

# A novel prediction model for the probability of mediastinal lymph node metastases detected by endobronchial ultrasound-transbronchial needle aspiration in non-small cell lung cancer: possible applications in clinical decision-making

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*Provenance:* This is an invited Editorial commissioned by the Section Editor Dr. Luigi Ventura (Thoracic Surgery, Surgical Unit, Department of Medicine and Surgery, University Hospital of Parma, Parma, Italy).

*Comment on:* O'Connell OJ, Almeida FA, Simoff MJ, *et al.* A Prediction Model to Help with the Assessment of Adenopathy in Lung Cancer: HAL. *Am J Respir Crit Care Med* 2017;195:1651-60.

Received: 17 March 2018; Accepted: 08 May 2018; Published: 01 June 2018.

doi: 10.21037/med.2018.05.02

**View this article at:** <http://dx.doi.org/10.21037/med.2018.05.02>

Surgery is the most successful radical approach to non-small cell lung cancer (NSCLC), provided accurate preoperative systemic and mediastinal staging for stratification of patients with potentially resectable disease (1). In particular, pre-surgical mediastinal nodal staging (N staging) is performed by a combination of diagnostic tests with different levels of accuracy and invasiveness (2,3), as well as cumulative costs and risks. The optimal diagnostic option is composed by selection of a clinically relevant combination from among computed tomography (CT), positron emission tomography (PET), endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA), and endoscopic ultrasound-needle aspiration (EUS-NA) (4). O'Connell and colleagues systematically analysed the factors that should drive the most appropriate diagnostics for pre-surgical N staging and provided a prediction model to help with the assessment of adenopathy in lung cancer (HAL).

A prediction model estimates the probability of an event on the basis of risk factors, thus driving the most appropriate resource in the subpopulation that is likely to get the most value from it (5). Thereby, a prediction model may firstly guide the use of staging procedures, and secondly inform about the likelihood of false negative requiring a further confirmatory test. In the scenario of a

known malignancy, like lung cancer, prediction models are particularly useful to reduce harms of over investigation and address the most appropriate therapy (e.g., surgery, radiation therapy, or medical treatment) (6).

Each of CT and PET show limitations in N staging, especially with smaller lymph nodes (7). As a consequence, the American College of Chest Physicians (ACCP) issued guidelines with four main categories on the basis of thoracic radiographic appearance to drive the most appropriate use of EBUS-TBNA according to likelihood of N2/N3 (*Table 1*), addressing invasive mediastinal staging in case of normal radiographic nodal appearance but relevant PET uptake. A similar approach is replicated by the guidelines from the European Society of Thoracic Surgeons (ESTS) (2)

Yet, those guidelines suffer from the lack of a specific algorithm for risk stratification. Furthermore, it cannot be overemphasised that there is an increasing proportion of lung adenocarcinoma that are not metabolically susceptible under conventional 18-Fluorodeoxyglucose (<sup>18</sup>FDG) PET (8). The HAL model aims to address such gaps.

The HAL model was developed on retrospective single-centre data, and validated on external cohorts from three further hospitals. The authors call it “parsimonious” because indeed it can be applied by only age and CT data, with

**Table 1** ACCP guidelines for stratification of N2/N3 probability based on imaging and optimal application of EBUS-TBNA

Category	Imaging finding	Mediastinal involvement
A	Obvious signs of direct disease extension and mediastinal infiltration	Supposed upon imaging
B	Mediastinal nodal enlargement (short axis >1 cm)	Need for invasive confirmation of mediastinal involvement
C	Normal mediastinal lymph nodes, suspected N1 or central tumour	Need for invasive confirmation of mediastinal involvement
D	Normal mediastinal lymph nodes, peripheral stage I tumour	Further invasive mediastinal staging not recommended

ACCP, the American College of Chest Physicians; EBUS-TBNA, endobronchial ultrasound-transbronchial needle aspiration.

further possible integration with PET and tumour histology.

The literature provides a number of models that stratify the risk of N metastases from lung cancer (5,9-17). The major effort of providing specific prediction models turned into the intrinsic limitation of several independent models that heterogeneously covered a variety of specific clinical scenarios (e.g., selection of cT1 lung cancer; *Table 2*). Most of them focus on stage I neoplasms (9-11,15,16), on a single histologic subtype (10,11), on patients with negative lymph nodes by morphological or metabolic findings (9-11,13,15-17). Also, there is a number of studies that do not include PET for mediastinal stratification (12,13,16,17), despite PET is currently included as standard of care for systemic staging (3). Thereof, compared to former models in the literature (*Table 2*), the HAL model has the major strength of wide applicability through age decades (e.g., 40–80), NSCLC histology types, and lung cancer stages. The integrity and the wide applicability of a single model through dozens of clinical scenarios make the model a good candidate for inclusion in guidelines. Risk factors retained in the HAL for the probability of N2/N3 (prN2/N3) disease were younger age, adenocarcinoma histology, central location of the tumour (i.e., in the inner one-third of lung parenchyma), and higher N stage demonstrated by PET and CT. Tumour size wasn't retained in the HAL, in contrast with a previous study from Farjah and colleagues (14).

One could argue that prediction models might perform differently according to several clinical variables that might change between individual hospitals. The external validation is the method of testing the broad applicability of a proposed model (6). The previously proposed models almost entirely missed external validation, with the exception of the study from Farjah *et al.* (5). It is interesting that indeed the first version of the HAL model was found overestimating prN2/N3 in the three external validation cohorts. Of note, the technique for EBUS-TBNA was consistent between the developing and validation cohort: sampling of each lymph

node >0.5 cm (e.g., minimized likelihood of false negative). In this regard, the external validation operated by O'Connell *et al.* clarifies the adjustment needed for its universal application. Noteworthy, this model accounts for inter-centre variability, and a method of calibration was proposed to grant consistent performance of the model over a range of different local patient patterns. This latter feature is particularly convenient in clinical practice where accuracy and reproducibility are quite debated at the level of the diagnostic test. Indeed, the calibration proposed by O'Connell comes with an upper hierarchical degree that aims to minimize differences in the final outcome: prN2/N3 by EBUS-TBNA.

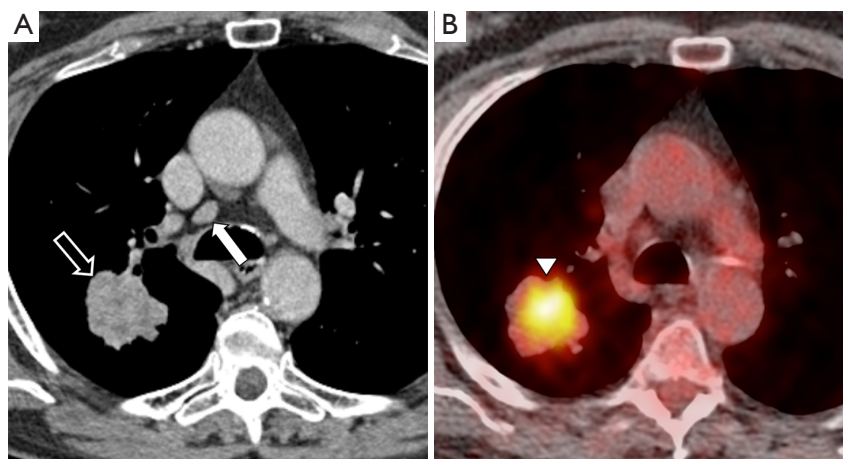
A potential limitation of the study by O'Connell lays in the use of EBUS-TBNA as standard of reference for nodal status assessment, rather than thoracotomy. In fact, lymph node sampling by EBUS-TBNA could underestimate the real prevalence of disease: the ACCP guidelines report a sensitivity 89% and specificity 100%. However, it should be noted that such 10% variability in sensitivity is still acceptable, as long as specificity is perfect. Indeed, the ESTS guidelines (2) deem acceptable up to 10% of unforeseen pathologic N2 patients (mainly represented by single N2 stations) revealed by surgical resection despite preoperative accurate staging. Hence, as advocated by O'Connell and colleagues, a second and relevant possible application of the aforementioned model is to estimate the probability of a false negative EBUS-TBNA result with the attempt to determine whether a confirmatory mediastinoscopy should be considered.

Secondary purpose of the study by O'Connell and colleagues was to investigate the role of PET in the diagnostic algorithm, after a chest CT scan. The model showed that, in case of obvious N2 disease at CT, the clinical yield of PET imaging is limited to detection of distant metastases. Apart from systemic metastases, CT findings combined to clinical data would consistently indicate appropriateness of EBUS-TBNA, irrespective of

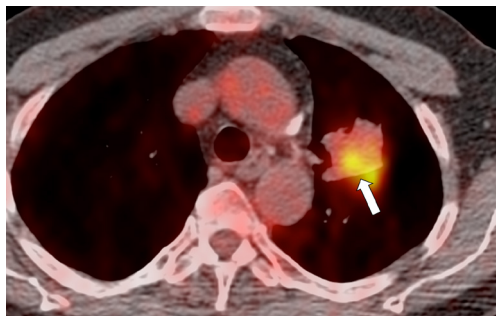
**Table 2** Summary of scientific studies focusing on risk-predictors of lymph node metastases in NSCLC

Authors	Year	Development cohort; validation cohort	Selection criteria	Pathologic reference	Predictors of nodal metastasis	Comments
Shafazand S <i>et al.</i> (12)	2006	566; internal, cross-validation	Potentially resectable NSCLC	Mediastinoscopy and thoracotomy results	Higher probability of pN2: adenocarcinoma or large-cell histology, apparent metastatic disease on chest radiography, central location, tumour size, younger age	No PET or CT inclusion, only CXR for non-invasive mediastinal staging
Zhang Y <i>et al.</i> (17)	2012	530; internal, bootstrapping	cT1 N0 (by CT) M0	Intraoperative lymph nodes dissection	Higher probability of pN2: younger age, larger tumour size, central location, invasive adenocarcinoma histology	No PET inclusion
Tsutani Y <i>et al.</i> (10)	2012	502; x	cT1 N0 (by CT and PET-CT) M0 adenocarcinomas	Intraoperative lymph nodes dissection	Higher probability of pN0: lower solid tumour size, lower maximized standardized uptake value (SUVmax)	PET-CT inclusion
Takenaka T <i>et al.</i> (9)	2012	94; x	cT1 N0 (by CT and PET-CT) M0	Intraoperative lymph nodes dissection	Higher probability of nodal metastases: higher SUVmax	PET-CT inclusion
Koike T <i>et al.</i> (16)	2012	894; x	Peripheral cT1 N0 (only by CT or by CT and PET-CT) M0	Intraoperative lymph nodes dissection	Higher probability of nodal metastases: younger age, preoperative serum carcinoembryonic antigen level, tumour size on preoperative imaging, consolidation/ tumour ratio	PET-CT not uniformly performed
Chen K <i>et al.</i> (13)	2013	605; internal, cross-validation; external, (211 patients, same institution)	Resectable cN0 (by CT)	Intraoperative lymph nodes dissection	Higher probability of pN2: younger age, larger tumour size, central location, adenocarcinoma or adenosquamous carcinoma histology	No PET inclusion
Farjah F <i>et al.</i> (14)	2013	625; internal (313 patients, same institution)	cT1/T2 (by CT) and N0/N1 (by PET) M0	Preoperative invasive staging or intraoperative lymph nodes dissection	Higher probability of pN2: larger tumour size, nodal status by CT, SUVmax, N1 by PET	PET inclusion
Tsutani Y <i>et al.</i> (11)	2014	100; x	cT1N0 (by CT and/ or PET-CT) M0 squamous cell carcinomas	Intraoperative lymph nodes dissection	No useful predictors	PET-CT inclusion
Park SY <i>et al.</i> (15)	2015	139; x	Peripheral cT1 N0 (by PET-CT) M0	Intraoperative lymph nodes dissection	Higher probability of nodal metastases (pN1/N2): SUVmax and volume-based parameters (especially metabolic tumour volume, MTV)	PET-CT inclusion
Farjah F <i>et al.</i> (5)	2015	239; external validation	cT1/T2 (by CT) and N0/N1 (by PET) M0	Preoperative invasive staging or intraoperative lymph nodes dissection	Higher probability of pN2: larger tumour size, nodal status by CT, SUVmax, N1 by PET	PET inclusion; external validation of a previously published model (14)
O'Connell <i>et al.</i> (18) Evaluation, and Education	2017	633; external validation [722]	cT1-T3, M0	EBUS-TBNA	Higher probability of pN2/N3: younger age, central tumour, adenocarcinoma histology, higher PET-CT N stage	PET inclusion

NSCLC, non-small cell lung cancer; PET, positron emission tomography; CT, computed tomography; CXR, chest X-ray; MTV, metabolic tumor volume.



**Figure 1** An 80-year-old male with a right peripheral adenocarcinoma. (A) Axial CT image obtained after intravenous injection of iodinated contrast agent (mediastinal window) highlights the primary lung cancer (black arrow) and an enlarged lymph node in 4R station (white arrow) which would make N2 stage; (B) PET image shows FDG uptake only at the pulmonary mass (white arrowhead) and no relevant metabolic activity within the mediastinal lymph node in 4R, which makes N1 stage. The HAL model calculated a 7% predicted probability of N2/N3 disease before EBUS-TBNA, and a 0.8% post-test probability following a negative EBUS-TBNA. This could make an EBUS-TBNA not necessary, while the ESTS and ACCP Guidelines recommend such procedure to be performed, given the presence of an enlarged mediastinal lymph-node. The HAL model correctly predicted the post-surgical mediastinal staging (N1). PET, positron emission tomography; CT, computed tomography.

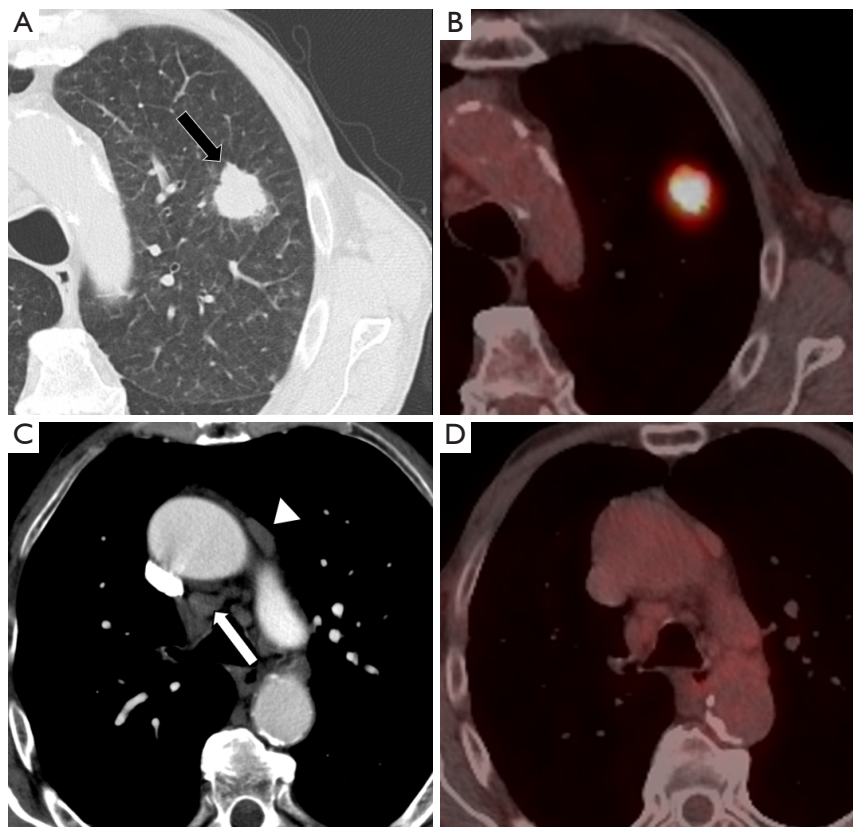


**Figure 2** A 70-year-old male with a left adenocarcinoma (white arrow in the PET image). No FDG-uptake could be observed at any mediastinal and hilar lymph nodal station. The HAL model calculated a 4% predicted probability of N2/N3 disease before EBUS-TBNA, and a 0.4% post-test probability of nodal involvement following a negative EBUS-TBNA. This value could make an EBUS-TBNA not necessary, while the ESTS Guidelines recommend such procedure to be performed in presence of a lesion greater than 3 cm. The HAL model correctly predicted the post-surgical mediastinal staging (N1). PET, positron emission tomography; EBUS-TBNA, endobronchial ultrasound-transbronchial needle aspiration; FDG, Fluorodeoxyglucose; ESTS, the European Society of Thoracic Surgeons; HAL, help with the assessment of adenopathy in lung cancer.

PET results. On the other hand, in N0 patients by CT, the HAL underscores the additional value of PET imaging.

Furthermore, three additional multivariable models are provided by the authors to inform decision making in different clinical scenarios, demonstrating good similar performance of the prediction rule also when both PET and histology are not known. In particular, the area under the receiving operator curve (AUC) was 0.88 for the full model including histology characterization. Nonetheless, the AUC for a restricted model without histology still performed well (AUC 0.87), suggesting that the HAL might be used even before biopsy of the primary lung cancer. On the other hand, the detrimental effect of pre-PET and pre-biopsy application of the model seems to be more conspicuous (AUC 0.76) and might lead to a greater level of uncertainty between predicted and observed nodal N2/N3 involvement. Further studies are warranted to test the performance of such model for alternative preoperative diagnostic algorithms.

Finally, it seems that there might be some degree of association between the prN2/N3 and the risk of false negatives at EBUS-TBNA. As clearly demonstrated, the main goal of the HAL model is to determine whether EBUS-TBNA is recommended in different clinical settings, advising a 10% threshold of predicted N2/N3 involvement



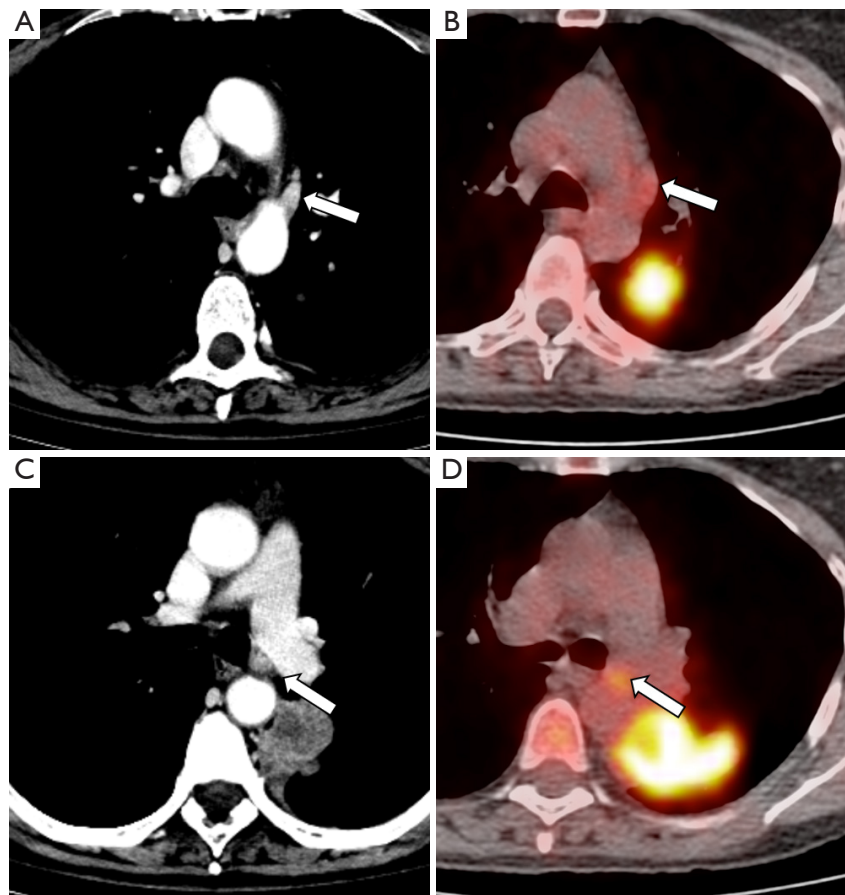
**Figure 3** A 73-year-old male with a left peripheral squamous cell carcinoma. (A) Axial CT image with lung window shows a 3 cm lung cancer in the periphery of the lung (black arrow); (B) PET image shows FDG uptake of the primary lung cancer; (C) axial CT image obtained after intravenous injection of iodinated contrast agent showing enlarged lymphnodes in 4R station (white arrow) and 6 station (white arrowhead); (D) PET image does not show FDG uptake in mediastinal lymph nodes. The HAL model calculated a 4% predicted probability of N2/N3 disease, and a 0.5% post-negative EBUS-TBNA. This value could make the EBUS-TBNA avoidable, while the ESTS and ACCP Guidelines recommend EBUS-TBNA for investigation of the lymph node in 4R station, and even mediastinoscopy for investigation of the lymph node in 6 station. The HAL model correctly predicted the post-surgical mediastinal staging (N1). PET, positron emission tomography; CT, computed tomography; EBUS-TBNA, endobronchial ultrasound-transbronchial needle aspiration; FDG, Fluorodeoxyglucose; ESTS, the European Society of Thoracic Surgeons; HAL, help with the assessment of adenopathy in lung cancer; ACCP, the American College of Chest Physicians.

(Figures 1-3). Moreover, the model shows that negative EBUS-TBNA might be found with a likelihood of actual N2/N3 positivity still above the 10% (Figure 4). Should this be an indication to proceed directly to mediastinoscopy in such high-risk patients, and maybe use the HAL to leave the EBUS-TBNA to cases with more limited risk of false negative? Furthermore, it should be remembered that the ESTS guidelines (2) generally recommend a further confirmatory invasive investigation (i.e., video-assisted mediastinoscopy) in patients suspected for mediastinal involvement by PET-CT but negative after EBUS-TBNA. The possibility of a future integration of a prediction model

in the guidelines follows the importance of estimating the pre-test and post-test probability of nodal metastases with the aim to minimize the number of unnecessary invasive procedures performed. The HAL model is made available for further validation, we foster the literature will provide more evidence and critical testing of this promising novel comprehensive predictor of mediastinal involvement in lung cancer.

In conclusion, prediction models may be considered a useful tool to guide decision-making for patients with potentially resectable lung cancer, with the aim of reducing the number of invasive mediastinal staging procedures. The HAL model seems to have the potential for medical





**Figure 4** A 60-year-old female with a left central adenocarcinoma. (A) Axial CT image obtained after intravenous injection of iodinated contrast agent highlights an enlarged lymph node in 6 station (white arrow); (B) PET image shows FDG uptake at the same level (white arrow); (C) axial CT image highlights an enlarged lymph node in the station 4L (white arrow); (D) PET image shows FDG-uptake at the same level (white arrow). The HAL model calculated an 80% predicted probability of N2/N3 disease and a 31% estimated post-test probability N2/N3 disease after a negative EBUS-TBNA performed to evaluate the 4L lymph node. Conversely, ACCP and ESTS guidelines would have recommended EBUS-TBNA for investigation of the enlarged PET positive lymph nodes. The HAL model correctly predicted the post-surgical mediastinal staging (N2). PET, positron emission tomography; CT, computed tomography; EBUS-TBNA, endobronchial ultrasound-transbronchial needle aspiration; FDG, Fluorodeoxyglucose; ESTS, the European Society of Thoracic Surgeons; HAL, help with the assessment of adenopathy in lung cancer; ACCP, the American College of Chest Physicians.

decision support to guide invasive mediastinal staging, also warranting a further confirmatory investigation (i.e., mediastinoscopy) after a first EBUS-TBNA result suspicious for false-negative.

### Acknowledgements

None.

### Footnote

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

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doi: 10.21037/med.2018.05.02

**Cite this article as:** Carnevale A, Milanese G, Sverzellati N, Silva M. A novel prediction model for the probability of mediastinal lymph node metastases detected by endobronchial ultrasound-transbronchial needle aspiration in non-small cell lung cancer: possible applications in clinical decision-making. *Mediastinum* 2018;2:43.