APPLICATION OF WHOLE EXOME SEQUENCING IN METACHRONOUS LUNG CANCERS EVALUATION

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Multiplicity and metachronous tumours are recurrent management problems. Morphological resemblance, in-situ carcinoma, cancer driver mutations, etc. have been used to distinguish intrapulmonary metastasis and metachronous primary lung cancers but these criteria are often insufficient. Next generation sequencing promises to advance personalized cancer management but finding a practicable approach remains a problem. We explored the utility of whole exome sequencing for cancer nature determination in a 74 year-old female non-smoker with 2 sequential lung cancers of unknown relation. Initially, she had an *EGFR-L858R* adenocarcinoma (Tumour-A) treated by excision and adjuvant gefitinib for metastatic pleural tumours. Two years later while still on gefitinib, she developed a contralateral, morphologically indistinguishable adenocarcinoma with no other metastasis (Tumour-B).

Genetically, it was *EGFR* wild-type. We performed WES on formalin-fixed-paraffin-embedded(FFPE) and frozen(FZ) tissues from each tumour with raw sequencing depths 240x (FFPE), and 150x(FZ/leukocytes control), respectively. Both tissue types yielded good quality data with no significant difference in on-target coverage or mutation type distribution, suggesting both are amenable to WES. Amongst 12108 significantly over-represented variants in tumours, <20% were common to both tumours-A and -B. The resistant *EGFR-T790M* genotype was undetected in either tumour. We further narrowed the candidate genes list using computational prediction (Condel) of exonic SNV effects on protein functions and compared mutation frequencies with lung adenocarcinomas registered in TCGA followed by Sanger sequencing for confirmation. Substitution mutations of *POT1* (reported frequency 2.81%) and *CKAP4* (1.80%) were proposed as cancer genes for tumour-B while *POU6F2* (3.50%) might be involved in tumour-A. Using WES, we have shown tumour-B is likely a metachronous second primary or have developed through selection of metastatic bypass pathways. Various candidate genes are proposed as surveillance targets for tumour A or B, respectively. Further, those in tumour-B are likely resistant to tyrosine kinase inhibitors.