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· 综述 ·

早期舌鳞癌颈淋巴转移的规律及评估因素研究进展

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【摘要】 早期舌鳞癌易发生隐匿性淋巴转移,因此早期舌鳞癌是否进行颈淋巴清扫一直是众多学者争议的问题。为了准确评估患者颈部情况,确定是否同期进行颈淋巴清扫,本文就性别、年龄、原发灶部位、术前辅助检查、浸润深度、病理分级、神经以及血管淋巴管浸润等评估因素进行综述。文献复习结果表明,早期舌鳞癌颈淋巴主要回流至 I、II、III 区,跳跃性转移较为罕见,早期舌鳞癌的颈淋巴转移主要受浸润深度、病理分级、神经浸润、血管淋巴管浸润等因素影响,为了使早期舌鳞癌患者获得较高的生存率,对于术前通过超声或磁共振成像(magnetic resonance imaging, MRI)显示肿瘤浸润深度超过 5 mm、病理分级高、已经存在麻木或者疼痛等临床症状的患者以及在冰冻结果中已存在神经、血管淋巴管浸润的 T1 期和 T2 期患者,应考虑切除原发灶同时行选择性颈淋巴清扫。

【关键词】 舌; 癌; 鳞状细胞癌; 肿瘤分期; T1 期; T2 期; 颈淋巴转移; 浸润深度; 神经侵犯; 血管淋巴管浸润; 评估因素; 颈淋巴清扫

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Research progress on the consistency and evaluation factors of cervical lymphatic metastasis in early tongue cancer ZHANG Haifeng¹, NAN Xinrong², HUA Yongqing¹. 1. Shanxi Medical University School and Hospital of Stomatology, Taiyuan 030001, China; 2. First Hospital of Shanxi Medical University of Oral and Maxillofacial Surgery, Taiyuan 030001, China.

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【Abstract】 Early tongue cancer is more prone to occult lymphatic metastasis than other oral cancers. Therefore, the decision of whether to perform neck dissection in the early stage of tongue cancer has been a controversial issue among many scholars. To accurately evaluate the neck condition of patients and determine whether neck dissection should be performed, this article reviews evaluation factors such as sex, age, tumor site, preoperative auxiliary examination results, depth of invasion, pathological grade, and nerve, lymphatic and vascular invasion. A literature review showed that the cervical lymphatics of early tongue cancer mainly migrated to regions I, II and III, and distant metastasis was rare. The cervical lymphatics of early tongue cancer were mainly affected by the depth of invasion, pathological grade, and nerve, lymphatic and vascular invasion. To achieve a high survival rate for patients with early tongue cancer, patients with preoperative ultrasound or MRI showing a tumor invasion depth of more than 5 mm, a tumor with a higher pathological grade, and clinical symptoms such as numbness or pain who are in stage T1 and T2 and who have already have nerve and vascular lymphatic infiltration according to the frozen sectioning results should be considered for primary simultaneous cervical lymphatic dissection.

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【Key words】 tongue; cancer; squamous cell carcinoma; tumor stage; stage T1; stage T2; cervical lymphatic metastasis; depth of invasion; perineural invasion; lymphatic and vascular invasion; evaluation factors; neck dissection

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舌鳞癌是口腔癌中最常见的恶性肿瘤,由于舌体血供和淋巴回流丰富,使舌鳞癌成为口腔癌中最易发生淋巴转移者,有较高的局部复发率^[1],研究表明近20年来5年生存率为45%~50%^[2]。早期舌鳞癌常表现为舌部较小的原发灶,临床触诊、B超、电子计算机断层扫描(computed tomography, CT)、磁共振成像(magnetic resonance imaging, MRI)等影像学检查颈部淋巴阴性,但颈淋巴清扫术后病理检查发现淋巴结内有微小转移灶,称为隐匿性淋巴转移,至今仍没有一种合适的检测手段可以无创检测出是否存在隐匿性淋巴转移^[3]。因此早期舌鳞癌是否进行颈淋巴清扫一直是研究的热点。

目前早期舌鳞癌治疗的主要方法是手术切除原发灶^[4],但手术治疗合并选择性颈淋巴清扫仍有争议,对此有两种颈部处理的方式:①保守观察,密切随访,一旦发现颈淋巴转移立即行治疗性颈淋巴清扫;②为切除原发灶同期进行选择性颈淋巴清扫,由于临床上N0期患者隐匿性淋巴结转移的检出率较高,如同期未进行颈淋巴清扫,而在随访过程中出现颈淋巴转移,甚至是包膜外扩散,会严重影响患者的预后^[5]。大多数研究也认同早期舌鳞癌同期选择性颈清扫对患者的预后是有帮助的^[3,6],但此方法对于病理上未发生淋巴结转移却同期行选择性颈清的患者,将会承受不必要的术中及术后并发症的风险^[4]。因此,针对这两种颈部处理方式,有必要对早期舌鳞癌患者进行合理分层,得到更合理的手术方式。

本文就性别、年龄、原发灶部位、术前辅助检查、浸润深度、病理分级、神经以及血管淋巴管浸润等评估因素进行综述,总结早期舌鳞癌颈淋巴转移规律,为临床早期舌鳞癌的患者寻找更合理的治疗方法提供理论依据。

1 早期舌鳞癌颈淋巴转移规律

由于临床样本量、病理学检测方法、原发部位分类不同,国内外文献对于早期舌鳞癌隐匿性颈淋巴转移率报道不一,大部分文献转移率均高于25%^[7-8],这也反映出舌鳞癌淋巴结转移的早期

性。根据舌的淋巴回流解剖学,舌鳞癌颈淋巴转移具有一定的规律,即通常先到达I、II区淋巴结,再到达III区淋巴结,遵循“瀑布学说”,早期舌鳞癌淋巴结转移局限在I、II、III区,IV、V区淋巴结的转移通常合并有相邻解剖区域的受累^[9],而且研究证实颈部III区淋巴结转移时,IV区出现转移的可能性也会明显增大^[10]。在极少情况下,不出现I、II、III区颈淋巴转移时,可能会出现IV、V区转移,即跳跃性转移^[11]。但出现在IV区孤立的跳跃性淋巴转移的概率极小,V区淋巴结跳跃性淋巴转移发生也鲜有报道^[12]。

2 早期舌鳞癌颈淋巴转移的评估因素

2.1 性别和年龄

大多数人认为早期舌鳞癌在男性中发病率较高,这可能是因为男性有更多烟酒等不良嗜好,而烟草、酒精均被认为是导致舌鳞癌发病的重要危险因素^[13]。但研究发现,早期舌鳞癌与性别关系不大,舌鳞癌的发病年龄高峰约在50~65岁之间^[14],老年人由于自身免疫力较差,受不良因素刺激或接触致癌物时间更长,年老患者较年轻患者也更容易复发以及出现颈淋巴转移。但在舌鳞癌发病率上越来越呈现年轻化趋势^[15],Miller等^[16]研究表明年轻早期舌鳞癌患者(<45岁)比例正在逐年上升,并且预后较老年人更差。并且目前一项多中心研究证明,性别及年龄与早期口腔癌复发并无明显相关性^[17]。由此可见,性别及年龄仅可作为临床诊断的参考因素。

2.2 原发灶部位

早期舌鳞癌颈淋巴转移与原发灶生长部位有密切关系,舌鳞癌大部分发生于舌体,舌根也可发生,舌尖最为少见^[18]。研究表明舌后1/3受侵犯时,术后复发率及颈淋巴转移率均比舌前2/3高^[19],但不能说明舌后1/3受侵犯就会提高复发率,可能是受临床技术等原因,术中由于视野暴露问题导致肿瘤切缘未能足够,也因其部位较靠后,早期不易发现导致。而且研究表明,肿瘤部位对复发及颈淋巴转移并无明显相关性^[9],因此,原发灶部位并不能作为判断颈淋巴转移的方法,在临

床上也需要参考辅助检查来进一步诊断。

2.3 术前辅助检查

术前评估颈部淋巴尤为重要,大多临床医生依靠自身经验通过触诊来诊断,由于检查者的经验不同,淋巴结较深、较小,患者颈部脂肪较多等原因使诊断较为困难,因此,辅助诊断是必要的,一方面常采用影像学检查,目前以超声(ultrasonography, US)、CT、MRI、正电子发射断层显像(positron emission tomography, PET)最为常见。Liao等^[20]通过meta分析研究被诊断为临床N0期的头颈鳞癌患者,比较了US、CT、MRI及PET对于检查颈淋巴结转移的准确性,其灵敏度分别为66%,52%,65%,66%,认为上述影像学检查提供了相似的诊断准确性。然而,Chen等^[18]认为MRI很难检测到直径小于1 cm颈淋巴结转移,PET对目前检测颈淋巴结转移的敏感性最高,但在评估单侧淋巴结转移时可能由于某些炎症性病变影响可以导致较高的假阳性率,因此MRI与PET联合诊断准确率会更高。另一方面,一些非影像学检测方法也被采用,包括细针穿刺细胞学检查(fine needle aspiration cytology, FNAC),前哨淋巴结活检(sentinel lymph node biopsy, SLNB)等技术。Souren等^[21]比较了FNAC、US、MRI对于颈部淋巴结的诊断价值,最后认为MRI相较US和FNAC有更高的灵敏度(83%),而FNAC特异度最高(100%)。Yang等^[22]通过对1 084名早期舌鳞癌患者进行统计分析得出SLNB的颈淋巴检出率高达98%。SLNB对于判断早期舌鳞癌颈部淋巴结显示出较高的准确性,但在临床上由于对操作者要求较高,并没有广泛开展。由此可见,目前还没有一种确切的辅助检查来准确评估颈部淋巴,这意味着寻找影响颈淋巴转移的独立指标很有必要。

2.4 浸润深度(depth of invasion, DOI)

越来越多的证据表明,肿瘤浸润深度作为评估口腔舌鳞癌颈淋巴转移的独立预测指标有重要的意义^[23],所谓浸润深度^[24],即在显微镜下测量肿瘤的最深浸润边缘与正常上皮基底膜垂直方向的最大深度,而肿瘤厚度(tumor thickness, TT)指的是肿瘤的最深浸润缘与肿瘤表面或溃疡型的基底膜在垂直方向的距离,这两种概念并不相同,美国癌症协会(American Joint Committee on cancer, AJCC)主张使用DOI而不是肿瘤厚度,因为DOI可能影响高达5.7%的口腔癌患者的T分期^[25],但这在很多研究中并未区分开来。传统的TNM分期并没有考

虑到肿瘤的浸润深度,但在2017年最新颁布的UICC/AJCC标准(第8版)^[26]中指出,T1期为肿瘤最大直径 < 2 cm,DOI < 0.5 cm;T2期为肿瘤最大直径 < 2 cm, 0.5 cm $< DOI \leq 1.0$ cm,或者肿瘤最大直径 > 2 cm,但 < 4 cm,DOI ≤ 1.0 cm,这表明T分期不仅仅依赖于肿瘤的直径大小,还依靠浸润深度作为参考指标,证明了浸润深度的重要性。

Mücke等^[27]通过Roc分析和Youden指数分析相结合的统计分析,最终得出当肿瘤厚度为3~6 mm时,是淋巴结未转移的极限深度,当肿瘤厚度为8 mm时,对于淋巴结转移的预测来说是最准确的,另一项前瞻性研究也同样证实了上述结论^[28]。肿瘤浸润深度与早期舌鳞癌颈淋巴转移相关,但对于决定颈淋巴清扫临界值尚未达成共识^[29-30]。

目前准确测量DOI要靠永久性病理切片,而不是冰冻检查,无法同期切除原发灶时迅速判断肿瘤DOI,从而无法同期判断是否进行选择性颈清,使浸润深度测量在应用上受到限制^[31]。Berdugo等^[32]通过进行组织病理学分析提出在测量早期舌鳞癌浸润深度存在两个问题,即无法判断肿瘤切除后有无微小的残留病灶,其次肿瘤最深浸润边缘为阳性时测量较为困难。在DOI测量方法上,通过研究证明超声、MRI在判断肿瘤浸润深度有一定的指导意义^[33-35]。

2.5 病理分级(pathological grading, PG)

早期舌鳞状细胞癌分化程度高,预后较好,这一观点已被广泛接受^[3,36],PG越差通常表明肿瘤恶性程度越高,侵袭能力越强,浸润范围越广,淋巴结转移概率越高^[37]。Ahmed等^[36]通过研究78例早期舌鳞癌患者,统计得出颈淋巴转移率为25.6%,其中高分化占4.3%,中分化及低分化患者占25.6%及56.2%,得出病理分级与颈淋巴转移存在显著正相关的结论。但也有学者持反对观点,Montoro等^[38]通过分析早期口腔癌的生存率曲线,认为没有充足的证据来证实病理分级对颈淋巴转移有影响。但总的来说,早期舌鳞癌的病理分级也是评估颈淋巴转移的重要参考指标之一。

2.6 神经浸润(perineural invasion, PNI)

PNI是一种转移性肿瘤的扩散形式,临床上可以表现出疼痛、持续生长的症状,它具有长期的临床过程,还可发生晚期的转移^[39]。

Yang等^[40]对221例早期舌鳞癌患者进行前瞻性研究,发现PNI是预测颈淋巴结转移、局部复发、

颈部复发的重要指标。同时表明对于存在PNI的患者,选择性颈清扫不能提高患者的生存率。也有研究发现受到PNI的早期舌鳞癌患者5年局部和总体生存方面差异无统计学意义^[41]。这可能由于侵犯神经大小的差异,一旦侵犯主要神经,预后很可能恶化,主要发生在晚期舌鳞癌,而对T1期和T2期伴PNI的舌鳞癌患者的颈淋巴转移并无明显影响^[42]。因此,PNI是早期舌鳞癌颈淋巴转移的可靠预测指标之一,一旦发生PNI的早期舌鳞癌患者,建议行选择性颈淋巴清扫术。

2.7 血管淋巴管浸润(lymphatic and vascular invasion, LVI)

LVI包括淋巴管浸润及血管浸润,肿瘤侵袭血管是实体恶性肿瘤转移灶形成的第一步,也被认为是淋巴转移和血行转移的开始^[43]。Michikawa等^[43]回顾性分析63例口腔舌鳞癌患者,结果显示LVI是淋巴结转移的独立危险因素。Chen等^[42]将神经浸润与血管淋巴管浸润合并研究,认为LVI可以作为判断早期舌鳞癌颈淋巴转移的独立因素。然而,Adel等^[44]认为虽然淋巴和血管浸润与许多临床病理表现有关,但均不影响治疗后局部复发和颈淋巴转移。

3 小 结

综上所述,早期舌鳞癌颈淋巴主要回流至I、II、III区,跳跃性转移较为罕见,早期舌鳞癌的颈淋巴转移主要受浸润深度、病理分级、神经浸润、血管淋巴管浸润等的影响,为了使早期舌鳞癌患者获得较高的生存率,对于术前通过超声或MRI显示肿瘤浸润深度超过5 mm、病理分级高、已经存在麻木或者疼痛等临床症状的患者以及在冰冻结果中已存在神经、血管淋巴管浸润的T1期和T2期患者,应考虑切除原发灶同时行选择性颈淋巴清扫。

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