甲状腺球蛋白抗体对甲状腺乳头状癌^{131}I清甲疗效的影响

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［摘要］ **背景与目的：**甲状腺球蛋白抗体(thyroglobulin antibody，TgAb)在甲状腺乳头状癌(papillary thyroid carcinoma，PTC)中较为常见。该研究旨在探讨PTC患者术后TgAb对^{131}I清甲疗效的影响。**方法：**纳入329例非远处转移性PTC患者，根据^{131}I清甲前TgAb水平分为G1组(大于115 U/mL，*n*=84)和G2组(<115 U/mL，*n*=245)，G2组再以40 U/mL为界分为S1(大于40 U/mL，*n*=31)和S2(小于40 U/mL，*n*=214)两个亚组，中位随访时间24个月，比较两组患者清甲疗效并分析其影响因素，观察^{131}I清甲剂量对患者疗效的影响。**结果：**G1组女性居多，年龄更小(*P*=0.000，*P*=0.004)，其余临床病理基线资料差异均无统计学意义(*P*均>0.05)。G1组清甲成功率为35.7%，G2组为72.7%，差异有统计学意义(*P*=0.000)；S1和S2两个亚组清甲成功率分别为54.8%和75.2%，差异有统计学意义(*P*=0.017)；G1组高、低剂量^{131}I清甲后成功率分别为34.1%、37.2%，与G2组的71.9%、73.2%差异均有统计学意义(*P*均=0.000)；G1组与G2组内分别采用低剂量^{131}I与高剂量^{131}I清甲的成功率差异均无统计学意义(*P*均>0.05)。多因素分析显示，清甲疗效仅与清甲前TgAb值有关(*P*=0.018)。**结论：**TgAb可以影响PTC患者的^{131}I清甲疗效，TgAb越高者清甲疗效越差。增加^{131}I治疗剂量未能进一步提高患者的清甲成功率。

［关键词］ 甲状腺乳头状癌；甲状腺球蛋白抗体；^{131}I清甲；疗效

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The impact of thyroglobulin antibody on efficacy of ^{131}I ablation in patients with papillary thyroid carcinoma

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［**Abstract**］ **Background and purpose:** Thyroglobulin antibody (TgAb) is often positive in papillary thyroid carcinoma (PTC) patients. This study aimed to investigate the effect of TgAb on radioiodine ablation efficacy in PTC patients. **Methods:** A total number of 329 PTC patients with no distant metastasis were included and classified into 2 groups ［G1 group (>115 U/mL，*n*=84) and G2 group (<115 U/mL, *n*=245)］, G2 group was further divided into 2 subgroups ［S1 (>40 U/mL, *n*=31) and S2 (<40 U/mL, *n*=214)］, before ^{131}I ablation. The median follow-up time was 24 months after a total or subtotal thyroidectomy and subsequent ^{131}I ablation. The efficacy in terms of ^{131}I ablation success rates (IBR) between two groups were compared and the influencing factors were analyzed according to criteria posed by 2015 American Thyroid Association Guidelines, then the effect of ^{131}I dose on IBR was also explored. **Results:** Female and younger age were more prevalent in patients with high TgAb (*P*<0.05). The G1 group presented lower IBR over the G2 group (35.7% *vs* 72.7%, *P*=0.000). Moreover, S1 group also presented lower IBR over S2 group (54.8% *vs* 75.2%, *P*=0.017), indicating the adverse effect from high titer TgAb on IBR. No matter high or low dose, the G1 group presented lower IBR (34.1% *vs* 71.9%, 37.2% *vs* 73.2%; *P*=0.000). However, IBR did not differ in G1 or G2 group

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either with high or low dose ^{131}I (P>0.05). TgAb was the only adverse indicator correlating with IBR in multi-logistic regression analysis (P=0.018). **Conclusion:** TgAb could negatively affect ^{131}I ablation efficacy, while increasing the dose of ^{131}I failed to improve the success rate in such cases.

［**Key words**］ Papillary thyroid carcinoma; Thyroglobulin antibody; ^{131}I ablation; Efficacy

目前中高危甲状腺乳头状癌(papillary thyroid carcinoma，PTC)患者一线治疗方案主要包括甲状腺全切或次全切除术、选择性^{131}I治疗及促甲状腺激素(thyroid stimulating hormone，TSH)抑制治疗。25%～30%的PTC患者的甲状腺球蛋白抗体(thyroglobulin antibody，TgAb)呈阳性[1-2]，TgAb是针对血清甲状腺球蛋白(thyroglobulin，Tg)产生的抑制性自身免疫抗体，高滴度TgAb干扰了Tg检测，影响Tg作为肿瘤标志物在患者随访过程中的作用[3-4]。因此，有关高TgAb水平患者的治疗及随访一直是临床工作中的难题。目前研究主要侧重于TgAb是否可以预测PTC发生与复发以及其对Tg检测的影响[5-8]，有关TgAb与PTC患者^{131}I清甲疗效间的关系尚不清楚。本研究旨在探讨TgAb对PTC患者^{131}I清甲疗效的影响并分析其可能影响因素。

1 资料和方法

1.1 对象及分组

2012年1月—2016年1月在中国医学科学院北京协和医院就诊的经病理证实的PTC患者329例，其中男性103例，女性226例，平均年龄(39.2±11.2)岁(13～69岁)。所有患者均接受甲状腺全切或次全切除术、术后行^{131}I清甲及TSH抑制治疗，经^{131}I清甲前评估无远处转移，具有术后、^{131}I清甲前TgAb测定值，治疗后规律随访，均具备^{131}I全身显像或其他影像学检查结果及血清学检查结果，中位随访时间24个月(13~40个月)。依据TgAb检测的正常参考值上限115 U/mL，将^{131}I治疗前患者分为G1组(大于115 U/mL，n=84)和G2组(小于115 U/mL，n=245)，G2组再以40 U/mL为界值分为S1(大于40 U/mL，n=31)和S2(小于40 U/mL，n=214)两个亚组[6]。

1.2 方法

所有患者^{131}I清甲准备和方案均参照2015年美国甲状腺协会(American Thyroid Association，ATA)发布的《成人甲状腺结节与分化型甲状腺癌诊治指南》及《中国^{131}I治疗分化型甲状腺癌指南(2014年)》[9-10]。^{131}I清甲前评估采用血清学检查(包括Tg、TgAb检测)、影像学检查(包括^{131}I全身显像、胸部高分辨CT、颈部超声、全身骨显像、PET/CT)及病理活检(证实无远处转移病灶)。^{131}I清甲前通过综合评估术后病理及治疗前检查，给予不同剂量的^{131}I清甲治疗(本研究定义30 mCi为低剂量，100～150 mCi为高剂量)。Tg和TgAb的测定采用E170电化学发光免疫分析法［购自罗氏诊断产品(上海)有限公司］，检测范围分别是0.04～500 ng/mL和10~4 000 U/mL。TgAb正常范围上限是115 U/mL。Tg、TgAb的测定值若超过其测定范围则分别记作500 ng/mL、4 000 U/mL。所有患者于^{131}I清甲后3 d开始口服甲状腺激素(L-T4)，治疗后7 d行全身显像，半年左右停服L-T4，待TSH大于30 mU/L时测定Tg水平，行诊断性全身显像(3 mCi，静态扫描，16 cm/min)，并定期复查Tg、TgAb、胸部高分辨CT及颈部超声。

将患者^{131}I清甲疗效分为成功与未成功2类，根据《成人甲状腺结节与分化型甲状腺癌诊治指南》，符合以下条件视为清甲成功：① 清甲后随访半年以上诊断性全身显像甲状腺床未见放射性浓聚影；② 其他影像学检查无复发或转移发现。

1.3 统计学处理

采用SPSS 22.0统计软件，采用t检验、χ^2检验及Mann-Whitney U检验比较两组间的年龄、性别、癌灶大小、多灶性、被膜侵犯及TNM分期，采用χ^2检验比较两组^{131}I清甲后的疗效，

采用多元线性回归分析性别、年龄、清甲前后TgAb、^{131}I清甲距手术的时间、^{131}I剂量与^{131}I清甲疗效的关系，P<0.05为差异有统计学意义。

2 结　果

2.1 一般情况

两组患者的年龄、性别差异有统计学意义(P=0.004、P=0.000)，G1组女性(85.7%)明显多于G2组(62.9%)，且年龄较G2组更小［(36.2±11.7) *vs* (40.2±10.8)］，其余临床病理基线资料(癌灶大小、多灶性、被膜侵犯及TNM分期)差异均无统计学意义(P均>0.05，表1)。

2.2 清甲疗效

G1组清甲成功率为35.7%，G2组为72.7%，差异有统计学意义(P=0.000)；S1和S2两个亚组清甲成功率分别为54.8%和75.2%，差异有统计学意义(P=0.017)；G1组高、低剂量^{131}I治疗成功率为34.1%、37.2%，与G2组的71.9%、73.2%差异均有统计学意义(P均=0.000)。两组低剂量^{131}I与高剂量^{131}I清甲的成功率差异均无统计学意义(P均>0.05，表2)。

2.3 ^{131}I清甲疗效的影响因素

多元线性回归结果显示，^{131}I清甲疗效与清甲前TgAb值有关(P=0.018)，与年龄(P=0.694)、性别(P=0.097)、^{131}I剂量(P=0.524)、^{131}I清甲距手术的时间(P=0.685)及清甲后TgAb值(P=0.201)无关(表3)。

表 1　两组患者临床病理特征比较

Tab. 1　Comparison of clinicopathologic features between two groups

[*n* (%)]

Clinicopathologic features	G1 group (N=84)	G2 group (N=245)	P value
Gender			0.000 (χ^2=15.196)
Male	12 (14.3)	91 (37.1)	
Female	72 (85.7)	154 (62.9)	
Age/year ($\bar{x}\pm s$)	36.2±11.7	40.2±10.8	0.004 (F=0.490)
Tumor size d/cm	1.2 (0.6-1.9)	1.0 (0.6-1.6)	0.172 (U=9 264.50)
Multifocality			0.481 (χ^2=0.497)
Yes	50 (59.5)	135 (55.1)	
No	34 (40.5)	110 (44.9)	
Extracapsular invasion			0.185 (χ^2=1.755)
Yes	41 (48.8)	140 (57.1)	
No	43 (51.2)	105 (42.9)	
TNM stage			0.391 (χ^2=3.003)
Ⅰ	62 (73.8)	158 (64.5)	
Ⅱ	1 (1.2)	2 (0.8)	
Ⅲ	10 (11.9)	36 (14.7)	
Ⅳ	11 (13.1)	49 (20.0)	

表 2 两组患者^{131}I清甲疗效比较

Tab. 2 Comparison of ^{131}I ablation efficacy between two groups

[*n* (%)]

Group	^{131}I ablation efficacy		*P* value
	Success	Failure	
G1 group (*n*=84)	30 (35.7)	54 (64.3)	0.000 (χ^2=36.708)
G2 group (*n*=245)	178 (72.7)	67 (27.3)	
S1 (*n*=31)	17 (54.8)	14 (45.2)	0.017 (χ^2=5.669)
S2 (*n*=214)	161 (75.2)	53 (24.8)	
Low dose (*n*=192)			0.000 (χ^2=18.978)
G1 group	16 (37.2)	27 (62.8)	
G2 group	109 (73.2)	40 (26.8)	
High dose (*n*=137)			0.000 (χ^2=17.126)
G1 group	14 (34.1)	27 (65.9)	
G2 group	69 (71.9)	27 (28.1)	
G1 group (*n*=84)			0.770 (χ^2=0.086)
Low dose	16 (37.2)	27 (62.8)	
High dose	14 (34.1)	27 (65.9)	
G2 group (*n*=245)			0.826 (χ^2=0.048)
Low dose	109 (73.2)	40 (26.8)	
High does	69 (71.9)	27 (28.1)	

表 3 多元线性回归分析结果

Tab. 3 Results of multiple linear regression analysis

Factor	*B*	*SE*	*Wald*	*Df*	*Sig*	*Exp* (*B*)
TgAb before ablation	-0.001	0.001	5.612	1	0.018	0.999
TgAb after ablation	0.001	0.001	1.632	1	0.201	1.001
Gender	-0.434	0.261	2.762	1	0.097	0.648
Age	0.004	0.011	0.155	1	0.694	1.004
^{131}I dose	-0.001	0.002	0.407	1	0.524	0.999
Interval between surgery and ^{131}I ablation	0.001	0.003	0.164	1	0.685	1.001

B: Partial regression coefficient; *SE*: Standard error; *Wald*: Chi-square values; *df*: Degree of freedom; *Sig*: Significance; *Exp* (*B*): Odds ratio

3 讨 论

TgAb是针对Tg产生的抑制性自身抗体，主要来源于甲状腺内淋巴细胞，多存在于甲状腺自身免疫性疾病患者体内，是机体免疫功能紊乱的标志，与PTC有关的主要是IgG1、IgG3及IgG4[11]。有研究发现，桥本甲状腺炎(Hashimoto thyroiditis，HT)可以增加PTC的发生概率[12]，而TgAb作为HT等自身免疫性甲状腺疾病(autoimmune thyroid diseases，ATID)的特征性指标，出现在约51%的HT患者中[13]，但TgAb与PTC之间的关系仍有争议[5-6]。Kim等[14]研究发现，在TgAb阳性的PTC患者中，肿瘤复发的概率显著增加(18% *vs* 1%，*P*<0.001)；Seo等[15]报告了TgAb高于140 U/mL的PTC患者与低于此滴度的患者相比，肿瘤复

发率显著增加。此外，有研究发现，甲状腺切除术后不久检测到TgAb的患者，在长期随访期间具有较高的疾病持续或复发风险，且TgAb水平越高，风险越高[16-17]。上述研究均是从疾病复发的角度阐述了TgAb与PTC的关系，未涉及TgAb与清甲成功率的关系。

PTC患者的清甲是利用^{131}I清除术后残留的甲状腺组织，其疗效有赖于^{131}I进入残留的甲状腺组织的剂量，这一过程由位于甲状腺细胞基底膜的钠碘同向转运体(sodium iodide symporter，NIS)介导。有研究发现，HT患者的NIS表达水平下降，并且在ATID中发现了可以抑制NIS表达的自身抗体，而TgAb与ATID的出现呈正相关；此外，有学者报告了Tg可以作为NIS表达的抑制剂，TgAb是针对Tg产生的抗体，因此，由于上述机制，高TgAb患者其NIS表达水平可出现下降[18-19]，这是否会影响^{131}I清甲治疗的疗效尚不清楚。本研究发现，G1组患者的清甲成功率仅为35.7%，显著低于G2组(72.7%)，将G2组以40 U/mL为界再分为两个亚组，结果显示，大于此值的患者清甲成功率亦低于小于此值的患者，提示高滴度TgAb的PTC患者^{131}I清甲疗效下降，并且TgAb水平越高清甲疗效越差，推测主要是由于高TgAb者其NIS水平下降，进一步降低了其清甲疗效。为了进一步统一基线，我们分别比较了两组患者经低剂量^{131}I与高剂量^{131}I清甲的疗效，结果显示，G1组的清甲成功率均低于G2组。有文献报道，在碘摄入过量的地区TgAb阳性率增高[20-21]；高TgAb水平与甲状腺内淋巴细胞浸润有关[22]，由此进一步推测，高TgAb水平患者体内碘负荷较高或淋巴浸润的环境，也有可能会造成其清甲成功率降低。此外，本研究发现，G1组女性(85.7%)明显多于G2组(62.9%)，且患者年龄较G2组更小，与文献报道的一致，提示高TgAb水平更易出现在年轻女性中[23]。另有学者发现，HT合并PTC也常见于女性患者[5,12]，这可能预示着女性PTC患者较男性具有更高的疾病危险性。

此外，为进一步观察清甲疗效的影响因素，我们采用Logistic回归分析，在纳入的性别、年龄、清甲前后TgAb、^{131}I 剂量及^{131}I清甲距手术的时间等因素中，发现只有清甲前TgAb水平对清甲疗效有影响，其偏回归系数为负值，意味着^{131}I清甲前TgAb水平越高，清甲疗效越差。有学者发现，残留的甲状腺组织越少，清甲疗效越好[24]，但由于目前如何正确进行残留的甲状腺组织质量估算仍无明确的方法，常用的甲状腺B超、核素平面和断层显像对残留的甲状腺组织质量估算的准确性均有待进一步研究，故本研究未将残留的甲状腺组织质量列入观察影响因素中。

本研究发现， G1与G2组分别经低剂量^{131}I与高剂量^{131}I清甲后的成功率差异均无统计学意义，提示增加^{131}I清甲的剂量不能提高其清甲成功率，Hackshaw等[25]的研究亦认为小剂量(30 mCi)的^{131}I清甲疗效不比大剂量(100 mCi)差，这可能与甲状腺基底膜上的NIS有关。当NIS达到饱和状态的时候，即使加大^{131}I 清甲治疗剂量也不能增加甲状腺组织的摄碘率，因而清甲疗效未见提高。

综上所述，TgAb可以影响^{131}I清甲疗效，TgAb越高者清甲疗效越差，但是增加^{131}I清甲的剂量未能进一步提高其清甲成功率。对于治疗前高TgAb水平的PTC患者，可以通过降低其TgAb水平来提高清甲疗效。

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