

Nodal upstaging: effects of instrumentation and three-dimensional view in clinical stage I lung cancer

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Abstract: Nodal upstaging after surgical intervention for non-small cell lung cancer (NSCLC) is defined as the presence of unsuspected pathologic hilar (pN1) or mediastinal (pN2) disease detected during the final histopathologic evaluation of surgical specimens. The prevalence of pathologic nodal upstaging is used as a quality measure for the definition of the completeness of the nodal dissection. Risk factors for nodal upstaging may be patient-related (history of tuberculosis, rheumatoid arthritis, and diabetes mellitus), or tumor-related (central tumor, higher T stage, higher SUVmax value, or adenocarcinoma). Actually, the theoretical superiority of a minimally invasive resections is the lymph node dissection. Studies may suggest that, expert video-assisted thoracoscopic surgery (VATS) surgeon could do similar lymph node dissection as it is done in open. Robotic surgeons may replicate the results of lymph node dissection in the open techniques. The possible reason for this is the instrumental superiority provided by the higher technology.

Keywords: Video-assisted thoracic surgery; robotic-assisted thoracic surgery (RATS); thoracotomy; lung cancer; nodal upstaging

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Introduction

Definition of the ideal surgery for lung cancer patients could be concluded as follows: an approach with minimal morbidity allowing patients to return to daily activities in short time, but without any compromises in the oncologic principles. Minimally invasive surgeries are performed to the lung cancer patients with abovementioned expectations. Unfortunately, very few data exists to define the oncologic quality and equivalence of the minimally invasive surgery versus open surgery.

To define the oncologic equivalence, the prevalence of pathologic nodal upstaging is used as a quality measure for the definition of the completeness of the nodal dissection, and surgery by comparing video-assisted thoracoscopic

surgery (VATS) and thoracotomy patients (1,2). Several studies have shown that VATS has less nodal upstaging than thoracotomy, suggesting a difference in the completeness of nodal evaluation. However, none has demonstrated a difference in overall or disease-free survival (2).

Here, in this study we will try to define the effects of instrumentation and three-dimensional view in clinical stage I lung cancer for nodal upstaging.

How is nodal upstaging for lung cancer defined?

Nodal upstaging after surgical intervention for non-small cell lung cancer (NSCLC) is defined as the presence of unsuspected pathologic hilar (pN1) or mediastinal (pN2)

disease detected during the final histopathologic evaluation of surgical specimens, in patients presumed to have clinical N0 diseases (1,2). Nodal upstaging may occur in a significant proportion of the patients. According to Cancer and Leukemia Group B prospective clinical trial (CALGB 9761), 28% of clinical stage I lung cancer patients were upstaged (14% stage II and 14% stage III) (3).

Are there any predictors for nodal upstaging in lung cancer?

Hilar and mediastinal lymph nodes can be evaluated either by non-invasive (chest computed tomography, positron emission tomography, etc.) or by invasive (mediastinoscopy, endobronchial ultrasound, VATS, etc.) methods. Each of these techniques has its own false-positive or negative predictive rates. As imaging did not identify the nodal metastases, nodal upstaging is likely dependent on the efficacy of the surgical lymph node evaluation. Therefore, the prevalence of nodal upstaging may be a landmark for the completeness of nodal evaluation (1,2). Incomplete staging might also happen since invasive staging of both hilar and peribronchial lymph nodes remains challenging with more recent techniques including endobronchial or endoscopic ultrasound (2).

Rocha *et al.* (4) investigated the predictors of upstaging in 109 patients with clinical stage I/II lung cancer. Their study is of limited value, since the authors did not analyse specifically the predictors of upstaging due to N stage, but included patients upstaging due to T stage. They concluded that early-stage NSCLC located in the lower lobes was associated with upstaging after surgery. Another study investigating nodal upstaging was reported by Al-Sarraf *et al.* (5). This study evaluated the risk factors of inaccuracy in N staging (both downstaging and upstaging), and concluded that inaccurate nodal staging was common in patients with history of tuberculosis, rheumatoid arthritis, and diabetes mellitus. In patients with abovementioned comorbidities, especially interlobar lymph nodes are adhesive to pulmonary artery and its branches. Many times surgeons would not perform a proper dissection in the benefit of the patient to prevent bleeding. Robotic surgery is an excellent type of surgery to dissect these adhesive nodes in our experience.

Contrary to the abovementioned studies, the study of Lee *et al.* (6) is more specific. The authors investigated the risk factors of occult mediastinal metastases in clinical stage I NSCLC patients (n=224) with CT and PET-CT

negative results for mediastinal lymph nodes. According to this study, risk factors for N2 upstaging in stage I NSCLC were the presence of a central tumor, tumor size larger than 2 cm, and a SUVmax value of more than 4 for primary tumor. Besides, the authors concluded that there was a trend to occult nodal mediastinal metastasis in patients with adenocarcinoma. In a recent study, Decaluwé and colleagues (7) pointed out that centrally located tumors had a significant impact on N1 upstaging.

Some other studies also reported that the rate of nodal upstaging generally may increase with increasing clinical T stage (2,8-10). Licht *et al.* (2) also reported a significant nodal upstaging in lower lobe tumors. The type of the operation also affected the rate of nodal upstaging. Khullar and colleagues (11) demonstrated that lobar resections was associated with a higher rate of nodal upstaging compared to sublobar resections.

Based on the abovementioned studies, we can specifically describe the candidate patients for nodal upstaging. N1 and N2 level proper lymph node dissection should be a must in lung cancer patients to define the adjuvant treatment after the surgery.

VATS as a minimally invasive technique and its effects on nodal upstaging compared to thoracotomy

Too many articles have been published on VATS lobectomy during the past two decades. VATS has been generally shown to have its benefits, including decreased pain, lesser trauma, shortened length of postoperative stay, and increased compliance to adjuvant chemotherapy compared to thoracotomy. But the level of evidence for its superiority is low.

Survival rates of VATS are similar with those of thoracotomy, but orthodox surgeons maintained the criticisms for VATS resections as if there is a concern for a less systematic lymph node dissection. There are many studies which have demonstrated no difference in the number of lymph nodes and lymph node stations dissected (12-14). Some other groups have found the LN dissection to be incomplete during VATS (15).

Several studies compared VATS with thoracotomy in terms of nodal upstaging, and reported that the rate of both techniques were similar (12,16-18). Contrary to these studies, there are major studies based on larger number of patients favored thoracotomy to detect unsuspected nodal metastasis. Boffa *et al.* (1) investigated 11,513 patients

from the Society of Thoracic Surgeons database undergoing anatomical pulmonary resections in clinical stage T1N0M0 or T2N0M0 lung cancer. They concluded that upstaging from N0 to N1 was more common in the thoracotomy group, however upstaging from N0 to N2 was similar between both approaches. Licht *et al.* (2) recruited their patients from the Danish Lung Cancer Registry database (n=1,513). The authors demonstrated that the rates of upstaging from N0 to both N1 and N2 were higher in patients undergoing thoracotomy. A very recent study reported by Medbery and colleagues (19) consisted of 16,983 patients collected from the National Cancer database undergoing lobectomy for early stage lung cancer revealed that the overall nodal upstaging was more common in thoracotomy group.

We can claim that expert VATS surgeons could provide similar lymph node dissection with VATS techniques. However, novice VATS surgeons may not provide similar capabilities, as they could do in open techniques. One other possible explanation for lower rate of nodal upstaging in VATS may be the selection of fissureless technique to prevent air-leak after VATS surgery. In this technique, as the fissure is not dissected, lymph node may remain undissected.

Theoretical superiorities of robotic surgery and its possible reflections

In the past decade, robotic assisted thoracic surgery (RATS) approach to anatomic lung resection became the newest minimally invasive technique, and studies have shown its feasibility and safety (20-22). Three-dimensional high-definition camera, dexterity, and precision in dissection are its superiorities compared with VATS. An important aspect of the RATS is the depth and accuracy of hilar and mediastinal nodal dissection (23). In comparative studies by Veronesi *et al.* (20) and Cerfolio *et al.* (21) the median numbers of lymph nodes removed by RATS and thoracotomy procedures were closely similar, suggesting that RATS achieves similar oncological radicality to that achieved by thoracotomy. In our recent study comparing three approaches (thoracotomy *vs.* VATS *vs.* RATS), we demonstrated that RATS could yield more peribronchial (number 11 and 12) compared to the other two techniques (24). We believe that this higher rate of interlobar lymph node dissection is due to our preference in performing segmentectomy operations more often which increases the number of dissected level 11 and 12 nodes.

Another reason may be the fact that as the table surgeon staples the vessels, the console surgeon wants to provide a very clean field around the vessels for an easy stapling.

The reflections of RATS in the nodal upstaging remains controversial. Wilson and colleagues (25) reported that the rate of nodal upstaging of RATS was greater than that of VATS. Contrary to this study, Lee *et al.* (26) demonstrated that both techniques achieved similar rates of nodal upstaging. A very recent study by Yang *et al.* (27) compared 7,824 VATS and 2,025 RATS lobectomy patients using propensity score matching, and concluded that both approaches yielded similar results in terms of nodal upstaging.

The only study comparing three approaches (RATS, VATS and thoracotomy) in terms of nodal upstaging was recently reported. In their study, Martin *et al.* (10) demonstrated that nodal upstaging rates of RATS and thoracotomy were similar, but there was a lower upstaging rate with VATS. This study and our study claims that the robotic surgery even in the earliest experience may replicate the open surgery results.

Scrutiny of robotic surgeons

The systematic lymph node sampling or complete lymphadenectomy were accepted as the standarts for lymph evaluation after a resection either with VATS or RATS. Many times the comparisons are retrospective, however, the participating surgeons in these studies, in common, share similar philosophy regarding the role of hilar and mediastinal lymph node dissection. When VATS lobectomy was accused for not having any possibility for complete lymph evaluation, all VATS surgeons tried to demonstrate that the lymph node dissection was equal to open surgery (28). Having such an experience before, the robotic surgeons did their best to prevent the claims of incomplete lymph node dissection before any suspects rose.

Conclusions

One of the oncologic quality predictor of a resection is the lymph node dissection. Actually, the theoretical superiority of a minimally invasive resections to recently developed radiotherapy techniques is the lymph node dissection. Nodal upstaging in clinical stage I lung cancer has been shown to be around 10–30%. Studies performed up to now, may suggest that, expert VATS surgeon could do similar lymph node dissection as it is done in open. Robotic

surgeons, even in the early experience may replicate the results of lymph node dissection in the open techniques. The possible reason for this is the instrumental superiority provided by the high technology.

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Footnote

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