Managing screening-detected subsolid nodules—the Asian perspective

Masaaki Sato¹*, Shun-Mao Yang¹,²#, Dong Tian¹,³,⁴, Nakajima Jun¹, Jang-Ming Lee⁵

¹Department of Thoracic Surgery, University of Tokyo Hospital, Tokyo, Japan; ²Department of Thoracic Surgery, National Taiwan University Hospital, Hsin-Chu Branch, Hsinchu; ³Department of Thoracic Surgery, Affiliated Hospital of North Sichuan Medical College, Nanchong, China; ⁴Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu, China; ⁵Department of Thoracic Surgery, National Taiwan University Hospital, Taipei

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*These authors contributed equally to this work and are first co-authors.

Correspondence to: Jang-Ming Lee, MD, PhD. Department of Surgery, National Taiwan University Hospital, No. 7, Chung Shan South Road, 100, Taipei. Email: jangminglee@gmail.com.

Abstract: The broad application of low-dose computed tomography (CT) screening has resulted in the detection of many small pulmonary nodules. In Asia, a large number of these detected nodules with a radiological ground glass pattern are reported as lung adenocarcinomas or premalignant lesions, especially among female non-smokers. In this review article, we discuss controversial issues and conditions involving these subsolid pulmonary nodules that we often face in Asia, including a lack or insufficiency of current guidelines; the roles of preoperative biopsy and imaging; the location of lesions; appropriate selection of localization techniques; the roles of dissection and sampling of frozen sections and lymph nodes; multifocal lesions; and the roles of non-surgical treatment modalities. For these complex issues, we have tried to present up-to-date evidence and our own opinions regarding the management of subsolid nodules. It is our hope that this article helps surgeons and physicians to manage the complex issues involving ground glass nodules (GGNs) in a balanced manner in their daily practice and provokes further discussion towards better guidelines and/or algorithms.

Keywords: Lung cancer screening; subsolid nodules; sublobar resection; localization

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Introduction

The widely adopted use of computed tomography (CT) for lung cancer screening has led to detection of large numbers of pulmonary nodules that require further evaluation and management. Among the detected nodules, those with a radiological ground glass pattern are classified as subsolid or ground glass nodules (GGNs), which include both non-solid nodules (pure GGNs) and part-solid nodules (mixed GGNs). In Asia, many GGNs are detected by screening that is either specifically targeted to find them or done for other medical purposes, particularly among female non-smokers and those with a family history of lung cancer (1,2). Because of their reportedly high probability of being lung adenocarcinoma or premalignant lesions (3), detected GGNs tend to be directly referred to thoracic surgeons for surgical evaluation. Although the growth of GGNs is generally slow or even indolent, some grow rapidly during follow-up (4), which often makes it challenging to make a decision regarding the management of these nodules (5-7).

To facilitate a more concrete discussion, we present three typical clinical case scenarios that highlight particularly...
important issues: a small pure GGN the resection of which is strongly desired by the patient against the guidelines; a centrally located GGN; and multifocal GGNs.

**Clinical scenarios**

**Case 1**

A 50-year-old male banker received an industry-provided health examination. A subcentimeter peripheral GGN was found in the right upper lobe (RUL) on chest CT (*Figure 1A*), and it remained stable on the follow-up CT 6 months later. Continuous long-term follow-up until the lesion size increased or a solid component emerged was initially recommended; however, the patient insisted on receiving surgical resection after considering the risk of minimally invasive surgery and the impact of pulmonary functional loss after a simple wedge resection, although the size and the growth pattern of the GGN did not yet meet the criteria to mandate resection. The patient received thoracoscopic wedge resection 7 months after detection, and the pathology reported minimally invasive adenocarcinoma. The cost of surgery and hospitalization was totally covered by the national health insurance system.

**Case 2**

A 35-year-old female office worker who worked in a hospital received the annual health-examination in her workplace. A 1 cm centrally located GGN was found in the RUL (*Figure 1B*), and the GGN became heterogeneous during the 2 years of imaging follow-up. However, she hesitated to undergo lobectomy directly without tissue diagnosis of the lesion, and she instead went to another hospital to receive semi-anatomical segmentectomy under the guidance of lesion localization with a fiducial marker (microcoil). The pathology report indicated minimally invasive adenocarcinoma and the resection margin was sufficient.

**Case 3**

A 58-year-old female, who had retired from work, received low-dose CT screening in a medical center. Four small lung nodules were detected bilaterally and the doctor suggested follow-up with low-dose CT. However, she visited several hospitals for second opinions during the 1-year follow-up period. She received a positron emission tomography (PET) scan in one of the hospitals, and it showed three nodules with higher standardized uptake value (SUV) and no evidence of nodal metastasis. She finally underwent thoracoscopic RUL anterior segmentectomy for the RUL lesion (*Figure 2A*), and one month later, thoracoscopic left upper lobe (LUL) wedge resection for another peripheral LUL lesion (*Figure 2B*) with apical trisegmentectomy for the central LUL lesion (*Figure 2C*). The pathology report indicated primary lung adenocarcinomas for all the three lesions, and the lymph nodes from both sides were all negative. A chest X-ray taken 3 months after surgery is shown in *Figure 2D*. Her functional status remained excellent during the 2 years of follow-up after surgery.
Challenges of guidelines

There may or may not be clinical guidelines on the management of pulmonary nodules in Asian countries and where guidelines are provided, they vary widely. There are national society guidelines in Japan (8), Korea (9) and China, and in other countries healthcare practitioners optionally refer to individual institutional standards or to western guidelines. To provide common guidelines for practitioners throughout Asia, consensus-based expert recommendations were used to produce a set of consensus guidelines by adapting the guidelines of the American College of Chest Physicians (CHEST) (1). However, the above guidelines do not seem to be utilized commonly in practice, and most clinicians tend to manage those detected nodules according to their own experience in the interpretation of CT images and the personality of individual patients, even in countries with national society guidelines. Ideally, every patient should be discussed at a multidisciplinary team meeting (MDT) to determine optimal diagnostic and therapeutic strategy. In general, the guidelines may often not be utilized for several reasons: (I) national health insurance covers the medical expenses of all treatments for screened nodules, including those outside the regulations of the existing guidelines, causing ultimate clinical decisions to be readily affected by either the physician’s experience or sometimes the patient’s own will. (II) In Asia, many institutes have in actuality adopted the concept of shared decision making (SDM) with patients in the management of screened nodules, although this is not formally documented. SDM has, in fact, been adopted in many western medical systems for lung cancer screening (10-12), including in ongoing randomized trials (13). Because of anxiety, some patients prefer to have the small GGNs removed as long as there is some probability of malignancy. The cost and radiation exposure involved in long-term monitoring of GGNs is another cause of concern leading to premature removal. (III) Many specialists with different backgrounds, including pulmonology, radiology, thoracic surgery, and family medicine, are involved in the management of small GGNs. However, different specialists and their associated medical societies might not adopt other

Figure 2 A 58-year-old female with bilateral multifocal subsolid nodules treated with sequential sublobar resections for the suspicious nodules (arrows), which all proved to be primary lung cancers. (A) RUL lesion treated with anterior segmentectomy; (B) LUL peripheral lesion treated with simple wedge resection; (C) another LUL central lesion treated with apical trisegmentectomy; (D) chest X-ray taken 3 months after surgery. LUL, left upper lobe.
society’s guidelines, or guidelines may not exist in their own society.

Role of preoperative biopsies and imaging work-ups

Increased experience in managing small GGNs has led to a great decline in the importance of preoperative biopsy. Although nonsurgical biopsy still remains the standard diagnostic option for a suspicious nodule, many thoracic surgeons prefer direct surgical resection for diagnosis and treatment. The main reason in support of this practice is a better understanding of the correlation between CT characteristics and histopathological findings (14-16), which has prompted surgical removal of these small GGNs on the basis of radiological diagnosis. Although a high specificity (0.94; 95% CI, 0.84–0.98) and sensitivity (0.92; 95% CI, 0.88–0.95) of percutaneous CT-guided biopsy for GGNs has been reported in meta-analyses (17,18), the diagnostic accuracy of small-sized (<1 cm) GGNs with a lower percentage of ground glass component tended to be lower, which made thoracic surgeons reluctant to perform preoperative biopsy for these small-sized GGNs. Additionally, the risk of complications, such as pneumothorax, hemoptysis and air embolism, is also a reason against biopsy. Compared with percutaneous CT-guided biopsy, the complication rate of transbronchial biopsy is relatively lower, but the reported diagnostic rate is also lower than CT-guided biopsy in general (19-21). However, a negative biopsy still does not totally preclude the possibility of malignancy. Thoracic surgeons may feel the necessity of preoperative biopsy for centrally located lesions in which pulmonary lobectomy is required for resection of the lesion, and tissue diagnosis might be needed to justify such a major surgical procedure.

When treating lung cancers, complete staging with a brain and whole-body imaging workup is considered mandatory in current clinical practice (22,23). An imaging workup using brain MRI in combination with whole body PET/CT scan is the first choice to detect possible distant metastasis of lung cancer. However, to save cost and time, a brain CT and whole-body bone scan is an optional alternative in some institutes, although this combination is less sensitive in detecting metastasis. On the basis of wanting a complete imaging workup for lung cancer, most countries in Asia adopt the more sensitive imaging policy for suspicious GGNs before undertaking surgery. However, the value of routine imaging workups for the GGNs is still questionable and sometimes considered unnecessary (24) because there is very little chance of distant metastasis, especially for pure GGNs (25). Interestingly, sometimes incidental findings on these PET/CT scans include second primary cancers of other organs, but this might not be able to justify the routine use of such advanced imaging modalities. In our opinion, it is quite reasonable to adopt these stringent preoperative imaging workups for the part-solid GGNs, which are considered relatively invasive with higher probability of nodal involvement compared with pure GGNs; however, the debate on differentiating benign and malignant GGNs with PET scans goes beyond the discussion of complete staging before surgery (26,27).

Location of GGNs: what really matters

The current guidelines for GGN management mainly focus on the size, solidity, and growth rate of the nodules (1,8,9). However, the location of the nodules, which is less mentioned in the guidelines, is critical in decision making in real clinical practice. Because the technical difficulty and the loss of lung tissue for acquiring adequate resection margins varies depending on the location of small GGNs, clinicians should always think of the potential risks and benefits for individual patients, especially when the benefit of surgical resection for small GGNs remains controversial. For example, when treating a small peripheral pure GGN such as the one shown in Figure 1A, a simple wedge resection by thoracoscopic surgery would be an easy decision because of the low technical demand for a surgeon and also minimal loss of lung tissue for the patient. However, if a similar lesion is located centrally as shown in Figure 1B, the decision would be more difficult, especially for elderly patients with limited function and/or limited expected prognosis. Indeed, some thoracic surgeons tend to continue observation of such central lesions until pulmonary lobectomy is strongly indicated. Alternatively, if sublobar resection is attempted, there should be enough confidence of success in complete resection with adequate margin for the target lesion. For the resection of central lesions, obtaining sufficient resection margins with a direct wedge resection appears challenging. Conventional anatomical segmentectomy is also sometimes inadequate because the lesion is located too close to an adjacent segment or even between two segments, which necessitates various types of segmentectomy to secure the resection margins—including extended segmentectomy, semi-anatomical segmentectomy, or combined subsegmentectomy—and the determination
of the appropriate resection plane between segments or subsegments is critical (28).

**Localization: beyond what we think for sublobar resection**

For surgical management of small subsolid nodules, preoperative localization is important when performing sublobar lung resection. In addition to localization of the targeted tumor, acquisition of sufficient resection margins is critical to prevent local recurrence (29-31). The conventional marking strategy is to place a single marker on the lung surface, which is effective especially when the target lesion is located near the surface. Most CT-guided percutaneous localization utilizes a single surface marking strategy, and this is probably the most commonly used localization method; however, with this method there is still concern about localization-related complications (32,33) including pneumothorax, pulmonary hemorrhage and most importantly air embolism, which is rare but critical (34-36). Because of the above concerns, the authors prefer to use a transbronchial localization method, which has been demonstrated to be relatively safe with no reported fatal complications. Transbronchial localization can be guided by virtual bronchoscopy software (37), an electromagnetic bronchoscopy system (38,39) and a cone-beam CT with augmented fluoroscopy (40,41). Additionally, multiple surface markings can be made easily with the transbronchial approach. Compared with conventional point-directed single-dimensional localization, multiple surface markings, which can be referred to as “lung mapping,” can provide two-dimensional geometric information for better control of the resection border, and the system of virtual-assisted lung mapping (VAL-MAP) has already been widely adopt and covered by public health insurance in Japan as one of the main approaches to localize small GGNs (42). However, for some deeply-seated GGNs, even two-dimensional localization might not guarantee sufficient resection margins at greater depths (43), and the concept of three-dimensional localization or mapping with centrally placed fiducial markers has been raised for acquiring adequate deep margins in a standardized and reproducible manner. Therefore, a next-generation lung mapping system (VAL-MAP 2.0) has been developed (44), and a phase III prospective trial is also in progress to evaluate the effectiveness of small-nodule resections with optimal resection margins (45). Because the new technologies and modalities for localization will continue to progress, surgeons in different institutions should choose a suitable method, based on the facilities they can use, while balancing efficacy, safety, and cost. The priorities for adopting new localization technology should be the reproducibility of surgery and the acquisition of resection margins.

**Intra-operative frozen section: when is it needed?**

Varoli et al. (46) reported their surgical experience [1991–2006] of performing resections of 370 solitary pulmonary nodules without preoperative diagnosis. Frozen sections were performed on all the 276 wedge resections with nodules included, while the other patients received lobectomy directly because of the difficulty of wedge resection. When the frozen pathology showed primary lung cancer, the procedure was converted to lobectomy in the same session. In the modern era of numerous small nodules, frozen sections are still routinely performed in many centers. However, now that lobectomy as the standard final procedure for lung cancer has been greatly replaced by sublobar resection, the practice of routinely performing frozen sections on indeterminate lung nodules has raised some questions. Regarding the role of intraoperative frozen section, the possibility of having to alter the final surgical plan was the only reason to justify this urgent examination. In the following situations, frozen section analysis could be necessary for intraoperative decision making: (I) when a further planned resection—lobectomy, segmentectomy, or additional wedge—would need to be completed if malignancy is confirmed; (II) to evaluate the existence of a high-grade invasive component, which might also change the resection plan, although the validity of such a decision remains controversial (47,48); (III) to confirm that the target lesion was successfully resected when success cannot be judged by gross examination, especially for small GGNs; (IV) when the surgical procedure would be extended to lymphadenectomy if malignancy of the lesion is confirmed. In the current practice, most surgical procedures are decided prior to surgery according to the findings of CT images, although many current series still report that frozen section is routinely performed without changing the subsequent surgical procedures. The critical point in real clinical practice is: should the diagnosis be made right after the surgery, even when there is no chance of changing the surgical plan? If the answer is negative, it may be preferable to save the specimen for a permanent section, which could provide more comprehensive pathological evaluation of the
Mediastinal lymph node (MLN) dissection, sampling, or omitting assessment?

Lymph node staging was long considered mandatory for lung cancer, and surgical exploration of MLN nodes was usually performed as a standard procedure of lung cancer surgery. However, more thoracic surgeons are now adopting a less aggressive manner of MLN dissection when doing surgery for part-solid nodules because of the rarity of lymph node metastasis (50). Also, there is still risk of complications, including hoarseness, chylothorax, and injury to adjacent structures (51,52). For a pure GGN, although there is still up to a 40% probability of the final diagnosis being invasive adenocarcinoma (53), most current literature has reported negative nodal involvement (50,54,55) even when the lesion size exceeds 3 cm (56). Moon et al. (57) reported 358 cases of clinical nodal negative (N0) GGNs (<3 cm in size), which received either MLN dissection, MLN sampling or no MLN assessment. In 129 GGNs with consolidation/tumor (C/T) ratio <0.5, only one case had intralobar (N1) nodal metastasis. For the other 229 GGNs with C/T ratio >0.5, twenty-five cases had nodal upstaging after resection. Among such consolidation-dominant GGNs, although the 5-year recurrence free survival was comparable in patients receiving MLN sampling and MLN dissection, the recurrence free survival was significantly poorer in the group where MLN assessment was omitted. In another cohort with cT1N0 peripheral lung cancers undergoing lobectomy and MLN dissection, nodal upstaging was observed among nodules with C/T ratio >0.61 or size >1.3 cm (58). Aside from lymph node sampling, selective or lobar-specific lymph node dissection has also been reported as an effective alternative to systemic dissection (59-61). In our current opinion, for pure-GGNs, omitting MLN assessment is a reasonable option. For part-solid GGNs, MLN sampling or selective MLN dissection could be an alternative to systemic MLN dissection; however, there is still no consensus on this issue.

Management of multifocal subsolid nodules

Among patients with screened nodules, there are many who present with synchronous multifocal subsolid nodules, which are considered to be separate primary lesions instead of intrapulmonary metastasis (62). The patient shown in Figure 2 is a typical example. In current series of surgically managed early stage lung cancers, similar multifocal lesions have been found in up to 5–20% of all patients (63–66). Although the long-term survival of these patients is usually favorable, management of these multifocal lesions with different characteristics, sizes and locations is challenging due to the lack of consensus or established algorithms, which results in clinical judgement being almost totally dependent on the surgeons’ own experience. To exclude the possibility of extrapulmonary and nodal metastasis, PET/CT is the recommended examination for multiple lung lesions according to the National Comprehensive Cancer Network (NCCN) guidelines (67). Additionally, the 18F-fluorodeoxyglucose (FDG) uptake in PET scans provides information associated with the aggressiveness of each lesion (68–71), indicating the priority of surgical intervention, although it is considered less useful to perform PET scans for multifocal pure GGNs (66). In current practice, according to recent reports, the most common strategy is to prioritize treatment of the dominant lesion, defined by its size and radiological invasiveness, because it is considered to have the most effect on patient survival (64), and any residual GGNs with the risk of progression should not rule out the resection of the dominant lesion (72). Neither the growth nor the need for subsequent intervention for residual GGNs, influenced patient survival (72), strongly suggesting that these multifocal lesions should be treated in a separate, sequential manner with staged interventions during close, long-term observation (73). At the planning of such staged interventions, laterality of lesions should also be taken into consideration. For example, if the prioritized lesion accompanies a small pure GGN on the same side and it could be easily resected, concurrent resection is an option rather than waiting for a third operation (which would likely be accompanied by pleural and possibly hilar adhesions) following the second surgery on the other side for the second-dominant lesion. In the authors’ opinion, preserving the patient’s lung function and quality of life after surgery is most important. In addition to image surveillance for non-dominant lesions, comprehensive preoperative planning for each patient that includes precise localization, a lung-preserving surgical strategy, anatomy of the remaining lung, and estimation of residual lung function (74) is necessary to keep the balance between the resection of suspicious nodules and the preservation of the patient’s lung function.

Nonsurgical management of subsolid nodules

If patients are not amenable to surgery or if surgical
Resection seems unjustified in terms of the balance among functional loss, invasiveness, and radicality, non-surgical treatments such as stereotactic body radiotherapy (SBRT) and other local ablation therapies can be adopted as alternatives with curative intent for suspicious nodules. Particularly in the case of multifocal GGNs, combining surgery with such nonsurgical management is also a viable option. A major drawback of this approach is that in many cases the pathological diagnosis cannot be made without biopsy.

**SBRT**

SBRT typically involves delivery of a steep dose gradient beyond the small target while simultaneously avoiding the surrounding normal tissue. This technique relies on technological advances in image-guided radiation therapy to visualize the tumor both before and during treatment delivery, as well as to monitor respiratory motion (75). Currently, the NCCN and the European Society for Medical Oncology (ESMO) guidelines consider SBRT as the first-line non-surgical treatment option for medically inoperable patients with stage I non-small cell lung cancer (NSCLC). Population-based analyses (76,77) have demonstrated an improvement in overall survival following the introduction of SBRT in clinical practice for elderly patients with stage I NSCLC, and large retrospective observational studies have also confirmed the promising results of SBRT (78-80). Several research groups conducted phase I-II trials of SBRT for inoperable early-stage NSCLC, with 2–3-year local control (LC) rates and 1–3-year overall survival rates ranging between 84–98% and 43–72%, respectively (81). The role of SBRT for medically operable patients is yet to be determined and concerns remain about the risk of local or nodal recurrence after SBRT. Several population-based and retrospective analyses suggested that overall survival and disease-specific survival are similar compared to surgery (82-87); however, a recent phase II trial reported that the pathological complete response rate of early stage lung cancer after SBRT was only 60%, which was lower than expected (88). Although SBRT toxicity is generally mild, the risk of skin and rib toxicity when treating peripheral tumors and the risk of severe complications when treating central tumors are still issues of concern, and the optimal fractionation scheme for safe and effective SBRT delivery is under evaluation. The need for accurate nodal staging and pathological information is still challenging, and difficulties remain in the interpretation of radiological findings after SBRT, which appear similar in regard to local relapse and radiation-induced changes (75).

**Radiofrequency ablation (RFA)**

RFA is a common technique for the ablation of solid organs and also a relatively new treatment option for medically inoperable primary lung cancer. Advantages of RFA compared to surgery include treatment in an outpatient setting and the use of local anesthesia before placement of the ablation probe via CT guidance. Limitations of RFA include: (I) lesions greater than 3 cm in diameter are not recommended for RFA due to poor LC. (II) A heat sink effect occurs when tumors are located in close proximity to large vessels (>3 mm), reducing the energy delivered to the target through convection within the circulatory system. (III) Location is critical as a result of the risk of damage to adjacent structures, such as the esophagus and trachea (89,90). Several studies have examined the results of RFA as definitive therapy for early stage NSCLC (91-93). However, RFA has generally been associated with inferior LC compared to surgery and SBRT, with a 3-year LC rate of approximately 80% to 95% (94). Trials that are designed to evaluate RFA use in high-risk patients, such as ACOSOG Z4033, will help determine the indications for its use.

**Microwave ablation (MWA)**

MWA has theoretical advantages over RFA in treatment of the lung because microwaves are less prone to the heat sink effect and able to penetrate deeper into low-conductivity tissue such as lung parenchyma (95). Current applications of MWA in pulmonary lesions mostly involve metastatic lesions, and reported LC rates are comparable with SBRT without major adverse events (96-98). Interestingly, cancer-specific mortality is reportedly not significantly affected by tumor size larger than 3 cm, which may attribute to increased intratumoral temperatures with a larger ablation zone in MWA compared to RFA (94). However, limited data are available to support the use of MWA in the treatment of suspicious subsolid nodules.

**Conclusions**

Because of their high probability of being lung cancer, surgical resection of screening-detected subsolid nodules is the common practice in Asia. As clinical judgement is largely affected by the physician’s experience and the
patient’s own will, the current treatment guidelines might frequently not be followed. However, guidelines continue to evolve and may more closely match actual clinical practice in the near future. With a better understanding of the oncological characteristics of these subsolid nodules, including patterns of disease progression, surgery will be performed in the manner of early intervention, reducing the need for whole-body scans. Such surgical intervention is likely to comprise a less extensive lymph node exploration and limited resection with increased lung preservation. To ensure the adequacy of performing sublobar resection with sufficient safety margins, precise localization plays an essential role, not only for the lesion itself, but also for the resection borders and deep margins. We believe it is most important for thoracic surgeons to keep a balance between surgical and oncological achievement and preservation of the patient’s lung function and quality of life after surgery. This is especially true for the management of multifocal nodules.

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