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· 甲状腺外科专题研究 ·

甲状腺髓样癌侧颈淋巴结转移危险因素的单中心回顾性分析

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摘要

背景与目的: 甲状腺髓样癌 (MTC) 恶性程度较高, 常伴颈部淋巴结转移, 对预后影响显著。然而, 目前对 MTC 侧颈淋巴结转移 (LLNM) 的风险因素尚缺乏统一认识。本研究旨在分析 MTC 患者发生 LLNM 的危险因素, 以期为制定个体化手术方案提供依据。

方法: 回顾性分析 2011—2019 年在天津医科大学肿瘤医院接受手术治疗的 242 例 MTC 患者临床病理资料, 评估术前降钙素水平、CEA 水平等肿瘤标志物与 LLNM 的关系, 并采用单因素与多因素 Logistic 回归分析探讨 LLNM 的独立危险因素。

结果: 术前降钙素水平与肿瘤直径、淋巴结转移数量及淋巴结转移数范围明显有关, 而术前 CEA 水平与肿瘤直径明显有关 (均 $P < 0.05$); 术前降钙素水平诊断 LLNM 的 ROC 曲线下面积为 0.750 ($P = 0.000$), 最佳截断值 266.00 ng/L (敏感度 0.854, 特异度 0.577), 术前 CEA 水平对 LLNM 的诊断价值有限。单因素分析显示, 性别、侵出腺叶、T 分期、中央区淋巴结转移 (CLNM)、双侧、术前降钙素水平、肿瘤直径和多灶性与 MTC 患者 LLNM 明显有关 (均 $P < 0.05$); 多因素分析显示, CLNM ($OR = 17.645$, 95% $CI = 7.728 \sim 40.290$) 和术前降钙素 ≥ 266.00 ng/L ($OR = 7.832$, 95% $CI = 3.132 \sim 19.582$) 是 MTC 患者发生 LLNM 的独立危险因素。

结论: CLNM 及术前降钙素水平升高与 MTC 患者发生 LLNM 密切相关。联合这两项指标可有效筛选 LLNM 高风险人群, 推动 MTC 治疗的个体化与精准化。

关键词

甲状腺肿瘤; 淋巴转移; 降钙素; 癌胚抗原; 危险因素
中图分类号: R736.1

Risk factors for lateral cervical lymph node metastasis in medullary thyroid carcinoma: a single-center retrospective analysis

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Abstract

Background and Aims: Medullary thyroid carcinoma (MTC) is an aggressive malignancy that is frequently associated with cervical lymph node metastasis, significantly affecting patient prognosis. However, the risk factors for lateral cervical lymph node metastasis (LLNM) in MTC remain inconclusive. This study aims to identify the risk factors associated with LLNM in MTC patients, in

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order to inform individualized surgical decision-making.

Methods: The clinicopathologic data of 242 patients with MTC who underwent surgical treatment at Tianjin Medical University Cancer Institute and Hospital from 2011 to 2019 were retrospectively collected. The relationships between preoperative tumor markers, including calcitonin and carcinoembryonic antigen (CEA), and LLNM were evaluated. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for LLNM.

Results: Preoperative calcitonin level was significantly associated with tumor diameter, the number of lymph node metastases, and the extent of lymph node involvement, while preoperative CEA level was significantly associated with tumor diameter (all $P<0.05$). The area under the ROC curve for preoperative calcitonin in diagnosing LLNM was 0.750 ($P=0.000$), with an optimal cutoff value of 266.00 ng/L (sensitivity 0.854, specificity 0.577). The diagnostic value of preoperative CEA for LLNM was limited. Univariate analysis showed that sex, extracapsular extension, T stage, central lymph node metastasis (CLNM), bilateral lesions, preoperative calcitonin, tumor diameter, and multifocality were significantly associated with LLNM in MTC patients (all $P<0.05$). Multivariate analysis revealed that CLNM ($OR=17.645$, 95% $CI=7.728-40.290$) and preoperative calcitonin ≥ 266.00 ng/L ($OR=7.832$, 95% $CI=3.132-19.582$) were independent risk factors for LLNM.

Conclusion: CLNM and elevated preoperative calcitonin level are closely associated with LLNM in patients with MTC. The combination of these two indicators may help identify high-risk patients for LLNM, thereby promoting individualized and precise treatment strategies for MTC.

Key words

Thyroid Neoplasms; Lymphatic Metastasis; Calcitonin; Carcinoembryonic Antigen; Risk factors

CLC number: R736.1

甲状腺髓样癌 (medullary thyroid carcinoma, MTC) 是一种起源于甲状腺滤泡旁 C 细胞的神经内分泌肿瘤, 占甲状腺癌的 1%~2%, 但占甲状腺癌所致死亡的 13.4%^[1]。手术是 MTC 的唯一治愈性治疗手段, 但约 50%~70% 的患者确诊时已存在颈淋巴结转移, 而颈淋巴结转移与局部复发及不良预后密切相关。国内外指南^[2-3]推荐在全甲状腺切除的基础上行治疗性或预防性中央区淋巴结清扫; 对于侧颈淋巴结, 推荐治疗性颈淋巴结清扫。但关于预防性侧颈淋巴结清扫仍存在争议, 因此, 临床上对于侧颈淋巴结转移 (lateral lymph node metastasis, LLNM) 的准确诊断尤为重要, 是实施个体化、精准化治疗的基础。指南^[2-3]推荐 MTC 颈淋巴结转移的诊断首选超声检查, 但超声检查不足以预测大量亚临床淋巴结转移^[4]。近年来, 一些有关预测 MTC LLNM 危险因素的研究结论并不统一^[5-9], 因此本研究旨在分析影响 MTC LLNM 的危险因素。

1 资料与方法

1.1 一般资料

采用回顾性队列设计, 纳入 2011—2019 年间首诊于天津医科大学肿瘤医院并行手术的 242 例 MTC 患者。纳入标准: (1) 术后病理确诊为 MTC; (2) 接受至少中央区淋巴结清扫 (或) 单侧侧颈淋巴结清扫; (3) 随访资料完整。排除标准: (1) 合并其他恶性肿瘤; (2) 既往颈部放疗或甲状腺手术史。本回顾性研究经天津医科大学肿瘤医院伦理委员会批准 (伦理批件号: bc2023122), 所有患者均签署知情同意书。

1.2 观察指标及分组

收集患者相关临床病理资料, 包括性别、年龄、肿瘤直径, 侵出腺叶、多灶性、手术切除范围、美国癌症联合委员会第 8 版 pTNM 分期、术前降钙素水平及癌胚抗原 (CEA) 水平、淋巴结转移范围及数量。按照肿瘤直径, 将患者分为 ≤ 1 cm 组、 >1 cm 组, ≤ 2 cm 组、 >2 cm 组, ≤ 4 cm 组和 >4 cm 组。按照淋巴结转移范围将患者分为 N0 组、N1a 组、

N1b组。按照淋巴结转移数量，将患者分为0枚组、1~3枚组和≥4枚组。

1.3 统计学处理

应用SPSS 26.0软件对数据结果进行统计学分析。计数资料以例数(百分比)[$n(\%)$]表示，连续变量以均数±标准差($\bar{x} \pm s$)或中位数(四分位间距)[$M(IQR)$]表示，组间比较采用Kruskal-Wallis H 检验。绘制受试者工作特征(receiver operating characteristic, ROC)曲线评估术前降钙素及CEA的预测效能。采用 χ^2 检验分析MTC LLNM与临床病理资料的关系，Logistic回归模型分析影响LLNM的危险因素。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 基本资料

242例患者中，男性102例，女性140例，中位年龄51(11~77)岁。原发灶为单发174例，多发者68例，其中多发者以最大肿瘤作为研究对象。行术前降钙素检测233例，术前降钙素正常者5例，降钙素正常上限~100 ng/L者55例，降钙素>100~1 000 ng/L者84例，降钙素>1 000~2 000 ng/L者41例，降钙素>2 000 ng/L者48例。行术前CEA检测83例，CEA正常者11例，CEA正常上限~100 ng/mL者54例，CEA 100~300 ng/mL者10例，CEA>300 ng/mL者8例。甲状腺切除范围：行全甲状腺切除114例，单侧腺叶及峡叶切除128例。淋巴结清扫范围：全部患者均至少行患侧中央区淋巴结清扫术。仅行中央区淋巴结清扫术120例，患侧中央区及侧颈淋巴结清扫122例，其中14例行双侧颈淋巴结清扫。27例合并甲状腺乳头状癌。原发灶最大直径中位数1.50(0.80~2.50) cm，侵出腺叶101例。中央区淋巴结转移(central lymph node metastasis, CLNM)115例，未转移127例。LLNM 100例。I期70例，II期40例，III期33例，IV期99例(表1)。

2.2 术前降钙素及CEA水平与肿瘤直径、淋巴结转移的关系

分析降钙素与CEA两种肿瘤标志物与MTC患

者临床病理特征的关系，结果显示，术前降钙素水平与肿瘤直径、淋巴结转移范围、淋巴结转移数量明显有关($H=106.249$, $P=0.000$; $H=41.424$, $P=0.000$; $H=42.612$, $P=0.000$)。术前CEA水平与肿瘤直径明显有关($H=33.888$, $P=0.000$)，但与淋巴结转移范围、淋巴结转移数量无明显关系($H=2.825$, $P=0.243$; $H=3.362$, $P=0.186$)(表2)。

表1 242例MTC患者临床病理资料

Table 1 Clinicopathologic data of 242 patients with MTC

参数	数值
年龄岁, $M(IQR)$	51(42.75~59.00)
降钙素[ng/L, $M(IQR)$] ¹⁾	439.00(93.70~1 714.50)
CEA[ng/mL, $M(IQR)$] ²⁾	26.95(8.76~81.78)
肿瘤最大直径[cm, $M(IQR)$]	1.50(0.80~2.50)
性别[$n(\%)$]	
男	102(42.1)
女	140(57.9)
原发灶切除范围[$n(\%)$]	
腺叶及峡叶	128(52.9)
全甲状腺	114(47.1)
TNM分期[$n(\%)$]	
I	70(28.9)
II	40(16.5)
III	33(13.6)
IV	99(40.9)
淋巴结切除范围[$n(\%)$]	
中央区	120(49.6)
中央区+侧颈区	122(50.4)
T分期[$n(\%)$]	
T1	108(44.6)
T2	28(11.6)
T3	97(40.1)
T4	9(3.7)
N分期[$n(\%)$]	
N0	109(45.0)
N1a	33(13.6)
N1b	100(41.3)
侵出腺叶[$n(\%)$]	
否	141(58.3)
是	101(41.7)
病灶数[$n(\%)$]	
单发	174(71.9)
多发	68(28.1)

注:1)233例术前行降钙素检测;2)83例术前行CEA检测

Note: 1) 233 patients undergoing calcitonin detection before the operation; 2) 83 patients undergoing CEA detection before the operation

表2 术前降钙素、CEA水平与MTC患者肿瘤直径、淋巴结转移范围、淋巴结转移数量的关系[M(IQR)]

Table 2 The associations of preoperative calcitonin and CEA levels with tumor diameter, extent of lymph node metastasis, and number of metastatic lymph nodes in patients with MTC [M(IQR)]

项目	降钙素(ng/L)	H	P	CEA(ng/mL)	H	P
肿瘤直径(cm)						
≤1	80.30(20.10~176.50)			8.13(2.97~8.13)		
>1~2	715.00(296.00~1 496.00)	106.249	0.000	21.68(13.05~73.56)	33.888	0.000
>2~4	1 994.00(775.00~2 000.00)			67.24(30.55~202.60)		
>4	2 000.00(1 100.00~2 000.00)			178.00(88.59~305.07)		
淋巴结转移范围						
N0	172.50(40.43~1 019.75)			27.340(8.13~67.240)		
N1a	166.00(78.30~1 034.00)	41.424	0.000	19.36(2.603~54.770)	2.825	0.243
N1b	1 258.50(388.75~2 000.00)			27.655(9.323~173.025)		
淋巴结转移数量(枚)						
0	161.50(40.43~991.50)			21.68(6.78~59.21)		
1~3	172.00(80.25~1 110.50)	42.612	0.000	26.24(7.92~38.99)	3.362	0.186
≥4	1 339.00(429.500~2 000.000)			32.00(10.200~174.700)		

2.3 术前降钙素及CEA水平对LLNM的诊断效能

术前降钙素水平诊断LLNM的ROC曲线下面积(AUC)为0.750(P=0.000),最佳截断值266.00 ng/L(敏感度0.854,特异度0.577)(图1A)。术前CEA

水平诊断LLNM的价值有限,其AUC为0.587(P=0.174),最佳截断值88.4 ng/mL(敏感度0.375,特异度0.907)(图1B)。

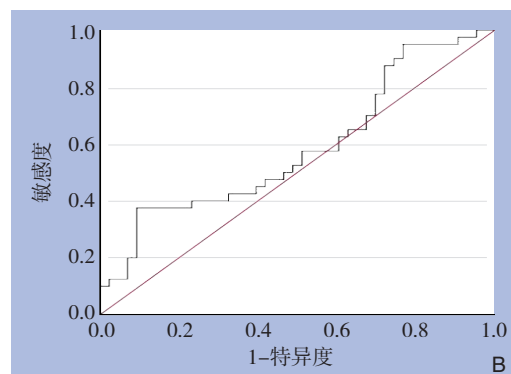
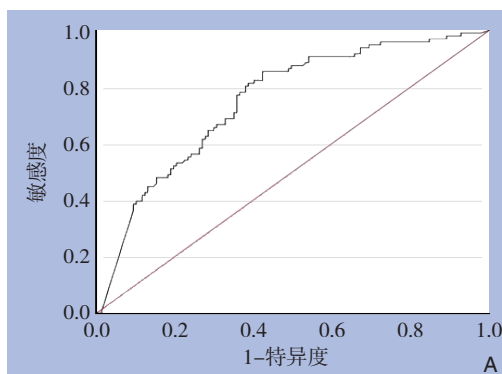


图1 术前降钙素、CEA水平预测MTC LLNM的ROC曲线 A: 术前降钙素水平; B: 术前CEA水平

Figure 1 ROC curve of preoperative calcitonin, CEA and lateral lymph node metastasis of medullary thyroid carcinoma A: Preoperative calcitonin; B: Preoperative CEA

2.4 MTC患者LLNM的影响因素

单因素分析结果显示,LLNM与性别、双侧、侵出腺叶、肿瘤直径、多灶性、T分期、术前降钙素水平、CLNM明显有关(均P<0.05);与年龄、

家族史无明显关系(均P>0.05)(表3)。多因素分析结果显示,CLNM、术前降钙素水平是MTC LLNM独立影响因素(均P<0.05)(表4)。

表3 影响MTC患者发生LLNM的单因素分析[n(%)]
Table 3 Univariate analysis of factors influencing the occurrence of LLNM in MTC patients [n(%)]

因素	LLNM		χ^2	P
	否(n=142)	是(n=100)		
年龄(岁)				
<51	65(45.77)	51(51.00)	0.642	0.423
≥51	77(54.23)	49(49.00)		
性别				
男	46(32.39)	56(56.00)	13.409	0.000
女	96(67.61)	44(44.00)		
侵出腺叶				
是	99(69.72)	42(42.00)	18.539	0.000
否	43(30.28)	58(58.00)		
家族史				
是	5(3.52)	9(9.00)	3.232	0.072
否	137(96.48)	91(91.00)		
T分期				
T1+T2	96(67.61)	40(40.00)	18.166	0.000
T3+T4	46(32.39)	60(60.00)		
CLNM				
否	106(74.65)	14(14.00)	86.336	0.000
是	36(25.35)	86(86.00)		
双侧				
否	134(94.37)	84(84.00)	7.058	0.008
是	8(5.63)	16(16.00)		
术前降钙素(ng/L) ¹⁾				
<266	79(55.63)	14(14.00)	43.682	0.000
≥266	58(40.85)	82(82.00)		
肿瘤直径(cm)				
≤1.5	94(66.20)	42(42.00)	13.957	0.000
>1.5	48(33.80)	58(58.00)		
多灶性				
否	115(80.99)	59(59.00)	14.039	0.000
是	27(19.01)	41(41.00)		

注: 1) 9例患者未检查术前降钙素

Note: 1) Preoperative calcitonin levels were not measured in 9 patients

表4 影响MTC患者发生LLNM的多因素分析
Table 4 Multivariate analysis of factors influencing the occurrence of LLNM in MTC patients

参数	β	S.E.	Wald	P	OR(95% CI)
性别	-0.622	0.384	2.624	0.105	0.537(0.253~1.139)
双侧	0.273	0.697	0.154	0.695	1.314(0.335~5.150)
侵出腺叶	0.992	1.213	0.669	0.413	2.698(0.250~29.090)
多灶性	0.620	0.506	1.500	0.221	1.859(0.689~5.013)
CLNM	2.870	0.421	46.433	0.000	17.645(7.728~40.290)
术前降钙素	2.058	0.468	19.375	0.000	7.832(3.132~19.582)
T分期	-0.958	1.220	0.617	0.432	0.383(0.035~4.191)
直径	0.171	0.433	0.156	0.693	1.187(0.507~2.775)
常量	-3.346	0.549	37.082	0.000	0.035

3 讨论

手术是MTC患者唯一治愈性治疗手段。MTC的预后及复发取决于初次手术的彻底性^[10-11]。指南^[2-3]推荐MTC患者应至少行甲状腺切除术及中央区淋巴结清扫术,然而,关于预防性切除侧颈淋巴结仍存在争议。虽然较大范围的淋巴结清扫可减少疾病复发的机会,却对患者的生活质量产生不利影响^[12]。

指南^[2-3]推荐评估MTC LLNM首选超声检查,而CT、PET/CT^[13-14],包括¹⁸F-DOPA PET^[15]和⁶⁸Ga PET^[16],对于淋巴结转移的诊断准确率仍较低。CTR-FAPI PET展现出更高的诊断准确率^[17],但仍需大样本进一步验证。临床上,对于可疑转移性的淋巴结,结合穿刺活检及洗脱液降钙素测定可进一步提高诊断准确率。如何提高亚临床淋巴结转移的诊断率,是减少局部复发,改善预后的关键。

本研究结果显示,降钙素水平和CLNM是预测LLNM的独立危险因素,而降钙素水平与肿瘤直径、淋巴结转移数量及范围相关。MTC发生同侧CLNM、侧颈区及对侧CLNM、LLNM的降钙素截断值分别是20、50、200和500 pg/mL^[18]。也有文章^[5]报道,患者发生同侧LLNM的降钙素截断值为90 pg/mL。而本研究预测同侧LLNM的降钙素截断值为266 pg/mL (AUC=0.750, 敏感度85.4%, 特异度57.7%)。以50 pg/mL为截断值分析本文的数据,敏感度95.8%,特异度为27.0%;而以90 pg/mL为截断值分析本文的数据,敏感度90.6%,特异度为35.0%。出现不同降钙素截断值的原因可能与检测方法、人种异质性及纳入人群分期偏倚有关。本研究中,在降钙素>2 000 pg/mL的患者当中,仍有13例患者未发生淋巴结转移。也有研究^[19]显示,术前降钙素水平并不能预测MTC患者是否需要预防性侧淋巴结清扫。临床上,单依靠降钙素水平可能出现漏诊、误诊风险,需结合影像学、分子标志物及淋巴结穿刺洗脱液降钙素水平综合评估。因此,降钙素作为一种检测建立的截断值并不是普遍适用于所有患者。这也是目前指南并没有制定一个参考范围用于MTC的诊断及预测LLNM的原因^[2]。

本研究显示,术前CEA水平与肿瘤直径有关,但是与淋巴结转移数量及范围无明显关系,提示

术前CEA水平对于LLNM的预测作用弱。但也有研究^[5]显示,CEA水平与LLNM具有一定相关性,截断值分别为29.68 ng/mL (AUC: 0.831)。将CEA水平作为预测LLNM的指标还需更多临床数据的验证。

关于不同临床病理特征在预测MTC LLNM方面的说法并不统一。相关研究显示肿瘤直径^[6,20]、性别^[7-9]、多灶性^[6]、腺外侵犯^[6,21]、中央区转移^[7,21-22]是预测LLNM的危险因素。出现上述原因的结果可能与纳入患者分期偏倚、多为单中心数据及纳入患者例数偏少等有关。也有研究^[23-24]显示,借助术中冷冻检测肿瘤间质增生反应来预测MTC LLNM。近期研究^[25-26]显示,结合术前降钙素水平与间质增生反应程度可以更好地预测MTC LLNM。本研究结果显示CLNM是MTC患者发生LLNM的独立危险因素。英国国家多学科指南^[27]推荐对于有CLNM的MTC患者行预防性侧颈部淋巴结清扫。但是,临床上我们还应注意存在跳跃转移的现象^[28]。本研究中,CLNM且降钙素水平 ≥ 266 ng/L患者发生LLNM的比率为83.7%。因此,建议针对存在高危因素患者应结合其他相关检查,权衡获益与手术并发症风险综合决定,必要时行预防性侧颈清扫。

本研究尚存在一定的局限性。首先,本研究为单中心的回顾性研究,所得结论还需多中心、大样本的数据资料进一步深入分析和研究论证。其次,本研究中48例患者降钙素水平 ≥ 2000 ng/L,但未对该部分患者进一步进行检测或分层分析。最后,本研究未纳入RET基因突变状态,将在未来研究中进一步完善、深入。

综上所述,CLNM和降钙素水平 ≥ 266 ng/L是MTC患者发生LLNM的危险因素。基于此提出的风险模型可为个体化手术决策提供可靠依据。

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