Original Article
Metastatic rate of lymph nodes in clinical stage I non-small-cell lung cancer patients with mixed ground-glass opacity versus pure ground-glass opacity: a systematic review and meta-analysis

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Abstract: Objective: This systematic review and meta-analysis aimed to investigate the metastatic rate of hilar lymph node (N1) and mediastinal lymph node (N2) in clinical stage I non-small-cell lung cancer patients with either a pure ground-glass opacity (Pure-GGO) or mixed ground-glass opacity (Mixed-GGO), to indicate how to dissect lymph nodes in patients with GGO. Methods: A systematic search of the published literature was conducted using the main databases (Science Direct, PubMed, Springer Link and Wiley Online Library) to collect relevant case-control studies that compared Pure-GGOs and Mixed-GGOs in clinical stage I non-small-cell lung cancer patients. Meta-analysis was performed extracting data from the published literature using STATA 12.0. The results of the meta-analysis were expressed as an odds ratio (OR) and their corresponding 95% confidence interval (CI). Results: We extracted data from three case-control studies, with a total of 736 patients. There were no significant differences (OR=3.66, 95% CI: 0.68-19.58, P=0.13) in the rates of metastases in all lymph nodes in patients with either Pure-GGO or Mixed-GGO. In addition, there were no significant differences (OR=4.22, 95% CI: 0.77-23.19, P=0.10) in the rates of metastases in N1 hilar lymph nodes in patients with either Pure-GGO or Mixed-GGO. However, we found that the study by Aritoshi Hattori showed an OR of 20.18 (95% CI: 0.94-432.12). There are no significant differences in rates of metastases of N2 mediastinal lymph nodes in patients with either Pure-GGO or Mixed-GGO (OR=1.10; 95% CI: 0.19-6.32, P=0.92). Conclusions: The results indicated no statistically significant difference in metastatic rates of N1 hilar lymph nodes and N2 mediastinal lymph nodes in patients with either Pure-GGO or Mixed-GGO. However, we must be particularly cautious about metastasis in N1 hilar lymph nodes in patients with Mixed-GGO.

Keywords: Pure-GGO, mixed-GGO, metastatic rate of lymph nodes, meta analysis

Introduction

Lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer deaths in both men and women [1]. In recent years, there have been rapid developments in imaging modalities and the worldwide use of radiographic screening methods such as low-dose helical computed tomography (CT), high-resolution computed tomography and positron emission tomography/computed tomography for the screening of early lung cancer [2-5]. This has therefore helped ensure an increase in the detection rate of ground-glass opacity (GGO) in patients with early-stage lung cancer [6-8]. Pure ground-glass opacity (Pure-GGO) is defi-

ned as a hazy increase in lung attenuation which does not obscure the underlying vascular markings excluding any solid component, whereas Mixed-GGO is defined as an increase in attenuation which obscures the underlying lung structures including both the GGO and solid component (the rate of GGO component ranges from 1% to 99%) [9-11]. On a CT scan, early-stage lung cancer often contains the GGO component and can be treated by surgical intervention [12-17]. Several authors have reported that patients with GGO-dominant small lung cancer have a favourable postoperative prognosis [18-21]. Unfortunately, regional and mediastinal lymph node metastases are found

in some patients with clinical stage I disease including those with Mixed-GGO [22-26].

Whether surgeons must dissect lymph nodes for patients with different types of GGOs and even how to dissect lymph nodes is still controversial. Surgeons also want to know whether the same mode of dissection of lymph nodes could be applicable to patients with Pure-GGOs and Mixed-GGOs. The most likely sites of metastases include the hilar and mediastinal lymph nodes which therefore need to be removed whilst causing patients the least amount of harm.

Clearly, a systematic review and meta-analyses are required to resolve these questions with definitive analysis providing stronger rationales for choosing a specific ways to dissect the lymph nodes in either Pure-GGOs or Mixed-GGOs. For this reason, we performed a meta-analysis of pooled data from existing case-control studies to evaluate the rate of metastases to lymph nodes in clinical stage I non-small-cell lung cancer patients with either pure-GGOs or mixed-GGOs.

Methods

Literature search strategy

We carried out and reported this systematic review and meta-analyses according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27]. The published reports were identified and selected by searching the following databases: Science Direct, PubMed, Springer Link, and Wiley Online Library, from their date of inception to February 2016, with no lower date limit applied. The search used combinations of the following text strings ((((lymphadenectomy) OR mediastinal lymph node dissection) OR hilar lymph node dissection) OR lymph node sampling) AND ((non-small cell lung cancer) OR NSCLC) AND ((GGO) OR grand glass opacity). The searches were restricted to the English language although there was no restriction of origin. We also reviewed the reference lists of all retrieved studies to identify any potentially related articles. All retrieved studies and many potentially relevant articles were carefully read, including the names of authors and the time of publishing, to avoid duplication of data.

Selection criteria

Studies were selected for inclusion in this meta-analyses based on the following criteria: (1) studies using case-control methods to research the operation procedure and lymph node dissection for Pure-GGOs and Mixed-GGOs in early stage lung cancer patients; (2) patients with Pure-GGOs and Mixed-GGOs must be divided into two groups for research at the same time; (3) no previous treatment for Pure-GGOs and Mixed-GGOs had been carried out; (4) including N1 and N2 lymph node dissection; (5) studies were limited to human trials and those written in English. Exclusion criteria for this meta-analyses were as follows: (1) studies researched patients with either Pure-GGOs or Mixed-GGOs; (2) where no operation or lymph node dissection was performed; (3) review articles or case reports; (4) letters, editorials, and expert opinions without original data; (5) the clinical data from patients with Pure-GGOs and Mixed-GGOs was not analysed separately in the reports; (6) studies lacked control groups and did not clearly report the outcomes of interest.

Data extraction and quality assessment

Two reviewers, ZF and SYG, independently selected the eligible studies and performed the data extraction according to a standard protocol. All the data were extracted from three eligible studies [28-30]. When the two reviewers initially disagreed, this was resolved by discussion whereby a consensus was eventually reached. According to a standard protocol, data comprising several necessary characteristics were extracted: the first author(s) or the name of the study group, the journal the article had been published in, the year of the publication, the country of the study, the number of the patients enrolled, the surgical procedures, the N1 and N2 lymph node dissection (LND), and the number of patients with N1 and N2 lymph node metastasis. When data were missing or unclear in a paper, the corresponding authors were contacted through mail or email to obtain the necessary information. An article was excluded if there were no response after two contact attempts were made.

Statistical analysis

The Review Manager 5.3 and STAT 12.0 software was used for the statistical analysis of

Figure 1. Flow diagram showing the process used for selecting articles.

tified from reading the bibliographies. We identified 155 studies after 219 duplicates removed. By scanning titles and abstracts, we excluded 132 studies including 36 case reports, 8 reviews, 41 studies with no apparent relevance to GGO, and 47 studies with no apparent relevance to the present study. In total, 23 studies were therefore included in the next round of review. After reading the full text of these articles, we removed 20 studies that did not meet the selection criteria. A diagram represents the flow of identification and inclusion of trials (**Figure 1**), as recommended by the PRISMA statement. As a result, three studies [28-30] that included a total of 736 patients were selected for meta-analysis.

Comparison of metastatic rates of all lymph nodes in patients with Mixed-GGO and Pure-GGO

A total of 3 papers reported results that simultaneously divided Mixed-GGO and Pure-GGO into two groups. We analysed the metastatic rates of all lymph nodes in patients with Mixed-GGO and Pure-GGO including N1 and N2 lymph nodes. The homogeneity test on these 3 studies resulted in P=0.96 and I^2=0%. An analysis using the fixed-effects model showed an OR of 3.66 (95% CI: 0.68-19.58) although this was not statistically significant (P=0.13), indicating that there are no significant differences in rates of metastases for all lymph nodes in patients with either Pure-GGO or Mixed-GGO (**Figure 2**).

Comparing the rates of metastases of N1 lymph nodes in patients with either Mixed-GGO or Pure-GGO

A total of 3 papers reported results that simultaneously divided Mixed-GGO and Pure-GGO into two groups. We analysed the metastatic rates of N1 hilar lymph nodes in patients with Mixed-GGO and Pure-GGO. The homogeneity test on these 3 studies resulted in P=0.44 and

studies. The OR and 95% CI were used to present the statistical values derived from the efficacy analysis for dichotomous variables. All statistical assessments were 2-sided and the significance level was defined as P<0.05. The fixed-effects model was adopted for the pooled analysis if a statistical homogeneity existed among the studies (P>0.05, I^2<50%), and the random-effects model was utilized for the analysis if a statistical heterogeneity existed among the studies (P<0.05, I^2>50%). Egger's test was used to evaluate publication bias. Contour-enhanced funnel plots were used to help interpret, and to further explore publication bias in the case of funnel asymmetry.

Results

Search results and trial characteristics

A total of 374 studies were identified by the searches. Out of all the studies, 372 were identified by database searching whilst 2 were identified
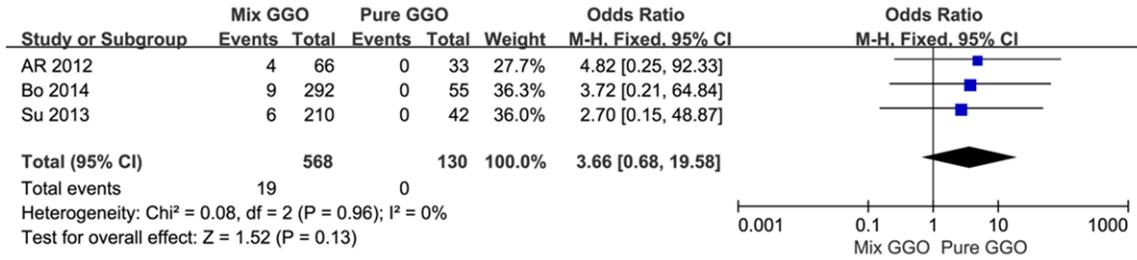
Figure 2. Forest plot of metastatic rates of all lymph nodes for the Mixed-GGO vs. Pure-GGO groups. GGO, Ground-Glass Opacity; OR, odds ratio; CI, confidence interval.
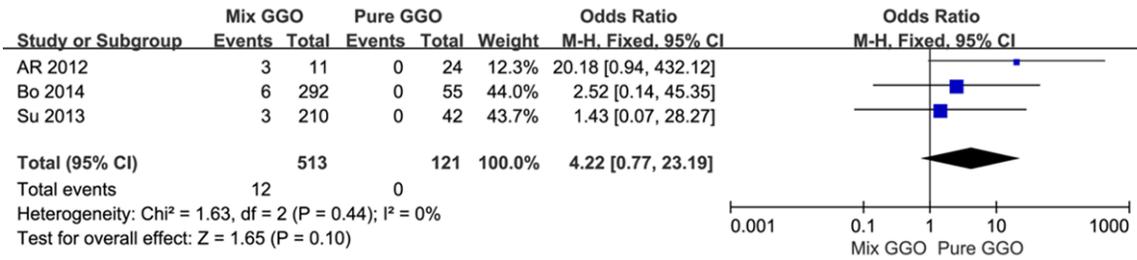

Figure 3. Forest plot of metastatic rates of N1 hilar lymph nodes for the Mixed-GGO vs. Pure-GGO groups. GGO, Ground-Glass Opacity; OR, odds ratio; CI, confidence interval.
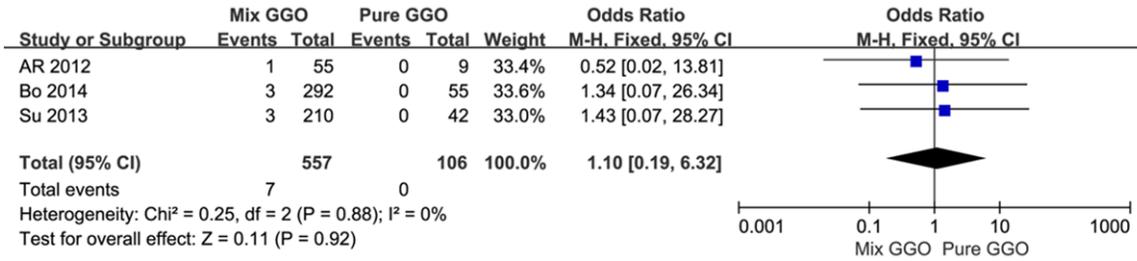

Figure 4. Forest plot of metastatic rates of N2 mediastinal lymph nodes for the Mixed-GGO vs. Pure-GGO groups. GGO, Ground-Glass Opacity; OR, odds ratio; CI, confidence interval.
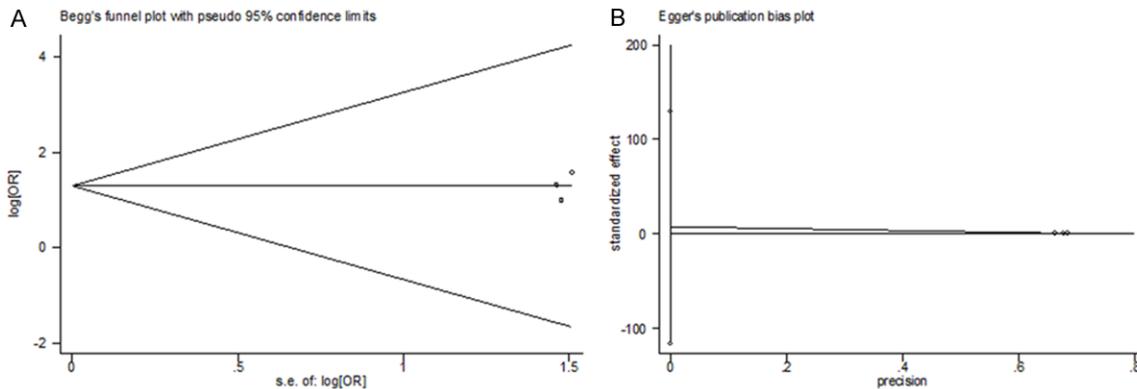

Figure 5. Publication bias detection using both Begg's (A) and Egger's (B) bias indications in the analysis of metastatic rates of all mediastinal lymph nodes for the Mixed-GGO vs. Pure-GGO groups.

Figure 6. Publication bias detection using both Begg's (A) and Egger's (B) bias indications in the analysis of metastatic rates of N1 hilar mediastinal lymph nodes for the Mixed-GGO vs. Pure-GGO groups.
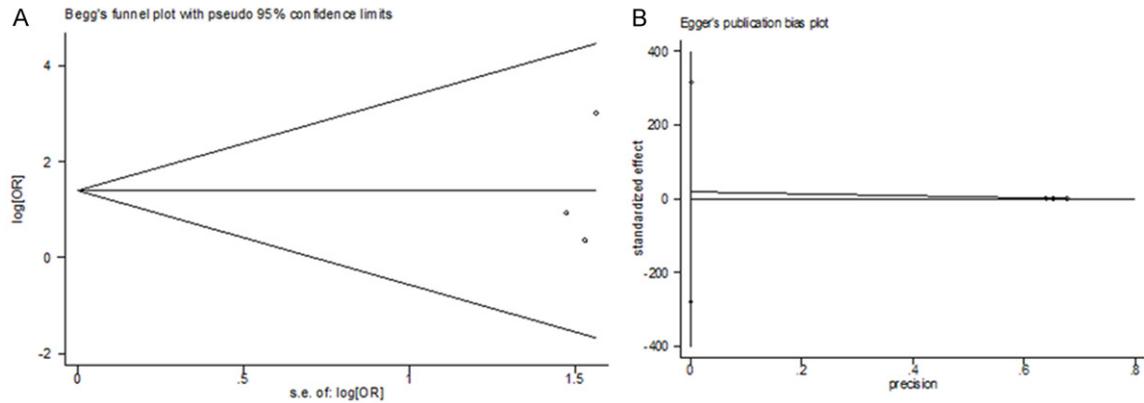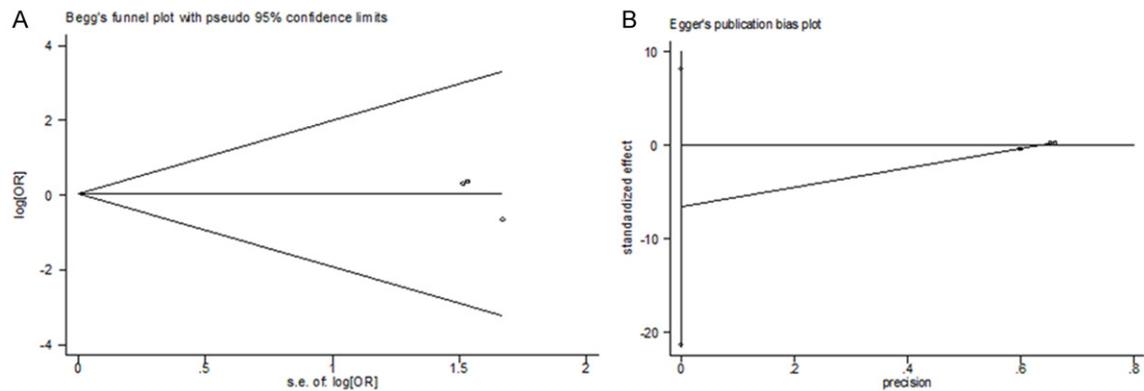

Figure 7. Publication bias detection using both Begg's (A) and Egger's (B) bias indications in the analysis of metastatic rates of N2 mediastinal mediastinal lymph nodes for the Mixed-GGO vs. Pure-GGO groups.

I^2=0%. An analysis using the fixed-effects model showed an OR of 4.22 (95% CI: 0.77-23.19) although, again, this was not statistically significant (P=0.10), indicating that there are no significant differences in rates of metastases to N1 hilar lymph nodes in patients with either Pure-GGO or Mixed-GGO. However, we found that the study from Hattori et al. (REF) in 2012 showed an OR of 20.18 (95% CI: 0.94-432.12) indicating that metastatic rates in N1 hilar lymph nodes in patients with Mixed-GGO are probably greater than those with Pure-GGO. However, since there were too few patients in this study, the weight of this study was only 12.3% in total (**Figure 3**).

Comparing the rates of metastases of N2 lymph nodes in patients with either Mixed-GGO or Pure-GGO

A total of 3 papers reported results that simultaneously divided Mixed-GGO and Pure-GGO into two groups. We analysed the metastatic rates of N2 mediastinal lymph nodes in patients with Mixed-GGO and Pure-GGO. The homogeneity test on these 3 studies resulted in P=0.88 and I^2=0%. An analysis using the fixed-effects model showed an OR of 1.10 (95% CI: 0.19-6.32) which was not statistically significant (P=0.92), indicating that there are no significant differences in the rates of metastases in N2 mediastinal lymph nodes in patients with either Pure-GGO or Mixed-GGO (**Figure 4**).

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias in this study. These two tests estimated the publication bias of the rates of metastases to all lymph nodes (**Figure 5**), N1 lymph nodes (**Figure 6**), and N2 lymph nodes (**Figure 7**) in patients with Mixed-GGO and Pure-GGO. The shape of the funnel plots did not reveal any evidence of obvi-

ous asymmetry for the meta-analysis. Egger's test was then used to provide statistical evidence of funnel plot symmetry. In all, the results still did not present any obvious evidence of publication bias (P>0.05).

Discussion

With development of new technology in CT scanning, small-sized lung cancers such as GGO are routinely found in daily clinical practice [4, 31]. Because GGO was normally defined as an early-stage lung cancer such as adenocarcinoma *in situ* or minimally invasive adenocarcinoma, many people considered that the possibility of lymph node metastasis would be very low in these patients. With further research about GGO, GGO lesions are now always classified into either pure GGO or mixed GGO depending on the solid components. Some researchers were sure that lymph node metastasis had never been discovered in patients with pure GGO lesions. Unfortunately, tumours less than 1 cm in size, including GGO, were simply considered to not have spread through the lymphatic or vasculature although some of these tumours are already in the advanced stage [19].

Controversies still exist as to whether surgeons must dissect lymph nodes and how to dissect lymph nodes for patients with different type of GGOs. Many researchers assert that it is not necessary for patients with pure GGOs to have their lymph nodes dissected. However, surgeons do not know whether dissection of lymph nodes is appropriate for patients with mixed-GGOs. Moreover, if surgeons do need to perform a dissection of lymph nodes, what is the extent of dissection they should perform for N1 or N2 lymph nodes?

Our meta-analysis included 3 case-control studies, according to the inclusion criteria. Our results showed that there are no significant differences in rates of metastases of all lymph nodes including N1 and N2 lymph nodes in patients with either Pure-GGO or Mixed-GGO (OR=3.66, 95% CI: 0.68-19.58). From these results, we generally concluded that surgeons can use the same surgical procedures to treat Pure-GGO and Mixed-GGO without dissecting all lymph nodes, including N1 and N2. If analysis of the rates of metastases for N1 and N2 lymph nodes for each type of GGO was not per-

formed, some evidences would be neglected. For this reason, we separately analysed the metastatic rates of N1 hilar lymph nodes and N2 mediastinal lymph nodes. Our results showed that there are no significant differences in rates of metastases of N1 hilar lymph nodes in patients with either Pure-GGO or Mixed-GGO (OR=4.22, 95% CI: 0.77-23.19). However, the study by Hattori et al. (REF) in 2012 showed an OR=20.18 (95% CI: 0.94-432.12), indicating that the metastatic rates of N1 hilar lymph nodes in patients with a Mixed-GGO are probably greater than with Pure-GGO. However, because this study only made up 12.3% of the total, it cannot have a defining effect on the final results. Despite this, the study warned us that surgeons must pay more attention to the metastasis of hilar lymph nodes in patients with Mixed-GGO. For patients with Mix-GGO, surgeons should dissect the hilar lymph nodes as clearly as possible when metastasis in N1 lymph nodes is suspected. On the other hand, we found that there were no significant differences in metastatic rates of N2 mediastinal lymph nodes in patients with either Pure-GGO or Mixed-GGO (OR=1.43, 95% CI: 0.19-6.32). The value of OR was always low in these three studies, so we concluded that surgeons do not need to completely dissect N2 mediastinal lymph node in all patients with GGO.

Conclusions

The results of our meta-analysis indicated that there was no statistically significant difference in metastatic rates of N1 hilar lymph nodes and N2 mediastinal lymph nodes in patients with either Pure-GGO or Mixed-GGO. However, as thoracic surgeons, we should still be concerned about metastasis of N1 hilar lymph nodes in patients with Mixed-GGO to ensure the possibility of missing metastases in lymph nodes is as low as possible.

Disclosure of conflict of interest

None.

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