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髓母细胞瘤术后放射治疗

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摘 要

髓母细胞瘤为儿童颅内常见肿瘤之一。手术后放疗为常规治疗手段。根据术后残留分为中危组和高危组。随着放疗技术提高，调强治疗和质子治疗在术后应用越来越广泛。不同放疗技术对生存影响和不良反应也存在差异。本文对髓母细胞瘤手术后放疗的现状进行了综述。

关键词

髓母细胞瘤，放疗，质子治疗

Postoperative Radiation Therapy for Medulloblastoma

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Abstract

Medulloblastoma is one of the most common intracranial tumors in children. Postoperative radi-

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otherapy is the conventional treatment. The patients were divided into the standard risk group and the high risk group according to the postoperative residue. With the improvement of radiotherapy technology, intensity modulated therapy and proton therapy are more and more widely used in postoperative patients. Different radiotherapy techniques also have different effects on survival and adverse reactions. This article reviews the current status of postoperative radiotherapy for medulloblastoma.

Keywords

Medulloblastoma, Radiotherapy, Proton Therapy

1. 引言

髓母细胞瘤是儿童常见的颅内肿瘤之一，Cushing 于 1930 年首次报道[1]，约占小儿颅内肿瘤的 20%左右，占整个后颅窝肿瘤的 40%以上。高发年龄为 5~6 岁，约有 20%左右发生在 2 岁以下的婴儿，85%的病例在 15 岁以前发病，男性发病略多于女性，5 年生存率在 50%~80%。现在认为有髓母细胞瘤 4 种分子亚型，分别为 WNT、SHH、Group3 和 Group4，不同亚型之间具有明显的统计学、临床和遗传学特征[2]-[8]。

髓母细胞瘤的治疗包括手术、放疗和辅助化疗。建议对所有患者做最大程度的手术切除。如果影像学支持诊断，没有必要行活检手术。术后行放疗患者全切除或次切除与单纯活检手术相比总生存率明显提高[9] [10]。除外科手术外，放射治疗和内科治疗方案也因疾病程度和年龄差异较大。对 3 岁以上儿童，根据术后残留肿瘤体积和有无肿瘤播散分为中危组和高危组。中危组定义为术后肿瘤残留体积 < 1.5 平方厘米，脑脊液细胞学阴性，核磁检查无脑部和脊柱转移证据。高危组定义术后肿瘤残留体积 ≥ 1.5 平方厘米和/或出现扩散[11]。

2. ≥3 岁患者术后放疗

对于中危组年龄 ≥ 3 岁术后患者，以前全脑全脊髓放疗(craniospinal irradiation, CSI) 36 Gy，局部后颅窝加量总量为 54 Gy。近年来由国际儿科肿瘤学会和儿童肿瘤组共同主导研究，CSI 剂量已由原来的 36 Gy 降 23.4 Gy~24 Gy，同时辅助化疗[12] [13] [14] [15]。Thomas E. Merchant 采取全脑全脊髓放疗 23.4 Gy，后颅窝放疗 36 Gy，局部瘤床 54 Gy，同时配合化疗。5 年无事件生存(event-free survival, EFS)和后颅窝复发率分为 83%和 4.9%，颞叶、耳蜗和下丘脑剂量明显降低[14]。放疗期间的化疗方案通常为每周应用长春新碱。目前对于中危组患者推荐术后放疗后化疗持续大约 1 年，方案为 8 周期顺铂、洛莫司汀(Lomustine, CCNU)和长春新碱，间隔 6 周。Packer 等人在 1988 年首次提出此方案，5 年的无病生存大约为 80% [16]。用环磷酰胺替代洛莫司汀类似方案中在统计学上无差异[17] [18] [19]。

对于高危组年龄 ≥ 3 岁术后患者术后通常给予“标准剂量”放疗，CSI 36 Gy，后颅窝及转移病灶给予推量至 55.8 Gy，同步给予化疗。尽管理想的化疗方案尚未有数据支持。II 期试验对于就诊已出现转移的患者放疗同步长春新碱，随后应用洛莫司汀、长春新碱和顺铂显示 5 年无进展生存率 67%。需说明此试验是对分期为 M1、M2 和 M3 的患者一起分析[19]。出现转移的患者 5 年无进展生存仅为 40% [20]。

有研究通过加速超分割放射减轻放疗毒性反应。在此研究中 33 名患者接受了术后 2 个月诱导化疗，方案包括依托泊苷、甲氨蝶呤、环磷酰胺和卡铂。随后对 10 岁以下患者超分割放疗 CSI 31.2 Gy，后颅窝推量至 59.7 Gy。对 10 岁以上患者超分割放疗 CSI 39 Gy，后颅窝推量至 60 Gy，另外对结节转移灶再增加 9 Gy。超分割治疗达到完成缓解(complete response, CR)后再应用长春新碱和洛莫司汀维持化疗一年。对没有达到 CR 患者接受高剂量塞替派为基础的自身移植。5 年 EFS 为 70% [20]。

关于放疗介入的时机，研究表明放疗延期会导致疗效的下降，即便是应用诱导化疗。在 SIOP PNET4 研究中术后超过 49 天放疗与术后早放疗相比 5 年 EFS 明显下降[15]。目前推荐术后放疗不超过 40 天，最好在术后 28 天内开始放疗[21]。

3. <3 岁患者术后放疗

对于<3 岁患者可以采用应用维持化疗(丙卡巴嗪、甲氨蝶呤和长春新碱)来推迟放疗或者对后颅窝和瘤床行放疗。低风险组术后 2~4 周开始行化疗，维持化疗直至 3 岁后或进展后开始行放疗。2.5~3 岁高风险组(术后残留或出现转移)患者 2 后期化疗后维持化疗，直至 3 岁后行放疗[22]。一项针对 8 个月至 3 岁无转移髓膜细胞瘤前瞻性试验(P9934 试验)中入组 8 个月至 3 岁患者，术后诱导 4 周期化疗后行后颅窝(18 或 23.4 Gy)和瘤床(累积 50.4 或 54 Gy)适形放疗。4 年 EFS 和总生存(overall survival, OS)分别为 50% ± 6% 和 69% ± 5.5%。促纤维增生性/结节性髓母细胞瘤预后较好，4 年 EFS 为 58% ± 8% [23]。

4. 复发后治疗

髓母细胞瘤复发性患者预后较差，5 年存活率大约为 25% [24] [25]。多种治疗策略包括再次手术、再程放疗、立体定向放射外科、自身干细胞挽救的高剂量化疗、低剂量口服依托泊苷、使用生物靶向制剂或以上组合使用。治疗局限性复发比弥漫性复发治疗更有利[25]-[34]。复发后行再程放疗在中危组和高危组均提高了 5 年和 10 年 OS，再程放疗做为姑息治疗延长了复发患者生存时间。从影像表现可以看出再程放疗增加了组织坏死发生率[28] [29]。对于放疗后复发患者，有研究应用大剂量卡铂、塞替派和依托泊苷联合自身干细胞移植治疗[26]。也有研究对复发患者应用贝伐珠单抗联合伊利替康 ± 替莫唑胺方案化疗，中位进展时间 11 个月，中位 OS 为 13 个月，能够达到客观缓解且毒性反应较小[31]。

5. 光子与质子治疗比较

髓母细胞瘤的特点是沿脑膜扩散，因此需要 CSI。这将导致治疗后晚期的毒副作用，包括智力低下、激素下降、身材矮小和听力丧失。CSI 体积较大，晚期毒性反应和第二原发肿瘤发生率较高。在 20 世纪 90 年代开始 CSI 剂量开始减少。有报道经过长期随访仍有半数患者出现 3~4 级晚期中枢神经毒性反应[35]。故对儿童肿瘤治疗，应尽量减少照射剂量并保护正常组织，维持认知功能和内分泌功能，减轻对生长发育的影响。

有研究对调强放疗(Intensity modulated radiation therapy, IMRT)与传统放疗计划进行比较，IMRT 对≥110%处方剂量体积降低了 7%，对于≥95%处方剂量体积增加了 8%。IMRT 提高靶区的均匀性[9]。Parker W 等对 IMRT、三维放疗和二维放疗进行比较，三者 V95%分别为 100%、96%和 98%，V107%分别为 3%、38%和 37%。IMRT 具有更好的适形性和能够更好保护正常组织[10]。

质子治疗的优势可以使儿童肿瘤患者正常组织受照射明显减少。日本研究发现儿童恶性肿瘤质子治疗晚期毒性反应发生率较低[36] [37]。质子治疗能够明显减少耳蜗、颞叶、海马和下丘脑垂体轴剂量。由于保护了这些结构的功能，质子治疗与光子放射治疗相比，能更有效保持智力[38] [39] [40]。有研究比较质子组患者在智商、记忆力和理解力方面均优于光子治疗组[41]。Torunn I Yock 应用质子治疗后 3~4 级

耳毒性双侧发生率9%，单侧发生率为7%。神经内分泌下降5年发生率为55%，生长激素缺乏最常见。无心脏、肺和胃肠道晚期毒性反应[40]。单侧海马受照射剂量与神经认知功能存在明显相关。N. Patrik Brodin等对质子、调强和适形放疗比较，质子治疗能够更好的保护海马区域[42]。质子治疗或IMRT能够减少在全脑全脊髓照射中心脏和肝脏受量[43] [44] [45] [46]。质子和IMRT与普通放疗相比90%耳蜗剂量从101.2%降低到2.4%和33.4%，50%心脏范围剂量降低到29.5%和0.5% [44]。

Bree R Eaton等对中危组髓母细胞瘤行多中心研究化疗加光子治疗和化疗加质子治疗疗效分析，认为光子和质子治疗在无复发生存和总生存率方面无差别，光子和质子显示相同的疾病控制[39] [47]。

全脑全脊髓放疗普遍存在导致内分泌失调的问题。Bree R. Eaton等对77例患者化疗联合质子或光子内分泌影响研究。质子治疗明显降低甲状腺功能减退(23% vs 69%, $P < 0.001$)和性激素缺乏(3% vs 19%, $P = 0.025$)的发生风险。对生长激素(53% vs 57%)、肾上腺功能不全(5% vs 8%)和性早熟(18% vs 16%)方面无明显差别[38]。Benjamin J Moeller等对23例脊索瘤患者质子治疗后进行听力监测。平均耳蜗照射剂量30 Gy和平均累积顺铂303 mg/m^2 (范围298~330 mg/m^2)时听力明显下降($P < 0.05$)。Rui Zhang等对儿童接受放疗引起的第二原发癌风险进行研究。4 岁髓母细胞瘤患者行全脑全脊髓质子治疗和光子治疗，全脑全脊髓给予23.4 Gy处方剂量，3野6 MV光子治疗和4野质子治疗，使用基于电离辐射生物学效应的剂量风险模型来评估八个组织/器官的第二次癌症风险。质子全中枢放疗和光子全中枢放疗第二原发癌发病率的总归因风险分别为7.7%和92%，终生风险比率为0.083。在儿童髓母细胞瘤患者质子治疗比光子治疗引起第二原发癌风险低[48]。质子治疗在国内开展较少，费用也比光子治疗明显增加。在巴西的研究中质子治疗更具有成本效益[49]。

6. 预后分析

在过去30年，髓母细胞瘤患儿的无进展生存率和总生存率逐步提高，在2000年开始逐渐趋于稳定，5年生存率50%~80%。髓母细胞瘤分为中危组和高危组，中危组全脑全脊髓放疗后局部加量同时应用化疗，5年无进展生存率为80%和85%之间[17]。Roger J. Packer报道大于3岁患者5年EFS和总生存率为81%和86%。EFS与年龄、性别，种族及脑干受累均无关[16]。大部分患者5年内无病生存保持稳定，后期5%~10%出现复发。然而后期复发可能是继发高级别胶质瘤，十年内第二恶性肿瘤发生率大约为4.2% [50]。高危组患者在诊断时已出现扩散，5 年存活率在 50%~65%之间，与中危组的复发率类似。在诊断时有无转移对复发模式没太大差别。也有报道不同病理类型生存预后差异，促纤维增生型预后明显好于大细胞间变型[51]。

发病时小于三岁的患儿比相对较大患儿预后差。目前仍不清楚是存在生物学差异，还是因为未行全脑全脊髓放疗。化疗后无论是否对原发部位行放疗，报道生存率范围在25%~45% [52]。分子分型对预后和治疗有潜在启示价值。未来将分子亚型纳入治疗方案中有望改善生存率和治疗后的生活质量。

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