Is it really necessary to perform mediastinal lymphadenectomy in surgery for ground glass opacity-featured lung adenocarcinoma?

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Abstract: An increasing number of lung ground-glass opacity (GGO) are detected along with the popularity of low-dose computed tomography (LDCT) screening. Despite the excellent prognosis of GGO-featured lung cancers, systematic lymphadenectomy is still recommended for all resectable lesions. Much effort has been made to determine the conditions surrounding a limited resection for subsolid nodules. However, the necessity to perform systematic lymphadenectomy in radiologic GGO-featured lung adenocarcinomas (LUADs) remains controversial. Pure GGOs were reported had a 100% 5-year survival rate with no lymphatic metastasis, and the lymphatic metastasis rate in part-solid nodules (PSNs), especially in GGO-predominant PSNs, was significantly lower than that in pure solid nodules. The impact of lymphadenectomy on the prognosis and the specific predictors for lymphatic metastasis in PSNs are also discussed. Systematic lymphadenectomy was not yet proved to confer a survival benefit in patients with GGO-featured lung cancers. Integration of pre-/intra-operative information such as tumor size, consolidation tumor ratio (CTR) and pathological information is warrant for solid-predominant PSNs. Pre-invasive lesions rarely occurred lymph node metastasis and intraoperative frozen section (FS) results might provide pathological information before lymphadenectomy strategy determination. Finally, although randomized controlled trials are difficult to conduct in LUAD manifesting as GGO, more prospective studies are required to justify the indication of systematic lymphadenectomy.

Keywords: Ground-glass opacity (GGO); systematic lymphadenectomy; lymphatic metastasis rate; necessity

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Introduction

Lung cancer is the leading cause of cancer death worldwide (1). Low-dose computed tomography (LDCT) screening for lung cancer is being implemented in China and the United States and is under consideration in many other countries (2-4). Along with the popularity of LDCT screening, an increasing number of lung ground-glass opacity (GGO) lesions are detected. Pure-GGO and part-solid nodules (PSNs) present different degrees of malignancy from those of pure-solid tumors, since even a

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small proportion of GGO components is associated with a favorable prognosis (5).

Surgery is the main treatment for early-stage non-small cell lung cancer (NSCLC) (6) using a standard procedure of lobectomy or pneumonectomy with systematic lymph node dissection (SND) (7,8). Although major randomized trials have not demonstrated that SND confers a survival benefit (9-12), the current guidelines still recommend SND for all resectable NSCLC irrespective of the stage, location and GGO component of the tumor. Several studies have reported that unlike radiologic pure-solid tumor without any GGO component, the estimated rate of lymph node metastasis in part-solid lung adenocarcinoma (LUAD) is approximately less than 5% (13-15). Moreover, animal model experiments even demonstrated lymphadenectomy altered endogenous antitumor mechanisms and accelerates the growth of tumor (16). The necessity to perform systematic lymphadenectomy in radiologic GGO-featured LUADs still remains controversial. In this review, therefore, we discuss this issue from aspects concerning prognosis, lymph node metastasis rates, corresponding predictive factors and random clinical trials (RCTs) of SND in radiological GGO-featured lung cancers.

Prognosis and resection strategy

It is well known that GGO presence is associated with excellent survival in LUAD (17-21). Hattori *et al.* (20) demonstrated the 5-year overall survival (OS) among clinical stage IA LUAD was 91.2% for GGO and 68.9% for solid nodules. Similarly, Miyoshi *et al.* (18) reported that the survival rate of the patients having a GGO nodule was significantly higher than that without GGO components. Fu *et al.* (22) further separated GGO lesions and reported the 5-year recurrence-free survival (RFS) for patients with pure GGO, part-solid, and solid nodules among invasive stage I NSCLC was 100%, 87.6%, and 73.2%, respectively. Under such circumstance, whether to perform lobectomy for GGO-featured NSCLC remains controversial. Appropriate determination of the extent of lung excision and lymph node dissection (LND) is important, and there has been much effort to determine the conditions surrounding a limited resection for a subsolid adenocarcinoma. Studies have demonstrated that limited resection for GGOs smaller than 20 mm have similar results to those obtained with standard lobectomy (23,24) while lobectomy is indicated for GGOs with over 25% of the solid component. National Comprehensive Cancer Network (NCCN) guidelines (25) recommend that limited resection is appropriate for peripheral GGO lesions with size ≤2 cm and ≥50% ground-glass appearance, which mainly based on several recent RCTs. The Japan Clinical Oncology Group (JCOG 0201) (26) defined GGO with size ≤3 cm and consolidation tumor ratio (CTR) ≤0.5 as "radiological noninvasive", and the 5-year OS of this "noninvasive" group was 96.7%. Another JCOG0804 (27) investigated the application of sublobar resection in peripheral GGO lesions with size ≤2 cm and CTR ≤0.25 and reported the 5-year RFS was 99.7%. However, there is still no consensus on the most appropriate surgical treatment for GGO with CTR >0.5 and two RCTs (JCOG 0802 in Japan and CALGB 140503 in the United States) are undergoing.

The lymph node metastasis rate in GGO

Similar to the discussion of resection, the introduction of a subsolid LUAD fueled a debate about the necessity of SND. SND has been considered as an important factor in radical surgical resection for lung cancer patients. However, it is not always necessary. Proponents emphasize that it is more accurate with the respect to staging, than the limited LND. Gajra *et al.* (28) reported that SND increased chance of survival of the patient by removing the occult N2 disease. Darling *et al.* (10) conducted a RCT comparing complete mediastinal LND with lymph node sampling and the former identified occult N2 disease in 4% of patients, although it did not improve survival compared with lymph node sampling. Conversely, opponents of SND have asserted that it could potentially result in more adverse events, such as bleeding, chylothorax, or longer hospitalization.

Nevertheless, we have to know the exact rate of nodal involvement in subsolid LUAD before determining the proper LND strategy. Yoshida *et al.* (29) first reported that in patients with lung carcinoma smaller than 1 cm, only 1% of part-solid LUAD had node metastasis. Ye *et al.* (30) demonstrated that pN1 was observed at 2% and pN2 at 1% in patients with clinical stage 1A, part-solid lung cancer. It is noteworthy that the entire cohorts in these two studies performed SND testing, which made the conclusions more meaningful. Our group (13) also reported that among clinical stage IA LUAD, no patients with pure GGOs had lymphatic metastasis, and the lymphatic metastasis rate in PSNs (7/312, 2.2%) was significantly lower than that in pure solid nodules (41/152, 27.0%). A summary of studies regarding lymph node metastasis rate of patients with lung cancer presenting as GGO was shown in *Table 1*. In addition

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Table 1 Summary of studies regarding lymph node metastasis of patients with lung cancer presenting as ground-glass opacity

First author, year	No. of patients	Staging	Lymph node metastasis rate	
			Pure GGOs	PSNs
Ye, 2014	651 (pGGOs: 55, PSNs: 292, solid nodules: 304)	Clinical stage IA	0%	2% of pN1and 1% of pN2
Hattori, 2017	497 (PSNs with 0.5≤ CTR <1: 177, solid nodules: 320)	Clinical stage IA	NA	2% of pN1and 2% of pN2
Hattori, 2018	634 (PSNs: 356, solid nodules: 278)	Clinical stage IA	NA	2.8%
Ye, 2019	988 (pGGOs: 501, PSNs: 329, solid nodules: 158)	Clinical stage IA	0%	2.2%
Tsutani, 2014	239 [pGGO and PSNs (0< CTR <0.5)]	Clinical stage IA	0.8%	
Hattori, 2017	1,029 (nodules containing GGO: 503, solid nodules: 526)	Clinical stage I	1% of pN1and 1% of pN2	
Zhang, 2019	2,749 (pGGOs and PSNs: 581, solid: 2,168)	Pathological stage I–III	There was no lymph node metastasis in PSNs with CTR ≤0.5	

GGO, ground-glass opacity; PSN, part-solid nodule; pGGO, pure ground-glass opacity; CTR, consolidation tumor ratio.

to lymph node metastasis, the impact of lymphadenectomy on the prognosis of patients with GGO-featured lung cancers was also analyzed in several studies. Moon *et al.* (31) retrospectively reviewed 358 patients with clinical stage IA NSCLC and found that in GGO-predominant patients, the 5-year RFS rate among no mediastinal lymph node evaluation (NoMLE) group, mediastinal lymph node sampling (MLS) group, and mediastinal lymph node dissection (MLND) group showed no difference. Hattori *et al.* (32) reviewed 462 patients with radiological part-solid LUAD and found the extent of lymphadenectomy was not associated with survival outcomes after propensity score matching. Based on the above findings, SND may be unnecessary for pure GGO-featured lung cancer as well as some with PSNs.

The necessity of SND in PSNs

To further determine the necessity of SND, as well as develop a standardized guideline for LND in part-solid lung cancer, a model based on pre-/intra-operative information, such as tumor size, CTR and intraoperative frozen section (FS) pathology, is warrant. Okada *et al.* (33) revealed that adenocarcinoma with high SUVmax and low GGO ratio is more closely associated with LN metastasis. However, measuring SUVmax value greatly affected by measurement methods, which may provide no advantage in predicting LN metastasis. As aforementioned, Hattori *et al.* (32) also showed that none of part-solid LUAD with CTR ≤0.5 had a LN metastasis. Similarly, Zhang *et al.* (34) revealed there was no LN metastasis in 151 patients with invasive part-solid LUAD with CTR ≤0.5. Among them, the tumor size of six patients even exceeded 3cm. Our previous studies have indicated that tumor histology such as atypical adenomatous hyperplasia (AAH)/adenocarcinoma in situ (AIS)/minimally invasive adenocarcinoma (MIA) might be able to guide lymphadenectomy (35,36), since pre-invasive lesions rarely occurred LN metastasis and FS might provide pathological information before lymphadenectomy strategy determination. For cases diagnosed as AAH/AIS/MIA by FS intra-operatively, SND might not be necessary. Nevertheless, whether FS could be an efficient method to diagnose invasive degree of lung cancers and to guide final lymphadenectomy strategy mostly depends on the discrimination accuracy. Liu *et al.* (37) showed the accuracy of FS to distinguish AAH/AIS/MIA from invasive adenocarcinoma was 96%. Moreover, patients undergoing limited resection of invasive LUAD misdiagnosed as AAH/AIS/MIA by FS analysis showed excellent prognoses (38). Sublobar resection without lymphadenectomy was consequently conducted for patients with AAH/AIS/MIA and the 5-year RFS turned out to be 100% (37). In this regard, there is the possibility of setting up the prediction model for the pathologic LN status and effectively guide lymphadenectomy strategy for PSNs.

RCTs for GGO

Nevertheless, considering the excellent survival of GGO-featured lung cancer, RCTs regarding LND strategies require excessive sample size and follow-up time. It may be very difficult or even impossible to conduct such RCTs. There is an ongoing prospective observational clinical trial validating the selective LND strategy based on radiologic

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and pathologic features in Fudan University Shanghai Cancer Center (FUSCC) (NCT03216551) (39). All enrolled patients are still performed systematic mediastinal LND, and the accuracy of mediastinal lymph node metastasis determination by selective mediastinal LND strategy is then analyzed. Specifically, CTR ≤0.5 is one of the conditions for predicting no mediastinal lymph node metastasis, which indicated the systematic lymphadenectomy might be unnecessary. Another prospective observational study using paraffin pathological whole sections to determine the correlation between ground glass components and pathological subtypes is also ongoing in FUSCC, which may provide extra pathological information for lymph node status prediction preoperatively.

Conclusions

Whether systematic lymphadenectomy should be used in GGO-featured lung cancers depends on numerous clinical-pathological variables. SND may be unnecessary for GGO-predominant lesions and especially for pure GGO nodules. However, the necessity of systematic lymphadenectomy in solid-predominant nodules and corresponding predictors for lymph node status remains controversial. Given the difficulty to conduct such RCTs in LUAD manifesting as GGO, RCTs may not be necessary to determine the optimal lymphadenectomy strategy. Nevertheless, the necessity to perform systematic lymphadenectomy, no matter in GGO- or solid-predominant lung cancers, requires more prospective studies to justify the indication.

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