

Accuracy of transbronchial needle aspiration for mediastinal staging of non-small cell lung cancer: a meta-analysis

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ABSTRACT

Background: The reported accuracy of transbronchial needle aspiration (TBNA) for mediastinal staging in non-small cell lung cancer (NSCLC) varies widely. We performed a meta-analysis to estimate the accuracy of TBNA for mediastinal staging in NSCLC.

Methods: We searched Medline, Embase and the bibliographies of retrieved articles, with no language restriction, for studies evaluating TBNA accuracy. We used meta-analytic methods to construct summary receiver-operating characteristic curves and to pool sensitivity and specificity.

Results: Thirteen studies met inclusion criteria, including six studies that surgically confirmed all TBNA results and enrolled at least 10 patients with and without mediastinal metastasis (tier 1). Methodologic quality varied, but did not affect diagnostic accuracy. In tier 1 studies, the median prevalence of mediastinal metastasis was 34%. Using a random effects model, the pooled sensitivity and specificity were 39% (95% CI, 17% to 61%) and 99% (95% CI, 96% to 100%), respectively. Compared with tier 1 studies, median prevalence of mediastinal metastasis (81%; $p=0.002$) and pooled sensitivity (78%; 95% CI, 71% to 84%; $p=0.009$) were higher in non-tier 1 studies. Sensitivity analysis confirmed that the sensitivity of TBNA depends critically on the prevalence of mediastinal metastasis. The pooled major complication rate was 0.3% (95% CI, 0.01% to 4%).

Conclusions: When properly performed, TBNA is highly specific for identifying mediastinal metastasis in patients with NSCLC, but sensitivity depends critically on the study methods and patient population. In populations with a lower prevalence of mediastinal metastasis, the sensitivity of TBNA is much lower than reported in recent lung cancer guidelines.

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the most common malignancy in the world and accounts for an estimated 1 million deaths each year.[1] The overall 5-year survival is approximately 15%.[2] However, the survival rate approaches 70% in some patients with resectable disease.[3] Metastasis to the mediastinal lymph nodes is one of the most important factors in determining resectability and prognosis.[4] Careful mediastinal staging is essential to identify appropriate candidates for surgery and to avoid futile thoracotomy in patients with more advanced disease.

Currently, computed tomography (CT) is the most frequently utilized pre-surgical staging modality. However, large benign hyperplastic lymph nodes are commonly found in patients with NSCLC [5] and normal sized lymph nodes frequently harbor metastases.[6] Preoperative clinical staging with CT differs from surgical staging in as many as 40% of cases.[7][8] Newer imaging modalities such as positron emission tomography (PET) have limitations in diagnostic accuracy as well.[9] Given the limitations of CT and PET, invasive surgical staging techniques such as mediastinoscopy are often used to exclude or confirm mediastinal lymph node metastasis, especially in patients who are candidates for surgical resection. However, mediastinoscopy is associated with a complication rate of 2% to 3% and a surgical mortality rate of around 0.1%.[10][11][12]

Transbronchial needle aspiration (TBNA) using a flexible fiberoptic bronchoscope was developed in the early 1980's to obviate the need for more risky surgical staging procedures. Compared with mediastinoscopy, TBNA is generally more convenient, less risky and less expensive.[13] A recent systematic review for mediastinal staging with TBNA found the sensitivity to be similar to that of mediastinoscopy (76% versus 81%).[14] This analysis,

however, was not restricted to patients having non-small cell lung cancer, did not assess study methodologic quality, and did not attempt to identify sources of variation in study results. We performed a meta-analysis to estimate the diagnostic accuracy of TBNA in patients with non-small cell lung cancer and to identify technical factors and patient characteristics that have an impact on accuracy.

METHODS

A more detailed description of our methods is available as an online data supplement on the *Thorax* website at www.thoraxjnl.com/supplemental.

Literature search & study identification

We searched Medline and Embase (January 1966 to July 2003; Medline updated through April 2004) to identify studies that examined TBNA for mediastinal staging in NSCLC (fig S1A and B, online supplement). In addition, we manually searched reference lists of included studies and review articles. We considered all articles regardless of language.

Selection of studies

We included studies that 1) examined TBNA using a flexible bronchoscope for mediastinal staging in patients with NSCLC; 2) enrolled at least 10 subjects with and/or 10 subjects without mediastinal metastasis; 3) provided sufficient data to permit calculation of sensitivity and/or specificity; and 4) enrolled no more than 10% of patients with a diagnosis other than NSCLC, or provided separate data for patients with NSCLC. More rigorous (tier 1) studies enrolled at least 10 subjects with and 10 subjects without mediastinal lymph node involvement, surgically confirmed all TBNA results (e.g. with mediastinoscopy, mediastotomy and/or thoracotomy), and utilized the patient as the unit of analysis. We contacted the authors of abstracts and studies not reporting sufficient data to request additional information.

Study quality

We adapted an existing instrument to describe study methodological quality,[15] as we have done previously (fig S2, online supplement).[9] [16] We developed criteria for the technical quality of TBNA based on our clinical experience and by reviewing published guidelines.[17][18][19]

Data abstraction

One investigator abstracted primary data regarding patient characteristics and the sensitivity and/or specificity of TBNA for identifying mediastinal metastasis in patients with NSCLC.

When possible, we separated staging characteristics of TBNA for patients with and without enlarged lymph nodes on CT, and for biopsies performed at hilar, subcarinal, paratracheal or other lymph node stations. We also separately tabulated test characteristics for studies utilizing ‘real-time’ imaging (e.g. CT fluoroscopy, endobronchial ultrasound or transthoracic ultrasound).

Data synthesis & statistical analysis

We constructed a 2 x 2 contingency table for each study to summarize the results of TBNA and the reference test(s). For each study, we calculated the true positive rate (TPR;

sensitivity), the false-positive rate (FPR; 1-specificity) and the log odds ratio (LOR). When necessary, we added 0.5 as a correction factor to calculate the LOR.

Because many studies of TBNA did not confirm positive test results surgically, they were unable to report false positive rates. Therefore, we calculated a weighted kappa-1 coefficient, which does not require information about the false positive rate to measure test accuracy with respect to avoiding false negative results.[20][21]

We used a random effects model to pool sensitivity, specificity, LOR and kappa-1.[22] When pooling sensitivity and specificity, we excluded studies with <10 subjects with or without mediastinal lymph node involvement, respectively, in the calculations. We constructed summary receiver operating characteristic (SROC) curves as described by Moses *et al.*,[23] to quantitatively summarize the results of studies.

To assess sources of variation in study results, we performed sensitivity analyses, discriminate function analysis and meta-regressions. Sensitivity analysis included stepwise single study elimination, adjusting the correction factor, and varying the reference test result in studies that employed a suboptimal reference standard. To compare sensitivity and specificity jointly in studies grouped by tier and prevalence, we used discriminant function analysis. To compare reported sensitivities and LORs in studies with high and low prevalence of lymph node metastasis ($\geq 60\%$ or $< 60\%$) and year of study publication (≥ 1995 or < 1995), we used multivariate analysis of variance (ANOVA).[24] [25] To assess for the presence of publication bias, we constructed inverted funnel plots of standard error versus estimated effect size (LOR) for each individual study.[26] We also assessed how the exclusion of small-cell cancer cases from the included studies impacted TBNA test accuracy.

We programmed all biostatistical models with Excel 8.0 for Windows (Microsoft Corporation, Redmond, Washington, USA). We performed discriminant function analysis with SAS 9.0 for Windows (SAS Corp, Cary, North Carolina). We calculated 95% confidence intervals (CI's) for the TPR and the FPR by using the quadratic method.[27] A normal approximation to the binomial of the standard error was used in calculating all other CI's, as appropriate. When making comparisons between groups of studies, we used an unpaired t-test or the Mann-Whitney U test as appropriate. A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS

Literature search and study selection

Our literature search identified 525 potentially eligible studies (fig 1). We eliminated 398 studies that were judged not to be relevant after carefully reviewing their titles and abstracts. A hand search of the bibliographies of the remaining articles identified 203 additional studies that were potentially relevant. A preliminary review of these 330 articles eliminated 268 studies, leaving 62 articles for detailed analysis (table S1, online supplement). After detailed review, 13 studies met inclusion criteria (table 1).[28][29][30][31][32][33][34][35][36][37][38][39][40] Studies were most often excluded because they provided insufficient data to calculate sensitivity or specificity (76%) or enrolled more than 10% of subjects with a diagnosis other than NSCLC (60%). Interrater agreement for study inclusion was high (mean kappa $\sim 80\%$; table S2, online supplement). Five authors provided additional information that enabled us to include their studies [28][29] [32][33] [37].

Table 1. Characteristics of studies in the meta-analysis*

Study (ref)	Year	Prevalence [§] (%)	NSCLC (%)	TBNA results ^{††}				Inclusion criteria & comments
				TP	FN	FP	TN	
Tier 1 studies[†]								
Harrow et al. [28] [‡]	2000	34	100	8	17	1	48	Patients with suspected lung cancer were included. Patients without lung cancer, or TBNA from a lymph node confluent with the tumor mass were excluded by the authors.
Bilaceroglu et al. [29] [‡]	1998	60	100	24	9	0	22	Patients with potentially resectable extra-or endobronchial mass suggestive of lung cancer and without extrathoracic metastases were included. We excluded patients with N0 or N1 disease on pre-TBNA CT. [¶]
Disdier et al. [30]	1998	52	100	5	9	1	12	Patients with potentially resectable lung cancer without evidence of extrathoracic metastases and with enlarged mediastinal LAD on CT or CXR were included.
Ratto et al. [31]	1988	30	96	2	12	0	33	Patients with potentially resectable lung cancer (no preoperative SCLC) without evidence of extrathoracic metastases were included. Only subcarinal lymph nodes were biopsied.
Schenk et al. [32] [‡]	1986	29	100	8	13	2	50	Patients with CXR evidence of lung cancer and who were potentially resectable without evidence of extrathoracic metastases were included. One FP had scanty neoplastic cells without lymphocytes.
Studies not meeting tier 1 criteria								
Herth et al. [33] ^{‡**}	2002	82	100	30	6	0	8	Patients with central lung cancer and enlarged mediastinal LAD by CT without evidence of extrathoracic metastases were included. Needle placement via endobronchial ultrasound.
Wang R. et al. [34]	2002	100	93 ^{††}	10	0	0	0	Inclusion criteria not specified. Unable to calculate specificity (100% prevalence). Patients with NSCLC, N2 disease by CT and a negative bronchoscopy for lung cancer were included. Statistical analysis was by TBNA specimen. Data was collected by a retrospective chart review. Non-surgically confirmed negative TBNA specimens (total: 49) were assumed to be false negative.
Patelli et al. [35]	2002	NA	100	127	52	-	15	Patients with CXR evidence of lung cancer and enlarged mediastinal LAD on CT and who were potentially resectable and without evidence of extrathoracic metastases were included.
Rong et al., [37] ^{‡**}	1998	79	100	26	2	0	5	Patients undergoing thoracotomy for mediastinal adenopathy on CT and suspected lung cancer were included. Bronchoscopist was not experienced with TBNA. Real-time CT assisted needle placement.
Schenk et al. [38]	1993	81	100	32	6	-	9	Patients with resectable lung cancer and paratracheal LAD without extrathoracic metastases were included. Four of the 32 TPs were confirmed surgically.
Schenk et al. [39]	1989	81	100	14	3	-	4	Patients with CXR evidence of lung cancer and who were potentially resectable and without evidence of extrathoracic metastases were included.
Wang K. P. et al. [40]	1983	55	100	13	3	-	13	Patients with suspected lung cancer and who were potentially resectable and without evidence of extrathoracic metastases were included.

* Five studies [30][31] [33][34] [36] reported age (median, 60) and six studies [30][31] [33][34][35][36] reported gender characteristics (median proportion male, 91%). A “-“ in the FP column denotes studies in which positive TBNA results were not confirmed surgically but were assumed to be true positives. **Abbreviations:** TBNA = transbronchial needle aspiration; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; LAD = lymphadenopathy; CT = chest computed tomography; CXR = chest roentgenogram; NA = not applicable; TP = true positive; FN = false negative; FP = false positive; TN = true negative.

† Studies meeting tier 1 criteria surgically confirmed all TBNA’s, had at least 10 subjects with and without mediastinal lymph node metastasis and used the patient as the unit of analysis.

‡ Additional information obtained from original study author(s).

§ Prevalence of mediastinal lymph node metastasis. Studies that did not surgically confirm all TBNA results assumed that the false positive rate was zero.

¶ All mediastinal and hilar lymph nodes ($\geq 8\text{mm}$) identified by CT in this study were sampled by TBNA. To estimate TBNA diagnostic accuracy for identifying mediastinal metastasis, we excluded patients with N0 or N1 disease on pre-TBNA CT from the analysis (the combined mediastinal/hilar TBNA results for NSCLC were: TP 49, FN 18, FP 0, TN 16). The sensitivity (73% versus 73%; $p=0.97$) and specificity (100% versus 100%; $p=1.0$) were similar whether or not N0/N1 disease on CT was excluded.

** Two studies utilized real-time radiological assistance to guide needle placement during CT.

†† Three of 42 patients undergoing TBNA had SCLC. Thirty-two patients who had hilar lymph node biopsies (not mediastinal) were excluded.

‡‡ Number of patients (except for the study by Patelli et al.,[35] where statistical analysis was by TBNA specimen).

Study description

The median number of participants per study was 44 (range, 10 to 183). Six studies [30][31] [33][34] [36][37] reported statistics about the age of participants (median, 60) and seven studies [30][31] [33][34][35][36][37] reported gender characteristics (median proportion male, 89%). One study reported results by using individual lymph nodes as the unit of analysis.[35] For the other studies that reported results by using the patient as the unit of analysis, the median prevalence of mediastinal metastasis was 70% (interquartile range, 47% to 83%). The size and type of TBNA needle utilized, as well as the number of aspirate passes per lymph node station varied between studies (table S3, online supplement). None of the studies stratified results according to nodal station or lymph node size on CT in patients with NSCLC. In eight studies, all positive and negative TBNA results were confirmed by mediastinoscopy, mediastinotomy or thoracotomy [28][29][30][31][32][33][34] [37]. Six studies enrolled fewer than 10 subjects without mediastinal lymph node involvement [33][34] [36][37][38][39]. Two studies [33] [37] utilized real-time imaging (CT or endobronchial ultrasound) to guide needle placement during TBNA. Five studies met criteria for tier 1 analysis [28][29][30][31][32].

Study quality

Studies met between 12 and 23 out of 34 prespecified criteria for methodologic quality. Seven studies met at least 50% of the criteria.[28][29][30] [32][33] [36] [38] Table S4 (online supplement) shows selected aspects of methodologic quality for each study. In general, tier 1 studies met more criteria (mean: 18.8; 95% CI: 15.8 to 21.8) than non-tier 1 studies (mean: 15.8; 95% CI: 14.0 to 17.5), but this difference was not statistically significant ($p=0.13$).

Diagnostic accuracy of TBNA

Tier 1 analysis (5 studies). In these studies, the median prevalence of mediastinal metastasis was 34% (range, 29% to 60%). The median sensitivity and specificity of TBNA were 36% (interquartile range, 32% to 38%) and 98% (interquartile range, 96% to 100%), respectively (table 2). The pooled (random effects) sensitivity was 39% (95% CI, 17% to 61%) and the pooled specificity was 99% (95%CI, 96% to 100%) (table 2, fig 2). The corresponding positive

and negative likelihood ratios were 29.0 and 0.62, respectively. The summary ROC curve is shown in fig 3.

The pooled (random effects) kappa-1 coefficient was 30% (95% CI, 15% to 46%), suggesting that the accuracy of TBNA with respect to false negative results was poor to fair in tier 1 studies.

Table 2. Summary of results*

	Median sensitivity (IQR)	Median specificity (IQR) [¶]	Pooled sensitivity (95% CI) [‡]	Pooled specificity (95% CI) [‡] [¶]	Likelihood ratio (95% CI) [‡] [¶]	
					Positive	Negative
Tier 1 studies	0.36 (0.32-0.38)	0.98 (0.96-1.00)	0.39 (0.17-0.61)	0.99 (0.96-1.00)	29.0 (21.9-38.4)	0.62 (0.53-0.72)
Non-tier 1 studies	0.82 (0.79-0.84)	-	0.78 (0.71-0.84)	-	-	-
P-value[§]	0.001	-	0.009	-	-	-

* For studies that did not use ‘real-time’ radiological guidance for needle placement. **Abbreviations:** TBNA = transbronchial needle aspiration; IQR = interquartile range.

† Pooled sensitivity and specificity were calculated using a random effects model.

‡ The positive and negative likelihood ratios were calculated from the pooled sensitivity and specificity.

§ P-value is for the comparison between tier 1 and non-tier 1 studies.

¶ The median and pooled specificities for non-tier 1 studies were not calculated because only two studies allowed calculation of specificity (both 100%),[33] [37] however, both of these studies had fewer than 10 patients without mediastinal metastases. We were thus unable to calculate likelihood ratios for non-tier-1 studies.

Non-tier 1 analysis (8 studies). Two non-tier 1 studies utilized ‘real-time’ radiological needle guidance during TBNA.[33] [37] In the remaining six studies, the median prevalence of mediastinal metastasis was 81% (range: 55% to 100%; p=0.002 for comparison with tier 1 studies). None of these six studies provided sufficient information to calculate specificity (e.g. did not surgically confirm positive TBNA results). The median sensitivity of TBNA in studies not utilizing real-time radiological needle guidance was 82% (interquartile range, 79% to 84%; table 2). The pooled (random effects) sensitivity was 78% (95% CI, 71% to 84%; table 2, fig 2). The pooled kappa-1 coefficient (random effects) was 40% (95% CI, 19% to 62%; table 2), suggesting that the accuracy of TBNA with respect to false negative results was fair in non-tier 1 studies.

The median prevalence of mediastinal metastasis in the two non-tier 1 studies that utilized ‘real-time’ radiological needle guidance was 83% (p=0.84 for comparison with the six other non-tier 1 studies). The pooled (85%) and median sensitivities (88%) in these two studies were not significantly different (p=0.36 and p=0.38, respectively) as compared to the pooled and median sensitivities of the six non-tier 1 studies that did not use ‘real-time’ radiological guidance.

Summary analysis (11 studies). The Q statistic from the random effects model showed that there was statistically significant heterogeneity in sensitivity (p<0.001), but not specificity (p=0.90). Discriminant function analysis confirmed that there was a statistically significant difference in the joint sensitivity and specificity of tier 1 and non-tier 1 studies (p=0.002 by

parametric Wilks' Lambda test) (fig 4). Hence, we did not pool the results of tier 1 and non-tier 1 studies.

Complication rate

One study did not report complications.[30] Of the remaining studies, two reported major complications,[28] [40] including two major bleeds and one pneumothorax requiring a chest tube. Two other cases of pneumothoraces [35] and one case of pneumomediastinum [28] spontaneously resolved under observation. The mean rate of major complications per patient in tier 1 and non-tier 1 studies was 0.32% (95%CI, 0.01% to 6%) and 0.25% (95%CI, 0.01% to 6%), respectively (p=0.65). The overall major complication rate was 0.26% (95% CI, 0.01% to 4%).

Sensitivity analysis and meta-regressions

An inverted funnel plot showed no evidence of publication bias (fig S4, online supplement). Stepwise single study elimination did not substantially affect the magnitude of the pooled LOR or sensitivity in tier 1 or non-tier 1 studies (table S5, online supplement). In one study, one of two false positive results had scanty neoplastic cells and no lymphocytes.[32] Recategorizing this result as a true negative had no effect on pooled sensitivity, specificity, LOR or the kappa-1 coefficient. Varying the correction factor from 0.5 to 0.1 had no impact on the LOR or the kappa-1 coefficient. Using a 0.1 correction tended to shift the summary ROC curve to the left (increasing specificity), but had little discernable impact on sensitivity.

Study sensitivity was positively correlated with the prevalence of lymph node metastasis (fig 5). When the prevalence rose from 40% to 80%, sensitivity increased from 42% to 78%. For the seven studies in which the prevalence of mediastinal disease was $\geq 60\%$, the median sensitivity (83% versus 36%; p=0.005) and pooled sensitivity (84% versus 40%; p=0.005) were higher as compared to the five remaining studies in which prevalence was $<60\%$ (fig S3, online supplement). Discriminant function analysis confirmed that the joint sensitivity and specificity were different in studies with high versus low prevalence (p=0.01 by parametric Wilks' Lambda test).

For the eight studies published since 1995, the pooled sensitivity (71% versus 60%; p=0.52) was not significantly different from the five remaining studies published prior to 1995. However, the median prevalence of lymph node metastasis in more recent studies (82% versus 55%; p=0.09) was higher as compared to the five earlier studies.

We assessed these and other potential sources of heterogeneity by using a multivariate ANOVA to compare reported sensitivities and LORs in studies with respect to the prevalence of lymph node metastasis ($\geq 60\%$ or $<60\%$) and year of publication (≥ 1995 or <1995). Because only two included studies utilized 'real-time' radiological needle guidance we were unable to assess this potential source of heterogeneity and excluded these two studies from the analysis. Sensitivity was higher in studies with a higher prevalence of lymph node metastasis (difference=60%; 95%CI, 51% to 69%) and in more recently published studies (difference=10%; 95%CI, 1% to 18%). Prevalence of lymph node metastasis, but not year of publication had a significant effect on the LOR.

Excluding small-cell lung cancer patients from the included studies had no impact on the pooled sensitivity in tier 1 (39% versus 41%, p=0.92) or non-tier 1 (78% versus 80%, p=0.71) studies.

DISCUSSION

We found that TBNA is highly specific for identifying mediastinal metastasis in patients with NSCLC, but sensitivity depends critically on the prevalence of mediastinal disease. Specificity is excellent, but not perfect. In three of eight studies that surgically confirmed all TBNA results, a total of 4 false positive results were reported. One of the four false positive results would have been avoided if biopsy specimens were considered negative when they lacked nodal tissue or when the cytopathologist identified the specimen as “contaminated” or containing “atypical” cells. It is essential to avoid contamination of the bronchoscope channel and to follow stringent criteria to define positive or negative biopsy specimens in order to minimise the risk of false positive TBNA results. We found that TBNA is generally safe with a major complication rate of approximately 0.3%.

We identified several sources of variation in study results. Sensitivity was much lower in tier 1 studies than non-tier 1 studies. Tier 1 studies surgically confirmed all TBNA results, enrolled at least 10 patients with and without mediastinal metastasis, and used the patient as the unit of analysis. Sensitivity was also lower in studies with a low prevalence (<60%) of mediastinal metastasis. Not surprisingly, TBNA appears to be less sensitive than mediastinoscopy for identifying mediastinal metastasis. A recent meta-analysis of 14 studies of mediastinoscopy reported a pooled sensitivity of 81% (95% CI, 76% to 85%).^[14] In these studies, the pooled prevalence of mediastinal disease was 37%, which is similar to the median prevalence (34%) of lymph node metastasis in tier 1 studies of TBNA.

The difference in diagnostic accuracy between tier 1 and non-tier 1 studies was statistically significant. We believe that this difference is probably related to a lower prevalence of mediastinal metastasis in tier 1 as compared to non-tier 1 studies. Higher disease prevalence and enrollment of patients with a more severe spectrum of disease are sources of variation in studies of diagnostic accuracy leading to an increase in sensitivity.^{[41][42]} We speculate that the higher prevalence of mediastinal metastasis in non-tier 1 studies may reflect enrollment of study cohorts with a more severe spectrum of mediastinal disease, resulting in more positive TBNA results. For example, non-tier 1 (high prevalence) studies may have enrolled a greater number of patients with bulky lymphadenopathy in whom TBNA was being used to confirm the diagnosis of unresectable disease. In contrast, tier 1 (lower prevalence) studies may have enrolled potential surgical candidates with less impressive lymph node enlargement. A recent meta-analysis of 39 studies comparing positron emission tomography (PET) to computed tomography (CT) for mediastinal staging in NSCLC found that the median prevalence of malignant lymph nodes in enrolled patients was 32% (range, 5% to 64%), which is similar to the median prevalence of mediastinal metastasis in the tier 1 studies in our analysis.^[9] Most of the studies of PET and CT enrolled patients with potentially resectable NSCLC. Furthermore, the bronchoscopist’s technique may be more proficient when the pretest probability of obtaining a positive result is high (e.g. higher prevalence of mediastinal disease within the study cohort). For example, more diligence may be taken to identify endobronchial landmarks, more TBNA needle passes attempted and more aggressive sedation given to minimize cough and patient movement during the procedure.

The difference in pooled sensitivities between tier 1 and non-tier 1 studies may also be due to methodological differences. Non-tier 1 studies utilized suboptimal methodological criteria by not confirming all TBNA results against a reference standard (verification bias), having insufficient numbers of participants with and without mediastinal metastasis and/or not using the patient as the unit of analysis. Verification bias has been shown to lead to overestimates of test sensitivity.^[41]

A previous meta-analysis showed that the pooled sensitivity of 12 studies analyzing TBNA in patients with either small-cell or NSCLC was 76%.^[14] Our estimates of sensitivity were lower for tier 1 studies (39%), because several studies that were included in this previous meta-analysis did not meet criteria for our tier 1 analysis. Interestingly, the exclusion of small cell lung cancer patients from the included studies in our analysis did not significantly impact sensitivity.

Despite the relatively low sensitivity of TBNA in detecting mediastinal metastasis as compared to other invasive staging procedures, TBNA continues to be an appropriate diagnostic test in the sampling of mediastinal lymph nodes, especially if concurrently performed with routine bronchoscopic examination for suspected lung cancer. TBNA is generally more convenient, less risky and less expensive as compared to other invasive staging procedures, such as mediastinoscopy.^[13] A formal assessment of the cost-effectiveness of staging TBNA is beyond the scope of this analysis.

Although we were unable to directly assess how newer needles, use of on-site cytological analysis and/or improved techniques may impact TBNA accuracy, our multivariate ANOVA demonstrated that more recent studies, which presumably utilized more up-to-date techniques and equipment, had a slightly higher sensitivity when we controlled for prevalence of mediastinal metastasis.

Our study has several limitations. First, only a small number of studies met our inclusion criteria (five tier 1 and eight non-tier 1 studies). Most studies enrolled fewer than 100 participants and were performed at single centers where experience with TBNA is likely to be extensive. Large, multi-center, prospective studies of TBNA should be performed in consecutively enrolled patients with NSCLC. Studies should explicitly define inclusion criteria and should report separate results for patients with non-bulky versus bulky lymphadenopathy. Second, because needle type and size, as well as the number of aspiration passes varied between studies, we were unable to control for these test characteristics. Likewise, because most studies did not report age or gender characteristics, we were unable to control for these demographic features. Third, few of the included studies provided information on whether TBNA results altered patient management. Clearly, positive results on TBNA obviate the need for mediastinoscopy, because specificity and positive predictive value are high. However, simple calculations based on our results indicate that when prevalence is relatively low (~35%), approximately 85% of patients will have negative TBNA results, and 25% of such results will be falsely negative. Fourth, despite an exhaustive search, we may not have identified all studies, especially ones with unpublished results. We identified one potentially relevant abstract, but we were unable to obtain sufficient additional information to assess it for inclusion.^[43] However, an inverted funnel plot showed no evidence of publication bias. Finally, the thirteen included studies utilized a variety of reference tests (cervical mediastinoscopy, anterior mediastinotomy and/or thoracotomy with ipsilateral lymph node sampling), raising the possibility of differential verification bias.^[41] Because none of the reference tests has perfect sensitivity, the true sensitivity of TBNA may be even lower than our estimates. Future studies of the diagnostic accuracy of TBNA should require thoracotomy with systematic sampling of both normal and abnormal appearing lymph nodes at all accessible mediastinal stations to exclude the presence of lymph node metastasis.^[44]

In conclusion, we found that TBNA is highly specific for detecting mediastinal lymph node metastasis in patients with NSCLC, but that sensitivity depends critically on the prevalence of mediastinal lymph node involvement. In patient populations with a relatively low prevalence of mediastinal disease (e.g. patients with potentially resectable NSCLC), the sensitivity of TBNA is poor.

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FIGURE LEGENDS

Figure 1. Literature search and selection. Studies could meet one or more exclusion criteria. For simplicity, only one primary exclusion criterion per study is shown.

Figure 2. Individual study estimates of sensitivity and 1-specificity of TBNA for identifying mediastinal metastasis. Error bars represent 95% CI's. Point estimates and 95% CI's for tier 1 studies and studies meeting inclusion criteria but not tier 1 criteria are shown. Tier 1 and non-tier 1 summary point estimates and corresponding 95% CI's are shown and were calculated by using a random effects model.

* Specificity was not calculated for the study by Wang, R. et. al.,[34] because the prevalence of mediastinal lymph node metastasis was 100%.

† Specificity is not shown for studies that did not surgically confirm all TBNA results but instead assumed that all positive results were true positives.

‡ Summary non-tier 1 specificity not shown because only two studies allowed calculation of specificity (both 100%),[33] [37] though both of these studies had fewer than 10 patients without mediastinal metastases.

Figure 3. Summary receiver-operating characteristic curve for mediastinal staging with TBNA for tier 1 studies. Individual study estimates of sensitivity and 1-specificity are shown (open circles). Median (solid square) and pooled sensitivities (solid triangle) are shown.

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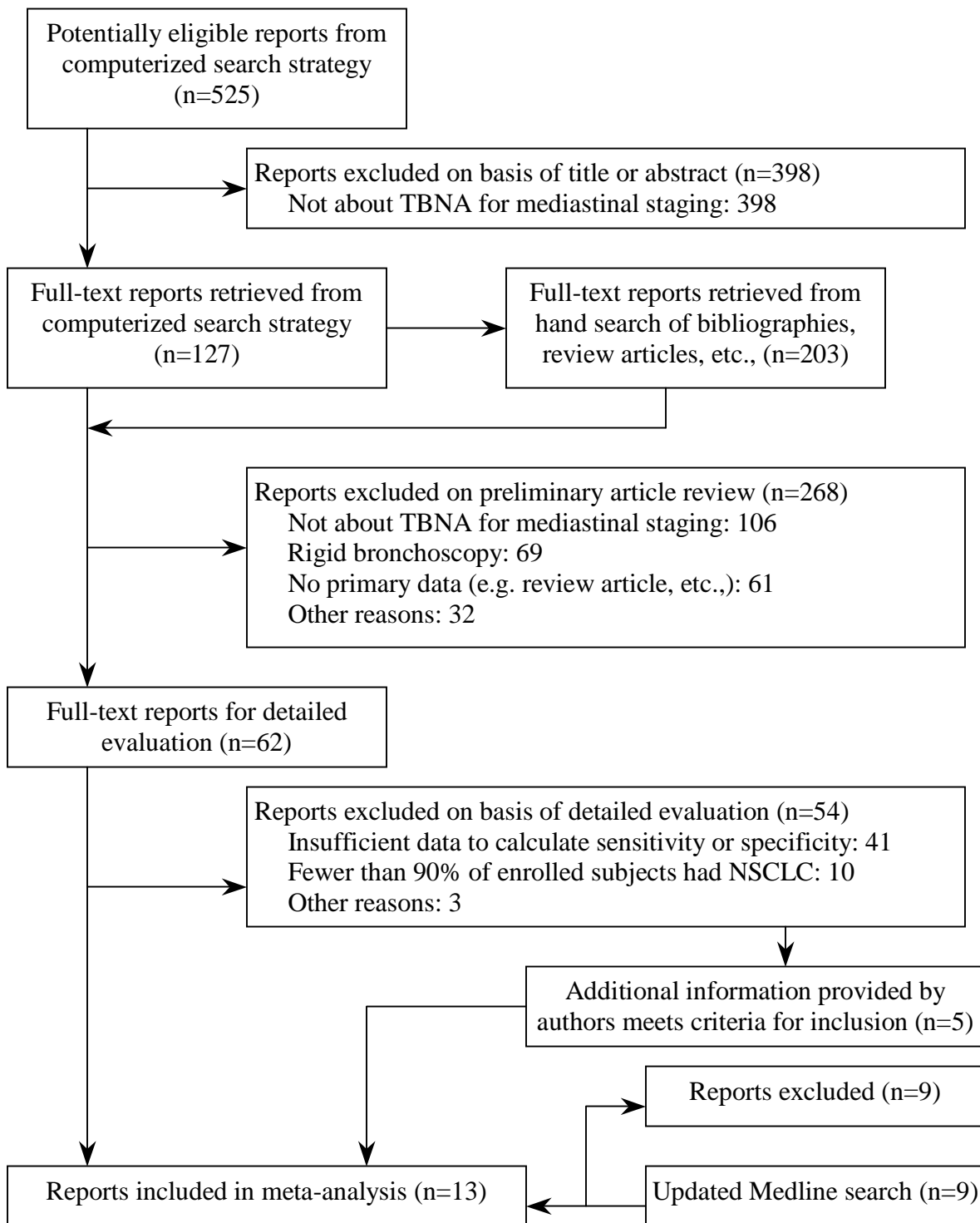


Figure 1. Literature search and selection. Studies could meet one or more exclusion criteria. For simplicity, only one primary exclusion criterion per study is shown.

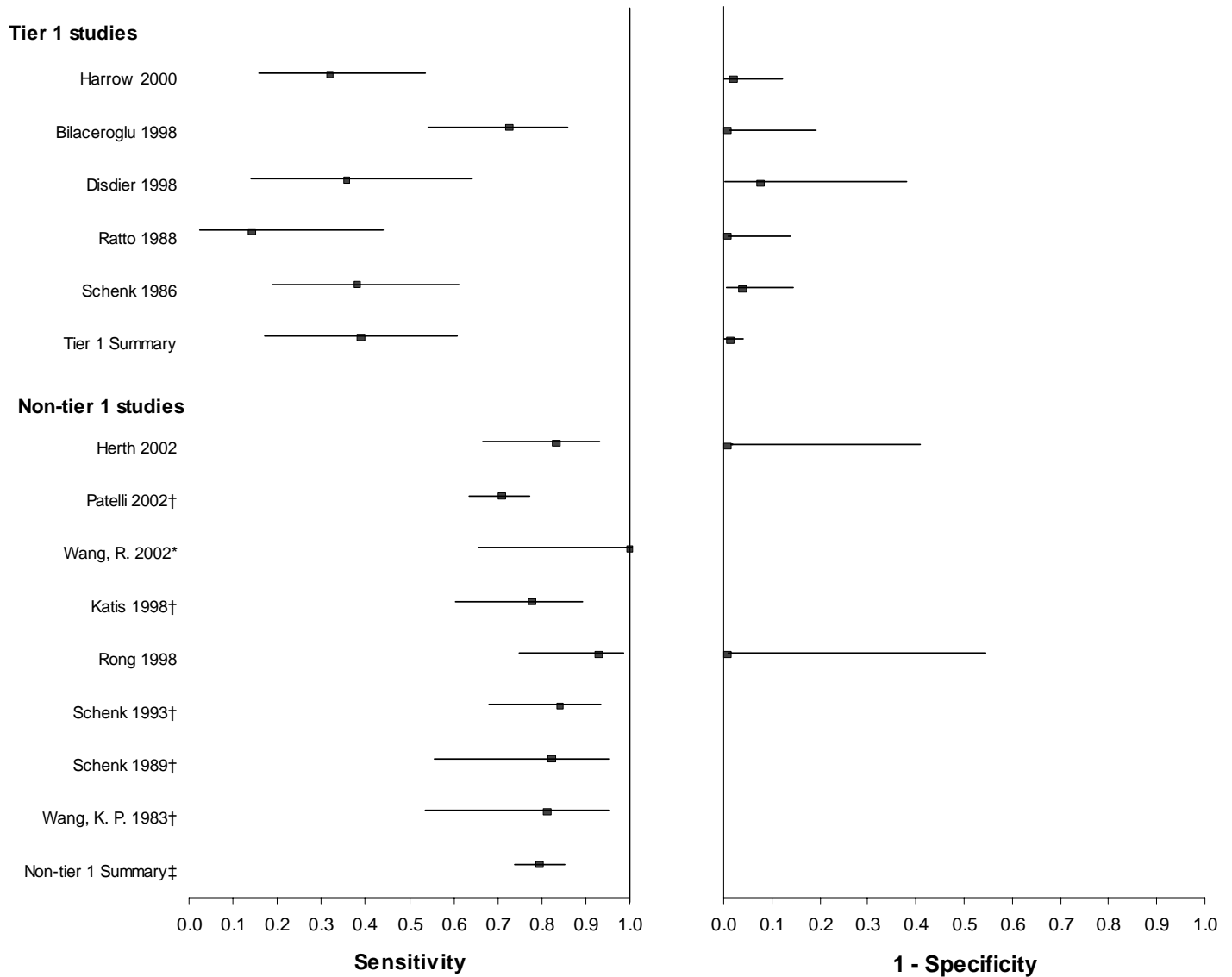
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Figure 2. Individual study estimates of sensitivity and 1-specificity of TBNA for identifying mediastinal metastasis. Error bars represent 95% CI's. Point estimates and 95% CI's for tier 1 studies and studies meeting inclusion criteria but not tier 1 criteria are shown. Tier 1 and non-tier 1 summary point estimates and corresponding 95% CI's are shown and were calculated by using a random effects model.

* Specificity was not calculated for the study by Wang, R. et. al.,[34] because the prevalence of mediastinal lymph node metastasis was 100%.

† Specificity is not shown for studies that did not surgically confirm all TBNA results but instead assumed that all positive results were true positives.

‡ Summary non-tier 1 specificity not shown because only two studies allowed calculation of specificity (both 100%),[33] [37] though both of these studies had fewer than 10 patients without mediastinal metastases.

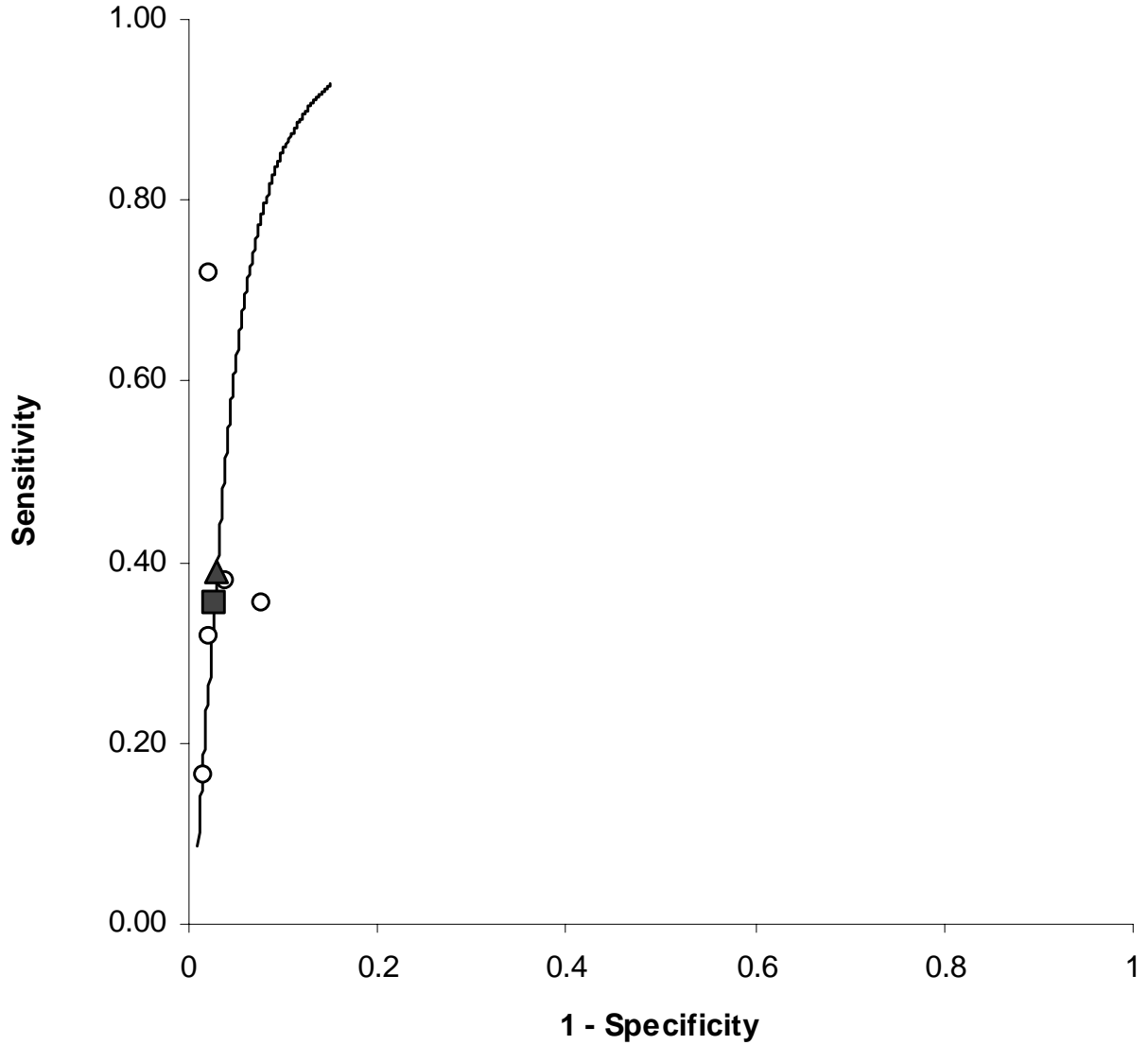


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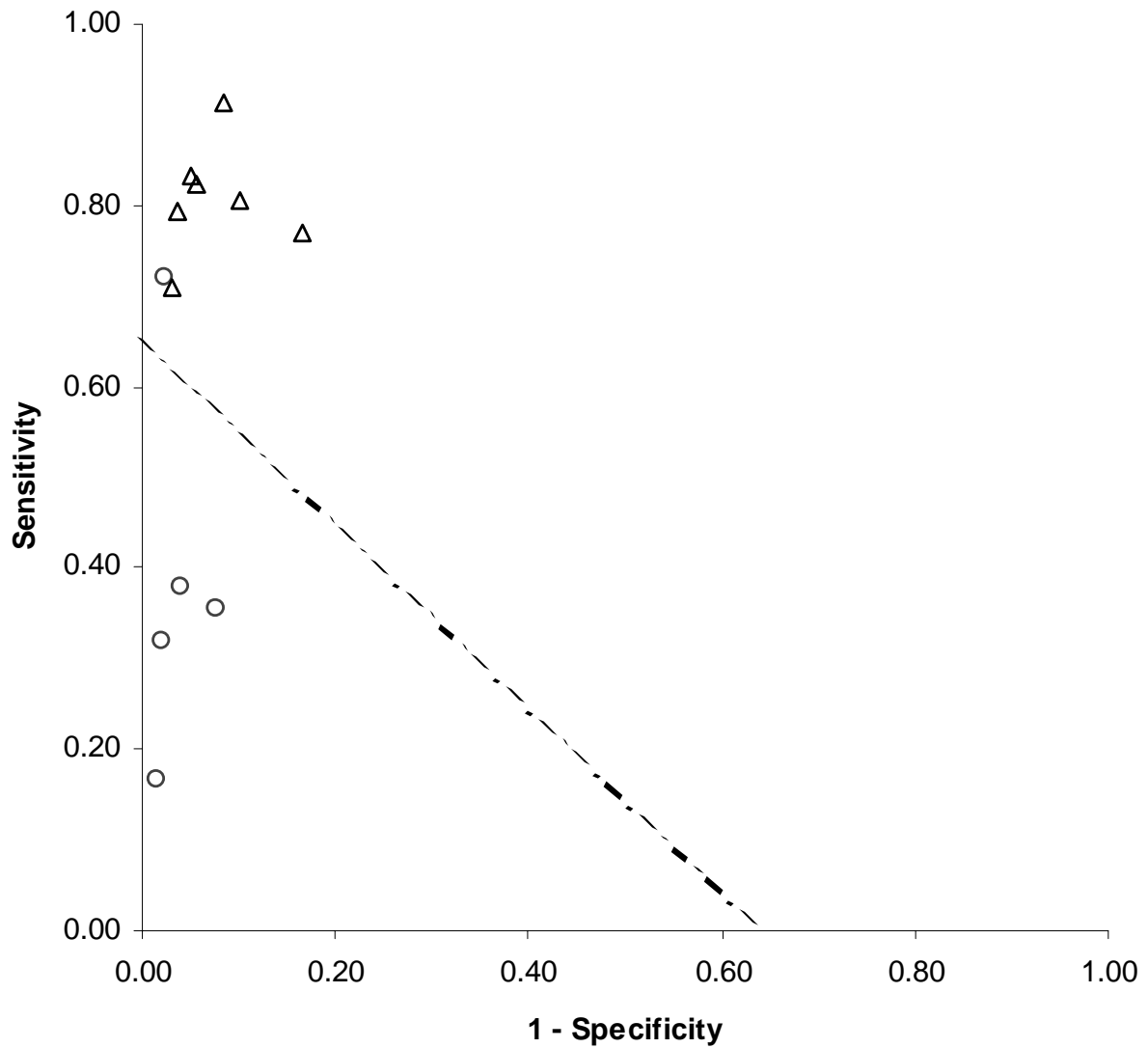


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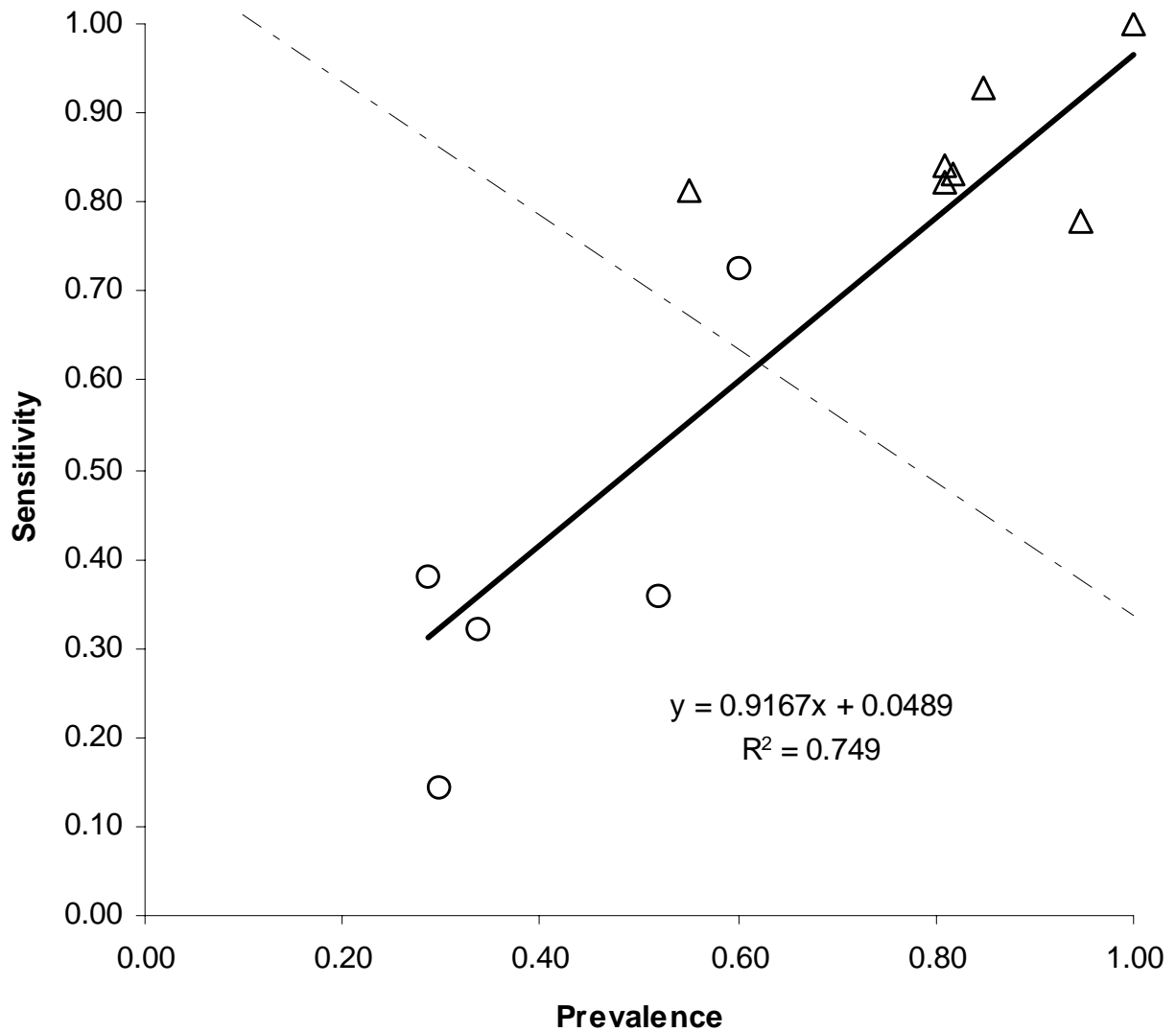


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Individual study estimates of prevalence and sensitivity are shown for tier 1 (circles) and non-tier 1 (triangles) studies. Both the linear regression equation and R^2 are shown. One study reported results by using individual lymph nodes as the unit of analysis and was not included (unable to calculate prevalence of mediastinal metastasis).[35] The discriminant function that separates tier 1 from non-tier 1 studies (dashed line) was significant ($p=0.002$ by parametric Wilks' Lambda test).



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