegmental pathway group and a segmental pathway group. The intersegmental pathway group appeared to have larger tumors, a higher rate of visceral pleura tumoral involvement, and a shorter distance between the visceral pleura and the

tumor (Table 4). The histology and nodal involvement were similar between the two groups. Ten patients were diagnosed with N2 disease. Among them, four of eight in the intersegmental pathway group showed a strict skip-N2 disease and neither of the two patients in the segmental pathway group showed skip-N2 disease (50% vs 0%, *p = 0.47*) (Table 4). When considering patient with clinical I-A stage with a tumor of 2cm or less (patient eligible for sublobar resection such as segmentectomy), 9/20 (45%) showed an intersegmental lymphatic pathway, which was lower than in patient with clinical stage I-A with tumor >2cm or higher with 26/33 (78.8%) of intersegmental lymphatic pathway. Logistic regression with multivariate analysis of these preoperative variables and tumor characteristics showed only the peripheral location of the tumor, represented by a shorter distance between the visceral pleura and the tumor, to be a risk factor for intersegmental visceral pleura lymphatic drainage (OR = 0.87 [079-0.95], *p = 0.003*) (Table 5).

## Discussion

Lymphatic drainage of lung cancer in the visceral pleura appears to largely follow an intersegmental pathway, especially when the tumor is peripheral, close to the visceral pleura, as suggested by our prior cadaveric study (Figure 4).

The first mention of lung lymphatic drainage not following the bronchi, which could be defined as intersegmental, was reported by Hovelacque in 1912 [12]. Riquet et al. showed that peri-bronchial lymphatic drainage can follow an intersegmental pathway in 9.5% of cases (483 injections in 260 specimens), although this observation mainly concerned the peribronchial lymphatic drainage pathway [13]. In a previous feasibility study in cadavers, we performed the first specific assessment of visceral pleura lymphatic drainage, demonstrating that the intersegmental pathway was more common in visceral pleura drainage than peribronchial drainage [10]. The current prospective study allowed us to transpose such an evaluation of visceral pleura lymphatic drainage to a cohort of patients after resection for NSCLC, with immediate ex-vivo assessment of the surgical specimens, confirming that lymphatic drainage within the visceral pleura is mainly intersegmental. Moreover, risk factor analysis allowed us to determine that peripheral tumors are more likely to show intersegmental lymphatic drainage in the visceral pleura.

There has been growing interest in the segmental/intersegmental characteristics of lung cancer due to the increasing practice of sublobar resection for early-stage NSCLC surgery. This has been primarily to spare the parenchyma to preserve postoperative lung function [14], but there is yet no clear evidence that it lowers postoperative complications [15]. Nonetheless, such sublobar resections are required because of the increasing incidence of early-stage NSCLC following radiological screening protocols in an aging population with a high rate of comorbidities. The indication of sublobar resection is nevertheless still a subject of debate, but segmentectomy has been recently suggested as an alternative to lobectomy in NSCLC surgery for peripheral tumors < 2 cm [1], even though such patients show a higher rate of local recurrence following segmentectomy than lobectomy [1,2]. These studies have been mainly clinical and few have evaluated the physiopathology behind the higher rate of local recurrence.

Several hypotheses have arisen to explain this higher rate of local recurrence. First, and above all, an inadequate lymphadenectomy may result in inaccurate staging, leading to a false comparison of outcomes in patients with different oncological prognoses, as nodal involvement may be undiagnosed [16]. Second, the role of STAS is yet to be determined, as it appears to be a risk factor for the local recurrence in stage I NSCLC, especially after sublobar resection relative to lobar resection [17]. It is also a risk factor for occult lymph node

metastasis [18]. Third, we previously highlighted the high incidence of an intersegmental pathway for lymphatic drainage within the visceral pleura, with a 55.8% rate in our prior cadaveric study [10], reaching 66% in the present study, probably because of the lymphophilic characteristics of lung cancer. This incidence is much higher than the 9.5% described by Riquet et al., who evaluated peribronchial lymphatic drainage. Based on this evidence, it is possible that a sublobar resection, such as wedge resection or segmentectomy, may result in an incomplete resection of the lymphatic drainage of the lung cancer in patients with intersegmental drainage within the visceral pleura, leading to a higher rate of local recurrence, especially in cases of lymphatic embolism.

The main strengths of this study were its prospective design, with a homogenous cohort, and its solid methodology, consisting of immediate ex-vivo assessment of the specimen to mimic in-vivo conditions using a validated tumor injection protocol based on a previous feasibility study [10]. The main limitation of the study was the modest sample size, which was mainly due to the non-inclusion of patients requiring planned intraoperative wedge resection for frozen section examination. In addition, the impact of intersegmental tumor lymphatic drainage in the visceral pleura on the completeness of resection and the risk of local recurrence, while strongly suggested, is still theoretical. Interestingly, visceral pleura involvement was not retained as a risk factor in the multivariate analysis while tumor distance to pleura was statistically significant. One possible explanation, other than lack of statistical power, is the fact that visceral pleura involvement is defined by an extension of the tumor beyond the elastic layer, but lymphatic vessels are draining the pleura beneath this elastic layer (thus, a peripheral tumor may potentially drains in these vessels, without visceral pleura involvement). Another limitation is that identification of STAS was not performed, as it was not a routine practice at the time of the study. Lastly, regarding skip-metastasis, because specimen injection was performed ex-vivo as defined by the study protocol, it was not possible to determine if the tumour drained directly in the mediastinal stations, or through the interlobar/hilar stations first. Thus, these results are not applicable in the field of sentinel lymph node.

In conclusion, we demonstrate that lymphatic drainage of lung cancer in the visceral pleura largely follows an intersegmental pathway. Contrary to what might be expected, intersegmental lymphatic drainage in the visceral pleura particularly occurs when the tumor is located peripherally. The role of the mainly intersegmental drainage of lung cancer should be further evaluated in clinical studies to assess its impact on local recurrence after sublobar resection for NSCLC.

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| Patient characteristics and outcomes | Value |
|---|---|
| Preoperative | |
| Male sex | n = 37 (69.8%) |
| Age (years) | 66.7 ± 8.2 |
| Comorbidities | |
| Cardiac | |
| Preoperative FEV1 (%) | 88 ± 18 |
| BMI (kg/m²) | 26.5 ± 4.8 |
| cTNM stage | |
| IA | n = 30 (56.6%) |
| IB | n = 4 (7.6%) |
| IIA | n = 8 (15.1%) |
| IIB | n = 5 (9.4%) |
| IIIA | n = 5 (9.4%) |
| IIIB | n = 1 (1.9%) |
| Intraoperative | |
| VATS surgical approach | n = 35 (66%) |
| Surgical resection | |
| Lobectomy | n = 49 (92.4%) |
| Bilobectomy | n=3 (5.7%) |
| Lobectomy + Segmentectomy | n=1 (1.9%) |
| Postoperative complications | n = 10 (18.9%) |
| Length of stay (days) | 6.5 ± 6.8 |
| Postoperative mortality (90 days) | n = 0 (0%) |

Table 1. Patient characteristics and postoperative outcomes

| Intersegmental Pathway | Value |
|---|---|
| Right upper lobe | n = 16/24 (66.7%) |
| Right middle lobe | n=1/4 (25%) |
| Right lower lobe | n = 10/13 (76.9%) |
| Left upper lobe | n = 2/4 (50%) |
| Left lower lobe | n = 6/8 (75%) |
| | |
| Number of adjacent segment reached | |
| 1 segment | n = 21/35 |
| 2 segments | n =12/35 |
| 3 segments | n = 2/35 |

Table 2. Characteristics of the intersegmental pathway of lymphatic drainage in the visceral pleural

| Characteristic | Value |
|---|---|
| Mean number of LN harvested | 15.4 +/- 8 |
| Mean number of LN harvested in N1 station | 5.5 +/- 4.1 |
| Number of dissected N1 station | |
| 0 | n = 2 (3.8%) |
| 1 | n = 5 (9.4%) |
| 2 | n = 12 (22.6%) |
| 3 | n = 24 (45.3%) |
| ≥4 | n = 10 (18.9%) |
| Mean number of LN harvested in N2 station | 9.9 +/- 5.6 |
| Number of dissected N2 station | |
| 0-1 | n = 0 (0%) |
| 2 | n = 4 (7.6%) |
| 3 | n = 37 (69.8%) |
| ≥4 | n = 12 (22.6%) |
| Positive higher removed LN | n = 1 (1.9%) |
| Positive pleural lavage cytology | n = 1 (1.9%) |
| Bronchial margin with carcinoma in situ | n = 1 (1.9%) |
| Uncertain resection status | n = 22 (41.6%) |
| Less rigorous LN evaluation among skip-N2 | n=1/4 (25%) |

Table 3: Detailed data regarding lymphadenectomy and uncertain resection metrics. LN: lymph node; N1 station: intrapulmonary and/or hilar station; N2 station: mediastinal station.

| Patient Characteristic | Inter-segmental group (n = 35) | Segmental group (n = 18) | p value |
|---|---|---|---|
| CT-scan aspect | | | 0.84 |
| Solid | n= 30 | n = 16 | |
| GGO | n = 1 | n = 1 | |
| Mixed GGO | n = 4 | n = 1 | |
| cTNM stage | | | 0.02 |
| I-A ≤ 2cm | n = 9 | n = 11 | |
| IA > 2cm or higher | n = 26 | n = 7 | |
| VATS Surgical approach | n = 23 (65.7%) | n = 12 (66.7%) | 0.94 |
| Surgical resection | | | 0.54 |
| RUL | 14 | 7 | |
| ML | 1 | 3 | |
| RLL | 9 | 3 | |
| LUL | 2 | 2 | |
| LLL | 6 | 2 | |
| Other | 3 | 1 | |
| Histology | | | 0.18 |
| Adenocarcinoma | n = 24 | n =8 | |
| Squamous | n = 8 | n = 5 | |
| Other | n = 2 | n = 4 | |
| Benign | n = 1 | n = 1 | |
| Tumor size (mm) | 35.3 ± 16.5 | 24.5 ± 11 | 0.008 |
| Pleural involvement - T2a | n = 17/34 (50%) | n = 2/14 (13.3%) | 0.01 |
| Nodal status | n = 34 | n = 14 | 0.87 |
| N0 | n = 23 | n = 11 | |
| N1 | n = 3 | n = 1 | |
| N2 | n = 8 | n = 2 | |
| Skip N2 | n= 4/8 (50%) | n = 0/2 (0%) | 0.47 |
| Distance tumor /segmental bronchus (mm) | 35.7 ± 15.4 | 37.6 ± 17.3 | 0.71 |
| Distance tumor /pleura (mm) | 3.4 ± 5.1 | 14.6 ± 11.8 | < 0.001 |

Table 4. Clinical and histological characteristics of the intersegmental and segmental pathway groups. CT-scan: computerized tomography scanner; GGO: ground-glass opacity. Other histology subtype in intersegmental group: adenosquamous carcinoma (n=1), sarcomatoid carcinoma (n=1); and in segmental group: large cell neuroendocrine lung cancer (n=1), clear cell renal carcinoma (n=1), type B lymphoma (n=1) and pleiomorphic sarcoma (n=1).

| Patient characteristic | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | Odds ratio [95%CI] | p value | Odds ratio [95%CI] | p value |
| Age | | 0.622 | | |
| Cardiac comorbidities | | 0.945 | | |
| preop FEV1 > 80% (vs < 80%) | 3.10 [0.75 - 12.80] | 0.119 | | 0.103 |
| BMI | | 0.843 | | |
| Surgical resection (Lobectomy vs Bilobectomy vs other) | | 0.605 | | |
| Surgical approach (VATS vs Thoracotomy) | | 0.945 | | |
| Histology (adenocarcinoma vs squamous vs other vs benign) | | 0.270 | | |
| Tumor size | 1.06 [1.01 - 1.12] | 0.028 | | 0.647 |
| Pleural involvement (T2a) | 0.17 [0.03 - 0.86] | 0.032 | | 0.297 |
| Nodal involvement (N0 vs N1 vs N2) | | 0.976 | | |
| Skip N2 disease vs non-Skip N2 disease | | 0.950 | | |
| Distance between tumor and pleura | | 0.001 | 0.87 [0.79 - 0.95] | 0.003 |
| Distance between tumor and origin of segmental bronchus | | 0.692 | | |

Table 5. Logistic regression with univariate and multivariate analysis of risk factors for the intersegmental pathway of lymphatic drainage in the visceral pleura

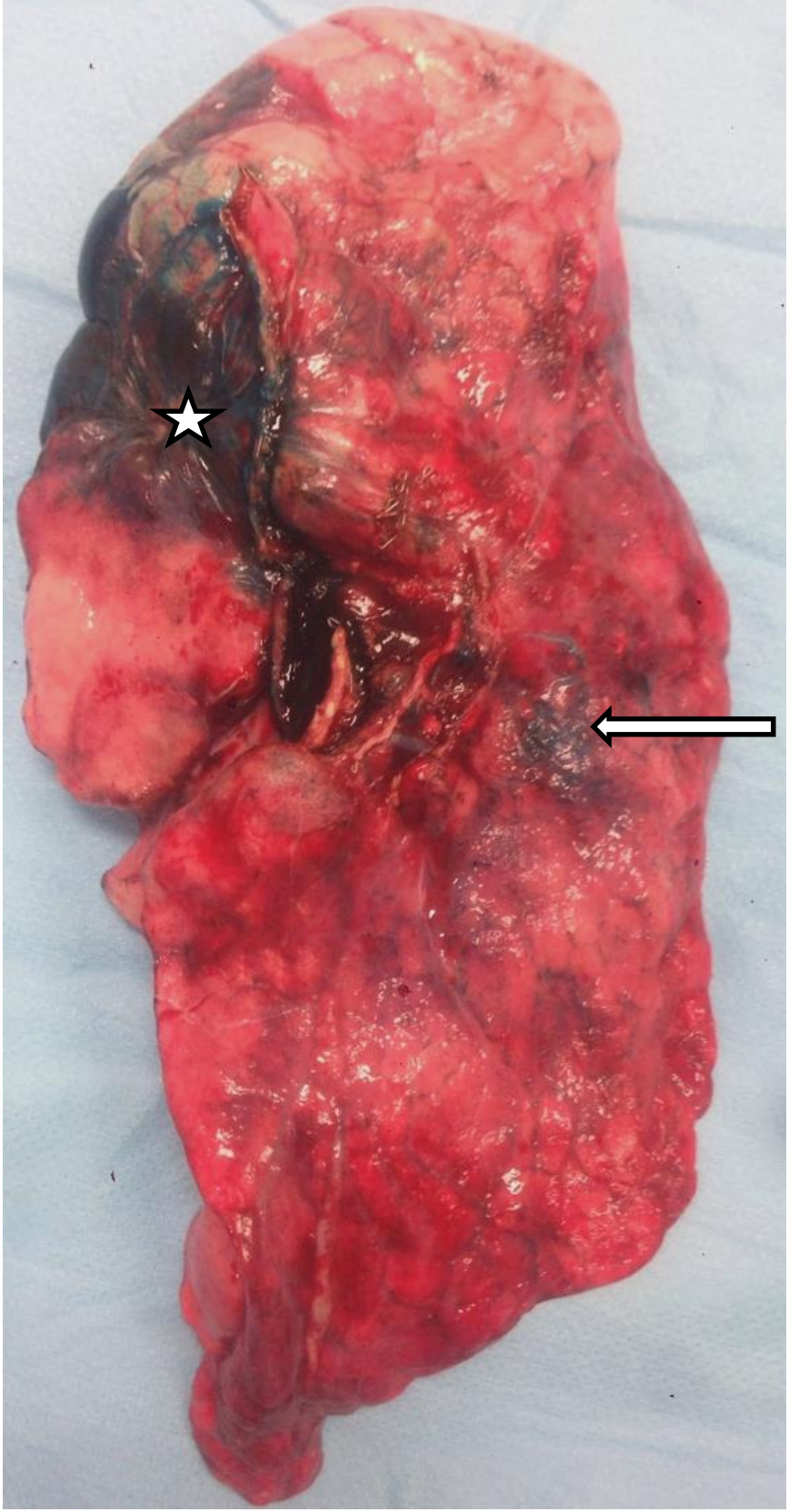
Figure legends

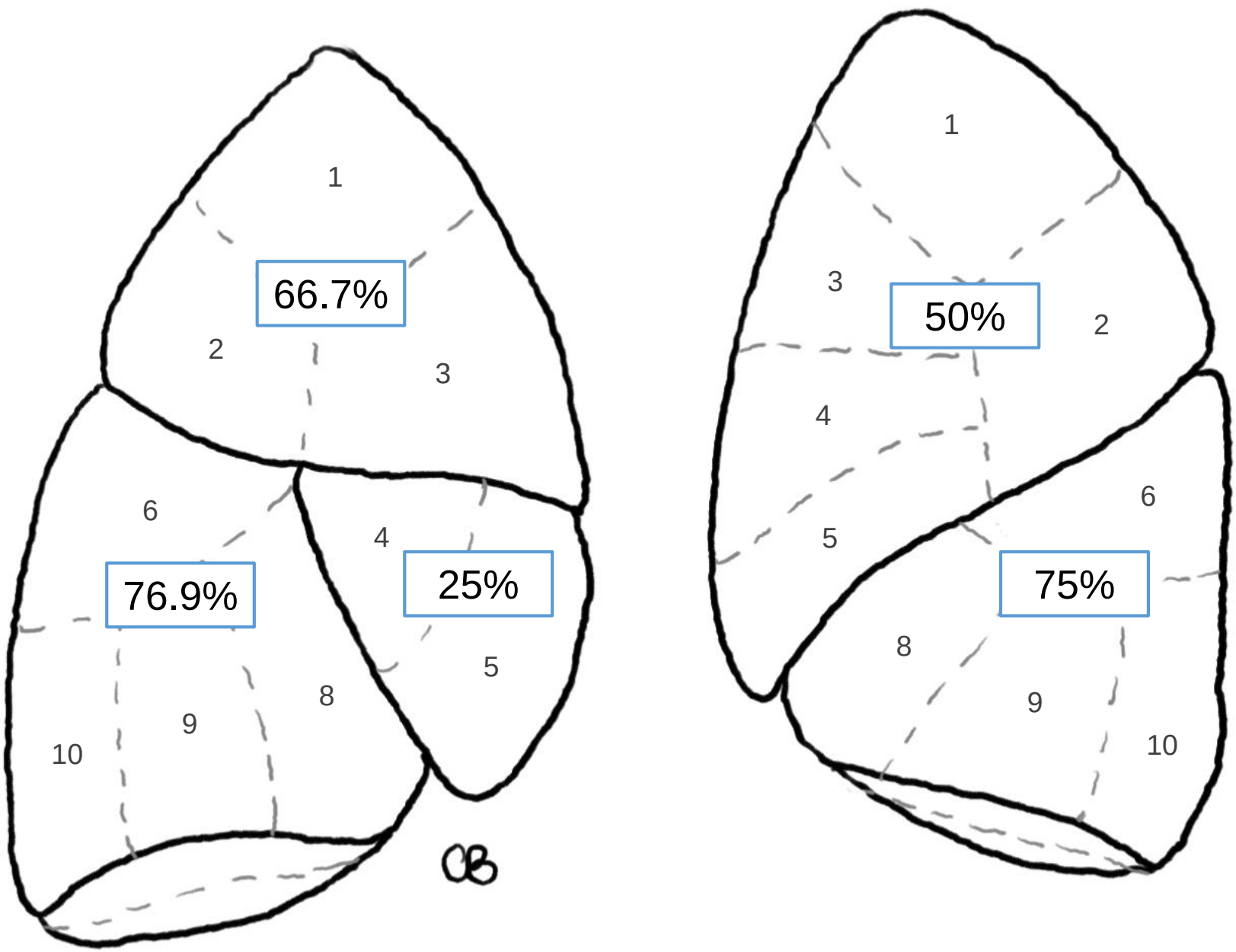
Figure 1. Left upper lobe specimen, showing intersegmental lymphatic drainage from S2 toward S4. The white star shows the injected tumor in S2 and the white arrow the pleural lymphatic vessel with blue dye in S4.

Figure 2. Proportion of intersegmental pathway of lymphatic drainage in the visceral pleural among the different pulmonary lobes

Figure 3. Histological sample showing lymphatic vessels within the visceral pleura, marked with white arrows (x200)

Figure 4. Lymphatic drainage of a lung tumor through segmental peribronchial pathway and intersegmental visceral pleura pathway

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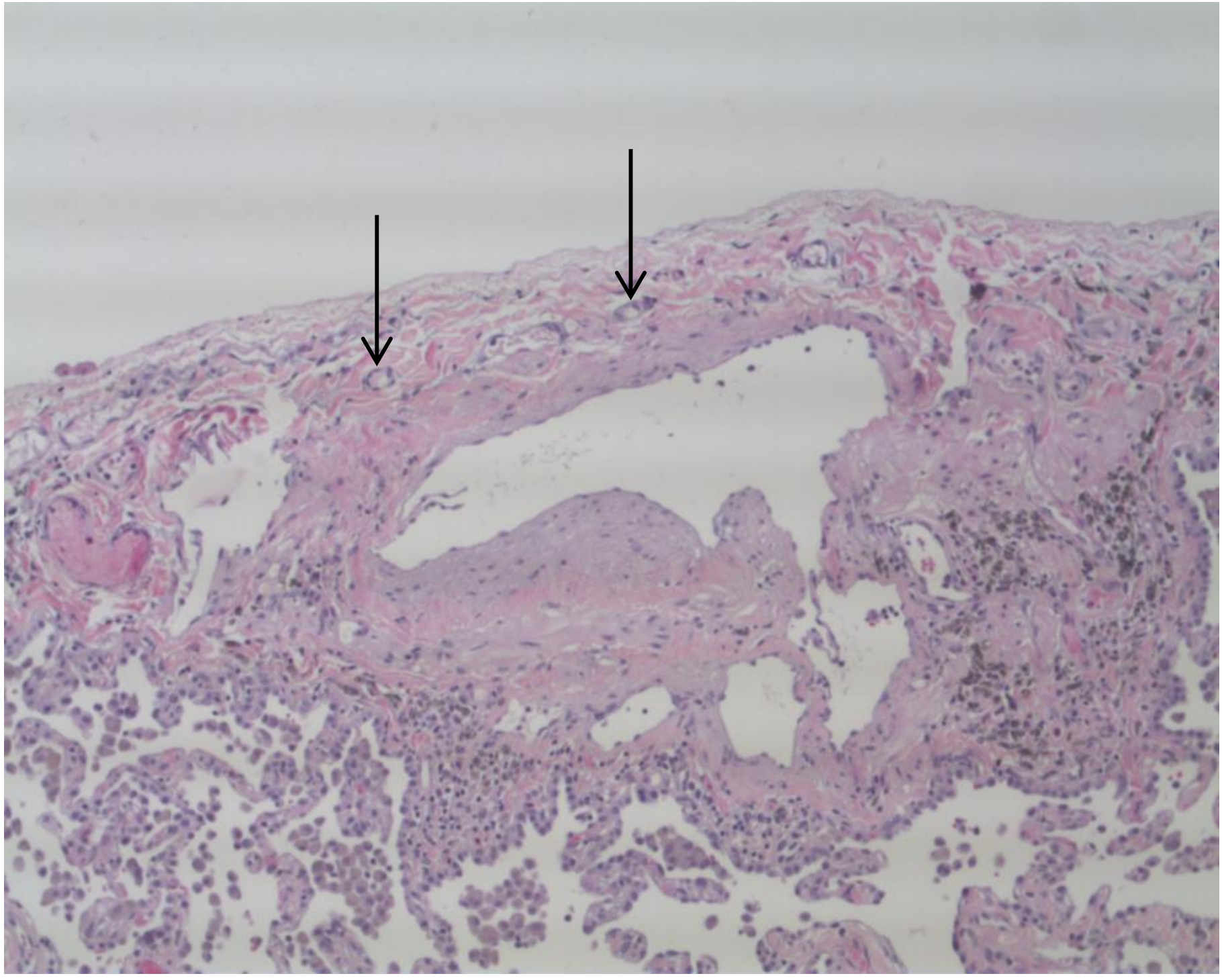

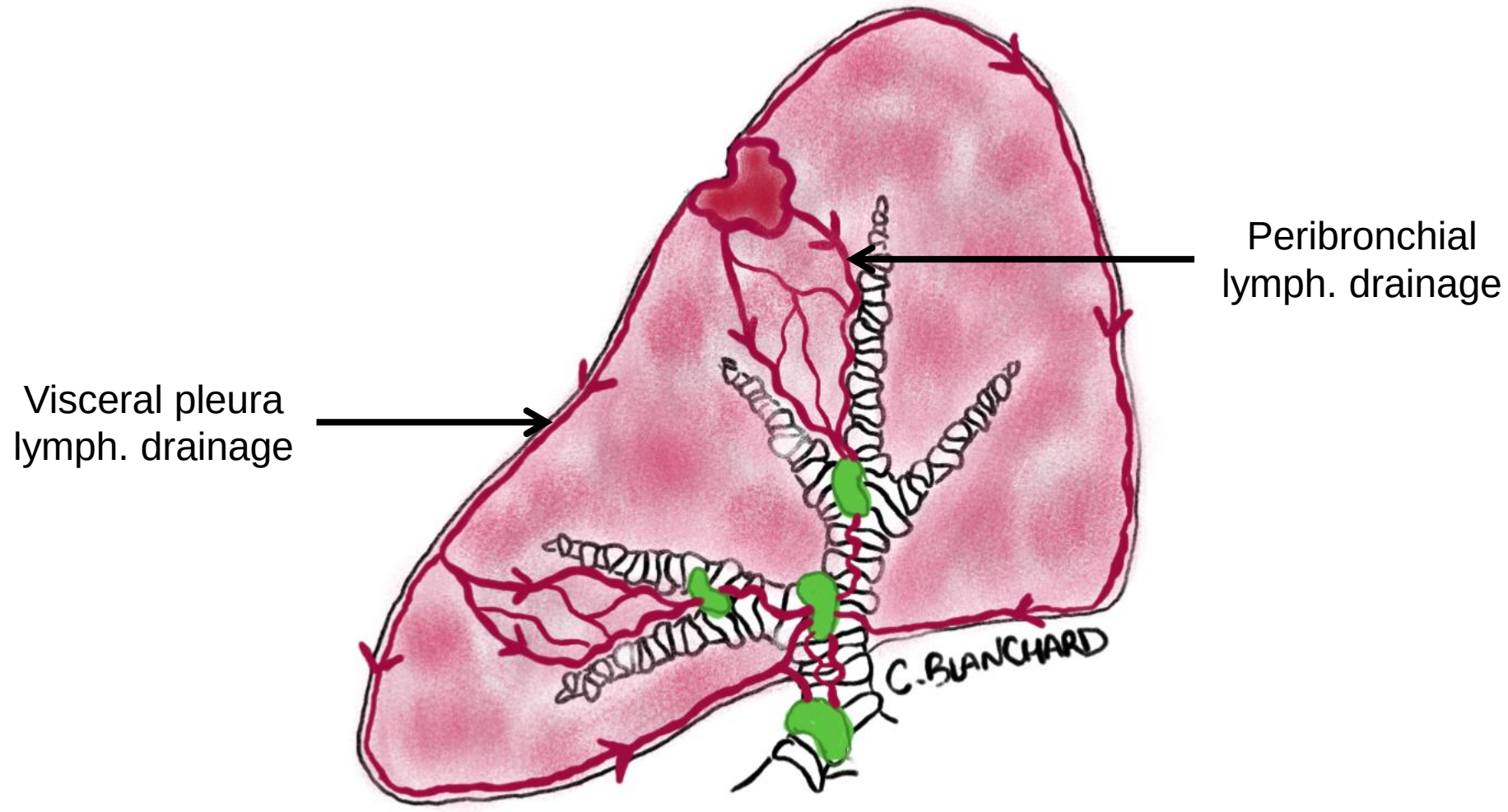
Peribronchial
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