· 共识 ·

放射性口腔黏膜炎防治策略专家共识(2019)

中华医学会放射肿瘤治疗学分会

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【摘要】 放射性口腔黏膜炎(RTOM)是放疗导致的口腔黏膜炎症,是头颈部肿瘤患者放疗中最常见的并发症,重度 RTOM 可导致治疗中断,影响疗效。近年来,针对 RTOM 的防治研究不断有报道,但国内尚缺乏规范和指南。本共识参考国外相关临床实践指南,对国内外 RTOM 的防治药物和方法进行回顾、总结,为 RTOM 的预防与治疗提供推荐和建议。

【关键词】 头颈部肿瘤/放射疗法; 放射性口腔黏膜炎; 共识

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Expert consensus on prevention and control strategy of radiotherapy-induced oral mucositis (2019)

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【**Abstract**】 Radiotherapy-induced oral mucositis (RTOM) is a category of oral mucosal injury caused by radiotherapy, which is the most common complication of radiotherapy in patients with head and neck tumors. Severe RTOM may interrupt the treatment and lower the clinical efficacy. In recent years, new accomplishment on the prevention and treatment of RTOM has been reported. Nevertheless, unified standards and guidelines are still lacking in China. This expert consensus refers to clinical practice guideline abroad, reviews and summarizes the prevention and management of RTOM at home and abroad, aiming to provide recommendations and suggestions for the prevention and treatment of RTOM in patients with head and neck tumors in China.

【**Key words**】 Head and neck neoplasm/radiotherapy; Radiotherapy-induced oral mucositis; Consensus

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放射性口腔黏膜炎(radiotherapy-induced oral mucositis, RTOM)是头颈部肿瘤放疗常见且严重并发症之一,表现为口腔黏膜充血、红斑、糜烂、溃疡及纤维化等,患者出现疼痛、进食困难、口干、味觉障碍等(Ⅰ级证据)[1-3]。80%以上头颈部放疗患者在放疗过程中都会发生 RTOM,半数以上患者甚至会发生 3-4 级口腔黏膜炎[4]。临床常用的口腔黏膜炎分级标准有 WHO 口腔毒性量表、RTOG 急性放射性黏膜炎分级标准及 NCI/CTC;其中 WHO 分级标准偏向于进食情况的评估,RTOG 及 NCI/CTC 标准偏重于口腔病理生理状况评估[5-8]。2004 年MASCC/ISOO 发表了第 1 个黏膜炎相关的循证临床实践指南,2014 年更新了第 2 版[9-10]。ESMO 也更新了口腔黏膜炎防治指南[11]。然而,RTOM 尚缺乏相关临床专家共识或临床诊疗指南。本共识参考国外相关临床实践指南,对国内外 RTOM 防治药物和方法进行回顾、总结,并且纳入对临床诊疗指导意义较大的新药物和新方法,最终形成符合国人的最新指导性专家共识。

一、RTOM 危险因素评估

尽管 RTOM 发生发展的危险因素中还有许多尚未解答的问题,但根据既往研究结果得出危险因素主要包括患者自身因素以及治疗相关的因素(Ⅰ级证据)[12]。

1.患者自身因素:不良的口腔卫生习惯、既往牙周疾病史、吸烟以及营养不良是目前比较公认的危险因素(Ⅰ级证据)[13]。而另一些因素包括年龄、体重、性别、心理因素、肿瘤的性质以及是否合并糖尿病等也可能是影响口腔炎严重程度的影响因素(Ⅲ-Ⅳ级证据)[14-15]。

2.治疗相关因素:治疗会影响 RTOM 发生率和严重程度。治疗相关的危险因素包括放疗技术,放疗分割模式、剂量及放疗部位、化疗药物(靶向药物)的使用等。

(1)放疗技术:放疗技术的革新,不仅带来疗效的提升,同时不良反应也降低。研究显示,调强放疗能减少口腔黏膜的照射剂量,与二维放疗相比,能降低放射性口腔炎的严重程度(Ⅲ级证据)[16]。近年来质子、重离子及中子也越来越多的运用于头颈部肿瘤治疗,使头颈部肿瘤急性口腔黏膜炎发生率降低[17-18]。研究数据显示,质子治疗头颈肿瘤的口腔黏膜炎的发生率明显低于光子调强放疗(P=0.019)[19]。

(2)放疗分割模式:与常规分割相比,超分割和加速分割均增加 RTOM 严重程度和持续时间(Ⅰ级证据)[20-21]。头颈部肿瘤患者≥3 级 RTOM 发生率常规分割放疗为 25%~34%(Ⅰ级证据),超分割放疗为 42%~57%(Ⅲ级证据)[22-24]。改变分割方式导致的 RTOM 风险不仅高于单纯常规分割放疗,也高于同期放化疗,是同期放化疗的 1.57 倍(Ⅰ级证据)[25]。

(3)放疗剂量:RTOM 的严重程度与 PTV 外口腔黏膜接受的剂量相关。Narayan 等[26]对 12 例头颈肿瘤患者的研究结果显示,口腔黏膜累积剂量<32 Gy 者 RTOM 反应≤1 级(Ⅳ级证据)。基于这一结果,Wang 等[27]将 24 例舌鳞癌术后调强放疗患者 PTV 外口腔黏膜剂量控制在 32 Gy 以下,2、3 级黏膜炎发生率分别为 25%和 0%(Ⅲ级证据)。

(4)放疗联合化疗和(或)分子靶向药物引起的 RTOM:化疗和表皮生长因子受体(epidermal growth factor receptor,EGFR)单克隆抗体可能增加黏膜对低剂量放射的敏感性,使得联合化疗和 EGFR 单克隆抗体后调强放疗的口腔黏膜炎程度比非调强放疗严重(Ⅰ级证据)[28]。因此,在同期化疗和(或)分子靶向药物增敏时代,调强放疗的中低剂量区不容忽视。单纯放疗的急性 RTOM 往往在放疗达 12 Gy 后开始出现,24 Gy 时最严重,40~46 Gy 后逐渐好转[29]。同步放化疗急性 RTOM 的出现时间提前,持续时间延长,3-4 级急性 RTOM 发生率增加(Ⅰ级证据),发生风险是单纯放疗的 1.40~1.51 倍(Ⅰ级证据)[30-36]。大多数患者 RTOM 可在放疗后 2~4 周逐渐缓解,而放疗后行辅助化疗可能会导致口腔黏膜炎迁延不愈。Chen 等[37]针对局部晚期鼻咽癌同期放化疗加辅助化疗的随机对照研究中,辅助化疗组在放疗结束 28 d 后开始 3 个疗程辅助化疗;该组患者有 31%在放疗期间出现 3-4 级口腔黏膜炎,而 21%的患者在辅助化疗期间口腔黏膜炎无法缓解(Ⅰ级证据)。EGFR 单克隆抗体联合放疗能提高头颈部肿瘤区域控制率和存活率。一项针对晚期鼻咽癌的随机对照研究中,采用放疗联合西妥昔单抗同期治疗组因 3-4 级口腔黏膜炎发生率高达 89%,在中期分析时停止了试验(Ⅱ级证据)[22]。另一项回顾性研究也显示西妥昔单抗同期治疗组 3-4 级口腔黏膜炎发生率上升(Ⅲ级证据)[38]。

专家推荐:放疗前从患者自身因素和治疗相关因素两方面评估患者发生 RTOM 的风险。自身危险因素主要包括:既往牙周疾病史、是否吸烟、营养状况和口腔卫生习惯及是否并发糖尿病等(Ⅰ级证据)。治疗相关危险因素包括:放疗技术,放疗分割模式、剂量及放疗部位、化疗/靶向药物的使用等(Ⅰ级证据)。

二、RTOM 的预防

1.非药物预防:放疗期间建议患者戒烟、戒酒,多喝水,避免热、酸性及辛辣的食物[39-40]。良好的口腔卫生有助于预防和减轻 RTOM[15]。建议患者放疗前进行口腔检查、改善口腔卫生。推荐每天 4~6 次采用柔软的牙刷,使用不含氟的牙膏、牙线和不含酒精的生理盐水或碱性(碳酸氢钠)漱口水清洁口腔(Ⅲ级证据)[41]。氯己定漱口液长期以来一直用于预防化疗引起的口腔黏膜炎,但不推荐用于 RTOM (Ⅱ级证据)[42]。同时可采用口腔保湿剂或人工唾液、水溶性果冻、干口含片或干口胶润滑口腔[24]。对装有金属牙的患者,可在金属牙和口腔黏膜之间填充保护材料,减小摩擦[43]。

2.药物预防

(1)细胞因子:临床报道预防用于 RTOM 的细胞因子包括重组人粒细胞巨噬细胞刺激因子(granulocyte-macrophage colony stimulating factor,GM-CSF)、EGF 等[44]。早期一项非随机对照研究显示,16 例局部晚期头颈部肿瘤患者在放疗前连续皮下注射 GM-CSF 5 d 后 RTOM 较对照组患者轻(P=0.011)[45]。类似一项 40 例头颈部肿瘤患者的随机对照研究结果显示 GM-CSF 漱口水在预防 RTOM 和缓解黏膜相关疼痛方面比硫糖铝漱口水更有效,可减少黏膜炎引起的放疗过程中断。另一项比较局部预防性使用 GM-CSF 的非随机Ⅱ期研究也发现预防组患者口腔黏膜炎平均分级及持续时间低于治疗组(P<0.05)[46]。最近一项多中心随机双盲、对照研究调查了 36 个机构的 130 例患者,结果显示 GM-CSF 组(放疗前 1 周起至放疗后 2 周,每周皮下注射 GM-CSF,250 μg/m^2)和安慰剂组的平均黏膜炎评分相近(P=0.401)[47-48]。2013 年一项系统分析认为

没有足够的证据支持局部或全身使用 GM-CSF 能改善头颈部肿瘤患者的 RTOM[49]。2014 年 MASCC/ISOO 指南[10]和 2015 年 ESMO[11]未推荐 GM-CSF 用于预防 RTOM。一项中国的随机研究显示预防性外喷重组人 EGF 可推迟放射性黏膜炎的发生，预防用药可降低 3、4 级黏膜炎发生率[50]。另一项韩国的多中心随机双盲前瞻性研究也显示局部 EGF 的使用可减轻 RTOM 发生和程度[51]。

（2）黏膜保护剂：临床使用的黏膜保护剂包括自由基清除剂、必需氨基酸及过饱和钙磷酸盐等。2013 年 Nicolatou 等[52]进行了一项系统性分析，纳入 30 篇用氨磷汀处理口腔黏膜炎的文献。其中有 16 篇文献显示氨磷汀可减轻口腔黏膜炎的严重程度，有 10 篇未能显示相应的获益，另外 4 篇文章未得出任何结论。Tsujimoto 等[53]研究发现，谷氨酰胺（10 g/d）对头颈部癌症患者 RTOM 有预防作用，谷氨酰胺组和安慰剂组的 2 级黏膜炎发生率分别为 0 和 10%（$P=0.023$），4 级黏膜炎发生率分别为 0 和 25%。Quinn 等[54]回顾性分析了 30 项关于过饱和钙磷酸盐漱口水预防 RTOM 的研究，其中 24 项研究证实该药能保持口腔卫生、湿润和润滑口腔，有效地降低了放射性口腔炎发病率、严重程度和持续时间。然而，另一项前瞻性随机研究却显示，过饱和钙磷酸盐并不能改善口腔黏膜炎的发生频率、持续时间或严重程度[55]。

（3）非甾体抗炎药：盐酸苄达明漱口水能抑制炎症细胞因子 TNF-α 和 IL-1β 的产生[56-57]。Epstein 等[58]随机双盲对照 135 例头颈部肿瘤患者 RTOM 的研究显示，盐酸苄达明能使红斑和溃疡发生率降低约 30%（$P=0.037$），从而减少全身止痛剂的使用（$P<0.05$）。Kazemian 等[59]进一步对 100 例头颈部肿瘤患者进行随机双盲对照研究发现，安慰剂组 RTOM 的发生率是盐酸苄达明漱口水组的 2.6 倍（Ⅰ级证据）。Nicolatou-Galitis 等[60]荟萃了 40 篇关于 RTOM 的文献，推荐对将接受 50 Gy 及以上放疗的头颈部肿瘤患者使用盐酸苄达明漱口水，预防 RTOM 发生。基于以上研究，欧洲已将苄达明作为预防头颈部癌症患者的放射性黏膜炎的Ⅰ级证据推荐[42]。

（4）预防性抗菌素：Saunders 等[61]对癌症患者应用抗菌素预防口腔黏膜炎的文献进行回顾分析后，不推荐抗菌多肽以及抗菌合剂含片（多粘菌素-妥布霉素-两性霉素含片和杆菌肽-克霉唑-庆大霉素含片）用于头颈放疗患者口腔黏膜炎的预防（Ⅲ级证据）。

（5）中药：中医认为放射线属于火热毒邪，导致人体热毒过盛，日久热毒伤津耗气，因此阴虚和热毒是放疗最常见的不良反应，清热解毒、益气养阴、滋阴生津是中药治疗 RTOM 的最主要原则[62]。多项成品中药复方制剂预防 RTOM 的研究陆续发表，包括双花百合片、口炎清颗粒、康复新液等[63-65]。一项纳入 240 例鼻咽癌患者的多中心随机、双盲、前瞻性临床试验结果显示，服用双花百合片能减少 RTOM 发生率，延迟口腔黏膜炎出现时间，以及降低严重 RTOM 发生率（$P<0.001$）（Ⅰ级证据）[63]。另一项随机、平行、多中心临床研究纳入 240 例患者随机接受康复新溶液（试验组）或复方硼砂漱口剂（对照组）预防 RTOM。与对照组相比，试验组口腔黏膜炎的发生率、严重程度及口腔疼痛发生率低于对照组（$P<0.01$）（Ⅰ级证据）[65]。

（6）其他：另外，还有如免疫球蛋白、芦荟、蜂蜜等用于预防 RTOM[66-68]。但其临床疗效尚需大样本的临床随机试验来证实。

专家推荐：针对患者自身相关因素和治疗因素采取个性化的预防策略，尽早联合多种方法进行预防。①非药物性预防：放疗前对患者进行口腔黏膜护理教育，营养指导，建议戒烟、戒酒，避免刺激性食物，糖尿病患者严格控制血糖。保持口腔卫生至关重要。推荐每天 4~6 次采用柔软的牙刷，使用不含氟的牙膏、牙线和不含酒精的生理盐水清洁口腔。放疗计划设计时尽可能降低口腔黏膜受量。②药物性预防：推荐碳酸氢钠液、盐酸苄达明漱口，或含漱、口服中药制剂。由于各研究的结论不相一致以及证据因级别不够的原因，尚不推荐重组人粒细胞巨噬细胞刺激因子、谷氨酰胺以及过饱和钙磷酸盐漱口水用于 RTOM 的预防。也不推荐局部预防性使用抗生素、抗菌多肽和激素。

三、RTOM 的治疗

1.非药物治疗：口腔黏膜炎的非药物性治疗十分重要，需要从心理、营养、卫生习惯等多方面进行。研究表明，头颈部癌患者尤其是 RTOM 患者是最易患抑郁症的患者之一，发病率高达 44%[69]。医护人员应积极进行健康宣教，帮助患者以积极的态度面对疾病。同时帮助患者养成良好的口腔卫生习惯，根据口腔 pH 值选择合适的漱口液。鼓励患者每日做张口、鼓腮、叩齿等锻炼，增加口腔黏膜皱襞与外界的气体交换，破坏厌氧菌的生存环境，防止发生继发感染。治疗期间避免辛辣食物，以防止对口腔黏

膜的刺激(Ⅳ级证据)[11]。积极的营养支持将增强口腔黏膜抵抗能力,减少感染的机会,促进 RTOM 修复。另外,低能量激光治疗(low level laser therapy,LLLT)能通过调节活性氧以及促炎性细胞因子(TNF-α、IL-6 以及 IL-8)的产生而起到治疗 RTOM 的作用(Ⅲ级证据)[70]。2014 年 MASCC/ISOO 推荐 LLLT 用于化疗(Ⅱ级证据)和单纯放疗(Ⅲ级证据)所致导致的口腔黏膜炎[10]。

2.药物治疗:大多数 RTOM 在治疗结束后能痊愈,因此症状控制是关键,措施以局部对症治疗为主,系统全身治疗为辅。除上述细胞因子、黏膜保护剂和中药外,镇痛和控制局部及全身的继发感染亦非常重要。

(1)细胞因子:除预防外,前述细胞因子如 GM-CSF 和 EGF 等也有临床报道用于治疗 RTOM[71]。早期的一项非随机对照研究显示,10 例患者在接受头颈部放疗 20 Gy 后,皮下注射 GM-CSF (1 μg/kg, qd)患者的 1、2、3 级 RTOM 分别为 40%、60%、0[72]。此后又有小样本前瞻性、随机、双盲、对照试验提示接受皮下注射 GM-CSF (2 μg/kg,qd)的患者黏膜炎严重程度明显低于对照组的患者(P<0.05)[73]。但另一项前瞻性、随机、对照研究则认为 GM-CSF 治疗 RTOM 与常规漱口水对比无差异[74]。2013 年的系统分析认为 GM-CS 治疗头颈部肿瘤患者 RTOM 的证据不充分[49]。鉴于有关研究的不一致性 2014 年的 MASCC/ISOO 指南和 2015 年的 ESMO 也未将 GM-CSF 纳入治疗 RTOM 的专家推荐[10-11]。

(2)镇痛剂:RTOM 伴轻度疼痛时,可以使用利多卡因或吗啡等漱口液。有研究证实 2%吗啡含漱液能有效控制黏膜炎相关性疼痛,并减少全身性吗啡的需求[11]。当引起重度疼痛时推荐系统使用吗啡或芬太尼等强阿片类药物(Ⅲ级证据)[42]。

(3)抗菌素治疗:RTOM 合并感染需要抗菌素治疗。治疗前需要送口腔黏膜拭子进行细菌和真菌培养及做药物敏感试验,指导抗菌药物使用。

(4)糖皮质激素:局部使用含糖皮质激素能减轻水肿,抑制炎症反应,缓解患者的症状,但长期使用有增加口腔真菌感染的风险[74]。而全身使用糖皮质激素有减少放疗中断的趋势,但并不能减少 RTOM 的发病率和严重程度[75]。

(5)中药:文献提示前述多项成品中药复方制剂包括双花百合片、口炎清颗粒、康复新液等均能在一定程度上降低 RTOM 的严重程度和缓解疼痛[63-65]。

专家推荐:非药物性治疗为从心理、营养、卫生习惯等方面进行。积极进行健康宣教,加强营养支持,避免粗糙食物和酸性食物的刺激,保持口腔清洁、湿润,同时应避免酒精、烟草和辛辣的食物。有条件患者的可使用细胞因子或黏膜保护剂,明显感染征象时采用抗生素治疗。具体实施原则如下:①1-2 级为强烈推荐(80%以上专家推荐)口腔卫生指导及营养支持,碳酸氢钠水及中药漱口,局部使用 EGF 等。推荐(50%以上专家推荐)采用利多卡因漱口液漱口缓解轻度疼痛,吗啡或芬太尼等强阿片类药物治疗中重度疼痛。不推荐采用抗生素、激素以及全身使用黏膜保护剂。②3 级:强烈推荐口腔卫生指导及营养支持(包括鼻饲饮食及肠外营养支持,尽可能采用肠内营养),碳酸氢钠水及中药漱口,局部使用 EGF 等。强烈推荐采用利多卡因漱口液漱口缓解轻度疼痛,吗啡或芬太尼等强阿片类药物治疗中重度疼痛。推荐局部或系统性使用抗生素、激素以及口服中药治疗。不推荐全身使用黏膜保护剂。抗感染治疗前需要送口腔黏膜拭子进行细菌和真菌培养及做药物敏感试验,指导抗菌药物使用。如果联合西妥昔单抗治疗,可暂停西妥昔单抗 1~2 周直到黏膜反应降至 2 级以下。③4 级:除上述处理外,暂停放疗,如果联合西妥昔单抗治疗/化疗,则暂停西妥昔单抗/化疗直到黏膜反应降至 2 级以下。

四、总结

RTOM 可以在一定程度上加以预防。良好的口腔卫生环境及护理是预防 RTOM 的主要措施。放射性黏膜炎的预防和治疗目前无特效药,治疗主要在于减轻症状和减少并发症的发生,包括营养支持、疼痛控制、预防和/或治疗继发感染,被认为是 RTOM 管理的主要基石。尽管放射性黏膜炎发病率很高,但对大多数头颈部肿瘤患者是一种剂量限制性的毒性反应,放疗结束后能慢慢恢复。然而,对重症患者来说,这可能是致命的伤害。虽然对于放射性黏膜炎的预防和治疗已进行了许多研究,但由于缺乏大规模的多中心随机对照研究,很多预防和治疗策略仍有争议。RTOM 重在预防,期待开展多中心症状管理的大数据分析,以期发现更完整的 RTOM 危险因素,找到更为安全、有效的防治策略。

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《中国临床案例成果数据库》征稿启事

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· 头颈部肿瘤 ·

原发腮腺淋巴上皮癌临床特征与诊断及疗效分析

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【摘要】 **目的**　分析原发腮腺淋巴上皮癌的临床特征、诊断特点及预后。**方法**　回顾性分析 2009-2017 年经中国医学科学院肿瘤医院确诊的 13 例腮腺淋巴上皮癌患者临床资料，中位随访时间 38.5 个月，所有患者均先行手术+放疗。**结果**　全组 13 例患者中男 9 例，女 4 例，中位年龄 33 岁。确诊时局限于腮腺 9 例、区域淋巴结转移 4 例，均为 Ⅰb、Ⅱ区。UICC2010 分期Ⅰ、Ⅱ、Ⅲ、Ⅳ期患者分别为 1、1、6、5 例。11 例患者手术病理标本 EBER 检测 10 例阳性。全组无死亡事件，3 年总生存率 100%，3 年无进展生存率 76%，3 年局部控制率 92%，3 年无远处转移率 84%。**结论**　腮腺淋巴上皮癌发病率较低，病变与 EBV 相关，容易发生颈部淋巴结转移，疗前应除外鼻咽癌转移至腮腺的可能。目前治疗模式是以手术+放疗，总体预后较好，治疗失败主要原因为局部复发和远处转移。

【关键词】 涎腺淋巴上皮癌；　EB 病毒；　治疗结果

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Clinical characteristics, diagnosis and efficacy of primary lymphoepithelial carcinoma of the parotid gland

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【**Abstract**】 **Objective**　To analyze the clinical features, diagnosis and prognosis of patients with primary lymphoepithelial carcinoma of the parotid gland. **Methods**　Clinical data of 13 patients diagnosed with lymphoepithelial carcinoma of the parotid gland in our hospital from 2009 to 2017 were retrospectively analyzed. The median follow-up time was 38.5 months. All patients received radiotherapy after operation. **Results**　Of 13 patients, 9 cases were male and 4 female. The median age was 33 years. At the initial diagnosis, 9 cases had primary lesions limited to the parotid gland, and 4 cases of lymph node metastases located in Ⅰb and Ⅱ regions of the neck. According to UICC2010 staging, 1 case was classified as stage Ⅰ, 1 as stage Ⅱ, 6 as stage Ⅲ and 5 as stage Ⅳ, respectively. Eleven surgically pathological specimens were tested with EBER in-situ, and 10 cases were positive for EBER. No patient died in the whole group. The 3-year overall survival rate was 100%. The 3-year progression-free survival rate was 76%. The 3-year local control rate was 92%. The 3-year metastasis-free survival rate was 84%. **Conclusions**　The incidence of lymphoepithelial carcinoma of the parotid gland is relatively low. The pathological features are associated with EB virus. It is prone to present with cervical lymph node metastasis. The possibility of lymph node metastasis of nasopharyngeal carcinoma to the parotid gland should be excluded before treatment. At present, surgery combined with postoperative radiotherapy is the main treatment. The overall survival is favorable. Local recurrence and distant metastasis are the main causes of treatment failure.

【**Key words**】 Lymphoepithelial carcinoma of the parotid gland;　EB virus;　Treatment outcome

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涎腺淋巴上皮癌（lymphoepithelial carcinoma，LEC）是一种较为少见涎腺肿瘤，于 1921 年首次报道，