

· 临床研究 ·

ROSE 在肺部病变活检病理诊断中的价值

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[摘要] **目的:**探讨经支气管镜肺活检(transbronchial lung biopsy, TBLB)及超声引导下经支气管针吸活检(endobronchial ultrasound-guided transbronchial needle aspiration, EBUS-TBNA)联合细胞学现场快速评估(rapid on-site evaluation, ROSE)在肺恶性肿瘤细胞学诊断中的应用价值。**方法:**收集2018年1月—2019年8月在南京市第一医院进行的TBLB和EBUS-TBNA的患者174例,根据有无进行ROSE,分为两组,ROSE组106例,非ROSE组68例。以组织学病理结果为金标准,分析两种方法对肺恶性肿瘤细胞学诊断的灵敏度,并评估两种方法对肺恶性肿瘤的细胞学诊断价值是否有差异。**结果:**ROSE组和非ROSE组的总确诊率分别为88.7%和77.9%,诊断肺部恶性肿瘤的灵敏度分别为90.1%和71.4%,ROSE组的总确诊率及恶性肿瘤诊断灵敏度高于非ROSE组,两组之间差异有统计学意义($P < 0.05$)。ROSE组二次检查率小于非ROSE组,两组之间差异有统计学意义($P < 0.05$)。ROSE组的活检时间大于非ROSE组,出血发生率小于非ROSE组,但差异均无统计学意义。ROSE组标本满意度(96.2%)高于非ROSE组(86.8%),两组之间差异有统计学意义($P < 0.05$)。**结论:**联合ROSE可提高TBLB和EBUS-TBNA在取样过程中的标本满意度,提高肺部病变的确诊率,尤其是提高恶性肿瘤细胞学诊断的灵敏度,在肺肿瘤诊断中有一定应用价值。

[关键词] 细胞学现场快速评估;经支气管镜肺活检;超声引导下经支气管针吸活检;细胞学

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The value of ROSE in pathological diagnosis of the pulmonary biopsy

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[Abstract] **Objective:** This study aims to assess the utility of rapid on-site evaluation (ROSE) for transbronchial lung biopsy (TBLB) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in cytological diagnosis of lung malignant tumor. **Methods:** Total 174 cases performed TBLB and EBUS-TBNA procedures prospectively collected between January 2018 to August 2019 at the Affiliated Nanjing Hospital of Nanjing Medical University. They were randomly divided into the two groups according to with or without ROSE. There were 106 cases in ROSE group, while there were 68 cases in non-ROSE group. Histological findings was the gold standard. The accuracy of TBLB or EBUS-TBNA with and without ROSE was compared. The sensitivity of the two methods in cytological diagnosis of lung malignant tumor was analyzed, and the differences between the two methods in cytological diagnosis of lung malignant tumor was compared. **Results:** Overall accuracy in ROSE group and non-ROSE group was 88.7% and 77.9%, respectively. Sensitivity to detect malignant lesions in ROSE group and non-ROSE group was 90.1% and 71.4%, respectively. The diagnostic accuracy rate and sensitivity rate in ROSE group were higher than those in non-ROSE group ($P < 0.05$), and the rate of secondary inspection in ROSE group was lower than that in non-ROSE group ($P < 0.05$). The time of inspection in ROSE group was higher than that in non-ROSE group, but there were no significant differences between two groups. Specimen satisfaction (96.2%) of ROSE group was higher than that of non-ROSE group (86.8%), and there were significant differences between two groups ($P < 0.05$). **Conclusion:** The combination of ROSE can improve the satisfaction of TBLB and EBUS-TBNA in the sampling process, improve the diagnostic accuracy rate of lung lesions, especially the sensitivity of cytological diagnosis for malignant tumor, which has certain application value in the diagnosis of lung tumors.

[Key words] rapid on-site evaluation; TBLB; EBUS-TBNA; cytology

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快速现场评估(rapid on-site evaluation, ROSE)是一种采用穿刺、活检、刷片等方法收集标本进行现场细胞病理学评价的技术^[1]。该技术是在支气管镜检查过程中,由细胞病理学医师现场对所得标本的满意度进行快速评价,判断穿刺是否成功,并提供初步诊断,指导下一步操作。但是,ROSE是否能够提高经支气管镜肺活检(transbronchial lung biopsy, TBLB)和超声引导下经支气管针吸活检(endobronchial ultrasound-guided transbronchial needle aspiration, EBUS-TBNA)的诊断准确性仍存在争议^[2-4]。国内在临床工作中应用TBLB或EBUS-TBNA联合ROSE不如国外广泛,也缺乏相关研究。本研究旨在回顾性分析并探讨TBLB或EBUS-TBNA联合ROSE对肺恶性肿瘤诊断的临床价值。

1 对象和方法

1.1 对象

收集2018年1月1日—2019年8月31日在南京医科大学附属南京医院气管镜室进行TBLB或EBUS-TBNA,并有组织病理学诊断的病例174例,其中男103例,女71例,年龄17~85岁。在进行活检手术之前将其随机分为两组,其中ROSE组患者106例,男62例,女44例,年龄25~84岁,平均(63.8±11.4)岁。非ROSE组患者68例,男41例,女27例,年龄17~85岁,平均(62.5±12.8)岁。两组一般资料差异无统计学意义($P>0.05$),具有可比性。本项目取得医院伦理委员会批准(KY20201102-01),所有患者知情同意。

1.2 方法

非ROSE组对明确或怀疑病变区域取材(钳夹、刷检、灌洗、针吸活检),采用拉片法将刷取的细胞涂至一张载玻片上,再用另一张载玻片叠放并轻压,反向拉开,制成两张涂片,迅速置入95%的酒精中固定30 min后取出干燥。

ROSE组按照ROSE指导操作,其涂片采用WHO推荐的ROSE染色方法——迪夫快速染色(Diff-quickstain)方法进行染色,并在显微镜下进行现场快速评估。采用试剂:迪夫A溶液、迪夫B溶液、磷酸盐缓冲液(PBS)。染色方法:把玻片浸泡于迪夫A溶液(10~30 s);再置于PBS染缸中洗掉迪夫A溶液,甩干缓冲液;然后再把涂片浸泡于迪夫B溶液(20~40 s);最后置于清水染缸中水洗,以吸水纸吸干、擦干玻片残留液体,完成染色、干燥,光学显微镜下诊断。评价内容:①是否采集到癌细胞;②

恶性肿瘤细胞比例以及其数量是否足够;③细胞是否完整。阅片后,判断取样是否有效,以确定是否需继续取样。当标本为无法诊断或恶性细胞比例低,则再次取样;若ROSE结果为阳性则在同样的部位进行取样,若ROSE结果为阴性则更换取样部位后再次进行ROSE分析,最多不超过7次。同时采用非ROSE组相同的拉片法,制作涂片两张。

ROSE组和非ROSE组操作结束后所有涂片及活检组织送病理科行常规组织及细胞学检查,由2名高年资病理科医师阅片。若获得明确的病理诊断结果,此为最终诊断,若TBLB或EBUS-TBNA的病理诊断为阴性,但患者行其他有创性操作,如经皮肺穿刺、胸腔镜及开胸手术等获得明确的阳性诊断,则以阳性诊断为最终诊断。所有标本的满意度由病理科医师确定。

1.3 统计学方法

采用SPSS 22.0统计学软件进行数据分析,符合正态分布的计量资料用均数±标准差($\bar{x} \pm s$)描述,并采用 t 检验,组间计数资料比较采用 χ^2 检验, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 ROSE组和非ROSE组的临床资料及诊断结果

174例病例中,组织学最终诊断为恶性病变99例,其中非小细胞肺癌79例(包括鳞癌31例,腺癌48例),小细胞癌18例,其他恶性病变2例;非肿瘤性病变75例。

ROSE组106例,非小细胞肺癌57例,其中鳞癌22例,腺癌35例;小细胞肺癌12例;其他恶性病变2例;非肿瘤性病变35例。非ROSE组共68例,非小细胞肺癌22例,其中鳞癌9例,腺癌13例;小细胞肺癌6例;非肿瘤性病变40例(表1)。

2.2 ROSE与非ROSE组细胞学检查的诊断效能比较

ROSE组106例,94例ROSE细胞学诊断与最终组织学病理结果一致,总确诊率为88.7%(94/106),其中恶性肿瘤诊断灵敏度为90.1%(64/71);非ROSE组68例,53例细胞学诊断与最终组织学病理结果一致,总确诊率为77.9%(53/68),其中恶性肿瘤诊断灵敏度为71.4%(20/28);ROSE组的总确诊率及恶性肿瘤诊断灵敏度高于非ROSE组,差异有统计学意义($P<0.05$)。两组的非恶性肿瘤诊断灵敏度之间差异无统计学意义($P>0.05$,表2)。

2.3 ROSE组和非ROSE组的相关指标比较

ROSE组二次检查率为1.89%(2/106),非ROSE

表1 ROSE 组和非 ROSE 组的临床资料及诊断结果
Table 1 Comparison of the clinical data and diagnosis results between ROSE group and non-ROSE group

观察指标	非 ROSE 组 (n=68)	ROSE 组 (n=106)	P 值
性别[n(%)]			0.81
男	41(60.29)	62(58.49)	
女	27(39.71)	44(41.51)	
平均年龄(岁)	62.5 ± 12.8	63.8 ± 11.4	0.49
肿块大小(最大径)[n(%)]			0.36
< 20 mm	26(38.24)	39(36.79)	
≥ 20 mm	42(61.76)	67(63.21)	
恶性肿瘤[n(%)]	28(41.18)	71(66.98)	0.21
非小细胞肺癌[n(%)]	22(32.35)	57(53.74)	0.29
鳞癌	9(40.91)	22(38.60)	0.21
腺癌	13(59.09)	35(61.40)	0.06
小细胞肺癌[n(%)]	6(8.82)	12(11.32)	0.59
其他恶性病变[n(%)]	0(0)	2(1.96)	0.52
非肿瘤性病变[n(%)]	40(58.82)	35(33.02)	0.48

表2 ROSE 组和非 ROSE 组的诊断效能
Table 2 Comparison of the diagnostic efficacy between ROSE group and non-ROSE group [% (n/N)]

诊断效能	非 ROSE 组 (n=68)	ROSE 组 (n=106)	χ ² 值	P 值
总确诊率	77.9(53/68)	88.7(94/106)	3.75	0.04
诊断灵敏度				
恶性肿瘤	71.4(20/28)	90.1(64/71)	4.89	0.03
非恶性肿瘤	82.5(33/40)	85.7(30/35)	0.26	0.61

组二次检查率为 8.82% (6/68), ROSE 组二次检查率

小于非 ROSE 组, 差异有统计学意义 ($P < 0.05$), 两组活检时间及出血发生率差异均无统计学意义 ($P > 0.05$, 表 3)。

2.4 ROSE 组和非 ROSE 组的标本满意率比较
ROSE 组标本满意率为 96.2% (102/106), 非 ROSE 组为 86.8% (59/68), ROSE 组的标本满意率高于非 ROSE 组, 两组差异有统计学意义 ($P < 0.05$)。

2.5 细胞学染色结果
不同类型肺癌及正常柱状上皮的镜下典型细胞学特征: 腺癌细胞胞浆丰富, 细胞核增大, 排列呈腺样或成团。小细胞癌胞浆少, 细胞核有典型的“粉尘样”改变, 往往挤压明显。正常的柱状上皮排列规整, 有极向, 可见纤毛 (图 1)。

3 讨 论

TBLB 和 EBUS-TBNA 是国内外开展的应用十分成熟的内镜介入技术, 其创伤小、安全性及耐受性较好^[5-6]。对肺癌及纵隔淋巴结病变的诊断及分期有着非常重要的价值。操作过程中获取的组织标本质量直接影响到随后的病理诊断及分子检测, 如何取到合适的组织标本尤为重要。ROSE 是一种基于细胞形态学的诊断技术, 可以对标本进行快速评价、确定有无取得靶部位标本, 判断标本是否满意, 进而做出初步诊断及进行分流, 实时指导下一步操作, 是现代化介入肺脏病诊疗中心常用的一种诊疗技术^[7-8]。

但是, ROSE 能否有效提高 TBLB 或 EBUS-TBNA 的细胞学诊断效率, 仍然存在争议。Mondoni 等^[9]进行的随机试验显示 ROSE 可将 TBLB 的细胞学诊断

表3 ROSE 组和非 ROSE 组的相关指标比较 Table 3 Comparison of the relevant indexes between ROSE group and non-ROSE group				
指标	非 ROSE 组(n=68)	ROSE 组(n=106)	χ ² 值/t 值	P 值
活检时间(min)	28.98 ± 0.72	38.15 ± 0.94	3.64	0.06
出血发生[n(%)]	4(5.88)	4(3.77)	0.42	0.52
二次检查[n(%)]	6(8.82)	2(1.89)	4.54	0.03

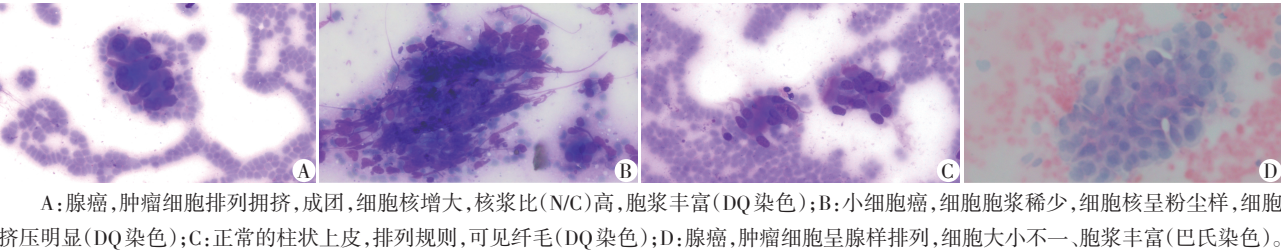


图1 不同类型的肺癌及正常柱状上皮的镜下特征(×400)
Figure 1 Microscopic features of different types of lung cancer and normal columnar epithelium (×400)

灵敏度从76%提高至97%。回顾性研究也表明ROSE可以提高细胞学诊断率^[10]。但Griffin等^[11]和Nakajima等^[12]进行的回顾性研究,提示ROSE并没有提高肺活检的诊断率。不过Griffin研究报告指出ROSE提高了采样组织的质量。此外,多项研究表明EBUS-TBNA中采用ROSE未能提高其细胞学诊断率,但是ROSE组可减少穿刺次数,缩短手术操作时间^[13-15]。有研究表明ROSE可用于EBUS-TBNA中判断肺癌的分期,并确定手术切除方式^[16]。所有研究都与患者是否有可疑肺癌有关,对肺的非肿瘤性病变,没有数据表明联合ROSE有诊断价值。

TBLB或EBUS-TBNA联合ROSE在我国临床工作中还没有得到普遍应用,也缺乏相关经验。本研究主要将肺占位和纵隔/肺门淋巴结肿大患者作为研究对象,在TBLB及EBUS-TBNA手术过程中,评价ROSE是否对细胞学诊断效能产生影响。本研究分析了ROSE对TBLB和EBUS-TBNA的影响,以术后组织病理学检查作为金标准,ROSE组和非ROSE组对肺部病变的确诊率分别为88.7%和77.9%、对肺部恶性肿瘤细胞学诊断的灵敏度分别为90.1%和71.4%,本研究结果显示,TBLB和EBUS-TBNA联合ROSE可提高肺部病变的总确诊率及肺部恶性肿瘤细胞学诊断的灵敏度($P < 0.05$),两组标本满意率分别为96.2%和86.8%,ROSE组的标本满意率高于非ROSE组,提示ROSE能减少无效标本,提高取材满意率,进而提高肺部病变总确诊率以及恶性肿瘤的诊断灵敏度。两组非恶性肿瘤诊断灵敏度之间差异无统计学意义。TBLB和EBUS-TBNA操作过程中,仅仅凭医生经验及肉眼观察难以保证每次都能取到有效标本,有时需要二次检查,这就增加操作风险及费用。本研究中,ROSE组二次检查率小于非ROSE组($P < 0.05$),可能是ROSE技术为取材提供了指导,减少无效的重复操作,提高了取材的准确性,避免了二次检查。虽然ROSE组的活检时间长于非ROSE组,差异却无统计学意义,这提示虽然ROSE过程需要进行制片、染色及阅片,只要操作熟练并不会显著延长整个术程;ROSE组的出血发生率小于非ROSE组,两组之间差异无统计学意义,可能与样本数量较少有关,需要更大规模的研究及多中心合作的数据。

本研究结果显示TBLB或EBUS-TBNA联合ROSE提高了术中取样过程中的标本满意度,提高肺部病变的确诊率及恶性肿瘤的诊断灵敏度,减少了二次检查率。此外,在阳性部位多次取材,可以

为常规病理检查、免疫组化和基因检测提供尽可能多的有效标本,并且减少无效重复操作。因此,TBLB或EBUS-TBNA联合使用ROSE值得临床应用推广。

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