Editorial

Does oncogenic mutation status influence tumor spread in resectable lung cancer?

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Skip N2 metastasis of lung cancer is known to involve the mediastinum, but not the hilar lymph nodes. This phenomenon itself is not especially rare, as the incidence in resected pN2 disease is reported to range from 17.6% to 40.4% (*Table 1*) (1-13). Prognosis after resection is favorable for skip N2 cases compared with that of pN2 cases accompanied with hilar disease. Based on data from the International Association for the Study of Lung Cancer, Asamura *et al.* (15) documented no significant survival differences between the skip N2 phenotype and multistation pN1 disease, and thus recommend that physicians record N categories using new descriptors for further testing. With regard to factors predictive of skip N2 metastasis, several authors suggested that the histological type and tumor-containing lobe are predictive of skip pN2. An investigation on resected non-small-cell lung cancer cases conducted by Misthos *et al.* (3) reported that skip N2 occurred more frequently in squamous cell carcinoma than in adenocarcinoma. Li *et al.* (13) documented that acinar adenocarcinoma was more frequently associated with skip N2 metastasis in pN2 cases. In terms of the tumor-containing lobe, Riquet *et al.* (5) actually revealed a higher incidence of skip N2 metastasis involving tumors of the upper lobe and suggested potential contributions of lymph drainage patterns and visceral pleural invasion (VPI) to the spread patterns. In a study of 422 cases of cStage IA adenocarcinoma, Gorai *et al.* (12) identified 21 instances of skip N2 in 52 pN2 cases and found a significant association between skip pN2 and VPI and concluded that lymph node dissection was essential in cN0 VPI cases.

Over the past decade, the impact of oncogenic mutational status, including the epidermal growth factor receptor (*EGFR*) gene, has been emphasized. Specifically, the presence of EGFR-sensitive mutations predicts favorable responses and survival outcomes of advanced lung cancer after the administration of EGFR-tyrosine kinase inhibitors (TKIs), which is currently the standard first-line treatment for genetically selected cases. However, the biological nature of spread patterns and the significance of the genotype remain unclear, especially in resected cases.

In a recent study of 177 pN2 adenocarcinoma cases, which included 45 cases with the skip N2 phenotype, Li *et al.* (13) found no significant impact of molecular alterations on lymph metastatic patterns in this cohort. On the other hand, the results of the present study on 279 cases of pN2 adenocarcinoma, which included 22 limited resection cases in which there was some concern regarding the diagnostic accuracy of skip N2, found a higher frequency of skip N2 in EGFR-mutated tumors than that of the non-skip N2 phenotype of pN2 adenocarcinoma (14). As described, although correlations between genetic status and tumor spread patterns remain poorly understood and controversial, the findings of this study provide a novel biological aspect of lung adenocarcinoma. Furthermore, the associations among variables, including the tumor-containing lobe, VPI, and EGFR status, remain a matter of interest. It is possible that EGFR-mutated tumors may develop in locations that favor skipping spread, such as the peripheral lung parenchyma, which may be correlated with VPI.

In spite of the small number of resected cases, it is assumed that oncogenic mutation status was not investigated

Table 1 Summary of the reports about skip pN2

Author	Year	Study cohort	pN2	Skip pN2	%	Skip pN2 associated factors
Prenzel *et al.* (1)	2003	pN2	45	17	37.8	None
Kotoulas *et al.* (2)	2004	cN0	138	27	19.6	NA
Misthos *et al.* (3)	2004	IIIA/pN2	151	44	29.1	Right side tumor, SQ histology, MDL
Okada *et al.* (4)	2005	NS	87	19	21.8	NA
Riquet *et al.* (5)	2005	pN2	731	209	28.6	Upper lobe tumor, single station
Benoit *et al.* (6)	2006	pN2	142	42	29.6	NA
Ilic *et al.* (7)	2007	NS	85	21	24.7	SQ histology
Ito *et al.* (8)	2012	pN2	40	13	32.5	NA
Li *et al.* (9)	2012	pN2	256	44	17.2	Tumor size
Saeteng *et al.* (10)	2012	NS	50	18	36.0	NA
Shimada *et al.* (11)	2012	pN2	207	55	26.6	NA
Gorai *et al.* (12)	2015	cIA	52	21	40.4	VPI
Li *et al.* (13)	2015	pN2 AD	177	45	25.4	Lymphatic invasion, histological subtype, tumor differentiation
Guerrera *et al.* (14)	2017	pN2 AD	279	54	19.4	Non-smoker, limited resection
						No adjuvant therapy, EGFR mutation

NS, non-small cell lung cancer; AD, adenocarcinoma; NA, not available; SQ, squamous cell carcinoma; MDL, mediastinal lymph node dissection; VPI, visceral pleural invasion.

before surgical resection. Accordingly, the usefulness of this knowledge is limited to planning a strategy before treatment by subclassification of the cohort based on clinical stage, which may be of more clinical use. However, partial elucidation of the biological nature of resectable lung adenocarcinoma harboring EGFR mutations could overcome such limitations.

In both overall survival (OS) and time to recurrence (TTR) analyses, the difference between skip N2 and non-skip N2 was not evident by the Kaplan-Meier method, whereas skip N2 status was identified as an independent prognostic factor by Cox proportional hazard model analysis. According to the TTR curve, the majority of pN2 cases experienced recurrence after resection. The impact of post-recurrence treatment, including the use of TKIs, on OS was also of interest in their cohort.

At present, no initial or adjuvant treatment strategies for surgery cases have been developed based on oncogenic status. The results of the RADIENT trial, which compared adjuvant erlotinib and a placebo, found that the period of disease-free survival was longer in the EGFR mutation-positive subgroup treated with adjuvant erlotinib; however, this result was not statistically significant (16). The results of ongoing randomized trials in Japan (IMPACT; WJOG6401L), China (ADJUVANT; CTONG 1104), and the United States (ALCHEMIST trials) have yet to be reported (17).

The results of this study show that oncogenic status strongly affects both choices of treatment strategies and outcomes of advanced disease, but not resectable cases. Hence, further studies on this issue are expected to provide useful information regarding multimodal treatment, including surgery, and follow-up after resection.

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