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·专题研究·

甲状腺乳头状癌患者侧颈区淋巴结转移影响因素分析

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摘 要

背景与目的：甲状腺乳头状癌（PTC）是甲状腺癌中占比最大的病理类型，PTC 的侧颈区淋巴结转移（LLNM）是导致患者复发和再手术的主要原因。因此，本研究分析 PTC 患者的临床特征，探讨发生 LLNM 的影响因素，并构建临床预测模型，为制定合理的手术范围提供参考依据。

方法：回顾性分析锦州医科大学附属第一医院 2018 年 3 月—2022 年 1 月行手术治疗的 PTC 患者临床资料，比较发生 LLNM 与未发生 LLNM 患者临床病理因素的差异，将有统计学意义的因素纳入多因素 Logistic 回归分析，用 R 4.1.3 建立 PTC 患者 LLNM 风险预测列线图模型，并绘制校准曲线评价该模型的精准度，用 ROC 曲线界定 LLNM 独立危险因素的诊断截断值。

结果：共纳入 597 例 PTC 患者，其中，187 例（31.32%）发生 LLNM。单因素分析显示，年龄、肿瘤直径、多发癌灶、腺外侵犯、颈中央区淋巴结转移（CLNM）与 *BRAF*^{V600E} 基因突变为 PTC 患者发生 LLNM 的影响因素（均 P<0.05）。年龄、肿瘤直径、发生腺外侵犯、存在 CLNM 和 *BRAF*^{V600E} 基因突变是 LLNM 的独立危险因素（均 P<0.05）。基于以上影响因素构建 PTC 患者 LLNM 风险预测列线图模型。列线图显示，肿瘤直径对 LLNM 的影响最大，多发癌灶对 LLNM 的影响最小。校准曲线分析结果显示，该列线图模型预测 PTC 患者发生 LLNM 的校准曲线接近于理想曲线。根据 ROC 曲线显示，LLNM 的独立危险因素中肿瘤直径的诊断截断值为 1.05 cm，年龄的诊断截断值为 32.5 岁。

结论：存在年龄较小、肿瘤直径>1.05 cm、发生腺外侵犯、存在 CLNM 和 *BRAF*^{V600E} 基因突变等因素的 PTC 患者发生 LLNM 的风险相对较高，基于以上因素构建的列线图模型对 PTC 患者发生侧颈区淋巴结转移具有良好的校准度。当 PTC 患者存在以上特征且列线图评分较高时，应对其侧颈区淋巴结情况更为谨慎地进行术前评估及术中探查，并采取相应的治疗措施，以改善其预后状况。

关键词 甲状腺肿瘤；癌，乳头状；淋巴转移；危险因素；列线图

中图分类号：R736.1

Analysis of influencing factors for lateral neck lymph node metastasis in patients with papillary thyroid carcinoma

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Abstract **Background and Aims:** Papillary thyroid carcinoma (PTC) is the most prevalent pathological type

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among thyroid cancers, and lateral neck lymph node metastasis (LLNM) in PTC is the primary cause of patient recurrence and reoperation. Therefore, this study was conducted to analyze the clinical characteristics of PTC patients, explore the influencing factors for LLNM, and construct a clinical prediction model to provide a reference basis for determining an appropriate surgical scope.

Methods: The clinical data of patients with PTC who underwent surgical treatment at the First Affiliated Hospital of Jinzhou Medical University from March 2018 to January 2022 were retrospectively analyzed. The clinicopathologic factors between patients who experienced LLNM and those who did not were compared. Factors that showed statistical significance were included in a multiple Logistic regression analysis. Using R 4.1.3, a predictive nomogram model for LLNM risk in PTC patients was established, and a calibration curve was plotted to evaluate the accuracy of the model. The diagnostic cut-off values for independent risk factors for LLNM were determined using the ROC curve.

Results: A total of 597 PTC patients were included, and 187 cases (31.32%) had LLNM. Univariate analysis showed that age, tumor diameter, multifocal lesions, extrathyroidal invasion, central neck lymph node metastasis (CLNM), and $BRAF^{V600E}$ gene mutation were significant factors influencing LLNM in PTC patients (all P<0.05). Age, tumor diameter, extrathyroidal invasion, presence of CLNM and $BRAF^{V600E}$ gene mutation were identified as independent risk factors for LLNM (all P<0.05). Based on these factors, a predictive nomogram model for LLNM risk in PTC patients was constructed. The nomogram demonstrated that tumor diameter had the greatest impact on LLNM, while multifocal lesions had the least. Calibration curve analysis indicated that the nomogram model had a close fit to the ideal curve for predicting LLNM in PTC patients. According to the ROC curve analysis, the diagnostic cut-off value for tumor diameter as an independent risk factor for LLNM was 1.05 cm, and the cut-off value for age was 32.5 years.

Conclusion: PTC patients who have factors such as younger age, tumor diameter >1.05 cm, extrathyroidal extension, presence of CLNM, and $BRAF^{V600E}$ gene mutation have a relatively higher risk of developing LLNM. The nomogram model constructed based on these factors demonstrates good calibration for predicting LLNM in PTC patients. When PTC patients exhibit these characteristics and have high nomogram scores, a more cautious approach should be taken in the preoperative assessment and intraoperative exploration of their lateral neck lymph nodes, and appropriate treatment measures should be implemented to improve their prognosis.

Key words Thyroid Neoplasms; Carcinoma, Papillary; Lymphatic Metastasis; Risk Factors; Nomograms

CLC number: R736.1

甲状腺乳头状癌（papillary thyroid carcinoma，PTC）是甲状腺癌中最常见的病理类型，约占甲状腺恶性肿瘤 80%[1]，约有 40%~90%[2-3]的 PTC 患者有早期发生转移现象，颈部淋巴结是最常见的转移部位。现有研究[4]普遍认为颈部淋巴结转移是导致 PTC 患者复发和再手术的主要原因，在手术治疗中全面彻底地进行颈部淋巴结清扫对于患者的预后具有重要意义。术前进行的超声与细针穿刺活检（fine needle aspiration，FNA）对 PTC 原发病灶的诊断准确率高达 90% 以上，但对淋巴结转移的诊断评估却相对局限，尤其是一些体积较小或位于血管后方的淋巴结存在漏诊的可能性[5-6]，增加术后复发的风险。因此，本研究通过对 PTC 患者的临床病理特征的分析，探讨侧颈区淋巴结发生转移（lateral lymph node metastasis，LLNM）的危险因素，为制定合理的手术范围提供参考依据。

1　资料与方法

1.1　研究对象

选择 2018 年 3 月—2022 年 1 月在锦州医科大学附属第一医院普外甲状腺科行手术治疗的患者为

　

研究对象。纳入标准：(1) 年龄>18岁的患者；(2) 经术后病理证实为PTC的患者；(3) 接受甲状腺全切术并行颈部淋巴结清扫术的患者；(4) 病理资料完整。

1.2 研究方法

采用回顾性研究的方法对有无侧颈淋巴结转移的甲状腺癌患者的性别、年龄、BMI、肿瘤最大直径、多发癌灶、腺外侵犯、肿瘤分布、肿瘤位置、中央区淋巴结转移、合并桥本氏甲状腺炎和$BRAF^{V600E}$基因突变等临床特征进行分析，确定PTC患者LLNM的影响因素。

1.3 统计学处理

使用SPSS 26.0统计软件进行数据分析。计量资料采用均数和标准差（$\bar{x} \pm s$）表示，组间比较采用t检验，计数资料采用χ^2检验。影响因素采用二分类Logistic回归分析，以二分类Logistic回归模型为基础制作列线图，绘制ROC曲线，检验水准α=0.05。

2 结 果

2.1 一般情况

共纳入597例患者，其中，男性132例，女性465例；年龄18~79岁，平均年龄（46.20±11.36）岁；肿瘤直径0.1~7.0 cm，平均为（1.21±0.95）cm；187例（31.32%）发生LLNM，410例（68.68%）未发生LLNM。

2.2 PTC患者发生LLNM的单因素分析

发生与未发生LLNM的PTC患者间比较结果显示，年龄、肿瘤最大直径、多发癌灶、腺外侵犯、中央区淋巴结转移（central lymph node metastasis，CLNM）、$BRAF^{V600E}$基因突变等因素差异有统计学意义（均P<0.05）；性别、BMI、肿瘤分布、肿瘤位置和合并桥本氏甲状腺炎等因素差异无统计学意义（均P>0.05）（表1）。

2.3 PTC患者发生LLNM的多因素分析

以是否有LLNM为因变量，以单因素分析有统计学意义的影响因素为自变量进行二分类Logistic回归分析，结果显示年龄、肿瘤直径、腺外侵犯、CLNM和$BRAF^{V600E}$基因突变为LLNM的独立危险因素（均P<0.05）（表2）。

表1 LLNM影响因素的单因素分析

Table 1 Univariate analysis of factors for LLNM

因素	LLNM组（n=187）	非LLNM组（n=410）	t/χ^2	P
性别[n(%)]				
男	48(25.67)	84(20.49)	2.001	0.157
女	139(74.33)	326(79.51)		
年龄(岁)	43.3±12.7	47.5±10.4	3.916	<0.001
BMI[kg/m^2,n(%)]				
<18.5	4(2.14)	7(1.71)	3.071	0.381
18.5~<24	71(37.97)	149(36.34)		
24~<28	69(36.90)	179(43.66)		
≥28	43(22.99)	75(18.29)		
肿瘤最大直径(cm,$\bar{x} \pm s$)	1.7±1.11	0.99±0.75	8.268	<0.001
多发癌灶[n(%)]				
是	66(35.29)	95(23.17)	9.584	0.002
否	121(64.71)	315(76.83)		
腺外侵犯[n(%)]				
是	91(48.66)	50(12.20)	94.676	<0.001
否	96(51.34)	360(87.80)		
肿瘤分布[n(%)]				
上极	104(55.61)	190(46.34)	4.835	0.089
中极	54(78.88)	152(37.07)		
下极	29(15.51)	68(16.59)		
肿瘤位置[n(%)]				
左侧	64(34.22)	153(37.31)	0.582	0.748
右侧	88(47.06)	181(44.15)		
双侧	35(18.72)	76(18.54)		
CLNM [n(%)]				
是	143(76.47)	133(32.44)	100.165	<0.001
否	44(23.53)	277(67.56)		
合并桥本氏甲状腺炎[n(%)]				
是	15(8.02)	28(6.83)	0.273	0.601
否	172(91.98)	382(73.17)		
$BRAF^{V600E}$基因突变[n(%)]				
是	48(25.67)	63(15.37)	9.006	0.003
否	139(74.33)	347(84.63)		

表2 LLNM影响因素的二分类Logistic分析

Table 2 Binary Logistic analysis of influencing factors for LLNM

因素	β	$S.E$	$Wald$	P	OR(95% CI)
常数项	−2.121	0.515	16.954	<0.001	0.120
年龄	−0.200	0.010	4.463	0.035	0.980(0.961~0.999)
肿瘤直径	0.606	0.123	24.305	<0.001	1.833(1.440~2.332)
多发癌灶	0.367	0.234	2.472	0.116	1.444(0.913~2.282)
腺外侵犯	1.375	0.242	32.172	<0.001	3.957(2.460~6.364)
CLNM	1.549	0.226	46.829	<0.001	4.708(3.021~7.337)
$BRAF^{V600E}$基因突变	0.618	0.263	5.527	0.019	1.856(1.108~3.107)

2.4　LLNM 影响因素列线图

以 LLNM 二分类 Logistic 回归分析模型为基础制作列线图，结果显示，肿瘤直径对 LLNM 的影响最大，多发癌灶对 LLNM 的影响最小（图 1）。

2.5　ROC 曲线与列线图模型的构建及验证

ROC 曲线分析显示，肿瘤直径诊断 LLNM 的截断值 1.05 cm，AUC=0.737（95% *CI*=0.695~0.779，*P*<0.001），敏感度为 0.668，特异度为 0.676（图 2A）。年龄诊断 LLNM 的截断值为 32.5 岁，AUC=0.601（95% *CI*=0.550~0.652，*P*<0.001），敏感度为 0.262，特异度为 0.92（图 2B）。在校正曲线图中，理想预测，预测值与偏差校正三条曲线走势基本一致，表示本模型具有较好的预测价值（图 3）。

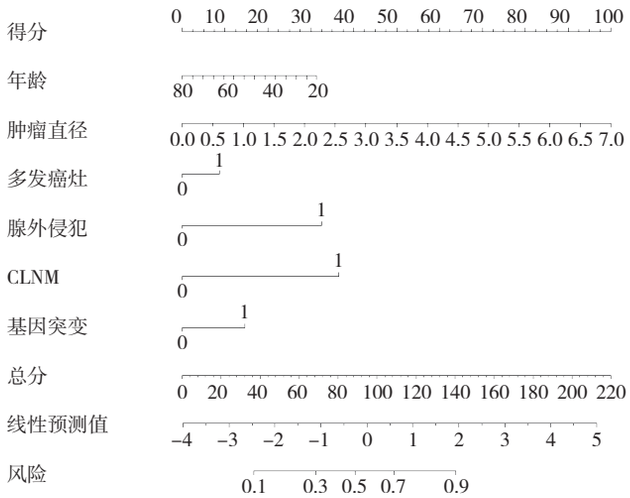

图 1　以 LLNM 二分类 Logistic 回归模型为基础的列线图

Figure 1　Nomogram based on binary Logistic regression model for LLNM

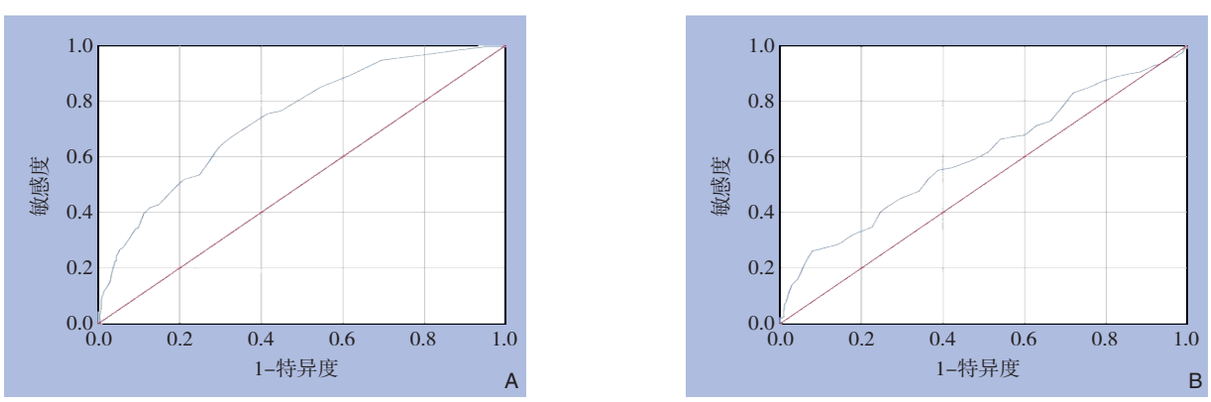

图 2　危险因素诊断 LLNM 的 ROC 曲线　A：肿瘤直径；B：年龄

Figure 2　ROC curves of risk factors for diagnosing LLNM　A: Tumor diameter; B: Age

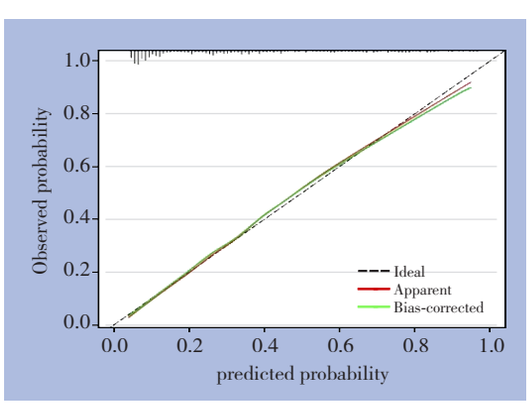

图 3　LLNM 列线图模型的校准曲线

Figure 3　Calibration curve for the LLNM nomogram model

3　讨　论

PTC 作为最常见的甲状腺癌病理类型，具有恶性程度较低，预后较好的特征[7-8]。但容易发生颈部淋巴结转移[9-10]，约有 15%~50% 的患者在确诊时检出淋巴结转移[11]。大量研究[12-13]表明，颈部淋巴结转移与 PTC 患者的复发与预后存在密切联系，LLNM 与较短的无病生存期存在显著关联[14-17]。若能在手术中彻底清扫发生转移的颈部淋巴结，即可降低患者的复发与远处转移风险。《分化型甲状腺癌颈侧区淋巴结清扫专家共识（2017 版）》[18]与 2015 年的美国甲状腺协会（ATA）指南[19]均建议对侧颈区淋巴结仅治疗性清扫，不主张进行预防性侧淋巴结切除术。

但近期研究表明，约有 20%~69% 的 cN0 期 PTC 患者出现了 LLNM[20]，因侧颈区淋巴结的隐匿性特征，目前采用的超声、磁共振成像、计算机断层扫描、细针穿刺活检等术前检查方式均对其诊断敏感度略低[21]。因此，评估 PTC 患者 LLNM 需要更

加直观准确的方法。本研究建立Logistic回归模型并构建列线图预测模型与ROC曲线分析PTC患者的临床病理特征，预测LLNM，帮助进一步确定手术范围，降低患者复局部复发与转移的风险。改善患者的生活质量并降低局部复发的概率。

在既往研究[22-24]中显示，PTC患者出现LLNM与其临床特征密切相关。甲状腺癌的多灶性是指甲状腺癌灶个数≥2个。Zhuo等[25-26]与在研究中发现，肿瘤的多灶性与淋巴结转移有关，癌灶数量越多，发生淋巴结转移的风险越高。在本研究的单因素分析中显示，多灶性为PTC患者发生LLNM的影响因素（P<0.05），但在进一步的多因素回归分析中，肿瘤的多灶性并非独立危险因素。

在大量的既往研究[27-28]中显示，肿瘤最大直径与LLNM有关。肿瘤最大直径通常与发生LLNM的风险呈正相关，转移率随着肿瘤最大直径的增加而升高[29]，这与本研究列线图模型中所显示的结果一致，肿瘤最大直径对PTC患者发生LLNM影响最大。但纵观以往研究，均对肿瘤最大直径的截断值存在分歧。Feng等[22,25]认为肿瘤最大直径>1.0 cm是LLNM的危险因素，Wu等[30]建议肿瘤最大直径的截断值应为>0.7 cm，而Kim等[31-32]则报告称PTC>2 cm甚至>3 cm是LLNM的独立危险因素。在本研究中，笔者与近期研究观点相接近，认为肿瘤最大直径>1.05 cm时，发生LLNM的风险明显升高。

此外，年龄常用于评估分化型甲状腺癌的分期。根据Lu等[33]调查显示，年轻的PTC患者比老年患者更容易发生LLNM。这与本研究的多因素研究结果相一致，年龄每增大1岁，发生LLNM的风险随之降低，通过绘制ROC曲线得出年龄截断值为32.5岁。发生这种情况可能与肿瘤活性降低和隐匿性转移的存在有关。然而，尽管各种分期系统将年龄列为PTC预后的预测指标，但有关于其的最佳临界值仍然有不同意见。在先前的一项Meta分析[34]中，发现45岁以下的PTC患者与LLNM风险增加有关。而在第8次AJCC分期系统[19]中，年龄<55岁被认为是比年龄<45岁更合适的预后临界值。笔者认为应对目前年轻的PTC患者群体增加LLNM的关注，年龄与PTC肿瘤进展的关联仍需要更多前瞻性研究进行探索。

恶性肿瘤对被膜的侵犯正是其侵袭行为的表现，通常被认为是导致转移淋巴结的危险因素。Liu等[23,35]对PTC患者进行分析，甲状腺腺外侵犯不仅与颈部淋巴结转移有关，还是中央区与侧颈区淋巴结转移的独立危险因素。本研究的结果与此一致，多因素研究结果表明，存在腺外侵犯的PTC患者发生LLNM的风险是无腺外侵犯的3.957倍。颈部淋巴结转移通常遵循一定规律，中央区淋巴结作为甲状腺癌淋巴结转移的首站，该区域发生淋巴结转移则发生其他区域转移的可能性增加，近期国内外研究[36-39]结果均表明，PTC患者CLNM与LLNM存在关联，CLNM发生转移的数目与LLNM相关。本研究同样证实CLNM是LLNM发生的独立危险因素，存在CLNM的PTC患者发生LLNM的风险增加4.708倍。在纳入的597例PTC患者中，有46.23%（276/597）发生CLNM，31.32%（187/597）发生LLNM，LLNM率高于一般研究结果，可能由于纳入研究的多数患者肿瘤位于甲状腺上极，这与So等[40-42]研究结果相一致。Ⅱ、Ⅲ、Ⅳ、Ⅴ区淋巴结的转移率分别为28.87%（54/187），35.83%（67/187），34.22%（67/187）和2.14%（4/187），符合一般LLNM规律[43]，应按照规律择区进行清扫。

BRAF^{V600E}是近年来PTC诊断中常检的基因靶点，其中*BRAF*是丝裂原活化蛋白激酶（MAPK）信号通路的一部分，*V600E*突变导致缬氨酸转化为谷氨酸，导致*BRAF*的组成性激活，从而导致参与细胞增殖的基因转录，促进肿瘤发生、细胞增殖和转移[44]。*BRAF*^{V600E}基因突变常被认为与PTC的腺外侵犯、肿瘤直径、多灶性、淋巴结转移等侵袭性表现相关[43,45-48]。在本研究中显示*BRAF*^{V600E}基因突变是LLNM的独立危险因素，发生*BRAF*^{V600E}基因突变的PTC患者发生LLNM的风险是未发生基因突变患者的1.856倍，印证了以上研究对*BRAF*^{V600E}基因突变增强PTC侵袭性的观点。而Liu等[49]的分析却认为*BRAF*^{V600E}基因突变与PTC患者发生淋巴结转移的无关，可能与纳入研究的不同种族、地区或样本量有关。本次研究并未纳入其他甲状腺癌基因位点检测结果，有研究[50]显示，*TERT*与*BRAF*可能对PTC患者的临床结局产生协同作用，有待于进一步探索。

综上所述，年龄、肿瘤直径、腺外侵犯、CLNM和*BRAF*^{V600E}基因突变为LLNM的独立危险因素，依据以上影响因素构建的列线图模型具有良好的校准度。但本研究为回顾性研究，存在一定选择性偏倚，且本次仅纳入了单中心数据进行研

究，未进行外部验证，存在地域局限性。因此该列线图预测模型对PTC患者发生LLNM的预测效能仍需多中心的后续研究进行证实。临床应对存在以上独立危险因素的PTC患者更为谨慎地判断淋巴结转移的范围，对其实行针对性的淋巴结探查及清扫手段，以达到降低复发风险、延长存活期，改善患者预后生活质量的目的。

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