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REVIEW ARTICLE

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Ewing sarcoma

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ABSTRACT

Ewing sarcoma is a group of low-differentiated, high-grade, small-cell tumours. It is the third most common malignancy among primary bone tumours in adults. The prognosis of Ewing sarcoma is bad, and very often at the time of diagnosis the disease is highly advanced. For patients with localized disease, who have no metastases diagnosed at baseline, it is necessary to use combined treatment. It consists of induction chemotherapy (12–18 weeks) + local treatment (surgery ± radiotherapy or radiotherapy), and is followed by adjuvant consolidation chemotherapy. The whole treatment takes about 48–52 weeks. Advances in multidisciplinary treatment, including combined chemotherapy, surgery and radiotherapy have resulted in a significant improvement in patients' quality of life and prognosis. Clinical trials are currently underway and new treatment standards are being developed.

Key words: Ewing sarcoma, diagnosis, therapy, prognosis

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Introduction

Ewing's tumours (ET) are a group of high-grade, small-cell tumours that present high malignancy potential. The group include Ewing sarcomas (both soft tissue and bone sarcomas), primitive neuroectodermal tumours (PNET), and small-cell sarcomas of the chest wall (Askin's tumour), currently all named as Ewing sarcoma. Chromosome 22 rearrangements of the EWS gene are present in whole Ewing's family of tumours. Due to the homogenic nature and low differentiation of small cancer cells present in Ewing's tumours, the actual tissue of origin — either mesodermal or neuroectodermal — is still unknown. Ewing's tumours are the third most common primary bone cancer in adults. Under the age of 20 years, Ewing sarcoma is the second most common (after osteosarcoma) primary bone cancer. About half of patients are between 10 and 20 years old. The disease is more common in the Caucasian race. The number of new cases in Poland is estimated to be about 40–60 per year (0.25/100,000/year) [1–4].

Ewing sarcomas occur mostly in shafts of long bones and in the axial skeleton (vertebrae and pelvis). Symptoms are determined by the size and localisation of the primary lesion. Pain is an early sign of the disease, usually more severe during nights, and gradually increasing with tumour growth. Tumours arising in the axial skeleton and pelvis are often asymptomatic until advanced. In about 40% of small cell sarcomas, the symptoms are caused by localised inflammation, without clear tumour formation. Soft-tissue infiltration is present in about 60% of cases. In more advanced cases of Ewing sarcoma systemic symptoms may occur (fever, night sweats, anaemia, fatigue).

Radiological imaging of small cell sarcomas is often atypical, especially at the early stage of the disease. The tumour invades normal bone structures, causing osteolysis or growth in a more infiltrating pattern. Additionally, pathological calcification of tissue (bone or cartilage) or malignant periosteal changes (such as Codman triangle or spicules) may be present. In children and adolescents with Ewing sarcoma osteolytic lesions are usually seen, but osteosclerotic changes may also coexist. Lamellated periosteal changes, formatting "onion-skin" sign, are typical. Pathological bone fracture is detected in about 15% of patients. Ewing sarcomas often create vast un-mineralised infiltrations of bones and surrounding soft tissues.

The range of tumour invasion should be evaluated with computed tomography (CT) and magnetic reso-

nance (MR). Additional information on the stage of the disease can be provided by positron emission tomography (PET-CT), which can detect bone, lymph node, or bone marrow metastases. With proper diagnostics, metastases to lung might be found in 10% of cases, to bone or bone marrow in 10%, and in 5% to multiple organs or other sites.

The most important prognostic factors in ET are: size of the primary lesion, serum activity of lactate dehydrogenase (LDH), axial localisation, age over 15 years, and presence and localisation of metastases (five-year survival is less than 20% in patients with bone metastases and about 20–40% in patients with lung metastases).

General principles of treatment

Patients with localised disease, without the presence of metastases in radiological evaluation, require multimodality treatment: induction chemotherapy (12–18 weeks), locoregional treatment (surgical resection ± radiotherapy or radiotherapy alone), and then adjuvant/consolidation chemotherapy for about 48–52 weeks (Fig. 1) [1–6]. The only exception is cases requiring immediate intervention with surgery or radiotherapy, e.g. spinal cord compression due to tumour or malignant cardiac tamponade. These cases require urgent chemotherapy as soon as possible after surgical debulking. In locoregional treatment, surgical resection is the preferred option [1–8]. Radiotherapy should be reserved for inoperable tumours and as an adjuvant treatment after non-radical resection. Locoregional treatment plays an important role in patients with primarily metastatic form of Ewing sarcoma. In the EURO-EWING99 trial, patients with primarily metastatic disease, who received locoregional treatment, had better three-year recurrence-free survival than patients without locoregional treatment [9]. Patients with inoperable primary tumour should receive radical radiotherapy [1–6, 10, 11]. The effectiveness of primary lesion treatment impacts the rates of qualified patients, if necessary, to radical resection of metastases. In cases when the primary tumour exceeds 8 cm in size and achievement of negative surgical margins is questionable, pre-operative radiotherapy (radiochemotherapy) should be considered because this provides an opportunity to achieve radical resection. Additionally, the volume and dose of radiotherapy required post-operatively can be reduced. Available data do not provide evidence that whole bone irradiation improves local control. Similarly, doses of radiotherapy exceeding 60 Gy do not provide better results than standard dosing. Planned therapy volume should enclose the tumour volume with a 2–3-cm margin, requiring smaller fields with reduced toxicity and

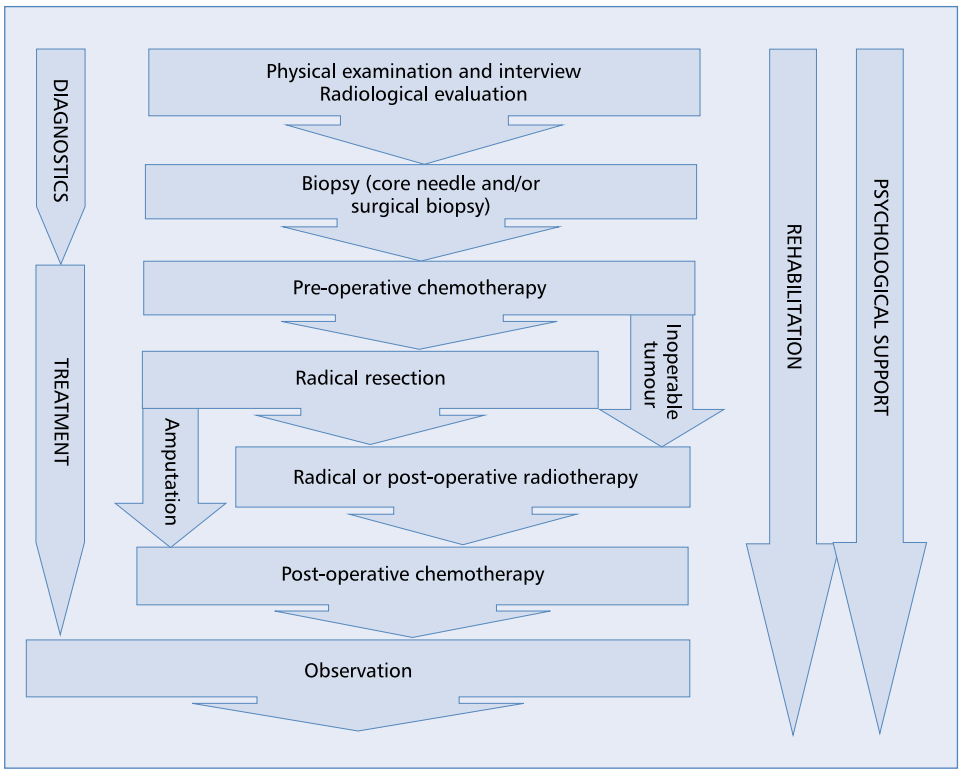

Figure 1. Schedule of assessment and treatment of patients with Ewing' tumours

maintained local control. Depending on localisation, doses of 40–60 Gy are required, fractioned in 1.8–2.0 Gy per day. Inoperable primary tumours require radical radiotherapy, recommended in patients with M1 trait and axial localisation of the primary tumour, as an alternative to vast and difficult resection. Patients with tumours less than 8 cm in diameter and with favourable response to neoadjuvant chemotherapy might not require adjuvant radiotherapy after radical resection. No randomised phase III trial has compared radical radiotherapy with radical surgical resection. Some trials indicate (CESS) that better local control without long-term impact can be achieved with surgery ± radiotherapy when compared to radiotherapy alone [9, 10]. After locoregional treatment, consolidation chemotherapy is continued until maximal cumulative drug dose is achieved (in practice at least six months, to reach at least 48–52 weeks in total) or until occurrence of grade 3 and 4 toxicity. Due to the long treatment duration (about 12 months), significant toxicity of chemotherapy and radiotherapy, and functional disability after surgery (both in limb-sparing procedures and amputations), most patients require intensive rehabilitation and clinical psychological counselling (Fig. 1).

Radiotherapy

Radiotherapy is, beside surgery, the basic modality in radical treatment of Ewing sarcomas. No single randomised phase III trial has compared radical radiotherapy with radical surgery. Some trials (CESS, Tab. 2) indicate that improved locoregional control, without impact on overall survival, can be achieved with a combination of surgery and radiotherapy when compared to radiotherapy alone. In the case of large, inoperable tumours — with infiltration of pelvis, retroperitoneum, or vertebrae — radiotherapy is the treatment of choice, providing locoregional control in about 25% of cases. Radical radiotherapy should begin between 12 and 18 weeks of multimodality treatment. Standard doses used in radical radiotherapy, 40–60 Gy, give primary tumour control in 53–86% of patients. The dose is usually given in 150–200 cGy per daily fraction. Depending on the localisation of the primary tumour and the extent of growth, radiotherapy can be delivered in two-dimensional and three-dimensional techniques or using IMRT. Available data suggest that local control is strictly correlated with radiotherapy dose and size of tumour. In adjuvant radiotherapy, which should begin no more than 60 days after surgery, a dose of 45 Gy is given after R0 and R1 resection. After R2 resection, a larger dose of 56 Gy is required. If the tumour is localised within the chest wall and invades the pleura, additional radiotherapy to the entire half of the chest is advised (up to 15–20 Gy). Evidence from clinical trials does not support whole bone irradiation or overall survival benefit from doses higher than 60 Gy when compared to standard dosing. In some situations, such as in locally advance tumours difficult to resect radically, pre-operative radiotherapy at doses 35–45 Gy can be used. Optimally, radiotherapy is administered simultaneously with systemic treatment. In adult patients receiving radiotherapy on considerable bone volume (such as Ewing sarcomas of the pelvis), concurrent intensive systemic treatment is challenging. Sometimes, temporary interruption of chemotherapy for the length of radiotherapy or usage of less intensive double-drug schedules with vincristine and dactinomycin might be considered. To limit the duration of radiotherapy and thus to limit chemotherapy interruption, some schedules use hyperfractionated radiotherapy. Additionally, radiotherapy plays an important role in palliative treatment of patients with systemic ET. In patients with numerous lung metastases, treated with systemic treatment with or without metastasectomy, whole-lung irradiation of up to 18 Gy might be considered, despite inconclusive data regarding the effect of this procedure on overall survival.

Systemic treatment

The first schedules of chemotherapy that provided statistically significant improvement in overall survival of patients with ET included vincristine, dactinomycin, and cyclophosphamide (VAC). Subsequent studies proved improvement of recurrence-free survival from 24% to 60% with the addition of doxorubicin to the VAC schedule (VACD). Further gain in overall survival was obtained with aggressive initial cytoreductive treatment with alkylating agents (cyclophosphamide in doses larger than 1.4 g/m^2). The addition of ifosfamide and etoposide to standard treatment (VCD) in patients without metastases improved recurrence-free survival and overall survival. Currently, basic schedules used in the treatment of patients with Ewing's family sarcomas include doxorubicin, vincristine, cyclophosphamide, ifosfamide, etoposide, and dactinomycin (Tab. 1) [1–6, 11–16].

In 2018 the results of the EURO-EWING 99/EWING study were published, showing a modest benefit from intensified consolidation chemotherapy with subsequent autologous haematopoietic stem cell transplantation in patients with high-risk disease. The trial included 214 patients who received six cycles of chemotherapy based on vincristine, ifosfamide, doxorubicin, and etoposide. Qualification criteria included age under 50 years with a poor histological response (76% of patients), or tumour volume at the time of diagnosis > 200 ml. The patients were randomly allocated to receive either one cycle of busulfan and melphalan with subsequent autologous haematopoietic stem cell transplantation or seven cycles of standard chemotherapy (vincristine, dactinomycin, and ifosfamide). After a median follow-up time

Table 1. Basic chemotherapy schedules used in ET treatment

Schedules	Doses (cycles every 14–21 days, based on schedule type)
VCD	Day 1: vincristine 2 mg/m^2 (max 2 mg) Day 1: cyclophosphamide 1200 mg/m^2 Day 1: doxorubicin 75 mg/m^2 OR Day 1: vincristine 2 mg/m^2 (max 2 mg) Day 1–2: cyclophosphamide 600 mg/m^2 Day 1–2: doxorubicin 37.5 mg/m^2
IE	Day 1–5: ifosfamide 1.8 g/m^2 Day 1–5: etoposide100 mg/m^2 + mesna
VIDE	Day 1: vincristine 1.5 mg/m^2 (max 2 mg) Day 1–3: ifosfamide 3000 mg/m^2 + mesna Day 1–3: doxorubicin 20 mg/m^2 Day 1–3: etoposide 150 mg/m^2
VAI	Day 1: vincristine 1.5 mg/m^2 (max 2 mg) Day 1–2: dactinomycin 0.75 mg/m^2 Day 1–2: ifosfamide 3000 mg/m^2 + mesna
VAC	Day 1: vincristine 1.5 mg/m^2 (max 2 mg) Day 1–2: dactinomycin 0.75 mg/m^2 Day 1: cyclophosphamide 1500 mg/m^2 + mesna
VACA (VACD)	Day 1: vincristine 1.5 mg/m^2 (max 2 mg) Day 1: cyclophosphamide 1200 mg/m^2 + mesna Day 1–2: doxorubicin 30 mg/m^2 alternately with dactinomycin 0.75 mg/m^2, day 1–3
VAIA (VAID)	Day 1: vincristine 1.5 mg/m^2 (max 2 mg) Day 1: ifosfamide 2000 mg/m^2 + mesna Day 1–2: doxorubicin 30 mg/m^2 alternately with dactinomycin 0.75 mg/m^2, day 1–3
EVAIA (EVAID)	Day 1: vincristine 1.5 mg/m^2 (max 2 mg) Day 1: ifosfamide 2000 mg/m^2 + mesna Day 1–3: etoposide 150 mg/m^2 Day 1–2: doxorubicin 30 mg/m^2 alternately with dactinomycin 0.75 mg/m^2, day 1–3

of 7.8 years, eight-year event-free survival (EFS) and overall survival (OS) were significantly better in patients who received high-dose chemotherapy (respectively, 61% *vs.* 47% and 65% *vs*. 56%). However, high-dose chemotherapy was associated with significant acute toxicity that led to death in three patients. No secondary neoplasms were reported in patients with long-term follow-up [17, 18]. It seems that high-dose chemotherapy with subsequent autologous haematopoietic stem cell transplantation might be a therapeutic option for children with high-risk disease, treated according to the European induction schedule. However, those results cannot be extrapolated or included in standard treatment, because the effectiveness and toxicity of such an approach was not included in the results of the EURO-EWING trial [17, 18].

Currently, the randomised phase III trial Euro Ewing 2012 is recruiting. The trial has accrued 301 patients out of 600 planned [19]. In the Euro Ewing 2012 trial there are two randomisations: patients R1 and R2 are randomised at two different time points. The study design is presented in Figure 2 [19].

The aims of Euro Ewing 2012 trial are as follows:

1. R1: comparison of the two most commonly used treatment schedules — induction treatment schedule VIDE + post-operative schedule VAC/VAI versus VCD/IE schedule — in terms of effectiveness and toxicity profiles. Systemic treatment is planned for 48 weeks [19].
2. R2: determination whether addition of zoledronic acid to consolidation therapy is associated with improved clinical outcomes [19].
   Both *in vitro* and *in vivo* data suggest that bisphosphonates show anticancer activity against ET cells [20, 21]. Pamidronate suppressed growth in eight different ET cell lines through inhibition of mevalonate pathway. Zhou et al. showed significantly lower rates of bone metastasis formation after administration of zoledronic acid *in vivo* [20]. Additionally, bisphosphonates induced apoptosis and inhibited bone metastasis formation. Zoledronic acid exhibits direct activity against ESFT cells *in vitro* through induction of apoptosis via activation of caspase 3 and suppression of cell cycle in the S phase. This effect can be amplified with the addition of alkylating agents. In a mouse model *in vivo*, zoledronic acid suppressed growth of ET in bone lesions, with a smaller effect on growth of intramuscularly injected ET cells. In combination with ifosfamide, zoledronic acid exhibited a synergistic effect in a soft-tissue model: one cycle of ifosfamide combined with zoledronic acid gave results similar to three cycles of ifosfamide IV alone [20, 21].
3. Identification of prognostic biomarkers evaluating disease status and response assessed throughout treatment [19].

In October 2018 at the ESMO congress in Munich, the results of a phase II trial that evaluated cabozantinib in the treatment of patients with advanced Ewing sarcoma and osteosarcoma were presented. Cabozantinib is a small-molecule tyrosine kinase inhibitor (TKI) with potential anticancer activity. Cabozantinib inhibits several receptor-related kinases, including hepatocyte growth factor receptor (MET), rearranged during transfection (RET) oncogene, vascular endothelial growth factor receptor 1, 2, and 3 (VEGFR-1, -2, -3), and mast/stem cell growth factor receptor (KIT). This may suppress both tumour growth and angiogenesis, leading to cancer cell death and tumour regression. Cabozantinib is currently used in the treatment of advanced and metastatic medullary thyroid cancer and in the second-line treatment of renal cell carcinoma.

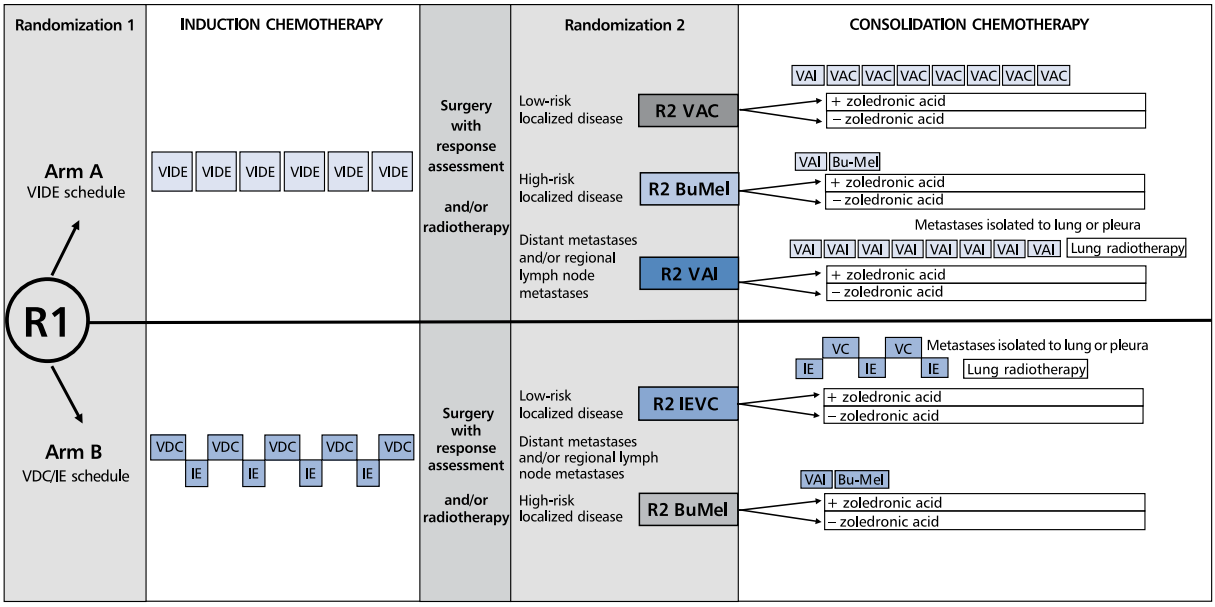

Figure 2. Schedule of the Euro Ewing 2012 trial based on original version of protocol [19]. VIDE — vincristine, ifosfamide, doxorubicin, etoposide; VAI — vincristine, dactinomycin, ifosfamide; VDC — vincristine, doxorubicin, cyclophosphamide; VAC — vincristine, dactinomycin, cyclophosphamide; IE — ifosfamide, etoposide; VC — vincristine, cyclophosphamide; Bu — busulfan; Mel — melphalan

Results of the aforementioned phase II trial are promising. 57.6% of patients with advanced Ewing sarcoma had tumour volume reduction, including 27.7% with partial response (PR) and 30.3% with stable disease (SD) as per RECIST 1.1. Rate of six-month progression-free survival was 24.2% [22].

Results from other important trials dedicated to Ewing's family sarcomas are shown in Table 2 [5].

Progression of Ewing's family sarcomas — both as a local relapse and/or distant progression in lungs, bones or other organs — can develop after or during first-line treatment. Late relapses have better prognosis. Both local and distal relapse are associated with worse outcomes. Particularly poor prognosis is associated with progression during first-line treatment. In this situation, due to low effectiveness of second-line treatment and development of multi-drug resistance in cancer cells, patient's participation in clinical trials of drugs with a mechanism of action other than standard cytotoxic drugs should be encouraged. If clinical trials are not available, second-line systemic treatment should be initiated. Trials undertaken in the 1980s in patients who relapsed after standard schedules (VCR, DACT, DOX, CPM) showed improvement in survival and recurrence-free survival after a combination of ifosfamide and etoposide. If ifosfamide and etoposide were used as part of first-line treatment, schedules using platinum compounds or camptothecin may be considered (Tab. 3). In patients with isolated relapse, including lung parenchyma only, metastasectomy with or without radiotherapy on lung volume may provide survival benefit.

The best option to assess response to systemic treatment in ET is histopathological evaluation of tumour resected after induction treatment. Response may also be evaluated with CT and MR imaging. Reduction in tumour size and decrease in contrast enhancement is usually associated with good response. Decrease in glucose metabolism in PET-CT before and after systemic treatment has similar prognostic value.

The most important long-term consequence of intensive multimodality treatment of Ewing sarcoma is an increased risk of secondary malignancies, which can develop in up to 10% of patients cured of ET. The risk of developing secondary haematological malignancy after chemotherapy is estimated at 3–8%. Acute lymphocytic leukaemia and myelodysplastic syndromes develop in 1–2% of patients treated for Ewing sarcoma. The risk of developing other long-term complications of multimodality treatment, such as heart failure, infertility, chronic kidney disease, or prostheses dysfunction, justifies observation of patients even many years after completed treatment.

Summary

The introduction of multimodality treatment, with neoadjuvant and adjuvant chemotherapy and postponed locoregional treatment, significantly improved

Table 2. Results from main trials dedicated to patients with Ewing sarcoma

Trial (period)	Treatment schedule	Number of patients	5-year disease-free survival
IESS (Intergroup Ewing Sarcoma Study)			
IESS-I (1973–1978)	VAC *vs*. VAC + radiotherapy on lung volume *vs*. VACD	342	24% *vs*. 44% *vs*. 60%
IESS-II (1978–1982)	VACD — high dose *vs.* VACD — intermediate dose	214	68% *vs*. 48%
The North American Intergroup Ewing Sarcoma study	VCD *vs*. VCD + IE	518	54% *vs*. 69%
POG-CCG (Pediatric Oncology Group–Children's Cancer Group)			
POG-CCG (1988–1993)	VACD *vs*. VACD + IE	398	54% *vs.* 69%
POG-CCG (1995–1998)	VCD + IE 48 weeks *vs*. VCD + IE 30 weeks	492	75% (3-year) *vs*. 76% (3-year)
MSKCC (Memorial Sloan-Kettering Cancer Centre)			
T2 (1970–1978)	VACD	20	75%
P6 (1990–1995)	VCD + IE	36	77% (2-year)
P6 (1991–2001)	VCD+ IE	68	Localised disease — 81% (4-year); metastatic disease — 12% (4-year)
St. Jude Children's Research Hospital studies			
ES-79 (1978–1986)	VACD	52	Primary lesion < 8 cm — 82% (3-year); primary lesion ≥ 8 cm — 64% (3-year)
ES-87 (1987–1991)	IE	26	Response rate 96%
EW-92 (1992–1996)	VCD-IE × 3	34	78% (3-year)
ROI (Rizzoli Orthopaedic Institute), Italy			
REN-3 (1991–1997)	VDC + VIA + IE	157	71%
SFOP (French Society of Paediatric Oncology), France			
EW–88 (1988–1991)	VD + VD/VA	141	58%
SSG (Scandinavian Sarcoma Group)			
SSG IX (1990–1999)	VID + PID	88	58% (metastasis-free survival)
UKCCSG/MRC (United Kingdom Children's Cancer Study Group/Medical Research Council)			
ET-1 (1978–1986)	VACD	120	41%; localised in limbs 52%; axial localisation 38%; pelvis 13%
ET-2 (1987–1993)	VAID	201	62%; localised in limbs 73%; axial localisation 55%; pelvis 41%
CESS (Cooperative Ewing Sarcoma Studies) group studies			
CESS-81 (1981–1985)	VACD	93	< 100 ml, 80%; ≥ 100 ml 31% (3-year) alive tissue < 10%, 79%; alive tissue > 10%, 31%
CESS-86 (1986–1991)	< 100 ml: VACD	301	52% (10-year)
	≥ 100 ml: VAID		51% (10-year)
EICESS (European Intergroup Cooperative Ewing Sarcoma Studies) studies (CESS + UKCCSG)			
EICESS-92 (1992–1999)	VAID *vs.* VACD (low-risk)	155	68% *vs*. 61%
	VAID *vs*. EVAID (high-risk)	326	51% *vs*. 61%
COG (Children's Oncology Group) study			
2001–2005	VCD + IE (cycles every 21 days) *vs*. VCD + IE (cycles every 14 days)	587	65% *vs*. 73%

V — vincristine; A — dactinomycin; D — doxorubicin; C — cyclophosphamide; I — ifosfamide; E — etoposide; P — cisplatin

Table 3. Chemotherapy schedules used in the treatment of relapsed ESFT-type sarcomas

Schedules	Doses
TopoCTX*	Topotecan 0.75 mg/m^2, day 1–5 Cyclophosphamide 250 mg/m^2, day 1–5, cycle every 21 days
Irinotecan/ /temozolomide	Irinotecan 10 mg/m^2, day 1–5, 8–12 Temozolomide 100 mg/m^2, day 1–5, cycle every 21–28 days
AP	Doxorubicin 50 mg/m^2 48-hour infusion Cisplatin 30 mg/m^2, day 1–3, cycle every 21 days
PE	Cisplatin 30 mg/m^2, day 1–3 Etoposide 150 mg/m^2, day 1–3, cycle every 21 days
IE	Ifosfamide 1.6–1.8 g/m^2, day 1–5 + mesna Etoposide 100 mg/m^2, day 1–5, cycle every 21 days
ICE*	Carboplatin 400 mg/m^2, day 1–2 Ifosfamide 1.8 g/m^2, day 1–5 Etoposide 100 mg/m^2, day 1–5, cycle every 21 days

*G-CSF primary prophylaxis required

long-term results in adult patients with Ewing's family sarcomas. Five-year survival rates rose from 5–10% to 40% in adults. Localisations within the pelvis and vertebrae, as well as extraosseous tumours, are associated with worse prognosis. The presence of distant metastases at treatment initiation lowers the rate of cured patients to 30%. Bone metastases is associated with a five-year survival rate < 20%, in contrast to a 20–40% survival rate in patients with pulmonary metastases. Patients who relapse after treatment have detrimental prognosis. Adults with small-cell sarcomas have worse prognosis than children, usually due to more common presence of unfavourable prognostic factors.

Clinical trials dedicated to improvement of long-term treatment effectiveness are difficult due to the low number of new cases per year, and they require international collaboration. Nevertheless, efforts undertaken during the last 30 years, including introduction of multimodality treatment consisting of chemotherapy, surgery, and radiotherapy, have radically improved patient's prognosis.

References

1. Casali PG, Bielack S, Abecassis N, et al. ESMO Guidelines Committee, PaedCan and ERN EURACAN. Bone sarcomas: ESMO-PaedCan-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; 29(Supplement_4): iv79–iv95, doi: 10.1093/annonc/mdy310, indexed in Pubmed: 30285218.
2. Gerrand C, Athanasou N, Brennan B, et al. British Sarcoma Group. UK guidelines for the management of bone sarcomas. Clin Sarcoma Res. 2016; 6: 7, doi: 10.1186/s13569-016-0047-1, indexed in Pubmed: 27148438.
3. Rutkowski P, Świtaj T. Bone sarcomas. Oncol Clin Pract. 2018; 14(3): 115–128.
4. NCCN Clinical Practice Guidelines in Oncology: Bone Cancer. 2018; 1.
5. Rutkowski P. Mięsaki kości. Viamedica Gdańsk. 2016.
6. Le Deley MC, Paulussen M, Lewis I, et al. Cyclophosphamide compared with ifosfamide in consolidation treatment of standard-risk Ewing sarcoma: results of the randomized noninferiority Euro-EWING99-R1 trial. J Clin Oncol. 2014; 32(23): 2440–2448, doi: 10.1200/JCO.2013.54.4833, indexed in Pubmed: 24982464.
7. Denbo JW, Shannon Orr W, Wu Y, et al. Timing of surgery and the role of adjuvant radiotherapy in ewing sarcoma of the chest wall: a single-institution experience. Ann Surg Oncol. 2012; 19(12): 3809–3815, doi: 10.1245/s10434-012-2449-5, indexed in Pubmed: 22752372.
8. Schuck A, Ahrens S, Paulussen M, et al. Local therapy in localized Ewing tumors: results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials. Int J Radiat Oncol Biol Phys. 2003; 55(1): 168–177, indexed in Pubmed: 12504050.
9. Ladenstein R, Pötschger U, Le Deley MC, et al. Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. J Clin Oncol. 2010; 28(20): 3284–3291, doi: 10.1200/JCO.2009.22.9864, indexed in Pubmed: 20547982.
10. Schuck A, Hofmann J, Rübe C, et al. Radiotherapy in Ewing's sarcoma and PNET of the chest wall: results of the trials CESS 81, CESS 86 and EICESS 92. Int J Radiat Oncol Biol Phys. 1998; 42(5): 1001–1006, indexed in Pubmed: 9869222.
11. Bacci G, Palmerini E, Staals EL, et al. Ewing's sarcoma family tumors of the humerus: outcome of patients treated with radiotherapy, surgery or surgery and adjuvant radiotherapy. Radiother Oncol. 2009; 93(2): 383–387, doi: 10.1016/j.radonc.2009.06.009, indexed in Pubmed: 19576648.
12. Cotterill SJ, Ahrens S, Paulussen M, et al. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. J Clin Oncol. 2000; 18(17): 3108–3114, doi: 10.1200/JCO.2000.18.17.3108, indexed in Pubmed: 10963639.
13. Nesbit ME, Gehan EA, Burgert EO, 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. 1990; 8(10): 1664–1674, doi: 10.1200/JCO.1990.8.10.1664, indexed in Pubmed: 2213103.
14. Miser JS, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med. 2003; 348(8): 694–701, doi: 10.1056/NEJMoa020890, indexed in Pubmed: 12594313.
15. Paulussen M, Craft AW, Lewis I, et al. European Intergroup Cooperative Ewing's Sarcoma Study-92. Results of the EICESS-92 Study: two randomized trials of Ewing's sarcoma treatment — cyclophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients. J Clin Oncol. 2008; 26(27): 4385–4393, doi: 10.1200/JCO.2008.16.5720, indexed in Pubmed: 18802150.
16. Ladenstein R, Pötschger U, Le Deley MC, et al. Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. J Clin Oncol. 2010; 28(20): 3284–3291, doi: 10.1200/JCO.2009.22.9864, indexed in Pubmed: 20547982.
17. 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. 2018; 36(31): 3110–3119.
18. Gorlick R, Janeway KA, Adamson PC. Dose Intensification Improves the Outcome of Ewing Sarcoma. J Clin Oncol 2018; 36(31): 3072–3073.
19. Euro Ewing 2012 protocol_version 5.0. http://www.euroewing.eu/clinical-trials/ee2012-trial/ee2012-update (2 Jun 2017).
20. Zhou Z, Guan H, Duan X, et al. Zoledronic acid inhibits primary bone tumor growth in Ewing sarcoma. Cancer. 2005; 104(8): 1713–1720, doi: 10.1002/cncr.21383, indexed in Pubmed: 16121404.
21. Odri GA, Dumoucel S, Picarda G, et al. Zoledronic acid as a new adjuvant therapeutic strategy for Ewing's sarcoma patients. Cancer Res. 2010; 70(19): 7610–7619, doi: 10.1158/0008-5472.CAN-09-4272, indexed in Pubmed: 20841471.
22. Italiano A, Katz D. Cabozantinib in patients with advanced osteosarcomas and Ewing sarcomas: a French Sarcoma Group (FSG)/US National Cancer Institute phase II collaborative study. Presented at: the ESMO 2018 Congress; Munich, Germany: October 19-23, 2018. Abstract LBA67.