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FULL PAPER

Meta-analysis of CT-guided transthoracic needle biopsy for the evaluation of the ground-glass opacity pulmonary lesions

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Objective: This meta-analysis is to determine the overall diagnostic yield of CT-guided transthoracic needle biopsy (TNB) of ground-glass opacity (GGO) lesions.

Methods: A PubMed search was performed using "ground-glass opacity" crossed with "core biopsy" and "needle biopsy". Test performance characteristics with the use of forest plots, summary receiver operating characteristic curves and bivariate random effects models were summarized. Adverse events, if reported, were recorded.

Results: Our search identified 52 citations, of which 6 diagnostic studies evaluated 341 patients. Pooled specificity estimates were 0.94 [95% confidence interval (CI), 0.84–0.98] and sensitivity estimates were 0.92 (95% CI, 0.88–0.95), respectively. The positive likelihood ratio was

11.27 (95% CI, 4.2–30.6), the negative likelihood ratio was 0.1 (95% CI, 0.06–0.19), the diagnostic odds ratio was 131.38 (95% CI, 39.6–436.0) and the area under the curve was 0.97.

Conclusion: Our data suggest that the CT-guided TNB is likely to be a useful tool for tissue diagnosis and may serve as an alternative for further patient management with GGO lesions. However, considering the limited studies and patients included, large scale studies are needed to verify these findings.

Advances in knowledge: Some studies about CT-guided TNB of GGO lesions have been published, most have been small, single-institution case series. To our knowledge, our study is the first systematic analysis about CT-guided TNB of GGO lesions.

Owing to the prevalence of lung cancer screening with low-dose CT, an increase in the detection of ground-glass opacity (GGO) lesions has been noted.^{1–3} GGO is a finding on thin-section CT that is defined as "hazy increased attenuation of the lung with preservation of bronchial and vascular margins".⁴ These characteristics may be caused by partial filling of air spaces, interstitial thickening, partial collapse of alveoli, normal expiration or increased capillary blood volume. It is known that GGO is a non-specific finding that may be caused by various disorders, including inflammatory disease, pulmonary fibrosis, alveolar haemorrhage or neoplasm.^{5,6} The clinical significance of localized GGO is its high incidence of malignancy compared with solid nodules.^{7,8} Kim et al⁹ reported that approximately 75% of focal pure GGO lesions are adenocarcinoma. Although it has been reported that the morphologic classification is helpful to differentiate malignant GGO

lesions from benign conditions,⁸ it is generally considered very difficult based on CT findings alone.⁹ CT-guided biopsy is an established diagnostic technique that has high diagnostic yield and is used mainly for solid lung lesions.^{10,11} Although some studies about CT-guided TNB of GGO lesions have been published, most have been small, single-institution case series. Figure 6 shows the procedure of CT-guided TNB for GGO lesions. The aim of this study was to systemically and quantitatively assess the diagnostic performance of CT-guided transthoracic needle biopsy (TNB) of GGO lesions.

METHODS AND MATERIALS

Literature search strategy

A systematical literature search was undertaken for any (from inception to August 2013) research of the diagnostic efficacy of CT-guided TNB in GGO lesions. No systematical

Figure 1. A flow chart of study identification and inclusion.

research was found. We then performed a search in PubMed without language restrictions using the keyword “ground-glass opacity” crossed with “core biopsy” and “needle biopsy”. Our search was limited to human studies. A similar search strategy and similar search terms were used in EMBASE and Cochrane Library databases. All searches were conducted independently by two authors. To ensure a comprehensive acquisition of literature, independent supplemental manual searches were performed on the reference lists of relevant articles. Any inconsistencies between the two investigators in the article inclusion and exclusion were resolved by consensus.

Study selection and data extraction

We included studies that met all of the following inclusion criteria: (i) CT-guided TNB was adopted to obtain histological diagnosis before starting the next treatment in the study; and (ii) sufficient data to construct a 2×2 table for meta-analysis was present. Two authors assessed all full-text articles and extracted data from each of the included studies independently.

Figure 2. Quality assessment of diagnostic accuracy studies criteria for included studies.

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Hur J 2009 ¹⁴	+	+	+	+	+	+	+
Inoue D 2012 ¹⁷	+	+	+	+	+	+	+
Kim TJ 2008 ¹³	+	+	+	+	+	+	+
Lu CH 2012 ¹⁶	+	+	+	+	+	+	+
Yamagami T 2013 ¹⁸	+	+	+	?	+	+	+
Yamauchi Y 2011 ¹⁵	+	+	+	+	+	+	+

● High ? Unclear + Low

The quality of the selected studies was assessed by quality assessment of diagnostic accuracy studies (QUADAS) criteria.¹²

Data synthesis and analysis

The data synthesis for the accuracy of CT-guided TNB in GGO lesions was made by calculating pooled estimates of sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-) and diagnostic odds ratio (DOR). We also generated a summary receiver operating characteristic (SROC) curve as a way of summarizing the global test performance from different diagnostic studies. The average sensitivity, specificity and other related indexes across studies were calculated using a random effects model. Spearman rank correlation was performed as a test for threshold effect. χ^2 and Fisher's exact tests were used to detect statistically significant heterogeneity across studies. All analyses were performed using one statistical software program (Meta-DiSc v. 1.4; www.hrc.es/investigacion/metadisc_en.htm), all statistical tests were two-sided, and significance was set at $p < 0.05$.

Table 1. Summary of characteristics of the included studies

No.	Study	Year	n	Technology	Type of needle	True positive	False positive	False negative	True negative
1	Kim et al ¹³	2008	46	CT	Core biopsy 18 G/20 G	33	1	3	9
2	Hur et al ¹⁴	2009	28	CT-fluoroscopy	Aspiration biopsy 20 G/22 G	12	0	5	11
3	Yamauchi et al ¹⁵	2011	67	CT-fluoroscopy	Core biopsy 18 G	59	0	2	6
4	Lu et al ¹⁶	2012	49	CT	Core biopsy 20 G	44	0	3	2
5	Inoue et al ¹⁷	2012	66	CT-fluoroscopy	Core biopsy 20 G	58	0	3	5
6	Yamagami et al ¹⁸	2013	85	CT-fluoroscopy	Core biopsy 18 G	58	0	8	19

Figure 3. Forest plots of sensitivity: the point estimates of sensitivity from each study are shown as solid circles. Error bars indicate 95% confidence interval (CI). df. degrees of freedom.

RESULTS

Characteristics of studies

The systematic search that we conducted is summarized in Figure 1. The search initially yielded 52 potential literature citations through database searching. 44 citations were excluded based on screening titles and abstracts. After reading the full texts, two of the remaining eight articles were excluded, since they lacked sufficient information to complete a 2×2 contingency table. Finally, six studies were included in the study.^{13–18} The abstract data of these individual studies are summarized in Table 1. Figure 2 provides an overall picture of the methodological quality of studies as evaluated by the QUADAS tool.

Diagnostic accuracy

The forest plots of sensitivity and specificity of CT-guided TNB for the diagnosis of GGO lesions are shown in Figures 3 and 4. The sensitivity ranged from 0.71 to 0.97 [pooled 0.92; 95% confidence interval (CI), 0.88–0.95], while specificity ranged from 0.80 to 0.97 (pooled 0.94; 95% CI, 0.84–0.98). The LR+ was 11.27 (95% CI, 4.2–30.6), LR– was 0.1 (95% CI, 0.06–0.19) and DOR was 131.38 (95% CI, 39.6–436.0). χ^2 values of sensitivity, specificity, LR+, LR– and DOR were 11.37 ($p = 0.04$), 1.48 ($p = 0.92$), 1.35 ($p = 0.93$), 11.67 ($p = 0.04$) and 1.31 ($p = 0.93$), respectively, suggesting heterogeneity among studies to some extent.

Figure 5 shows the SROC curve plotting the true-positive against the false-positive rates of individual studies. As a global measure of test efficacy, we used the Q-value, the intersection point of the SROC curve with a diagonal line from the left upper corner to the right lower corner of the receiver operating characteristic space, which corresponds to the highest common value of

sensitivity and specificity for the test. This point does not indicate the only or even the best combination of sensitivity and specificity for a particular clinical setting but represents an overall measure of the discriminatory power of a test. In this meta-analysis, the maximum joint sensitivity and specificity of our study was 0.92 (the Q-value) and the area under the curve (AUC) was 0.97, indicating a high level of overall accuracy.

Complications

The incidence of pneumothorax was reported in all six studies and ranged from 16% to 51.8% (pooled incidence rate, 29.8%; 95% CI, 25.2–34.3; test of homogeneity, $p = 0.001$). A total of seven patients from four of the studies required chest tube drainage. The incidence of haemoptysis ranged from 8% to 23%, and no patient with haemoptysis required treatment.

DISCUSSION

According to the guidelines of managing small lung nodules from the Fleischner Society, small GGO lesions usually require more than 2 years follow-up.¹⁹ However, malignant GGO lesions can remain stable in size for as long as 36 months.²⁰ In addition, during the observation period, some malignant tumours will progress from being resectable to unresectable.²¹ GGO lesions have been reported to have a good prognosis, and, in most cases, their pathological features are minimally invasive.^{22–24} Thus, these tumours are considered to be candidates for limited surgical resection, such as segmentectomy and wedge resection, although some would consider lobectomy as most appropriate.^{25,26} Additionally, treatment options for adenocarcinoma *in situ* and minimally invasive adenocarcinoma, based on the perspective that it is an early phase cancer that has not metastasized, would not be limited to surgical resection but could also include less

Figure 4. Forest plots of specificity: the point estimates of specificity from each study are shown as solid circles. Error bars indicate 95% confidence interval (CI). df. degrees of freedom.

Figure 5. Summary receiver operating characteristic (SROC) curve: the size of each solid circle represents the size of each study included in the present meta-analysis. The regression SROC curve indicates the overall diagnostic accuracy. AUC, area under the curve; SE, standard error.

invasive strategies, such as radiofrequency ablation, cryoablation therapy, stereotactic radiotherapy and heavy charged particle radiotherapy.¹⁵ Other lesions might also be considered for less invasive treatments. Thus, a process to confirm the diagnosis of GGO histologically before starting treatment is required.

Although CT-guided lung biopsy has widespread acceptance as a preferred method of diagnosing lung nodules and its diagnostic

Figure 6. CT-guided core biopsy in 76-year-old male with ground-glass opacity (GGO) lesion in left lower lobe. CT scan obtained during biopsy shows biopsy needle targeting GGO lesion. Histologic diagnosis of core biopsy and surgical resection was adenocarcinoma.

accuracy has been reported to be as high as 81–96%, few investigations have focused on GGO lesions.^{10,11,13–18} To our knowledge, this is the first pooled estimation of the diagnostic performance of CT-guided TNB of GGO lesions.

This meta-analysis investigated the overall diagnostic role of CT-guided TNB in the differential diagnosis of GGO lesions with a high specificity (0.94; 95% CI, 0.84–0.98) and sensitivity (0.92; 95% CI, 0.88–0.95). The SROC curve presents a global summary of test performance and indicates the trade-off between sensitivity and specificity.²⁷ Our meta-analysis based on the SROC curve showed that the maximum joint sensitivity and specificity was 0.92 and the AUC was 0.97, indicating a high level of overall accuracy. We can conclude that CT-guided TNB plays an important role in the diagnosis of GGO lesions. DOR is another indicator of test accuracy, combining the data from sensitivity and specificity into a single value.²⁸ In this study, the DOR was 131.38 (95% CI, 39.6–436.0), indicating that CT-guided TNB was valuable in the diagnosis of GGO lesions.

Previous studies have reported that diagnostic yield is dependent on size and site of the lesion, operator experience, needle type and length, choice of biopsy technique and availability of cytopathology expertise in solid pulmonary nodules.^{10,11} For GGO lesions, to our knowledge, some reports have studied the factors affecting the diagnostic yield according to the component and lesion size. The diagnostic accuracy tended to be lower in the small-sized lesions <10 mm and in lesions with lower percentage of GGO component; however, statistical significances were not reached.^{13–18} In our study, we also tried to perform subgroup analysis by dividing the diagnostic yield into two groups according to size (>2 vs <2 cm) and GGO component (>90% vs 50–90%). This is contrary to the general expectation

that it is more difficult to obtain adequate samples for further subgroup analysis. Further studies on the factors affecting the diagnostic yield may be needed.

Currently, no guideline exists for the management of GGO lesions. In some institutes, lesions of <1 cm in diameter are followed up with thin-section CT 2–3 months later and those of ≥1 cm in diameter are examined with CT-guided needle biopsy or video-assisted thoracoscopic surgery (VATS). Although VATS biopsy can provide larger tissue specimens and improve accuracy, the morbidity and length of stay are greater than those with needle biopsy. The results of this study suggest that CT-guided TNB for GGO lesions can yield high diagnostic accuracy. Based on a high incidence of malignancy and a good prognosis after radical operation for GGO in those patients, for whom lesions that increase beyond 1 cm or develop a new solid component at follow-up CT, we recommend the use of CT-guided needle biopsy as the first-line histologic diagnostic modality.

The incidence of adverse effects was considered to be within an acceptable range. Pneumothorax is the most frequently encountered

complication of CT-guided TNB, with an incidence of 16.0–51.8%. Out of 341 patients, only 7 required chest tube drainage. The incidence of haemoptysis ranged from 8% to 23%, and no patient with haemoptysis required treatment.

There is one limitation in this meta-analysis. Although we used a comprehensive search strategy, with screening, study selection, data extraction and quality assessment carried out independently and reproducibly by two reviewers, only six studies were included. The limited number of patients may have influenced the results we obtained, so further studies on a larger scale may be needed.

CONCLUSION

The results of this study suggest that CT-guided TNB of GGO lesions can yield high diagnostic accuracy and acceptable complication rates. The study can provide useful information for further patient management.

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REFERENCES

- Kaneko M, Eguchi K, Ohmatsu H, Kakinuma R, Naruke T, Suemasu K, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. *Radiology* 1996; **201**: 798–802. doi: [10.1148/radiology.201.3.8939234](https://doi.org/10.1148/radiology.201.3.8939234)
- Sone S, Takashima S, Li F, Yang Z, Honda T, Maruyama Y, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet* 1998; **351**: 1242–5. doi: [10.1016/S0140-6736\(97\)08229-9](https://doi.org/10.1016/S0140-6736(97)08229-9)
- Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS, et al. Early lung cancer action project: overall design and findings from baseline screening. *Lancet* 1999; **354**: 99–105. doi: [10.1016/S0140-6736\(99\)06093-6](https://doi.org/10.1016/S0140-6736(99)06093-6)
- Koshihashi T, Munechika H, Ri K, Kubota H, Ukisu R, Satoh S, et al. Bronchioloalveolar adenoma of the lung: CT-pathologic correlation. *Radiology* 1994; **193**: 789–93. doi: [10.1148/radiology.193.3.7972826](https://doi.org/10.1148/radiology.193.3.7972826)
- Nakajima R, Yokose T, Kakinuma R, Nagai K, Nishiwaki Y, Ochiai A. Localized pure ground-glass opacity on high-resolution CT: histologic characteristics. *J Comput Assist Tomogr* 2002; **26**: 323–9.
- Collins J, Stern EJ. Ground-glass opacity at CT: the ABCs. *AJR Am J Roentgenol* 1997; **169**: 355–67. doi: [10.2214/ajr.169.2.9242736](https://doi.org/10.2214/ajr.169.2.9242736)
- Henschke CI, Yankelevitz DF, Mirtcheva R, McGuinness G, McCauley D, Miettinen OS, et al. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. *AJR Am J Roentgenol* 2002; **178**: 1053–7. doi: [10.2214/ajr.178.5.1781053](https://doi.org/10.2214/ajr.178.5.1781053)
- Li F, Sone S, Abe H, Macmahon H, Doi K. Malignant versus benign nodules at CT screening for lung cancer: comparison of thin-section CT findings. *Radiology* 2004; **233**: 793–8. doi: [10.1148/radiol.2333031018](https://doi.org/10.1148/radiol.2333031018)
- Kim HY, Shim YM, Lee KS, Han J, Yi CA, Kim YK. Persistent pulmonary nodular ground-glass opacity at thin-section CT: histopathologic comparisons. *Radiology* 2007; **245**: 267–75. doi: [10.1148/radiol.2451061682](https://doi.org/10.1148/radiol.2451061682)
- Hiraki T, Mimura H, Gobara H, Iguchi T, Fujiwara H, Sakurai J, et al. CT fluoroscopy-guided biopsy of 1,000 pulmonary lesions performed with 20-gauge coaxial cutting needles: diagnostic yield and risk factors for diagnostic failure. *Chest* 2009; **136**: 1612–17.
- Montaudon M, Latrabe V, Pariente A, Corneloup O, Begueret H, Laurent F. Factors influencing accuracy of CT-guided percutaneous biopsies of pulmonary lesions. *Eur Radiol* 2004; **14**: 1234–40. doi: [10.1007/s00330-004-2250-3](https://doi.org/10.1007/s00330-004-2250-3)
- Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; **155**: 529–36. doi: [10.7326/0003-4819-155-8-201110180-00009](https://doi.org/10.7326/0003-4819-155-8-201110180-00009)
- Kim TJ, Lee JH, Lee CT, Jheon SH, Sung SW, Chung JH, et al. Diagnostic accuracy of CT-guided core biopsy of ground-glass opacity pulmonary lesions. *AJR Am J Roentgenol* 2008; **190**: 234–9. doi: [10.2214/AJR.07.2441](https://doi.org/10.2214/AJR.07.2441)
- Hur J, Lee HJ, Nam JE, Kim YJ, Kim TH, Choe KO, et al. Diagnostic accuracy of CT fluoroscopy-guided needle aspiration biopsy of ground-glass opacity pulmonary lesions. *AJR Am J Roentgenol* 2009; **192**: 629–34.
- Yamauchi Y, Izumi Y, Nakatsuka S, Inoue M, Hayashi Y, Mukai M, et al. Diagnostic performance of percutaneous core needle lung biopsy under multi-CT fluoroscopic guidance for ground-glass opacity pulmonary lesions. *Eur J Radiol* 2011; **79**: e85–9. doi: [10.1016/j.ejrad.2011.03.088](https://doi.org/10.1016/j.ejrad.2011.03.088)
- Lu CH, Hsiao CH, Chang YC, Lee JM, Shih JY, Wu LA, et al. Percutaneous computed tomography-guided coaxial core biopsy for small pulmonary lesions with ground-glass attenuation. *J Thorac Oncol* 2012; **7**: 143–50. doi: [10.1097/JTO.0b013e318233d7dd](https://doi.org/10.1097/JTO.0b013e318233d7dd)
- Inoue D, Gobara H, Hiraki T, Mimura H, Kato K, Shibamoto K, et al. CT fluoroscopy-guided cutting needle biopsy of focal pure ground-glass opacity lung lesions: diagnostic yield in 83 lesions. *Eur J Radiol* 2012; **81**: 354–9. doi: [10.1016/j.ejrad.2010.11.025](https://doi.org/10.1016/j.ejrad.2010.11.025)
- Yamagami T, Yoshimatsu R, Miura H, Yamada K, Takahata A, Matsumoto T, et al. Diagnostic performance of percutaneous lung biopsy using automated biopsy needles under CT-fluoroscopic guidance for ground-glass opacity lesions. *Br J Radiol* 2013; **86**: 20120447. doi: [10.1259/bjr.20120447](https://doi.org/10.1259/bjr.20120447)

19. MacMahon H, Austin JH, Gamsu G, Herold CJ, Jett JR, Naidich DP, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. *Radiology* 2005; **237**: 395–400. doi: [10.1148/radiol.2372041887](https://doi.org/10.1148/radiol.2372041887)
20. Park JH, Lee KS, Kim JH, Shim YM, Kim J, Choi YS, et al. Malignant pure pulmonary ground-glass opacity nodules: prognostic implications. *Korean J Radiol* 2009; **10**: 12–20.
21. Gould MK, Fletcher J, Iannettoni MD, Lynch WR, Midthun DE, Naidich DP, et al; American College of Chest Physicians. Evaluation of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; **132**(Suppl. 3): 108S–30S.
22. Noguchi M, Morikawa A, Kawasaki M, Matsuno Y, Yamada T, Hirohashi S, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer* 1995; **75**: 2844–52.
23. Suzuki K, Asamura H, Kusumoto M, Kondo H, Tsuchiya R. “Early” peripheral lung cancer: prognostic significance of ground glass opacity on thin-section computed tomographic scan. *Ann Thorac Surg* 2002; **74**: 1635–9.
24. Suzuki K, Koike T, Asakawa T, Kusumoto M, Asamura H, Nagai K, et al. A prospective radiological study of thin-section computed tomography to predict pathological non-invasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). *J Thorac Oncol* 2011; **6**: 751–6.
25. Hattori A, Suzuki K, Matsunaga T, Fukui M, Kitamura Y, Miyasaka Y, et al. Is limited resection appropriate for radiologically “solid” tumor in small lung cancers? *Ann Thorac Surg* 2012; **94**: 212–15.
26. Lee HY, Lee KS. Ground-glass opacity nodules: histopathology, imaging evaluation, and clinical implications. *J Thorac Imaging* 2011; **26**: 106–18. doi: [10.1097/RTI.0b013e3181fbaa64](https://doi.org/10.1097/RTI.0b013e3181fbaa64)
27. Walter SD. Properties of the summary receiver operating characteristic (SROC) curve for diagnostic test data. *Stat Med* 2002; **21**: 1237–56. doi: [10.1002/sim.1099](https://doi.org/10.1002/sim.1099)
28. Glas AS, Lijmer JG, Prins MH, Bossel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol* 2003; **56**: 1129–35.