Does the location make the difference in predicting mediastinal spreading of clinical N0 non-small cell lung cancer?

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Comment on: Decaluwé H, Moons J, Fieuws S, *et al.* Is central lung tumour location really predictive for occult mediastinal nodal disease in (suspected) non-small-cell lung cancer staged cN0 on 18F-fluorodeoxyglucose positron emission tomography-computed tomography? Eur J Cardiothorac Surg 2018;54:134-40.

Received: 11 June 2018; Accepted: 18 July 2018; Published: 31 July 2018.

doi: 10.21037/jovs.2018.07.13

View this article at: http://dx.doi.org/10.21037/jovs.2018.07.13

Lung cancer is one of the worldwide "big killers", being the first cause of death among malignant tumours (1). Mediastinal nodal disease is one of the most important predictive factor of survival in patients with non-small-cell lung cancer (NSCLC) and it guides clinicians in the decision of the proper treatment (2). In patients with clinical N0 imaging at computed tomography (CT) and/or positron emission tomography (PET), central location of lung cancer has been found to be associated with unexpected positive mediastinal nodes (pN2–3), with a prevalence variable between 16% and 36% among authors (3-7); thus, invasive mediastinal staging by endosonography or mediastinoscopy is recommended by current guidelines in patients with lung cancer with central location and negative mediastinal nodes at PET and CT (2,8-10).

However, central location of a lung cancer has different definitions in the literature, as it can be a lesion: (I) within the inner two-thirds of the lung; (II) within the inner one-third; (III) with endobronchial visualization by the standard bronchoscope; (IV) in contact with lobar or first segmental branches of vessels or bronchus; (V) at a distance of less than 2 cm from the bronchial tree (8-14). Therefore, a uniform, standard definition of "central lung tumour" is necessary, as well as a better understanding of the role of this location as predictor of occult mediastinal nodal disease in patients with cN0 at PET-CT.

Recently, an article entitled "*Is central lung tumour location really predictive for occult mediastinal nodal disease in (suspected) non-small-cell lung cancer staged cN0 on 18F-fluorodeoxyglucose positron emission tomography—computed tomography?*" has been published on the *European Journal of Cardio-Thoracic Surgery* (12). In this article, Decaluwé *et al.* investigated on which type of central location of NSCLC would have the highest predictive value on detection of occult mediastinal nodal disease (pN2–3) and on its prevalence in clinical N0 patients staged by PET-CT.

It is a large and single institutional study, unique in its objectives. The study cohort consisted of 813 patients with suspected NSCLC, cN0 after PET-CT, and referred for mediastinal staging and/or surgical resection after multidisciplinary team meeting, over a 10-year period, from a center with an excellent track record on lung cancer patients (Leuven Lung Cancer Group).

The authors evaluated five definitions of centrally located NSCLC: inner 1/3, inner 2/3, contact with bronchovascular structures, <2 cm from bronchus, endobronchial visualization.

The main aim of the study was to evaluate the association between each of these 5 different definitions of central tumour location and the prevalence of positive mediastinal nodal disease (pN2–3); the secondary aim was the detection of the association between central tumour location and any unforeseen positive lymph nodes (pN1 and pN2–3 combined: pN+) (12).

Considering the five different definitions of central tumour, lung lesions were defined as being central because "visualized by bronchoscopy" in 23% of cases, "located in the inner 1/3 of the lung", "in contact with bronchovascular structures" or "distant <2 cm from the bronchial tree" in 32–36% of cases, "located in the inner 2/3 of the lung" in

51% of cases.

Invasive mediastinal nodal staging was performed in 248 of 813 patients (31%), in most of them (93%) by video mediastinoscopy. Primary lung resection was performed in 751 patients, in 189 cases after invasive staging; 3 patients underwent explorative surgery only; 39 patients were submitted to induction therapy followed by surgery; 20 patients did not receive surgery after invasive mediastinal staging. Surgical resection was performed by video-assisted thoracic surgery (VATS) in 42% of patients; the median number of examined lymph node stations was 5 and the median number of mediastinal lymph node stations was 3 and the authors found no difference in the number of lymph node stations assessed between VATS and open surgery (P=0.33); however, more stations were evaluated in case of central tumour location versus peripheral (P<0.001). The mean follow-up was 84 months and the 5-year survival was 61%.

In 21% of patients (n=171) the authors found a nodal upstaging (cN0 to pN+): pN1 in 13% of patients (n=106) and pN2–3 in 8% of patients (n=65).

In response to the primary aim of the study, considering the five different definitions of central tumour location, univariate analysis did not reveal an association between any of them and occult mediastinal node disease (pN2–3). Considering the entire cohort of patients, the prevalence of N2–3 was only 8%, varying between 6% and 10% according to the 5 definitions of central tumour location used. Even multivariate analysis did not show a significant relationship between any of the five different definitions of central tumour location and pN2–3 upstaging.

As concern the secondary aim of the study, univariate analysis showed a relationship between central tumour location and overall nodal upstaging (from cN0 to pN+), with odds ratios between 3.36 and 4.21 according to the definition of central tumour location.

This article is innovative as it is the first reported study considering and comparing five different definitions of central lung tumour location and their relationship with occult mediastinal node disease in patients with clinical N0, suspected NSCLC, who were submitted to invasive mediastinal staging and/or surgery. However, among the five definitions of central tumour location, the authors did not find any of them having a higher predictive value for unforeseen mediastinal disease: in fact, both univariate and multivariate analyses did not demonstrate relationships between any of the 5 definitions and pN2–3 disease. Moreover, they postulate that further studies would be recommended to establish which is the best definition of central tumour location, though they also point out that the impact on the clinical history would be of minor importance if the prevalence of unforeseen mediastinal disease at integrated PET-CT is confirmed to be less than 10% from other studies.

Furthermore, even if the authors found that central tumour location had four times higher odds for any pN+, the discriminating capacity for pN+ was not significantly different between the various definitions of central tumour.

Thus, their results question whether the indication of current guidelines, to perform an invasive mediastinal staging in patients with central lung cancer and cN0 PET-CT (2,8-10), is correct.

In fact, previous studies demonstrating a correlation between central tumour location and unexpected positive mediastinal nodes after negative imaging were based on CT only or on non-integrated PET-CT, or considered together cN0 and cN1 patients (4-6). Three other studies have been published in which no difference in mediastinal upstaging between central and peripheral tumours has been demonstrated (15-17), as in this study (12), while only one recent study found that central tumour location was predictive of pN2 disease in patients with cN0 imaging at integrated PET-CT (7).

The authors conclude that to predict the probability of occult mediastinal nodal disease and to make a correct indication to an invasive mediastinal staging, a more complex model should be developed than central location alone.

Despite being original, the study has some limitations: it is retrospective and the low number of patients of different subgroups cannot allow to make definitive conclusions based on their prevalence of mediastinal disease; moreover, the authors did not consider the maximal standardized uptake value (SUVmax) of the primary tumour, that could be correlated to occult mediastinal nodal disease, as found in a metanalysis by Wang *et al.* (18). Among other significant factors that the Clinicians should consider seems also of paramount importance the histology: also in the cited paper of the Leuven group, the multivariate analysis found significant predictor of any nodal upstaging the squamous histology.

In conclusion, this research advanced the knowledge on the relationship between central lung tumour location and unexpected mediastinal nodal disease in patients with cN0, suspected NSCLC, after imaging with integrated PET-CT: no correlation was found between the five considered

different definitions of central tumour location and occult mediastinal disease (pN2–3), the prevalence of pN2 was 8% and that of any nodal upstaging (pN+) was 21%, with all definitions of central tumour location predictive for pN+. Thus, in patients with central NSCLC location, further studies are necessary to develop a better and more complex model of prediction of mediastinal nodal disease and the current guidelines about indication to invasive mediastinal staging for this group of patients should be revised.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Visualized Surgery*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jovs.2018.07.13). The 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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doi: 10.21037/jovs.2018.07.13
Cite this article as: Marulli G, De Palma A. Does the location make the difference in predicting mediastinal spreading of clinical n0 non-small cell lung cancer? J Vis Surg 2018;4:157.