

• 综述 •

进展期喉癌患者甲状腺侵犯概况及其预后价值*

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[摘要] 喉癌是第二常见的头颈部恶性肿瘤,指南推荐对进展期喉癌患者进行预防性甲状腺切除,但其预后价值尚不明确。本文综述了喉癌患者甲状腺侵犯的发生率、高危因素、预后价值及预防性切除甲状腺对进展期喉癌患者结局的影响。

[关键词] 喉肿瘤;预防性甲状腺切除;危险因素;预后价值

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Overview of thyroid gland involvement and its prognostic value on advanced laryngeal cancer

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Abstract Laryngeal cancer is the second most common malignancy in the head and neck region. The guidelines recommend prophylactic thyroidectomy for patients with advanced laryngeal cancer, but its prognostic value remains elusive. In this review, the incidence, risk factors, prognostic value of thyroid invasion in patients with laryngeal cancer were reviewed. The effect of prophylactic thyroidectomy on the outcome of advanced laryngeal cancer patients was also discussed.

Key words laryngeal neoplasms; prophylactic thyroidectomy; risk factors; prognostic value

喉癌是一种常见的头颈部恶性肿瘤,根据其发生部位主要可分为声门上型、声门型、声门下型和贯声门型^[1]。据估计,2020年全球有184 615名新发喉癌患者(约占所有癌症患者的1%),有99840名患者死于喉癌^[2]。而既往数据显示我国喉癌的年发病率约为1.84/100 000,年死亡率约为1/100 000^[3],是第二常见的头颈部恶性肿瘤^[4]。尽管由于吸烟模式的改变,喉癌的发生率近年呈下降趋势^[5-6],但喉癌的5年生存率在过去的数十年里并没有随着医疗卫生水平的提升而得到显著改善^[7]。据统计,早期喉癌患者的5年生存率可达80%~90%,而进展期喉癌患者(T3/T4期)的5年生存率不足50%^[8],且60%的患者在首次诊断时即已进入进展期^[9],因此,如何为进展期喉癌患者选择最佳的治疗方式,已成为提高喉癌患者总体生存率及生活质量的关键问题。

目前进展期喉癌首选手术治疗^[10],然而其手术方式及手术范围的选择仍有较大争议。1955年Ogura^[11]开创性地提出行全喉切除术的患者应同时切除同侧甲状腺叶及甲状腺峡部,该结论于1973年被Harrison^[12]再次证实,并于此后的数十年内成为应用最广的手术方式。目前该标准仍被最新版美国国家综合癌症网络(National Comprehensive Cancer Network, NCCN, <https://www.nccn.org/home>)头颈肿瘤诊治指南所推荐,但也有部分学者认为该方式缺乏充足的循证医学证据支撑。近年来,针对头颈肿瘤患者有选择性地进行器官保护性外科治疗已逐渐发展为一种新兴趋势,而进展期喉癌患者是否需要同时进行甲状腺切除也受到越来越多的质疑。目前已有多个研究提示喉癌患者甲状腺侵犯的发生率较低^[13-14],且部分患者在接受全/部分甲状腺切除术后容易发生甲状腺功能减退,或因切除甲状腺时损伤甲状旁腺而导致钙磷代谢失调^[15];反之,保留甲状腺并不会导致患者局部复发风险的升高或无疾病生存时间的缩短^[16]。因此,部分研究者认为全喉切除术联合全/

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部分甲状腺切除术仅适用于部分具有特定指征的进展期喉癌患者,但该结论的可靠性仍有待进一步验证。本文就进展期喉癌患者甲状腺侵犯的发生率和高危因素,甲状腺侵犯对预后的影响,及切除甲状腺的预后影响等进行综述。

1 喉癌的甲状腺侵犯

1.1 喉癌侵犯甲状腺的发生率

根据第 8 版美国癌症联合会(American Joint Committee on Cancer, AJCC, <https://cancerstaging.org/references-tools/deskreferences/pages/default.aspx>)的喉癌分期标准,进展期(T3 和 T4 期)喉癌患者均可以没有甲状腺侵犯,而一旦原发肿瘤侵犯到甲状腺则分期为 T4 期。大多数回顾性研究显示进展期喉癌的甲状腺侵犯率为 12.6%~21.0%^[17-19],另有多项针对喉癌人群的 meta 分析结果则显示喉癌患者的甲状腺侵犯率仅为 8.0%~10.9%^[13-14,20-21],尽管上述研究存在样本量较少和人群异质性较大等缺陷,无法完全反映喉癌患者甲状腺侵犯的真实发生率,但根据现有数据可推测进展期喉癌患者的甲状腺侵犯率并不高。

1.2 喉癌发生甲状腺侵犯的高危因素

目前已有多项研究认为对喉癌患者行甲状腺切除仅适用于具有特定高危因素者,如喉癌扩展到声门下、甲状软骨和环状软骨侵蚀等,其他的一些因素包括前连合侵犯和气管旁淋巴结侵犯等。

1.2.1 肿瘤的原发部位和局部扩展 早在 1995 年, Yuen 等^[22]的研究结果就显示在 12 例累及声门下的喉癌患者中,多达 5 例有甲状腺侵犯。此后多项研究结果表明,声门下扩展是喉癌患者甲状腺侵犯的高危因素^[13-14,17-18,23-24],且有研究认为声门下扩展>10 mm 者具有甲状腺切除的指征^[25];但也有一些研究给出了相反的结论^[26-28],他们认为声门下侵犯与甲状腺侵犯无关,这可能是由于其研究的样本数量过少或是有部分 T2 期患者混杂。除声门型喉癌扩展到声门下外, Muhammad 等^[20]认为喉癌起源于声门下(即声门下型喉癌)也是甲状腺侵犯的高危因素,且该结论得到了 meta 分析的支持^[13-14];但也有研究^[19,29]并不支持声门下起源与甲状腺侵犯之间的关系。另有研究观察到行全喉切除术联合甲状腺切除的患者中有甲状腺侵犯者均为贯声门型喉癌^[30-31],且二者之间的相关性也被后续研究及相关 meta 分析所证实^[13,20,27,32]。此外,也有少数研究其他局部扩展与甲状腺侵犯之间的关系,如环甲膜^[23,33]、前连合^[13,17,32]者,但尚无一致的结论。

1.2.2 淋巴结转移 有研究显示喉癌患者中部分区域淋巴结转移(如气管旁淋巴结^[19]、VI 区淋巴结^[26])与甲状腺侵犯相关,而其他区域的淋巴结转移^[18]与甲状腺侵犯间的相关性仍有待进一步证

实,同时,淋巴结包膜外扩展与甲状腺侵犯之间的关联性尚无一致结论^[19,26]。

1.2.3 软骨侵蚀 Brennan 等^[34]研究的 107 例喉癌患者中,8 例患者有甲状腺侵犯,这些患者均同时伴有喉软骨的侵蚀。随后,多项研究观察到甲状软骨侵蚀与喉癌患者甲状腺侵犯之间的相关性^[23,28,32-33],有研究也认为甲状软骨侵蚀是进行甲状腺切除的指征^[25],且有 meta 分析^[21]的支持。然而,也有回顾性研究^[19]或其他的 meta 分析^[13]并未发现甲状软骨侵蚀与甲状腺侵犯之间的相关性。因此,尽管大多数研究支持二者之间的相关性,但甲状软骨侵蚀与甲状腺侵犯之间的关联尚待进一步证实。

此外,在环状软骨侵蚀与甲状腺侵犯之间相关性的研究方面, Gaillardin 等^[18]观察到 CT 影像上环状软骨破坏与甲状腺侵犯之间的相关性,同时, Mangussi-Gomes 等^[17]针对 83 例喉癌患者的研究也证实了环状软骨受侵会显著增加甲状腺受侵犯的风险。然而 Nayak 等^[27]的研究则不支持二者之间的关联,故环状软骨与甲状腺侵犯之间的关联性也需要更多大样本队列研究的证实。

1.2.4 其他因素 Sparano 等^[23]认为术前声带固定可以预测甲状腺侵犯,而 Hilly 等^[19]观察到术前声带固定无法预测甲状腺侵犯与否,由于喉癌声带固定和甲状腺侵犯均与肿瘤分期之间具有显著相关性,因而在未对肿瘤分期进行校正的情况下探究声带固定对甲状腺侵犯的预测意义具有较大的偏差。此外, Hilly 等^[19]还观察到 73% 的患者同时具有甲状腺侵犯和血管侵犯,另外在 1 例甲状腺侵犯的患者中观察到淋巴管受侵,提示脉管侵犯可能与甲状腺侵犯之间存在关联。 Elteley 等^[35]观察到 T4a 期、分化程度差、非鳞状细胞癌的病理类型等也是甲状腺侵犯的潜在危险因素,但也有部分研究认为人口学因素(年龄、性别)、肿瘤的 TNM 分期、分化程度、病理类型、有无淋巴管和周围神经受累、手术方式等与甲状腺侵犯无关^[17,28,31]。因此,其他的一些临床病理因素与甲状腺侵犯之间的关联尚不明确。

2 全喉切除术是否联合甲状腺切除

2.1 进展期喉癌的治疗概览

目前已有多个单中心回顾性研究结果表明进展期喉癌患者接受全喉切除术可以获得更好的预后^[36-38],而美国临床肿瘤学会临床实践指南(American society of clinical oncology, ASCO, <https://www.asco.org/>)建议,对于局部进展期喉癌,可行器官保护手术(与放化疗结合或单独手术),但是对符合特定特征的患者、扩展性 T3 或较大的 T4a 患者及术前喉功能极差者,最好采用全喉切除术^[8]。同时, NCCN 2021 版指南推荐进展期

喉癌患者在行全喉切除术的同时应切除甲状腺(<https://www.nccn.org/home>),但对于甲状腺未受侵犯的进展期喉癌患者行预防性全切或部分切除的这一推荐做法尚缺乏有力的证据支撑。

2.2 进展期喉癌甲状腺侵犯的术前判断依据

Mourad 等^[39]建议根据喉癌累及双侧、可触及甲状腺异常,或可疑甲状腺异常(定义为对侧的质韧结节、有临床证据的钙化灶或可见的结节)等指征判断行全甲状腺切除的必要性。目前主要通过体格检查和影像学手段对进展期喉癌患者的甲状腺侵犯情况进行术前判断,主要判断依据是影像结果显示的甲状软骨侵蚀或肿瘤浸润甲状腺等。但在实际有甲状腺侵犯的患者中,超过 1/3^[18]乃至半数^[25,40]患者的术前 CT 并未观察到甲状腺侵犯的证据,因此根据术前 CT 判断甲状腺有无侵犯具有一定的局限性,这与翟姣等^[41]进行文献综述后所得结论类似。有研究者认为通过 MRI 判断进展期喉癌和下咽癌患者甲状腺侵犯的敏感性和准确性虽然较高^[42]但存在一定的假阳性^[43]。因此,有研究者推荐联合使用多种影像学证据来判断甲状软骨侵蚀的情况^[44]。术前未发现甲状腺侵犯证据时,则主要根据术中甲状腺的形态进行判定^[18,30,45]。

2.3 甲状腺侵犯对喉癌患者预后的影响

Muhammad 等^[20]对 92 例喉癌患者进行回顾性分析,结果显示有甲状腺侵犯的喉癌患者肿瘤复发率更高,且甲状腺侵犯与肿瘤的早期复发而非晚期复发相关。然而,Dequantier 等^[31]未观察到有甲状腺侵犯组和无甲状腺侵犯组之间在肿瘤复发率上的差别,同时 Panda 等^[26]的结果也显示甲状腺侵犯与患者的 5 年总体生存率和 5 年无病生存率无关,因此认为需要严格把握全喉切除术时甲状腺切除的指征。综上所述,喉癌患者甲状腺侵犯是否具有显著的预后价值仍然存疑,而甲状腺是否应同步切除更需要进一步的研究。

2.4 全喉切除联合甲状腺切除与否的预后对比

McGuire 等^[16]分析了保留甲状腺的全喉切除术对喉癌患者预后的影响,该研究纳入了 69 例保留甲状腺和 73 例切除甲状腺的全喉切除术患者,结果显示接受两种不同手术方式的患者在肿瘤的局部复发和总体生存率上没有显著差异,基于该结果,他们提出对于行全喉切除术的患者,当术前影像学提示无甲状腺侵犯时,需要在术中仔细地进行甲状腺检查和评估,仅当术中发现喉癌有甲状腺侵犯的高危因素,如喉外扩展、侵犯到甲状腺、累及声门下或梨状窝而需要切除 level 6 水平的淋巴结时才切除甲状腺,在其他情况下保留甲状腺,并不会影响患者的预后情况。此外,Viljoen 等^[15]对比了保留整个甲状腺与保留一叶甲状腺的患者($n=84$)

术后甲状腺功能减退情况,结果显示,与未切除甲状腺的患者相比,切除了一叶甲状腺加峡部的患者发生甲状腺功能减退的风险显著提升。综上所述,这些研究结果对是否进行甲状腺切除提出了挑战:切除甲状腺并不能为所有的进展期喉癌患者带来收益,NCCN 指南所推荐的甲状腺无差别切除尚缺乏充分的证据支持。

3 结论

喉癌是一种常见的恶性肿瘤,多数患者在首次诊断时即已进入进展期,因而具有较低的 5 年生存率。目前根据 NCCN 指南推荐,进展期喉癌患者多在接受全喉切除术的同时行甲状腺切除,但现有研究表明进展期喉癌患者甲状腺侵犯的发生率较低,且对于不伴甲状腺侵犯的进展期喉癌患者行预防性甲状腺切除,并不能显著改善预后,反而会导致甲状腺功能减退等术后并发症的发生率增高。因而,尚需更多的大型前瞻性队列研究及临床试验等来验证甲状腺切除对进展期喉癌患者的预后价值,以确定进展期喉癌患者切除甲状腺的适应证。

利益冲突 所有作者均声明不存在利益冲突

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