XXXX DOI:

甲状腺球蛋白在分化型甲状腺癌中的研究进展

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【摘 要】甲状腺癌是一种常见的内分泌系统恶性肿瘤,其中分化型甲状腺癌占绝大多数,因为甲状腺球蛋白仅由甲状腺滤泡上皮细胞合成,所以可以作为甲状腺切除术后监测疾病进展和诊断淋巴结转移的生物标志物。由于检测技术的限制,甲状腺球蛋白检测可能受到抗甲状腺球蛋白抗体等因素的干扰,影响其临床价值。本文主要探讨了不同标本来源的甲状腺球蛋白对于分化型甲状腺癌的临床意义,并分析了甲状腺球蛋白检测的干扰因素及存在的问题。

【关键词】甲状腺球蛋白;分化型甲状腺癌;淋巴结转移;监测
【中图分类号】R446.1 【文献标志码】A

Research advances in thyroglobulin in differentiated thyroid cancer

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【**Abstract**】Thyroid cancer is a common malignant tumor of the endocrine system, among which differentiated thyroid cancer accounts for the vast majority of cases. Since thyroglobulin is synthesized only by thyroid follicular epithelial cells, it can be used as a biomarker for monitoring disease progression and diagnosing lymph node metastasis after thyroidectomy for differentiated thyroid cancer. Due to the limitations of detection technology, the measurement of thyroglobulin may be interfered by the factors such as anti-thyroglobulin antibodies, thereby affecting its clinical value. This article mainly explores the clinical significance of thyroglobulin from different specimens in differentiated thyroid cancer and analyzes the interfering factors and existing problems in the measurement of thyroglobulin.

【**Key words**】thyroglobulin; differentiated thyroid cancer; lymph node metastasis; monitoring

我国是甲状腺癌的高发国,据统计,2022年我国甲状腺癌新发病例数约46.61万,占全球甲状腺癌新发病例数的56.76%;在我国全部恶性肿瘤新发病例中占9.66%,排名第3,相比之下全球甲状腺癌占比仅4.11%,我国年龄标准化率发病率也将近全球平均水平的3倍(男性:13.25 vs. 4.6,女性:36.51 vs. 13.6,单位:/10万),我国甲状腺癌发病率远高于全球平均水平;并且,我国甲状腺癌发病人数迅速增多,与2016年比较增加一倍多[1-3]。以上数据显示,甲状腺癌已成为我国重要的疾病之一,是我国的公共健康问题,对甲状腺癌的诊疗对于提高人民生活幸福感至关重要。

根据第5版世界卫生组织分类,甲状腺肿瘤分为滤泡上皮起源和非滤泡上皮起源,甲状腺滤泡上皮细胞起源的恶性肿瘤包括分化型甲状腺癌(differentiated thyroid carcinoma, DTC)等类别,DTC占甲状腺癌的90%以上[4]。DTC患者容易出现颈部淋巴结转移[5],有转移的患者更易复发、预后不佳[6]。

甲状腺球蛋白(thyroglobulin, Tg)是一种由甲状腺滤泡上皮细胞产生的大分子糖蛋白,具有合成甲状腺激素等生理功能。DTC细胞仍可产生甲状腺球蛋白,在甲状腺全部切除术后,一般仅有残留的甲状腺产生极少量甲状腺球蛋白,并且正常甲状腺几乎不可再生,因此通过监测血清中的甲状腺球蛋白水平能够诊断分化型甲状腺癌的复发或转移。同理,对于颈部淋巴结,如果检测到细针穿刺洗脱液甲状腺球蛋白(thyroglobulin in fine-needle aspirate washout, FNA-Tg),就表明有分化型甲状腺癌细胞转移至所穿刺的淋巴结中。依照我国甲状腺癌诊疗指南2022年版,DTC以外科手术治疗为主,术后在放射性碘治疗清除残余甲状腺组织后可通过检测血清Tg监测疾病进展,即使未进行放射性碘治疗的患者仍

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基金项目:国家自然科学基金委员会青年科学基金资助项目(编号:82202832);重庆市科卫联合医学科研资助项目(编号:2024MSXM105)。

推荐术后每6个月定期随访血清Tg，如呈持续升高趋势，可结合其他检查进一步评估[7]。DTC患者常通过细针穿刺细胞学（fine-needle aspiration cytology，FNAC）检查、超声、颈部增强CT等检查来诊断有无颈部淋巴结转移，也可通过FNA-Tg检测来诊断颈部淋巴结转移[8]。

因为检测技术的限制，Tg检测容易受到抗甲状腺球蛋白抗体（thyroglobulin antibody，TgAb）、嗜异性抗体等因素的干扰，从而使临床价值下降。有研究表明，影像学阳性而血清Tg检测阴性患者的标本中分别有23%和2%受到TgAb和嗜异性抗体的干扰[9]。通过改进检测方法可以在一定程度上避免干扰因素，也可采用与Tg相关的生物标志物作为替代。

因此，Tg的准确检测可以使DTC术后患者尽早地明确是否疾病进展，从而及时得到治疗，改善预后；还能使诊断颈部淋巴结转移，辅助确定手术范围，改善患者生活质量。本文主要探讨了不同标本来源的甲状腺球蛋白对于分化型甲状腺癌的临床意义，并分析了甲状腺球蛋白检测的干扰因素及存在的问题。

1 血清Tg

血清是检测Tg最常采用的标本来源，主要用于监测DTC术后的疾病进展，但无法定位病灶的具体位置，需结合影像检查进一步明确。

1.1 不同促甲状腺激素水平下检测Tg

由于促甲状腺激素可能使DTC进展，DTC患者在术后进行促甲状腺激素抑制治疗可以降低疾病进展风险[10]。根据患者复发风险的不同，通过服用左甲状腺素将促甲状腺激素抑制在2 mIU/L以下或更低水平；而由于促甲状腺激素会促进Tg分泌，DTC随访的血清Tg测定包括基础甲状腺球蛋白（basal thyroglobulin，b-Tg）和刺激性甲状腺球蛋白（stimulated thyroglobulin，s-Tg），b-Tg是在促甲状腺激素抑制治疗时进行检测，s-Tg是通过停用左甲状腺素或应用重组人促甲状腺激素使血清促甲状腺激素水平升高至>30 mIU/L时检测[7]。s-Tg的2种促甲状腺激素刺激方法对监测疾病进展同样有效[11-14]，但研究提示这2种方法得到的促甲状腺激素、s-Tg水平可能存在差异，需选取合适的阈值[15-19]，重组人促甲状腺激素刺激一般采用1 ng/mL[20-23]；停用左甲状腺素采用2 ng/mL[24-25]。

由于检测技术的限制，在以前b-Tg的阈值定为1 ng/mL，因为更低的水平在当时检测不到，s-Tg相比b-Tg对于监测疾病进展的敏感性更高[21-27]。随着检测技术的进步，高灵敏度Tg检测能更灵敏地检测低水平Tg，定量限<0.2 ng/mL的检测方法即为高灵敏度Tg检测[28]。当高灵敏度b-Tg检测不到时，s-Tg也往往低于1 ng/mL，很少发生疾病进展，s-Tg并不能提高诊断性能[29-31]；而高灵敏度b-Tg可检测到但低于1 ng/mL时，s-Tg对于疾病进展更敏感[20]。

由于DTC患者的整体复发率偏低，而s-Tg检测需要患者提前准备，不够便利、舒适，特别是对于低危患者，随访应当优先选择高灵敏度b-Tg监测。当高灵敏度b-Tg检测不到时，不需进一步检测；当高灵敏度b-Tg可检测但<1 ng/mL时，可进行s-Tg检测，如果s-Tg<2 ng/mL则不需重复s-Tg监测，仅常规随访高灵敏度b-Tg；而当高灵敏度b-Tg>1 ng/mL或s-Tg>2 ng/mL时，应当怀疑疾病进展，进一步完善影像学检查以确认。

1.2 血清Tg的临床意义

血清Tg主要用于DTC患者术后监测疾病进展。一般在全甲状腺切除术后1年内大多数患者的b-Tg会下降至1 ng/mL以下[32]。而在甲状腺切除和放射性碘治疗后的短期内，由于甲状腺组织的破坏释放Tg，会出现Tg的短暂升高然后恢复至基线水平[33]。全甲状腺切除术后但没有放射性碘治疗的患者采用Tg监测疾病进展的敏感性偏低，但仍有很好的阴性预测值[34]。甲状腺部分切除术后患者在各研究中Tg水平的变化、阈值不同[35-39]，难以通过Tg判断有无疾病进展。并且，通过Tg检测来诊断术后疾病进展也可能存在假阴性与假阳性，需要结合影像检查综合分析。Tg阳性而影像检查阴性时，Tg水平可能会逐渐下降而无疾病继续进展的表现[40-41]，这可能是因为即便在放射性碘治疗后，仍存在少部分残余的甲状腺组织在释放Tg. Tg阴性但影像检查阳性时也应警惕疾病进展，假阴性可能是因为病灶过小[42]，也可能因为肿瘤去分化等因素。

Tg与影像检查不匹配时如何进行临床决策仍待进一步研究。碘131全身显像是一种利用碘131特异性检查甲状腺组织的影像检查，Tg阳性而碘131全身显像阴性时，被称为TENIS综合征（thyroglobulin elevation and negative iodine scintigraphy syndrome，TENIS sysdrome）。这种现象可能是由于诊断性碘131全身显像所用碘剂量不够，而采用更大剂量的治疗性碘131全身显像进行检查则大多为阳性[43]；也可能是因为检查前促甲状腺激素升高不足等原因造成的碘摄取能力下降。TENIS综合征患者利用18F-FDG PET/CT检查可使40%的患者治疗方案发生变化，且准确性高[44]，Tg水平与PET/CT阳性率正相关[45]。对于TENIS综合征患者，也可直接进行放射性碘治疗，治疗后大多数患者的Tg下降[46-47]。但部分研究显示未放射性碘治疗患者Tg可能自行下降或与治疗组的差异无统计学意义[48-51]。

Tg并非DTC的特异性标志物，不能完全反映DTC的疾病进展，并且存在正常甲状腺组织、其他甲状腺疾病的干扰，使得Tg在DTC的术前诊断、甲状腺部分切除术后的随访监测方面临床价值有限。目前已有DTC相关的多组学、多模态研究，但主要应用于术前诊断和预测预后，未来还应注重治疗后监测随访的方向。

2 血清以外来源的Tg

2.1 FNA-Tg

2.1.1 FNA-Tg的检测流程 FNA-Tg一般是对甲状腺癌患者在超声引导下对有可疑超声表现的淋巴结行细针穿刺活检，采用针头冲洗液（囊性结节可直接使用穿刺液）检测Tg，以诊断有无淋巴结转移。除了颈部淋巴结转移外，FNA-Tg

还可用于诊断肺部转移[52]，当DTC患者出现可疑肺转移时对肺结节进行FNA-Tg检测以辅助诊断。

有关FNA-Tg检测的具体流程尚未标准化[53]，一般采用1 mL生理盐水对针头进行冲洗[54]，但所用基质类型与体积对于检测结果的具体影响尚未明确。研究显示穿刺洗脱液加入不同采血管中会得到不同的FNA-Tg结果[55]，因此盛装容器应选用不含抗凝剂的红帽管或离心管。为了取得足够的样本以供FNAC检查，术者会对淋巴结进行来回穿刺，研究显示对同一淋巴结不同位置多次穿刺并不会提高FNA-Tg水平[56]。

2.1.2 FNA-Tg的临床价值 FNAC可能因所取标本过少或未穿刺到恶性部位而结果为良性或可疑，FNA-Tg可用于辅助诊断FNAC无法确定的淋巴结转移，从而为DTC患者在术前决定手术范围、在术后监测转移等方面提供价值。研究显示当淋巴结在超声下有囊性、液化、钙化、最大直径小等特征时，FNAC诊断性能下降而FNA-Tg依然可诊断[57-59]。FNAC联合FNA-Tg相对于单独一项检查可以提高诊断性能，但两者联合时仍与粗针穿刺活检的诊断性能差异无统计学意义[60-61]。不过FNA创伤更小，仅当FNAC不能明确诊断、可疑淋巴结最大直径>1.5 cm等情况时才推荐粗针穿刺[8]。

诊断有无淋巴结转移的FNA-Tg阈值尚未有明确标准，各研究计算最大曲线下面积时得到的阈值不同。荟萃分析显示：当以1 ng/mL为准时，敏感性好；FNA-Tg相比血清Tg的比值>1为准时，特异性好[62]。

2.1.3 术中FNA-Tg检测 甲状腺癌患者一般在术前进行细针穿刺以检查有无颈部淋巴结转移，从而决定手术范围是否清扫颈部淋巴结。在术中分离出淋巴结进行FNA-Tg检测[63-65]，可以避免术前的细针穿刺，也便于术者在术中判断有无淋巴结转移，但缺乏超声引导，只能靠术者肉眼判断来选取可疑的淋巴结检测FNA-Tg，依赖于术者的经验。

术中检测需要更快的检测速度，否则可能延长手术时间，可以尝试使用胶体金、电化学传感器等快速检测方法。胶体金免疫层析测定是将一定量的穿刺洗脱液加入胶体金检测卡的加样孔中，经过一定时间后利用仪器读取检测区条带显色的强度得出定量的Tg结果。胶体金免疫层析测定法与电化学发光免疫测定法相比最大曲线下面积差异无统计学意义[66]，胶体金法存在显色强度可能随时间发生变化的问题，但研究显示检测3、10、15 min时采用对应时间的阈值对诊断性能无明显影响[67]。电化学传感器利用抗体捕获所需检测的Tg，将电化学信号放大来进行检测，检测灵敏度高[68-69]。

但需要注意FNA-Tg仅对DTC患者颈部淋巴结转移有诊断价值，若术中冰冻病理检查提示非DTC则不应作为诊断依据。此外，术前超声引导下穿刺的淋巴结要在术中精确定位十分困难，不能保证在术后病理报告与所穿刺淋巴结的一致性，而术中进行穿刺可以确定该淋巴结，能为患者提供更准确的诊断，还能将FNA-Tg与术后病理结果对应起来，有助于确定FNA-Tg的阈值。

2.2 *尿外泌体Tg*

有研究提出对甲状腺癌患者检测尿外泌体Tg，这是无创的检测方法，提示了尿外泌体Tg与肿瘤分期或术前淋巴结转移相关，在术后尿外泌体Tg下降[70]。尽管观察到部分患者术后尿外泌体Tg升高，但没有发现复发[71]，未能揭示其随访意义，仍待进一步研究。

3 Tg检测干扰因素

由于检测技术的限制，Tg检测容易受到TgAb、嗜异性抗体等物质的干扰，不同方法间也会存在检测水平的差异。

3.1 TgAb干扰

TgAb是一种自身抗体，DTC患者术后血清TgAb的阳性率在20%~29%[72-74]，在1年内TgAb水平一般会显著下降[75]，术前已是TgAb阳性的患者在术后更有可能长期TgAb阳性[76-78]。术后随访期间，即便之前TgAb阴性的患者也有可能TgAb转阳，因此推荐TgAb阴性患者仍在监测Tg时同时监测TgAb。

3.1.1 不同方法间TgAb干扰差异 临床应用于Tg检测的技术有放射免疫分析法（radioimmunoassay，RIA）、免疫测定法（immunoassay，IMA）和液相色谱串联质谱法（liquid chromatography-tandem mass spectrometry，LC-MS/MS）等，IMA包括免疫放射分析法、免疫化学发光分析法等。由于更高的灵敏度、自动化等优点，目前大多数实验室采用IMA进行检测。

用IMA法检测Tg时，TgAb会结合Tg从而阻断检测所用抗体所需结合的表位干扰检测。回收试验反映了干扰使所得结果偏低，可能导致假阴性[79]。不同患者TgAb对于Tg抗原表位识别的异质性不同，因此即便用针对不同表位的特异性单克隆抗体进行检测依然会被TgAb干扰[80-81]。采用单克隆抗体进行检测可能提高Tg回收试验的回收率，但Tg检测水平仍与采用多克隆抗体检测无明显差异[82]。所以IMA法受其检测原理限制，难以避免TgAb干扰。

LC-MS/MS是基于胰蛋白酶消化后的肽定量和Tg特异性肽的免疫捕获来测定Tg的方法，可以消除内源性自身抗体包括TgAb和嗜异性抗体等对检测的干扰。当TgAb阴性时，RIA、IMA与LC-MS/MS结果比较一致；而当TgAb阳性时，LC-MS/MS对Tg检测到的水平一般比IMA法高，而RIA法往往更高[83-86]。RIA法受TgAb干扰时根据TgAb浓度等因素不同可能出现假阳性与假阴性[87]。

虽然LC-MS/MS可以避免TgAb的干扰来准确检测Tg，但由于LC-MS/MS的检测灵敏度较低（定量限在0.5 ng/mL），对于TgAb阳性且Tg水平较低的样本，可检出率不如高灵敏度的IMA法，在43.7%的疾病进展患者中检测不到Tg[88]。有研究在LC-MS/MS基础上，通过改进检测方法，实现了0.02 ng/mL的定量限，能够在35%TgAb阳性且用IMA法检测不到（Tg<0.1 ng/mL）的样本中检测出定量的Tg水平，但这些患者在该研究的随访中并未发现疾病进展[87]。LC-MS/MS检测Tg能否有效识别疾病进展患者仍待验证。

3.1.2 FNA-Tg可能不受TgAb干扰 大部分研究显示FNA-Tg对淋巴结转移的诊断价值不会受血清TgAb的干

扰[57,67,89-93]，即使血清TgAb阳性时，FNA-Tg也足够敏感以发现淋巴结转移。然而少有研究检测穿刺洗脱液中的FNA-TgAb，虽然以血清TgAb的阈值来判断FNA-TgAb大多为阴性，但研究显示FNA-Tg与FNA-TgAb正相关[58,93-94]，淋巴结转移中FNA-TgAb比良性的更高[58,95]。FNA-TgAb的存在对于FNA-Tg的诊断价值无明显干扰可能是因为淋巴结转移患者的FNA-Tg水平足够高忽略了FNA-TgAb的干扰，也要考虑是否因为检测方法在FNA-Tg很高时出现FNA-TgAb假阳性的情况。有研究提示FNA-TgAb的存在可能会使FNA-Tg阈值提高[93]，伴有桥本甲状腺炎患者的FNA-Tg可能偏低[58,96]。FNA-Tg与FNA-TgAb的关系仍待进一步研究。

3.1.3 减轻TgAb干扰的改进措施与替代方法 通过改进检测方法可以在一定程度上避免TgAb的干扰。通过缓冲液处理血清标本破坏Tg-TgAb复合物释放Tg，能够在TgAb阳性时用IMA检测到更高水平的Tg[97]。利用筛选出的Tg不同表位的单克隆抗体对Tg进行检测可能减轻TgAb干扰[98]。采用多克隆抗体对Tg进行竞争性检测能够在IMA与LC-MS/MS检测不到Tg时识别疾病进展[99]。

即便通过改进检测技术能排除TgAb的体外干扰来更准确地检测Tg，然而对于部分有疾病进展且TgAb阳性的患者，IMA和LC-MS/MS均无法检测到Tg，可能是因为病灶去分化；也可能是因为TgAb加速Tg在体内代谢而使Tg浓度降低[100]，该机制曾通过标记Tg在兔子上验证[101]。TgAb结合Tg加速体内清除也许会使Tg水平难以真实反映体内产生Tg的情况，尚未有研究具体量化其效果。

作为替代，有研究显示可以将TgAb变化趋势作为替代标志物监测肿瘤的复发和转移[76]。还有研究尝试在TgAb阳性时，将Tg的mRNA水平作为替代标志物[102-103]，但其诊断性能可能不佳[104-105]。肿瘤细胞中mRNA剪接会产生异质性Tg，人Tg的mRNA有至少16种剪接，研究显示某一变异在DTC患者和良性人群中占Tg的mRNA总量的比例一样高[106]，Tg的mRNA检测可能不受mRNA剪接的干扰。

3.2 其他干扰因素

使用IMA检测时过高的Tg浓度会超出所用于检测的抗体的结合能力，造成假性低值，这种情况被称为钩状效应。在临床上，当DTC患者全身广泛转移时可能会出现此种情况[107]，将样本进行稀释后检测，可以得到正常结果。当患者病情严重而与低水平Tg结果不匹配时，需警惕钩状效应。

通过IMA方法检测Tg，有0.4%~2.9%的标本会被嗜异性抗体干扰[108-110]，结果可能出现假阳性与假阴性。换用采取另一种抗体进行检测的IMA法可能有效，或用LC-MS/MS进行检测[111]。RIA法也不易受嗜异性抗体干扰。

由于mRNA剪接产生的Tg分子变异，不同检测方法采用的检测抗体对相关表位的亲和力各不相同，TgAb的干扰效应也可能因检测而异，各检测方法所得结果会有差异。即使实验室参考国际标准CRM-457进行校准，在不同检测方法间有些方法之间的检测结果相关性好，但有的方法间结果差距较大[112-113]。患者术后随访期间推荐选择同一实验室用同一检测方法随访。

Tg检测也可能受外源性干扰，有病例显示输注免疫球蛋白可能导致TgAb和Tg检测水平短期升高，在1~2个月后会恢复至基线水平[114-115]。

Tg检测主要受到自身抗体TgAb的干扰，不光会在体外检测时造成妨碍，在体内也会加速Tg清除而影响其临床价值，因此Tg应与TgAb同时进行检测。当TgAb阳性时，根据检测方法评估Tg检测水平受到的影响，并结合超声、穿刺病理等检查综合判断。

4 总结与展望

DTC在我国发病率迅速提高，Tg检测能在术后监测、诊断淋巴结转移等方面提供价值。但目前仍存在一些难点，Tg与影像检查结果不匹配时临床决策收益不确定；FNA-Tg检测流程与诊断阈值尚未规范化；血清Tg检测容易受到TgAb干扰，需要既能准确检测又有足够敏感性以区分出疾病进展患者的检测方法或新的标志物，并且对于TgAb阳性患者体内代谢加速清除Tg的动力学研究有待探索。未来对Tg检测与应用的进一步研究对于DTC患者的治疗与预后至关重要。

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(收稿:2025-06-18;修回:2025-09-05;录用2025-09-24)

(责任编辑:李青颖)