Editorial

Comment on prognostic value of epidermal growth factor receptor mutation subtypes in surgically resected non-small cell lung cancer

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Personalization of lung cancer treatment requires predictive biomarkers that have been validated by correlation between tumor features and outcomes after therapy. Several mutations have been identified in the epidermal growth factor receptor (EGFR) in non-small cell lung cancer (NSCLC). Mutations in this gene are considered an important predictor of response to EGFR tyrosine kinase inhibitors (TKIs) with 70–80% of NSCLC patients receiving substantial benefits from this targeted therapy (1). The EGFR mutation is both a predictive and prognostic factor of EGFR-TKI therapy outcome (1,2). Testing for these mutations in all patients with recurrent or metastatic lung adenocarcinoma is therefore recommended for standard practice.

Several studies have reported that EGFR mutations have an impact on prognosis after surgical resection of NSCLCs (3,4). Izar *et al.* demonstrated that the mutation status of EGFR can serve as an independent prognostic marker associated with decreased recurrence and improved progression-free survival and overall survival (OS) in patients with stage I lung adenocarcinoma (3). This study was restricted to patients who had no adjuvant or neoadjuvant systemic therapy administered and focused solely on the postoperative prognostic differences among different genotypes. On the other hand, Kosaka *et al.* reported that the significant prognostic impact of EGFR mutations was lost after adjusting for other confounding prognostic factors (4). Several other studies in the literature corroborate this finding (5,6). Additionally, EGFR mutation status and the use of EGFR-TKI therapy particularly affected the postoperative recurrence survival (PRS), which is survival after disease recurrence, among patients who underwent surgical resection for lung cancers (7). The results could also affect OS in general.

Exon 19 deletion (Ex19) and the L858R point mutation in exon 21 (Ex21) of EGFR comprise approximately 90% of all EGFR mutation positive lung adenocarcinomas (8) and are strongly associated with robust responses to EGFR-TKI. Patients with Ex19 advanced NSCLC have consistently shown improved outcomes with afatinib *vs.* chemotherapy compared with those with Ex21 NSCLC (9). The cause for these differences in response to EGFR-TKIs among EGFR mutation subtypes is not known. However, another trial that demonstrated survival curves of patients with Ex19 and Ex21 advanced NSCLC showed no statistically significant differences between afatinib or gefitinib and the EGFR mutation subtypes (10).

In the study by Isaka *et al.* published in the *Annals of Thoracic Surgery*, the authors demonstrated that different EGFR mutation subtypes were associated with different prognoses among patients with surgically resected pathologic N1-N2 lung adenocarcinoma (11). This

Table 1 Summary of EGFR mutation subtypes (exon19 deletion *vs.* L858R point mutation in exon 21) as a prognostic factor in surgically resected lung cancer patients

Authors	Journal	N (Ex19 *vs.* Ex21)	Stage	5 y-DFS, median DFS, comment	5 y-OS, MST, comment	Multivariate analysis for EGFR mutation subtypes (Ex19 *vs.* Ex21) as a prognostic factor
Ex19: better prognosis						
W Liu, *et al.* (14)	*Med Oncol*, 2014	30 *vs.* 23	Stage I–IIIA	Ex19, 46.2 mo; Ex21, 21.9 mo (P=0.056)	3 y-OS; Ex19, 93.3%; Ex21, 60.9% (P=0.01)	No data
T Isaka, *et al.* (11)	*Ann Thorac Surg*, 2016	55 *vs.* 41	N1-2	Ex19, 38.8%; Ex21, 11.8% (P=0.001)	Ex19, 78.3%; Ex21, 48.3% (P=0.123)	DFS: HR 2.25, P=0.011; OS: HR 1.48, P=0.299
Ex21: better prognosis						
YJ Lee, *et al.* (15)	*J Cancer Res Clin Oncol*, 2009	38 *vs.* 11	Stage I–IIIA	Ex19 had higher recurrence rate than Ex21 (HR 4.13, P=0.03)	No data	No data
T Nishi, *et al.* (16)	*Asia Pac J Clin Oncol*, 2016	55 *vs.* 85	Stage I	No significant difference in Stage IA (P=0.681); DFS better in Ex21 than in Ex19 in Stage IB (P=0.008)	No significant difference in Stage IA or IB (P=0.503 and 0.134, respectively)	No data
T Okamoto, *et al.* (17)	*Anticancer Research*, 2016	27 *vs.* 45	Stage I–III	Ex19, 53.3%; Ex21, 84.4% (P=0.027)	Ex19, 95.0%; Ex21, 84.8% (P=0.70)	DFS: HR 0.41, P=0.067
H Shigematsu, *et al.* (18)	*J Natl Cancer Inst,* 2005	31 *vs.* 31	Stage I–IV	No data	Ex21 has better survival rate than Ex19 (P=0.05) in patients without EGFR-TKI therapy	No data
No difference between Ex19 and Ex21						
N Nose, *et al.* (19)	*J Clin Oncol*, 2009	74 *vs.* 92	Stage I–IV	No significant difference (P value unknown)	No data	No data
Y Jin, *et al.* (20)	*Scientific Reports*, 2016	53 *vs.* 51	Stage I–III	Ex19, 29.4 mo; Ex21, 25.7 mo (P=0.941, analysis includes wild-type)	No data	No data
JL Marks, *et al.* (5)	*J Thorac Oncol*, 2008	19 *vs.* 19	Stage I–III	No data	No significant difference (P=0.499)	No data
T Kosaka, *et al.* (4)	*J Thorac Oncol*, 2009	65 *vs.* 80	Stage I–IV	No data	No significant difference (P=0.4144)	No data
K Sugio, *et al.* (21)	Br J Cancer, 2006	52 *vs.* 70	Stage I–IV	No data	No significant difference (P=0.5625)	No data

EGFR, epidermal growth factor receptor; Ex19, exon19 deletion of EGFR; Ex 21, L858R point mutation in exon 21 of EGFR; DFS, disease free survival; MST, median survival time; HR, hazard ratio; mo, months; EGFR-TKI, EGFR tyrosine kinase inhibitor.

meaningful work showed that patients with Ex19 displayed statistically significant better 5-year disease-free survival (DFS) rate (38.8%) than those with Ex21 (11.8%, P=0.001). In this study, pathologic N status (N1 or N2) or pathologic stage (stage II or III) were determined to not be statistically informative prognostic factors for DFS using multivariate analysis (HR 1.71; P=0.353, or HR 0.75; P=0.627, respectively). Additionally, patients with Ex21 tumors

displayed a significantly higher prevalence of pN2 (70.7%) than those with Ex19 tumors (45.5%, P=0.014). However, in this case, the EGFR mutation subtype was a prognostic factor for DFS using multivariate analysis (HR 2.25; 95% CI, 1.21–4.20, P=0.011). Therefore, they hypothesized that tumors with Ex19 might possess lower proliferative potential, making them more susceptible to cell death than those tumors with Ex21.

Meanwhile, two conflicting *in vivo* assessments have been reported. Carey *et al.* showed that the growth rate of the NR6-EGFR del [746-752] cell line was more aggressive *in vivo* than the NR6-EGFR L858R cell line (12). This data might support the results and hypothesis of Isaka's study. However, Politi *et al.* demonstrated that lung tumors from EGFR L858R expressing mice developed faster and exhibited a preponderance of lepidic growth with a more aggressive nature compared with lung tumors derived from EGFR del [L747-S752] expressing mice. It is to be noted that both EGFR mutation subtypes promoted lung adenocarcinomas with lepidic growth features in transgenic mice (13).

Table 1 summarizes ten studies that reported a relationship between EGFR mutation subtypes and prognosis (4,5,11,14-21). In focusing on the association between DFS or recurrence and EGFR mutation subtype, Liu *et al.* also reported that patients with Stage I-IIIA lung adenocarcinoma harboring Ex19 had a better DFS rate than those with Ex21 (P=0.056) (14). Conversely, Okamoto *et al.* demonstrated that patients with Stage I-III lung adenocarcinoma harboring Ex21 showed statistically significant better DFS than those with Ex19 (P=0.027), and that the EGFR mutation subtype was a potential prognostic factor for DFS (HR 0.41, P=0.067) (17). In the study reported by Nishi *et al.*, whose institution was the same as Isaka *et al.*, the DFS rate of Stage IB lung adenocarcinoma harboring Ex21 was better than that of Ex19 (P=0.008), with no differences in DFS observed among patients with stage IA adenocarcinoma (P=0.681) (16). Furthermore, several other groups reported there to be no significant differences of DFS between tumors with Ex19 and those with Ex21 (19,20).

Possibilities for the discrepancies in survival might be due to clinicopathological factors, studies containing small cohorts of patients, or selection bias in the examination of EGFR mutation analysis. For instance, Isaka *et al.* determined the EGFR mutation status in their cohort and identified mutations in 72.9% of 277 patients with pN1–2, and EGFR mutation status was also examined for not all of the patients in other studies. Moreover, it might be necessary to interpret that DFS were affected by death from other cause as well as lung cancer recurrence or death and by follow-up assessment schedule after operation.

The current study demonstrated the association between EGFR mutation subtype and prognosis, especially DFS among patients with pN1–N2 lung adenocarcinoma. This study could provide additional evidence to support EGFR mutation analysis for surgically resected lung adenocarcinoma. Large prospective and multicenter studies with appropriate EGFR mutation detection methods are warranted to validate the prognostic effect of EGFR mutation subtypes.

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Footnote

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