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Next generation sequencing: A novel approach to distinguish multifocal primary lung adenocarcinomas from intrapulmonary metastases

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Distinguishing between multiple lung primaries and intrapulmonary metastases is imperative for accurate staging. The American Joint Committee on Cancer (AJCC) criteria are routinely used for this purpose but can yield equivocal conclusions. We evaluated whether next generation sequencing using the 50 gene AmpliSeq Cancer Hotspot Panel v2 can be used to facilitate this distinction. Sequencing was performed on known primary-metastatic pairs (8 patients) and multiple lung adenocarcinomas (11 patients). Primary-metastatic pairs showed high mutational concordance: Seven pairs shared mutations and 1 was concordant for having no mutations. Driver mutations in KRAS (4), EGFR (2) and BRAF (1) were always concordant. Multiple lung tumors from 3 patients were completely concordant and therefore, were predicted by sequencing to be intrapulmonary metastases, whereas 8 had completely discordant mutations and therefore, were predicted to be primaries. The sequencing prediction correlated with the AJCC (8th edition) prediction in all patients for whom the latter was unequivocal (8 of 11). Furthermore, it separated patients by overall survival: Patients with predicted multiple primaries had better survival than those with distant metastases (p=0.016, log-rank test), whereas those with predicted intrapulmonary metastases showed no difference (p=0.527). With further validation, the 50 gene panel has the potential to serve as an adjunct to the AJCC criteria, especially in patients for whom the latter is equivocal.

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