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·乳腺甲状腺精准诊疗新径·

基于临床病理特征预测甲状腺乳头状癌喉前淋巴结转移的列线图模型构建

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[摘 要] **目的** 基于临床诊疗中易获取的临床病理特征,筛选甲状腺乳头状癌(PTC)患者喉前淋巴结转移的独立危险因素,并构建及验证列线图预测模型,为术前风险分层和个体化手术决策提供参考。**方法** 回顾性分析271例PTC患者的临床资料,按7∶3的比例随机分为训练集(n=189)和验证集(n=82)。收集患者临床资料,采用单因素和多因素Logistic回归分析筛选喉前淋巴结转移的独立危险因素,构建列线图预测模型。通过受试者工作特征(ROC)曲线、校准曲线和决策曲线分析(DCA)分别评估模型的区分度、校准度和临床实用性。**结果** 多因素Logistic回归分析显示,肿瘤位于中份、多发PTC、中央区淋巴结转移和男性是喉前淋巴结转移的独立危险因素。基于上述独立危险因素构建的列线图模型在训练集和验证集中的曲线下面积(AUC)分别为0.866(95%*CI*:0.815~0.917)和0.833(95%*CI*:0.746~0.919),显示出良好的区分度。校准曲线显示模型预测概率与实际概率具有良好的一致性,DCA证实该模型具有较高的临床净收益。**结论** 肿瘤位于中份、多发PTC、中央区淋巴结转移和男性是PTC患者喉前淋巴结转移的独立危险因素。基于以上因素构建的列线图模型能够有效预测PTC患者喉前淋巴结转移风险,可为临床个体化治疗决策提供参考依据。

[关键词] 甲状腺乳头状癌;喉前淋巴结转移;预测模型;列线图

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Construction of a nomogram model based on clinicopathological features for predicting delphian lymph node metastasis of papillary thyroid carcinoma

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Abstract: Objective To screen the independent risk factors for delphian lymph node metastasis in patients with papillary thyroid carcinoma (PTC) based on readily available clinicopathological characteristics in daily clinical practice, and a nomogram prediction model was constructed and verified to provide references for preoperative risk stratification and individualized surgical decisions. **Methods** A retrospective analysis was conducted on the clinicopathological data of 271 PTC patients. All participants were randomly divided into the training set (n=189) and the validation set (n=82) at a 7∶3 ratio. The clinical data of patients were collected. Univariate and multivariate Logistic regression analyses were used to identify the independent risk factors for delphian lymph node metastasis, and a nomogram prediction model was established. Receiver operating characteristic (ROC) curve, calibration curve and decision curve analysis (DCA) were applied to evaluate the discrimination, calibration and clinical applicability of the model, respectively. **Results** Multivariate Logistic regression analysis revealed that tumor location in the middle, multifocal PTC, central lymph node metastasis and male gender were the independent risk factors for delphian lymph node metastasis. The area under the curve (AUC) of the nomogram model constructed based on the above independent risk factors was 0.866 (95%*CI*: 0.815 to 0.917) in the training set and 0.833 (95%*CI*: 0.746 to 0.919) in the validation set, suggesting good discriminatory ability. Calibration curves showed good consistency between model-predicted probability and actual incidence. DCA confirmed that the model possessed favorable clinical net benefit. **Conclusion** Tumor location in the middle, multifocal PTC, central lymph node metastasis and male gender are the independent risk factors for delphian lymph node metastasis in patients with PTC. The nomogram model constructed based on the above factors can effectively predict the risk of delphian lymph node metastasis in patients with PTC and provide a reference basis for individualized clinical treatment decisions.

Keywords: papillary thyroid carcinoma; delphian lymph node metastasis; predictive model; nomogram

甲状腺乳头状癌(papillary thyroid carcinoma, PTC)是最常见的甲状腺恶性肿瘤,占所有甲状腺癌的80%~90%[1-2]。尽管PTC整体预后良好,但淋巴结转移仍是影响患者复发与长期生存的重要因素[3-4]。喉前淋巴结位于环状软骨与甲状软骨之间的正中线区域,

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是甲状腺癌淋巴引流的首站淋巴结之一,其转移状态与中央区、颈侧区淋巴结转移及肿瘤局部复发密切相关,对手术方案制定与清扫范围选择具有关键指导意义[5-7]。

由于喉前淋巴结体积小、解剖位置深,术前超声、CT等影像学检查难以准确判断其转移状态[8]。现有研究多关注肿瘤大小、BRAF基因突变等指标,对肿瘤部位、病灶数量、性别、中央区淋巴结转移等临床病理特征的整合预测价值缺乏系统建模[9-10]。本研究基于上述术前易获取的临床病理特征,筛选喉前淋巴结转移的独立危险因素,构建可视化列线图模型,旨在为临床提供无创、便捷、精准的术前风险预测工具。

1 资料与方法

1.1 临床资料

回顾性收集2020年1月至2023年12月在陆军军医大学第一附属医院接受甲状腺手术治疗的PTC患者的临床资料。纳入标准:①术后病理证实为PTC;②接受甲状腺全切或近全切除术+中央区淋巴结清扫;③临床病历资料完整。排除标准:①术前接受过放化疗;②合并其他恶性肿瘤;③既往有甲状腺手术史。最终纳入271例患者,按7∶3的比例随机分为用于危险因素筛选与模型构建的训练集(n=189)和用于模型效能独立验证的验证集(n=82)。本研究经陆军军医大学第一附属医院伦理委员会批准[批准号:(B)KY2023099]。

1.2 数据收集

收集患者以下临床资料:①一般资料,包括年龄、性别、体质量指数(body mass index,BMI)、病程;②实验室指标,包括促甲状腺激素(thyroid-stimulating hormone,TSH)、游离三碘甲状腺原氨酸(free triiodothyronine,FT3)、游离甲状腺素(free thyroxine,FT4)、三碘甲状腺原氨酸(triiodothyronine,T3)、甲状腺素(thyroxine,T4)、甲状腺球蛋白(thyroglobulin,TG)、甲状腺球蛋白抗体(thyroglobulin antibody,TGAb)、甲状腺微粒体抗体(thyroid microsomal antibody,TMAb)、甲状腺过氧化物酶抗体(thyroid peroxidase antibody,TPOAb)、BRAF基因突变状态;③肿瘤特征,包括肿瘤最大径、肿瘤部位(分为上极、中份、峡部、下极)、是否多发PTC、包膜有无侵犯;④合并疾病,包括合并桥本甲状腺炎、结节性甲状腺肿;⑤淋巴结转移情况,即喉前淋巴结转移、中央区淋巴结转移等。

1.3 统计学方法

采用R4.2.0软件进行统计分析。计量资料采用均数±标准差($\bar{x}\pm s$)或中位数(四分间距)[$M(Q_1,Q_3)$]表示,组间比较采用t检验或Mann-Whitney U检验。计数资料采用率(%)表示,组间比较采用χ^2检验或Fisher精确检验。单因素Logistic回归分析筛选P<0.05的候选变量;多因素Logistic回归分析确定独立危险因素;以多因素回归系数为权重,构建列线图预测模型。采用受试者工作特征(receiver operating characteristic,ROC)曲线评估模型的区分度,计算曲线下面积(area under the curve,AUC)。采用DeLong检验比较列线图模型与各单一危险因素的AUC差异,以评估模型性能提升的统计学显著性。采用校准曲线评估模型的校准度,采用Bootstrap法(重复抽样500次)进行内部验证,计算平均绝对误差。采用决策曲线分析(decision curve analysis,DCA)评估模型的临床实用性。P<0.05为差异有统计学意义。

2 结果

2.1 患者临床资料

本研究共纳入271例PTC患者,其中喉前淋巴结转移130例,男101例、女170例,平均年龄(39.86±12.03)岁。多发PTC 94例,肿瘤位于中份150例,中央区淋巴结转移227例。详细的临床数据见表1。

2.2 喉前淋巴结转移的危险因素分析

将上述所有变量纳入Logistic回归分析,在训练集中以是否发生喉前淋巴结转移为因变量进行单因素Logistic回归分析,结果显示:性别、肿瘤部位、多发PTC、中央区淋巴结转移与喉前淋巴结转移相关(P<0.05);进一步行多因素Logistic回归分析,结果显示:肿瘤位于中份、多发PTC、中央区淋巴结转移、男性均是喉前淋巴结转移的独立危险因素(P<0.05),见表2、3。

2.3 列线图模型构建

基于上述4项独立危险因素,构建PTC喉前淋巴结转移的列线图预测模型。该模型可通过累加各个预测因子的得分,计算总分后对应预测喉前淋巴结转移的概率,为临床医生提供直观、便捷的预测工具,见图1。

2.4 模型的区分度评估

ROC曲线分析显示,该预测模型在训练集中的AUC为0.866(95%CI:0.815~0.917),在验证集中的AUC为0.833(95%CI:0.746~0.919),表明模型具有良好的区分能力,见图2。为了进一步验证列线图模型的有效性,本研究将列线图模型的预测性能与各独立

表1 PTC患者临床资料

变量		总量(n=271)	验证集(n=82)	训练集(n=189)	$\chi^2/t/Z$	P
喉前淋巴结转移[例(%)]	未转移	141(52.03)	38(46.34)	103(54.50)	1.215	0.270
	转移	130(47.97)	44(53.66)	86(45.50)		
性别[例(%)]	女	170(62.73)	48(58.54)	122(64.55)	0.646	0.422
	男	101(37.27)	34(41.46)	67(35.45)		
中央区淋巴结转移[例(%)]	未转移	44(16.24)	13(15.85)	31(16.40)	0.000	1.000
	转移	227(83.76)	69(84.15)	158(83.60)		
多发PTC[例(%)]	否	177(65.31)	54(65.85)	123(65.08)	0.000	1.000
	是	94(34.69)	28(34.15)	66(34.92)		
肿瘤部位[例(%)]	下极	67(24.72)	21(25.61)	46(24.34)	0.632	0.889
	中份	150(55.35)	47(57.32)	103(54.50)		
	峡部	22(8.12)	6(7.32)	16(8.47)		
	上极	32(11.81)	8(9.76)	24(12.70)		
包膜侵犯[例(%)]	无	201(74.17)	61(74.39)	140(74.07)	0.000	1.000
	有	70(25.83)	21(25.61)	49(25.93)		
桥本甲状腺炎[例(%)]	无	167(61.62)	52(63.41)	115(60.85)	0.069	0.792
	有	104(38.38)	30(36.59)	74(39.15)		
结节性甲状腺肿[例(%)]	无	228(84.13)	66(80.49)	162(85.71)	0.811	0.368
	有	43(15.87)	16(19.51)	27(14.29)		
BRAF基因突变[例(%)]	无	45(16.61)	15(18.29)	30(15.87)	0.099	0.753
	有	226(83.39)	67(81.71)	159(84.13)		
年龄(岁)		39.86±12.03	40.30±10.91	39.67±12.51	0.176	0.676
病程(月)		2.00(1.00,10.00)	2.00(0.62,9.50)	2.00(1.00,12.00)	0.786	0.375
BMI(kg/m^2)		24.3±3.47	25.05±3.81	23.97±3.26	4.999	0.027
肿瘤最大径(cm)		1.48±1.07	1.31±0.72	1.56±1.18	4.499	0.035
T3(nmol/L)		1.75(1.56,1.97)	1.78(1.56,1.98)	1.75(1.56,1.95)	0.031	0.862
T4(nmol/L)		103.40(92.26,118.90)	103.40(91.72,116.62)	104.10(93.30,119.60)	0.357	0.549
FT3(nmol/L)		5.10(4.56,5.55)	5.07(4.71,5.58)	5.12(4.53,5.55)	0.440	0.507
FT4(nmol/L)		16.72(15.27,18.4)	17.05(15.33,18.59)	16.60(15.19,18.30)	0.792	0.372
TSH(μIU/mL)		2.01(1.31,2.81)	2.08(1.21,2.71)	1.98(1.35,2.81)	0.002	0.962
TG(ng/mL)		16.49(2.99,53.02)	18.81(4.64,56.37)	14.98(2.87,46.79)	0.418	0.518
TGAb(IU/mL)		14.32(1.3,40.11)	12.35(1.30,43.59)	14.56(1.30,37.87)	0.329	0.566
TMAb(%)		5.47(3.17,13.63)	5.03(2.63,17.05)	5.59(3.38,12.11)	0.443	0.506
TPOAb(IU/mL)		28.00(13.49,51.34)	30.00(12.49,76.67)	28.00(13.85,49.00)	0.192	0.661

表2 PTC喉前淋巴结转移的单因素分析

影响因素	β	SE	OR(95%CI)	Waldχ^2	P
BRAF基因突变	0.433	0.411	1.542(0.699~3.549)	1.111	0.292
TPOAb	−0.001	0.001	0.999(0.998~1.001)	1.073	0.300
TMAb	−0.001	0.012	0.999(0.975~1.023)	0.009	0.922
TGAb	0.000	0.000	1.000(1.000~1.001)	0.608	0.435
TG	0.000	0.001	1.000(0.998~1.003)	0.068	0.794
TSH	0.002	0.015	1.002(0.969~1.038)	0.026	0.873
FT4	−0.027	0.027	0.973(0.908~1.013)	1.000	0.317
FT3	0.037	0.051	1.038(0.980~1.283)	0.527	0.468
T4	−0.006	0.006	0.994(0.982~1.006)	0.903	0.342
T3	−0.104	0.317	0.901(0.465~1.675)	0.109	0.741
结节性甲状腺肿	−0.226	0.422	0.798(0.340~1.810)	0.287	0.592
桥本甲状腺炎	−0.150	0.300	0.861(0.476~1.548)	0.250	0.617
包膜侵犯	0.522	0.334	1.685(0.877~3.268)	2.434	0.119
肿瘤位于上极			1.000(Reference)		
肿瘤位于峡部	1.695	0.797	5.444(1.222~30.060)	4.524	<0.050
肿瘤位于下极	0.049	0.757	1.050(0.250~5.367)	0.004	0.949
肿瘤位于中份	2.698	0.652	14.840(4.708~66.070)	17.106	<0.001
肿瘤最大径	0.119	0.125	1.126(0.882~1.445)	0.904	0.342
BMI	0.039	0.045	1.040(0.952~1.137)	0.759	0.384
病程	0.000	0.008	1.000(0.984~1.017)	0.003	0.958
多发PTC	1.786	0.338	5.965(3.122~11.810)	27.868	<0.001
中央区淋巴结转移	1.452	0.482	4.274(1.763~12.010)	9.096	<0.010
性别	1.091	0.315	2.978(1.618~5.583)	11.985	<0.001
年龄	0.001	0.012	1.001(0.978~1.024)	0.002	0.961

表3 PTC喉前淋巴结转移的多因素分析

影响因素	β	SE	OR(95%CI)	Waldχ^2	P
多发PTC	1.577	0.416	4.841(2.143~10.937)	14.387	<0.001
中央区淋巴结转移	1.256	0.625	3.511(1.032~11.950)	4.040	<0.050
性别	1.299	0.433	3.666(1.567~8.574)	8.982	<0.010
肿瘤位于上极			1.000(Reference)		
肿瘤位于峡部	1.552	0.892	4.720(0.821~27.128)	3.024	0.082
肿瘤位于下极	−0.665	0.867	0.514(0.094~2.815)	0.587	0.443
肿瘤位于中份	2.136	0.727	8.469(2.038~35.183)	8.644	<0.010

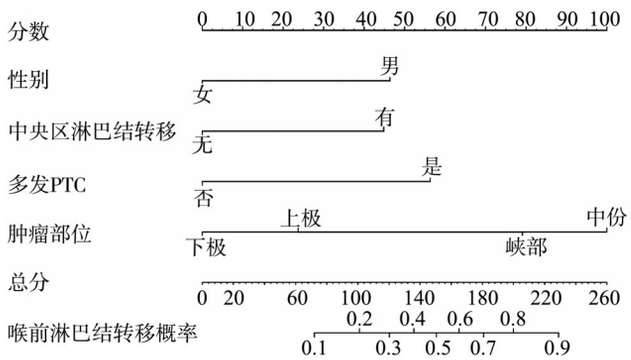
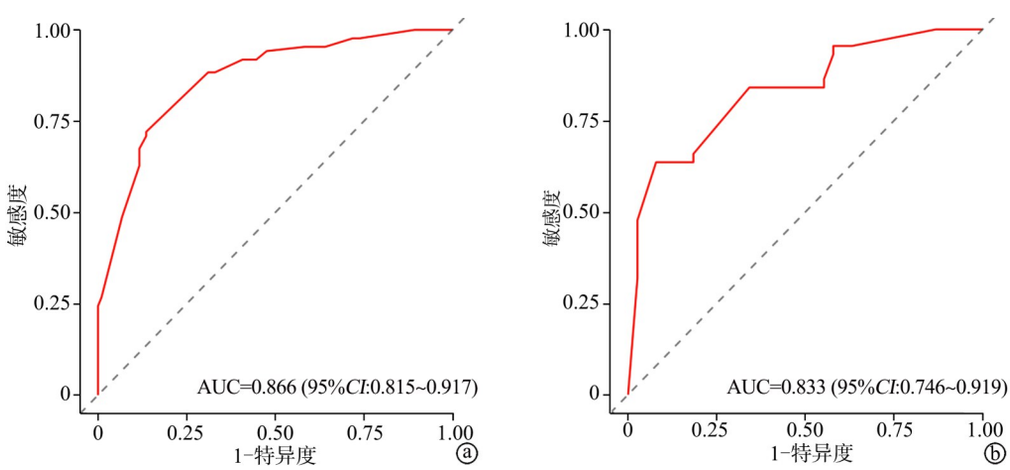


图1 PTC喉前淋巴结转移的列线图预测模型

危险因素进行了比较。列线图模型的AUC值达到0.833(95%CI:0.746~0.919),显著高于任何单一危险因素的预测效能(P<0.001),见图3。

2.5 模型的校准度评估

校准曲线分析显示,训练集和验证集中模型预测概率与实际概率均表现出良好的一致性,见图4。Bootstrap法(重复抽样500次)内部验证结果显示,训练集的平均绝对误差为0.018,验证集为0.044,均较小,表明模型具有良好的校准度。



a:训练集;b:验证集

图2 喉前淋巴结转移ROC曲线

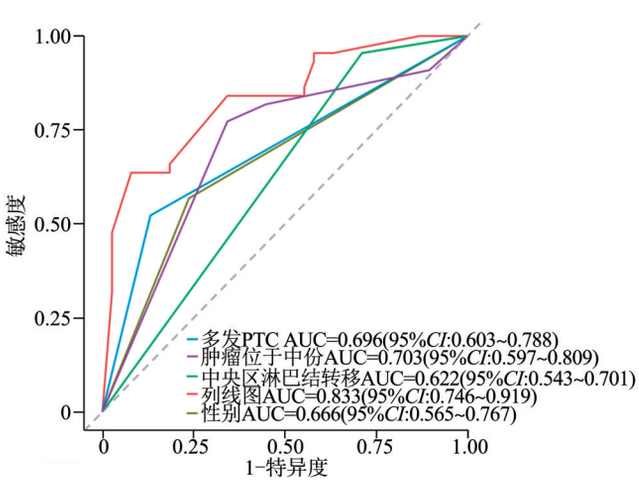


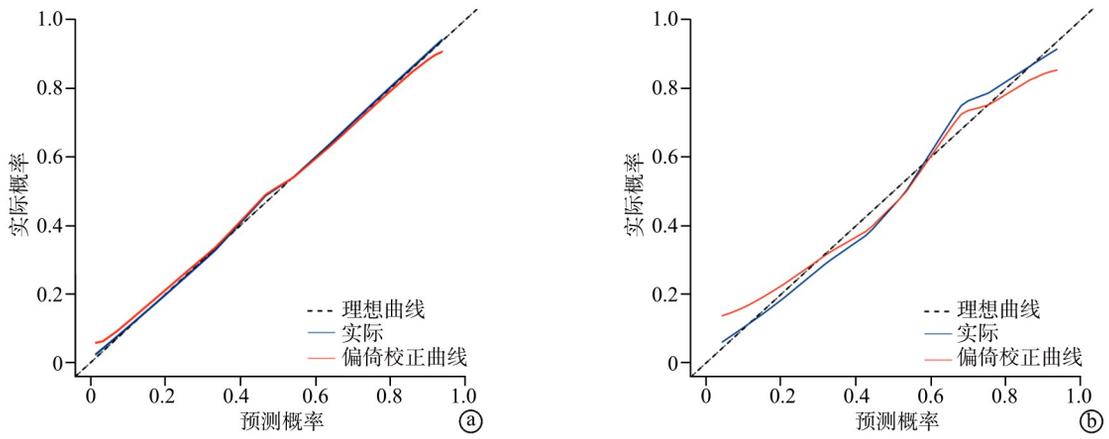
图3 列线图模型与单一危险因素预测喉前淋巴结转移的ROC曲线比较

2.6 模型的临床实用性评估

DCA显示,在合理的阈值概率范围内(30%~70%),该预测模型的净收益明显高于“全部治疗”和“全不治疗”两种极端策略,具备良好临床应用价值,见图5。

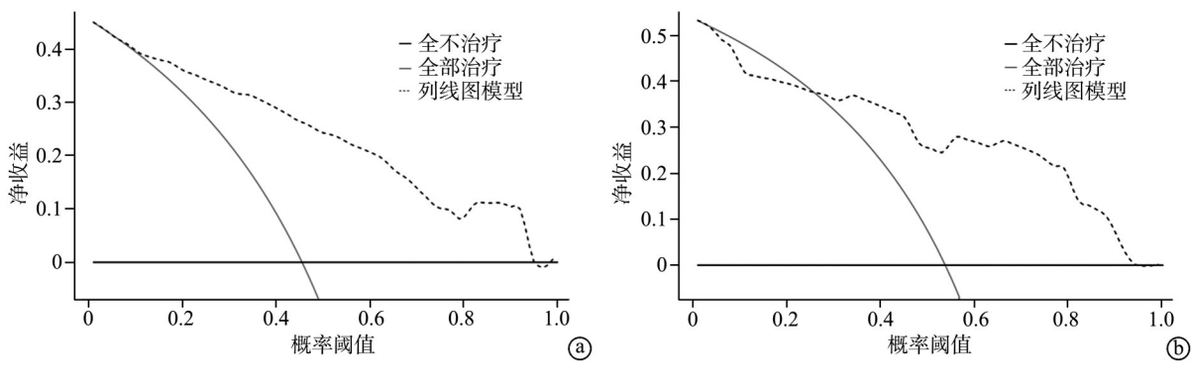
3 讨论

本研究基于性别、肿瘤部位、病灶数量、中央区淋巴结转移4项术前易获取的临床病理特征,成功构建并验证了预测PTC喉前淋巴结转移的列线图模型。多因素分析证实,肿瘤部位是预测喉前淋巴结转移最重要的危险因素;肿瘤位于甲状腺中份者发生喉前淋巴结转移的风险显著升高。喉前淋巴结是甲状腺淋巴引流的第一站淋巴结,主要接收甲状腺峡部、中上份区域的淋巴回流[11]。甲状腺中份具有丰富的交通淋



a:训练集;b:验证集

图4 喉前淋巴结转移列线图的校准曲线



a:训练集;b:验证集

图5 喉前淋巴结转移列线图的DCA

巴网,可同时向上引流至喉前淋巴结、向下引流至气管前淋巴结[12],因此位于中份的病灶更易出现喉前淋巴结转移[13]。多发PTC提示甲状腺实质受累范围更广,癌细胞进入淋巴系统的概率更高[10],同时也反映肿瘤具有更强的侵袭性生物学行为[9]。既往关于多发PTC与淋巴结转移的关系存在争议,部分研究认为二者无明确关联[14],但更多大样本研究支持多发PTC可使淋巴结转移风险升高[15-17]。本研究通过单因素与多因素校正,明确证实多发PTC对喉前淋巴结转移具有独立预测价值,提示临床对多发PTC患者应积极评估喉前淋巴结受累风险。本研究进一步证实,中央区淋巴结转移是喉前淋巴结转移的独立危险因素,符合甲状腺癌淋巴结阶梯式转移规律[7]。喉前淋巴结本身即属于中央区淋巴结组,其转移常伴随中央区转移[18]。Huang等[18]对1 237例PTC患者的研究显示,82.4%的喉前淋巴结阳性患者合并其他中央区淋巴结转移,65.3%合并颈侧区淋巴结转移。因此,喉前淋巴结转移并非孤立事件,而是中央区淋巴结广泛受累的重要标志。术前识别这一规律,有助于更合理地规划淋巴结清扫范围。尽管PTC以女性高发,但男性患者肿瘤侵袭性更强、淋巴结转移率更高、预后更差已被多项研究证实[19-21]。性别差异的机制可能与雌激素信号、遗传易感性、免疫状态及就诊延迟等因素相关[22]。无论其潜在机制如何,本研究进一步确认,男性PTC患者应被列为喉前淋巴结转移的高危人群,临床需对该群体进行更严格的术前评估,并采取更积极的手术干预措施。

本研究构建的预测模型仅整合性别、肿瘤部位、多发PTC、中央区淋巴结转移4项术前易获取指标,无需超声组学、CT或分子检测,即可达到训练集AUC=0.866、验证集AUC=0.833的良好预测效能,优于单一因素预测。校准曲线显示预测概率与实际概率高度一致;DCA证实模型在30%~70%阈值概率范围内具有显著临床净收益,整体性能与近年国际同类模型相当,甚至更优[8,23]。

然而本研究仍存在一些局限性:首先,作为回顾性研究,可能存在选择偏倚和信息偏倚。其次,单中心数据可能限制了结果的外推性,需要多中心、前瞻性研究进一步验证。第三,样本量相对有限,特别是某些亚组,如峡部肿瘤的病例数较少。第四,未纳入

影像学特征如超声或CT表现,这些信息可能进一步提高模型的预测能力。第五,缺乏长期随访数据,未能评估喉前淋巴结转移对患者预后的影响。未来研究应当扩大样本量,进行多中心验证;纳入影像学特征,构建综合预测模型;整合分子标志物,提高预测准确性;开展前瞻性研究,验证模型的临床效能;探索喉前淋巴结转移与长期预后的关系。

综上所述,肿瘤位于中份、多发PTC、中央区淋巴结转移和男性是PTC患者喉前淋巴结转移的独立危险因素。基于上述4项临床病理特征构建的列线图模型具有良好的区分度、校准度和临床实用性,可为PTC患者喉前淋巴结转移风险评估及个体化手术决策提供参考。

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