

儿童骨和软骨肉瘤：诊断及治疗的新型进展和未来方向

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摘 要

原发性骨肿瘤(Primary bone sarcomas)是一类对于临床医生、放射科医生和病理科医生来说难以识别和分类的罕见恶性肿瘤, 具有较高的致死率。最常见的原发性骨肿瘤包括骨肉瘤(osteosarcoma)、软骨肉瘤(chondrosarcoma)和尤文肉瘤(Ewing sarcoma)。儿童骨肉瘤和软骨肉瘤已经成为新的儿童原发性骨肿瘤的研究关注焦点, 其恶性程度往往较高, 预后较差, 死亡率较高, 因此进行早期诊治非常重要。如何提高骨肉瘤和软骨肉瘤患儿的生存率和生活质量也是目前治疗研究的重点。我们回顾了相关文献, 在此试对儿童骨肉瘤和软骨肉瘤现有的诊断和治疗进行分析, 对新型相关进展进行述评, 以明确临床诊治要点和分析未来发展方向。

关键词

儿童, 骨肉瘤, 软骨肉瘤, 诊断, 治疗

Pediatric Osteosarcoma and Chondrosarcoma: Recent Advances and Future Directions in Diagnosis and Treatment

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Abstract

Primary bone sarcomas are a group of rare malignant tumors can be challenging for clinicians, radiologists, and pathologists to identify and classify, and they are associated with a high mortality rate. The most common primary bone tumors include osteosarcoma, chondrosarcoma, and Ewing sarcoma. Recent research has focused on pediatric osteosarcoma and chondrosarcoma, as these tumors tend to be more aggressive, have a poorer prognosis, and result in a higher mortality rate in children. This underscores the importance of early diagnosis and treatment. Current therapeutic research aims to improve the survival and quality of life for children with osteosarcoma and chondrosarcoma. In this context, we reviewed the relevant literature to analyze the existing methods for diagnosing and treating pediatric osteosarcoma and chondrosarcoma. We will also discuss recent advancements in this field to clarify key points in clinical diagnosis and treatment while exploring future directions for development.

Keywords

Children, Osteosarcoma, Chondrosarcoma, Diagnosis, Treatment

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1. 引言

原发性骨肿瘤(Primary bone sarcomas)是一类对于临床医生、放射科医生和病理科医生来说难以识别和分类的罕见恶性肿瘤。世界卫生组织的研究提示,原发性骨肿瘤发病率在登记的恶性肿瘤中占比不到0.2% [1],但是具有较高的致死率[2]。最常见的原发性骨肿瘤包括骨肉瘤(osteosarcoma)、软骨肉瘤(chondrosarcoma)和尤文肉瘤(Ewing sarcoma),骨肉瘤主要来源于成骨细胞、间充质细胞,尤文肉瘤主要来源于骨髓、原始神经外胚层或神经嵴细胞的圆形细胞,软骨肉瘤则可来自于透明细胞、间充质细胞转化产生的软骨细胞[3] [4]。原发性骨肿瘤中骨肉瘤最为常见,通常发生于长骨的干骺端,如股骨远端、胫骨近端和肱骨近端等,最常见于膝关节周围[5];第二常见的为软骨肉瘤[3] [6] [7],通常发生于长骨近端,尤其是下肢,其次是骨盆和肋骨[8]-[10]。通常认为,骨肉瘤的发生频率存在两个特异的年龄峰值,第一个峰值在生后的第二个十年间,也即儿童和青少年发病高峰[5] [8];第二个峰值则从生后第四个十年开始增加,在第六个十年后到达顶峰[9] [11]。软骨肉瘤虽然在儿童及青少年中并不多见[12] [13],但其通常在生长板闭合后数年内可能存在急性发展[14],并可以通过先前存在的软骨帽是否重新生长来进行识别[15],在近二十余年中也出现多例有关儿童软骨肉瘤报道[7] [16]-[18],已经成为新的儿童原发性骨肿瘤的研究关注点。

对于儿童和青少年骨肉瘤及软骨肉瘤而言,进行早期诊治是非常重要的。研究表明,实现早期诊治的儿童软骨肉瘤生存率明显高于成人软骨肉瘤[7]。儿童骨肉瘤发展至晚期发生肺转移后,5年生存率可降低23%至33%,并且生存时间更短[19]-[22]。虽然儿童骨肉瘤和软骨肉瘤预后较差,死亡率较高,但是随着现代医疗技术水平逐渐提升,儿童骨肉瘤和软骨肉瘤生存率有明显升高[23]-[25]。如何提高骨肉瘤和软骨肉瘤患儿的生存率和生活质量是目前治疗研究的重点。我们回顾了相关文献,在此试对儿童骨肉瘤和软骨肉瘤诊断和治疗的新型进展进行述评。

2. 诊断现状和探索

儿童骨肉瘤最初常表现为病变部位局部肿大,伴频繁且持续的进行性非机械性骨骼疼痛,症状表现主要集中在夜间,应当对其进行有效的影像学检查。初步影像学检查一般为两个平面的常规X线检查,当X线检查不能明确排除恶性肿瘤时,应当对整个受累部位及相邻关节进行磁共振成像检查(Magnetic Resonance Imaging, MRI)。MRI在目前被认为是判断四肢、脊柱和骨盆肿瘤分期的最佳的检查方式[3]。此外,计算机断层扫描(Computed tomography, CT)可以提供更多有关骨骼受累的额外信息,如是否存在钙化、骨膜形成、骨质破坏等,可以作为其他原发部位的首选影像学检查,以及用于明确肿瘤是否发生远处转移。儿童骨肉瘤的明确诊断主要基于病理形态学检查结果,目前尚没有特别明确的特异性分子检测诊断。但是有学者通过研究发现,骨肉瘤中存在一部分骨肉瘤干细胞(osteosarcoma stem cells, OSCs),能够自我更新以维持自身的干细胞样特性,他们认为骨肉瘤最初可能是起源某个单细胞克隆,通过不断复制最终形成了一个多克隆、异质性巨大的实体肿瘤[26][27]。OSCs最初由Gibbs等人发现[28][29],其他学者完成了一系列研究相继确认了人骨肉瘤以及犬骨肉瘤中OSCs的存在,并证实了OSCs具备较强致癌能力以及对化疗药的耐药性[30]-[32]。在这些研究基础上,更多的学者尝试进行了细胞分选,即利用OSCs表面的某些特异性蛋白,使用免疫学方法以及流式细胞技术将其分选出来,并取得了一定的研究成果,CD133、CD117、Stro-1以及CD271在先前的研究中均相继被证明可能是OSCs的表面标记[33]-[37],但目前上述细胞表面标记物尚缺乏作为OSCs表面的特异性蛋白的权威数据与研究,尚不支持确保分离出来的细胞是OSCs。有研究针对骨肉瘤发生肺转移的患儿进行采用iTRAQ标记的蛋白组学技术筛查,发现骨肉瘤肺转移患儿血清中存在多种差异表达蛋白,一定程度上证实了相关临床应用的价值[38]。除针对OSCs的研究,还有学者对醛脱氢酶(aldehyde dehydrogenase, ALDH)进行研究发现,其活性不仅被用于在某些恶性肿瘤如白血病、乳腺癌等中作为鉴定肿瘤干细胞的关键表面标记,在骨肉瘤细胞中ALDH的活性表达同样明显升高[39][40]。骨肉瘤可以自然发生,其发生的危险因素包括既往放射治疗(radiotherapy, RT)、骨骼Paget病、存在家族性遗传异常的Li-Fraumeni综合征、Werner综合征、Rothmund-Thomson综合征、Bloom综合征和遗传性视网膜母细胞瘤相关的家族性遗传异常等[41]。从上述介绍中可以发现,骨肉瘤中相当一部分患者是发生在遗传性疾病的情况下,因此对每个儿童骨肉瘤病例都应当详细了解其家族史,如果有可疑的家族遗传病史,则建议可以与医学遗传学医生合作进行适当遗传学检查,以求在早期阶段得到有效诊治[42][43]。这种由遗传学因素引发骨肉瘤发生的情况可能是某些地区人群的发病率较高的主要原因。

原发性软骨肉瘤包括传统软骨肉瘤(conventional chondrosarcoma)、去分化软骨肉瘤(dedifferentiated chondrosarcoma, DCS)、间充质软骨肉瘤(mesenchymal chondrosarcoma, MCS)、透明细胞软骨肉瘤(clear-cell chondrosarcoma)和粘液样软骨肉瘤(myxoid chondrosarcomas);继发性软骨肉瘤则通常是由良性软骨病变的进展演变而来,包括骨软骨瘤、内生软骨瘤、多发性遗传性外生骨疣、Ollier病和Maffucci综合征等。值得说明的是,在过去较长时间段中,骨骼外的粘液样软骨肉瘤被认为是软骨性肿瘤的一种,但由于其未显示明确的软骨分化,2020年世界卫生组织更新了新的肿瘤分期和分类,开始建议其归类为分化不明

确的间充质肿瘤[14][44]。Rosenberg 等[45]将软组织肉瘤依据组织病理学特征分为三个等级：高分化(1级)、中分化(2级)和低分化(3级)。成人中最常见的原发性骨肿瘤就是传统软组织肉瘤，通常发生在 20 至 30 岁之间[8]，大多数是局部侵袭性或低级别、高分化(1级)、非转移性的肿瘤。另外的去分化软组织肉瘤、间充质软组织肉瘤和透明细胞软组织肉瘤则是罕见的原发性软组织肉瘤亚型[3]，却在儿童软组织肉瘤中频频出现，它们是高级别、中低分化(2、3级)的肉瘤，往往具有严重的侵袭性，预后较差[46]。儿童软组织肉瘤主要的初始症状是病变部位肿胀和疼痛。大多数病例的首发表现是局部肿块，后来可能伴有不同程度的疼痛[47][48]。这些临床表现通常是非特异性的症状和体征，加上患儿往往不能有效地进行病情表达，这些因素都加大了儿童软组织肉瘤的识别难度，尤其是当病变部位位于脊柱或较为深部的部位，如腹膜后和骨盆时，通常难以及时发现[49]。影像学检查对于儿童软组织肉瘤具有较大的诊断意义。软组织肉瘤病变位于髓腔内时，在 X 线检查中通常可发现有不同程度的钙化灶，表现为点状、弧形或环状高密度影[47][48][50]；同时由于儿童软组织肉瘤具有侵袭性，还有可能观察到成骨破坏、骨皮质侵蚀以及骨膜反应等表现，少数情况下可能还存在有软组织包块。有研究指出，去分化软组织肉瘤和间充质软组织肉瘤更容易在诊治期间发生肿瘤转移[51]，行骨扫描和肺部 CT 扫描可以明确有否远处转移，并可以通过先前存在的软骨帽是否重新生长来进行识别[15]。同时该研究也指出，一般影像学检查在良性骨软骨瘤与低级别、高分化(1级)的传统软组织肉瘤之间可能很难有效区分，使用动态增强磁共振成像(Dynamic Contrast-Enhanced Magnetic Resonance Imaging, DCE-MRI)即 MR 增强扫描可以有效地提供帮助[51]。儿童软组织肉瘤的明确诊断同样基于病理形态学检查结果，分子检测诊断并不是常规的必要条件。Amary 等[52]的一项研究中发现约 56% 的中央型和去分化软组织肉瘤患者中携带异柠檬酸脱氢酶 1(isocitrate dehydrogenase 1, IDH1)和异柠檬酸脱氢酶 2(isocitrate dehydrogenase 2, IDH2)的基因突变。另一项研究则发现在间充质软组织肉瘤中 HEY1 基因和 Nuclear Receptor Coactivator 2 (NCOA2)基因之间存在高度特异性的基因片段融合[53]。

3. 治疗方法和时机

常规骨肉瘤的不良预后因素包括原发性转移、肿瘤存在于近端肢体部位、肿瘤体积大、血清碱性磷酸酶(alkaline phosphatase, AP)或 LDH 水平升高以及年龄较大等[54]-[56]。手术治疗是治疗骨肉瘤的主要手段，但是在发现骨肉瘤后很长一段治疗中，使用单纯截肢手术治疗的效果并不理想，患者的生存率是通常 15%~17%之间，并且约 80% 的患者发生了肿瘤肺转移[57]-[59]。自 20 世纪 70 年代以来，应用大剂量甲氨蝶呤、长春新碱、阿霉素等作为手术辅助治疗的辅助化疗逐渐开始应用，非转移性骨肉瘤患者的总生存率随着辅助化疗的应用从 20% 增加到 70% 以上[23][60]。现阶段，非转移性骨肉瘤患者使用的新辅助化疗常用药物包括阿霉素、异环磷酰胺、顺铂或甲氨蝶呤[61]。针对儿童和青少年骨肉瘤的一线新辅助化疗方案最常选择阿霉素、顺铂、大剂量甲氨蝶呤的方案[62]-[64]。骨肉瘤与其他恶性原发性骨肿瘤一样可以通过血行扩散转移，儿童骨肉瘤最常见的转移类型是肿瘤肺转移，一旦发生将严重影响患者的预后，死亡率高且发生时间短[21][22]。在现阶段儿童骨肉瘤的手术治疗中，如何在不增加肿瘤复发率的前提下提供更好的肢体外观和功能进行保肢手术、对特定年龄的儿童完成生长重建，如生长中的骨骼重建等，相关议题已经成为热点研究内容[3][65]-[67]。孙寅等[68]回顾性分析了儿童骨肉瘤保肢手术的相关文献研究，认为保留骨骺的保肢手术能够节段性切除骨干区域肿瘤，保留骨骺与自身关节，有望完成生长重建。此外也有研究观点认为，得益于新辅助化疗-手术治疗-辅助化疗的模式的应用，有效提高了骨肉瘤手术保肢率[54][69]。同时有研究证实骨肉瘤的新辅助化疗药物往往是通过杀死免疫抑制调节性 T 细胞和骨髓来源的抑制细胞(Myeloid-derived suppressor cells, MDSCs)来激活免疫效应细胞而引起免疫抗肿瘤活性[70]，而在儿童骨肉瘤中，化疗后淋巴细胞数量与预后恢复良好程度正相关[71]，可能提示对于儿童转移性和复发性骨肉瘤的治疗，免疫疗法可能具有巨大的潜力[60]。针对转移性骨肉瘤，靶向

骨肉瘤相关抗原的嵌合抗原受体基因修饰的 T 细胞(CAR-T)疗法是一种很有前景的新型免疫治疗方式[72], 已有研究报道包括针对靶向 GD2、HER-2、IL-11R α 和 ROR1 等骨肉瘤相关抗原的特异性 CAR-T 治疗在基础和临床应用中有良好的治疗效果[72] [73]。此外, 有研究证实程序性死亡蛋白 1 (programmed death protein-1, PD-1)及其配体 1 (programmed cell death ligand 1, PD-L1)可以介导骨肉瘤发生免疫逃逸并在其进展中发挥重要作用[74], 还有研究介绍了褪黑素可由多种途径和机制发挥抗骨肉瘤的作用[75], 这些方面的研究内容都将为儿童骨肉瘤的药物治疗带来新的契机。

据报道, 软骨肉瘤的预后因素包括诊治中是否发生转移、肿瘤的组织学分级、肿瘤大小以及发病部位[76]。对于儿童间充质软骨肉瘤的最佳治疗方法尚无普遍共识, 但是手术治疗被认为是主要治疗手段, 关键在于对于病变部位完成较宽的手术切缘以实现局部根除[47]。有研究发现手术治疗可以显著提升儿童软骨肉瘤的生存率[7]。间充质软骨肉瘤与尤文氏肿瘤相似[77], 被认为对化疗和放疗耐药[78] [79], 历史上一直被认为与不良预后有关[80]。然而, 最近的现代疗法显著提高了患者的生存率[24] [25]。针对去分化软骨肉瘤的研究中, 截肢或保肢手术被认为具有明显的生存收益[81]-[83], 宽切缘切除术的应用也具有关键价值[84], 去分化软骨肉瘤切除术后远处转移的风险非常高, 尤其是发生病理性骨折的情况下。如果手术治疗不能可靠地实现较宽的切缘保肢手术, 应考虑充分截肢手术。此外还可对难以进行手术的软骨肉瘤进行放射治疗, 包括质子放射治疗。传统放疗技术治疗肿瘤时可能出现严重的放疗反应[85], 质子束剂量能在治疗靶区处大量沉积, 优于传统的光子治疗, 在儿童软骨肉瘤中已有应用并取得了一定效果[86]-[88]。但同时也需要注意到质子放射治疗的成本目前仍远高于现有放疗技术[89]。

4. 总结与展望

骨肉瘤和软骨肉瘤作为原发性骨肿瘤中最常见的两种恶性肿瘤。与成人相比, 儿童骨肉瘤和软骨肉瘤的恶性程度往往较重, 预后较差, 死亡率较高。近年来, 儿童原发性骨肿瘤一直在得到越来越多的学者关注, 关于新的协助诊断方式、实验室指标、新的治疗方案和方式选择层出不穷, 随着现代医疗技术水平逐渐提升, 儿童骨肉瘤和软骨肉瘤生存率有明显升高[23]-[25]。儿童和青少年骨肉瘤及软骨肉瘤而言, 进行早期诊治十分关键。对于影像表现上怀疑为原发性骨肿瘤的儿童, 应当转诊至儿童医疗机构中心, 避免可能存在的管理差异影响病情, 儿童医疗机构中心则需要为不同年龄的儿童提供特定专业技能。现阶段, 儿童骨肉瘤和软骨肉瘤确诊依旧主要依靠病理形态学检查结果, 为明确诊断所采取的病理标本活体组织检查, 应当由之后同样进行根治性肿瘤切除术的手术团队完成, 或在与骨肿瘤外科医生讨论后由专门的介入放射科医生进行操作, 以提高患者生存率[90]。所取得每位患者的组织学标本必须由经验丰富的骨肿瘤外科医生、病理科医生、与放射科医生合作进行解读, 并在多学科团队(Multi-Disciplinary Treatment, MDT)中进行讨论。位于北欧的斯堪的纳维亚的一项研究评估了 106 例胸壁软骨肉瘤, 发现大约 60%的患者在综合医院接受治疗, 而不是在骨肿瘤中心接受治疗。在非骨肿瘤中心接受治疗的患者复发率较高, 生存率较低[91]。此外, 不断涌现出的有关儿童骨肉瘤和软骨肉瘤的分子检测内容必将会取得更多成果。

在儿童骨肉瘤和软骨肉瘤的综合治疗中, 最为关键的是如何降低肿瘤肺转移率和以及提高患者长期生存率, 相较于传统单纯手术治疗, 新辅助化疗 - 手术治疗 - 辅助化疗模式的应用在一定程度上为提升手术保肢率、患者存活率产生了重要意义。靶向治疗、质子放射治疗以及免疫治疗有可能为儿童骨肉瘤和软骨肉瘤的综合治疗提供新的机会。与成人骨肉瘤和软骨肉瘤不同的是, 儿童骨肉瘤和软骨肉瘤的手术方法和处理原则具有其独特性。如何对不同特定年龄段的儿童, 最大程度地减少术后肢体长度差异, 保留儿童生长中的机体重建功能, 在治疗安全有效的前提下最大程度保障肢体功能等一系列问题, 成为了骨科医生现阶段一项艰巨的“重建挑战”。综上所述, 要推动儿童骨肉瘤和软骨肉瘤诊治的进一步

进展,无疑需要骨外科、肿瘤科、病理科、放射科、介入放射科的相互协作,共同对新型诊断和治疗的多学科内容持续交叉学习,以求做到进一步提升诊治效果和针对不同个体的情况 and 需求制定个性化诊疗方案。

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