Editorial

Editorial on "Long-term outcomes after near-infrared sentinel lymph node mapping in non-small cell lung cancer"

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It has been a real pleasure to be invited to write an Editorial comment on the paper of Digesu *et al.* published in the *Journal of Thoracic and Cardiovascular Surgery* (1).

We read with great interest the paper reporting the first analysis of long-term outcomes using near-infrared (NIR) image-guided sentinel lymph node (SLN) mapping in non-small cell lung cancer (NSCLC). NSCLC represents, worldwide, the most common cause of cancer-related death, and, unfortunately, still shows high recurrence rates at nearly 40%, with an overall 5-year survival of 52.2% even for patients with early stage disease thought to have undergone curative surgery (2).

Local lymph nodes involvement seems to represent the most important prognostic factor in NSCLC, as demonstrated by the 5-year survival decreasing by one half in presence of nodal involvement.

Underestimation, and, consequently, undertreatment of the disease, may be responsible of recurrence in early stage NSCLC. The accuracy of nodal staging during an anatomic resection is mandatory because adjuvant chemotherapy is now the standard of care for patients with pN2 where an appropriate administration of chemotherapy offers an additional survival of 1–7% at 5 years (3).

While it is widely accepted that accurate staging of mediastinal lymph node is of foremost importance to offer patients the best chance of cure, the therapeutic role of mediastinal lymph node dissection (MLND) is still under discussion.

A recent systematic review and meta-analysis evaluating overall survival (OS), local recurrence (LR), distant metastasis and complications of MLND *vs.* mediastinal lymph node sampling (MLNS) in stage I–IIIA NSCLC found similar results between MLND and MLNS in early stage NSCLC patients (4). Nevertheless, on the basis of the evidence that recurrence of mediastinal LN cancer seems to be significantly higher in patients underwent lobe-specific nodal dissection than in those undergoing systematic MLND (5,6) the lymphatic spread of NSCLC should not be considered lobe-specific. The high incidence of skip metastases in mediastinal LNs in absence of hilar adenopathy (7,8), suggests that the key to the best accurate staging of the mediastinum may be not the most extensive nodal dissection, but, instead, the possibility to identify the SLN.

The modern concept of SLN biopsy was made popular by Morton *et al.* (9), in 1992, in patients with melanoma. Their reported results, using blue dye, showed that biopsy and analysis of SLNs accurately describe the neoplastic involvement of the lymph node basin. Since then, SLN biopsy is deemed as accurate method in the identification of patients at greatest risk of locoregional recurrence and metastatic spread and, therefore, most likely to benefit from adjuvant therapy in most solid tumors. Unfortunately, due to the challenging and bizarre anatomy of lymphatic system of the chest, SLN biopsy has—until now—never been

considered trustworthy in the accurate nodal staging of NSCLC.

As demonstrated by Takeda *et al.* (10) using an indocyanine green fluorescence (ICG) imaging method to examine lymph flow in pleura and lung, the lymphatic fluid from primary lung lesions not always flows along bronchi, but sometimes spread directly into the mediastinum, explaining the high incidence of skip metastasis in mediastinal nodes.

The identification of the most clinically relevant node might not only guide the surgeon to the excision of the most predicting lymph node (LNF), but also might prevent an unnecessary MLND in true pathologic node negative (pN0) cases as suggested by the ACOSOG Z0030 randomized trial comparing MLNS with MLND in early-stage NSCLC (11). In addition, the identification and isolation of the most clinically relevant node, should maximize the accuracy of pathological examination. Taking into account that micrometastatic disease is detectable in nearly 16% of patients with pN0 NSCLC (12), when sampled lymph nodes are analyzed with additional immunohistochemistry staining and polymerase chain reaction, the identification of SLN could be helpful for the pathologist in selecting which nodes must undergo these molecular examinations.

The introduction of a new, trustworthy technique in the identification of SLN in NSCLC is, therefore, very desirable.

The paper we refer to, describes, for the first time, the long term results of a retrospective analysis of patients with NSCLC enrolled in 2 prospective phase I near infrared/indocyanine green (NIR/ICG)-guided SLN mapping trials.

The Group, which has a great wide experience in the field of SLN mapping, had previously reported the safety and feasibility of intraoperative NIR/ICG SLN mapping in NSCLC (13,14) using an optimized dose of NIR-detectable ICG dye of 2,500 μg (at least one SLN was identified in all patients with a dosage of 2,500 μg ICG). The main highlights of the referenced paper are the reported sensitivity, specificity, positive predictive value, and negative predictive value for NIR-identified SLN mapping of 100% yielded by the detection of metastatic disease within the SLN in all pN+ cases, and the absence of disease in the SLN when all other nodes were negative.

SLNs were identified in 100% of patients after transpleural peritumoral injection of ICG.

It is surprising that the results showed have never been described before with other techniques. Previous experiences with blue dye or radioisotopes for lymphatic mapping have never reached a so high rate of SLN identification. Intraoperative or preoperative injection of technetium-99m resulted in successful radioisotope migration in 81% of patients and SLN identification in 83–87% of patients (15,16). The recently completed CALGB 140203 multicenter phase II trial investigating the use of intraoperative technetium-99m colloid found an identification rate of only 51% (17). The routine use of vital blue dyes in the chest is limited because of the presence of anthracotic mediastinal nodes that decrease the signal-to-background ratio (SBR), making the visibility poor, and consequently, lowering the nodal detection (18). Neither the association of both, blue dye and radioisotopes to aid in the detection of the SLN in NSCLC patients revealed better results, with a SLN identification rate of 81% (19).

Despite gamma ray-emitting radiotracers and blue dyes are routinely used as the standard of care in surgical treatment of many solid cancer, they are not suitable as a standard approach to the thousands of patients with NSCLC.

Several trials have demonstrated initial safety and feasibility of NIR/ICG imaging, and have achieved SLN detection rates ranging from 80.3% to 100% (20,21).

The great advantage of the NIR/ICG system is that NIR imaging allows for a real-time intraoperative SLN identification and is ideal for *in vivo* intraoperative imaging due to low scatter, absorption, and tissue autofluorescence within the NIR spectrum (700–1,000 nm) (22).

NIR fluorescent lymphatic tracers, as ICG, permit surgical dissection without distortion of critical anatomy in absence of laser bean and radioactivity. ICG is a water soluble FDA-approved tricarbocyanine dye with a peak spectral absorption at 800 nm and an emission peak around 822 nm, perfectly located within the NIR window.

ICG is absolutely safe to be used, has a very low toxicity and very low number of allergic reactions (1:10,000, as reported by manufacturer). The dose used for standard diagnostic procedures lies between 0.1 and 0.5 mg/kg, that is below the hypothesized toxicity level. The incidence of immediate allergic reactions increases above 0.5 mg/kg. The mechanism of ICG uptake in solid tumors remains not completely clarified. In non-hepatic tumors, the enhanced permeability and retention (EPR) effect is hypothesized as the primary mechanism by which molecules of certain sizes as ICG, tend to accumulate in tumor tissue much more than they do in normal tissues (23).

Following the ICG flow within the lymphatic system, is possible to identify the SLN in the chest. Actually, due to

the development of modern imaging systems, is possible to obtain simultaneous acquisition of surgical anatomy (white light, color video) and NIR fluorescence signal. Because the human eye is insensitive to NIR wavelengths, the use of NIR light does not alter the surgical field.

In the referenced paper 42 patients were enrolled: 23 patients, underwent NIR/ICG SLN mapping, represented the SLN-group, while 19 patients enrolled prior to ICG dose optimization, represented the non-SLN group. Both groups underwent multistation MLNS and pathological assessment.

Following the optimization of ICG dosing, at least 1 SLN was identified in 23 patients with 17 SLNs in the N1 station and 12 SLNs in the N2 station. Most node positive cases had N1 disease (73%), with the SLN group containing 5 patients with N1 disease alone, 1 with both N1 and N2 disease, and 1 with N2 disease alone after examination of the SLN and MLNS specimens. Of the non-SLN patients, 3 had N1 disease and 1 patient had N2 disease within the MLNS specimen.

Among the 23 patients in whom at least 1 SLN was identified, 7 (30%) were found in pathological stage N^+. It should be underlined that the SLN was the only node containing metastases in 3 patients. The overall, occult metastatic disease was identified in 30% of the SLN specimens (7 of 23 patients).

This result is remarkable and absolutely better than previously reported in several studies were the incidence ranged between 10% and 18% (24). Based on these results, NIR/ICG SLN biopsy seems to be able to identify occult metastases better than MLNS and MLND. On the other hand, we must keep in mind that in several solid tumors, like melanoma, breast cancer, gynecological cancer, SLNs alone accurately described the neoplastic involvement of the lymph node basin. Despite the complex anatomy of the pleura, lung and mediastinum it's advisable that the improvement in the technique for SLN identification in NSCLC will lead to consider SLN in lung cancer predictable as in other solid tumors. The results reported by Digesu with NIR/ICH SLN mapping seem to encourage the adoption of SLN identification in NSCLC treatment.

In the above mentioned study, although 4 patients with metastatic disease in the SLN also showed disease in additional nodes, no patient with a pathologically negative SLN had evidence of nodal metastases in any other node within the MLNS specimen.

No evidence of disease recurrence has been found in any patient in the pN0 SLN group, while 4 patients developed nodal and/or distant recurrent disease in the non-SLN group.

Based on these results we could argue that the N0 status in the SLN correlate with the absence of nodal metastases in whole lymphatic chain.

By comparing the long-term outcomes of N0 patients belonging to SNL group and N0 patients belonging to non-SNL group, the Author found a 0% of recurrence rate within the SLN *vs.* 26.7% in the non-SLN group patients (P=0.04).

The 5-year OS and DFS for pN0 patients were 100% *vs.* 70.0% (P=0.062), and 100% *vs.* 66.1% (P=0.036), for SLN and non-SLN patients, respectively.

Given that no statistically significant differences between the SLN and non-SLN pN0 cohorts have been reported by the authors in terms of numbers of patients, lobar *vs.* sublobar resections, histology or tumor differentiation, we can hypothesize that patients with pN0 SLN are true N0 patients and consequently show more favorable long-term outcomes.

The paper comes with several new, positive, encouraging results. The most important one is that NIR/ICG SLN mapping seems to guarantee the possibility to get the correct node. Nevertheless, also debatable aspects arise.

In regard to the obtained results, it should be mentioned at first, that patients enrolled in the study underwent MLNS and no MLND, with an average number of lymph node stations sampled per patient of 2.9±2 (i.e., hilar, level 4 and 7). The mean number of dissected lymph nodes per patient in the MLND is usually significantly greater than that in the MLNS (15.59±3.08 *vs.* 6.46±2.21, P<0.001) (25). So, we can argue that, more increases the number of lymph nodes harvested, more increases the possibility to find occult nodal metastases, leading to a better selection per stadium of the patient and consequently to a better 3- and 5-year survival.

A second criticism is that preoperative assessment of nodal status has been performed through EBUS or mediastinoscopy. Although, for the best of our knowledge, there is no evidence in literature that these maneuvers could modify the lymphatic flow in the chest, it remains to be demonstrated if no changes in SLN occur after preoperative biopsy. Of course, this question cannot be easily answered and further studies are needed.

In conclusion, on the basis of the surgical results reported in the paper, the technique appears safe and very promising for the future of NSCLC nodal management, especially in the optics of even more minimally invasive surgery and lung

cancer screening programs.

Results on OS and DFS obtained in SLN-group are encouraging, but the sample is too small to get definitive conclusions.

Although this is a retrospective and single-institution study on a limited number of patients, the hope is that the encouraging results and the reproducibility of technique will stimulate larger and multicenter trials to validate the NIR/ICG approach in the detection of SLN for patient affected by NSCLC.

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Footnote

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

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