

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

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20 **JAMA Clinical Evidence Synopsis**

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

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

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

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

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.

44

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 review¹.

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

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 Physicians²⁻⁵. 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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109 MSH and JZ had full access to all the data in the study and take responsibility for the integrity of
110 the data and the accuracy of the data analysis

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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.

