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· 文献综述 ·

## 甲状腺癌上纵隔淋巴转移的外科诊疗策略进展

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### 摘要

甲状腺癌是全球范围内发病率不断上升的恶性肿瘤之一, 其中甲状腺乳头状癌(PTC)和甲状腺髓样癌(MTC)有时可发生上纵隔淋巴转移, 虽仍属区域转移, 但是病期较晚的表现之一, 容易漏诊漏治。对于常见的PTC和MTC, 彻底清扫中央区、颈侧区和少见的上纵隔淋巴结转移(SMLNM)显著提高了无病生存率。在解剖学上, 甲状腺有着广泛的引流淋巴管网, 其中腺内淋巴网通过甲状腺峡部连同两侧腺叶, 而腺外淋巴则引流至纵隔淋巴结。目前尚无专门的成熟的甲状腺癌SMLNM分区, 因此参考借鉴肺癌分区成为一种常见做法。甲状腺癌SMLNM最常见的区域为2R、2L区, 而4R、3a区则相对少见。SMLNM的发病率从不等幅的0.7%到48.1%, PTC的纵隔淋巴结转移率约为6%~12%, 而MTC更容易发生淋巴结转移, 转移率可高达18%左右。临床上, SMLNM往往无明显症状, 常通过影像学检查或肿瘤标志物检测发现。超声检查难以发现SMLNM, 颈胸部增强CT的典型表现为强化、钙化、囊性变、外侵等; 增强MRI、PET、<sup>131</sup>I显像也能协助诊断。对于甲状腺癌SMLNM患者, 进行安全、规范和彻底的手术仍然是获得良好疗效的关键, 需根据患者的具体情况制定个体化的手术方案。手术原则包括尽可能一期完成R<sub>0</sub>切除, 保证手术安全的前提下彻底清扫, 以达到解剖治愈和生化治愈。手术方式可以包括经颈部开放手术、劈胸手术、腔镜辅助手术以及胸腔镜下手术等。其中多数可通过颈部入路完成清扫; 低位广泛转移或严重侵犯周围大血管等则需要劈开胸骨, 有时可借助腔镜辅助或/和胸腔镜完成手术。在手术后应注意避免并发症的发生, 如大血管撕裂、气管和食管损伤等。鉴于上纵隔解剖结构复杂、从颈部难以显露, 手术风险较大, 甲状腺或头颈外科医师相对陌生和困难, 往往需要多学科协作。虽然甲状腺癌转移至上纵隔的患者预后相对较差, 但采用适合患者的个体化手术入路及方案, 联合胸心外科, 进行上纵隔转移灶的彻底清扫, 仍然可以明显改善患者的预后和生活质量。本文对甲状腺癌SMLNM的外科诊疗进行综述, 以期对甲状腺外科医师诊疗提供参考。

### 关键词

甲状腺肿瘤/治疗; 淋巴转移; 外科手术; 综述

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## Advances in surgical diagnosis and treatment strategies for mediastinal lymph node metastasis in thyroid cancer

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**Abstract**

Thyroid cancer is one of the malignant tumors with an increasing incidence worldwide, in which, papillary thyroid carcinoma (PTC) and medullary thyroid carcinoma (MTC) occasionally exhibit superior mediastinal lymph node metastasis (SMLNM). Although this is still considered regional metastasis, it is indicative of a later stage of the disease and is prone to being misdiagnosed or undertreated. For common types of PTC and MTC, thorough dissection of the central compartment, lateral neck, and the rare superior mediastinal lymph node metastases (SMLNM) can significantly improve disease-free survival rates. Anatomically, the thyroid has an extensive lymphatic drainage network. The intrathyroidal lymphatic network connects both lobes of the gland through the isthmus, while the extrathyroidal lymphatics drain to the mediastinal lymph nodes. Currently, there is no specialized and mature classification for SMLNM in thyroid cancer, hence the classification of lung cancer is commonly used. The most common regions for thyroid cancer SMLNM are zones 2R and 2L, with zones 4R and 3a being relatively less common. The incidence of SMLNM ranges from 0.7% to 48.1%. The mediastinal lymph node metastasis rate for PTC is approximately 6% to 12%, while MTC, which more readily metastasizes to lymph nodes, has a metastasis rate of up to 18%. Clinically, SMLNM often presents without obvious symptoms and is commonly detected through imaging examinations or tumor marker tests. Ultrasound examination has difficulty detecting SMLNM. Typical features on enhanced neck and chest CT scans include enhancement, calcification, cystic changes, and invasion. Enhanced MRI, PET, and <sup>131</sup>I scans can also assist in the diagnosis. For thyroid cancer patients with SMLNM, safe, standardized, and thorough surgery remains key to achieving good outcomes, with individualized surgical plans tailored to the specific circumstances of each patient. Surgical principles include aiming for R<sub>0</sub> resection in a single session whenever possible, ensuring complete dissection while maintaining surgical safety to achieve both anatomical and biochemical cures. Surgical approaches may include open neck surgery, sternotomy, endoscopic-assisted surgery, and thoracoscopic surgery. Most dissections can be completed through the cervical approach; however, extensive low-level metastasis or severe invasion of surrounding major blood vessels may require sternotomy, sometimes with endoscopic assistance and/or thoracoscopic surgery. Postoperative care should focus on avoiding complications such as major vessel tears and injuries to the trachea and esophagus. Given the complex anatomical structure of the superior mediastinum, its difficult exposure from the neck, and the high surgical risk, thyroid or head and neck surgeons often face relative unfamiliarity and challenges, necessitating multidisciplinary collaboration. Although patients with thyroid cancer metastasis to the superior mediastinum generally have a poorer prognosis, the use of individualized surgical approaches and plans, in conjunction with thoracic and cardiovascular surgeons, for complete dissection of mediastinal metastases can significantly improve patient prognosis and quality of life. This article reviews the surgical diagnosis and treatment of thyroid cancer SMLNM to provide a reference for thyroid surgeons in their clinical practice.

**Key words**

Thyroid Neoplasms/ther; Lymphatic Metastasis; Surgical Procedures, Operative; Review

**CLC number:** R736.1

近几十年来,虽然甲状腺癌的发病率在全球范围内持续上升<sup>[1]</sup>,但甲状腺癌相关病死率仍然较低,这与人们健康意识提高及早期精准诊治密不可分,也与晚期难治性或特殊类型甲状腺癌的部分诊疗策略不断改进有关<sup>[2]</sup>。对常见的甲状腺乳头

状癌(papillary thyroid carcinoma, PTC)和甲状腺髓样癌(medullary thyroid carcinoma, MTC)进行中央区、颈侧区和罕见的上纵隔淋巴结转移(superior mediastinal lymph node metastasis, SMLNM)彻底清扫明显提高了患者的无病生存率。

## 1 上纵隔淋巴结应用解剖学

甲状腺有广泛的引流淋巴管网，包括腺内和腺外。腺内淋巴网通过甲状腺峡部连同两侧腺叶。甲状腺峡部和腺体下极的腺外淋巴由气管前和气管旁（气管食管沟）引流至纵隔淋巴结。目前尚无专门的成熟的甲状腺癌SMLNM分区，仍参考借鉴肺癌分区：高位气管旁淋巴结：(1) 2R区气管右侧，左无名静脉下缘与气管左侧壁交叉处上缘的上方淋巴结；(2) 2L区气管左侧，主动脉弓上方淋巴结。低位气管旁淋巴结：(1) 4R区气管右侧，左无名静脉下缘的下方至隆突/奇静脉水平淋巴结；(2) 4L区气管左侧主动脉弓上缘至左肺动脉上缘/隆突水平淋巴结。前纵隔淋巴结：3a区纵隔大血管前方淋巴结，包括胸腺区。后纵隔淋巴结：3p区气管后方淋巴结（图1A-B）<sup>[3-4]</sup>。甲状腺癌SMLNM最常见的区域为2R、2L区，而4R、3a区少见，4L、3p区极少见<sup>[5]</sup>。中国医学科学院肿瘤医院<sup>[6]</sup>报道122例分化型甲状腺癌SMLNM清扫阳性率为2R区73.1%、2L区61.3%、4R区16.0%、4L区5.0%、3a区10.9%和3p区0。甲状腺癌行胸骨劈开SMLNM清扫阳性率明显提高：2R区（82.4%，28/34）、2L区（58.8%，20/34）、4R区（58.8%，20/34）、3区（23.5%，8/34）、4L区（11.8%，4/34）<sup>[7]</sup>。

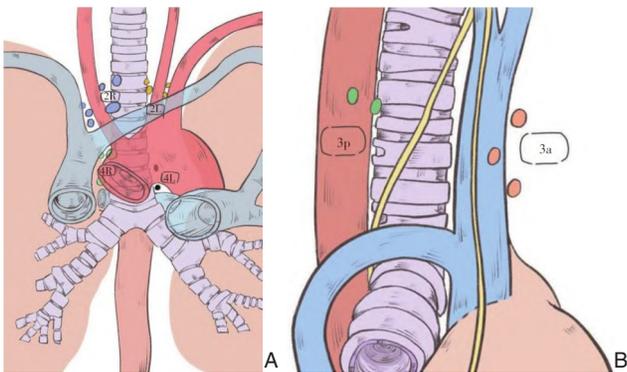


图1 部分上纵隔淋巴结示意图<sup>[4]</sup> A: 2R、2L、4R、4L区；B: 3a、3p区

Figure 1 Schematic diagram of partial upper mediastinal lymph nodes<sup>[4]</sup> A: Zones 2R, 2L, 4R, and 4L; B: Zones 3a and 3p

## 2 SMLNM的发病率和危险因素预测

SMLNM仍属区域转移，是病期较晚的表现之一。文献<sup>[8-9]</sup>报道SMLNM的发病率0.7%~48.1%。PTC纵隔淋巴结转移率约为6%~12%<sup>[10]</sup>。MTC更容

易发生淋巴结转移<sup>[11-13]</sup>，其纵隔淋巴结转移率可高达18%左右<sup>[14]</sup>。也有甲状腺滤泡状癌、嗜酸细胞甲状腺癌和甲状腺未分化癌纵隔淋巴结转移的个案报道<sup>[8-9]</sup>。

韩国前瞻性研究<sup>[15]</sup>217例甲状腺癌，发现上纵隔淋巴结隐匿性转移率为15.7%（34/217）。SMLNM与再次手术、气管前淋巴结阳性和双侧区淋巴结阳性相关，而与肿瘤细胞学分类、BRAF<sup>V600E</sup>突变、肿瘤大小、T分期、甲状腺周围侵犯、淋巴管侵犯、多灶性和气管旁淋巴结阳性无关<sup>[16]</sup>。Rendl等<sup>[17]</sup>随访MTC SMLNM术后患者，严格规范彻底清扫上纵隔淋巴结，而不是摘除，易获得生化缓解，实现生化治愈和未实现生化治愈的十年生存率分别是100%和73%。

## 3 SMLNM的临床特征

SMLNM本身一般无明显症状，多因为术后肿瘤标志物下降不理想，颈胸部增强计算机断层扫描（contrast-enhanced computed tomography, CE-CT）、核磁共振成像（magnetic resonance imaging, MRI）、正电子发射计算机断层成像（positron emission tomography/CT, PET/CT）、<sup>131</sup>I全身平面显像（whole-body scanning, <sup>131</sup>I-WBS）发现。但严重SMLNM可侵犯附近的气管、食道、肺、无名动脉和主动脉弓<sup>[18-19]</sup>，可引起声音嘶哑、呼吸困难、吞咽困难、咯血。有文献<sup>[20]</sup>报道气管压迫症状是甲状腺癌纵隔复发的首发症状。

甲状腺癌发生SMLNM时，超声检查由于胸骨的遮挡往往难以发现，但颈胸部增强CT及三维重建等检查可以发现淋巴结强化、钙化、囊性变、外侵等典型转移表现。进行安全、规范和彻底的手术仍是获得良好疗效的关键<sup>[21-23]</sup>。鉴于上纵隔解剖结构复杂、手术风险较大的特点，对胸部手术不熟悉的甲状腺外科或头颈外科医生可请胸外科会诊、联合手术，以提高手术彻底性，降低手术风险和并发症发生率<sup>[24]</sup>。

<sup>131</sup>I-WBS和18-氟-脱氧葡萄糖（<sup>18</sup>F-FDG）PET/CT对分化型甲状腺癌SMLNM有着较为重要的诊断价值。由于诊断性<sup>131</sup>I-WBS使患者暴露于潜在辐射风险，且部分SMLNM患者病灶不摄碘，所以不做常规推荐<sup>[25-27]</sup>。对于上纵隔检查PET阳性而<sup>131</sup>I-WBS阴性（不摄碘）的患者应追加手术清扫<sup>[28]</sup>。

PET/CT检查是检测降钙素、癌胚抗原(CEA)升高的MTC患者转移的一种高度敏感且无创的方法。其敏感度超过其他影像学检查(超声、MRI、CT、 $^{131}\text{I}$ -WBS),特别是在上纵隔淋巴结受累的定位<sup>[28-30]</sup>。在一项纳入55例初次手术治疗后降钙素水平仍然升高的MTC患者的研究<sup>[31]</sup>中,纵隔淋巴结转移的CT和PET检查阳性率分别为31%和20%。MTC初次确诊患者降钙素 $>500\text{ pg/mL}$ 或虽降钙素 $<500\text{ pg/mL}$ ,但属于复发拟再次手术者的绝大多数MTC患者,容易发生上纵隔和远处转移,DOPA PET/CT比 $^{18}\text{F}$ -FDG PET/CT更有优势<sup>[32]</sup>。

在MTC中,区域淋巴结转移需要再次积极外科治疗<sup>[33]</sup>。存在淋巴结转移预示着预后较差,这是局部复发率和病死率增加的原因<sup>[16-17]</sup>。而且纵隔淋巴结转移患者的存活率明显低于颈部淋巴结转移的患者<sup>[11]</sup>。虽然多数病例死于肿瘤远处转移,但也有一些因肿瘤侵犯重要结构而死于局部复发。上海肿瘤医院Zhang等<sup>[21]</sup>回顾分析了73例甲状腺癌SMLNM患者,发现发生SMLNM尤其是数目较多的患者预后较差<sup>[9,21]</sup>,及时追加纵隔清扫对改善预后非常重要。晚期MTC的病死率较高,早期诊断并接受手术治疗对患者至关重要。殷德涛等<sup>[34]</sup>研究表明,血清降钙素检测对于MTC的早期诊断、术式选择及患者预后有十分重要的意义。

## 4 SMLNM的手术适应证、原则和手术方式

### 4.1 SMLNM的手术适应证

甲状腺癌上纵隔淋巴结清扫术(superior mediastinal lymph nodal dissection, SMLND)是甲状腺癌SMLNM的首选治疗方法<sup>[18]</sup>。其适应证为:(1)上纵隔肿大淋巴结,短径一般 $>1\text{ cm}$ ,增强CT扫描有明显强化;(2)颈部肿瘤 $\text{R}_0\sim\text{R}_1$ 切除;(3)术前未发现远处转移或远处转移仍可有效治疗;(4)初次确诊MTC患者降钙素 $>500\text{ pg/mL}$ 或虽降钙素 $<500\text{ pg/mL}$ ,但属于复发再次手术者的绝大多数MTC患者;(5)一般情况较好,可耐受手术。

上纵隔淋巴结术前评估为阴性,是否需要行SMLND仍存在争议,Kikumori等<sup>[35]</sup>不建议对可治愈的PTC患者进行预防性胸骨劈开SMLND。但Woo等<sup>[15]</sup>认为,如甲状腺癌肿瘤 $>1\text{ cm}$ 、气管前淋巴结转移、多发侧区转移和再次手术的患者仍可有效预测SMLND,可选择经颈清扫。Ducic等<sup>[36]</sup>认为对

PTC、MTC和甲状腺未分化癌疑有SMLNM的患者,选择性行SMLND后通常显示有转移。MTC若有甲状腺外侵犯和颈淋巴结转移,再次手术时应考虑SMLND<sup>[37-40]</sup>。对晚期MTC患者再次进行SMLND的姑息治疗也是有益的<sup>[41]</sup>。

### 4.2 SMLNM的手术原则

甲状腺癌SMLND的手术原则为:在保证手术安全的前提下尽可能一期完成 $\text{R}_0$ 切除,以达到解剖治愈和生化治愈。Ito等<sup>[42]</sup>指出纵隔的淋巴结清扫必须积极、彻底,以防止清扫过的区域复发。一般将受累区域的淋巴结、胸腺和非重要结构的软组织(脂肪组织等)完整切除,尽量不要肉眼下残留病灶,万一清扫十分困难时,镜下可能有少许病灶残留( $\text{R}_1$ 切除),可术后辅以 $^{131}\text{I}$ 治疗。尽量整块清扫,有时因不便暴露,也可分区分块清扫。

### 4.3 SMLNM的手术方式

SMLND需由经验丰富的外科医生进行。SMLNM最常见的区域为2R、2L区,多数可通过经颈部入路顺利完成清扫。少数情况下,如低位广泛转移或严重侵犯周围大血管等需要劈开胸骨或借助腔镜辅助或联合胸腔镜手术<sup>[43]</sup>。(1)颈部开放手术:经颈部低位颌状切口入路。术前影像学显示仅2R或2L区较少转移病灶,无严重的血管外侵,基本上可从颈部切口行开放手术清扫<sup>[36,44]</sup>。宜充分暴露无名动脉,小心寻找无名静脉,无需劈开胸骨即可安全完成清扫<sup>[36]</sup>,减少了不必要的创伤,缩短了手术时间。此时,术者站在头顶位或佩戴放大镜或借助腔镜照明放大或使用特制拉钩,均有利于SMLND。(2)劈胸手术:胸骨劈开入路。术前影像学提示上纵隔转移淋巴结严重粘连或外侵上纵隔大血管,或淋巴结转移较多、融合成团、范围较广,可直接劈胸以充分暴露手术区域<sup>[5,41,45]</sup>。临床上可根据肿瘤转移情况及术者擅长术式,选择“L”形、反“L”形、倒“T”形或全长纵向劈胸<sup>[6]</sup>。“L”形或反“L”形劈胸甚至一侧锁骨内侧段切除可用于一侧上纵隔转移患者;倒“T”形劈胸适用于双侧转移患者;考虑到充分暴露,也可直接行全长胸骨劈开<sup>[6,46-48]</sup>。日本学者<sup>[49]</sup>还报道改良倒“T”形胸骨切开术,横向分割线于胸骨上呈现上下错位状态,以使切开的胸骨上、下段完美对位。相对于传统胸骨劈开方式,改良倒“T”形更稳定,更安全,并发症发生率更低,患者接受

度更高。经颈入路一旦术中发现淋巴结不活动侵犯周围血管或位置较低时,不可粗暴操作,马上用胸骨锯正中锯开胸骨,充分暴露,直视下保护大血管及神经,完整清扫,同时注意保护纵隔胸膜。手术中发生意外大出血或置换血管时,常需要与血管外科或胸心外科专家共同完成手术。胸骨劈开入路虽可直视手术,但创伤明显增大,术后并发症增加。特别是再次纵隔手术时,因为重要器官粘连多,清扫难度和手术风险也明显增大。

(3) 腔镜辅助手术:对于无严重外侵上纵隔大血管的患者,也可考虑用腔镜(或纵隔镜)辅助行规范化的上纵隔淋巴结分区清扫,腔镜的放大、照明和视野拓展功能有利于精细解剖;有时还可联合胸腔镜同时进行SMLND;以减少劈胸创伤、增加手术清扫的便利性和彻底性<sup>[48,50-51]</sup>。但在内镜手术操作困难或术中发生意外时,仍需要及时中转为劈胸手术<sup>[43,52]</sup>。腔镜辅助手术在保证切除范围的同时,尽可能地保留功能及兼顾美观,但要求术者熟练掌握颈部和前上纵隔的解剖结构以及腔镜操作技巧。内镜辅助手术或胸腔镜下手术的手术顺序较传统开放手术多了一步建腔,即层次间预分离+组织牵张成腔。(4) 胸腔镜下手术:为了最大限度地减少甲状腺癌上纵隔淋巴结可疑转移患者的手术创伤,Song等<sup>[52]</sup>探索出经颈电视纵隔镜辅助下行上纵隔淋巴结活检或清扫。4R, 4L, 3a区淋巴结转移较多时,可选择胸腔镜下行清扫<sup>[41]</sup>。胸腔镜下SMLND有三种入路,左侧入路可清扫2L、4L、3a区淋巴结;右侧入路可清扫2R、4R、3a、3p区淋巴结;剑突下入路可完成3a、2R、2L、4R区淋巴结清扫。同样也需要在保证切除范围的同时,尽可能地保留功能及兼顾美观。

中国医学科学院肿瘤医院刘杰等<sup>[46]</sup>回顾性分析119例行SMLND PTC患者发现,不同的SMLND方式与术后上纵隔肿瘤复发无关,双侧气管旁淋巴结转移是纵隔复发的独立危险因素。我院采用上述三种个体化手术方案进行SMLND,也证实是安全有效的。

围手术期应避免出现大血管撕裂、气管和食管损伤、神经损伤(霍纳综合征等)、纵隔感染、胸腔积液、乳糜胸、血肿<sup>[6,53]</sup>等并发症,一旦出现需要积极治疗。

## 5 总结与展望

尽管甲状腺癌转移至上纵隔的患者预后相对较差,但由经验丰富的甲状腺或头颈外科专科医师采用适合患者的个体化手术入路及方案,必要时联合胸心外科,进行上纵隔转移灶的彻底清扫,并防止严重并发症,仍可明显改善患者预后,提高患者生活质量。

利益冲突:所有作者均声明不存在利益冲突。

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## 本刊对来稿中统计学处理的有关要求

1. 统计研究设计: 应交代统计研究设计的名称和主要做法。如调查设计(分为前瞻性、回顾性或横断面调查研究); 实验设计(应交代具体的设计类型, 如自身配对设计、成组设计、交叉设计、正交设计等); 临床试验设计(应交代属于第几期临床试验, 采用了何种盲法措施等)。主要做法应围绕4个基本原则(随机、对照、重复、均衡)概要说明, 尤其要交代如何控制重要非试验因素的干扰和影响。

2. 资料的表达与描述: 用 $\bar{x} \pm s$ 表达近似服从正态分布的定量资料, 用 $M(IQR)$ 表达呈偏态分布的定量资料; 用统计表时, 要合理安排纵横标目, 并将数据的含义表达清楚; 用统计图时, 所用统计图的类型应与资料性质相匹配, 并使数轴上刻度值的标法符合数学原则; 用相对数时, 分母不宜小于20, 要注意区分百分率与百分比。

3. 统计分析方法的选择: 对于定量资料, 应根据所采用的设计类型、资料所具备的条件和分析目的, 选用合适的统计分析方法, 不应盲目套用 $t$ 检验和单因素方差分析; 对于定性资料, 应根据所采用的设计类型、定性变量的性质和频数所具备条件以分析目的, 选用合适的统计分析方法, 不应盲目套用 $\chi^2$ 检验。对于回归分析, 应结合专业知识和散布图, 选用合适的回归类型, 不应盲目套用简单直线回归分析, 对具有重复实验数据的回归分析资料, 不应简单化处理; 对于多因素、多指标资料, 要在一元分析的基础上, 尽可能运用多元统计分析方法, 以便对因素之间的交互作用和多指标之间的内在联系进行全面、合理地解释和评价。

4. 统计结果的解释和表达: 当 $P < 0.05$  (或 $P < 0.01$ ) 时, 应说明对比组之间的差异有统计学意义, 而不应说对比组之间具有显著性(或非常显著性)的差别; 应写明所用统计分析方法的具体名称(如: 成组设计资料的 $t$ 检验、两因素析因设计资料的方差分析、多个均数之间两两比较的 $q$ 检验等), 统计量的具体值(如 $t=3.45$ ,  $\chi^2=4.68$ ,  $F=6.79$ 等) 应尽可能给出具体的 $P$ 值(如 $P=0.0238$ ); 当涉及总体参数(如总体均数、总体率等)时, 在给出显著性检验结果的同时, 再给出95%置信区间。

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