N2 involvement in lung cancer: the Danaïdes’ barrel

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In the article ‘Time to refine N2 staging’ [1], Matsunaga et al. investigated the relationship between the prognosis and the location of the primary tumour and nodes (LN) involved. They suggested a classification of these patients to either cN2a, which consisted of an upper lobe tumour with clinical positive ipsilateral upper mediastinal LN (station: 2R and 4R on the right and 2L, 4L, 5 and 6 on the left), or cN2b, which was a lower lobe tumour with clinical positive ipsilateral mediastinal LN (station: 7, 8 and 9 on both sides) [1]. They found that survival was better in the cN2a subgroup regardless of the number of LN stations involved.

The following points need to be considered:

(i) cN2 diagnosis based on tomodensitometry (TDM) and positron emission tomography (PET), available in only 10 patients, lacks sensitivity and specificity, and comparing cN2 in this manner without considering pN2 may result in reflecting a Will Rogers ‘phenomenon’.

(ii) Upper or lower mediastinal LN involvement related to tumour location was considered an important prognostic factor, which is not demonstrated on a pathological basis [2].

(iii) Single- and multiple-station involvements were mixed as visible in Figure 1 [1]: two stations could be located in the same anatomical LN chain in cN2a, and in two different LN chains in cN2b. Such a mixture might shift the results in favour of a non-difference between single- and multiple-station involvements.

Refining N2 staging in this manner is only adding one more paper to many already published papers during the last 30-year period (at least 1850 available in PubMed), which sought a solution to understanding the N2-involvement effects on prognosis, classification and grouping (stations, zones and lobe-specific drainage) and management (sampling, radical or extended lymphadenectomy or nothing).

Lymphatic drainage of tumours follows an anatomical pathway. Therefore, returning to anatomical landmarks may be crucial to a better understanding of lung cancer lymphatic spread [3]. This could avoid the perpetual filling of an N2 Danaïdes’ barrel and permit the escape of a vicious cycle impeding any consistent progress.

REFERENCES


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Reply to Riquet et al.

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We would like to thank Riquet et al. for their interest in our paper [1, 2]. Firstly, our classification is based on the location of the primary tumour and nodes involved, regardless of whether the mediastinal lymph node metastasis is single station or multiple station. We defined cN2a as the involvement of an upper mediastinal lymph node in a main tumour located in the upper lobe or as that of a lower mediastinal lymph node in a main tumour located in the lower lobe. cN2b was defined as other situations. For example a main tumour located on the lower right lobe that involved Station #7 was classified as cN2a, and a main tumour located on the upper left lobe that involved Station #7 was classified as cN2b [2].

Sensitivity and specificity of diagnosis for cN2 using computed tomography (CT) only, as in this study, were decreased compared with those using positron emission tomography-computed tomography (PET–CT) as Riquet et al. pointed out. Although, in these 4 years, we have always staged patients with lung cancer using not only CT but also PET–CT, we have considered the definition of mediastinal metastasis as unclear, causing it to differ among institutions or radiologists.

There were two reasons why our discussion was mainly on clinical factors but not pathological factors in our paper even though the Will Rogers phenomenon might occur when cN2 is compared without considering pN2. The first is about N2 involvement in lung cancer: the Danaïdes’ barrel was clinical N2 and not resected pathological N2. Adjuvant chemotherapy was recommended for lung cancer patients with resected pathological N2. On the other hand, treatment for clinical N2 lung cancer is controversial although, in general, radical chemoradiotherapy is recommended for cN2 Stage IIIA lung cancer patients. Secondly, there is report on prognosis based on the location of the primary tumour and the pathologically involved node. As such, we considered clinical status to be important in deciding the treatment strategy, and therefore investigated mainly the clinical status.

Our classification of mediastinal lymph node was based on the concept of the anatomical pathway of lymphatic drainage in lung cancer. We therefore suggested that prognosis of patients with N2 non-small-cell lung cancer was poor as the distance between the primary tumour and the lymph node involved was farther in the same mediastinal lymph node. Moreover, in our paper, the 5-year disease-free survival rate for cN2a was significantly better than that for cN2b (29.6 vs 9%, P < 0.001). We assumed that our result was supported by Riquet et al. [3]. In their report, the patterns of pN2 distribution in the right and left lobectomies showed that the incidence of upper mediastinal involved lymph nodes was much higher than that of lower mediastinal involved lymph nodes in upper lobectomy. Moreover, the incidence of lower mediastinal involved lymph nodes was much higher than that of upper mediastinal involved lymph nodes in lower lobectomy.

We believe that the anatomical pathway of lymphatic drainage could provide a clue as we resolve N2 involvement in lung cancer: the Danaïdes’ barrel.