动态监测 ^{131}I 治疗前刺激性 Tg 在 DTC 远处转移诊治中的增益效应

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摘　要:[目的]探讨动态监测 ^{131}I 治疗前刺激性甲状腺球蛋白(sTg)在伴有远处转移的分化型甲状腺癌(DTC)诊治中的意义。[方法]221 例甲状腺全切或次全切术后拟行 ^{131}I 治疗的 DTC 患者,根据是否存在远处转移分为 M_1 组(50 例)和 M_0 组(171 例)。动态监测 ^{131}I 治疗前 sTg 及相应促甲状腺激素(TSH)水平(首次测量值记为 Tg1、TSH1,末次记为 Tg2、TSH2)。分别计算 sTg 变化值(△Tg)及其变化速度(vTg)、Tg/TSH 变化值(△Tg')及其变化速度(vTg'),以及 sTg 随 TSH 变化比值(△Tg/△TSH)。将以上各 sTg 变化指标分别与 Tg1、Tg2 结合,建立 Logistic 回归方程,并用 ROC 曲线及最佳诊断界值点(DCP)评估各指标单独及联合应用在判断远处转移性 DTC 的价值。[结果]sTg 变化指标中,△Tg/△TSH 对远处转移性 DTC 的诊断更有价值,界值范围为-0.40~0.44ng/μIU,对应灵敏度、特异性、准确率分别为 90.00%、88.89%和 89.14%。△Tg/△TSH 结合 sTg 水平(Tg1 或 Tg2)联合判断 DTC 远处转移的 ROC 曲线下面积(AUC)可达 0.971,特异性 93.57%,准确率 92.31%,较两者单独应用时均有提高。[结论]^{131}I 治疗前动态监测 sTg 对伴有远处转移 DTC 的诊疗具有增益效应,sTg 随 TSH 变化比值(△Tg/△TSH)与 sTg 水平结合有助于提高 DTC 远处转移诊断的准确率和特异性,为 DTC ^{131}I 治疗前评估及治疗策略的制定提供依据。

主题词:分化型甲状腺癌;甲状腺球蛋白;^{131}I 治疗;诊断
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The Incremental Effect of Dynamically Tracing Pre-ablation Stimulated Thyroglobulin in the Diagnosis and Treatment for Distant Metastasis in Differentiated Thyroid Cancer

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Abstract: [Purpose] To investigate the value of dynamically tracing pre-ablation stimulated thyroglobulin (sTg) in the diagnosis and treatment for differentiated thyroid cancer (DTC) with distant metastasis. [Methods] The 221 cases with DTC undergoing total or subtotal thyroidectomy were divided into 2 groups: M_1 (n=50) and M_0 (n=171) according to the presence or absence of distant metastases. Pre-ablation sTg and the corresponding thyroid stimulating hormone(TSH) values were dynamically surveilled. The pre-ablation sTg and corresponding TSH collected at the first time were marked as Tg1 and TSH1, while as Tg2 and TSH2 at the last time. Variation indexes including pre-ablation sTg variation (ΔTg) and its velocity (vTg), Tg/TSH variation (ΔTg') and its velocity (vTg'), as well as ΔTg/ΔTSH ratio were calculated. Logistic regression equation was established based on the above variation indexes combining with Tg1 and Tg2, respectively. All of the indexes, independent or combined were compared by receiver operating characteristic (ROC) curves and diagnostic critical point (DCP) to evaluate their value in judging distant metastasis of DTC. [Results] Among all of the sTg variation indexes, ΔTg/ΔTSH, whose reference range was -0.40~0.44ng/μIU, worked best in judging distant metastasis of DTC with sensitivity of 90.00%, specificity of 88.89%, and accuracy of 89.14%. The area under the ROC curve of ΔTg/ΔTSH combining with either of pre-ablation sTg (Tg1 or Tg2) in judging distant metastasis was 0.971. This combination, compared with each of the independent indexes, helped improve the accuracy to 92.31% with a higher specificity (93.57%). [Conclusions] Dynamically tracing sTg before radioiodine therapy might offer more incremental effect to the diagnosis and treatment for distant

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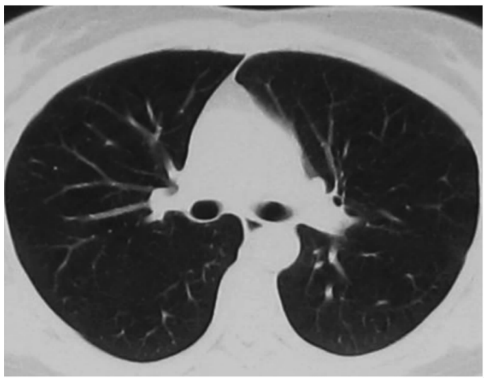
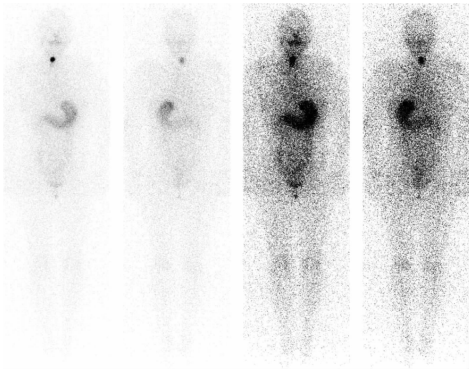
metastasis in DTC. Combining ΔTg/ΔTSH with either of pre-ablation sTg (Tg1 or Tg2) would be helpfull to improve the accuracy and specificity of judging distant metastasis in DTC patients as well as providing evidence for pre-ablative assessment and strategies of radioiodine treatment.
Subject words: differentiated thyroid cancer; thyroglobulin; radioiodine therapy; diagnosis

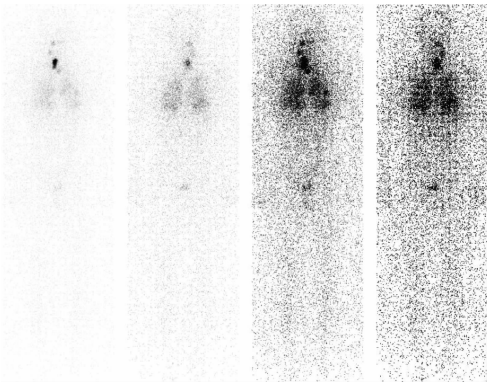
甲状腺癌是内分泌系统和头颈部最常见的恶性肿瘤,因其发病率近 30 年来持续快速增长引起广泛关注[1]。其中约 90%为分化型甲状腺癌(differentiated thyroid cancer,DTC),1%~23%的 DTC 患者在诊断时已发生远处转移(distant metastasis,DM)[2,3]。然而目前影像学手段对于微小隐匿性 DM 的检出仍存在一定局限性, 部分患者 ^{131}I 治疗前胸部 CT 甚至 ^{131}I 诊断性全身显像 (diagnostic whole-body scintigraphy, DxWBS)均未能及时发现远处转移灶,仅在进行治疗后全身显像 (post treatment whole-body scintigraphy, RxWBS) 甚至 2-氟-2-脱氧-D-葡萄糖(^{18}F-FDG)正电子发射断层成像(PET)时才被正确判断(Figure 1),因此良好的血清学指标对于 DTC 远处转移的早期识别具有重要意义。甲状腺球蛋白(thyroglobulin,Tg)已作为 DTC ^{131}I 治疗后长期随访的重要指标被广泛应用, 但 ^{131}I 治疗前刺激性甲状腺球蛋白(stimulated thyroglobulin,sTg)在 DTC 诊断和治疗中的价值尚存争议[4]。目前研究主要侧重于 ^{131}I 治疗前单次静止sTg 对于 DTC 缓解、复发或远处转移的预测价值[5~8],鲜有报道关注其动态变化在病情评估及治疗决策中的意义。本课题组近期一项研究显示,动态监测 ^{131}I 治疗前 sTg 并计算其随 TSH 变化的比值(△Tg/△TSH)较单次 sTg 测量值在 DTC 远处转移的诊断上可获更高的准确性和特异性。本文旨在分析 ^{131}I 治疗前 sTg 动态变化相关参数,以期寻找提高 DTC 远处转移诊断效能的最佳指标。



A: Chest CT with no nodule in lung before radioiodine therapy



B: DxWBS showed no abnormal uptake in lung



C: RxWBS showed diffused bilateral pulmonary uptake (pulmonary metastasis) except thyroid bed

Figure 1 Female, 40 years old, differentiated thyroid carcinoma

1 资料与方法

1.1 一般资料

2012 年 3 月至 2014 年 8 月在北京协和医院就诊且病理检查确诊为 DTC 的术后 (全切或次全切)患者 221 例,其中男性 80 例,女性 141 例,年龄 12~68 岁。根据是否存在远处转移分为远处转移组 M_1

(50 例,其中男性 21 例,女性 29 例;平均年龄 41.7±13.2 岁)和非远处转移组 M_0(171 例,其中男性 59 例,女性 112 例;平均年龄 40.8±11.7 岁)。

1.2 检查方法

治疗前常规检查包括胸部 CT、颈部超声,^{131}I 治疗前血清 sTg [术后未服或停服甲状腺激素后 TSH 升高(>30μIU/ml)状态下测定的血清 Tg 水平]、TSH 及甲状腺球蛋白抗体 (thyroglobulin antibody,TgAb) 水平,部分患者根据病情评估需要考虑进行 DxWBS 检查。所有患者 ^{131}I 治疗准备均参照 ATA 指南[4],并于治疗后 5~8d 进行 RxWBS 检查。远处转移的确定根据 CT、DxWBS 或 RxWBS 结合病理检查综合判断。患者 ^{131}I 治疗前血清 sTg 及相应 TSH、TgAb 首次测量值分别记为 Tg1、TSH1、TgAb1,末次(通常为治疗当天服碘前检测)记为 Tg2、TSH2、TgAb2。TSH 测定采用化学发光免疫分析法(德国拜耳公司,ADVIA CENTAVRXP),检测范围是 0.004~150μIU/ml。Tg 和 TgAb 测定采用电化学发光免疫分析法 (美国罗氏公司,E170),检测范围分别是 0.1~1 000ng/ml 和 10~4 000IU/ml。TSH 和 Tg 测量值超过其检测范围时分别记为>150μIU/ml 和>1 000ng/ml,TgAb 测量值高于其参考值范围上限(115IU/ml)者不纳入本研究。

1.3 统计学处理

应用 SPSS22.0 软件进行统计学分析。计算 sTg 变化值(ΔTg=Tg2−Tg1)、sTg 变化速度[vTg=(Tg2−Tg1)/t]、Tg/TSH 变化值(△Tg'=Tg2/TSH2−Tg1/TSH1)、Tg/TSH 变化速度 [vTg'=1000×(Tg2/TSH2−Tg1/TSH1)/t]及 sTg 随 TSH 变化比值 [△Tg/△TSH=(Tg2−Tg1)/(TSH2−TSH1)],并用 Mann-Whitney 秩和检验比较两组差异。采用 Logistic 回归模型将以上各 sTg 变化指标分别与 Tg1、Tg2 联合建立 Logistic 回归方程,并建立各指标单独及指标间联合应用判断 DTC 远处转移 ROC 曲线,获得最佳诊断界值点。比较各指标判断DTC 远处转移的灵敏度、特异性、准确率、阳性预测值 (positive predictive value,PPV) 和阴性预测值 (negative predictive value,NPV)。P<0.05 为差异有统计学意义。

2 结 果

2.1 sTg 变化指标与 DTC 远处转移的关系

M_0 组与 M_1 组间△Tg、vTg、△Tg/△TSH 差异均有统计学意义(P 均<0.01),△Tg'和 vTg'差异无统计学意义(Table 1)。根据△Tg、vTg、△Tg/△TSH 升高和降低两种情况分别做 ROC 曲线,△Tg、vTg、△Tg/△TSH>0(即 sTg 呈升高趋势)时 ROC 曲线下面积分别为 0.900(95%CI:0.842~0.959)、0.917(95%CI:0.866~0.968)和 0.914(95%CI:0.855~0.972),约登指数(灵敏度+特异性−1)最大值分别为 0.666、0.704、0.799,判断远处转移的最佳临界值分别为 7.75ng/ml、0.71ng/(ml·d)和 0.44ng/μIU;△Tg、vTg、△Tg/△TSH<0(即 sTg 呈降低趋势) 时 ROC 曲线下面积分别为 0.835 (95%CI:0.689~0.982)、0.860 (95%CI:0.723~0.996) 和 0.890 (95%CI:0.747~1.000),约登指数最大值分别为 0.622、0.653 和 0.765,对应的最佳诊断界值点分别为−10.50ng/ml、−0.60ng/(ml·d)和−0.40ng/μIU(Table 2)。其中,△Tg/△TSH 的 ROC 曲线下面积较大,且其以−0.40~0.44ng/μIU 为界值判断远处转移的约登指数最大,对应灵敏度、特异性、准确率最佳,分别为 90.00%、88.89%和 89.14%,阳性预测值、阴性预测值分别为 70.31%和 96.82%,提示 sTg 变化指标中△Tg/△TSH 对远处转移性 DTC 的诊断更有价值。

2.2 sTg 变化指标联合 ^{131}I 治疗前 sTg 水平对 DTC 远处转移的判断

M_1 组 ^{131}I 治疗前 sTg 测量值(Tg1 和 Tg2)显著高于 M_0 组(P 均<0.001)(Table 1)。Tg1、Tg2 与远处

Table 1 Serological characteristics and their changes of the 221 cases with DTC

Parameters	Median (25%~75% quartile)		U	P
	M_0 (n=171)	M_1 (n=50)		
Tg1(ng/ml)	4.40(2.30~9.90)	110.20(42.25~377.90)	534.0	< 0.001
Tg2(ng/ml)	5.20(2.80~14.00)	143.55(45.30~457.55)	396.0	< 0.001
△Tg(ng/ml)	0.50(0.00~2.70)	11.80(−0.23~86.95)	2603.5	< 0.001
vTg[ng/(ml·d)]	0.080(0.000~0.238)	2.336(−0.035~10.002)	2537.5	< 0.001
△Tg'(ng/μIU)	−0.005(−0.030~0.003)	−0.081(−1.841~0.189)	3755.5	0.191
vTg'[ng/(μIU·d)]	−0.685(−4.445~0.341)	−12.281(−185.258~21.340)	3734.0	0.174
△Tg/△TSH(ng/μIU)	0.024(−0.001~0.120)	1.178(0.011~3.886)	2400.5	< 0.001

转移关系的 ROC 曲线下面积分别为 0.938(95%CI：0.896~0.979)和 0.954(95%CI：0.927~0.980)(Figure 2)，约登指数最大值分别为 0.767 和 0.800，对应的最佳诊断界值点分别为 12.35ng/ml 和 24.45ng/ml，诊断远处转移性 DTC 的灵敏度较高，分别为 96.00%和 94.00%，但特异性、准确性均低于△Tg/△TSH (Table 2)。

进一步将 sTg 变化指标(△Tg、vTg 及△Tg/△TSH)与 ^{131}I 治疗前 sTg 水平(Tg1 和 Tg2)联合建立 Logistic 回归方程及计算其 ROC 曲线下面积(Table 3)。其中，△Tg/△TSH 与 ^{131}I 治疗前 sTg 水平(Tg1 或 Tg2)联合应用判断远处转移性 DTC 的回归方程 ROC 曲线下面积最大，均为 0.971，最佳诊断界值点分别为 0.370 和 0.386，约登指数分别为 0.816 和 0.822。通过上述回归方程计算：当△Tg/△TSH 在 −0.40~0.44ng/μIU 界值范围内时，Tg1、Tg2 诊断远处转移的界值分别为 128.73ng/ml 和 128.13ng/ml；当△Tg/△TSH 超出−0.40~0.44ng/μIU 界值范围时，Tg1、Tg2 诊断远处转移的界值分别为 12.44ng/ml 和 25.51ng/ml。应用此联合诊断方法对研究纳入的 221 例患者重新进行分析，结果显示，△Tg/△TSH 与 ^{131}I 治疗前 sTg 水平(Tg1 或 Tg2)联合应用诊断远处转移性 DTC 的特异性、准确率较两者单独应用时明显提高，分别达 93.57%和 92.31%，阳性预测值、阴性预测值分别为 80.00%和 96.39%(Table 2)。提示△Tg/△TSH 与 ^{131}I 治疗前 sTg 水平(Tg1 或 Tg2)联合应用有助于提高 DTC 远处转移的诊断效能。

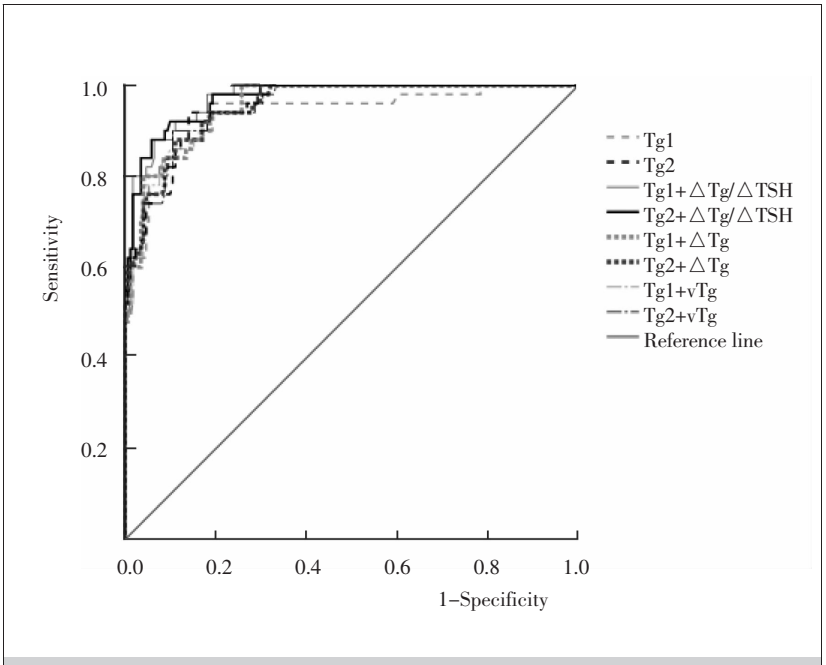


Figure 2 The ROC curves of each parameter regarding to sTg change combining with a single sTg measured at different time before radioiodine therapy in identifying distant metastatic DTC

Table 2 Serological characteristics and their changes before radioiodine therapy in identifying distant metastatic DTC

Parameters	Cut-off	TP	FP	TN	FN	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
Tg1	12.35ng/ml	48	33	138	2	96.00	80.70	84.16(186/221)	59.26	98.57
Tg2	24.45ng/ml	47	24	147	3	94.00	85.96	87.78(194/221)	66.20	98.00
△Tg	−10.50~7.75ng/ml	40	25	146	10	80.00	85.38	84.16(186/221)	61.54	93.59
vTg	−0.60~0.71ng/(ml·d)	43	29	142	7	86.00	83.04	83.71(185/221)	59.72	95.30
△Tg/△TSH	−0.40~0.44ng/μIU	45	19	152	5	90.00	88.89	89.14(197/221)	70.31	96.82
△Tg/△TSH and Tg1	When ΔTg/ΔTSH is in the range of −0.40~0.44ng/μIU, Tg1>128.73ng/ml; When ΔTg/ΔTSH is out of the range of −0.40~0.44ng/μIU, Tg1>12.44ng/ml	44	11	160	6	88.00	93.57	92.31(204/221)	80.00	96.39
△Tg/△TSH and Tg2	When ΔTg/ΔTSH is in the range of −0.40~0.44ng/μIU, Tg2>128.13ng/ml; When ΔTg/ΔTSH is out of the range of −0.40~0.44ng/μIU, Tg2>25.51ng/ml	44	11	160	6	88.00	93.57	92.31(204/221)	80.00	96.39

Table 3 Logistic regression equation and the corresponding ROC curves of parameters regarding to sTg changes combining with a single sTg measured at different time before radioiodine therapy in identifying distant metastatic DTC

Parameters	Parameters or regression equation	AUC	Standard error	*P*	95%CI
Tg1	Tg1	0.938	0.021	<0.001	0.896~0.979
Tg2	Tg2	0.954	0.013	<0.001	0.927~0.980
Tg1+△Tg/△TSH	$P=1/[1+e^{-(-0.868+0.027Tg1-3.140\triangle Tg/\triangle TSH)}]$	0.971	0.010	<0.001	0.952~0.990
Tg2+△Tg/△TSH	$P=1/[1+e^{-(-1.204+0.029Tg2-2.976\triangle Tg/\triangle TSH)}]$	0.971	0.010	<0.001	0.951~0.991
Tg1+△Tg	$P=1/[1+e^{-(-1.547+0.032Tg1-1.902\triangle Tg)}]$	0.956	0.013	<0.001	0.931~0.981
Tg2+△Tg	$P=1/[1+e^{-(-2.064+0.033Tg2-1.447\triangle Tg)}]$	0.954	0.014	<0.001	0.927~0.980
Tg1+vTg	$P=1/[1+e^{-(-1.457+0.028Tg1-2.119vTg)}]$	0.956	0.013	<0.001	0.931~0.981
Tg2+vTg	$P=1/[1+e^{-(-1.897+0.029Tg2-1.730vTg)}]$	0.953	0.014	<0.001	0.926~0.980

3 讨 论

Tg 已成为 DTC 患者术后及 ^{131}I 治疗后监测肿瘤残留或复发的重要手段[9]，对于 ^{131}I 治疗前 sTg，由于易受术后残余甲状腺组织的影响，一些研究者认为其在病情评估和治疗决策中的意义仍存在争议[10~12]。Ciappuccini 等[6]的研究发现停服甲状腺激素后 sTg>28ng/ml 或人重组 TSH 下 sTg>2.8ng/ml 时对判断疾病复发或持续状态有一定价值。本课题组亦有前期研究表明术后 ^{131}I 治疗前 sTg 异常升高对 DTC 远处转移有重要预测价值[8]。但上述研究主要侧重于 ^{131}I 治疗前单次静止 sTg 测量值与 DTC 缓解、复发或远处转移的关系[5-8]，有关 sTg 随 TSH 的动态变化及其在 DTC^{131}I 治疗前评估和决策中的意义鲜有报道。

本研究首次通过动态监测 DTC 患者 ^{131}I 治疗前 sTg，发现 ^{131}I 治疗前 sTg 变化值(△Tg)、sTg 变化速度(vTg)及 sTg 随 TSH 变化比值(△Tg/△TSH)对远处转移性 DTC 均有一定诊断价值。其中，以△Tg/△TSH 为 sTg 变化指标诊断远处转移性 DTC 时灵敏度、特异性和准确率最佳。笔者认为由于 TSH 是正常甲状腺或 DTC 细胞产生和释放 Tg 最重要的刺激因子[13-15]，△Tg/△TSH 校正了 TSH 水平对 sTg 的影响，因而该指标一定程度上能够较为真实地反映肿瘤负荷，对于远处转移性 DTC 具有较为稳定的诊断价值。△Tg/△TSH 在用于 DTC 远处转移的诊断时可分为两种情况：①当△Tg/△TSH>0(sTg 随 TSH 升高而升高)时，M_1 组△Tg/△TSH 较高，提示这部分患者的远处转移灶受 TSH 升高刺激时产生 Tg 较不伴远处转移者增多；②当△Tg/△TSH<0(sTg 随 TSH 升高而降低或 sTg 随 TSH 降低而升高) 时，M1 组△Tg/△TSH 绝对值较 M_0 组大，推测可能与远处转移灶随停药产生大量内源性甲状腺激素反馈抑制 TSH 使其下降或肿瘤负荷过大造成的 Tg 下降与 TSH 上升不平衡有关。

采用单一诊断指标对疾病作出判断时，提高灵敏度必然会降低特异性，即减少漏诊必然增加误诊，反之亦然。本研究结果中，尽管△Tg/△TSH 在诊断远处转移性 DTC 方面灵敏度、特异性、准确率均较高，分别为 90.00%、88.89%和 89.14%，但假阳性率仍达 11.11%。因此本研究进一步将各 sTg 变化指标(△Tg、vTg 和△Tg/△TSH) 分别与 ^{131}I 治疗前不同时间 sTg 测量值(Tg1、Tg2)联合，结果显示△Tg/△TSH 与 ^{131}I 治疗前 sTg 水平 (Tg1 或 Tg2) 联合应用判断 DTC 远处转移时诊断效能最佳，特异性及准确率均较两者单独应用时进一步提高，分别达 93.57%和 92.31%，且将假阳性率降低到了 6.43%，减少了过度治疗的风险，提示这种联合诊断对于临床上远处转移性 DTC 的正确诊断(特别是减少误诊)以及治疗策略的合理制定具有增益效应。

综上，本研究通过动态观察 ^{131}I 治疗前 sTg 变化，计算并比较了几种 sTg 变化指标与 sTg 水平联合判断 DTC 远处转移的诊断效能。结果显示，△Tg/△TSH 与 ^{131}I 治疗前 sTg(首次或末次测量值)联合应用有助于提高判断 DTC 远处转移的特异性和准确率，可在 ^{131}I 治疗前为远处转移性 DTC 的诊断及治疗策略的合理制定提供良好依据。

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