Review Article

Mediastinal lymph node staging for lung cancer

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Abstract: Mediastinal lymph node staging is crucial in deciding the treatment strategy for lung carcinoma. The diagnosis rate of computed tomography is not high; however, it is a standard examination. Although the contrast computed tomography is necessary for an accurate diagnosis, images from the positron emission tomography are excellent, and these two technologies are independent and complementary. Positron emission tomography has a disadvantage of false positives and false negatives, but it should also be used in cases where lymph node diameters are 1 cm or more. However, image-based diagnostic methods are not an alternative to histological examination. The results of a transbronchial needle biopsy are extremely dependent on the inspection method, the diagnostic ability of the physician, and the staging of the case. The transesophageal ultrasound endoscope is useful for reaching parts inaccessible by a mediastinoscope. Although its employment requires technical training, it is becoming popular as a minimally invasive method of obtaining cell and the tissue samples. A thoracoscopic biopsy is considered as a last resort for mediastinal lymph node diagnosis. Carefully-chosen invasive procedures are necessary to diagnose swollen lymph nodes. Although mediastinoscopy is still considered as the gold standard, most procedures will be replaced by a comparatively minimally invasive method in the future.

Keywords: Mediastinum; lymph node; staging

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Introduction

The presence or absence of lymph node metastasis in lung carcinoma has a significant effect on the treatment policy and prognosis. Recent advances in medical technology has helped establish several new methods for diagnosis—fluorodeoxyglucose positron emission tomography (FDG-PET), PET-computed tomography (CT), transbronchial needle aspiration (TBNA), endobronchial ultrasound-guided TBNA (EBUS-TBNA), convex type EBUS-TBNA, endoscopic ultrasound-guided needle aspiration (EUS-NA), mediastinoscopy (MED), video-assisted MED (VAM), and video-assisted thoracoscopic surgery (VATS). The combined use of non-invasive and invasive methods for the diagnosis of lymph node metastasis is challenging and the features of each method must be carefully considered before choosing them (*Table 1*).

Non-invasive methods (diagnostic imaging)

Non-invasive diagnostic imaging such as CT, FDG-PET, and PET-CT, can detect all lymph nodes in the chest, however positive predictive values (PPVs) are not high in spite of a relatively high negative predictive value. Presently, there is no substitute for histological examination, and invasive methods are required only for the final diagnosis

CT

Various criteria for the diagnosis of mediastinal lymph node metastasis by CT have been proposed such as the product of the major and minor axis, size of the transition by station, and change of the standard by tissue type (1). Since there is presently no consensus, lymph nodes measuring more than 1 cm at the minor axis are considered as metastatic. Several

Table 1 Lymph node staging modalities

Staging modality	Lymph node access	Sensitivity (%)	Specificity (%)	PPV	NPV
Non-invasive					
CT	All	44	89	56	85
PET	All	74	82	63	92
PET-CT	All	58	69	65	89
Invasive					
Mediastinoscopy	2R, 2L, 4R, 4L,7	85	100	100	92
Video-assisted mediastinoscopy	2R, 2L, 4R, 4L,7	87	100	100	93
VATS	4R, 4L, 7, 10R, 10L, 11R, 11L, 5, 8, 9	89	100	100	96
TBNA	2R, 2L 4R, 4L, 7, 10R, 10L, 11R, 11L	72	100	100	63
EBUS-TBNA	2R, 2L 4R, 4L, 7, 10R, 10L, 11R, 11L	87	100	100	88
EUS-NA	4L, 5, 7, 8, 9	81	100	100	80
Combined EBUS/EUS	2R, 2L 4R, 4L, 5, 7, 8, 9, 10R, 10L, 11R, 11L	82	99	100	91

CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; VATS, video-assisted thoracoscopic surgery; TBNA, transbronchial needle aspiration; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EUS-NA, endoscopic ultrasound-guided needle aspiration; PPV, positive predictive value; NPV, negative predictive value.

Table 2 Computed tomography for mediastinal lymph node staging

First author	Year	No.	Sensitivity (%)	Specificity (%)	PPV	NPV
Jolly (2)	1996	336	71	86	69	87
Suzuki (3)	1999	440	33	92	56	82
Takamochi (4)	2000	401	30	82	30	83
Osada (5)	2001	335	56	93	77	83
Kamiyoshihara (6)	2001	456	33	90	46	84
Reed (7)	2003	302	37	91	58	81
Kimura (8)	2003	203	63	97	88	89
Ebihara (9)	2006	205	32	83	26	87
Total/mean	–	2,678	44	89	56	85

Inclusion criteria: studies reporting test characteristics of chest CT scanning to identify benign or malignant mediastinal nodes in patients with lung cancer, involving more than 200 patients. PPV, positive predictive value; NPV, negative predictive value; CT, computed tomography.

reports have used this method to confirm metastasis in case of a surgical adaptation; mean sensitivity and specificity are 44% and 89% (*Table 2*).

FDG-PET/FDG-PE-CT

FDG-PET use has been ubiquitous due to the development of the delivery system. It was initially considered as a substitute for cytology or tissue sampling for the diagnosis of cancer, but it should be used with care as false positives and false negatives are seen occasionally (*Table 3*), and careful evaluation is necessary for the diagnosis of mediastinal lymph nodes. However, a good quality image, and fusion PET-CT provides accurate information for diagnosis (*Table 4*). An FDG is known to accumulate in lymph nodes in non-malignant conditions such as inflammation and the results

Table 3 Accuracy of PET scanning for staging of mediastinum in patients with lung cancer

First author	Year	No.	Sensitivity (%)	Specificity (%)	PPV	NPV
Kernstine (10)	2002	237	82	82	51	95
Gonzalez-Stawinski (11)	2003	202	66	78	48	88
Reed (7)	2003	302	61	84	56	87
Ebihara (9)	2006	205	74	90	58	95
Lee (12)	2007	210	61	64	69	92
Nosotti (13)	2008	413	97	97	97	97
Total/mean	–	1,569	74	82	63	92

Inclusion criteria: studies reporting test characteristics of PET scanning to identify benign or malignant mediastinal nodes in patients with lung cancer, involving more than 200 patients. PPV, positive predictive value; NPV, negative predictive value; PET, positron emission tomography.

Table 4 Accuracy of PET-CT scanning for staging of mediastinum in patients with lung cancer

First author	Year	No.	Sensitivity (%)	Specificity (%)	PPV	NPV
Yi (14)	2007	143	56	100	100	88
Lee (12)	2007	126	86	81	56	95
Yi (15)	2008	150	62	94	82	85
Yang (16)	2008	122	52	73	33	86
Shin (17)	2008	184	48	95	58	93
Lee (18)	2009	182	81	73	42	94
Carnochan (19)	2009	194	42	87	50	83
Billé (20)	2009	159	48	93	63	88
Maziak (21)	2009	167	48	93	74	82
Bugge (22)	2014	130	78	88	64	94
Naur (23)	2017	115	42	99	90	90
Ozturk (24)	2018	483	75	84	78	80
Total/mean	–	2,155	58	89	65	89

Inclusion criteria: studies reporting test characteristics of PET-CT scanning to identify benign or malignant mediastinal nodes in patients with lung cancer, involving more than 100 patients. CT, computed tomography; PET, positron emission tomography; PPV, positive predictive value; NPV, negative predictive value.

can be pseudo positive as the specificity or negative predictive values are relatively low. The Z0050 trial (7) which analyzed the use of PET for staging in 303 cases of non-small cell lung carcinoma with surgical adaptation revealed an N1 detection rate of 13% *vs.* 42%, N2 and N3 detection of 32% *vs.* 58%, and sensitivity of 37% *vs.* 61%, by CT and PET scans respectively. This makes it possible to prevent unnecessary thoracotomies; however, a definite diagnosis is still necessary for confirmatory findings.

Invasive methods (cytological-pathological diagnosis)

It is necessary to perform an invasive procedure such as MED, VAM, VATS, TBNA, EBUS-TBNA, or EUS-NA (sensitivity of the needle biopsy is lower in the case of N0) even after PET scans show positive or negative lymph nodes. The most appropriate method is chosen according to the surgeon's skill, experience, and lymph node position (*Figure 1*).

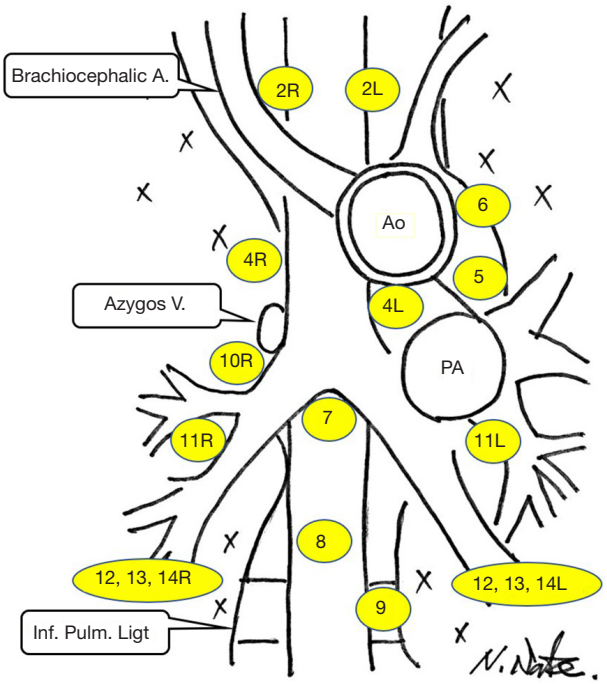

Figure 1 Lymph node position at the mediastinum, the hilum, and the lung. A., artery; V. vein; inf., inferior; pulm., pulmonary; Ligt., ligament.

MED and VATS

Traditionally, lymph nodes sampling is carried under direct visualization, but currently it is done by viewing an image on the video monitor and is performed with more safety. Additionally, the accuracy of MED is similar to MED and VAM (*Table 5*). A report on MED in 202 cases after a PET scan (11) revealed that only 29 cases were PET-positive, while 65 cases were positive in MED; N2 and N3 stages were observed in 16 out of 137 PET negative cases. MED is considered to be a standard procedure by some for the diagnosis of mediastinal lymph nodes. VATS has been used to assess aorto-pulmonary window lymph nodes (level 5) and paraaortic lymph nodes (level 6). The overall results of this technique are summarized in *Table 6*. Specific results for stations 5 and 6 have not been reported but are likely to be better because these are easier to access than other mediastinal node stations. In specific cases, a combination of VAM and VATS is performed for the management of lung cancer (39).

TBNA

Although TBNA has been used for some time, the rate

Table 5 Accuracy of mediastinoscopy in patients with lung cancer

First author	Year	No.	Stage	Sensitivity (%)	Specificity (%)	PPV	NPV
MED							
Coughlin (25)	1985	1,259	cN0-3	92	100	100	97
Luke (26)	1986	1,000	cN0-2	85	100	100	91
De Leyn (27)	1996	500	cN0-2	76	100	100	87
Hammoud (28)	1999	1,369	cN0-3	85	100	100	92
Lemaire (29)	2006	1,362	cN0-3	86	100	100	95
Total/mean	–	5,490	–	85	100	100	92
VAM							
Venissac (30)	2003	154	cN2-3	97	100	100	94
Lardinois (31)	2003	195	cN0-3	87	100	100	92
Kimura (8)	2003	125	cN0-3	85	100	100	92
Kimura (32)	2007	209	cN0-3	78	100	100	91
Sayar (33)	2011	104	cN0-2	90	100	100	96
Sayar (34)	2016	216	cN0-2	87	100	100	95
Total/mean	–	1,003	–	87	100	100	93

Inclusion criteria: studies of mediastinoscopy (MED) for lung cancer staging for mediastinal lymph adenopathy, involving more than 500 and video-assisted mediastinoscopy (VAM), involving more than 100 patients. PPV, positive predictive value; NPV, negative predictive value.

Table 6 Surgical staging of the mediastinum with video-assisted thoracic surgery

First author	Year	No.	Stage	Sensitivity (%)	Specificity (%)	PPV	NPV
Eggeling (35)	2002	73	cN2-3	98	100	100	96
Massone (36)	2003	55	cN2	100	100	100	100
Sebastián-Quetglás (37)	2003	79	cN0-2	58	100	100	88
Cerfolio (38)	2007	39	cN2	100	100	100	100
Total/mean	–	246	–	89	100	100	96

Inclusion criteria: studies of video-assisted thoracoscopic surgery for staging of the mediastinal nodes, involving more than 30 patients. PPV, positive predictive value; NPV, negative predictive value.

Table 7 Transbronchial needle aspiration of the mediastinum in patients with lung cancer

First author	Year	No.	c-stage	Sensitivity (%)	Specificity (%)	PPV	NPV
Bilaçeroğlu (40)	1998	134	cN1-N3	75	100	100	36
Harrow (41)	2000	264	cN1-N3	93	99	99	80
Patelli (42)	2002	182	cN2	98	100	100	83
Shah (43)	2006	129	cN1-N3	68	100	100	56
Bernasconi (44)	2006	113	cN2-N3	54	100	100	91
Wallace (45)	2008	138	cN2-N3	36	100	100	78
Fernández-Villar (46)	2010	280	cN1-N3	68	100	100	10
Rakha (47)	2010	182	cN1-N3	84	100	100	70
Total/mean	–	1,422	–	72	100	100	63

Inclusion criteria: studies of transbronchial needle aspiration (TBNA) for staging of the mediastinal nodes, involving more than100 patients. PPV, positive predictive value; NPV, negative predictive value.

of diagnosis is greatly affected by the experience of the examiner and is no longer used as a standard diagnostic tool. The results of studies on TBNA containing more than 100 cases is shown in *Table 7*, and reveals that mean specificity, sensitivity, PPV, and negative predictive values were 72%, 100%, 100%, and 63%, respectively.

EBUS-TBNA/EUS-NA

The method of identifying the position of lymph nodes using ultrasound to increase the accuracy of the lymph node metastasis has progressed. The combined results of lymph node metastasis by EBUS-TBNA from various studies are summarized in *Table 8*.

The convex-operated ultrasonic bronchoscopic needle biopsy method (Convex probe EBUS-TBNA) has recently emerged as a popular technique. Yasufuku et al. was the first to perform an EBUS-TBNA using a convex type model (64). A total of 70 patients with a confirmed or suspected malignant tumor, with lymph nodes of more than 1 cm on CT (mediastinal lymph nodes 58 cases, hilar lymph nodes 12 cases) were analyzed in real-time. According to the report, 68 positive cases were identified from the patients with lymph nodes, and two cases were found to be negative. Forty-five cases were found to be malignant and 25 were benign. The test results showed that sensitivity, specificity, and accuracy were 95.7%, 100%, and 97.1%, respectively. The patients had good results, and no complications were reported. In another study, Yasufuku et al. compared CT, PET, and EBUS-TBNA in patients with lung cancer or suspected surgical adaptation in published reports and reported that their respective sensitivities were 76.9%, 80.0%, 92.3%; specificities were 55.3%, 70.1%, 100%; and accuracies were 60.8%, 72.5%, 98.0%. EBUS-TBNA was found to have excellent results (65).

The CT is inaccurate and so is the PET, although

Table 8 Endobronchial ultrasound-guided transbronchial needle aspiration of the mediastinum in patients with lung cancer

First author	Year	No.	c-stage	Sensitivity (%)	Specificity (%)	PPV	NPV
Yasufuku (48)	2005	108	cN1-N3	95	100	100	90
Yasufuku (49)	2006	102	cN1-N3	92	100	100	97
Herth (50)	2006	100	cN0	92	100	100	96
Bauwens (51)	2008	106	cN1-N3	95	100	100	91
Lee HS (52)	2008	102	cN2-N3	94	100	100	97
Wallace (45)	2008	138	cN2-N3	69	100	100	88
Hwangbo (53)	2009	117	cN2-N3	90	100	100	97
Rintoul (54)	2009	109	cN1-N3	91	100	100	60
Ømark Petersen (55)	2009	151	cN2-N3	85	100	100	89
Szlubowski (56)	2009	226	cN0-N3	89	100	100	84
Szlubowski (57)	2010	120	cN0	46	99	96	86
Hwangbo (58)	2010	150	cN2-N3	84	100	100	93
Memoli (59)	2011	100	cN1-N3	87	100	100	89
Steinfort (60)	2011	117	cN1-N3	95	100	100	67
Ye (61)	2011	101	cN1-N3	95	100	100	93
Yasufuku (62)	2011	153	cN0-N3	80	100	100	91
Oki (63)	2015	150	cN2-N3	52	100	100	88
Ozturk (24)	2018	483	cN1-N3	97	100	100	97
Total/mean	–	2,633	–	85	100	100	89

Inclusion criteria: studies of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for staging of the mediastinal nodes, involving more than 100 patients. PPV, positive predictive value; NPV, negative predictive value.

it increased the possibility of different diagnoses. The TBNA is a blind procedure, and the CT-guided cytology is more restrictive than the conventional ultrasound guided cytology, and the standard MED is also restricted and invasive. Although a TBNA cannot reach levels 5, 6, 8, 9 of lymph nodes, it is possible to access levels 10 and 11, and the total mediastinum can be reached when combined with EUS-NA. In addition, if the MED and EBUS-TBNA are compared, the EBUS-TBNA may reduce the necessity of a MED without complications; however, it is necessary to assess the possibility of micro metastases by EBUS-TBNA.

An EUS-NA is a transesophageal ultrasound endoscope, which can access parts unreachable by mediastinoscope and is more accurate than a PET or CT; its PPV is particularly good (*Table 9*). An EUS-NA and an EBUS-TBNA are complementary technologies and can be adapted to be used together (*Table 10*).

Conclusions

Although techniques for mediastinal lymph node diagnosis should be chosen depending on the experience and skill of the surgeon, the relatively minimally invasive EBUS-TBNA is preferred to obtain a histological diagnosis. However, more advanced technologies to match the pathological diagnosis by PET imaging are expected in the future.

Table 9 Endoscopic ultrasound-guided fine-needle aspiration of the mediastinum in patients with lung cancer

First author	Year	No.	c-stage	Sensitivity (%)	Specificity (%)	PPV	NPV
Wallace (66)	2001	121	cN2-N3	87	100	100	68
Annema (67)	2005	215	cN0-N3	91	100	100	74
Eloubeidi (68)	2005	104	cN2-N3	93	100	100	96
Tournoy (69)	2008	100	cN0-N3	95	100	100	81
Wallace (45)	2008	138	cN2-N3	69	100	100	88
Annema (70)	2010	551	cN2-N3	83	100	100	75
Talebian (71)	2010	152	cN2-N3	74	100	100	73
Hearth (72)	2010	139	cN1-N3	89	100	100	82
Szlubowski (57)	2010	120	cN0	50	99	93	87
Oki (63)	2015	150	cN2-N3	45	100	100	86
Total/mean	–	1,790	–	81	100	99	80

Inclusion criteria: studies of endoscopic ultrasound-guided needle aspiration (EUS-NA) for staging of the mediastinal nodes, involving more than 100 patients. PPV, positive predictive value; NPV, negative predictive value.

Table 10 Endobronchial ultrasound-guided transbronchial needle aspiration and endoscopic ultrasound-guided fine-needle aspiration

First author	Year	No.	c-stage	Sensitivity (%)	Specificity (%)	PPV	NPV
Wallace (45)	2008	138	cN2-N3	93	100	100	97
Annema (73)	2010	123	cN1-N3	82	100	100	80
Herth (72)	2010	139	cN1-N3	96	100	100	96
Hwangbo (58)	2010	150	cN2-N3	91	100	100	96
Szlubowski (57)	2010	120	cN2	68	91	98	91
Ohnishi (74)	2011	110	cN0-N3	72	100	100	87
Oki (61)	2015	150	cN2-N3	73	100	100	93
Total/mean	–	930	–	82	99	100	91

Inclusion criteria: studies of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guided needle aspiration (EUS-NA) for staging of the mediastinal nodes, involving more than 100 patients. PPV, positive predictive value; NPV, negative predictive value.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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