Editorial

Occult pN2 disease in lung cancer patients: a wide range of diseases endangering the long term prognosis

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Occult pN2 disease is the discovery of non-small-cell lung cancer (NSCLC) metastases in mediastinal lymph nodes (LNs) considered clinically disease free (cN0) after clinical staging (cTNM) established by increasingly precise work procedures, such as current imaging studies [computed tomography (CT) and positron emission tomography (PET)] and bronchoscopy or esophagoscopy with ultrasound directed biopsies (EBUS, EUS). That topic was recently revisited by Bille and coworkers (1), who reviewed 1,667 patients with cT1/T2aN0M0 NSCLC who underwent surgery with a mediastinal lymph node dissection (MLND). They defined MLND as resection of at least two mediastinal stations (2), always including station 7 LNs. cN0 consisted in LNs with a short axis diameter of less than 10 mm and non-fluoro-2-deoxyglucose (FDG)-avid on PET [standard uptake value (SUV) max <2.5]. Patients with any clinical suspicion of N2 disease based on PET or CT findings underwent surgical staging of their mediastinum (i.e., mediastinoscopy, EBUS biopsy) and were excluded from the analysis regardless of the results of those staging studies. Nine percent (146/1,667) of patients had occult pN2 disease. This important incidence deserves to be underlined all the more because it is even higher in series including any cT. In that case, the incidence of occult N2 disease with negative mediastinal uptake of FDG on PET-CT may be between 14% and 16% (3,4).

Another important observation of Bille and coworkers (1) was that 16% of pN2 patients had mediastinal LN metastasis that did not follow a lobe-specific lymphatic drainage pattern. In left and right upper lobe tumors, station 7 nodes were involved in 5% and 13% of pN2 positive cases, respectively. Station 5 and station 2/4 nodes were involved in 29% and 18% of left and right lower lobe pN2 tumors, respectively. Such finding was similar in one of our studies (5). Thus, if a lobe-specific lymphadenectomy had been performed in that series and ours, about 16% of pN2 patients could have been understated, not offered evidence-based adjuvant therapy, and furthermore, not been offered a R0 resection. Therefore, the resulting recommendation (1,5) is that a complete lymphadenectomy should be performed, even in clinical stage I NSCLC.

In the light of this article, it is necessary to review more fully the notions of complete lymphadenectomy and occult pN2 disease.

The need for complete lymphadenectomy and its setbacks

As remembered (6), complete MLND was routinely performed as part of the surgical procedure at the beginning of NSCLC surgery in the forties. It was progressively replaced by LNs "picking" or sampling for questionable reasons, the main one probably being the fear of increasing the operative risks of the surgical procedure whereas its usefulness was not flagrant.

To assess the role of MLND and mediastinal lymph node sampling (MLNS), a multicentric prospective randomized study was performed by the American College of Surgery

Oncology Group (SOG). The first results demonstrated the harmlessness of MLND (7), but further analysis showed that MLNS offered similar results to MLND in patients with clinically stage I NSCLC (8). Those results suggested that complete MLND was not mandatory and thus, was indirectly an encouragement not to do it. Cerfolio and coworkers (9) pointed out that the study only randomized patients after thorough samplings that were negative on frozen section in several N2 and N1 nodal stations, which might have biased the results (9). They reviewed 1,358 patients clinically staged as N0 who underwent lobectomy or segmentectomy and MLND (not MLNS) (9). The incidence of pathologic N2 disease in 1,107 patients who underwent lobectomy was 10.6% whereas it was 9.4% in the 24,896 SOG lobectomy patients (P=0.196). The incidence of pathologic N2 disease in 251 patients who underwent segmentectomy was 13.0% whereas it was 5.3% in the 2,150 SOG segmentectomy patients (P<0.001). Thus, when complete MLND was performed in cN0 patients without using intraoperative frozen section of N2 or N1, more patients were pathologically staged with N2 disease which confirmed the need to perform complete MLND.

Besides minimizing the risk of incomplete NSCLC resection induced by lobe-specific lymphadenectomy, a complete MLND was also mentioned as the best way to rule out the question of the number of lymph node (NLN) to sample during lung cancer surgery (6). Recent studies advocate removing 10 LNs. In fact, the NLN is variable from one patient to another and the only way to ensure the best number of lymph node sampled (NLNsS) and the best pN-staging is to remove all LNs from the ipsilateral mediastinal and hilar LN-stations as they are discovered by thoroughly dissecting their anatomical locations. In doing so, a deliberate lack of harvest of LNs is unlikely, and a low NLNsS does not mean any longer incomplete surgery. This is important in view to correctly evaluate the quality of surgery. This prevents from judging as incomplete a complete LN dissection in a patient with a small NLNsS and from considering as complete a true incomplete one in a patient with a great NLNsS. It is mandatory to stress that precise information describing the course of the operation and furnished in the surgeon's reports is also advisable to further improve the quality of LN-dissection, which ultimately might be beneficial in the long-term to patients. Indeed, that procedure is of limited interest in pN-staging if LNs are not thoroughly examined and also described by the pathologist.

Thus, all surgical studies advocate the need for correctly dissecting the LNs. Accurate mediastinal staging is important for prognostic reasons as well as to determine the need for adjuvant therapies. The role and the extension of the lymphadenectomy is currently available in surgical guidelines (10,11). In spite of all that, lymphadenectomy is still a stumbling block and the state of the art remains discouraging as illustrated by two recent papers (12,13).

Verhagen and coworkers (12) evaluated the extent of MLND in 216 patients who underwent surgery in four different hospitals. Interlobar and hilar LNs were dissected in one-third of patients. A mediastinal LN exploration was performed in 75% of patients; however, subcarinal LNs were dissected in <50% of patients and at least three mediastinal LN stations were investigated in 36% of patients. In 35% of the mediastinal stations explored, LNs were sampled instead of a complete dissection of the entire station. A complete LN dissection according to the guidelines of the ESTS (10) was performed in only 4% of patients. Osarogiagbon and coworkers (13) audited operative summaries and pathology reports in a NSCLC resection cohort. The operating surgeons mentioned to have performed a MLND in 45% of all resections but the review of pathology reports revealed that only 8% of all resections met systematic sampling criteria, 50% had random sampling, and 42% had no mediastinal LN examined. Thus, it is amazing that in daily practice, a resection cannot be considered complete and curative in the majority of patients, just because of inadequate LN management. Such unreliable MLNDs will not only question the prognosis but also falsify and bias the results of studies concerning adjuvant therapy and long-term survival. Consequently, all those reasons urge to imperatively follow the current guidelines.

Characteristics of occult pN2 disease

Some characteristics are specific to occult pN2 disease. Bille and coworkers (1) observed that independent risk factors for occult pN2 disease were adenocarcinoma and vascular invasion. Histology seems important. In effect, other studies have confirmed that adenocarcinoma histology is associated with a higher risk for occult pN2 disease (4,14,15). Moon and coworkers (16), even reported that those adenocarcinomas displayed micropapillary and lepidic component positivity with significantly greater frequency; the frequency of epidermal growth factor receptor (EGFR) mutation was also significantly greater in this subset. Multivariate analysis indicated a significant correlation between micropapillary positivity and nodal upstaging.

In patients upstaged postoperatively to N1 or N2 stage of NSCLC, occult LN metastasis and MPC positivity appeared significantly related. Haruki and coworkers (17), reviewed 876 patients with c-stage I NSCLC whose 9.1% proved to have mediastinal LN metastasis. There were no cases with hilar and mediastinal LN metastasis in ground glass opacity-predominant tumors. There was no significant association of clinical factors with subcarinal LN metastasis in right upper-lobe and left upper-division adenocarcinoma.

Some other characteristics have been found. Al-Sarraf and coworkers (3), mentioned that the following were independent predictors of occult N2 disease in multivariate analysis: centrally located tumours, right upper lobe tumours and PET positive uptake in N1 nodes (P<0.05). They suggested that such patients should have preoperative cervical mediastinoscopy to rule out N2 nodal involvement, especially in LN stations 7 and 4 as the incidence of occult nodal metastasis in these nodes is high. Gómez-Caro and coworkers (4), also observed that occult pN2 metastases were more frequent in women (P<0.01) and in case of pN1 (P<0.05). Pathological N2 prevalence for pN1 was 34 (27.7%).

Occult pN2 metastasis and mini pN2

Occult pN2 metastases are clinically undetectable because they are predominantly small. Their prognosis could be much better. Andre and coworkers (18), reviewed 686 patients who underwent surgical resection of N2 NSCLC and distinguished among them patients with clinical N2 (cN2: n=332) and those with minimal N2 (mN2: n=354) disease, that is patients in whom N2 disease was and was not detected preoperatively at CT scan, respectively. A multivariate analysis identified four negative prognostic factors, namely, cN2 status (P<0.0001), involvement of multiple LN levels (P<0.0001), pT3 to T4 stage (P<0.0001), and no preoperative chemotherapy (P<0.01). For patients treated with primary surgery, 5-year overall survival (OS) rates were as follows: mN2, one level involved (n=244): 34%; mN2, multiple level involvement (n=78): 11%; cN2 one level involved (n=118): 8%; and cN2 multiple level involvement (n=122): 3%. Those results were obtained from a multicentric study.

In reviewing our series (19), we also observed that the survival was better when only one N2 station was involved: out of 586 N2 patients, metastases involved one N2 stations in 386 (66%) and two or more in 200 (34%). When considering one N2 stations, capsular rupture, number, and size of LNs were not significant prognostic factors. When the size of LNs was analyzed (micrometastases, 53; non-bulky, 207; or bulky metastases, 126), OS differences between non-bulky and bulky N2 were significant: 5-year OS was 34% *vs.* 23%, respectively (P=0.026). Presence of micrometastases was associated with a poor prognosis: 5-year OS of 21.4%. Roh and colleagues (20) reported that a micropapillary component might be a manifestation of aggressive behavior for stage I lung adenocarcinomas. They observed that there was a relationship between the micropapillary component and micrometastases in regional LNs of those patients. The 5-year OS of the cases with and without nodal micrometastases were 71.4% and 35.7%, respectively (P=0.03). The indicator of the aggressive behavior might be reflected by the frequency of LN-micrometastases.

However, Garelli and coworkers (21), reported findings similar to what Andre and coworkers (18), observed. Out of 982 pathologically stage IIIA-N2 patients who underwent surgery with curative intent for NSCLC, microscopic pN2 disease, defined as a nodal metastasis ranging from 0.2 to 2 mm in size was observed in 309 (31.5%) patients. Microscopic N2 was associated with better median survival compared with macroscopic N2 (5-year survival rate of 39% and 21%, respectively). In multivariate analysis, microscopic N2 remained a favourable independent prognostic factor.

The prognostic value of LN-micrometastasis (mini-pN2) is still a matter of debate. LN-micrometastasis might enjoy the best prognosis among the pN2 group in its whole. Nevertheless the prognosis remains poor as soon as there is the slightest trace of cancer in the mediastinal LN.

Occult cancer cells in mediastinal LNs

In effect, despite histologically negative LNs some patients may still suffer from local recurrence and die from their disease. The rate of recurrence after complete resection in node negative patients may be as high as 30–40% and suggest that their nodal staging is suboptimal (22). Le Pimpec-Barthes and coworkers (23), designed a study to screen occult cancer cells by CK19 mRNA detection using reverse transcriptase-polymerase chain reaction (RT-PCR) in mediastinal LNs in NSCLC. In 49 NSCLC patients free of mediastinal adenopathy on computed tomography, 254 mediastinal LNs were evaluated by histopathology, immunohistochemistry (IHC) and RT-PCR. Of 225 non-tumoral mediastinal LNs on histopathology, 32 (14.2%) were positive by RT-PCR. IHC did not provide significant additional results. The patients were further divided in

three groups. Seventeen patients were without mediastinal tumoral extension on histopathology and RT-PCR (Group 1), 16 were upgraded by RT-PCR (Group 2) and 16 pN2 on histopathology (Group 3). The 2-year cancer-related death survival in Groups 1 (100%) and 2 (64.5%) was significantly different (P=0.04). The relative risk of recurrence in Group 2 compared with Group 1, evaluated by the Cox model multivariate analysis, was 5.61 (P=0.02). In conclusion, CK19 mRNA detected by RT-PCR in mediastinal LNs was significantly associated with an increased risk of rapid recurrence.

Similar findings may be demonstrated by using different tumor markers. In Dai and coworkers' (22) study, primary tumor samples from 62 patients with resected stage I–IIB NSCLC were screened for fragile histidine triad (FHIT) and CDKN2A mRNA deletion using RT-PCR. The molecular alternations were found in tumors of 49 patients. A total of 269 LNs from these 49 NSCLC patients with FHIT or/and CDKN2A deletion tumors were examined. Thirty-nine (22%) and 22 (18%) LNs from the 49 patients with FHIT and CDKN2A mRNA deletion in primary tumor had FHIT and CDKN2A mRNA deletion, respectively. The types of FHIT and CDKN2A mRNA deletion in LNs were identical with those in their primary tumors. By combination of two markers, 16 patients (32.7%) were found to have nodal micrometastasis. Survival analysis showed that patients with nodal micrometastasis had reduced disease-free survival (P=0.001) and OS (P=0.002) rates. Multivariate analysis demonstrated that nodal micrometastasis was an independent predictor for worse prognosis. Martin and coworkers (24), reviewed 304 patients with pathologic stage I NSCLC. Primary tumor and LNs were assayed for occult metastasis using IHC for cytokeratin (AE1/AE3) and real-time RT-PCR for carcinoembryonic antigen. LNs from 298 patients were analyzed by IHC; 41 (14%) were IHC-positive (42% in N1 position, 58% in N2 position). LNs from 256 patients were analyzed by RT-PCR; 176 (69%) were PCR-positive (52% in N1 position, 48% in N2 position). Thus, NSCLC tumor markers were detected in histologically negative LNs by AE1/AE3 IHC and carcinoembryonic antigen RT-PCR. In that prospective, multi-institutional trial, the presence of occult metastasis by IHC staining in N2 LNs of patients with NSCLC correlated with decreased survival.

Conclusions

Complete lobar, hilar and mediastinal lymphadenectomy is the gold standard in NSCLC surgery with curative intent. It is the only way to remove occult pN2 disease, to insure an unequivocal NLNs, and to prevent from leaving cancer cells behind.

PN2 is a heterogeneous group with a wide range of pLN diseases each with different poor prognostic values; each subtype of pN2 should be assigned its own pTNM stage. Range includes mini-N2 clinically unsuspected and discovered at surgery. It is itself a multifaceted subset, the outcome of which might not be so poor.

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Footnote

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

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