Editorial

Can mathematics replace anatomy to establish recommendations in lung cancer surgery?

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Provenance: This is an invited Editorial commissioned by the Section Editor Min Zhang (The First Affiliated Hospital of Chongqing Medical University, Chongqing, China).

Comment on: David EA, Cooke DT, Chen Y, *et al*. Does Lymph Node Count Influence Survival in Surgically Resected Non-Small Cell Lung Cancer? Ann Thorac Surg 2017;103:226-35.

Abstract: The greater the number of lymph node (LN) sampled (NLNsS) during lung cancer surgery, the lower the risk of underestimating the pN-status and the better the outcome of the pN0-patients due to stage-migration. Thus, regarding LN sampling "to be or not to be", number is the question. Recent studies advocate removing 10 LNs. The most suitable NLNsS is unfortunately impossible to establish by mathematics. A too high NLNsS variability exists, based on anatomy, surgery and pathology. The methodology may vary according to Inter-institutional differences in the surgical approach regarding LN inspection and number sampling. The NLNsS increases with the type of resection: sublobar, lobectomy or pneumonectomy. Concerning pathology, one LN may be divided into several pieces, leading to number overestimation. The pathological examination is limited by the number of slices analyzed by LN. The examined LNs can arbitrarily depend on the probability of detecting nodal metastasis. In fact, the only way to ensure the best NLNsS and the best pN-staging is to remove all LNs from the ipsilateral mediastinal and hilar LN-stations as they are discovered by thoroughly dissecting their anatomical locations. In doing so, a deliberate lack of harvest of LNs is unlikely, number turns out not to be the question anymore and a low NLNsS no longer means incomplete surgery. This prevents from judging as incomplete a complete LN dissection in a patient with a small NLNsS and from considering as complete a true incomplete one in a patient with a great NLNsS. Precise information describing the course of the operation and furnished in the surgeon's reports is also advisable to further improve the quality of LN-dissection, which ultimately might be beneficial in the long-term to patients. However, that procedure is of limited interest in pN-staging if LNs are not thoroughly examined and also described by the pathologist.

Keywords: Lung cancer; TNM; lymphadenectomy; lymph node number (LN number)

Submitted Feb 06, 2017. Accepted for publication Feb 09, 2017.
doi: 10.21037/jtd.2017.03.46
View this article at: http://dx.doi.org/10.21037/jtd.2017.03.46

Introduction

The effect on outcome of the number of lymph nodes sampled (NLNsS) during surgery in patients with stage I non-small cell lung cancer (NSCLC) was disclosed more than 12 years ago (1), but the minimum number of lymph nodes (LNs) to be sampled is still controversial and undefined. Recent surgical studies analyzed the effect of NLNsS on survival by operating NSCLC at early clinical N0 stage (2,3). David and coworkers (2) stratified patients by NLNsS into groups of zero LN, one to three LNs, four to 10 LNs, and more than 10 LNs, and Samayoa and coworkers (3) grouped them according to the number of LNs pathologically examined: one to four LNs, five to eight, nine to 12, 13 to16, and more than 17 LNs. NLNsS significantly influenced the overall and cancer-specific

survivals with longer survival seen in patients with greater NLNsS (2). A greater NLNsS was also correlated with a more favorable prognosis in pathologically LN-negative patients (3). Both studies advocated the removal of a minimum of 10 LNs (2,3). It is therefore understood that this threshold limit is considered necessary and sufficient to satisfactorily avoid non-curative operations.

The greater the NLNsS, the lower the risk of underestimating the status of pLNs (2): the potential of resecting unidentified micrometastases in the LNs increases and the better outcome of the remaining pN0 patients may be attributable to p-stage migration of the others (3). This p-stage migration can be illustrated in other ways. Bott and coworkers (4) demonstrated pathologic upstaging in 17% of 55,653 clinical stage I NSCLC patients: upstaged patients had greater NLNS than patients who were not upstaged (10.9 *vs.* 8.2, P<0.001). Osarogiagbon and coworkers (5) observed that patients with no LN examined (pNX resections) had survival equivalent to pN1 patients and not pN0, suggesting the importance of LN retrieval for adequate staging and treatment. Consequently, the establishment of a threshold in order to avoid, as far as possible, an under-staging that could question the curative value of surgery has become an issue of paramount importance. However, the risk of under-staging will never be reduced with certainty by setting a 10 LNs threshold for the simple reason that a greater NLNsS may be harvested in about 50% of the patients (6). Furthermore, an unquestionable numerical standard for NLNsS cannot be mathematically established because of the high variability inherent to NLNsS which is based not only on the patient (2,6) but also on surgeon and pathologic factors (2,3).

Mathematics is an accurate science but is not suitable in establishing a right NLNsS

The variability of NLNsS is related to many factors based on surgery and pathology.

The methodology may vary according to the authors. The NLNsS strongly relies on the mode of calculation and may differ from one study to another. Some studies analyze both intrapulmonary and mediastinal LNs (7-9), and others only mediastinal LNs (6,10). One study excluded patients with less than 11 LNs (9), so eliminating a potentially high percentage of patients that may have biased the results (6).

Some operative factors may be implicated. Inter-institutional differences in the surgical approach regarding LN inspection, sampling (11), and resection (10) have been reported. The staging accuracy increases with the extension of the LN dissection, and random sampling is less accurate than a complete mediastinal LN dissection (1,12). The quality of a complete mediastinal LN dissection relies on its anatomical boundaries rather than on the number of LNs harvested (13,14).

The type of lung resection is also decisive. David and coworkers (2) reported that 43.8% of the patients who underwent sublobar resection had no LN sampled. Patients who underwent sublobar resection with LN sampled had significantly fewer LNs removed compared with lobectomy or pneumonectomy (P<0.0001) (2). Razi and coworkers (15) observed that only 36.2% of patients undergoing wedge resection had LNs sampled, compared with 92.8% of patients undergoing lobectomy. Samayoa and coworkers (3) shown that the NLNsS is also correlated with increasing tumor size and not only extent of resection. Having a larger tumor was associated with more LNs removed: 53.5% of tumors >7 cm had 9 or more LNs sampled, versus 36.9% of those with tumors <3 cm. The patients who underwent less than a lobectomy had a mean of 5.6 LNs removed, compared with a mean of 9.2 LNs for those who underwent a lobectomy or bi-lobectomy, and 12.8 LNs with pneumonectomy (P<0.001). In theory, none of these operations preclude complete mediastinal dissection of the LNs, even the sublobar resections. The problem is different concerning intrapulmonary LN dissection, which may prove very difficult in case of wedge resection and to a lesser extent in case of segmentectomy. In case of lobectomy, LN dissection may seem easier; however it would be imprudent to neglect LNs from the remaining lobes. The main pitfall concerns the possibility of direct lymphatic drainages originating from the lower lobes that connect into LNs located at the level of the upper lobar bronchi. Thus, removing the upper lobar LNs is advisable, even in case of clinical N0 NSCLC of lower lobes (16).

The pathologic characteristics are inconstant. The assessment and numbering of LN specimens vary greatly between laboratories and pathologists (1,17,18). Sometimes nodal tissue is not extracted intact and one LN may be divided into several pieces, leading to an overestimation of the NLNsS (4,10,19). On the other hand, it may sometimes be difficult to separate the LNs from each other within a tissue dissected as a whole, which may lead to underestimating the actual number of LN (10).

The number of pathology examinations and the number of examined LNs may be hazardous (20): retrieval of hilar and mediastinal LNs (stations 2 to 10) entirely

depends on the surgeon, but most intrapulmonary LNs (stations 11 to 14) are sampled during gross dissection of the lung resection specimen in the pathology laboratory. Despite rigorously standardized surgical hilar/mediastinal LNs dissection, the number of LNs examined can be dictated by the probability of detecting nodal metastasis. Thus, the pathological examination may be incomplete. Meltzer and coworkers (21) conducted a prospective cohort study to evaluate inadvertently discarded LNs in redissected remnant lung resection specimens from lung cancer patients. The study included 110 patients. Discarded LNs with metastasis were found in 25 patients (23%). Patients with missed LN metastasis had an increased risk of death; patients with more than 2 missed LNs with metastasis had 4.8 times the hazard of death (P=0.0005) compared with patients without missed LN metastasis (adjusted hazard ratio 6.5, P=0.0001).

The accuracy of the NLNs may be guaranteed by the anatomy, but the number of LNs is still submitted to many variations and fluctuations

At the time of surgery, the total number of LNs in the lung and the ipsilateral mediastinum of a given individual are determined and limited: it is easy to collect some of them by sampling, but it is impossible to harvest more than they are, their number being by definition limited. The most precise number might be obtained by pneumonectomy and complete ipsilateral mediastinal lymphadenectomy.

Complete mediastinal lymphadenectomy was routinely performed as part of the surgical procedure at the beginning of NSCLC surgery in the forties (22). Nevertheless, it was progressively replaced by LNs "picking" or sampling for questionable reasons, the main one probably being the fear of increasing the operative risks of the surgical procedure whereas its usefulness was not flagrant. An international randomized trial demonstrated its harmlessness (23), but further analysis failed to demonstrate its usefulness in early stages of NSCLC (24). That study randomized patients after thorough samplings that were negative on frozen section in several N2 and N1 nodal stations, which biased the results (25). In a multicentric cross-sectional study comparing sampling with lymphadenectomy, sampling adequately recognized N2 disease in only 52% of the pN2 patients diagnosed by lymphadenectomy (26). Despite this, skepticism still prevails in the world of thoracic surgery and pneumo-oncology, the complete mediastinal dissection of LNs has difficulty to be recognized by some as the best option and many authors still look for the ideal NLNsS that might offer the least reproachable surgery possible.

We observed that the number of LNs harvested during complete LN dissection varied greatly among patients with NSCLC (6), in the mediastinum as well as in the lungs.

The NLNsS was also subject to large interindividual variations: it was higher on the right side than on the left. The NLNsS also varied from one mediastinal LN station to another. Darling and coworkers (24) found similar results and reported a median of at least 6 LNs from at least 3 stations in 99% of patients. The largest numbers of LNs were resected from stations 7 and 4R, with a median of 3 and 4 LNs, respectively. Occasionally, a few or even no LNs were found in some stations, such as stations 8 and 9. Our observations also demonstrated this high intra-individual variability.

In our study, the number of LNs also varied according to the pN status increase. Saji and colleagues (7) also reported that the mean NLNsS was greater in N1 and N2/N3 than in N0 cases. Similarly, Darling and coworkers (24) reported higher N stage to be associated with increased NLNsS. The similar results that we observed were not dependent on the surgeon's will, contrary to one of their assumptions. In effect, a complete LN dissection being systematically performed, no accessible LN was left behind. It is now recognize that tertiary lymphoid organs may appear in lymphatic malformations (27) and chronic inflammatory diseases (28). Tertiary lymphoid organs mimicking LNs represent sites of lymphoid neogenesis that also develop in most solid cancers (29-31). Our suggestion is that they might also be induced by and associated with tumoral LNs. We noticed that the NLNsS was also greater after induction therapy, which may benefit from the same hypothesis, induction therapy being performed mainly for advanced disease. The number of LNs was greater in squamous cell carcinoma than in adenocarcinoma, which may be attributable to a probably more important N1 involvement encountered in squamous cell carcinomas or to the higher proportion of pneumonectomy performed in these patients.

A complete anatomical LN dissection may offer other advantages regarding the quality of surgery

Osarogiagbon and colleagues (32) audited operative summaries and pathology reports in a NSCLC resection cohort and discovered wide discordances in identifying the extent of lymphadenectomy performed. The operating

surgeons mentioned to have performed a mediastinal LN dissection in 45% of all resections but the review of pathology reports revealed that only 8% of all resections met systematic sampling criteria, 50% had random sampling, and 42% had no mediastinal LN examined. They suggested that the discordance might arise from three sources: poor surgical LN examination practice (failure to collect nodes), problems in the transfer of specimens (loss in transit or improper communication of the source of specimens), and poor pathology examination practice (incomplete examination or inaccurate reportage). Osarogiagbon and colleagues (33) demonstrated that improvement could be obtained by avoiding poor and delayed draft operation notes, incorrect interpretation of operation narratives, and nonstandardization of LN identification during removal by using a specimen collection kit and a checklist. The concordance rate between surgeons' claims and pathology reports significantly improved from 39% to 80% (33). That study does not provide a numerical standard for NLNsS, but stress the importance of clearly describing the different procedures in order to improve the quality of the lymphadenectomy.

The complete anatomical dissection of the LNs that we advocate can offer other advantages regarding the quality of the surgery in addition to allowing the NLNsS as large and exact as possible. Lymphadenectomy should include as far as possible, as we already discussed (34), en bloc removal of surrounding fat to prevent LN-rupture and LN-splitting up, which means complete LN removal in each systematic surgically explored mediastinal LN stations, rather than random station LN sampling. Not describing the technique could question the quality of data used in clinical trials and thus their validity, and adjuvant therapy might be reliant upon such a technical data description. Thus, it is also necessary to clearly describe the technical aspect of LN dissection in the surgical reports. The idea of following a checklist during the operation as proposed by Osarogiagbon and colleagues (33), the surgeon systematically indicating whether or not LNs were present and removed in the listed stations, is probably a step forward to clarify the dissection procedure, but might remain insufficient without providing precise information concerning how LN removal was performed (34). The macroscopic characteristics of LN dissection should be provided: systematic surgical exploration of all stations, complete LN removal in each, en bloc resection including surrounding fat to prevent any LN rupture, absence of visible LN left after dissection, unchecked LN stations if any, LN splitting up during dissection when it occurred. In case of lobectomy or segmentectomy, care must be taken of reporting how the LNs within the remaining lung were explored and managed.

Conclusions

The only way to ensure the greatest NLNsS and the best pLN-staging is to remove all available LNs in the hilar ipsilateral and mediastinal LN-stations based on anatomical knowledge. This strategy eliminates a deliberate lack of harvest of LNs. A low NLNsS might not mean incomplete surgery. Relying on mathematics alone cannot replace anatomical aspect in NSCLC surgery. A theoretical cutoff remains arbitrary and does not adequately guarantee the quality of LN dissection. The first risk is to estimate as incomplete a correct and complete LN dissection in a patient with a small number of LNs and the second risk is to consider as complete a true incomplete one in a patient with a great number of LNs. Precise information describing the course of the operation in the surgeon's reports is likely to further improve the quality of LN dissection. A LN dissection of best quality may improve the surgical and adjuvant treatment and thus the natural history of the NSCLC, and ultimately presents potential benefits to patients in the long term. However, the procedure is of limited interest in pLN-staging if the LNs are not thoroughly examined and also described by the pathologist.

Acknowledgements

None.

Footnote

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

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Cite this article as: Riquet M, Pricopi C, Legras A, Arame A, Badia A, Le Pimpec Barthes F. Can mathematics replace anatomy to establish recommendations in lung cancer surgery? J Thorac Dis 2017;9(3):E327-E332. doi: 10.21037/jtd.2017.03.46

