Ground-glass opacities: a problem bound to get more challenging

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Comment on: Peng JZ, Bie ZX, Li YM, *et al.* Diagnostic performance and safety of percutaneous fine-needle aspiration immediately before microwave ablation for pulmonary ground-glass nodules. Quant Imaging Med Surg 2023;13:3852-61.

In the article, "Diagnostic performance and safety of percutaneous fine-needle aspiration immediately before microwave ablation for pulmonary ground-glass nodules", the authors address a novel approach to a traditionally challenging diagnostic entity, ground-glass nodules (GGNs) (1). Higher utilization and improved resolution of computed tomography (CT) imaging has led to an increase in the detection of pulmonary GGNs, which are nodules with varying degrees of malignant potential. Roughly 75% of GGNs are malignant, and, for these nodules, lobectomy remains the definitive treatment. For the remaining GGNs, however, especially those with characteristics on imaging that favor a premalignant or benign etiology (e.g., small size, absence of solid components), more conservative approaches may be undertaken. Segmentectomy and wedge resection, without lymph node resection, represent two such alternatives to lobectomy.

However, even when surgery is possible, the occult nature of these GGN is prohibitive for a targeted resection. Furthermore, patients may often be poor surgical candidates and hence would benefit from non-surgical techniques such as microwave ablation (MWA). It involves thermally destroying lesions under CT guidance and may offer an additional benefit for patients with multiple primary nodules distributed across different lobes, for whom surgical resection is less feasible. Ablative techniques however do not allow for histopathologic diagnoses, which are necessary with GGN as they may be malignant. As such, there is concomitant need for a biopsy-proven histologic diagnosis for which there are two options: a CT-guided fine needle aspiration (FNA) or core-needle biopsy (CNB).

CNB offers the advantage of procuring more adequate tissue specimens for histopathologic analysis than FNA, but it is also associated with higher rates of complications, including pneumothorax, hemorrhage, and hemoptysis. In the setting of MWA, CNBs prior to MWA can affect the vasculature of the GGN and compromise the ablative effect. Meanwhile, performing a post-ablation CNB runs the risk of having an inadequate sample. FNA has shown high diagnostic accuracy in providing a histologic diagnosis prior to MWA (2). Meanwhile, a study by Kiranantawat *et al.* established that CNB and FNA had a similar diagnostic accuracy in identifying GGN. This study however addresses the performance of these biopsies at the same time the MWA ablation is taking place. The purpose of which is to avoid having patients undergo multiple visits and the associated higher complication risk.

The authors conclude that the positive rates of FNA and CNB did not differ significantly and that sequential FNA and CNB showed better diagnostic performance than did

either alone when coupled to MWA. There were minor complications associated with both procedures. Previous studies have reported similar findings of improved efficacy with sequential FNA and CNB while others do not observe significant benefits over FNA or CNB alone (3). Physicians may need to consider the tradeoff between additional costs of sequential biopsies and potential improvements to diagnostic performance.

The were no significant differences in the baseline characteristics of patients who underwent FNA or CNB. The fact that they performed a subgroup analysis on whether the GGN is pure or part-solid or whether the lesion is greater than or smaller than 1.5 cm, and had no statically significant differences, shows that the diagnostic studies are agnostic to tumor composition and size which is consistent with other studies (2). However, this comparison is conducted by splitting patients into two groups based on proportion and size thresholds that they established. Instead, when categorizing patients into low, medium, and high groups, others find that diagnostic yields are better for larger lesions and GGNs with more solid components (4). Hence, there must be additional tumor or patient characteristics that contribute to the diagnostic yield. Performing a multivariate logistic regression do identify other potential contributors to the diagnostic yield might have provided a more granular understanding of the differences between this study and others. It might highlight other considerations that might be factored in when selecting patients for MWA and FNA or CNB.

This study is limited in several respects. Firstly, it is inherently limited in its design. The study is a retrospective cohort study, which predisposes it to potential selection bias. Secondly, it is a single-institution study that enrolled only 92 patients, which limits the study's power and generalizability. Other studies that looked at differences between CNB and FNA in establishing a histologic diagnosis found no statistically significant differences (5). However, these studies did not factor in MWA and only looked at the ability of the biopsy modalities to identify a nodule.

Thirdly, the study did not consider the use of Rapid On-Site Evaluations (ROSEs)—a practice that allows for specimens to be sent intraoperatively for real-time evaluation by cytopathologists to confirm adequate tissue procurement. Another concern is that using a smaller gauge needle in FNA will result in a lower sample adequacy rate (5). Although this has not shown to affect diagnostic efficacy, supplementing CT-guided FNA with ROSE

can compensate for potential shortcomings and improve sensitivity and specificity (6). This study also addresses pre-procedural FNA compared to post-procedural CNB or a combination of the two. Though addressed in the study, having an arm whereby CNB is done pre-procedurally or FNA done post-procedurally would have provided a more comprehensive picture of these procedures in yielding an accurate histologic diagnosis. Also, although low risk overall, the patients are ultimately getting 2 to 3 separate procedures. It would be interesting to compare the complication risk on a larger scale between those who undergo either FNA or CNB diagnosis compared to those who undergo both.

Finally, the study does not directly address the effects that the experience levels of the performing interventional radiologists may have had on the diagnostic yield.

Performing CNB prior to GGN ablation may induce hemorrhaging that can interfere with ablation accuracy. Peng *et al.* (6) recommend the use of percutaneous FNA as an alternative diagnostic method to CNB because of its low complication rate. Compared to studies using CNB pre-ablation, they find that the rates of pulmonary hemorrhage and pneumothorax immediately after biopsy are lower when using FNA (7). However, other studies report unclear or insignificant differences between the two techniques, indicating that center-specific factors may also influence post-biopsy complication rates (8). Patient characteristics might be a contributing factor. In light of that, a predictive model for the development of pneumothoraxes after CT-guided biopsy of the lung has been described (9). For instance, patients who have emphysematous disease are likely to experience a higher risk of pneumothoraxes. Given that the risk profile is different for MWA with biopsy compared to surgical resection, patient-specific risks should be factored in the decision-making process on what treatment modality to proceed with.

In conclusion, the manuscript addresses a novel approach to GGN that uses already existing technologies in a sequential combination. This methodology presents a way to target and eradicate occult GGN. While CT-guided localization is one way, it is not always feasible intraoperatively and can be quite labor intensive. We also presented all the associated risk of the CT-guided biopsies needed for MWA. Alternatively, using other localization techniques can be considered. One that has shown promise is intraoperative molecular imaging (IMI).

In IMI, patients receive a fluorescent contrast agent the day of or the day before surgeries. The contrast agent is tumor specific and is excited and detected by a near-infra

red (NIR) laser and camera respectively. That will guide the surgeon intraoperatively as the lesion will fluoresce and indicate the area of concern. The lesion is then evaluated on the back table for margin positivity. This modality has been externally validated for localizing occult disease, identifying synchronous lesions, and identifying positive margins (10). It has been shown to work with great success in identifying GGN. Prior to IMI, surgeons would have had to perform a more extensive procedure to assure that the lesion of interest has been located and resected. As a result, patients would unnecessarily lose normal parenchyma, which is a more serious concern when they have a more limited physiologic reserve. IMI altered the procedure from a more extensive lobar resection to a more targeted localized wedge resection. It also does not necessitate an additional invasive procedure and provides histologically intact moieties that can be assessed by the pathologist.

Indeed, each patient and surgeon are unique. Identifying the best combination of tools to assure that the disease in question is addressed with the minimum toll on normal parenchyma is the goal. The authors presented one possible way of addressing GGNs and identified a methodology that optimized yield and minimizes risk. However, we encourage a multidisciplinary approach that also integrates other options to localize disease such as IMI into the decision-making process on how to treat our patients best. Also, ideally a procedure specific risk stratification model can help calculate the predict risk from each procedure. Physicians can then select the treatment plan that minimizes risk while improving outcomes.

Acknowledgments

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Quantitative Imaging in Medicine and Surgery.* The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims. amegroups.com/article/view/10.21037/qims-23-797/coif). GTK has a grant from the National Insitite of Health (No. F32 CA254210). FA was supported by the training grant in Surgical Oncology by the National Institutes of Health (No. T32CA251063-01). The other authors have no conflicts of

interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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