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Title: Assessment of SHOX2 methylation in EBUS-TBNA specimen improves accuracy in lung cancer staging

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Body: Introduction:EBUS-TBNA is a well established method to assess mediastinal lymph nodes for lung cancer staging. However, due to the low negative predictive value a high proportion of patients with negative results require further investigations or invasive procedures. The level of SHOX2 gene methylation is a known diagnostic biomarker but its usefulness for lung cancer staging in EBUS-TBNA specimen is unknown. Methods:EBUS-TBNA was performed from 264 suspicious lymph nodes of 161 patients. Histologic evaluation and SHOX2 DNA methylation real time PCR analysis was performed on EBUS-TBNA specimen. Relative methylation in form of $\Delta\Delta Ct$ was used to classify the samples. Negative or ambiguous histologic results were confirmed by surgical means and clinical follow up over 6 months. Results:In average a 70 fold higher SHOX2 methylation level was measured for positive compared to negative lymph nodes. Using a cutoff from 6.5 $\Delta\Delta Ct$, the SHOX2 assay in combination with EBUS-TBNA histopathological evaluation correctly identified 96% of the lymph nodes with a sensitivity of 94% and a specificity of 100%. Negative predictive value could be improved from 80% to 92% when assessing SHOX2 methylation level to histopathological evaluation of EBUS-TBNA specimen alone. Conclusion:The combination of histological evaluation and the assessment of SHOX2 methylation level in EBUS-TBNA specimen strongly improves mediastinal lung cancer staging and such avoiding unnecessary surgical exploration.