

基于超声影像组学及深度神经网络预测甲状腺乳头状癌pN分期

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Prediction of pN Staging of Papillary Thyroid Carcinoma Using Ultrasonography Radiomics and Deep Neural Networks

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Abstract: Objective To assess the accuracy of pN staging prediction in papillary thyroid carcinoma (PTC) using ultrasound radiomics and deep neural networks (DNN). **Methods** A retrospective analysis was conducted on 375 patients with pathologically confirmed PTC, comprising 261 cases in the training set and 114 in the test set. Staging was categorized as pN0 (no cervical lymph node metastasis), pN1a (central neck lymph node metastasis), and pN1b (lateral neck lymph node metastasis). An ultrasound physician manually segmented the regions of interest (ROIs) for PTC, extracting 1 899 radiomic features. Dimensionality reduction was performed using the least absolute shrinkage and selection operator (LASSO) regression. A DNN model for predicting PTC pN staging was developed using the H2O deep learning platform, trained on the training set, and validated on the test set to assess the accuracy of the optimal model. **Results** A total of 153 patients were in the pN0 stage, 131 patients in the pN1a stage, and 91 patients in the pN1b stage. LASSO regression selected 15 radiomic features for each PTC. The optimal DNN model, constructed using these 15 features, achieved accuracies of 85.82% on the training set and 81.57% on the test set. **Conclusion** Ultrasound radiomics of PTC demonstrates high accuracy in predicting pN staging and shows potential for automating N staging in patients.

Key words: Thyroid Cancer; Papillary; Ultrasonography; pN staging; Predicting; Lymph nodes

Competing interests: The authors declare that they have no competing interests.

摘要: 目的 基于超声影像组学及深度神经网络(DNN)预测甲状腺乳头状癌(PTC)pN分期的准确性。**方法** 回顾性收集经病理确诊的PTC患者375例(训练集261例,测试集114例)。将无颈部淋巴结转移定义为pN0,中央区淋巴结转移定义为pN1a,颈侧区淋巴结转移定义为pN1b。由超声科医师手动分割PTC的兴趣区(ROI)并提取1 899个影像组学特征。采用最小绝对收缩与选择算子(LASSO)对上述影像组学特征进行降维。基于H2O深度学习平台在训练集构建预测PTC pN分期的DNN模型,并在测试集验证最优模型准确性。**结果** pN0期患者153例, pN1a期131例, pN1b期91例。每个PTC的影像组学特征经LASSO回归筛选出15个影像组学特征。基于该15个影像组学特征构建的最优DNN模型在训练集及测试集的准确性分别为85.82%及81.57%。**结论** PTC

的超声影像组学预测pN分期的准确性较高,有为患者自动化N分期的潜力。

关键词: 甲状腺癌; 乳头状; 超声检查; pN分期; 预测; 淋巴结

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0 引言

甲状腺乳头状癌 (Papillary thyroid carcinoma, PTC) 作为分化型甲状腺癌 (Differentiated thyroid cancer, DTC) 最常见类型, 远处转移率低, 5年及10年生存率高。但当原发肿瘤很小且局限在甲状腺内时, 常已有颈部淋巴结转移^[1-4]。研究表明伴有淋巴结转移的PTC患者复发率高且生存率低^[5-8]。颈部中央区淋巴结作为PTC淋巴结转移的第1站最为常见。但有28%~33%的术前影像学未检出中央区转移淋巴结, 而在预防性中央区淋巴结清扫后发现转移者达30%以上^[9]。因此美国甲状腺协会 (American Thyroid Association, ATA) 指南建议在有效保留甲状旁腺和喉返神经的基础上行原发肿瘤同侧中央区淋巴结清扫。颈侧区淋巴结转移率低于中央区, 切除该区转移淋巴结可降低PTC复发率和死亡率, 因此推荐对影像学可疑颈侧区淋巴结转移的PTC患者行颈侧区淋巴结清扫^[10-11]。也有文献指出不同pN分期的PTC患者有不同的复发风险^[12]。因此颈部淋巴结转移状态及位置对PTC患者手术决策至关重要, 同时也是其pN分期和复发危险分层的重要依据^[13]。

超声检查对甲状腺的评估方便易行, 性价比高。对颈部淋巴结转移的评价特异性高但敏感性低^[14-16]。因此部分转移淋巴结在术前常未被发现。近年来, 影像组学在肿瘤的分级分期、精确诊断及预后预测方面展现出巨大潜力^[17]。再结合当前如火如荼的机器学习及深度学习技术强劲的非线性映射能力, 在解决分类问题上有较好的表现。故本研究拟探讨基于超声影像组学联合深度学习技术预测PTC pN分期的诊断性能。

1 资料与方法

1.1 患者资料

本回顾性研究放弃患者知情同意, 遵守2013年修订版《赫尔辛基宣言》。回顾性收集空军军医大学第一附属医院2019年3月—2022年5月的PTC患者, 符合以下纳入及排除标准。纳入标准: (1) 原发肿瘤及颈部淋巴结转移经手术或细针抽吸活检确诊; (2) PTC术前行甲状腺超声检查; (3) 甲状腺肿瘤为单发。排除标准: (1) 图像质量差, 影响影像组学特征提取; (2) 超声检查前接受过针对PTC局部或全身性治疗。最终共纳入375例患者, 其中女性324例, 男性51例, 年龄 44.5 ± 11.7 岁, 年龄范围25~65岁。采用分层抽样按照7:3比例随机将患者分为训练集 (261例) 及测试集 (114例)。本研究通过空军军医大学第一附属医

院伦理委员会批准 (KY20211356-C-1)。

1.2 超声数据采集

超声检查采用GE LOGIQ E9及百胜-MyLab90超声诊断仪, 探头频率3~11 MHz。检查时患者取平卧位, 暴露颈前及颈侧区, 扫查甲状腺及颈部淋巴结。检查完成后保存PTC最大长轴切面图。

1.3 PTC的pN分期

pN分期采用美国肿瘤联合委员会 (AJCC) 2018年版DTC的TNM分期标准。将无颈部淋巴结转移定义为pN0; 将VI及VII区转移淋巴结定义为颈部中央区淋巴结, 为pN1a; 将I~V区转移淋巴结定义为颈侧区淋巴结, 为pN1b。

1.4 PTC的分割及影像组学特征提取

将PTC图像导入一款免费开源的影像图像分析软件ITK-Snap^[18] (版本3.4.0, <http://www.itksnap.org/>)。由一名超声科医师 (5年超声诊断经验) 手动分割PTC感兴趣区 (Region of interest, ROI), 分割完成后由另外一名超声科医师 (6年超声诊断经验) 修正上述ROI用于后续分析, 见图1。进一步在uAI Research Portal平台 (联影智能, 中国上海) 中提取PTC影像组学特征, 包括7类特征: 一阶特征、形状、灰度共生矩阵、灰度行程矩阵、灰度大小区域矩阵、灰度相关矩阵及邻域灰度差矩阵, 以上影像组学特征符合《图像生物标志物标准化倡议》^[19]。

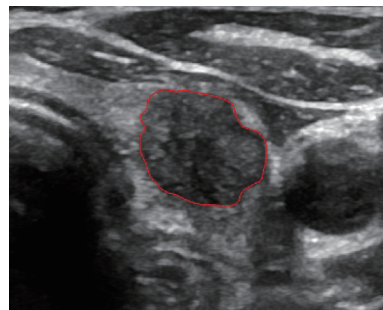


图1 超声科医师手动分割PTC的ROI

Figure 1 ROI of PTC manually segmented by ultrasound physicians

1.5 统计学方法

数据分析采用R语言 (版本3.5.3, <https://www.r-project.org>)。训练集影像组学特征降维采用最小绝对收缩与选择算子 (LASSO), 采用交叉验证确定最优超参数 (λ 值)。降维后的影像组学特征采用H2O平台 (基于R语言的深度学习平台, <https://h2o.ai>) 构建预测PTC pN分期的深度神经网络 (Deep neural network, DNN) 模型。采用网格搜索确定DNN模型最优超参数, 以对数损失函数 (Logloss) 作为损失函数。训练完成后, 分别计

算最优模型在训练集及测试集的准确性评价模型性能。以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 患者一般资料

375例患者中，pN0期153例，pN1a期131例，pN1b期91例。不同pN分期患者的性别、年龄及原发肿瘤最大径差异均无统计学意义（ $P>0.05$ ），见表1。

2.2 影像组学特征降维

每个PTC共提取1 899个影像组学特征，采用LASSO回归进行特征降维，经交叉验证确定最优 λ 值为0.054 457 45（ $\ln\lambda=-2.910$ ），见图2。最终共筛选出15个影像组学特征，其中一阶特征3个、形状特征2个、灰度共生矩阵特征7个、灰度行程矩阵特征2个、灰度大小区域矩阵特征1个，分别为original_firstorder_Kurtosis、original_firstorder_MeanAbsoluteDeviation、original_firstorder_Variance、original_shape_Elongation、original_shape_MaximumDiameter、original_glcmlm_Idmn、original_glcmlm_MaximumProbability、original_glcmlm_SumEntropy、original_glcmlm_DifferenceVariance、curvatureflow_

glcm_Imc2、wavelet_glcmlm_wavelet-LLH-DifferenceVariance、wavelet_glcmlm_DifferenceAverage、wavelet_glcmlm_wavelet-HLH-GrayLevelVariance、discretegaussian_glcmlm_LowGrayLevelRunEmphasis及original_glcmlm_GrayLevelNonUniformity。

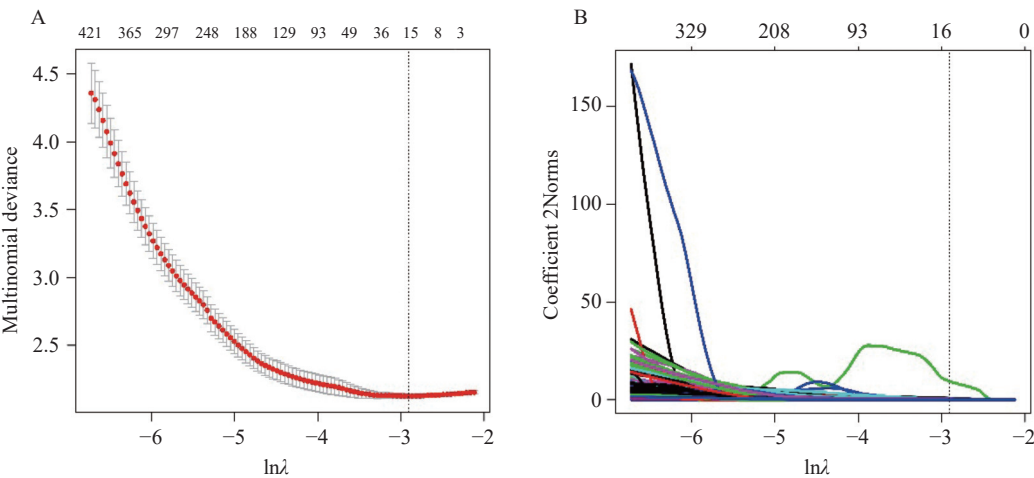
2.3 DNN建模及性能

基于上述15个影像组学特征采用DNN建模，经网格搜索共生成100个神经网络模型，将准确性最高的模型作为最优模型。该模型在训练52回合收敛，学习率为0.01。其拓扑结构为：输入层包含15个神经元，即降维后的15个影像组学特征，输入神经元无丢弃；隐藏层为两层，每层分别包含5个神经元，激活函数为无丢弃的修正线性单元，两个隐藏层平均权重分别为-0.031 427及-0.247 374，平均截距为0.821 876及0.732 502；输出层包含3个神经元，即PTC pN分期（pN0、pN1a及pN1b），激活函数为Softmax，该层平均权重为0.722 072，平均截距为-0.329 600。结果显示，最优DNN模型在训练集准确性为85.82%，损失函数值为0.25。该模型在测试集准确性为81.57%，测试集损失函数值为0.28，见图3。

表 1 PTC患者不同pN分期的一般资料比较

Table 1 Comparison of general data of PTC patients with different pN staging

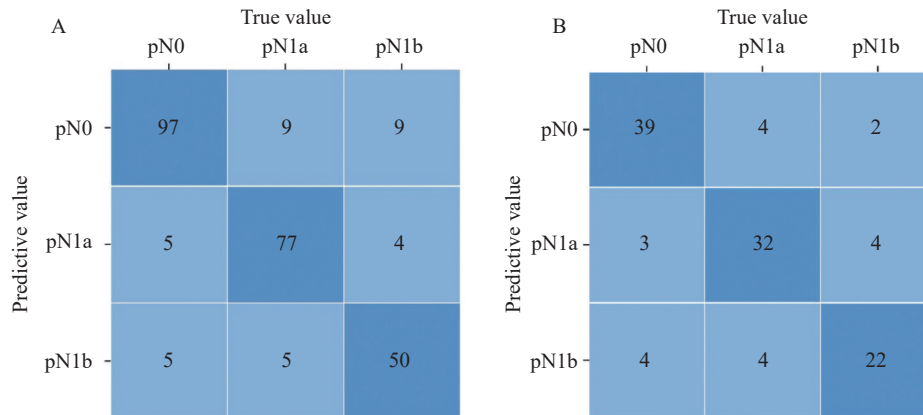
Parameters	pN0(n=153)	pN1a(n=131)	pN1b(n=91)	χ^2/F	P
Gender				0.785	0.675
Female	135(88.2%)	111(84.7%)	78(85.7%)		
Male	18(11.8%)	20(15.3%)	13(14.3%)		
Age(years)	44.9±11.8	43.4±11.7	45.4±11.8	1.103	0.333
Maximum diameter(mm)	17.0±9.8	16.6±9.0	15.2±9.2	0.899	0.408



A: optimal $\ln\lambda$ value determined by cross-validation (the lowest multinomial deviance); B: an increase in $\ln\lambda$ value causes a change in the radiomic feature coefficients; optimal $\ln\lambda$ value (vertical dashed line) corresponds to the number of radiomic features (upper horizontal axis).

图 2 甲状腺乳头状癌提取影像组学特征的LASSO回归交叉验证图及回归系数图

Figure 2 Lasso regression cross-validation diagram and regression coefficient diagram for extracting radiomic features of papillary thyroid carcinoma



A: training set confusion matrix; B: test set confusion matrix.

图3 最优神经网络模型的预测值与真实值分别在训练集和测试集的混淆矩阵

Figure 3 Confusion matrices of the predictive and true value of the optimal neural network model in the training and testing sets

3 讨论

早期有研究者采用甲状腺癌的超声纹理特征或影像组学分析预测颈部淋巴结转移状态、颈侧区淋巴结 (pN1b) 转移状态的效能均较差^[20-21]。但另外一项类似研究的AUC达到中等诊断效能为0.727^[22]。该团队在另一项研究中发现进一步联合普通B型超声和应变弹性成像的影像组学对PTC淋巴结转移的预测性能更高^[23]。黄云霞等^[24]研究结果也表明超声影像组学在预测Ⅵ区淋巴结转移的性能高于传统超声及CT。Jiang等^[25]利用超声横波弹性成像的影像组学列线图预测颈部淋巴结转移的AUC达到了0.832 (95%CI: 0.749~0.916)。以上诸多研究表明新超声成像方法较普通超声成像的影像组学在预测PTC患者N分期的二分类问题上有更高价值。因为新超声成像方法有更高的分辨率、对比度及功能性成像等优势,但新超声成像方法更依赖于操作者的经验和技巧,操作者间和设备间存在较强的异质性,会严重影响影像组学特征提取的准确性和分析结果^[26]。

当前传统超声检查方法因其经济性和成熟性在临床上广泛应用,尤其在基层医疗单位,因此基于传统超声图像建模更具普适意义。另外,从数据分析角度来看二分类问题建模更容易,因为涉及的变量和决策边界更少,模型结构通常也更为简单。而多分类问题由于需要处理更多的类别,模型复杂度更高,因此在实践中可能会遇到更多的挑战^[27]。DNN具有较强的非线性映射能力,高度自学习和自适应的能力,以及较强泛化及容错能力。因此本研究利用DNN建立的模型,结果表明其在传统超声成像方法中对三分类问题依然能获得较高的诊断效能。

DNN建模也受多种因素影响,其中超参数对其性能的影响最大,如隐藏层结构、激活函数、训练回合以及学习率等。这些超参数的选择目前尚无参考标准。本研究中为降低神经网络超参数对模型性能的影响,提高三分类问题准确性,采用了网格搜索算法,其大致原理是在指定的选择范围内检索所有的超参数组合,最终选择模型性能最高的超参数组合。本研究采用了较大的搜索范围和较小的步长来确定全局的最优超参数组合,最终获得的DNN模型在训练集及测试集均达到了较高的准确性。

本研究尚存在以下局限性:(1)仅选择了单发PTC,因多发肿瘤时无法确定是哪个PTC继发的淋巴结转移,故有可能对真实原发肿瘤的影像组学特征提取产生偏差。(2)本研究为回顾性研究,PTC超声图像只选择了最大长轴切面提取影像组学特征,因肿瘤的异质性,该层面代表性可能有所缺乏。

综上所述,本研究结果表明甲状腺乳头状癌的超声影像组学预测pN分期的准确性较高,有为患者进行自动化N分期的潜力。

利益冲突声明:

所有作者均声明不存在利益冲突。

参考文献:

- [1] Chow SM, Law SC, Chan JK, *et al.* Papillary microcarcinoma of the thyroid-Prognostic significance of lymph node metastasis and multifocality[J]. *Cancer*, 2003, 98(1): 31-40.
- [2] Lim YC, Choi EC, Yoon YH, *et al.* Central lymph node metastases in unilateral papillary thyroid microcarcinoma[J]. *Br J Surg*, 2009, 96(3): 253-257.
- [3] Shaha AR. Prognostic factors in papillary thyroid carcinoma and implications of large nodal metastasis[J]. *Surgery*, 2004, 135(2): 237-239.

- [4] Haugen BR, Alexander EK, Bible KC, *et al.* 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer[J]. *Thyroid*, 2016, 26(1): 1-133.
- [5] Podnos YD, Smith D, Wagman LD, *et al.* The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer[J]. *Am Surg*, 2005, 71(9): 731-734.
- [6] Zaydfudim V, Feurer ID, Griffin MR, *et al.* The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma[J]. *Surgery*, 2008, 144(6): 1070-1078.
- [7] Liu FH, Kuo SF, Hsueh C, *et al.* Postoperative recurrence of papillary thyroid carcinoma with lymph node metastasis[J]. *J Surg Oncol*, 2015, 112(2): 149-154.
- [8] Luo XY, Chen AM, Zhou Y, *et al.* Analysis of risk factors for postoperative recurrence of thyroid cancer[J]. *J BUON*, 2019, 24(2): 813-818.
- [9] Moo TA, McGill J, Allendorf J, *et al.* Impact of prophylactic central neck lymph node dissection on early recurrence in papillary thyroid carcinoma[J]. *World J Surg*, 2010, 34(6): 1187-1191.
- [10] Goropoulos A, Karamoshos K, Christodoulou A, *et al.* Value of the cervical compartments in the surgical treatment of papillary thyroid carcinoma[J]. *World J Surg*, 2004, 28(12): 1275-1281.
- [11] Genssenjäger E, Perren A, Seifert B, *et al.* Lymph node surgery in papillary thyroid carcinoma[J]. *J Am Coll Surg*, 2003, 197(2): 182-190.
- [12] American thyroid association (ATA) guidelines taskforce on thyroid nodules and differentiated thyroid cancer, Cooper DS, Doherty GM, *et al.* Revised American thyroid association management guidelines for patients with thyroid nodules and differentiated thyroid cancer[J]. *Thyroid*, 2009, 19(11): 1167-1214.
- [13] Randolph GW, Duh QY, Heller KS, *et al.* The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension[J]. *Thyroid*, 2012, 22(11): 1144-1152.
- [14] Kim E, Park JS, Son KR, *et al.* Preoperative diagnosis of cervical metastatic lymph nodes in papillary thyroid carcinoma: comparison of ultrasound, computed tomography, and combined ultrasound with computed tomography[J]. *Thyroid*, 2008, 18(4): 411-418.
- [15] Jeong HS, Baek CH, Son YI, *et al.* Integrated 18F-FDG PET/CT for the initial evaluation of cervical node level of patients with papillary thyroid carcinoma: comparison with ultrasound and contrast-enhanced CT[J]. *Clin Endocrinol (Oxf)*, 2006, 65(3): 402-407.
- [16] hoi JS, Kim J, Kwak JY, *et al.* Preoperative staging of papillary thyroid carcinoma: comparison of ultrasound imaging and CT[J]. *Am J Roentgenol*, 2009, 193(3): 871-878.
- [17] Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data[J]. *Radiology*, 2016, 278(2): 563-577.
- [18] Paul AY, Joseph P, Heather CH, *et al.* User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability[J]. *Neuroimage*, 2006, 31(3): 1116-1128.
- [19] Zwanenburg A, Vallières M, Abdalah MA, *et al.* The image biomarker standardization initiative: standardized quantitative radiomics for high-throughput image-based phenotyping[J]. *Radiology*, 2020, 295(2): 328-338.
- [20] Kim SY, Lee E, Nam SJ, *et al.* Ultrasound texture analysis: association with lymph node metastasis of papillary thyroid microcarcinoma[J]. *PLoS One*, 2017, 12(4): e0176103.
- [21] Park VY, Han K, Kim HJ, *et al.* Radiomics signature for prediction of lateral lymph node metastasis in conventional papillary thyroid carcinoma[J]. *PLoS One*, 2020, 15(1): e0227315.
- [22] Liu T, Zhou S, Yu J, *et al.* Prediction of lymph node metastasis in patients with papillary thyroid carcinoma: a radiomics method based on preoperative ultrasound images[J]. *Technol Cancer Res Treat*, 2019, 18: 1533033819831713.
- [23] Liu T, Ge X, Yu J, *et al.* Comparison of the application of B-mode and strain elastography ultrasound in the estimation of lymph node metastasis of papillary thyroid carcinoma based on a radiomics approach[J]. *Int J Comput Assist Radiol Surg*, 2018, 13(10): 1617-1627.
- [24] 黄云霞, 周瑾, 刘桐桐, 等. 超声影像组学与传统影像模式对甲状腺乳头状癌颈部中央区淋巴结转移的诊断价值比较[J]. *中华超声影像学杂志*, 2019, 28(10): 882-887. [Huang YX, Zhou J, Liu TT, *et al.* Comparison of ultrasound radiomics with conventional imaging models: diagnosis of central cervical lymph node metastasis in papillary thyroid carcinoma[J]. *Zhonghua Chao Sheng Ying Xiang Xue Za Zhi*, 2019, 28(10): 882-887.]
- [25] Jiang M, Li C, Tang S, *et al.* Nomogram based on shear-wave elastography radiomics can improve preoperative cervical lymph node staging for papillary thyroid carcinoma[J]. *Thyroid*, 2020, 30(6): 885-897.
- [26] Xiao Q, Zhu W, Tang H, *et al.* Ultrasound radiomics in the prediction of microvascular invasion in hepatocellular carcinoma: A systematic review and meta-analysis[J]. *Heliyon*, 2023, 9(6): e16997.
- [27] 葛晓燕, 韩红娟, 罗艳虹, 等. 基于神经影像数据的阿尔茨海默病多分类诊断模型的研究进展与挑战[J]. *郑州大学学报(医学版)*, 2020, 55(1): 1-7. [Ge XY, Han HJ, Luo YH, *et al.* Research progress and challenges of multi class diagnosis model for Alzheimer's disease based on neuroimaging data[J]. *Zhengzhou Da Xue Xue Bao (Yi Xue Ban)*, 2020, 55(1): 1-7.]

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