·论著·

乳头状甲状腺微小癌不宜作为术后 ^{131}I治疗的决策依据

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[摘要] **目的：**分析术后接受^{131}I治疗的乳头状甲状腺微小癌（papillary thyroid microcarcinoma, PTMC）与乳头状甲状腺非微小癌（papillary thyroid non-microcarcinoma, non-PTMC）病人的临床病理特征，并比较治疗转归的差异，以期指导PTMC的^{131}I治疗决策。**方法：**纳入2015年1月至2020年12月在天津医科大学总医院核医学科^{131}I治疗的1 118例PTC病人，采用卡方检验及秩和检验比较PTMC组与non-PTMC组病人临床病理特征、^{131}I治疗情况及治疗反应的差异，Kaplan-Meier法绘制两组的治疗反应不佳(incomplete response, IR)率曲线。**结果：**PTMC组病人多灶性、累及双叶的比例均高于non-PTMC组，腺外侵犯、T4、N1b、刺激性甲状腺球蛋白(stimulated thyroglobulin, sTg)＞10 μg/L及高危复发风险的比例低于non-PTMC组（$P<0.05$）。PTMC组多数病人首次接受清甲治疗，而non-PTMC组中更多病人接受辅助及清灶治疗（$P<0.05$）。两组病人^{131}I治疗反应、疗效满意(excellent response, ER)率和IR率的差异均无统计学意义，IR率曲线差异也无统计学意义（$P>0.05$）。**结论：**PTMC具有一定的侵袭性。经综合评估和规范^{131}I治疗后，PTMC和non-PTMC病人治疗转归大致相同。PTMC的界定对^{131}I治疗决策的指导价值极其有限。

关键词：甲状腺肿瘤； 甲状腺乳头状癌； 放射疗法； 碘放射性同位素； 治疗转归

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Papillary thyroid microcarcinoma should not be used as the basis for postoperative ^{131}I therapy

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[Abstract] Objective To analyze the clinicopathological data of patients with papillary thyroid microcarcinoma (PTMC) and papillary thyroid non-microcarcinoma (non-PTMC) who received ^{131}I therapy retrospectively, and compare the therapeutic response of the two groups of patients, so as to guide ^{131}I therapy decisions for PTMC patients. **Methods** A total of 1 118 patients with papillary thyroid carcinoma (PTC) underwent ^{131}I therapy in the Department of Nuclear Medicine, Tianjin Medical University General Hospital from January 2015 to December 2020 were enrolled. Chi-square test and Mann-Whitney *U* test were used to compare the differences of clinicopathological features and ^{131}I therapy, therapeutic response between two groups. The incomplete response (IR) rate curves of the two groups were plotted by Kaplan-Meier analysis. **Results** The proportion of patients with multifocal, involvement of bilateral thyroid lobes in PTMC group were higher than those in non-PTMC group, and the proportion of patients with extra-thyroid extension, T4, N1b, stimulated thyroglobulin (sTg)>10 μg/L, and high risk stratified were lower than those in non-PTMC group (P<0.05). Most patients in PTMC group received remnant ablation for the first time, while more patients in non-PTMC group received adjuvant therapy and therapy for known disease (P<0.05). There was no statistically significant difference in ^{131}I therapeutic response, the rates of excellent response(ER) and IR in two groups, and the differences in curves of IR rate between the two groups were also no statistically significance (P>0.05). **Conclusions** PTMC has a certain degree of invasiveness. As long as the patients were comprehensively evaluated and the standard ^{131}I therapy was adopted, the treatment outcomes of patients with PTMC and non-PTMC were roughly the same. Therefore, the clinical value of the definition of PTMC is extremely limited in the

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formulation of ^{131}I therapeutic dose regimens.

Key words: Thyroid tumor; Papillary thyroid carcinoma; Radiotherapy; Iodine radioisotope; Treatment outcome

早在1988年，世界卫生组织(World Health Organization, WHO)将肿瘤最大直径≤10 mm的乳头状甲状腺癌(papillary thyroid carcinoma, PTC)定义为乳头状甲状腺微小癌(papillary thyroid microcarcinoma, PTMC)[1]。它是近年来增长速度最快的甲状腺癌，发病占全部甲状腺癌的50%以上[2]。尽管PTMC预后良好，但多项研究提示PTMC似乎不能简单地等同于低危癌症，其临床意义及最佳治疗方法仍存在争议[3-5]。

临床上是否有必要对PTMC病人行^{131}I治疗仍存在争议[6]。有学者认为^{131}I治疗并不能进一步改善其预后[7-8]；而另一些研究则表明^{131}I治疗可以降低这些病人的复发及转移风险[9-11]。PTMC概念的提出，似更多强调肿瘤的大小在临床工作中的价值，而忽略其分子表型、病理学等反映肿瘤侵袭性的特征对预后的影响。接受^{131}I治疗的PTMC病人是否具有更低的侵袭性和远处转移发生率，是否可以因此适当降低^{131}I治疗剂量，是否较甲状腺非微小乳头状癌(papillary thyroid non-microcarcinoma, non-PTMC)远期预后更好，尚有待研究。本研究将肿瘤最大直径＞10 mm的PTC定义为non-PTMC，回顾性分析接受^{131}I治疗的PTMC和non-PTMC病人临床病理特征的差异，并进一步评估不同初治目标病人的临床转归。

1 资料和方法

1.1 一般资料

检索自2015年1月至2020年12月天津医科大学总医院核医学科PTC病人术后^{131}I治疗数据库资料，研究分析该数据库中保存完整的PTMC与non-PTMC病人的临床病理特征及^{131}I治疗反应。本方案获得天津医科大学总医院医学伦理委员会批准(IRB2021-WZ-047)，所有病人均于治疗前签署知情同意书。

纳入标准：已行全甲状腺切除术及颈部淋巴结清扫术，术后病理检查证实为PTC且癌灶大小及淋巴结转移分区明确，术后于我科进行一次或多次^{131}I治疗。排除标准：①病理诊断癌灶大小不详，淋巴结转移分区不明确；②首次^{131}I治疗前甲状腺球蛋白抗体(thyroglobulin antibody, TgAb)阳性(≥20 U/mL，参考范围0~40 U/mL)；③同时接受其他抗肿瘤治疗。

1.2 方法

1.2.1 ^{131}I治疗与随访

结合病人组织病理特征及入院后血清及影像实时评估结果，拟定个体化^{131}I治疗剂量。对于低TNM分期、低sTg且无明确肿瘤存在的影像学证据者，首次行清甲治疗，^{131}I剂量1.11 GBq或3.7 GBq；对于存在不良病理特征(具备T4分期、软组织侵犯、转移淋巴结最大径≥3 cm或伴有结外侵犯中的一项或多项)或sTg＞10 μg/L者，首次行辅助治疗，^{131}I剂量5.55 GBq；对于明确存在结构和(或)功能性病灶，或sTg高度提示存在远处转移者，首次行清灶治疗，^{131}I剂量7.4 GBq。

随访与评价：^{131}I治疗后6个月，基于血清及影像学检查结果，动态评估前次^{131}I治疗反应。对于评估提示仍有摄碘性病灶，在无法手术根治且前次^{131}I治疗有效(血清Tg水平明显下降、影像学检查显示病灶缩小)时，行再次^{131}I治疗，两次^{131}I治疗间隔6~12个月。

1.2.2 研究内容

收集病人一般临床病理资料，包括病人性别、年龄以及病灶数量、累及腺叶、病理亚型，是否甲状腺外侵犯、颈部淋巴结转移、远处转移，术后sTg水平、初始复发危险度分层和随访时间。分析比较PTMC组与non-PTMC组病人临床病理特征的差异。

进一步比较两组病人首次^{131}I治疗目标、^{131}I治疗次数、累积治疗剂量及治疗反应等的差异。在治疗反应的分析中，将病人按照首次治疗目标分为清甲治疗组、辅助治疗组和清甲兼顾清灶治疗组，分析^{131}I治疗后6个月及末次随访时的治疗反应。治疗反应参照2015年美国甲状腺协会(American Thyroid Association, ATA)指南分为疗效满意(excellent response, ER)、疗效不确切(indeterminate response, IDR)、生化疗效不佳(biochemical incomplete response, BIR)及结构性疗效不佳(structural incomplete response, SIR)，BIR和SIR统称为治疗反应不佳(incomplete response, IR)。

1.3 统计学处理

采用IBM SPSS 23.0统计软件包、以回顾性分

析方法对临床病理资料进行统计分析。采用Kolmogorov-Smirnov分析进行正态性检测，非正态分布计量资料以中位数和四分位数间距[M(Q_1, Q_3)]描述。两组间率比较采用卡方检验，非正态计量资料两组间比较采用曼-惠特尼 U(Mann-Whitney U)秩和检验。采用Kaplan-Meier法绘制IR率曲线，对数秩和检验(Log-rank test)比较两组间曲线差异。以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 病人临床病理特征

研究共有1 118例PTC病人符合纳入标准，其中PTMC 458例（41.0%），non-PTMC 660例（59.0%）。入组病人手术确诊为PTC时中位年龄为44(11~76)岁，男353例，女765例，中位随访时间为12(6~113)个月。接受^{131}I治疗的PTMC组病人多灶性、累及双叶的比例均高于non-PTMC组病人；而non-PTMC组病人腺外侵犯、T4、N1b、sTg > 10 μg/L及高危复发风险的比例均高于PTMC组病人($P<0.05$)。两组病人的年龄、性别、病理亚型及是否伴有远处转移的差异均无统计学意义($P>0.05$)(见表1)

2.2 接受^{131}I治疗情况

PTMC组和non-PTMC组病人接受^{131}I治疗的情况如表2所示。两组病人首次治疗目标的分布存在差异，多数PTMC病人首次接受了清甲治疗，而non-PTMC组中更多的病人接受了辅助及清灶治疗($P<0.05$)。83.6%的PTMC组病人累积治疗剂量≤7.4 GBq，高于non-PTMC病人的70.5%($P<0.05$)。另外，PTMC组中76.9%的病人仅接受单次^{131}I治疗，高于non-PTMC组的63.2%($P<0.05$)(表2)。

2.3 ^{131}I治疗转归

2.3.1 接受清甲治疗病人的转归

294例PTMC和308例non-PTMC病人接受了清甲治疗，两组病人的ER、IDR、BIR和SIR率如表3

表1 PTMC与non-PTMC病人临床病理特征比较[*n*(%)]

Tab 1 Comparisons of clinicopathological characteristics between PTMC and non-PTMC patients[*n*(%)]

Characteristics		PTMC(n=458)	non-PTMC(n=660)	Test value	P value
Age(year)	<55	359(78.4)	507(76.8)	0.380	0.561
	≥55	99(21.6)	153(23.2)		
Gender	Male	130(28.4)	223(33.8)	3.654	0.058
	Female	328(71.6)	437(66.2)		
Number of lesions	Unifocal	132(28.8)	263(39.8)	14.390	0.000
	Multifocal	326(71.2)	397(60.2)		
Involvement of thyroid lobes	Unilateral thyroid lobe	193(42.1)	325(49.2)	5.485	0.021
	Bilateral thyroid lobes	265(57.9)	335(50.8)		
Pathological subtype	Non-invasive	451(98.5)	642(97.3)	1.778	0.220
	Invasive	7(1.5)	8(2.7)		
Extra-thyroid extension	No	350(76.4)	413(62.6)	23.910	0.000
	Yes	108(23.6)	247(37.4)		
T4 stage	No	431(94.1)	593(89.8)	6.361	0.012
	Yes	27(5.9)	67(10.2)		
lymph node metastasis	N0	91(19.9)	102(15.5)	23.382	0.000
	N1a	224(48.9)	257(38.9)		
	N1b	143(31.2)	301(45.6)		
Distant metastasis	No	441(96.3)	625(94.7)	1.544	0.249
	Yes	17(3.7)	35(5.3)		
sTg of pre-therapy(μg/L)	<1	162(35.4)	158(23.9)	24.321	0.000
	1-10	209(45.6)	307(46.5)		
	≥10	87(19.0)	195(29.5)		
Recurrence risk stratification	Low risk	65(14.2)	50(7.6)	30.800	0.000
	Moderate risk	272(59.4)	340(51.5)		
	High risk	121(26.4)	270(40.9)		

表2　PTMC与non-PTMC病人接受^{131}I治疗情况比较[*n*(%)]

Tab 2　Comparisons of ^{131}I therapy between PTMC and non-PTMC patients[*n*(%)]

Item		PTMC(*n*=458)	non-PTMC(*n*=660)	Test value	*P* value
Goal of the initial therapy	Remnant ablation	294(64.2)	308(46.7)	34.492	0.000
	Adjuvant therapy	138(30.1)	282(42.7)		
	^{131}I therapy	26(5.7)	70(10.6)		
Initial therapeutic doses(GBq)	≤3.7	294(64.2)	308(46.7)	34.492	0.000
	5.55	138(30.1)	282(42.7)		
	7.4	26(5.7)	70(10.6)		
Cumulative therapeutic doses(GBq)	≤7.4	383(83.6)	465(70.5)	26.724	0.000
	7.4-22.2	72(15.7)	190(28.8)		
	>22.2	3(0.7)	5(0.8)		
Times of ^{131}I therapy	Single	352(76.9)	417(63.2)	23.545	0.000
	Multiple	106(23.1)	243(36.8)		

表3　接受清甲治疗的PTMC与non-PTMC病人治疗反应比较[*n*(%)]

Tab 3　Comparisons of therapeutic response between PTMC and non-PTMC patients received remnant ablation[*n*(%)]

Item		6 months after ^{131}I therapy				Last follow-up			
		PTMC(*n*=458)	non-PTMC(*n*=660)	Test value	*P* value	PTMC(*n*=458)	non-PTMC(*n*=660)	Test value	*P* valu
Therapeutic response	ER	189(64.3)	178(57.8)	4.911	0.189	220(74.8)	235(76.3)	4.662	0.147
	IDR	103(35.0)	122(39.6)			74(25.2)	68(22.1)		
	BIR	1(0.3)	4(1.3)			0	3(1.0)		
	SIR	1(0.3)	4(1.3)			0	2(0.6)		
ER	ER	189(64.3)	178(57.8)	2.665	0.113	220(74.8)	235(76.3)	0.176	0.705
	Non-ER	105(35.7)	130(42.2)			74(25.2)	73(23.7)		
IR	IR	2(0.7)	8(2.6)	2.312	0.128	0	5(1.6)	—	0.062
	Non-IR	292(99.3)	300(97.4)			294(100.0)	303(98.4)		

所示。初治后6个月，两组间ER及IR率差异均无统计学意义（$P>0.05$）。随着随访时间延长，两组的ER率均有所提高，而IR率逐渐下降，末次随访时PTMC组无IR病人，non-PTMC组的IR率下降至1.6%，但两组间差异仍无统计学意义。如图1所示，病人并不会因肿瘤最大径≤10 mm而降低IR发生率（$P>0.05$）。

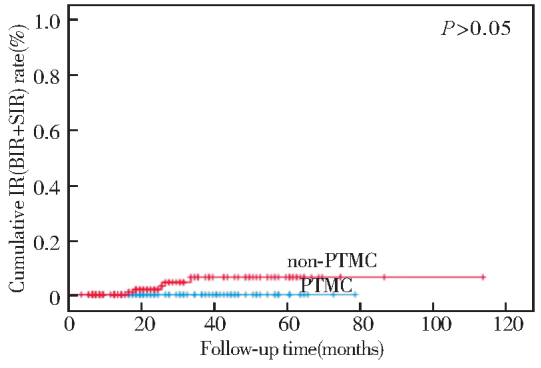

图1　接受清甲治疗的PTMC与non-PTMC病人IR率图

Fig 1　Curves of IR rate in PTMC and non-PTMC patients received remnant ablation

2.3.2　接受辅助治疗病人的转归

如表4所示，在接受辅助治疗的138例PTMC和282例non-PTMC病人中，与治疗后6个月相比，末次随访时PTMC组ER率从38.4%上升至51.4%，IR率从34.8%下降至18.8%，非SIR率从88.4%上升至93.5%；non-PTMC组ER率从30.5%上升至47.2%，IR率从39.4%下降至21.6%，非SIR率从91.5%上升至95.0%。PTMC组IR率略低于non-PTMC组，但差异无统计学意义（$P>0.05$）。可见对于接受辅助治疗的PTC病人，肿瘤最大径≤10 mm并不会降低IR发生率（见图2）。

2.3.3　接受清灶治疗病人的转归

26例PTMC和70例non-PTMC病人接受了清灶治疗，两组病人的治疗反应如表5所示。末次随访时，PTMC组有1例达到ER，IR率为88.5%，非SIR率为26.9%；non-PTMC组3例达到ER，IR率为87.1%，非SIR率达到40.0%，两组差异无统计学意义（$P>0.05$）。如图3所示，肿瘤最大径≤10 mm并不会降低IR发生率（$P>0.05$）。

表 4　接受辅助治疗的 PTMC 与 non-PTMC 病人治疗反应比较[*n*(%)]

Tab 4　Comparisons of therapeutic response between PTMC and non-PTMC patients received adjuvant therapy[*n*(%)]

Item		6 months after ^{131}I therapy				Last follow-up			
		PTMC(*n*=458)	non-PTMC(*n*=660)	Test value	*P* value	PTMC(*n*=458)	non-PTMC(*n*=660)	Test value	*P* value
Therapeutic response	ER	53(38.4)	86(30.5)	4.950	0.173	71(51.4)	133(47.2)	1.978	0.575
	IDR	37(26.8)	85(30.1)			41(29.7)	88(31.2)		
	BIR	32(23.3)	87(30.9)			17(12.3)	47(16.7)		
	SIR	16(11.6)	24(8.5)			9(6.5)	14(5.0)		
ER	ER	53(38.4)	86(30.5)	2.618	0.122	71(51.4)	133(47.2)	0.681	0.467
	Non-ER	85(61.6)	196(69.5)			67(48.6)	149(52.8)		
IR	IR	48(34.8)	111(39.4)	0.862	0.393	26(18.8)	61(21.6)	0.439	0.525
	Non-IR	90(65.2)	171(60.6)			112(81.2)	221(78.4)		
SIR	SIR	16(11.6)	24(8.5)	1.022	0.376	9(6.5)	14(5.0)	0.434	0.649
	Non-SIR	122(88.4)	258(91.5)			129(93.5)	268(95.0)		

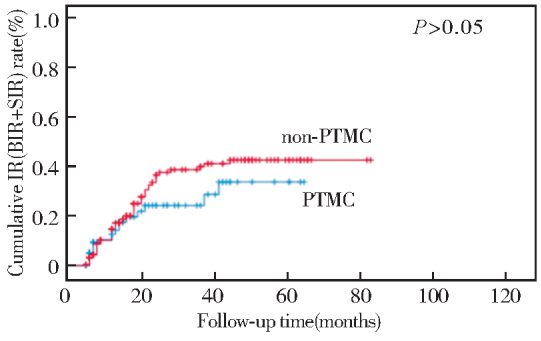

图 2　接受辅助治疗的 PTMC 与 non-PTMC 病人 IR 率图

Fig 2　Curves of IR rate in PTMC and non-PTMC patients received adjuvant therapy

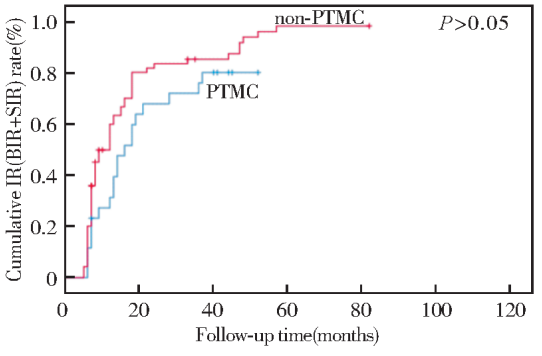

图 3　接受清灶治疗的 PTMC 与 non-PTMC 病人 IR 率图

Fig 3　Curves of IR rate in PTMC and non-PTMC patients received therapy for known disease

表 5　接受清灶治疗的 PTMC 与 non-PTMC 病人末次随访治疗反应比较[*n*(%)]

Tab 5　Comparisons of therapeutic response at the last follow-up between PTMC and non-PTMC patients received therapy for known disease[*n*(%)]

Item		PTMC (*n*=458)	non-PTMC (*n*=660)	Test value	*P* value
Therapeutic response	ER	1(3.8)	3(4.3)	1.693	0.685
	IDR	2(7.7)	6(8.6)		
	BIR	4(15.4)	19(27.1)		
	SIR	19(73.1)	42(60.0)		
ER	ER	1(3.8)	3(4.3)	—	1.000
	Non-ER	25(96.2)	67(95.7)		
IR	IR	23(88.5)	61(87.1)	0.000	1.000
	Non-IR	3(11.5)	9(12.9)		
SIR	SIR	19(73.1)	42(60.0)	1.399	0.340
	Non-SIR	7(26.9)	28(40.0)		

3　讨论

WHO 将肿瘤直径≤10 mm 的甲状腺癌定义为微小癌(thyroid microcarcinoma, TMC),其中 90% 是 PTMC[12]。与 non-PTMC 相比,PTMC 具有相对不活跃、临床预后更好等特征,但也有研究发现 PTMC 与较大的 PTC 有着相似的临床病理特征,如多灶性、腺外侵犯、颈部淋巴结转移等[5]。本研究纳入的 PTMC 与 non-PTMC 病人中分别有 71.2% 和 60.2% 肿瘤表现为多灶性,且 PTMC 多病灶的概率比 non-PTMC 高。本研究还发现所有 PTC 病人不论肿瘤大小均易累及双叶,且 PTMC 比 non-PTMC 更易累及双侧腺叶,与文献报道[13-14]PTMC 大多为单叶发病的结果不一致,考虑可能与研究纳入的病人群体不同有关(经术后评估需进行 ^{131}I 治疗)。

本研究 458 例 PTMC 病人中有 367 例(80.1%)

合并淋巴结转移，其中仅中央区淋巴结(N1a)转移有224例(48.9%)，均高于此前的研究[15-17]，这可能是因为本研究对象大多为多病灶、累及双侧腺叶的PTMC病人。此外，non-PTMC比PTMC更易发生颈侧区淋巴结转移和腺外侵犯。之前也有研究报道，癌灶越大越容易发生甲状腺外浸润和淋巴结转移[18-20]，但也有学者认为颈侧区的淋巴结转移是因为肿瘤进展而导致受累范围不断扩大，与肿瘤大小并无直接关系[14]。

《甲状腺微小乳头状癌诊断与治疗中国专家共识(2016版)》指出，根据长期的临床实践以及国内、外的相关研究报道，对合并有转移(尤其是远处转移)的PTMC病人，^{131}I治疗有助于消除残留病灶和转移灶，有助于缓解病情和降低复发风险，且对于PTMC病人的治疗原则与PTC基本一致[21]。研究表明，PTMC是PTC的早期病变，二者的基因表达演变并无差异，不应简单地认为PTMC是一种惰性的甲状腺癌[22]。本研究也发现接受^{131}I治疗的PTMC病人淋巴结转移率很高，有一定的腺外侵犯甚至远处转移率。PTMC并不等于惰性癌，在确定^{131}I治疗方案时应综合考虑多方面因素，不应单纯因肿瘤直径≤10 mm而减少治疗剂量。

为了优化PTC术后^{131}I治疗的决策，^{131}I治疗前的实时评估是十分重要的步骤。根据病人TNM分期、相关血清学(如Tg、TgAb等)及影像学检查[颈部超声、^{131}I诊断性全身显像(diagnostic whole body scan, Dx-WBS)、CT、MRI等]等各项指标，动态评估病人复发风险，可将术后首次^{131}I治疗目的分为清甲治疗、辅助治疗、清灶治疗三种[23]。^{131}I治疗后的再次动态评估更能实时反映前期治疗的效果和病人的疾病状态以指导后续的^{131}I治疗。如果首次治疗后评估病人治疗反应已达ER，或病人接受其他治疗方案可能更大获益时，则无需再次进行^{131}I治疗；若评估提示仍有摄碘性病灶且前次^{131}I治疗有效时，可再次行^{131}I治疗[23-24]。

为了比较PTMC与non-PTMC病人的^{131}I治疗转归，本研究按照首次治疗目标进行分组分析。结果发现，以清甲、辅助或清灶为治疗目的，PTMC与non-PTMC病人治疗反应的差异均无统计学意义。到末次随访时，接受清甲治疗的PTMC和non-PTMC组ER率分别为74.8%和76.3%，两组接受辅助治疗后非SIR率分别高达93.5%和95.0%，接受清灶治疗的两组病人非SIR率分别为26.9%和40.0%。PTMC与non-PTMC病人接受清甲、辅助或清灶治疗后，IR率分别为0和1.6%、18.8%和21.6%、88.5%和87.1%。可见无论^{131}I治疗目标及策略如何，均不会因为肿瘤最大径≤10 mm而降低IR发生率。因此，只要在治疗前对病人进行综合评估，采取恰当的^{131}I治疗方案，同样治疗目的之PTMC和non-PTMC病人转归大致相同，non-PTMC病人的预后并不会较差。综合考虑，在制定^{131}I治疗方案时，PTMC的界定其临床价值极其有限。

本研究仍存在一些不足，首先，本研究中位随访时间仅为16个月，未进行总生存期(overall survival, OS)、无病生存期(disease free survival, DFS)、无进展生存期(progression free survival, PFS)等的研究；其次，长期的随访对^{131}I长期治疗反应的评估应更准确。

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