

• 综 述 •

头颈肿瘤放疗后咽鼓管功能障碍机制研究进展*

邓 锐 综述, 骆文龙, 王朝永[△] 审校

(重庆医科大学, 重庆 400016)

[摘要] 头颈部恶性肿瘤是常见的恶性肿瘤之一。头颈肿瘤放疗后分泌性中耳炎、粘连性中耳炎、中耳胆脂瘤、化脓性中耳炎、慢性乳突炎等中耳疾病发生率高,且治疗效果欠佳,严重影响患者生活质量。咽鼓管功能障碍是头颈恶性肿瘤放疗导致中耳疾病的核心因素,放疗导致咽鼓管功能障碍形成的机制较为复杂,该文从其形成机制方面进行了综述,旨在为临床治疗头颈肿瘤放疗后中耳疾病提供参考。

[关键词] 咽鼓管功能障碍; 中耳疾病; 头颈肿瘤; 放疗

DOI:10.3969/j.issn.1009-5519.2024.08.029

中图法分类号:R764.21

文章编号:1009-5519(2024)08-1397-03

文献标识码:A

**Research progress on the mechanism of eustachian tube dysfunction
after radiotherapy for head and neck tumors***

DENG Rui, LUO Wenlong, WANG Chaoyong[△]

(Chongqing Medical University, Chongqing 400016, China)

[Abstract] Head and neck malignant tumors are one of the common malignant tumors. The incidence of middle ear diseases such as secretory otitis media, adhesive otitis media, middle ear cholesteatoma, purulent otitis media, and chronic mastoiditis is high after radiotherapy for head and neck tumors, and the treatment effect is poor, seriously affecting the quality of life of patients. Eustachian tube dysfunction is the core factor of middle ear disease caused by radiotherapy for head and neck malignant tumors. The mechanism of eustachian tube dysfunction caused by radiotherapy is relatively complex. The article reviews its formation mechanism, aiming to provide reference for clinical treatment of middle ear disease after radiotherapy for head and neck tumors.

[Key words] Eustachian tube dysfunction; Middle ear disease; Head and neck tumors; Radiotherapy

头颈肿瘤为全球第 6 大常见肿瘤,每年包括鼻咽癌、喉癌、下咽癌、口咽癌、鼻腔鼻窦恶性肿瘤等在内的新发头颈部恶性肿瘤超过 88 万例,死亡病例超过 45 万例^[1-2]。头颈恶性肿瘤的治疗方式主要为放疗为代表的综合治疗,随着综合治疗水平的进步,患者存活率逐年提高,但放疗所致的中耳疾病如分泌性中耳炎、粘连性中耳炎、胆脂瘤、化脓性中耳炎、慢性乳突炎等疾病发生率较高,且治疗效果不佳,严重影响患者生活质量^[3]。头颈肿瘤放疗所致中耳疾病的病因通常认为与咽鼓管功能障碍、放疗辐射损伤、肿瘤侵犯、局部免疫炎症反应、细菌感染等有关,且各种因素之间相互影响^[4-7],其中咽鼓管功能障碍被认为是放疗后引起各型中耳疾病的核心因素^[8]。但放疗后咽鼓管功能障碍形成机制较为复杂,本文就头颈部恶性肿瘤放疗后咽鼓管功能障碍机制进行了综述,以期为临床提供参考。

1 咽鼓管解剖结构与生理功能

咽鼓管是人体鼻咽部与耳部相连的重要通道,咽

鼓管由外侧的骨部、内侧的软骨部及连接处的峡部构成,具有维持中耳与外界的压力平衡、引流中耳分泌物、防治中耳逆行感染等重要生理功能^[9]。

2 放疗对咽鼓管影响机制

2.1 直接辐射损伤咽鼓管黏膜、肌肉、软骨及被支配的神经 (1)放疗辐射可致咽鼓管黏膜受损,直接影响咽鼓管黏膜纤毛系统。放疗前期会导致咽鼓管黏膜细胞空泡化、气孔水肿、纤毛活动减弱甚至停止,以及纤毛之间分泌物停止流动、纤毛脱落、融合、塌陷、排列紊乱;放疗后期,咽鼓管黏膜会出现瘢痕修复和粘连及膜性粘连、狭窄、闭锁,严重时甚至出现咽鼓管软骨部全部粘连,造成中耳分泌物引流障碍^[10]。(2)辐射可直接损害咽鼓管软骨弹性,导致咽鼓管塌陷,引起咽鼓管开放功能障碍^[11]。(3)放疗后腭帆张肌可出现不同程度萎缩现象,当萎缩程度大于 30% 时,可出现明显咽鼓管功能障碍^[12-13]。当放疗剂量超过 40 Gy 时,可同时出现腭帆张肌肌源性损伤,即出现肌肉炎症、肌纤维数量减少和肌肉畸形,以及支配腭帆张

* 基金项目:重庆市科卫联合医学科研面上项目(2021MSXM279)。

[△] 通信作者, E-mail: cqwchy@sina.com。

肌的神经冲动传导受阻,致腭帆张肌电生理瘫痪。二者均可引起咽鼓管开放功能失调^[14]。相比于传统二维放疗,20 世纪末开发的强调放疗能更精确地规划受辐射的肿瘤区域,增加保护咽鼓管正常结构的可能性,降低放疗后因腭帆张肌、腭帆提肌受辐射损伤致咽鼓管功能障碍的发生率^[15]。有学者通过辐射剂量分析显示,咽鼓管、腭帆张肌、腭帆提肌所受到的辐射剂量与咽鼓管功能障碍的发展并无相关性,认为强调放疗对咽鼓管功能没有保护作用^[16-18]。因此,辐射剂量与咽鼓管功能障碍的机制有待进一步探究。

2.2 电离辐射致血管、淋巴管内皮细胞损伤 放疗后,颈部淋巴管肿胀导致咽鼓管周围淋巴管压力增高时可导致咽鼓管功能障碍^[19]。AVRAHAM 等^[20]认为,放疗可通过直接损伤或消耗淋巴管内皮细胞,使得内皮细胞对辐射损伤高度敏感并发生细胞凋亡,以及通过使淋巴管软组织纤维化,使其失去顺应性,从而损害淋巴管功能,导致组织渗出,产生内毒素及回流障碍。有研究将豚鼠以 60 Gy 放疗剂量照射后,豚鼠中耳黏膜下间质水肿,血管壁增厚伴管腔变窄,毛细血管扩张、破裂,微循环减少,组织渗出增加^[21]。BASELET 等^[22]研究认为,辐射可损害血管舒张功能,导致血管张力恶化,诱导线粒体功能障碍和过早衰老,以及内皮细胞回缩和死亡,导致血管完整性丧失,从而引起组织液渗出增加。

2.3 细菌感染及其产生的炎症反应 头颈部肿瘤放疗后常并发鼻-鼻窦炎、鼻咽炎、放射性口咽黏膜炎等^[23]。鼻腔、鼻窦、鼻咽、口咽、喉咽等黏膜上皮损伤、腺体分泌减少、黏膜纤毛功能障碍,会导致引流不畅,造成相关部位干燥、结痂、易滋生细菌、继发细菌感染,加重黏膜炎症,引起鼻-鼻窦炎、鼻咽炎、放射性咽炎长期反复发作,从而导致细菌上行感染至咽鼓管,引起咽鼓管功能障碍^[23]。NG 等^[24]研究发现,在放疗后的 3 个月内鼻窦炎发病率迅速增加,其鼻窦炎患者数量在 6~9 个月时达到高峰。研究表明,放疗后鼻窦炎患者革兰阳性菌感染率高于单纯鼻窦炎患者^[25]。当放疗剂量达到 40 Gy 时,鼻窦黏膜、鼻咽黏膜及口咽黏膜可发生类似的炎症反应^[24]。在接受单纯放疗的头颈部肿瘤患者中,有约 60% 患者发生放射性口咽黏膜炎,而同步放化疗患者发生比例高达 90% 以上^[26],其原因是放疗所致组织损伤部位的上皮、血管和结缔组织细胞释放了各种促炎细胞因子,致正常黏膜屏障丧失后形成溃疡面,可继发细菌感染^[27],而长期反复发作可导致感染上行至咽鼓管。何光耀等^[28]研究发现,放疗后咽鼓管堵塞程度与中耳积液白细胞介素-1 等细胞因子表达呈正相关,提示放疗后咽鼓管功能障碍可能与一种免疫反应介导的病理过程有关。

3 小 结

咽鼓管是维持中耳通气引流的重要通道,其在放疗后极易引发咽鼓管组织病理和生理功能的改变,从

而导致中耳相关疾病。本文通过复习国内外相关文献时发现,头颈部肿瘤放疗后咽鼓管功能障碍机制大致分为三类:辐射直接损害咽鼓管及其周围组织、咽鼓管周围组织内毒素增加及回流障碍、局部黏膜物理及免疫屏障受损致感染概率增加。头颈肿瘤放疗引起咽鼓管功能障碍常常由多种因素共同参与、相互影响,因此放疗后中耳疾病发生率高。临床应结合患者实际情况综合分析,针对致病因素采取个性化的防治措施。

参考文献

- [1] SUNG H, FERLAY J, SIEGEL R L, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2021, 71(3): 209-249.
- [2] CHEN S M Y, KRINSKY A L, WOOLAVER R A, et al. Tumor immune microenvironment in head and neck cancers[J]. Mol Carcinog, 2020, 59(7): 766-774.
- [3] 方玲, 刘泓毅, 苏晓磊, 等. 分泌性中耳炎伴有咽鼓管功能障碍行球囊扩张治疗的中长期疗效分析[J]. 中华耳科学杂志, 2023, 21(1): 41-46.
- [4] MOSLEH-SHIRAZI M A, AMRAEE A, MOHAGHEGH F. Dose-response relationship and normal-tissue complication probability of conductive hearing loss in patients undergoing head-and-neck or cranial radiotherapy: A prospective study including 70 ears[J]. Phys Med, 2019, 61: 64-69.
- [5] KANEKO T, KOTO M, IKAWA H, et al. Dosimetric analysis for otitis media with effusion due to eustachian tube dysfunction after carbon-ion radiation therapy for head and neck cancers[J]. Adv Radiat Oncol, 2023, 8(1): 101115.
- [6] MAZUMDER M D, PHOOKAN J T M, SAIKIA N J T, et al. Pure tone audiometry findings before and after radiotherapy in head and neck cancer patients: A hospital-based prospective interventional study[J]. J Clin Diagn Res, 2023, 17(1): MC05-MC09.
- [7] MO Y X, ZHUO S Q, TIAN L, et al. Functional MRI of the eustachian tubes in patients with nasopharyngeal carcinoma: correlation with middle ear effusion and tumor invasion[J]. AJR Am J Roentgenol, 2016, 206(3): 617-622.
- [8] 王胜资, 程庆芳. 头颈部肿瘤放射治疗后分泌性中耳炎的研究进展[J]. 中国癌症杂志, 2001, 11(2): 178-180.
- [9] HUISMAN J M L, VERDAM F J, STEGEM-

- AN I, et al. Treatment of eustachian tube dysfunction with balloon dilation: A systematic review[J]. *Laryngoscope*, 2018, 128(1): 237-247.
- [10] 李敏, 班莫璐, 唐凤珠. 鼻咽癌放疗后咽鼓管功能障碍机制、评估和治疗[J]. *中国临床新医学*, 2023, 16(1): 13-19.
- [11] SUN H C, CAO C, QIU X W, et al. Efficacy of balloon dilatation of the eustachian tube in patients with refractory otitis media with effusion after radiotherapy for nasopharyngeal carcinoma [J]. *Am J Otolaryngol*, 2020, 41(6): 1027-24.
- [12] 张钦华, 邹雨荷, 程霞, 等. 腭帆张肌横截面积对鼻咽癌患者放射性中耳炎的影响[J]. *上海医药*, 2017, 38(9): 39-40, 44.
- [13] 郭丽青, 苗春雨, 付衍朋, 等. 鼻咽癌放疗后分泌性中耳炎影响因素的 Meta 分析[J]. *中国耳鼻咽喉颅底外科杂志*, 2022, 28(6): 53-60.
- [14] HE G Y, ZHU M C, QIN Y, et al. Electrophysiological change in the tensor veli palatini muscle after radiotherapy [J]. *Acta Otolaryngol*, 2015, 135(6): 608-614.
- [15] SLEVIN F, PAN S, MISTRY H, et al. A multi-centre UK study of outcomes of nasopharyngeal carcinoma treated with Intensity-Modulated radiotherapy ± chemotherapy [J]. *Clin Oncol (R Coll Radiol)*, 2020, 32(4): 238-249.
- [16] VAINER I, TZELNICK S, POPOVTZER A, et al. Post radiation middle ear effusion in NPC Patients—Analysis of patient, tumor and radiation factors [J]. *Laryngoscope*, 2013, 123(9): 2148-2153.
- [17] LIANG K L, SU M C, TWU C W, et al. Long-term result of management of otitis media with effusion in patients with post-irradiated nasopharyngeal carcinoma [J]. *Eur Arch Otorhinolaryngol*, 2011, 268(2): 213-217.
- [18] HSIN C H, CHEN T H, LIANG K L, et al. Post-irradiation otitis media with effusion in nasopharyngeal carcinoma patients treated by intensity-modulated radiotherapy [J]. *Laryngoscope*, 2013, 123(9): 2148-2153.
- [19] 零兴勤. 鼻咽癌放疗后并发分泌性中耳炎形成机制及治疗研究进展 [J]. *基层医学论坛*, 2022, 26(22): 117-120.
- [20] AVRAHAM T, YAN A, ZAMPELL J C, et al. Radiation therapy causes loss of dermal lymphatic vessels and interferes with lymphatic function by TGF-beta1-mediated tissue fibrosis [J]. *Am J Physiol Cell Physiol*, 2010, 299(3): C589-C605.
- [21] 龚桃根, 文忠, 柯朝阳. 鼻咽癌放疗后分泌性中耳炎的病因及发病机制 [J]. *中华耳科学杂志*, 2018, 16(6): 903-906.
- [22] BASELET B, SONVEAUX P, BAATOUT S, et al. Pathological effects of ionizing radiation: endothelial activation and dysfunction [J]. *Cell Mol Life Sci*, 2019, 76(4): 699-728.
- [23] 胡燕萍, 李勇, 滕尧树, 等. 鼻咽癌放化疗后慢性鼻窦炎的内镜治疗临床效果评价 [J]. *中国耳鼻咽喉头颈外科*, 2022, 29(6): 363-366.
- [24] NG W, SOONG Y, AHN Y, et al. International recommendations on reirradiation by intensity modulated radiation therapy for locally recurrent nasopharyngeal carcinoma [J]. *Int J Radiat Oncol Biol Phys*, 2021, 110(3): 682-695.
- [25] KUHAR H N, TAJUDEEN B A, HEILINGOETTER A, et al. Distinct histopathologic features of radiation-induced chronic sinusitis [J]. *Int Forum Allergy Rhinol*, 2017, 7(10): 990-998.
- [26] TAO Z C, GAO J, QIAN L T, et al. Factors associated with acute oral mucosal reaction induced by radiotherapy in head and neck squamous cell carcinoma: A retrospective single-center experience [J]. *Medicine (Madr)*, 2017, 96(50): e8446.
- [27] MARIA O M, ELIOPOULOS N, MUANZA T. Radiation-Induced oral mucositis [J]. *Front Oncol*, 2017, 7: 89.
- [28] 何光耀, 唐军, 尧振兴, 等. 鼻咽癌放疗后分泌性中耳炎中 IL-1 β 和内毒素的表达与咽鼓管功能障碍的关系 [J]. *中国耳鼻咽喉颅底外科杂志*, 2018, 24(3): 202-207.

(收稿日期: 2023-09-16 修回日期: 2024-01-05)