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

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Highlights:

- This review focuses on the two most frequent bone sarcomas in AYAs: osteosarcoma and Ewing sarcoma.
- There is international consensus for current standard of care for upfront chemotherapy treatment and multidisciplinary input within specialized sarcoma centers to individualize important variations in timing, sequence and type of local control.
- Targeted therapies with promising efficacy for osteosarcoma and Ewing sarcoma are still in development.

Abbreviations:

Abbreviation	**Full term**
AYA	Adolescent and Young Adult
ES	Ewing sarcoma
OS	Osteosarcoma
EFS	Event-free survival
FDG- PET/CT	18F-fluorodeoxyglucose positron emission tomography with computerized tomography
WB-MRI	Whole body magnetic resonance imaging
TKI	Tyrosine kinase inhibitor
RT	Radiotherapy
PBT	Proton beam therapy
IMRT	Intensity modulated radiotherapy
Gy	Gray
PEEK	Polyether ether ketone
COG	Children's Oncology Group
EURAMOS	The European and American Osteosarcoma Study
VEGFR	Vascular endothelial growth factor receptor
SEER	Surveillance, Epidemiology and End Results
FDA	Food and Drug Administration
NICE	National Institute for Health and Care Excellence

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 morbidity to enhance quality of care for AYA survivors.

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) and gender (Fig 1B). The commonest bone sarcomas, OS and ES, have a peak incidence in AYAs, with a nadir in older AYAs and a progressive incidence increase of OS thereafter (Fig. 1A). 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, such as *CDKN2A*, *MEN1*, *VHL*, *POT1*, *APC*, *MSH2*, *ATRX* and *TP53*, 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 such as *BRCA1*, *FANCC, ERCC, POLE, RET* and *TP53* or inactivating variants associated with cancer predisposition syndromes -such as Fanconi anemia and familial breast cancer.[14-16]

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 incorporates multidrug chemotherapy and surgical resection is the current standard of care for resectable OS, with neoadjuvant chemotherapy generally advocated in the AYA population. 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. 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.[26] Several independent risk factors, including histologic response, age, presence of metastases, primary tumor site and volume are associated with propensity to OS recurrence.[22,26-30] 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%).[25,26] 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.[31]

Despite combined treatment, 40 to 50% of patients experience recurrent disease most frequently within 3 years from diagnosis.[32,33] 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%.[33,34] Early relapse (within 24 months) is associated with a less favorable prognosis.[35] Achieving a second complete surgical remission is crucial as some patients, ~30% will remain disease free.[33,36] Retrospective data

suggest that repeated metastasectomies may improve survival and should be considered whenever possible.[34,36-38] However, this is dependent on patient selection and lacks high quality prospective evaluation.[39,40]

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.[33,41,42] Outcomes depend on disease-free interval with late relapses faring better.[33] There is no accepted standard regimen but cytotoxic agents include, ifosfamide ± etoposide, single agent ifosfamide, gemcitabine and docetaxel, cyclophosphamide, and carboplatin.[43] 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 prolonged intensive chemotherapy regimens through the addition of cytotoxic agents, (notably- doxorubicin, ifosfamide and etoposide) to vincristine, dactinomycin and cyclophosphamide (VAC).[44-49] 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).[50,51] 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).[51] 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.[52,53] 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.[53] 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.[54] 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.[55,56]

Recurrent ES, which is mostly systemic relapse, occurs in 30-40% of primary localized disease and 60-80% of metastatic ES.[57] Survival is less than 25% overall for patients with relapsed ES, better in later relapses >2y after treatment.[58,59] 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.[60,61] The median PFS across all cohorts was 4.7 months with overall survival of 13.7 months across all therapies.[60]

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.[62] The failure rate after RT alone is higher in extremity and pelvic tumors, reflecting patients with often, locally advanced or unresectable tumors.[62,63] Indications for combination treatment include the expectation or confirmation of inadequate resection margins, large tumors and poor response to induction chemotherapy.[64,65] Definitive RT is recommended where surgery would result in unacceptable morbidity.[43,62,66-71] RT dose ranges from 45Gy to 66Gy depending on anatomical location, tumor size and timing of RT in relation to surgery.[71,72] 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.[73]

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.[74] 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. An increased overall survival (from 70 to 78% at 6y, *P*=0.03) was reported for the mifamurtide arms, however, the lack of significantly improved EFS and concerns about trial design and a possible interaction between mifamurtide and ifosfamide ensured the results were insufficient to support global approval by regulatory authorities, such as the US FDA, restricting the use of mifamurtide to selected countries.[74-76] The agent is approved through the NICE in the UK, however, even amongst expert sarcoma centers, there is no consensus on its use. We await the results of a phase II randomized trial for patients with high risk, localized and metastatic disease, (NCT03643133 at https://ClinicalTrials.gov/).

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.[43,77-79] Doses of 60Gy or higher, and ideally 70Gy are indicated.[77,80-82] 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.[33-36,41]

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.[83-85] Surgical

sampling is undertaken in some centers but its value in determining overall survival and guiding treatment is unproven.[84,86] 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.[87-89]

Approaches to **follow-up after treatment** vary in visit intervals, pulmonary imaging modalities and monitoring for late effects of treatment.[90,91] There is considerable variation in recommendations and practice, indicating a need for collaborative prospective evaluation and evidence-seeking.[90-93] Access to rehabilitation services, assistance in resuming progress on achieving life skills and psychosocial support are all vital parts of effective follow-up to restoring quality of life for AYA patients.[94] Screening to identify rehabilitation needs and physical rehabilitation with exercise and physical activity prescription, improves physical sequelae of therapy, with a resultant positive impact on wellbeing and quality of life.[95-97] The psychological, social and physical needs of AYA sarcoma survivors require a personalized approach and holistic guidance and care from a proactive multidisciplinary team that understands psychological adaptation and recovery as dynamic systems.[98]

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.[99-103] WB-MRI appears comparable to FDG-PET/CT and superior to bone scintigraphy, without requiring ionising radiation.[87,104] In centers with access to these imaging modalities, it is possible to avoid an invasive bone marrow biopsy.[105] 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.[106-109] 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.[110] No benefit from BuMel, compared with conventional VAI with whole lung irradiation, was seen in patients with pulmonary metastases.[111] Additional treosulfan and melphalan HD chemotherapy over standard VIDE induction/ VAC consolidation demonstrated no benefit in patients >14 years with primary metastatic ES.[112] 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.[107,113]

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.[65] There has been a move towards delivering RT pre-operatively, to reduce surgical morbidity by allowing limb/ organ salvage surgery in selected patients, to reduce the impact of surgical fixation on the quality of RT and to reduce the risk of late effects with lower doses. There is however, an increased risk of wound complications which in turn may compromise complex bone reconstructions.[114] Complete resection of chest wall tumors appear superior to treatment with RT in improving survival.[115] Sacral tumors demonstrate improved survival with definitive RT, compared to non-sacral pelvic tumors that do better with combined surgery and RT.[63] 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.[116] 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.[117-120] 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.[121]

The risk of ovarian dysfunction from pelvic RT increases with radiation dose. [122-124] Cumulative irradiation doses of 2Gy to the testes and 6-15Gy to ovaries, depending on age, can cause gonadal failure.[125] 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, a procedure that can be achieved laparoscopically, may be used to move one or both ovaries away from the RT target if indicated.[126,127] If concurrent gonadotoxic chemotherapy is planned, ovarian cortex can be obtained for cryopreservation at the same time.

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.[82,128] 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%.[80] 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.[129]

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 resect tumors with subsequent reconstruction to maximize long term functional outcome, of particular importance in the AYA population. In any procedure, surgeons and patients must balance the oncological benefits of wider resections with the morbidity of resecting 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.[104,130] Preoperative imaging however, is unfortunately not able to assess the response of tumors to neoadjuvant chemotherapy with sufficient reliability to influence surgical options.[131] 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, (Fig. 3).[132] 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. 4).[133]

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

391 the best option. Reconstruction with the uninvolved part of the limb, for example, by
392 rotationplasty or tibial turn-up may be helpful, particularly in children.[134] Advances in
393 prosthetics and other technologies including transosseous fixation devices offer the
394 potential for improved function for some amputees.[135]
395
396 Limb preservation carries a risk of local recurrence. In OS, retrospective studies have
397 evaluated the risk in terms of the surgical margins, chemotherapy response and
398 proximity to major vessels,[136,137] but the application of these systems in prospective
399 decision making has yet to be established.
400
401 Growth and the long-term complications of surgical reconstructions are further issues
402 for adolescents. Growing endoprostheses contain a mechanism which is activated in
403 outpatients using a magnetic coil. Although these implants have reduced the number
404 of operations required after endoprosthetic reconstruction, patients do not escape
405 further surgery, but the rate of limb preservation remains high. Bone-compatible
406 collars encourage bone growth onto the surface of implants and reduce the risk of
407 aseptic loosening when successful integration occurs. New porous designs may have
408 some advantages but these remain to be proven.[138] Antibacterial silver surface
409 treatments have also become widely adopted with the aim of reducing the risk of deep
410 infection. However, studies of their efficacy are retrospective and they have not been
411 subjected to a prospective randomized trial.[139]
412
413
414 **Emerging targeted therapeutics**

Targeted therapies are under investigation for recurrent ES and OS but are not standard of care at this time.

Multitargeted tyrosine kinase small molecule inhibitors have been investigated in phase 1 and 2 clinical trials in ES and OS with a number of agents including regorafenib,[140-143] carbozantinib,[144] apatinib,[145] and lenvatinib,[146] demonstrating single agent activity- (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.[146] 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 have been 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.[147] Olaparib trialled as a single agent in a prospective phase II trial was disappointing with no objective responses in heavily pre-treated ES,[148] 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.[149-151] These demonstrated varied efficacy in pediatric and AYA patients with refractory/ recurrent ES with toxicity limiting dose intensity, Table II. Additional trials with Olaparib are ongoing. Pre-clinical programs 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.[152-154]

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.[155-158] Disialogangliosides, GD2 is a potential cell surface target expressed by ES and OS.[159,160] 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,[161] 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;[162] 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.[163] 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.[164]

Challenges of care for bone sarcoma AYA and recommendations

Provision of AYA care varies globally. AYA often falls between pediatric centers and adult oncology models of care, none of which meet the specific complex needs of AYA. Disparities in access to expert cancer care specifically adapted to AYA needs and the modest improvement in survival outcomes compared to older adult and pediatric cancers is well documented.[165-169] There are many reasons for inferior AYA outcomes, including unique biologic and genetic features to AYA, as yet largely undefined.[47,170] AYA with bone tumors often experience delays in diagnosis; with presenting complaints and nonspecific features often not recognized due to young age and rarity.[171] Importance should be attributed to community awareness and GP education programs with concurrent strong referral pathways to expert AYA bone sarcoma centers.[172,173] There are psychosocial factors related to the developmental transition of AYA that are magnified by a cancer diagnosis; these include the pressures of normality, maintaining peer and family relationships, discovering sexuality and body image, balancing education and work commitments and compliance with treatment protocols. Environments and models of care have developed that are tailored to meet the specific needs of AYA with sarcoma to provide flexibility and better quality of care by avoiding inpatient admissions, with administration of chemotherapy in the ambulatory setting being demonstrated to be safe, practical and cost effective. [174-176]

The AYA disparities in cancer care have been identified by the European consortiums, ESMO and SIOPE that demonstrated underprovision and inequity of specialized AYA cancer care across Europe with almost 70% of healthcare professionals with no access to specialized services for AYA including management of late effects.[169] In response, ESMO have published a position paper that addresses the special cancer

care issues in AYA.[177] Several recommendations from ESMO and NICE focus on the need for a large multidisciplinary team that uses a developmental, patient and family centered approach, supports AYA trial accrual and defines the minimal essential requirements for AYA centers such as, disease expertise resources and age appropriate- psychosocial supports, palliative care, transition services, fertility preservation programs, genetic counselling and sustainable AYA programs.[177,178]

Gonadotoxic chemotherapy and radiotherapy are risks to future fertility and reproductive health in AYA survivors. Early AYA consultation with a fertility expert is recommended for patients and parents of children diagnosed with bone sarcoma to prepare for the possibility of infertility and to discuss potential fertility preservation options.[179] Sperm storage is recommended for post pubertal males and if not possible, surgical exploration of the testes (OncoTESE) can be performed to extract sperm. In pre-pubertal males, testicular tissue may be stored on an experimental basis. Fertility preservation options for females of reproductive age are complex and include, oocyte/ ovarian tissue cryopreservation and gonatrophin-releasing hormone agonists.[179] Fertility preservation methods, such as gonadotrophin- releasing hormone agonists and auto-transplantation of ovarian tissue in sarcomas, may be limited by conflicting scientific evidence, variable resources and health care policies internationally.[179,180] It is important to have a holistic discussion about options to parenthood rather than concentrating on fertility preservation alone. Gamete donation is an effective means of assisted conception. The possible effect of radiotherapy on the uterus also needs to be discussed. The risk of miscarriage, preterm delivery and small for gestational age babies increase after pelvic radiotherapy.[181] Discussion should also include late effects of cancer such as premature ovarian insufficiency, need for hormone

515 replacement therapy, vaginal stenosis and possible vaginal dilatation after
516 radiotherapy.
517
518 Teenagers and AYA have typically been underrepresented in clinical cancer trials,
519 especially in the 20-29y age group and this correlates with only modest gains in
520 survival.[182,183] There is evidence that AYA recruitment will increase with improved
521 awareness of trial availability, acceptability of trial design to AYA specific lifestyle and
522 education and more appropriate age eligibility criteria to increase trial access for
523 AYA.[165] Greater efforts are unfolding internationally to increase access to specialist
524 centers and clinical trials, particularly of novel agents with age inclusion criteria across
525 the AYA spectrum,[177] and supported by multi-stakeholder platforms such as the
526 ACCELERATE Fostering Age Inclusive Research (FAIR) trial[184] to include
527 adolescents from 12 years age, as evidenced by the novel agent trials in Table II.
528
529 A multidisciplinary approach to standard of care for AYA with sarcoma requires the
530 expertise and collaboration of both pediatric and adult medical oncologists.[173,177]
531 Accrual of young adults to many trials remains low, such as Womer et al[51] with
532 compressed VDC IE chemotherapy being accepted as standard upfront therapy for
533 young adults with ES, despite only 12% of all patients enrolled being 18 years or over.
534 Support for the inclusion of young adults into pediatric protocols for pediatric type
535 cancers with no upper age limit, is just as important as supporting inclusiveness of
536 adolescents into adult early phase clinical trials. To this effect, trial development that
537 is centered on the molecular target and cancer biology should be prioritized over age.
538 Development of dedicated AYA sarcoma units allows centralization of care, expertise
539 and access to trials.[173] Greater collaboration and networking between established

pediatric and medical oncology bone sarcoma groups also leads to increased development and access to trials with opportunities existing through, for example- The Connective Tissue Oncology Society (CTOS), and EuroEwing consortium which has strong representation across medical and pediatric oncology across Europe and trial recruitment across the AYA spectrum.[52]

AYA with cancer require specialized clinical care and survivorship programs that address mental health. A Canadian study identified survivors that had been diagnosed with cancer between 15-21 years, including bone sarcomas, are at increased risk of adverse mental health outcomes.[185] Cancer survivors treated in adult centers have an 80% higher rate of outpatient mental health visits usually anxiety related, compared to those treated in the pediatric sector.[185] The allocation of resources to tailor guidance on the psychosocial challenges and address the mental health needs of AYA during and after treatment should be prioritized and surveillance for psychiatric disorders built into long term effects guidelines.[186,187]

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 compared to younger children. The reasons are multifactorial, including aggressive complex biology that remains ill-understood as well as delayed diagnosis, lack of prognostic biomarkers and 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 with expert multidisciplinary collaboration 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 and improve outcome.

Conflict of Interest

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

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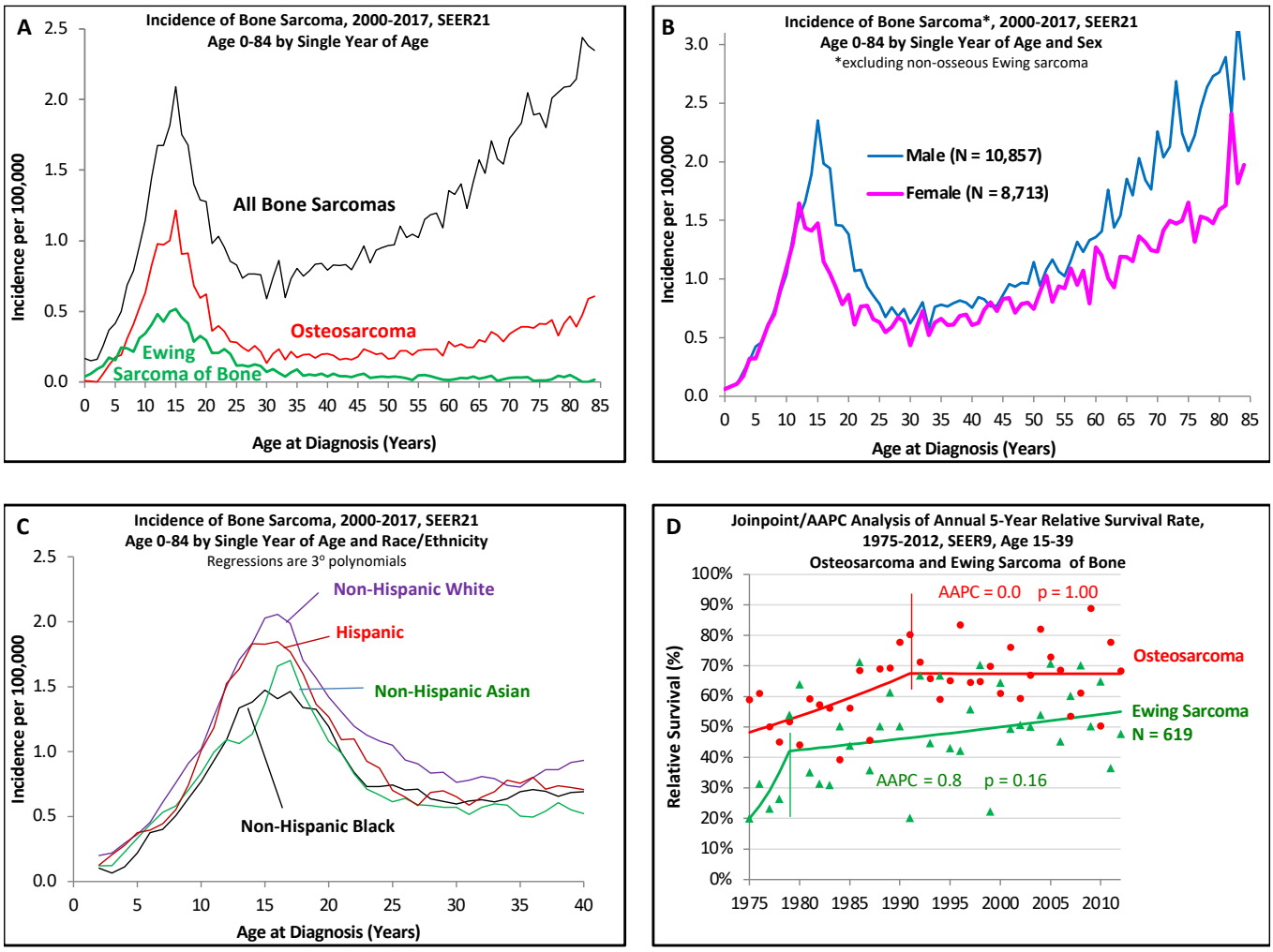

Figure 1. The incidence and outcomes of primary bone sarcoma using Surveillance, Epidemiology, and End Results (SEER) data.

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.[188,189]

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

Ref.	Trial	Population	Pts *(n)*	Treatment	Survival outcomes
Standard risk, localized					
Paulussen[48]	EICESS-92	Localized, Tumor volume <100ml	155	Induction (VAIA x4) + Randomization: VAIA x10 vs. VACA x10 (cyclophosphamide vs ifosfamide)	3y EFS 74% vs. 73%, HRs for EFS and overall survival 0.91 VAIA vs. VACA
Le Deley[49]	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[47]	INT-0091 (CCG-7881 and POG-8850)	<30yo	398	Standard (VACA) vs experimental (VACA + IE)	5yr EFS and overall survival for standard vs. experimental, 54% vs. 69% (*p* 0.005) and 61% vs. 72% (*p* 0.01)
Granowetter[190]	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%
Womer[51]	COG AEWS0031	<50yr age Localized	568	Randomization: VDC/IE standard (q3/52) vs.	3y EFS and overall survival for std vs.

				VDC/IE intensified (q2/52)	intensified, 65% vs. 73% (*p* 0.048) and 77% vs. 83% (*p* 0.056) Similar toxicity
High risk, localized*					
Whelan[110]	Euro-Ewing99/ Ewing-2008	<50yo Poor histologic response (≤90%), Tumor volume ≥200ml	240	Induction (VIDEx6, VAIx1) Randomization: VAI vs. Bu-Mel/ ASCT	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[111]	Euro-Ewing99 R2Pulm/ EWING-2008	<50yo Pulmonary/pleural metastases, nil other	287	VAI + WLI vs. Bu-Mel	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[48]	EICESS-92	Volume ≥100ml or ±Metastases (any)	492	VAIA x14 vs. EVAIA x4 + EVAIAx10 (addition of etoposide)	3y EFS 47% vs. 52% (*p*=0.47)
Brennan[53]	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, ifosfamide, doxorubicin, etoposide.
Bu-Mel/ ASCT: Busulphan Melphalan conditioning with autologous stem cell transplant.
WLI: whole lung irradiation.

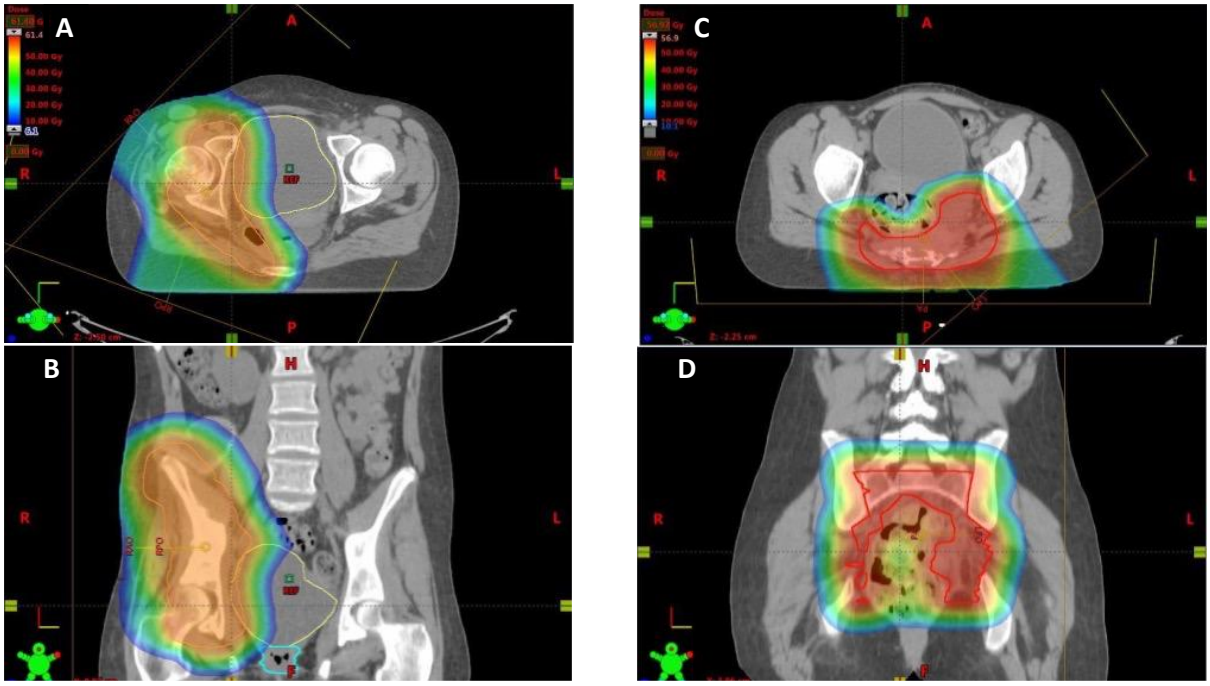

Figure 2. Example PBT plans for pelvic and sacral tumors in AYAs.[191]

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.

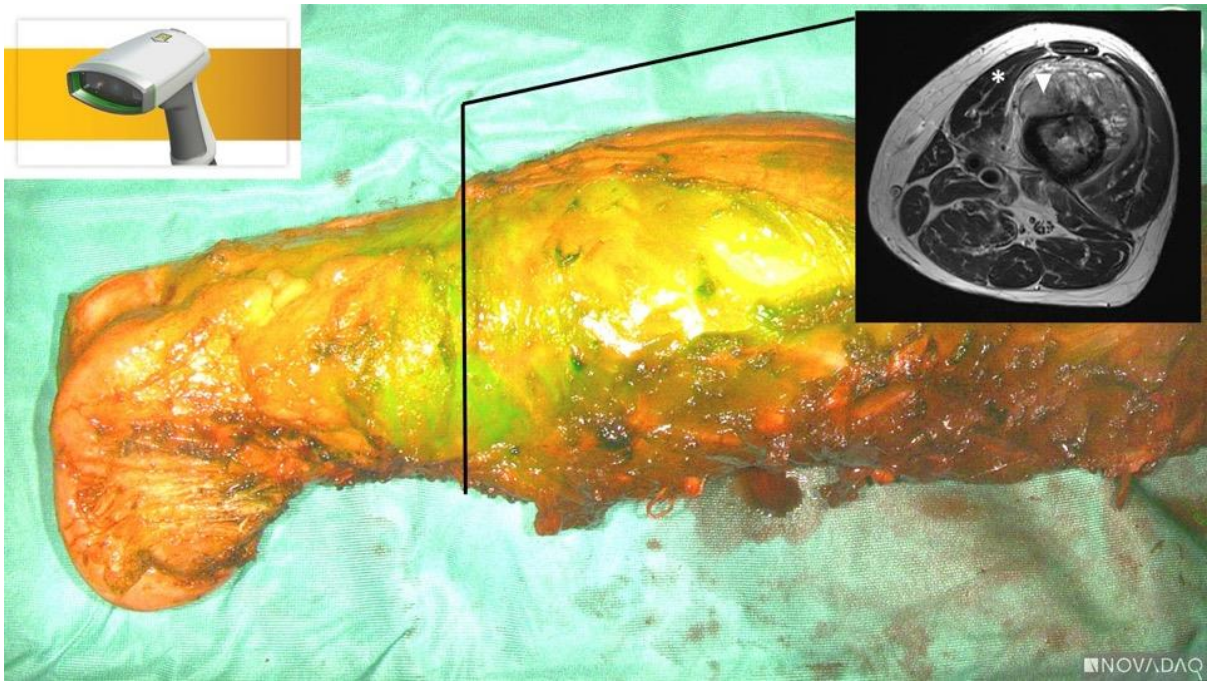

Figure 3. Fluorescence guided surgery in osteosarcoma.

Assessment of an osteosarcoma specimen following resection with fluorescence guided surgery using a handheld infrared camera (top left inset). The patient was injected with 75mg indocyanine green intravenously the day prior to surgery. The soft tissue component of the tumor (annotated with the white arrowhead on the MRI axial slice inset on the top right) is fluorescing through the vastus medialis muscle (annotated with * on the MRI).

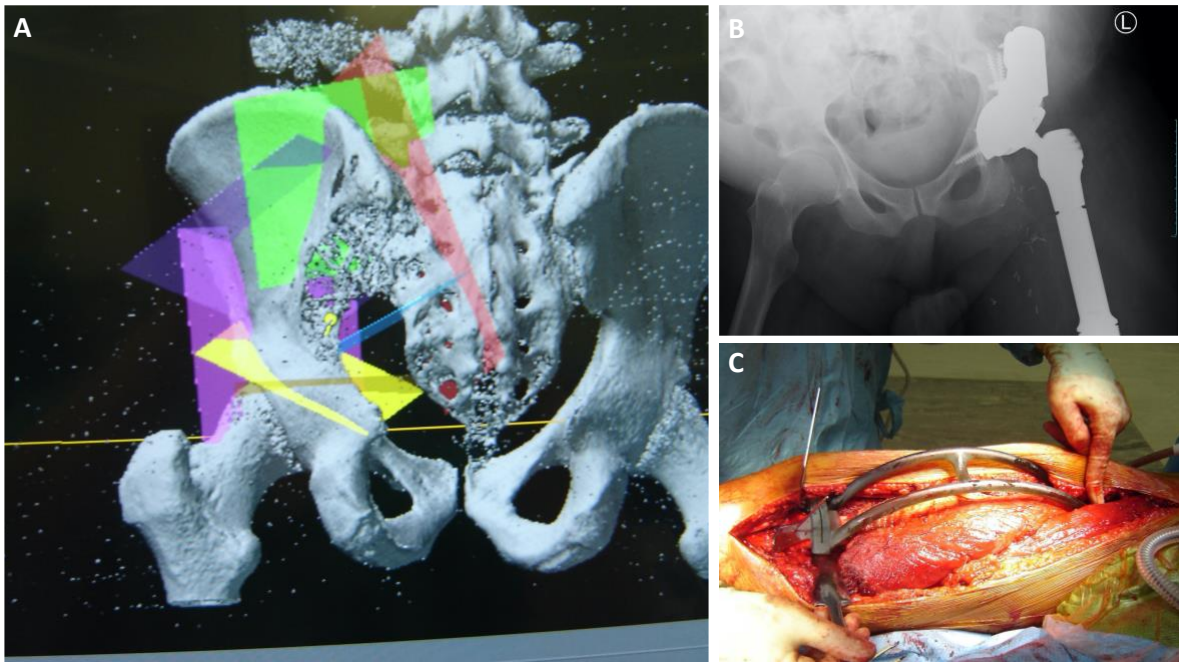

Figure 4. Surgical techniques for primary bone sarcoma.

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.

634 **TABLE II. Trials investigating new therapeutics for advanced or metastatic ES and OS.**
635

	Clinical trial	Drugs	Patient group	Outcome measures	Common / significant grade 3 or 4 toxicity (>10%)
Multi-targeted TKIs					
Italiano *et al*, 2020.[144]	CABONE-multicenter, single arm, phase 2	Cabozantinib	Advanced ES (n=39) and OS (n=42), ≥12yo	ORR 26% in ES, median PFS 4.4 mo, ORR 12% in OS with 33% PFS at 6 mo	Hypophosphataemia, raised AST, palmar-plantar syndrome, pneumothorax, neutropenia
Duffaud *et al*, 2019.[141]	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, hypophosphataemia, chest pain
Duffaud *et al*, 2020.[143]	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
Davis *et al*, 2019.[140]	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.[145]	Single arm, phase 2	Apatinib	Relapsed/ unresectable OS, n=37, ≥16yo	ORR 43%, 4mo PFS 57%	Pneumothorax, wound dehiscence
Gaspar *et al*, 2018.[192]	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, hypothyroidism, hypertension, pyrexia, weight loss
Gaspar *et al*, 2019.[146]	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					
Choy *et al*, 2014.[148]	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.[150]	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.[149]	Single arm, phase 1/2	Talazoparib plus temozolomide	Recurrent/ refractory	ES- 2/10 prolonged SD (8 cycles)	DLTs: haematologic

			solid tumors, n=40, 4-25yo		
Federico *et al*, 2020.[193]	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.[164]	TK216-01, phase 2 dose (RP2D)	TK216± vincristine	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	CR 7%, SD 39%, PD 54%, SD median duration 113 days (B) 3 patient tumor responses	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.

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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.[188,189]

Figure 2. Example PBT plans for pelvic and sacral tumors in AYAs.[191]

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. Fluorescence guided surgery in osteosarcoma.

Assessment of an osteosarcoma specimen following resection with fluorescence guided surgery using a handheld infrared camera (top left inset). The patient was injected with 75mg indocyanine green intravenously the day prior to surgery. The soft tissue component of the tumor (annotated with the white arrowhead on the MRI axial slice inset on the top right) is fluorescing through the vastus medialis muscle (annotated with * on the MRI).

Figure 4. 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.