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术前CT双能量成像联合血清甲状腺球蛋白水平对 甲状腺乳头状癌颈部淋巴结转移的诊断价值

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[摘要] 目的: 探讨术前CT双能量成像联合血清甲状腺球蛋白(thyroglobulin, Tg)对甲状腺乳头状癌(papillary thyroid carcinoma, PTC)颈部淋巴结转移(cervical lymph node metastasis, CLNM)的诊断价值。方法: 回顾性分析2019年5月至2021年10月在合肥京东方医院完成甲状腺癌根治术治疗的81例PTC患者的相关资料, 患者术前均接受CT双能量成像扫描检查和血清Tg水平检测。以手术病理结果为金标准, 将81例PTC患者按是否发生过CLNM分别分为CLNM组($n=34$)和非颈部淋巴结转移组(non-cervical lymph node metastasis, N-CLNM; $n=47$)。比较两组术前Tg水平和CT双能量成像检查资料。采用受试者工作特征(receiver operator characteristic, ROC)曲线评价术前血清Tg水平、术前CT双能量成像检查以及联合诊断对PTC患者CLNM的诊断价值。结果: CLNM组术前血清Tg水平为97.85(75.01, 117.51) ng/mL, 明显高于N-CLNM组的71.30(41.79, 92.34) ng/mL, 2组比较有统计学意义($P<0.001$)。CLNM组淋巴结短径长于N-CLNM组, CLNM组淋巴结短径 >10 mm、钙化征、明显强化、囊性或坏死、侵犯周围组织的比例均高于N-CLNM组(均 $P<0.05$)。ROC曲线显示: 术前血清Tg水平联合术前CT双能量成像征象诊断PTC患者CLNM的曲线下面积为0.832(95% CI: 0.763~0.901), 灵敏度为82.41%, 特异度为100.00%, 均高于术前血清Tg水平、术前CT双能量成像征象单一诊断。结论: PTC患者术前血清Tg水平和CT双能量成像形态学征象均与CLNM的发生紧密相关, 二者联合应用可为术前CLNM的诊断提供依据。

[关键词] 甲状腺乳头状癌; 淋巴结转移; 甲状腺球蛋白; CT双能量成像; 诊断

Diagnostic value of preoperative dual-energy CT imaging combined with serum thyroglobulin level in cervical lymph node metastasis of thyroid papillary carcinoma

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ABSTRACT

Objective: To investigate the value of preoperative dual-energy CT combined with serum

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thyroglobulin (Tg) in the diagnosis of cervical lymph node metastasis (CLNM) of thyroid papillary carcinoma (PTC).

Methods: The data of 81 patients with PTC who completed radical thyroidectomy in Hefei BOE Hospital from May 2019 to October 2021 were analyzed retrospectively. All patients underwent dual-energy CT scanning and serum Tg level detection before operation. Taking the surgical and pathological results as the gold standard, 81 patients with PTC were divided into a CLNM group (34 patients with CLNM) and a N-CLNM group (47 patients without CLNM). The preoperative Tg levels and dual-energy CT examination data of the 2 groups were compared. The receiver operator characteristic (ROC) curve was used to evaluate the diagnostic value of preoperative serum Tg level, preoperative dual-energy CT examination and combined diagnosis for CLNM in PTC patients.

Results: The preoperative serum Tg level of the CLNM group was 97.85 (75.01, 117.51) ng/mL, which was significantly higher than that of the N-CLNM group [71.30 (41.79, 92.34) ng/mL], the difference was statistically significant ($P < 0.001$). The short diameter of lymph nodes in the CLNM group was longer than that in the N-CLNM group, and the proportions of short diameter > 10 mm, calcification, obvious enhancement, cystic or necrosis and invasion of surrounding tissues in the CLNM group were higher than those in the N-CLNM group (all $P < 0.05$). ROC curve showed that the area under the curve of preoperative serum Tg level combined with preoperative dual-energy CT features in diagnosing CLNM in PTC patients was 0.832, 95% confidence interval was 0.763 to 0.901, the sensitivity was 82.41%, and the specificity was 100.00%, which were all higher than those of preoperative serum Tg level and preoperative dual-energy CT features alone.

Conclusion: The preoperative serum Tg level and dual-energy CT morphological features of PTC patients are closely related to the occurrence of CLNM. The combined application of the serum Tg level and dual-energy CT features can provide a basis for the diagnosis of CLNM before operation.

KEY WORDS papillary thyroid carcinoma; lymph node metastasis; thyroglobulin; dual-energy CT; diagnosis

甲状腺癌是常见内分泌系统恶性肿瘤类型, 可表现为甲状腺肿大/结节、呼吸/吞咽困难等典型症状。甲状腺乳头状癌 (papillary thyroid carcinoma, PTC) 是甲状腺癌的主要病理分型, 占成人甲状腺癌患者的 70%~80%^[1]。虽然 PTC 呈低度恶性, 预后优于滤泡状癌、未分化型癌或髓样癌, 但 PTC 早期易发生颈部淋巴结转移 (cervical lymph node metastasis, CLNM), 术后复发和转移风险较高。因此术前准确诊断淋巴结是否存在转移对指导术中淋巴结清扫和降低术后复发并转移风险尤为重要^[2]。甲状腺球蛋白 (thyroglobulin, Tg) 是甲状腺上皮滤泡细胞分泌的一种特异性糖蛋白, 在甲状腺疾病如甲状腺功能减退、甲状腺癌和甲状腺肿瘤等中均有应用, 但对于术前诊断 PTC 患者有无 CLNM 发生的价值有待探究^[3]。目

前影像学在 PTC 患者术前淋巴结检查中占有重要地位, 但常用超声检查的敏感性较低, 且易受操作者主观性影响较大。CT 的密度分辨率和空间分辨率均较高, 且图像后处理技术的进步可一定程度上弥补超声检查的不足^[4], 因此在 PTC 患者术前影像学检查中 CT 的地位日益凸显。本研究回顾性分析 81 例 PTC 手术患者的资料, 旨在探讨术前 CT 双能量成像联合血清 Tg 水平对 PTC 患者 CLNM 的诊断价值。

1 对象与方法

1.1 对象

收集 2019 年 5 月至 2021 年 10 月在合肥京东方医院确诊治疗的 81 例 PTC 患者资料, 进行单中心回顾

性队列研究。其中男31例,女50例;年龄22~75(47.23±10.19)岁。PTC患者入选标准:1)年龄18~75岁,首次确诊PTC,均为单发结节,征得同意后均成功接受根治术治疗,行均行扩大淋巴结清扫术获得病理证实;2)围手术期实验室、CT影像学 and 手术病理等相关资料均保留完整;3)术前未接受过PTC相关治疗。排除标准:1)既往颈部或颅脑部肿瘤病史或放疗史;2)病理证实为其他分型的甲状腺分化癌,如甲状腺滤泡状癌或甲状腺髓样癌;3)合并甲状腺炎、甲状腺功能亢进等其他甲状腺疾病;4)资料残缺不宜纳入研究者。本研究得到合肥京东方医院伦理委员会批准。

所有PTC患者由同组甲状腺外科医师完成手术,术前发现CLNM或可疑CLNM者行扩大淋巴结清扫术,术后常规病理送检且均证实为PTC。依据手术病理结果,将其分为CLNM组($n=34$)和非颈部淋巴结转移(non-cervical lymph node metastasis, N-CLNM)组($n=47$),手术病理切片分别诊断CLNM 108枚、N-CLNM 75枚。CLNM组男12例,女22例,年龄(47.51±9.60)岁;N-CLNM组男19例,女28例,年龄(47.03±9.53)岁。两组性别、年龄差异均无统计学意义(均 $P>0.05$)。

1.2 方法

1.2.1 术前CT双能量成像检查

术前3~7 d由同组资深影像科医师进行CT双能量成像检查,检查仪器为德国Siemens SoMATOM Force双源CT扫描仪,包括平扫和增强双期扫描。患者取仰卧体位,头先进,扫描范围为纵隔上部至颅底底部下缘,扫描期间正常平静呼吸,勿做吞咽或咳嗽动作。先行CT平扫,探测器准直128×0.6 mm,管电压为Sn150 kVp,管电流为118 mAs,螺距0.7,扫描层厚1.5 mm,层间距为1.5 mm,视野(field of view, FOV)为252 mm×252 mm,球管旋转时间为0.5 s/周。增强扫描对比剂为碘佛醇,注射剂量1.5 mL/kg,经肘静脉用高压注射器团注,注射速率3.0 mL/s,动脉期扫描的触发阈值为100 HU,延迟30 s后行静脉期扫描。所得原始图像传送至后处理工作者进行1 mm重建。本研究由1名从事甲状腺影像学诊断工作>8年的主治医师在不知手术病理结果前提下进行阅片。

1.2.2 血清Tg水平检测

同组检验科医师完成术前7 d内血清Tg水平检测。术前抽取患者晨起空腹肘静脉血5 mL,以3 000 r/min离心10 min,离心半径为10 cm,提取血清样本。采用罗氏Cobas e60电化学发光仪进行检查,血清Tg水平正常参考值范围:1.40~78 ng/mL。

1.3 观察指标

统计CLNM组和N-CLNM组基线资料和术前血清Tg水平,评价术前血清Tg水平对PTC患者CLNM的诊断价值;统计两组PTC患者术前CT双能量成像相关征象,包括淋巴结最短径、有无钙化、有无明显强化、有无囊变或坏死、有无侵犯周围组织等,其中淋巴结短径正常情况下 ≤ 10 mm;增强扫描下淋巴结CT值-平扫下CT值 ≥ 40 HU为明显强化;病灶突破甲状腺被膜外缘,被膜边缘中断为侵犯周围组织。由负责阅片工作的医师根据上述CT征象评估PTC患者是否为CLNM;根据手术病理学结果计算术前CT双能量成像检查的灵敏度、特异度和准确度。

1.4 统计学处理

用Excel表格归类整理CLNM组和N-CLNM组相关资料,并导入SPSS 23.0统计学软件进行数据分析。计数资料组间比较用 χ^2 或Fisher确切概率法检验,用例(%)描述;经Levene法和Kolmogorov-Smirnov法检验后,满足正态分布和方差齐性的计量资料,组间比较采用独立 t 检验,用均数±标准差($\bar{x}\pm s$)描述;非正态分布则用中位数(第1四分位数,第3四分位数)[$M(P_{25}, P_{75})$]表示,组间比较采用秩和检验。用受试者工作特征(receiver operator characteristic, ROC)曲线评价术前血清Tg水平、术前CT双能量成像检查以及联合诊断对PTC患者CLNM的诊断价值,曲线下面积(area under curve, AUC) >0.7 表示具有较好的诊断价值。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组术前血清Tg水平比较

CLNM组术前血清Tg水平为97.85(75.01, 117.51) ng/mL,明显高于N-CLNM组的71.30(41.79, 92.34) ng/mL,2组比较差异有统计学意义($Z=5.557$, $P<0.001$)。

2.2 两组术前CT双能量成像征象比较

比较手术病理证实的CLNM组108枚和N-CLNM组75枚淋巴结的术前CT征象资料,CLNM组淋巴结短径长于N-CLNM组,CLNM组淋巴结短径 >10 mm、钙化征、明显强化、囊性或坏死、侵犯周围组织的比例均高于N-CLNM组(均 $P<0.05$,表1)。

2.3 CLNM组和N-CLNM组术前CT征象的病例分析

PTC患者颈部N-CLNM和CLNM的CT征象分别见图1A和图1B。N-CLNM,女,51岁,甲状腺

右叶上极见一类圆形低密度影, 边界清晰, 直径约 17 mm, 其内密度均匀; CT 值约 46 HU; 相应甲状腺右叶部分受压, 增强后动脉期、静脉期未见强化, 甲状腺左侧叶及峡部未见异常密度影, 增强后强化均匀。双侧颈部未见明显肿大淋巴结影(图 1A)。CLNM, 女, 47 岁, 甲状腺左侧叶稍

增大, 其内可见一 16 mm × 13 mm 之实质占位性病灶, 密度欠均匀, 其内夹杂点状钙化, 增强扫描呈明显不均匀强化, 边界欠清, 周围肌间隙清晰; 甲状腺右叶及峡部未见明显异常强化灶。双侧颌下及颈动脉鞘区见多发淋巴结, 大者短径 < 1.0 cm (图 1B)。

表 1 两组术前 CT 双能量成像征象比较

Table 1 Comparison of preoperative dual-energy CT signs between the 2 groups

组别	n	淋巴结短径/mm	淋巴结数[例(%)]		钙化[例(%)]	
			≤10 mm	>10 mm	阳性	阴性
CLNM 组	108	9.51±2.63	51 (47.22)	57 (52.78)	79 (73.15)	29 (26.85)
N-CLNM 组	75	7.76±2.45	48 (64.00)	27 (36.00)	35 (46.67)	40 (53.33)
χ^2/t		4.552		5.018		13.215
P		<0.001		0.025		<0.001

组别	明显强化[例(%)]		囊变或坏死[例(%)]		侵犯周围组织[例(%)]	
	阳性	阴性	阳性	阴性	阳性	阴性
CLNM 组	86 (79.63)	22 (20.37)	24 (22.22)	84 (77.78)	16 (14.81)	92 (85.19)
N-CLNM 组	23 (30.67)	52 (69.33)	0 (0.00)	75 (100.00)	0 (0.00)	75 (100.00)
χ^2/t		44.057		19.182		12.176
P		<0.001		<0.001		<0.001

CLNM: 颈部淋巴结转移; N-CLNM: 非颈部淋巴结转移。

2.4 不同诊断方式对 PTC 患者 CLNM 的诊断价值

ROC 曲线显示: 术前血清 Tg 水平联合术前 CT 双能量成像征象诊断 PTC 患者 CLNM 的 AUC 为

0.832, 95% 置信区间 0.763~0.901, 灵敏度为 82.41%, 特异度为 100.00%, 均高于术前血清 Tg 水平、术前 CT 双能量成像征象单一诊断(表 2, 图 2)。

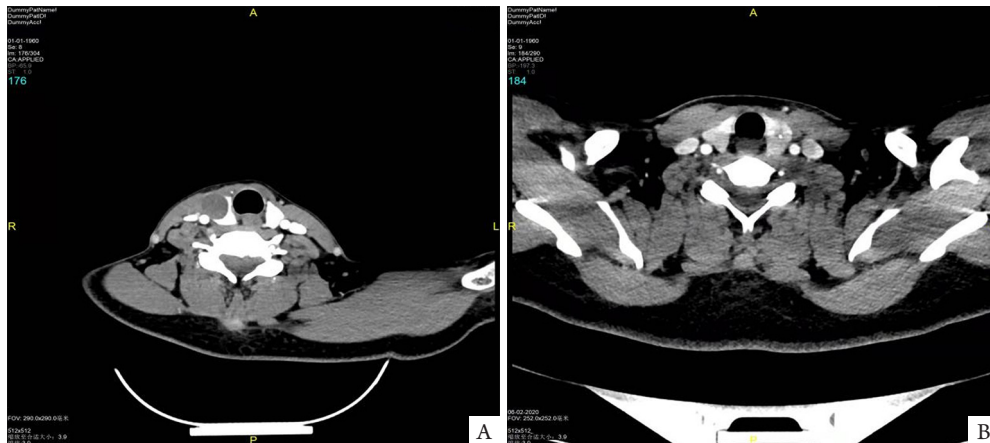


图 1 患者的 CT 征象

Figure 1 CT signs of patients

A: N-CLNM; B: CLNM. N-CLNM: Non-cervical lymph node metastasis; CLNM: Cervical lymph node metastasis.

表2 不同诊断方式诊断PTC患者CLNM的诊断价值

Table 2 Diagnostic value of different diagnostic methods for CLNM in PTC patients

诊断方式	AUC	标准误	截断值	灵敏度/%	特异度/%	95% CI
术前血清Tg水平	0.742	0.036	91.28*	63.89	81.33	0.671~0.813
术前CT双能量成像征象	0.772	0.037	—	82.41	72.00	0.699~0.845
联合诊断	0.832	0.035	—	82.41	100.00	0.763~0.901

*单位为ng/mL。PTC：甲状腺乳头状癌；CLNM：颈部淋巴结转移；AUC：曲线下面积；Tg：甲状腺球蛋白。

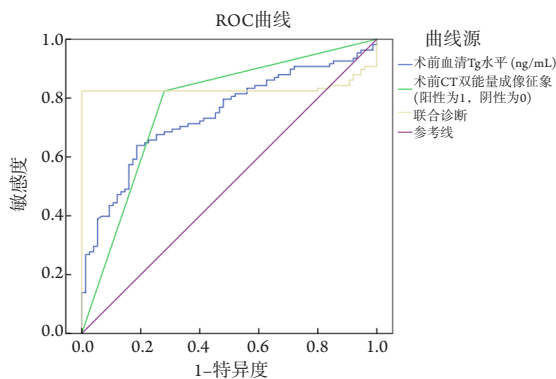


图2 不同诊断方式诊断PTC患者CLNM的ROC曲线

Figure 2 ROC curves of CLNM in PTC patients diagnosed by different methods

ROC: Receiver operator characteristic; Tg: Thyroglobulin; PTC: Papillary thyroid carcinoma; CLNM: Cervical lymph node metastasis.

3 讨论

CLNM是PTC的重要病理特征，较多PTC患者初诊时已存在CLNM。普遍认为，术前CLNM是PTC患者术后复发转移的重要危险因素，因此术前准确评估CLNM意义重大。2015年美国甲状腺学会(American Thyroid Association, ATA)发布的《成人甲状腺结节与分化型甲状腺癌治疗指南》^[5]中也明确强调了术前淋巴结诊断对制订手术和术后随访策略、评估预后的重要性。细针穿刺活检是评估CLNM的准确手段，但存在一定创伤性，而且也不可能对所有区域的淋巴结进行穿刺，尤其是隐匿性淋巴结转移，故存在漏诊可能。实验室和影像学是术前PTC检查的重要手段，本研究主要探讨血清Tg水平和CT双能量成像对PTC患者CLNM术前诊断的应用价值。

Tg主要是由甲状腺细胞合成并释放进入甲状腺滤泡腔中，溶解体水解Tg表面甲状腺素、三碘甲状腺原氨酸后使之释放入血，同时少量Tg释放入血。

目前Tg已被认为是甲状腺体形完整性的特殊标志物，也是分化型PTC的肿瘤标志物。

术前血清Tg水平监测常用于术后复发风险和预后评估，术后Tg水平升高者，往往提示肿瘤复发或存在转移灶^[6-7]。术前血清Tg水平与PTC患者CLNM的关系有待探究，本研究显示：CLNM组术前Tg水平明显高于N-CLNM组，AUC为0.742，截断值91.28 ng/mL，灵敏度和特异度分别为63.89%和81.33%。可见术前Tg水平对PTC患者CLNM有一定诊断价值，特异度较好。孙少坤等^[8]报道显示：术前血清Tg水平判断PTC患者中央区 and 颈侧区淋巴结有无转移的AUC分别为0.710和0.728，截断值分别为92.28 ng/mL和117.20 ng/mL。本研究支持上述结论。本研究因样本量偏少，故未能将CLNM组进一步分组。在临床实践中，PTC患者术前Tg水平较高者，其T分期往往级别更高，推测PTC患者Tg水平可一定程度上反映肿瘤生长活跃程度，肿瘤生长活跃对甲状腺组织的破坏程度越明显，释放入血的Tg含量增多；另外肿瘤自身也可大量合成释放Tg，导致血清Tg水平明显升高^[9-10]。但血清Tg水平诊断PTC CLNM的灵敏度偏低，故单独应用效果不佳，还应结合影像学依据。

CT设备和技术近些年发展迅猛，CT双能量成像扫描下患者受到的辐射剂量降低，也不影响后续放射性碘消融术治疗，安全性明显提高。而且与常用超声手段相比，CT在判断颈部淋巴结状态的敏感度方面明显更优。磁共振(magnetic resonance imaging, MRI)虽然能多方位、多层次观察淋巴结转移病灶，能辨别淋巴结病变和周围组织的关系，但与CT相比，MRI存在检查耗时长、对患者检查配合度要求高、禁忌证多等不足，而且MRI对淋巴结钙化欠敏感。CT扫描和增强扫描能显示淋巴结病灶的详细信息，能良好显示低位、颈深部淋巴结，有助于判断淋巴结侵犯范围和与气管、食管等周围组织的关系；CT形态学征象可为术前CLNM诊断和手术方案制订

提供影像学依据^[11]。本研究显示: CLNM组淋巴结短径长于N-CLNM组, CLNM组淋巴结短径>10 mm、钙化征、明显强化、囊性或坏死、侵犯周围组织的比例均高于N-CLNM组, AUC为0.772, 灵敏度和特异度分别为82.41%和72.00%, 与以往研究^[12-13]报道相符。借助术前CT双能量成像征象能够为诊断PTC患者是否发生淋巴结转移提供重要参考, 其中淋巴结强化程度是最重要的CT征象。分析原因为, PTC患者的转移淋巴结具有摄碘的组织学特性, 血供较丰富, 因此增强扫描下尤其是动脉期转移淋巴结的强化程度可在一定程度反映内微循环的情况, 且随淋巴结增大和淋巴门血管增粗, 上述强化程度更加明显^[14-15]。

另外, 本研究比较不同诊断方式的诊断效能, 结果显示术前血清Tg水平联合术前CT双能量成像征象诊断PTC患者CLNM的AUC为0.832(95% CI 0.763~0.901), 灵敏度为82.41%, 特异度为100.00%, 均高于术前血清Tg水平、术前CT双能量成像征象单一诊断。术前血清Tg水平、术前CT双能量成像征象能够从不同角度对PTC患者是否发生CLNM进行评估, 二者联合能够进一步提升其诊断准确率。

本研究的样本量偏少, 且未能进一步细分中央区 and 颈侧区CLNM与血清Tg水平的关系, 后续需不断完善。总的来说, 术前血清Tg水平和CT双能量成像征象对PTC患者是否发生CLNM转移均有一定判断价值, 但也具有各自不足, 二者联合可为临床诊断PTC患者CLNM提供更详细的诊断依据。

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