Review Article

Mediastinal up-staging: risk factors and prognosis: a narrative review

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Objective: Mediastinal nodal upstaging is defined as increased nodal stage (pN2) at pathological analysis after surgical resection in patients staged as cN0-1. The aim of this narrative review is to analyze the principal risk factors for mediastinal nodal upstaging and to evaluate the prognostic implications for patients affected by non-small cell lung cancer (NSCLC).

Background: Lymph node involvement after surgery is one of the most important prognostic factors in NSCLC and the main determinant for adjuvant therapy after surgery. Several studies evaluated any possible factors involved in postoperative nodal upstaging.

Methods: All works were reviewed and results summarized in order to identify the main risk factors and prognostic variables in mediastinal upstaging.

Conclusions: The main risk factors recognized and confirmed by authors are: tumor size, tumor centrality, adenocarcinoma histology and number of nodes retrieved. Other factors like surgical approach, upper lobe tumors, consolidation/tumor ratio or clinical comorbidities (like diabetes, pneumonia or tubercolosis history) were reported only by some authors. In patients at risk for nodal upstaging, limited or sublobar lung resections are not recommended because the type of resection often precludes a radical lymphadenectomy for an accurate staging. In NSCLC patients with a mediastinal involvement at postoperative staging, adjuvant chemotherapy is the treatment of choice. The role of adjuvant or concomitant radiotherapy is still a debated topic. However, as all studies underlined, the rate of unexpected pN2 can be low if all international guidelines are followed in preoperative staging.

Keywords: Nodal upstaging; lymphadenectomy; non-small cell lung cancer (NSCLC); risk factors

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Introduction

Mediastinal nodal upstaging after surgical resection for non-small cell lung cancer (NSCLC) is defined as the finding of mediastinal node disease (pN2) at pathological staging in presumed clinical N0-1 tumors (1,2).

Pathological mediastinal lymph node involvement is one of the most important prognostic factors in NSCLC and the main determinant for adjuvant therapy after surgery.

The aim of this review is to analyze the principal risk factors for mediastinal nodal upstaging and to evaluate the prognostic implications for patients affected by NSCLC.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/vats-21-24).

Background

The 2014 revision of the European Society of Thoracic Surgeons (ESTS) guidelines (3) for preoperative mediastinal lymph-node staging consider computed tomography (CT) and 18F-fluordeoxyglucose positron emission tomography (FDG PET) the starting point for mediastinal staging. When CT and/or PET-CT identify positive lymph-nodes, endobronchial ultrasound (EBUS) and/or endoscopic ultrasound (EUS) fine-needle biopsy (TBNA) must be performed for tissue confirmation. If nodes are negative at radiological evaluation, mediastinoscopy or video-assisted mediastinoscopy (VAM) is indicated.

The tissue confirmation is also indicated when CT and/or PET scan are negative on the mediastinum but may underestimate the nodal involvement, like when hilar positive nodes are suspected or the tumor is greater than 3 cm and has an adenocarcinoma histology or located close to the hilar structure.

Each biopsy methodology has a proper sensitivity and specificity in particular contests.

In patients with tumors classified as clinical N0 at PET-CT, EBUS-TBNA has a sensitivity of 0.17–0.41 to detect mediastinal nodal disease. In resectable patients classified as clinical N1 at PET-CT, it has a sensitivity of 0.38–0.53 to detect mediastinal nodal disease (3).

The use of a videomediastinoscope (VAM) over a standard mediastinoscope improves the visualization of the operative field, which may increase accuracy and facilitate possible teaching process.

Staging values described for VAM are: sensitivity ranging from 0.78 to 0.97, and negative predictive value ranging from 0.83 to 0.99, with a complication rate of 2%.

American College of Chest Physicians (ACCP) guidelines [2013] (4) and ESTS guidelines [2014] (3) are in agreement for preoperative mediastinal staging in NSCLC.

Instead, in case of central tumors, tumors greater than 3 cm or cN1 (on CT or PET/CT), there is a little disagreement between American and European guidelines about the best staging procedure to start with. The ACCP guidelines suggest endosonography methods over surgical procedures as the best first test (level of evidence 2B), while the ESTS guidelines describe that the choice between mediastinoscopy with biopsies, or with pre-surgical lymphadenectomies (VAMLA or TEMLA) or endoscopic staging by EBUS/EUS with FNA depends on local expertise (level of evidence V). The guidelines of the European Society of Gastrointestinal Endoscopy (ESGE), produced in cooperation with the European Respiratory Society (ERS) and ESTS, also suggest the use of endobronchial and/or esophageal sonography for mediastinal staging (recommendation grade C); and if sonography is negative, mediastinoscopy must be considered (5).

In this setting, video-assisted thoracic surgery (VATS) can have a role in surgical staging of ipsilateral nodes, in particular the aorto-pulmonary window nodes (stations 5–6), if enlarged on CT and/or PET-CT positive (3). Staging values of VATS show a sensitivity ranging from 0.58–1 (median 0.99) and a false-negative rate of 4%, with an average complication rate of 2%. There is only one study by Jaklitsch *et al.* (6) addressing VATS as a restaging technique. The study enrolled 75 patients between 1998 and 2003. Sensitivity, specificity and negative predictive value of VATS for restaging were 67%, 100% and 73%, respectively. The authors reported a feasibility of 40%.

Minimally invasive endoscopic techniques (EBUS-TBNA and EUS-FNA or their combination) are included in the staging algorithms as the first invasive technique, when they are available.

However, their negative results should be validated by surgical methods. To date, mediastinoscopy remains the gold standard in the staging process. It provides reliable information on the mediastinal nodal status and/or direct mediastinal invasion of the primary tumor (7).

Nevertheless, not all thoracic centers follow all the recommendations expressed in international guidelines for preoperative NSCLC staging. In particular, often a mediastinoscopy was not performed in patients with suspicious nodal enlargement but negative PET-CT after a negative EBUS (8), or in patients with large tumor but negative PET-CT. A retrospective revision of Italian VATS group data showed how only 3.5% of patients underwent any form of invasive mediastinal staging (with a proportion of clinical T2 and T3 of 22.1% and 1.8%, respectively), having a postoperative N2-upstaging of 6.5% (8). According to Cancer and Leukemia Group B prospective clinical trial (CALGB 9761), 28% of patients affected by stage I NSCLC were upstaged.

In particular, previous studies reported a 10–15% prevalence of mediastinal occult lymph node metastases (9) after surgery.

On the other hand, the ongoing MEDIASTrial (10)

has been comparing results of two different diagnostic strategies, with or without mediastinoscopy, to test the hypothesis that omitting mediastinoscopy after negative endosonography, in patients with central/large tumor or suspicious lymph nodes on PET-CT, not only does not increase the percentage of pathological N2-upstaging but also reduce time until final surgery.

Methods

In order to identify the studies evaluating the mediastinal nodal upstaging and the implicated prognostic factors, PubMed, Web of Science, Scopus and Google Scholar were interrogated. The literature research was conducted by combining Medical Subject Headings terms such as "mediastinal nodal upstaging", "NSCLC nodal upstaging", "mediastinal nodal upstaging and risk factors", "NSCLC and occult mediastinal nodal disease". Only English literature was examined.

All works were reviewed and results summarized in order to identify the main risk factors and prognostic variables in mediastinal upstaging.

Mediastinal upstaging risk factors

Each preoperative staging method has its own false-positive and false-negative predictive values. Therefore, postoperative upstaging can reflect or an inaccurate preoperative staging or—if all international guidelines were respected, as desired in any good study—the intrinsic efficacy of the staging methodologies for some hilar and peribronchial nodal stations (2). Furthermore, the nodal upstaging is also a parameter of the efficacy of surgical lymphadenectomy and therefore of the surgical approach employed (11).

There are several works investigating the risk factors for nodal upstaging in early stage lung cancer—after open, VATS surgery or both—that in the present work will be analyzed and summarized (*Table 1*).

Rocha and colleagues (12), in their study on 109 patients with clinical stage I/II, concluded that lower lobe location is a risk factor for upstaging in early stage NSCLC. The same conclusion was reached by Licht *et al.* (2) analyzing the data of 1,523 patients from the Danish Lung Cancer Registry (from 2007 to 2011), operated on by Thoracotomy or VATS. Indeed, at logistic regression analysis, they found as risk factors for nodal-upstaging: T stage (P=0.01), invasive mediastinal staging (P<0.001), number of lymph node stations dissected (P=0.02), thoracotomy approach (P<0.001), and lower lobes (P=0.045).

Al-Sarraf *et al.* (13) retrospectively analyzed the main risk factors for postoperative nodal upstaging on a group of 100 patients; they found out at multivariate analysis that rheumatoid arthritis, non-insulin dependent diabetes, tuberculosis history, atypical adenomatous hyperplasia and pneumonia were associated to an inaccurate mediastinal node staging. The highest rate of upstaging was in nodal station 4 (11%, P=0.01) followed by station 7 (10%, P=0.02) and station 9 (3.5%, P=0.01).

Another retrospective study on 224 patients affected by stage I NSCLC with a negative mediastinal staging at CT and PET (14), registered a pN2 upstaging in 6.5% cT1 patients and in 8.7% cT2 patients. The main predictors of occult N2 disease were: central tumors (P<0.001), larger clinical T size (P<0.001), adenocarcinoma histology (p:0.082) and a higher PET maximum standardized uptake value (SUV_{max}) of the primary tumor (P=0.017).

Decaluwé *et al.* (9) evaluated centrality of lung tumors as risk factor for nodal upstaging and tested 5 definitions of central tumors (1/3, inner 2/3, contact with bronchovascular structures, <2 cm from bronchus or endobronchial visualization) in cN0 patients after PET-TC. On this study on 813 patients, a nodal upstaging (pN+) was found on 21% cases, of whom 8% was pN2-N3. Central tumor locations had 4 times higher odds for pN+ upstaging (P<0.001), while no significant odds were found for pN2-3. Furthermore, no one of the 5 centrality-definition had a discriminative predictive value for occult pN2-3. The same topic was also investigated by Boada and colleagues (20) that confirmed tumor centrality as risk factor for hilar upstaging (P=0.006) on 323 patients underwent anatomical resections for NSCLC <IIB. They also stated that differences in hilar upstaging related to different approach (VATS *vs.* thoracotomy) were only related to selection biases (in several centers, large or central tumors are often operated by open approach and centrality is a risk factor for hilar upstaging); indeed, these differences between techniques vanished when central tumors were excluded from the analysis. The same findings were also confirmed in a retrospective analysis by Nachira *et al.* (23) on 160 patients affected by cN0 NSCLC underwent anatomical resection by open or Uniportal VATS approach [the only significant risk factor for a pN1 upstaging was central or larger (>3 cm) tumor (P=0.0004)].

Marulli *et al.* (17) found tumor size (P=0.0275) and adenocarcinoma histology (P=0.0382) as risk factor

Table 1 Studies that evaluated mediastinal nodal upstaging and risk factors

Study	Patients (n)	Clinical stage	Surgical access	pN2-upstaging	Risk factors (P value)
Rocha (12), 2004 (retrospective)	109	I–II	Thoracotomy	8.30%	Lower lobe location (<0.006)
Al-Sarraf (13), 2007 (retrospective)	100	I–IIIA	Thoracotomy (?)	3.5–11%	Rheumatoid arthritis (0.048) Type 2 diabetes (0.017) History of tuberculosis (0.038) Pneumonia (0.012) Atypical adenomatous hyperplasia (0.041)
Lee (14), 2007 (retrospective)	224	I	Thoracotomy (?)	6.5–8.7%	Central tumors (<0.001) Larger clinical T size (<0.001) Adenocarcinoma histology (0.082) Higher tumor PET-SUV_{max} (0.017)
Licht (2), 2013 (retrospective on a National registry)	1,513	I	Thoracotomy *vs.* VATS	11.5% *vs.* 3.8%	Clinical T stage (0.01) Invasive mediastinal staging (<0.001) Number of lymph node stations dissected (0.02) Surgical approach (<0.001) Lower lobe (0.045)
Wilson (15), 2014 (retrospective)	302	I	RATS	4.30%	–
Lee (16), 2015 (retrospective)	211	I–II	VATS/RATS	6.9% (VATS) *vs.* 3.8% (RATS)	–
Decaluwé (9), 2018 (retrospective)	813	II	Thoracotomy	8%	Central tumor location (<0.001)
Marulli (17), 2018 (retrospective)	231	I–IIB	VATS	7.40%	Tumor size (0.0275) Adenocarcinoma histology (0.0382)
Ismail (18), 2018 (retrospective)	136	I–IIB	VATS	5.20%	Positive nodes in stations 2–4 (0.009) and 5–6 (0.027)
Moon (19), 2018 (retrospective)	486	II	Thoracotomy	3.90%	Nodule diameter (0.039) Consolidation/tumor ratio (0.001)
Boada (20), 2019 (retrospective)	323	I–IIA	Thoracotomy *vs.* VATS	6% (thoracotomy) *vs.* 6.5% (VATS)	Tumor centrality (0.006)
Marulli (21), 2020 (retrospective on a National registry)	3,276	I–IIB	VATS	2.40%	Adenocarcinoma histology (<0.001) Higher tumor grade (<0.001) Higher pathologic T status (<0.001) Tumor size >3 cm (<0.001) Upper lobe tumors (0.049) Interestingly >12 nodes resected (<0.001)
Yang (22), 2016 (retrospective on a National registry)	30,040	I	VATS/RATS *vs.* open	3.8% (open) *vs.* 4.1% (RATS/VATS)	–

RATS, robot-assisted thoracic surgery; VATS, video-assisted thoracic surgery.

for nodal upstaging on 231 patients underwent VATS lobectomy for NSCLC. On a wider analysis on 3,276 patients from Italian VATS group (21) underwent VATS lobectomy for cT1–T3N0 NSCLC, nodal upstaging was found in 12.7% of cases (6.2% pN1, 2.4% pN2 and 4% pN1+N2). The main risk factors associated with nodal upstaging were: adenocarcinoma histology (P<0.001), higher tumor grade (P<0.001), higher pathologic T status (P<0.001), tumor size >3 cm (P<0.001), upper lobe tumors (P=0.049) and, interestingly, more than 12 nodes resected (P<0.001). In contrast, Lich *et al.* (2) reported a higher risk of nodal upstaging in lower lobe tumors. Ismail and colleagues (18) showed that the resection of 18 nodes was the best predictors of general nodal upstaging (13.3% of cases in a series of 136 patients), while the resection of 7 hilar lymph nodes for N1 upstaging and the resection of 11 mediastinal nodes for N2 upstaging.

Moon and colleagues (19) evaluated the role of the consolidation/tumor ratio (a radiologic parameter for identifying pathologic subsolid lesions on chest CT) in postoperative nodal upstaging. They found that in peripheral cN0 lung tumors, nodule diameter and consolidation/tumor ratio were significant predictors for nodal upstaging [hazard ratio (HR) =2.259, P=0.039; HR =173.645, P=0.001, respectively].

Several studies were published about safety and effectiveness of VATS in lymphadenectomy compared to standard open surgery and robot-assisted thoracic surgery (RATS) surgery. While according to some authors (16,22) VATS and RATS can have the same results in terms of nodal upstaging, Wilson (15) and colleagues reported a superior nodal upstaging after RATS. Toker *et al.* (11) believed that expert VATS surgeons can perform a lymph node dissection similar to open surgery, that probably can't be achieved by novice surgeons. On this aspect RATS surgery seems to show its superiority according to Toker, giving even to surgeons in early experience the possibility to replicate open dissection, thanks to the high technology of instrumentations, that supports the operator in his surgical movements. Therefore, in expert hands, surgical approach should not be considered a predictor for nodal upstaging.

Prognostic implications of nodal upstaging

If the preoperative staging is improved in all categories of patients at risk of postoperative upstaging, the treatment planning can be more effective and overall survival increased.

Some authors (24,25) showed how lymph node involvement in post-operative staging and unexpected pN2 disease worsen survival, in general.

However, in a recent study, Obiols *et al.* (26) found a reasonable survival rate (40% at 5-year follow-up) compared to the 10–30% of previous studies (24,25).

They explained the result by an accurate preoperative staging. Indeed, the rate of unexpected pN2 is low if preoperative staging is conducted according to the ESTS guidelines.

Therefore, they concluded that surgery may have a role and should not be excluded in unexpected pN2 patients if a compete resection can be achieved.

Furthermore, due to the impossibility to perform a radical lymphadenectomy, limited or sublobar resection should be avoided in patients having risk factors for unexpected lymph node metastases and subsequent post-operative nodal upstaging. Indeed, the correct staging in this subset of patients allows the most accurate adjuvant treatment.

Chemotherapy is recommended as adjuvant treatment, while the role of postoperative radiotherapy is not well established yet (25).

Conclusions

As emerged by the studies on postoperative nodal upstaging, tumor size, tumor centrality, adenocarcinoma histology and number of nodes retrieved seem to be the most common and recognized risk factors for nodal upstaging.

All studies available and analyzed on the topic were retrospective and most of them related to single center experience.

However, all of them contributed in corroborating and promoting the application of ESTS and ACCP guidelines on the correct preoperative staging of NSCLC patients, above all in patients at risk, in order to plan the most appropriate pathway of care and to improve postoperative survival.

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