

• 临床研究 •

细针穿刺洗脱液甲状腺球蛋白测定在甲状腺乳头状癌淋巴结转移诊断中的价值*

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[摘要] 目的: 探讨细针穿刺细胞学(fine needle aspirates cytology, FNAC)及穿刺洗脱液甲状腺球蛋白测定(the measurement of thyroglobulin (Tg) in the washout of the needle used to perform the fine needle aspiration cytology, FNA-Tg)在甲状腺乳头状癌(papillary thyroid carcinoma, PTC)淋巴结转移诊断中的价值。方法: 回顾性分析我院 104 例行 FNAC 和 FNA-Tg 并最终经病理证实的初次诊断 PTC 的患者资料。评价不同 FNA-Tg 阳性标准的敏感性、特异性, 比较 FNAC、FNA-Tg 以及二者联合诊断 PTC 淋巴结转移的诊断效能, 分析淋巴结大小、血清甲状腺球蛋白抗体(thyroglobulin antibody, TgAb)对诊断效能的影响。结果: FNA-Tg 的最佳截断值为 5.88 ng/mL; 以 FNA-Tg/血清甲状腺球蛋白 > 1、FNA-Tg > 1.00 ng/mL、FNA-Tg > 5.88 ng/mL 为阳性标准诊断淋巴结转移的敏感性分别为 91.95%、98.85%、96.55%; 特异性分别为 81.82%、86.36%、100.00%。FNA-Tg 联合 FANC 诊断的敏感性、特异性分别为 97.70%、100.00%, 诊断效能优于单独使用 FNAC ($P=0.008$)。淋巴结大小影响 FNAC 的诊断效能 ($P=0.005$) 而并不影响 FNA-Tg 的诊断效能 ($P=0.120$); 血清 TgAb 水平对 FNAC、FNA-Tg 的诊断效能影响均不明显 ($P>0.05$)。结论: FNA-Tg 诊断 PTC 淋巴结转移有较高的敏感性、特异性, 且不受淋巴结大小、血清 TgAb 是否阳性的影响; 联合 FANC 能提高诊断的敏感性和准确度。当 FNAC 阴性或诊断存疑时, FNA-Tg 能为 PTC 颈部淋巴结转移的诊断提供重要信息。

[关键词] 甲状腺乳头状癌; 淋巴结转移; 细针穿刺细胞学; 细针穿刺洗脱液甲状腺球蛋白测定; 甲状腺球蛋白抗体

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Value of FNA-Tg in the Diagnosis of Lymph Node Metastasis in Papillary Thyroid Carcinoma

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[Abstract] **Objective:** To evaluate the value of fine-needle aspiration cytology (FNAC) and the measurement of thy-

roglobulin (Tg) in the washout of the needle used to perform the fine needle aspiration cytology (FNA-Tg) in the diagnosis of lymph node metastasis in papillary thyroid carcinoma (PTC). **Methods:** In this retrospective study, 104 patients initially diagnosed as PTC underwent FNAC and FNA-Tg, and were finally confirmed by pathology. Sensitivity and specificity of FNA-Tg with different positive criteria were evaluated. Efficacy of FNAC alone, FNA-Tg alone and the combination of the two in the diagnosis of lymph node metastasis in PTC were compared. Effects of the size of the lymph node and serum thyroglobulin antibody (TgAb) on the diagnosis of FNAC and FNA-Tg were analyzed. **Results:** The optimal cut-off value of FNA-Tg was 5.88 ng/mL. With the positive criteria of FNA-Tg/sTg > 1, FNA-Tg > 1 ng/mL and FNA-Tg > 5.88 ng/mL, the sensitivity were 91.95%, 98.85% and 96.55%; and the specificity were 81.82%, 86.36% and 100%, respectively. The sensitivity and specificity of FNA-Tg + FNAC were 97.7% and 100%, with the diagnostic efficacy better than FNAC alone ($P=0.008$). The size of lymph nodes affected the accuracy of FNAC ($P=0.005$), while it did not affect the accuracy of FNA-Tg ($P=0.12$). Serum TgAb level affected neither the accuracy of FNAC nor that of FNA-Tg ($P>0.05$). **Conclusion:** FNA-Tg is highly sensitive and specific in the diagnosis of metastatic lymph nodes even, which is not prone to be affected by the size of lymph nodes and serum TgAb level. FNA-Tg combines with FNAC can improve the sensitivity and accuracy of diagnosis. FNA-Tg can provide important information for the diagnosis of lymph node metastasis in PTC for FNAC negative patients or those with dubious results.

[**Key words**] Papillary thyroid carcinoma; Lymph node metastasis; Fine needle aspiration cytology; FNA-Tg; Thyroglobulin antibody

在过去的三十年中,分化型甲状腺癌已成为全球增长最快的恶性肿瘤,其中甲状腺乳头状癌(papillary thyroid carcinoma, PTC)约占 85%~90%,恶性程度低,预后较好^[1]。PTC 生物学行为和临床预后相对良好,但在初始诊断时仍有约 30%~80% 的患者已经合并区域淋巴结转移^[2]。因此,准确区分颈部淋巴结的性质能避免多余的颈侧区淋巴结清扫。

超声在 PTC 颈部淋巴结转移诊断中敏感性高但特异性较低;超声引导下细针穿刺细胞学(fine needle aspirates cytology, FNAC)检查是术前诊断 PTC 患者颈部淋巴结性质最常用、最直接的方法,敏感度、特异度也较高,但受穿刺操作者、细胞病理学者的经验等因素影响较大^[3],FNAC 约有 6%~8% 的假阴性^[4-7]。细针穿刺洗脱液甲状腺球蛋白测定(the measurement of thyroglobulin (Tg) in the washout of the needle used to perform the fine needle aspiration cytology, FNA-Tg)基于甲状腺球蛋白为甲状腺滤泡上皮细胞分泌的特异性分子这一特征,在 PTC 淋巴结转移的诊断作用日益显著,该法最早在 1992 提出^[8],并在 2015 美国甲状腺协会(American Thyroid Association, ATA)指南上推荐可作为术前可疑淋巴结转移的诊断(弱推荐,低质量证据)^[1]。作为 FNAC 的附属检测,FNA-Tg 并不会增加病人创伤,而且 FNA-Tg 联合 FNAC 能将 PTC 淋巴结转移诊断敏感性提升约 13%,还有助于降低假阴性率^[9-14]。FNA-Tg 只是一种半定量指标,目前尚无统一的检测方法和阳性诊断参考值^[15],本文通过回顾性分析,

比较 FNA-Tg 在不同阳性诊断标准间的诊断效能,并比较单独使用 FNA-Tg、联合 FNA-Tg + FNAC 的诊断效能,以期能为诊断 PTC 颈部淋巴结转移提供更多信息。

1 资料与方法

1.1 研究对象

回顾性分析 2019 年 4 月至 2020 年 4 月因初次诊断 PTC 于我院行颈部淋巴结穿刺的患者 368 例,其中同时行 FNAC 和 FNA-Tg 测定 150 例(191 个淋巴结)。以术后病理检查为金标准,最终纳入行对应颈侧区淋巴结清扫并取得病理结果的患者 104 例共 131 个淋巴结。根据参考文献^[1],以穿刺目标淋巴结大小将病例分为 ≥ 8 mm、 < 8 mm 组;以患者血清甲状腺球蛋白抗体(thyroglobulin antibody, TgAb)大于试剂参考值范围上限(即 100 IU/mL)为阳性标准分为 TgAb 阳性组、TgAb 阴性组。

1.2 方法

穿刺前患者签署知情同意书,取 2 mL 静脉血送检血清甲状腺球蛋白(serum thyroglobulin, sTg)、TgAb。在超声引导下对可疑淋巴结穿刺,避免穿刺到结外组织,涂片立即送病理行 FNAC 检查;将穿刺针用 1 mL 生理盐水反复冲洗 10 次制成洗脱液,3 000 r/min 离心 10 min,取上清液测量 FNA-Tg。上述 sTg、FNA-Tg、TgAb 均采用化学发光免疫分析法检测。

1.3 结果判定

FNA-Tg 分别选择以下三种阳性诊断标准诊断

转移性颈部淋巴结^[1,16-17]: 1) FNA-Tg 高于 sTg, 即 FNA-Tg/sTg > 1; 2) FNA-Tg > 1.00 ng/mL; 3) FNA-Tg > 受试者工作特征 (receiver operating characteristic, ROC) 曲线最佳截断值。FNAC 及术后石蜡病理切片均由 2 位经验丰富的病理医生共同诊断。

1.4 数据分析

应用 SPSS 23.0 统计软件, 计量资料使用均数 ± 标准差表示, 组间使用 *t* 检验或秩和检验; 采用卡方检验分别比较淋巴结是否 ≥ 8 mm、血清 TgAb 阳性及阴性组间的 FNAC、FNA-Tg 诊断效能。使用 MedCalc 19.0, 以术后病理为金标准绘制 FNA-Tg 的 ROC 曲线并计算曲线下面积 (area under curve, AUC) 及最佳截断值, 比较 FNA-Tg 不同阳性诊断标

准间的 AUC 以及 FNAC、FNA-Tg 的诊断效能。以 $P < 0.05$ 为差异有统计学意义。

2 结果

最终纳入患者 104 例共 131 个淋巴结, 其中男性 40 例共 47 个淋巴结, 女性 64 例共 84 个淋巴结。从表 1 可知, 131 个淋巴结中有 87 个转移性淋巴结及 44 个非转移性淋巴结; 转移性与非转移性淋巴结组间性别、FNA-Tg 差异有统计学意义 ($P < 0.05$), 而淋巴结的大小、sTg 差异无统计学意义 ($P > 0.05$); 淋巴结 ≥ 8 mm 组共 109 个, < 8 mm 组共 22 个, TgAb 阳性组淋巴结 41 个, 阴性组 90 个。

表 1 131 个淋巴结的临床特征

Table 1. Clinical Characteristics of 131 Cases

Variable	Pathology		χ^2/Z	<i>P</i>
	Metastasis (<i>n</i> = 87)	Non-metastasis (<i>n</i> = 44)		
Sex [<i>n</i> (%)]			$\chi^2 = 4.980$	0.026
Male (<i>n</i> = 47)	37 (78.72%)	10 (21.28%)		
Female (<i>n</i> = 84)	50 (59.52%)	34 (40.48%)		
Lymph node size [<i>n</i> (%)]			$\chi^2 = 0.635$	0.425
≥ 8 mm (<i>n</i> = 109)	74 (67.89%)	35 (32.11%)		
< 8 mm (<i>n</i> = 22)	13 (59.09%)	9 (40.91%)		
TgAb [<i>n</i> (%)]			$\chi^2 = 0.240$	0.624
+	26 (63.41%)	15 (36.59%)		
- (<i>n</i> = 90)	61 (67.78%)	29 (32.22%)		
FNA-Tg (ng/mL)	704.72 ± 412.43	0.58 ± 1.00	$Z = -9.489$	< 0.001
sTg (ng/mL)	56.03 ± 147.29	21.36 ± 30.36	$Z = -0.203$	0.839
Lymph node size (mm)	14.30 ± 7.40	12.70 ± 5.90	$Z = -0.993$	0.321

TgAb: Thyroglobulin antibody; FNA-Tg: The measurement of thyroglobulin (Tg) in the washout of the needle used to perform the fine needle aspiration cytology; sTg: Serum thyroglobulin.

通过 ROC 曲线发现 FNA-Tg 最佳截断值为 5.88 ng/mL, AUC 为 0.990 (图 1)。以 FNA-Tg/sTg > 1、FNA-Tg > 1.00 ng/mL、FNA-Tg > 5.88 ng/mL 为阳性标准诊断 PTC 颈部淋巴结转移的 AUC 分别为: 0.869、0.926、0.983, 诊断的敏感性分别为 91.95%、98.85%、96.55%, 特异性分别为 81.82%、86.36%、100.00%, 准确度分别为 88.55%、94.66%、97.71%; 其中以 FNA-Tg > 5.88 ng/mL 为阳性标准时的诊断效能最高 ($P < 0.05$) (图 2, 表 2)。

表 3 显示, 87 个转移性淋巴结中 FNAC 正确诊断 75 个, 假阴性 12 个; 44 个非转移性淋巴结 FNAC 均正确诊断, 假阳性 0 个; 诊断颈部淋巴结转移的敏感性为 86.21%, 特异性 100.00%, 准确率 90.84%。

12 个 FNAC 诊断假阴性淋巴结中 3 个含囊性结构的淋巴结 FNA-Tg 均正确诊断, 另 9 个较小淋巴结 (< 8 mm) FNA-Tg 正确诊断 7 个, FNAC + FNA-Tg 诊断假阴性 2 个 (淋巴结分别为 6 mm、5 mm), 但 FNAC 正确诊断中有 1 例在 FNA-Tg 诊断中却为假阴性。以 FNA-Tg > 5.88 ng/mL 为阳性标准的 FNA-Tg 诊断颈部淋巴结转移效能优于 FNAC ($P = 0.005$); FNA-Tg + FNAC 的诊断敏感性为 97.70%, 特异性为 100%, 准确度为 98.47%; 两者联合诊断的敏感性、准确度最高并且优于单独应用 FNAC ($P = 0.001$), 但与 FNA-Tg 诊断效能差异无统计学意义 ($P = 0.317$) (表 3, 图 3)。

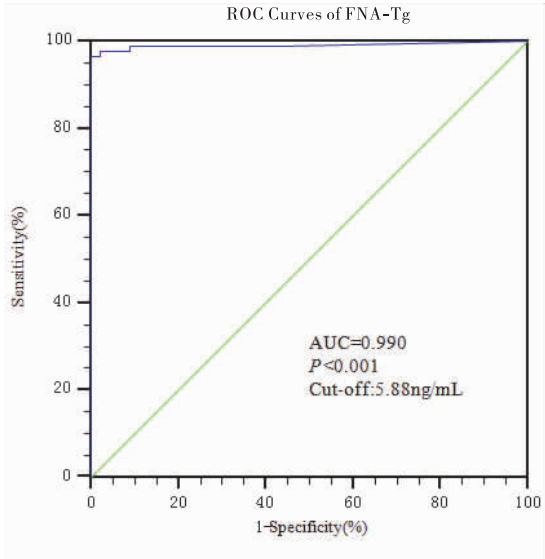


图 1 FNA-Tg 的 ROC 曲线

Figure 1. ROC Curve of FNA-Tg

The AUC of FNA-Tg was 0.990 ($P < 0.001$); the optimal cut-off value of FNA-Tg was 5.88 ng/mL. Abbreviations as indicated in Table 1.

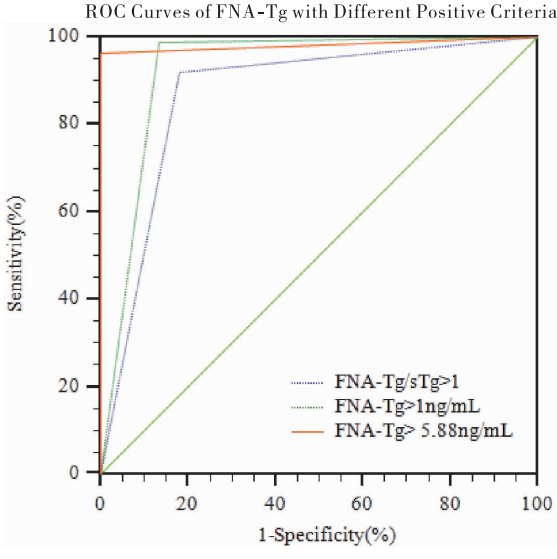


图 2 不同 FNA-Tg 阳性标准的 ROC 曲线

Figure 2. ROC Curves of FNA-Tg with Different Positive Criteria

With positive criteria of FNA-Tg/sTg > 1, FNA-Tg > 1 ng/mL and FNA-Tg > 5.88 ng/mL, AUC were 0.869, 0.926 and 0.983, respectively ($P < 0.001$). Abbreviations as indicated in Table 1.

表 2 不同 FNA-Tg 阳性标准的诊断效能 ($N = 131$)

Table 2. Diagnostic Efficacy of FNA-Tg with Different Positive Criteria ($N = 131$)

Positive criteria	TP	FP	FN	TN	Sensitivity	Specificity	Accuracy	AUC	Z	P
FNA-Tg/sTg > 1	80	8	7	36	91.95%	81.82%	88.55%	0.869	1.479	0.139 ^a
FNA-Tg > 1 ng/mL	86	6	1	38	98.85%	86.36%	94.66%	0.926	2.070	0.039 ^b
FNA-Tg > 5.88 ng/mL	84	0	3	44	96.55%	100.00%	97.71%	0.983	3.500	0.001 ^c

^a Compared with FNA-Tg > 1 ng/mL; ^b compared with FNA-Tg > 5.88 ng/mL; ^c compared with FNA-Tg/sTg > 1.

TP: True positive; FP: False positive; FN: False negative; TN: True negative; other abbreviations as indicated in Table 1.

表 3 不同检测方法的诊断效能 ($N = 131$)

Table 3. Diagnostic Efficacy of Different Detection Methods ($N = 131$)

Detection Method	TP	FP	FN	TN	Sensitivity	Specificity	Accuracy	AUC	Z	P
FNAC	75	0	12	44	86.21%	100.00%	90.84%	0.931	2.820	0.005 ^a
FNA-Tg	84	0	3	44	96.55%	100.00%	97.71%	0.983	1.000	0.317 ^b
FNAC + FNA-Tg	85	0	2	44	97.70%	100.00%	98.47%	0.989	3.342	0.001 ^c

The positive criterion of >5.88 ng/mL was adopted.

^a Compared with FNA-Tg; ^b compared with FNAC + FNA-Tg; ^c compared with FNAC.

Abbreviations as indicated in Table 2.

表 4 显示,淋巴结 ≥ 8 mm 与 < 8 mm 组间的 FNAC 诊断效能差异有统计学意义 ($\chi^2 = 7.972, P = 0.005$),而组间 FNA-Tg 的诊断效能差异并无统计

学意义 ($\chi^2 = 2.423, P = 0.120$); TgAb 阳性与阴性组间 FNAC、FNA-Tg 的诊断效能差异均无统计学意义 ($\chi^2 = 0.028, P = 0.862$; $\chi^2 = 0.306, P = 0.578$)。

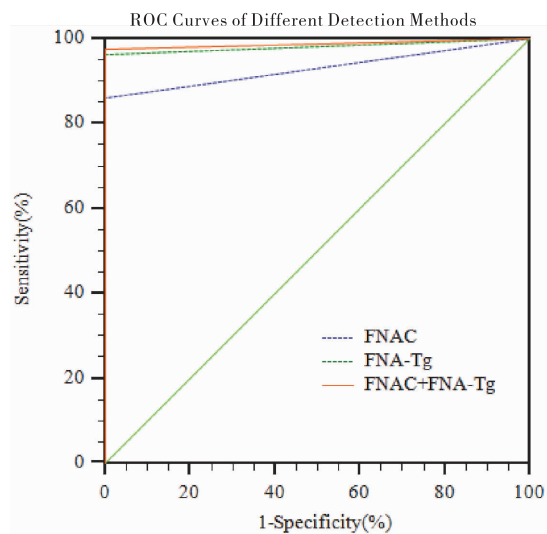


图3 不同诊断方法的 ROC 曲线

Figure 3. ROC Curves of Different Detection Methods

AUC of FNAC, FNA-Tg and FNAC + FNA-Tg were 0.931, 0.983 and 0.989, respectively.

Abbreviations as indicated in Table 1.

表4 淋巴结大小、TgAb 对 FNAC、FNA-Tg 诊断效能的影响

Table 4. Effects of Lymph Node Size and TgAb on Diagnostic Efficacy of FNAC and FNA-Tg

Variable	FNAC (n = 131)				FNA-Tg (n = 131)			
	Non-metastasis	Metastasis	χ^2	P	Non-metastasis	Metastasis	χ^2	P
TgAb			0.028	0.862			0.306	0.578
Positive								
Non-metastasis	15	0			15	0		
Metastasis	4	22			1	25		
Negative								
Non-metastasis	29	0			29	0		
Metastasis	8	53			2	59		
Lymph size			7.972	0.005			2.423	0.120
≥8 mm								
Non-metastasis	35	0			35	0		
Metastasis	6	68			1	73		
<8 mm								
Non-metastasis	9	0			9	0		
Metastasis	6	7			2	11		

The positive criterion of >5.88 ng/mL was adopted.

Abbreviations as indicated in Table 1.

3 讨论

甲状腺球蛋白 (thyroglobulin, Tg) 是甲状腺滤泡上皮细胞分泌的特异性大分子糖蛋白, 通常情况下, 与 T3、T4 结合储存于甲状腺滤泡腔内, 经溶酶体酶水解后, 释放出 T3、T4 的同时伴有少量 Tg 入血。因此在非甲状腺组织中 (如淋巴结) 检测到 Tg 可以间接证明其可能是甲状腺来源, 倾向转移。大量研究表

明, FNA-Tg 能提高 PTC 颈部淋巴结转移诊断敏感性、准确度, 并降低假阴性率^[12,18-21], 但目前 FNA-Tg 诊断 PTC 颈部淋巴结转移阳性截断值并无统一论。既往研究发现男性是 PTC 颈部淋巴结转移的危险因素^[22-23], 与之类似, 本研究中男性 PTC 出现淋巴结转移的比例高于女性 (78.72% vs 59.52%)。本研究参考 2015 年 ATA《成人甲状腺结节与分化型甲状腺癌诊治指南》等定义了三种不同的 FNA-Tg 阳性诊

断标准^[1,16-17]: FNA-Tg/sTg > 1、FNA-Tg > 1.00 ng/mL、FNA-Tg > 5.88 ng/mL, 结果显示以 FNA-Tg > 5.88 ng/mL 为阳性标准诊断 PTC 颈部淋巴结转移的效能优于另外两种, 敏感性、特异性、准确度分别为 96.55%、100.00%、97.71%。同时与以 FNA-Tg > 1.00 ng/mL 为阳性诊断标准的文献比较, 敏感性、特异性均较高^[12,18-21], 但由于不同的超声医师对穿刺目标淋巴结的选择、洗脱液的处理方式及不同化学发光仪器的影响, 此差异尚待进一步验证。

超声引导下 FNAC 检查是诊断 PTC 患者颈部淋巴结性质最常用也是最直接的方法, 敏感性、特异性较高但仍有一定的假阴性^[3,5,24]。我们发现淋巴结大小影响 FNAC 的诊断效能: FNAC 对 < 8 mm 的转移淋巴结诊断效能低于 ≥ 8 mm 淋巴结组, 而淋巴结大小对 FNA-Tg 诊断效能则没有影响。在 12 个 FNAC 诊断假阴性淋巴结中, 3 例含囊形结构淋巴结 FNA-Tg 均正确诊断, 9 例较小 (< 8 mm) 淋巴结 FNA-Tg 正确诊断 7 个。这可能是由于淋巴结较小或含有囊性结构时, FNAC 可能因采集不到足够的样本导致从细胞形态学上没能对淋巴结的性质进行准确鉴别, 而 FNA-Tg 检查是基于分子特征, 受淋巴结大小、是否有囊形结构的影响较小^[3,18,25-26]。与既往研究类似^[27-28], 我们发现以 > 5.88 ng/mL 为阳性标准的 FNA-Tg 诊断 PTC 颈部淋巴结转移的敏感性、准确度均高于 FNAC, 而且二者联合时的敏感性、特异性及准确度均为最高, 明显优于单独使用 FNAC。

血清 TgAb 是血清 Tg 的特异性抗体, TgAb 能影响 sTg 的测量^[29], 但目前对 FNA-Tg 测定的影响仍无定论^[19,30-33]。本研究中, TgAb 是否阳性对 FNAC、FNA-Tg 诊断 PTC 颈部转移淋巴结的诊断效能并没有影响, 这可能是由于 FNA-Tg 阳性标本中 Tg 的浓度过高使 TgAb 结合位点过饱和所致^[19,30]。

不过, 本研究尚有许多不足。首先本研究样本量较小, 我们并未深入讨论 FNA-Tg 假阴性的原因; 其次我们没有在方法学上、样本处理方面进行深入探讨; 第三, 作为回顾性研究, 某些 FNA-Tg 阴性的患者并未行对应淋巴结的清扫, 甚至某些穿刺淋巴结可能在术中难以准确定位, 这都可能会影响 FNA-Tg 诊断效能; 因此我们仍需前瞻性、大样本及标准化流程的研究来做进一步的验证。

总之, FNA-Tg 诊断 PTC 颈部淋巴结转移的敏感性、特异性、准确度较高, 并且受淋巴结的大小、是否有囊性结构影响较小; 而且该技术相对简单, 在能

行 FNAC 穿刺的单位均可使用; 当 FNAC 为阴性或结果难以判断时, 作为 FNAC 附属检测的 FNA-Tg 能为 PTC 颈部淋巴结转移的诊断提供重要信息。但 FNA-Tg 仍需标准化的样本处理流程和阳性判断标准, 以期能在未来为诊断 PTC 颈部淋巴结转移提供更准确的信息。

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