

# Validating guideline concordant care in lung cancer also validates good surgical judgement and skill

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Surgical therapy with curative-intent continues to remain an important pillar in the treatment of non-small cell lung cancer (NSCLC). For thoracic surgical oncologists, integral to the long-term success of surgery for NSCLC is the preoperative identification of patients who will reap the benefits of a curative-intent treatment paradigm. Key to this selection process is ascertaining those patients who have NSCLC confined to the portion of lung being removed without any evidence of lymph node involvement. In 2014, the European Journal of Cardio-Thoracic Surgery Guidelines provided a revised algorithm for using PET-CT for mediastinal staging (1). Specifically, these guidelines rely solely on PET-CT imaging for patients with peripheral tumors less than 3 cm that are not adenocarcinoma to deem if there is clinically negative mediastinal lymph node involvement (cN0). If the PET-CT scan is negative in the mediastinum, the next step is to proceed with surgical resection for cure. For essentially all other patients, invasive mediastinal staging is advocated.

The contribution by Turna *et al.*, *Validity of the updated European Society of Thoracic Surgeons staging guidelines in lung cancer patients*, reports their validation of these guidelines among a retrospective cohort (2). This study found evidence to support PET-CT imaging for mediastinal staging in those patients with cN0 disease and peripheral tumors less than 3 cm. Forty-five patients with negative PET-CT scans underwent video-assisted mediastinoscopy (VAM) or video-assisted mediastinal lymphadenectomy (VAMLA). Even though the invasive mediastinoscopy procedure in these

45 patients would be considered unnecessary according to the 2014 European guidelines, they all underwent VAM or VAMLA. All 45 patients underwent surgical resection because the mediastinal staging procedure, in fact, did not reveal any mediastinal lymph node involvement prior to resection. This observation alone would suggest that the 2014 guidelines are appropriate to rely upon PET-CT imaging exclusively for mediastinal staging in the type of patient generally described. Moreover, only one patient had false negative lymph node staging on final surgical pathology (2.2%). This incidence is in keeping with other data that rely upon PET-CT imaging (3).

For all the other patients who did not meet the criteria for relying on PET-CT scanning as sufficient mediastinal staging, 26.4% (66/250 patients) were ultimately found to have positive mediastinal lymph node involvement on VAM/VAMLA or surgical resection. In reality, most of the 57 of these 66 patients were found to have their mediastinal disease detected prior to surgery, suggesting that only 9 patients underwent a futile operation. This finding clearly supports the role of high quality operative technique as evidenced by a thorough lymphadenectomy or lymph node sampling that ultimately detected the previously “unsuspected” mediastinal lymph node involvement by PET-CT imaging. Awareness of a differential quality in surgical invasive mediastinal staging has been raised previously (4,5). Again, the authors have shown that meticulous technical competence of the surgeons performing the surgical mediastinal staging procedures

goes hand-in-hand with the rationale to support staying guideline concordant. For the 9 patients who eventually were found to have N2 disease at surgical pathology, a larger question then looms: how biologically relevant is this N2 disease compared to N2 disease that is detected upon invasive mediastinal staging? Assuming the burden of disease is less, one could argue that surgical resection under these circumstances is particularly valuable as mediastinal lymph node involvement otherwise would not have been detected.

We would be remiss to exclude the fact that proceeding with invasive mediastinal staging in patients with clinical N1 disease is not only guideline concordant with the ESTS, but also follows other international recommendations (3,6,7). Turna *et al.* demonstrate that 50% of their patients with N1 disease were ultimately found to have positive N2 disease at the time of invasive mediastinal staging or surgical resection. Despite the fact that most patients with N1 disease are considered to have resectable disease, more often than not, its presence has been shown to be a marker for mediastinal lymph node involvement. As the authors show, N1 disease discovered on PET-CT imaging reaffirms the belief that it is a potential marker for mediastinal lymph node involvement and merits further investigation.

While the value of not operating on patients with confirmed N2/N3 disease is certainly one of obvious value in staying guideline concordant, a very interesting aspect of the study by Turna *et al.* centers around the number of these patients who were found on PET-CT imaging to have false positive mediastinal lymph node involvement. The fact that they demonstrated 24.3% (67/275) of patients with N2/N3 on PET-CT had negative invasive staging and of these 67 patients, 61 actually had true negative disease as evidenced from their pathology from surgical resection must be highlighted as another notable aspect of their study. Depending on the clinical context, the incidence of false positive PET imaging in the mediastinum is not insignificant and has been reported to range from 10% to 32% (3,8,9). Generally speaking, we would hazard an opinion that there is often a temptation to assume that these positive nodes on PET-CT scans truly represent malignancy more often than not. The impact of this assumption cannot be overstated since, as the authors note, in some parts of the world, the belief that N2 disease is present may not necessarily lead to the inclusion of surgery as part of a multimodality therapy treatment paradigm.

With more PET-CT scans being used for staging, it is useful to know what degree of FDG avidity is considered

actionable or decidedly abnormal. It has been suggested that the optimal maximum standard uptake value (maxSUV) threshold for declaring positive mediastinal lymph nodes is 5.3 (10). In that study, the investigators stratified PET-CT scan results into four categories based on primary tumor maxSUV and mediastinal lymph node maxSUV. The group of patients with low uptake in both the primary tumors (maxSUV <10) and their mediastinal lymph nodes (maxSUV <5.3) all had false negative lymph node staging on final pathology, despite having a high maxSUV lymph node-to-primary tumor ratio. This subpopulation may be the one in which the benefits of surgical mediastinal staging outweigh its inherent risks. This observation also may have accounted for the false negatives or positives in the current study, which did not specify a threshold maxSUV value. Another possible confounding factor includes the effect of smoking status on PET-CT diagnostic accuracy. An inverse dose response of pack-years to PET-CT imaging diagnostic accuracy has been demonstrated previously (11). Here, the accuracy of integrated PET-CT imaging among smokers (64%) was significantly lower relative to former smokers (80%) and never smokers (83%) ( $P=0.03$ ). The authors of the current study did not stratify their study population by smoking status, but perhaps future studies can further test the European Guidelines by using smoking status and maxSUV as fine-tuned variables to improve accuracy.

The current study emphasizes the added value of re-examining published guidelines with investigations such as this one to gain greater confidence in using them. It is only through this process of validating guidelines that they ultimately become practice changing. While some may consider it an afterthought, critical to the validation of the ESTS revised guidelines is the execution of high quality surgical technique both during invasive mediastinal staging and operative resection. It is a tacit assumption that these occur in any multidisciplinary setting that relies upon guidelines and Turna *et al.* certainly demonstrate these points in their outstanding investigation. The authors should be applauded for demonstrating that the coupling of guideline concordant care in NSCLC with superb caliber surgical technique results in excellent clinical outcomes for their patients. These outcomes clearly support remaining both guideline concordant on the programmatic level and technically sharp on the individual surgeon level.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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