



· 综述 ·

# 多模态超声术前评估右侧喉返神经后方淋巴结转移的应用与意义

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[摘要] 甲状腺癌的发病率近年逐渐升高。右侧喉返神经后方淋巴结 (lymph node posterior to right recurrent laryngeal nerve, LN-prRLN) 是甲状腺乳头状癌 (papillary carcinoma of the thyroid, PTC) 淋巴结转移的重要路径之一, 具有转移率较高、隐蔽性较强、与癌症进展高度相关的特点。由于LN-prRLN清扫术伴随风险较高, 准确评价LN-prRLN受累情况对手术方式的选择、患者预后预测意义重大。超声作为评价LN-prRLN的首选影像学检查方法, 在LN-prRLN术前诊断中发挥重要作用, 并随着人工智能的发展而具有更广阔的应用前景。常规超声可直接识别并定位可疑淋巴结, 结合超声造影和超声弹性成像增加评估准确度, 淋巴超声造影对显示LN-prRLN有极大优势, 新兴的超声影像组学可客观、定量提取特征, 构建LN-prRLN转移的联合预测模型辅助诊断。本文就超声及其新技术在术前诊断和评估LN-prRLN转移中的应用现状进行综述。

[关键词] 甲状腺乳头状癌; 超声; 右侧喉返神经后方淋巴结; 人工智能

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**Application and significance of multimodal ultrasound for preoperative assessment of metastasis in lymph nodes posterior to the right recurrent laryngeal nerve in papillary carcinoma of the thyroid** ZHENG Yiman, XU Chaoli, YE Xinhua (Department of Ultrasound, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu Province, China)

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[Abstract] The incidence of thyroid cancer has gradually increased in recent years. The lymph node posterior to the right recurrent laryngeal nerve (LN-prRLN), which is characterized by higher metastasis rate, poor preoperative diagnosis rate, and high correlation with cancer progression, is one of the important pathways for lymph node metastasis in papillary carcinoma of the thyroid (PTC). Due to the complication accompanying LN-prRLN dissection, accurate evaluation of LN-prRLN involvement is significant for the surgical approach and patient prognosis. Ultrasound, as the primary choice for PTC and its cervical lymph node metastasis, plays an important role in the preoperative diagnosis and evaluation of LN-prRLN and has a broad application prospect with the development of artificial intelligence. Conventional ultrasound can directly identify and localize suspicious lymph nodes, combined with contrast-enhanced ultrasound and ultrasound elastography to increase the accuracy of assessment. Lymphatic contrast-enhanced ultrasound is extremely advantageous for the display of LN-prRLN, and emerging ultrasound imaging histology can objectively and quantitatively extract features to construct a joint prediction model for LN-prRLN metastasis to aid in diagnosis. This article reviewed the current status of the application of ultrasound and its new technologies in the preoperative diagnosis and evaluation of LN-prRLN metastasis.

[Key words] Papillary carcinoma of the thyroid; Ultrasound; Lymph node posterior to the right recurrent laryngeal nerve; Artificial intelligence

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甲状腺癌的发病率在世界范围内呈上升趋势<sup>[1]</sup>。在世界卫生组织国际癌症研究机构（International Agency for Research on Cancer, IARC）发布的2022年全球癌症统计数据中，甲状腺癌全球发病率排第7位，发病例数82.1万，较2020年的59万大幅增加<sup>[2]</sup>。甲状腺癌最常见的病理学分型是甲状腺乳头状癌（papillary carcinoma of the thyroid, PTC），约占甲状腺癌的80%<sup>[3]</sup>。绝大多数PTC较少发生远处转移，但往往伴随着早期淋巴结转移，这与患者预后、肿瘤复发密切相关<sup>[4-5]</sup>。

一般而言，颈部中央区淋巴结（central lymph node, CLN）是PTC转移的第一站<sup>[6-8]</sup>。中央区淋巴结由喉前淋巴结、气管前淋巴结和左右气管旁淋巴结组成。由于左右侧喉返神经（recurrent laryngeal nerve, RLN）的解剖学差异，右侧气管旁淋巴结又被分为右侧喉返神经前方淋巴结（lymph node anterior to right recurrent laryngeal nerve, LN-arRLN）和右侧喉返神经后方淋巴结（lymph node posterior to right recurrent laryngeal nerve, LN-prRLN）或右侧食管旁淋巴结（right paraesophageal lymph node, RPELN）<sup>[9]</sup>。

目前，美国甲状腺协会（American Thyroid Association, ATA）指南和美国内分泌外科医师协会指南都已强调PTC治疗性中央区淋巴结清扫（central neck dissection, CND）的重要性，而对于预防性CND则存在广泛争议<sup>[10-11]</sup>，尤其是位于中央区深处的LN-prRLN，缺乏相关指南的明确规范。在实际临床操作中，由于LN-prRLN位于喉返神经后方，位置较深，清扫时易发生出血、喉返神经和甲状旁腺损伤等并发症<sup>[8]</sup>，是否需要LN-prRLN清扫未能达成统一意见。因此，能够术前诊断是否有LN-prRLN转移将最大化平衡手术的收益与风险，对手术方式的选择至关重要。

本文主要就LN-prRLN转移的临床意义及其术前诊断方式展开综述，以期对PTC患者术前评估LN-prRLN转移和制订手术方案提供参考。

### 1 LN-prRLN转移术前诊断的临床意义

据Shao等<sup>[12]</sup>开展的一项meta分析显示，

PTC的LN-prRLN转移率可达9.36%。Du等<sup>[13]</sup>的研究也得出了与之相近的结论，并且发现LN-prRLN转移往往伴随着其他淋巴结的并发转移，更有甚者报道LN-prRLN转移率达30.4%<sup>[14]</sup>，提示LN-prRLN在PTC的淋巴结转移中具有重要地位。LN-prRLN还与其他颈部淋巴结转移有关。Chang等<sup>[15]</sup>证实，95.9%的LN-prRLN转移者还存在其他CLN转移，且颈侧区淋巴结转移的发生率显著高于无LN-prRLN转移者（分别为63.5%，14.3%），这表明LN-prRLN可能是癌细胞由中央区转移到颈侧区的首要途径。更重要的是，PTC的复发被公认与LN-prRLN转移相关<sup>[16]</sup>。Kim等<sup>[17]</sup>首次提出LN-prRLN转移是右侧PTC患者局部复发的预测因素之一，且转移淋巴结数量和淋巴结转移率（即转移淋巴结个数与检出淋巴结总数的比值）是PTC复发的独立预测因素<sup>[18]</sup>。有学者<sup>[19]</sup>对近几年的数据进行meta分析后发现，行LN-prRLN清扫可显著降低手术局部区域复发率。

即便如此，考虑到PTC恶性程度较低以及LN-prRLN清扫伴随的并发症，对于cN0期PTC患者是否需要常规行LN-prRLN清扫，国内外学者尚未达成一致意见。首先，由于LN-prRLN解剖位置较深，周围血运丰富，适宜淋巴结隐藏，田文等<sup>[20]</sup>认为诊断真正低危PTC难度较大，对PTC的保守治疗将可能引起中国PTC死亡率的上升，因此应行常规LN-prRLN清扫。据报道，复发患者LN-prRLN转移的发病率明显高于首次接受手术的患者<sup>[21]</sup>。相较于原发，PTC复发更易侵犯周围喉返神经、食管等组织，再次手术时，瘢痕组织粘连会加大手术难度，加重术后并发症<sup>[22-23]</sup>。反对者则认为PTC进展缓慢、恶性程度较低，即便出现复发，对生存率无明显影响，行清扫术反而增加甲状旁腺功能减退和喉返神经损伤等并发症的风险，影响患者预后<sup>[24-27]</sup>，所以仅应在影像学检测到可疑淋巴结或超声引导下穿刺病理学检查证实转移后，才有必要行治疗性LN-prRLN清扫。

基于以上，术前诊断是否有LN-prRLN转移至关重要。早期明确LN-prRLN转移不仅可以预

测PTC颈部淋巴结扩散的风险、评估预后, 还可制订个体化手术方案, 规避不必要的手术, 减少术后并发症的发生。

## 2 LN-prRLN转移的术前诊断

### 2.1 超声成像

#### 2.1.1 常规超声

相较其他区域淋巴结, 常规超声对CLN转移的检出效能较低。据报道超声诊断CLN转移的灵敏度为30%~50%, 特异度为80%~90%<sup>[28]</sup>, 漏诊率可达44%<sup>[29]</sup>。一般认为, CLN转移的超声征象包括淋巴结体积增大、形态变圆、淋巴门结构消失、边缘血流而非淋巴门型血流、内见局部高回声团块、点状钙化、囊性变等<sup>[30-31]</sup>。相较于其他转移性淋巴结, PTC转移可呈高回声, 周边有钙化, 表现为强回声斑伴声影, 这多由凝固性坏死引起。并且转移淋巴结易发生囊性坏死, 即结内出现无回声区或整体囊性变, 这在CLN转移中尤为常见<sup>[29, 32-33]</sup>。

由于LN-prRLN处于中央区深层, 前方组织较多干扰超声成像, 术前超声对LN-prRLN转移检出率极低<sup>[34]</sup>, 目前几乎未有超声直接提示LN-prRLN转移。因此, 寻找相关危险因素对LN-prRLN转移进行评估具有重大意义。既往研究<sup>[35-37]</sup>通过回顾并分析PTC原发肿块和其他颈部淋巴结的术前超声检查结果, 明确其与LN-prRLN的关联, 间接评估有无LN-prRLN转移, 结果显示, LN-prRLN转移危险因素主要包括肿瘤大小、肿瘤位置、肿瘤微钙化、多灶性、包膜浸润、甲状腺外浸润、颈侧部淋巴结转移和LN-arRLN转移。

术前超声测量PTC病灶大小被广泛认为可用于预测LN-prRLN的转移, 但具体的测量径线及标准尚未达成一致。杨旭芬等<sup>[4]</sup>的研究认为, 病灶左右径是预测转移风险发生的独立危险因素, 当病灶左右径 $>1.05$  cm时应行LN-prRLN清扫术。Zhang等<sup>[38]</sup>在收集了615例PTC患者术前超声图像后, 认为 $\geq 20$  mm的肿瘤是LN-prRLN转移的预测因素。

部分预测因素如甲状腺包膜侵犯、甲状腺腺外浸润、甲状腺影像报告和数据库系统 (Thyroid

Imaging Reporting And Data System, TI-RADS) 分级等是否与淋巴结转移有关仍然存在争议。杨旭芬等<sup>[4]</sup>和Zou等<sup>[39]</sup>都认为两者间无相关性; 这与徐骁诚等<sup>[40]</sup>于2018年开展的一项回顾性分析所得结论相矛盾。后者基于术后病理学检查结果指出, 肿瘤被膜侵犯、右侧喉返神经前方淋巴结转移个数 $\geq 2$ 、转移灶直径 $\geq 0.45$  cm和右侧颈侧区淋巴结转移时极大概率伴有LN-prRLN的转移, 是其清扫术的指标。刘文等<sup>[41]</sup>的研究佐证了该观点。这种差异可能与淋巴结分区规范性、超声探查精度有关。此外, 也有学者<sup>[42-43]</sup>提出较高的血流阻力指数和血流丰富也可作为CLN转移的独立危险因素, 由于相关研究较少, 该观点目前尚未获得普遍认可。

综上所述, 术前超声虽然对LN-prRLN诊断灵敏度较低, 但通过对原发灶和其他颈部淋巴结图像特点进行分析, 可用于评估LN-prRLN淋巴结转移。当前的研究还存在着样本量较小、超声科医师技术差异限制, 以及灵敏度较低、假阴性等问题。这可能与LN-prRLN的特殊解剖位置、纳入标准不统一、超声报告欠缺规范化等有关, 有待以后大样本、多中心、前瞻性的研究进一步探索。

#### 2.1.2 超声造影 (contrast-enhanced ultrasound, CEUS)

CEUS具有更高的时空分辨率, 可通过时间-强度曲线定性定量评估肿瘤组织的微血管状况。PTC转移淋巴结往往表现出不均质的向心性增强、混杂血流和灌注缺损等征象<sup>[44]</sup>。目前, 对用于预测PTC患者LN-prRLN转移的CEUS参数探索较少, 仅有1例文献报道<sup>[45]</sup>, PTC的离心灌注模式与周边环状增强与LN-prRLN转移紧密相关, 且前者是其发生的独立预测因子。

对CLN转移的研究或许能为LN-prRLN的研究提供参考和方向。Ye等<sup>[46]</sup>直接研究了127例PTC CLN转移患者的CLN图像, 发现CLN转移常表现出高增强、异质性增强、向心灌注、环状增强、峰值强度 (peak intensity, PI)  $> 1$ 和曲线下面积 (area under curve, AUC)  $> 1$ , 异质性增强和向心灌注增强是其独立特征。Hong

等<sup>[47]</sup>指出,伴有CLN转移的PTC更易呈现为高增强或等增强,并有更高的峰值指数( $\geq 1$ )。Jiang等<sup>[48]</sup>则建立B型超声和CEUS影像组学评分,表明它们是CLN转移的独立危险因素,并将后者与其他临床因素相结合,建立临床影像组学列线图,经验证其具有良好的预测效用。淋巴CEUS通过在淋巴管内注入微泡并观察其增强模式,可在术前观察并定位淋巴结转移。据报道,该方法可有效判断 $< 1$  cm的深层CLN转移,恰巧弥补了常规超声探查深度的不足<sup>[49-50]</sup>。

### 2.1.3 超声弹性成像

剪切波弹性成像(shear wave elastography, SWE)可以对组织弹性进行精准测量,已广泛应用于甲状腺结节良恶性的判断<sup>[51]</sup>。Li等<sup>[52]</sup>对172例PTC患者进行灰阶超声和SWE检查,发现伴有CLN转移的弹性值( $E_{\max}$ 、 $E_{\text{mean}}$ 、 $E_{\min}$ )显著高于无CLN转移组,提示SWE弹性值与CLN转移有关,并且联合使用SWE和灰阶超声时,对CLN转移预测的AUC(0.825)显著高于单独使用灰阶超声(0.774),证实SWE有助于提高对CLN转移的诊断准确度。Chang等<sup>[31]</sup>扫描了22例患者的87个淋巴结,发现转移性淋巴结较非转移性淋巴结更硬,且 $E_{\text{SD}}$ 可能是评估VI区淋巴结的最佳SWE指标,不过该项研究并未对CLN进行精确分区,这可能是因为LN-prRLN较小且位置较深,难以探查。基于影像组学建模联合SWE参数预测PTC CLN转移也被证明有良好的效能(AUC 0.853)<sup>[53]</sup>。然而,Hong等<sup>[47]</sup>对127例患者行应变弹性成像(strain elastography, SE)则得出了截然不同的结果,他们的结果表明PTC肿瘤的硬度与CLN转移无明显相关性。需要注意的是,目前的弹性成像研究均聚焦于VI区而非LN-prRLN,提示我们对后者还需要进一步关注。

### 2.1.4 超声纹理分析、影像组学和人工智能

近年来,随着精准医学的发展与科技的进步,影像组学结合人工智能通过深度挖掘图像信息,提取相关特征并建立预测模型,在医疗领域的运用得到飞速发展,并被广泛应用于PTC颈部淋巴结转移的预测<sup>[54-55]</sup>,Zhang等<sup>[56]</sup>指出,相

较于临床模型,超声影像组学模型表现出更高的灵敏度。目前,针对LN-prRLN的预测模型相对较少。Shen等<sup>[57]</sup>分析了570例PTC患者的超声图像,勾画并分析得到105个影像组学特征,二次提取出15个特征并建立LN-prRLN转移的影像组学特征和临床因素联合预测模型,对照病理学检查结果,其AUC为0.849,灵敏度高达96.40%,相较于常规超声,极大地提高了LN-prRLN的预测效能。该研究同时指出,超声测量肿瘤大小、颈侧区淋巴结转移、微钙化、喉前淋巴结转移、VIa区淋巴结转移和影像组学评分是转移的重要危险因素。该相关性提示超声影像组学模型或联合模型在预测LN-prRLN转移方面有良好的效能。然而,想要将其用于临床决策还需要更多的前瞻性队列进行模型验证,需要更大的、多中心的样本量进行深度学习<sup>[55]</sup>。

### 2.2 超声-计算机体层成像(computed tomography, CT)融合技术

目前,CT常被用于评估CLN转移,针对LN-prRLN的相关研究较少。相较于超声,CT特异度较低<sup>[58]</sup>,但其更高的空间分辨率使淋巴结观察更容易、对CLN的分区更精准,灵敏度更高<sup>[59]</sup>。不同于其他转移淋巴结,CLN转移形态上主要表现为淋巴结短径 $\geq 5$  mm和短长径比值 $\geq 0.5$ <sup>[60]</sup>。

研究<sup>[61]</sup>显示,当增强CT值 $> 132$ 时,其诊断LN-prRLN转移的特异度和灵敏度分别为84.1%和71.4%(该研究报告超声分别为95.8%和11.1%),并且随着增强的CT值的增加,LN-prRLN转移的检出率也迅速增加,这可为术前诊断提供辅助参考。

双能CT碘浓度在预测LN-prRLN转移中也有着广阔的发展前景。其原理是甲状腺正常组织摄碘能力与PTC病灶的摄碘能力存在差异,因此可利用不同组织摄碘能力的能谱衰减测定两者区别<sup>[62]</sup>。虽然目前能谱CT定量参数存有争议<sup>[63]</sup>,但其诊断效能依旧高于以形态学特征评估淋巴结转移,具有更高的特异度(分别为96.77%, 54.84%),这为后续研究的开展提供了方向。

近年来, 超声-CT融合技术(虚拟导航技术)获得广泛关注。这是一种通过对同一部位进行多平面重建, 将动态对比CT的三维容积数据与超声实时同步成像的新技术<sup>[64-65]</sup>。既往有研究<sup>[66]</sup>表明, 相较于单一超声检查, 超声联合CT检查淋巴结转移具有更高的灵敏度。CT可更清晰地轴向反映咽、食管、气管周围等深层结构的肿瘤浸润状况, 弥补了LN-prRLN解剖学位置较深, 超声无法探查的缺陷。若能将两者联合同步成像, 甚至在超声引导下穿刺, 将极大地提高术前诊断的准确度和安全性。

### 3 总结

随着现代诊断技术的不断进步和甲状腺癌发病率的增高, 如何预测甲状腺癌侵袭性、复发性以及确定相应的手术方式成为研究焦点。作为颈CLD与颈侧淋巴结转移路径的重要环节, LN-prRLN转移极大地影响着PTC的复发与预后, 是决定甲状腺癌手术方式的重要因素, 因此, 术前评估有无LN-prRLN转移至关重要。

超声是临床术前评估甲状腺癌及其淋巴结转移的主要影像学检查, 内见高回声团块、伴有声影的钙化和囊性变被认为是LN-prRLN转移的典型表现。基于原发甲状腺癌病灶的联合预测模型, 通过分析原发病灶、其他区域淋巴结明确LN-prRLN转移的危险因素, 解决LN-prRLN解剖位置较深、体积较小, 以致常规超声灵敏度、特异度较低的问题, 在一定程度上可辅助评估LN-prRLN。其中, 通过勾画感兴趣区、提取相关特征建立的影像组学模型可定量获取病灶特点, 减少医师评估主观性的干扰, 大幅提高模型准确度, 将成为未来研究的焦点。超声弹性成像有助于提高诊断淋巴结转移准确度。CEUS, 尤其是淋巴CEUS可显示小而深的淋巴结及其血供状态, 尤为适用于LN-prRLN, 具有极高的应用潜能。

然而, 目前针对LN-prRLN的研究较少, CEUS、超声弹性成像的实际应用价值还需未来大样本量研究数据的支持。超声弹性成像极为依赖常规超声的定位能力, 并受操作者影响较大, 在实际临床应用中可能存在较大的误差。影像组

学和人工智能相关研究开展时间较短, 未能形成统一的、广泛认可的评估体系, 尚存在样本量较小、单中心为主、随访时间较短、缺乏前瞻性等问题。后续的研究将聚焦于LN-prRLN而非广泛的CLD, 一方面依托超声新技术, 增强对LN-prRLN的直接观测能力, 减少误差, 另一方面结合人工智能、综合提取各项预测因素, 建立客观、可靠的预测模型, 为手术方式的选择提供参考, 并应建立完善、长期的随访队列, 以明确LN-prRLN转移和手术方式选择的长远影响。

综上所述, 作为PTC转移的重要途径之一, LN-prRLN具有较大的临床意义、极高的研究价值、广阔的探索空间。作为评估LN-prRLN的首选检查, 相信超声及其新技术通过未来大范围、多中心研究的开展, 能有效地诊断LN-prRLN转移。

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