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Detection of short stature homeobox 2 and RAS-associated domain family 1 subtype A DNA methylation in interventional pulmonology

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Abstract

One of the most important aspects of interventional pulmonology is to obtain tissue or liquid samples of the chest to diagnose a respiratory disease; however, it is still possible to obtain insufficient tissue or cytologic specimens. Indeed, methylation detection is an effective method by which to establish a diagnosis. This review focuses on the clinical application of short stature homeobox 2 and RAS-associated domain family 1 subtype A DNA methylation detection in interventional pulmonology, including bronchoscopic fluid biopsy, transbronchial needle aspiration, and pleural effusion.

Key Words: DNA methylation; Interventional pulmonology; Short stature homeobox 2; RAS-associated domain family 1 subtype A; Fluid biopsy; Transbronchial needle aspiration

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Core Tip: Lung cancer is the most common cancer in the world. Although the diagnosis and treatment are improved, there are still a large number of cases found with advanced stage when diagnosed. DNA methylation is key to regulate gene expression and maintain cell characteristics. Studies have showed that short stature homeobox 2 (*SHOX2*) promoter methylation and RAS-associated domain family 1 subtype A (*RASSF1A*) DNA methylation have been identified as biomarkers for the diagnosis of lung cancer. We review the application of *SHOX2* and *RASSF1A* in interventional pulmonology, and introduce some of our research results in this field.

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INTRODUCTION

Lung cancer (LCA) is the most common cancer worldwide and has the highest mortality of all cancers[1]. Although the diagnosis and treatment of LCA have improved, there are still a large number of LCA cases in an advanced stage when diagnosed and the 5-year survival rate is only 16%[2]. Timely diagnosis and identification of recurrences can facilitate early intervention and improve prognosis in patients with LCA[3-5]. Interventional pulmonology is a method of diagnosis and treatment of respiratory diseases *via* tracheoscopy and other instruments using minimally invasive technology, including many techniques to obtain tissue or liquid biopsy samples, such as biopsy, brushing, lavage, washing, and needle aspiration biopsy. The samples obtained using these methods can be further tested for tumor-specific biomarkers, which can be used for early warning and assistant diagnosis of cancer[6,7].

DNA methylation is the key by which gene expression and cell characteristics are maintained. Epigenetic changes through DNA methylation play an important role in the occurrence of multiple cancers[6,7]. Currently, methylation detection is considered to be a valuable auxiliary diagnostic method for LCA.

Studies have shown that short stature homeobox 2 (*SHOX2*) promoter methylation and RAS-associated domain family 1, subtype A (*RASSF1A*) DNA methylation have been identified as biomarkers for the diagnosis and prognosis of LCA[8,9]. The detection of *SHOX2* and/or *RASSF1A* in respiratory samples indicates that patients are highly likely to suffer from LCA. This method does not require complete tumor cells, thus it is suitable for application in interventional pulmonology, which often involves micro-tissue or liquid biopsy samples. Herein we review the application of *SHOX2* and *RASSF1A* in interventional pulmonology and introduce our research results.

SHOX2 AND RASSF1A DNA METHYLATION

SHOX2

SHOX2 is a homologue of the short stature homeobox gene. The *SHOX2* gene, also known as the *OG12*, *OG12X*, or *SHOT* gene, is another gene of the *SHOX* gene family and is located on chromosome 3q25-q26.1[10]. A meta-analysis showed that *SHOX2* DNA methylation is an important diagnostic biomarker for LCA[11]. Studies involving lymph node samples obtained from bronchial needle aspiration, bronchial lavage fluid, pleural effusion (PE), plasma, and tumor tissue under the guidance of endobronchial ultrasound showed that *SHOX2* DNA methylation is a useful and powerful biomarker for the detection of LCA[8,9,12-14].

RASSF1A

The *RASSF1* gene consists of eight exons and seven transcripts that are produced by different promoters and alternative splicing (*RASSF1A-G*). *RASSF1A* is the main subtype, which is transcribed from an independent CpG island promoter region[15]. *RASSF1A* methylation inactivation was initially described in LCA and breast cancer[16], and since then *RASSF1A* has been one of the most common hypermethylated genes reported in human cancer. Inactivation is often observed in a wide range of tumors. Inactivation is absent in primary tumors of the lung, breast, bladder, stomach, bile duct, and esophagus[16-21]. *RASSF1A* methylation can also be detected in several body fluids from cancer patients, which highlights its potential as a disease marker[15]. Race subgroup analysis showed that methylated *RASSF1A* gene was significantly associated with LCA in Caucasians and Asians[22].

High expression of *SHOX2* and deletion of *RASSF1A* plays important regulatory roles in the occurrence, apoptosis, and transformation of LCA cells. The combination of *RASSF1A* and *SHOX2* methylation has a high sensitivity and specificity for LCA

detection, which can provide a valuable biomarker for LCA screening and progression monitoring[23].

METHYLATION IN LIQUID BIOPSY SPECIMENS UNDER BRONCHOSCOPY

We can usually obtain airway lavage fluid, bronchoalveolar lavage fluid, mucosal brushing, and mucosal biopsy specimens, including transbronchial lung biopsy specimens, *via* bronchoscopy. Mucosal brushing, biopsy, and TBLB specimens are not included in this review because they are direct tumor tissues, and detection of the methylation level does not significantly improve the LCA diagnosis rate. In this paper, methylation detection of bronchoalveolar and airway lavage fluid is reviewed.

Airway lavage fluid is the specimen obtained by injecting 10-20 mL of isotonic saline into the target bronchus, which is then aspirated. Bronchoalveolar lavage fluid is the fluid recovered after injecting 20-40 mL of normal saline into the target lung segment. Schmidt *et al*[9] detected *SHOX2* methylation in 523 samples of airway lavage fluid obtained by bronchoscopy. Compared with benign diseases, *SHOX2* methylation detection showed a high sensitivity (68%) and specificity (95%) in the diagnosis of malignant lung disease. Compared with adenocarcinoma (47%), the sensitivity was increased in squamous (82%) and small cell carcinoma (97%). In a similar study involving 250 patients conducted by Dietrich *et al*[24], the sensitivity was 78% and the specificity was 96%. Compared with adenocarcinoma (77%), the sensitivity was increased in squamous (91%) and small cell carcinoma (93%). Ilse *et al* [25] tested *SHOX2* and *RASSF1A* DNA methylation in airway lavage fluid from 118 patients. *SHOX2* methylation had a sensitivity of 64% and specificity of 98%. *RASSF1A* DNA methylation had a sensitivity of 29% and specificity of 100%. The sensitivity (72%) and specificity (98%) were increased when *SHOX2* and *RASSF1A* DNA methylation testing was combined. In a systemic analysis on methylation detection of airway lavage fluid by Ni *et al*[22], the pooled sensitivity, specificity, and the area under the curve (AUC) of the *SHOX2* methylation status were 0.75, 0.94, and 0.94, respectively. The methylated *RASSF1A* gene had a sensitivity of 40%, specificity of 99%, and AUC of 0.66.

Ren *et al*[26] detected DNA methylation of *SHOX2* and *RASSF1A* in 305 bronchoalveolar lavage fluid samples. The sensitivity of the cytologic examination was only 5.7%, while the sensitivity of the combined detection was 71.5%. Zhang *et al*[27] detected DNA methylation of *SHOX2* and *RASSF1A* in bronchoalveolar lavage fluid samples from 322 patients. The sensitivity of combined detection was 81%. For early LCA (stage I), the sensitivity was as high as 85.7%, which was significantly higher than that of the carcinoembryonic antigen (10.7%) and cytology (46.4%). The specificity, positive predictive value, and negative predictive value (NPV) of combined detection among all enrolled patients were 97.4%, 99.6%, and 40.7%, respectively.

Based on methylation detection of liquid samples under bronchoscopy, we can predict LCA in patients without visualizing bronchoscopic abnormalities, and facilitate making full use of the samples acquired under bronchoscopy, shorten the diagnosis time, and reduce the need for additional examinations. Based on current research data, the combined detection of *SHOX2* and *RASSF1A* DNA methylation has high predictive value for LCA. Patients may be unwilling to undergo multiple bronchoscopies because it is an invasive examination. While an airway lavage is easy to obtain during bronchoscopy, methylation detection of airway lavage is safe and fast, and has good predictive value for LCA, which can improve the diagnostic efficacy of patients with a negative bronchoscopy, so that more patients can get receive a timely diagnosis and early treatment.

METHYLATION OF TBNA SPECIMENS

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is the gold standard for N staging of LCA[28] and an important method for the pathologic diagnosis of mediastinal lymph node metastasis in some LCA patients[29-31]; however, micro-metastases may be missed by needle aspiration biopsy, which results in a low NPV and the need for further examination of some patients[32,33]. Indeed, it may be useful to detect methylation in these patients. Darwiche *et al*[8] detected *SHOX2* DNA methylation in 105 patients with TBNA and found that the

accuracy of pathologic diagnosis alone was 52%. Combining pathology and *SHOX2* detection, the diagnostic accuracy could reach 99% and the NPV increased from 80% to 99%. Leiro *et al*[34] detected *SHOX2* and *RASSF1A* DNA methylation in 218 lymph node samples of 112 patients acquired by EBUS-TBNA. Gender, age, lymph node short diameter, standardized uptake value of lymph nodes, and methylation of *SHOX2* DNA were included in a multivariate regression model, which yielded a cross-validation sensitivity of 82.7% and specificity of 82.4% in detecting malignant lymph node lesions in negative cytology samples. The proposed prediction method can supplement the application of EBUS-TBNA in mediastinal staging. It is also suggested that single methylation marker test is not suitable for the detection of malignant tumors.

During an EBUS-TBNA examination, it is necessary to flush the needle track with liquid[35,36]. We collected the syringe washing fluid and detected the methylation in small samples. The results of *SHOX2* and *RASSF1A* DNA methylation detection of 18 needle tract washing fluid samples are shown in the Table 1 below. Although the number of cases is small, it is suggested that the syringe washing fluid can be used as a sample source for methylation detection, which provides a new way to make full use of TBNA samples.

METHYLATION IN PE

Medical thoracoscopic biopsies of abnormal pleural tissue have adequate diagnostic rates. Thus, there is no need for methylation testing to establish a diagnosis; however, when there is no apparent abnormality under the microscope, methylation testing of a PE may have clinical significance. Dietrich *et al*[37] detected *SHOX2* methylation in 114 patients with PEs and found that the combined analysis of cytology and DNA methylation increased the positive PEs by 71% compared with cytologic analysis alone. The specificity of *SHOX2* methylation was 100% for benign PEs. A study by Ilse *et al*[12] showed that among 1270 patients, the sensitivity and specificity of *SHOX2* DNA methylation for benign and malignant PEs were 39.5% and 96.2%, respectively. Based on the results, the sensitivity of methylation detection for PEs was lower than that of liquid biopsy by bronchoscopy; the underlying reason was not clear.

CONCLUSION

The above is a summary of the application of *SHOX2* and *RASSF1A* DNA methylation detection in interventional respiratory diseases. Interventional pulmonology has many indications in the diagnosis and treatment of respiratory diseases, including percutaneous lung biopsy and electromagnetic navigation bronchoscopy. At present, there is no data on methylation detection of samples obtained by percutaneous lung biopsy due to the high diagnosis rate of this type of specimen. The significance of methylation detection has mainly focused on the cases in which samples are difficult to obtain and few samples are obtained. In view of this situation, further research is urgently needed. In addition, electromagnetic navigation bronchoscopy provides the feasibility for tunnel biopsy of peripheral nodules and extrabronchial lesions, and the research on the diagnostic rate of methylation detection for these specimens is still lacking. In conclusion, *SHOX2* and *RASSF1A* DNA methylation detection may help interventional respiratory physicians improve the accuracy of LCA screening and guide personalized clinical medication in a timely fashion to improve the 5-year survival rate of LCA patients.

Table 1 Short stature homeobox 2 and RAS-associated domain family 1 subtype A DNA methylation detection of needle tract washing fluid samples during transbronchial needle aspiration

Diagnostic result	Total number	Cases	Controls	Sensitivity	Specificity
SHOX2 +	10/18	9/9	1/9	100%	-
SHOX2 -	8/18	0/9	8/9	-	89%
RASSF1A +	6/18	6/9	0/9	67%	-
RASSF1A -	12/18	3/9	9/9	-	100%
SHOX2 + or RASSF1A +	10/18	9/9	1/9	100%	-
SHOX2 - and RASSF1A -	8/18	0/9	8/9	-	89%

SHOX2: Short stature homeobox 2; RASSF1A: RAS-associated domain family 1 subtype A.

REFERENCES

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
- Lu S, Kong H, Hou Y, Ge D, Huang W, Ou J, Yang D, Zhang L, Wu G, Song Y, Zhang X, Zhai C, Wang Q, Zhu H, Wu Y, Bai C. Two plasma microRNA panels for diagnosis and subtype discrimination of lung cancer. *Lung Cancer* 2018; **123**: 44-51 [PMID: 30089594 DOI: 10.1016/j.lungcan.2018.06.027]
- Mahvi DA, Liu R, Grinstaff MW, Colson YL, Raut CP. Local Cancer Recurrence: The Realities, Challenges, and Opportunities for New Therapies. *CA Cancer J Clin* 2018; **68**: 488-505 [PMID: 30328620 DOI: 10.3322/caac.21498]
- Schiffman JD, Fisher PG, Gibbs P. Early detection of cancer: past, present, and future. *Am Soc Clin Oncol Educ Book* 2015; 57-65 [PMID: 25993143 DOI: 10.14694/EdBook_AM.2015.35.57]
- Sak K. A Hypothetical Approach on Gender Differences in Cancer Diagnosis. *J Transl Int Med* 2019; **7**: 90-92 [PMID: 31637178 DOI: 10.2478/jtim-2019-0020]
- Schwarzenbach H, Hoon DS, Pantel K. Cell-free nucleic acids as biomarkers in cancer patients. *Nat Rev Cancer* 2011; **11**: 426-437 [PMID: 21562580 DOI: 10.1038/nrc3066]
- Wan JCM, Massie C, Garcia-Corbacho J, Mouliere F, Brenton JD, Caldas C, Pacey S, Baird R, Rosenfeld N. Liquid biopsies come of age: towards implementation of circulating tumour DNA. *Nat Rev Cancer* 2017; **17**: 223-238 [PMID: 28233803 DOI: 10.1038/nrc.2017.7]
- Darwiche K, Zarogoulidis P, Baehner K, Welter S, Tetzner R, Wohlschlaeger J, Theegarten D, Nakajima T, Freitag L. Assessment of SHOX2 methylation in EBUS-TBNA specimen improves accuracy in lung cancer staging. *Ann Oncol* 2013; **24**: 2866-2870 [PMID: 24026539 DOI: 10.1093/annonc/mdt365]
- Schmidt B, Liebenberg V, Dietrich D, Schlegel T, Kneip C, Seegebarth A, Flemming N, Seemann S, Distler J, Lewin J, Tetzner R, Weickmann S, Wille U, Liloglou T, Raji O, Walshaw M, Fleischhacker M, Witt C, Field JK. SHOX2 DNA methylation is a biomarker for the diagnosis of lung cancer based on bronchial aspirates. *BMC Cancer* 2010; **10**: 600 [PMID: 21047392 DOI: 10.1186/1471-2407-10-600]
- De Baere E, Speleman F, Van Roy N, De Paepe A, Messiaen L. Assignment of SHOX2 (alias OG12X and SHOT) to human chromosome bands 3q25-->q26.1 by in situ hybridization. *Cytogenet Cell Genet* 1998; **82**: 228-229 [PMID: 9858825 DOI: 10.1159/000015108]
- Zhao QT, Guo T, Wang HE, Zhang XP, Zhang H, Wang ZK, Yuan Z, Duan GC. Diagnostic value of SHOX2 DNA methylation in lung cancer: a meta-analysis. *Onco Targets Ther* 2015; **8**: 3433-3439 [PMID: 26640383 DOI: 10.2147/OTT.S94300]
- Ilse P, Biesterfeld S, Pomjanski N, Fink C, Schramm M. SHOX2 DNA methylation is a tumour marker in pleural effusions. *Cancer Genomics Proteomics* 2013; **10**: 217-223 [PMID: 24136974 DOI: 10.5732/cjc.012.10221]
- Kneip C, Schmidt B, Seegebarth A, Weickmann S, Fleischhacker M, Liebenberg V, Field JK, Dietrich D. SHOX2 DNA methylation is a biomarker for the diagnosis of lung cancer in plasma. *J Thorac Oncol* 2011; **6**: 1632-1638 [PMID: 21694641 DOI: 10.1097/JTO.0b013e318220e99a]
- Schneider KU, Dietrich D, Fleischhacker M, Leshchber G, Merk J, Schäper F, Stapert HR, Vossenaar ER, Weickmann S, Liebenberg V, Kneip C, Seegebarth A, Erdogan F, Rappold G, Schmidt B. Correlation of SHOX2 gene amplification and DNA methylation in lung cancer tumors. *BMC Cancer* 2011; **11**: 102 [PMID: 21426551 DOI: 10.1186/1471-2407-11-102]
- Hesson LB, Cooper WN, Latif F. The role of RASSF1A methylation in cancer. *Dis Markers* 2007; **23**: 73-87 [PMID: 17325427 DOI: 10.1155/2007/291538]
- Dammann R, Li C, Yoon JH, Chin PL, Bates S, Pfeifer GP. Epigenetic inactivation of a RAS association domain family protein from the lung tumour suppressor locus 3p21.3. *Nat Genet* 2000; **25**:

- 315-319 [PMID: [10888881](#) DOI: [10.1038/77083](#)]
- 17 **Burbee DG**, Forgacs E, Zöchbauer-Müller S, Shivakumar L, Fong K, Gao B, Randle D, Kondo M, Virmani A, Bader S, Sekido Y, Latif F, Milchgrub S, Toyooka S, Gazdar AF, Lerman MI, Zbarovsky E, White M, Minna JD. Epigenetic inactivation of RASSF1A in lung and breast cancers and malignant phenotype suppression. *J Natl Cancer Inst* 2001; **93**: 691-699 [PMID: [11333291](#) DOI: [10.1093/jnci/93.9.691](#)]
- 18 **Byun DS**, Lee MG, Chae KS, Ryu BG, Chi SG. Frequent epigenetic inactivation of RASSF1A by aberrant promoter hypermethylation in human gastric adenocarcinoma. *Cancer Res* 2001; **61**: 7034-7038 [PMID: [11585730](#) DOI: [10.1097/00002820-200110000-00014](#)]
- 19 **Kuroki T**, Trapasso F, Yendamuri S, Matsuyama A, Alder H, Mori M, Croce CM. Allele loss and promoter hypermethylation of VHL, RAR-beta, RASSF1A, and FHIT tumor suppressor genes on chromosome 3p in esophageal squamous cell carcinoma. *Cancer Res* 2003; **63**: 3724-3728 [PMID: [12839965](#) DOI: [10.1097/00130404-200307000-00015](#)]
- 20 **Lee MG**, Kim HY, Byun DS, Lee SJ, Lee CH, Kim JI, Chang SG, Chi SG. Frequent epigenetic inactivation of RASSF1A in human bladder carcinoma. *Cancer Res* 2001; **61**: 6688-6692 [PMID: [11559536](#) DOI: [10.1002/1097-0142\(20010915\)61:12<1155::AID-CNCR1506>3.0.CO;2-0](#)]
- 21 **Wong N**, Li L, Tsang K, Lai PB, To KF, Johnson PJ. Frequent loss of chromosome 3p and hypermethylation of RASSF1A in cholangiocarcinoma. *J Hepatol* 2002; **37**: 633-639 [PMID: [12399230](#) DOI: [10.1016/s0168-8278\(02\)00269-6](#)]
- 22 **Ni S**, Ye M, Huang T. Short stature homeobox 2 methylation as a potential noninvasive biomarker in bronchial aspirates for lung cancer diagnosis. *Oncotarget* 2017; **8**: 61253-61263 [PMID: [28977861](#) DOI: [10.18632/oncotarget.18056](#)]
- 23 **Li N**, Zeng Y, Huang J. Signaling pathways and clinical application of RASSF1A and SHOX2 in lung cancer. *J Cancer Res Clin Oncol* 2020; **146**: 1379-1393 [PMID: [32266538](#) DOI: [10.1007/s00432-020-03188-9](#)]
- 24 **Dietrich D**, Kneip C, Raji O, Liloglou T, Seegebarth A, Schlegel T, Flemming N, Rausch S, Distler J, Fleischhacker M, Schmidt B, Giles T, Walshaw M, Warburton C, Liebenberg V, Field JK. Performance evaluation of the DNA methylation biomarker SHOX2 for the aid in diagnosis of lung cancer based on the analysis of bronchial aspirates. *Int J Oncol* 2012; **40**: 825-832 [PMID: [22108652](#) DOI: [10.3892/ijo.2011.1264](#)]
- 25 **Ilse P**, Biesterfeld S, Pomjanski N, Wrobel C, Schramm M. Analysis of SHOX2 methylation as an aid to cytology in lung cancer diagnosis. *Cancer Genomics Proteomics* 2014; **11**: 251-258 [PMID: [25331797](#)]
- 26 **Ren M**, Wang C, Sheng D, Shi Y, Jin M, Xu S. Methylation analysis of SHOX2 and RASSF1A in bronchoalveolar lavage fluid for early lung cancer diagnosis. *Ann Diagn Pathol* 2017; **27**: 57-61 [PMID: [28325362](#) DOI: [10.1016/j.anndiagpath.2017.01.007](#)]
- 27 **Zhang C**, Yu W, Wang L, Zhao M, Guo Q, Lv S, Hu X, Lou J. DNA Methylation Analysis of the SHOX2 and RASSF1A Panel in Bronchoalveolar Lavage Fluid for Lung Cancer Diagnosis. *J Cancer* 2017; **8**: 3585-3591 [PMID: [29151944](#) DOI: [10.7150/jca.21368](#)]
- 28 **Monaco SE**, Khalbuss WE, Pantanowitz L. Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA): A Practical Approach. Basel, Switzerland: Karger, 2014
- 29 **Zhang Y**, Xie F, Mao X, Zheng X, Li Y, Zhu L, Sun J. Determining factors of endobronchial ultrasound-guided transbronchial needle aspiration specimens for lung cancer subtyping and molecular testing. *Endosc Ultrasound* 2019; **8**: 404-411 [PMID: [31670289](#) DOI: [10.4103/eus.eus_8_19](#)]
- 30 **Cornelissen CG**, Dapper J, Dreher M, Müller T. Endobronchial ultrasound-guided transbronchial needle aspiration under general anesthesia versus bronchoscope-directed deep sedation: A retrospective analysis. *Endosc Ultrasound* 2019; **8**: 204-208 [PMID: [30880723](#) DOI: [10.4103/eus.eus_65_18](#)]
- 31 **Adler DG**, Gabr M, Taylor LJ, Witt B, Pleskow D. Initial report of transesophageal EUS-guided intraparenchymal lung mass core biopsy: Findings and outcomes in two cases. *Endosc Ultrasound* 2018; **7**: 413-417 [PMID: [29786035](#) DOI: [10.4103/eus.eus_13_18](#)]
- 32 **Groth SS**, Andrade RS. Endobronchial and endoscopic ultrasound-guided fine-needle aspiration: a must for thoracic surgeons. *Ann Thorac Surg* 2010; **89**: S2079-S2083 [PMID: [20493985](#) DOI: [10.1016/j.athoracsur.2010.03.018](#)]
- 33 **Liran L**, Rottem K, Gregorio FZ, Avi A, Neville B. A novel, stepwise approach combining conventional and endobronchial ultrasound needle aspiration for mediastinal lymph node sampling. *Endosc Ultrasound* 2019; **8**: 31-35 [PMID: [28879863](#) DOI: [10.4103/eus.eus_29_17](#)]
- 34 **Leiro V**, De Chiara L, Rodríguez-Girondo M, Botana-Rial M, Valverde D, Núñez-Delgado M, Fernández-Villar A. Methylation Assessment for the Prediction of Malignancy in Mediastinal Adenopathies Obtained by Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in Patients with Lung Cancer. *Cancers (Basel)* 2019; **11** [PMID: [31547177](#) DOI: [10.3390/cancers11101408](#)]
- 35 **Guo J**, Li H, Chen Y, Chen P, Li X, Sun S. Robotic ultrasound and ultrasonic robot. *Endosc Ultrasound* 2019; **8**: 1-2 [PMID: [30777939](#) DOI: [10.4103/eus.eus_69_18](#)]
- 36 **Costa-Moreira P**, Vilas-Boas F, Moutinho-Ribeiro P, Macedo G. Macroscopic on-site evaluation during EUS-fine needle biopsy with combined cyto and histological analysis may overcome the need of rapid on-site evaluation. *Endosc Ultrasound* 2019; **8**: 432-433 [PMID: [31854347](#) DOI: [10.4103/eus.eus_72_19](#)]

- 37 **Dietrich D**, Jung M, Puetzer S, Leisse A, Holmes EE, Meller S, Uhl B, Schatz P, Ivascu C, Kristiansen G. Diagnostic and prognostic value of SHOX2 and SEPT9 DNA methylation and cytology in benign, paramalignant and malignant pleural effusions. *PLoS One* 2013; **8**: e84225 [PMID: [24386354](#) DOI: [10.1371/journal.pone.0084225](#)]



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