

听神经瘤治疗进展

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【摘要】 听神经瘤是脑桥小脑角区常见的良性肿瘤,治疗方法主要包括随访观察、立体定向放射治疗和显微外科手术,各有优缺点,标准治疗方法尚存争议。随着对肿瘤进程和治疗认识的深入,较为认可的治疗方案是,初诊的无症状性听神经瘤可采取随访观察或立体定向放射治疗,随访期间若每年肿瘤生长 > 2 mm 即建议放射治疗;体积较大(直径 > 20 mm)的听神经瘤可采取显微外科手术切除,肿瘤体积大、向腹侧生长较多和脑干压迫严重者,可考虑近全切除或次全切除等相对保守的手术策略,并辅以适当的放射治疗;难治性听神经瘤可将靶向药物作为辅助治疗选择。

【关键词】 神经瘤,听; 放射外科手术; 显微外科手术; 药物疗法; 综述

Progress on the treatment of vestibular schwannoma

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【Abstract】 Vestibular schwannoma is a common benign tumor in the cerebellopontine angle (CPA). The treatment strategy mainly includes follow-up observation, stereotactic radiosurgery (SRT) and microsurgery. Although there are still disputes about the standard treatment methods, each method has its advantages and disadvantages. With the deep understanding of tumor progression and various treatment methods, the widely acceptable treatment is follow-up observation or SRT for the early asymptomatic vestibular schwannoma. During the follow-up period, if the annual tumor growth is more than 2 mm, SRT should be recommended. Large vestibular schwannoma (diameter > 20 mm) can be resected by microsurgery. For large tumors with more ventral growth and severe brain stem compression, relatively conservative surgical strategies such as near total resection (NTR) or subtotal resection (STR) can be considered, supplemented with appropriate SRT. Targeted drug therapy can be used as adjunctive therapy selection for refractory vestibular schwannoma.

【Key words】 Neuroma, acoustic; Radiosurgery; Microsurgery; Drug therapy; Review

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听神经瘤亦称前庭神经鞘瘤,是临床常见的颅内占位性病变,约占颅内肿瘤的 5%^[1],可引起耳鸣、眩晕等症状,并最终导致听力下降,因此恰当的治疗十分重要。听神经瘤的治疗受多种因素影响,如患者年龄、一般状况、治疗选择、医疗机构、医师主观经验、肿瘤大小等,尤其在很大程度上取决于肿

瘤大小^[2]。治疗方法主要包括随访观察、立体定向放射治疗(SRT)和显微外科手术,尽管关于标准治疗方法一直存有争议,但每种方法各有其优缺点^[3],体积较小(直径 ≤ 20 mm)的肿瘤通常采用随访观察或立体定向放射治疗;体积较大(直径 > 20 mm)或生长较快者,建议通过显微外科手术予以切除。本文对目前听神经瘤的治疗观点进行综述,以期规范治疗提供参考。

一、随访观察

听神经瘤的生长速度十分缓慢,肿瘤直径每年仅增长约 1 mm^[1]。从肿瘤进展角度看,约 67.3% 的患者在为期 5 年的随访观察期间无肿瘤进展^[4];从

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听力角度看,初诊有实用听力的患者随访观察 3 年实用听力保留率为 75%、5 年时为 60%、10 年时仍有 40%^[5];而且肿瘤体积越大、肿瘤增长速度越快,随访观察期间实用听力损失风险越高^[6]。由此可见,早期无症状性听神经瘤可采取随访观察的治疗策略,但应定期行 MRI 检查以监测肿瘤进展,尽早发现短期内肿瘤生长过快的患者^[4,7]。Ismail 等^[8]对随访观察与立体定向放射治疗效果进行比较,发现肿瘤直径 < 2 cm 且保留实用听力的听神经瘤患者,随访观察(5.9 ± 1.6)年,约 68.75% 患者保留实用听力;而放射治疗组随访(7.1 ± 1.9)年仅 15.38% 患者保留实用听力,因此建议,直径 < 2 cm 的听神经瘤应随访观察,随访期间若出现肿瘤进展再考虑立体定向放射治疗。最新研究显示,即使肿瘤无进展,患者听力下降仍逐渐加重,但肿瘤进展与性别、年龄、初始听力和肿瘤大小无关联性,仅与延迟诊断有关,其结论是,随访观察期间主动接受监测和管理(即定期行 MRI 检查和听力监测)的患者有望达到与积极治疗患者相当的生活质量^[9]。

二、立体定向放射治疗

目前认为,立体定向放射治疗适用于 Koos I ~ III 级听神经瘤^[1],此类患者若就诊时听力正常,放射治疗的肿瘤控制率可达 92% 且面神经功能障碍发生率低于显微手术(2% 对 10%),其疗效(肿瘤控制率)虽略低于显微手术(98%),但听力保留率与显微手术相当(59% 对 56%)^[10]。初诊采取随访观察的小体积听神经瘤患者,若随访期间每年肿瘤增长 > 2 mm 则应行立体定向放射治疗,可获得较好的肿瘤控制率^[4],但约 4% 患者治疗后出现迟发性肿瘤再生长,故需继续进行密切的临床和影像学随访^[11]。对于 Koos IV 级听神经瘤,立体定向放射治疗可取得与 Koos I ~ III 级听神经瘤相当的长期肿瘤控制率和神经功能保留率,提示立体定向放射治疗的适应证可进一步扩大^[12]。(1)伽马刀放射外科(GKRS):以 γ 射线照射肿瘤是放射治疗的主要方法^[13],可持续改善患者听力并使肿瘤体积明显缩小,其并发症发生率与显微手术相当,约为 19%^[1]。研究显示,伽马刀放射治疗的短期疗效良好,肿瘤控制率高达 92% ~ 97.1%^[1],尤其是 Gardner-Robertson 听力分级 I 级患者,经伽马刀放射治疗后实用听力及其他脑神经功能长期预后良好,虽然各项研究纳入对象的年龄不同(< 40 或 < 54 岁),但均推荐听力良好的年轻患者采取伽马刀放射治疗^[1]。Teyateeti 等^[14]对放

射治疗剂量进行研究,发现 40% 等剂量线可获得 50% 等剂量线相同的长期肿瘤控制率,且更利于听力保留。Huang 等^[15]研制了一种人工智能(AI)算法,可自动分割和区分听神经瘤囊性与实体成分,他们发现囊性成分占比大、信号强度高的听神经瘤对伽马刀放射治疗的反应更佳,但伽马刀放射治疗的长期疗效并不理想,治疗 10 年后仅有 23% 患者保留实用听力,且肿瘤控制率与听力保留率之间并不平衡,即肿瘤控制率较高的患者听力保留率可能较低。亦有研究显示,肿瘤体积 < 0.3 cm³^[1]和肿瘤直径每年增长 \geq 2.5 mm 的患者,伽马刀放射治疗后肿瘤体积进一步增大的可能性较大^[16]。因此,临床应严格把握伽马刀放射治疗的适应证。(2)分次立体定向放射治疗(FSRT):分次放射治疗系指随着时间的推移自小剂量逐渐增量照射肿瘤,可以有效阻止肿瘤生长,但需长期随访方能确认肿瘤的完全缓解。分次立体定向放射治疗结合了立体定向放射治疗的准确性和分次放射治疗的有效性,使 53% 患者听力保留、9% 患者听力提高,同时使 35% 患者肿瘤体积缩小^[1];其并发症发生率低于立体定向放射治疗(10% 对 19%)且症状轻微,仅表现为皮肤红斑、疲劳和头痛等,是治疗听神经瘤的有效方法^[1]。(3)其他:其他放射治疗方法的综合效果欠佳,如单次分割直线加速器立体定向放射外科(SFSRT)仅可使 48% 患者听力保留、38% 患者肿瘤体积缩小,但其并发症发生率高达 37%,主要是神经功能障碍和视乳头水肿^[1]。质子重离子技术具有独特的电离辐射剂量学特性,分割质子放射治疗(FPRT)可以更好地保留听力,但晚近一项 II 期临床试验并未发现分割质子放射治疗可以达到保留实用听力的目的^[17],且耳蜗的照射剂量越高、听力损失越严重,提示听力与耳蜗照射剂量相关,而与治疗方式无关联性。

三、外科手术治疗

近年来,显微外科手术在听神经瘤治疗中的占比逐渐下降,一般认为,直径 > 20 mm 的听神经瘤可考虑手术切除^[4]。而晚近研究对手术指征更新,Macielak 等^[18]认为,肿瘤向脑桥小脑角区延伸 14 ~ 20 mm,应考虑手术切除;Gadot 等^[19]通过机器学习(ML)算法提出,肿瘤直径 > 16 mm 或症状进行性加重者,应考虑手术切除。手术的目的是全切除肿瘤、保留面神经和前庭蜗神经功能并减少并发症,随着手术显微镜的普及和应用,对脑桥小脑角的显微解剖研究更加深入,手术疗效日益提高。研究显

示,肿瘤大小、Koos 分级和切除程度是术后肿瘤进展或再次干预(手术或放射治疗)的预测因素,肿瘤切除程度是无进展生存期(PFS)的独立预测因素,年龄、肿瘤大小和切除程度是面神经功能预后的预测因素^[20]。总体而言,肿瘤体积越小、切除程度越高,术后无进展生存期越长,再次干预的可能性越小;而肿瘤体积越大、切除程度越高,虽可减少肿瘤进展或复发风险,但手术相关并发症发生率越高^[7]。术后实用听力保留率亦与肿瘤大小相关,肿瘤越小、实用听力保留率越高^[21],直径 < 3 cm 的听神经瘤,若就诊时听力正常,显微手术后肿瘤控制率较高,听力保留率与放射治疗相当,但面神经功能障碍发生率较高^[10]。由此可见,体积较小但症状呈进行性加重的听神经瘤患者,应在尚有实用听力时尽早手术切除,如果肿瘤体积较大、向腹侧生长较多且脑干压迫症状较严重,可选择近全切除或次全切除等相对保守的手术策略,并辅以放射治疗,可在较好控制肿瘤生长的同时,降低并发症发生率^[22]。对于放射治疗后复发的听神经瘤,可以选择显微手术切除,即使无法达到全切除,术后残留的少量肿瘤灶也相对稳定,因此不宜追求全切除^[23];对于伽马刀放射治疗失败的听神经瘤患者,显微手术切除仍可获得较好的面神经功能保留率和长期肿瘤控制率^[24]。

显微手术可使约 50% 的患者保留术前听力,仅 1% 的患者术后听力提高,但手术相关并发症发生率约 19%,主要为脑脊液漏、脑水肿、头痛、硬膜外血肿和脑膜炎等^[1]。常用的手术入路包括乙状窦后入路、中颅窝入路、迷路入路等,其中,乙状窦后入路手术后听力保留率为 12% ~ 57%,与肿瘤大小相关^[25];中颅窝入路手术更利于实用听力的保留且听力维持更稳定^[26-27];迷路入路手术可获得更好的肿瘤控制以及面神经和前庭蜗神经功能预后^[4]。de Boer 等^[28]通过对迷路入路手术后肿瘤复发预测模型的观察,发现约 63% 患者复发率 < 1%。经迷路入路手术的常见体位是侧卧位,该体位易摆放,但存在脑脊液释放困难、解剖位置不明确和助手操作困难等缺点;半坐位可通过重力引流血液和脑脊液,有助于术野显露、手术解剖和连续双手操作,因此认为,对于体积较大的听神经瘤,半坐位手术的肿瘤切除率更高、面神经功能保留率更高^[29],但存在静脉空气栓塞等潜在风险。一项对比分析侧卧位与半坐位对临床结局(肿瘤切除率、面神经功能保

留率、听力保留率、体位摆放时间、手术时间、住院时间、住院费用、手术相关并发症)影响的单中心随机对照临床试验正在进行中,以期可以为体积较大听神经瘤的个体化手术体位的选择提供依据^[30]。

随着神经内镜技术越来越多地应用于颅底手术,虽然大多仅作为显微手术的辅助方法,但亦有神经内镜下听神经瘤切除术的报道^[31-33]。神经内镜技术可减小手术创伤,有助于解剖结构的观察和术区重要结构的识别。对于散发性听神经瘤,神经内镜手术的肿瘤切除率和术后面神经功能保留率与显微手术相当,甚至在 Koos I ~ II 级体积较小的听神经瘤中,肿瘤切除率和面神经功能保留率更高,但听力保留率差异较大(50% ~ 77.8%)^[31]。神经内镜技术不仅可以辅助经典入路手术,还有助于开拓新入路,例如,神经内镜下耳囊入路听神经瘤切除术可显著提高患者生活质量,尤其适用于局限于内听道且无实用听力的体积较小听神经瘤的切除^[33]。

术中电生理监测包括脑干听觉诱发电位(BAEP)和面神经肌电图等,有助于提高手术安全性和面神经功能保留率。如果术前即存在面神经麻痹,术中面神经监测可能出现假阴性结果,此类患者的肿瘤切除率较低^[34]。近年来,中间神经逐渐受到关注,显微手术切除听神经瘤时可能损伤中间神经,从而出现术后功能障碍(79%),尤以干眼症最常见^[35]。为保护面神经及中间神经功能,手术不全切除肿瘤,但残留肿瘤大小与术后残留肿瘤生长相关,因此术后第 1 年应密切监测临床症状及 MRI 等影像学改变,之后每年进行一次 MRI 检查,至少持续 5 年,此后继续规律监测,但可延长监测间隔^[36]。

四、靶向药物治疗

对于手术治疗或伽马刀放射外科治疗存在高风险的难治性听神经瘤,亟待延缓肿瘤生长的药物。针对放射治疗耐受的 II 型神经纤维瘤病(NF2)相关听神经瘤,血管内皮生长因子-A(VEGF-A)/血管内皮生长因子受体(VEGFR)靶向药物(如贝伐单抗)有可能成为一线治疗选择。研究显示,NF2 相关进行性听神经瘤患者接受贝伐单抗治疗后,约 41% 肿瘤体积缩小、20% 听力改善^[37],中位治疗时间为 16 个月^[38]。进行性散发性听神经瘤患者接受贝伐单抗治疗后肿瘤体积亦明显缩小^[39]。NF2 一线免疫治疗药物——VEGFR1/2 多肽疫苗正在 NF2 相关进行性听神经瘤患者中进行临床试验,目前已显示出其可缩小肿瘤体积和改善听力的疗效^[40]。针对

SH3PXD2A-HTRA1 融合基因产物的靶向药物可能对散发性听神经瘤有效^[41]。蛋白激酶抑制剂有助于阻止肿瘤进展, He 等^[42]探讨 P53 在听神经瘤中的作用机制, 即通过关键蛋白 Merlin 调节细胞周期以抑制肿瘤进展, 他们发现伊拉斯汀在体外可触发铁死亡以发挥抗肿瘤作用, 进而提出伊拉斯汀有可能作为听神经瘤的靶向治疗药物。肿瘤微环境在听神经瘤的发生发展中具有重要作用^[43], 也有可能成为显微手术或放射治疗的辅助方法^[44-46]。

五、展望

上述治疗方案各有其优缺点, 且单一学科医师制定治疗决策时可能受个人经验与认知的限制, 因此, 应采用多学科诊疗模式以为听神经瘤患者提供最佳的个体化治疗方案^[47]。多学科诊疗模式由神经外科、耳鼻咽喉头颈外科、放射科、肿瘤放疗科等学科参与其中, 可以对患者进行全面的症状评估和神经影像学检查, 进行高度专业化的协作手术和团队内诊断与治疗, 从而改善面神经和前庭蜗神经功能、提高生活质量、减少失访。听神经瘤患者的预后应重点关注肿瘤的控制、听力和面神经功能的保留。研究显示, 肿瘤大小[包括肿瘤体积($r = 0.340$, $P < 0.01$)、肿瘤直径($r = 0.400$, $P < 0.01$)、Koos 分级($r = 0.360$, $P < 0.01$)和 Samii 分级($r = 0.360$, $P < 0.01$)]与术后面神经功能呈中等相关, 且术后重度面神经麻痹主要见于体积较大(Koos IV 级和 Samii 4b 级)的听神经瘤患者^[48]。由此可见, 肿瘤体积预测术后面神经功能的价值优于肿瘤直径, 因此, 根据肿瘤大小尤其是体积以及肿瘤进展速度等, 开展多学科诊疗模式, 进行个体化综合治疗, 有助于提高听神经瘤的治疗效果。然而, 目前关于听神经瘤多学科诊疗模式的研究较少, 尚待开展更多临床实践进一步探讨。

利益冲突 无

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· 小词典 ·

中英文对照名词词汇(一)

- 癌胚抗原 carcinoembryonic antigen(CEA)
- 半高全宽 full width half maximum(FWHM)
- 标准摄取值 standardized uptake value(SUV)
- 标准摄取值率 standard uptake value rate(SUVR)
- 表观扩散系数 apparent diffusion coefficient(ADC)
- 表皮生长因子受体 epidermal growth factor receptor(EGFR)
- 病情稳定 stable disease(SD)
- 波形蛋白 vimentin(Vim)
- 哺乳动物雷帕霉素靶蛋白 mammalian target of rapamycin(mTOR)
- 部分缓解 partial response(PR)
- 常染色体显性视神经萎缩 dominant optic atrophy(DOA)
- 超声吸引手术刀 cavitron ultrasonic surgical aspirator(CUSA)
- 迟发性面瘫 delayed facial paralysis(DFP)
- 纯音听阈均值 pure tone average(PTA)
- 磁共振波谱 magnetic resonance spectrum(MRS)
- 大脑脚性幻觉 peduncular hallucinosis(PH)
- 单胺氧化酶B monoamine oxidase B(MAO-B)
- 单纯疱疹病毒 herpes simplex virus(HSV)
- 单次分割直线加速器立体定向放射外科 single-fraction linac stereotactic radiosurgery(SFSRS)
- S-100蛋白 S-100 protein(S-100)
- 等剂量线 isodose line(IL)
- 第三脑室脊索样胶质瘤 chordoid glioma of the third ventricle(CGTV)
- 动脉自旋标记 arterial spin labeling(ASL)
- 端粒酶逆转录酶 telomerase reverse transcriptase(TERT)
- 短时间反转恢复 short-tau inversion recovery(STIR)
- 多学科诊疗模式 multi-disciplinary team(MDT)
- 额颞叶变性 frontotemporal lobar degeneration(FTLD)
- 额颞叶痴呆 frontotemporal dementia(FTD)
- 恶性外周神经鞘膜瘤 malignant peripheral nerve sheath tumor(MPNST)
- 耳蜗电图 electrocochleography(EcochG)
- 分次立体定向放射治疗 fractionated stereotactic radiotherapy(FSRT)
- 分割质子放射治疗 fractionated proton radiotherapy(FPRT)
- Brodmann分区 Brodmann's area(BA)
- 复合动作电位 compound action potential(CAP)
- 伽马刀放射外科 Gamma knife radiosurgery(GKRS)
- 高分辨率磁共振成像 high-resolution magnetic resonance imaging(HRMRI)
- 骨外黏液样软骨肉瘤 extraskeletal myxoid chondrosarcoma(EMC)
- 国际行为异常型额颞叶痴呆诊断联盟 International Behavioural Variant Frontotemporal Dementia Criteria Consortium(FTDC)
- 国家食品药品监督管理局 State Food and Drug Administration(SFDA)
- 横窦-乙状窦夹角 transverse-sigmoid sinus junction(TSSJ)
- 横纹肌样肿瘤易感综合征 rhabdoid tumor predisposition syndrome(RTPS)
- 肌阵挛性癫痫伴破碎红纤维 myoclonic epilepsy with ragged-red fibers(MERRF)
- 基底动脉 basilar artery(BA)
- 基于体素的分析 voxel-based analysis(VBA)
- 基于体素的形态学分析 voxel-based morphometry(VBM)
- 脊髓前动脉 anterior spinal artery(ASA)
- 加拿大蒙特利尔神经病学研究所 Montreal Neurological Institute(MNI)
- O⁶-甲基鸟嘌呤-DNA 甲基转移酶 O⁶-methylguanine-DNA methyltransferase(MGMT)
- 甲胎蛋白 alpha-fetoprotein(AFP)
- 甲状腺转录因子-1 thyroid transcription factor-1(TTF-1)
- 简易智能状态检查量表 Mini-Mental State Examination(MMSE)
- 胶质纤维酸性蛋白 glial fibrillary acidic protein(GFAP)
- 进行性核上性麻痹 progressive supranuclear palsy(PSP)
- 聚合酶 γ 相关疾病 polymerase γ -related disorders(POLG-RDs)
- 扩散张量成像 diffusion tensor imaging(DTI)
- 酪氨酸激酶抑制剂 tyrosine kinase inhibitors(TKIs)
- 立体定向放射治疗 stereotactic radiotherapy(SRT)
- X连锁 α 地中海贫血伴精神发育迟滞综合征蛋白 X-linked α -thalassaemia retardation syndrome protein(ATRX)
- 临床痴呆评价量表 Clinical Dementia Rating Scale(CDR)