Review Article on Lung Cancer Screening

Should sublobar resection be offered for screening-detected lung nodules?

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Abstract: The increasing use of low-dose CT for screening for lung cancer will inevitably identify many small, asymptomatic lung nodules and ground-glass opacities (GGOs). Current guidelines for the management of screening-detected lesions tend to advise a conservative approach based on serial imaging and intervention only if 'suspicious' features emerge. However, more recent developments in thoracic surgery and in the understanding of the screening-detected lesions themselves prompt some pertinent questions over this conservatism. Is CT surveillance sufficiently reliable to exclude malignancy? Is it really necessary to hold back on operative biopsy and resection given modern surgical safety and efficacy? Is the option for early surgical therapy a viable one—especially with the availability of sublobar resection today? Modern data suggests that the risk of inaction for some screening-detected lesions may be higher than expected, whereas the potential harm of surgical intervention may be substantially reduced by sublobar resection and the latest minimally invasive surgical techniques. A more pro-active approach towards offering surgery for screening-detected lesions should now be considered.

Keywords: Ground-glass opacity (GGO); lung cancer; screening; sublobar; video-assisted thoracic surgery (VATS)

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Lung cancer screening: the promise and the challenge

Despite the massive progress made with target therapy, immunotherapy and modern variations of radiotherapy, there is still only one realistic hope of cure for the vast majority of patients with lung cancer: surgical resection of early stage disease (1). Modern lung resection surgery—coupled with a complete lymph node dissection—is capable of yielding 5-year recurrence-free survival rates of over 80% for patients with stage I disease (2,3). However, the crucial factor for good survival is that the disease must be at an early stage, and it has for years been a challenge to diagnose lung cancer in its early stages because patients tend to be asymptomatic (4).

In recent years, low-dose computed tomography (LDCT) of the thorax has emerged as a viable tool for lung cancer screening in asymptomatic adults (5-9). LDCT has been proven in large randomized trials to both increase the rate of early stage detection of lung cancer and to reduce the mortality of this disease (5,8,9). More than any improvement in pharmaceutical or surgical therapy, this screening has the greatest current potential to save countless patients from dying of lung cancer.

The flip-side of the coin, some would argue, is that widespread use of LDCT screening will inevitably detect many small lung lesions that may mimic lung cancer but are actually benign (10,11). These small lesions include both solid nodules, and also ground-glass opacities (GGOs) defined as any hazy lung opacities on CT scan that do not obscure the underlying bronchial structures or pulmonary vessels (12,13). While many may be benign, a proportion actually do represent malignancy, and hence the clinician must decide on how to manage these screening-detected lesions to exclude cancer. This quandary may possibly result in 'over-diagnosis', 'over-investigation', and even 'over-treatment' (14-16). These rather sensationalist terms are frequently used to argue in favor of conservative

management, but the pragmatic consideration must be to weigh the costs of action versus the risks of inaction.

What do current guidelines say?

A number of guidelines have been published in recent years by authoritative bodies to help clinicians in managing screening-detected lung nodules and GGOs (17-22). This author has previously reviewed these in a previous article (11). It is noted that essentially all current guidelines for LDCT detected lesions share some common features:

(I) The initial management is invariably further imaging;
(II) The type of and interval until that further imaging depends solely on the number, size and solidity of the lesion(s) seen on the initial CT/LDCT;
(III) On follow-up imaging, further investigation is recommended only if a lesion is unchanged or growing in size and is deemed 'suspicious' for malignancy radiologically;
(IV) That further investigation may consist of further follow-up imaging, non-surgical biopsy or 'surgical excision'. The guidelines generally do not suggest any preference of any one of these over the others;
(V) No specific advice is given regarding what 'surgical excision' should entail.

Overall, the current guidelines therefore favor a very conservative approach. The first instinct should be for watchful waiting and offering as little intervention as possible. Even when intervention is required, there appears to be a general reluctance to recommend surgery outright. This is reasonable given that these guidelines were constructed based on clinical data showing that the majority of these small screening-detected lesions tend to be benign (19-22).

However, as this author has pointed out in the previous review, the clinical data on which these guidelines are based were reported from a number of years ago (11). Since then, much progress has been made in thoracic surgery that is pertinent to the management of such small screening-detected nodules and GGOs. These include newer minimally invasive surgical approaches and sublobar resections (23-25), which promise to reduce the morbidity from the surgery. Greater understanding of the natural history of these screening-detected lesions are also revealing that a more nuanced approach may be required in different populations around the world (26,27). The risk of malignancy may actually be greater than previously estimated in some parts of the world (27,28). In other words, the costs of action are reducing while the risks of inaction may be higher than expected. In view of this, three important questions have emerged for clinicians to seriously contemplate.

"Why are we just relying on imaging for initial management?"

The guidelines recommend follow-up imaging—usually CT—as initial management in most cases of screening-detected lung lesions. This is based on two assumptions: (I) that the initially detected lesions are most likely benign; and (II) that follow-up LDCT or CT can safely identify which lesions are 'suspicious' for malignancy that warrant further investigation. The first assumption is based on previously published data from multiple studies (usually retrospective) that suggest that 10% to 43% of screening-detected lung lesions are 'false positives' (22,29). In the well-known National Lung Screening Trial (NLST), the false positive rate with LDCT was reported to be 23.5%, with these mostly due to intrapulmonary benign lymph nodes and non-calcified granulomas (5). Even amongst the lung cancers found in the NLST, it was estimated that 18% were indolent tumors and were hence cases of 'over-diagnosis' (30). The second assumption is that on follow-up CT, some lesions may disappear while those that are stable or growing have higher risk of being malignant (12,19,22).

The problem with these assumptions is that CT differentiation between benign and malignant lesions is never fully reliable. Multiple studies have confirmed that CT alone can never exclude malignancy with absolute accuracy (11,19,20,22). In one study on the use of CT to estimate the presence of invasive cancer in small adenocarcinoma lesions of more than 5 mm, a sensitivity of 78% and specificity of 58% was reported (31). In 2016, Hattori and colleagues further demonstrated that the use of size and solidity to determine prognosis—as favored by the guidelines—is invalid for all lesions other than the completely solid ones (32). More alarmingly, a study by Lee and colleagues looked at the use of CT features to distinguish invasive and pre-invasive pathologies in GGOs, and found that even experienced radiologists could not consistently reach an agreement on whether any particular lesion was malignant or not (33). External validation of prediction models based on CT find that these generally offer area under the receiver operating characteristic curve values of 0.73 to 0.90 (34). These findings all suggest that by relying on imaging follow-up only based on initial CT findings, there will always be a possibility of missing some truly malignant

tumors. The same concerns also hold true for the use of follow-up imaging alone. In the guidelines issued by the British Thoracic Society (BTS), the authors themselves acknowledge that there is "*no growth rate threshold beneath which, nor duration of radiological stability beyond which, malignancy is definitely excluded*" (20).

Another emerging concern is that the risk of malignancy in screening-detected lung nodules may not be as low as assumed. Studies from North America suggest that the risk of malignancy in such nodules may range from 3.7% to 23% (35,36). However, other studies from East Asia report that 53% to 75% of resected pulmonary nodules were malignant (37,38). This suggests that disease patterns may vary in different parts of the world, and that guidelines recommending a conservative approach may not be globally applicable. Adenocarcinoma, for example, may be especially prevalent in East Asia (2,3,27,28,37).

Clearly, the reassurance that initial and follow-up CT alone can absolutely preclude further investigation is a shaky if not false one. Even if the risk of malignancy on a screening-detected lesion is considered 'low', the cost of failure to investigate or intervene could be the progression of a malignant tumor to an advanced or incurable stage.

"Why are we avoiding surgery for diagnosis?"

The guidelines only recommend investigation of screening-detected lung nodules or GGOs when they persist or grow on follow-up imaging. However, regarding the nature of this investigation, the guidelines are non-specific and non-committal. The options include further CT surveillance, non-surgical biopsy, or 'surgical excision' (17-22).

The limitations of further CT surveillance have been discussed above. Regarding non-surgical biopsy, today there are a number of techniques available. These include conventional bronchoscopy, percutaneous imaging-guided biopsy, and different systems of navigation bronchoscopy (39,40). Conventional bronchoscopy—even with fluoroscopy-guidance—has a sensitivity for identifying malignant nodules of 5% to 76% (41,42), with the figure for benign diagnosis even lower. Newer techniques of endobronchial ultrasound (EBUS), electromagnetic navigation bronchoscopy (ENB), and virtual bronchoscopy navigation (VBN) are said to give similar or higher diagnostic yields (39,40). However, the accumulated volume of experience with these is still not huge, and the probability that publication bias exists skewing reports towards the positive side cannot be ruled out. Ultimately, most screening-detected lesions tend to be away from central airways, and hence a percutaneous approach if favored (19). It has been estimated that the sensitivity of CT-guided transthoracic needle biopsy (TTNB) for identifying malignancy in lung nodules was 90% or greater (19,41). However, the frequency of non-diagnostic results with TTNB has been reported to be as high as 55% (19,41). For GGOs 2 cm or smaller, the sensitivity of TTNB has been reported to be only 50–51% (43,44). At the same time, 33% of patients receiving TTNB may experience a pneumothorax, with over a third of those requiring a chest drain insertion (43). Even the bronchoscopic techniques may incur a pneumothorax risk of 1.6% to 7.5% (19,39,41).

Despite the imperfect diagnostic yields and the definite risk of minor complications, the guidelines still rank these non-surgical biopsy modalities on an equal footing with surgical excision. For example, the American College of Chest Physicians (ACCP) guidelines note that surgery is "the gold standard for diagnosis", and warn of the "imperfect sensitivity and limited negative predictive value" of TTNB (19). However, it still does not recommend surgery over non-surgical methods due to considerations of 'surgical risk'. Indeed, the ACCP lists one condition for surgery as "when nonsurgical biopsy is suspicious for malignancy" (19), clearly placing surgery behind non-surgical biopsy. The concerns about surgery are based on the evidence reviewed by the ACCP, which suggest a nonfatal complications rate of about 5% for diagnostic wedge resection using video-assisted thoracic surgery (VATS) (45,46). Should surgery progress to a lobectomy, the ACCP quoted North American databases showing a mortality rate of 2% to 3.4% (47,48). In the review for the BTS guidelines, an inpatient mortality rate of 0.4% was noted for wedge resection/segmentectomy in the UK, rising to a 90-day mortality of 4.2% (20,49). In writing their lung cancer screening guidelines, the National Comprehensive Cancer Network (NCCN) considered that the average mortality rate for major lung surgery in the USA was 5%, and the risk of serious complications was over 20% (22,50). Given these figures, it is understandable that the current guidelines are reluctant to give stronger recommendations for surgery.

However, the reality is that thoracic surgery has progressed significantly in recent years. The actual 30-day mortality rate from major lung cancer surgery is now only 0.48% in Japan (51). In ultra-high-volume centers (UHVCs) now emerging in China, the peri-operative mortality of thoracic surgery is now less than 0.1% (52,53). Mortality and significant morbidity from lesser wedge resections

are almost non-existent amongst normal-risk patients nowadays. On top of this, minimally invasive thoracic surgery has evolved beyond conventional VATS and robot-assisted thoracic surgery (RATS) (23). Modern approaches such as uniportal VATS have become established which promise even less morbidity than ever before (25,54). These techniques can be coupled with modern strategies of enhanced recovery after surgery (ERAS) to further improve patient outcomes post-operative (55-57). Altogether, these advances mean that surgery can be performed with morbidity rates that are significantly lower than those considered by the guidelines, and which are not much more than what can be expected from non-surgical biopsy (58).

In return, surgery gives a much higher diagnostic yield than non-surgical biopsy (59). If a wedge resection is performed, the specificity should in theory be 100%. More importantly, surgical biopsy can be performed with intra-operative frozen section (60). This can give a diagnostic accuracy of up to 97% for small peripheral invasive adenocarcinoma. The importance of this is that if such malignant pathology exists, the surgeon can proceed immediately in the same operation to a curative resection. This significantly reduces the interval between initial presentation and final treatment for each patient, which in turn may potentially improve survival (61). It is therefore disappointing that current guidelines do not even mention the feasibility of combining diagnosis and therapy using surgery in this way for screening-detected lesions.

"Why are we giving up on the golden opportunity for surgical treatment?"

That surgery can provide both diagnosis and treatment are worthy of further consideration. Screening-detected lung nodules and GGOs tend to be small (5-8). In the NLST, 40% of the cancers found by CT were stage IA (5). In the European NELSON trial of lung cancer screening, that figure is closer to 50% (8). The significance of these observations is that many screening-detected lung lesions are therefore amenable to sublobar resection.

For many years, sublobar resection was almost taboo for lung cancer therapy. This largely was a result of the Lung Cancer Study Group's randomized trial in 1995 which concluded that sublobar resection resulted in significantly worse survival and a higher local recurrence rate than lobectomy for T1N0 lung cancer (62). However, oncologic outcomes with sublobar resection have substantially improved since then, and modern results show no difference in survival compared to lobectomy for tumors at 2 cm diameter or smaller (63). The keys to good outcomes have also been well delineated now: (I) stage IA disease with a tumor diameter of 2 cm or smaller; (II) a higher consolidation: tumor ratio on CT for GGO; (III) achieving a wide resection margin (at least 1 cm or more); and (IV) adequate nodal dissection (24). In addition, anatomical segmentectomy tends to give better survival than wedge resection—perhaps because of the greater resection margins usually obtained with the former (64). Because screening detected lung nodules and GGOs frequently all these criteria for good survival, they are ideal for sublobar resection with curative intent. Indeed, the rate of performing segmentectomy has seen a marked increase in recent years, particularly in East Asia (52,53).

The advantage of sublobar resection is of course that minimizing the lung volume resected should in turn minimize the harm and morbidity caused to the patient. A good volume of evidence has been published demonstrating that compared to lobectomy a sublobar resection can better preserve lung function (in terms of spirometry results, pulmonary gas exchange, anaerobic threshold, and so on), and also reduce post-operative morbidity (62,65-67). This is especially important in elderly and frail patients who may not tolerate a lobectomy (68,69). The ACCP recommends that in considering surgery for lung cancer: "*In patients with major increased risk or perioperative mortality… (due to age related or other co-morbidities), an anatomic sublobar resection (segmentectomy) over a lobectomy is suggested.*" (1). In normal risk patients, 'elective' sublobar resection can also be considered (24). As discussed above, current clinical evidence confirms that in well-selected patients, elective sublobar resection does not compromise oncological outcomes compared to lobectomy. At the time of this writing, large randomized trials comparing sublobar resection versus lobectomy for small lung cancers have been conducted in the USA and Japan respectively and their final findings are eagerly awaited (70,71). However, it is also expected that their conclusions are likely to only confirm what we already know: that elective sublobar resection is a viable alternative to lobectomy in those selected patients with small tumors. The value of the randomized trials may be in ushering elective sublobar resection into current guidelines in the same way as sublobar resection for high risk patients.

Of course, sublobar resection is not the only option available for the treatment of screening-detected nodules once they are diagnosed to be lung cancer. For patients

with these lesions, another choice would be advanced radiotherapy techniques including stereotactic body radiotherapy (SBRT) and the newer proton beam therapy (72-74). At first glance, the ability to effect potentially curative therapy using SBRT without making a single incision should be very attractive to patients. Reports from the radio-therapy literature point to promising treatment results for SBRT that compare favorably with surgery at 1-year follow-up (72,74). However, careful scrutiny of the current clinical evidence shows that sublobar resection remains a better option for several reasons. First, many patients receiving SBRT did not actually have a biopsy-confirmed cancer—and this would skew results towards better observed 'survival' (75). Second, if non-surgical biopsy is performed before the SBRT, then the morbidity from the biopsy (as discussed above) needs to be added to that of the SBRT (76), and the combined risk to the patient may not be less than that of surgery. Third, on follow-up for longer periods, multiple studies have confirmed that the survival following sublobar surgery is superior to that following SBRT in the medium- to long-term (77-80). Fourth, the assumption that SBRT causes less harm than sublobar surgery may be false. In an elegant study by Crabtree and colleagues, patients receiving SBRT, sublobar resection and radio-frequency ablation were compared (81). Despite patients in the sublobar group having significantly worse pre-treatment lung function, they did not experience more post-treatment adverse events than those in the other study arms. In this context, it would appear that for patients with screening-detected lung nodules, sublobar surgery offers potentially better diagnosis, better cure and no added morbidity compared to the alternative of SBRT with or without non-surgical biopsy.

A stitch in time saves nine

Reviewing the development of minimally invasive surgery (MIS) for lung cancer since the 1990s, Prof. Chen Haiquan of Shanghai has espoused the idea of "MIS 3.0" (28). It is clear that the first phase (MIS 1.0) was the reduction of surgical access trauma from open thoracotomy to VATS and its evolutions, such as uniportal VATS and RATS. In more recent years, a trend has emerged for reducing the extent of the resection itself (MIS 2.0) by offering effective sublobar resection to selected patients as discussed above. The next phase of this progression—MIS 3.0—would seek to minimize the overall harm of the disease and the surgery to the patient through better strategizing. This could be effected in a variety of ways, including streamlining surgery to reduce overall operating times or developing effective peri-operative management pathways (such as enhanced recovery after surgery programmes) (28,56,57).

In the context of screening-detected lung nodules and GGOs, this concept of MIS 3.0 could be applied to managing the patient over the course of his or her lifetime. According the current guidelines, any screening-detected lesion is followed up with repeated imaging, involving cost and radiation exposure to the patient repeatedly. Should any change or persistence be noted on follow-up, non-surgical biopsy may be performed which incurs a certain morbidity risk. Because of the inherent limitations in their diagnostic accuracy, such non-surgical biopsies may even have to be repeated, multiplying the risk of morbidity. At this time, if malignancy is ultimately confirmed, major resection—such as lobectomy—may have to be considered because of the interval progression of the lesion which prompted the biopsy. Generally, lobectomy for early stage lung cancer carries a mortality risk of 0.5–3.0%, and provides a 5-year survival of around 70–80% (20,22,74). During follow-up with imaging or investigation of a persistent/growing lesion, a small proportion of patients may even be found to have more advanced inoperable disease, or they may be found to be unsuitable for the required lobectomy—thereby losing any realistic chance at 'cure'.

The MIS 3.0 alternative would be to consider a more pro-active approach to screening-detected lung nodules and GGOs that steers away from the guidelines. At the individual level, certain screening-detected lesions may be higher risk for malignancy—for example, the risk of adenocarcinoma in younger, non-smoking females in East Asia is recognized to be higher (2,3,27,28). Pursuing an agenda of individualized care, if the cancer risk is deemed high and the operative risk low, it is not unreasonable to consider upfront surgery. VATS—perhaps uniportal VATS with pre-operative lesion localization—can be performed, removing the lesion very simply by sublobar resection. The lesion is analyzed by intra-operative frozen section, and surgical biopsy in this way has superior accuracy to any non-surgical modality. If the lesion is benign, the operation is concluded and the risk of intervention-related morbidity is nowadays very low (not necessarily higher than non-surgical biopsy). The patient is spared the mental stress and anxiety of carrying an indeterminate lung lesion for months or years, and the exposure to repeated imaging and investigations. If the lesion is found to be malignant, immediate surgical therapy can be given in the same operation. Because the

lesion is likely to be small at this time, many if not most cases may even be amenable to curative therapy by sublobar resection alone. The risk of mortality and morbidity is less than if a lobectomy were performed later when the lesion has progressed. More importantly, the disease is more likely to be in its earliest stage, and hence the survival is better after surgery. If the lesion is pre-malignant, the survival with a minimally invasive sublobar resection can reach virtually 100%. This contrasts with waiting until a lesion becomes larger, when the lobectomy is more traumatic and has lower chance of 'cure'.

The old saying '*a stitch in time saves nine*' may sound indecipherable to those who are not native English speakers. It basically means: if there is a tear in your dress then you can either repair it now with just one stitch, or wait until the tear becomes big—by which time you will need nine stitches to repair it. This is perhaps exactly the consideration that clinicians should make with screening-detected lung lesions.

Conclusions

As screening becomes more widely used, clinicians will face more and more screening-detected nodules being discovered. Current guidelines advocate a conservative approach, predicated on the assumptions that most lesions are benign and that intervention (surgery) carries high risks. However, there is emerging understanding that the risk of malignancy in screening-detected lesions may actually be higher than assumed, especially in certain parts of the world. Progress with surgery has also meant that the risk of morbidity is now very low—especially with modern MIS approaches and the availability of sublobar surgery. If the risk of inaction is higher than anticipated, and the cost of surgery is lower than ever before, it is time to consider whether a more pro-active strategy should now be considered.

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