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EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONS ARE LINKED TO SKIP N2 LYMPH NODE METASTASIS IN RESECTED NON-SMALL CELL LUNG CANCER ADENOCARCINOMAS

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Objectives: Skip-N2 metastases (e.g. N2 lymph node metastases without N1) impact on survival in surgically resected non-small lung cancer remains an intriguing and rarely investigated topic. Our study aimed to elucidate: (1) Skip-N2 influence on overall survival (OS) and disease free survival (DFS) in resected lung adenocarcinoma patients; (2) its link with epidermal growth factor receptor (EGFR) and KRAS mutations.

Methods: A retrospective analysis of 279 consecutive lung pN2 adenocarcinoma patients, operated in two institutions between 2003 and 2013, was conducted. OS and DFS were calculated using Kaplan-Meyer. Crude and multivariate-adjusted comparisons by skip-N2 for OS and DFS was performed using the Cox method with shared frailty (accounting for the within-centre correlation). Associations between skip-N2 metastasis, clinical-pathological characteristics and EGFR/KRAS mutations were investigated using Chi-square, Fisher's exact test and Cramer's V, when appropriate.

Results: Mean age at time of surgery was 63 years (+/-12), median follow-up time was 36 months (min 3; max 101). Skip-N2 was observed in 54 patients (19%). EGFR mutations were observed in 38 patients (14%), while *KRAS* mutations in 86 patients (31%). Patients with skip-N2 metastasis were predominantly non-smokers ($P = 0.001$), underwent segmentectomy ($P = 0.004$), and were not submitted to adjuvant therapy ($P = 0.022$). Multivariate-adjusted model showed a skip-N2 protective effect on OS (OR: 0.5, 95% CI: 0.285–0.875, $P = 0.015$) but not on DFS (OR: 0.8, 95% CI: 0.428–1.454, $P = 0.45$). Moreover, there was a correlation between EGFR mutations and skip-N2 (Cramer's V: 0.25, $P < 0.001$). Indeed, EGFR mutations were significantly more frequent in skip-N2 tumours (33%) compared to non-skip (10%), $P < 0.001$. No correlation between skip-N2 and KRAS mutations was observed (Cramer's V: 0.05, $P = 0.46$).

Conclusion: In our series, lung adenocarcinoma skip-N2 metastases showed a better prognosis. Presence of EGFR mutations could have significance in the specific anatomic pattern of lymphatic metastases in skip-N2 tumours.

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