Published in final edited form as:

Ann Surg. 2016 August ; 264(2): e7. doi:10.1097/SLA.0000000000001103.

Addition of *RAS* Mutation Status May Strengthen the Predictive Model for Progression of Indeterminate Pulmonary Nodules

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To the Editor

We read with interest the report by Kim et al. regarding a predictive model for progression of indeterminate pulmonary nodules (IPNs) in patients with colorectal cancer (CRC).¹ This topic is clinically relevant given that the presence of IPNs can affect the treatment strategy, especially in patients with liver metastases who may require sequential or combined liver and lung resections.^{2,3} The predictive model was developed on the basis of a thorough analysis of clinicopathological data. However, we believe that consideration of *RAS* mutation status would have improved the accuracy of the model, given the evidence reported in modern series.

During the past decade, somatic mutation of the *RAS* oncogene family has become a focus of CRC research, and studies have demonstrated that *RAS* mutation status correlates with the tumor biology of CRC.⁴ Especially, growing evidence reveals a propensity for *RAS*-mutated tumors to metastasize to the lung.^{5–7} Tie et al. demonstrated that *KRAS* mutation prevalence was significantly higher in lung (62%) and brain metastases of CRC (57%) than in liver metastases (32%), indicating the metastatic-site-specific association of *KRAS* mutation status.⁶ In addition, we recently reported that patients with mutant *RAS* had a lower 3-year lung recurrence-free survival rate (35% vs. 59%, $P < 0.01$) but not a lower liver recurrence-free survival rate (44% vs. 50%, $P = 0.18$) than patients with wild-type *RAS* after hepatectomy for colorectal liver metastases.⁷

As we previously proposed, these findings suggest that *RAS* mutation may also predict a high propensity for lung metastases in patients with IPNs.⁷ From a practical perspective, the reported high concordance of mutation status between primary and metastatic tumors may allow for early identification of patients at risk for progression of IPNs—i.e., patients with *RAS* mutation in their primary tumors.^{6–9} In the study by Kim et al., multivariate analysis revealed that primary tumor characteristics (rectal primary tumor, positive node status, and perineural invasion) as well as IPN characteristics (metachronous and bilateral presentation)

were strong predictors of progression of IPNs. We believe that additional investigation of the genetic profile of the primary tumor would have resulted in a more powerful predictive model for progression of IPNs. We thank Dr. Kim and colleagues for investigating an important issue and for providing a thorough predictive model for progression of IPNs.

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