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累及前联合的早期声门型喉癌治疗：现在与未来

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摘　要

喉癌是全球常见的头颈部肿瘤，声门型喉癌是最常见的喉癌类型。累及前联合的肿瘤因解剖结构特殊，局部复发率较高，为治疗提出了挑战。针对累及前联合的早期声门型喉癌的最佳治疗方法仍存在争议。本文系统评述了累及前联合的早期声门型喉癌的现有主流治疗方式——经口激光显微手术(TLM)与放射治疗(RT)的肿瘤学结局及功能预后。现有有限证据提示，放射治疗在局部控制率及嗓音质量保留方面可能较手术更具优势。但缺乏大样本、前瞻性随机对照研究的更强证据指导临床治疗决策。此外，本文探讨了新兴手术和放射治疗技术的临床应用进展及未来潜力。

关键词

早期声门型喉癌，前联合，放射治疗，经口激光显微手术

Treatment of Early Glottic Laryngeal Cancer Involving the Anterior Commissure: Now and Future

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Abstract

Laryngeal cancer is a common head and neck malignancy worldwide, with glottic laryngeal cancer

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representing the most prevalent subtype. Tumors involving the anterior commissure pose a clinical challenge due to their unique anatomical location, which is associated with higher local recurrence rates. Despite ongoing debates, the optimal treatment for early-stage glottic cancer with anterior commissure involvement remains controversial. This review systematically evaluates the current standard therapeutic approaches—transoral laser microsurgery (TLM) and radiotherapy (RT)—focusing on their oncological outcomes and functional prognosis. Limited evidence suggests that RT may offer advantages over TLM in terms of local control rates and voice quality preservation. However, high-level evidence from large-scale, prospective randomized controlled trials is lacking to guide definitive clinical decision-making. Additionally, this review highlights the clinical advancements and future potential of emerging surgical and radiotherapeutic technologies in managing this complex patient population.

Keywords

Early Glottic Laryngeal Cancer, Anterior Commissure, Radiotherapy, Transoral Laser Microsurgery

1. 引言

喉癌是全球第二常见的头颈部肿瘤[1]。2022 年，我国新增喉癌 2 万 9 千余人，死亡 1 万 6 千余人[2]。虽然喉癌仅占我国所有新发癌症病例的 0.6%，但由于喉功能在患者发声、吞咽和生活质量方面发挥着至关重要的作用，因此具有重要的社会意义。喉癌的发病率存在性别的差异，男性患者发病率高于女性。喉癌的早期表现通常包括声音嘶哑、发音困难、呼吸困难、吞咽障碍等。鼻咽镜检查有助于直接观察，并可获取组织活检，进一步的影像学检查对疾病分期至关重要。超过 95%的喉部恶性肿瘤是鳞状细胞癌，按照解剖结构和肿瘤的病变部位可分为声门型、声门上型、声门下型，其中声门癌是最常见的类型。临床上，早期声门型喉癌是指 Tis、T1a、T1b 和 T2 分期且没有淋巴结转移及远处转移的声门癌[3]。

早期声门癌推荐采用单一治疗，常规的治疗方案包括：经口激光显微手术、开放性喉部分切除术和放射治疗[4]。由于区域淋巴结转移率低，通常无需对颈部淋巴结进行选择性治疗。过去的几十年间，喉癌的治疗取得了显著的进展，增加了非手术治疗方法的使用，内窥镜激光手术的使用，相对减少了开放性保留手术和全切手术[5]。喉癌的治疗从单纯根除肿瘤为目标，发展到保留喉功能同时保证良好的局部控制率。

尽管内镜手术治疗和根治放射治疗在早期喉癌中均取得了良好的肿瘤学结局，但累及前联合的早期声门癌的最佳治疗仍存在争议，尚缺乏治疗共识。

2. 累及前联合的早期声门型喉癌的治疗

2.1. 前联合的重要意义

前联合通常理解为声门前方位于两个声带之间插入甲状软骨的区域[6]。前联合与声带、后联合一起，属于声门解剖的亚部位[7]。前联合很少是声门肿瘤的起源部位，但约 20%的声门肿瘤存在前联合受累[8]。

声门癌前联合受累已被认为是治疗预后中应考虑的危险因素，前联合累及与局部控制率下降相关，并且会增加治疗后局部复发的风险[9]-[12]。累及前联合的肿瘤可能会进入前声门下间隙并穿透环甲膜，

由于前联合粘膜与甲状软骨之间的距离仅仅几毫米，表面上很小的肿瘤实际可能侵犯软骨并扩散至喉外结构[12]，外加该区域的面积很小、软骨早期钙化，给放射学分期和软骨侵犯的诊断带来困难[13]；此外，由于未侵犯声带肌，累及前联合的肿瘤并不一定会损害声带活动性[7]。因此，单纯的临床或内窥镜评估很可能会低估肿瘤分期，对前联合受累情况的正确评估对治疗决策意义重大。

2.2. 经口激光显微手术

自 1972 年被首次用于治疗喉部恶性病变[14]，激光显微手术(Transoral laser microscopic, TLM)已经取代传统开放手术成为近几十年早期声门肿瘤手术治疗的主要手段，经口窥镜激光显微手术与传统手术治疗效果相当，避免了气管切开术，并发症显著降低，治疗时间更短，术后功能更好。众多学者指出，经口激光显微手术患者的总生存期和局部控制率与单独使用放射治疗相当，并为潜在的可能复发保留了更多治疗选择[15]。欧洲喉科协会将经口激光喉切除术分为六种类型。I 型仅涉及粘膜，应用于白斑等癌前病变。II~III 型涉及不同深度的声带韧带和甲杓肌，适用于小病灶(T1~T2)，IV 型从声带延伸至前联合，V 型是扩大的声带切除术(Va 包括对侧声带和前联合，Vb 包括杓状软骨，Vc 包括声门下，Vd 包括室带)。2007 年提出了一种新的内镜下声带切除术(VI 型)，用于治疗源于前联合的疾病：包括前联合和两侧声带前部，如果肿瘤与软骨紧密接触，还包括声门下粘膜和甲状软骨前角[16]。

尽管经口激光治疗早期声门型喉癌效果显著，当肿瘤累及前联合时，经口激光手术的应用存在争议。诊断为早期声门癌并接受经口激光手术治疗的患者中，前联合受累的患者表现出较低的五年生存率、较低的器官保存率和较高的局部复发率[9]。外科医生将手术的失败总结为：分期不准确，病灶暴露不充分以及经验不足。累及前联合的肿瘤可能会延伸到更难以直接观察的平面，如何获得充分暴露是一个挑战；粘膜与甲状软骨之间的距离仅为 2~3 mm，难以满足足够宽的安全边界，经口激光手术可能存在边缘阳性或边缘无法判断，需要术后辅助放疗[17]。此外，前联合手术切除后不可避免的粘连问题也尚未有有效解决手段[18]。尽管如此，许多学者认为，前联合受累并非激光手术治疗的禁忌：在保证肿瘤的完全暴露、充分的术前诊断检查和评估、丰富操作经验的前提下，大部分患者依然可以从经口激光手术中受益[19]。一项关于 444 例患者的回顾分析发现在经口激光显微手术治疗的早期声门癌中，前联合累及会影响 T1a 和 T1b 肿瘤的局部控制率，但鉴于经口激光显微手术保留了后续治疗选择，大多数复发患者可以通过再次经口显微手术或经口激光显微手术加放疗进行器官保留挽救治疗，整体的喉部保留率达到 95% [20]。

2.3. 放射治疗

放射治疗一直是早期声门癌广泛接受的器官保留疗法。传统喉部放疗技术使用平行的相对侧向野，大概 4*5 cm 至 6*6 cm 的靶区范围覆盖声带、周围声门和杓状软骨，在肿瘤控制方面取得较好的疗效但对颈部其他邻近结构造成一定副作用。之后，调强放射治疗等较新的技术为靶区域提供了更好的适形性覆盖，显著减少附近颈动脉等结构的辐射剂量[21]。在过去的几十年，调强适形放疗取代旧技术，成为早期声门癌放射治疗的主要手段。近几年有学者指出，如果病变只累及一侧声带，单侧声带放疗也可获得满意的局部控制率和无病生存率，并且急性毒性和晚期毒性少[22]。

前联合对早期声门癌放疗效果的影响存在争议。有回顾研究提示前联合受累不影响早期声门癌的放射治疗结果[23] [24]，但更多的研究显示前联合受累是放射治疗局部预后的重要影响因素，前联合浸润的患者局部复发的风险增加两到三倍[25] [26]。更高的生物有效剂量和大分割方案(>2 Gy)可能可以减少该影响[27]。

早期的研究报告前联合受累的早期声门癌根治放疗的局部控制率仅 43%~51% [25] [28]，这可能与早期放疗简单的侧向场设计或缺乏推注造成的前联合剂量不足有关[1] [29]。随着适形放疗的发展，前联合

的剂量覆盖得到保证，局部控制率在近年的研究中有显著提高。

3. 疗效评估

迄今为止，只有少数研究基于早期声门癌前联合受累患者治疗后的长期随访，有 1 项回顾性研究比较放疗与喉部分切除术对涉及前联合对早期声门癌治疗中的结果，另有 1 项更小型的回顾研究报告了放疗和经口激光手术治疗在累及前联合的早期声门癌中的治疗效果。目前尚无比较经口激光手术与放疗治疗累及前联合早期声门癌的前瞻队列。表 1 列举了部分经口激光手术和放疗治疗累及前联合的早期喉癌的回顾性研究[20] [26] [30]-[39]。

Table 1. Oncological outcomes of patients with early glottic cancer with anterior commissure following radiotherapy, partial laryngectomy, or transoral laser microsurgery
表 1. 累及前连合的早期声门癌患者接受放射治疗或开放喉部分切除术或经口激光显微手术后的肿瘤结局

作者/年份	治疗时间	治疗方式	肿瘤分期	患者数量	5 年 LC (%)	*p*	5 年 OS (%)	*p*	5 年 DSS (%)	5 年 LP (%)	*p*
Li/2021 [40]	2005~2017	PL	T1~T2	140	84.5	0.127	83.9	0.302	89.7	91.4	0.628
		RT		70	79.3		82.8		88.3	90	
Alkan/2017 [30]	2006~2013	TLM	T1	16	75	0.037	87.5	0.26			
		RT		38	87		78.9				
Rödel/2009 [20]	1993~2001	TLM	T1a	55	73		85			94	
			T1b	34	68		93			88	
			T2a	64	76		80			89	
Piazza/2018 [38]	2005~2015	TLM	T1b	61	89.4					90.1	
Hoffmann/2016 [36]	2001~2013	TLM	Tis~T1a	33	93.9		92.7		100	93.9	
			T1b~T2	63	63.2		69.9		85.5	93	
Ansarin/2017 [32]	1999~2013	TLM	Tis~T3	102	79.4				87.2		
Carta/2018 [33]	1993~2016	TLM	Tis~T2	105	89.7		78.6		98.4	95.3	
Steiner/2004 [39]	1986~1996	TLM	T1a	28	84				93		
			T1b	16	73				88		
			T2a	45	79				93		
Gultekin/2012 [35]	1998~2007	RT	T1	31	79		78		81		
Al-Mamgani/2013 [31]	1985~2011	RT	T1~T2	553	84						
Laskar/2012 [37]	1975~2000	RT	T1	228	86.3						
Cellai/2005 [34]	1970~1999	RT	T1a	184	79						
			T1b	98	76						
Mucha-Małecka/2019 [26]	1988~2007	RT	T1	179	77		79		75		

PL：喉部分切除术；TLM：经口激光手术；RT：放射治疗；LC：局部控制率；OS：总生存率；DSS：疾病特异生存率；LP：喉部保留率。

3.1. 肿瘤学结局

3.1.1. 局部控制率和总体生存率

在 Li 等人的研究中，对于早期累及前联合的声门型喉癌，放射治疗与喉部分切除术相比，局部控制率(79.3% vs 84.5%, $p = 0.127$)、总存活率(82.8% vs 83.9%, $p = 0.302$)、和喉部保存率(89.7% vs 89.8%, $p = 0.628$)的结果相当，而区域控制率更好(100% vs 87.1%, $p = 0.014$) [40]。在 Alkan 等人对前联合累及的 T1 声门癌不同治疗方式肿瘤结局的回顾研究中，放射治疗相比经口激光手术治疗显示了更好的局部控制率(87% vs 75%, $p = 0.037$)，更长的无病生存率(11.6 ± 0.8 年 vs 5.4 ± 1.4 年，$p = 0.002$)；经口激光手术治疗组相比放射治疗组的总生存率似乎较高(87.5% vs 78.9%, $p = 0.26$)，但没有统计学差异[30]。在其他对研究中，经口激光手术治疗的患者 5 年局部控制率在 63.2%~93.9%，放射治疗的患者在 76%~87%。

遗憾的是，大部分研究受限于回顾性本质：患者没有被随机分配到治疗组，每种治疗的有效性评估可能存在选择偏移。部分研究的样本量也较小，不具有代表性。此外，研究之间的异质性很大，这可能受到不同 T 分期、前联合浸润程度等混杂因素的影响。几项研究的时间跨度较大，其间诊疗技术(如手术器械、激光系统、放疗计划与照射技术)的不断进步可能引入治疗效果的时序性偏倚；同时，原始研究普遍缺乏对放疗方案(如剂量、分割方式、靶区定义)和手术细节(如切除深度、切缘评估方法)的充分描述。不同医疗机构及术者/放疗团队在技术水平、操作规范和临床经验上的差异，也会增加异质性，限制了结果的可比性。

3.1.2. 器官保留

经口激光显微手术治疗的患者 5 年喉部保留率均在 88%以上，有关放射治疗的研究未统计此项数据。在系统评价和荟萃分析中发现，经口激光显微手术在早期声门癌喉部保留总生存率方面有一定优势[41]，这可能是因为大多数放射失败无法通过保守手术来挽救，通常需要全喉切除术；而经口激光切除术为局部失败提供了更开放的再治疗选择[42]。然而尚未有研究在前联合受累的早期声门癌中比较喉部保留率。

3.2. 生活质量

在现在的技术下，手术和放疗对累及前联合的早期声门癌疾病控制率都较好，因此声音质量成为方案选择的重要考量因素。欧洲的随机对照研究显示放射治疗相比激光手术治疗，患者的呼吸音更少，声门闭合保持更好[43]，其他研究也提及了放疗在语音质量方面的优势[44]。

传统的头颈部放疗可能涉及对甲状腺、颈动脉等邻近结构的不良影响。但 3D 适形放疗、调强放疗等较新的放疗技术可以控制甲状腺区域较低的剂量，预防甲状腺功能减退的发生；尽可能地减少颈动脉剂量，降低中风的风险；也为未来其他可能的头颈部放疗保留选择[45] [46]。

4. 未来发展

4.1. 进一步分层

尽管大量数据表明前联合受累与较差的预后相关，但现有 TNM 系统难以描述前联合的累及情况。在治疗前进行详细的影响学检查，特别是 MRI 检查[47]，可以有效评估前联合受累情况，避免对肿瘤分期的低估，这对不论最终选择何种治疗方式都是重要的。

Piazza 等人制定了有关喉部暴露的临床预测评分，暴露不佳的患者手术边缘阳性率是暴露良好患者的两倍以上，通过充分的术前评估有助于判断经口激光手术对患者的适用情况[19] [48] [49]。

4.2. 技术进步

4.2.1. 立体定向放射治疗

立体定向放射治疗(SBRT)，是一种将高剂量外束放射治疗分几次准确地递送到小而明确的靶区的方

法。与传统放疗相比，剂量急剧下降可以最大程度地保护正常组织，并且较短的疗程也让治疗更加方便[50]。目前，SBRT 用于原发性头颈部肿瘤的证据较少，在喉癌中的应用还处于探索阶段。传统放疗方案的临床靶区 CTV 包括假声带、真声带、前联合、后联合、杓状软骨和杓状会厌皱襞以及声门下间隙，通常 CTV 周围留出 5 mm 余量形成 PTV [26]，这覆盖了几乎整个声门区域，而如今的手术目标通常只包括声带甚至肿瘤本身，也取得了较好的预后结局。SBRT 有望提供一种“从开放手术过渡到切除体积更少的经口显微手术”类似的策略，在放疗中实现类似手术的狭窄边缘，获得相当的局部控制和功能结果。影像分析证实静止时最大呼吸声带运动小于 1.3 毫米[51]，测算呼吸引起的声带位移，并指导患者控制吞咽，可以为患者提供安全高效的大分割方案[52]。基于此，SBRT 治疗声门癌将 GTV 外扩 2 mm 形成 CTV，对于前联合 2 mm 内的病变则将整个联合加上 2 mm 内的对侧声带，通常在 CTV 基础上再扩大 3 mm 来创建 PTV [50]，这相比以往的放疗方案，大幅度减少了对周围正常组织的照射。已有一期临床研究显示 5 次 SBRT 治疗早期声门癌的效果和标准放疗效果相当[50] [53]。

4.2.2. 质子治疗

目前，世界范围内广泛开展质子疗法治疗肿瘤的研究。由于布拉格峰值剂量分布，质子治疗可能在不牺牲靶点覆盖范围的情况下更大程度地保护正常组织，被认为比 IMRT 毒性更低。已有文章报道质子治疗用于口咽癌、鼻窦恶性肿瘤等头颈部肿瘤等应用，但在声门癌中的应用还有待探索[54]。

4.2.3. 经口机器人手术

经口机器人手术(TORS)的发展为外科医生提供了新的治疗方法。2010 年，TORS 被批准用于治疗扁桃体、咽喉部的疾病，但目前的研究显示 TORS 在声带切除术中的优势有限，气管插管率和并发症发生率高于经口激光治疗[55]，但值得注意的是，TORS 的视线限制较少且具有 3D 高倍放大的优势，可以一定程度弥补经口激光显微手术在累及前联合疾病中暴露不足的问题，可能是累及前联合的声门癌的初始治疗和复发后治疗的有效手段之一[56]。

4.3. 分子医学指导治疗选择

随着个性化医疗的不断推进，测序技术的不断发展，肿瘤生物学的分子标记物可能对患者预后具有提示意义，并指导最佳治疗选择。例如 pFADD (磷酸化 Fas 相关死亡域蛋白)的过度表达与早期声门鳞癌的局部控制率改善相关；HIF1-alpha，一种血管生成因子，过表达与放射治疗后较差的局部控制相关；表皮生长因子受体 EGFR 的表达与放射抗性正相关，是影响早期声门癌局部控制的重要预后因素[57] [58]，根据分子标记物对放射抗性或肿瘤复发的预测对于个体化选择治疗至关重要。

5. 总结

前联合是声门结构的重要亚部位，是早期声门癌治疗的一大挑战，虽然不在声门癌的分期标准里，前联合受累情况的评估对疾病分期、治疗选择和肿瘤结局及预后有重要作用。对于前联合受累的早期声门癌，放射治疗和经口激光显微手术仍然是可行的治疗方案，但前联合受累的早期声门癌的最佳治疗尚无定论，现有的研究发现放射治疗可能在局部控制率上更好，但在生存率上和经口激光显微手术类似；因为为复发提供更多治疗选择，经口激光显微手术的喉部保留率可能较高；放射治疗的患者声音质量较经口激光手术治疗更好。然而，尚缺少大样本、前瞻性的随机对照研究进一步指导治疗。目前而言，治疗的选择基于疾病分期，患者的发声要求和偏好，内窥镜及激光设备、手术技术和经验以及放射技术和设备也成为治疗决策的驱动因素，最佳的治疗决定需要患者和医生共同进行个体化的制定。

在未来，根据前联合受累情况进一步对早期声门癌患者进行分层可能有助于最佳治疗的制定。立体定向技术等新兴放疗技术的发展有助于获得更好的疾病控制的同时减少对正常组织的影响并减少治疗时

间，激光和机器人手术的进步可能会实现更精准的切除，相关分子标记物的发展有助于指导个体化治疗。

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