Queen Mary
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# FDG-PET/CT imaging for mediastinal staging in patients with potentially resectable non-small cell lung cancer.

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1 **Title:** FDG PET-CT for mediastinal staging in patients with potentially resectable non-small cell

2 lung cancer.

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**JAMA Clinical Evidence Synopsis**

**Title:** FDG PET-CT for mediastinal staging in patients with potentially resectable non-small cell lung cancer.

**Clinical question**: What is the sensitivity and specificity of PET-CT for detecting mediastinal lymph node involvement in patients with potentially resectable non-small cell lung cancer (NSCLC)?

**Bottom line**: The sensitivity and specificity of ($^{18}$F)-2-fluoro-deoxy-D-glucose (FDG) PET-CT ranged from 0.77-0.81 and 0.79-0.90, respectively, and were related to the brand of scanner, NSCLC subtype, FDG dose, and country of study origin. These sensitivities and specificities are not sufficiently accurate to warrant reliance on PET-CT scanning alone to make decisions about whether or not to offer about suitability for surgery as a single option for patients with potentially resectable NSCLC. PET-CT should instead be used to determine whether the next step should be a biopsy (with endobronchial ultrasound-guided (EBUS) biopsy or mediastinoscopy) or surgical resection.

**Introduction**: Therapeutic options for patients with NSCLC are determined in part by the presence or absence of intrathoracic mediastinal lymph node metastases. If disease has not spread beyond the ipsilateral hilar nodes (N1) then proceeding directly to lung resection is an appropriate therapeutic option. PET-CT is a non-invasive staging method which is increasingly

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39  available and used by lung cancer multidisciplinary teams. This systematic review from a

40  published Cochrane review specifically examined the accuracy of PET-CT in differentiating

41  N0/N1 (no lymph node involvement or involvement limited to the ipsilateral hilar, peribronchial

42  or intrapulmonary nodes) from N2/N3 (involvement of ipsilateral mediastinal, subcarinal or

43  contralateral lymph nodes) disease.

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45  **Evidence Profile:**

46  Number of studies: 45 diagnostic test accuracy studies

47  Years studies published: 2006-2013

48  Literature search date: 30 April 2013

49  Number of patients:  6095 patients with potentially resectable NSCLC

50  Male: 69.5% Female: 30.5%

51  Race/ethnicity: Unavailable

52  Age, mean (range): 63.6 (23-90) years

53  Setting: Nuclear imaging, radiology and thoracic surgery departments

54  Countries: United Kingdom, Italy, USA, China, Poland, Canada, Belgium, Egypt, Denmark,

55  Turkey, South Korea, Taiwan, Japan, France, Germany, Switzerland.

56  Comparison: Not applicable.

57   Gold standard: Pathological confirmation of PET-CT results from mediastinal nodal sampling

58   via EBUS biopsy, mediastinoscopy, or resection of the primary tumor with lymph node

59   resection.

60   Primary outcome measures: Sensitivity and specificity.

61   Secondary outcome measures: Adverse events.

62   This evidence comes from a new original Cochrane Collaboration review[1].

63   **Summary of Findings**: Different criteria were used to define a positive PET-CT in the reviewed

64   studies. The summary sensitivity and specificity estimates for the *'FDG uptake in the lymph node*

65   *> background uptake'* PET-CT positivity criterion (18 studies, N = 2823) were 0.77 (95% CI

66   0.65-0.86) and 0.90 (95% CI 0.85-0.94), respectively, but the high variability between the studies

67   means that in practice sensitivity and specificity may differ from these estimates.

68   The summary sensitivity and specificity estimates for the '*Maximum Standardized Uptake Value*

69   *≥ 2.5'* PET-CT positivity criterion (12 studies, N = 1656) were 0.81 (95% CI 0.70-0.89) and

70   0.79% (95% CI 0.70-0.87), respectively, and they were also associated with high between-study

71   variability and uncertainty about the estimates.

72   Sensitivity and specificity estimates were related to country of study origin, percentage of

73   participants with adenocarcinoma, FDG dose, brand of PET-CT scanner, and study size

74   (FIGURE). None of the studies reported on adverse events.

75   **Discussion**: The accuracy of PET-CT is insufficient to allow a decision about whether or not to

76   proceed directly to surgery as a single option in people with potentially resectable NSCLC to be

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77  based on PET-CT alone. Instead PET-CT can be used to define the need for further

78  characterisation of mediastinal lymph nodes with minimally invasive sampling or

79  mediastinoscopy. Sufficient sensitivity and specificity should both be >0.95 because the

80  consequences of an incorrect evaluation of mediastinal metastases may have a major influence

81  on outcome. The difference between the two main brands of PET-CT scanner is important and

82  may influence the detection of nodal involvement and consequently treatment decisions in some

83  circumstances. The differences in PET-CT accuracy between scanner brands, NSCLC subtypes,

84  FDG dose, and country of study origin, along with the variability of results, suggest that all large

85  centres should monitor their accuracy against the gold standard of pathological confirmation.

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87  Limitations: The high level of heterogeneity may be partly explained by the variation in the

88  criteria used for test positivity. Few studies examined the sensitivity and specificity of PET-CT

89  in lymph nodes that were not significantly enlarged by CT criteria or in populations with a high

90  prevalence of comorbidities or exposures known to produce false positive results (e.g.

91  tuberculosis and industrial dust exposure).

92  Comparison of findings with current practice guidelines: Findings from this systematic review

93  are consistent with the practice guidelines from the National Institute for Health and Clinical

94  Excellence, Scottish Intercollegiate Guidelines Network, European Society of Thoracic Surgeons

95  and American College of Chest Physicians[2-5]. These guidelines do not recommend the use of

96  PET-CT alone: When PET-CT is positive, these guidelines recommend that mediastinal

97  sampling should be performed with EBUS or mediastinoscopy; when the nodes are small (<10

98  mm) or not visualized by PET-CT, lung resection without mediastinoscopy may be pursued, but

99  systematic nodal dissection is recommended as part of the surgery

100 Areas in need of future study: It is not known how different PET-CT scanners perform in

101 populations with a -high prevalence of tuberculosis or industrial dust exposure or in populations

102 with lymph nodes of different sizes.

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130   **Figure legend**: Meta-analysis by Subgroup for sensitivity and specificity of PET-CT for

131   Mediastinal Staging in Patients With Non-Small Cell Lung Cancer ("Criteria for test positivity"

132   refers to the criteria used by the studies to define a positive PET-CT result; SUVmax =

133   maximum standardized uptake value of FDG; "mixed" brand of scanner refers to studies that

134   used more than one brand of PET-CT scanner for obtaining the study data, but collapsed the data

135   across all the brands used). Adapted with permission from John Wiley & Sons, Inc.

| Subgroups | Studies | Patients | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|
| **Criteria for test positivity** | | | | |
| - Activity > background | 18 | 2823 | 0.77 (0.65, 0.86) | 0.90 (0.85, 0.94) |
| - SUVmax | 12 | 1656 | 0.81 (0.70, 0.89) | 0.79 (0.70, 0.87) |
| - Other/Mixed | 15 | 1616 | 0.68 (0.57, 0.77) | 0.92 (0.84, 0.96) |
| **Brand of scanner** | | | | |
| - Discovery | 19 | 3135 | 0.71 (0.62, 0.79) | 0.93 (0.88, 0.96) |
| - Biograph | 14 | 1516 | 0.84 (0.74, 0.91) | 0.84 (0.75, 0.90) |
| - Other/mixed/unclear | 12 | 1444 | 0.69 (0.52, 0.83) | 0.84 (0.76, 0.89) |
| **FDG dose (MBq)** | | | | |
| - =300 | 12 | 1519 | 0.74 (0.61, 0.84) | 0.95 (0.91, 0.97) |
| - 301-500 | 25 | 3097 | 0.74 (0.65, 0.81) | 0.87 (0.81, 0.90) |
| - >500 | 4 | 910 | 0.91 (0.76, 0.97) | 0.80 (0.65, 0.90) |
| - Not reported | 4 | 569 | 0.64 (0.36, 0.85) | 0.74 (0.58, 0.86) |
| **Adenocarcinoma (%)** | | | | |
| - 0-55% | 24 | 3175 | 0.77 (0.70, 0.83) | 0.84 (0.77, 0.89) |
| - 55.1-100% | 8 | 1385 | 0.53 (0.40, 0.66) | 0.96 (0.90, 0.98) |
| - Not reported | 13 | 1535 | 0.82 (0.69, 0.91) | 0.87 (0.81, 0.92) |
| **Country** | | | | |
| - Asia | 22 | 3331 | 0.69 (0.60, 0.77) | 0.91 (0.86, 0.95) |
| - Europe/USA/other | 23 | 2764 | 0.81 (0.72, 0.88) | 0.84 (0.79, 0.89) |
| **Sample size** | | | | |
| - <100 | 19 | 1079 | 0.85 (0.76, 0.91) | 0.87 (0.80, 0.91) |
| - 100-200 | 20 | 2872 | 0.66 (0.56, 0.75) | 0.87 (0.80, 0.91) |
| - >200 | 6 | 2144 | 0.75 (0.60, 0.85) | 0.94 (0.86, 0.98) |