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The major thoracic vascular invasion of lung cancer

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HIGHLIGHTS

- We actually investigated tumor invasion of the major thoracic vessels.
- We analyzed 30 patients in whom pulmonary artery (PA) invasion was suspected.
- We analyzed 11 patients in whom pulmonary vein (PV) or left atrium (LA) invasion was suspected.
- The positive predictive value of CT findings was low.

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ABSTRACT

Background: We actually investigated the surgical and pathological findings in cases which tumor invasion of the major thoracic vessels was suspected based on the preoperative Computed tomography (CT) findings.

Materials and methods: We retrospectively reviewed our prospective database of all patients, who underwent lung resection for lung cancer from 2012 to 2014. 387 patients underwent lung cancer surgery. Among these patients, we analyzed 30 patients in whom pulmonary artery (PA) invasion was suspected and 11 patients in whom pulmonary vein (PV) or left atrium (LA) invasion was suspected based on the preoperative CT findings.

Results: Among the 30 patients with suspected PA invasion, there were 9 patients in whom the tumor could be peeled off the PA in actual thoracotomy. Pathological invasion of the PA was observed in 6 of these patients. The positive predictive value of the preoperative CT findings was 20%. Among the 11 patients with suspected PV or LA invasion, there were 2 patients in whom the tumor could be peeled off the PV or LA in actual thoracotomy. Pathological tumor invasion of the PV or LA was observed in 4 of these patients. The positive predictive value of the preoperative CT findings was 36%.

Conclusion: The positive predictive value of the preoperative CT findings for tumor invasion of the thoracic vessels was low. Therefore, surgical opportunities that offer the chance of a cure shouldn't be missed in advanced lung cancer patients because the tumor is located near the major thoracic vessels on preoperative CT.

1. Introduction

Lung cancer is a leading cause of death worldwide; it is the primary cause of cancer death in men and the secondary cause in women [1].

Computed tomography (CT) scans have been considered the reference standard for the preoperative evaluation of the intrathoracic spread and invasion of lung cancer [2]. However, the

Abbreviations: NSCLC, non-small cell lung cancer; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; PA, pulmonary artery; PV, pulmonary vein; LA, left atrium.

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assessment of the preoperative T stage in lung cancer on CT is not always satisfactory, due to the limited ability to evaluate tumor invasion in the adjacent structures [3]. We therefore considered the possibility that the assessment major thoracic vessel invasion based on the preoperative CT findings might not be accurate.

The vascular wall is constructed from three membranes (the outer, media, and inner membranes). The media membrane structure of an artery, which includes elastic fiber and smooth muscle, is thicker and stronger than the media membrane structure of a vein (Fig. 1). Thus, the artery is able to withstand blood pressure. The thickness of the vascular wall also affects tumor invasion. In other words, the tumor can invade a vein wall more easily than an artery wall. In general, it is more difficult for a tumor to penetrate an artery wall than a vein wall.

Surgeons, radiologists, and physicians classify vascular invasion differently. For a surgeon, vascular invasion is defined by the inability to peel the tumor off the vascular wall. Thus, vascular invasion is defined based on the presence of adhesion due to inflammation—a condition which is difficult to detect before surgery.

Harman et al. reported three criteria for diagnosing vascular invasion on CT: 1) the disappearance of the fat layer; 2) the angle of tumor contact >90°; and 3) stenosis and deformation of the vascular lumen [4]. Thus, Munden et al. reported that the CT-based diagnosis of vascular and mediastinal tumor invasion was of limited use [5].

In the present study, we investigated the surgical and pathological findings of cases in which major thoracic vessel invasion was suspected based on the preoperative CT findings.

2. Materials and methods

We retrospectively reviewed our prospective database of all patients who underwent lung resection for lung cancer between January 2012 and December 2014 at the University of Occupational and Environmental Health Hospital (a single institution). Informed consent was obtained from all of the patients with written. Three hundred eighty-seven patients underwent lung cancer surgery during this period. Among these patients, we analyzed 30 patients in whom pulmonary artery (PA) invasion was suspected and 11 patients in whom pulmonary vein (PV) or left atrium (LA) invasion was suspected based on the preoperative CT examination. The presence of vascular invasion on the preoperative CT scans was independently evaluated by a thoracic surgeon and radiologist. Furthermore, vascular invasion was pathologically evaluated by a thoracic surgeon and two pathologists. The degree of vascular invasion is classified as follows: 1) invasion outside the outer membrane; 2) invasion of inflammatory cells; 3) invasion of the outer membrane; 4) invasion of the media membrane; 5) invasion of the inner space (Fig. 2).

2.1. Image acquisition

Whole lung CT scans were obtained with a 32-detector row CT scanner (Aquilion 32, Toshiba Medical Systems) or a 64-detector row CT scanner (Aquilion 64, Toshiba Medical Systems) using the following technique: collimation, 1 mm; rotation time, 0.5 s; reconstruction thickness, 2 mm; and pitch (ratio of table travel per rotation to total beam width), 27 or 53, 120 kV. Automatic tube current modulation (z-axis modulation with the Real E.C. technique, Toshiba Medical Solutions) was used with the noise level set at10 SD. Each CT image was displayed and evaluated using a standard lung window (window width, 1600 HU; window level, −600 HU) and a mediastinal window (window width, 350 HU; window level, 50 HU) on a high-resolution monitor.

3. Results

We encountered 30 patients in whom pulmonary artery (PA) invasion was suspected and 11 patients in whom pulmonary vein (PV) or left atrium (LA) invasion was suspected based on the preoperative CT findings. Among the 30 patients with suspected PA invasion, there were 9 patients in whom the tumor could be peeled off the PA in actual thoracotomy. Thus, there were 21 patients in

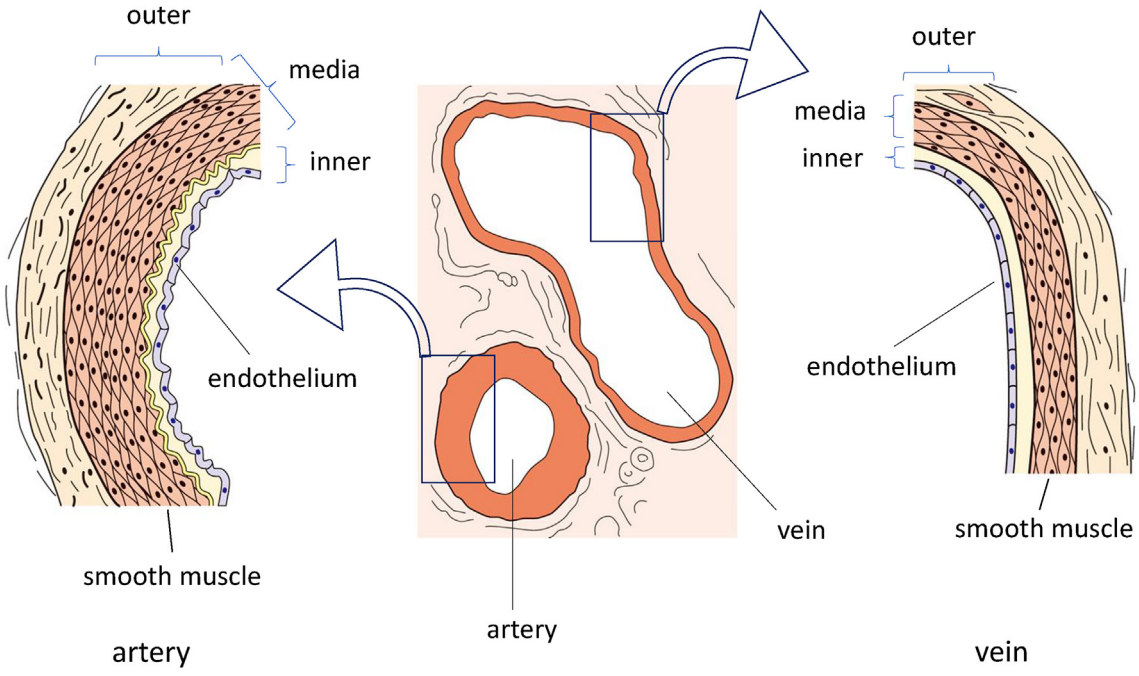

Fig. 1. This figure shows the structures of artery and vein.

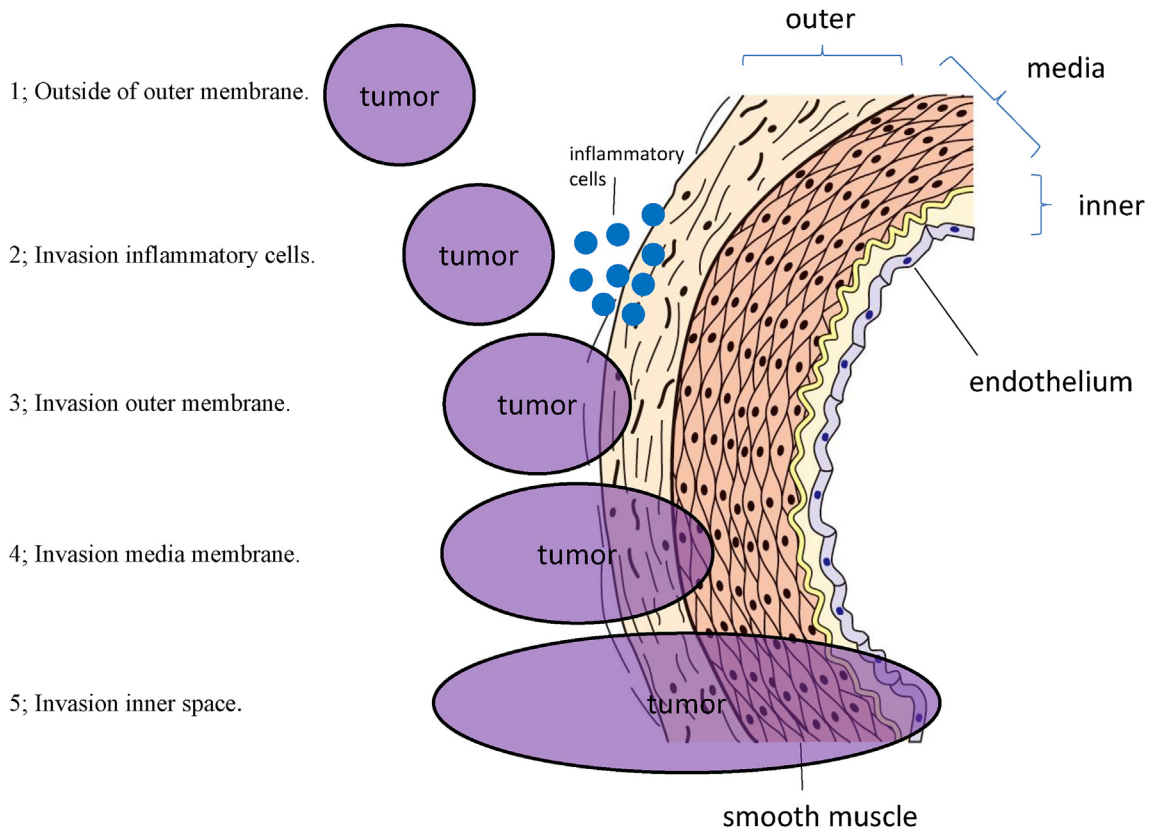

Fig. 2. The degree of vascular invasion is classified as follows: 1) invasion outside the outer membrane; 2) invasion of inflammatory cells; 3) invasion of the outer membrane; 4) invasion of the media membrane; 5) invasion of the inner space.

whom the tumor could not be peeled off. We performed the combined excision of the tumor and the PA in these cases. Pathological tumor invasion of the PA was observed in 6 of these patients. The positive predictive value of the preoperative CT findings was 20% (6/30) (Fig. 3).

Among the 11 patients with suspected PV or LA tumor invasion, there were 2 patients in whom the tumor could be peeled off the PV or LA in actual thoracotomy. Thus, there were 9 patients in whom the tumor could not be peeled off. We performed the combined excision of the tumor and PV or LA in these cases. Pathological tumor invasion of the PV or LA was observed in 4 of these patients. The positive predictive value of the preoperative CT findings was

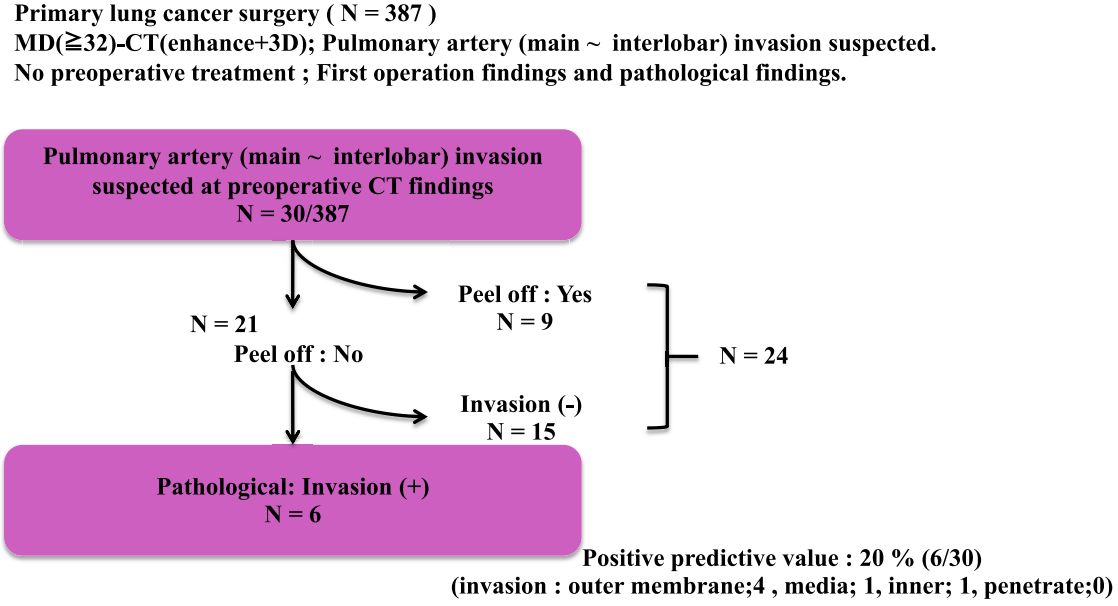

Fig. 3. This figure shows whether tumor invasive pulmonary artery (PA) wall in practically.

36% (4/11) (Fig. 4).

Pathological tumor invasion of a vessel wall was observed in 2 of the cases in the overall study population (Fig. 5).

90-days mortality was not occurred in these operations.

3.1. Case presentations

Case: The tumor (squamous cell carcinoma) was suspected to have invaded the left main PA based on the preoperative CT findings. We could not peel the tumor off the PA. We therefore performed the combined excision of the tumor and PA, followed by PA plasty. Invasion of the PA wall was not detected in the pathological examination (Fig. 6).

4. Discussion

Few reports have evaluated the difference between the detection of thoracic vascular invasion on preoperative CT images and the real-world pathological findings. Our present study is one of the first reports to clearly show these differences.

The present study yielded three important findings. First, the positive predictive value, which represents the invasion of the thoracic vessels on preoperative CT, was low (20 - 36%). Munden et al. reported that the invasion of the primary tumor into the mediastinum is important for assessing patients for surgical resection. The sensitivity, specificity, and accuracy of CT imaging for confirming invasion into the mediastinum have been reported to be 40–84%, 57–94%, and 56–89%, respectively [5]. In particular, the invasion of the major thoracic vessels is rare. We should not lose surgical opportunities that offer a chance of a cure in cases of advanced lung cancer because a tumor is found to be located near major thoracic vessels on preoperative CT.

Second, vascular endothelial growth factor (VEGF) promotes tumor angiogenesis, which is critical for tumor progression [7–10]. In non-small cell lung cancer (NSCLC), the increased expression of VEGF is common and is associated with adverse clinical outcomes. Bevacizumab, a humanized monoclonal anti-VEGF antibody [11], has demonstrated significant clinical benefit as a first-line and second-line treatment for colorectal cancer and as a first-line treatment for nonsquamous NSCLC, metastatic breast cancer, and renal cell cancer [12–15]. Bevacizumab, which is an anti-angiogenic monoclonal antibody, targets the VEGF signaling pathway and has been shown to provide additional efficacy when used in combination with first-line platinum-based chemotherapy in several trials for non-squamous NSCLC [16–18]. Bleeding events such as pulmonary hemorrhage and hemoptysis were among the most common adverse events (AEs) associated with bevacizumab therapy in clinical trials for non-squamous NSCLC; some of these events led to fatal outcomes [19]. In the phase II AVF0757g study, 3.8% of bevacizumab-treated patients experienced life-threatening bleeding events [20]. Thus, some major studies have demonstrated that bevacizumab should not be administered to patients with tumors invading or abutting major blood vessels [17,21]. The profile of hemoptysis occurrence with the real-world use of bevacizumab in Japan and the risk factors for its hemoptysis remain unclear. Goto et al. reported that prior thoracic radiotherapy, tumor exposure in the central airway, and concomitant radiotherapy were risk factors for hemoptysis. Thus, these factors should be considered when selecting patients for bevacizumab treatment [19]. A retrospective case control analysis of the E4599 study suggested that tumor cavitation at baseline could be a potential risk factor in bevacizumab-treated patients who developed hemoptysis, while lesion location, size, or vascular involvement did not appear to be significantly associated with severe pulmonary hemorrhage or hemoptysis [22]. The suspicion of major vascular invasion is very important for the indication of bevacizumab in the treatment of non-squamous NSCLC. In our experience, there were two cases (2/41) in which the tumor was found to penetrate a thoracic vessel. In these cases, the penetration of the vessel by the tumor could be clearly recognized on the preoperative CT scans. When patients with advanced non-squamous NSCLC are treated with bevacizumab, cases in which the invading tumor penetrates the vessel wall require attention because of the risk of bleeding; however, most of the cases in the present study did not involve penetrating vascular invasion. Bevacizumab has been shown to be very effective for the treatment of non-squamous NSCLC [16,17]. Thus, the

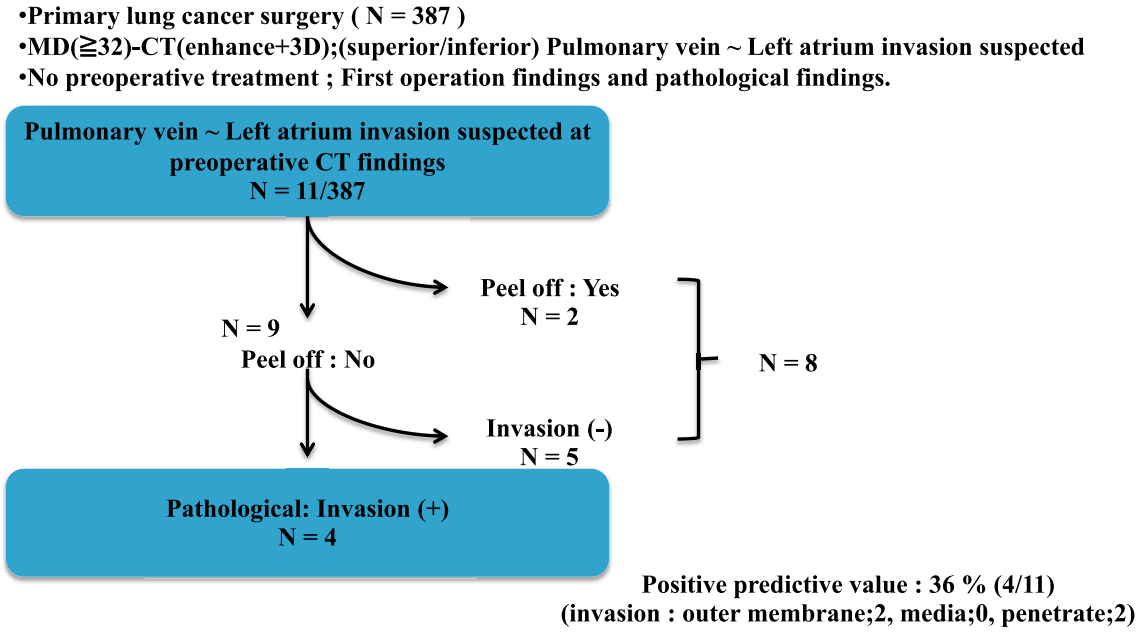

Fig. 4. This figure shows whether tumor invasive pulmonary vein (PV) or left atrium (LA) wall in practically.

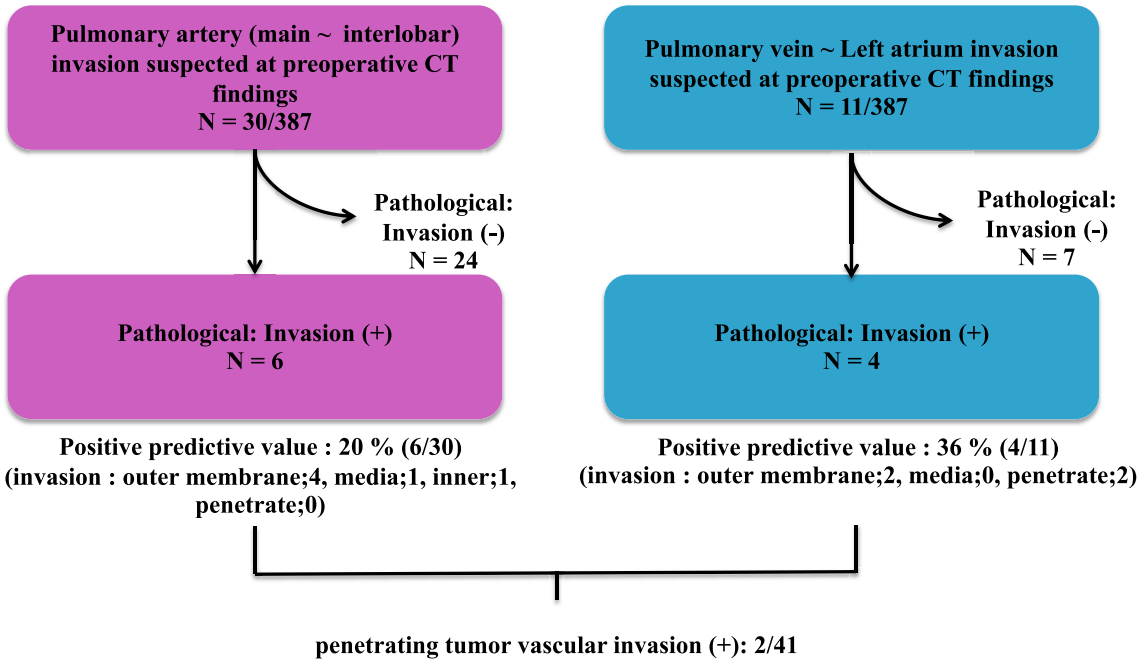

Fig. 5. This figure shows whether tumor invasive pulmonary artery (PA) or pulmonary vein (PV) or left atrium (LA) wall in practically.

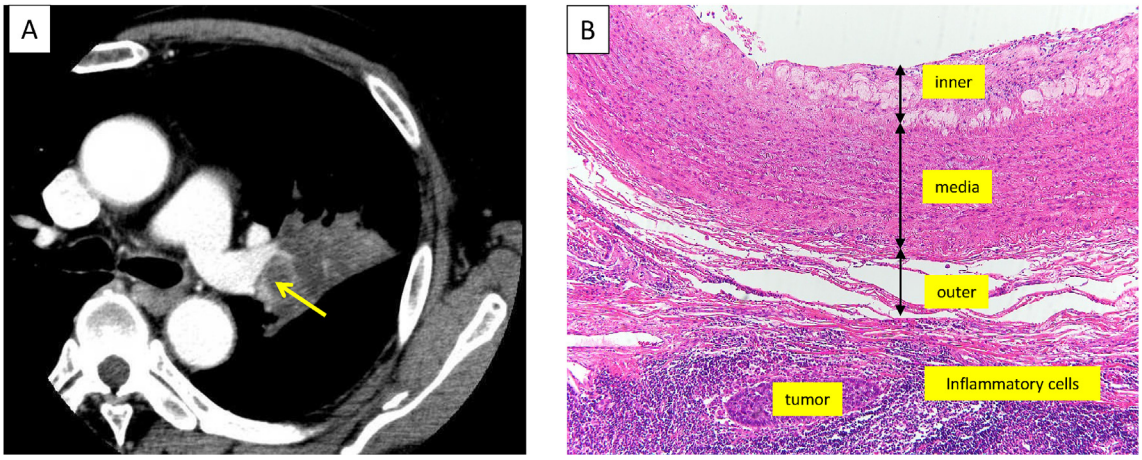

Fig. 6. CT of the chest showing the localization of this tumor. This tumor located in hilar left upper lobe. This tumor was suspected invasive left main pulmonary artery at preoperative CT findings (A). This figure shows pathological finding relationship between PA wall and tumor invasion. This tumor was not invasive PA vascular wall. There were inflammatory cells in near outside of outer membrane (B).

practice of avoiding the administration of bevacizumab when tumors are located near major vessels in patients with advanced non-squamous NSCLC might not be valid.

Finally, thoracic surgeons must acquire high-level techniques to enable them to perform combined excision and reconstruction for advanced NSCLC. Recently, video-assisted thoracic surgery (VATS) is becoming a standard in thoracic surgery in Japan. VATS is very effective for reducing invasion. However, VATS is not useful for complex and aggressive thoracic surgery (PA plasty, Br plasty, etc). Aggressive surgery (PA plasty, Br plasty, etc) requires high-level thoracotomy. Thoracic surgeons must learn several aggressive thoracic surgeries to facilitate the performance of completely curative surgery for advanced NSCLC [23–25].

Next our study, we must pursue follow up these patient's data (for example, overall survival, disease free survival, etc).

Ethical approval

We got ethical approval from ethical committee of University of Occupational and Environmental health, Japan.

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None.

Author contributions

Soichi Oka; Study design, writing.
Shuichi Shinohara; Other.
Taiji Kuwata; Other.
Masaru Takenaka; Other.

Yasuhiro Chikaishi; Other.
Ayako Hirai; Other.
Yoshinobu Ichiki; Other.
Shohei Shimajiri; Other.
Takatoshi Aoki; Other.
Fumihiro Tanaka; Study design, Others.

Conflict of interest statement

There were no conflicts of interest or financial interests for any of the authors.

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Guarantor

Soichi Oka.
Fumihiro Tanaka.

Consent

Written and signed consent from the patient to publish a case report has been obtained.

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