Diagnosis and staging of locally advanced non-small cell lung cancer

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Abstract: T4 non-small cell lung cancer (NSCLC) might include a wide range of clinical scenarios. In very selected cases a surgical treatment might be indicated, after careful staging and thorough functional evaluation. Performance status, cardiac and pulmonary function should be evaluated in detail, in a tailored fashion according to the planned surgical operation. Besides the anatomical lung unit (lobectomy or pneumonectomy), resection may involve several vital structures, including great vessels and some portion of the atria. Given the particular nature of T4, surgery is often a part of a multimodal approach. In case of induction therapies, pulmonary function should be re-assessed, to rule out any deterioration that could eventually jeopardize survival. Computed tomography (CT) scan and positron emission tomography (PET)-CT should be always performed to stage the disease, but in case of chest wall, airways or other mediastinal organs involvement, more detailed exams, such as Magnetic Resonance, echocardiography or CT angiography (CTA) and magnetic resonance angiography (MRA) should be carried out. Additionally, a careful investigation for possible mediastinal nodal involvement should be routinely performed, given the detrimental effect of nodal diffusion on survival in this subset of patients. Nowadays endobronchial ultrasound (EBUS), endoscopic (esophageal) ultrasound are reliable and semi-invasive tools that can be used as first step prior to more invasive surgical diagnostic procedures such as video assisted mediastinoscopy or even video-assisted mediastinoscopic lymphadenectomy (VAMLA) and transcervical extended mediastinal lymphadenectomy (TEMLA). Bronchoscopy and EBUS can be safely used for yield diagnostic tissue in case of central tumors, while in case of peripheral masses, transthoracic biopsy is more sensitive.

Keywords: Advanced non-small cell lung cancer (advanced NSCLC); T4; staging

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Introduction

According to the recent update of the staging of non-small cell lung cancer (NSCLC) by the International Association on the Study of Lung Cancer (IASLC), T4 classifier encompasses rather different entities: a tumour larger than 7 cm; a tumour with a satellite neoplastic nodule in another lobe of the ipsilateral lung, a tumour involving the vertebral body, great vessels, heart, mediastinum, trachea, esophagus, recurrent laryngeal nerve and diaphragm (that was upstaged in the latest version of the TNM from T3) (1). Although a detailed survival sub-analysis of different T4 subcategories was not possible due to the relatively small amount of data, a slightly worse prognosis has been observed in patients with a second nodule in a different lobe of the same lung.

Farjah et al. (2) investigated the trends in treatment of T4 NSCLC in the last decades finding out that, among 13,000 patients T4-NSCLC patients taken from the Surveillance,
Epidemiology and End Result program (SEER) database, just 9% received surgery which is reserved for highly selected patients. Moreover, evidences regarding outcomes of resected T4 are poor and often retrospective analysis of a single institution experience (3); nevertheless, long term outcomes of T4 patients is generally dismal, relying mainly on N status. Consequently, preoperative staging of T4 tumours plays a key role and it should be carried out thoughtfully and carefully. As a consequence, T4 NSCLC staging may require several steps according to the anatomical and pathological situation; furthermore a proper management of the preoperative workup showed to have a direct impact on survival (4). The initial evaluation relies upon an accurate clinical evaluation of the patient, a detailed medical history including possible risk factors, a computed tomography (CT) with contrast and a 2-(18) fluoro-2-deoxy-D-glucose (FDG-PET)-CT (5).

Recently, magnetic resonance imaging (MRI) and PET-MRI have been proposed to have a role in the diagnosis of lung cancer, but benefits compared with CT have still not been demonstrated in prospective studies (6) and their routinary use is currently left for selected patients.

**Functional assessment**

Surgery of T4 NSCLC might require extended procedures which account for not only resection of surrounding structures, but also large parts of lung parenchyma up to complete pneumonectomy. It is therefore of paramount importance a detailed evaluation of the pulmonary and cardiac function prior to any planned treatment. It is mandatory that such factors as life expectancy, tumor stage, performance status, and comorbidities should be taken into account.

Risk of cardiovascular complication after thoracic surgery is about 2–3% (7) and a cardiological preoperative evaluation is therefore needed. Not all the patients should undergo invasive cardiological tests, but only those with a higher risk of complication which might be selected and stratified according to the presence of comorbities or their medical history (8,9).

Pulmonary function should be evaluated using both pulmonary function tests (PFTs) and diffusing capacity for carbon monoxide (DLCO). Forced expiratory volume in the first second (FEV1) and DLCO showed to be strictly related with morbidity and mortality in particular a preoperative FEV1 lower than 30% and more than 60% were related to and incidence of respiratory morbidity of 43% and 12% respectively (10), while a preoperative DLCO lower than 60% was associated to a 40% pulmonary morbidity and up to 25% of postoperative mortality (11). Interestingly, up to 40% of patients with a preoperative FEV1 higher than 80% has a DLCO lower than 80% and among them the 7% has a postoperative DLCO lower than 40%; DLCO should therefore be always investigated regardless the values of FEV1 (12,13). Together with preoperative values, predicted postoperative (PPO) FEV1 and DLCO can be calculated and they are very sensitive prognostic factors (9,14).

In this cohort of patients an induction therapy is often performed before surgery. Some authors reported a detrimental effect of induction treatment on pulmonary function; in particular DLCO seems to be the most affected parameter (15), even if the long term effect is not clear (16). Consequently, PFTs and DLCO tests should be repeated after neoadjuvant therapy.

In patients undergoing a pneumonectomy, lung function is usually more severely impaired and functional reserve is decreased as well (17,18); consequently, a more careful evaluation of lung and cardiac function is mandatory in the work up of this kind of patients (19). Brunelli and colleagues (18) suggest a routinary a cardiopulmonary exercise test (CPET) before pneumonectomy regardless PFTs and DLCO preoperative and PPO data. Concurrently, echocardiography has been advocated as necessary in the perioperative management of pneumonectomy to evaluate right ventricular function for the risk of developing or worsen pulmonary hypertension (20).

**Diagnosis of T category**

Diagnostic tests should aim to maximize the yield for both diagnosis and staging avoiding unnecessary invasive tests (21). In large and centrally located NSCLC, in particular with previous episodes of haemoptysis, sputum cytology could be the first diagnostic step in with sensitivity and specificity ranging from 42% to 97% and from 68% to 100% respectively. Nevertheless, this results are strongly influenced by the position of the cancer and the number of specimen collected (22); as a consequence, sputum cytology might be performed, but a negative results required further investigation (21). In case of centrally located masses, bronchoscopy is the procedure of choice to yield specimen either for histologic or cytological examination; overall sensitivity is 88% (21), but it has been reported to be 74%, 48% and 59% for forceps biopsy, washing and brushing respectively. Furthermore, an endobronchial needle aspiration can increase sensitivity of bronchoscopy (23).
In case of peripheral lesions, data are less encouraging with an overall sensitivity of 78% and transbronchial needle aspiration seems to be the most sensitive tool in this setting (65%) (22). Nonetheless, sensitivity might be increased by the use of fluoroscopy (24), by a larger number of specimen (25) and by larger tumor diameter (in particular if larger than 2 cm) (26,27). Radial-endobronchial ultrasound (r-EBUS) and electromagnetic navigation (EMN) are relatively new techniques that might increase sensitivity of endoscopic procedures for peripheral nodules. In a meta-analysis, r-EBUS showed to have a sensitivity of 73% and specificity of 100% for peripheral nodules, with higher diagnostic yield for lesion larger than 2 cm (28); additionally, a single centre prospective study showed a diagnostic yield rate of 74% for peripheral nodules (29). Concurrently, a combined use of EBUS and EMN might lead to an interesting diagnostic yield of 93% (30). Nonetheless, transthoracic needle aspiration (TTNA) is currently considered the gold standard for peripheral NSCLC with a sensitivity of 90% (21); CT guided TTNA seems to lead to better results in terms of sensitivity rather than fluoroscopy (92% versus 88%) (22). Moreover, the use of a needle core biopsy seems to bring some advantages compared to fine needle aspiration (FNA); as a matter of fact, despite similar sensitivity for malignancies, it can reach better results in defining non-malignant lesion and to yield enough tissue for genetic and mutation analysis. Importantly, TTNA has a relatively high rate of false negative results (31) and has a moderate complication rate (32).

**Superior vena cava (SVC) involvement**

Lung cancer invading SVC are quite rare accounting for less than 1% of operable patients. These tumors are often centrally located, possibly requiring pneumonectomy, and might infiltrate the phrenic nerve, which therefore must be sacrificed in the majority of cases.

In the preoperative management of NSCLC involving SVC extension of the infiltration can be studied with cavography with simultaneous injection of contrast agent from both upper limbs, even if this technique might be heavily biased by the presence of overlaying structures which might results in inconclusive images (33,34). Recently, CT angiography (CTA) and magnetic resonance angiography (MRA) has been proposed to assess vessel involvement (Figure 1). Both CTA and MRA showed a higher sensibility compared to cavography in discriminating different anatomical structures and eventually extent of vascular invasion (33); interestingly, some authors reported a similar sensibility both for un-enhanced and enhanced MRA, which might further reduce invasiveness of the test (35,36). Additionally, Ohno and colleagues (37) report a better quality of radiological images with the use of electrocardiographically (ECG)-triggered MRA. Lastly, a echocardiography is mandatory to exclude the presence of thrombus in the right atrium (34).

**Tracheal and carinal involvement**

Bronchoscopy is fundamental in the work up of airways involvement. Mitchell and colleagues (38) suggest the preoperative the use of rigid bronchoscopy not only to verify feasibility of the resection, but also to plan it in details. Furthermore, preoperative rigid bronchoscopy could be useful to perform an endoscopic debulking to prevent the development of postoperative pneumonia.

**Aorta involvement**

In one large European multicentre study (39) and a single institution paper (40) of NSCLC invading thoracic aorta, authors suggest that possible aortic infiltration should be investigated both by contrasted CT and MRI, which can adequately define particular of vascular invasion. On the other hand, none of the authors suggest the routinely use of angiographic tests.

**Left atrial involvement**

Intrapericardial invasion of the heart by NSCLC is generally considered a contra-indication for surgery;
nevertheless, left atrium might be involved either by a direct diffusion of the tumor or by a neoplastic thrombus arising from the pulmonary vein. Echocardiography is the first-level test to assess heart involvement; in particular, transesophageal echocardiography can be used both in the preoperative workup and as intraoperative monitoring to verify haemodynamic impact of left atrium clamping, as described by Stella colleagues in a series of 31 consecutive cases (41). Beside echocardiography, Galvaing et al. (42) suggests a routinary use of preoperative cardiac MRI to assess a possible infiltration of interatrial septa. In case of heart involvement, a cardio-pulmonary bypass (CPB) should be used, even if many authors reported the use of a clamp-and-suture technique.

**Superior sulcus tumors**

Superior sulcus tumor might be considered as T3 or T4 according to the extension to the vertebræ, the subclavian vessels or the brachial plexus beside the chest wall. Although T4 are not uniformly considered operable, Waseda and colleagues (43) report similar long term outcomes compared with T3 in experienced hands. Preoperative staging should always consider MRI for a better definition of the involvement of the surrounding structures and better define the surgical approach.

**Diagnosis of N category**

N status should probably be considered the most important prognostic factors in the management of T4 tumors. As a matter of fact, beside the technical evaluation of surgical resectability of the T component, lymph-node involvement is crucial to decide the better therapeutic path to follow. In a multicentre study, Reed et al. (44) confirmed the utility of PET scan, in particular for the staging of mediastinal nodes and unexpected metastasis, while Cerfolio et al. (45) suggested that, in case of positivity at PET scan in a mediastinal lymph-node station or a distant organ, further analysis and possibly histological biopsy should be always performed to confirm the positivity. The routinely use of PET scan is strongly recommended also by the National Comprehensive Cancer Network (NCCN) and the European Society of Thoracic Surgeons (ESTS) (46) guidelines for its higher sensitivity (80–90%) and specificity (85–95%), compared with other radiological techniques. Concurrently, a recent meta-analysis (47) comparing PET-CT and diffusion-weighted MRI finding a better sensitivity for the latter; nevertheless, to date, no high grade evidences justify the routinary use of Magnetic Resonance for the specific diagnosis of N component. In addition to this, ESTS guidelines (46) pointed out some exception in the solely use of PET-CT for the staging of mediastinal lymph-nodes, which are: tumors larger than 3 cm, suspected N1 and centrally located tumour without suspected nodes on CT or PET scan. It is therefore clear that in case of a T4 tumour, the negative predictive value (NPV) of PET-CT in the investigation of mediastinal lymph node should be always taken with caution and further analysis should be performed, also in case of a completely negative preoperative radiological work up.

EBUS techniques and endoscopic ultrasounds (EUS), are commonly used by endoscopists and thoracic surgeons and they allow the exploration of almost all mediastinal lymph-node stations (48), except station 5 and 6 which are not recommended to be explored with these techniques. Trials and meta-analysis (49-54) investigated the specificity and sensitivity of each technique, finding the best results with the combined use of EUS and EBUS (sensitivity of 83% to 94% for mediastinal staging of lung cancer), reducing the need for further invasive diagnostic procedures (46,55,56). Surgical approaches for lymph-node staging account for video-assisted mediastinoscopy (VAM), video-assisted mediastinoscopic lymph-adenectomy (VAMLA) (57) transcervical extended mediastinal lymphadenectomy (TEMLA) (58) and VATS; although they are standardized and safe procedures, they are plagued by a higher incidence of morbidity compared to endoscopic procedures. VAM is the most diffuse surgical procedure for the evaluation of pathological mediastinal lymph-nodes; it allows a histological sampling of all paratracheal stations, subcarinal and the most proximal hilar stations; conversely, stations 5, 6, 8, 9 are not reachable (46). The use of VAMLA and TEMLA have been described by several institutions, but their use it is neither largely diffuse nor even suggested by ESTS guidelines as morbidity and mortality rates are significantly higher than VAM. On the other hand, investigation of station 5 and 6 might require different approaches. VAMLA and TEMLA showed the highest NPV, which reaches an impressive 98.7% (46). Furthermore, also VATS and anterior mediastinotomy (Chamberlain procedure) can be performed as diagnostic procedures.

Interestingly, Mitchell and his colleagues advocated for the use of mediastinoscopy just before surgical resection of tumors invading trachea, as it allows not only a correct
analysis of nodal status prior to a complex surgical procedure, but also it can free the trachea by creating the pretracheal space (38).

Induction therapy is frequently requested for locally advanced NSCLC. Restaging is therefore mandatory after neoadjuvant treatment to re-assess the nodal status and consequently give the proper indication (59). CT scan and PET-CT lose part of their sensitivity, specificity and NPV in the restaging after induction therapy and are therefore not fully reliable leading to over- or down-staging (60). As a matter of fact, EBUS and EUS should be used as first line procedures to assess possible persistence of disease, but their sensitivity and false negative rate suggest the use of a surgical staging in case of negative results (59,61,62). Although mediastinoscopy in naïve patients is feasible and safe even after induction therapy (63), remediastinoscopy is a feasible, but challenging procedures that should be performed with caution in experienced centres (59,61).

**Diagnosis of M category**

Presence of distant metastasis is a contraindication for surgical resection in T4 NSCLC and they should be investigated prior to any invasive procedure. In a meta-analysis investigating accuracy of 18F-FDG PET-CT in detecting lung cancer metastasis, Li and colleagues (64) reported a sensitivity and specificity of 92% and 97% respectively. Concurrently, two meta-analysis (65,66) comparing PET-CT and MRI found similar results in terms of sensitivity and specificity suggesting that a combined use might improve the preoperative staging. Nevertheless, due to the baseline cerebral activity, PET-CT is not suitable to a correct staging of the brain. In stage III or IV tumors, American College of Chest Physicians (ACCP) guidelines suggest to investigate the brain using MRI or CT scan even in patients with no clinical sign of cerebral involvement (5). Concurrently, a single-institution Korean study suggested that evaluation of the brain might be suggested only in patients with higher risk factors (67).

**Summary**

T4 tumors represent a rare presentation of NSCLC and they can be considered a double challenge for thoracic surgeons: they imply a correct staging and a correct evaluation of technical feasibility of surgical resection. In fact, both N status and radicality of the intervention are two fundamental prognostic factors that strongly affect long term results. In order to choose the correct treatment, multidisciplinary discussion is mandatory and should include thoracic surgeons, oncologists, radiation oncologists and interventional pneumonologists. Moreover, three main points should be always followed in the management of T4 NSCLC: firstly, surgical treatment of T4 tumors usually required skills and experience and they should be referred to higher volume institutions with an acceptable expertise (9); secondly, CT scan, PET-CT, and any further analysis should be performed on a case-by-case fashion according to anatomic and oncologic features; lastly, pulmonary and cardiac functionality should be investigated in details.

In conclusion, management of T4 NSCLC require a multidisciplinary and multimodality work-up in order to decide the better and more correct treatment for the disease.

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**Footnote**

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

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