鼻咽癌调强放射治疗后颞叶损伤预测与预防研究现状

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摘要 现代放射治疗技术的进步和综合治疗策略的优化,使得鼻咽癌(NPC)的治疗效果取得长足进步。随着长期存活患者的增加,如何降低放射治疗相关晚期并发症变得越来越重要。放射性颞叶损伤作为NPC放射治疗后相对少见,但严重影响患者生活质量的并发症之一,目前治疗手段有限,因此尚以预防为主。本文主要针对调强放射治疗年代颞叶损伤的变化、剂量学预测研究以及预防策略进行简要综述。

关键词 鼻咽癌;放射治疗;颞叶损伤;预测;预防

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Current research status on prediction and prevention of temporal lobe injury after intensity-modulated radiotherapy for nasopharyngeal carcinoma

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Abstract The advancement of modern radiotherapy technology and the optimization of comprehensive treatment strategies have led to significant improvements in the efficacy of nasopharyngeal carcinoma (NPC) treatment. With the increase in long-term survivors, the prevention of radiation-related late complications has become increasingly important. Radiation temporal lobe injury is a relatively rare complication after NPC radiation therapy, but it seriously affects patients’ quality of life. Currently, treatment options are limited, so prevention remains the primary focus. This review mainly summarizes the changes in the temporal lobe injury during the era of intensity-modulated radiotherapy, dosimetric prediction studies, and comprehensive prevention strategies.

Keywords nasopharyngeal carcinoma; radiotherapy; temporal lobe injury; prediction; prevention

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鼻咽癌(nasopharyngeal carcinoma,NPC)是我国最常见的头颈部恶性肿瘤,放射治疗是唯一的根治性治疗手段[1]。随着调强放射治疗(intensity-modulated radiotherapy,IMRT)的应用以及综合治疗策略的优化,NPC患者的总体生存率显著改善[2]。既往多项研究显示,接受以IMRT为主的综合治疗后的NPC患者5年总生存率超过80%[3-5]。然而,长期存活患者普遍存在不同程度的晚期放射性损伤,如口干、张口受限、放射性龋齿、听力下降、颞叶损伤、颅神经损伤、颌骨骨髓炎、皮肤及皮下纤维化等,严重影响患者生活质量,甚至危及生命[6-7]。其中,放射性颞叶损伤可导致头痛、癫痫发作、局灶性神经功能障碍和认知功能障碍,作为NPC放射治疗后最严重的晚期损伤之一,一直以来都是临床研究的热点[8]。本文主要针对IMRT年代颞叶损伤的变化、剂量学预测研究以及预防策略进行综述。

1 IMRT年代颞叶损伤的变化

由于鼻咽部解剖位置的特殊性,且NPC极易局部侵犯至毗邻的颅底骨质,为达到肿瘤控制,周围邻近脑组织尤其是双侧颞叶中、下部不可避免受到照射。IMRT作为目前主流的放射治疗技术,具有高度适形性和剂量均匀性,使得剂量聚焦于靶区内,周围正常组织受量降低。相比于常规放射治疗(two-dimensional radiation therapy,2DRT)及三维适形放射治疗(three-dimensional conformal radiation therapy,3D-CRT),IMRT的剂量学优势也转化为晚期放射性损伤减少,从而改善了长期存活患者的生活质量[9]。2012年发表的一项Ⅲ期随机对照研究对比了IMRT与2DRT治疗NPC的疗效和毒副反应,中位随访42个月,IMRT组和2DRT组颞叶损伤发生率分别为13.1%和21.0%(P=0.01)[10]。另外一项中山肿瘤防治中心的大样本回顾性研究报道了NPC患者接受IMRT或2DRT的10年随访结果,发现与2DRT组相比,IMRT组3～4级的颞叶坏死的发生率显著降低(2% *vs.* 4%)[11]。

除颞叶损伤发生率显著下降以及严重程度明显减轻外,IMRT后放射性颞叶损伤的影像学征象也与常规放射治疗年代明显不同:2DRT年代因两侧对穿水平设野,故颞叶损伤多为双侧,坏死和水肿范围相对广泛;而IMRT后颞叶损伤以单侧病变为主,且坏死和水肿范围相对局限[12-13]。

2 颞叶损伤的剂量学预测研究现状

IMRT年代颞叶损伤的中位潜伏期通常在36个月左右[13],其影像学征象主要表现为颞叶水肿伴坏死。明确放射性颞叶损伤与颞叶剂量—体积的效应关系可预测颞叶损伤的发生概率。目前已有多项回顾性研究开发了颞叶损伤的正常组织并发症概率(normal tissue complication probability,NTCP)模型以预测颞叶损伤的发生风险[14-17]。在Wang等[15]开发的定量预测模型中,0.5 mL体积接受的最大剂量(D0.5cc)和10%体积接受的最大剂量(D10%)是颞叶损伤的关键预测因素,这表明颞叶高剂量区剂量与损伤发生显著相关。一项纳入30项研究的系统性综述和荟萃分析发现,颞叶损伤的粗发生率在2.3%～47.3%,颞叶最大剂量(Dmax)和1 mL体积接受的最大剂量(D1cc)为接受3D-CRT和IMRT治疗的NPC患者颞叶损伤的潜在预测因素,Dmax＞72 Gy和D1cc＞62 Gy与颞叶损伤风险增加有关[18]。而Su等[14]的另一项研究则发现限制颞叶V40绝对体积(aV40)＜10%和占颞叶百分比(rV40)＜5 mL,颞叶损伤发生率不足5%;而aV40≥15%或rV40≥10 mL时,颞叶损伤发生风险超过20%。由此可推测,除颞叶的高剂量区剂量外,低剂量区受照体积也可能影响颞叶损伤的发生。

既往研究发现,结合临床参数及剂量学参数可进一步提高由单剂量学参数构建的NTCP模型的预测能力[19]。一项来自四川肿瘤医院的研究利用多元逻辑回归方法构建了由T分期、中性粒细胞与淋巴细胞比值比、Dmax及D1cc组成的颞叶损伤的Nomogram模型,C指数为0.847,外部数据验证该模型区分度同样良好(C指数为0.811)[16]。另外一项来自中山大学肿瘤防治中心的研究纳入了8 194例接受IMRT治疗的NPC患者,并通过机器学习算法和单因素COX分别筛选剂量学参数和临床因素,最终将年龄、T分期及D0.5cc共同构建Nomogram模型,其C指数显著优于单剂量学参数模型(0.780 *vs.* 0.737,P＜0.001),内部数据验证结果保持一致。近年来,有研究发现联合剂量组学可进一步提高颞叶损伤模型的预测能力[20-21]。最新发表的一项研究通过将多基因评分与年龄、分期等临床因素以及剂量学因素结合,颞叶损伤预测准确性显著提高(C指数为0.78 *vs.* 0.85,P=0.016 3)[22]。因此,在评估颞叶损伤发生风险时,结合剂量学和临床因素共同评估可能更加准确,此外遗传易感性也在颞叶损伤预测方面显示出极大潜力。

3 颞叶损伤的预防策略

在不牺牲肿瘤控制率的同时尽量减少颞叶损伤的发生,重点在于平衡治疗靶区和颞叶的剂量分布,其中精准勾画颞叶、合理降低剂量或缩小靶区、

优化物理计划是关键环节。此外，质子、重离子技术因其明显的Bragg峰，使得靶区外邻近组织剂量迅速跌落，从而能够更好地保护周围正常器官和组织，降低颞叶损伤的发生。

3.1 颞叶的精准勾画　针对危及器官边界的主观解释及其客观轮廓变化是导致危及器官勾画差异性的主要因素[23]。2014年发布的NPC危及器官解剖图谱和勾画指南针对包括颞叶在内的33种危及器官开发了CT-MRI融合图谱，减少了勾画的主观多样性[24]，然而观察者之间和观察者内部的差异同样影响放射治疗计划优化的质量[25]。基于人工智能技术的自动勾画显著减少了观察者间的差异，提高了包括颞叶在内的危及器官剂量学参数的一致性[23]。

在放射治疗期间，由于患者体重减轻、腮腺萎缩或肿瘤退缩等情况，NPC患者可能出现明显的解剖结构变化，从而导致靶区欠量和（或）周围正常器官遭受过多且不必要的照射[26]。自适应放射治疗（adaptive radiotherapy，ART）可通过图像引导观察患者体位变化情况、治疗过程中正常组织结构及肿瘤形态位置变化，从而及时调整放射治疗计划。既往研究显示，治疗中IMRT再计划可明显降低NPC患者颞叶等危及器官Dmax、Dmean等剂量学参数[27-29]。目前对于自适应放射治疗再计划的时机、频率以及患者的选择仍存在争议，同时尽管有研究显示IMRT再计划可显著提高NPC患者的无局部区域复发生存[30]，但颞叶受量的减少是否能够带来颞叶损伤发生率的降低尚需更长时间的随访。

3.2 合理降低治疗强度　根据诱导化疗反应降低治疗强度是近年来NPC研究的热点之一，旨在实现不牺牲疗效的同时降低患者毒副反应的目标[31]。ARAR0331研究根据不同诱导化疗反应对儿童和青少年NPC分别给予61.2 Gy和71.2 Gy剂量放射治疗并同步化疗，结果表明对诱导化疗有效者适当降低放射治疗剂量仍可获得较好的肿瘤控制率，但长期毒副反应尚未评估[32]。最近发表的一项单臂Ⅱ期研究仅纳入EBV-DNA＜4 000拷贝/mL的Ⅲ期NPC患者，对2个周期诱导化疗后达完全缓解或部分缓解者采用降低剂量（60 Gy）的放化疗，同样降低了外周神经病变等毒副反应发生率[33]。尽管上述降低放射治疗剂量的研究均未报道颞叶损伤的发生情况，但理论上降低放射治疗剂量是减少颞叶损伤最直接的方式，期待后续随访结果的更新。

对于局部晚期NPC，根据诱导化疗后肿瘤范围进行放射治疗靶区勾画似乎也是可行的策略。Zhao等[34]的一项单臂Ⅱ期研究纳入112例局部晚期NPC患者，根据诱导化疗后的肿瘤勾画靶区，对于诱导化疗后残存肿瘤给予68 Gy，诱导化疗后消失区域为CTV1，给予60 Gy，其10年局部区域控制和生存结果与历史对照相似，全组颞叶损伤发生率仅9%，且均为1级。一项Ⅲ期多中心随机对照研究初步结果显示，根据诱导化疗后的大体肿瘤勾画靶区可以缩小靶区体积，显著降低两侧颞叶的2%体积接受的最大剂量（D2%），且不影响3年总生存[35]。尽管未提及颞叶损伤的发生率，但是根据诱导化疗后的肿瘤范围勾画靶区显著改善了患者的认知功能（认知功能评分为65.13分 *vs.* 75.61分，P=0.003）。

3.3 质子、重离子技术的应用　早年的一项研究显示，在复发NPC中，质子治疗计划与IMRT计划相比肿瘤覆盖度和适形度相似，颞叶的平均剂量均显著减低[36]，相似的结果也在之后的一项研究中得到证实[37]。最新发表的一项包含77例非转移性NPC的小样本研究显示，调强质子放射治疗（intensity-modulated proton therapy，IMPT）仅3.8%出现3级以上晚期毒性，而IMRT组3级以上晚期毒性为16.3%，经过倾向配比后，IMPT组3年总生存稍高于IMRT组，但差异无统计学意义[38]。Wang等[39]的研究则分别采用调强碳离子放射治疗（intensity-modulated carbon-ion radiotherapy，IMCT）和IMRT制定了10例复发NPC患者的计划，肿瘤覆盖度和适形度无明显差异，而IMCT计划中颞叶、脑干等剂量学参数显著降低。综上，质子、重离子的物理学特性确实转化为剂量学上的优势，但能否带来晚期毒性的减少仍需大样本研究和长时间随访证实。

4 总结与展望

总体而言，放射治疗技术的进步使得NPC放射性颞叶损伤的发生率降低、严重程度减轻，但仍然无法完全避免。合理的剂量限制是维持肿瘤覆盖度欠佳与邻近颞叶潜在损伤之间平衡的主要策略，精准勾画颞叶、合理减低治疗强度、放射治疗再计划以及放射治疗新技术的应用为更好地保护正常组织提供了可能，有助于降低颞叶损伤的发生率。

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