Pathologic N1 disease in lung cancer: the segmental and subsegmental lymph nodes

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N1 disease represents a heterogeneous group of non-small cell lung carcinoma (NSCLC). Pathologic N1 disease may involve one or more lymph node (LN) in the lung classified by Mountain and Dressler (1) in five stations corresponding to their anatomical locations: the hilar LNs, the Interlobar LNs, the lobar LNs, the segmental LNs and the subsegmental LNs being termed station 10, 11, 12, 13 and 14, respectively. In the seventh edition of the TNM classification for lung cancer (2), N1 disease was classified in two zones, hilar/interlobar zone regrouping stations 10 and 11 and peripheral zone regrouping stations 12, 13 and 14.

Wang and coworkers (3) questioned the impact of omission of station 13 and 14 LN retrieval on outcome evaluation of NSCLC in a series of 435 post-surgery pN0 patients. LNs from stations 10 to 12 had been routinely collected during the operation in all patients but segmental station 13 and subsegmental station 14 had been retrieved at the surgeons' discretion. Segmental station 13 was collected from 163 patients (95.9%), and subsegmental station 14 was collected from 103 patients (60.6%). Overall survival (OS) and disease-free survival (DFS) was significantly improved in the 13–14 station group compared to the other (5-year OS rate, 89.3% *vs.* 77.4%, P=0.027; 5-year DFS rate, 81.4% *vs.* 67.4%, P=0.021). They concluded that pN0 patients with station 13 and 14 collected were truly pN0, whereas patients with station 13 and 14 pN1 involvement were probably present among the pN0 patients without that LN retrieval. Their study draws attention on the importance of

intrapulmonary LN collection for accurate diagnosis of true pN0. The role of segmental LNs in the pathological staging of NSCLC had also been previously underlined by Li and coworkers (4), and Huang and coworkers (5) who confirmed the presence of involved LNs in those stations. Li and coworkers (4) observed that in 113 patients (pN0 n=68, pN1 n=16 and pN2 n=29), 6 patients (37.5% of pN1) would have been down-staged to N0, and that two cases of multiple-zone pN1 disease would have been misdiagnosed as single-zone N1 disease without segmental LNs dissection. Similar results were reported by Huang and coworkers (5) who discovered that among 370 patients (pN0 n=238, pN1 n=62 cases and pN2 n=69), 16 patients (25.8% of pN1) would have been down-staged to N0, and that five cases of multiple-station N1 disease would have been misdiagnosed as single-station N1 disease.

In fact, these intrapulmonary LNs deserve special attention because they occupy an original place not only with regard to the prognosis of the NSCLCs when they are metastatic but also because of their anatomical and pathogenic characteristics

Considerations on the prognosis of pN1 NSCLC

The number of involved LNs or the LN-stations in the lung may influence the 5-year survival rates. We reviewed 1,174 patients in 1999 (6): 50.25% were pN0, 21.8% pN1 and 27.95% were pN2. The 5-year survival was

significantly better when N1 involvement was intralobar (levels 12 and 13, n=102), as compared with extralobar (hilar) involvement (levels 10 and 11, n=154): 53.6% *vs.* 38.5% (P=0.02). Ten years later, Demir and coworkers reviewed 540 pN1 patients (7). The 5-year survival rates for patients with hilar N1 (station 10), interlobar (station 11), and peripheral N1 (stations 12 to 14) involvement were 39%, 51% and 53%, respectively. Patients with hilar LN metastasis showed a shorter survival period than patients with peripheral LN involvement (P=0.02). Patients with hilar zone N1 (stations 10 and 11) involvement tended to show poorer survival than patients with peripheral zone N1 (12 to 14) metastasis (P=0.08). The same kinds of results have subsequently been commonly reported. Maeshima and coworkers (8) reported that the 5-year DFS rates for pN0, level 13/14 pN1, lobar (level 12), interlobar (level 11), and hilar (level 10) pN1 were 90.5%, 69.4%, 46.4%, 46.7% and 37%, respectively. Reviewing stage II (T1a-T2bN1M0) NSCLC, Li and coworkers (9) observed that peripheral zone LN involvement was a statistically significant indicators of higher OS and DFS by univariate analyses, and Liu and coworkers (10), that hilar/interlobar nodal zone involvement was significant predictors for worse OS by multivariate analysis (P=0.001). Rena and coworkers (11) reported that the 5-year survival rates for pN0, level 13+14, level 11+12, level 10 pN1, and pN2 was 93%, 81%, 58%, 48% and 25%, respectively.

Concerning the peripheral LNS, some curiosities of the prognostic value of their invasion raise some questions. In the previous papers (8-11), patients who had only level 13/14 LN metastasis seemed to have an intermediate 5-year DFS rate between that of patients with pN0 status and other patients with pN1 status. However, we observed that Intralobar pN1 5-year survival was similar to that of pN0 (53.6% *vs.* 56.5%, P=0.01), and that extralobar pN1 5-year survival was comparable with that of pN2 (38.5 *vs.* 28.3%, P=0.01) when pN2 was only located in one station of the ipsilateral mediastinum (6). Wang and coworkers (3) have reported other results that prompt reflection. They observed that the patients whose intrapulmonary nodes were retrieved from 2 stations (13 and 14), showed better survival than those without any intrapulmonary LNs retrieved (5-year OS rate, 90.3% *vs.* 77.3%, P=0.010). In contrary, survival of patients from whom intrapulmonary LNs were retrieved from only one station was not significantly different when compared to that of patients without any retrieved intrapulmonary LNs (5-year OS rate, 85.5% *vs.* 77.3%, P=0.147).

In a more recent study, we analyzed a larger series of pN1 patients (n=450) (12). Only one station was metastatic in 340 patients (75.6%, single station disease) and two stations or more were involved in 110 patients (24.4%, multiple station disease). The presence of intralobar metastatic LN (station 12-13-14) did not impact the 5-year survival (P=0.71). The location of metastatic stations was of prognostic significance only in case of multi-station disease, with hilar (station 10) involvement. Thus, since three-quarters of patients had a single station with metastatic LNs, it is not surprising that the impact on survival could be equivalent to those of Wang and coworkers (3) when they indicated that the difference is not significant in cases where only one station has been recovered (possible pN1) compared to cases where no intrapulmonary LN recovery has been performed. This may also support the finding that pN1 involvement of stations 13 or 14, when isolated, shares a prognosis similar to that of pN0 patients. Also, it may be possible, as previously suggested (6), that pN1 disease is a compound of two subgroups: one located peripherally inside the lobes behaving as uninvolved LN (pN0), and the other (extralobar or hilar) behaving like an early stage of N2 disease. Those two groups correspond to the two zones (2), hilar/interlobar zone (stations 10 and 11) and peripheral zone (stations 12, 13 and 14). This particularity of the prognosis of the peripheral LNs could be correlated with their anatomical, embryological and pathogenetic aspects.

Peripheral LN: anatomy, subpleural LNs, embryology and pathogenesis

Anatomically, the number of peripheral LNs varies. Wang and coworkers (3) collected a total of 5.0±3.0 (mean ± SD) intrapulmonary LNs, the study concerned pN0 patients. This included 3.1±1.9 nodes from station 13 and 2.0±2.2 nodes from station 14. In case of pN1 patient, metastasis can be found in about 60% of cases. In the paper of Rena and coworkers (11) the median number of examined level 13+14 LNs was 2 (range, 0–6) and 57% of pN1 patients had metastasis at that level. Maeshima and coworkers (8) found a median number of examined 13/14 LNs of 3 (range, 0–22; 13/14 LNs), and metastases to these LNs were detected in 61% of patients who had pN1 status. In the series reviewing pN0, pN2 and pN1 patients, the frequency of segmental LN involvement is not so high. Huang and coworkers (5) reported that the detection rates of hilar nodes, interlobar nodes, lobar nodes and segmental nodes were 69.7%, 86.8%, 84.0%,

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67.0%, respectively. The metastasis rates of hilar nodes, interlobar nodes, lobar nodes and segmental nodes were 6.5%, 10.8%, 15.7% and 10.3%, respectively. In their paper, Li and coworkers (4) mentioned that the detection rates of hilar nodes, interlobar nodes, lobar nodes and segmental nodes were 61.1%, 85.0%, 75.2% and 80.5%, respectively, and that the metastasis rates were 5.3%, 10.5%, 16.8% and 14.2%, respectively. Thus, the number of LNs was different from an individual to another. This may be observed whatever the LN station (mediastinal or/and intrapulmonary) (13). There were stations where no LN could be found (13). Stations without LN were also observed in the reports concerning peripheral LNs (3-5,8,11).

To be complete, it should be pointed out that those papers do not mention the most peripheral and distal LNs, the sub-pleural LNs. They lie beneath the visceral pleura and are not very frequent. They first were reported by Greenberg in 1961 (14). They may be misdiagnosed with peripheral NSCLC. Since the development and progress of computed tomographic imaging, those LNs have become increasingly described and are now well-known entities (15,16). They appear as a solitary pulmonary nodular shadow or sometimes as multiple nodules masquerading as carcinoma metastases. These subpleural LNs may also be metastatic (17).

In terms of pathogenesis, peripheral LNs have some other characteristics. Wang and coworkers (3), observed that the tumor-bearing segments harbored 2.8±2.2 LNs compared to the non-tumor-bearing segments (2.2±2.3 LNs; P=0.006). The reason for this difference is unknown, but they thought that factors such as immune response to the tumor and inflammation cannot be ruled out. The fact that more LNs were collected from the tumor-bearing segments than from the none-tumor-bearing segments is similar to another constatation. We also observed (13) that the number of LNs increased in the LN stations when some of them were metastatic. Other hypotheses may help explain that phenomenon. Tertiary lymphoid organs have been reported to appear in lymphatic malformations (18) and chronic inflammatory diseases (19). Tertiary lymphoid organs mimicking LNs that represent sites of lymphoid neogenesis may also develop in most solid cancers (20). We suggest that tertiary "LNs" might also be induced by and associated with tumoral LNs.

Another characteristic also mentioned by Wang and coworkers (2) is that the left lower lobe contained the maximum number of intrapulmonary nodes (5.7±2.9),

followed by the right lower lobe (5.2±3.0), left upper lobe (5.1±3.1), right upper lobe (4.7±2.8), and right middle lobe (1.7±0.6). The subpleural LNs behave in the same way: 72% are located in the lower-lobes (15); 25% are multiple nodes (21). According to Kradin and coworkers (21), most of them may be considered to be acquired highly organized lymphoid nodules formed along interlobular lymphatic drainage routes. In fact, bronchial and bronchiolar lymphoid tissue is sparse at birth (22). Distal LNs, with germinal centers and a definite sinusoidal structure, located along the segmental bronchi lymphatics probably develop during the years following birth in human, as bronchial and bronchiolar lymphoid tissue (system known as bronchus – associated lymphoid tissue BALT) does in animals. Because they usually contain only a small number of cells, LNs are difficult to identify within the lung except when they are enlarged owing to a pathologic process (22).

Peripheral LN dissection: who retrieves? Is it the Pathologist or the surgeon?

For Wang and coworkers (3) and Li and coworkers (9), the procedure of LN retrieval is at best to be performed by the surgeons. However, many other teams confer this responsibility to pathologists. In our case, a dissection protocol for the recovery of intrapulmonary and mediastinal LNs has been used by pathologists for a long time (6). On the other hand, the role of the surgeon and of him alone is of paramount importance in a particular situation which is not part of what is mentioned by Wang and coworkers (3) and the others. In effect, in all series (3-5,8,11), the resection considered as "lesser resection" is a lobectomy that allows surgeons or pathologists to dissect intralobar LNs in the resected part of the lung. In the case of still lesser resections the quality of surgery actually depends upon the surgeon's skill and this point must be emphasized here. Thus, although this may go beyond the considerations of Wang and coworkers (3), it seems appropriate to broaden the debate on these LNs. LN-dissection completeness is particularly difficult to obtain with sublobar resections (segmentectomy and wedge resection). Intralobar LN-dissection, obligatory to be performed by the surgeon, requires care and patience when dissecting along the bronchi after segmentectomy. It is impossible within the remaining lobe during wedge resection and exposes wedge resections to local recurrence risk. Omission of segmental and intralobar LN retrieval might explain the high incidence of loco-regional recurrence observed after segmentectomy

by Hattori and coworkers (23) and after wedge resection by Stiles and coworkers (24). Given the major impact on the prognosis of peripheral LN metastasis, the absence of intrapulmonary resection of these LNs should be a warning signal when considering local surgical therapy or local non-surgical procedures such as stereotactic body radiation therapy. Patients receiving stereotactic body radiotherapy for stage I NSCLC are typically staged clinically with PET/CT. Up to 7.6% of patients may be found to have occult N1 metastasis on pathologic review (25). In conclusion, peripheral LNs must be collected not only for better staging of NSCLC but also for performing a curative operation if a local therapy of peripheral lesions is scheduled.

Acknowledgements

Footnote

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