pN_{1a}甲状腺乳头状癌中央区淋巴结清扫数与临床转归的关系

赵 腾[1,2]，高 文[3]，梁 军[4]，李 欣[1]，林岩松[1]

1. 中国医学科学院，北京协和医学院，北京协和医院核医学科，北京 100730；
2. 首都医科大学附属北京世纪坛医院耳鼻咽喉头颈外科，北京 100038；
3. 青岛大学附属医院肿瘤科，山东 青岛 266003；
4. 北京大学肿瘤医院肿瘤内科，北京 100142

［摘要］ **背景与目的：**甲状腺乳头状癌(papillary thyroid carcinoma，PTC)常发生颈部淋巴结转移，多见于颈部中央区。该研究旨在探讨转移淋巴结数小于等于5枚的pN_{1a} PTC患者颈部中央区淋巴结清扫数与^{131}I“清甲”治疗后临床转归的关系。**方法：**回顾性分析2012年2月—2014年12月北京协和医院收治的167例经术后病理证实存在1～5枚淋巴结转移的pN_{1a} PTC患者的临床资料，均行全甲状腺切除或近全甲状腺切除联合中央区淋巴结清扫术。经过^{131}I“清甲”治疗后中位随访26个月，将患者的临床转归根据美国甲状腺协会(American Thyroid Association，ATA)2015年发布的《成人甲状腺结节与分化型甲状腺癌诊治指南》分为：满意(excellent response，ER)、不确切(indeterminate response，IDR)、血清学反应欠佳(biochemical incomplete response，BIR)和影像学反应欠佳(structural incomplete response，SIR)。计算不同淋巴结清扫数对应的累计ER率(以ER_n表示，n为淋巴结清扫数，ER_n为清扫数小于等于n枚淋巴结后达到ER的患者数占清扫数小于等于n枚淋巴结的总人数的百分比)，分析中央区淋巴结清扫数与ER_n的关系。**结果：**随着中央区淋巴结清扫数增多，ER_n总体呈上升趋势，ER_1、ER_5、ER_{10}和ER_{30}分别为25.0%、66.7%、74.7%和79.1%，且n由1至10时ER_n升高明显。n大于等于10的患者的满意率高于n小于10的患者，差异有统计学意义(85.7% *vs* 73.3%，P=0.05)。多因素Logistic回归分析显示，中央区淋巴结清扫数大于等于10枚(OR=2.720，95%CI：1.052~7.033，P=0.039)、^{131}I治疗前刺激性甲状腺球蛋白(stimulated thyroglobulin，sTg)水平(OR=0.955，95%CI：0.926~0.984，P=0.003)是影响ER的独立预后因素。**结论：**随着中央区淋巴结清扫数的增多，pN_{1a} PTC患者^{131}I“清甲”治疗后更易达到ER；对于淋巴结转移数小于等于5枚的pN_{1a} PTC患者，中央区淋巴结清扫数大于等于10枚有助于其^{131}I“清甲”治疗后达到ER。

［关键词］ 甲状腺乳头状癌；颈淋巴结清扫术；临床转归；淋巴结转移

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The relationship between the number of dissected central lymph nodes and clinical outcome in pN_{1a} papillary thyroid carcinoma

ZHAO Teng[1,2], GAO Wen[3], LIANG Jun[4], LI Xin[1], LIN Yansong[1]
(1. Department of Nuclear Medicine, PUMC Hospital, CAMS and PUMC, Beijing 100730, China; 2. Department of Otorhinolaryngology Head and Neck Surgery, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China; 3. Department of Oncology, the Affiliated Hospital of Qingdao University, Qingdao 266000, Shandong Province, China; 4. Department of Oncology, Peking University Cancer Hospital & Institute, Beijing 100142, China)
Correspondence to: LIN Yansong E-mail: linys@pumch.cn

［**Abstract**］ **Background and purpose:** Neck lymph node metastasis, most of which presents in central neck compartment, is common in patients with papillary thyroid carcinoma (PTC). The objective of this study was to investigate the relationship between the number of dissected central neck lymph nodes and clinical outcome after radioactive iodine (RAI) ablation in pN_{1a} PTC with no more than 5 lymph nodes involvement. **Methods:** A total of 167 PTC patients who had

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通信作者：林岩松　E-mail: linys@pumch.cn

1–5 proven metastatic lymph nodes according to postoperative pathological diagnosis were retrospectively analyzed, all of whom underwent total or near total thyroidectomy and central lymph node dissection. After a median follow–up period of 26 months, the clinical outcome of each patient was evaluated as excellent response (ER), indeterminate response (IDR), biochemical incomplete response (BIR), or structural incomplete response (SIR) according to the new American Thyroid Association guidelines. The accumulative ER rate (ER_n) was calculated in patients with different numbers of dissected lymph nodes (ER_n was defined as the proportion of patients who achieved ER with the dissected lymph node number of $\leqslant n$). The relationship between the number of dissected central neck lymph nodes and ER_n were investigated. **Results:** As the increase in the number of dissected central neck lymph nodes, there was also an overall increase in ER_n, especially when n rose from 1 to 10. The values of ER_1, ER_5, ER_{10} and ER_{30} were 25.0%, 66.7%, 74.7% and 79.1%, respectively. Besides, the proportion of patients who achieved ER was higher in those with 10 or more dissected lymph nodes than in those with less than 10 (85.7% *vs* 73.3%, P=0.05). In the multivariate logistic regression analysis, both the dissected central lymph node number of $\geqslant$10 (OR=2.720, 95%CI: 1.052–7.033, P=0.039) and the level of preablation stimulated thyroglobulin (OR=0.955, 95%CI: 0.926–0.984, P=0.003) were shown to contribute independently to ER. **Conclusion:** As the increasing number of dissected central neck lymph nodes, the percentage of pN_{1a} PTC patients that achieved ER after RAI ablation generally rises. In pN_{1a} PTC patients with no more than 5 lymph nodes involvement, a central compartment dissection with 10 or more lymph nodes might help them achieve ER after RAI ablation.

［**Key words**］ Papillary thyroid carcinoma; Neck lymph node dissection; Clinical outcome; Lymph node metastasis

甲状腺乳头状癌(papillary thyroid carcinoma，PTC)是最常见的甲状腺恶性肿瘤，尽管其生长缓慢且较少发生远处转移，但20%~60%的患者确诊时即伴有颈部淋巴结转移[1-3]，且多见于颈部中央区。有研究显示，伴有淋巴结转移的PTC患者复发率高于不伴有淋巴结转移者[4]。随着体检及筛查意识的普及，许多PTC患者虽伴有淋巴结转移，但术后病理证实转移数较少(小于等于5枚)且仅局限于中央区(pN_{1a})。对于此类患者，中央区淋巴结清扫可使其有相对明确的获益。目前，关于淋巴结的研究主要侧重于位置、大小、数量和结外侵犯与疾病复发和无病生存期的关系[5-10]，本课题组近期研究发现，淋巴结转移率(转移淋巴结数/清扫淋巴结总数)大于52.3%的患者^{131}I“清甲”治疗后更易出现较差的临床转归[11]，该指标纳入了淋巴结清扫范围即“清扫数”这一变量，并通过分析转移淋巴结数小于等于5枚的pN_{1a} PTC患者中央区淋巴结清扫数与^{131}I“清甲”治疗后临床转归的关系，探讨此类患者的合适淋巴结清扫数。

1 资料和方法

1.1 一般资料

回顾性分析2012年2月—2014年12月于北京协和医院行手术及^{131}I“清甲”治疗的167例pN_{1a} PTC患者的临床资料。纳入标准：① 手术方式为全甲状腺切除或近全甲状腺切除+中央区淋巴结清扫术，术后行^{131}I治疗及促甲状腺激素(thyrotropin，TSH)抑制治疗；② 术后病理证实为PTC，且仅存在1~5枚中央区转移淋巴结；③ 手术及^{131}I“清甲”治疗时无颈侧区淋巴结转移或远处转移的证据。在167例伴有1~5个淋巴结转移的pN_{1a} PTC患者中，男性42例，女性125例，平均年龄(40.9±10.5)岁，其中63.5%为甲状腺微小乳头状癌(papillary thyroid microcarcinoma，PTMC)，即病灶直径小于等于1 cm。

1.2 ^{131}I“清甲”治疗

^{131}I治疗准备和方案制定均参照美国甲状腺协会(American Thyroid Association，ATA)2015年发布的《成人甲状腺结节与分化型甲状腺癌诊治指南》(简称《2015版指南》)[12]，^{131}I治疗前

常规检测术后未服或停服甲状腺激素致TSH升高(大于30 mU/L)状态下的血清刺激性甲状腺球蛋白(stimulated thyroglobulin，sTg)及相应甲状腺球蛋白抗体(thyroglobulin antibody，TgAb)水平。^{131}I治疗剂量为1.1～5.5 GBq (30～150 mCi)。治疗后规律随访。

1.3 临床转归分析方法

根据ATA《2015版指南》，将^{131}I“清甲”治疗后患者的临床转归依据血清学证据(Tg、TgAb)和影像学证据(颈部超声、^{131}I全身显像、胸部CT、必要时加做全身骨显像及PET/CT等检查)分为：满意(excellent response，ER)、不确切(indeterminate response，IDR)、血清学反应欠佳(biochemical incomplete response，BIR)和影像学反应欠佳(structural incomplete response，SIR) 4类[12]。分别针对不同颈部中央区淋巴结清扫数计算累计ER率以ER_n表示，其中n为淋巴结清扫数，公式为：ER_n=清扫≤n枚淋巴结后达到ER的患者人数/清扫≤n枚淋巴结的患者总数。观察n与ER_n的关系。根据淋巴结清扫数以5、10和15为界进行分组，比较小于5组与大于等于5组、小于10组与大于等于10组、小于15组与大于等于15组3种分组形式中ER率的差异。进一步分析ER与年龄、性别、T分期、中央区淋巴结转移数、中央区淋巴结清扫数、^{131}I治疗前sTg及^{131}I治疗剂量之间的关系。

1.4 统计学处理

应用SPSS 22.0软件进行数据分析。不同组间ER率比较采用χ^2检验，采用Logistic回归模型进行ER影响因素的多因素分析。P<0.05为差异有统计学意义。

2 结 果

167例转移淋巴结数小于等于5枚的pN_{1a} PTC患者均手术顺利，未发生永久性甲状旁腺损伤或喉返神经损伤。^{131}I“清甲”治疗后中位随访26个月(14～40个月)，临床转归达到ER、IDR、BIR和SIR者分别占79.0%、13.8%、3.6%和3.6%。

2.1 中央区淋巴结清扫数与临床转归的关系

随着中央区淋巴结清扫数的不断增多，ER_n总体呈上升趋势，ER_1、ER_5、ER_{10}和ER_{30}分别为25.0%(1/4)、66.7%(32/48)、74.7%(74/99)和79.1%(129/163)，其中以n由1提高至10时上升趋势更显著(图1)。

分别以5、10、15为界按中央区淋巴结清扫数将患者各分为2组，即小于5组与大于等于5组、小于10组与大于等于10组、小于15组与大于等于15组，其中大于等于5组ER率高于小于5组，差异有统计学意义(83.6% *vs* 60.6%，χ^2=8.44，P=0.004)；大于等于10组ER率高于小于10组，差异有统计学意义(85.7% *vs* 73.3%，χ^2=3.84，P=0.05)；而大于等于15组ER率仅略高于小于15组，差异无统计学意义(82.9% *vs* 78.0%，χ^2=0.39，P=0.533)。

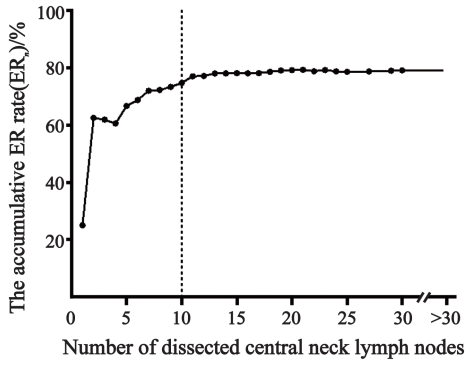

图 1 pN_{1a} PTC中央区淋巴结清扫数与累计ER率的关系

Fig. 1 The relationship between the number of dissected central lymph nodes and the accumulative ER rate in pN_{1a} PTC

2.2 临床转归满意率影响因素分析

单因素分析结果显示，T分期pT_1、pT_3或pT_4、淋巴结清扫数大于等于10枚、^{131}I治疗前sTg水平小于5 ng/mL及接受低剂量^{131}I治疗者ER率更高(表1)。多因素分析结果显示，仅中央区淋巴结清扫数大于等于10枚和^{131}I治疗前sTg水平是ER的独立预后因素(表2)。

表 1 PTC临床转归满意的相关临床病理特征单因素分析结果

Tab. 1 Univariate analysis for the clinicopathologic characteristics associated with excellent response in patients with PTC

Characteristics	Rate of excellent response	χ^2	*P* value
Age/year		0.026	0.872
< 45	78.6%(81/103)		
≥45	79.7%(51/64)		
Gender		2.776	0.096
Male	88.1%(37/42)		
Female	76.0%(95/125)		
T stage		11.762	0.006
pT_1	83.0%(73/88)		
pT_2	25.0%(2/8)		
pT_3	81.3%(39/48)		
pT_4	78.3%(18/23)		
No. of metastatic lymph nodes		2.676	0.613
1	81.5%(44/54)		
2	82.1%(32/39)		
3	81.6%(31/38)		
4	71.4%(15/21)		
5	66.7%(10/15)		
No. of dissected lymph nodes		3.840	0.050
< 10	73.3%(66/90)		
≥10	85.7%(66/77)		
Coexisting with Hashimoto's thyroiditis			
Yes	81.0% (34/42)	0.124	0.725
No	78.4% (98/125)		
Level of preablative stimulated thyroglobulin ρ_B/ng·mL^{-1}		18.353	0.000
< 5	86.6%(110/127)		
≥5	55.0%(22/40)		
Dose of radioiodine ablation *D*/mCi		12.413	0.000
30	84.4%(114/135)		
150	56.3%(18/32)		

表 2 PTC临床转归满意的相关临床病理特征多因素分析结果

Tab. 2 Multivariate analysis for the clinicopathologic characteristics associated with excellent response in patients with PTC

Characteristics	β	SE	Wald	OR (95%CI)	*P* value
Age	0.074	0.467	0.025	1.077(0.431–2.688)	0.874
Gender	–0.743	0.573	1.681	0.476(0.155–1.462)	0.195
T stage	–0.025	0.199	0.015	0.976(0.661–1.440)	0.901
Number of metastatic lymph nodes	–0.082	0.180	0.209	0.921(0.647–1.311)	0.648
Number of dissected lymph nodes≥10	1.001	0.485	4.265	2.720(1.052–7.033)	0.039
Coexisting with Hashimoto's thyroiditis	–0.042	0.525	0.006	0.959(0.343–2.684)	0.936
Level of preablative stimulated thyroglobulin	–0.046	0.016	8.799	0.955(0.926–0.984)	0.003
Dose of radioiodine ablation	–0.705	0.549	1.650	0.494(0.169–1.448)	0.199

3 讨 论

PTC常伴有颈部淋巴结转移，由于中央区淋巴结易受累及，ATA发布的《2015版指南》建议对伴有临床发现的中央区淋巴结转移者，临床颈部淋巴结转移阴性(cN_0)的T_{3-4}期患者，以及伴有临床发现的颈侧区淋巴结转移者，均应考虑行中央区淋巴结清扫[12]，但目前尚无指南对合适的淋巴结清扫数作出明确推荐。在其他肿瘤治疗中已有充分的证据提示淋巴结清扫数与患者的临床转归密切相关，目前美国国家综合癌症网络(National Comprehensive Cancer Network，NCCN)发布的指南推荐将淋巴结清扫数小于12枚作为Ⅱ期结肠癌的高危因素；淋巴结清扫数大于等于15枚可使Ⅱ、$Ⅲ_a$和$Ⅲ_b$期胃癌患者存活率明显提高[13]。目前，临床多认为pN_{1a} PTC患者死亡风险较低，ATA《2015版指南》甚至将淋巴结转移数小于等于5枚的pN_1患者(最大径小于0.2 cm)划分为低危复发风险组[12]。但这一评估标准未充分考虑淋巴结清扫范围的影响。

本研究纳入淋巴结转移数小于等于5枚的pN_{1a} PTC患者，发现其中63.5%为PTMC，提示PTMC的局部侵袭性亦不容忽视。随访观察发现，即便是对于中央区淋巴结转移数小于等于5枚的pN_{1a} PTC患者，经过规范的手术、^{131}I“清甲”治疗后中位26个月的时间，临床转归达到ER者仅占79.0%，且随淋巴结清扫数由1至10，ER_n可由25.0%提高至74.7%，这提示ATA《2015版指南》仅以淋巴结转移数小于等于5枚作为低危复发风险分层的依据尚显不足，而更应在考虑转移数的同时兼顾清扫范围即“清扫数”等因素。随着中央区淋巴结清扫数从1到10不断增加，患者更易达到ER，这说明充分的中央区淋巴结清扫在一定程度上有助于改善患者的临床转归。为了进一步探索淋巴结清扫数的合适界值范围，进一步比较淋巴结清扫数小于5组与大于等于5组、小于10组与大于等于10组、小于15组与大于等于15组3种情况ER率的差异，发现大于等于5组ER率显著高于小于5组，说明仅评估1~5个中央区淋巴结可能相对不足；以10为界时，大于等于10组ER率高于小于10组(P=0.05)，但两组间差异缩小，而以15为界时，两组间差异无统计学意义，提示中央区淋巴结清扫数大于等于10枚在判断ER方面可能是一个较好的临界点，清扫数大于等于10枚时因手术清扫相对更充分，更有利于对伴有少量淋巴结转移的pN_{1a}患者进行评估；反之，中央区淋巴结清扫数小于10时，可能因部分患者术后仍存在微小淋巴结转移灶，导致其后续经过^{131}I“清甲”治疗后临床转归仍不满意。

针对pN_{1a} PTC临床转归的影响因素分析结果显示，中央区淋巴结清扫数大于等于10个及^{131}I治疗前sTg水平均为ER的独立预后因素。因此，对于淋巴结转移数小于等于5枚的pN_{1a} PTC患者，清扫大于等于10枚中央区淋巴结有助于对颈部淋巴结的充分评估并改善患者预后；^{131}I治疗前sTg低水平亦有助于预测较好的临床转归，这与文献报道的结果基本一致[14-15]。而对于这些患者，是否达到ER与具体的淋巴结转移数(小于等于5枚时)无相关性，提示对于中央区淋巴结转移数小于等于5枚的pN_{1a} PTC患者，相较于淋巴结转移数更应关注其清扫范围对临床转归的影响。此外，在单因素分析中，T分期pT_1、pT_3或pT_4，接受低剂量^{131}I治疗者ER率更高，笔者认为这与pT_2病例数较少、接受高剂量^{131}I治疗者本身具备更多的与不良预后相关的临床病理特征有关。多因素分析结果显示，应用低剂量^{131}I“清甲”治疗即可能达到与高剂量治疗后相似的临床转归，这与以往研究的结果一致[16-18]。

综上所述，随着中央区淋巴结清扫数的增加，pN_{1a} PTC患者经^{131}I“清甲”治疗后更易达到满意的临床转归；对于淋巴结转移数小于等于5枚的pN_{1a} PTC患者，常规清扫大于等于10枚中央区淋巴结有助于其^{131}I“清甲”治疗后达到更好的临床转归。

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