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颅底脊索瘤放射治疗

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摘　要

颅底脊索瘤为少见肿瘤之一，生长缓慢，但具有高的复发倾向。手术是主要治疗手段，由于局部解剖结构影响，手术受到一定限制。通常采取手术后放疗或根治性放疗。随着放疗技术提高，立体定向放疗、调强治疗、质子治疗和碳离子治疗应用越来越广泛。不同放疗技术对生存影响和不良反应也存在差异。本文对颅底脊索瘤放疗的现状进行了综述。

关键词

颅底脊索瘤，放疗，质子治疗，碳离子放射治疗

Radiotherapy for Chordoma of Skull Base

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Abstract

Chordoma of skull base is one of the rare tumors with slow growth but high recurrence tendency. Surgery is the main method of treatment. Due to the influence of local anatomical structure, surgery is limited, usually taking postoperative radiotherapy or radical radiotherapy. With the im-

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provement of radiotherapy technology, stereotactic radiotherapy, intensity modulated therapy, proton therapy and carbon ion radiotherapy are more and more widely used. Different radiotherapy techniques also have different effects on survival and adverse reactions. In this paper, the current status of radiotherapy for chordoma of skull base is reviewed.

Keywords

Chordoma of Skull Base, Radiotherapy, Proton Therapy, Carbon Ion Radiotherapy

1. 引言

脊索瘤是一种特殊类型的骨肿瘤，来源于脊索残余物[1]。属于低度恶性肿瘤，发病率低，仅占原发恶性骨肿瘤的 1%~4% [2]。最常见发病部位是脊柱两端，位于骶尾部脊索瘤占 50%~60%，位于颅底约为 25%~35%，位于脊柱约为 15% [2] [3] [4]。男性多于女性，与其他骨和软组织肿瘤相比，较少出现转移[5]。颅底脊索瘤约占中枢神经系统肿瘤 0.2%，主要有 3 种病理类型，经典型、软骨样型和去分化型，去分化型约占 5% [6] [7]。病程较长，起病隐匿，解剖结构复杂造成手术难度较大，术后复发率较高[8]。疾病后期可出现肺脏、肝脏、骨骼、皮下和淋巴结等器官转移[7]。对放化疗不敏感，5 年和 10 年总生存率约为 65%和 30% [6]。

2. 放疗在治疗中的地位

手术是治疗原发性和/或复发性脊索瘤的主要手段。手术的结果与预后相关。手术针对特定的肿瘤部位，目的是能够取得清晰的切除边界。多个回顾性研究显示手术对预后存在影响。有证据表明斜坡脊索瘤侵袭性手术应当谨慎，通常不选择广泛的切除术。放疗在手术治疗存在局限性的脊索瘤中起到重要作用，特别是大部分切除或次全切术后辅助治疗和不能手术患者根治性治疗。Choy 等认为辅助放疗是最重要的影响进展时间的变量[9]。手术应以边缘阴性、没有局部浸润为目标，辅助高剂量放疗达到最佳肿瘤控制[7]。这种情况仅适合部分患者，临床预后结果取决于初次就诊治疗。对于手术后残存和不能完全手术切除患者应当建议性高剂量放射治疗。病理是一个影响外科手术的重要方面。肿瘤含有胶状物可流入到手术腔内，导致肿瘤切缘常常出现复发。脊索瘤的这特性显示多学科治疗的重要性。最近一项研究显示术前放疗可降低手术区域污染种植的风险[10]。

颅底区域肿瘤对放疗医师具有挑战性。近年来，放疗技术不断进步，包括影像技术、治疗计划、剂量传递和患者重复摆位的准确性。应用伽马刀、射波刀和专用直线加速器进一步提高靶区覆盖、适形度和降低危及器官受量。另外，质子治疗(proton therapy, PT)和碳离子治疗(carbon-ion radiotherapy, CIRT)放疗技术的进步，对粒子治疗肿瘤产生了巨大影响，成为关注的热点[11]。

3. 术后辅助放射治疗

颅底脊索瘤通常采用手术加辅助放疗的方法，单独手术后局部复发率为 58% [12]。化疗作用有限，辅助放疗能够提高局部控制率[12] [13]。Masaru Takagi 等对 24 例颅底脊索瘤患者回顾性研究发现，手术后放疗较单纯放疗明显提高了局部控制率(local control, LC)、无进展生存(progression-free survival, PFS)和

总生存(overall survival, OS)，P 值分别为 0.048、0.028 和 0.012 [14]。术后立即放疗与复发后再放疗相比 10 年生存率为 65% vs 0% [15]。放疗一般采用高剂量 PT、伽马刀和射波刀[6]。Rich 报道低于 60 Gy 放疗 LC 仅有 28% [16]。脊索瘤对放疗不敏感，需要给与更高的放疗剂量。在常规分割(1.8~2 Gy/次)至少 74 Gy [16]。这也明显超出了周围正常器官限量。随着放疗技术的进步，调强放疗(intensity modulated radiation therapy, IMRT)或容积调强(volumetric modulated arc therapy, VMAT)也能够达到危及器官限量要求。IMRT 比适形放疗(conformal radiotherapy, CRT)存在明显优势，特别是一些不规则靶区和临近重要器官[17]。

Sunil Krishnan 等对 25 例颅底脊索瘤患者放疗，中位剂量为 50.4 Gy (45~54 Gy)，大部分患者采用外照射结合放射外科。2 年和 5 年 LC 分别为 89%和 32%。分析认为放射外科剂量<15 Gy 和≥15 Gy 的 4 年射野内局部控制率分别为 50%和 100% (P = 0.03) [18]。Jürgen Debus 等术后采用立体定向放疗(stereotactic radiotherapy, SRT)，中位等中心剂量为 66.6 Gy，2 年和 5 年 LC 分别为 82%和 50%，OS 分别为 97%和 82%。没有患者因急性反应中断治疗，1 例出现晚期反应，在治疗后 25 个月出现右侧偏瘫[19]。Arjun Sahgal 等对 24 例颅底脊索瘤采用图像引导 IMRT，中位放疗剂量为 76 Gy。5 年 OS 和 LC 分别为 85.6%和 65.3%。其中有 8 例患者出现晚期放射损伤，包括听力损伤、甲状腺功能减退、垂体功能减退、前庭神经损伤、复视和第二原发肿瘤[20]。随着放疗剂量增加，局部控制率明显提高，同时不良反应也会增加，特别是晚期不良反应。

4. 立体定向放疗

现代立体定向放疗技术包括立体定向放疗外科(stereotactic radiosurgery, SRS)和立体定向放疗(stereotactic radiotherapy, SRT)，主要通过伽马刀、射波刀或专用直线加速器来实施。进一步提高了靶区适形度和降低了危及器官受量。Hasegawa 等报道 30 例患者应用 SRS 边缘平均剂量为 14 Gy，平均靶区体积为 19.7 cm^3。5 年和 10 年 LC 分别为 76%和 67% [12]。Martin 等对 18 例患者应用 SRS，边缘平均剂量为 16.5 Gy，5 年 LC 为 53% [21]。Linton T. Evans 等对放疗后复发或转移患者行 SRS 治疗。与再次手术或化疗相比 SRS 提高了无治疗部位进展(P = 0.006)。经过 SRS 治疗病灶均无进展，也无严重放疗反应[22]。

5. 粒子放射治疗

脊索瘤对化疗及传统光子放疗并不敏感。由于 PT 的精确剂量分布，与传统光子放疗相比较可给予高的放射剂量和危及器官更低的受量[23]。几个研究报道了脊索瘤对放疗抗拒，需要 60 Gy 及更高剂量达到局部控制[24]。由于超过周围正常组织耐受(脊髓、脑干和视神经)，传统 X 线放疗很难达到高的剂量[25]。近几十年，PT 和 CIRT 用于颅底脊索瘤[26] [27]。PT 的物理特性减少了横向散射，与 X 线放疗相比更好的剂量分布。因此，PT 能够加强局部控制，减少晚期毒性反应。

Matthias Uhl 等报道 CIRT 治疗 155 例颅底脊索瘤长期随访结果，中位剂量 60 Gy，每次 3 Gy。3 年、5 年和 10 年 LC 分别为 82%、72%和 54%，3 年、5 年和 10 年 OS 分别为 95%、85%和 75%。年龄和推量计划体积是预后影响因素[27]。Alberto Iannalfi 进行前瞻性研究比较 PT 和 CIRT 在治疗颅底脊索瘤。入组 135 例患者，分别给于 74 Gy，37 次和 70.4 Gy，16 次。5 年 LC 分别为 71%和 84% (P = 0.15)，5 年 OS 分别为 82%和 83%。严重毒性(3~4 级)反应发生率为 12%，两组之间无差异[28]。Jinpeng Zhou 等对 25 篇文章进行荟萃分析显示术后 CRT、SRT、PT 和 CIRT 四种放疗措施 3 年 OS 分别为 70%、92%、89%和 93%，5 年 OS 分别为 46%、81%、79%和 87%，10 年 OS 分别为 21%、40%、60%和 45%。3 年 OS、5 年 OS 和 10 年 OS 可见 CRT 相比 SRT、PT 和 CIRT 明显生存优势(P < 0.001)。5 年 OS 统计中 SRT、PT 和 CIRT 之间无差异。在 10 年 OS 统计中 PT 比 SRT 具有生存优势(P = 0.004)，SRT 与 CIRT 之间无

差异[29]。在这研究中均为手术后辅助放疗，PT 随着时间延长逐渐显示出生存获益。目前尚无大型随机对照试验提高有利证据，根据回顾性研究和荟萃分析认为粒子治疗优于光子放疗。

6. 复发模式和预后因素

尽管进行根治手术和辅助放疗，仍有超过 50%出现复发，大部分复发在治疗后 5 年以上[30]。Jacob L Freeman 等报道 5 年内、5~10 年和>10 年复发率分别为 55%、10%和 35%，局部和远处进展的中位时间分别为 13.5 个月和 51 个月[31]。Shaan M Raza 等报道中位进展时间为 24.9 个月，单独手术患者占 55%，手术后辅助放疗患者占 45% [32]。复发后存活时间数据有限，再行局部治疗后 5 年和 10 年 LC 分别为 47%~76%和 42%~71% [33]。尽管 PT 存在优势，仍然有较高复发率。Mohammed Alahmari 分析 11 个质子治疗的研究，共 511 例患者，平均复发时间为 34.5 ± 15.2 个月[34]。Linton T Evans 等对复发患者行再次手术、SRS 或化疗，显示 SRS 唯一提高无治疗部位进展[22]。

研究发现肿瘤体积、部分切除、高龄和 KI-67 > 3%是不良预后因素[35]。Xiyin Guan 等对 91 例患者进行 PT 或 CIRT，多因素分析肿瘤体积(>60 cc)是影响 PFS 的因素(P = 0.045)，再程放疗和肿瘤体积是影响 OS 的预后因素[36]。E.R. Gatfield 等研究认为 PTV (Planned target volume)与 LC 相关，PTV ≤ 110 ml 患者的预后更好[37]。也有研究认为免疫微环境与预后相关，T 细胞免疫球蛋白和 TIM3^{+}TIL (mucin-domain 3 tumor infiltrating lymphocyte)计数与肿瘤浸润(P = 0.01)和 KPS (Karnofsky score) (P = 0.037)相关。TIM3^{+}TIL 是 LRFS (Local progression free survival)和 OS 的独立预后因素[38]。VEGF (Vascular endothelial growth factor)与肿瘤免疫微环境相关，VEGFR1 和 VEGFR2 不仅在血管内皮表达，在肿瘤细胞内也存在表达。复发患者较初诊患者 VEGFR1 表达明显增加[35]。

7. 结论

综上，颅底脊索瘤尽管生长缓慢，复发率较高，目前仍然难以治愈。采取多种模式治疗延缓肿瘤复发，提高总生存率。放疗在术后辅助中占有重要地位，采用何种策略能够提高局部控制率和减轻后期放疗反应需要不断探索。

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