

doi: 10.13241/j.cnki.pmb.2018.10.036

甲状腺微小乳头状癌发生隐匿性颈部淋巴结转移的危险因素分析*

蒋倩楠¹ 王 斐^{1Δ} 王 萍¹ 赵 慧² 迟静薇³ 赵世华¹

(1 青岛大学附属医院内分泌与代谢病科 山东 青岛 266555; 2 青岛市海慈医院内分泌科 山东 青岛 266033;

3 青岛大学附属医院甲状腺重点实验室 山东 青岛 266555)

摘要 目的:分析甲状腺微小乳头状癌(PTMC)发生隐匿性颈部淋巴结转移的危险因素。**方法:**收集2013-2017年于青岛大学附属医院确诊的PTMC患者共1524例,按其术前、术后是否有颈部淋巴结转移分为显性淋巴结转移、隐匿性淋巴结转移及无淋巴结转移三组,比较各组之间的临床病理特征,包括性别(男性)、年龄、肿瘤大小、双叶、多灶、侵犯包膜、合并桥本病、术前TSH水平等是否具有差异性。**结果:**单因素分析结果显示:与无淋巴结转移患者相比,隐匿性淋巴结转移组男性患者比例、年龄、肿瘤大小、肿瘤累及双叶、多灶比例均有统计学差异($P<0.05$),其中隐匿性淋巴结转移组中的发病年龄较低($P<0.05$),合并桥本病的比率无显著差异($P>0.05$);与显性淋巴结转移相比,隐匿性淋巴结转移肿瘤大小、合并多灶及合并病理桥本病的转移率较后者低($P<0.05$)。多因素分析表明以无淋巴结转移的患者为对照组,男性患者、年龄、大小、多灶为隐匿性淋巴结转移的危险因素(OR值分别为0.525, 1.033, 0.169, 0.562);与隐匿性淋巴结转移相比,合并桥本病的患者发生显性颈部淋巴结转移的风险更高,而发病年龄较前者大(OR值分别为0.370, 0.979)。**结论:**男性、肿瘤累及双叶、多灶者为PTMC早期淋巴结转移的危险因素,合并桥本病者发生显性颈部淋巴结转移的风险更高;但没有发现桥本病与隐匿性颈部淋巴结转移存在相关性。

关键词: 甲状腺微小乳头状癌; 颈部淋巴结转移; 危险因素**中图分类号:** R736.1 **文献标识码:** A **文章编号:** 1673-6273(2018)10-1977-05

Analysis of the Risk Factors of Occult Cervical Lymph Node Metastasis in Papillary Thyroid Microcarcinoma*

JIANG Qian-nan¹, WANG Fei^{1Δ}, WANG Ping¹, ZHAO Hu², CHI Jing-wei³, ZHAO Shi-hua¹

(1 The Affiliated Hospital of Qingdao University, Department of Endocrinology and Metabolism, Qingdao, Shandong, 266555, China;

2 Hiser medical center of Qingdao, Department of Endocrinology, Qingdao, Shandong, 266033, China;

3 The Affiliated Hospital of Qingdao University, Laboratory of thyroid, Qingdao, Shandong, 266555, China)

ABSTRACT Objective: To investigate the risk factors of occult cervical lymph node metastasis in papillary thyroid microcarcinoma.

Methods: The clinical records of 1524 cases of PTMC patients diagnosed in the Affiliated Hospital of Qingdao University from 2013 to 2017 were reviewed. The pathological and clinical characteristics were analyzed of dominant lymph node metastasis, occult lymph node metastasis and patients without lymph node metastasis, including gender (male), age, number of lesions, capsular invasion and Hashimoto's disease. **Results:** In the univariate analysis, patients without lymph node metastasis, age, tumor with double blade, multifocality had statistic difference ($P<0.05$). And the age of the occult lymph node metastasis group is lower ($P<0.05$), there was no significant difference in the ratio of Hashimoto's disease ($P>0.05$). Compared with dominant lymph node metastases, patients with occult lymph node metastasis had lower tumor size, multifocality and the pathological Hashimoto's disease ($P<0.05$). Multivariate analysis showed that gender, age, tumor size and multifocality were risk factors for occult lymph node metastasis (OR=0.525, 1.033, 0.169, 0.562). Compared with the occult lymph node metastasis, patients with Hashimoto's disease had a higher risk of dominant cervical lymph node metastasis, and the age of onset was larger than that of the former (OR=0.370, 0.979). **Conclusion:** The risk factors for early lymph node metastasis of PTMC were male, tumor involving double lobeS and multifocality. The risk of dominant cervical lymph node metastasis was higher in patients with Hashimoto's disease, but there was no correlation between Hashimoto's disease and occult cervical lymph node metastasis.

Key words: Papillary thyroid microcarcinoma; Lymph node metastasis; Risk factors**Chinese Library Classification(CLC):** R736.1 **Document code:** A**Article ID:** 1673-6273(2018)10-1977-05

前言

近年来,随着影像学技术的提高及人们的广泛关注,甲状腺乳头状癌(papillary thyroid carcinoma, PTC)的检出率逐年上

* 基金项目:山东省中青年科学家科研奖励基金项目(BS2009YY030);青岛市民生计划项目(13-1-3-58-nsh)

作者简介:蒋倩楠(1992-),硕士研究生,主要研究方向:甲状腺疾病,电话:18754230131, E-mail: 1101241658@qq.com

Δ 通讯作者:王斐,博士,主任医师、教授,硕士研究生导师,主要研究方向:甲状腺疾病, E-mail: wf18661802019@163.com

(收稿日期:2017-12-30 接受日期:2018-01-31)

升,已成为内分泌系统最为常见的恶性肿瘤,尤以甲状腺微小乳头状癌(papillary thyroid microcarcinoma,PTMC)(肿瘤最大直径 ≤ 10 mm)增多为主。虽其具有恶性程度低、预后较好的生物学特点,但早期也可发生颈部淋巴结转移,有研究报道^[1,2],PTMC 术后证实中央区淋巴结转移率高达 24-64%,可影响患者远处转移、复发率甚至整体预后。

本研究将显性颈部淋巴结转移定义为患者术前经触诊、颈部超声或 CT 检查已经发现有颈部淋巴结转移且术后病理得到证实者。将隐匿性颈部淋巴结转移定义为患者术前经触诊、颈部彩超或 CT 检查未发现颈部淋巴结转移,而术后病理明确诊断为有淋巴结转移,视为甲状腺乳头状癌的早期转移。PTMC 患者术前已经发现有颈部淋巴结转移时,应首先选择手术治疗;而术前检查未发现颈部淋巴结转移者,是否启动手术治疗,目前存在较大争议。由于存在隐匿性淋巴结转移的可能性,术前检查未发现颈部淋巴结转移的 PTMC 患者是否启动手术治疗,尚需结合患者的其他临床病理特征。本研究主要探讨了 PTMC 发生隐匿性淋巴结转移的危险因素,结果报道如下。

1 资料与方法

1.1 一般资料

收集 2013-2017 年在青岛大学附属医院确诊为 PTMC 并行手术治疗的患者,患者均在我院行术前颈部触诊、甲状腺及颈部淋巴结彩超或 CT 检查,行甲状腺全切除或单侧甲状腺及峡部切除,包括或不包括中央区淋巴结清扫术,术中行快速冰冻病理,术后病理组织学检查,且诊断均以术后病理为主。

1.2 纳入及排除标准

纳入标准:术后病理证实为 PTMC,且为初治患者,术前均行颈部彩超及 CT 等影像学检查;首次行手术治疗;临床病理中淋巴结资料相对完善。排除标准:复发再次手术患者;术中未行淋巴结清扫术;术前行甲状腺及颈部淋巴结超声或 CT 检查者,或无术后淋巴结病理资料者。经筛选,本研究共纳入 1524 例 PTMC 患者,对其临床和病理资料进行分析。

1.3 方法

根据 PTMC 患者术前术后是否发生淋巴结转移,分为显性淋巴结转移、隐匿性淋巴结转移及无淋巴结转移三组,回顾所有患者临床资料,对性别(男性)、年龄、肿瘤大小、双叶、多灶、

侵及包膜、合并桥本病、术前 TSH 水平等指标进行统计学分析,明确 PTMC 隐匿性淋巴结转移的相关危险因素。

1.4 统计学方法

采用 SPSS 21.0 统计学软件进行处理,病灶数较多者选用肿瘤最大直径纳入统计中,年龄、肿瘤大小、术前 TSH 水平等计量资料选用(均数 $\pm$ 标准差)表示,比较选用 t 检验;性别、双叶、多灶等计数资料率的比较选用卡方检验,将指标进一步纳入多因素 Logistic 回归分析模型, $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 各组临床病理特征比较

本研究共 1524 例患者,包括男性 356 例 (23.4%),女性 1168 例(76.6%),男女比例为 1:3.3;年龄 18-79 岁,平均年龄为 (45.49 $\pm$ 11.33)岁,其中年龄 <45 岁的患者有 723 例(47.4%), ≥ 45 岁的患者有 801 例(52.6%);肿瘤直径 0.05-10 mm,平均直径为 (0.59 $\pm$ 0.25) cm;病灶数为 1-8 灶,其中单灶 1140 例 (74.8%),多灶 384 例(25.2%);病灶累及单叶者 1305 例(85.6%),累及双叶者 259 例(14.4%);术后证实有淋巴结转移者 504 例,其中显性淋巴结转移有 126 例(8.3%),隐匿性转移者 378 例(24.8%),术后无淋巴结转移者 1020 例(66.9%);术后发现甲状腺包膜侵犯者 214 例(14%),合并病理桥本病者 224 例(14.7%)。术前 TSH 缺失 56 例,TSH 平均水平为 (2.30 $\pm$ 2.21) mIU/mL。

单因素分析中,两两比较结果显示:与无淋巴结转移患者相比,隐匿性淋巴结转移男性患者比例、年龄、肿瘤大小、肿瘤累及双叶、多灶比例均有统计学差异($P<0.05$),其中隐匿性淋巴结转移组中发病年龄较小($P<0.05$),见表 1;与无淋巴结转移的患者相比,显性淋巴结转移的患者年龄及术前 TSH 水平无统计学差异($P>0.05$),男性、双叶肿瘤、多灶比例、肿瘤大小、肿瘤外侵、合并病理桥本病等的比例均显著高于无淋巴结转移组 ($P<0.05$),见表 2;与显性淋巴结转移相比,隐匿性淋巴结转移肿瘤大小、合并多灶及合并病理桥本病的转移率较低 ($P<0.05$),而性别、发病年龄、肿瘤累及双叶、术前 TSH 水平均无统计学差异($P>0.05$),见表 3。

表 1 隐匿性淋巴结转移与无淋巴结转移的临床特点的单因素分析

Table 1 Single factors analysis of clinical features between occult and negative lymph node metastasis

Variable	Lymph node metastasis(%)		P value
	Occult(n=378)	No(n=1020)	
Gender(male)	120(31.7%)	195(19.1%)	<0.001
Age/year	43.11 $\pm$ 11.53	46.42 $\pm$ 11.08	<0.001
Tumor size/cm	0.66 $\pm$ 0.24	0.54 $\pm$ 0.24	<0.001
Involving double lobes	70(18.5%)	122(12.0%)	0.002
Multifocality	115(30.4%)	218(21.4%)	<0.001
Capsular invasion	58(15.3%)	129(12.6%)	0.188
PTMC with HT	46(12.2%)	146(14.3%)	0.301
Preoperative TSH / mIU/mL	2.32 $\pm$ 3.23	2.30 $\pm$ 1.82	0.879

表 2 显性淋巴结转移与无淋巴结转移的临床特点单因素分析

Table 2 Single factors analysis of clinical features between dominant and negative lymph node metastasis

Variable	Lymph node metastasis(%)		P value
	Dominant(n=126)	No(n=1020)	
Gender(male)	41(32.5%)	195(19.1%)	0.001
Age/year	45.14± 11.75	46.42± 11.08	0.227
Tumor size/cm	0.71± 0.26	0.54± 0.24	<0.001
Involving double lobes	27(21.4%)	122(12.0%)	0.003
Multifocality	51(40.5%)	218(21.4%)	<0.001
Capsular invasion	27(21.4%)	129(12.6%)	0.007
PTMC with HT	32(25.4%)	146(14.3%)	0.001
Preoperative TSH / mIU/mL	2.27± 1.53	2.30± 1.82	0.874

表 3 显性淋巴结转移与隐匿性淋巴结转移的临床特点单因素分析

Table 3 Single factors analysis of clinical features between dominant and occult lymph node metastasis

Variable	Lymph node metastasis(%)		P value
	Dominant(n=126)	Occult(n=378)	
Gender(male)	41(32.5%)	120(31.7%)	0.869
Age/year	45.14± 11.75	43.11± 11.53	0.089
Tumor size/cm	0.71± 0.26	0.66± 0.24	0.040
Involving double lobes	27(21.4%)	70(18.5%)	0.473
Multifocality	51(40.5%)	115(30.4%)	0.038
Capsular invasion	27(21.4%)	58(15.3%)	0.114
PTMC with HT	32(25.4%)	46(12.2%)	<0.001
Preoperative TSH / mIU/mL	2.27± 1.53	2.32± 3.23	

2.2 PTMC 发生隐匿性颈部淋巴结转移的多因素分析

多因素分析表明与无淋巴结转移组比较,隐匿性淋巴结组性别、年龄、大小、多灶为隐匿性淋巴结转移的危险因素(OR 值分别为 0.525,1.033,0.169,0.562);与无淋巴结组比较,显性淋

巴结转移组性别、肿瘤大小、多灶、合并桥本为前者的危险因素(OR 值分别为 0.357,0.078,0.329,0.446)。与显性淋巴结转移组相比,隐匿性淋巴结转移组合并桥本、年龄较小患者发生隐匿性淋巴结转移的风险低(OR 值分别为 0.370,0.979)。

表 4 隐匿性与无淋巴结转移的多因素 Logistic 回归分析

Table 4 Multiple factors Logistic regression analysis of occult and negative lymphatic metastasis

Variable	B	S.E.	wald	df	sig.	Exp(B)	95%CI.forExp(B)	
							Lower	Upper
Gender(male)	-0.644	0.158	16.718	1	0.000	0.525	0.385	0.715
Age	0.032	0.006	26.363	1	0.000	1.033	1.020	1.045
Tumor size/cm	-1.779	0.280	40.429	1	0.000	0.169	0.098	0.292
Involving double lobes	-0.092	0.262	0.122	1	0.727	0.912	0.546	1.525
Multifocality	-0.576	0.216	7.110	1	0.008	0.562	0.368	0.859
Capsular invasion	-0.064	0.189	0.116	1	0.733	0.938	0.648	1.358
PTMC with HT	0.410	0.214	3.670	1	0.055	1.506	0.991	2.291
Preoperative TSH/ mIU/mL	-0.011	0.028	0.154	1	0.695	0.989	0.935	1.046

Note: No lymph node metastasis as a reference group.

表 5 显性与无淋巴结转移的多因素 Logistic 回归分析

Table 5 Multiple factors Logistic regression analysis of dominant and negative lymphatic metastasis

Variable	B	S.E.	wald	df	sig.	Exp(B)	95%CI.forExp(B)	
							Lower	Upper
Gender(male)	-1.030	0.237	18.941	1	0.000	0.357	0.224	0.568
Age	0.009	0.009	0.958	1	0.328	1.009	0.991	1.028
Tumor size/cm	-2.545	0.419	36.852	1	0.000	0.078	0.034	0.178
Involving double lobes	0.187	0.350	0.287	1	0.592	1.206	0.608	2.393
Multifocality	-1.112	0.292	14.550	1	0.000	0.329	0.186	0.582
Capsular invasion	-0.293	0.263	1.238	1	0.266	0.746	0.445	1.250
PTMC with HT	-0.808	0.259	9.756	1	0.002	0.446	0.268	0.740
Preoperative TSH/ mIU/mL	0.064	0.065	0.960	1	0.327	1.066	0.938	1.211

Note: No lymph node metastasis as a reference group.

表 6 显性与隐匿性淋巴结转移的多因素 Logistic 回归分析

Table 6 Multiple factors Logistic regression analysis of dominant and occult lymphatic metastasis

Variable	B	S.E.	wald	df	sig.	Exp(B)	95%CI.forExp(B)	
							Lower	Upper
Gender(male)	-0.320	0.247	1.680	1	0.195	0.726	0.448	1.178
Age	0.022	0.010	4.845	1	0.028	0.979	0.960	0.998
Tumor size/cm	-0.768	0.462	2.767	1	0.096	0.464	0.188	1.147
Involving Double lobes	0.290	0.372	0.610	1	0.435	1.337	0.645	2.771
Multifocality	-0.315	0.313	1.009	1	0.315	0.730	0.395	1.349
Capsular invasion	-0.333	0.278	1.431	1	0.232	0.717	0.416	1.237
PTMC with HT	-0.993	0.295	11.368	1	0.001	0.370	0.208	0.660
Preoperative TSH/ mIU/mL	0.010	0.045	0.044	1	0.834	1.010	0.924	1.104

Noet: Dominant lymph node metastasis as a reference group.

3 讨论

甲状腺癌是内分泌系统中最常见的恶性肿瘤,其中乳头状癌是最常见的病理类型,近年来发病率逐渐上升,其中微小乳头状癌(PTMC)发病率的上升尤为显著^[3]。PTMC 因其肿瘤直径小,无明显自觉症状,通常不易被早期诊断。即使临床上有学者把PTMC 作为甲状腺乳头状癌(PTC)的早期病变^[4],仍会发生颈部淋巴结转移,且手术后 15-30 %以局部淋巴结转移复发为主^[5],受到临床关注。2015 年,美国甲状腺协会(ATA)指南中尚未提及 PTMC 隐匿性颈部淋巴结转移的定义,但提出了淋巴结微小转移的概念(淋巴结直径低于 0.2 cm),结合相关文献^[6],将临床 N0 期(cN0)患者,即术前通过体格检查、超声、CT 等影像学检查均未见淋巴结转移,术后病理证实存在淋巴结转移的情况认为甲状腺癌的隐匿性颈部淋巴结转移,虽然 PTMC 淋巴结转移基本不影响患者的整体预后,但仍与肿瘤的早期转移及

局部复发有关。有研究表明^[7,9]预防性的清扫患者颈部淋巴结可以降低局部复发率及延长患者的远期生存率^[10]。目前,国内外对于术前检查未发现颈部淋巴结转移的 PTMC 患者是否启动手术治疗颇具争议,主要考虑有发生隐匿性颈部淋巴结转移的可能性。

目前,关于 PTMC 隐匿性淋巴结转移的危险因素的研究尚少,部分报道尚存在争议。本研究纳入的 PTMC 患者隐匿性淋巴结转移率为 24.8 %,淋巴结转移与临床资料的相关性研究显示以无淋巴结转移的患者为对照组,男性、年龄、大小、多灶为隐匿性淋巴结转移的危险因素 (OR 值分别为 0.525,1.033,0.169,0.562),且其发病年龄较无淋巴结转移组小,肿瘤直径较后者大;与无淋巴结转移组相比,显性淋巴结转移组男性、肿瘤大小、多灶、合并桥本为前者的危险因素(OR 值分别为 0.357,0.078,0.329,0.446)。这与 Mao 等^[11]相关研究结果一致,表明 PTMC 患者中男性、年龄较小者,更易发生早期淋

巴结转移,可能与之细胞代谢较旺盛、淋巴结反应性较高有关^[12]。多因素分析显示合并桥本病者发生显性颈部淋巴结转移的风险更高,这与 Xie Li-wo 等^[13]和 Deng Jiang-bo^[14]的部分研究结论不一致;同时,本研究并没有发现桥本病与隐匿性颈部淋巴结转移存在相关性,是否与不存在 PTC 的某些致癌基因有关尚待进一步研究。有学者认为桥本甲状腺炎为自身免疫性疾病,其病变中存在的甲状腺特异性抗原可破坏肿瘤细胞,同时可以抑制肿瘤血管生成及肿瘤基质的重建,从而抑制肿瘤的增殖^[15],可能是不易发生早期(隐匿性)颈部淋巴结转移的机制,但不能解释本研究结果显示的 PTMC 并显性颈部淋巴结转移者合并桥本病的比率高。另外,有研究表明^[16,18]肿瘤侵犯包膜为 PTMC 颈部淋巴结转移的独立危险因素,在本研究中未得到证实。

由于影像学技术的不断提高,目前 PTMC 的颈部淋巴结转移率逐渐增高,但因其分辨率有限,尚不能发现组织学上已发生颈部淋巴结转移而淋巴结形态尚未发生明显改变的早期淋巴结转移的 PTMC 患者。有研究显示术前通过甲状腺超声及颈部 CT 判断出颈部淋巴结转移的敏感度仅为 50-70 %^[19,20]。尽管 2015 年 ATA 指南不主张对所有 cN0 的 PTC 患者行预防性淋巴结清扫,对于原发肿瘤直径为 T3、T4 期的患者,建议进行颈部中央区淋巴结清扫;也有学者^[21]认为 PTMC 发病隐匿、预后良好,可随访观察,切莫过度治疗,但本研究的结果显示 PTMC 患者隐匿性颈部淋巴结转移的发生率为 24.8% (378/1524),且与男性患者、肿瘤累及双叶、多灶性临床病理特征相关,所以我们认为临床上对男性、肿瘤累及双叶、多灶性的 PTMC 患者,应尽早手术切除并行预防性淋巴结清扫。

综上所述,尽管术前未发现有颈部淋巴结转移,但对于具备男性患者、肿瘤累及双叶、多灶性临床病理特征的 PTMC 患者,由于可能存在隐匿性颈部淋巴结转移,仍应选择手术切除及颈部淋巴结清扫治疗。关于 PTMC 隐匿性淋巴结转移的研究尚少,本研究为回顾性研究,虽然样本量较大,但缺少随访预后的证据支持,今后的研究进一步随访患者,完善随访资料,观察对 PTMC 患者的预后的影响,从而为 PTMC 的治疗提供更有力的依据。

参考文献(References)

- [1] Cho SY, Lee TH, Ku YH, et al. Central lymph node metastasis in papillary microcarcinoma can be stratified according to the number, the size of metastatic foci, and the presence of desmoplasia [J]. *Surgery*, 2014, 157(1): 111-118
- [2] Zhao Q, Ming J, Liu C, et al. Multifocality and total tumor diameter predict central neck lymph node metastases in papillary thyroid microcarcinoma[J]. *Ann Surg Oncol*, 2013, 20(3): 746-752
- [3] Hayat MJ, Howlader N, Reichman ME, et al. Cancer statistics,trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program[J]. *Oncologist*, 2007, 12(1): 20-37
- [4] Kim HY, Park WY, Lee KE, et al. Comparative analysis of gene expression profiles of papillary thyroid microcarcinoma and papillary thyroid carcinoma[J]. *Cancer Res Ther*, 2010, 6(4): 452-457
- [5] Hartl DM, Le Boulleux S, Al Ghuzlan A, et al. Optimization of staging of the neck with prophylactic central and lateral neck dissection for papillary thyroid carcinoma[J]. *Ann Surg*, 2012, 255: 777-783
- [6] Chen R, Wei T, Zhang M, et al. Lateral neck lymph node metastasis in cN0 papillary thyroid carcinoma [J]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*, 2012, 47: 662-667
- [7] Wang WT, Gu J, Shang J, et al. Correlation analysis on central lymph node metastasis in 276 patients with cN0 papillary thyroid carcinoma [J]. *Int J Clin Exp Pathol*, 2013, 6: 510-515
- [8] Kim MK, Mandel SH, Baloch Z, et al. Morbidity following central compartment reoperation for recurrent or persistent-thyroid cancer[J]. *Arch Otolaryngol Head Neck Surg*, 2004, 130: 1214-1216
- [9] Liang J, Liz, Fang F, et al. Is prophylactic central neck dissection necessary for cNO differentiated thyroid cancer patients at initial treatment? A meta-analysis of the literature[J]. *Acta Otorhinolaryngol Ital*, 2017, 37: 1-8
- [10] 张奥博,刘良发,路承,等.cN0 期甲状腺乳头状癌颈部中央区淋巴结转移的危险因素分析[J].*临床耳鼻咽喉头颈外科杂志*, 2017, 31 (15): 1141-1145
Zhang Ao-bo, Liu Liang-fa, Lu Cheng, et al. Risk factors of central neck lymph node metastasis in cN0 papillary thyroid carcinoma[J]. *Clin Otorhinolaryngol Head Neck Surg (China)*, 2017, 31 (15): 1141-1145
- [11] Mao LN, Wang P, Li ZY, et al. Risk factor analysis for central nodal metastasis in papillary thyroid carcinoma[J]. *Oncology Letters*, 2015, 9(1): 103-107
- [12] 张宇皓,文开学,马培如.1 例甲状腺微小乳头状癌临床诊治分析[J].*中国癌症杂志*, 2016, 26(1): 102-105
Zhang Yu-hao, Wen Kai-xue, Ma Pei-ru. Diagnosis and treatment of papillary thyroid micro-carcinoma: An analysis of 61 cases [J]. *China Oncology*, 2016, 26(1): 102-105
- [13] Xie Li-wu, Xi Yan-feng. Analysis of mutation status of BRAFV600E in Hashimoto's thyroiditis and thyroid papillary carcinoma[J]. *Chinese Remedies & Clinics*, 2017, 17(10): 1447-1451
- [14] 邓江波. 甲状腺乳头状癌合并桥本氏甲状腺炎的临床和病理特点 [J].*深圳中西医结合杂志*, 2016, 26(13): 90-92
Deng Jiang-bo. Clinical and pathological characteristics of papillary thyroid carcinoma with Hashimoto's thyroiditis [J]. *Shenzhen Journal of Integrated Traditional Chinese and Western Medicine*, 2016, 26 (13): 90-92
- [15] Sabharwal SS, Schumacker PT. Mitochondrial ROS in cancer: initiators, amplifiers or an Achilles' heel [J]. *Nat Rev Cancer*, 2014, 14 (11): 709-721
- [16] Yang Y, Chen C, Chen Z, et al. Prediction of central compartment lymph node metastasis in papillary thyroid microcarcinoma [J]. *Clin Endocrinol (Oxf)*, 2014, 81(2): 282-288
- [17] Kim KE, Kim EK, Yoon JH, et al. Preoperative prediction of central lymph node metastasis in thyroid papillary microcarcinoma using clinicopathologic and sonographic features[J]. *World J Surg*, 2013, 37 (2): 385-391
- [18] Park JP, Roh JL, Lee JH, et al. Risk factors for central neck lymph node metastasis of clinically noninvasive, node- negative papillary thyroid microcarcinoma[J]. *Am J Surg*, 2014, 208(3): 412-418
- [19] White ML, Gauger PG, Doherty GM. Central lymph node dissection in differentiated thyroid cancer[J]. *World J Surg*, 2007, 31: 895-904

- [46] Sanjabi S, Oh SA, Li MO. Regulation of the Immune Response by TGF-beta: From Conception to Autoimmunity and Infection[J]. Cold Spring Harb Perspect Biol, 2017, 9(6): 1-34
- [47] Wan YY, Flavell RA. Regulatory T cells, transforming growth factor-beta, and immune suppression [J]. Proc Am Thorac Soc, 2007, 4(3): 271-276
- [48] Conte E, Gili E, Fruciano M, et al. Human lung fibroblasts increase CD4(+)CD25(+)Foxp3(+) T cells in co-cultured CD4(+) lymphocytes [J]. Cell Immunol, 2013, 285(1-2): 55-61
- [49] Al-Alawi M, Hassan T, Chotirmall SH. Transforming growth factor beta and severe asthma: a perfect storm [J]. Respir Med, 2014, 108(10): 1409-1423
- [50] Stumm CL, Halesik E, Landgraf RG, et al. Lung remodeling in a mouse model of asthma involves a balance between TGF-beta1 and BMP-7[J]. PLoS One, 2014, 9(4): e95959
- [51] Johnson JR, Nishioka M, Chakir J, et al. IL-22 contributes to TGF-beta1-mediated epithelial-mesenchymal transition in asthmatic bronchial epithelial cells[J]. Respir Res, 2013, 14(1): 1-12
- [52] Minshall EM, Leung DY, Martin RJ, et al. Eosinophil-associated TGF-beta1 mRNA expression and airways fibrosis in bronchial asthma [J]. Am J Respir Cell Mol Biol, 1997, 17(3): 326-333
- [53] McMillan SJ, Xanthou G, Lloyd CM. Manipulation of allergen-induced airway remodeling by treatment with anti-TGF-beta antibody: effect on the Smad signaling pathway [J]. J Immunol, 2005, 174(9): 5774-5780
- [54] Itoigawa Y, Harada N, Harada S, et al. TWEAK enhances TGF-beta-induced epithelial-mesenchymal transition in human bronchial epithelial cells[J]. Respir Res, 2015, 16(1): 1-15
- [55] Chakir J, Shannon J, Molet S, et al. Airway remodeling-associated mediators in moderate to severe asthma: effect of steroids on TGF-beta, IL-11, IL-17, and type I and type III collagen expression[J]. J Allergy Clin Immunol, 2003, 111(6): 1293-1298
- [56] Huang YC, Leyko B, Frieri M. Effects of omalizumab and budesonide on markers of inflammation in human bronchial epithelial cells [J]. Ann Allergy Asthma Immunol, 2005, 95(5): 443-451
- [57] Brown SD, Brown LA, Stephenson S, et al. Characterization of a high TNF-alpha phenotype in children with moderate-to-severe asthma[J]. J Allergy Clin Immunol, 2015, 135(6): 1651-1654
- [58] Camille T, Claire P, Sylvain M-A, et al. Monoclonal Anti-TNF-alpha Antibodies for Severe Steroid-Dependent Asthma: A Case Series [J]. Open Respir Med J, 2013, 7(1): 21-25
- [59] Blume C, Reale R, Held M, et al. Cellular crosstalk between airway epithelial and endothelial cells regulates barrier functions during exposure to double-stranded RNA [J]. Immunity, inflammation and disease, 2017, 5(1): 45-56
- [60] Brown SD, Lou AB, Stephenson S, et al. Characterization of a "high" TNF-alpha phenotype in moderate-to-severe asthmatic children [J]. J Allergy Clin Immunol, 2015, 135(6): 1651-1654
- [61] Kips JC, Tavernier J, Pauwels RA. Tumor necrosis factor causes bronchial hyperresponsiveness in rats [J]. Am Rev Respir Dis, 1992, 145(2 Pt 1): 332-336
- [62] Howarth PH, Babu KS, Arshad HS, et al. Tumour necrosis factor (TNFalpha) as a novel therapeutic target in symptomatic corticosteroid dependent asthma[J]. Thorax, 2005, 60(12): 1012-1018
- [63] Kim J, Mckinley L, Natarajan S, et al. Anti-tumor necrosis factor-alpha antibody treatment reduces pulmonary inflammation and methacholine hyper-responsiveness in a murine asthma model induced by house dust[J]. Clin Exp Allergy, 2006, 36(1): 122-132
- [64] Berry MA, Hargadon B, Shelley M, et al. Evidence of a role of tumor necrosis factor alpha in refractory asthma[J]. N Engl J Med, 2006, 354(7): 697-708
- [65] Holgate ST, Noonan M, Chanez P, et al. Efficacy and safety of etanercept in moderate-to-severe asthma: a randomised, controlled trial[J]. Eur Respir J, 2011, 37(6): 1352-1359
- [66] Kikuchi S, Kikuchi I, Takaku Y, et al. Neutrophilic inflammation and CXC chemokines in patients with refractory asthma [J]. Int Arch Allergy Immunol, 2009, 149(Suppl 1): 87-93
- [67] Pepe C, Foley S, Shannon J, et al. Differences in airway remodeling between subjects with severe and moderate asthma [J]. J Allergy Clin Immunol, 2005, 116(3): 544-549
- [68] Shannon J, Ernst P, Yamauchi Y, et al. Differences in airway cytokine profile in severe asthma compared to moderate asthma [J]. Chest, 2008, 133(2): 420-426
- [69] Hasegawa T, Uga H, Mori A, et al. Increased serum IL-17A and Th2 cytokine levels in patients with severe uncontrolled asthma [J]. Eur Cytokine Netw, 2017, 28(1): 8-18
- [70] Agache I, Ciobanu C, Agache C, et al. Increased serum IL-17 is an independent risk factor for severe asthma[J]. Respir Med, 2010, 104(8): 1131-1137

(上接第 1981 页)

- [20] 张奥博, 刘良发, 路承, 等. cN0 期甲状腺乳头状癌颈部中央区淋巴结转移的危险因素分析[J]. 临床耳鼻咽喉头颈外科杂志, 2017, 31(15): 1141-1145
- Zhang Ao-bo, Liu Liang-fa, Lu Cheng, et al. Risk factors of central neck lymph node metastasis in cN0 papillary thyroid carcinoma[J]. Clin Otorhinolaryngol Head Neck Surg (China), 2017, 31(15): 1141-1145
- [21] Ito Y, Miyauchi A, Inoue H, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients [J]. World J Surg, 2010, 34(1): 28-35