Comparison of Rearranged During Transfection (RET) Gene Rearrangements in Primary Versus Metastatic Non-Small Cell Lung Cancer (NSCLC)

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Background: RET rearrangements have been reported in 30% of papillary thyroid carcinomas and 1–2% of non-small cell lung cancer (NSCLC). In these tumors, RET gene fusion product provides a constitutively active tyrosine kinase (TKR), leading to uncontrolled cellular proliferation, differentiation, and migration. In this investigation we assessed the positivity rate of RET gene rearrangement in primary and metastatic non-small cell lung cancer and explored their relationships.

Material/Methods: Between January 2013 and May 2015, we collected 384 cases of primary metastatic non-small cell lung cancer, which included 246 matched metastatic tumors cases from multiple centers. The RET rearrangement uniformity in metastatic lymph nodes and tumor specimens were contrasted and the relationships between RET rearrangement and patients’ clinical features were investigated.

Results: For those 384 cases, 7 (1.82%) cases had tumors with identified RET rearrangement. Among the 246 paired cases, 3 (1.22%) cases of primary tumor had identified RET rearrangement and 2 (0.81%) cases of metastases had identified RET rearrangement. The sensitivity was 66.67% (2/3) and the specificity was 100% (243/243).

Conclusions: The results of this research indicate that the metastases of non-small cell lung cancer can predict RET rearrangement of the primary tumor tissue in the majority of cases. Testing for RET rearrangement in metastases can be used as an alternative to testing of primary tumor tissue if it is inaccessible.

MeSH Keywords: Genetic Heterogeneity • Lung Neoplasms • Transfection

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Background

Lung cancer is a major cause of cancer-related mortality worldwide, and it is classified into small cell lung cancer and non-small cell lung cancer. Non-small cell lung cancer represents about 80% of all lung cancers, which includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [1]. Recent progress in sequencing technology has facilitated the detection of gene rearrangements in the cancer genome and transcriptome, and chromosomal rearrangements involving receptor tyrosine kinases (RTKs) are considered as drivers of cancer progression.

Rearrangements in the rearranged during transfection (RET) gene, including inversions on chromosome 10 or translocations with other chromosomes involving different gene partners, have been reported in 30% of papillary thyroid carcinomas and in 1–2% of NSCLC [2]. The RET gene rearrangement product provides a constitutively active RTK, leading to uncontrolled cellular proliferation, differentiation, and migration [3–6]. Targeted therapy has reshaped the therapeutic landscape for patients with lung cancers [7]. RET rearrangements have been associated with clinical benefit from multi-kinase inhibitors such as cabozantinib and vandetanib [8]. At least 12 forms of RET rearrangements have been identified in NSCLC, including KIF5B-RET, CCDC6-RET, NCOA4-RET, MYOSC-RET, EPHAS-RET, CLIP1-RET, ERC1-RET, PICALM-RET, FRMD4A-RET, RUFY2-RET, TRIM24-RET, and TRIM33-RET gene fusions. Kinesin family member 5B (KIF5B) has been identified as the most common partner combined with RET (72%) to date [9]. However, further molecular screening for RET fusions is warranted. RET rearrangements have mainly been discovered in younger patients aged <60 years, who are former light smokers or never smokers [10]. In this investigation, the aim was to assess the positivity rate of RET gene rearrangement in primary and metastatic non-small cell lung cancer and their relationships with clinical characteristics.

Material and Methods

Sample collection

Between January 2013 and May 2015, we collected patients with pathologically confirmed non-small cell lung cancer from multiple centers. Eligible patients were enrolled from Fujian Cancer Hospital, Zhejiang Rongjun Hospital, and Zhejiang Cancer Hospital, China. The diagnosis of non-small cell lung cancer was determined according to pathological examination of the lesion, and the histological type was based on the World Health Organization (WHO) standards [11]. The stage of tumor was determined according to the 7th version of the Tumor, Node, and Metastasis (TNM) Classification of Lung Cancer [12]. All Ethics Committees of the 3 institutions evaluated and authorized the study. All the patients provided informed consent to take part in this research and agreed to use of their pathological specimens. None of the patients received any neoadjuvant treatment before the study. Surgery and biopsy samples from 384 NSCLC patients were examined for RET rearrangements, including matched primary and metastatic samples from 246 patients.

RET detection

Paraffin-embedded tissues (4–8 slices) were cut into 4-μm slices and dewaxed. RET was detected using a RET Detection Kit (Amoy Diagnostics, Xiamen, China) based on reverse transcriptase-polymerase chain reaction. Genomic RNA was extracted based on the kit instructions, using EB solution as a blank control, and 1 μl of the RNA sample was amplified using an ABI7500 real-time fluorescence quantitative PCR instrument (Applied Biosystems Life Technologies, Foster City, CA, USA) according to the methods provided in the 9 RET fusion detection kits for lung cancer. Positive and negative controls were established as described in the kit instructions. RET rearrangements were detected using a method previously described. RET gene rearrangements were detected and compared between primary and metastatic tissue samples. The relationships between RET rearrangements and clinical data were also analyzed statistically.

Statistical and database analyses

The prevalence of RET rearrangements was compared between primary and metastatic tissues using the χ² test. For clinical characteristics, categorical variables were evaluated with the Fisher’s exact test. P values of less than 0.05 were statistically significant; χ²>0.75 was considered remarkable consistency, 0.45<χ²<0.75 represented good consistency, and χ²<0.4 represented inconsistency. All analyses were completed using SPSS software (version 19.0 for Windows, IBM Corp., Armonk, NY, USA).

Results

RET rearrangements in primary and metastatic tissue samples

Altogether, 384 NSCLC patients participated in this study. RET rearrangements were detected in 1.82% (7/384) of primary tumors. Among the 246 paired primary and metastatic samples, RET rearrangements were detected in 1.22% (3/246) of primary tumors and 0.81% (2/246) of metastases. All patients who had RET rearrangement in the metastatic sample had RET rearrangement in the primary sample, but 1 patient had rearrangement in the primary but not the metastatic sample.
Table 1. RET rearrangement in advanced primary NSCLC tissues and matched metastatic samples.

| M       | Cases (n=246) | P         | P value | \( \kappa \) value |
|---------|---------------|-----------|---------|--------------------|
| +       | 2             | 2         | 0       | <0.001             |
| -       | 244           | 1         | 243     | 0.798              |
| Cases   | 246           | 3         | 243     |                    |

M – metastatic samples; NSCLC – non-small cell lung cancer; P – primary cancerous tissue.

Table 2. Correlation of RET rearrangement in advanced primary NSCLC tissue and basic patient characteristics.

| Characteristics | Cases (n=384) | RET rearrangement | RET non-rearrangement | % | \( \chi^2 \) and P values |
|-----------------|---------------|-------------------|-----------------------|---|-------------------------|
| Sex             |               |                   |                       |   |                         |
| Male            | 181           | 2                 | 178                   | 1.66% | \( \chi^2=0.000 \) P=1.000 |
| Female          | 203           | 4                 | 199                   | 1.97% |                         |
| Age (year)      |               |                   |                       |   |                         |
| \( \geq 60 \)   | 189           | 2                 | 187                   | 1.06% | \( \chi^2=0.520 \) P=0.471 |
| \(< 60 \)       | 195           | 5                 | 190                   | 2.56% |                         |
| Smoking status  |               |                   |                       |   |                         |
| Smoker          | 177           | 2                 | 175                   | 1.13% | \( \chi^2=0.309 \) P=0.578 |
| Non-smoker      | 207           | 5                 | 202                   | 2.42% |                         |
| Pathological type|             |                   |                       |   |                         |
| Adenocarcinoma  | 242           | 7                 | 235                   | 2.89% | \( \chi^2=2.724 \) P=0.099 |
| Non-adenocarcinoma | 142      | 0                 | 142                   | 0 |                         |

NSCLC – non-small cell lung cancer.

(Table 1). The prevalence of RET rearrangements was significantly higher in primary lesions compared with metastases \( \chi^2=91.117, P<0.001 \). RET rearrangement in the primary tumor were predicted by rearrangement in the corresponding metastasis \( \kappa=0.798, P<0.001 \), with a sensitivity of 66.67% (2/3) and specificity of 100% (243/243).

**RET rearrangement and clinical characteristics**

Among the 384 cancerous tissue specimens, active RET rearrangement was detected in 7, giving a rearrangement rate of 1.82%. The frequency of RET rearrangement in primary cancerous tissue was not significantly related to patient age, sex, pathological type, or smoking history (P>0.05) (Table 2). There was also no relationship between RET rearrangement in the primary or metastatic samples and clinical details among the 246 patients with paired primary and metastatic samples (Tables 3, 4).

**Discussion**

Recent progress in sequencing technology has enabled the extensive detection of gene rearrangements in the cancer genome and transcriptome. Chromosomal rearrangements involving RTKs are an important class of cancer-related somatic variation and have emerged as oncogenic drivers in solid tumors and hematologic malignancies[13,14]. The main potentially targetable gene fusions in NSCLC involve the ALK, ROS1, NTRK, and RET genes. Although these represent a small fraction of NSCLC patients (3–7%, 3.3%, 1–2%, and 0.7–2%, respectively) [15–19], the significance of treating these rare chromosome rearrangements is profound, given that about 1.8 million new cases of lung cancer per year are reported worldwide [20].

RET gene fusion accounts for about 1% to 2% of all NSCLC[2], with a high rate of KIF5B-RET gene fusion (72%) [8,9]. RET gene fusion rarely occurs simultaneously with other driver
genes, such as EGFR, ALK, or KRAS [21], suggesting that RET fusion genes are an independent driver in NSCLC. Patients with NSCLCs harboring RET rearrangements can be sensitive to cytotoxic chemotherapies, including pemetrexed-based regimens, which have an objective response rate (ORR) of 45% and median progression-free survival 19 months, similar to

### Table 3. Correlation of RET rearrangement in primary and metastasis tissue paired with advanced primary NSCLC tissue and basic patient characteristics.

| Characteristics | Cases (n=384) | RET rearrangement | RET non-rearrangement | % | \( \chi^2 \) and P values |
|-----------------|-------------|-------------------|------------------------|---|--------------------------|
| Sex             |             |                   |                        |   |                          |
| Male            | 121         | 1                 | 120                    | 0.83% | \( \chi^2 = 0.000 \) P=1.000 |
| Female          | 125         | 2                 | 123                    | 1.60% |                          |
| Age (year)      |             |                   |                        |   |                          |
| ≥60             | 112         | 1                 | 111                    | 0.89% | \( \chi^2 = 0.000 \) P=1.000 |
| <60             | 134         | 2                 | 132                    | 1.49% |                          |
| Smoking status  |             |                   |                        |   |                          |
| Smoker          | 113         | 1                 | 112                    | 0.88% | \( \chi^2 = 0.000 \) P=1.000 |
| Non-smoker      | 133         | 2                 | 131                    | 1.50% |                          |
| Pathological type|           |                   |                        |   |                          |
| Adenocarcinoma  | 145         | 3                 | 142                    | 2.07% | \( \chi^2 = 0.747 \) P=0.388 |
| Non-adenocarcinoma | 101     | 0                 | 101                    | 0 |                          |

NSCLC – non-small cell lung cancer.

### Table 4. Correlation of RET rearrangement in primary and metastasis tissue paired with advanced metastatic NSCLC tissue and basic patient characteristics.

| Characteristics | Cases (n=384) | RET rearrangement | RET non-rearrangement | % | \( \chi^2 \) and P values |
|-----------------|-------------|-------------------|------------------------|---|--------------------------|
| Sex             |             |                   |                        |   |                          |
| Male            | 121         | 1                 | 120                    | 0.83% | \( \chi^2 = 0.000 \) P=1.000 |
| Female          | 125         | 1                 | 124                    | 0.80% |                          |
| Age (year)      |             |                   |                        |   |                          |
| ≥60             | 112         | 1                 | 111                    | 0.89% | \( \chi^2 = 0.000 \) P=1.000 |
| <60             | 134         | 1                 | 133                    | 0.75% |                          |
| Smoking status  |             |                   |                        |   |                          |
| Smoker          | 113         | 1                 | 112                    | 0.88% | \( \chi^2 = 0.000 \) P=1.000 |
| Non-smoker      | 133         | 1                 | 132                    | 0.75% |                          |
| Pathological type|           |                   |                        |   |                          |
| Adenocarcinoma  | 145         | 2                 | 143                    | 1.38% | \( \chi^2 = 0.215 \) P=0.643 |
| Non-adenocarcinoma | 101     | 0                 | 101                    | 0 |                          |

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Conclusions

Our results show that RET gene fusion status differed be-
tween metastatic and primary tumors. For most molecular al-
terations, there is no good evidence to favor testing of either
primary or metastatic tumors. It is therefore important to es-
ablish, for each driver alteration in NSCLC, whether the alter-
ation is homogeneous or heterogeneous between primary and
metastatic tumor. In conclusion, there is growing evidence to
suggest that testing for RET gene rearrangements will be im-
portant in personalizing treatment of NSCLC in the future. We
showed that RET rearrangement in NSCLC metastases could
predict rearrangement in the primary lesion in the majority of
cases, and it could thus be used as an alternative means of
detecting RET rearrangements in cases where it is difficult to
obtain a primary specimen. Nevertheless, molecular targeted
therapy should consider the possible heterogeneity of gene
rearrangements between primary and metastatic samples.
Furthermore, although we found no significant association
between RET gene rearrangements in either primary or meta-
static samples and clinical characteristics, this may have been
due to the small sample size, and further studies with larger
samples are needed to verify our results.

Conflict of interest

None.

of RET gene rearrangements and any of the tested clinical
characteristics, based on either primary or metastatic tumor
samples. No RET rearrangements were identified in non-ad-
encarcinomas, but the overall sample size was too small to
demonstrate a statistically significant difference in RET re-
arrangement prevalence between adenocarcinomas and non-
adenocarcinomas. It is possible that our sample size was too
small to demonstrate a significant difference. It is also possible
that the apparent discrepancy with previous studies was due
to dissimilarities in sample size, race, and/or the rate of lung
adenocarcinoma and squamous cell cancer.

In the present study, we detected RET gene rearrangements in
384 patients with advanced primary NSCLC by RT-PCR and
found a RET gene rearrangement rate of 1.82%, which was con-
sistent with the results of Takeuchi et al. [18]. We also found
a higher prevalence of RET gene rearrangements in primary
compared with metastatic lesions (χ²=91.117, P<0.001). The
presence of RET rearrangement in the primary tumor could be
predicted by rearrangement in the corresponding metastatic
lesion (κ=0.798, P<0.001) with a sensitivity of 66.67% (2/3)
and specificity of 100% (243/243). Furthermore, Wang et al.
found that patients with RET rearrangements had small pri-
mary lesions (<3 cm) but were more likely to have N2 dis-
ease compared with other LADCs with small lesions (54% vs.
23%) [16], meaning that primary samples are more difficult to
obtain than metastatic specimens. However, our results sug-
gest that metastatic samples may be used as a surrogate to
predict RET gene rearrangement in the primary tumor when
it is difficult to acquire the primary tumor tissue.

Wang et al. and Gautschi et al. found that RET gene fusion
was more common in patients who had never smoked or who
had lung adenocarcinomas (LADCs) [8,16]. However, our re-
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