

• 临床研究 •

## 高频超声及其新技术在评估甲状腺乳头状癌喉前淋巴结转移中的应用

何佳美, 曹琨芃, 王欣玥, 徐超丽, 叶新华\*

南京医科大学第一附属医院超声诊断科, 江苏 南京 210029

**[摘要]** 甲状腺乳头状癌是最常见的甲状腺恶性肿瘤组织学类型。颈部中央区淋巴结, 尤其是喉前淋巴结, 是甲状腺乳头状癌最先累及的部位。早期诊断喉前淋巴结转移对患者的治疗方式及生存预后具有重要意义。超声是诊断甲状腺乳头状癌淋巴结转移的首选方式, 文章针对高频超声及其新技术在评估甲状腺乳头状癌喉前淋巴结转移中的研究进展及应用进行综述。

**[关键词]** 超声; 甲状腺乳头状癌; 喉前淋巴结; 转移

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### The application of high-frequency ultrasound and new ultrasonic techniques in the evaluation of Delphian lymph node metastasis in papillary thyroid carcinoma

HE Jiamei, CAO Kunpeng, WANG Xinyue, XU Chaoli, YE Xinhua\*

Department of Ultrasound Diagnosis, the First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China

**[Abstract]** Papillary thyroid carcinoma is the most common histological type of malignant thyroid tumor. The central cervical lymph nodes, particularly Delphian lymph nodes, are the first areas affected by metastasis in papillary thyroid carcinoma. Early diagnosis of Delphian lymph node metastasis is crucial for determining the treatment approach and improving survival prognosis of patients. Ultrasound is the preferred method for diagnosing lymph node metastasis in papillary thyroid carcinoma. This review focuses on the research progress and applications of high-frequency ultrasound and its advanced technologies in detecting Delphian lymph node metastasis in papillary thyroid carcinoma.

**[Key words]** ultrasound; papillary thyroid carcinoma; Delphian lymph node; metastasis

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根据国际癌症研究中心最新发布的全球恶性肿瘤统计数据, 甲状腺癌的发病率显著上升, 现已成为全球范围内第7大常见恶性肿瘤; 在国内, 甲状腺癌的发病率甚至高居第3位<sup>[1]</sup>。甲状腺癌按照病理类型分为乳头状癌、滤泡状癌、髓样癌和未分化

癌, 其中甲状腺乳头状癌是最常见的甲状腺恶性肿瘤组织学类型<sup>[2]</sup>。喉前淋巴结转移(Delphian lymph nodes metastasis, DLNM)是甲状腺乳头状癌具有较强侵袭性的表现, 与局部复发息息相关<sup>[3]</sup>。术前常规超声检查是检测转移淋巴结最敏感的方法。但是, 喉前淋巴结上覆甲状腺, 位置深在, 且超声表现上易与甲状腺峡部结节混淆, 术前常规超声的准确性很容易受操作者临床经验的影响, 这些原因导致DLNM的临床重要性被低估。因此, 利用超声新技术找到可靠的DLNM征象以帮助术者制定合理诊疗

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\*通信作者(Corresponding author), E-mail: yexh-0125@163.com  
(ORCID: 0000-0002-9628-660X)

方案尤为重要。

## 1 喉前淋巴结解剖及临床价值

### 1.1 解剖

喉前淋巴结位于喉部正前方,是中央区淋巴结的一个亚群,其横跨于环状软骨和舌骨之间,紧邻甲状腺峡部上方,藏于颈深筋膜内,主要负责甲状腺(上部、峡部、锥状叶)与喉部(会厌、声门下区)的淋巴回流。喉前淋巴结的数量因人而异,一般为1~4个。

### 1.2 临床价值

DLNM已被证实是喉癌淋巴结转移的可靠预测因素,近期相关研究认为,相较其他前哨淋巴结如气管旁和气管前淋巴结,DLNM有望成为甲状腺乳头状癌预后不良的预测指标<sup>[4-5]</sup>。DLNM阳性对于甲状腺乳头状癌在预测其他中央区淋巴结转移、双侧颈侧区淋巴结转移及对侧腺叶隐匿性癌方面具有重要临床意义<sup>[5-9]</sup>。Zhu等<sup>[9]</sup>对乳头状癌术后患者随访发现DLNM可能还与预后不良有关,DLNM阳性组更易出现新、远处转移,且转移生存率、无远处转移生存率均较未转移者低。研究建议DLNM患者彻底清扫同侧中央区淋巴结,必要时加做对侧中央区淋巴结清扫,同时提示需要更充分评估颈侧区淋巴结转移,制定更为积极的个体化治疗方案<sup>[10]</sup>。当甲状腺乳头状癌患者术前超声或术中冰冻切片提示DLNM时,提示临床医师谨慎制定手术方式,确定淋巴结清扫范围及手术范围。

## 2 DLNM的危险因素

大量临床实践表明,准确判断DLNM的出现情况有助于预测其他中央区淋巴结转移及术后复发,肿瘤直径>1 cm、甲状腺淋巴管和腺叶外侵犯、肿瘤位于甲状腺腺叶上部或峡部是DLNM的独立危险因素<sup>[5-13]</sup>。近期也有研究表明,DLNM在分子水平上与BRAF<sup>V600E</sup>突变和TERT启动子突变有关<sup>[8-9]</sup>;还有一些其他因素如年龄、性别、与桥本甲状腺炎的关系及病理分型等也值得参考。上述危险因素关系密切,通过对多个风险因素的联合评估对准确判断DLNM有重要指导意义。

### 2.1 肿瘤数目和直径

多发病灶及较大的肿瘤直径意味着更高的恶性程度和转移侵袭性,从而导致其发生DLNM的风险明显增加。相关研究均发现甲状腺乳头状癌肿瘤大小与DLNM密切相关,Yan等<sup>[7]</sup>和Zheng等<sup>[8]</sup>更

认为甲状腺癌直径>1 cm是DLNM的独立危险因素,且直径越大,肿瘤越易侵犯至被膜,DLNM的风险也越大。也有研究表明多灶癌结节更容易出现DLNM,病灶的数量越多,表示肿瘤的侵袭性越强,DLNM的风险越大;尽管多因素分析未发现多发病灶是DLNM的独立危险因素,但多发病灶往往具有更高的恶性特征、更大的肿瘤尺寸、更严重的腺叶外侵犯和淋巴管侵犯<sup>[7-11]</sup>。

### 2.2 肿瘤位置

喉前淋巴结主要接受来自峡部和甲状腺上部的淋巴引流,从而导致其发生淋巴结转移的风险明显增加。因此,DLNM的发生与峡部和甲状腺上部这两个部位的甲状腺癌密切相关<sup>[12]</sup>。峡部组织相对较薄,肿瘤细胞易突破包膜浸润生长。当包膜侵犯时,原本局限于甲状腺组织内部的肿瘤细胞会侵入并突破包膜,沿包膜外的淋巴组织向周围转移,更易引发DLNM<sup>[13]</sup>。

### 2.3 淋巴管和腺叶外侵犯

甲状腺内淋巴系统广泛,喉前淋巴结亦引流甲状腺中央区其他亚群的淋巴液,如果发生DLNM,中央区甚至颈侧区淋巴结转移风险便随之升高<sup>[14]</sup>。研究也发现淋巴管侵犯是DLNM的独立风险因素<sup>[7,10]</sup>。甲状腺癌跳跃性转移较为少见,当甲状腺癌侵犯包膜并突破包膜,形成腺外侵犯时,将使得原本局限于甲状腺内部的肿瘤细胞沿腺外的淋巴组织向周围转移,从而更易引起DLNM,几乎所有的单因素分析都发现腺叶外侵犯是DLNM的风险因素<sup>[3,5-12]</sup>。

### 2.4 BRAF<sup>V600E</sup>突变和TERT启动子突变

BRAF<sup>V600E</sup>和TERT启动子突变是甲状腺乳头状癌中最常见的基因突变类型且与术后复发风险紧密相关,甲状腺乳头状癌患者出现DLNM可能在分子水平上提示其预后不良,且肿瘤可能具有更强的侵袭性。Zheng等<sup>[8]</sup>发现甲状腺乳头状癌伴颈部DLNM与BRAF<sup>V600E</sup>突变存在相关性;而Zhu等<sup>[9]</sup>的研究发现DLNM与TERT启动子突变之间存在显著关联,并且当这两种突变共同存在时,提示患者同位素治疗不敏感,预后更差。

### 2.5 其他因素

近年研究表明,男性较女性更易出现DLNM,且是甲状腺乳头状癌DLNM的独立危险因素<sup>[9,11]</sup>。年龄与DLNM的相关性还存在争议,Zhu等<sup>[9]</sup>的研究认为年龄>55岁的患者更容易出现DLNM,而Li等<sup>[11]</sup>的研究却发现,年轻患者的DLNM阳性率高于老年患者。在病理类型方面,Yan等<sup>[7]</sup>的研究发现甲状

腺乳头状癌中高侵袭性病理亚型的比例在DLNM组中更高。

### 3 超声新技术在DLNM诊断中的应用

虽然其他影像技术如计算机断层扫描、磁共振成像和正电子发射计算机断层显像也可以用于淋巴结转移的检测<sup>[14-16]</sup>,但由于存在辐射暴露、价格昂贵及灵敏度低等问题,超声检查仍是甲状腺及淋巴结检查最重要的手段,而高频超声及其新技术的出现使得DLNM的诊断效能进一步提高。

#### 3.1 高频超声

高频超声具有高空间分辨率、高对比度、高信噪比,对直径<1 mm的甲状腺癌和淋巴结细微结构及血流检测的灵敏度较传统超声高。因此国内外诊疗指南和共识均建议进行术前颈部超声检查以评估手术策略和范围<sup>[14-16]</sup>。2022年中国甲状腺癌诊疗指南<sup>[14]</sup>指出颈部淋巴结异常征象主要包括:淋巴结内部出现微钙化、囊性变、高回声、周边血流,此外还包括淋巴结呈圆形、边界不规则或模糊、内部回声不均匀、淋巴门消失或皮髓质分界不清等。然而,一项荟萃分析显示在颈部超声检查中,超声检测中央区淋巴结转移的敏感度仅为33%<sup>[17]</sup>。DLNM的检出率更低,主要原因是其位置隐蔽,易与峡部甲状腺结节混淆,且缺乏上述淋巴结转移的典型超声特征<sup>[18]</sup>。Qi等<sup>[19]</sup>发现将高频超声特征联合病理特征用于预测甲状腺乳头状癌患者DLNM诊断效能更高:DLNM组的甲状腺结节形状不规则、微钙化和腺外侵犯的比例更高,曲线下面积(area under the curve, AUC)高达0.877。Zhou等<sup>[20]</sup>通过超声和临床病理参数联合建模发现,DLNM组患者更容易表现出结节边界不清晰、后方回声衰减及中央区淋巴结转移的特征;而周娜等<sup>[21]</sup>在研究甲状腺微小乳头状癌DLNM影响因素时也发现,中央区淋巴结转移是独立危险因素,且结节更易出现纵横比 $\geq 1$ 及被膜侵犯的超声特征。上述研究为超声预测DLNM提供了新的思路,也表明利用超声及临床病理特征建立的预测模型能更有效地识别DLNM风险。

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

CEUS可以弥补常规超声在淋巴结内出现微转移灶时,难以做出明确诊断这一不足。CEUS在检测乳腺癌、甲状腺癌、子宫内膜癌、宫颈癌、黑色素瘤等多种恶性肿瘤的前哨淋巴结转移方面展现出了显著的临床价值,特别是在乳腺癌的检测中,CEUS能够实现高灵敏度和特异度,其性能与传统

的放射性同位素及蓝染法相当<sup>[22-26]</sup>。研究显示,CEUS超强化、向心灌注和环状强化特征与甲状腺癌颈部淋巴结转移独立相关,而CEUS诊断中央区淋巴结转移的特征是不均匀强化和向心灌注<sup>[26-28]</sup>。Wei等<sup>[28]</sup>通过与病理学对照后发现:灌注缺损与淋巴结髓质肿瘤转移相关,亮环中断与淋巴结边缘窦肿瘤播散相关。这两个体征诊断的AUC可达0.899和0.904,体现出CEUS识别中央区淋巴结转移的优势大。现有的CEUS技术主要用于整体评估中央区淋巴结,但未精确区分这些不同区域的功能性和病理学差异,这一局限性对医生在制定更精确的肿瘤分期和治疗规划时构成了挑战,有待今后更多的研究。

#### 3.3 超微血流成像(superb microvascular imaging, SMI)

SMI旨在通过提高血流检测的灵敏度来显示微小的血管结构,能够通过先进的算法去除噪声和组织运动伪影,同时保留真正的血流信号,捕捉到传统彩色多普勒超声难以检测到的低速血流信号<sup>[29]</sup>。SMI技术在显示血流方面与CEUS表现出良好的一致性,而SMI无需造影剂就能高分辨度、高灵敏度地显示低速血流及微小血管,可用于评价淋巴结的微血流灌注情况,目前已被逐渐应用于淋巴结良恶性病变的诊断<sup>[30]</sup>。由于病灶内部滋养血管网越丰富,增殖能力就越强,肿瘤越容易侵入微血管而发生转移,血供丰富的结节发生中央区淋巴结转移的可能性较高<sup>[31]</sup>。Guang等<sup>[32]</sup>根据Adler标准<sup>[33]</sup>将结节的SMI血流分为3个级别:0级,结节内无血流;I级,结节显示少量血流,只有少量血流或1条长血管穿入结节;II级,结节内血流丰富,有5个及以上点状血流或2条长血管;证实了SMI血流丰富(Adler II级)的特征是甲状腺乳头状癌中央区淋巴结转移的独立危险因素,甲状腺乳头状癌内血流情况可以用来预测中央区淋巴结转移。喉前淋巴结作为中央区淋巴结中最有诊断意义的亚群,通过SMI技术预测DLNM有望成为未来研究的新方向。

#### 3.4 超声引导下细针穿刺细胞学(ultrasound guided fine needle aspiration cytology, US-FNAC)检查及术中淋巴结活检

US-FNAC能够精准地获取细胞样本进行病理学分析,评估细胞的形态和特征,以确定是否存在癌变。US-FNAC是术前诊断原发性甲状腺病变和淋巴结转移的首选方法,也是准确性最高的方法之一<sup>[14-16]</sup>。甲状腺癌术中淋巴结活检于1998年首次报道<sup>[33]</sup>。目前绝大部分应用亚甲蓝染色法、放射性

同位素或纳米碳标记甲状腺癌引流区淋巴结。喉前淋巴结在术中通常比较容易发现,但有时会包埋在包绕环甲肌的颈深筋膜浅层之下,沿着染色的淋巴管更容易找到。但示踪剂均需要通过淋巴管进入淋巴结,一旦淋巴结转移较重,癌栓堵塞淋巴管,淋巴示踪剂将起不到示踪作用,导致术中淋巴结活检假阴性率增高<sup>[34]</sup>。

甲状腺球蛋白在正常甲状腺组织内、甲状腺癌组织及转移的淋巴结组织中均有较高含量;甲状腺球蛋白由甲状腺滤泡上皮细胞合成,可随着甲状腺癌细胞的淋巴结转移呈升高表达<sup>[35]</sup>。临床医生可通过实验室检查和淋巴结细针穿刺活检获取标本进行甲状腺球蛋白检测<sup>[36]</sup>。淋巴结穿刺洗脱液中甲状腺球蛋白浓度较高说明淋巴结组织中包含具有分泌功能的甲状腺组织,从细胞的生物学特性上可诊断为转移癌<sup>[37-38]</sup>。Pacini等<sup>[39]</sup>于1992年首次报道颈部肿块细针穿刺后洗脱液中的甲状腺球蛋白浓度升高强烈提示甲状腺分化癌淋巴结转移。许多研究称,在洗脱液中检测到甲状腺球蛋白可提高甲状腺分化癌患者可疑淋巴结的评估效能,但洗脱液中甲状腺球蛋白的阈值标准尚存争议<sup>[35-38]</sup>。一项纳入21项研究的荟萃分析显示,细针穿刺细胞学的诊断特异度更高,洗脱液中检测甲状腺球蛋白的诊断灵敏度更高,而联合使用能获得更好的诊断性能(AUC=0.986)<sup>[40]</sup>。目前研究显示,甲状腺球蛋白并非DLNM的独立危险因素,但甲状腺球蛋白作为一种特异性标志物,能反映残余甲状腺组织或癌细胞的存在,而DLNM通常与肿瘤侵袭性增加、复发风险升高等因素相关<sup>[41]</sup>。

### 3.5 影像组学

影像组学通过对超声图像的高通量数据进行定量分析,以提取图像中难以通过传统视觉方法识别的细节特征。影像组学结合机器学习和人工智能算法,分析从医学图像中提取的大量特征数据,帮助进行疾病诊断、预后预测和治疗方案的制定,目前已广泛用于甲状腺癌、乳腺癌等疾病的早期诊断与筛查<sup>[41-43]</sup>。此外,超声影像组学还可以整合超声弹性成像、CEUS等超声新技术,进一步提高预测DLNM的准确性<sup>[44-45]</sup>。超声影像组学使得基于甲状腺结节图像的影像组学预测DLNM成为可能。一项荟萃分析显示,基于高频超声的影像组学可在术前有效评估甲状腺乳头癌的淋巴结转移,影像组学特征在训练集中预测中央区淋巴结转移的AUC为0.839,在3个验证集中分别为0.819、0.799、0.797;

在训练集预测颈侧区淋巴结转移的AUC为0.908,在3个验证队列中分别为0.888、0.796、0.793;表明影像组学特征对甲状腺乳头癌颈部淋巴结的判别性能优于超声医生的主观预测<sup>[46]</sup>。Dai等<sup>[47]</sup>提出了通过高频超声-弹性成像-超声组学特征建立多模态超声模型预测甲状腺乳头状癌中央淋巴结转移,在验证集和测试集中的AUC分别达到了0.910和0.851,均高于单模态模型。Jiang等<sup>[48]</sup>通过多因素逻辑回归分析,结合患者的性别、年龄、超声淋巴结情况以及CEUS影像组学评分,建立的联合模型在预测乳头状癌中央区淋巴结转移训练集和验证集中的AUC值分别为0.820和0.814,展现出较好的预测性能。这种临床-超声影像组学联合模型为甲状腺乳头状癌患者的个性化治疗规划提供了重要参考,有望成为术前无创评估淋巴结状态的有效工具,减少了不必要的活检。人工智能的发展纠正了传统超声诊断淋巴结的可变性,还可缩短诊断时间,减轻医生负担。目前用于预测DLNM的超声证据相对较少且为未联合影像组学,相信随着研究日益完善,人工智能将成为未来甲状腺及淋巴结超声诊断发展的主要趋势。

## 4 总结和展望

综上所述,DLNM情况能指导手术方案,且甲状腺乳头癌患者出现DLNM往往预示着预后较差。因此,术前超声检查十分必要,可以将高频超声、弹性成像、超声造影及血流成像等新技术与影像组学相结合以提高诊断的灵敏度、特异度和准确性。预测DLNM的临床病理因素也有助于进一步确定手术范围以避免过度治疗或治疗不足。甲状腺颈部淋巴结超声诊断随着临床的重视仍在继续标准化和技术创新,人工智能作为一种先进技术的发展,将成为甲状腺及淋巴结超声诊断发展的主要趋势。针对DLNM的诊断仍需要进一步完善和更系统的研究,以造福广大患者。

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### Author's Contributions:

HE Jiamei was responsible for literature review, data orga-

nization, and manuscript writing. CAO Kungpeng and WANG Xinyue were responsible for literature review, data organization, and manuscript revision. XU Chaoli and YE Xinhua designed, guided, and revised the manuscript.

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