

# Quantification of regional lymph node involvement in lung cancer

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Regional lymph node involvement in lung cancer is heterogeneous. From micro-metastases in intrapulmonary lymph nodes—coded as N1(mi)—to bulky contralateral nodal disease—coded as N3—the different situations in between vary in anatomic extent and prognosis. However, regardless of the amount of tumour burden in the regional lymph nodes, the present nodal staging of the tumour, node and metastases (TNM) classification of lung cancer defines the extent of nodal involvement solely via anatomic location.<sup>1</sup>

Several studies have found that within every N category, there are prognostic modifiers. Thus, for pathologically staged I tumours, the number of removed lymph nodes at thoracotomy seems to have prognostic impact, although the cut-off varies in different studies from six to more than 15 removed lymph nodes.<sup>2–3</sup> Within the N1 category, involvement of hilar (main bronchi) lymph nodes has been consistently associated with worse prognosis compared with involvement of intrapulmonary lymph nodes.<sup>4–5</sup> Other indicators of worse prognosis in N1 disease are macroscopic nodal involvement and multiple nodal involvement,<sup>6</sup> involvement of multiple nodal stations,<sup>7</sup> and metastatic involvement—as opposed to direct nodal invasion, at least, in squamous cell carcinomas.<sup>8</sup> As for N2 disease, skip pathologic (p) N2 (ie, pN2 without pN1 disease) is associated with better prognosis than pN2 with pN1.<sup>9</sup> Single nodal station pN2 also has better prognosis than multiple nodal station pN2.<sup>10</sup> Clinically evident multilevel N2 disease and bulky disease also have an adverse effect on prognosis, as well as the involvement of the highest mediastinal lymph node and extranodal extension. Even the specific nodal involvement depending on the lobar location of the primary tumour seems to have prognostic

impact: superior mediastinal and aortic nodal disease with right and left upper lobe tumours, respectively, seem to have a better prognosis than the involvement of lower mediastinal nodes with lower lobe tumours.<sup>11</sup>

Most of the situations described above qualify more than quantify regional nodal disease, and, although they might be clinically relevant for patient management, they have not found their way into the TNM classification for lung cancer. There are several reasons for that: most findings are based on relatively small, single-centre studies; the findings are derived from pathologic data with no clinical validation; and results may be inconsistent among different series. However, increased nodal tumour burden, grossly quantified by the presence of multiple involved nodes and nodal stations, is consistently associated with worse prognosis. This fact has recently been confirmed by the survival analyses of a selected group of patients with pathologically staged tumours obtained from the International Association for the Study of Lung Cancer (IASLC) database. In this case, the traditional nodal stations were amalgamated into nodal zones. While single pN1 zone had a significantly better prognosis than multiple pN1 zones, which had the same prognosis as single pN2 zone; multiple pN2 zones had the worst prognosis.<sup>12</sup> These findings, although clinically relevant, could not be used to subdivide the N1 and N2 categories because they could not be validated clinically, across geographic areas and databases, or by the different T categories. However, despite this, they significantly quantify pathologic nodal disease.

Another way to quantify nodal disease is through the number of involved lymph nodes. This N descriptor is already used in several tumours, either in isolation or in combination with other parameters. The number of involved lymph nodes alone is an N descriptor that is used for carcinomas of the digestive tract and malignant melanoma of the skin. For head and neck tumours, the number of involved lymph nodes is combined with location and nodal greatest dimension. Number

and size are combined for carcinomas of the vulva, testis and urethra; and number and location, for carcinoma of the urinary bladder. Breast and penis cancers are exceptions to the staging guidelines and have different descriptors for clinical and pathologic N classifications. While mobility and fixation are parameters to define the clinical N categories, the number of involved lymph nodes is fundamental to the establishment and classification of pathologic N status.<sup>13</sup> This exception to the rule reflects, first, the difficulty in counting involved nodes in the clinical assessment of tumours (when no test is so reliable as a properly performed systematic dissection of the regional lymph nodes to determine their involvement), and, second, the importance of the number of involved lymph nodes in pathologic staging.

Wisnivesky *et al*<sup>14</sup> report on the prognostic impact of lymph node ratio (LNR), that is, the ratio of involved lymph nodes to the total number of removed nodes, in patients over 65 years of age with pN1 non-small cell lung cancer. Their study included 1682 patients of the Surveillance, Epidemiology and End Results registries, diagnosed between 1992 and 2005. A median of eight lymph nodes had been resected. Based on previous studies, they divided their patients into three groups according to the LNR:  $\leq 0.15$ ,  $>0.15-0.5$ , and  $>0.5$ . They found that cancer-specific and overall survival was significantly worse as LNR increased in the whole population of studied patients, among those with T1, T2 and T3 tumours, and among those with more than 10 lymph nodes removed. Cox regression analysis showed that LNR stood as an independent prognostic factor for cancer-specific and overall mortality, and survival.

The results obtained by Wisnivesky *et al*<sup>14</sup> (see page 287) derived from a large series of patients and show that quantification of pN1 is important. Quantification is clinically relevant, because it can be used to refine postoperative prognosis, and to intensify postoperative follow-up and treatment; and may be used to stratify patients in future clinical trials. This study is a step forward in the understanding of tumour spread and prognosis. It shows there is a certain logic to the anarchy of cancer: the larger the tumour burden, the worse the prognosis. This could be reliably proved in the analyses of tumour size performed by the IASLC that allowed the separation of five groups of tumours, based on tumour size, with significantly different prognosis.<sup>15</sup> The same can be

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said of nodal tumour burden, quantified by number of involved nodes, nodal stations, nodal zones, and by the LNR, as confirmed by this study.<sup>14</sup> Tumour volume also has a prognostic role in early<sup>16</sup> and advanced<sup>17</sup> non-small cell lung cancer.

The authors discuss that the LNR may be better than the number of involved lymph nodes to quantify nodal disease, because the latter depends on the extent of the intraoperative nodal assessment performed. However, the LNR tells us little about this type of assessment, and the way that it is carried out is vital to the classification and completeness of resection.<sup>18</sup> The LNR is 0.2 if one node out of five removed nodes is involved, or if two nodes out of 10 removed nodes are involved. However, in the first case, the minimum number of required lymph nodes (six) in systematic nodal dissection is not met, while in the second case, it is. Consequently, as other authors have suggested, a better way to quantify nodal involvement might involve a combination of the total number of removed lymph nodes and the LNR. In the study of Wisnivesky *et al*<sup>14</sup> it would have been informative to know whether there were differences between the HRs for patients with less than 10 lymph nodes removed and those for patients with more than 10 lymph nodes removed. If there were significant differences, it could be suggested that there is an association between the extent of nodal resection and prognosis.

The results of Wisnivesky *et al*<sup>14</sup> cannot be used, however, to modify the N descriptors of the present TNM classification. They are, indeed, clinically useful, a *sine qua non* condition to modify the classification, but they should be validated in the clinical setting, and in larger populations of patients of all ages. Although counting the number of involved lymph nodes in clinical staging is harder than in pathologic staging, the Prospective Phase of the IASLC Lung Cancer Staging Project is using a detailed dataset that includes all the necessary information to provide evidence on the impact of nodal involvement and its quantification in clinical and pathologic staging.<sup>19</sup> The success of this project will very much depend on the generosity of proprietors of databases on lung cancer around the world. The contribution of their data to the IASLC database is of paramount importance to

the collection of an adequate amount of well-registered information, that will hopefully provide the researchers with answers to many of the key questions.

If any reader wishes to take part in this project, then there is still time to participate. Simply send an email to the data managers and statisticians of Cancer Research And Biostatistics at [information@crab.org](mailto:information@crab.org), stating 'IASLC Staging Project' in the subject line, and all the necessary instructions and documentation will be provided.

Clinical, biological and molecular parameters can complement tumour classification based on anatomic extent, but anatomic extent, imperfect as it may be, still stands as the most important factor in lung cancer classification.<sup>20–22</sup> Therefore, for the time being, and until there is something better, any research to refine the present TNM classification will be useful to medicine and its patients, and the quantification of regional nodal involvement certainly deserves further investigation.

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