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EGFR mutational status in a large series of Caucasian European NSCLC patients: data from daily practice

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Background: The prognosis of metastatic non-small cell lung cancer (NSCLC) is still poor. Activating epithelial growth factor receptor (EGFR) mutations are important genetic alterations with dramatic therapeutical implications. Up to now, in contrast to Asian populations only limited data on the prevalence of those mutations are available from patients with Caucasian and especially European ethnicity.

Methods: In this multicentre study, 1201 unselected NSCLC patients from Southern Germany were tested in the daily clinical routine for EGFR mutation status.

Results: Activating EGFR mutations were found in 9.8% of all tumours. Mutations in exons 18, 19 and 21 accounted for 4.2%, 61.9% and 33.1% of all mutations, respectively. Non-smokers had a significantly higher rate of EGFR mutations than smokers or ex-smokers (24.4% *vs* 4.2%; $P<0.001$). Non-lepidic-non-mucinous adenocarcinomas (G2) accounted for 45.5% of all activating EGFR mutations and 3.5% of all squamous cell carcinomas were tested positive. Thyroid transcription factor 1 protein expression was significantly associated with EGFR mutational status.

Conclusion: These comprehensive data from clinical routine in Germany add to the knowledge of clinical and histopathological factors associated with EGFR mutational status in NSCLC.

In contrast to other tumour entities like colorectal or breast cancer, the overall prognosis of non-small cell lung cancer (NSCLC) is still poor and has not much improved over the recent 20 years (Jemal *et al*, 2009). However, one milestone in the field of lung cancer was the detection of epithelial growth factor receptor (EGFR) as a target oncogenic driver in a subset of patients. Epithelial growth factor receptor is a member of the HER family of tyrosine kinase receptors and is expressed in more than half of all NSCLC (Sharma *et al*, 2007; Hynes and MacDonald, 2009). Recently, it could be shown that somatic activating mutations in the ATP-binding region of the receptor lead to a more effective binding of EGFR tyrosine kinase inhibitors (TKIs; Lynch *et al*, 2004; Paez *et al*, 2004). This translates into better response and longer progression-free survival (PFS) for patients with metastatic NSCLC treated with

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EGFR-TKIs (Jackman *et al*, 2007). In a landmark study by Mok *et al* (2009), PFS in tumours with activating mutations treated with an EGFR-TKI was significantly higher when compared with chemotherapy (9.5 *vs* 6.5 months). In contrast, patients with tumours tested as EGFR wild type had no benefit from treatment with EGFR-TKI (PFS 1.5 months). This beneficial treatment effect of EGFR-TKI in EGFR mutated tumours has been confirmed in other phase III trials (Maemondo *et al*, 2010; Zhou *et al*, 2011; Rosell *et al*, 2012). As a consequence, the TKIs gefitinib and erlotinib have been approved for first-line treatment of those tumours in patients with EGFR mutations, for example, the European Medicines Agency.

However, most studies in this field have been performed in East Asia. In those studies, it has been shown that especially adenocarcinomas, tumours in female patients and tumours in non-smokers harbour activating mutations in the EGFR gene (Pao *et al*, 2004; Shigematsu *et al*, 2005a, b). To date, only limited data on activating EGFR mutations and their relation to clinicopathological features are available from patients with Caucasian ethnicity, especially from European patients.

Histology is an important predictor of activating EGFR mutations. It has been demonstrated that most tumours with activating EGFR mutations present with a non-squamous histology. There are only a few studies where patients with squamous histology were included and tested for EGFR mutations. Retrospective data from East Asian populations (Tanaka *et al*, 2009) show that not >3–8% of NSCLC patients with squamous histology present with activating EGFR mutations. Systematic data on European Caucasian patients presenting with squamous type NSCLC are missing up to date.

An important marker to distinguish between different types of NSCLC is the thyroid transcription factor 1 (TTF1); TTF1 has a crucial role in normal lung function and morphology and is regarded as a lineage marker of the terminal respiratory unit. Strong nuclear TTF1 expression detected by immunohistochemistry is an important diagnostic marker to identify adenocarcinomas of the lung in daily routine histopathology (Yatabe *et al*, 2002). As TTF1-positive tumours are more frequently found in female patients and in non-smokers and as TTF1-positive tumours are associated with a longer survival (Tanaka *et al*, 2007; Anagnostou *et al*, 2009; Ordonez, 2012; Sun *et al*, 2012), it would be interesting to find out, whether there is a correlation between TTF1 status and EGFR mutation status in European Caucasian patients.

In this study from a group of tertiary care centres for lung cancer in Southern Germany, patients with NSCLC were tested for EGFR mutation status in the daily clinical routine in four molecular pathology laboratories and basic biometric data were collected. The aim of our study was to quantify and correlate clinical, pathohistological and molecular characteristics from unselected NSCLC patients in Germany.

PATIENTS AND METHODS

We enrolled 1201 consecutive patients with newly diagnosed, histologically proven NSCLC tested for EGFR mutational status in the routine clinical setting between January and December 2010. The indication for EGFR mutation testing was provided by the physicians caring for the individual patients based on the individual patients' clinical situation. In general, all patients were tested on whom a positive test result might lead to first-line palliative treatment with an EGFR-TKI. Although stage according to TNM was no selection criterion for these analyses, the whole majority of patients presented with stage IV disease. Epithelial growth factor receptor mutation testing was performed at four different departments of pathology in Bavaria, located in Southern Germany (Erlangen, Coburg, Regensburg and Wuerzburg). Clinical data were aggregated for all tested patients. The smoking status was classified as never smoker, former smoker (>1 year of quitting), active smoker and the number of pack years of smoking (one pack year is defined as 20 cigarettes per day per 1 year) was retrieved (Patel *et al*, 2006). All clinical, pathological, histological and molecular data were transferred to a central database after strict pseudonymisation. The study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki (1995, revised Edinburgh, 2000).

Histological classification. All initial histological findings were crosschecked by at least one board-certified pathologist. Histological type (for details see Table 3) and grading was defined using haematoxylin and eosin (HE)-stained biopsies after serial sectioning. In cases without unequivocal diagnosis in HE stainings, the recommended panel of antibodies for classification of NSCLC (TTF1, CK7, CK5/6 and/or p63) was stained by immunohistochemistry and also reviewed (Ring *et al*, 2009; Travis *et al*, 2011; Thunnissen *et al*, 2012). Subsequently, each sample was discussed by the pathologists of all four departments of pathology. In cases of uncertainty, a majority decision by the involved pathologist was taken.

EGFR mutational status. All tumours were analysed for EGFR mutational status in one of the four participating departments of pathology. In all cases, exons 18, 19 and 21 of the EGFR gene were sequenced by the Sanger method as described by Savic *et al* (2008) or by pyrosequencing (Ronaghi *et al*, 1996, 1998). Both techniques are broadly accepted for routine in detection of EGFR mutational status. All four participating Molecular Pathology laboratories successfully completed the round robin test of the quality initiative pathology of the German Society of Pathology (Penzel *et al*, 2011). All sequence analyses were checked for plausibility.

Statistical analyses. All patients of the study could be classified as either EGFR mutation positive or wild type. Tumours, where either molecular testing was not possible (e.g., because of quantity of material) or no result could be performed (e.g., because of quality of material), were excluded from this study. Differences in the variables between the two groups and associations with clinical and histological data were tested using the Fisher's exact or two-sided χ^2 test. Significance was determined by a P-value of <0.05. All statistics were performed using SPSS software (SPSS version 17.0 for Windows, SPCC Inc., Chicago, IL, USA).

RESULTS

General data. Between January and December 2010, the EGFR mutation status could be determined in 1201 tumour samples at four Departments of Molecular Pathology in Southern Germany (Coburg $n=235$, Erlangen $n=443$, Regensburg $n=325$, Wuerzburg $n=198$). In all, 1122 (93.4%) of those samples had an interpretable result for the histological subtype, the other 79 were not other specified. In 884 samples (73.6%), TTF1 expression was determined. In 684 patients (56.9%), the smoking status was obtained and in 625 patients (52%) quantitative data on smoking (pack years) were available.

Frequency of EGFR mutations and clinical characteristics. A total of 118 out of 1201 patients (9.8%) presented with EGFR mutations (Table 1). There were significantly more EGFR mutations detected in females than in males (17.4% *vs* 5.0%; $P<0.001$). In male patients, there was no age-dependent difference in EGFR mutation rate. In contrast, female patients $\geqslant$65 years of age had a significantly higher rate of EGFR mutations in

Table 1. Clinical characteristics in association to the EGFR mutation status

	N total	Wild type *N* (%)	EGFR mutation *N* (%)	*P*-value
Age at diagnosis				
<65 years	532	489 (91.9)	43 (8.1)	
>65 years	669	594 (88.8)	75 (11.2)	NS
Gender				
Male	735	698 (95.0)	37 (5.0)	
Female	466	385 (82.6)	81 (17.4)	<0.001
Age and gender				
Male<65 years	301	286 (95.0)	15 (5.0)	
Male>65 years	434	412 (94.9)	22 (5.1)	NS
Female<65 years	231	203 (87.8)	28 (12.2)	
Female>65 years	235	182 (77.4)	53 (22.6)	<0.001
Smoking status				
Smoker	291	279 (95.9)	12 (4.1)	
Former smoker	237	227 (95.8)	10 (4.2)	
Non-smoker	156	118 (75.6)	38 (24.4)	<0.001
Smoking (pack years)				
>15 pack years	205	197 (96.1)	8 (3.9)	
⩽15 pack years	25	22 (88.0)	3 (12.0)	NS

Abbreviations: EGFR = epithelial growth factor receptor; NS, not significant. Smoking status was collected for 684 patients, pack year status for 230 patients.

Table 2a. Frequency of EGFR mutations

Exon	*N*	(%)	% Of mutated cases
Exon 18	5	0.4	4.2
Exon 19	73	6.1	61.9
Exon 21	39	3.2	33.1
Exon18 and 21	1	0.1	0.8
Total	118	9.8	100.0

Abbreviation: EGFR = epithelial growth factor receptor.

Table 2b. Characteristics and number of EGFR mutations

Localisation (exon) and description of mutations on protein level	*n*	(%)
Total (*n* = 1201)		
Wild type	1083	90.2
Exon 18: p.G719A	3	0.2
Exon 18: p.G724D	1	0.1
Exon 18: p.G724S	1	0.1
Exon 19: p.E746_A750del	42	3.5
Exon 19: p.E746_S 752delinsV	1	0.1
Exon 19: p.E746_S752del	2	0.2
Exon 19: p.E746_S752delinsA	1	0.1
Exon 19: p.E746_S752delinsV	5	0.4
Exon 19: p.E746_T751delinsA	4	0.3
Exon 19: p.K745_E746delinsIPVAIK	1	0.1
Exon 19: p.L747_A750delinsP	2	0.2
Exon 19: p.L747_P750delinsP	1	0.1
Exon 19: p.L747_P753delinsQ	1	0.1
Exon 19: p.L747_P753delinsS	4	0.3
Exon 19: p.L747_T751del	4	0.3
Exon 19: p.L747P	1	0.1
Exon 19: p.R748_S753del	1	0.1
Exon 19: p.T751_I759delinsN	3	0.2
Exon 21: p.D855N and p.E868G	1	0.1
Exon 21: p.E866K	1	0.1
Exon 21: p.G863D	1	0.1
Exon 21: p.L851I	1	0.1
Exon 21: p.L858R	27	2.2
Exon 21: p.L858R and exon18: p.E709G	1	0.1
Exon 21: p.L861Q	4	0.3
Exon 21: p.N826D	2	0.2
Exon 21: p.N842S and p.T847A	1	0.1
Exon 21: p.P848L	1	0.1

Abbreviation: EGFR = epithelial growth factor receptor.

comparison with younger female patients (22.6% *vs* 12.2%; $P<0.001$). In addition, a significantly higher rate of EGFR mutations was found in non-smokers in comparison with smokers or ex-smokers (24.4% *vs* 4.2%; $P<0.001$). In detail, smokers featuring ⩽15 pack years had a three-fold higher EGFR mutation rate than those with >15 pack years (12% *vs* 3.9%; *NS*).

Characteristics of EGFR mutations. Among EGFR mutations, deletions in exon 19 (61.9%) were the most common, followed by mutations in exon 21 (33.1%) and exon 18 (4.2%). In one case, EGFR mutations were detected both in exon 18 and in exon 21 (0.8%; Table 2a).

In all, 41.9% of all EGFR mutations were deletions, 39% were substitutions and 19.5% were complex deletion-insertions (delins). Among all mutations detected, the p.E746_A750deletion in exon 19 (35.6% of all mutations) and the p.L858R substitution in exon 21 (22.9%) were most common. An overview of all detected mutations is given in Table 2b.

Distribution of EGFR mutations in histological subtypes. The histological subtype could be defined in 1122 tumours (Table 3). Non-mucinous adenocarcinomas without lepidic (bronchioloalveolar) growth pattern and intermediate differentiation (G2) accounted

Table 3. Characteristics and number of EGFR mutations

	Analysable cases		Wild type		EGFR mutation			
Histology	***n***	**(%)**	***n***	**(%)**	***n***	**(%)**	**% Of all mutated cases**	***P*-value**
Total ($n=1201$), NOS ($n=79$)	1122	100	1021	91.0	101	9.0		
Separated categories								
SQC-Ca	144	12.8	139	13.6	5	0.4	5.0	1.000
LEP-muc. (G1)	24	2.1	23	2.3	1	0.1	1.0	
LEP-non-muc. (G1)	84	7.4	62	6.1	22	2.0	21.8	
Non-LEP-muc. (G1)	7	0.6	6	0.6	1	0.1	1.0	
Non-LEP-non-muc. (G1)	30	2.6	27	2.6	3	0.3	3.0	
Non-LEP-muc. (G2)	24	2.1	24	2.4	0	0.0	0.0	
Non-LEP-non-muc. (G2)	299	26.6	253	24.8	46	4.1	45.5	
Non-LEP-muc. (G3)	12	1.1	12	1.2	0	0.0	0.0	
Non-LEP-non-muc. (G3)	464	41.4	444	43.5	20	1.8	19.8	
LC undiff.	34	3.0	31	3.0	3	0.3	3.0	
Grouped categories								
SCQ-Ca	144	12.8	139	13.6	5	0.4	5.0	<0.001
AC G1 and G2, muc.	55	4.9	53	5.2	2	0.2	2.0	
AC G1 and G2, non-muc.	413	36.8	342	33.5	71	6.3	70.3	
AC G3, muc.	12	1.1	12	1.2	0	0.0	0.0	
AC G3, non-muc.	464	41.4	444	43.5	20	1.8	19.8	
LC undiff.	34	3.0	31	3.0	3	0.3	3.0	
Immunohistochemical data								
TTF1								
Positive	627	73.4	526	83.9	101	16.1		
Negative	227	26.6	220	96.9	7	3.1		<0.001

Abbreviations: AC = adenocarcinoma; EGFR = epithelial growth factor receptor; G(1,2,3) = grade(1,2,3); muc = mucinous; NOS = not other specified; LEP = lepidic (bronchioloalveolar) growth pattern; SQC = squamous cell carcinoma; TTF1 = thyroid transcription factor 1. TTF1 was determined in 854 patients.

for 45.5% of all EGFR mutations followed by non-mucinous adenocarcinomas with lepidic growth pattern and good differentiation (G1) (21.8% of all EGFR mutations,) and non-mucinous adenocarcinomas without lepidic growth pattern and poor differentiation (G3) (19.8% of all EGFR mutations).

In total, 5% and 3% of the mutated tumours were classified as squamous carcinomas and large cell lung cancers, respectively. In mucinous adenocarcinoms (all gradings), the mutational rate was significantly lower than in non-mucinous adenocarcinomas (2.0% *vs* 90.1%; $P<0.001$). The rate of EGFR mutations was significantly higher in TTF1-positive tumours in contrast to TTF1-negative tumours (16.1% *vs* 3.1%; $P<0.001$).

DISCUSSION

In our cohort of Caucasian patients from Southern Germany, we could demonstrate an overall rate of 9.8% EGFR mutations. There was an obvious gender difference with significantly more women presenting with an EGFR mutation as men. These results are consistent with previously reported data for Northern European populations (Marchetti *et al*, 2005; Rosell *et al*, 2009; Helland *et al*, 2011; Ludovini *et al*, 2011; Smits *et al*, 2012). However, in comparison with Asian or North American populations the EGFR mutation rate in our German cohort was significantly lower. The much higher rate of EGFR mutations in women with NSCLC had also been demonstrated in earlier reports (Table 4). In addition to this effect of gender on EGFR mutation rates, we could demonstrate that in women of advanced age ($\geqslant 65$ years) EGFR mutation rates were significantly higher than in younger women. The reasons for these effects of gender and age on EGFR mutation rates are not completely understood. Sex hormones and differential smoking habits between men and women might contribute to these effects (Perkins *et al*, 2009; Sofuoglu and Mooney, 2009).

It was hypothesised that different molecular mechanisms are active in tumours of smokers and non-smokers (An *et al*, 2012; Lee *et al*, 2012; Paik *et al*, 2012). Although tumours of smokers frequently exhibit KRAS mutations (a downstream effector in the EGFR pathway; Riely *et al*, 2009), in non-smokers the EGFR itself can be found mutated in many cases (Pham *et al*, 2006). In addition, there seems to be a strong association between EGFR mutational status and the duration and the amount of cigarette smoking with the highest incidence of EGFR mutations seen in never smokers (Pao *et al*, 2004; Shigematsu *et al*, 2005a; Pham *et al*, 2006; Huang *et al*, 2011). Pham *et al* (2006) described that patients with limited cigarette exposure (<15 pack years) had a high incidence of EGFR mutations like never smokers (51%). Patients who have been smoking >15 pack years had significantly fewer EGFR mutations. This 'dose-dependent' effect of smoking on EGFR mutation status is confirmed by our findings. In our study, non-smokers had a significant higher rate of EGFR mutations than smokers or ex-smokers and in more detail, smokers with <15 pack years had a significantly higher rate of EGFR mutations than those with >15 pack years of smoking. Taking our data together with previously published findings, the effect of smoking on the EGFR mutation rate seems to be independent of ethnic origin (Table 4).

Table 4. Comparison of EGFR mutations in NSCLC in reports of the USA, Europe and Asia

Author	Country, year	n=	Exons analysed	EGFR-mutation in %	Median age with EGFR-mutation (years)	Men EGFR mut+ in %	Women EGFR mut+ in %	Non-smoker EGFR mut+ in %	Former smoker EGFR mut+ in %	Adeno-CA EGFR mut+ in %	Squam. CA EGFR mut+ in %	Comments
Paik, PK	USA, 2012	675	No data	24%	63	21%	26%	38%		24%	—	Selected-only adenocarcinomas, not only Caucasians
Jänne, PA	USA, 2012	164	Exons 19, 21, 20	40%	58	36%	43%	40%	42%	41%	37% (others)-	Selected-only adenocarcinomas and bronchioalveolar cancer, not only Caucasians
D'Angelo, SP	USA, 2011	2142	Exons 19, 21	23%	51	19%	26%	52%	15%	23%	—	Selected-only adenocarcinomas, probably not only Caucasians
Tsao, AS	USA, 2006	159	Exons 18-21	8%	66	3.5%	15%	35%	7%	16%	0%	87% Caucasians
Yang, SH	USA, 2005	219	Exons 18-21	12%	67	9%	16.5%	35%	13%	15%	2%	81% Caucasians
Smits, AJ	Holland, 2012	778	Exons 19, 21, 20	9%	61.6	3%	13%	48%	8%	11%	0%	Selected- mainly adenocarcinomas, a few SCC, Caucasians
Ludovini, V	Italy, 2011	166	Exons 18-21	25%	—	20%	32%	33%	25%	30%	10%	Caucasians
Helland, A	Norway, 2011	240	Exons 18-21	7%	—	3%	12%	53%	10%	11%	3%	Caucasians
Rosell, R	Spain, 2009	2105	Exon 19, exon 21	17%	—	8%	30%	38%	9%	17%	15% (others)	Caucasians
Marchetti, A	Italy, 2005	375	Exons 18,19,21	10%	62.5	6%	30%	25%	5%	10%	—	Caucasians, selected-identification of EGFR mutation only in adenocarcinomas
Gao, B	China, 2010	86	Exons 18-21	66%	—	53%	84%	80%	—	66%	—	Asian patients, selected-only adenocarcinoma, smoker and former smoker in one group
Tanaka, T	Japan, 2009	308	Exon 18, exon 19, exons 19+21, exons 19+20, exon 21, exons 21+20	36%	—	25%	59%	61%	—	43%	12%	Asian patients, never smoker and smoker<20 py in one group
Kosaka, T	Japan, 2004	224	Exons 18-21	49%	—	36%	62%	68%		49%	—	Asian patients, Selected-mainly adenocarcinomas, smoker and former smoker in one group

Abbreviations: CA=carcinoma; EGFR=epithelial growth factor receptor; NSCLC= non-small cell lung cancer; py=pack years; SCC=small cell carcinoma.

In addition, no major difference between different races can be identified with reference to distribution of mutations in the EGFR gene. In Asia and Northern American populations, deletions in exon 19 account for 45–50% of all EGFR mutations and a further 35–40% derive from the L858R mutation in exon 21 (Kosaka *et al*, 2004; Marchetti *et al*, 2005; Shigematsu *et al*, 2005a). About 3% of the EGFR mutations are located in exon 18 and exon 20, respectively (Gazdar, 2009). Similarly, in our study the most prevalent mutations detected were deletions in exon 19, which accounted for 61.9% of all EGFR mutations, more frequent as published in other populations (Sharma *et al*, 2007; Tanaka *et al*, 2009; Penzel *et al*, 2011).

The rate of EGFR mutations in exon 18 (4.2% of all EGFR mutations) was in accordance to other studies (Tanaka *et al*, 2009), but in contrast to an increased rate of mutations (10.4%) reported by Penzel *et al* (2011). In exon 21, the rate of EGFR mutations (33.1% of all EGFR mutations) resembled the results with 34.4% observed by Penzel *et al* (2011), while other studies described higher rates (Sharma *et al*, 2007; Tanaka *et al*, 2009). Interestingly, the frequency and distribution of EGFR mutations in exons 18, 19 and 21 were in agreement in each of the four Departments of Molecular Pathology. We therefore hypothesise that different frequencies and distributions of EGFR mutations described in the literature may be attributable to different populations.

The clinical and prognostic impact of exon 19 mutations is still a debate of controversy. It has been postulated by some research groups that deletions in exon 19 might have a better prognosis than mutations in exon 21 when patients are treated with TKI (Jackman *et al*, 2009; Rosell *et al*, 2009). However, other studies could not confirm these results (Maemondo *et al*, 2010; Won *et al*, 2011). Interestingly, a double mutation, for example, two different types of mutation of the EGFR gene in one tumour was found in our cohort in one case. Double mutations of EGFR are described rarely in the literature. Tanaka *et al* (2009) found six double mutations in a sample of 112 EGFR mutations (5.3%) similar to Penzel *et al* (2011) detecting four double and one triple mutation in a sample of 169 EGFR mutations (2.9%). The clinical and therapeutical relevance of such double/triple mutations is unknown.

Up to now, there are only very limited data on the association of TTF1 positivity and EGFR mutation status in NSCLC. Thyroid transcription factor 1 is a 38 kDa homeodomain containing DNA-binding protein of the Nkx-2 gene family (Lazzaro *et al*, 1991). It is mainly expressed in lung and thyroid during embryogenesis and important for the regulation of organ development, maturation and morphogenesis (Bingle, 1997). The expression of TTF1 has been considered as a predictor of prolonged survival in patients with NSCLC (Puglisi *et al*, 2001; Rosell *et al*, 2003; Saad *et al*, 2004). In reports from the literature, TTF1 is expressed in 0–25% of large cell carcinoma, in 0–27% of squamous cell carcinoma and in 60–90% of adenocarcinoma, respectively (Pelosi *et al*, 2001; Zamecnik and Kodet, 2002). Owing to its high frequency in adenocarcinomas, TTF1 is used as a marker to distinguish pulmonary adenocarcinoma from other NSCLC (Yatabe *et al*, 2002; Myong, 2003; Moldvay *et al*, 2004) and to discriminate pulmonary adenocarcinomas from adenocarcinoma of other origin. According to these published data we found TTF1 expression in 4.9% squamous cell carcinomas, which showed EGFR wild type. This result is in accordance with Pelosi *et al* (2001). In contrast, 80% of adenocarcinoma showed TTF1 positivity. In our cohort, we could find a significant association between TTF1 protein expression and EGFR mutational status. All together, 93.5% of all tumours with EGFR mutations were TTF1 positive. This is in accordance with data from Asian patients. As reported by Sun *et al* (2012), 92.7% of EGFR mutation-positive adenocarcinomas were also TTF1 positive.

In summary, our data on EGFR mutation status from a large German cohort of NSCLC patients in the daily clinical practice are in agreement with data from other populations around the world with regard to associations with gender, smoking habits and TTF1 expression. However, we found a considerably higher frequency of mutations in exon 19 than in exon 21. We could demonstrate a spectrum of different EGFR mutations on the EGFR gene in good agreement with data from other ethnicities. Even in subgroups with clinical characteristics associated with EGFR wild type, like male gender, squamous histology, TTF1 negativity and heavy smoking, we found tumours tested positive for activating EGFR mutations. These comprehensive data provide a valid basis for the development of strategies for clinical care for patients with NSCLC.

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