Editorial

Is tumor location an independent prognostic factor in locally advanced non-small cell lung cancer treated with trimodality therapy?

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Provenance: This is an invited Editorial commissioned by the Section Editor Claudio Caviezel (Division of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland).

Comment on: Kamel MK, Rahouma M, Ghaly G, *et al*. Clinical predictors of persistent mediastinal nodal disease after induction therapy for stage IIIA N2 non-small cell lung cancer. Ann Thorac Surg 2017;103:281-6.

Submitted Feb 23, 2017. Accepted for publication Mar 23, 2017.
doi: 10.21037/jtd.2017.03.183
View this article at: http://dx.doi.org/10.21037/jtd.2017.03.183

To improve the prognosis of patients with locally advanced (LA) non-small cell lung cancer (NSCLC), it is necessary to control local disease and to decrease relapse from distant disease by combining systemic chemotherapy with surgery and/or radiotherapy. Since 1990s, induction therapy with chemotherapy or chemoradiotherapy (CRT) followed by surgery has been used for clinical (c) Stage IIIA-N2 NSCLC to downstage tumors, to render them completely resectable, and to possibly eradicate lymph node metastasis in the mediastinum (1). To further improve the outcome of induction therapy, prognostic factors for this treatment setting needed to be identified. The histological response of resected specimens has been reported to be a prognostic factor for induction therapy followed by surgery (2,3).

In a recent study, Kamel *et al*. conducted a retrospective review of a database of patients with cStage IIIA-N2 NSCLC who had received induction therapy followed by surgery. They identified clinical predictors associated with persistent (chemotherapy or CRT refractory) N2 disease after induction therapy, potentially contributing to the selection of patients most likely to benefit from surgical resection (4). They reviewed the treatment outcomes of 203 patients with cStage IIIA-N2 NSCLC who had undergone lung resection after induction treatment at a single institution in the USA between 1990 and 2014. The majority of the patients (87%) were pathologically confirmed to have N2 disease before induction therapy, and 87.5% received induction chemotherapy alone and the remaining 12.5% received induction CRT. After induction therapy, 72% underwent a lobectomy, 8% underwent a bilobectomy, and 20% underwent a pneumonectomy. They found that patients who had nodal downstaging after induction therapy (ypN0/ypN1, n=97) had a significantly improved overall survival (OS) rate, compared with patients who had persistent N2 disease (ypN2, n=106) (5 years OS, 56% *vs*. 35%, respectively; P=0.047). In a limited analysis of 116 patients using complete positron emission tomography (PET) data obtained before and after induction therapy, they reported that a tumor location in the upper or middle lobe [odds ratio (OR), 3.44; 95% confidence interval (CI), 1.46 to 8.12; P=0.005] and a less than 60% reduction in the mediastinal nodal PET maximum standardized uptake value (SUV_{max}) after induction therapy (OR, 4.99; 95% CI, 1.10 to 22.63; P=0.037) were found to be independent predictors of persistent mediastinal nodal metastasis after induction therapy (ypN2) in a multivariate logistic regression analysis. In their study, several of the 203 originally enrolled patients had single cN2 station metastasis before induction therapy (median number of cN2 station was 1; range was 1–2), and the upper or middle lobe tumors had a significantly higher number of involved cN2 stations, compared with the lower lobe tumors (P=0.035). Moreover, the upper or middle

lobe tumors were more likely to have multiple station ypN2, compared with the lower lobe tumors (P=0.010), although the actual number of these stations analyzed in the multivariate logistic regression analysis was not reported. Regarding the locations of involved N2 stations according to the primary tumor location, they analyzed the details of ypN2 stations (not cN2 stations). The upper lobe tumors had a higher ypN2 involvement rate at the superior mediastinal lymph node stations (levels 2–6), compared with the lower lobe tumors (P<0.001), although the pN2 involvement rate of subcarinal or inferior mediastinal lymph node stations (levels 7–9) was similar between upper lobe and lower lobe tumors (P=0.729). In summary, many of the lower lobe tumors analyzed in their study seemed to have single station cN2 involvement in subcarinal or inferior mediastinal lymph nodes, and these background factors likely led to some biases in their results.

Regarding the tumor location-specific prognosis of NSCLC patients, several investigators have reported that a lower lobe origin was associated with an unfavorable prognosis in surgically resected patients (5-7). On the other hand, there is a report showing that tumor location was not an independent prognostic factor in patients with early-stage NSCLC (8). At present, we could not find any studies showing a clear relation between a lower lobe origin and a better prognosis.

Since 1998, our group has also applied induction CRT using mainly cisplatin and docetaxel with a total of 40–46 Gy of concurrent radiotherapy, followed by surgery, for the treatment of LA-NSCLC (9,10). We reported an advantage of induction CRT over induction chemotherapy in a retrospective analysis (11). In addition, we have found that a lower lobe origin could be a poor prognostic factor in LA-NSCLC patients treated with induction CRT followed by surgery (12). In our study, we conducted a retrospective analysis to identify prognostic factors in patients receiving induction CRT followed by surgery for LA-NSCLC. We analyzed 76 patients with cStage IIIA/IIIB-N2/N3 NSCLC who were treated with trimodality therapy. As a result, lower lobe tumors were associated with a significantly shorter OS and disease-free survival (DFS) than upper or middle lobe tumors (P=0.022 for OS and P<0.001 for DFS, respectively).

What are the possible causes for this discrepancy in tumor location-specific treatment responses between Kamel *et al.*'s study and ours? Kamel *et al.* mentioned in their report that a difference in tumor biology arising from ethnicity might have caused this discrepancy, since the incidence of non-adenocarcinoma is higher among Asian patients than among Western patients (4). Indeed, 69.5% of the tumors in their study were adenocarcinomas, while only 56.6% of the tumors in our study were adenocarcinomas; however, we feel that this difference was unlikely to have had a major impact on the results (12). Many of our patients had multiple cN2/3 station involvements (43.4%), and many of the lower lobe tumors in our cohort had involvement of the superior mediastinal or N3 lymph nodes before induction therapy (61.1%). We defined regional mediastinal lymph nodes for each lobe tumor as follows: right upper lobe for superior mediastinal nodes (level 2R and 4R), right middle lobe for superior mediastinal and subcarinal nodes (level 2R, 4R, and 7), left upper lobe for superior mediastinal nodes (level 4L, 5, and 6), and right and left lower lobe for subcarinal and inferior mediastinal nodes (level 7, 8, and 9). Metastatic lymph nodes extending over regional lymph nodes were defined as beyond regional nodes (i.e., superior mediastinal nodes for lower lobe tumors). As a result, the lower lobe tumors were associated with a higher incidence of beyond regional node metastasis, compared with the upper or middle lobe tumors (61.1% *vs.* 20.7%, respectively; P=0.0016). In addition, the patients with beyond reginal node metastasis had significantly shorter OS and DFS outcomes than the patients with regional node metastasis (P=0.037 for OS and P<0.01 for DFS). Moreover, the lower lobe tumors were associated with significantly shorter OS and DFS outcomes, compared with the upper or middle lobe tumors, as described above. Thus, we suggested that the lower lobe tumors were associated with a significantly higher incidence of beyond regional node metastases than the upper or middle lobe tumors, resulting in the poor outcomes.

These findings suggest that the majority of lower lobe tumors with multiple mediastinal station metastases, including superior mediastinal nodes, would not have been candidates for trimodality therapy in the study conducted by Kamel *et al.* Indeed, it has been reported that most institutions (90.5%) that belong to the National Comprehensive Cancer Network in the USA consider surgery in patients with a single lymph node station smaller than 3 cm, while 47.6% of the institutions consider surgery in patients with multiple station involvement (as long as no lymph node is larger than 3 cm), and some institutions (16.7%) consider surgery in patients with multiple stations even if the lymph node is larger than 3 cm (13). The 2013 American College of Chest Physicians (ACCP) guideline categorized the resectability of tumors based on these cN2 statuses, such as infiltrative or discrete nodes type, and recommendations for treatment were made according to the cN2 status (14). In patients with

infiltrative cStage III-N2/N3 NSCLC and a performance status of 0–1 who are being considered for curative-intent treatment, a combination of platinum-based chemotherapy and radiotherapy is recommended, while treatment with induction chemotherapy or CRT followed by surgery is not recommended. For discrete cN2-involved NSCLC identified preoperatively, the ACCP recommends that a treatment plan be made with input from a multidisciplinary team that includes a medical oncologist, radiation oncologist and thoracic surgeon, and they recommend either definitive CRT or induction therapy followed by surgery over either surgery or radiation alone (14).

In summary, identifying factors for selecting patients likely to benefit from trimodality therapy is crucial for determining the optimal therapeutic strategy. As Kamel *et al*. mentioned in their report, future studies need to further analyze the relation between tumor location and response to induction therapy as well as survival outcomes, to improve the management of patients with LA-NSCLC.

Acknowledgements

None.

Footnote

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

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Cite this article as: Shien K, Toyooka S, Soh J, Yamamoto H, Miyoshi S. Is tumor location an independent prognostic factor in locally advanced non-small cell lung cancer treated with trimodality therapy? J Thorac Dis 2017;9(5):E489-E491. doi: 10.21037/jtd.2017.03.183

