·诊疗指南·

文章编号：2095-9958（2018）04-0260-16
DOI：10.3969/j.issn.2095-9958.2018.04.003

尤文肉瘤肿瘤家族（ESFT）临床循证诊疗指南

中国医师协会骨科医师分会骨肿瘤专业委员会
郭卫[1*] 王臻[2*] 郭征[2*] 董扬[3*]

（1.北京大学人民医院骨肿瘤科，北京 100044；2.空军医科大学附属西京医院骨科，西安 710032；
3.上海市第六人民医院骨科，上海 200233）

【摘要】尤文肉瘤是常见的原发恶性骨肿瘤，严重危害青少年的身体健康。通过规范的化疗、手术及放疗，很多患者可达到痊愈，但不当的诊疗过程可能造成严重的不良后果。中国医师协会骨科医师分会骨肿瘤专业委员会依据循证医学方法制定了《尤文肉瘤肿瘤家族（ESFT）临床循证诊疗指南》，就诊断流程、化疗、放疗、不同部位的手术方式及挽救性治疗等临床问题进行总结，依据文献证据等级给出相应的推荐等级。旨在为骨肿瘤医师的临床诊疗提供最佳的、有效的意见参考，从而使患者达到最佳的治疗效果。本指南仅为学术性指导意见，具体实施时必须依据患者的个体医疗情况而定。

【关键词】尤文肉瘤；骨肿瘤；指南

Guideline for clinical evidence-based diagnosis and treatment of Ewing sarcoma family tumor (ESFT)

Musculoskeletal Tumor Society, Chinese Association of Orthopaedic Surgeons
GUO Wei[1*], WANG Zhen[2*], GUO Zheng[2*], DONG Yang[3*]

(1.Musculoskeletal Tumor Center, Peking University People's Hospital, Beijing 100044; 2.Department of Orthopaedics, Xijing Hospital, Air Force Medical University, Xi'an 710032; 3.Department of Orthopaedics, Shanghai No.6 People's Hospital, Shanghai 200233,China)

【Abstract】Ewing sarcoma family tumors (ESFTs) are common primary malignancies of the bone and severely jeopardize teenagers' health. Standardized multi-modality treatment including chemotherapy, surgery and radiotherapy can achieve cure of disease for many patients, while improper treatments could lead to severe consequences. The Musculoskeletal Tumor Society from Chinese Association of Orthopaedic Surgeons proposes the "Guideline for clinical evidence-based diagnosis and treatment of Ewing sarcoma family tumor (ESFT)". This guideline addresses several clinical problems (e.g. diagnostic process, chemotherapy, radiotherapy, surgical options for lesions of different locations, and salvage treatments) and provides recommendations with categories of evidence and consensus. The aim of the guideline is to provide the most effective references for practitioners of oncologic orthopaedics in order to achieve ideal outcomes for patients. But this guideline provides only academic recommendations and should be adapted to individualized treatments during clinical practice.

【Key words】Ewing Sarcoma Family Tumor; Bone Tumor; Guidebooks

1 方法学

证据推荐等级方法采用GRADE（Grading of Recommendations Assessment, Development and Evaluation）方法，详见表1。

2 尤文肉瘤肿瘤家族概述

尤文肉瘤肿瘤家族（Ewing sarcoma family tumor, ESFT）是一组小圆细胞肿瘤的统称，包括尤文肉瘤、原始神经外胚层瘤（primitive neuroectodermal tumor, PNET）、骨PNET和骨外软组织尤文肉瘤。尤文肉瘤以22q12染色体上EWS基因（EWSR1）与ETS基因家族的几种基因（FLI1、ERG、ETV1、ETV4、FEV）融合为特征[1,2]。EWS与11号染色体上的FLI1融合，以及相应的t(11;22)(q24;q12)染色体易位导致的EWS-FLI1融合基因转录，出现在约85%的尤文肉瘤患者中[1]。在5%~10%病例中，EWS与ETS基因家族的其他基因相融合。在极少数病例中，FUS可以替代EWS，导致没有EWS的重新排列，即由t(16;21)(p11;q24)易位引起的FUS-ERG融合基因转录或t(2;16)(q35;p11)易位引起的FUS-FEV融合基因转录[3,4]。尤文肉瘤还有高表达细胞表面糖蛋白MIC2（CD99）的特征[5,6]。虽然MIC2表达不是特异性的，但可能有助于尤文肉瘤/

*通信作者：郭卫，E-mail：bonetumor@163.com；王臻，E-mail：wangzhen@fmmu.edu.cn；郭征，E-mail：guozheng@fmmu.edu.cn；董扬，E-mail：dongyang6405@163.com

表1 GRADE推荐等级和证据分级

推荐等级	证据等级
1.强烈推荐:利大于弊或弊大于利	A.荟萃分析、高质量RCT、高质量回顾性研究
2.利弊相当或不确定	B.随机或回顾性研究存在方法学瑕疵
	C.随机或回顾性研究存在方法学瑕疵、个案、专家经验、共识

PNET与其他小圆细胞肿瘤的鉴别[7]。

ESFT好发于青少年及年轻人。可见于全身任何骨骼,最常见的初始发病部位为骨盆、股骨以及胸壁[8]。长骨病变骨干最易受累。影像学多表现为溶骨性破坏。骨膜反应呈典型"洋葱皮"样改变。

ESFT患者与大多数骨组织肉瘤患者一样常因局部疼痛或肿胀就诊。与其他骨起源肉瘤不同的是,全身性症状如发热、体重下降及疲劳在发病时常见。实验室检查异常包括血清乳酸脱氢酶(lactate dehydrogenase, LDH)升高及白细胞增多。

2.1 预后因素

预后较好的重要因素包括:原发肿瘤位于肢体、肿瘤体积 < 100 ml、发病时LDH水平正常[9-13]。与其他部位的ESFT相比,脊柱及骶骨ESFT预后更差[14]。

发病时即有转移是ESFT最显著的不良预后因素,与其他骨起源肉瘤相同,转移最常见于肺、骨和骨髓[13,15,16]。EICESS研究组975例患者的回顾性分析中,诊断时即有转移的患者5年无复发生存率为22%,而诊断时无转移的患者为55%[15]。在有转移灶的患者中,单纯肺转移的患者比骨转移或肺骨同时转移的患者生存时间更长[15]。一个30例患者的回顾性分析表明,肿瘤转移至肺和骨以外的其他位置(如脑、肝、脾)时预后更差[17]。无转移的患者对化疗反应不佳,是无事件生存率的一个不良预后因素[12,18,19]。

IESS的303例尤文肉瘤患者的临床病理学特征回顾资料显示,原发病变位于骨盆的患者较四肢起病患者生存率低[20]。在一个对53例尤文肉瘤化疗患者预后的多因素分析中,Gupta等发现,骨盆是否受累、何时接受局部治疗与无事件生存率相关[21]。Lee等将成年人、西班牙裔、有转移灶、肿瘤大、低社会经济水平认定为总生存率的不良预后因素[22]。

2.2 检查

怀疑ESFT的患者,在活检前应进行全面的肿瘤分期。应包括胸部CT,原发病变部位MRI、CT、PET扫描和(或)骨扫描以及骨髓活检,同时建议行脊柱及骨盆MRI除外骨髓侵犯。在一个系统性回顾和Meta分析中,Treglia等报道了将PET/CT与传统影像学结合对ESFT的分期及再分期很有价值,敏感性96%,特异性92%[23]。活检标本应进行细胞遗传学和(或)分子生物学分析评估t(11;22)易位。初步报道认为EWS-FLI1易位较其他变异预后更好[24-26]。与上述观点不同,来自EURO-EWING99及儿童肿瘤组的研究报道认为运用当前有效的治疗后尤文肉瘤患者的疗效预后与融合基因亚型无关[27,28]。除了EWS以外,在分子学诊断上为了确诊罕见的带有FUS-ERG或FUS-FEV融合基因转录的ESFT病例,FUS也应该作为融合基因检测靶点[3,4]。为完善诊断和分期,应常规进行骨髓活检。血清LDH已被证明是一种具有判断肿瘤预后意义的肿瘤标志物,指南将该检验列为尤文肉瘤患者的初步评估手段。(1B级)

3 诊疗规程

3.1 诊断

所有怀疑ESFT的患者都应进行详细的病史采集及体格检查,首先对原发肿瘤部位行MRI和CT检查。为评估疾病的分期,还需行胸部CT、PET扫描和(或)骨扫描检查以便早期发现经血行转移至肺或骨的病灶。ESFT还容易出现骨髓浸润,所以还需行骨髓活检、脊柱及盆腔的MRI的筛查。由于ESFT有显著的遗传易感性(90%尤文氏瘤家族肿瘤拥有4种特定染色体易位),因此强烈建议患者行细胞遗传学和(或)分子生物学检测(可能因此需要再次活检)。另外,除常规血液学检查外,ESFT患者还需监测LDH的变化。患者在接受放化疗前建议至生殖医学科进行相关咨询。(1B级)

3.2 治疗

由于ESFT多为化疗高度敏感的肿瘤,因此建议在局部治疗之前至少进行12周的化疗(1A级)。并在化疗后对肿瘤进行再次分期。对初诊无转移的局灶病变患者,再次分期评估包括胸部及原发部位影像检查,可考虑行PET扫描或骨扫描检查。而对转移性ESFT患者,除行上述检查外,还需对初次检查过程中所有异常结果做再次检查评估。若肿瘤对化疗有反应(病情稳定或改善),则对可切除的局部病灶进行广泛切除,对不可切除的病灶行根治性放疗或继续化疗(根据治疗的反应,对转移性疾病可考虑延长初始化疗时间)。

手术切除后需对手术切缘进行病理学评估,对切缘阳性的病例,术后继续化疗后放疗,或放疗后化疗。化疗时长28~49周,具体化疗周期数取决于化疗

方案及剂量的使用，此后进行定期随访。对切缘阴性的病例，术后继续辅助化疗，此后进行定期随访。（1A级）

对初始化疗后再评估肿瘤进展的病例，则考虑先对原发病灶行放疗和（或）手术治疗，以达到局部控制或姑息治疗的目的。此后继续化疗或行最佳的支持治疗。

3.3 随访与监测

患者治疗结束后，需每3个月进行原发部位的体格检查、影像学检查以及胸部CT检查，并同时进行血常规以及其他实验室检查，可考虑应用PET扫描或骨扫描进行监测。24个月后体格检查、胸部CT和局部影像检查的间隔可延长至6个月。5年后延长至每年1次。在随访过程中发现早期或晚期复发的病例，需再次接受化疗（对晚期复发的病例，可考虑应用前期有效的治疗方案再治疗）和（或）放疗。（1B级）

4 治疗方法说明

4.1 局部控制治疗

手术切除及放疗是非转移尤文肉瘤患者最常用的局部控制方法。目前没有比较此两种方法的随机研究。（1B级）

多中心研究显示，治疗非转移性尤文肉瘤患者时，局部控制手段的选择（手术、放疗或手术加放疗）没有对总体生存率或无事件生存率产生显著影响[29,30]。在CESS86临床试验中，虽然根治性手术和手术加放疗后的局部控制率（分别为100%和95%）较单纯适形放疗（86%）更高，但因为术后存在转移风险，总体生存率方面没有提高[29]。在INT-0091研究中，患者单用手术或放疗治疗后局部控制失败的发生率是相近的（25%），但手术加放疗后的局部控制失败发生率更低（10.5%）[30]。5年无事件生存率同样在组间没有显著差别（手术、放疗、手术加放疗组分别为42%、52%、47%）。其他回顾性分析的数据表明手术（加或不加术后放疗）对于局限性病变的局部控制能力优于单纯放疗[31]。1058例CESS81、CESS86及EICESS92临床试验联合分析表明手术（加或不加术后放疗）后局部控制失败率，较单纯适形放疗明显降低（分别为7.5%和26.3%，P=0.001），而术前放疗组的局部控制率与手术组（5.3%）相当[31]。由儿童肿瘤组开展的回顾性分析（INT-0091、INT-0154或AEWS0031）表明：适形放疗与手术加放疗相比有更高的局部控制失败风险，但对远隔部位治疗失败没有影响。

适形放疗可以作为对肿瘤部位难以手术广泛切除的一种有效治疗方法[32,33]。一个针对CESS81/86与EICESS92研究中，治疗椎体尤文肉瘤患者的回顾性分析显示，适形放疗的局部控制率为22.6%，与其他部位肿瘤接受适形放疗后的水平相当；5年无事件生存率和总生存率分别为47%和58%[33]。对于接受化疗和适形放疗的非转移性尤文肉瘤患者，肿瘤大小和放疗剂量被证实可以用于预测局部控制率[34,35]。

尤文肉瘤家族肿瘤放疗原则如下。

4.1.1 原发肿瘤治疗

4.1.1.1 根治性放疗：应在VAC/IE化疗方案12周或VIDE化疗方案18周后开始。

放射治疗范围和剂量：①肿瘤区（GTV）45 Gy照射剂量，临床靶区1（CTV1）扩大1~1.5 cm，计划靶区1（PTV1）再扩大0.5~1 cm；②锥形下区（CD）覆盖病变骨范围，化疗后软组织区（GTV2）总量55.8 Gy照射剂量，CTV2扩大1~1.5 cm，PTV2再扩大0.5~1 cm；③化疗反应度＜50%肿瘤，考虑增加到总量59.4 Gy的增强剂量。

4.1.1.2 术前放疗：对拟边缘切除肿瘤考虑术前放疗，对巩固性化疗患者同时进行。

放射治疗范围和剂量：36~45 Gy照射剂量对初始GTV，扩大2 cm。

4.1.1.3 术后放疗：术后60 d内开始放疗，对巩固性化疗患者同时进行。

照射范围和剂量：①R0切除：组织学反应差，即使边界切除充分，仍考虑放疗（GTV2：45 Gy照射剂量，CTV1：扩大1~1.5 cm，PTV1：扩大0.5~1 cm）；②R1切除：GTV2 45 Gy照射剂量，CTV1扩大1~1.5 cm，PTV1再扩大0.5~1 cm；③R2切除：GTV2 45 Gy照射剂量，CTV1扩大1~1.5 cm，PTV1再扩大0.5~1 cm，继续对残余病灶行CD照射，GTV2总量55.8 Gy照射剂量，CTV2扩大1~1.5 cm，PTV2再扩大0.5~1 cm。

4.1.1.4 半胸照射：原发于胸壁合并胸膜受累15~20 Gy（1.5 Gy/fx），继续对原发病灶行CD照射（最终剂量以切除边缘为基础）。

4.1.2 转移病灶治疗：全肺照射后行彻底化疗/转移灶切除：①14岁以下患者15 Gy（1.5 Gy/fx）；②14岁以上患者行18 Gy。目前COG研究以年龄在6岁上下进行分层（12 Gy∶15 Gy）。

4.2 化疗（1A级）

美国和欧洲的单中心及多中心合作临床研究表明，包含异环磷酰胺和（或）环磷酰胺、依托泊苷、多

柔比星和(或)放线菌素D、长春新碱的多药联合化疗对非转移性尤文肉瘤有效。术前的新辅助化疗可缩减肿瘤体积,增加完整切除并获得镜下阴性边缘的几率。外科切除术后辅助化疗可提高大部分患者的RFS和OS[32,36-39]。

IESS-Ⅰ和IESS-Ⅱ证明,在病灶局限的、非转移性患者中,放疗联合VACD方案辅助化疗(长春新碱、放线菌素D、环磷酰胺和多柔比星)比VAC方案(长春新碱、环磷酰胺和多柔比星)疗效好[37]。其5年RFS分别为60%和24%(P<0.001),相应的OS分别为65%和28%(P<0.001)。

对于初治无转移的尤文肉瘤患者,在标准方案的基础上可单独加用异环磷酰胺或同时联合依托泊苷[36,40-44]。在儿童癌症协作组(POG-COG)的研究中(INT-0091),共398例非转移性ESFT患者随机接受共计17周期VACD或VACD-IE(VACD-异环磷酰胺+依托泊苷)方案化疗[36]。5年EFS VACD-IE组显著高于VACD组(分别为69%及54%,P=0.005)。5年OS VACD-IE组也显著提高(分别为72%及61%,P=0.01)。无论局部治疗方式如何,与VACD组相比,VACD-IE组局部复发率更低(分别为30%和11%);5年累积局部控制失败率在VACD组为30%,VACD-IE组为11%[30]。

VAC-IE方案中烷化剂剂量的提高不能改善非转移性患者的预后[45],但缩短化疗间期可改善非转移性患者的预后[46]。在一项针对50岁以内非转移性尤文肉瘤(n=568)的随机临床试验中,Womer等报道VAC-IE2周方案比3周方案更有效,且药物毒性没有增加;两组患者5年EFS分别为73%、65%[46]。

研究发现,对于初治即有转移的患者,加用异环磷酰胺/依托泊苷并不能改善其预后[36,40,42,47]。在INT0091试验中,共120例转移性患者,VACD-IE组与VACD组在EFS和OS均无显著区别[36]。二者五年EFS均为22%,5年OS在VACD-IE组为34%,在VACD组为35%。在68例患者中(44例非转移性,24远处转移),Kolb等报道4年EFS和OS分别为82%和89%,其中非转移性患者接受密集化疗[多柔比星和长春新碱和(或)大剂量环磷酰胺]并加用异环磷酰胺和依托泊苷[40]。在远处转移患者中,相应的生存率为12%和18%。Miser等也报道了在转移性尤文肉瘤/PNET患者中的类似情况[47]。

EICESS-92试验旨在探索在标准危险度尤文肉瘤患者(小的局限性肿瘤)中环磷酰胺是否与异环磷酰胺有类似的疗效,以及在高危患者(肿瘤体积大或初治即有转移)已使用异环磷酰胺的基础上再加用依托泊苷能否提高生存率[48]。标准危险度患者被随机分配,在VAIA(长春新碱、放线菌素D、异环磷酰胺和多柔比星,n=76)后接受VAIA或VACA(长春新碱、放线菌素D、环磷酰胺和多柔比星,n=79)[48]。VACA组和VAIA组的3年EFS分别为73%和74%,说明在此类型患者中,环磷酰胺与异环磷酰胺疗效相当。高危组患者被随机分配至VAIA组以及VAIA加依托泊苷(EVAIA组),3年EFS在两组患者中无明显差异(EVAIA组为52%,VAIA组为47%)。但有证据表明,加用依托泊苷的非转移性患者(P=0.18)比转移性患者获益更多(P=0.84)[48]。

作为对EICESS-92试验的随访,Euro-EWING99-R1试验评估了856例标准危险度的尤文肉瘤患者使用VIDE(长春新碱,异环磷酰胺,多柔比星,依托泊苷)后,联用长春新建和放线菌素D时以环磷酰胺代替异环磷酰胺(VAC *vs* VAI),VAC方案相对于VAI方案并无统计学优势,但时间发生率稍低(3年EFS降低2.8%)。发生严重血液学毒性的患者比例在VAC组略高,但VAI组患者肾小管功能损伤更为显著[49]。

4.3 大剂量化疗后行干细胞移植(2B级)

大剂量化疗后行干细胞移植(HDT/SCT)在非转移性及转移性ESFT患者中均有评估。HDT/SCT在未转移性患者中可提高生存率[50,51]。但是针对转移性患者的研究得出相反结论[51-57]。

EURO-EWING 99是第一个大型随机临床试验,旨在评估6周期VIDE的多药联合方案,局部治疗(手术和/或放疗),和HDT/SCT在281例初治转移性尤文肉瘤患者中的疗效[53]。在中位随访3.8年后,全部患者3年的EFS和OS分别为27%和34%[55]。HDT/SCT后获得完全或部分缓解的患者,其EFS分别为57%和25%。患者年龄、肿瘤体积、疾病进展程度都是相关危险因素。由于非移植组早期偏倚较大(82%未进行HDT/SCT的患者在平均1年内死亡),HDT/SCT对预后的影响没有得出最终结论。

4.4 治疗方法小结

所有尤文肉瘤患者均采取以下方案治疗:初始诱导化疗后接受局部控制治疗[手术和(或)放疗]和辅助治疗。

初始治疗包括多药化疗以及粒细胞集落刺激因子支持,至少12周。已有转移灶的患者根据化疗反

应可以适当延长初始诱导化疗周期。VAC/IE(长春新碱、阿霉素和环磷酰胺与异环磷酰胺和依托泊苷交替)是局部尤文肉瘤的首选方案,而VAC(长春新碱、阿霉素和环磷酰胺)是有转移灶患者的首选方案[36,40,47]。

初始治疗后应根据病变部位MRI和胸部检查再分期。根据初始诊断时所用的影像学技术,PET扫描和(或)骨扫描也可以用于再分期。初始治疗后患者维持稳定状态或肿瘤缩小应进行局部控制治疗。

局部控制治疗方法包括局部切除、适形放疗,甚至截肢[31,33,34,58]。局部控制方法的选择应个性化,根据肿瘤位置、大小、对化疗的反应、患者年龄、功能预期来制定。

无论手术切缘如何,建议对所有患者进行术后辅助化疗。强烈建议广泛切除后的化疗持续时间为28~49周,根据方案和剂量制定具体时间[36,37,39]。对于切缘阳性或外科边缘非常邻近的患者,建议在化疗的基础上增加术后放疗[31]。Denbo等最近报道在小体积肿瘤(<8 cm)及切缘阴性的患者中,可以不采用术后放疗而总体生存率无降低[59]。接受辅助放疗患者的15年预计总体生存率为80%,未经辅助放疗的患者为100%。本指南建议对广泛病灶切除及切缘阴性患者单用辅助化疗。(1B级)

初始治疗后的进展性疾病的最好治疗方法是对原发病灶进行放疗和(或)手术,之后采取化疗或最好的支持性治疗。

4.5 复查监测

尤文肉瘤患者的复查包括3个月进行1次体格检查、血常规和其他实验室检查、胸片和局部病灶影像学检查。复查间隔在2年后应延长至6个月。5年后的长期监测应每年进行1次[60]。(2B级)

4.6 复发或难治性疾病

30%~40%ESFT患者会复发[局部复发和(或)远处转移],预后很差。首次复发的间隔时间越长,患者的生存机会越大。晚期复发(首诊后≥2年)、只有肺部转移、可以用积极性手术切除的局部复发和密集化疗是最有利的预后因素,而有肺部和(或)其他部位转移的早期复发(首诊后<2年)、局部及远处都有复发、首诊LDH升高以及首次即有复发被认为是不良预后因素[61~63]。在一个近期的回顾性分析中,初次复发的部位及间隔时间对于成人局限性尤文肉瘤患者来说是重要的预后因素[64]。局部和远处复发患者的复发后5年预计生存几率分别为50%和13%。晚期复发患者的复发后5年预计生存率显著高于早期复发患者[64,65]。

有临床试验评估联合异环磷酰胺与依托泊苷(加或不加卡铂)治疗复发或难治性肉瘤患者效果[66,67]。在一个Ⅱ期研究中,对于儿童及年轻人的复发性肉瘤患者采用异环磷酰胺及依托泊苷联合治疗在可接受的毒性范围内有明显效果[66]。由儿童肿瘤组开展的Ⅰ/Ⅱ期研究表明,复发性或难治性肉瘤患者的总体反应率为51%;1年及2年的总体生存率分别为49%和28%。肿瘤有完全或部分反应的患者的总体生存率明显提高[67]。

不以异环磷酰胺为基础的化疗方案在复发性或难治性骨组织肉瘤患者中也显示有效。多西他赛与吉西他滨联合被证实有很好的耐受性,治疗后患有难治性骨组织肉瘤的儿童及年轻人的总体客观反应率为29%;中位反应持续时间为4.8个月[68]。拓扑异构酶Ⅰ抑制剂(拓扑替康和伊立替康)与环磷酰胺与替莫唑胺联合治疗复发或难治性骨组织肉瘤时有可观的反应率[69~75]。对54例复发或难治性肉瘤患者,环磷酰胺和拓扑替康在44%患者中展现了治疗反应(35%患者完全反应,9%部分反应)[71]。在中位随访时间23个月后,26%患者位于持续性缓解期。对患有复发性或进展期尤文肉瘤患者的回顾性分析中,伊立替康和替莫唑胺治疗后的总体客观反应率为63%。所有可评估患者(20例)的肿瘤进展中位时间(TTP)为8.3个月(复发患者为16.2个月)[70]。与诊断后两年内复发和诊断时即有转移的患者比较,2年初次缓解和原发局限性肿瘤患者的中位TTP更好。复发或难治性尤文肉瘤患者对长春新碱、伊立替康与替莫唑胺联合用药的反应好且耐受性好,总体反应率为68.1%[76]。

总之,复发或难治性患者的治疗方法包括参加临床试验和化疗(加或不加放疗)。ESFT有时会出现延迟复发,采用以前有效的治疗方案可能有作用。所有复发和转移的患者均应考虑参加研究新型治疗方法的临床试验。

4.7 尤文肉瘤化疗方案汇总

4.7.1 一线治疗方案(初始/新辅助/辅助治疗):①VAC/IE(长春新碱、阿霉素联合环磷酰胺或异环磷酰胺联合足叶乙甙)[36];②VAI(长春新碱、阿霉素联合异环磷酰胺)[19,48];③VIDE(长春新碱、异环磷酰胺、阿霉素联合足叶乙甙)[53]。

4.7.2 就诊即存在转移病灶初始治疗:①VAdriaC(长

春新碱、阿霉素联合环磷酰胺)[47];②VAC/IE[36];③VAI[19,48];④VIDE[53]。

4.7.3 二线治疗方案(复发/难治性或转移):①环磷酰胺联合拓扑替康[69,71-73];②伊立替康±替莫唑胺[70,74,75,77-80];③异环磷酰胺联合足叶乙甙[66];④异环磷酰胺、卡铂、足叶乙甙[67];⑤多西紫杉醇联合吉西他滨[68]。

5 不同部位的外科治疗

5.1 四肢尤文肉瘤的外科治疗

5.1.1 外科边界的选择与预后:对于肢体尤文肉瘤来说,在完成术前新辅助化疗后且可以保肢时,应首选切缘阴性的广泛切除或根治性手术[81-88]。

肢体尤文肉瘤患者的5年生存率在50%~75%之间[31,89-92],高于脊柱及骨盆尤文肉瘤的5年生存率[30,90,93-95]。尤文肉瘤恶性程度高,易发生远处转移,尤其是肺[16,85,86,96],其远处转移率为60%左右[85,86,96]。因此肢体尤文肉瘤必须选择切缘阴性的广泛切除或根治性手术[81-88]。

Sluga等在2001年于Eur J Surg Oncol发表的数据显示,无转移的肢体尤文肉瘤做切缘阴性的广泛切除后与囊内切除患者的五年生存率分别为60.2%和40.1%[97]。其他肢体尤文肉瘤的回顾性研究显示,切缘阴性的广泛切除或根治性手术的局部复发率为10%左右[98-100],而囊内刮除术后局部复发率较高约为30%[98,99]。因此,切缘阴性的广泛切除或根治性手术较囊内刮除术可以减少肢体尤文肉瘤的局部复发率,并且五年生存率亦有所提高。

由此看来,外科边界的满意程度是肢体尤文肉瘤预后重要的影响因素之一。(1B级)

5.1.2 复发病例的处理:肢体尤文肉瘤局部复发率为10%~30%[65,101-104],复发病例是否接受二次手术需根据个体情况决定,部分患者可能从中受益[64]。

初次手术外科边界的满意程度是肢体尤文肉瘤局部复发最重要的影响因素[105]。局部复发与预后不良密切相关[65,105]。局部复发患者要根据患者实际情况考虑推荐给予放疗、再次手术或化疗[58,105]。(1B级)

5.1.3 截肢和保肢的选择:当肢体尤文肉瘤体积巨大且新辅助化疗效果不佳,肿瘤累及主要血管神经,或复发、放疗等因素造成局部软组织条件不良的情况下应选择截肢。(1B级)

截肢和保肢手术对于尤文肉瘤患者的生存率、局部复发率无统计学差异[106-108],Schrager的数据显示,截肢组和保肢组的生存率分别为63.1%和71.8%[108]。保肢与截肢患者的生存质量没有明显差异,但截肢患者较保肢患者社会适应性更差[109];保肢患者术后功能有好于截肢患者的趋势,但研究的统计学差异不显著[110-112]。亦有学者认为保肢患者的功能比截肢患者好[113]。随着影像学和计算机技术的发展,目前对肢体尤文肉瘤的诊断、外科边界已经更加精确[114-116]。

肢体尤文肉瘤切除方式的选择需充分考虑新辅助化疗后肿瘤累及主要的血管神经、周围软组织条件等因素,综合评判选择保肢或截肢术。

5.1.4 肢体尤文肉瘤切除后的功能重建:对于接受保肢手术的尤文肉瘤患者,在切除肿瘤后应进行缺损区域的功能重建,以恢复肢体的功能。重建方法的选择应根据患者年龄、病变部位等因素综合考虑。重建主要有生物学重建、机械性重建以及复合重建。(1B级)

对于肿瘤切除后的缺损区域可以采用机械性重建的方法,比如邻近关节的缺损可以采用关节假体置换的重建方法[117-121],全部骨干的缺损则可以采用全骨假体置换的方法重建[122,123]。此外,也可以采取生物学重建方法,针对不同部位可以采用肿瘤灭活再植、大段异体骨、游离腓骨移植等方法进行重建[124-126]。复合型重建亦可用于缺损的重建[124,127]。

5.2 脊柱尤文肉瘤的外科治疗

5.2.1 新辅助化疗有利于提高总的生存率和手术方式的制定(1A级):原发脊柱尤文肉瘤占所有尤文肉瘤的3.5%~10%[128-132]。平均发病年龄为13岁,通常源于单一脊椎(61%)的后半部分(65%),胸腰椎占绝大多数(91%)[133]。脊柱尤文肉瘤单纯手术或放疗的5年生存率为5%~20%[134,135]。多药联合化疗结合手术或放疗使得脊柱尤文肉瘤的5年生存率提高至41%~80%[33,136,137],局部控制率达到50%~80%[37,138,139]。Oberlin等报道一组67例患者,化疗对尤文肉瘤的有效率为61%[129]。

新辅助化疗的益处包括三个方面[140]:①对化疗敏感的脊柱尤文肉瘤的软组织包块能够很快缩小,脊髓受压能够很快减轻[141],并使得部分原先不能切除的肿瘤可以切除。Vogin等报道了一组脊柱尤文肉瘤病例,实行新辅助化疗组的患者37%获得了R0切除,而未行新辅助化疗直接行椎板减压组无一例获得R0切除[133]。②系统化疗可以消灭循环肿瘤细胞和微转移灶。③肿瘤对于化疗的敏感性有利于制定术后化疗方案。对于脊髓神经功能稳定的患者,活检

确诊后即开始新辅助化疗，对于确诊时脊髓功能已经受到损害的患者，行椎管减压后开始化疗[136]。

5.2.2 术前动脉栓塞有利于手术的安全进行（1B级）：动脉栓塞逐渐成为原发和继发脊柱肿瘤治疗有效和安全的方法。术前栓塞可以有效减少肿瘤的血供，使瘤体缩小，减少术中出血，改善总体预后[142,143]。脊柱尤文肉瘤的出血倾向虽不如肾癌、甲状腺癌等转移瘤，但仍推荐患者接受术前栓塞治疗[144]。

5.2.3 就诊时有脊髓功能损害需紧急进行椎管减压手术（1B级）：虽然脊柱尤文肉瘤体的初始体积不大（平均60 ml），但肿瘤向椎管内生长导致脊髓或马尾症状时，需行紧急椎管减压手术（全椎板切除减压或前方减压）[140,141]。Vogin等报道了75例脊柱尤文肉瘤，57例（79%）就诊时表现为神经受压的症状，69%行减压手术[133]。Marco等报道13例脊柱尤文肉瘤患者中10例行椎板切除减压术[141]。Indelicato等报道27例脊柱尤文肉瘤中6例行紧急椎板切除减压[136]。Sharafuddin等报道的7例脊柱尤文肉瘤中4例行椎板切除减压，1例行前方减压[140]。椎管减压后超过三分之二的患者神经功能可以恢复[136,140,145]。

5.2.4 切缘阴性的整块切除是无转移脊柱尤文肉瘤局部治疗的首选方法（1B级）：与瘤内切除或单纯放疗相比，整块切除局部复发风险低，并可能提高长期生存率[141,146]。Boriani等报道了27例脊柱尤文肉瘤，总生存率为40.7%，而6例行整块切除且切缘阴性的患者中5例长期无瘤生存，总生存率为83.3%[147]。Ulf等报道了7例行整块切除的脊柱尤文肉瘤，5例达到广泛切除，1例边缘切除，1例瘤内切除，随访10~96个月，5例无瘤生存，1例由于其他疾病死亡，1例带瘤生存[98]。李晓等[148]报道整块切除可降低局部复发率，7例中1例复发，2例出现肺转移。分块切除20例，局部复发8例。但脊柱肿瘤整块切除技术要求高[141]，容易出现大的并发症，死亡率可达7.7%（0~7.7%），最常见的死亡原因为呼吸衰竭[149]，术后并发症的发生率为10%~30%，主要包括血管神经损伤、伤口预后不良、感染和内固定失败等[133,150]，故采取整块切除应根据肿瘤的分期和患者的状况在专业的骨肿瘤中心进行。

5.2.5 脊柱尤文肉瘤是否采用瘤内切除尚存在争议（2B级）：瘤内切除相对于整块切除技术要求低，对脊柱稳定性影响小，多数医师可以实施，手术后局部症状可以很快部分缓解[141]。但由于局部仍有肿瘤残留，局部复发率较整块切除高[146]，术后需要进行辅助放疗。瘤内切除或边缘切除后辅助放疗是否比单纯根治性放疗更使患者获益尚存在争议。Vogin等报道一组病例脊柱尤文肉瘤，56例行手术切除，其中R0切除11例、R1切除8例、R2切除37例，术后50例行辅助放疗，与19例单纯行根治性放疗患者相比，前者局部控制率为83%，后者为74%，两者无统计学差异[133]。Schuck等观察了111例脊柱尤文肉瘤，单纯放疗组75例局部控制率为77.4%，手术结合放疗组32例局部控制率为81.3%，两组无统计学差异，47例患者出现放疗相关的急性并发症[33]。Indelicato等报道了一组27例脊柱尤文肉瘤，其中5例在确诊时已有转移。单纯放疗21例，手术结合放疗6例，单纯放疗组平均放疗剂量为55 Gy。肿瘤局部控制率在单纯放疗组为84%，手术结合放疗组为100%，两组无统计学差异。5年总生存率分别为50%和80%，无瘤生存率分别为35%和69%，两组之间均无统计学差异。10例患者（37%）出现严重并发症，其中3例与放疗相关，包括食道狭窄、顽固性恶心呕吐和膀胱肥大导致的双肾积水[136]。Boriani等报道27例脊柱尤文肉瘤，其中瘤内切除并辅以放疗的11例患者均死亡，而单纯放疗的9例中5例存活[147]。但术后放疗与单纯放疗相比，由于瘤内切除后局部只有少量肿瘤残留，所需的放疗剂量低[141]，低剂量放疗也降低了放疗相关的肉瘤变[151-154]和放射性脊髓病的风险[155-157]。

5.2.6 放疗在脊柱尤文肉瘤局部治疗中具有重要作用，瘤内切除或单纯椎板减压术后需行辅助放疗（1B级）：尤文肉瘤对放疗相对敏感，长期以来放疗在尤文肉瘤局部控制中占有重要的地位，单纯放疗所需剂量为55~60 Gy，超过了脊髓的耐受剂量，易于引起放射性脊髓病[136]。另外放疗可以导致脊柱畸形、软组织纤维化、挛缩和第二恶性肿瘤的发生风险[158,159]。多数学者对于肿瘤较大，侵及范围较广，无法手术的倾向于单纯放疗[148]。放疗的范围为包括病变脊椎和其上下各一个脊椎[136]。Marco等报道13例单纯局部放疗的治疗结果：放疗剂量为30~66 Gy，平均48 Gy，5年无瘤生存率为49%，局部控制率率为77%[141]。瘤内切除或单纯椎板减压术后由于局部有肿瘤的残留，需行术后辅助放疗，放疗的剂量一般低于45 Gy，以降低放疗相关的脊髓病的发生[133,155-157]，也可降低放疗相关的肉瘤发生的风险[151-154]。放疗后局部复发的原因在于在放疗区域内有活的肿瘤细胞残存[141]。Tellers等通过尸解在化疗结合放疗的20例患者中13例发现肿瘤残留[160]。

5.2.7 椎板切除减压或整块切除术后需进行脊柱稳定

性重建(1B级):单纯椎板减压后易于发生远期脊柱的畸形和神经系统的并发症。Vogin报道一组脊柱尤文肉瘤病例,在存活超过5年的患者中神经和脊柱畸形的并发症发生率分别为32%和73%[133],而在儿童患者中,脊柱畸形的发生率可达95%~100%[161-163]。最常见的脊柱畸形为椎板减压后的后凸畸形,其发生率为40%~75%[141,145]。单纯放疗可以导致椎体前方或一侧的楔形变,随后发生脊柱的侧弯或后凸畸形,其发生率为10%~100%[164]。脊柱尤文肉瘤行椎板减压后的患者一般需行辅助放疗,已经行椎板减压的患者再行放疗可导致严重的脊柱畸形[165,166]。故在行单纯椎板切除减压后需行脊柱稳定手术[136,141],如椎板成形术或后外侧融合术并辅以外固定以预防脊柱畸形的发生[164],行全脊椎整块切除的患者则应进行包括前柱在内的360°稳定性重建。

5.3 骨盆/骶骨尤文肉瘤的外科治疗

5.3.1 外科边缘(1B级):建议采用国际抗癌联盟(UICC)手术切缘("R"切缘),因为多数患者需要考虑术后放疗。对于骨盆/骶骨的尤文肉瘤病例来说,在放疗或(和)化疗的基础上,为使患者获得更高的局部控制率以及更好的预后,首选外科初始治疗方案均为切缘阴性(R0切除)的广泛切除,尽量避免囊内切除[94,95,167-169]。

国际抗癌联盟手术切缘定义为:手术切缘镜下观察,R0为无微小病灶残留,R1为微小病灶残留,R2为肉眼可见病灶残留。经多学科的协作治疗,骨盆/骶骨尤文肉瘤患者的5年生存率在45%~75%[95,167,169,170],而四肢尤文肉瘤患者的5年无进展生存期、总体生存率以及局部控制率分别为:24.1%,43.5%~64%,以及55%[171,172]。骨盆/骶骨尤文肉瘤患者的预后差[14,172],对于骨盆/骶骨的尤文肉瘤病例来说,无论病理分级如何,外科手术都首选切缘阴性的广泛切除[94,95,167-169]。满意的外科边界可能降低局部复发的风险[81]。Hoffmann等报道的大样本对照研究长达13年的随访结果显示,接受外科手术的骨盆/骶骨尤文肉瘤患者,广泛切除使得无转移的入组治疗患者无进展生存率达到60%,而边缘切除与囊内切除为52%;广泛切除使得无转移的随访患者其无进展生存率达到37%,而边缘切除与囊内切除为0%[93]。尽量避免囊内切除,因为此种手术与单纯放疗相比并无获益[15]。非常接近肿瘤的骨盆/骶骨尤文肉瘤R0边缘,也建议采用术后放疗[31]。由于骨盆/骶骨的尤文肉瘤来源特性、解剖部位、放化疗敏感性等特征,NCCN推荐的广泛切除的概念即为R0切除。

局部治疗中手术切除是最佳方法;外科手术边界不足时应予以术后放疗;术后组织学反应不良时应考虑放疗(与放疗医师讨论)。

如果可能,切缘阴性的广泛切除是局部的最佳选择,局部放疗也是对局限性病变的局部控制方法,但是目前没有比较此两种方法的随机研究。合作性研究小组的尤文肉瘤局部控制方式的对比研究发现,局部控制手段(手术、放疗或手术加放疗)没有对总体生存率以及无进展生存率产生十分显著的影响[29,30,173]。在CESS86临床试验中,虽然积极的手术和切除再加放疗后的局部控制率(分别为100%和95%)较适形放疗(86%)更高,但因为外科手术后发生转移的风险更高,在无复发生存率或总体生存率方面没有显著提高[29]。在INT-0091研究中,患者单独手术或放疗治疗后局部控制失败的发生率是相近的(25%),但手术加放疗后的局部控制失败的发生率更低(10.5%)[169]。5年无事件生存率同样在组间没有显著差别(手术、放疗、手术加放疗组分别为42%、52%、47%)。其他回顾性分析的数据表明手术(加或不加术后放疗)对于局限性病变的局部控制能力优于单纯放疗[31,168]。1058例CESS81、CESS86及EICESS92临床试验联合分析表明手术(加或不加术后放疗)后局部控制失败率,较适形放疗明显降低(分别为7.5%和26.3%,P=0.001),而术前放疗组的局部控制率与手术组(5.3%)相当[31]。由儿童肿瘤组开展的对于序贯性研究(INT-0091、INT-0154和AEWS0031)的回顾性分析表明:适形放疗与手术加放疗相比有更高的局部控制失败风险,但对远隔部位治疗失败没有影响[168]。然而,对于手术边界不足的患者,术后应当给予局部放疗,以期提高局部控制率。当术后标本的组织学应答不良(即肿瘤细胞存活率>10%)时应与放疗科医师讨论是否予以术后放疗[15]。

5.3.2 复发、转移病例的处理(1B级):建议对骨复发或转移病灶进行手术治疗或放疗。建议对单纯肺转移患者行全肺放疗。

尤文肉瘤较易复发,单纯局部病灶患者的复发率为30%~40%,存在原发转移以及播散的患者的复发率为60%~80%[48,62]。对于复发患者,目前发现唯一的预后因素是复发的时间:初始诊断2年以后复发者预后较好(P<0.0001)[15,65]。而且,局部复发患者的5年生存率为13%~30%,优于全身或者合并复发患者[54,65]。对于复发性骨病灶,建议行手术切除和(或)

放疗[58]，部分患者可以从中获益。20%~25%患者在诊断时已有转移（肺：10%；骨/骨髓：10%；上述两种部位或其他：5%）[15,16,19,69,174]，单纯肺转移患者预后优于骨转移患者以及同时肺转移、骨转移的患者[15,19,174]，5年无进展生存率分别为29%、19%和8%（P<0.001）[15]。对单纯骨转移患者建议行外科手术切除和（或）放疗[58]，对肺转移患者进行全肺放射治疗可能会提高生存率[175]。

5.3.3 骨盆重建手术（1B级）：在术中条件允许的情况下应进行恢复肢体功能的骨盆重建。

骨盆的功能是传导躯体的重量和参与构成髋关节。如果在肿瘤切除后，股骨-骶骨之间的骨连续性和髋关节的结构不完整，则需要进行重建。对于Ⅲ型或骶髂关节稳定性未受到影响的Ⅰ型切除，通常不需要重建。对于骶髂关节的稳定性受到影响的Ⅰ型或Ⅰ+Ⅳ型切除，需要进行重建，恢复骨盆环的连续性[176,177]。骨盆恶性肿瘤切除后的功能重建是骨肿瘤医师的一大挑战，重建方法包括人工假体和骨水泥[178-180]、马鞍式假体[181]、病灶骨灭活[182,183]或者辐照[184,185]再植、近端股骨自体骨移植[186]、同种异体骨移植[187-192]以及带血管蒂的腓骨瓣移植[193]等，国内王臻教授团队也提出了儿童及青少年尤文肉瘤“髋臼挽救”的概念[194,195]。同种异体移植骨重建方法的优点在于能够重建复杂的骨盆骨结构，但是文献报道此种方法的并发症[187-191]，如：感染、异体骨吸收等发生率较高[187,189,190,192]。而且可调式人工半骨盆假体的术后功能及并发症发生率均优于马鞍式假体[179-181]。

5.3.4 截肢手术的选择（1B级）：当体积巨大的骨盆软骨肉瘤累及主要血管神经，或复发、放疗等因素造成局部软组织条件不良的情况下应选择截肢。

局部控制可通过保肢或截肢来实现。对部分病例而言，截肢可能是达到这一目标的最佳选择。但是，能够合理保全功能，应选择保肢手术[31,176,196]。保留髋臼患者MSTS评分高于髋臼切除的骨盆尤文肉瘤患者MSTS评分[197]。截肢和保肢手术获得满意的外科边界的比例无统计学差异[198]。

5.3.5 切除技术与重建技术（1B级）：建议采用数字导航技术以及数字化骨科技术（3D打印模型与假体、3D打印截骨导板）。

骨盆肿瘤导航手术便于骨盆区域深部骨性结构和肿瘤的观察，可以做到内植物的精确放置，减少并发症，避免因反复透视增加辐射危害。计算机导航侧重于术中影像学辅助肿瘤定位，引导切除肿瘤和骨盆截骨[199,200]。计算机导航辅助肿瘤切除和个体化定制髋臼假体重建能够满足髋臼肿瘤精确切除和重建的要求，肿瘤切除彻底、髋臼重建满意、并发症发生率低、近期效果良好，是外科治疗恶性髋臼肿瘤的一种有效方法。3D打印手术导板很好地适应了骨肿瘤手术个体化要求，可实现术前设计，不同3D打印技术制备的手术导板各有优势，需根据具体手术方式选择。

5.3.6 腰骶稳定（1B级）：建议对骶髂关系不稳的进行稳定性重建。

国内郭卫教授团队报道了新的骶骨恶性肿瘤的外科分区系统，对于低位骶骨（骶2、3间盘以下）的恶性肿瘤来说，外科切除后无需重建。高位骶骨（骶2、3间盘以上）恶性肿瘤切除后需重建骶髂关节连续性[201]。也有其他研究支持这一结论[196,202]。

参 考 文 献

[1] Delattre O, Zucman J, Melot T, et al. The Ewing family of tumors--a subgroup of small-round-cell tumors defined by specific chimeric transcripts. N Engl J Med, 1994, 331(5): 294-299.

[2] Denny CT. Gene rearrangements in Ewing's sarcoma. Cancer Invest, 1996, 14(1): 83-88.

[3] Shing DC, McMullan DJ, Roberts P, et al. FUS/ERG gene fusions in Ewing's tumors. Cancer Res, 2003, 63(15): 4568-4576.

[4] Ng TL, O'Sullivan MJ, Pallen CJ, et al. Ewing sarcoma with novel translocation t(2;16) producing an in-frame fusion of FUS and FEV. J Mol Diagn, 2007, 9(4): 459-463.

[5] Ambros IM, Ambros PF, Strehl S, et al. MIC2 is a specific marker for Ewing's sarcoma and peripheral primitive neuroectodermal tumors. Evidence for a common histogenesis of Ewing's sarcoma and peripheral primitive neuroectodermal tumors from MIC2 expression and specific chromosome aberration. Cancer, 1991, 67(7): 1886-1893.

[6] Perlman EJ, Dickman PS, Askin FB, et al. Ewing's sarcoma--routine diagnostic utilization of MIC2 analysis: a Pediatric Oncology Group/Children's Cancer Group Intergroup Study. Hum Pathol, 1994, 25(3): 304-307.

[7] Olsen SH, Thomas DG, Lucas DR. Cluster analysis of immunohistochemical profiles in synovial sarcoma, malignant peripheral nerve sheath tumor, and Ewing sarcoma. Mod Pathol, 2006, 19(5): 659-668.

[8] Bernstein M, Kovar H, Paulussen M, et al. Ewing's sarcoma family of tumors: current management. Oncologist, 2006,

11(5): 503-519.

[9] Glaubiger DL, Makuch R, Schwarz J, et al. Determination of prognostic factors and their influence on therapeutic results in patients with Ewing's sarcoma. Cancer, 1980, 45 (8): 2213-2219.

[10] Ahrens S, Hoffmann C, Jabar S, et al. Evaluation of prognostic factors in a tumor volume-adapted treatment strategy for localized Ewing sarcoma of bone: the CESS 86 experience. Cooperative Ewing Sarcoma Study. Med Pediatr Oncol, 1999, 32(3): 186-195.

[11] Göbel V, Jürgens H, Etspüler G, et al. Prognostic significance of tumor volume in localized Ewing's sarcoma of bone in children and adolescents. J Cancer Res Clin Oncol, 1987, 113(2): 187-191.

[12] Bacci G, Longhi A, Ferrari S, et al. Prognostic factors in non-metastatic Ewing's sarcoma tumor of bone: an analysis of 579 patients treated at a single institution with adjuvant or neoadjuvant chemotherapy between 1972 and 1998. Acta Oncol, 2006, 45(4): 469-475.

[13] Rodríguez-Galindo C, Liu T, Krasin MJ, et al.Analysis of prognostic factors in ewing sarcoma family of tumors: review of St. Jude Children's Research Hospital studies. Cancer, 2007, 110(2): 375-384.

[14] Bacci G, Boriani S, Balladelli A, et al. Treatment of nonmetastatic Ewing's sarcoma family tumors of the spine and sacrum: the experience from a single institution. Eur Spine J, 2009, 18(8): 1091-1095.

[15] Cotterill SJ, Ahrens S, Paulussen M, et al. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. J Clin Oncol, 2000, 18(17): 3108-3114.

[16] Cangir A, Vietti TJ, Gehan EA, et al. Ewing's sarcoma metastatic at diagnosis. Results and comparisons of two intergroup Ewing's sarcoma studies. Cancer, 1990, 66(5): 887-893.

[17] Paulino AC, Mai WY, Teh BS. Radiotherapy in metastatic ewing sarcoma. Am J Clin Oncol, 2013, 36(3): 283-286.

[18] Oberlin O, Deley MC, Bui BN, et al. Prognostic factors in localized Ewing's tumours and peripheral neuroectodermal tumours: the third study of the French Society of Paediatric Oncology (EW88 study). Br J Cancer, 2001, 85(11): 1646-1654.

[19] Paulussen M, Ahrens S, Dunst J, et al. Localized Ewing tumor of bone: final results of the cooperative Ewing's Sarcoma Study CESS 86. J Clin Oncol, 2001, 19(6): 1818-1829.

[20] Kissane JM, Askin FB, Foulkes M, et al. Ewing's sarcoma of bone: clinicopathologic aspects of 303 cases from the Intergroup Ewing's Sarcoma Study. Hum Pathol, 1983, 14(9): 773-779.

[21] Gupta AA, Pappo A, Saunders N, et al. Clinical outcome of children and adults with localized Ewing sarcoma: impact of chemotherapy dose and timing of local therapy. Cancer, 2010, 116(13): 3189-3194.

[22] Lee J, Hoang BH, Ziogas A, et al. Analysis of prognostic factors in Ewing sarcoma using a population-based cancer registry. Cancer, 2010, 116(8): 1964-1973.

[23] Treglia G, Salsano M, Stefanelli A, et al. Diagnostic accuracy of ^{18}F-FDG-PET and PET/CT in patients with Ewing sarcoma family tumours: a systematic review and a meta-analysis. Skeletal Radiol, 2012, 41(3): 249-256.

[24] Avigad S, Cohen IJ, Zilberstein J, et al. The predictive potential of molecular detection in the nonmetastatic Ewing family of tumors. Cancer, 2004, 100(5): 1053-1058.

[25] de Alava E, Kawai A, Healey JH, et al. EWS-FLI1 fusion transcript structure is an independent determinant of prognosis in Ewing's sarcoma. J Clin Oncol, 1998, 16(4): 1248-1255.

[26] Zoubek A, Dockhorn-Dworniczak B, Delattre O, et al. Does expression of different EWS chimeric transcripts define clinically distinct risk groups of Ewing tumor patients? J Clin Oncol, 1996, 14(4): 1245-1251.

[27] Le Deley MC, Delattre O, Schaefer KL, et al. Impact of EWS-ETS fusion type on disease progression in Ewing's sarcoma/peripheral primitive neuroectodermal tumor: prospective results from the cooperative Euro-E.W.I.N.G. 99 trial. J Clin Oncol, 2010, 28(12): 1982-1988.

[28] van Doorninck JA, Ji L, Schaub B, et al. Current treatment protocols have eliminated the prognostic advantage of type 1 fusions in Ewing sarcoma: a report from the Children's Oncology Group. J Clin Oncol, 2010, 28(12): 1989-1994.

[29] Dunst J, Jürgens H, Sauer R, et al. Radiation therapy in Ewing's sarcoma: an update of the CESS 86 trial. Int J Radiat Oncol Biol Phys, 1995, 32(4): 919-930.

[30] Yock TI, Krailo M, Fryer CJ, et al. Local control in pelvic Ewing sarcoma: analysis from INT-0091--a report from the Children's Oncology Group. J Clin Oncol, 2006, 24(24): 3838-3843.

[31] Schuck A, Ahrens S, Paulussen M, et al. Local therapy in localized Ewing tumors: results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials. Int J Radiat Oncol Biol Phys, 2003, 55(1): 168-177.

[32] Krasin MJ, Davidoff AM, Rodriguez-Galindo C, et al. Definitive surgery and multiagent systemic therapy for patients with localized Ewing sarcoma family of tumors: local outcome and prognostic factors. Cancer, 2005, 104(2): 367-373.

[33] Schuck A, Ahrens S, von Schorlemer I, et al. Radiotherapy in Ewing tumors of the vertebrae: treatment results and local relapse analysis of the CESS 81/86 and EICESS 92 trials. Int J Radiat Oncol Biol Phys, 2005, 63(5): 1562-1567.

[34] Krasin MJ, Rodriguez-Galindo C, Billups CA, et al. Definitive irradiation in multidisciplinary management of localized Ewing sarcoma family of tumors in pediatric patients: outcome and prognostic factors. Int J Radiat Oncol Biol Phys, 2004, 60(3): 830-838.

[35] Paulino AC, Nguyen TX, Mai WY, et al. Dose response and local control using radiotherapy in non-metastatic Ewing sarcoma. Pediatr Blood Cancer, 2007, 49(2): 145-148.

[36] Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med, 2003, 348(8): 694-701.

[37] Nesbit ME Jr, Gehan EA, Burgert EO Jr, et al. Multimodal therapy for the management of primary, nonmetastatic Ew-

ing's sarcoma of bone: a long-term follow-up of the First Intergroup study. J Clin Oncol, 1990, 8(10): 1664-1674.
[38] Shamberger RC, LaQuaglia MP, Gebhardt MC, et al. Ewing sarcoma/primitive neuroectodermal tumor of the chest wall: impact of initial versus delayed resection on tumor margins, survival, and use of radiation therapy. Ann Surg, 2003, 238(4): 563-567; discussion 567-568.
[39] Burgert EO Jr, Nesbit ME, Garnsey LA, et al. Multimodal therapy for the management of nonpelvic, localized Ewing's sarcoma of bone: intergroup study IESS-II. J Clin Oncol, 1990, 8(9): 1514-1524.
[40] Kolb EA, Kushner BH, Gorlick R, et al. Long-term event-free survival after intensive chemotherapy for Ewing's family of tumors in children and young adults. J Clin Oncol, 2003, 21(18): 3423-3430.
[41] Rosito P, Mancini AF, Rondelli R, et al. Italian Cooperative Study for the treatment of children and young adults with localized Ewing sarcoma of bone: a preliminary report of 6 years of experience. Cancer, 1999, 86(3): 421-428.
[42] Wexler LH, DeLaney TF, Tsokos M, et al. Ifosfamide and etoposide plus vincristine, doxorubicin, and cyclophosphamide for newly diagnosed Ewing's sarcoma family of tumors. Cancer, 1996, 78(4): 901-911.
[43] Bacci G, Picci P, Ferrari S, et al. Neoadjuvant chemotherapy for Ewing's sarcoma of bone: no benefit observed after adding ifosfamide and etoposide to vincristine, actinomycin, cyclophosphamide, and doxorubicin in the maintenance phase-- results of two sequential studies. Cancer, 1998, 82(6): 1174-1183.
[44] Oberlin O, Habrand JL, Zucker JM, et al. No benefit of ifosfamide in Ewing's sarcoma: a nonrandomized study of the French Society of Pediatric Oncology. J Clin Oncol, 1992, 10(9): 1407-1412.
[45] Granowetter L, Womer R, Devidas M, et al. Dose-intensified compared with standard chemotherapy for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study. J Clin Oncol, 2009, 27(15): 2536-2541.
[46] Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. J Clin Oncol, 2012, 30(33): 4148-4154.
[47] Miser JS, Krailo MD, Tarbell NJ, et al. Treatment of metastatic Ewing's sarcoma or primitive neuroectodermal tumor of bone: evaluation of combination ifosfamide and etoposide-- a Children's Cancer Group and Pediatric Oncology Group study. J Clin Oncol, 2004, 22(14): 2873-2876.
[48] Paulussen M, Craft AW, Lewis I, et al. Results of the EICESS-92 Study: two randomized trials of Ewing's sarcoma treatment-- cyclophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients. J Clin Oncol, 2008, 26(27): 4385-4393.
[49] Le Deley MC, Paulussen M, Lewis I, et al. Cyclophosphamide compared with ifosfamide in consolidation treatment of standard-risk Ewing sarcoma: results of the randomized noninferiority Euro-EWING99-R1 trial. J Clin Oncol, 2014, 32(23): 2440-2448.
[50] Ferrari S, Sundby Hall K, Luksch R, et al. Nonmetastatic Ewing family tumors: high-dose chemotherapy with stem cell rescue in poor responder patients. Results of the Italian Sarcoma Group/Scandinavian Sarcoma Group III protocol. Ann Oncol, 2011, 22(5): 1221-1227.
[51] Gaspar N, Rey A, Bérard PM, et al. Risk adapted chemotherapy for localised Ewing's sarcoma of bone: the French EW93 study. Eur J Cancer, 2012, 48(9): 1376-1385.
[52] Kushner BH, Meyers PA. How effective is dose-intensive/myeloablative therapy against Ewing's sarcoma/primitive neuroectodermal tumor metastatic to bone or bone marrow? The Memorial Sloan-Kettering experience and a literature review. J Clin Oncol, 2001, 19(3): 870-880.
[53] Juergens C, Weston C, Lewis I, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. Pediatr Blood Cancer, 2006, 47(1): 22-29.
[54] Burdach S, Thiel U, Schöniger M, et al. Total body MRI-governed involved compartment irradiation combined with high-dose chemotherapy and stem cell rescue improves long-term survival in Ewing tumor patients with multiple primary bone metastases. Bone Marrow Transplant, 2010, 45(3): 483-489.
[55] Ladenstein R, Pötschger U, Le Deley MC, et al. Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. J Clin Oncol, 2010, 28(20): 3284-3291.
[56] Oberlin O, Rey A, Desfachelles AS, et al. Impact of high-dose busulfan plus melphalan as consolidation in metastatic Ewing tumors: a study by the Société Française des Cancers de l'Enfant. J Clin Oncol, 2006, 24(24): 3997-4002.
[57] Rosenthal J, Bolotin E, Shakhnovits M, et al. High-dose therapy with hematopoietic stem cell rescue in patients with poor prognosis Ewing family tumors. Bone Marrow Transplant, 2008, 42(5): 311-318.
[58] Haeusler J, Ranft A, Boelling T, et al. The value of local treatment in patients with primary, disseminated, multifocal Ewing sarcoma (PDMES). Cancer, 2010, 116(2): 443-450.
[59] Denbo JW, Shannon Orr W, Wu Y, et al. Timing of surgery and the role of adjuvant radiotherapy in ewing sarcoma of the chest wall: a single-institution experience. Ann Surg Oncol, 2012, 19(12): 3809-3815.
[60] Bacci G, Forni C, Longhi A, et al. Long-term outcome for patients with non-metastatic Ewing's sarcoma treated with adjuvant and neoadjuvant chemotherapies. 402 patients treated at Rizzoli between 1972 and 1992. Eur J Cancer, 2004, 40(1): 73-83.
[61] Bacci G, Ferrari S, Longhi A, et al. Therapy and survival after recurrence of Ewing's tumors: the Rizzoli experience in 195 patients treated with adjuvant and neoadjuvant chemotherapy from 1979 to 1997. Ann Oncol, 2003, 14(11): 1654-1659.
[62] Leavey PJ, Mascarenhas L, Marina N, et al. Prognostic factors for patients with Ewing sarcoma (EWS) at first recur-

rence following multi-modality therapy: A report from the Children's Oncology Group. Pediatr Blood Cancer, 2008, 51 (3): 334-338.
[63] Rodriguez-Galindo C, Billups CA, Kun LE, et al. Survival after recurrence of Ewing tumors: the St Jude Children's Research Hospital experience, 1979-1999. Cancer, 2002, 94 (2): 561-569.
[64] Robinson SI, Ahmed SK, Okuno SH, et al. Clinical outcomes of adult patients with relapsed Ewing sarcoma: a 30-year single-institution experience. Am J Clin Oncol, 2014, 37(6): 585-591.
[65] Stahl M, Ranft A, Paulussen M, et al. Risk of recurrence and survival after relapse in patients with Ewing sarcoma. Pediatr Blood Cancer, 2011, 57(4): 549-553.
[66] Miser JS, Kinsella TJ, Triche TJ, et al. Ifosfamide with mesna uroprotection and etoposide: an effective regimen in the treatment of recurrent sarcomas and other tumors of children and young adults. J Clin Oncol, 1987, 5(8): 1191-1198.
[67] Van Winkle P, Angiolillo A, Krailo M, et al. Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the Children's Cancer Group (CCG) experience. Pediatr Blood Cancer, 2005, 44(4): 338-347.
[68] Navid F, Willert JR, McCarville MB, et al. Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma. Cancer, 2008, 113(2): 419-425.
[69] Bernstein ML, Devidas M, Lafreniere D, et al. Intensive therapy with growth factor support for patients with Ewing tumor metastatic at diagnosis: Pediatric Oncology Group/Children's Cancer Group Phase II Study 9457--a report from the Children's Oncology Group. J Clin Oncol, 2006, 24(1): 152-159.
[70] Casey DA, Wexler LH, Merchant MS, et al. Irinotecan and temozolomide for Ewing sarcoma: the Memorial Sloan-Kettering experience. Pediatr Blood Cancer, 2009, 53(6): 1029-1034.
[71] Hunold A, Weddeling N, Paulussen M, et al. Topotecan and cyclophosphamide in patients with refractory or relapsed Ewing tumors. Pediatr Blood Cancer, 2006, 47(6): 795-800.
[72] Kushner BH, Kramer K, Meyers PA, et al. Pilot study of topotecan and high-dose cyclophosphamide for resistant pediatric solid tumors. Med Pediatr Oncol, 2000, 35(5): 468-474.
[73] Saylors RL 3rd, Stine KC, Sullivan J, et al. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. J Clin Oncol, 2001, 19(15): 3463-3469.
[74] Wagner LM, Crews KR, Iacono LC, et al. Phase I trial of temozolomide and protracted irinotecan in pediatric patients with refractory solid tumors. Clin Cancer Res, 2004, 10(3): 840-848.
[75] Wagner LM, McAllister N, Goldsby RE, et al. Temozolomide and intravenous irinotecan for treatment of advanced Ewing sarcoma. Pediatr Blood Cancer, 2007, 48(2): 132-139.
[76] Raciborska A, Bilska K, Drabko K, et al. Vincristine, irinotecan, and temozolomide in patients with relapsed and refractory Ewing sarcoma. Pediatr Blood Cancer, 2013, 60 (10): 1621-1625.
[77] McNall-Knapp RY, Williams CN, Reeves EN, et al. Extended phase I evaluation of vincristine, irinotecan, temozolomide, and antibiotic in children with refractory solid tumors. Pediatr Blood Cancer, 2010, 54(7): 909-915.
[78] Blaney S, Berg SL, Pratt C, et al. A phase I study of irinotecan in pediatric patients: a pediatric oncology group study. Clin Cancer Res, 2001, 7(1): 32-37.
[79] Furman WL, Stewart CF, Poquette CA, et al. Direct translation of a protracted irinotecan schedule from a xenograft model to a phase I trial in children. J Clin Oncol, 1999, 17 (6): 1815-1824.
[80] McGregor LM, Stewart CF, Crews KR, et al. Dose escalation of intravenous irinotecan using oral cefpodoxime: a phase I study in pediatric patients with refractory solid tumors. Pediatr Blood Cancer, 2012, 58(3): 372-379.
[81] Ozaki T, Hillmann A, Hoffmann C, et al. Significance of surgical margin on the prognosis of patients with Ewing's sarcoma. A report from the Cooperative Ewing's Sarcoma Study. Cancer, 1996, 78(4): 892-900.
[82] Iwamoto, Y. Diagnosis and treatment of Ewing's sarcoma. Jpn J Clin Oncol, 2007, 37(2): 79-89.
[83] Avedian RS, Haydon RC, Peabody TD. Multiplanar osteotomy with limited wide margins: a tissue preserving surgical technique for high-grade bone sarcomas. Clin Orthop Relat Res, 2010, 468(10): 2754-2764.
[84] Ruggieri P, Angelini A, Montalti M, et al. Tumours and tumour-like lesions of the hip in the paediatric age: a review of the Rizzoli experience. Hip Int, 2009, 19 Suppl 6: S35-S45.
[85] Liu CY, Yen CC, Chen WM, et al. Soft tissue sarcoma of extremities: the prognostic significance of adequate surgical margins in primary operation and reoperation after recurrence. Ann Surg Oncol, 2010, 17(8): 2102-2111.
[86] McKee MD, Liu DF, Brooks JJ, et al. The prognostic significance of margin width for extremity and trunk sarcoma. J Surg Oncol, 2004, 85(2): 68-76.
[87] Kandel R, Coakley N, Werier J, et al. Surgical margins and handling of soft-tissue sarcoma in extremities: a clinical practice guideline. Curr Oncol, 2013, 20(3): e247-e254.
[88] Li J, Guo Z, Pei GX, et al. Limb salvage surgery for calcaneal malignancy. J Surg Oncol, 2010, 102(1): 48-53.
[89] Laurence V, Pierga JY, Barthier S, et al. Long-term follow up of high-dose chemotherapy with autologous stem cell rescue in adults with Ewing tumor. Am J Clin Oncol, 2005, 28(3): 301-309.
[90] Whelan J, McTiernan A, Cooper N, et al. Incidence and survival of malignant bone sarcomas in England 1979-2007. Int J Cancer, 2012, 131(4): p. E508-E517.
[91] Esiashvili N, Goodman M, Marcus RB Jr. Changes in incidence and survival of Ewing sarcoma patients over the past 3 decades: Surveillance Epidemiology and End Results data. J Pediatr Hematol Oncol, 2008, 30(6): 425-430.
[92] Elomaa I, Blomqvist CP, Saeter G, et al. Five-year results in Ewing's sarcoma. The Scandinavian Sarcoma Group experience with the SSG IX protocol. Eur J Cancer, 2000, 36(7):

875-880.
[93] Hoffmann C, Ahrens S, Dunst J, et al. Pelvic Ewing sarcoma: a retrospective analysis of 241 cases. Cancer, 1999, 85 (4): 869-877.
[94] Sucato DJ, Rougraff B, McGrath BE, et al. Ewing's sarcoma of the pelvis. Long-term survival and functional outcome. Clin Orthop Relat Res, 2000, (373): 193-201.
[95] Rödl RW, Hoffmann C, Gosheger G, et al. Ewing's sarcoma of the pelvis: combined surgery and radiotherapy treatment. J Surg Oncol, 2003, 83(3): 154-160.
[96] Gronchi A, Lo Vullo S, Colombo C, et al. Extremity soft tissue sarcoma in a series of patients treated at a single institution: local control directly impacts survival. Ann Surg, 2010, 251(3): 506-511.
[97] Sluga M, Windhager R, Lang S, et al. A long-term review of the treatment of patients with Ewing's sarcoma in one institution. Eur J Surg Oncol, 2001, 27(6): 569-573.
[98] Liljenqvist U, Lerner T, Halm H, et al. En bloc spondylectomy in malignant tumors of the spine. Eur Spine J, 2008, 17 (4): 600-609.
[99] Talac R, Yaszemski MJ, Currier BL, et al. Relationship between surgical margins and local recurrence in sarcomas of the spine. Clin Orthop Relat Res, 2002, (397): 127-132.
[100]Gherlinzoni F, Picci P, Bacci G, et al. Limb sparing versus amputation in osteosarcoma. Correlation between local control, surgical margins and tumor necrosis: Istituto Rizzoli experience. Ann Oncol, 1992, 3 Suppl 2: S23-S27.
[101]Akhavan A, Binesh F, Hashemi A, et al. Clinicopathologic characteristics and outcome of childhood and adolescent Ewing's sarcoma in center of Iran. Iran J Ped Hematol Oncol, 2014, 4(3): 97-102.
[102]Hong AM, Millington S, Ahern V, et al. Limb preservation surgery with extracorporeal irradiation in the management of malignant bone tumor: the oncological outcomes of 101 patients. Ann Oncol, 2013, 24(10): 2676-2680.
[103]Kutluk MT, Yalçin B, Akyüz C, et al. Treatment results and prognostic factors in Ewing sarcoma. Pediatr Hematol Oncol, 2004, 21(7): 597-610.
[104]Pérez-Muñoz I, Grimer RJ, Spooner D, et al. Use of tissue expander in pelvic Ewing's sarcoma treated with radiotherapy. Eur J Surg Oncol, 2014, 40(2): 197-201.
[105]Arpaci E, Yetisyigit T, Seker M, et al. Prognostic factors and clinical outcome of patients with Ewing's sarcoma family of tumors in adults: multicentric study of the Anatolian Society of Medical Oncology. Med Oncol, 2013, 30(1): 469.
[106]Marulanda GA, Henderson ER, Johnson DA, et al. Orthopedic surgery options for the treatment of primary osteosarcoma. Cancer Control, 2008, 15(1): 13-20.
[107]Mavrogenis AF, Abati CN, Romagnoli C, et al. Similar survival but better function for patients after limb salvage versus amputation for distal tibia osteosarcoma. Clin Orthop Relat Res, 2012, 470(6): 1735-1748.
[108]Schrager J, Patzer RE, Mink PJ, et al. Survival outcomes of pediatric osteosarcoma and Ewing's sarcoma: a comparison of surgery type within the SEER database, 1988-2007. J Registry Manag, 2011, 38(3): 153-161.
[109]Postma A, Kingma A, De Ruiter JH, et al. Quality of life in bone tumor patients comparing limb salvage and amputation of the lower extremity. J Surg Oncol, 1992, 51(1): 47-51.
[110]Malek F, Somerson JS, Mitchel S, et al. Does limb-salvage surgery offer patients better quality of life and functional capacity than amputation? Clin Orthop Relat Res, 2012, 470 (7): 2000-2006.
[111]Mei J, Zhu XZ, Wang ZY, et al. Functional outcomes and quality of life in patients with osteosarcoma treated with amputation versus limb-salvage surgery: a systematic review and meta-analysis. Arch Orthop Trauma Surg, 2014, 134(11): 1507-1516.
[112]Ottaviani G, Robert RS, Huh WW, et al. Sociooccupational and physical outcomes more than 20 years after the diagnosis of osteosarcoma in children and adolescents: limb salvage versus amputation. Cancer, 2013, 119(20): 3727-3736.
[113]Aksnes LH, Bauer HC, Jebsen NL, et al. Limb-sparing surgery preserves more function than amputation: a Scandinavian sarcoma group study of 118 patients. J Bone Joint Surg Br, 2008, 90(6): 786-794.
[114]Koudelová J, Kunesová M, Koudela K Jr, et al. Peripheral primitive neuroectodermal tumor -- PNET. Acta Chir Orthop Traumatol Cech, 2006, 73(1): 39-44.[Article in Czech]
[115]Masrouha KZ, Musallam KM, Samra AB, et al. Correlation of non-mass-like abnormal MR signal intensity with pathological findings surrounding pediatric osteosarcoma and Ewing's sarcoma. Skeletal Radiol, 2012, 41(11): 1453-1461.
[116]Sanford Z, Israelsen S, Sehgal R, et al. Atypical growth on MRI in a case of Ewing's sarcoma despite lower SUV on PET. Skeletal Radiol, 2014, 43(6): 819-25.
[117]Borkowski P, Pawlikowski M, Skalski K. Expandable non-invasive prostheses - an alternative to pediatric patients with bone sarcoma. Conf Proc IEEE Eng Med Biol Soc, 2005, 4: 4056-4059.
[118]Muscolo DL, Ayerza MA, Aponte-Tinao LA, et al. Partial epiphyseal preservation and intercalary allograft reconstruction in high-grade metaphyseal osteosarcoma of the knee. J Bone Joint Surg Am, 2004, 86-A(12): 2686-2693.
[119]Bernthal NM, Greenberg M, Heberer K, et al. What are the functional outcomes of endoprosthestic reconstructions after tumor resection? Clin Orthop Relat Res, 2015, 473(3): 812-819.
[120]Gebert C, Wessling M, Hoffmann C, et al. Hip transposition as a limb salvage procedure following the resection of periacetabular tumors. J Surg Oncol, 2011, 103(3): 269-275.
[121]Natarajan MV, Chandra Bose J, Viswanath J, et al. Custom prosthetic replacement for distal radial tumours. Int Orthop, 2009, 33(4): 1081-1084.
[122]Puri A, Gulia A. The results of total humeral replacement following excision for primary bone tumour. J Bone Joint Surg Br, 2012, 94(9): 1277-1281.
[123]Puri A, Gulia A, Chan WH. Functional and oncologic outcomes after excision of the total femur in primary bone tumors: Results with a low cost total femur prosthesis. Indian J Orthop, 2012, 46(4): 470-474.
[124]Campanacci DA, Puccini S, Caff G, et al. Vascularised fib-

ular grafts as a salvage procedure in failed intercalary reconstructions after bone tumour resection of the femur. Injury, 2014, 45(2): 399-404.
[125]Hu YC, Ji JT, Lun DX. Intraoperative microwave inactivation in- situ of malignant tumors in the scapula. Orthop Surg, 2011, 3(4): 229-235.
[126]Rabitsch K, Maurer-Ertl W, Pirker-Frühauf U, et al. Intercalary reconstructions with vascularised fibula and allograft after tumour resection in the lower limb. Sarcoma, 2013, 2013: 160295.
[127]Moran M, Stalley PD. Reconstruction of the proximal humerus with a composite of extracorporeally irradiated bone and endoprosthesis following excision of high grade primary bone sarcomas. Arch Orthop Trauma Surg, 2009, 129 (10): 1339-1345.
[128]Bacci G, Picci P, Gherlinzoni F, et al. Localized Ewing's sarcoma of bone: ten years' experience at the Istituto Ortopedico Rizzoli in 124 cases treated with multimodal therapy. Eur J Cancer Clin Oncol, 1985, 21(2): 163-173.
[129]Oberlin O, Patte C, Demeocq F, et al. The response to initial chemotherapy as a prognostic factor in localized Ewing's sarcoma. Eur J Cancer Clin Oncol, 1985, 21(4): 463-467.
[130]Pilepich MV, Vietti TJ, Nesbit ME, et al. Ewing's sarcoma of the vertebral column. Int J Radiat Oncol Biol Phys, 1981, 7(1): 27-31.
[131]Wilkins RM, Pritchard DJ, Burgert EO Jr, et al. Ewing's sarcoma of bone. Experience with 140 patients. Cancer, 1986, 58(11): 2551-2555.
[132]Himelstein BP, Dormans JP. Malignant bone tumors of childhood. Pediatr Clin North Am, 1996, 43(4): 967-984.
[133]Vogin G, Helfre S, Glorion C, et al. Local control and sequelae in localised Ewing tumours of the spine: a French retrospective study. Eur J Cancer, 2013, 49(6): 1314-1323.
[134]Phillips RF, Higinbotham NL. The curability of Ewing's endothelioma of bone in children. J Pediatr, 1967, 70(3): 391-397.
[135]Rosen G. Current management of Ewing's sarcoma. Prog Clin Cancer, 1982, 8: 267-282.
[136]Indelicato DJ, Keole SR, Shahlaee AH, et al. Spinal and paraspinal Ewing tumors. Int J Radiat Oncol Biol Phys, 2010, 76(5): 1463-1471.
[137]Mukherjee D, Chaichana KL, Gokaslan ZL, et al. Survival of patients with malignant primary osseous spinal neoplasms: results from the Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 2003. J Neurosurg Spine, 2011, 14(2): 143-150.
[138]Razek A, Perez CA, Tefft M, et al. Intergroup Ewing's Sarcoma Study: local control related to radiation dose, volume, and site of primary lesion in Ewing's sarcoma. Cancer, 1980, 46(3): 516-521.
[139]Rosen G, Caparros B, Nirenberg A, et al. Ewing's sarcoma: ten- year experience with adjuvant chemotherapy. Cancer, 1981, 47(9): 2204-2213.
[140]Sharafuddin MJ, Haddad FS, Hitchon PW, et al. Treatment options in primary Ewing's sarcoma of the spine: report of seven cases and review of the literature. Neurosurgery, 1992, 30(4): 610-8; discussion 618-619.
[141]Marco RA, Gentry JB, Rhines LD, et al. Ewing's sarcoma of the mobile spine. Spine (Phila Pa 1976), 2005, 30(7): 769-773.
[142]Hess T, Kramann B, Schmidt E, et al. Use of preoperative vascular embolisation in spinal metastasis resection. Arch Orthop Trauma Surg, 1997, 116(5): 279-282.
[143]Radeleff B, Eiers M, Lopez-Benitez R, et al. Transarterial embolization of primary and secondary tumors of the skeletal system. Eur J Radiol, 2006, 58(1): 68-75.
[144]林俊, 邱贵兴, 吴志宏. 脊柱原发性尤文氏肉瘤的治疗进展. 中国骨与关节外科, 2010, 3(3): 245-249.
[145]Grubb MR, Currier BL, Pritchard DJ, et al. Primary Ewing's sarcoma of the spine. Spine (Phila Pa 1976), 1994, 19 (3): 309-313.
[146]Tomita K, Kawahara N, Kobayashi T, et al. Surgical strategy for spinal metastases. Spine (Phila Pa 1976), 2001, 26 (3): 298-306.
[147]Boriani S, Amendola L, Corghi A, et al. Ewing's sarcoma of the mobile spine. Eur Rev Med Pharmacol Sci, 2011, 15 (7): 831-839.
[148]李晓, 郭卫, 杨荣利, 等. 脊柱原发尤文家族肿瘤的治疗及预后. 中国脊柱脊髓杂志, 2014, (2): 127-132.
[149]Yamazaki T, McLoughlin GS, Patel S, et al. Feasibility and safety of en bloc resection for primary spine tumors: a systematic review by the Spine Oncology Study Group. Spine (Phila Pa 1976), 2009, 34(22 Suppl): S31-S38.
[150]Boriani S, Bandiera S, Donthineni R, et al. Morbidity of en bloc resections in the spine. Eur Spine J, 2010, 19(2): 231-241.
[151]Bacci G, Toni A, Avella M, et al. Long-term results in 144 localized Ewing's sarcoma patients treated with combined therapy. Cancer, 1989, 63(8): 1477-1486.
[152]Patel SR. Radiation- induced sarcoma. Curr Treat Options Oncol, 2000, 1(3): 258-261.
[153]Strong LC, Herson J, Osborne BM, et al. Risk of radiation-related subsequent malignant tumors in survivors of Ewing's sarcoma. J Natl Cancer Inst, 1979, 62(6): 1401-1406.
[154]Tucker MA, D'Angio GJ, Boice JD Jr, et al. Bone sarcomas linked to radiotherapy and chemotherapy in children. N Engl J Med, 1987, 317(10): 588-593.
[155]Macbeth F. Radiation myelitis and thoracic radiotherapy: evidence and anecdote. Clin Oncol (R Coll Radiol), 2000, 12(5): 333-334.
[156]Maranzano E, Bellavita R, Floridi P, et al. Radiation- induced myelopathy in long-term surviving metastatic spinal cord compression patients after hypofractionated radiotherapy: a clinical and magnetic resonance imaging analysis. Radiother Oncol, 2001, 60(3): 281-288.
[157]Warscotte L, Duprez T, Lonneux M, et al. Concurrent spinal cord and vertebral bone marrow radionecrosis 8 years after therapeutic irradiation. Neuroradiology, 2002, 44(3): 245-248.
[158]Kuttesch JF Jr, Wexler LH, Marcus RB, et al. Second malignancies after Ewing's sarcoma: radiation dose-dependency of secondary sarcomas. J Clin Oncol, 1996, 14(10):

2818-2825.
[159]Mayfield JK. Postradiation spinal deformity. Orthop Clin North Am, 1979, 10(4): 829-844.
[160]Telles NC, Rabson AS, Pomeroy TC. Ewing's sarcoma: an autopsy study. Cancer, 1978, 41(6): 2321-2329.
[161]Albert TJ, Vacarro A. Postlaminectomy kyphosis. Spine (Phila Pa 1976), 1998, 23(24): 2738-2745.
[162]Herman JM, Sonntag VK. Cervical corpectomy and plate fixation for postlaminectomy kyphosis. J Neurosurg, 1994, 80(6): 963-970.
[163]Shikata J, Yamamuro T, Shimizu K, et al. Combined laminoplasty and posterolateral fusion for spinal canal surgery in children and adolescents. Clin Orthop Relat Res, 1990, (259): 92-99.
[164]de Jonge T, Slullitel H, Dubousset J, et al. Late-onset spinal deformities in children treated by laminectomy and radiation therapy for malignant tumours. Eur Spine J, 2005, 14 (8): 765-771.
[165]Lonstein JE. Post- laminectomy kyphosis. Clin Orthop Relat Res, 1977, (128): 93-100.
[166]Otsuka NY, Hey L, Hall JE. Postlaminectomy and postirradiation kyphosis in children and adolescents. Clin Orthop Relat Res, 1998, (354): 189-194.
[167]臧杰,郭卫,曲华毅. 骨盆尤文肉瘤31例治疗结果分析. 中华外科杂志, 2012, 50(6): 524-528.
[168]DuBois SG, Krailo MD, Gebhardt MC, et al. Comparative evaluation of local control strategies in localized Ewing sarcoma of bone: a report from the Children's Oncology Group. Cancer, 2015, 121(3): 467-475.
[169]Frassica FJ, Frassica DA, Pritchard DJ, et al. Ewing sarcoma of the pelvis. Clinicopathological features and treatment. J Bone Joint Surg Am, 1993, 75(10): 1457-1465.
[170]Evans RG, Nesbit ME, Gehan EA, et al. Multimodal therapy for the management of localized Ewing's sarcoma of pelvic and sacral bones: a report from the second intergroup study. J Clin Oncol, 1991, 9(7): 1173-1180.
[171]Biswas B, Rastogi S, Khan SA, et al. Outcomes and prognostic factors for Ewing-family tumors of the extremities. J Bone Joint Surg Am, 2014, 96(10): 841-849.
[172]Seker MM, Kos T, Ozdemir N, et al. Treatment and outcomes of Ewing sarcoma in Turkish adults: a single centre experience. Asian Pac J Cancer Prev, 2014, 15(1): 327-330.
[173]Raciborska A, Bilska K, Rychlowska-Pruszynska M, et al. Internal hemipelvectomy in the management of pelvic Ewing sarcoma - are outcomes better than with radiation therapy? J Pediatr Surg, 2014, 49(10): 1500-1504.
[174]Kushner BH, Meyers PA, Gerald WL, et al. Very-high-dose short-term chemotherapy for poor-risk peripheral primitive neuroectodermal tumors, including Ewing's sarcoma, in children and young adults. J Clin Oncol, 1995, 13(11): 2796-2804.
[175]Paulussen M, Ahrens S, Craft AW, et al. Ewing's tumors with primary lung metastases: survival analysis of 114 (European Intergroup) Cooperative Ewing's Sarcoma Studies patients. J Clin Oncol, 1998, 16(9): 3044-3052.
[176]Enneking WF, Dunham WK. Resection and reconstruction for primary neoplasms involving the innominate bone. J Bone Joint Surg Am, 1978, 60(6): 731-746.
[177]Hugate, R.J. and F.H. Sim, Pelvic reconstruction techniques. Orthop Clin North Am, 2006. 37(1): p. 85-97.
[178]Johnson JT. Reconstruction of the pelvic ring following tumor resection. J Bone Joint Surg Am, 1978, 60(6): 747-751.
[179]Guo W, Li D, Tang X, et al. Reconstruction with modular hemipelvic prostheses for periacetabular tumor. Clin Orthop Relat Res, 2007, 461: 180-188.
[180]Ji T, Guo W, Yang RL, et al. Modular hemipelvic endoprosthesis reconstruction--experience in 100 patients with mid-term follow-up results. Eur J Surg Oncol, 2013, 39(1): 53-60.
[181]Aboulafia AJ, Buch R, Mathews J, et al. Reconstruction using the saddle prosthesis following excision of primary and metastatic periacetabular tumors. Clin Orthop Relat Res, 1995, (314): 203-213.
[182]Harrington KD. The use of hemipelvic allografts or autoclaved grafts for reconstruction after wide resections of malignant tumors of the pelvis. J Bone Joint Surg Am, 1992, 74(3): 331-341.
[183]Satcher RL Jr, O'Donnell RJ, Johnston JO. Reconstruction of the pelvis after resection of tumors about the acetabulum. Clin Orthop Relat Res, 2003, (409): 209-217.
[184]Sys G, Uyttendaele D, Poffyn B, et al. Extracorporeally irradiated autografts in pelvic reconstruction after malignant tumour resection. Int Orthop, 2002, 26(3): 174-178.
[185]Wafa H, Grimer RJ, Jeys L, et al. The use of extracorporeally irradiated autografts in pelvic reconstruction following tumour resection. Bone Joint J, 2014, 96-B(10): 1404-1410.
[186]Laffosse JM, Pourcel A, Reina N, et al. Primary tumor of the periacetabular region: resection and reconstruction using a segmental ipsilateral femur autograft. Orthop Traumatol Surg Res, 2012, 98(3): 309-318.
[187]Bell RS, Davis AM, Wunder JS, et al. Allograft reconstruction of the acetabulum after resection of stage-IIB sarcoma. Intermediate-term results. J Bone Joint Surg Am, 1997, 79 (11): 1663-1674.
[188]Delloye C, de Nayer P, Allington N, et al. Massive bone allografts in large skeletal defects after tumor surgery: a clinical and microradiographic evaluation. Arch Orthop Trauma Surg, 1988, 107(1): 31-41.
[189]Langlais F, Lambotte JC, Thomazeau H. Long-term results of hemipelvis reconstruction with allografts. Clin Orthop Relat Res, 2001, (388): 178-186.
[190]Ozaki T, Hillmann A, Bettin D, et al. High complication rates with pelvic allografts. Experience of 22 sarcoma resections. Acta Orthop Scand, 1996, 67(4): 333-338.
[191]王威, 王岩, 毕文志. 骨盆肿瘤切除后同种异体骨移植重建骨盆的近期疗效. 中国修复重建外科杂志, 2014, 28 (3): 331-334.
[192]Delloye C, Banse X, Brichard B, et al. Pelvic reconstruction with a structural pelvic allograft after resection of a malignant bone tumor. J Bone Joint Surg Am, 2007, 89(3): 579-587.
[193]Clemens MW, Chang EI, Selber JC, et al. Composite extremity and trunk reconstruction with vascularized fibula

flap in postoncologic bone defects: a 10- year experience. Plast Reconstr Surg, 2012, 129(1): 170-178.
[194]范宏斌, 王臻, 郭征, 等. 经“Y”型软骨截骨髋臼挽救术治疗儿童和青少年TypeII型骨盆尤文肉瘤. 中华骨科杂志, 2014, 34(4): 460-465.
[195]付军, 郭征, 王臻, 等. 儿童骨盆尤文肉瘤的治疗以及对骨骼生长发育的影响. 中华肿瘤杂志, 2012, 34(12): 927-931.
[196]Tomita K. Reconstruction of the pelvic ring based on classification following resection of bone tumors. Gan To Kagaku Ryoho, 1988, 15(4 Pt 2-3): 1521-1527.
[197]Puri A, Pruthi M, Gulia A. Outcomes after limb sparing resection in primary malignant pelvic tumors. Eur J Surg Oncol, 2014, 40(1): 27-33.
[198]Shin KH, Rougraff BT, Simon MA. Oncologic outcomes of primary bone sarcomas of the pelvis. Clin Orthop Relat Res, 1994, (304): 207-217.
[199]Wong KC, Kumta SM, Chiu KH, et al. Precision tumour resection and reconstruction using image- guided computer navigation. J Bone Joint Surg Br, 2007, 89(7): 943-947.
[200]Wong KC, Kumta SM, Chiu KH, et al. Computer assisted pelvic tumor resection and reconstruction with a custom-made prosthesis using an innovative adaptation and its validation. Comput Aided Surg, 2007, 12(4): 225-232.
[201]Li D, Guo W, Tang X, et al. Surgical classification of different types of en bloc resection for primary malignant sacral tumors. Eur Spine J, 2011, 20(12): 2275-2281.
[202]Beadel GP, McLaughlin CE, Aljassir F, et al. Iliosacral resection for primary bone tumors: is pelvic reconstruction necessary? Clin Orthop Relat Res, 2005, 438: 22-29.

（上接259页）

[55] Dmytriw AA, Talla K, Smith R. Percutaneous sacroplasty for the management of painful pathologic fracture in a multiple myeloma patient: Case report and review of the literature. Neuroradiol J, 2017, 30(1): 80-83.
[56] Basile A, Tsetis D, Cavalli M, et al. Sacroplasty for local or massive localization of multiple myeloma. Cardiovasc Intervent Radiol, 2010, 33(6): 1270-1277.
[57] Sakellariou VI, Mavrogenis AF, Savvidou O, et al. Reconstruction of multiple myeloma lesions around the pelvis and acetabulum. Eur J Orthop Surg Traumatol, 2015, 25(4): 643-653.
[58] Wright JD, St Clair CM, Deutsch I, et al. Pelvic radiotherapy and the risk of secondary leukemia and multiple myeloma. Cancer, 2010, 116(10): 2486-2492.
[59] Rock MG, Harrington K. Pathologic fractures of the acetabulum and the pelvis. Orthopedics, 1992, 15(5): 569-576.
[60] Soutar R, Lucraft H, Jackson G, et al. Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma. Br J Haematol, 2004, 124(6): 717-726.
[61] Li QW, Niu SQ, Wang HY, et al. Radiotherapy alone is associated with improved outcomes over surgery in the management of solitary plasmacytoma. Asian Pac J Cancer Prev, 2015, 16(9): 3741-3745.
[62] Mendoza S, Urrutia J, Fuentes D. Surgical treatment of solitary plasmocytoma of the spine: case series. Iowa Orthop J, 2004, 24: 86-94.
[63] Venkatesh R, Tandon V, Patel N, et al. Solitary plasmacytoma of L3 vertebral body treated by minimal access surgery: Common problem different solution! J Clin Orthop Trauma, 2015, 6(4): 259-264.
[64] Finsinger P, Grammatico S, Chisini M, et al. Clinical features and prognostic factors in solitary plasmacytoma. Br J Haematol, 2016, 172(4): 554-560.