

对混合性毛玻璃样结节和单纯性毛玻璃样结节的临床 I 期非小细胞肺癌患者进行淋巴结转移率比较的 Meta 分析

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[摘要] 目的:比较单纯性毛玻璃样结节(pure ground-glass opacity, Pure-GGO)和混合性毛玻璃样结节(mixed ground-glass opacity, Mixed-GGO)的临床 I 期非小细胞肺癌患者肺门淋巴结与纵隔淋巴结的转移率,用以指导清扫毛玻璃样结节(ground-glass opacity, GGO)患者淋巴结的手术方式。方法:使用主要数据库(Science Direct、PubMed、Springer Link 和 Wiley Online Library),收集临床 I 期非小细胞肺癌 Pure-GGO 和 Mixed-GGO 患者的相关病例对照研究,对已出版的文献进行系统综述;使用 STATA 12.0 从已出版的文献中提取数据进行 Meta 分析。Meta 分析的结果用优势比(OR)及其相应的 95% 置信区间(CI)表示。结果:从 3 篇病例对照研究包括总计 736 例患者中提取数据。进行比较后发现,两组患者在总淋巴结转移率上没有显著性差异(OR=3.66, 95% CI: 0.68~19.58, $P=0.13$),在肺门淋巴结转移率上也没有显著性差异(OR=4.22, 95% CI: 0.77~23.19, $P=0.10$),但是有研究 OR 高达 20.18(95% CI: 0.94~432.12)。两组患者的纵隔淋巴结转移率没有显著差异(OR=1.10, 95% CI: 0.19~6.32, $P=0.92$)。结论:虽然结果显示两组患者在肺门淋巴结和纵隔淋巴结的转移率方面没有统计学差异,但是仍不能排除 Mixed-GGO 患者的肺门淋巴结转移情况。

[关键词] 单纯性 GGO;混合性 GGO;淋巴结转移率;Meta 分析

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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: Meta-analysis

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[Abstract] **Objective:** This systematic review and Meta-analysis aimed to investigate the metastatic rate of hilar lymph node and mediastinal lymph node in clinical stage I non-small-cell lung cancer patients with either pure ground-glass opacity (Pure-GGO) or mixed ground-glass opacity (Mixed-GGO), therefore 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 was no significant difference (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 hilar lymph nodes in patients with either Pure-GGO or Mixed-GGO, but one study showed an OR of 20.18 (95% CI: 0.94-432.12). There was no significant difference in rates of metastases of mediastinal lymph nodes in patients with either Pure-GGO or Mixed-GGO (OR=1.10; 95% CI: 0.19-6.32, $P=0.92$). **Conclusion:** The results indicated no statistically significant difference in metastatic rates of hilar lymph nodes and mediastinal lymph nodes in patients with either Pure-GGO or Mixed-GGO. However, as thoracic surgeon, we must be particularly cautious about metastasis in hilar lymph nodes in patients with Mixed-GGO.

[Key words] Pure-GGO; Mixed-GGO; metastatic rate of lymph nodes; Meta analysis

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肺癌在世界范围内的发病率逐年攀升,同时也是男性和女性癌症死亡的主要原因^[1]。近年来,随着医学影像学的迅速发展,使用CT对早期肺癌进行筛查已经在全世界范围内达成了共识,例如低剂量螺旋CT(low dose helical computed tomography)、高分辨率CT(high resolution computed tomography)等^[2-5,34]。这些技术的广泛应用,使得早期肺癌患者,特别是毛玻璃样结节(ground-glass opacity, GGO)患者的检出率迅速增多^[6-8]。单纯性GGO(pure ground-glass opacity, Pure-GGO)是指肿块的毛玻璃阴影不掩盖其下方的血管及肺结构,无任何实性成分。而混合性GGO(mixed ground-glass opacity, Mixed-GGO)是指肿块的毛玻璃阴影掩盖下方的肺结构,同时包含了毛玻璃样阴影和实性成分^[9-11]。通过CT扫描发现的GGO如果怀疑为早期肺癌,通常可以通过外科手术治疗^[12-17]。大部分胸外科的共识是,对Pure-GGO患者进行手术治疗后,患者的术后生存率及预后良好^[18-21]。然而一些包括Mixed-GGO患者在内的临床I期肺癌患者中发现了区域淋巴结如肺门(N1)和纵隔淋巴结(N2)的转移^[22-26]。

对于不同类型GGO患者,外科医生是否必须进行淋巴结清扫,以及如何选择淋巴结清扫方式都存在很多争议。如果需要清扫,相同的淋巴结清扫方式是否可以适用于Pure-GGO和Mixed-GGO患者。在肺癌根治术过程中的淋巴结清扫主要是对最有可能转移的肺门淋巴结和纵隔淋巴结进行切除,如果对于GGO患者使用与肺癌根治术相同的淋巴结清扫方式显然是不适宜的。

所以需要系统综述和Meta分析来解决这些问题,提供更有力的依据,以选择适合方式对Pure-GGO和Mixed-GGO患者进行淋巴结清扫。因此本研究对来自现有病例对照研究的数据进行了Meta分析,来比较Pure-GGO和Mixed-GGO的临床I期非小细胞肺癌患者的淋巴结转移率。

1 资料和方法

1.1 资料

依据系统综述和Meta分析指南(the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA)开展本次系统综述和Meta分析^[27]。通过检索以下数据库来选择和确定已发表的文献: Science Direct、PubMed、Springer Link 和 Wiley Online Library。检索时间范围从数据库开始投入使用时间至2016年2月。使用以下主题词检索式进行

查找:((((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)。本次检索仅限于英文文献。还查阅了所有检索文献的参考文献列表,以查找任何可能相关的文章。所有检索文献和许多可能相关的文章都经过仔细阅读,包括作者姓名和发表时间,以避免数据重复。

1.2 方法

1.2.1 选择标准

被选择纳入本次Meta分析的文献基于以下几个标准:①采用病例对照的方法研究Pure-GGO和Mixed-GGO早期肺癌患者的手术方式和淋巴结清扫情况;②每个病例对照研究中都将患者分为Pure-GGO和Mixed-GGO两组进行研究;③对Pure-GGO和Mixed-GGO没有进行过任何术前治疗;④每个患者都进行了N1组和N2组的淋巴结清扫;⑤限于英文文献。文献数据排除标准如下:①仅研究Pure-GGO或Mixed-GGO患者;②患者未进行过手术或淋巴结清扫;③综述或病例报告;④没有原始数据的文章、综述和病例报道;⑤文献中没有对Pure-GGO和Mixed-GGO患者的临床数据进行单独分析;⑥研究缺乏对照组,并且没有得到相关结果。

1.2.2 数据提取和质量评估

由2位研究员根据筛选程序独立选取符合条件的研究报告,并提取数据。所有数据均来自3个符合条件的病例对照研究^[28-30]。当2个研究员最初意见不统一时,通过讨论最终达成共识以解决问题。根据筛选程序,提取的数据包括几个必要要求:第一作者或研究小组的名字,文章发表期刊,出版年份,研究所属的国家,患者数量,手术方式,N1和N2组淋巴结清扫(lymph node dissection, LND)以及出现N1和N2淋巴结转移的患者数量。当数据在论文中丢失或不清楚时,研究员通过邮件或电子邮件联系相应作者来获取必要信息。若两次联系后该作者均未回复,则排除该篇论文。

1.3 统计学方法

应用Review Manager 5.3和STATA 12.0对研究进行统计分析。Meta分析的结果用优势比(odds ratio, OR)及其相应的95%CI表示。所有统计学评估都是双向的,并且显著性水平规定为 $P \leq 0.05$ 。如果研究之间存在统计学同质性($P > 0.05, I^2 < 50%$),则采用固定效应模型进行合并分析。如果研究之间存在统计学异质性($P \leq 0.05, I^2 > 50%$),则采用

随机效应模型进行分析。应用Egger法和Begg漏斗图评估发表性偏倚。

2 结果

2.1 检索结果和实验特点

通过对数据库的检索发现共有374项相关研究。其中372项研究通过数据库检索获得,2项通过阅读参考文献获得。在排除了219项重复研究后,确定了共155项研究。通过阅读标题和摘要,排除了132项研究,其中包括36项病例报告,8项综述,41项与GGO无明显相关性的研究,47项与本研究无明显相关的研究,总共剩余23项研究进入下一轮审查。在阅读了这些文章的全文后,共20项研究由于未达到选择标准被排除。图1参照PRISMA指南,显示了整个排除和纳入文献的流程。最终3项研究总计736例患者纳入最终的Meta分析^[28-30]。

2.2 两组淋巴结转移率的比较

这三篇文章同时将Pure-GGO和Mixed-GGO患者分为两组研究,并得出相应结果。我们分析了Pure-GGO和Mixed-GGO患者的总淋巴结转移率,包括N1和N2淋巴结。这三项研究同质性检验的结果显示 $P=0.96, I^2=0\%$ 。应用固定效应模型分析显示OR为3.66(95%CI:0.68~19.58),虽然OR值>1,但是Pure-GGO和Mixed-GGO患者的总淋巴结转移率差异无统计学意义($P=0.13$,图2)。

2.3 两组患者的N1淋巴结转移率

分析Pure-GGO和Mixed-GGO患者的N1肺门淋巴结转移率,这三项研究的同质性检验结果显示 $P=0.44, I^2=0\%$ 。应用固定效应模型分析显示OR为4.22(95%CI:0.77~23.19)。同样,尽管N1肺门淋巴结转移率在两组患者中差异无统计学意义($P=0.10$,图3),但是发现在Hattori等^[29]2012年研究中得出的OR值高达为20.18(95%CI:0.94~432.12),证明Mixed-GGO患者的N1肺门淋巴结转移率可能要高于Pure-GGO患者。然而这项研究的患者数量相对其他研究较少,

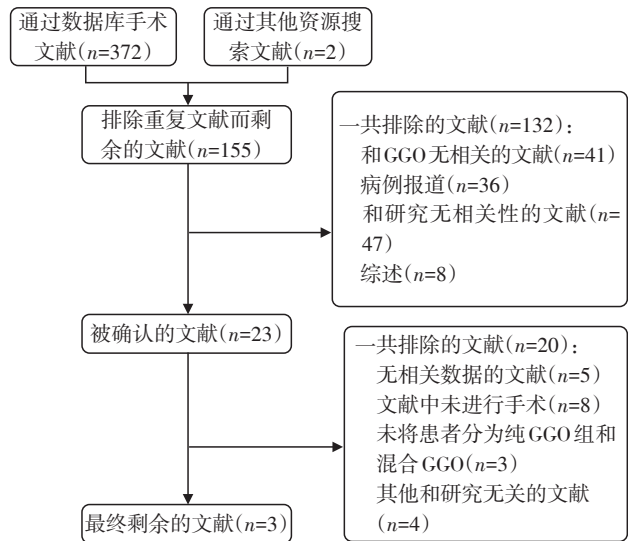


图1 选择文献的流程

Figure 1 Flow diagram showing the process for selecting articles

所以在整个Meta分析中的权重只有12.3%。

2.4 两组患者的N2淋巴结转移率

分析Pure-GGO和Mixed-GGO患者的N2纵隔淋巴结转移率,3项研究的同质性检验结果显示 $P=0.88, I^2=0\%$ 。应用固定效应模型分析显示OR为1.10(95%CI:0.19~6.32),OR值较小,但证明了两组N2纵隔淋巴结转移率差异无统计学意义($P=0.92$,图4)。

2.5 发表偏倚

应用Begg漏斗图以及Egger法来评估Pure-GGO和Mixed-GGO患者总淋巴结转移率的发表偏倚(图5)、N1淋巴结转移率的发表偏倚(图6)以及N2淋巴结转移率的发表偏倚(图7)。Meta分析的漏斗图形状并没有存在明显不对称。Egger法则在统计学上证明了漏斗图形状对称。总的来说,结果没有显示任何明显的发表偏倚($P > 0.05$)。

3 讨论

随着CT扫描技术的快速发展,早期肺癌如

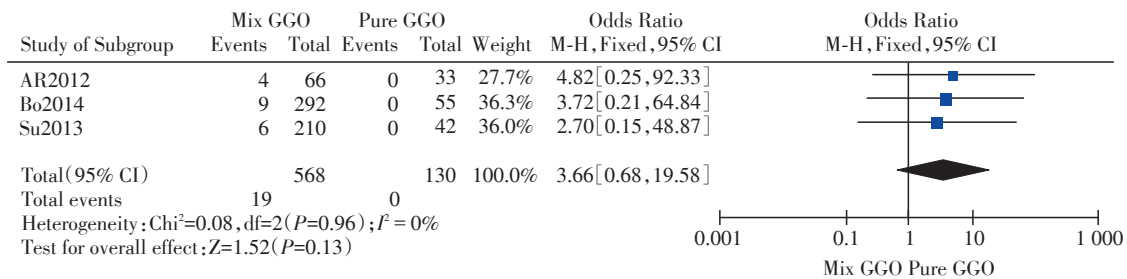


图2 关于Mixed-GGO和Pure-GGO的全部淋巴结转移率的对比

Figure 2 Forest plot of metastatic rates of all lymph nodes for the Mixed-GGO vs. Pure-GGO groups

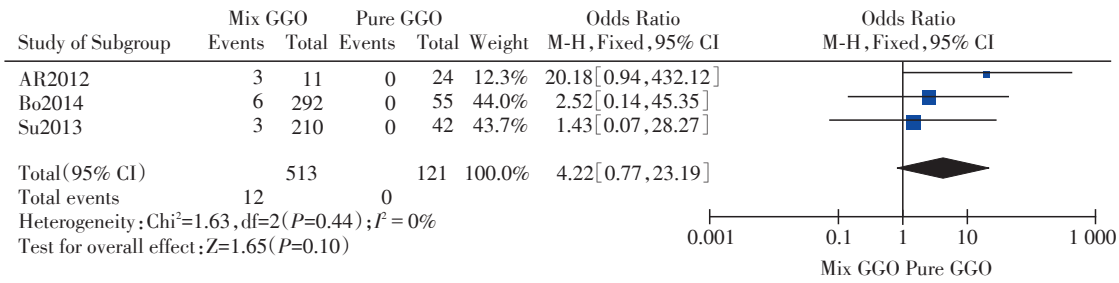


图3 关于Mixed-GGO和Pure-GGO的N1肺门淋巴结转移率的对比

Figure 3 Forest plot of metastatic rates of N1 hilar lymph nodes for the Mixed-GGO vs. Pure-GGO groups

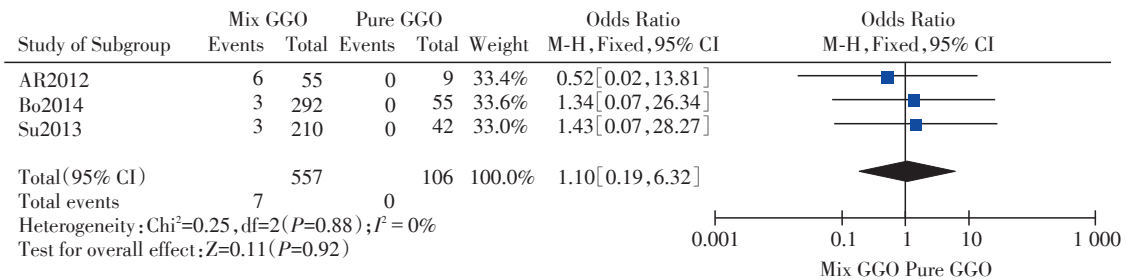


图4 关于Mixed-GGO和Pure-GGO的N2纵隔淋巴结转移率的对比

Figure 4 Forest plot of metastatic rates of N2 mediastinal lymph nodes for the Mixed-GGO vs. Pure-GGO groups

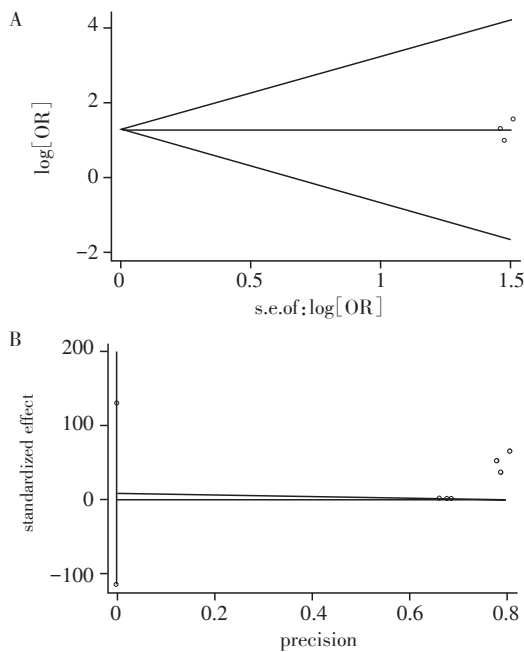


图5 Begg's (A)和Egger's (B)图显示全部淋巴结转移率对比的发表偏倚

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

GGO的检出率在日常临床实践中不断增高^[4,31]。由于GGO通常是指早期肺癌如原位腺癌或微浸润腺癌,大多数胸外科医生认为这些患者发生淋巴结转移的可能性很低。随着对GGO研究的进一步深入,

根据实性成分不同,分为Pure-GGO和Mixed-GGO。一些研究者证实在Pure-GGO患者中淋巴结转移发生极低。虽然小于1 cm的肿瘤,包括GGO,常常被认为并非通过淋巴和脉管系统转移,但是在这些早期病变中就已经出现了淋巴结转移^[19]。

外科医生对于不同类型的GGO患者是否必须进行淋巴结清扫以及如何选择淋巴结清扫的方式上依然存在许多争论^[32]。许多研究者坚信对于Pure-GGO患者是不需要清扫淋巴结的。但不清扫淋巴结的方式是否适用于Mixed-GGO患者。此外,如果确实需要清扫淋巴结,清扫范围如何,是清扫N1组、N2组,还是N1和N2组同时清扫需要明确。

根据纳入标准,本Meta分析包括3个病例对照研究。可见目前这方面的临床研究还处于起步阶段,不过许多学者已经开始重视此方向的深入研究。本研究结果显示Pure-GGO和Mixed-GGO患者包括N1和N2淋巴结在内的所有淋巴结的转移率差异并无统计学意义(OR=3.66, 95% CI: 0.68~19.58)。根据这些结果,外科医生可以通过相同的手术方式来治疗Pure-GGO和Mixed-GGO,即无须清扫所有淋巴结,包括N1和N2。如果没有对每种类型GGO的N1和N2淋巴结转移率进行分别分析,一些证据也许就会被忽视。因此,本研究分别分析了N1肺门淋巴结和N2纵隔淋巴结的转移率。结果显示Pure-GGO和Mixed-GGO患者的N1肺门淋巴结转移率差异无统计学意义(OR=4.22, 95% CI: 0.77~23.19),但

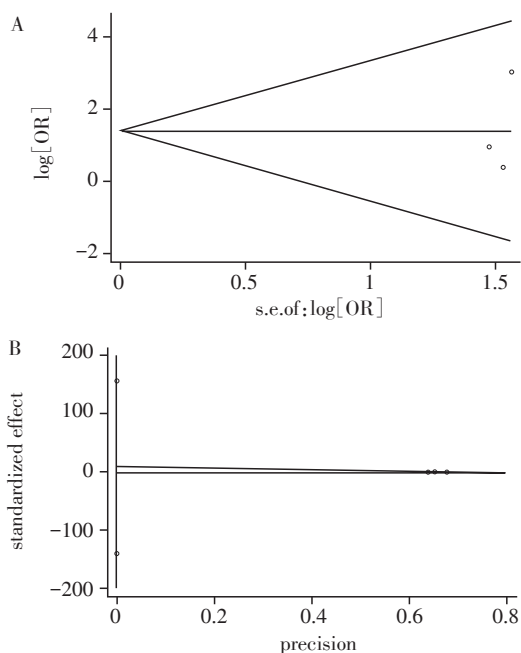


图6 Begg's(A)和Egger's(B)图显示N1肺门淋巴结转移率对比的发表偏倚

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

是,Hattori等^[29]研究表明Mixed-GGO患者的N1肺门淋巴结转移率很可能明显高于Pure-GGO患者。但是由于这个研究在Meta分析中的权重仅为12.3%,不能对最终结果起决定作用。尽管如此,这个研究仍然提醒必须更加注意Mixed-GGO患者肺门淋巴结的转移情况。对于Mixed-GGO患者,当怀疑N1肺门淋巴结有转移时,应该尽可能清扫N1组肺门淋巴结。另外,本研究发现Pure-GGO和Mixed-GGO患者的N2纵隔淋巴结转移率差异无统计学意义(OR=1.10,95% CI:0.19~6.32)。这3个研究中OR值都非常低,所以本研究认为对于所有GGO患者,不需要对N2纵隔淋巴结进行清扫。

本研究表明,Pure-GGO和Mixed-GGO患者包括N1和N2淋巴结在内的所有淋巴结的转移率并无显著统计学差异。但是作为胸外科医生,仍然应该关注Mixed-GGO患者的N1肺门淋巴结转移情况,以确保尽可能少地遗漏转移淋巴结。

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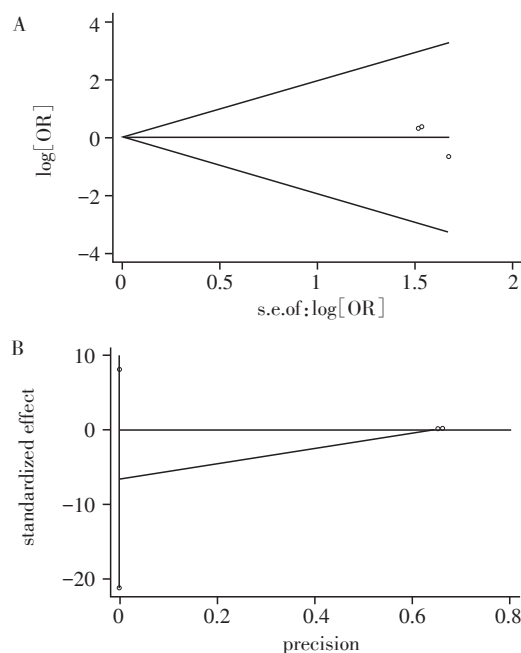


图7 Begg's(A)和Egger's(B)图显示N2纵隔淋巴结转移率对比的发表偏倚

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

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