Review
The size of mediastinal lymph nodes and its relation with metastatic involvement: a meta-analysis
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Summary
Positron emission tomography with 18-fluorodeoxyglucose (FDG-PET) seems to be superior to computed tomography (CT) in staging the mediastinum in patients with non-small-cell lung cancer (NSCLC). However, recent results suggest that FDG-PET performance characteristics are conditional for nodal size as shown by CT: FDG-PET is more sensitive but less specific with lymph node enlargement on CT. The association between size and the probability of malignancy needs to be known to predict the post-test probabilities after PET, and finally, stratify patients for mediastinoscopy or thoracotomy depending on the PET and CT results. Therefore, we performed a meta-analysis of available studies reporting on the prevalence of metastatic involvement for different size categories of enlarged lymph nodes in patients with NSCLC and were able to include 14 studies. The prevalence of metastatic involvement and conditional test performance of CT and FDG-PET were calculated for lymph nodes measuring 10—15 mm, 16—20 mm and >20 mm. We found a post-test probability for N2 disease of 5% for lymph nodes measuring 10—15 mm on CT in patients with a negative FDG-PET result, suggesting that these patients should be planned for thoracotomy because the yield of mediastinoscopy will be extremely low. For patients with lymph nodes measuring >16 mm on CT and a negative FDG-PET result a post-test probability for N2 disease of 21% was found, suggesting that these patients should be planned for mediastinoscopy prior to possible thoracotomy to prevent too many unnecessary thoracotomies in this subset.

Keywords: Carcinoma, non-small-cell lung; Fluorodeoxyglucose F18; Tomography, X-ray computed; Lymphatic metastasis; Sensitivity and specificity

1. Introduction
Since its introduction, computed tomography (CT) has been used to stage patients with non-small-cell lung cancer (NSCLC) and many studies have assessed its accuracy in staging the mediastinum, but with variable results. It has been shown that for CT, a threshold of 1 cm short-axis diameter has the best trade-off between sensitivity and specificity [1]. However, malignant lymph nodes may well be smaller than 1 cm and this explains the limited sensitivity of CT, which is estimated to be 57% [2]. Since specificity is about 82%, confirmation of the malignant nature of enlarged nodes is necessary [2]. Taken together, mediastinoscopy is required in all patients without distant metastases. Positron emission tomography with 18-fluorodeoxyglucose (FDG-PET) is superior to CT in staging the mediastinum [3, 4]. However, FDG-PET is not perfect either. False-negative test results occur when tumour size is well below the system’s highest resolution (typically 5—7 mm) and false-positive results may occur due to inflammatory disease and anthracosilicosis [5].

At present, there is debate about the diagnostic algorithm which combines performance characteristics of CT, FDG-PET and mediastinoscopy. In a recent meta-analysis, it was shown that FDG-PET is more sensitive but less specific with lymph node enlargement on CT [4]. A Bayesian model suggested that the post-test probability of malignant involvement is very low (6%) if the mediastinum is normal at both CT and FDG-PET. However, with enlarged nodes on CT and a negative PET scan the situation is less clear: e.g. the reported median prevalence of malignant involvement in enlarged nodes of 63% corresponds with a 17% post-test probability of malignancy in case of a negative PET scan [4]. The exact quantitative association of metastatic involvement and nodal size may have important implications for the implementation of these test results in daily practice. Therefore, we performed a meta-analysis of available studies to assess...
the prevalence of metastatic involvement for different size categories of enlarged lymph nodes.

2. Methods

A literature search was performed in the Medline database to identify all studies that assessed mediastinal lymph node size (with CT) and the prevalence of metastatic involvement in patients with NSCLC (Table 1).

This search covered the time frame from 1985 until August 2004, and it was followed by additional extensive cross-referencing. Studies were included if they presented sufficient data required to construct $2 \times 2$ contingency tables, and with a language restriction to English, German and Dutch. Studies were excluded if they comprised more than 10% small-cell lung carcinoma patients as well as if they were published before 1985 because of the inferior quality of the CT-scanners used.

2.1. Data analysis

The following information was extracted from the included articles: year of study (to be able to account for potential technological advances with CT), geographic origin (to account for endemic diseases leading to reduced specificity of CT), number of patients, histological subtype of lung cancer (adeno-, squamous cell, small cell carcinoma), number of hilar–mediastinal lymph nodes resected per patient, method of size measurement at CT (short-axis or other), CT-scanner generation, histopathological methods and prevalence of metastasis.

We set out to calculate the prevalence of metastatic involvement for the following size categories: 10–15 mm, 16–20 mm and >20 mm. However, since several researchers used different classifications, we chose to consider lymph node size groups with a difference of ≤1 mm as a single group (e.g., a size category of 10–15 mm in one study and of 10–14 mm in another study were considered to be one category).

2.2. Statistical analysis

Chi-square test was applied to test for heterogeneity of the study results for each lymph node size group. In case of statistical heterogeneity a random effect model was used for pooling, whereas in case of homogeneity a fixed effect model was used. The proportion of histologically proven metastatic lymph nodes and 95% confidence intervals (CI) were calculated for each size group. Z-test was used to compare the proportion of histologically proven metastatic lymph nodes between the different size categories. To predict the conditional test performance of CT and FDG-PET, we constructed $2 \times 2$ contingency tables for each lymph node size category, in which the FDG-PET test result and pathology result were outlined. The post-test probability for N2 disease after CT accounted for the percentage of positive test results (true-positive and false-positive). The sensitivity (91%) and specificity (78%) of FDG-PET for enlarged lymph nodes [4] were used to calculate the percentage of true-positive, false-positive, true-negative and false-negative test results. Additionally, we calculated the positive and negative predictive values (PPV and NPV, respectively) and the post-test probability for mediastinal metastasis.

3. Results

The initial search yielded 1537 hits, of which 73 articles were potentially eligible based on title and abstract. Cross-referencing yielded another 23 potentially eligible studies. After full-text analysis, 14 were included [7–20], all of which had been identified with the initial Medline search. In nine studies lymph node size was measured in the short axis with CT, in one in the long axis with CT and four studies did not mention whether the short or long axis was measured. Using these different methods of size measurement, the prevalence of malignant involvement ranged from 9% to 42% for lymph nodes measuring 10–15 mm [15,16], 19–75% for lymph nodes measuring 16–20 mm [9,16] and 27–100% for lymph nodes measuring >20 mm [11,15].

3.1. Description of CT-based studies for measuring lymph node size

For the 14 CT studies, the median number of patients per study was 64 (range, 48–387). The mean number of resected lymph nodes per patient was 2.2, while it was not recorded in two studies [9,19]. Two studies also examined hilar lymph nodes [10,11]. The mean percentage of SCLC patients was 3.6% (range, 0–10%).

3.2. Lymph node size measurement in the short axis with CT

The percentage of metastatic involvement for all lymph node size groups was calculated for each included study (Fig. 1). Four studies [12,15,18,19] provided data on the
prevalence of malignancy in lymph node size group 10—15 mm for a total number of 187 lymph nodes. Since the data were homogeneous (\( \chi^2: 6.22; P = 0.101 \)), we pooled it to obtain a prevalence of metastatic lymph nodes of 29% (95% CI: 0.23–0.36) (Fig. 2). Three eligible studies [12,15,19] reported on lymph node size group 16–20 mm to yield 38 lymph nodes. These data were also homogeneous (\( \chi^2: 0.07; P = 0.966 \)) and the pooled prevalence of malignancy was 68% (95% CI: 0.52–0.81). The mean prevalence of metastatic involvement was higher in the 16–20 mm group than in the 10–15 mm group (Z-test: \( P < 0.001 \)). For lymph node size group >20 mm, seven studies were found eligible [7,10–14,19], for a total of 131 lymph nodes. Here the data were heterogeneous (\( \chi^2: 35.7; P < 0.001 \)) due to one outlier [11] (Fig. 1). With exclusion of the outlier, the data were homogeneous (\( \chi^2: 6.95; P = 0.224 \)). With inclusion of all seven studies, the mean prevalence of metastatic involvement was higher in the >20 mm group, 66% (95% CI: 0.42–0.83), than in the 10–15 mm group (Z-test: \( P = 0.002 \)). However, it was not higher than that in the 16–20 mm group (Z-test: \( P = 0.879 \)). Exclusion of the outlier did not make a significant difference.

3.3. Modelling conditional test performance of FDG-PET and CT

We calculated the predicted positive and negative values of FDG-PET for identifying mediastinal lymph node metastasis in patients with enlarged lymph nodes of different size categories based on the calculated post-test probabilities after CT (Table 2).

<table>
<thead>
<tr>
<th>Lymph node size category</th>
<th>NPV (%)</th>
<th>PPV (%)</th>
</tr>
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<tbody>
<tr>
<td>CT 10—15 mm</td>
<td>95</td>
<td>62</td>
</tr>
<tr>
<td>CT 16—20 mm</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>CT &gt;20 mm, with outlier</td>
<td>82</td>
<td>90</td>
</tr>
<tr>
<td>CT &gt;20 mm, without outlier</td>
<td>80</td>
<td>90</td>
</tr>
</tbody>
</table>

NPV: negative predictive value; PPV: positive predictive value.

For patients with lymph nodes measuring 10—15 mm on CT and a negative FDG-PET result, the predicted post-test probability of malignancy was 5%. A positive FDG-PET result was predicted to yield a post-test probability of 62%. If CT showed lymph nodes of \( \geq 16 \) mm, the post-test probability of malignancy was 21% when the FDG-PET result was negative and 90% if it was positive. These results were similar for the subsets of 16–20 mm and >20 mm short-axis diameter.

4. Discussion

The results of this meta-analysis suggest that the probability of lymph node metastasis in mediastinal lymph nodes measuring 10–15 mm in the short axis on CT is 29%, and consistently two-fold higher in larger ones. We found 14 studies [7–20] that assessed the prevalence of metastatic involvement of enlarged lymph nodes of different size categories in patients with NSCLC. Although reports have been published that show no increase in prevalence of metastasis with increasing lymph node size or an increase at larger lymph node size (e.g. >20 mm), most of them measured either the long axis or did not specify the measured axis [8,9]. These studies were excluded on qualitative grounds. With pooling of the included studies, only one was responsible for heterogeneity [11]. In this study, the percentage of T2 tumours was relatively high (66%) and most were staged T2 based on associated atelectasis or an obstructive bronchitis, both of which can lead to benign hyperplasia of lymph nodes [21]. Therefore, we classified this study as an outlier and calculations were done both with and without this study.

Our data can be used to predict the conditional test performance of CT and FDG-PET for different size categories of enlarged lymph nodes on CT. Gould et al. [4] evaluated enlarged lymph nodes as one group and found a post-test probability for N2 disease of 17% when CT showed enlarged lymph nodes and the FDG-PET result was negative. The reported pre-test probability for enlarged lymph nodes was 63%. Our results suggest the added value of a subdivision of enlarged lymph nodes. We found a post-test probability for N2 disease of 5% for lymph nodes measuring 10–15 mm in the short axis on CT in patients with a negative FDG-PET result. Since, with extensive resection of lymph node stations, mediastinoscopy reaches a sensitivity of 85% [22], 25 of such patients should undergo mediastinoscopy to prevent one unnecessary thoracotomy. Looking at the morbidity of mediastinoscopy, we believe that patients in this group...
should be directly planned for surgery, without previous mediastinoscopy. However, for patients with lymph nodes measuring ≥16 mm in the short axis on CT and with a negative FDG-PET result, the post-test probability for N2 disease was 21%. This suggests that preoperative invasive mediastinal lymph node evaluation is useful in this subset (unless FDG-PET demonstrates extrathoracic spread). A prospective evaluation of the yield of mediastinoscopy in this subset is needed to show whether indeed five patients are needed to undergo invasive staging in order to obtain one positive biopsy. Since we assumed that the accuracy of FDG-PET is independent of size above the centimetre level, we performed a sensitivity analysis recalculating the results for sensitivity and specificity of FDG-PET of 85% and 70%, respectively. This shows that post-test probability for N2 disease will only moderately increase to 7% in patients having 10–15 mm lymph nodes on CT and a negative FDG-PET scan (vs 31% in patients having lymph nodes measuring ≥16 mm on CT).

We conclude that the prevalence of metastasis strongly increases above the 15 mm short-axis threshold at CT scanning, and that this may have implications for the positioning of mediastinoscopy in patients with negative lymph nodes on FDG-PET. The data suggest that patients with nodes measuring <15 mm on CT should be planned for thoracotomy if FDG-PET does not reveal mediastinal involvement, since the expected yield of mediastinoscopy is extremely low. Patients with lymph nodes measuring ≥16 mm on CT and a negative FDG-PET result should undergo mediastinoscopy before possible thoracotomy.

References

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