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ORIGINAL INVESTIGATION

Routine invasive mediastinal staging of lung cancer in elderly patients without lymph adenopathy on PET-CT scan: is an appropriate choice?

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We have reviewed the literature to clarify if routine invasive mediastinal staging is indicated also in Stage I elderly patients screened with PET/CT scan. Nineteen papers were chosen to answer the question. Occult pN2 disease was < 10% in five papers; between 10-16% in four papers; and > 16% in four papers.Significant risk factors for occult pN2 disease are the SUV value of primary tumor (seven papers), central tumor (four papers), tumor > 3 cm (five papers), adenocarcinoma histology (five papers) and cN1 disease(two papers). Two papers found that unexpected pN2 patients had a better survival than cN2 patients operated after induction therapy. Invasive mediastinal staging is recommended also in cN0 patients with central tumor or with peripheral tumor > 3 cm.

Key words: CT/PET, Invasive technique, Mediastinal staging, Non small cell lung cancer

INTRODUCTION

Increases in both life expectancy and cancer incidence with age, together to the exposure to pollutants including smoking habit, result in a significant rise in lung cancer rates among elderly patients [1-5].
At diagnosis, half of the patients are over 70 years of age, and most present with comorbidities and advanced disease for which chemotherapy provides limited benefit in terms of response rate and survival [6-16].
Better understanding cancer biology [17-37] is leading to renovated target based approaches also in elderly. Mediastinal lymph node (LN) staging represents the cornerstone in the diagnosis, treatment and prognosis of patient with non-small cell lung cancer (NSCLC). Despite the advances in radiological proceduresand the routine use of F-18 fluorodeoxy-D-glucose positron emission tomography(18-FDG-PET) [38-45] in diagnostic work-up of lung cancer, 5-15% of NSCLC patients clinically staged as N0 and undergoing surgery have an unexpected pN2 disease [46-54].

Thus, we have reviewed the literature to define if routine invasive mediastinal stage is indicated in NSCLC elderly patients without LN involvement on PET-CT, an issue still debate.

RESEARCH CRITERIA

Medline search was done on PubMed, EMBASE and Cochrane databases using the following terms: lung cancer, mediastinum, PET, staging, Endoscopy (Bronchial) Ultrasound-Endoscopy (EBUS, EUS), Video Assisted Thoracic Surgery (VATS), and mediastinoscopy. The time frame was restricted to articles published from January 2000 up to July 2015. Cited references of review articles on indication for invasive mediastinal staging were manually examined to find additional articles not found in the computerized databases. Additional articles were identified from reference lists of selected articles. No-English language papers, case reports, abstracts only, letters and unpublished data were excluded. Of the 293 papers founded, 19were identified for answering our question and summarized in Table I.

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RESULTS

Park et al. [55] attended mediastinoscopy in 78/147 (53%) patients with NSCLC Stage I. N2 disease was found in 7 (4.8%) cases of which 6 underwent mediastinoscopy with diagnosis of N2 involvement in only 3 cases (50%). Significant predictors of N1/N2 metastasis was a SUV of primary tumor > 7.3 (p = 0.001).

Cerfolio et al. [56] evaluated 153 NSCLC cN0 (n = 136) and cN1 (n = 17) patients screened with PET/CT. All patients underwent mediastinoscopy and EUS. N2 disease was found in 22/153 (14.3%) patients; among cN0 (n = 15) mediastinoscopy (n = 4; 2.9%) and EUS (5; 3.7%) correctly diagnosed N2 disease in 9 cases and failed in 6 (4.7%); among cN1 (n = 7) mediastinoscopy (n = 3; 17.6%) and EUS (n = 4; 23.5%) correctly diagnosed N2 disease in all cases. Significant risk factors were a SUV primary tumor > 10 (0.01) and poorly differentiated cancer (0.03).

Sivrikoz et al. [57] attended mediastinoscopy in 68 resectable patients. N2 disease was found in 11/68 (16%) cases. Mediastinoscopy correctly diagnosed N2 diseases in 9/11 patients (81.8%) and failed in 2/11 because sub-centimeters LNs.

Sanli et al. [58] studied 78 NSCLC patients. Mediastinoscopy (n = 33/78; 42%) was attended in cN2 patients and in those with adenocarcinoma or central tumors even without mediastinal involvement. Accuracy of mediastinoscopy was 96.9% with one false negative result.

Al-Sarraf et al. [59] evaluated 153 NSCLC patients without mediastinal adenopathy. No mediastinoscopy was performed. N2 disease was found in 25/153 (16%) patients; significant risk factors were central tumor (p = 0.007); right upper lobe (p = 0.01); and cN1 disease on PET (p = 0.002).

Perigaud et al. [60] evaluated 51 NSCLC. Mediastinoscopy was attended in only 2 patients to exclude N3 disease. N2 disease was found in 10/51 (19.6%) patients; of these, 6 sub-centimeters LNs were PET negative. Meyers et al. [61] evaluated 248 NSCLC early-stage patients. 14/248 (5.6%) had N2 disease; of these 13/14 (92.8%) underwent mediastinoscopy detecting metastasis in 5/13 (38%) patients. Only 1/70 patient who did not have mediastinoscopy had N2 disease. The 5 year progression free survival of patients undergoing mediastinoscopy or not was similar (72% *vs* 77%; p = 0.245). Zhang et al. [62] in 530 NSCLC T1N0 stage patients found N2 disease in 89/530 (16.8%) cases. No mediastinoscopy neither PET/CT was routinely carried-out. Significant risk factors were central tumor (p = 0.002); tumor size (p < 0.001), and invasive adenocarcinoma (p < 0.001). De Franchi et al. [63] in 968 pT1 patients found 59/968 (6.1%) occult N2 diseases. In 16/59 cases (27%) mediastinoscopy was attended revealing N2 disease in 3/16 (19%) cases and failing in 13 (81%). In 7/13 cases, metastases were in stations not accessible by mediastinoscopy whereas in 6/13 cases in 4R or 7 stations. The 5 year-survival-time of patients with occult N2 disease was better than cN2 patients (46% *vs* 31%).

Lee et al. [64] attended mediastinoscopy in 76/224 (34%) NSCLC Stage I patients. N2 disease was found in 16/224 (7.1%). Metastases were identified by mediastinoscopy in 11 and missed in 5 cases. Significant risk factors were central tumor location (p < 0.001); tumor size > 6.0 (p < 0.001), and SUV > 4.0 (p = 0.01). Kim et al. [65] found occult N2 disease in 34/150 (23%) cases. PET-CT had a low value of sensitity (47%) probably because LNs were sub-centimeters. Thus, the authors concluded that negative PET N2 disease did not obviate mediastinoscopy. Iskender et al. [66] evaluated 212 patients with NSCLC underwent to PET/CT and mediastinoscopy. Only 4/107 (3.7%) with negative mediastinal LN uptake on PET/CT had pN2 disease. Trister et colleagues [67] drew up a report, focusing on 201 patients with clinical stage I and II NSCLC screened with PET scan and undergoing invasive staging of the mediastinum. N2 disease was found in 63/201 (31%) patients. Multivariate analysis showed thatSUV of primary tumour > 6 was the only significant predictive factor (p = 0.02). Gomez-Caro et al. [68] investigated 79 patients with NSCLC Stage I screened with PET-CT scan. Occult pN2 diseases were found in 6/79 (7.6%) among patients with Stage IA and 11/74 (14.8%) among those with clinical Stage IB. Significant risk factors for occult pN2were tumor sizes ≥ 5 cm, pN1 disease, adenocarcinoma and female patients. Wang et al. [69] in a metanalysis including 10 studies and a total of 1122 patients with NSCLC stage I (T1-2N0) NSCLC evaluated the negative predictive value of PET-CT. Negative predictive value of PET/CT in detecting of mediastinal LN metastases was 94% in T1 and 89% in T2 patients. Significant risk factors were adenocarcinoma histology and high FDG uptake of the primary lesion.

Billé et al. [70] investigating 353 NSCLC stage I patients. PET/CT sensitivity, specificity and accuracy were 38.8%, 97.4%, and 85.7% for adenocarcinoma histology and 81.8%, 91.8% and 90.8% for squamous carcinoma histology.

The authors [71] evaluated 901 consecutive patients with Stage I NSCLC screened with PET/CT scan. 108/901 (12%) had unexpected pN2 disease. Central tumor location (p < 0.003), cT2a (p < 0.0001) and pT2a stage (p < 0.0001), pN1 disease (p = 0.004), and SUV of primary tumor > 4.0 (p = 0.007) were prognostic factors of occult pN2 disease. pN2 patients versus cN2 patients operated after induction therapy presented a betteroverall survival (56 *vs* 20 months; p = 0.001) and disease-free survival (46 *vs* 11 months; p < 0.0001).

<table>
<tr><th>Author, date and country, Study type (level of Evidence</th><th>Patient group</th><th>Outcomes</th><th>Key results</th><th>Comments</th></tr>
<tr><td>Park et al (2010). Respirology Korea [8]

Retrospective Single centre case series</td><td>From January 2005 to December 2007, 147 patients diagnosed as clinical stage IA by integrated PET-CT were enrolled

78/147 (53%) had preoperative mediastinoscopy
144/147 (98%) underwent resection with radical lymph adenectomy
3 patients were excluded from surgery because N2 involvement</td><td>N1 disease
N2 disease

Accuracy of mediastinoscopy

Predictors of N1/N2 disease</td><td>9.5% (14/147)
4.8% (7/147)

<table><tr><th>Occult N2 disease</th><th>Mediastinoscopy yes</th><th>Positive Mediastinoscopy</th><th>Negative Mediastinoscopy</th></tr><tr><td>4.8% (7/147)</td><td>6/7 (85%)</td><td>3 (50%)</td><td>*3 (50%)</td></tr></table>* Metastasis was missed because of false negative (n=1) or inaccessible nodal groups (n=2)

<table><tr><th>Characteristics</th><th>Odds Ratio</th><th>p</th></tr><tr><td>Age, years</td><td>1.860</td><td>0.237</td></tr><tr><td>Gender</td><td>0.985</td><td>0.594</td></tr><tr><td>SUV max primary tumor >7.3</td><td>7.574</td><td>0.001</td></tr><tr><td>Tumor size, cm</td><td>1.233</td><td>0.721</td></tr></table></td><td>The higher SUV max > 7.3 was an independent predictor of occult nodal metastasis in patients with clinical stage IA NSCLC. Because routine mediastinoscopy was not performed in all patients, its role in such patients remained unclear.</td></tr>
</table>

Right lower lobe tumor	47 (36%)	10 (45%)	0.4
Median tumor size	1.8	2.3	0.05

<table>
<tr>
<td>Sivrikoz et al (2012); Thorac Cardiovasc Surg Turkey [10]

Prospective Single centre case series</td>
<td>From February 2007 to May 2010, 68 with resectable NSCLC and undergoing integrated PET/CT were evaluated

All patients underwent standard and extended cervical mediastinoscopy and resection with radical lymph adenectomy if mediastinoscopy was negative</td>
<td>N2 disease

Diagnostic accuracy</td>
<td>16% (11/68)

<table>
<tr><th>Methods</th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>PPV (%)</th><th>NPV (%)</th><th>Accuracy (%)</th></tr>
<tr><td>Mediastinoscopy in all pts</td><td>81.8*</td><td>100</td><td>100</td><td>96.6</td><td>97</td></tr>
<tr><td>PET/CT in all pts</td><td>61**</td><td>98</td><td>91.7</td><td>87.5</td><td>88.2</td></tr>
<tr><td>PET/CT in only N2 and N3 pts</td><td>72.7</td><td>97.7</td><td>88.9</td><td>93.3</td><td>92.6</td></tr>
</table>
*In 2 cases, occult N2 disease was missed because lymph node < 1 cm

**3 patients with occult N2 disease (lymph node < 1cm) and 4 patients with N1 occult diasease (central tumor) were false negative</td>
<td>Positive PET results must be pathologically confirmed. Routine mediastinoscopy can be omitted in patients with negative PET/CT for mediastinal lymph node</td>
</tr>
<tr>
<td>Sanli et al (2009) Journal of Thoracic and Cardiovasc Surg, Turkey</td>
<td>From March 2006 to June 2008, 78 patients with NSCLC were enrolled.</td>
<td>Diagnostic accuracy of PET-CT scan</td>
<td>
<table>
<tr><th>Node station</th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>PPV (%)</th><th>NPV (%)</th><th>Accuracy (%)</th></tr>
<tr><td>N2</td><td>81.8</td><td>89.5</td><td>56.2</td><td>96.7</td><td>-</td></tr>
<tr><td>N1</td><td>34.6</td><td>88.8</td><td>64.2</td><td>70.1</td><td>69</td></tr>
</table>
</td>
<td>Mediastinoscopy is required in patients with positive</td>
</tr>
</table>

<table>
<tr>
<td>[11]

Prospective Single centre case series</td>
<td>All patients were clinically staged using integrated PET-CT scan.

Mediastinoscopy was attended in N2 clinically patients and in patients with a histology of adenocarcinoma or having central tumors even if N2 was not detected in radiological examinations.</td>
<td>Diagnostic accuracy of PET-CT scan compared to surgical stage

Accuracy of mediastinoscopy</td>
<td>
<table>
<tr><th>Up-stage</th><th>Down stage</th><th>Univariate</th></tr>
<tr><td>16</td><td>12</td><td>50</td></tr>
</table>
<table>
<tr><th>Number of procedures</th><th>True negative</th><th>False negative</th><th>True positive</th><th>Accuracy (%)</th></tr>
<tr><td>33/78 (42%)</td><td>25</td><td>1</td><td>7</td><td>96.9</td></tr>
</table>
</td>
<td>mediastinal lymph node on PET-CT scan but it might not be necessary in patients without radiological lymph nodes involvement</td>
</tr>
<tr>
<td>Al-Sarraf et al (2008), Eur. J. Cardio-Thorac Surgery, Ireland [12]

Retrospective Single centre case series</td>
<td>Over 30 period months, 153 patients with NSCLC undergoing curative intenteat surgical resection were</td>
<td>N2 disease</td>
<td>25/153 (16%) patients
16/25 (64%) within station 7
7/25 (28%) within station 4</td>
<td>Patients with centrally located tumor, with right upper lobe tumors, and with positive N1 lymph node on PET</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>enrolled.

All patients were staged using PET–CT scan which showed no uptake in the mediastinum. No preoperative mediastinoscopy was carryout.</td>
<td>N2 risk factors</td>
<td>
<table>
<tr><th>Variable</th><th>Odds Ratio</th><th>p</th></tr>
<tr><td>Central location</td><td>6.11</td><td>0.007</td></tr>
<tr><td>Right upper lobe</td><td>0.221</td><td>0.017</td></tr>
<tr><td>Positive N1 uptake on PET</td><td>0.164</td><td>0.002</td></tr>
</table>
</td>
<td>should have routine mediastinoscopy to rule out N2 metastasis especially in stations number 7 and 4.</td>
</tr>
<tr>
<td>Perigaud et al (2009), Eur. J. Cardio-Thorac Surgery, France [13]

Retrospective Single centre case series</td>
<td>From June 2006 to February 2008, 51 consecutive patients with NSCLC undergoing surgery. All patients were staged using integrated PET-CT scan. Peroperative mediastinoscopy was attended in</td>
<td>N2 disease

Diagnostic accuracy of integrated PET-CT</td>
<td>10/51 (19.6%) patients

<table>
<tr><th>Sensitivity</th><th>Specificity</th><th>PPV</th><th>NPV</th></tr>
<tr><td>40 ±30*</td><td>85 ±11</td><td>40 ±30</td><td>85 ±11</td></tr>
</table>
*In 6 cases, the negative N2 PET results were due to sub-centimetres lesions.</td>
<td>Positive mediastinal lymph node on integrated PET-CT scan required invasive procedure as mediastinoscopy to exclude false positive results. In contrast,</td>
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<td></td>
<td>only 2 patient to exclude N3 disease.</td>
<td></td>
<td></td>
<td>patients without mediastinal involvement on integrated PET-CT scan, can be operated without invasive procedures.</td>
</tr>
<tr>
<td>Meyers et al. (2006). J. Thorac and Cardiov. Surg, USA [14]

Retrospective Single centre case series</td>
<td>From May 1999 to April 2004, 248 patients with clinical stage I of NSCLC were enrolled

All patients had preoperative integrated PET-CT

178/248 (72%) patients underwent preoperative mediastinosc opy</td>
<td>Occult N2 metastasis

Accuracy of mediastino scopy

5 Year progressio n free survival (%)</td>
<td>14/248 (5.6%) patients

<table>
<tr><th>Occult N2 disease</th><th>Mediasti noscopy yes</th><th>Positive Mediastino scopy</th><th>Negative Mediastin oscopy</th></tr>
<tr><td>14 (5.6%)</td><td>13/14 (92.8%)</td><td>5 (38%)</td><td>8 (61%)</td></tr>
</table>
Of 70 patients in whom mediastinoscopy was omitted , only a patient had N2 disease

<table>
<tr><th>All patients (n=229*)</th><th>Mediastinoscopy (yes) (n=169)</th><th>Mediastinoscopy (no) (n=60)</th><th>p</th></tr>
<tr><td>73</td><td>72</td><td>77</td><td>0.245</td></tr>
</table>
*6 patients with diagnosis of benign disease after resection were excluded</td>
<td>Routine mediastinos copy in patients with clinically stage I lung cancer staged by PET and CT is clinically unproductiv e and excessively costly.</td>
</tr>
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<table>
<tr>
<td>Zhang et al (2012)
J Thorac and Cardiovasc Surg . China
[15]

Retrospective Single centre case series</td>
<td>From June 2007 to August 2011, 530 patients with NSCLC clinically staged as T1N0 and undergoing surgical resection with radical lymphadenectomy were enrolled.

PET scan was not routinley used in clinical stage</td>
<td>N2 disease

N2 risk factors</td>
<td>89/530 (16.8%) patients

<table>
<tr><th>Variable</th><th>OR</th><th>95%CI</th><th>p</th></tr>
<tr><td>Age</td><td>0.974</td><td>0.952-0.997</td><td>0.025</td></tr>
<tr><td>Tumor Size (cm)</td><td>2.769</td><td>1.818-4.217</td><td><.001</td></tr>
<tr><td>Central location</td><td>3.204</td><td>1.512-6.790</td><td>0.002</td></tr>
<tr><td>Invasive adenocarcinoma</td><td>3.537</td><td>1.740-7.191</td><td><.001</td></tr>
</table>
</td>
<td>No use of routine mediastinoscopy in patients with NSCLC clinically staged as T1N0</td>
</tr>
<tr>
<td>Defranchi et al (2009)
Ann Thorac Surg USA
[16]

Retrospective Single centre case series</td>
<td>Between 1998 and 2006, 968 patients with pT1 NSCLC undergoing surgical resection were</td>
<td>N2 disease

Diagnostic accuracy of mediastinoscopy</td>
<td>59/968 (6.1%) patients

<table>
<tr><th>N2 disease</th><th>Mediastinoscopy yes</th><th>Positive Mediastinoscopy</th><th>Negative Mediastinoscopy</th></tr>
<tr><td>59 (6.1%)</td><td>16 (27%)</td><td>3(19%)</td><td>*13 (81%)</td></tr>
</table>
*In 7 cases, lymph node metastasis were found in stations not accessible by standard mediastinoscopy (stations 9 ;5; and 6)</td>
<td>For patients with T1 NSCLC and negative mediastinal imaging, routine mediastinoscopy results</td>
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<td></td>
<td>enrolled.

CT scan was performed in all patients while PET in 27 (46%) of cases.

Mediastinoscopy performed in presence of significant lymph nodes observed on CT scan, by increased metabolic activity on PET or by surgeon preference</td>
<td>SYST</td>
<td><table><tr><th>All surgical T1N2 pts</th><th>Clinical N2 pts</th><th>Occult N2 pts</th><th>*p</th></tr><tr><td>41%</td><td>31%</td><td>46%</td><td>0.43</td></tr></table>*Clinical N2 versus Occult N2 pts</td>
<td>in a low yield of occult N2 disease discovery</td>
</tr>
<tr>
<td>Lee et al (2007)
Ann Thorac Surg
USA
[17]

Retrospective
Single centre
case series</td>
<td>From January 2000 to November 2006, 224 patients with clinical stage I NSCLC screened by CT and PET were enrolled Mediastinosc</td>
<td>N2 disease

Accuracy of mediastinoscopy</td>
<td>16/224 (7.1%)<table><tr><th>Occult N2 disease</th><th>Mediastinoscopy yes</th><th>Positive Mediastinoscopy</th><th>Negative Mediastinoscopy</th></tr><tr><td>16 (7.1%)</td><td>16</td><td>11(19%)</td><td>*5 (81%)</td></tr></table>*In only 1 case metastasis was in a station 5, not accessible by mediastinoscopy.</td>
<td>Patients with centrally located tumors, large tumor size, hystology of adenocarcinoma, and a</td>
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<td></td>
<td>opy was attended in 76 (34%) cases</td>
<td>N2 risk frators</td>
<td>
<table>
<tr><th>Variable</th><th>Occult N2 metastases (%)</th><th>p</th></tr>
<tr><td>Tumor location (central/peripheral)</td><td>21.6 vs 2.9</td><td><0.001</td></tr>
<tr><td>Tumor Size (cm) 0-2/2.1-4.0/4.1-6/>6.0</td><td>4.8/6.5/6.3/57.1*</td><td><0.001*</td></tr>
<tr><td>Histology (adeno/squamous carcinoma)</td><td>9.0 vs 0</td><td>0.082</td></tr>
<tr><td>SUV max (0-4.0/>4.0)</td><td>1.9/10.5</td><td>0.01</td></tr>
</table>
</td>
<td>PET uptake value > 4.0 should have mediastinos copy to rule out N2 occult metastasis. In the other cases it is no indicated.</td>
</tr>
<tr>
<td>Kim et al (2006) Radiology Korea [18]

Prospective Single centre case series</td>
<td>From June 2003 to February 2005, 150 patients with resectable lung cancer in Stage I screened by PET and CT were enrolled

Mediastinosc opy alone (n=15), mediastinosc opy +</td>
<td>N2 disease

Accuracy of PET</td>
<td>34/150 (23%) per patients
55/568 (10%) per nodal stations
<table>
<tr><th>Variable</th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>PPV (%)</th><th>NPV (%)</th><th>Accuracy (%)</th></tr>
<tr><td>Per patients</td><td>47</td><td>100</td><td>100</td><td>87</td><td>88</td></tr>
<tr><td>Per nodal stations</td><td>42</td><td>100</td><td>100</td><td>94</td><td>94</td></tr>
</table>
</td>
<td>Considering the low value of sensitivity, negative PET results do not obviate mediastinos copy for mediastinal nodal stage</td>
</tr>
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<tr><td></td><td>thoracotomy (n=101), and thoracotomy alone (n=34) were attended</td><td></td><td></td><td></td></tr>
<tr><td>Iskender et al (2012). Acta chir belg [19]

Retrospective Single centre case series</td><td>212 patients diagnosed with NSCLC between September 2005 and March 2008 were evaluated by PET/CT. Standard cervical medi astinoscopy was performed in all patients, and simultaneous extended cervical medi astinoscopy was performed in 52 patients with left sided lesions</td><td>N2 disease

Diagnostic accuracy</td><td>N2 occult disease: 4/107 (3.7%)
<table><tr><th>Sensitivity PET/CT</th><th>Specificity PET/CT</th><th>PPV and PNV PET/CT</th><th>Accuracy PET/CT</th></tr><tr><td>93.8%</td><td>69.6%</td><td>57.1%</td><td>96.3%</td></tr></table></td><td>In patients with positive mediastinal lymph node uptake on PET/CT invasive mediastinal staging appears necessary for exact staging. Me diastinoscop y can be omitted in NSCLC patients with negativ e mediastin al uptake on PET/CT.</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Trister et al (2014). Am J Clin Oncol. [20] **Retrospective single centre case series**	201 patients with clinical stage I and II NSCLC screened with PET scan **and unergoping invasive mediastinal staging**	**N2 disease**	**N2 occult disease: 63/201 (31%)** **Multivariate analysis showed that SUV of primary tumour > 6 was the only significant predictive factor (p=0.02) while** histology, tumor location (central vs. peripheral), sex, and age were not predictive for occult N2 disease.	Pathologic staging of the mediastinum should be strongly considered in patients with high SUV of primary tumor also in presence of negative mediastinum on PET.
Gomez-Caro et al (2012). Eur J Cardiothorac Surg [21] **Prospectly study**	Between January 2007 and December 2010, 402 patients with potentially operable NSCLC enrolled. 153 surgically treated patients (79 cIA and 74 cIB cases) were prospectively	**N2 disease Diagnostic accuracy**	**N2 occult disease founded:** **6 of 79 patients (7.6%) in clinical stage IA** **11 of 74 patients (14.8%) in clinical stage IB.**	**Principal risk factors to have occult (pN2) lymph nodes were tumour sizes ≥5 cm, pN1, adenocarcinoma and female patients. The report concluded**

	included in the study. Non-invasive surgical staging was carried out in this group, and curative resection plus systematic mediastinal dissection was performed except in the event of unexpected oncological contraindi-cation.			**that in tumours ≤1 cm (pT1a), surgical staging was unnecessary, while adenocarcinoma and non- central cIB required a more efficient invasive staging.**
Wang et al Clin Lung Cancer. 2012 [22] **Meta - analysis**	**Ten studies with a total of 1122 patients with stage I (T1-2N0) NSCLC analyzed from international literature**	**N2 disease** **Diagnostic accuracy**	**Negative predictive value of PET/CT in detecting of mediastinal lymph-node metastases is 94% in T1 and 89% in T2.**	**Risk factors of occult metastases are adenocarcinoma histology and high FDG uptake in the primary lesion. Low rate of NPV**

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<td>suggested unnecessariness of routine invasive staging procedures for T1 subgroup of patients.</td>
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<tr>
<td>Billé et al 2013 Eur J Cardiothorac Surg [23]

Retrospective study</td>
<td>353 consecutive patients with suspected or pathologically proven, potentially resectable non-small-cell lung cancer (NSCLC) who had integrated PET/CT scanning at the same centre. Lymph node staging was patho-logically confirmed on</td>
<td>N2 disease

Diagnostic accuracy</td>
<td>PET/CT values for the adenocarcinoma group
<table>
<tr><th>Sensitivity (%)</th><th>Specificity (%)</th><th>Accuracy (%)</th></tr>
<tr><td>38,8</td><td>97,4</td><td>85,7</td></tr>
</table>
PET/CT values in the squamous cell group
<table>
<tr><th>Sensitivity (%)</th><th>Specificity (%)</th><th>Accuracy (%)</th></tr>
<tr><td>81,8</td><td>91,8</td><td>90,8</td></tr>
</table>
</td>
<td>Principal risk factors to have occult (pN2) lymph nodes were tumour sizes ≥5 cm, pN1, adenocarcinoma and female patients. The report concluded that in tumours ≤1 cm (pT1a), surgical staging was</td>
</tr>
</table>

	tissue specimens obtained at mediastinoscopy and/or thoracotomy.			**unnecessary, while adenocarcinoma and non-central cIB required a more efficient invasive staging.**
Fiorelli et al (2015), Thorac Cardiovasc Surg., Italy [24] **Retrospective multicenter study**	901 consecutive patients with Stage I NSCLC screened with PET/CT scan undergoing surgery from January 2006 to December 2012	**pN2 disease** **Survival of occult pN2 patients**	108/901 (12%) had unexpected pN2 disease Central tumor location ($p < 0.003$), cT2a ($p < 0.0001$) and pT2a stage ($p < 0.0001$), pN1 disease ($p = 0.004$), and a standard uptake value > 4.0 (0.007) were prognostic factors of occult pN2 disease Patients with unexpected pN2 disease compared with patients with cN2 disease undergoing surgery after induction therapy presented a better median overall survival (56 versus 20 months; $p = 0.001$) and disease-free survival (46 versus 11 months; $p < 0.0001$).	The preoperative effort to discover unexpected pN2 disease in patients with clinical stage I non-small cell lung cancer is not justified, considering their good survival. indicated

De Leyn et al. (2014), Eur. J. Cardio-Thorac Surgery, Belgium [25] Systematic Review	ESTS guidelines for preoperative lymph node staging for NSCLC Systematic review into the pre-operative lymph node staging for NSCLC	Reccomandation	Preoperative mediastinal staging is advised in central tumors <3 cm, in every tumor larger than 3 cm or in CT or PET N1 nodes positivity. Instead, a systematic nodal dissection is indicated for tumors ≤3 cm, located in outer third of the lung cm and when there are no pathologic evidence on CT and or on PET or PET-CT. The choice of mini invasive technique (EBUC/EUS, mediastinoscopy or VATS) depends on local expertise to adhere to minimal requirements for staging.	
Silvestri et al (2014), Chest , USA [26] Systematic Review	ACCP guidelines for Invasive Mediastinal Staging of Lung Cancer	Reccomandation	Preoperative mediastinal staging is advised in central tumors <3 cm, in every tumor larger than 3 cm or in CT or PET N1 nodes positivity. Instead, a systematic nodal dissection is indicated for tumors ≤3 cm, located in outer third of the lung cm and when there are no pathologic evidence on CT and or on PET or PET-CT	

The update of European Society of Thoracic Surgery of 2014 [72] stated that preoperative mediastinal staging is advised in central tumors < 3 cm, in every tumor larger than 3 cm or in CT or PET N1 nodes positivity. Instead, a systematic nodal dissection is indicated for tumors ≤ 3 cm, located in outer third of the lung cm and when there are no pathologic evidence on PET-CT scan.
American College of Chest Physician [73] guidelines did not support mediastinoscopy in stage I NSCLC unless a PET scan finding is positive in the nodes. However, mediastinoscopy is indicated for central tumors, cN1 disease, or low FDG uptake of the primary tumor with N2 PET negative LNs 16 mm on CT scan.

DISCUSSION

The most of analyzed papers evaluated patients without mediastinal adenopaties on PET-CT undergoing resection. Invasive mediastinal staging was attended in all or in two/third of patients in four papers [55-58]; in half or less in two [63,64]; and in nobody patient in four [59 60 62 71]. Occult pN2 disease was < 10% in five [55 61 63-65]; between 10-16% in four [56 57 59 71]; and > 16% in four papers [60 61 65 67]. Diagnostic yield of mediastinoscopy was between 50-61% in two [55 61], and > 80% in four papers [57 58 63 64]. It missed N2 metastases because LNs were within inaccessible station or sub-centimeters [55 63]. Significant risk factors for occult pN2 disease are the SUV value of primary tumor ranging from 4 to 10 [56], central tumor [59 63 64 71], tumor larger than 3 cm [68 70], histology of adenocarcinoma [68-70] and presence of clinical hilar lymph node involvement (cN1 disease) [71]. However, the last guidelines of ESTS [54] and ACCP [53] in agreement with previous papers reported that invasive mediastinal staging is advised also for tumor < 3 cm if located in hilar region. Two papers [63 71] found that unexpected pN2 patients had a better survival than cN2 disease undergoing surgery after induction therapy.
From analysis of the literature [74-76], we can conclude that invasive mediastinal staging with mediastinoscopy, EBUS or EUS is recommended also in cN0 patients with central tumor or with peripheral tumor > 3 cm. Despite in the last years EBUS-TBNA is become the preferred approach for mediastinal sampling, mediastinoscopy or VATS remain the best options in case of lymph node with high suspicion of involvement but negative on EBUS.

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