Demarcated by bronchial or vascular landmarks? a study on the lower borders of the lower paratracheal lymph nodes

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lung cancer, stage, hilar-mediastinal lymph nodes, IASLC map, Wang‘s map

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Material and methods
One hundred patients with benign lung diseases, fifty with lung cancer diagnosed by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), and thirteen with right metastatic LNs confirmed by surgery were included. The lymph nodes (including W1, W3, W5, 10R below W5, W4, W6) were classified with Wang's and IASLC map concurrently, and the different outcomes of N stage were compared.

Results
The azygous arch and the left main pulmonary artery varied in relation to the airway, causing the following changes of classification, 9.4% benign LNs of W1 and 38.6% of W5 were down-regulated as IASLC-10R, 9.5% of 10R below W5 were up-regulated as IASLC-4R, 51.4% of W4 and 94% of W6 were down-regulated as IASLC-10L. In 50 patients diagnosed by EBUS-TBNA, the concordance between the two maps was 0.768 for the right 92 LNs, while it was 0.374 for the left 46 nodes. If based on the location of azygous arches, postoperative stages might be changed in 2 surgery patients.

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Introduction

Primary bronchogenic lung cancer is the leading cause of malignant-tumor-related death worldwide[1,2]. The precise assessment of lymph nodes (LNs) involvement is recognized as a pivotal component of tumor node metastasis (TNM) systems, which is closely related to treatment outcomes, prognosis and selecting therapy for individual patients[3]. The lymph nodes map of the International Association for the Study of Lung Cancer (IASLC) is a widely accepted map for N descriptors[4]. Both the National Comprehensive Cancer Network and the Chinese Society of Clinical Oncology guidelines give priority to recommend endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for diagnosing mediastinal LNs metastasis[5]. EBUS-TBNA is a milestone in the development of conventional TBNA (C-TBNA) [6]. C-TBNA technique is innovated and promoted by professor Ko-pen Wang in United States, which has been widely used for biopsy LNs[7-9]. There are several IASLC regions suitable for TBNA procedure, including upper paratracheal (station 2R & 2L), lower paratracheal nodes (station 4R & 4L), subcarinal nodes (station 7), hilar and interlobar nodes (station 10 and 11). Among them, the lower paratracheal LNs are most frequently involved[10], and may easily be confounded with mediastinal (4R & 4L) and hilar LNs (10R & 10L).

Distinguishing lower paratracheal (IASLC-4R and 4L) from hilar (IASLC-10R and 10L) lymph nodes is important because an error may result in misclassification of a stage N1 tumor as stage N2 or vice versa. In the IASLC map, the boundary of 4 and 10 LNs are the lower rim of the azygous arch (AZ) on the right and the upper rim of the left main pulmonary artery (PA) on the left, but some scholars have stated that the locations of the above vascular structures varied in relation to the airway, the tracheal bifurcation (anterior carina) was in mediastinum without necessarily referring to the vessels again[11,12]. In addition, as early as 1994, a nodal map using airway as landmarks to describe mediastinal and hilar LNs was proposed by Ko-pen Wang. He designed a TBNA puncture localization map for pulmonary LNs by visualizing endobronchial anatomical structure and chest CT images, which was called Wang's lymph node map (Wang's map), there was a detailed depiction of the locations and puncture sites for the eleven stations[13]. In Wang's map, the carina region consists of anterior carina (station W1), right paratracheal (station W3) and right main bronchus (station W5), left paratracheal (station W4, also referred to as aorta-pulmonary artery window LNs) and left main bronchus (station W6). Commonly, station W1, W3, and W5 are well corresponded to station 4R of the IASLC map, station W4 and W6 are correlated with station 4L of the IASLC map[14]. However, sometimes there are some inconsistencies between the two maps due to the variant vascular location. Until now, there are few clinical studies reporting the extent of such problems and how these problems affecting the staging of lung cancer, so further investigation is needed.

In this article, we used Wang's map and the IASLC map to analyze patients with benign and malignant LNs. Our purpose is to reveal the staging discrepancies for the classification of IASLC-4 and IASLC-10 LNs caused by vascular variation in the IASLC map, and the rationality of using bronchial landmarks as the borders.

Patients and Methods

Patients

The following three kinds of patients were enrolled: 1) 100 patients with benign respiratory diseases; 2) 50 patients with malignant pulmonary diseases diagnosed by EBUS-TBNA in the past year and; 3) 41 patients with lung cancer who underwent surgery in the past year, complicated by the hilar or mediastinal LNs metastases. Inclusion criteria: (1). Age from 18 to 90 years; (2). All patients underwent chest CT with the 1 mm slice thickness, and the structures of their mediastinal LNs on chest CT images were displayed clearly. Exclusion criteria: (1). Patients who had undergone thoracic or mediastinal surgery; (2). Mediastinal deviation caused by severe pleural diseases or chest deformity. The study was approved by the ethics committee of our hospital (2021-KY-090-01).

Radiological assessment

Patients' chest CT images were reviewed, Wang's and the IASLC map were used to analyse LNs at the lower segment of the trachea and main bronchus separately, the details of the two maps have been described well before[4,13]. We had drawn the chart to show the different classifications of paratracheal LNs (Figure 1). The LNs' sizes were divided into 6 grades according to their diameters of the long axis (cm): ≤0.5, 0.6~1, 1.1~1.5, 1.6~2.0, 2.1~2.5, 2.6~3.0. The LNs were labelled with station W1, 3, 5, 4, 6, 10R below W5 based on Wang's map and their corresponding station 4R, 4L, 10R, 10L in the IASLC map. Then the consistencies and differences between the two maps were analyzed. This evaluation was performed by two experienced physicians who were familiar with the two maps. If there was a disagreement between them, the third physician would make the final evaluation.

Classification of patients with lung cancer by EBUS-TBNA and surgery

For the patients with lung cancer, the metastatic lower paratracheal LNs were confirmed by EBUS-TBNA or surgery. The classification of these LNs was assessed by pulmonologists or surgeons who were familiarized with Wang's map and the IASLC map. The different outcomes of staging N1 or N2 were compared. For the patients with surgery, the postoperative TNM staging was evaluated.

Statistic analysis

Statistical analysis was performed by using the statistical analysis software SPSS 25.0 (SPSS Inc., Chicago, IL, USA). Continuous data were presented as mean ± standard deviation (SD). For the right benign lymph nodes and 50 patients with malignant pulmonary diseases diagnosed by EBUS-TBNA, Cohen's Kappa Statistic was used to evaluate the concordance between the results of their lymph nodes staging with the Wang's and IASLC map. Kappa value ≥0.75 indicates good consistency, 0.4-0.75 indicates moderate–high consistency, and ≤0.4 indicates poor consistency.

Results

One hundred patients with benign pulmonary diseases were randomly selected (59 men, 41women; mean age, 65.7±12.41), the most common diseases were lung infection, chronic obstructive pulmonary disease, asthma, interstitial lung disease, lung abscess, bronchiectasis, and et al. Fifty patients with lung cancer and metastatic LNs confirmed by EBUS-TBNA were collected (40 men, 10 women; mean age, 66.44±8.61), including 29 right and 21 left lung cancer. Among 270 patients with lung cancer who underwent surgery in the past year in our hospital, 41 patients with

hilar and mediastinal metastatic lymph nodes were enrolled (26 men, 15 women; mean age, 63±10), including 27 right and 14 left lung cancer.

Improper classification due to variant vascular landmarks in benign lymph nodes

A total of 702 lymph nodes were found at stations of W3, W1, W5, W4, W6 and 10R below W5 by Wang's map in 100 cases of benign lung diseases, 86% of all LNs were smaller than 1cm, 11% LNs between 1.1-1.5cm. A detailed depiction of the CT manifestation for the eleven stations was well documented before[13]. 10R below W5 (hilar LNs) indicated LNs below the right main proximal bronchus, 10L below W6 (hilar LNs) indicated LNs below the left main proximal bronchus in this paper (Figure 2).

We found that the relation of the azygous arch to the airway was varying. Some lower rims of azygous arches were at the level of the upper carina, some at the carina or near the right tracheobronchial angulation, and some near the orifice of the right upper lobe (Figure 3). According to the different locations of the lower rim of the azygous arch, Wang's and IASLC map were applied simultaneously to classify the right paratracheal LNs. High levels of the azygous arch relative to the trachea would result in down-staging LNs (Figure3A). Normal levels of the azygous arch wouldn't cause changes of stage (Figure3B). Low levels of the azygous arch would result in up-staging LNs (Figure 3C). All the LNs at W3 were classified as 4R, 9.4% (8/128) of the LNs at W1 and 38.6% (32/83) at W5 were misclassified as IASCL-10R, 9.5% (4/42) of the LNs at 10R below W5 were misclassified as IASLC-4R (Figure 4). According to Kappa analysis, the value was 0.550 which indicated the concordance between the two maps was moderate (Table1).

The locations of the upper rim of the left main pulmonary artery varied greatly, mostly at the tracheal terminal, carina or tracheobronchial angulation, but the variable sites could be from the lower segment trachea to the left main bronchus, parallel to the level of the orifice of the right upper lobe (Figure 5A, B, C). The location of the upper rim of the left main pulmonary artery is usually too high for distinguishing LNs between IASLC-4 and IASLC-10, a large portion of the mediastinal LNs at stations of W4 and W6 were mistaken for IASLC-10L, the different conditions of W4 and W6 below the upper margin of the left main PA were shown in Figure 5 (D, E, F). 51.4% (130/253) of the LNs at W4 and 94% (47/50) at W6 were misclassified as IASLC-10L (Figure 4).

The different N stages of metastatic lower paratracheal nodes by EBUS-TBNA with different landmarks

Among the 50 patients with lung cancer, there were 138 LNs metastases. Combined with the sites of the patient's primary lesion, we used Wang's bronchial landmarks and IASLC's vascular landmarks to analyze the metastatic lower paratracheal nodes respectively. For the right lower LNs, the Kappa value (0.768) indicated the substantial concordance between Wang's map and IASLC map, but for the left lower LNs, the concordance between the two maps was fair (Kappa 0.374) (Table 2).

Overall, if using vascular landmarks of IASLC-4 for the patients with lung cancer, it would lead to improper staging of the lower paratracheal nodes. For the right LNs, the LNs at station W5 in Wang's map were below the azygous arch, would be down-staged from N2 to N1 in 8 patients, the LNs below W5 were at the end of the azygous arch, would be up-staged from N1 to N2 in 2 patients, so the overall changes of N stage were found in 10 cases (34.5%). While for the left side, the LNs at W4

were often below the upper rim of the left pulmonary artery, they would be classified as IASLC-10L, leading to being down-staged from N2 to N1 in 11 patients (52.4%).

Changes of overall TNM staging confirmed by surgery with different landmarks

Since LNs of IASLC-4L were situated in the aorta-pulmonary window, which were inaccessible for surgery, thus the changes of stage for 14 patients with left lung cancer couldn't be analyzed.

Among the 27 patients with right metastatic LNs resected by surgery, 13 patients had metastases of 4R and/or 10R lymph nodes. In a patient, one lymph node situated at the right main bronchus (W5), but below the azygous arch, the surgeon usually dealt with it as 4R (N2), while if using vascular landmark, it would be classified by N1 (10R). In another patient, the LN was at the distal end of the right main bronchus, but at the end of the azygous arch, the surgeon dealt with it as 10R (N1), while if using vascular landmark, it would be classified by N2 (4R). Thus, for the above two patients, the overall postoperative stage would be downgraded and upgraded if based on different assessments, and the total percents of the TNM staging changes were 14.5%. For the third case, due to the presence of metastatic lymph node IASLC-7, the overall stage remained the same.

Discussion

IASLC lymph node map is used in tandem with the current eighth edition of the TNM stage classification for lung cancer. Its use is recommended following a long series of investigations and experiences. However, in clinical practice, some problems with node classification occur, especially with regard to the lower paratracheal lymph nodes in the IASLC map. Our study showed that the locations of the azygous arch and the left main pulmonary artery varied in relation to the airway, using such vascular

marks of the IASCL map would result in improper classification of some lower paratracheal lymph nodes. We have found that some parts of mediastinal LNs would be downgraded to hilar LNs, very few would be upgraded to mediastinal LNs on the right side, while many mediastinal LNs would be downgraded on the left. Although Wang's map was originally used to guide the biopsy of mediastinal and hilar adenopathy, it's bronchial landmarks can be helpful to complement the problem of IASLC using vessels as the boundaries[15,16].

In fact, the variability of the azygous arch and the pulmonary artery in relation to the airway had been reported in two previous articles[11,12]. Li et al used some chest CT images to show the improper staging of lymph nodes due to vascular variations. They found station 4L lymph nodes in the IASLC map were often below the upper border of the left pulmonary artery, which resulted in a risk of down-staging of the patient if vessels were used as landmarks. On the right side, the locations of azygous veins were varying too, if only vessels were visualized, the lymph node staging would be up-regulated or down-regulated[11]. In the other study, radiologists had also illustrated similar confusions in the IASLC staging map. If the definition of the lower boundary of IASLC-4 lymph nodes was strictly applied to CT, a territory occured (the region anterior to the tracheal bifurcation, also known as the precarinal space) in which the distinction between lower paratracheal lymph nodes and hilar lymph nodes was unclear. In clinical practice, the region anterior to the tracheal bifurcation is in the mediastinum regardless of vessels' locations, they should be typically grouped with station IASLC-4 at CT. Furthermore, surgical management of LNs anterior to the tracheal bifurcation mirrors that of mediastinal LNs[12]. However, such findings had been simply documented in a small part of both articles, and there were no solid data

to support these observations. In contrast, our study used clinical data to analyze the effects of vascular variants on the lymph node staging.

We have found the location of the azygous arch has the following varieties: (1) If the azygous arch is at the level of the end tracheal segment (Figure 3A), the LNs below the arch, including the terminal of the trachea, carina, all the right main bronchus, are belonged to IASLC-10R. We had found 9.3% (W1) and 38.6% (W5) of LNs were misclassified as IASLC-10R, resulting in down-staging mediastinal LNs to hilar LNs; (2) If the azygous arch is at the proximal right main bronchus (Figure 3B), using Wang's bronchial or IASLC' vascular landmarks can acquire the same classification for the paratracheal LNs regardless of which map is used; (3) If the azygous arch is at the end of the right main bronchus (Figure 3C), LNs at almost right main bronchus (about 9.5%) will be called as 4R, resulting in up-staging hilar LNs to mediastinal LNs. Then, the concordance between the two maps was analyzed, the kappa value (0.550) for the benign lymph nodes was not high as that of right lung cancer diagnosed by EBUS-TBNA (0.768), which might be resulted from different sizes of lymph nodes. The bigger lymph nodes in lung cancer would locate at two stations, which would cause the investigator more likely to evaluate the LNs as the right stations. At last, the variant sites of azygous arches caused improper classification of N stage in 34.5% of patients by EBUS-TBNA and changes of the TNM stage in 14.5% of patients by surgery.

In this study, it was found that variable locations of the upper rim of left main pulmonary artery could be from the terminal main trachea to the left main bronchus (Figure 5). According to the IASLC definition, the upper rim of the left main pulmonary artery is the boundary of 4L and 10L. However, such vascular landmark is set too high, many left lower tracheal LNs will be down-staged from 4L to 10L. This

misclassified percentage was more than 50% for the left lower paratracheal LNs. Such problem was further studied by EBUS-TBNA, which was recognized as the most diagnostic value in hilar/mediastinal (N1/N2) lymph node staging[17-19]. The concordance between these two maps for the left side LNs was poor (Kappa 0.374). If only pulmonary arteries were visualized, 52.4% of patients would be down-staged from N2 to N1, which would cause such patients without the opportunity for surgery to take surgery.

Actually, the range of IASCL-4R includes right paratracheal nodes, and pretracheal nodes extending to the left lateral border of the trachea; IASCL-4L includes nodes to the left of the left lateral border of the trachea, medial to the ligamentum arteriosum in the definition of IASCL map[4]. From the above definition of IASLC-4, it can be known that the demarcation of IASLC-4 contains the bronchial marks as the references, and it could also be speculated that the IASLC-4R and 4L in the IASLC map have included the proximal main bronchus (lower boundary of 4R and 4L), which belong to the mediastinum. Thus, the bronchial landmarks of Wang's map are consistent with the IASLC staging system in distinction of mediastinal and hilar classification. So, for accurate classification of lung cancer, we suggest that the more stable bronchial landmarks may be taken as the standard for staging lower paratracheal LNs, the LNs at proximal right main bronchus (W5) is always N2, which is not affected by the location of the azygous arch, the LNs (W4 and W6) at the left tracheobronchial angulation and the proximal left main bronchus should be mediastinal LNs. Therefore, we recommend the lower border of 4R should be the right proximal main bronchus(W5), and the lower border of IASLC-4L may extend to the left proximal main bronchus(W6).

There is no further nomenclature for the hilar LNs located around most of the right and left main bronchus in Wang's map, the reason is that the right main bronchus is short, except the proximal W5, and the lymph nodes in front of the right upper lobe (W7) are equivalent to IASLC-10R, and there is no left more space for 10R. The left main bronchus is long, except the proximal W6, IASLC-10L is present, but the meaning of which was equivalent to IASLC-11L. So, descriptions of 10R below W5 and 10L below W6 were adopted in Wang's map (Figure 1). This nomenclature can describe the upper rims of IASLC-10R and IASLC-10L more clearly, consistent with our suggestion about the lower borders of IASLC-4R and IASLC-4L from another view.

Conclusion

Our findings indicate the possibility of using more accurate and stable bronchial landmarks as boundaries to distinguish the paratracheal LNs. In particular, we recommend to consider the lower border of the proximal right main bronchus (W5) as the inferior margin of 4R, and to extend the boundary of 4L down to the region below the left proximal main bronchus (W6). In the future, we hope for more prospective and multi-centers studies to confirm it.

Limitation

There are limitations to our study. Firstly, this is a retrospective study. The number of subjects is relatively low, more studies on a large number of patients are warranted. Secondly, the patients diagnosed by EBUS-TBNA were almost at the advanced stage of lung cancer, so our paper did not show the final stage of such patients, just analyzed their LNs classification, but it did not affect the results of our study. Thirdly, this is just a preliminary exploration, follow-up data is lacking. More evidence-based data is needed.

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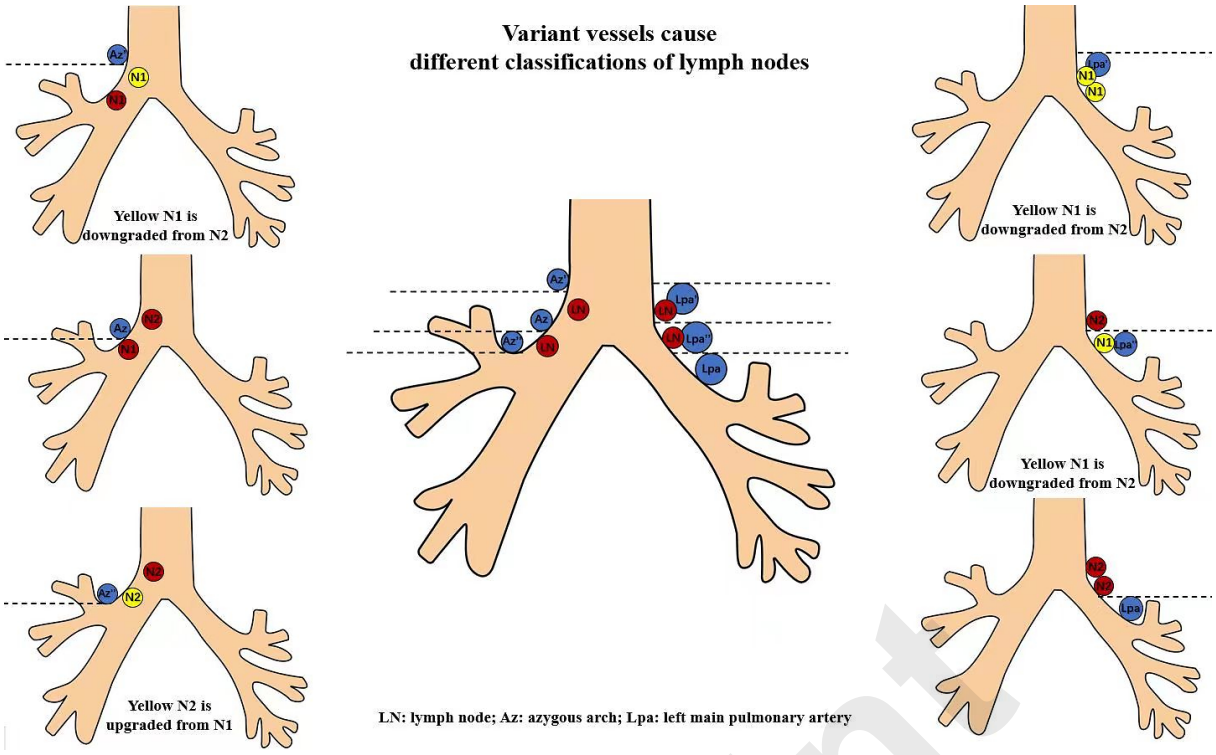
Variant vessels cause
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LN: lymph node; Az: azygous arch; Lpa: left main pulmonary artery

Table 1 Consistent analysis of different classifications of the benign right lower paratracheal lymph nodes by using IASLC map and Wang's map.

Wang's map	IASLC		Kappa(95%CI)	P Value
	4R	10R		
W1+W3+W5	313	44	0.550 (0.442-0.658)	p≤0.001
10R below W5	4	38		

Table 2 Concordance of metastatic lower paratracheal nodes staging between IASLC map and Wang's map.

	Wang's map	IASLC		Kappa(95%CI)	P Value
		N1	N2		
Right	N1	29	2	0.768(0.633-0.903)	p≤0.001
	N2	8	53		
Left	N1	8	0	0.374(0.160-0.588)	0.001
	N2	14	24		
Total	N1	37	2	0.629(0.502-0.756)	p≤0.001
	N2	22	77		

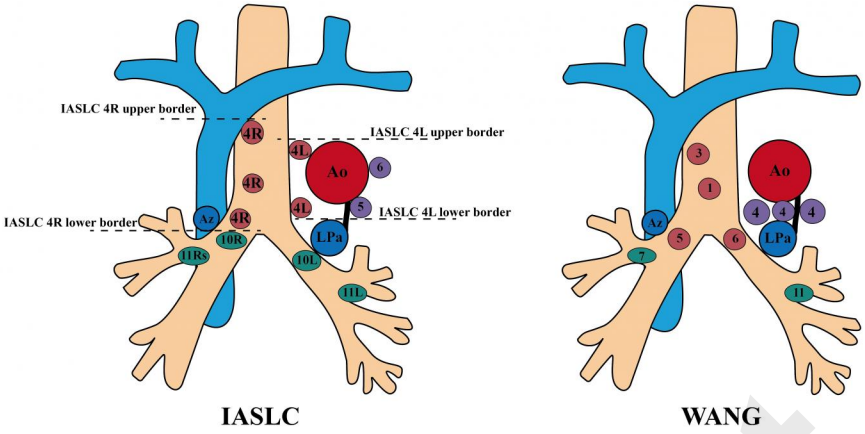

Figure 1 International Association for the Study of Lung Cancer (IASLC) and WANG maps. Ao, aortic arch; Az, azygos arch; Lpa, left pulmonary artery.

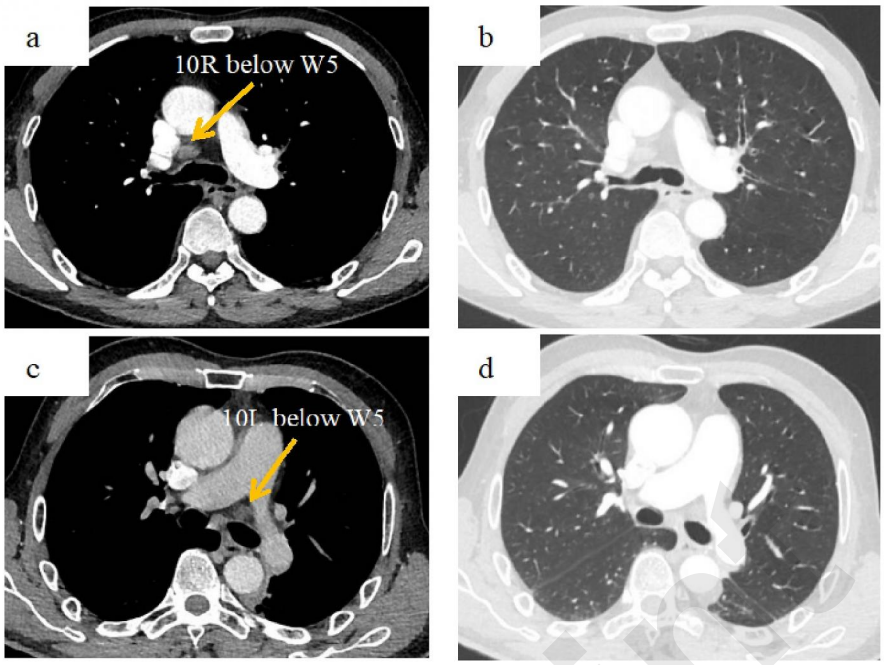

Figure 2 The manifestation of main bronchus hilar lymph node.(A) 10R below W5; (C) 10L below W6. (B) and (D) Lung window of (A) and (C) (yellow arrows).

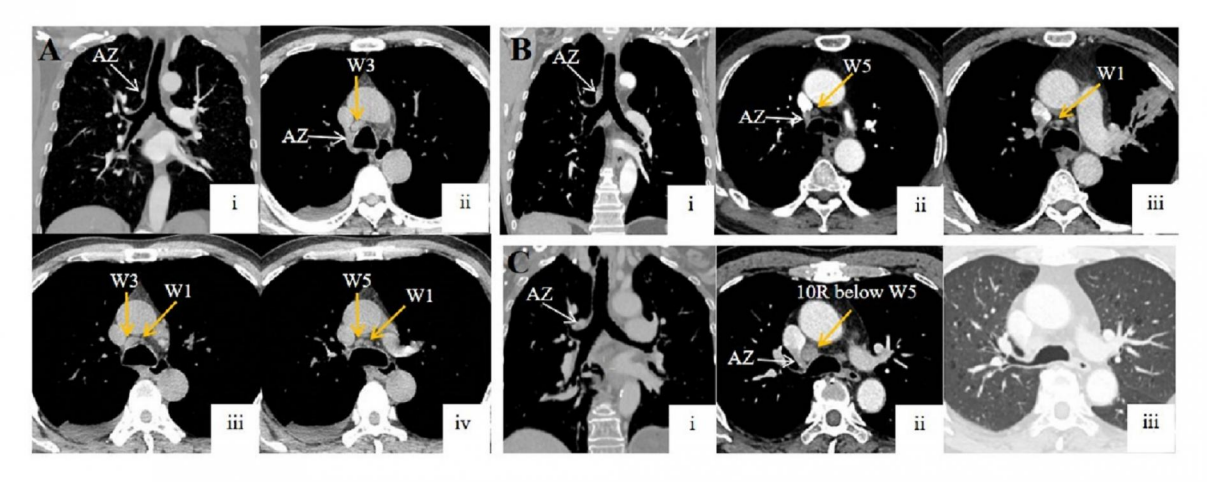

Figure 3 The inconsistent classification caused by the different locations of azygous arch (AZ, white arrow) relative to the trachea, coronal view reconstructed by MIP. (A) High level of AZ (i), (ii) W3 was classified as IASLC-4R, (iii) and (iv) W1, W3 and W5 were classified as IASLC-10R; (B) Normal level of AZ (i), (ii) and (iii) W1 and W5 were classified as IASLC-4R; (C) Low level of AZ (i), (ii) 10R below W5 was classified as IASLC-4R, (iii) the lung window of (ii) (yellow arrow).

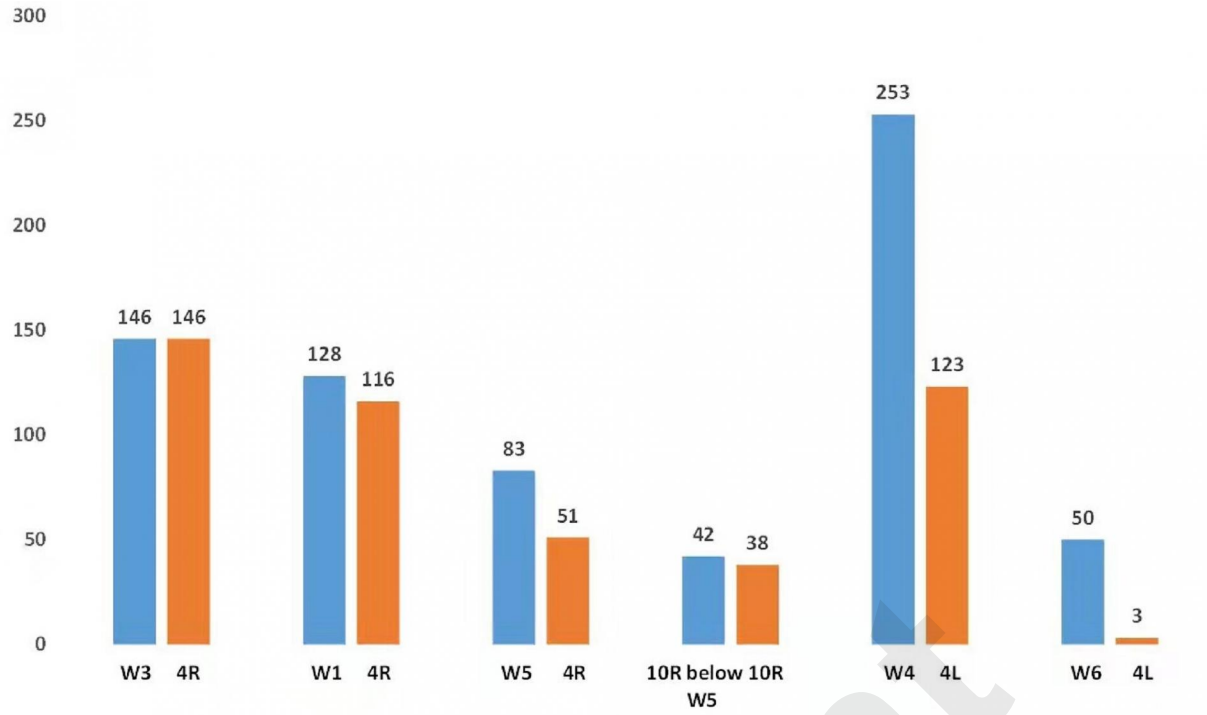

Figure 4 Comparison and correlation of the lower paratracheal mediastinal and hilar lymph nodes between Wang's map(blue histogram) and the IASLC map(yellow histogram) for the 702 lymph nodes in 100 benign patients.

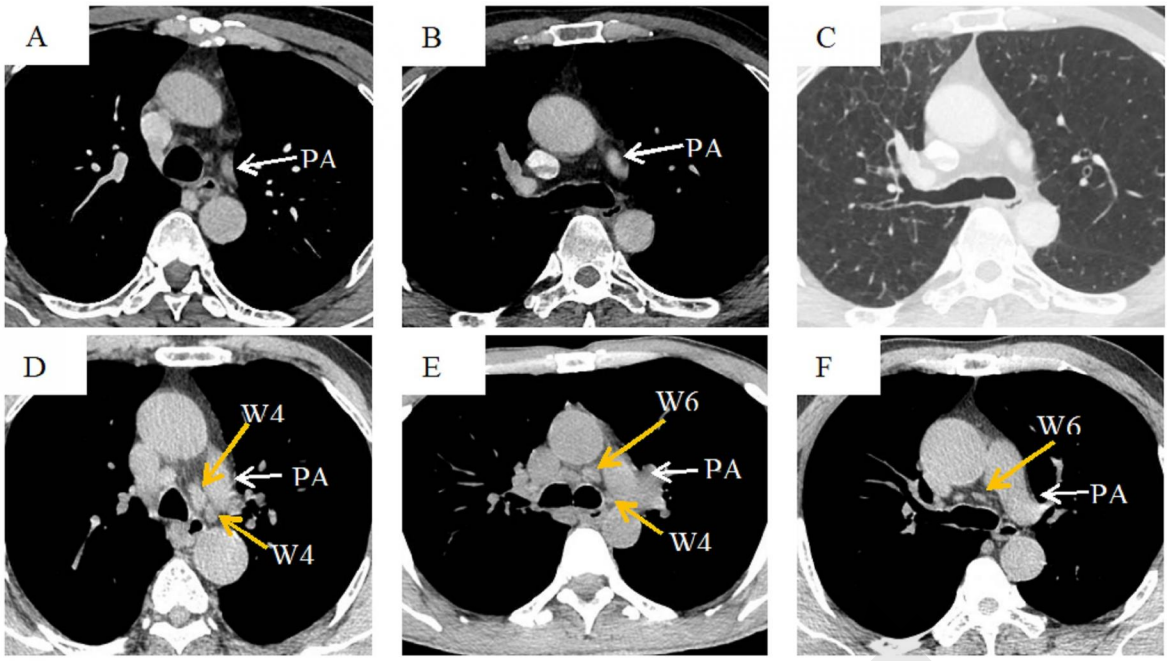

Figure 5.The improper classification caused by the variant location of the upper margin of the left main pulmonary artery (PA). (A) and (B), the variant locations of the upper margin of left main PA; (C) was the lung window of (B); (D), (E), (F): LNs (W4 and W6) were all misclassified to IASLC-10L (yellow arrow).