**Advances in Clinical Medicine** 临床医学进展, 2025, 15(9), 1977-1986
Published Online September 2025 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2025.1592708

Hans汉斯

# 骶尾部脊索瘤的治疗进展

**童　洁[1]，陈政宇[2*]**

[1]湖南中医药高等专科学校基础医学部，湖南　株洲
[2]湖南旺旺医院脊柱外科，湖南　长沙

收稿日期：2025年8月23日；录用日期：2025年9月17日；发布日期：2025年9月26日

## 摘　要

**脊索瘤是一种相对罕见的原发性骨肿瘤，起源于胚胎发育过程中脊索组织的残余物。骶尾部脊索瘤理想的治疗需要多学科联合协作完成。在此基础上，广泛完整地外科手术切除联合调强放射疗法(IMRT)是目前延长预后生存期的有效方式。分子靶向治疗和免疫治疗等辅助保守治疗也带来一线新的曙光，但因脊索瘤的罕见性，目前仍缺乏多中心、高质量的对比研究和前瞻性随机临床试验来评估真实疗效。完整的手术切除是治疗骶尾部脊索瘤的核心。切除范围不足、肿瘤体积过大、原发位置等因素与预后不良相关。在非手术治疗研究方面：探究新型放疗的最佳剂量、组合方式；阐明分子靶向治疗和免疫治疗的具体干预机制和疗效评估是下一步研究重心。这篇综述探讨了现阶段骶尾部脊索瘤的治疗方式和影响预后的相关因素，并根据目前的文献提供了最佳治疗方案的指导。**

## 关键词

**脊索瘤，骨肿瘤治疗，文献综述**

# Advances in the Treatment of Sacrococcygeal Chordoma

**Jie Tong[1], Zhengyu Chen[2*]**

[1]Department of Basic Medicine, Hunan Traditional Medical School, Zhuzhou Hunan
[2]Department of Spine, Hunan Want Want Hospital, Changsha Hunan

Received: Aug. 23rd, 2025; accepted: Sep. 17th, 2025; published: Sep. 26th, 2025

## Abstract

**Chordoma is a relatively rare primary bone tumor that originates from the remnants of notochordal tissue during embryonic development. The ideal treatment of sacrococcygeal chordoma requires**

*通讯作者。

文章引用: 童洁, 陈政宇. 骶尾部脊索瘤的治疗进展[J]. 临床医学进展, 2025, 15(9): 1977-1986.
DOI: 10.12677/acm.2025.1592708

**multidisciplinary collaboration. On this basis, extensive and complete surgical resection combined with intensity-modulated radiation therapy (IMRT) is currently an effective way to prolong the prognostic survival period. Adjuvant conservative treatments such as molecular targeted therapy and immunotherapy also bring a new ray of hope. However, due to the rarity of chordoma, there is still a lack of multi-center, high-quality comparative studies and prospective randomized clinical trials to evaluate the real efficacy. Complete surgical resection is the core of the treatment of sacrococcygeal chordoma. Factors such as insufficient resection range, excessive tumor volume, and primary location are associated with poor prognosis. In terms of non-surgical treatment research: exploring the optimal dose and combination mode of new radiotherapy; clarifying the specific intervention mechanisms and efficacy evaluation of molecular targeted therapy and immunotherapy are the focus of the next research. This review discusses the current treatment interventions for sacrococcygeal chordoma and the related factors affecting prognosis and provides guidance on the best treatment options based on current literature.**

## Keywords

**Sacrococcygeal Chordoma, Bone Tumor Treatment, Literature Review**



## 1. 引言

脊索瘤是一种在临床上相对罕见的原发性中低度恶性骨肿瘤，目前多数学者认为是起源于胚胎发育过程中残余的脊索组织恶变所致，多发生于人体中轴骨[1]。据美国最新大数据统计，其年平均发病率约为 8.8/1000 万人[2]，占所有恶性骨肿瘤的 1%~4%，主要多见于 50 岁以上中老年人，偶有儿童及青少年发病报道[3] [4]。脊索瘤的好发部位包括：骶尾部(约 56%)、蝶骨与枕骨交界处(约 38%)、脊柱的其他部位(约 6%)。脊索瘤在临床病例报道中常生长缓慢，具有发病隐匿、症状不典型、早期较少发生转移等特点[5]。但因伴有较强的局部侵袭性[6]，且常毗邻重要的神经和组织，随着时间增长会危害到人体的健康，影响日常生活质量甚至生命。然而，关于脊索瘤的标准化治疗方式，目前仍缺乏共识。对于骶尾部脊索瘤大多数学者认为在相对安全的范围内行最大程度的手术切除(Enbloc spondylectomy)，术后辅以精准靶向放射治疗，可取得一定的临床疗效和延长患者生存周期[7] [8]，是治疗骶尾部脊索瘤相对有效的手段。但因广泛切除容易损伤神经和骨组织、肌肉、韧带等稳定结构，同时带来了一系列不良并发症[9] [10]。因此，更优良、更合理的治疗方案有待进一步研究和完善。

本篇综述重点探讨关于骶尾部脊索瘤的治疗手段及相关预后因素。并从以下多方面进行了讨论：主要临床表现、外科手术治疗及肿瘤切除边缘、肿瘤节段位置和手术入路、肿瘤体积大小、术后的功能性缺陷、立体放射疗法、分子靶向药物化疗、免疫治疗前景、疾病复发率和生存率等。

## 2. 骶尾部脊索瘤概述

骶尾部脊索瘤的临床症状较隐匿且不典型，多数患者表现为慢性下腰部疼痛或骶尾部胀痛[11]，可放射至臀部。当局部肿瘤侵犯至骶孔或压迫邻近骶神经时可导致尿失禁、肠道功能障碍、会阴区感觉异常、下肢神经根症状等[1]。极少数病例报道：转移性脊索瘤可有皮肤、手足远端局部包块、或伴红斑与紫色结节等不典型表现[12] [13]。骶骨脊索瘤好发于 40 岁以上的中老年患者(男性发病率高于女性)。由于骶尾部脊索瘤生长缓慢，且骶骨前区容积较大，肿瘤往往生长至较大体积时才会出现明显的临床症状，当

患者出现症状再就诊时，大多数已处于疾病的中晚期[14]，在 Enneking 分期系统里多为 IIA、IIB 阶段表现。部分患者在确诊前，因非特异性的初期症状可维持长达 1~2 年，导致诊治不能及时。在起初，即便患者因“腰疼”行常规的腰椎计算机断层扫描(CT)和腰椎磁共振成像(MRI)检查，通常不会延伸扫描至骶 2 椎体以下水平，作者团队分析，这可能也是导致该疾病发生早期漏诊率的因素之一。

## 3. 治疗方法

### 3.1. 手术治疗

手术切除是骶尾部脊索瘤最主要的治疗方式[15]。而安全的外科切除边界是手术治疗的核心，是术后疾病局部复发和延长生存周期重要的预后指标之一[8] [16]。Xie 等[17]回顾性分析 54 例骶骨脊索瘤的治疗结果，未达到广泛切除患者 41 例(其中边缘切除 34 例、囊内切除 7 例)，经平均 3.8 年随访，术后整体复发率高达约 55.5% (30/54 例)。Varga 等[18]通过对已行手术治疗的 167 例骶尾部脊索瘤患者随访评估，研究结果表明：广泛的整体切除术(Enbloc resection)可明显减少术后的局部复发率。Zuckerman 等[10]对 50 名行骶骨脊索瘤整块切除术的患者行多因素 Cox 回归分析研究，平均随访 5.3 年统计得出：手术的病理切缘切除阴性者，发生局部复发的风险显著降低。综上分析，广泛安全的外科边界切除联合多学科治疗是改善患者预后较好的方案[7] [19]，并且术中尽量避免肿瘤破裂，减少医源性局部种植带来的复发风险[20]。总的来说，术前影像学资料分析和术后病理切片观察是评估手术是否达到切除安全范围的重要手段[7]。

临床中发现：由于骶尾部容积较大，给骶骨区脊索瘤的生长提供了空间条件，同时因骶骨脊索瘤的特殊位置和复杂解剖结构，术者出于对术后功能和生活质量方面考虑[21] [22]，希望能保留部分骶神经，所以在临床现实中手术切除往往较难达到广泛安全的外科边界，增加了术后疾病复发率。同时有研究表明，因广泛的骨切除会造成患者术后早期更大程度的疼痛和中轴骨稳定性丢失[23]，会直接影响患者日常生活质量。所以，当行高位骶骨切除或骶髂关节切除后，必须考虑骨盆重建，以维持躯体的生物力学稳定[24] [25]。

#### 3.1.1. 手术治疗影响因素

有研究表明，脊索瘤原发病灶在骶骨内的水平位置，同样也是一个重要的预后变量[14] [26]。Yang 等[27]，经一项 22 例骶骨脊索瘤患者采取选择性动脉栓塞联合手术切除治疗的回顾性研究，分析后发现：骶 3 (S3)远端以下节段肿瘤的连续无病生存周期(Continuous disease-free survival time, CDFS)明显大于 S3 以上水平的肿瘤，且随着骶骨脊索瘤的位置越高，CDFS 越短，两者差异具有统计学意义。同样，有国内学者对 34 例复发性骶骨脊索瘤患者经 12~144 个月时间随访分析表明，肿瘤平面高于 S3 者复发率显著高于 S3 以下节段患者，骶骨内肿瘤的水平位置也是局部复发的高危因素[26]。

另外一方面，作者团队考虑：由于骶尾部脊索瘤在生长过程中，大多是从尾端向头端缓慢延伸，当肿瘤延伸抵达至骶骨近端时，更大程度反映了病灶可能已穿透浸润骶骨近端，在一定程度上，这势必会增加疾病的复发率。

然而，对于骶尾部脊索瘤而言，手术入路应取决于肿瘤的节段位置、体积大小、侵袭范围、病理结果和手术团队的经验等[16] [24]。高位的骶骨脊索瘤(S3 以上)而言，众多学者认为前后联合入路更合适[28]-[30]，因肿瘤常累及骶骨、直肠、会阴区肌肉群或骶髂关节，前后联合入路可在保护骨盆前方脏器和血管的情况下[31]，行足够范围的截骨切除术。从解剖结构上分析，骶骨呈上宽下窄、后凸的形态。对于 S3 以下节段采取单纯后路骶骨切除术治疗[32]，即可达到广泛切除边界[33]，又能缩短一定手术时间。值得注意的是，无论是选择前后联合入路还是单纯后路，术前行选择性动脉栓塞术(Preoperative selective

arterial embolism, PSAE)，可明显减轻手术出血量、优化术中视野[34]-[36]，是作为术前一种辅助治疗的良好选择。

从原发肿瘤的体积方面分析预后和复发风险，目前众多学者尚未达成统一共识。但是较多数研究者认为：骶尾部脊索瘤 > 8 cm 是复发、转移以及降低总体生存率的指标之一[37]。Patel 等[15]，经一项大数据库的多变量分析表明，肿瘤体积大小 ≥ 10 cm 的患者，5 年生存率低于较小体积肿瘤患者(5 年生存率：0~5 cm: 72.2%；5~10 cm: 65.8%；≥10 cm: 54.8%)，且具有统计学差异。意味着肿瘤体积增大与生存率下降之间可能存在反比例关系，但仍然需要更多的样本量和多中心研究数据进一步证明。同时，较大体积的骶尾部脊索瘤在技术程度上更难以完整切除，术中操作过程中会增加周围组织被肿瘤细胞污染的风险。Pipola 等[38]，建议当肿瘤体积过大，且不允许阴性边缘切除的情况下，可以考虑氩气冷冻手术治疗，减少术中医源性肿瘤细胞污染概率，为术后放射治疗提高一定疗效。也有学者提出不同看法，Cherix 等[39]，经 5 年随访研究表明，骶尾部脊索瘤患者如果只行单纯冷冻消融术，术后复发率极高应慎重选择。

肿瘤生长率(Tumor growth rate, TGR)在基于影像学图像分析上，可提供肿瘤体积大小随时间变化的定量信息。Passeri 等[40]，对 32 例患者进行一项回顾性研究表明，术前 TGP 值较高的患者，与复发风险和远期预后较差有比较高的相关性，这对预测肿瘤的无进展生存期有一定指导作用。

#### 3.1.2. 手术后的功能性缺陷

为了保证安全的外科切除边界时，较大范围的切除可能会避免不了的牺牲双侧或单侧的腰骶丛神经，导致术后运动功能、膀胱、胃肠道和性功能障碍等。Moran 等[41]，经一项回顾性研究表明，神经根切除或损伤的节段范围与术后功能性缺陷大致相对应。接受了全骶骨切除术的患者大部分伴有会阴部鞍区麻木症状[24]。患者术后的行走步态、运动功能主要依赖于保留的 L5 和 S1 神经根；而 S2 神经根不仅在膀胱和肠道功能方面至关重要，在阴茎和阴蒂根部区域的感觉中也起重要作用[22] [42]；S3 神经与性功能方面较密切[43]。而 S4 神经根与肛周感觉相关。有研究表明，即便只保留了 S3 以上节段的单侧神经，也有较高的几率维持膀胱、胃肠道的部分正常生理功能[44] [45]。总而言之，在术后生理功能维持方面，即使只保留单侧骶神经也明显优于双侧全切者，特别是 S3 及以上节段的神经支配功能比远端更为关键[22]。所以，医师在术前沟通时，有必要向患者和家属告知肿瘤切除术后相关的功能性缺陷风险。

### 3.2. 放射疗法

虽然骶尾部脊索瘤较耐受辐射，但目前阶段，除了积极的外科手术之外，放射治疗仍然是相对重要的干预手段[8] [46] [47]。常规的光子放疗大多数不能满足肿瘤内的有效辐射剂量水平。相对而言，质子及重离子在脊索瘤的治疗中更具优势[48]-[50]。“粒子(质子、重离子)”在组织中的表现与光子不同：它们可在肿瘤限定的深度瞬间释放大剂量的能量，且不像光子会穿透组织。因此，向目标肿瘤内提供高剂量辐射的同时，又可限制或减少对周围正常组织的辐射剂量，具有靶向性[51]。Walser 等[52]，通过回顾性分析对 60 例确诊为骶骨脊索瘤患者，术后均接受质子放疗，4 年周期内局部控制率约 77%，且第 4 年后无毒副作用总体存活率约 91%。表明质子治疗骶骨脊索瘤具有一定安全性和有效性。Fujiwara 等[53]，对 11 例术后辅以放射治疗的回顾性研究表明，采取辅助质子放疗可较好地控制局部早期情况。同样，Patel 等[15]，经多中心的大数据研究分析后得出：与传统的放射治疗相比，接受质子放射疗法的患者总体存活率有显著提高。但仍然需要进一步探究质子治疗的最佳剂量和组合方式，以便更好的优化疗效。关于粒子剂量方面，学者 Dial 和 Tsugawa 等[54] [55]，认为采用大剂量(65~70.4 Gy)联合先进的调强放射治疗(IMRT)或立体定向放射技术(SRS)，对于手术切缘阳性的患者可以从辅助放疗中明显获益。在实际中，对于放射治疗的毒副作用也不可忽视。Beddok 等[56]，分析 41 例接受过放射治疗的骶骨脊索瘤患者，经

2 年以上随访研究表明：纤维化、马尾神经综合征、疲劳和疼痛是最常见的晚期毒性反应，直肠炎和膀胱炎在质子放疗后的发生率也占比较高。总之，多数文献的结果都表现出了比较积极的正面影响，但是围手术期多模式放射治疗策略的真正效果仍存在一定争议。在顾及临床疗效的同时，放疗的毒性风险和患者生活质量这两个方面也需高度重视[57]。

### 3.3. 分子靶向药物治疗

据往期多数文献报道，传统的化疗药物对脊索瘤的作用非常有限[58] [59]。随着研究进一步深入，采用药物控制脊索瘤在将来有望成为一种新的干预方式，特别是去分化型的变异脊索瘤患者中[60] [61]。作用于信号传导通路的分子靶向药物在脊索瘤治疗中也取得了一定价值的进展。

受体酪氨酸激酶(Receptor tyrosine kinase, RTK)信号通路靶向药物：脊索瘤行分子检测表明，在脊索瘤患者中，RTK 通路均有不同程度的过度活化表现[62]，作为一种特殊类型的跨膜蛋白酪氨酸激酶，RTK 基本多以单体形式存在，无明显活性。最常见的受体酪氨酸激酶有：表皮生长因子受体(EGFR)、血小板源生长因子受体(PDGFR)，均与脊索瘤预后负相关[63] [64]；如伊马替尼，通过抑制哺乳动物雷帕霉素 mTor 信号通路下调 EGFR 表达，从而控制脊索瘤进展[65]。

相关研究表明，以伊马替尼为首的靶向药物在脊索瘤的治疗中具有一定治疗或研究意义[66]。Stacchiotti 等[67]，行一项药物干预脊索瘤的II期研究，对纳入研究的 50 名脊索瘤患者每天服用 800 mg/d 伊马替尼，约 70%患者能达到病情稳定期，且中位无进展生存时间为 9 个月，表明伊马替尼在此疾病中可能具有相关抗肿瘤活性。随着时间的推移，也有学者持另类观点[68]，认为伊马替尼对进展期脊索瘤的治疗效果非常有限，还伴随着不可忽视的毒性作用。阿帕替尼作为 VEGFR 的一种抑制剂，近来也引起了多数研究者的关注。Liu 等[69]，对 30 名已确诊晚期脊索瘤患者行一项单中心研究表明，阿帕替尼具有良好活性，其毒副反应程度也可接受，可能是治疗晚期脊索瘤的一种新的选择。人们对脊索瘤的发生机制逐渐探究，现多数学者认为多模式联合靶向治疗可提高无进展生存周期[70] [71]，表现出新的可行性方向。但现阶段仍然缺乏多中心、大样本临床研究及更高级别的证据支持。

### 3.4. 免疫治疗

随着研究学者对免疫机制的深入研究，免疫应答、免疫逃逸机制、免疫微环境在肿瘤发病以及治疗作用方面逐渐引起重视[72]。对免疫微环境的研究表明，髓系细胞在脊索瘤肿瘤实质中存在显著浸润，而 T 细胞则倾向于被排除在肿瘤实质之外，且在间质中浸润程度较高。平均而言，髓系细胞相较于 T 细胞更接近靶肿瘤细胞，这可能导致效应 T 细胞功能受限。因此，未来脊索瘤免疫治疗联合方案应致力于降低髓系细胞的抑制功能，同时增强细胞毒性 T 细胞与 NK 细胞的杀伤能力[73]。

从脊索瘤方面分析，对于肿瘤相关的免疫治疗、预测肿瘤表型及进一步探究人体免疫系统与脊索瘤之间的相互作用至关重要[74] [75]。Brachyury 是一种参与脊索发育的重要调节转录因子[76]，在绝大部分脊索瘤患者中具有特异性高表达。它参与调控脊索瘤细胞的发育，Brachyury 蛋白被认为是脊索瘤的一种敏感、特异性标志物[77] [78]，同时也是重要的免疫治疗靶点[79]。现阶段正在积极研究 Brachyury 基因的免疫疗法，也许在治疗脊索瘤方面具有一定指导意义[80]。Heery 等[81] [82]，前期I期临床研究表明，将表达 Brachyury 基因的重组酵母菌疫苗(GI-6301)接种至脊索瘤患者中，可表现出特异性免疫反应，刺激 CD8+、CD4+等 T 淋巴细胞免疫应答。同时也首次证明了这种治疗性肿瘤疫苗的安全性和免疫原性，并为II期研究的探索提供了一定理论依据。近期，DeMaria 等[83]，在一项随机、对照实验中，对晚期不能手术切除的脊索瘤患者进行 GI-6301 疫苗(或安慰剂)联合放射治疗。研究结果虽提示重组 GI-6301 疫苗和放射联合疗法没有显示出协同的抗肿瘤作用。但该团认为 Brachyury 基因仍是脊索瘤发育及治疗方面

的一个良好靶点，值得更深入的研究。免疫治疗联合其他疗法(药物化疗、靶向治疗)的研究也在进行，但是在评估其对脊索瘤的真实疗效、治疗时机和策略方面任重道远[21] [80]。

## 4. 结论

骶尾部脊索瘤是一种罕见的原发性恶性骨肿瘤，局部侵袭性强、复发率高、预后效果不佳。总而言之，骶骨脊索瘤理想的治疗需要脊柱外科、肿瘤内科、病理科、放疗科和放射科及专科护理等多学科联合协作完成。在此基础上，广泛、完整地外科手术切除联合调强放射疗法(IMRT)是目前临床治疗的相对有效方式，可明显延长预后。然而，在制定治疗策略时，需与患者及家属沟通“手术/非手术”治疗的利弊，以及治疗后生活方式变化之间的平衡。分子靶向治疗和立体定向放射疗法在现阶段已表现出令人鼓舞的结果，免疫疗法联合其他保守治疗也带来一线新的曙光。但因骶尾部脊索瘤的罕见性，目前缺乏高质量的对比研究，且使得前瞻性随机临床试验具有较大挑战性。

结合文献综合分析，在非手术治疗研究方面，下一阶段的研究重心在：探究质子放疗的最佳剂量、时间和优化组合方式；阐明分子靶向治疗、肿瘤免疫治疗的具体干预机制、治疗时机和疗效评估。

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