



Seeking the holy grail of markers

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Comment on: Patella M, Bartolucci DA, Mongelli F, *et al.* Spiral wire localization of lung nodules: procedure effectiveness and oncological usefulness. *J Thorac Dis* 2019;11:5237-46.

Submitted Feb 29, 2020. Accepted for publication Apr 09, 2020.

doi: 10.21037/jtd.2020.04.56

View this article at: <http://dx.doi.org/10.21037/jtd.2020.04.56>

Because of increased indications for videothoroscopic (VATS) lung resection with different modalities (triportal, biportal, uniportal, subxiphoid approaches), the nodule localization has often become a challenge for surgeons. If in case of a superficial lesion, close to the pleura surface and solid the instrumental palpation instead of hand manipulation is usually easy, safe and helpful to completely remove it, the localization of a ground glass opacity (GGO) or a deep nodule may represent a huge problem to solve, in particular when a sublobar resection is planned. Although lobectomy is still the gold standard treatment for operable lung cancer, several experiences in the last ten years have given an important boost to perform limited resections as wedges and segmentectomies with curative intent in case of early stage lung cancers, GGOs, metastatic lesions or in patients with poor respiratory reserve. This extremely minimally invasive approach (VATS plus limited resection) poses two main difficulties: the correct localization of the nodule and its safe removal with wide free margins to avoid local recurrences.

Different ways have been attempted to overcome the first concern with contradictory results. Endofingers as tactile sensor and intraoperative ultrasound have been initially developed, but these methods were ineffective in case of GGOs due to air component similar to surrounding normal parenchyma and for lesions localized in depth (1,2). The placement of markers under CT scan guidance as hookwires shaped in different forms is the most preferred method; several types of products have been developed presenting different anchorage's systems, including the spiral wire proposed by Patella *et al.* (3-5), and all of these show advantages and some criticisms. The results showed by

Patella *et al.* (3) with the use of a spiral wire are encouraging in terms of feasibility, safety and stability during the patient transport towards operating room. As reported by authors, the particular shape of this marker is probably the key of their remarkable results. However, the gold standard marker should be easy to insert, stable during the transport after the insertion and during the surgical procedure, safe with a low complications rate and the technique should be easily reproducible worldwide. Actually none system seems to have all characteristics simultaneously, as also reported in the paper from Swiss experience that underlies how it is very important to have an high expertise on the procedure's planning and a technology adequate to perform it.

Also other types of markers as microcoils and dyes placed with fluoroscopy or fiberbronchoscopy with navigation systems require a dedicated instrumentation not always available (6,7); furthermore, many authors consider as a possible and desirable future scenario the use of hybrid operative theaters where to bring together in one place two moments: diagnostic and surgical (8). If this could reduce the operative time with a benefit for the patients, in other hand it should increase the healthy costs due to the technology required. Although an ideal system has been not still proposed, however the need to avoid larger incisions to detect small nodules and the impressive boost towards minimally invasive procedures enforce to develop new techniques and methods facilitating surgeons in the nodule localization.

The other relevant aspect is relative to the complete removal of the nodule with adequate free margins. Often also a correct localization with markers or other methods is not sufficient to assure an oncological complete resection, since the nodule's morphology as in case of a GGO with

a larger spread could be a limitation. To overcome this problem, a novel technique of lung mapping named Virtual-Assisted Lung Mapping (VAL-MAP) has been developed allowing with the use of fiberbronchoscopy information and virtual images derived from a CT and 3D reconstruction to have a geometric vision of the nodule in the lung due to multiple virtual markers (9). Of course, this method is expensive but it allows preoperatively planning in a more correct way the resection.

Finally, in this golden age of sublobar resections, there is another aspect that could add in the future some confounding factors in the diagnosis and treatment of GGOs: this is the spread through air spaces (STAS). This is a tumor's characteristic and well-defined histopathologic entity, it is included in the staging of lung cancer and it is not detectable with the standard techniques of imaging. Although it is not still clear which are the underlying mechanisms favoring STAS and how the neoplastic cells can survive without an evident contact with the alveolar walls, it is well known that the presence of STAS represents a factor associated with a poor prognosis (10). The definition of STAS is micropapillary clusters, solid nests, or single cells beyond the edge of the tumor into air spaces in the surrounding lung parenchyma (11); however, it is not specified how far is the surrounding parenchyma. Now, in our not yet published experience, we have found STAS up to 2 cm from the tumor edge; this could make unsafely a sublobar resection with a high risk of local recurrence. Although with conventional imaging techniques is not possible to detect STAS, new imaging algorithms based on radiomics could be useful to preoperatively discriminate its presence; this could be in the future a new tool in the planning of surgical strategy (12).

In conclusion, actually the need to have a way to localize small nodules in VATS is mandatory and several techniques are still available; the safety, the efficacy and the worldwide reproducibility should be the main purposes of these products. New studies must be performed to seek the holy grail of markers, but new technologies are already developing in the next future.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned

by the editorial office, *Journal of Thoracic Disease*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd.2020.04.56>). FV serves as the unpaid editorial board member of *Journal of Thoracic Disease* from Aug 2019 to Jul 2021. 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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Cite this article as: Anile M, Mantovani S, Vannucci J, Bassi M, Diso D, Venuta F. Seeking the holy grail of markers. *J Thorac Dis* 2020;12(10):5259-5261. doi: 10.21037/jtd.2020.04.56