Endobronchial ultrasound for T4 staging in patients with resectable NSCLC

Kuijvenhoven, J.C.; Livi, V.; Szlubowski, A.; Ninaber, M.; Stoger, J.L.; Widya, R.L.; ... ; Annema, J.T.

Lung Cancer 158 (2021) 18–24

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Endobronchial ultrasound for T4 staging in patients with resectable NSCLC

Jolanda C. Kuijvenhoven [a], Vanina Livi [b,c], Artur Szlubowski [d], Maarten Ninaber [e], J. Lauran Stöger [f], Ralph. L. Widya [f], Peter. I. Bonta [a], Laurence C. Crombag [a], Jerry Braun [g], Willem Jan van Boven [h], Rocco Trisolini [b,c], Daniël A. Korevaar [a], Jouke T. Annema [a,*]

[a] Department of Respiratory Medicine, Amsterdam University Medical Centers, Location Academic Medical Center (AMC), Amsterdam, the Netherlands
[b] Interventional Pulmonology Unit, Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[c] Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy
[d] Bronchoscopy Unit, Pulmonary Hospital Zakopane, Zakopane, Poland
[e] Department of Respiratory Medicine, Leiden University Medical Centre, Leiden, the Netherlands
[f] Department of Radiology, Leiden University Medical Centre, Leiden, the Netherlands
[g] Department of Cardio-thoracic Surgery, Leiden University Medical Centre, Leiden, the Netherlands
[h] Department of Cardio-thoracic Surgery, Amsterdam University Medical Centers, Location Academic Medical Center (AMC), Amsterdam, the Netherlands

ARTICLE INFO

Keywords:
EBUS
Lung cancer staging
T4
Non-small-cell carcinoma

ABSTRACT

Background: In lung cancer patients, accurate assessment of mediastinal and vascular tumor invasion (stage T4) is crucial for optimal treatment allocation and to prevent unnecessary thoracotomies. We assessed the diagnostic accuracy of linear endobronchial ultrasound (EBUS) for T4-status in patients with centrally located lung cancer.
Methods: This is a retrospective study among consecutive patients who underwent EBUS for diagnosis and staging of lung cancer in four hospitals in The Netherlands (Amsterdam, Leiden), Italy (Bologna) and Poland (Zakopane) between 04–2012 and 04−2019. Patients were included if the primary tumor was detected by EBUS and subsequent surgical-pathological staging was performed, which served as the reference standard. T4-status was extracted from EBUS and pathology reports. Chest CT's were re-reviewed for T4-status.
Results: 104 patients with lung cancer in whom EBUS detected the primary tumour, and who underwent subsequent surgical-pathological staging were included. 36 patients (35 %) had T4-status, based on vascular (n = 17), mediastinal (n = 15), both vascular and mediastinal (n = 3), or oesophageal invasion (n = 1). For EBUS, sensitivity, specificity, PPV and NPV for T4-status were (n = 104): 63.9 % (95 %CI 46.2–79.2 %), 92.6 % (83.7–97.6 %), 82.1 % (65.6–91.7 %), and 82.9 % (75.7–88.2 %), respectively. For chest CT (n = 72): 61.5 % (95 %CI 40.6–79.8 %), 37.0 % (23.2–52.5 %), 35.6 % (27.5–44.6 %), and 63.0 % (47.9–75.9 %), respectively. When combining CT and EBUS with concordant T4 status (n = 33): 90.9 % (95 %CI 58.7–99.8 %), 77.3 % (54.6–92.20 %), 66.7 % (47.5–81.6 %), and 94.4 % (721−99.1%), respectively.
Conclusion: Both EBUS and CT alone are inaccurate for assessing T4-status as standalone test. However, combining a negative EBUS with a negative CT may rule out T4-status with high certainty.

1. Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide [1]. Patients with non-small cell lung cancer (NSCLC) invading the mediastinum or large vessels (T4 stage) have a five-year survival rate that ranges from 44 % to less than 28 % [2,3]. T4 is defined according to the 8th TNM-classification as a tumor >7 cm in greatest dimension or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor, or invading any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, or vertebral body [4,5].

Accurate staging is crucial to ensure that patients receive optimal

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; EUS, esophageal ultrasound (using a Gastro-Intestinal endoscope); EUS-B, esophageal ultrasound (using an EBUS scope); MRI, magnetic resonance imaging; NPV, negative predictive value; NSCLC, non-small-cell lung cancer; PET, positron emission tomography; PPV, positive predictive value.

* Corresponding author at: Department of Respiratory Medicine, University Medical Centers Amsterdam, Location Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands.
E-mail address: j.t.annema@amsterdamumc.nl (J.T. Annema).

https://doi.org/10.1016/j.lungcan.2021.05.032
Received 28 February 2021; Received in revised form 11 May 2021; Accepted 26 May 2021
Available online 28 May 2021

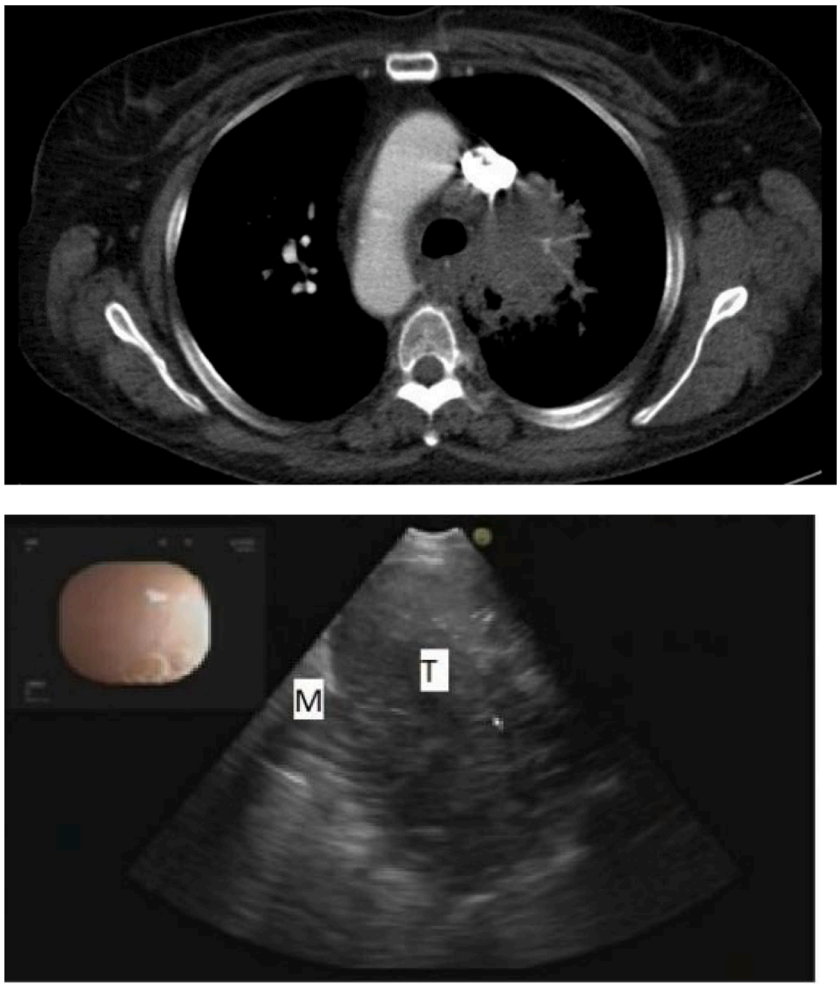

Fig. 1. EBUS evaluation of suspect T4 stage.
Chest CT image with a left upper lobe tumor with suspected mediastinal invasion (T4) note the right descending aorta.
Corresponding EBUS image. Demonstrating a clear plane between the lung tumor (T) and the mediastinum (M) (no T4). The final surgical pathological diagnosis was a pT2 tumor.

therapy. Patients with T4 lung tumors are most commonly treated with multimodality treatment including (neo-adjuvant) chemotherapy and/or radiotherapy, sometimes followed by surgery. However, accurate preoperative assessment of mediastinal tumor invasion is challenging. Computed tomography (CT) of the chest is of limited value, with reported sensitivity and specificity varying from 40 to 84% and 57 to 94 %, respectively [6,7]. FDG positron emission tomography (PET) offers minimal additional information due to its poor spatial resolution [8] and chest MRI has low specificity for T4 assessment [9]. As such, patients with suspected mediastinal or vascular tumor invasion are still at risk for futile thoracotomy or missed surgical opportunities [10].

Current lung cancer staging guidelines advocate the use of endosonography (endobronchial (EBUS) and/or esophageal (EUS(-B)) for regional nodal staging in patients with centrally located intrapulmonary tumors [11]. In cases where a tumor presents along the major airways, EBUS and EUS(-B) can also be used for diagnostic purposes [12–14]. However, the value of EBUS for assessing tumor invasion in the mediastinum and related structures has not yet been explored. The aim of this study was to evaluate the diagnostic accuracy of EBUS for assessing mediastinal or large vessel invasion (T4-status).

2. Methods

2.1. Study design and patient selection

We undertook a retrospective international multicentre study in the Netherlands (Amsterdam University Medical Centre (location Academic Medical Centre) and Leiden University Medical Centre, Leiden), Italy (Policlinico S. Orsola-Malpighi, Bologna) and Poland (Pulmonary Hospital Zakopane, Zakopane). Patients were selected from institutional endosonography databases. Records from 1−4-2012 until 1−4-2019 were analysed. Patients were eligible for enrolment in the study if all the following criteria were present: 1) EBUS was performed for the diagnosis and/or staging of (suspected) lung cancer; 2) the primary lung tumor was detected by EBUS; 3) surgical-pathological staging including verification of tumor status was performed within 6 weeks following EBUS. Patients were excluded if a diagnosis other than NSCLC was made, if neo-adjuvant therapy had been administered prior to surgical exploration or if the T4-status was not mentioned in the EBUS report.

For each included patient, we collected all the reports of the staging modalities, including chest CT imaging, EBUS and corresponding cytopathology, surgery and corresponding histopathology. In this study, T4-status was defined according to the international staging guidelines as a tumor invading the diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina [4,5].

2.2. EBUS procedure

All procedures were performed at the endoscopic units of the four referral centers by experienced interventional pulmonologists, who were not blinded to chest CT findings. Procedures were mainly

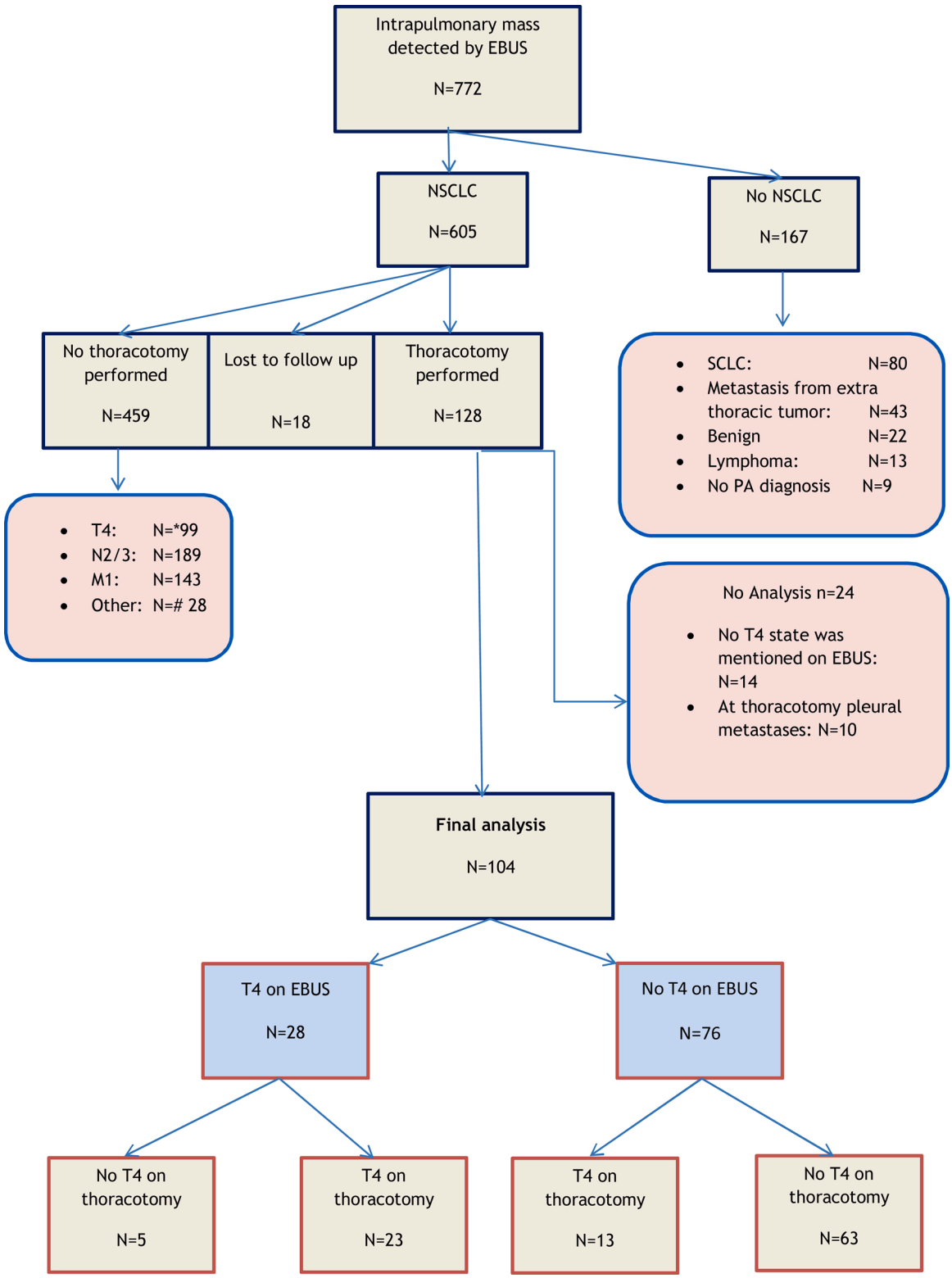

Fig. 2. Flowchart of patients with a centrally-located lung tumor that was detected by EBUS. *T4 as discussed in the tumor board meeting # no thoracotomy was performed mostly due to the clinical condition of the patient.

performed in an outpatient setting, either under conscious sedation using midazolam/fentanyl, or propofol/remifentanil sedation. A systematic EBUS examination (Olympus BF-UC180 F or UC 180 F, Olympus Medical Systems Europe, Ltd., or Pentax EB-1970 UK or Pentax EB19-J10U, Pentax, Hamburg, Germany) was performed according to EBUS assessment tool in all centers [15].

After visualizing a lung tumor by linear EBUS, the endoscopist evaluated the area for signs of mediastinal or vascular tumor invasion. The T4-status as reported by the endoscopist in the EBUS report was recorded and used for analysis. Mediastinal invasion was considered

Table 1
Patient characteristics of the patients included in de final analysis.

Number of patients	104
Median age (Range)	67.4 years (48–85 years)
Male sex	77 (74 %)
Female sex	27 (26 %)
Median long axis of the lesion on CT (Range)	54.0 mm (16–130 mm)
Location of the lesion	
RUL	44 (43 %)
RML	0
RLL	10 (10 %)
LUL	20 (19 %)
LLL	19 (18 %)
Central left	7 (7%)
Central right	4 (4%)
Final histological diagnosis	
Adenocarcinoma	30 (29 %)
Squamous cell carcinoma	63 (61 %)
Large Cell neuro-endocrine carcinoma	4 (4%)
NSCLC-NOS	7 (6%)
T stage after surgery	
pT4	36 (34 %)
pT3	21 (21 %)
pT2	33 (31 %)
pT1	14 (13 %)

diagnosed by EBUS if there was continuity of the tumor and the mediastinum, i.e. without a separation of the two structures by an endosonographically identifiable tissue plane. This evaluation could be further supported by dynamic maneuvers. Vascular invasion was considered diagnosed by EBUS when the tumor interrupted the intimal layer of a central extrapulmonary vessel or if there was evidence of tumor invasion into the vessel or atrium. In all cases, possible vascular tumor invasion was further assessed by color flow Doppler (Fig. 1). T4 status was extracted from the EBUS reports.

2.3. Chest CT scan

Chest CT-scans were collected for review. CT-scans of insufficient quality (i.e., absence of intravenous contrast administration, slice thickness >3 mm or low-dose CT for attenuation correction purposes) were excluded for final analysis. All available CT-scans were independently re-reviewed for T4-status by one board certified chest radiologist, who was blinded to the initial CT report, the EBUS report, and the intraoperative and pathology findings. These findings were used in the analysis of the diagnostic accuracy of chest CT for T4-status. Additionally, to assess inter-reviewer agreement, a second board certified chest radiologist who was also blinded to all earlier investigations, re-reviewed the chest CT-scans.

At chest CT scan, mediastinal invasion was documented as: replacement of mediastinal fat by soft-tissue mass, mass surrounding the trachea or esophagus, obvious invasion of mediastinal structures, tumor contact of >3 cm with the mediastinum, obliteration of the fat planes that are normally seen adjacent to mediastinal structures, compression of mediastinal structures by a mass, or mediastinal pleural or pericardial thickening. Vascular invasion was judged to be present when: the mass surrounded mediastinal vessels or clearly invaded them, the tumor was in contact with more than one fourth of the vessel's circumference, or the obliteration of fat planes that are normally seen adjacent to vessels was noticed [6,16,17].

2.4. Surgical pathological T4 assessment

All cases were reviewed in multi-disciplinary tumor board meetings as part of clinical practice, taking all available diagnostic tests into account. During these meetings, a decision was made whether there was an indication for lobectomy or pneumonectomy according to the current standards and guidelines at that time [18]. T4-status based on surgical-pathological staging after thoracotomy was the reference standard. In the pathological reports, T4 was defined in accordance with the 8th TNM classification [5].

2.5. Study endpoints and statistical analysis

The primary endpoint is the diagnostic accuracy of EBUS for the assessment of T4-status of lung malignancy. Secondary endpoints are the diagnostic accuracy of chest CT scan and of the combined CT/EBUS approach.

True positives were cases in which the test (EBUS or CT) was compatible with T4, and vascular/mediastinal invasion was confirmed by surgical pathological staging. True negatives were cases in which the test (EBUS or CT) showed no signs of T4, and this was confirmed by surgical pathological staging. False negatives were cases where the test (EBUS or CT) showed no signs of T4, but surgical pathological staging showed mediastinal/vascular invasion. False positives were cases where the test (EBUS or CT) was compatible with T4, but surgical pathological staging showed no mediastinal/vascular invasion.

When assessing the diagnostic accuracy of the combined CT/EBUS approach, we only included patients in whom both EBUS and CT findings were concordant regarding the T4 stage (i.e. both CT and EBUS showed T4, or both showed no T4). Accuracy estimates were calculated along with 95 % confidence intervals. Interobserver variability calculates for chest CT was assessed using the Kappa-statistic.

3. Ethics

This retrospective analysis was conducted in accordance with the amended Declaration of Helsinki, and collection and publication of the

Table 2
accuracy estimates for diagnosing T4-status in patients with NSCLC.

	EBUS (n = 104) (95 %CI)*	CT (n = 72) (95 %CI)**	CT/EBUS combined (n = 33) (95 %CI)***
Sensitivity	63.9 % (46.2%–79.2%)	61.5 % (40.5%–79.8%)	90.9 % (58.7%–99.8%)
Specificity	92.6 % (83.7%–97.6%)	37.0 % (23.2%–52.5%)	77.3 % (54.6%–92.2.%)
Positive predictive value	82.1 % (65.6%–91.7%))	35.6 % (27.5%–44.6%)	66.7 % (47.5%–81.6%)
Negative predictive value	82.9 % (75.7%–88.2%)	63.0 % (47.9%–75.9%)	94.4 % (72.1%–99.1%)
Accuracy	82.7 % (74.0–89.4%)	45.8 % (34.9%–58.0%)	81.8 % (64.5%–93.0%)

* For EBUS, all 104 patients were included in the analysis.

** For CT, 72 patients with a CT of sufficient quality (with contrast and less than 3 mm slice thickness) available for re-evaluation were included in the analysis.

*** For EBUS/CT combined, 33 patients where CT and EBUS had non-conflicting results for T4 evaluation (i.e. both were positive or both were negative) were included in the analysis.

data was approved by the local medical ethics committees.

4. Results

4.1. Patient selection

In 772 consecutive patients with known or suspected lung cancer undergoing EBUS in one of the participating centres, a primary lung lesion was identified by EBUS. Of these, 167 (22 %) patients had a final diagnosis other than NSCLC. Of the remaining 605 patients with NSCLC, 459 (76 %) individuals were excluded because they did not undergo thoracotomy, mostly due to N2/N3 disease or distant metastases, where 18 (3%) were lost to follow-up. In total, 128 patients with NSCLC underwent thoracotomy within 6 weeks of EBUS evaluation. In 14 cases, the EBUS report did not describe presence or absence of mediastinal tumor invasion, and these were excluded. An additional 10 patients were excluded for per operative detection of pleural metastasis and subsequent abrogation of the procedure. An overview of patient selection is represented in Fig. 2.

Overall, 104 cases were included. Patient characteristics are presented in Table 1. In summary, the median age of patients was 67.4 years (range 48−85) and 77 (74 %) were male. Primary tumors were located in the RUL (n = 44, 43 %), RLL (n = 10, 10 %), LUL (n = 20, 19 %), LLL (n = 19, 18 %), left hilum (n = 7, 7%), and right hilum (n = 4, 4%). The final histological diagnoses were adenocarcinoma (n = 30, 28 %), squamous cell carcinoma (n = 63, 61 %), large cell neuro-endocrine carcinoma (n = 4, 4%), and NSCLC-NOS (n = 7, 6%).

4.2. Final diagnosis

Of the 104 patients analysed, surgical-pathological staging showed tumor invasion (T4) in a total of 36 (34 %) patients, based on vascular invasion (n = 17), mediastinal invasion (n = 15), both vascular and mediastinal invasion (n = 3), or oesophageal invasion (n = 1). The remaining 68 (66 %) patients had no T4-status at surgical-pathological staging. An overview of accuracy estimates for EBUS, CT and combined CT/EBUS is provided in Table 2.

4.3. Diagnostic accuracy of EBUS

At EBUS, 28 patients were judged to have stage T4 tumors, of which 23 were confirmed at subsequent surgical-pathological staging. Of these 23 true positive cases, T4-status was established based on mediastinal invasion (n = 12) or vascular invasion (n = 11: pulmonary artery (n = 9), pulmonary vein (n = 1) or azygos vein (n = 1)). For the five false positive cases, the endoscopist reported invasion of the mediastinum (n = 1), the pulmonary artery (n = 3), or the pericardium (n = 1), which was not confirmed at surgical-pathological staging.

The remaining 76 patients did not demonstrate signs of tumor invasion at EBUS. Surgical-pathological staging showed T4 disease in 13 of them. These false negative cases included patients with mediastinal invasion (n = 3), vascular invasion (n = 9), both mediastinal and vascular invasion (n = 1). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of EBUS for diagnosing T4-status was 63.9 % (95 %CI 46.2–79.2 %), 92.6 % (83.7–97.6 %), 82.1 % (65.6–91.7 %), 82.9 % (75.7–88.2 %), respectively.

4.4. Diagnostic accuracy of chest CT scan

For six included patients, chest CT scan was not available for re-review, and for 26 patients, CT was deemed of insufficient quality for re-review, leaving 72 (69 %) patients suitable for CT reassessment.

Based on chest CT, 45 patients were judged to have T4 status, of which 16 were confirmed at subsequent surgical-pathological staging. Of these 16 true positive cases, T4-status was established based on mediastinal invasion (n = 8) or vascular invasion (n = 8: n = 6 pulmonary artery and n = 2 vena cava superior)). For the 29 false positive cases, the radiologist reported invasion of the mediastinum (n = 22) or vasculature (n = 7), which was not confirmed at surgical-pathological staging.

Out of 27 cases where tumor invasion was not detected through CT, surgical-pathological staging revealed T4 disease in 10 patients. These included patients with mediastinal invasion (n = 6) and vascular invasion (n = 4). The sensitivity, specificity, PPV, and NPV of chest CT for diagnosing T4-status was 61.5 % (95 %CI 40.6–79.8 %), 37.0 % (23.2–52.5 %), 35.6 % (27.5–44.6 %), 63.0 % (47.9–75.9 %), respectively (Table 2).

Due to technical reasons only 48 of the 72 CT scans were re-reviewed by the second radiologist. The Kappa statistic for this subset was 0.558 (95 %CI 0.331−0.785) which corresponds to moderate agreement.

4.5. Diagnostic accuracy of combined CT/EBUS

Overall, 33 of the 104 patients had concordant CT and EBUS outcomes regarding T4-status. Of these, 15 were judged to have T4 at both CT and EBUS, of which 10 were confirmed at subsequent surgical-pathological staging. Of the 18 patients without T4-status at combined CT/EBUS, only one patient (3%) turned out to have a T4 tumor at surgical-pathological staging. The sensitivity, specificity, PPV and NPV of combined CT/EBUS for diagnosing T4-status was 90.9 % (95 %CI 58.7–99.8 %), 77.3 % (54.6–92.20 %), 66.7 % (47.5–81.6 %), and 94.4 % (72.1–99.1 %), respectively.

5. Discussion

In this study, we retrospectively evaluated the diagnostic accuracy of EBUS for the assessment of T4-status in patients with NSCLC. We found that the overall sensitivity and specificity of EBUS is moderate and may be insufficient to rule-in or rule-out T4-status. Likewise, chest CT had limited sensitivity and specificity. However, a combination of a negative EBUS with a negative chest CT rules out T4-status with a relatively high level of certainty, and these patients may be referred for thoracotomy.

The role of endosonography in the diagnosis and staging of lung cancer has been expanding rapidly over the past decades. EBUS and EUS (-B) can be used for assessment of mediastinal lymph node metastases, and for diagnosis of centrally-located lung tumors [12,13,19]. Instead of linear EBUS, radial EBUS can also be used to assess a more peripheral location of the lung tumor, but it is inappropriate for T4 assessment [20]. In a recent retrospective study, we showed that among 74 subjects with lung cancer (26 % of whom were diagnosed as mediastinal or vascular T4, sensitivity and specificity of EUS for assessing T4-status were 42 % (95 %CI 20–67) and 95 % (95 %CI 85–99), respectively, compared to 76 % (50–93) and 61 % (46–75) for chest CT, and 83 % (36–100) and 100 % (88–100) for EUS and chest CT combined (in case of concordant results between both tests) [21].

The confirmation of direct mediastinal and/or great vessel invasion by a lung tumor (T4, stage IIIB), has profound consequences for the treatment and prognosis of patients with NSCLC. With the exception of some highly selected cases, who may benefit from a radical surgical approach [22,23], the majority of patients are best treated with combined chemo-radiotherapy with/without immunotherapy [24]. Therefore, accurate T4 assessment is crucial. So far, there has been limited evidence about the potential role of EBUS in this process. Alici et al. showed in a retrospective cohort of 55 patients that EBUS was able to discern vascular tumor invasion, although only nine cases had surgical-pathological confirmation of the tumour status [25].

In this analysis, we report the largest study so far on the potential role of EBUS in T4 assessment. Our findings show that EBUS alone may be insufficiently accurate for making a final diagnosis of T4-status. Sensitivity and specificity were 63.9 % and 92.6 %, which resulted in a PPV and NPV of 82.1 % and 82.9 %, respectively. This could imply an unacceptable number of false positives and negatives. However, when

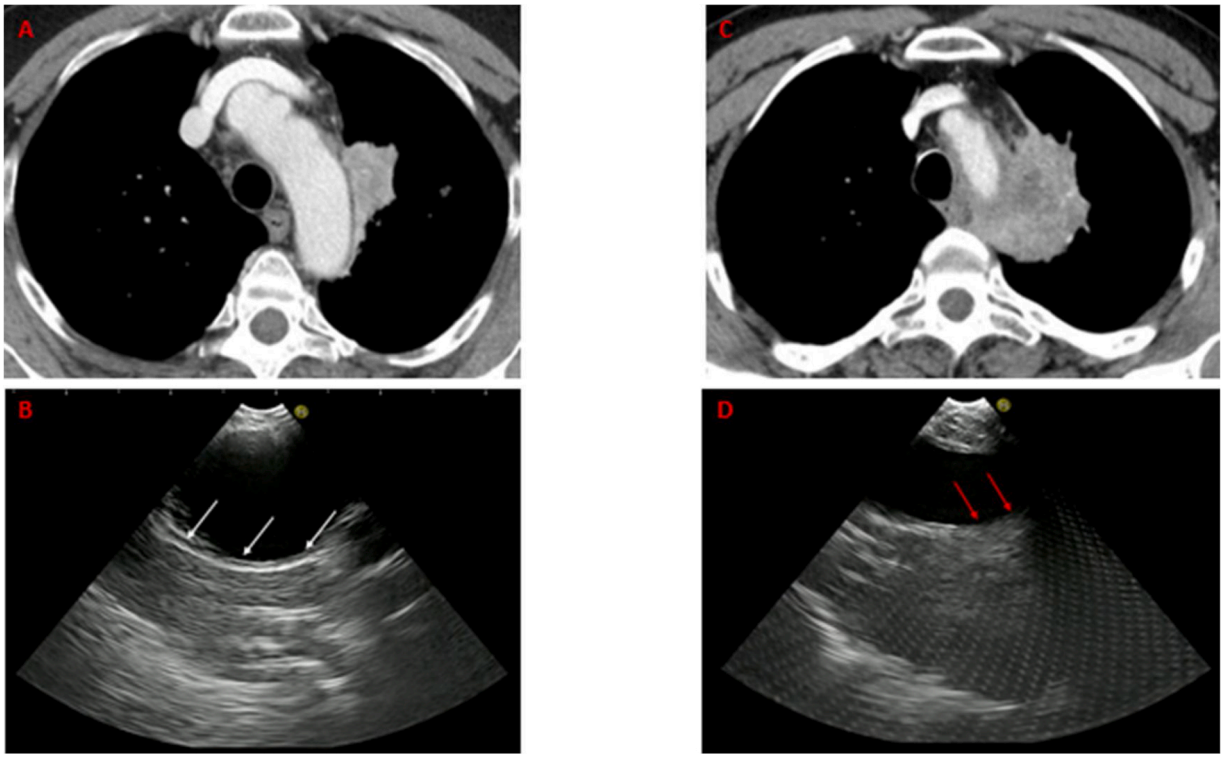

Fig. 3. EBUS assessment of aortic arch invasion from a left upper lobe central tumor.
Panel A: Chest CT demonstrating a clear separation between the aorta and a left upper tumor (no T4).
Panel B: corresponding EBUS image showing the intimal layer of the aorta is constantly visible at EBUS (with arrows), indicating lack of vessel infiltration by the tumor (no T4), this was confirmed after thoracotomy.
Panel C: demonstrates a chest CT scan where vascular invasion is readily recognizable (T4).
Panel D: shows the corresponding EBUS image showing a lack of visualization of the intimal layer of the aorta (red arrows) in a large part of the EBUS-window, indicating vessel wall invasion by the tumor. After tumor board meeting this patient was referred for chemo/radiation therapy.

combined with other clinical information, EBUS may certainly have added value for T4 assessment. This is illustrated in the subgroup of patients with both a negative chest CT and a negative EBUS, in which sensitivity and NPV were 90.9 % and 94.4 %, respectively. As such, T4-status may be ruled-out with a high level of certainty in these patients. Combined chest CT and EBUS seems less accurate for ruling-in T4-status: specificity was 77.3 % and PPV 66.7 %.

Compared to chest CT, endosonography (either EBUS or EUS(-B)) benefits from a higher spatial and temporal resolution, allowing for real-time, dynamic assessment of the relationship between tumour and adjacent structures. For instance, sliding of the lung tumor alongside the aorta excludes tumor invasion at this specific site. The use of color Doppler might be helpful in selected cases to visualize vascular structures and demonstrate or exclude tumor invasion at that location. Yet, assessment of intrapulmonary tumors through endosonography is limited to the immediate vicinity of the major airways as interposition of any aerated tissue between tumor and probe precludes adequate visualisation. Especially left upper lobe tumors with possible aortic arch invasion lend themselves for detailed assessment (Fig. 3).

Strong aspects of the current study are the large sample size, the international multicentre aspect and the excellent reference standard. However, some limitations do apply to this study. The interpretation of our findings is limited by inherent flaws related to the retrospective study design. A considerable proportion of potentially eligible patients needed to be excluded because the EBUS report did not specifically mention the T4-status. This could be due to a missing follow-up, or because they did not undergo thoracotomy, for example because the local tumor board meeting deemed T4-status sufficiently proven based on CT imaging and EBUS findings. Additionally, chest CT scans were not available/suitable for re-review in all patients. These issues may have introduced bias, which may have led to either under- or overestimation of test accuracy. The criteria for deciding which patient to refer for thoracotomy probably varied across local tumor board meetings, but could not be taken into account in this study. Endoscopists were not blinded to CT results and their T4-status interpretation may have been influenced by this, although this reflects clinical practice. Data were analysed from four centres with highly experienced endoscopists; less experienced endoscopists may not achieve similar results. Finally, the analysis of the combined use of CT and EBUS only included 33 patients in whom the results of both tests were consistent, which resulted in wide confidence intervals, and the point estimates around the accuracy estimates should be interpreted with care.

In our opinion, the findings of this study show that there is a role for EBUS in T4 assessment of patients with potentially resectable lung tumors adjacent to the airways, however not as a standalone test. Future studies need to show if our findings can be confirmed in a prospective setting, focusing on consecutive patients with suspected T4-tumors, and if there are subgroups of patients in whom EBUS may serve as an add-on to CT to rule-in or rule-out T4-status with a higher level of certainty.

Author contribution

JK had full access to all of the data in the study and takes responsibility for the integrity of the date and the accuracy of the data analysis.

VL, AS, MN, DAK, LS, RLW, JB, WJvB, RT and JTA contributed substantially to either study design, data acquisition or interpretation, evaluation of the manuscript and the writing of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

None.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (6) (2018) 394–424.

[2] D. Arslan, H. Bozcuk, S. Gunduz, D. Tural, A.M. Tattli, M. Uysal, S.S. Goksu, C. I. Bassorgun, L. Koral, H.S. Coskun, M. Ozdogan, B. Savas, Survival results and prognostic factors in T4 N0-3 non-small cell lung cancer patients according to the AJCC 7th edition staging system, Asian Pac. J. Cancer Prev. 15 (6) (2014) 2465–2472.

[3] Q. Li, P. Zhang, Y. Wang, D. Liu, L. Luo, R.B. Diasio, P. Yang, G. Jiang, T4 extension alone is more predictive of better survival than a tumour size &7 cm for resected T4N0-1M0 non-small-cell lung cancerdagger, Eur. J. Cardiothorac. Surg. 55 (4) (2019) 682–690.

[4] F.C. Detterbeck, The eighth edition TNM stage classification for lung cancer: what does it mean on main street? J. Thorac. Cardiovasc. Surg. 155 (1) (2018) 356–359.

[5] P. Goldstraw, K. Chansky, J. Crowley, R. Rami-Porta, H. Asamura, W.E. Eberhardt, A.G. Nicholson, P. Groome, A. Mitchell, V. Bolejack, S. International Association for the Study of Lung Cancer, A.B. Prognostic Factors Committee, I. Participating, S. International Association for the Study of Lung Cancer, B. Prognostic Factors Committee Advisory, I. Participating, The IASLC lung Cancer Staging project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung Cancer, J. Thorac. Oncol. 11 (1) (2016) 39–51.

[6] W. De Wever, S. Stroobants, J. Coolen, J.A. Verschakelen, Integrated PET/CT in the staging of nonsmall cell lung cancer: technical aspects and clinical integration, Eur. Respir. J. 33 (1) (2009) 201–212.

[7] R.F. Munden, S.S. Swisher, C.W. Stevens, D.J. Stewart, Imaging of the patient with non-small cell lung cancer, Radiology 237 (3) (2005) 803–818.

[8] F.M. Carnochan, W.S. Walker, Positron emission tomography may underestimate the extent of thoracic disease in lung cancer patients, Eur. J. Cardiothorac. Surg. 35 (5) (2009) 781–784, discussion 784-785.

[9] Y.J. Hong, J. Hur, H.J. Lee, Y.J. Kim, S.R. Hong, Y.J. Suh, B.W. Choi, Respiratory dynamic magnetic resonance imaging for determining aortic invasion of thoracic neoplasms, J. Thorac. Cardiovasc. Surg. 148 (2) (2014) 644–650.

[10] I. Ilonen, D.R. Jones, Initial extended resection or neoadjuvant therapy for T4 non-small cell lung cancer-What is the evidence? Shanghai Chest 2 (2018).

[11] P. Vilmann, P.F. Clementsen, S. Colella, M. Siemsen, P. De Leyn, J.M. Dumonceau, F.J. Herth, A. Larghi, E. Vazquez-Sequeiros, C. Hassan, L. Crombag, D.A. Korevaar, L. Konge, J.T. Annema, Combined endobronchial and oesophageal endosonography for the diagnosis and staging of lung cancer. European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS), Eur. Respir. J. 46 (1) (2015) 40–60.

[12] J.C. Kuijvenhoven, F. Leoncini, L.C. Crombag, R. Spijker, P.I. Bonta, D.A. Korevaar, J.T. Annema, Endobronchial ultrasound for the diagnosis of centrally located lung tumors: a systematic review and meta-analysis, Respiration 99 (5) (2020) 441–450.

[13] J.C. Kuijvenhoven, V. Livi, L. Morandi, A. Cancellieri, J.T. Annema, R. Trisolini, The expanding role of endobronchial ultrasound in patients with centrally located intrapulmonary tumors, Lung Cancer 134 (2019) 194–201.

[14] D.A. Korevaar, S. Colella, R. Spijker, P.M. Bossuyt, L. Konge, P.F. Clementsen, J. T. Annema, Esophageal endosonography for the diagnosis of intrapulmonary tumors: a systematic review and meta-analysis, Respiration 93 (2) (2017) 126–137.

[15] L. Konge, S. Colella, P. Vilmann, P.F. Clementsen, How to learn and to perform endoscopic ultrasound and endobronchial ultrasound for lung cancer staging: a structured guide and review, Endosc. Ultrasound 4 (1) (2015) 4–9.

[16] W. Higgins, Lung Cancer and Bronchopulmonary Neoplasms, Williams&Wilins, 2005.

[17] M.T. Truong, J.J. Erasmus, E.M. Marom, R.F. Munden, Imaging evaluation in the diagnosis and staging of malignant pleural mesothelioma, Semin. Roentgenol. 39 (3) (2004) 386–396.

[18] P.E. Postmus, K.M. Kerr, M. Oudkerk, S. Senan, D.A. Waller, J. Vansteenkiste, C. Escriu, S. Peters, E.G. Committee, Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 28 (suppl_4) (2017) iv1–iv21.

[19] D.A. Korevaar, L.M. Crombag, J.F. Cohen, R. Spijker, P.M. Bossuyt, J.T. Annema, Added value of combined endobronchial and oesophageal endosonography for mediastinal nodal staging in lung cancer: a systematic review and meta-analysis, Lancet Respir. Med. 4 (12) (2016) 960–968.

[20] B. Zaric, R. Eberhardt, F. Herth, V. Stojsic, V. Carapic, Z.P. Popovic, B. Perin, Linear and radial endobronchial ultrasound in diagnosis and staging of lung cancer, Expert Rev. Med. Devices 10 (5) (2013) 685–695.

[21] J.C. Kuijvenhoven, L. Crombag, D.P. Breen, I. van den Berk, M.I.M. Versteegh, J. Braun, T.A. Winkelman, W. van Boven, P.I. Bonta, K.F. Rabe, J.T. Annema, Esophageal ultrasound (EUS) assessment of T4 status in NSCLC patients, Lung Cancer 114 (2017) 50–55.

[22] M. Nonaka, M. Kadokura, D. Kataoka, S. Yamamoto, T. Kawada, T. Takaba, K. Kasahara, T. Kunimura, T. Kushihashi, [Incomplete resection for primary non-small cell lung cancer], Kyobu Geka 54 (7) (2001) 577–580.

[23] C. Dickhoff, M. Dahele, A.J. de Langen, M.A. Paul, E.F. Smit, S. Senan, K. J. Hartemink, R.A. Damhuis, Population-based patterns of surgical care for stage IIIA NSCLC in the Netherlands between 2010 and 2013, J. Thorac. Oncol. 11 (4) (2016) 566–572.

[24] B.D. Kozower, J.M. Larner, F.C. Detterbeck, D.R. Jones, Special treatment issues in non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: american College of Chest Physicians evidence-based clinical practice guidelines, Chest 143 (5 Suppl) (2013) e369S–e399S.

[25] I.O. Alici, S. Susam, M. Yuksel Yavuz, E. Bayramic, F. Guldaval, C. Anar, A. Ucvet, M. Buyuksirin, A promising tool for T-staging of lung cancer: Is convex probe endobronchial ultrasound superior to computed tomography in detecting invasion of mediastinal and hilar vessels? Turk Gogus Kalp Damar Cerrahisi Derg 27 (3) (2019) 355–359.