Current Approaches to Management of Bone Sarcoma in Adolescent and Young Adult (AYA) Patients

Katrina Ingley[1], Alessandra Maleddu[2], Franel Le Grange[2], Craig Gerrand[3], Archie Bleyer[4], Jeremy Whelan[2], and Sandra Strauss[2]

[1]BC Children's Hospital
[2]University College London Hospitals NHS Foundation Trust
[3]Royal National Orthopaedic Hospital NHS Trust
[4]Oregon Health & Science University

June 21, 2021

Abstract

Bone tumors are a group of histologically diverse diseases which occur across all ages. Two of the commonest, osteosarcoma (OS) and Ewing sarcoma (ES), are regarded as characteristic AYA cancers with an incidence peak in AYAs. They are curable for some but associated with unacceptably high rates of treatment failure and morbidity. The introduction of effective new therapeutics for bone sarcomas is slow, and to date, complex biology has been insufficiently characterized to allow more rapid therapeutic exploitation. This review focuses on current standards of care, recent advances that have or may soon change that standard of care and challenges to the expert clinical research community that we suggest must be met.

Introduction

Primary tumors arising in bone are characterized by an almost unique age incidence pattern, incompletely understood biology, complex and morbid treatments and patient outcomes in need of improvement. In the adolescent and young adult (AYA) age range, the two most common bone sarcomas are osteosarcoma (OS) and Ewing sarcoma (ES) of bone. While a significant proportion of young people with these diseases can be cured, their lives are often associated with lifelong consequences, especially in, but not limited to, physical functioning, so that survivorship issues are an essential consideration in providing care for AYA with bone sarcoma. Achieving improvements in survival has proved challenging despite greater levels of international collaboration in recent decades. This is likely multifactorial, including unequal access to expert multidisciplinary care. Recent observations of activity of new systemic agents against advanced disease hold hope for the future. A well-established multi-modality treatment approach for OS and ES focuses on systemic chemotherapy integrated with management of the primary tumor by surgery, radiotherapy (RT) or both. The challenge for specialists is to optimize these treatments to ensure the greatest number of young people survive with least long-term cost.

Epidemiology, Aetiology and Risk Factors

Primary bone sarcomas comprise <2% of all new malignancies in patients of all ages. In older adolescents aged 15-19 years, however, OS and ES account for 5.5% of new cases of all tumor types and in 15 to 24 year-olds they comprise 3.2% of all cancers.[1,2] A smaller proportion of chondrosarcomas, conventional type or mesenchymal, and very rare entities such as chordoma account for the rest of bone sarcomas in AYAs. The European age-standardized incidence rate for all bone sarcomas across all ages/ gender per year is 1.0 per 100,000 population, ˜0.3 per 100,000 person-years each for OS and ES.[3] Several population-based studies provide clear and consistent data about the relative incidence rates of these sarcomas and particularly the

relationship with age (Fig. 1A). The commonest bone sarcomas, OS and ES, have a peak incidence in AYAs, with a second peak in OS beyond 70 years (Fig. 1B). The male to female ratios for OS and ES are 1.2 and 1.1.[3] A racial disparity is notable for ES, with a higher incidence in Caucasians (Fig. 1C). While modest improvements in outcome for ES are seen in population data, due largely from wider implementation of multidisciplinary care and centralization, the same improvements are not apparent for OS (Fig. 1D).

OS is the most common primary bone sarcoma. In younger patients, most frequently diagnosed between ages 10 to 19 years.[4] It arises most commonly in the extremities compared to pelvic, axial and craniofacial primary locations in older patients.[5,6]Risk factors for OS include prior malignancy and radiation exposure, and particularly so in older patients,- underlying bone conditions such as Paget disease of bone and fibrous dysplasia.[7] While the majority of OS is sporadic, inherited cancer predisposition syndromes are recognized; these include Li- Fraumeni syndrome, hereditary retinoblastoma, Diamond-Blackfan anemia, Rothmund-Thompson, Werner and Bloom syndromes.[8] In a recent analysis, an estimated 28% of OS patients of all ages were found to carry a rare germline pathogenic, likely pathogenic variant in a cancer-susceptibility gene, with most of those variants in autosomal dominant cancer susceptibility genes, implicating an important role for germline genetic testing in younger patients.[9]

ES is a small round blue-cell tumor and the third most common primary bone sarcoma of all ages, also most frequently diagnosed between ages 10 to 19 years. It arises mostly in the extremities, followed by pelvis, ribs and vertebra and can also occur in soft tissue and viscera; 25% are metastatic at diagnosis.[4,10] ES is characterized by a recurrent balanced chromosomal translocation, resulting in the fusion of the FET family gene *EWSR1* with an ETS transcription factor *FLI1* in ˜80% cases.[11]Variant fusions will occur between EWSR1 and other genes, including ERG, ETV1, ETV4 and FEV.[12] Although somatic mutations in ES are rare; *STAG2* and *TP53* are associated with poor outcomes.[13] Well-defined genetic or other aetiological factors are present in a small proportion of AYAs diagnosed with ES. Germline sequencing and genealogy studies has identified pathogenic or likely pathogenic germline mutations in ˜13% of ES patients, commonly in DNA damage repair genes or inactivating variants associated with cancer predisposition syndromes -such as Fanconi anemia and familial breast cancer.[14,15]

A related entity of 'Ewing-like' sarcomas are a heterogeneous group of small round cell tumors considered genetically distinct entities without the typical ES fusions. Ewing-like sarcomas have a predilection for soft tissues in AYAs and have other specific gene rearrangements, including EWSR1-non ETS fusions, CIC-fused, BCOR- and NFATC2- rearrangements.[16-19] Differentiation from classical ES suggest the need for specific investigation of optimal treatment strategies.

Current standard of care for AYAs

Osteosarcoma

A multidisciplinary approach that includes multidrug chemotherapy and surgical resection is the current standard of care for resectable OS. About 80% of newly diagnosed patients have resectable disease and no radiological evidence of metastases. Historical uncontrolled trials reported before the era of chemotherapy, indicate that surgery alone was curative for less than 20%, while all others would experience rapid recurrence and death within 1-2 years.[20] The use of adjuvant chemotherapy in a randomized controlled trial between intensive multiagent chemotherapy and surveillance, improved 2y relapse free survival from 17% to 66%.[21] During the last four decades many trials were undertaken to define the most effective regimens to be used as standard of care. Multiple strategies were explored including different combination of agents, dose intensification and therapy adjustments according to the chemotherapy response seen in resection specimens.[22-25]

Currently, the internationally adopted standard of care for patients with resectable disease is a multidrug regimen including methothrexate, doxorubicin (adriamycin) and cisplatin (MAP) administered before and after surgical resection. In the AYA cohort there is an increased focus in administering chemotherapy in an outpatient setting.[26] The EURAMOS-1 collaboration including over 2000 patients with operable OS receiving MAP demonstrated a 5y EFS of 54% and overall survival ˜70% for all patients, increasing to 60% and 76% for localized disease.[27]Several independent risk factors, including histologic response, age, presence of metastases,

primary tumor site and volume are associated with propensity to OS recurrence.[22,27-31] Histological response of the primary tumor to preoperative chemotherapy has been reported as a key prognostic factor for relapse and efforts have been made to risk stratify for first line treatment, poor responders ([?]10% viable tumor) having a significantly worse 5y overall survival than good responders (<10% viable tumor), (45-55% vs 75-80%).[25,27] Adding ifosfamide and etoposide to MAP in poor responders did not significantly improve survival but increased toxicity.[25] Similarly, the addition of maintenance pegylated interferon alfa-2b in good responders did not impact 3y EFS.[32]

Despite combined treatment, 40 to 50% of patients experience recurrent disease most frequently within 3 years from diagnosis.[33,34] The commonest site of recurrence is the lungs in ˜80% patients. Bone metastases are less frequent, ˜15% and local recurrence occurs in less than 10%.[34,35] Early relapse (within 24 months) is associated with a less favorable prognosis.[36]Achieving a second complete surgical remission is crucial as some patients, ˜30% will remain disease free.[34,37] Retrospective data suggest that repeated metastasectomies may improve survival and should be considered whenever possible.[35,37-39] However, this is dependent on patient selection and lacks high quality prospective evaluation.[40,41]

Chemotherapy is widely used in the management of recurrent pretreated OS, although complete and partial responses are rare and survival benefit has not been well demonstrated in largely, retrospective analyses.[34,42,43] Outcomes depend on disease-free interval with late relapses faring better.[34] There is no accepted standard regimen but cytotoxic agents include, ifosfamide ± etoposide, single agent ifosfamide, gemcitabine and docetaxel, cyclophosphamide, and carboplatin.[44] Clinicians may witness clinical benefit from the use of chemotherapy that encourages its continued widespread use but a positive impact on quality of life has also not been documented.

Ewing sarcoma

Current standard of care for ES has evolved over decades through randomized trials into just-tolerated, prolonged intensive chemotherapy regimens through the addition of cytotoxic agents, (notably- doxorubicin, ifosfamide and etoposide) to vincristine, dactinomycin and cyclophosphamide (VAC).[45-50] Randomized trials by risk group for newly diagnosed ES are shown in Table I. More recently, the focus has shifted to dose-intensity of the alkylating agents and through several large, randomized trials, a clearer international consensus has emerged. The most recent prospective COG trial randomized patients <50years with localized ES to receive alternating vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide (VDC/IE) every 3 weeks (standard) compared to every 2 weeks, facilitated by the use of granulocyte colony stimulating factor (intensive).[51,52] 5y EFS was superior in the intensified regimen compared with the standard arm, (73% vs 65%, (P =0.048)), with no difference in toxicity ($P = 0.056$).[52] The Euro Ewing 2012 trial demonstrated a superior outcome for VDC/IE compared to the previous European standard, VIDE/VAI in patients with localized and metastatic ES: a Bayesian analysis demonstrated hazard ratios (HRs) of 0.70 for EFS and 0.64 for overall survival and a 98% posterior probability in favor of VDC/IE.[53,54] The 3-year EFS for VIDE/ VAI was 61% compared to 68% for VDC/IE and there was a similar difference in overall survival, with no excess acute toxicity with VDC/IE.[54] On the basis of these results, interval compressed VDC/IE therapy has become the international current standard of care for localized and metastatic ES. Dexrazoxane cardioprotection with short infusion doxorubicin allows for safe intensification of treatment without affecting tumor response.[55] The addition of chemotherapeutic agents to VDC/IE -such as vincristine-cyclophosphamide-topotecan in the COG trial AEWS1031 or irinotecan temozolomide showed no survival benefit in non-metastatic patients.[56,57]

Recurrent ES, which is mostly systemic relapse, occurs in 30-40% of primary localized disease and 60-80% of metastatic ES.[58] Survival is less than 25% overall for patients with relapsed ES, better in later relapses >2y after treatment.[59,60] The management of patients with primary refractory or recurrent ES is less well defined with several combinations of chemotherapy in use, largely dependent on institutional experience. An ongoing randomized multi-arm European trial (rEECur) is recruiting relapsed ES patients between ages 4 and 50, to multiple chemotherapy arms to determine a standard of care. Interim analyses suggest irinotecan plus temozolomide and gemcitabine and docetaxel are inferior to high dose ifosfamide and cyclophosphamide/ topotecan combination.[61,62] The median PFS across all cohorts was 4.7 months with overall survival of 13.7

months across all therapies.[61]

Local management of the primary tumor in ES includes surgery or RT or a combination of both. Complete surgical resection with clear margins (R0) remains the most important goal for local control. 5 year local failure rates after RT alone, surgery only, and surgery combined with RT were 15.3%, 3.9% and 6.6% respectively in 956 patients treated on COG protocols.[63] The failure rate after RT alone is higher in pelvic and extremity tumors reflecting patients with often locally advanced tumors unsuitable for surgery.[63,64]Indications for combination treatment include the expectation or confirmation of inadequate resection margins, large tumors and poor response to induction chemotherapy.[65,66] Definitive RT is recommended where surgery would result in unacceptable morbidity.[44,63,67-72] RT dose ranges from 45Gy to 66Gy depending on anatomical location, tumor size and timing of RT in relation to surgery.[72,73] Whole lung RT may be used to consolidate the response of lung metastases after chemotherapy and is well tolerated although the benefit has not been unequivocally demonstrated.[74]

Areas of clinical uncertainty for AYAs

Osteosarcoma

Mifamurtide is a macrophage modulator thought to be active in reducing the incidence of lung metastases in OS.[75] Its potential benefit has been investigated in a trial randomizing over 600 patients with localized OS to receive MAP alone or with the addition of mifamurtide and/or ifosfamide. Although increased overall survival (from 70 to 78% at 6y, P =0.03) was reported for the mifamurtide arms, the lack of significantly improved EFS and concerns about a possible interaction between mifamurtide and ifosfamide ensured the results were insufficient to support global approval by regulatory authorities, restricting the use of mifamurtide to selected countries.[75-77]

Surgical resectability is a cornerstone of curative treatment for OS. For some patients, especially with tumors of the pelvis, axial skeleton and skull, complete surgical resection is not possible. There is a lack of evidence for adjuvant or definitive RT in this situation. RT may be used where resection is not possible or anticipated to lead to unacceptable morbidity.[44,78-80] Doses of 60Gy or higher, and ideally 70Gy are indicated.[78,81-83]Strategies to improve outcomes, including comprehensive evaluation of particle beam therapy in this setting, are a priority. The role of**adjuvant chemotherapy in patients undergoing complete surgical resection of relapsed disease** , either local or distant, remains unclear.[34-37,42]

Identification of metastatic disease at diagnosis is essential for prognosis and management. Although only 20% of patients have clinically evident metastases at onset, sensitivity of cross sectional imaging demonstrates 30-45% have pulmonary nodules of uncertain clinical significance that do not meet defined COG criteria for metastases and about one third of these progress to metastatic disease.[84-86] Surgical sampling is undertaken in some centers but its value in determining overall survival and guiding treatment is unproven.[85,87] Data to support the use of FDG-PET/CT scanning both for accurate staging, especially of the skeleton, and to determine response to chemotherapy, supports its use in selected patients.[88-90]

Approaches to **follow-up after treatment** vary in visit intervals, pulmonary imaging modalities and monitoring for late effects of treatment. Access to rehabilitation, assistance in resuming progress on achieving life skills and identifying psychological impacts are all vital parts of effective follow up for AYAs but there is considerable variation in recommendations and practice, indicating a need for collaborative prospective evaluation and evidence-seeking.[91-94]

Ewing sarcoma

Risk stratification for ES lacks consistency and a unified consensus for stratifying localized disease may enable reliable interpretation of international trials. European collaborative groups have used primary site, tumor volume, metastases and histologic response to stratify consolidation treatment, whereas the presence of metastatic disease alone is used in North America. Histologic response varies depending on the number and type of treatment cycles prior to local therapy and with a recent move towards pre surgical RT may no longer be as relevant.

Staging of ES has conventionally included a bone marrow biopsy. With the advent and familiarity of functional imaging in solid tumors, excellent correlation rates have been demonstrated between bone marrow biopsy and FDG-PET/CT in patients with ES.[95-99] WB-MRI appears comparable to FDG-PET/CT and superior to bone scintigraphy, without requiring ionising radiation.[88,100] In centers with access to these imaging modalities, it is possible to avoid an invasive bone marrow biopsy. Widespread acceptance for PET-CT or alternatively, WB-MRI as the standard for staging bone marrow will require prospective trials that incorporate large homogenous cohorts of patients with ES.

The role of **high dose (HD) chemotherapy** in ES remains controversial due to an overreliance on uncontrolled data.[101-104] A randomized trial demonstrated consolidative HD chemotherapy using busulphan and melphalan (BuMel) confers a survival benefit in localized high-risk ES (large primary tumor, >200mls or poor response to induction VIDE chemotherapy) compared to standardized VIDE/VAI chemotherapy, with 3y EFS and overall survival of 69% vs. 56.7%(P =0.026), and 78% vs. 72.2% (P =0.028) respectively.[105] No benefit from BuMel, compared with conventional VAI with whole lung irradiation, was seen in patients with pulmonary metastases.[106] Additional treosulfan and melphalan HD chemotherapy over standard VIDE induction/ VAC consolidation demonstrated no benefit in patients >14 years with primary metastatic ES.[107] No randomized studies have been conducted in patients with recurrent or progressive disease in whom observational data indicates a potential greater benefit than seen in first line treatment.[102,108]

Debate often centers on choice of modality, sequence and timing for**local control management** . Combined modality treatment, favored in Europe, has resulted in excellent local control rates.[66] There has been a move towards delivering RT pre-operatively aiming to reduce the impact of surgical fixation on the quality of RT and reducing the risk of late effects with lower doses, but at the risk of increasing wound complications which in turn compromise complex bone reconstructions.[109] Complete resection of chest wall tumors appear superior to treatment with RT in improving survival.[110] Sacral tumors demonstrate improved survival with definitive RT, compared to non-sacral pelvic tumors that do better with combined surgery and RT.[64]The role of surgery for patients with spinal ES has to be considered carefully. Spinal decompressive surgery (usually in an emergency setting) is usually intralesional increasing the risk of local recurrence whereas definitive RT is associated with better outcomes.[111] Best practice is to tailor treatment for each patient individually with input from an expert multidisciplinary sarcoma panel.

New radiation techniques

The potential for RT to increase the late effects of treatment is particularly important in AYAs in whom ES is treated with curative intent. Modern RT techniques, image guided RT, intensity modulated photon radiotherapy (IMRT) and particle beam therapy such as proton beam therapy (PBT), deliver improved conformal RT to the target while reducing the volume of normal tissue that receive damaging doses of RT. As a result of the physical characteristics of PBT, significantly less whole-body dose is delivered compared to IMRT, reducing low as well as high doses outside the target (Fig. 2). This may reduce late effects of RT as well as the risk of radiation-induced malignancies and this dosimetric benefit has been sufficient to introduce PBT as the preferential radiation modality in the treatment of many pediatric and AYA cancers.[112-115] Data on outcomes for these techniques in ES is limited but PBT was well tolerated by a small series of children with ES with a low incidence of significant toxicity.[116]

The risk of ovarian dysfunction from pelvic RT pelvis increases with radiation dose. [117-119] PBT avoids significant dose to at least one of the ovaries potentially reducing the risk of infertility and premature menopause.[151] Surgical transposition or translocation may be used to move one or both ovaries away from the RT target if indicated.[120]

Modern RT techniques also facilitate dose escalation, both in ES at challenging sites (head and neck, pelvis and spine) and in the more radioresistant OS that require high RT doses.[83,121]PBT to treat OS, alone or in combination with photons to a mean dose of 68.4Gy, resulted in a 5 year LC rate of 72%.[81]Internal fixation with carbon fibre and PEEK, particularly along the spinal axis, is encouraged to improve the homogeneity and reliable delivery of RT at these sites.[122]

New surgical techniques

The decades since widespread adoption of limb-sparing surgery for primary bone tumors have seen incremental improvements in the ability of surgeons to remove tumors whilst maintaining as much function as possible in the affected limb. In any procedure, surgeons and patients must balance the oncological benefits of wider resections with the morbidity of removing normal tissues, such as muscle, bone and nerves.

To achieve this, surgeons have to define the anatomic location and extent of tumor to enable accurate complete resection. MRI remains the gold standard to identify the intramedullary extent of primary bone tumors, including skip metastases.[100,123] Preoperative imaging however, is unfortunately not able to assess the response of tumors to neoadjuvant chemotherapy with sufficient reliability to influence surgical options.[124] Intraoperative imaging techniques, such as fluorescence using indocyanine green, offer the prospect of guiding surgeons towards improved surgical margins, but have yet to be proven in large scale clinical trials.[125]Novel techniques including intraoperative navigation and personalized custom jigs to guide bone resections, are becoming more established, may increase safety, and when matched with implants using additive layer manufacturing and porous ingrowth surfaces, offer the ability to improve margins whilst preserving normal tissue, (Fig. 3).[126]

For some patients with large tumors where it may not be possible to preserve the limb, or when the expected functional differences between limb-sparing surgery and amputation are small and the risks of limb-sparing surgery high, amputation remains the best option. Reconstruction with the uninvolved part of the limb, for example, by rotationplasty or tibial turn-up may be helpful, particularly in children.[127] Advances in prosthetics and other technologies including transosseous fixation devices offer the potential for improved function for some amputees.[128]

Limb preservation carries a risk of local recurrence. In OS, retrospective studies have evaluated the risk in terms of the surgical margins, chemotherapy response and proximity to major vessels,[129,130] but the application of these systems in prospective decision making has yet to be established.

Growth and the long-term complications of surgical reconstructions are further issues for adolescents. Growing endoprostheses contain a mechanism which is activated in outpatients using a magnetic coil. Although these implants have reduced the number of operations required after endoprosthetic reconstruction, patients do not escape further surgery, but the rate of limb preservation remains high. Bone-compatible collars encourage bone growth onto the surface of implants and reduce the risk of aseptic loosening when successful integration occurs. New porous designs may have some advantages but these remain to be proven.[131] Antibacterial silver surface treatments have also become widely adopted with the aim of reducing the risk of deep infection. However, studies of their efficacy are retrospective and they have not been subjected to a prospective randomized trial .[132]

Emerging targeted therapeutics

Targeted therapies are under investigation for recurrent ES and OS but are not standard of care at this time. Trial accrual for AYAs has traditionally been poor, especially in the 20-29y age group and correlates with modest gains in survival.[133] Greater efforts are unfolding internationally to increase access to specialist centers and clinical trials, particularly of novel agents with age inclusion criteria across the AYA spectrum,[134] and supported by multi-stakeholder platforms such as ACCELERATE[135] to include adolescents >12yo, as evidenced by the novel agent trials in Table II.

Multitargeted tyrosine kinase small molecule inhibitorsinvestigated in OS and ES demonstrate single agent activity. Antiangiogenic TKIs, often multitargeted to various receptors such as VEGFR are accessible through phase 1 and 2 clinical trials for AYAs with relapsed or refractory ES and OS. They have been used either as a single agent or in combination with sarcoma responsive chemotherapy: regorafenib,[136-139] carbozatinib,[140]apatinib,[141] lenvatinib,[142](summarized in Table II). Lenvatinib has been demonstrated to be tolerated in combination with ifosfamide and etoposide in patients with relapsed OS and is the subject of an ongoing randomized phase II trial.[142] The challenge is how best to investigate these agents in the adjuvant

setting and integrate them into intensive combination therapy regimens.

Poly-ADP-ribose polymerase 1 (PARP1) inhibitors are under clinical evaluation in ES, based on promising preclinical activity and evidence that PARP1 inhibitors induced DNA damage in tumors deficient in DNA repair mechanisms.[143] Olaparib trialled as a single agent in a prospective phase II trial was disappointing with no objective responses in heavily pre-treated ES,[144]however potentiation of activity in combination with chemotherapeutic agents, especially temozolomide and or irinotecan in preclinical studies led to combination clinical trials of talazoparib and niraparib.[145-147] These demonstrated varied efficacy in pediatric and AYA patients with refractory/ recurrent ES with toxicity limiting dose intensity, Table II. Additional trials are ongoing. Pre-clinical programmes are currently evaluating PARP inhibition as a therapeutic target in OS based on potential evidence of a "BRCAness" phenotype that may lead to increased sensitivity to these agents, although validation using patient-derived models is required before embarking on clinical trials.[148-150]

The **role for immunotherapy** in ES and OS is currently limited with little evidence of efficacy in initial trials of checkpoint inhibition, particularly for ES which has a low mutation burden. Further work and trials are ongoing to determine biomarkers to identify subsets of patients or combination therapy that may be of more benefit.[151-154] Disialogangliosides, GD2 is a potential cell surface target expressed by ES and OS.[155,156] Current phase 1 clinical trials investigating anti-GD2 monoclonal antibodies with immunoadjuvants are recruiting AYAs with relapsed solid tumors including ES and OS, (NCT00743496 at https://ClinicalTrials.gov/). There is support for the utility of dinutuximab in combination with irinotecan and temozolomide in neuroblastoma,[157] cytotoxic agents also used in bone sarcoma and we await results of early phase clinical trials evaluating anti-GD2-CART cells in OS, (NCT02107963 at https://ClinicalTrials.gov/).

Targeting the FET-ETS translocation is challenging as the EWSR1-FLI fusion protein lacks enzymatic activity and binding sites for small molecules.[16] TK-216, a clinical derivative of YK-4-279 is a novel small molecule that inhibits EWS-FLI1 transcription by blocking co-immunoprecipitation with RNA helicase A;[158] this is under evaluation in a phase 1 clinical trial in combination with vincristine based on synergistic anti-tumor activity demonstrated by YK-4-279.[159] Very early interim trial analyses (NCT02657005, https://ClinicalTrials.gov/) report two pronounced clinical responses for more than 24 and 18 months following treatment with TK216 in relapsed/ refractory ES.[160]

Conclusion

Despite progress made in pathology, imaging and local control modalities coordinated by specialist sarcoma multidisciplinary centers, AYA patients with primary bone sarcomas continue to experience inferior outcomes. The reasons are multifactorial, including aggressive complex biology that remains ill-understood as well as reduced access to novel therapeutics and clinical trials along with unique psychosocial issues. There is now international consensus supporting standardized first line treatment for ES and OS. With evolving modern day imaging techniques (WB-MRI, FDG-PET/CT) and new RT and surgical approaches, local treatment should be tailored to the patient and multidisciplinary collaboration is crucial. New therapeutic agents show promise for AYA sarcomas. The challenge is to explore what value these agents may bring to first-line therapy and how they can be best delivered alongside standard of care treatments. Their inclusion into large randomized phase 3 international trials, along with the validation of biomarkers that signal refractory disease and can reliably predict response is required to fully evaluate their potential.

Conflict of Interest

The authors do not have any conflicts of interest to declare.

Acknowledgements

SJS is funded in part by UCLH NIHR Biomedical Research Centre.

Funding disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Hosted file

`image1.emf` available at https://authorea.com/users/420892/articles/527132-current-approaches-to-management-of-bone-sarcoma-in-adolescent-and-young-adult-aya-patients

Figure 1. The incidence and outcomes of primary bone sarcoma using Surveillance, Epidemiology, and End Results (SEER) data.

A-C. The incidence trends of bone sarcoma, SEER 21, overall from 2000 to 2017- histological type, gender and ethnicity by age of diagnosis. Data from SEER.[2] **D.** Five-year relative survival rates for osteosarcoma and Ewing sarcoma, SEER9, from patients diagnosed between 1975 to 2012 with at least 5-years follow-up for survival analyses. Data from SEER.[161,162]

TABLE I. Randomized trials by risk group for newly diagnosed Ewing sarcoma.

Ref.	Trial	Population	Pts *(n)*	Treatment	Survival outcomes
Standard risk, localized Paulussen[49]	Standard risk, localized EICESS-92	Standard risk, localized Localized, Tumor volume <100ml	Standard risk, localized 155	Standard risk, localized Induction (VAIA x4) + Randomization: VAIA x10 vs. VACA x10 (cyclophosphamide vs ifosfamide)	Standard risk, localized 3y EFS 74% vs. 73%, HRs for EFS and overall survival 0.91 VAIA vs. VACA
Le Deley[50]	Euro-Ewing99 R1	<50yo Localized, either good histologic response (>90%) or Tumor volume (<200ml)	856	Induction (VIDE x6, VAI x1) Randomization: VAIx7 vs. VACx7	3y EFS and overall survival for VAI vs. VAC, 78.2% vs. 75.4% and 85.5% vs. 85.9%
Localized Grier[48]	Localized INT-0091 (CCG-7881 and POG-8850)	Localized <30yo	Localized 398	Localized Standard (VACA) vs experimental (VACA + IE)	Localized 5yr EFS and overall survival for standard vs. experimental, 54% vs. 69% (p 0.005) and 61% vs. 72% (p 0.01)
Granowetter[163]	INT-0154	<30yo Localized, bone + soft tissue	478	VDC/IE (17 cycles, 48 weeks) vs. dose intensified VDC/IE (11 cycles, 30 weeks)	5y EFS and overall survival for standard vs. dose intensified, 72.1% vs. 70.1% and 80.5% vs. 77%

Ref.	Trial	Population	Pts *(n)*	Treatment	Survival outcomes
Womer[52]	COG AEWS0031	<50yr age Localized	568	Randomization: VDC/IE standard (q3/52) vs. VDC/IE intensified (q2/52)	3y EFS and overall survival for std vs. intensified, 65% vs. 73% (p 0.048) and 77% vs. 83% (p 0.056) Similar toxicity
High risk, localized* Whelan[105]	High risk, localized* Euro-Ewing99/ Ewing-2008	High risk, localized* <50yo Poor histologic response ([?]90%), Tumor volume [?]200ml	High risk, localized* 240	High risk, localized* Induction (VIDEx6, VAIx1) Randomization: VAI vs. Bu-Mel/ ASCT	High risk, localized* 8y EFS and overall survival for VAI vs. Bu-Mel, 47.1% vs. 60.7% (P 0.026) and 55.6% vs. 64.5% (p 0.028)
Metastatic (lungs only) Dirksen[106]	Metastatic (lungs only) Euro-Ewing99 R2Pulm/ EWING-2008	Metastatic (lungs only) <50yo Pulmonary/pleural metastases, nil other	Metastatic (lungs only) 287	Metastatic (lungs only) VAI + WLI vs. Bu-Mel	Metastatic (lungs only) 3y EFS 50.6% vs. 56.6%, HR= 0.79, p=0.16 3yr OS 68% vs. 68.2%, HR=1.00, p=0.99
Multisite-metastatic (other) Paulussen[49]	Multisite-metastatic (other) EICESS-92	Multisite-metastatic (other) Volume [?]100ml or ±Metastases (any)	Multisite-metastatic (other) 492	Multisite-metastatic (other) VAIA x14 vs. EVAIA x4 + EVAIAx10 (addition of etoposide)	Multisite-metastatic (other) 3y EFS 47% vs. 52% (p=0.47)
Brennan[54]	Euro-Ewing-2012	<50yo Localized +/- Metastases (lung or other)	640	VIDE/ VAI vs. VDC/ IE	HRs 0.70 for EFS, 0.64 for overall survival in favor of VDC/ IE

Definitions.

***** High risk localized defined as a tumor volume >200mls, poor response to neoadjuvant chemotherapy with <90% necrosis.

Chemo combinations- VAC: vincristine, dactinomycin, cyclophosphamide; VAI: vincristine, dactinomycin, ifosfamide; IE: ifosfamide, etoposide; VACA: vincristine, dactinomycin, cyclophosphamide, doxorubicin; VAIA: vincristine, dactinomycin, ifosfamide, doxorubicin; EVAIA: plus etoposide; VIDE: vincristine, ifos-

famide, doxorubicin, etoposide.

Bu-Mel/ ASCT: Busulphan Melphalan conditioning with autologous stem cell transplant.

WLI: whole lung irradiation.

Hosted file

`image2.emf` available at https://authorea.com/users/420892/articles/527132-current-approaches-to-management-of-bone-sarcoma-in-adolescent-and-young-adult-aya-patients

Figure 2. Example PBT plans for pelvic and sacral tumors in AYAs.[164]

Axial and coronal images of two definitive PBT plans to treat locally advanced pelvic ES. An iliac bone primary in a 16-year-old female (**A-B**) and sacral tumor in a 19-year-old female (**C-D**). Red colour wash represents high dose, green moderate and blue the low dose.

Hosted file

`image3.emf` available at https://authorea.com/users/420892/articles/527132-current-approaches-to-management-of-bone-sarcoma-in-adolescent-and-young-adult-aya-patients

Figure 3. Surgical techniques for primary bone sarcoma.

A . Complex navigation plan showing proposed resection planes for low grade osteosarcoma of the iliac wing. **B** . Reconstruction of the hip after navigated extraarticular resection using modular porous acetabular reconstruction system. **C** . 3D printed custom jig for resection of femoral diaphyseal Ewing sarcoma before insertion of custom implant.

TABLE II. Trials investigating new therapeutics for advanced or metastatic ES and OS.

	Clinical trial	Drugs	Patient group	Outcome measures	Common / significant grade 3 or 4 toxicity (>10%)
Multi-targeted TKIs Italiano *et al*, 2020.[140]	Multi-targeted TKIs CABONE- multicenter, single arm, phase 2	Multi-targeted TKIs Cabozantinib	Multi-targeted TKIs Advanced ES (n=39) and OS (n=42), [?]12yo	Multi-targeted TKIs ORR 26% in ES, median PFS 4.4 mo, ORR 12% in OS with 33% PFS at 6 mo	Multi-targeted TKIs Hypophosphataemia, raised AST, palmar-plantar syndrome, pneumotho-rax, neutropenia
Duffaud *et al*, 2019.[137]	REGOBONE- double blind, placebo-controlled, phase 2	Regorafenib	Progressive pretreated OS, n=43, [?]10yo	Median PFS 16.4w (regorafenib) vs 4.1w (placebo)	Hypertension, hand-foot skin reaction, fatigue, hypophos-phataemia, chest pain
Duffaud *et al*, 2020.[139]	REGOBONE- double blind, placebo-controlled, phase 2	Regorafenib	Metastatic relapsed pretreated ES, n=41, [?]10yo	ORR 22% (5/23), median PFS- 11.4w (regorafenib) vs 3.9w (placebo)	Diarrhoea, hand-foot skin reaction

	Clinical trial	Drugs	Patient group	Outcome measures	Common / significant grade 3 or 4 toxicity (>10%)
Davis *et al*, 2019.[136]	SARC024- randomized, double blind, phase 2	Regorafenib	Advanced/ metastatic pretreated OS, n=42, 18-76yo	Median PFS- 3.6mo and 1.7mo with regorafenib vs placebo, *P*.017	Hypertension
Xie *et al*, 2019.[141]	Single arm, phase 2	Apatinib	Relapsed/ unresectable OS, n=37, [?]16yo	ORR 43%, 4mo PFS 57%	Pneumothorax, wound dehiscence
Gaspar *et al*.[165]	Single arm, phase 1/2	Lenvatinib single agent	Relapsed OS, n=31, 2 to [?]25yo	ORR 6.9%, 4mo PFS 32%	Headache, diarrhoea, vomiting, decreased appetite, proteinuria, hypothy- roidism, hypertension, pyrexia, weight loss
Gaspar *et al*.[142]	Single arm, phase 2	Lenvatinib + etoposide + ifosfamide in phase 2 expansion cohort	Relapsed/ refractory OS, n=22 (8 evaluable patients in phase 2), 2 to [?]25yo	Phase 1 dose finding cohort: ORR 12.5%, 4mo PFS in 12/18 (68%) Phase 2 cohort: 4mo PFS in 5/8 (62%)	Pneumothorax, haematologic toxicity
PARP inhibitors	PARP inhibitors	PARP inhibitors	PARP inhibitors	PARP inhibitors	PARP inhibitors
Choy *et al*, 2014.[144]	Single arm, prospective phase 2	Olaparib	Metastatic/ recurrent ES, n=12, 18-70yo	Median PFS 5.7w, SD in 4/12	Haematologic, pain
Chugh *et al*, 2020.[146]	SARC025- multicenter, phase 1	Niraparib + temozolomide (Arm 1) or irinotecan (Arm 2)	Advanced ES, n=29, [?]13yo	Median PFS in Arm 1: 9w and in Arm 2: 16w Arm 1: ORR 0/17 Arm 2: ORR 8%- 1/12 PR and 6 SD	Arm 1- DLT: Haematologic, Arm 2- DLT: gastrointestinal toxicity, elevated ALT
Schafer *et al*, 2019.[145]	Single arm, phase 1/2	Talazoparib plus temozolomide	Recurrent/ refractory solid tumors, n=40, 4-25yo	ES- 2/10 prolonged SD (8 cycles)	DLTs: haematologic

	Clinical trial	Drugs	Patient group	Outcome measures	Common / significant grade 3 or 4 toxicity (>10%)
Federico *et al*, 2020.[166]	Single arm, phase 1	Talazoparib + irinotecan (A) plus temozolomide (B)	Recurrent/ refractory solid tumors (50% ES), n=41, median age 14.6yo	ORR 10% (A), ORR 25% (B)	Febrile neutropenia, diarrhoea
EWSR1-FLI1 target agents Ludwig *et al*, 2021.[160]	EWSR1-FLI1 target agents TK216-01, phase 2 dose (RP2D)	EWSR1-FLI1 target agents TK216± vincristine	EWSR1-FLI1 target agents Relapsed/ refractory metastatic ES, mean age 31yo A. Schedule escalation cohort, n=32 B. 14-day infusion 200mg/m^2/d (RP2D) expansion cohort, n=35	EWSR1-FLI1 target agents CR 7%, SD 39%, PD 54%, SD median duration 113 days (B) 3 patient tumor responses	EWSR1-FLI1 target agents Most common: haematologic toxicity, fatigue.

Definitions. ORR: objective response rate; PFS: progression free survival; w: weeks; mo: months; CR: complete response, PR: partial response; SD: stable disease; PD: progressive disease; DLT: dose limiting toxicity.

References

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2020. CA Cancer J Clin 70:7-30, 2020

2. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence- SEER Research Limited-Field DATA, 21 Registries, Nov 2020 Sub (2000-2018)- Linked to County Attributes- Time Dependent (1990-2018)- Income/ Rurality, 1969-2019 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2021, based on the November 2020 submission.,

3. Amadeo B, Penel N, Coindre JM, et al: Incidence and time trends of sarcoma (2000-2013): results from the French network of cancer registries (FRANCIM). BMC Cancer 20:190, 2020

4. Gatta G, Capocaccia R, Botta L, et al: Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. Lancet Oncol 18:1022-1039, 2017

5. Whelan J, McTiernan A, Cooper N, et al: Incidence and survival of malignant bone sarcomas in England 1979-2007. Int J Cancer 131:E508-517, 2012

6. de Pinieux G, Karanian M, Le Loarer F, et al: Nationwide incidence of sarcomas and connective tissue tumors of intermediate malignancy over four years using an expert pathology review network. PLoS One 16:e0246958, 2021

7. Mirabello L, Troisi RJ, Savage SA: Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. Cancer 115:1531-1543, 2009

8. Hameed M, Mandelker D: Tumor Syndromes Predisposing to Osteosarcoma. Adv Anat Pathol 25:217-222, 2018

9. Mirabello L, Zhu B, Koster R, et al: Frequency of Pathogenic Germline Variants in Cancer-Susceptibility Genes in Patients With Osteosarcoma. JAMA Oncol 6:724-734, 2020

10. Jawad MU, Cheung MC, Min ES, et al: Ewing sarcoma demonstrates racial disparities in incidence-related and sex-related differences in outcome: an analysis of 1631 cases from the SEER database, 1973-2005. Cancer 115:3526-3536, 2009

11. Turc-Carel C, Aurias A, Mugneret F, et al: Chromosomes in Ewing's sarcoma. I. An evaluation of 85 cases of remarkable consistency of t(11;22)(q24;q12). Cancer Genet Cytogenet 32:229-238, 1988

12. Sorensen PH, Lessnick SL, Lopez-Terrada D, et al: A second Ewing's sarcoma translocation, t(21;22), fuses the EWS gene to another ETS-family transcription factor, ERG. Nat Genet 6:146-151, 1994

13. Tirode F, Surdez D, Ma X, et al: Genomic landscape of Ewing sarcoma defines an aggressive subtype with co-association of STAG2 and TP53 mutations. Cancer Discov 4:1342-1353, 2014

14. Brohl AS, Patidar R, Turner CE, et al: Frequent inactivating germline mutations in DNA repair genes in patients with Ewing sarcoma. Genet Med 19:955-958, 2017

15. Abbott D, O'Brien S, Farnham JM, et al: Increased risk for other cancers in individuals with Ewing sarcoma and their relatives. Cancer Med 8:7924-7930, 2019

16. Grunewald TGP, Cidre-Aranaz F, Surdez D, et al: Ewing sarcoma. Nat Rev Dis Primers 4:5, 2018

17. Miettinen M, Felisiak-Golabek A, Luina Contreras A, et al: New fusion sarcomas: histopathology and clinical significance of selected entities. Hum Pathol 86:57-65, 2019

18. Antonescu CR, Owosho AA, Zhang L, et al: Sarcomas With CIC-rearrangements Are a Distinct Pathologic Entity With Aggressive Outcome: A Clinicopathologic and Molecular Study of 115 Cases. Am J Surg Pathol 41:941-949, 2017

19. Cohen-Gogo S, Cellier C, Coindre JM, et al: Ewing-like sarcomas with BCOR-CCNB3 fusion transcript: a clinical, radiological and pathological retrospective study from the Societe Francaise des Cancers de L'Enfant. Pediatr Blood Cancer 61:2191-2198, 2014

20. Dahlin DC, Coventry MB: Osteogenic sarcoma. A study of six hundred cases. J Bone Joint Surg Am 49:101-110, 1967

21. Link MP, Goorin AM, Miser AW, et al: The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med 314:1600-1606, 1986

22. Souhami RL, Craft AW, Van der Eijken JW, et al: Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. Lancet 350:911-917, 1997

23. Bramwell VH, Burgers M, Sneath R, et al: A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. J Clin Oncol 10:1579-1591, 1992

24. Lewis IJ, Nooij MA, Whelan J, et al: Improvement in histologic response but not survival in osteosarcoma patients treated with intensified chemotherapy: a randomized phase III trial of the European Osteosarcoma Intergroup. J Natl Cancer Inst 99:112-128, 2007

25. Marina NM, Smeland S, Bielack SS, et al: Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an

open-label, international, randomised controlled trial. Lancet Oncol 17:1396-1408, 2016

26. Anderson PW, P.; Lazarte, T.; Gore, L.; Salvador, L. & Salazar-Abshire, M.: Outpatient chemotherapy, family-centered care, electronic information, and education in adolescenets and young adults with osteosarcoma. Clinical Oncology in Adolescents and Young Adults. 3:1-11, 2013

27. Smeland S, Bielack SS, Whelan J, et al: Survival and prognosis with osteosarcoma: outcomes in more than 2000 patients in the EURAMOS-1 (European and American Osteosarcoma Study) cohort. Eur J Cancer 109:36-50, 2019

28. Jeys LM, Grimer RJ, Carter SR, et al: Post operative infection and increased survival in osteosarcoma patients: are they associated? Ann Surg Oncol 14:2887-2895, 2007

29. Kim MS, Lee SY, Lee TR, et al: Prognostic nomogram for predicting the 5-year probability of developing metastasis after neo-adjuvant chemotherapy and definitive surgery for AJCC stage II extremity osteosarcoma. Ann Oncol 20:955-960, 2009

30. Song WS, Jeon DG, Kong CB, et al: Tumor volume increase during preoperative chemotherapy as a novel predictor of local recurrence in extremity osteosarcoma. Ann Surg Oncol 18:1710-1716, 2011

31. Moore C, Eslin D, Levy A, et al: Prognostic significance of early lymphocyte recovery in pediatric osteosarcoma. Pediatr Blood Cancer 55:1096-1102, 2010

32. Bielack SS, Smeland S, Whelan JS, et al: Methotrexate, Doxorubicin, and Cisplatin (MAP) Plus Maintenance Pegylated Interferon Alfa-2b Versus MAP Alone in Patients With Resectable High-Grade Osteosarcoma and Good Histologic Response to Preoperative MAP: First Results of the EURAMOS-1 Good Response Randomized Controlled Trial. J Clin Oncol 33:2279-2287, 2015

33. Duffaud F, Digue L, Mercier C, et al: Recurrences following primary osteosarcoma in adolescents and adults previously treated with chemotherapy. Eur J Cancer 39:2050-2057, 2003

34. Kempf-Bielack B, Bielack SS, Jurgens H, et al: Osteosarcoma relapse after combined modality therapy: an analysis of unselected patients in the Cooperative Osteosarcoma Study Group (COSS). J Clin Oncol 23:559-568, 2005

35. Bielack SS, Kempf-Bielack B, Branscheid D, et al: Second and subsequent recurrences of osteosarcoma: presentation, treatment, and outcomes of 249 consecutive cooperative osteosarcoma study group patients. J Clin Oncol 27:557-565, 2009

36. Palmerini E, Torricelli E, Cascinu S, et al: Is there a role for chemotherapy after local relapse in high-grade osteosarcoma? Pediatr Blood Cancer 66:e27792, 2019

37. Bacci G, Briccoli A, Longhi A, et al: Treatment and outcome of recurrent osteosarcoma: experience at Rizzoli in 235 patients initially treated with neoadjuvant chemotherapy. Acta Oncol 44:748-755, 2005

38. Briccoli A, Rocca M, Salone M, et al: Resection of recurrent pulmonary metastases in patients with osteosarcoma. Cancer 104:1721-1725, 2005

39. Matsubara EM, T.; Koga, T.; Shibata, H.; Ikeda, K.; Shiraishi, K. & Suzuki, M.: Metastasectomy of pulmonary metastases from osteosarcoma: Prognostic factors and indication for repeat metastasectomy. Journal of Respiratory Medicine, 2015

40. Treasure T, Fiorentino F, Scarci M, et al: Pulmonary metastasectomy for sarcoma: a systematic review of reported outcomes in the context of Thames Cancer Registry data. BMJ Open 2, 2012

41. Treasure T, Milosevic M, Fiorentino F, et al: Pulmonary metastasectomy: what is the practice and where is the evidence for effectiveness? Thorax 69:946-949, 2014

42. Ferrari S, Briccoli A, Mercuri M, et al: Postrelapse survival in osteosarcoma of the extremities: prognostic factors for long-term survival. J Clin Oncol 21:710-715, 2003

43. Palmerini E, Setola E, Grignani G, et al: High Dose Ifosfamide in Relapsed and Unresectable High-Grade Osteosarcoma Patients: A Retrospective Series. Cells 9, 2020

44. Casali PG, Bielack S, Abecassis N, et al: Bone sarcomas: ESMO-PaedCan-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 29:iv79-iv95, 2018

45. 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 8:1514-1524, 1990

46. Nesbit ME, Jr., Gehan EA, Burgert EO, Jr., et al: Multimodal therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: a long-term follow-up of the First Intergroup study. J Clin Oncol 8:1664-1674, 1990

47. 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 5:1191-1198, 1987

48. 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 348:694-701, 2003

49. 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 26:4385-4393, 2008

50. 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 32:2440-2448, 2014

51. Womer RB, Daller RT, Fenton JG, et al: Granulocyte colony stimulating factor permits dose intensification by interval compression in the treatment of Ewing's sarcomas and soft tissue sarcomas in children. Eur J Cancer 36:87-94, 2000

52. 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 30:4148-4154, 2012

53. Anderton J, Moroz V, Marec-Berard P, et al: International randomised controlled trial for the treatment of newly diagnosed EWING sarcoma family of tumours - EURO EWING 2012 Protocol. Trials 21:96, 2020

54. Brennan BK, L.; Marec-Berard, P.; Martin-Broto, J.M.; Gelderblom, H.; Gasper, N.; Strauss, S.J.; Urgelles, A.S; Anderton, J.; Laurence, V.; et al. : Comparison of two chemotherapy regimens in Ewing sarcoma (ES): Overall and subgroup results of the Euro Ewing 2012 randmoized trial (EE2012). . J. Clin. Oncol. 38:11500-11500, 2020

55. Schwartz CL, Wexler LH, Krailo MD, et al: Intensified Chemotherapy With Dexrazoxane Cardioprotection in Newly Diagnosed Nonmetastatic Osteosarcoma: A Report From the Children's Oncology Group. Pediatr Blood Cancer 63:54-61, 2016

56. Mascarenhas L, Felgenhauer JL, Bond MC, et al: Pilot Study of Adding Vincristine, Topotecan, and Cyclophosphamide to Interval-Compressed Chemotherapy in Newly Diagnosed Patients With Localized Ewing Sarcoma: A Report From the Children's Oncology Group. Pediatr Blood Cancer 63:493-498, 2016

57. Meyers PA, SR.; Slotkin, EK.; Dela Cruz, F. & Wexier, LH.: The addition of cycles of irinotecan/ temozolomide (i/T) to cycles of vincristine, doxorubicin, cyclophosphamide (VDC) and cycles of ifosfamide, etoposide (IE) for the treatment of Ewing sarcoma (ES). Presented at the 2018 American Society of Clinical Oncology, May 20, 2018, 2018

58. Barker LM, Pendergrass TW, Sanders JE, et al: Survival after recurrence of Ewing's sarcoma family of tumors. J Clin Oncol 23:4354-4362, 2005

59. 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 18:3108-3114, 2000

60. Stahl M, Ranft A, Paulussen M, et al: Risk of recurrence and survival after relapse in patients with Ewing sarcoma. Pediatr Blood Cancer 57:549-553, 2011

61. McCabe MK, L.; Khan, M.; Fenwick, N.; Dirksen, U.; Gaspar, N.; Kanerva, J.; Kuehne, T.; Longhi, A.; Luksch, R.; Mata, C.; Phillips, M.; Safwat, A.; Strauss, S.; Sundby Hall, K.; Valverde Morales, CM.; Westwood, AJ.; Winstanley, M.; Whelan, J. & Wheatley, K.: Results of the second interim assessment of rEECur, an international randomized controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma (RR-ES). Journal of Clinical Oncology 38:11502-11502, 2020

62. McCabe MM, V.; Khan, M.; Dirksen, U.; Evans, A.; Fenwick, N.; Gaspar, N.; Kanerva, J.; Kuhne, T.; Longhi, A.; Luksch, R.; Mata, C.; Phillips, M.; Sundby Hall, K.; Valverde Morales, CM.; Westwood, AJ.; Winstanley, M.; Whelan, J. & Wheatley, K.: Results of the first interim assessment of rEECur, an international randomized controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma. American Society of Clinical Oncology 37:11007- 11007, 2019

63. Ahmed SK, Randall RL, DuBois SG, et al: Identification of Patients With Localized Ewing Sarcoma at Higher Risk for Local Failure: A Report From the Children's Oncology Group. Int J Radiat Oncol Biol Phys 99:1286-1294, 2017

64. Andreou D, Ranft A, Gosheger G, et al: Which Factors Are Associated with Local Control and Survival of Patients with Localized Pelvic Ewing's Sarcoma? A Retrospective Analysis of Data from the Euro-EWING99 Trial. Clin Orthop Relat Res 478:290-302, 2020

65. 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 55:168-177, 2003

66. Foulon S, Brennan B, Gaspar N, et al: Can postoperative radiotherapy be omitted in localised standard-risk Ewing sarcoma? An observational study of the Euro-E.W.I.N.G group. Eur J Cancer 61:128-136, 2016

67. Casey DL, Meyers PA, Alektiar KM, et al: Ewing sarcoma in adults treated with modern radiotherapy techniques. Radiother Oncol 113:248-253, 2014

68. Gerrand C, Athanasou N, Brennan B, et al: UK guidelines for the management of bone sarcomas. Clin Sarcoma Res 6:7, 2016

69. Balamuth NJ, Womer RB: Ewing's sarcoma. Lancet Oncol 11:184-192, 2010

70. Bernstein M, Kovar H, Paulussen M, et al: Ewing's sarcoma family of tumors: current management. Oncologist 11:503-519, 2006

71. 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 121:467-475, 2015

72. Indelicato DJ, Keole SR, Shahlaee AH, et al: Definitive radiotherapy for ewing tumors of extremities and pelvis: long-term disease control, limb function, and treatment toxicity. Int J Radiat Oncol Biol Phys 72:871-877, 2008

73. Donaldson SS: Ewing sarcoma: radiation dose and target volume. Pediatr Blood Cancer 42:471-476, 2004

74. Ronchi L, Buwenge M, Cortesi A, et al: Whole Lung Irradiation in Patients with Osteosarcoma and Ewing Sarcoma. Anticancer Res 38:4977-4985, 2018

75. Meyers PA, Schwartz CL, Krailo MD, et al: Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival–a report from the Children's Oncology Group. J Clin Oncol 26:633-638, 2008

76. Meyers PA, Schwartz CL, Krailo M, et al: Osteosarcoma: a randomized, prospective trial of the addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate. J Clin Oncol 23:2004-2011, 2005

77. Meyers PA: Muramyl tripeptide (mifamurtide) for the treatment of osteosarcoma. Expert Rev Anticancer Ther 9:1035-1049, 2009

78. DeLaney TF, Park L, Goldberg SI, et al: Radiotherapy for local control of osteosarcoma. Int J Radiat Oncol Biol Phys 61:492-498, 2005

79. Stacchiotti S, Sommer J, Chordoma Global Consensus G: Building a global consensus approach to chordoma: a position paper from the medical and patient community. Lancet Oncol 16:e71-83, 2015

80. Riedel RF, Larrier N, Dodd L, et al: The clinical management of chondrosarcoma. Curr Treat Options Oncol 10:94-106, 2009

81. Ciernik IF, Niemierko A, Harmon DC, et al: Proton-based radiotherapy for unresectable or incompletely resected osteosarcoma. Cancer 117:4522-4530, 2011

82. Oertel S, Blattmann C, Rieken S, et al: Radiotherapy in the treatment of primary osteosarcoma–a single center experience. Tumori 96:582-588, 2010

83. DeLaney TF, Liebsch NJ, Pedlow FX, et al: Phase II study of high-dose photon/proton radiotherapy in the management of spine sarcomas. Int J Radiat Oncol Biol Phys 74:732-739, 2009

84. Ghosh KM, Lee LH, Beckingsale TB, et al: Indeterminate nodules in osteosarcoma: what's the follow-up? Br J Cancer 118:634-638, 2018

85. Saifuddin A, Baig MS, Dalal P, et al: The diagnosis of pulmonary metastases on chest computed tomography in primary bone sarcoma and musculoskeletal soft tissue sarcoma. Br J Radiol:20210088, 2021

86. Cipriano C, Brockman L, Romancik J, et al: The Clinical Significance of Initial Pulmonary Micronodules in Young Sarcoma Patients. J Pediatr Hematol Oncol 37:548-553, 2015

87. Davison R, Hamati F, Kent P: What Effect Do Pulmonary Micronodules Detected at Presentation in Patients with Osteosarcoma Have on 5-Year Overall Survival? J Clin Med 10, 2021

88. Aryal A, Kumar VS, Shamim SA, et al: What Is the Comparative Ability of 18F-FDG PET/CT, 99mTc-MDP Skeletal Scintigraphy, and Whole-body MRI as a Staging Investigation to Detect Skeletal Metastases in Patients with Osteosarcoma and Ewing Sarcoma? Clin Orthop Relat Res, 2021

89. Liu F, Zhang Q, Zhou D, et al: Effectiveness of (18)F-FDG PET/CT in the diagnosis and staging of osteosarcoma: a meta-analysis of 26 studies. BMC Cancer 19:323, 2019

90. Palmerini E, Colangeli M, Nanni C, et al: The role of FDG PET/CT in patients treated with neoadjuvant chemotherapy for localized bone sarcomas. Eur J Nucl Med Mol Imaging 44:215-223, 2017

91. Rothermundt C, Seddon BM, Dileo P, et al: Follow-up practices for high-grade extremity Osteosarcoma. BMC Cancer 16:301, 2016

92. Paioli A, Rocca M, Cevolani L, et al: Osteosarcoma follow-up: chest X-ray or computed tomography? Clin Sarcoma Res 7:3, 2017

93. Puri A, Gulia A, Hawaldar R, et al: Does intensity of surveillance affect survival after surgery for sarcomas? Results of a randomized noninferiority trial. Clin Orthop Relat Res 472:1568-1575, 2014

94. Puri A, Ranganathan P, Gulia A, et al: Does a less intensive surveillance protocol affect the survival of patients after treatment of a sarcoma of the limb? updated results of the randomized TOSS study. Bone Joint J 100-B:262-268, 2018

95. Campbell KM, Shulman DS, Grier HE, et al: Role of bone marrow biopsy for staging new patients with Ewing sarcoma: A systematic review. Pediatr Blood Cancer 68:e28807, 2021

96. Newman EN, Jones RL, Hawkins DS: An evaluation of [F-18]-fluorodeoxy-D-glucose positron emission tomography, bone scan, and bone marrow aspiration/biopsy as staging investigations in Ewing sarcoma. Pediatr Blood Cancer 60:1113-1117, 2013

97. Cesari M, Righi A, Colangeli M, et al: Bone marrow biopsy in the initial staging of Ewing sarcoma: Experience from a single institution. Pediatr Blood Cancer 66:e27653, 2019

98. Inagaki C, Shimoi T, Sumiyoshi Okuma H, et al: Bone marrow examination in patients with Ewing sarcoma/peripheral primitive neuroectodermal tumor without metastasis based on (18)F-fluorodeoxyglucose positron emission tomography/computed tomography. Med Oncol 36:58, 2019

99. Kasalak O, Glaudemans A, Overbosch J, et al: Can FDG-PET/CT replace blind bone marrow biopsy of the posterior iliac crest in Ewing sarcoma? Skeletal Radiol 47:363-367, 2018

100. Kalus S, Saifuddin A: Whole-body MRI vs bone scintigraphy in the staging of Ewing sarcoma of bone: a 12-year single-institution review. Eur Radiol 29:5700-5708, 2019

101. 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 Societe Francaise des Cancers de l'Enfant. J Clin Oncol 24:3997-4002, 2006

102. McTiernan A, Driver D, Michelagnoli MP, et al: High dose chemotherapy with bone marrow or peripheral stem cell rescue is an effective treatment option for patients with relapsed or progressive Ewing's sarcoma family of tumours. Ann Oncol 17:1301-1305, 2006

103. Luksch R, Tienghi A, Hall KS, et al: Primary metastatic Ewing's family tumors: results of the Italian Sarcoma Group and Scandinavian Sarcoma Group ISG/SSG IV Study including myeloablative chemotherapy and total-lung irradiation. Ann Oncol 23:2970-2976, 2012

104. Ladenstein R, Potschger U, Le Deley MC, et al: Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. J Clin Oncol 28:3284-3291, 2010

105. Whelan J, Le Deley MC, Dirksen U, et al: High-Dose Chemotherapy and Blood Autologous Stem-Cell Rescue Compared With Standard Chemotherapy in Localized High-Risk Ewing Sarcoma: Results of Euro-E.W.I.N.G.99 and Ewing-2008. J Clin Oncol:JCO2018782516, 2018

106. Dirksen U, Brennan B, Le Deley MC, et al: High-Dose Chemotherapy Compared With Standard Chemotherapy and Lung Radiation in Ewing Sarcoma With Pulmonary Metastases: Results of the European Ewing Tumour Working Initiative of National Groups, 99 Trial and EWING 2008. J Clin Oncol 37:3192-3202, 2019

107. Dirksen UB, V.; Brichard, B.; Butterfass-Bahloul, T.; Cyprova, S.; Faldum, A.; Gelderblom, H.; Hardes, J.; Hauser, P.; Havemann, L.; Hjorth, L.; Juergens, H.; Kanerva, J.; Kuehne, T.; Ladenstein, RL.; Raciborska, A.; Rascon, J.; Timmermann, B.; Ranft, A. & Koch, R, on behlaf of the Cooperative Ewing Sarcoma Study Group Ewing 2008.: Efficacy of add-on treosulfan and melphalan high-dose therapy in patients with high-risk metastatic Ewing sarcoma: Report from the International Ewing 2008R3 trial. Journal of Clinical Oncology 38:11501-11501, 2020

108. Meyers PA, Krailo MD, Ladanyi M, et al: High-dose melphalan, etoposide, total-body irradiation, and autologous stem-cell reconstitution as consolidation therapy for high-risk Ewing's sarcoma does not improve prognosis. J Clin Oncol 19:2812-2820, 2001

109. Yang X, Zhang L, Yang X, et al: Oncologic outcomes of pre- versus post-operative radiation in Resectable soft tissue sarcoma: a systematic review and meta-analysis. Radiat Oncol 15:158, 2020

110. Bedetti B, Wiebe K, Ranft A, et al: Local control in Ewing sarcoma of the chest wall: results of the EURO-EWING 99 trial. Ann Surg Oncol 22:2853-2859, 2015

111. 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 49:1314-1323, 2013

112. Bekelman JE, Schultheiss T, Berrington De Gonzalez A: Subsequent malignancies after photon versus proton radiation therapy. Int J Radiat Oncol Biol Phys 87:10-12, 2013

113. Merchant TE: Clinical controversies: proton therapy for pediatric tumors. Semin Radiat Oncol 23:97-108, 2013

114. Chung CS, Yock TI, Nelson K, et al: Incidence of second malignancies among patients treated with proton versus photon radiation. Int J Radiat Oncol Biol Phys 87:46-52, 2013

115. Leroy R, Benahmed N, Hulstaert F, et al: Proton Therapy in Children: A Systematic Review of Clinical Effectiveness in 15 Pediatric Cancers. Int J Radiat Oncol Biol Phys 95:267-278, 2016

116. Rombi B, DeLaney TF, MacDonald SM, et al: Proton radiotherapy for pediatric Ewing's sarcoma: initial clinical outcomes. Int J Radiat Oncol Biol Phys 82:1142-1148, 2012

117. Sklar C: Maintenance of ovarian function and risk of premature menopause related to cancer treatment. J Natl Cancer Inst Monogr:25-27, 2005

118. Critchley HO, Wallace WH: Impact of cancer treatment on uterine function. J Natl Cancer Inst Monogr:64-68, 2005

119. Gross E, Champetier C, Pointreau Y, et al: [Normal tissue tolerance to external beam radiation therapy: ovaries]. Cancer Radiother 14:373-375, 2010

120. Haie-Meder C, Mlika-Cabanne N, Michel G, et al: Radiotherapy after ovarian transposition: ovarian function and fertility preservation. Int J Radiat Oncol Biol Phys 25:419-424, 1993

121. Yamada Y, Lovelock DM, Yenice KM, et al: Multifractionated image-guided and stereotactic intensity-modulated radiotherapy of paraspinal tumors: a preliminary report. Int J Radiat Oncol Biol Phys 62:53-61, 2005

122. Nevelsky A, Borzov E, Daniel S, et al: Perturbation effects of the carbon fiber-PEEK screws on radiotherapy dose distribution. J Appl Clin Med Phys 18:62-68, 2017

123. Barnett JR, Gikas P, Gerrand C, et al: The sensitivity, specificity, and diagnostic accuracy of whole-bone MRI for identifying skip metastases in appendicular osteosarcoma and Ewing sarcoma. Skeletal Radiol 49:913-919, 2020

124. Theruvath AJ, Siedek F, Muehe AM, et al: Therapy Response Assessment of Pediatric Tumors with Whole-Body Diffusion-weighted MRI and FDG PET/MRI. Radiology 296:143-151, 2020

125. Nicoli F, Saleh DB, Ragbir M, et al: Response to: Comment on "Intraoperative Near-infrared Fluorescence (NIR) Imaging with Indocyanine Green (ICG) Can Identify Bone and Soft Tissue Sarcomas which May Provide Guidance for Oncological Resection". Ann Surg, 2020

126. Laitinen MK, Parry MC, Albergo JI, et al: Is computer navigation when used in the surgery of iliosacral pelvic bone tumours safer for the patient? Bone Joint J 99-B:261-266, 2017

127. Tate R, Gerrand C, Hale J: Tibial turn-up procedure as an alternative to rotationplasty in a 4-year-old with osteosarcoma of the distal femur. J Pediatr Orthop B 24:50-55, 2015

128. Hebert JS, Rehani M, Stiegelmar R: Osseointegration for Lower-Limb Amputation: A Systematic Review of Clinical Outcomes. JBJS Rev 5:e10, 2017

129. Jeys LM, Thorne CJ, Parry M, et al: A Novel System for the Surgical Staging of Primary High-grade Osteosarcoma: The Birmingham Classification. Clin Orthop Relat Res 475:842-850, 2017

130. Fujiwara T, Medellin MR, Sambri A, et al: Preoperative surgical risk stratification in osteosarcoma based on the proximity to the major vessels. Bone Joint J 101-B:1024-1031, 2019

131. Mumith A, Coathup M, Chimutengwende-Gordon M, et al: Augmenting the osseointegration of endoprostheses using laser-sintered porous collars: an in vivo study. Bone Joint J 99-B:276-282, 2017

132. Parry MC, Laitinen MK, Albergo JI, et al: Silver-coated (Agluna(R)) tumour prostheses can be a protective factor against infection in high risk failure patients. Eur J Surg Oncol 45:704-710, 2019

133. Bleyer A, Tai E, Siegel S: Role of clinical trials in survival progress of American adolescents and young adults with cancer-and lack thereof. Pediatr Blood Cancer 65:e27074, 2018

134. Ferrari A, Stark D, Peccatori FA, et al: Adolescents and young adults (AYA) with cancer: a position paper from the AYA Working Group of the European Society for Medical Oncology (ESMO) and the European Society for Paediatric Oncology (SIOPE). ESMO Open 6:100096, 2021

135. Gaspar N, Marshall LV, Binner D, et al: Joint adolescent-adult early phase clinical trials to improve access to new drugs for adolescents with cancer: proposals from the multi-stakeholder platform-ACCELERATE. Ann Oncol 29:766-771, 2018

136. Davis LE, Bolejack V, Ryan CW, et al: Randomized Double-Blind Phase II Study of Regorafenib in Patients With Metastatic Osteosarcoma. J Clin Oncol 37:1424-1431, 2019

137. Duffaud F, Mir O, Boudou-Rouquette P, et al: Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study. Lancet Oncol 20:120-133, 2019

138. Attia SB, V.; Ganjoo, KN.; George, S.; Agulnik, M.; Rushing, DA.; Loggers, ET.; Livingston, MB.; Wright, JA.; Chawla, SP.; Okuno, SH.; Reinke, DK.; Riedel, RF.; Davis, LE.; Ryan, CW. & Maki, RG.: A phase II trial of regorafenib (REGO) in patients (pts) with advanced Ewing sarcoma and related tumors (EWS) of soft tissue and bone: SARC024 trial results. Presented at the ASCO, May 20, 2017

139. Duffaud FB, J.; Mir, O.; Chevreau, CM.; Boudou Rouquette, P.; Kalbacher, E.; Penel, N.; Perrin, C.; Laurence, V.; Bompas, E.; Saada-Bouzid, E.; Delcambre, C.; Bertucci, F.; Cancel, M.; Schiffler, C.; Monard, L.; Bouvier, C.; Vidal, C.; Gasper, N. & Chabaud, S.: LBA68 - Results of the randomized, placebo (PL)-controlled phase II study evaluating the efficacy and safety of regorafenib (REG) in patients (pts) with metastatic relapsed Ewing sarcoma (ES), on behalf of the French Sarcoma Group (FSG) and UNICANCER. Presented at the ESMO virtual conference 2020., 20 Sept 2020, 2020

140. Italiano A, Mir O, Mathoulin-Pelissier S, et al: Cabozantinib in patients with advanced Ewing sarcoma or osteosarcoma (CABONE): a multicentre, single-arm, phase 2 trial. Lancet Oncol 21:446-455, 2020

141. Xie L, Xu J, Sun X, et al: Apatinib for Advanced Osteosarcoma after Failure of Standard Multimodal Therapy: An Open Label Phase II Clinical Trial. Oncologist 24:e542-e550, 2019

142. Gaspar NBS, FJ.; Venkatramani, R.; Longhi, A.; Lervat, C.; Casanova, M.; Aerts, I.; Bielack, SS.; Entz-Werle, N.; Strauss, S.; He, C.; Thebaud, E.; Locatelli, F.; Morland, B.; Gallego Melcon, S.; Canete Nieto, A.; Marec-Berard, P.; Gambart, M.; Rossig, C. & Campbell- Hewson, Q.: Phase I combination dose-finding/phase II expansion cohorts of lenvatinib + etoposide + ifosfamide in patients (pts) aged 2 to[?]25 years with relapsed/refractory (r/r) osteosarcoma. Presented at the European Society for Medical Oncology (ESMO), 2019

143. Brenner JC, Feng FY, Han S, et al: PARP-1 inhibition as a targeted strategy to treat Ewing's sarcoma. Cancer Res 72:1608-1613, 2012

144. Choy E, Butrynski JE, Harmon DC, et al: Phase II study of olaparib in patients with refractory Ewing sarcoma following failure of standard chemotherapy. BMC Cancer 14:813, 2014

145. Schafer ES, Rau RE, Berg SL, et al: Phase 1/2 trial of talazoparib in combination with temozolomide in children and adolescents with refractory/recurrent solid tumors including Ewing sarcoma: A Children's Oncology Group Phase 1 Consortium study (ADVL1411). Pediatr Blood Cancer 67:e28073, 2020

146. Chugh R, Ballman KV, Helman LJ, et al: SARC025 arms 1 and 2: A phase 1 study of the poly(ADP-ribose) polymerase inhibitor niraparib with temozolomide or irinotecan in patients with advanced Ewing sarcoma. Cancer 127:1301-1310, 2021

147. Smith MA, Reynolds CP, Kang MH, et al: Synergistic activity of PARP inhibition by talazoparib (BMN 673) with temozolomide in pediatric cancer models in the pediatric preclinical testing program. Clin Cancer Res 21:819-832, 2015

148. Engert F, Kovac M, Baumhoer D, et al: Osteosarcoma cells with genetic signatures of BRCAness are susceptible to the PARP inhibitor talazoparib alone or in combination with chemotherapeutics. Oncotarget 8:48794-48806, 2017

149. Holme H, Gulati A, Brough R, et al: Chemosensitivity profiling of osteosarcoma tumour cell lines identifies a model of BRCAness. Sci Rep 8:10614, 2018

150. Jones DTW, Banito A, Grunewald TGP, et al: Molecular characteristics and therapeutic vulnerabilities across paediatric solid tumours. Nat Rev Cancer 19:420-438, 2019

151. Tawbi HA, Burgess M, Bolejack V, et al: Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol 18:1493-1501, 2017

152. D'Angelo SP, Mahoney MR, Van Tine BA, et al: Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. Lancet Oncol 19:416-426, 2018

153. Paoluzzi L, Cacavio A, Ghesani M, et al: Response to anti-PD1 therapy with nivolumab in metastatic sarcomas. Clin Sarcoma Res 6:24, 2016

154. Sundara YT, Kostine M, Cleven AH, et al: Increased PD-L1 and T-cell infiltration in the presence of HLA class I expression in metastatic high-grade osteosarcoma: a rationale for T-cell-based immunotherapy. Cancer Immunol Immunother 66:119-128, 2017

155. Dobrenkov K, Ostrovnaya I, Gu J, et al: Oncotargets GD2 and GD3 are highly expressed in sarcomas of children, adolescents, and young adults. Pediatr Blood Cancer 63:1780-1785, 2016

156. Wingerter A, El Malki K, Sandhoff R, et al: Exploiting Gangliosides for the Therapy of Ewing's Sarcoma and H3K27M-Mutant Diffuse Midline Glioma. Cancers (Basel) 13, 2021

157. Mody R, Yu AL, Naranjo A, et al: Irinotecan, Temozolomide, and Dinutuximab With GM-CSF in Children With Refractory or Relapsed Neuroblastoma: A Report From the Children's Oncology Group. J Clin Oncol 38:2160-2169, 2020

158. Erkizan HV, Kong Y, Merchant M, et al: A small molecule blocking oncogenic protein EWS-FLI1 interaction with RNA helicase A inhibits growth of Ewing's sarcoma. Nat Med 15:750-756, 2009

159. Zollner SK, Selvanathan SP, Graham GT, et al: Inhibition of the oncogenic fusion protein EWS-FLI1 causes G2-M cell cycle arrest and enhanced vincristine sensitivity in Ewing's sarcoma. Sci Signal 10, 2017

160. Ludwig JF, NC.; Anderson, PM.; Macy, ME.; Riedel, RF.; Davis, LE.; Daw, NC.; Wulff, J.; Kim, A.; Ratan, R.; Baskin-Bey, ES.; Toretsky, JA.; Breitmeyer, JB. & Meyers, PA.: TK216 for relapsed/ refractory Ewing sarcoma: Interim phase 1/2 results. Journal of Clinical Oncology 39:11500-11500, 2021

161. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence- SEER Research Data, 9 Registries, Nov 2019 Sub (1975-2017)- Linked to County Attributes- Time Dependent (1990- 2017) Income/ Rurality, 1969- 2018 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2020, based on the November 2019 submission.

162. Joinpoint Regression Program, Version 4.6.0.0. April, 2018; Statistical Research and Applications Branch, National Cancer Institute. Statistical Research and Applications Branch, National Cancer Institute. Kim HJ, Fay MP, Feuer, EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000; 19:335-351 (correction: 2001;20:655).

163. 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 27:2536-2541, 2009

164. Le Grange F: Advanced radiotherapy techniques: Improving outcomes in sarcoma., UCL (University College London), UCL Discovery., 2021

165. Gaspar NC, M.; Bautista Sirvent, FJ.; Venkatramani, R.; Morland, B.; Gambart, M.; Thebaud, E.; Strauss, S.; Locatelli, F.; Melcon, SG.; Canete, A.; Bielack, SS.; Rossig, C.; Aerts, I.; Marec-Berard, P.; Kraljevic, S.; Hayato, S.; He, C.; Dutcus, CE. & Campbell-Hewson, Q.: Single-agent expansion cohort of lenvatinib (LEN) and combination dose-finding cohort of LEN + etoposide (ETP) + ifosfamide (IFM) in patients (pts) aged 2 to [?]25 years with relapsed/refractory osteosarcoma (OS). Journal of Clinical Oncology 36:11527-11527, 2018

166. Federico SM, Pappo AS, Sahr N, et al: A phase I trial of talazoparib and irinotecan with and without temozolomide in children and young adults with recurrent or refractory solid malignancies. Eur J Cancer 137:204-213, 2020

Figure legends

Figure 1. The incidence and outcomes of primary bone sarcoma using Surveillance, Epidemiology, and End Results (SEER) data.

A-C. The incidence trends of bone sarcoma, SEER 21, overall from 2000 to 2017- histological type, gender and ethnicity by age of diagnosis. Data from SEER.[2] **D.** Five-year relative survival rates for osteosarcoma and Ewing sarcoma, SEER9, from patients diagnosed between 1975 to 2012 with at least 5-years follow-up for survival analyses. Data from SEER.[161,162]

Figure 2. Example PBT plans for pelvic and sacral tumors in AYAs.[164]

Axial and coronal images of two definitive PBT plans to treat locally advanced pelvic ES. An iliac bone primary in a 16-year-old female (**A-B**) and sacral tumor in a 19-year-old female (**C-D**). Red colour wash represents high dose, green moderate and blue the low dose.

Figure 3. Surgical techniques for primary bone sarcoma.

A . Complex navigation plan showing proposed resection planes for low grade osteosarcoma of the iliac wing. **B** . Reconstruction of the hip after navigated extraarticular resection using modular porous acetabular reconstruction system. **C** . 3D printed custom jig for resection of femoral diaphyseal Ewing sarcoma before insertion of custom implant.

Hosted file

`Table I.docx` available at https://authorea.com/users/420892/articles/527132-current-approaches-to-management-of-bone-sarcoma-in-adolescent-and-young-adult-aya-patients

Hosted file

TABLE II.docx available at https://authorea.com/users/420892/articles/527132-current-approaches-to-management-of-bone-sarcoma-in-adolescent-and-young-adult-aya-patients

Hosted file

Fig 1.pptx available at https://authorea.com/users/420892/articles/527132-current-approaches-to-management-of-bone-sarcoma-in-adolescent-and-young-adult-aya-patients

Hosted file

PBT in AYA.pptx available at https://authorea.com/users/420892/articles/527132-current-approaches-to-management-of-bone-sarcoma-in-adolescent-and-young-adult-aya-patients

Hosted file

10June_Surgical pics.pptx available at https://authorea.com/users/420892/articles/527132-current-approaches-to-management-of-bone-sarcoma-in-adolescent-and-young-adult-aya-patients