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Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap)

S. Dearden[1]*, J. Stevens[1], Y.-L. Wu[2] & D. Blowers[3]

[1]R&D Genetics, Personalised Healthcare & Biomarkers, AstraZeneca, Macclesfield, UK; [2]Guangdong Lung Cancer Institute, Guangdong General Hospital, Guangzhou, China; [3]Formerly: Oncology iMed, AstraZeneca, Macclesfield, UK

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Background: Meta-analyses were conducted to characterize patterns of mutation incidence in non small-cell lung cancer (NSCLC).
Design: Nine genes with the most complete published mutation coincidence data were evaluated. One meta-analysis generated a 'mutMap' to visually represent mutation coincidence by ethnicity (Western/Asian) and histology (adenocarcinoma [ADC] or squamous cell carcinoma). Another meta-analysis evaluated incidence of individual mutations. Extended analyses explored incidence of *EGFR* and *KRAS* mutations by ethnicity, histology, and smoking status.
Results: Genes evaluated were *TP53*, *EGFR*, *KRAS*, *LKB1*, *EML4-ALK*, *PTEN*, *BRAF*, *PIK3CA,* and *ErbB2*. The mutMap highlighted mutation coincidences occurring in ≥5% of patients, including *TP53* with *KRAS* or *EGFR* mutations in patients with ADC, and *TP53* with *LKB1* mutation in Western patients. *TP53* was the most frequently mutated gene overall. Frequencies of *TP53, EGFR, KRAS, LKB1, PTEN,* and *BRAF* mutations were influenced by histology and/or ethnicity. Although *EGFR* mutations were most frequent in patients with ADC and never/light smokers from Asia, and *KRAS* mutations were most frequent in patients with ADC and ever/heavy smokers from Western countries, both were detected outside these subgroups.
Conclusions: Potential molecular pathology segments of NSCLC were identified. Further studies of mutations in NSCLC are warranted to facilitate more specific diagnoses and guide treatment.
Key words: geography, histology, lung cancer, mutation coincidence, oncogenes

introduction

Non small-cell lung cancer (NSCLC) accounts for ~85% of primary lung cancers, the most common subtypes being adenocarcinoma (ADC) and squamous cell carcinoma (SCC) [1]. Recently, genetic profiling has identified driver mutations, believed to contribute to early carcinogenesis, in over 80% of ADC cases and ~47% of SCC cases. Supplementary Figure S1, available at *Annals of Oncology* online shows how understanding of driver mutations has evolved, from reports of *KRAS* mutations in ADC in 1987 [2], to reports of fusions between *KIF3B* and *RET* in 2012 [3].

Therapies targeting driver mutations have provided promising outcomes in relevant populations. For example, the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib have shown superiority (progression-free survival [PFS] and objective response rate [ORR]) over platinum-based doublet chemotherapy in the first-line treatment of stage IIIB/IV NSCLC with *EGFR* mutations [4–8]. Activating *KRAS* mutations also frequently occur in NSCLC; however, while compounds are in development, attempts to target these mutations or downstream signaling pathways have shown limited therapeutic success to date [9].

It is also important to consider mutations in tumor suppressor genes (TSGs) associated with NSCLC, including *TP53*, *LKB1*, and *PTEN*. As TSG mutations often coincide with oncogenic mutations [10], analyses of coincidence may facilitate subdivision of molecular pathology segments. Such analyses should account for ethnicity and histology, which can both impact on mutation incidence [11–13].

Here, we report two meta-analyses: the first investigated patterns of mutation coincidence, and the second investigated incidences of individual mutations, both according to ethnicity and histology. In addition, extended analyses explored the incidence of *EGFR* and *KRAS* mutations by ethnicity, histology, and smoking status. These analyses add to ongoing sequencing efforts in NSCLC [14].

*Correspondence to: Mr Simon Dearden, Personalised Healthcare and Biomarkers, AstraZeneca, 20G34/1 Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK. Tel: +44-1625-231294; Fax: +44-1625-510061; E-mail: simon.dearden@astrazeneca.com

materials and methods

literature search

A Medline search identified journal articles reporting studies of mutations in NSCLC (all stages) published before March 2012. The following search criteria were used: [lung OR non small cell lung OR NSCLC] AND [adeno* OR squamous] AND [tumour OR tumor] AND [mutation* OR fusion OR translocation]. The following were excluded: review articles; articles not in English; articles reporting studies where not all samples were screened for all reported genes (e.g. subsets of samples found to be positive/negative for one mutation were subsequently screened for additional mutations); articles with data not assigned to a defined ethnic group or collected from a single center in Europe, North America, Australia, or Asia; articles not reporting histology; articles reporting data exclusively from tumor-derived cell lines. If human tumors and tumor-derived cell lines were studied, only data from human tumors were included. If the same study was analyzed in several articles, only the article reporting the most complete data was included. Supplemental data, available at *Annals of Oncology* online were included from 126 patients at the Guangdong Lung Cancer Institute, China, and 84 at the Liverpool Heart and Chest Hospital, UK (supplementary Methods, available at *Annals of Oncology* online).

meta-analysis of mutation coincidence (mutMap)

Articles were reviewed to identify studies reporting the coincidence of mutations in ≥2 genes. References cited in these articles were also searched for additional relevant articles.

Mutation coincidence data were analyzed by ethnicity (Western [Europe, North America, or Australia] or Asian [China, Hong Kong, Jap an, Korea, Singapore, or Taiwan]) and histology (ADC or SCC). Overall, data were analyzed for four patient subgroups: Western/ADC, Western/SCC, Asian/ADC, and Asian/SCC. Data were collated for the nine genes with the most complete mutation coincidence data (not necessarily the most commonly mutated genes in NSCLC). A 'mutMap' was created to visually represent mutation coincidence.

meta-analysis of individual mutations

For the nine genes included in the mutMap, a separate meta-analysis evaluated incidences of individual mutations in the same four patient subgroups.

For a comprehensive evidence base, articles retrieved in the original literature search were reviewed again to identify additional articles reporting data for individual mutations. A further Medline search was also carried out using the Human Genome Organisation (HUGO) gene name (and any pseudonyms) together with the following criteria: [lung OR non small cell lung OR NSCLC] AND [adeno* OR squamous] AND [tumour OR tumor].

extended analyses of *EGFR* and *KRAS* mutations

Incidences of *EGFR* and *KRAS* mutations were explored further in a subsequent expansion of the meta-analyses. Articles were again reviewed to identify studies reporting *EGFR* or *KRAS* mutations in (i) NSCLC of non-ADC histology (excluding unclassified NSCLC) or (ii) NSCLC of any histology in patients with a defined smoking status (never/light or ever/heavy [according to the definitions of the original studies]). The incidence of these mutations was evaluated in NSCLC of non-ADC histology by ethnicity (Europe, North America, China [including Hong Kong and Taiwan], Japan, or Korea) and in NSCLC of any histology by ethnicity and smoking status.

statistical analyses

For the two meta-analyses, differences between the patient subgroups were tested for statistical significance using Fisher's exact test, with Bonferroni correction to account for multiple testing [15]; as 139 statistical tests were carried out, the Bonferroni correction factor was 139 times the uncorrected *P*-value (P_{corr}). Differences were considered statistically significant at $P_{corr} < 0.05$.

Extended analyses were only reported descriptively.

results

included studies

In total, 94 studies were included in one or more analyses: 27 in the mutMap, 68 in the meta-analysis of individual mutations, and 59 in each of the extended analyses (supplementary Figure S2, available at *Annals of Oncology* online).

The most common analysis method was sequencing: 71 studies carried out sequencing alone or with prescreening, and 16 used sequencing for part of the analysis alongside other methods (supplementary Table S1, available at *Annals of Oncology* online).

Articles reporting data on TSGs were examined to assess their scope. Studies of *LKB1* and *PTEN* mutations screened the full coding sequence of the genes. Screening of *TP53* was more variable; however, all reports included exons 5–8, where 90% of mutations have been reported [16].

Generally, studies included more males than females: the male : female ratio was 1.1 : 1 across studies of Western populations and 1.4 : 1 in Asian populations (supplementary Table S1, available at *Annals of Oncology* online). There were also more smokers than non smokers: the smoker : non smoker ratio was 3.0 : 1 in Western populations and 1.2 : 1 in Asian populations. Mean/median age was reported in 52 studies, 41 of which reported a mean/median age of 60–70 years.

mutation coincidence (mutMap)

The nine genes with the most complete mutation coincidence data across the four patient subgroups were *TP53*, *EGFR*, *KRAS*, *LKB1*, *EML4-ALK*, *PTEN*, *BRAF*, *PIK3CA*, and *ErbB2* (Figure 1).

There were several mutation coincidences with frequencies of ≥5%: *TP53* mutation with *KRAS* or *EGFR* mutation in the Western/ADC and Asian/ADC subgroups; *LKB1* mutation with *TP53* or *KRAS* mutation in the Western/ADC subgroup; and *TP53* mutation with *LKB1* mutation in the Western/SCC subgroup. These coincidences were not significantly different from what would be expected by chance given the individual mutation frequencies ($P_{corr} > 0.05$).

EGFR and *KRAS* mutations were generally mutually exclusive; these exclusivities were significant for the Western/ADC ($P_{corr} = 1.8 \times 10^{-36}$) and Asian/ADC ($P_{corr} = 1.9 \times 10^{-27}$) subgroups. *EGFR* and *KRAS* mutations were also exclusive of *EML4-ALK* mutation in the Western/ADC, Asian/ADC, and Asian/SCC subgroups (no data for Western/SCC subgroup). These exclusivities were significant in the Western/ADC subgroup for both *EGFR* and *EML4-ALK* ($P_{corr} = 6.8 \times 10^{-4}$) and *KRAS* and *EML4-ALK* ($P_{corr} = 6.6 \times 10^{-4}$). In the Asian/ADC subgroup, only the exclusivity between *EGFR* and

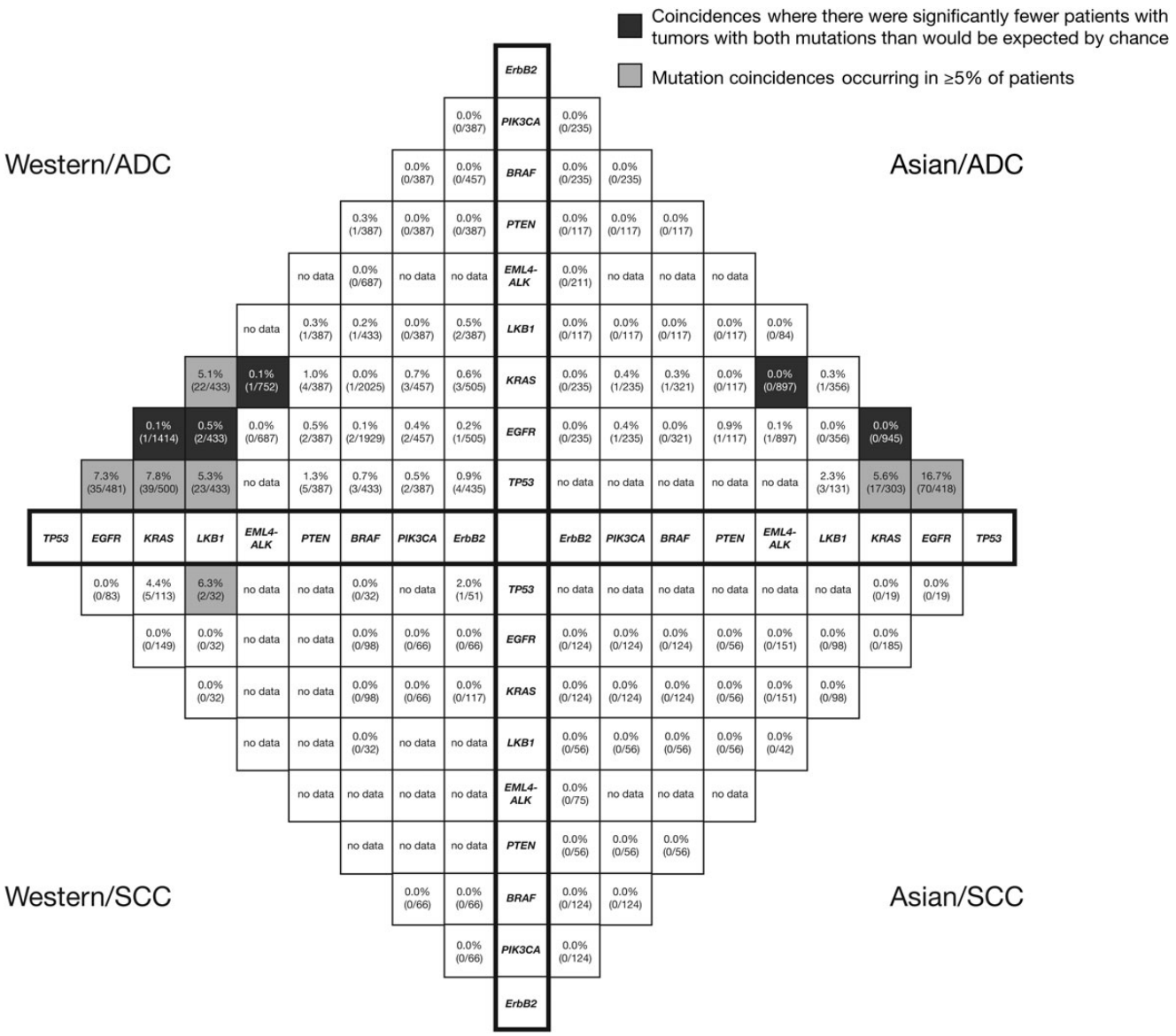

Figure 1. 'Compass' plot depicting the 'mutMap': coincidences of mutations across four non small-cell lung cancer patient subgroups (Western/ADC, Western/SCC, Asian/ADC, Asian/SCC). ADC, adenocarcinoma; SCC, squamous cell carcinoma.

EML4-ALK was significant ($P_{corr} = 7.7 \times 10^{-7}$). In addition, in the Western/ADC subgroup, there were fewer patients with both *EGFR* and *LKB1* mutations than would be expected by chance (observed frequency, 0.5%; expected frequency, 3.1%; $P_{corr} = 0.02$).

incidence of individual mutations

TP53 was the most frequently mutated gene (Table 1), with greater frequency in the Western/SCC subgroup than the Western/ADC subgroup (54.9% versus 30.8%; $P_{corr} = 3.2 \times 10^{-4}$). Similarly, *PTEN* mutations were more common in the Asian/SCC subgroup than the Asian/ADC subgroup (9.8% versus 1.6%; $P_{corr} = 8.3 \times 10^{-3}$). In contrast, *EGFR* and *KRAS* mutations were more common in ADC subgroups than SCC subgroups in both Western (*EGFR*, 19.2% versus 3.3%, $P_{corr} = 2.6 \times 10^{-15}$; *KRAS*, 26.1% versus 6.4%, $P_{corr} = 3.4 \times 10^{-9}$) and Asian populations (*EGFR*, 47.9% versus 4.6%, $P_{corr} = 1.8 \times 10^{-85}$; *KRAS*, 11.2% versus 1.8%, $P_{corr} = 1.6 \times 10^{-6}$). *BRAF* mutations were also more common in the Western/ADC subgroup than the Western/SCC subgroup (3.3% versus 0.2%; $P_{corr} = 1.3 \times 10^{-2}$).

Regarding ethnicity, for ADC, *EGFR* mutations occurred more frequently in Asian than Western patients (47.9% versus 19.2%; $P_{corr} = 1.7 \times 10^{-158}$), while *KRAS* and *LKB1* mutations were more frequent in Western than Asian patients (*KRAS*, 26.1% versus 11.2%, $P_{corr} = 1.1 \times 10^{-35}$; *LKB1*, 16.2% versus 4.0%, $P_{corr} = 3.2 \times 10^{-10}$). For SCC, *LKB1* mutations were significantly more frequent in the Western than Asian patients (9.5% versus 0.0%; $P_{corr} = 3.3 \times 10^{-3}$).

EML4-ALK mutations were relatively common in the Western/ADC (6.4%), Western/SCC (4.5%), and Asian/ADC

Table 1. Incidence of individual mutations across the four non small-cell lung cancer patient subgroups

Gene	Incidence of mutation, *n/N* (%)			
	Western/ADC	Western/SCC	Asian/ADC	Asian/SCC
TP53[a]	164/532 (30.8)	62/113 (54.9)	325/978 (33.2)	64/179 (35.8)
EGFR[a]	940/4890 (19.2)	11/334 (3.3)	1492/3117 (47.9)	22/474 (4.6)
KRAS[a]	613/2352 (26.1)	12/187 (6.4)	236/2114 (11.2)	5/284 (1.8)
LKB1[a]	99/610 (16.2)	13/137 (9.5)	22/550 (4.0)	0/166 (0.0)
EML4-ALK	55/856 (6.4)	4/89 (4.5)	71/1326 (5.4)	5/277 (1.8)
PTEN[a]	25/419 (6.0)	0/12 (0.0)	4/248 (1.6)	12/123 (9.8)
BRAF[a]	66/2028 (3.3)	1/408 (0.2)	5/321 (1.6)	0/124 (0.0)
PIK3CA	6/475 (1.3)	1/71 (1.4)	4/235 (1.7)	8/124 (6.5)
ErbB2	7/505 (1.4)	2/117 (1.7)	20/712 (2.8)	1/259 (0.4)

[a]Significant differences between patient subgroups were observed in the incidences of mutations in the following genes:
TP53: Western/ADC versus Western/SCC ($P_{corr} = 3.2 \times 10^{-4}$).
EGFR: Western/ADC versus Western/SCC ($P_{corr} = 2.6 \times 10^{-15}$); Western/ADC versus Asian/ADC ($P_{corr} = 1.7 \times 10^{-158}$); Asian/ADC versus Asian/SCC ($P_{corr} = 1.8 \times 10^{-85}$).
KRAS: Western/ADC versus Western/SCC ($P_{corr} = 3.4 \times 10^{-9}$); Western/ADC versus Asian/ADC ($P_{corr} = 1.1 \times 10^{-35}$); Asian/ADC versus Asian/SCC ($P_{corr} = 1.6 \times 10^{-6}$).
LKB1: Western/ADC versus Asian/ADC ($P_{corr} = 3.2 \times 10^{-10}$); Western/SCC versus Asian/SCC ($P_{corr} = 3.3 \times 10^{-3}$).
PTEN: Asian/ADC versus Asian/SCC ($P_{corr} = 8.3 \times 10^{-3}$).
BRAF: Western/ADC versus Western/SCC ($P_{corr} = 1.3 \times 10^{-2}$).
ADC, adenocarcinoma; SCC, squamous cell carcinoma.

(5.4%) subgroups; *PTEN* mutations were relatively common in the Western/ADC (6.0%) and Asian/SCC (9.8%) subgroups; and *PIK3CA* mutations were also relatively common in the Asian/SCC subgroup (6.5%). However, mutations in *EML4-ALK*, *PTEN*, *PIK3CA*, *ErbB2*, and *BRAF* were rarer (0.0%–3.3%) in all other cases.

extended analyses of *EGFR* and *KRAS* mutations

While *EGFR* and *KRAS* mutations occurred more frequently in ADC, these mutations also occurred in tumors of non-ADC histology, although pooled frequencies varied by ethnicity (*EGFR*, 5.1%–12.7%; *KRAS*, 0.0%–10.4%; supplementary Table S2, available at *Annals of Oncology* online). In general, *EGFR* mutations were more frequent in Asian populations and *KRAS* mutations were more frequent in Western populations.

In NSCLC of any histology, pooled frequencies of *EGFR* mutations ranged from 8.4% to 35.9% for ever/heavy smokers and from 37.6% to 62.5% for never/light smokers, depending on ethnicity (supplementary Table S3, available at *Annals of Oncology* online). Corresponding values for *KRAS* mutations were 6.7%–40.0% and 2.9%–11.4%, respectively.

discussion

These meta-analyses, which we believe are the largest such analyses to date, investigated mutation incidence in NSCLC to develop the first 'mutMap'—a visual tool describing mutation coincidence by ethnicity and histology.

Mutations in *EGFR*, *KRAS*, *EML4-ALK*, and *BRAF* were all exclusive, supporting the view that a single driver mutation is required for oncogene addiction in lung tumors [17]. There was some variation in *EGFR* and *KRAS* mutation frequencies between studies, even when grouped by ethnicity and smoking status. As the majority of studies used sequencing, this may reflect more than a variation in mutation testing technique. In addition to tobacco, other environmental factors may contribute to the development of NSCLC, including exposure to radon, air pollution, and cooking oil vapor [18]. Although the involvement of these factors in the development of *EGFR* and *KRAS* mutations is not currently understood, differing patterns of environmental factors may contribute to variability in *EGFR* and *KRAS* mutation frequencies.

There were several coincidences of driver mutations with TSG mutations: a relevant proportion (≥5%) of ADC tumors had *TP53* mutation with *KRAS* or *EGFR* mutation, and, in Western populations, relevant proportions of ADC or SCC tumors had *TP53* and *LKB1* mutations, and a relevant proportion of ADC tumors had *KRAS* and *LKB1* mutations. Such data could help subdefine molecular pathology segments of NSCLC, which may be associated with patient outcomes: higher numbers of coincident mutations correlate with higher tumor grade and stage in ADC, with *TP53* mutation rates specifically correlating with tumor grade [10].

Characterization of molecular pathology segments may help guide the development of novel targeted therapies and shape testing protocols, algorithms, or panels for diagnostic mutation testing in NSCLC. For example, combination therapies to target both oncogenic and TSG mutations may benefit patients within a relevant molecularly defined segment. There is already some precedent for this type of approach, including a planned trial of the erlotinib in combination with the phosphoinositide-3-kinase inhibitor BKM120 (which may be expected to compensate for inactivation of PTEN) [19].

EGFR mutations are known to occur most frequently in ADC tumors and those of non smoking patients [11, 12]. However, our analyses support screening for *EGFR* mutations outside of these groups, as *EGFR* mutations were present in non-ADC

tumors and those of ever/heavy smokers. Furthermore, although PFS and ORRs with EGFR TKIs may be lower for non-ADC tumors than ADC tumors [20], two studies among the limited available data show improved PFS in patients with *EGFR* mutation-positive tumors of non-ADC histology when treated with EGFR TKIs compared with chemotherapy [6, 7].

Caution is advised when using these data to infer mutation incidence in different populations, since the meta-analyses depended on the available published data, which represent a small sample size with intrinsic limitations. For example, only the genes with the most mutation data were included in the meta-analyses, but other genes may play key roles in some populations, e.g. amplification of *FGFR1* in SCC [21]. Also, analysis of the coincidence of three or more mutations was not practical due to the lack of published studies of large gene panels; however, some tumors may have more than 40 coincident mutations in putative oncogenes or TSGs [10]. The Cancer Genome Atlas [22, 23] and the Clinical Lung Cancer Genome Project [24] will provide further large-scale data on mutation coincidence in NSCLC in Western populations.

There were also insufficient data to include several key populations, including African and Latin American populations. Preliminary data suggest that *EGFR* and *KRAS* mutation frequencies in Latin American countries (*EGFR*, 33%; *KRAS*, 17%) lie between those in Western and Asian populations [25].

Variation in study design should also be considered. Although data were derived from NSCLC of any stage, there was some bias toward stage I/II tumors, as these are most commonly resected [26]. In addition, not all articles reported mutation types. Therefore, these meta-analyses categorized mutations by gene only, without reference to type or potential functional effect (e.g. synonymous substitutions, or non synonymous substitutions of unknown functional relevance).

Additionally, the meta-analyses were not designed to evaluate changes in mutation rates in patients who develop resistance to treatment. It is noted that, the *EGFR* T790M mutation, which has been reported at low frequency in untreated patients with stage IIIB/IV NSCLC and an Eastern Cooperative Oncology Group performance status of 0/1 (4.2%) [8], has been detected in 43.8%–50.0% of patients who become resistant to EGFR TKIs [27, 28].

Overall, these meta-analyses demonstrate that mutation profiles in NSCLC are heavily influenced by tumor histology, and the ethnicity and smoking history of patients. Despite these challenges, we have identified potential molecular pathology segments of NSCLC that combine oncogenic and TSG mutations. Advances in our understanding of mutation coincidence may be useful in enabling more specific diagnoses and guiding treatment paradigms. Large studies in Western populations are ongoing [23, 24], but similar studies in Asian populations are also warranted, particularly given the differences between mutation patterns in Western and Asian populations identified here.

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Solid tumor size on high-resolution computed tomography and maximum standardized uptake on positron emission tomography for new clinical T descriptors with T1 lung adenocarcinoma

Y. Tsutani[1], Y. Miyata[1], H. Nakayama[2], S. Okumura[3], S. Adachi[4], M. Yoshimura[5] & M. Okada[1]*

[1]Department of Surgical Oncology, Hiroshima University, Hiroshima; [2]Department of Thoracic Surgery, Kanagawa Cancer Center, Yokohama; [3]Department of Thoracic Surgery, Cancer Institute Hospital, Tokyo; [4]Departments of Radiology; [5]Thoracic Surgery, Hyogo Cancer Center, Akashi, Japan

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Background: To better describe clinical T descriptors using solid tumor size (the maximum dimension of the solid component of the tumor) on high-resolution computed tomography (HRCT) and maximum standardized uptake value (SUV_{max}) on F-18-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT).
Patients and methods: We examined 610 consecutive patients with clinical stage IA lung adenocarcinoma who underwent complete resection. Recurrence-free survival (RFS) was assessed on the basis of whole tumor size (maximum dimension of the tumor), solid tumor size, or a combination of solid tumor size and SUV_{max}.
Results: RFS based on whole tumor size was not significantly different between patients with tumors measuring ≤2 cm and 2–3 cm ($P = 0.089$), whereas RFS based on solid tumor size was significantly different ($P < 0.0001$). We divided patients into four groups on the basis of solid tumor size and SUV_{max}: group 1: solid tumor size ≤2 cm, SUV_{max} ≤1.8; group 2: solid tumor size ≤2 cm, SUV_{max} >1.8; group 3: solid tumor size 2–3 cm, SUV_{max} ≤3.6; and group 4: solid tumor size 2–3 cm, SUV_{max} >3.6. Groups 2 and 3 were combined because they showed similar RFS each other. RFS was significantly different among these groups: group 1 versus groups 2 + 3, $P < 0.0001$; groups 2 + 3 versus group 4, $P = 0.019$.
Conclusions: Both solid tumor size on HRCT and SUV_{max} on FDG-PET/CT reflect prognosis well in patients with clinical stage IA lung adenocarcinoma and may support new clinical T descriptors.
Key words: lung adenocarcinoma, positron emission tomography, T descriptor, TNM classification

*Correspondence to: Prof. Morihito Okada, Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, 1-2-3-Kasumi, Minami-ku, Hiroshima City, Hiroshima 734-0037, Japan. Tel: +81-82-257-5869; Fax: +81-82-256-7109; E-mail: morihito@hiroshima-u.ac.jp