Endoscopic ultrasound/endobronchial ultrasound pierce the veil of precision medicine for lung cancer

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Bugalho A, Martins C, Dias SS, *et al.* Cytokeratin 19, carcinoembryonic antigen, and epithelial cell adhesion molecule detect lung cancer lymph node metastasis in endobronchial ultrasound-guided transbronchial aspiration samples. Clin Lung Cancer 2013;14:704-12.
Patil S, Ayachit R. 'Unexplained intermittent hemoptysis with normal chest radiograph necessitates bronchoscopy'-mucoepidermoid carcinoma of lung: Case report. J Transl Intern Med 2014;2:40-4.

The time has arrived for personalized medicine (1). Now each individual is recognized to be special. The medicines prescribed and treatment in general will soon be decided taking individual variability into account. Each one will be recognized by his own medical fingerprint and treatment catered according to that for that particular individual. Generalization will not be there anymore.

Precision medicine is a new medical model for prevention and treatment of disease taking into account individual variability in genes, environment and lifestyle for each person. Molecular detection is often employed for selecting appropriate treatment protocol based on the context of a patient's genetic content or other molecular analysis (2,3). In the era of this medical model, we are now facing more challenges; this is especially true for lung cancer where clinical requirements of diagnosis have evolved dramatically. In the past, it was sufficient to select treatment protocol based on whether lung cancer is small cell carcinoma or non-small cell lung carcinoma (NSCLC). However, with the application of antiangiogenic therapy, a differential diagnosis between squamous and non-squamous NSCLC is necessary (4). Since epidermal growth factor receptor (EGFR) mutation analysis was performed in patients with lung adenocarcinomas and subsequent EFGR tyrosine kinase inhibitors treatment was applied (5), molecular analysis and sub-classification of NSCLC have become an

essential technique in the diagnosis and prognostication of NSCLC. Many other driver genes (2,4,6,7), such as c-ros oncogene 1, discoidin domain receptor tyrosine kinase 2, echinoderm microtubule associated protein like 4-AL-Kinase 1, receptor tyrosine kinase have been discovered, and many more are expected to be discovered in future.

The demand to harvest sufficient sample for EGFR mutational analysis is challenging. Especially for patients with an unresectable disease, the first diagnostic biopsy should be obtained by minimally invasive approaches. In fact, the sample types include pleural/peritoneal fluid samples, bronchial washings/brushings, and endoscopic ultrasound (EUS) or endobronchial ultrasound (EBUS) guided fine needle aspiration (FNA). Among all these approaches, the EUS and EBUS are the most promising, because they can provide very high-resolution images without vision impairment and can detect lesions only millimeters in size (8-11). At present, EUS plays a unique diagnostic role for many cancers, having been written into and recommended by numerous guidelines (12-14). Therefore, under the guidance of the high-resolution image of EUS/EBUS, we can puncture and acquire a sample of the lesion for cytopathological diagnosis by minimally invasive methods (15-18). In experienced hands, the accuracy of these procedures for malignant tumor is over 90% (19-21). So it is evident that EUS/EBUS-FNA has an impact on the

therapy of malignant tumors. The acquired FNA specimen can be used to determine the frequency and therapeutic potential of mutations identified, which would be very important in the subsequent evaluation of prognosis and targeted treatment protocol. Based on the unique sampling by FNA, some experts (22-24) have developed strategies to improve the diagnosis of gastrointestinal stromal tumor, rectal cancer and pancreatic cancer by analysis of KRAS mutation, microRNA expression, methylation, and mRNA expression using quantitative reverse transcription polymerase chain reaction (qRT-PCR) and Low Density Array Taqman analysis. These studies have shown the clinical and molecular advantages of EUS -FNA in the management of these conditions.

EGFR mutations are very useful in the prediction of therapeutic effectiveness and resistance of lung cancer. For the analysis, formalin-fixed paraffin-embedded samples including cell blocks are tested using Sanger sequencing or allele specific polymerase chain reaction, which may fail due to the lack of tumor cells (25). However, the cell pellet obtained from cytology specimens of EUS/EBUS-FNA, represents an alternative source for additional tissue. Leslie C *et al.* (26) found that cytology material can provide an adequate material for analysis of EGFR mutation, and there was no significant difference in the mutations detection between cytology and non-cytology material. Ulivi P *et al.* (27) found that for EUS/EBUS-FNA material, fixed and stained cytological samples seems to be more reliable than fresh material for molecular analysis.

Besides all these, new genetic test systems have been introduced such as next generation sequencing that enables detection of multiple mutations in different genes, amplifications and fusion genes. It increases the clinical sensitivity without decreasing the specificity of analysis and is useful to repeat the analysis starting from selectable material to avoid false negative results (19).

Besides EGFR mutations, more mutations have been analysed (4,6,28). In contrast to EGFR mutations, KRAS mutations are associated with the lack of response to tyrosine kinase inhibitors in patients with NSCLC. Anaplastic lymphoma kinase (ALK) fusion genes represent novel oncogenes for NSCLC (29). Several ALK inhibitors have been developed, and are being analysed in ALK-positive NSCLC. Based on the high accuracy of EUS-FNA/qRT-PCR, KS1/4 appears to be particularly useful for detecting metastatic disease. There are studies which show that patients in the cytology-negative/marker positive category might have high NSCLC recurrence rates (30).

EUS/EBUS-FNA holds promise for the detection and evaluation of mediastinal lymph nodes in patients with NSCLC. Combined with qRT-PCR and flow cytometry, EUS/EBUS-FNA can assess tumor-associated antigens (31-33), such as CK-19, CEA, and EPCAM, and detect SHOX2 methylation level. Wallace MB *et al.* found that approximately one-third of pathologically negative mediastinal lymph nodes in NSCLC patients express human telomerase reverse transcriptase mRNA. This is thought to improve the assessment of the nodal status and can be helpful for detecting NSCLC lymph node micrometastases (34).

Due to the explosion of techniques in biological databases such as genomics, proteomics, metabolomics, cellular assays and bioinformatics, EUS has shown its great value for accurate sampling and molecular diagnosis of the lung cancer. There is ample reason to believe that the application of EUS/EBUS-FNA based precision medicine will become more promising in this rapidly expanding field.

Each cancer has its own genomic signature with accumulated genomic damage during life compounded with inherited genetic variations. "Precision Oncology" will deal effectively with unexplained drug resistance, genomic heterogeneity of tumours, tumour recurrence and specific drug combinations custom made to each individual. Targeted therapies and novel immunologic approaches now offer spectacular benefits and will enrich the standard principles of oncology (35).

There is still a long way to go for precision medicine to be applied at the bedside. But time is not far when one is able to shop for one's treatment which is tailor made for just that particular person and that which will not fit all. The need of the hour rests on vigorous research programs based on genetic databases that will change the very meaning of medical practice in future.

Footnote

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