Introduction

Ewing sarcoma (ES) is a highly malignant tumor composed of small round cells. The origin of this tumor was unclear until recently, when electron microscopic and immunohistochemical analyses suggested that it is of neurogenic origin [1–3]. ES tumors often express a balanced translocation involving the EWS gene on chromosome 22 and a member of the ETS family of transcription factors [4, 5]. With the development of diagnostic radiological techniques such as magnetic resonance imaging (MRI), extraskeletal masses can be depicted clearly and the tumor area can be accurately evaluated. Due to improvements in intensive chemotherapy, the prognosis of ES patients has improved markedly [6–16]. The current chemotherapy protocols used to treat ES include various combinations of the following six drugs: doxorubicin (DOX), cyclophosphamide (CPM), vincristine (VCR), actinomycin-D (ACT-D), ifosfamide (IFO), and etoposide (ETO). Local ES lesions are usually treated via surgical excision or radiotherapy, or a combination of both. In cases in which surgical excision is not possible due to the large size of the tumor, its anatomical location, or the fact that the acquired surgical margin is not sufficient to achieve local control, pre- or postoperative radiotherapy is usually selected [14]. Better understanding of how local control can be achieved has helped to improve the oncological outcomes of ES. Although the survival rate of ES patients has improved, their prognosis remains unsatisfactory, and the treatment of ES is still challenging to the medical teams involved, which include orthopedic surgeons, pediatric oncologists, and radiotherapists.

This review was undertaken to update our current knowledge regarding the diagnosis and treatment of ES. The author hopes that this article will help to summarize the latest findings about ES for treatment teams and lead to further improvements in the prognosis of ES.
Management of Ewing sarcoma of the bone

History of ES

Lücke is considered to have been the first to describe this small round cell tumor [17, 18]. In 1918, Stout et al. [19] reported an undifferentiated round cell tumor that originated in the ulnar nerve and exhibited rosette formation, and he later proposed the concept of neuroepithelioma [20].

In 1921, Ewing reported a round cell sarcoma of the radius in a 14-year-old girl as a “diffuse endothelioma of bone” [21]. Radiotherapy produced a good response according to physical and plain X-ray examinations. In his report, Ewing reviewed six similar cases that he had experienced in the previous 4 months [21]. Ewing also documented the following specific radiographic findings: “A large portion or the whole of the shaft is involved, but the ends are generally spared. The shaft is slightly widened, but the main alteration is a gradual diffuse fading of the bone structure. Bone production is entirely absent”. Many of the features of ES described by Ewing in his original report are still very important, even after 90 years.

Angervall and Enzinger were the first to report the existence of ES of extraskeletal origin [22]. In 1976, Nesbitt and Vidone described a neuroepithelioma as a primitive neuroectodermal tumor (PNET) [23]. Since the latter report, the name PNET has been commonly used instead of neuroepithelioma. Askin et al. [24] described a small round cell tumor that originated in the thoracopulmonary region in 1979. In 1984, Jaffe et al. [1] reported a PNET of the bone composed of small round cells that exhibited rosette formation and were positive for the neural marker neuron-specific enolase.

In the 1980s, chromosome analysis detected the t(11;22)(q24;q12) translocation in ES cell lines [25, 26]. The EWS-FLI1 chimera, which is produced by a balanced translocation between FLI1 on chromosome 11q24 and EWS on chromosome 22q12, was identified in 1992 after the cloning of translocation breakpoints [5]. As the abovementioned small round cell tumors; i.e., ES, PNET, neuroepithelioma, and Askin’s tumor, exhibit similar types of chromosomal translocation, e.g., t(11;22)(q24;q12), they are classified as a single disease entity; i.e., the ES family of tumors. In this review paper, the name ES is used for all of these tumors.

Characteristics of ES

ES is the second most common bone tumor in childhood and adolescence. In Japan, approximately 30–40 patients with ES of the bone are registered in the bone tumor registry run by the Japanese Orthopaedic Association (JOA) Musculoskeletal Tumor Committee annually [27]. Males are affected more frequently than females (ratio 3:2). The peak age of ES patients ranges from 10 to 24 years (Fig. 1).

A total of 188 cases of ES of the bone were registered between 2006 and 2011 [27]. The sites that are most commonly affected by ES of the bone are the pelvis, ribs, and femur (Table 1). By comparison, 138 extraskeletal ES were registered in the same period, with 65 of these affecting males and 73 affecting females. The sites that were most frequently affected by extraskeletal ES were the thigh, gluteal region, back, lower leg, and the retroperitoneal region [28].

At the time of the diagnosis of ES of the bone, 34% of patients had distant metastases and 5% had regional lymph node metastases [27]. At the time of the diagnosis of
extraskeletal ES, 29% had distant metastases and 12% had regional lymph node metastases [28].

The incidence of ES differs markedly among races [29]; i.e., ES is rare among black children [29–31] and the Chinese population [29]. Conversely, Caucasian children display a 6 times higher incidence of ES than black children [32]. The ratio of ES to osteosarcoma is around 0.5 among Caucasians in the United States and less than 0.15 among non-Caucasian children in Shanghai, Beijing, and the United States [29]. Among Japanese patients, the ratio of ES of the bone to osteosarcoma was 0.21 [27].

### Symptoms and blood and serum findings

Patients with ES exhibit local symptoms such as tumor mass formation, induration, pain, swelling, venous dilation, and hyperemia. Pathological fractures sometimes occur due to bone metastasis, and spinal metastasis-associated back pain can progress to spinal paralysis. In cases in which an ES originates in the chest wall, pleural infiltration combined with carcinomatous pleurisy is often observed. The interval between the onset of the initial symptom and diagnosis has become shorter; i.e., it was 4.7 months in 2003, whereas it was 9.6 months in 1984 [33]. This change might have been due to improvements in diagnostic techniques.

Anemia and leukocytosis are often observed in ES, as are increases in the white blood cell count, blood sedimentation rate; and the serum levels of lactate dehydrogenase (LDH), alkaline phosphatase, and C-reactive protein. An elevated LDH level is associated with a poor prognosis [33]. Physicians must be aware that ES patients often exhibit similar blood and serum biochemical findings to those displayed by patients with inflammatory conditions such as osteomyelitis.

### Radiological findings

In ES of the bone, plain radiographs exhibit permeative and infiltrative destruction of the affected bone (often in the diaphysis of the long bone) (Fig. 2). In addition, an onion skin-like appearance and spiculae are indicative of periosteal reactions. The pelvis is the most commonly affected site; however, it is difficult to identify pelvic tumors on plain X-rays alone. Computed tomography (CT) is useful for depicting extraskeletal soft tissue masses, destruction of the bone cortex, and pulmonary metastasis (Fig. 3). On MRI, ES of the bone demonstrates low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, and appears as large extraskeletal soft tissue masses derived from bone. Skip lesions affecting the bone are often clearly depicted on MRI. On bone scans, ES of the bone demonstrates high 99mTc-MDP uptake. Similarly, it displays high 18F-fluorodeoxy glucose (18F-FDG) uptake on 18F-FDG-positron emission tomography (PET), [34] (Fig. 4).

From a radiological point of view, the differential diagnoses of ES include osteomyelitis, Langerhans cell histiocytosis, skeletal metastatic neuroblastoma, and malignant lymphoma of the bone.

### Histology

Histologically, ES is composed of sheets of uniform small round tumor cells with round nuclei and little cytoplasm that do not exhibit matrix formation (Fig. 5a). ES tumor cells are characterized by uniform findings with few mitoses. ES also demonstrates morphological features that are indicative of neural differentiation, such as rosette formation. Since ES tumor cells contain abundant amounts of

### Table 1 ES in Japan (2006–2011)

| Tissue          | Number |
|-----------------|--------|
| Bone            | 188    |
| Cranium         | 2      |
| Skull 1, mandible 1 |
| Trunk           | 112    |
| Pelvis 43, ribs 29, spine 23, clavula 9, clavicle 6 and sternum 2 |
| Upper extremities| 13     |
| Humerus 10, ulna 2 and phalanges 1 |
| Lower extremities| 50     |
| Femur 25, tibia 10, fibula 10, tarsals 3 and metatarsals 2 |
| Multiple sites  | 11     |

Data are derived from the Bone Tumor Registry in Japan, 2011 [27], and the Soft Tissue Tumor Registry in Japan, 2011 [28], run by the JOA Musculoskeletal Tumor Committee.
glycogen, periodic acid-Schiff (PAS)-positive granules are seen in their cytoplasm. Immunohistochemically, positivity for neural markers such as S-100 protein and PGP9.5 is sometimes detected, and vimentin positivity is also commonly observed. In over 90% of ES cases, positivity for CD99, a product of the MIC2 gene, is detected
the cytoplasmic membrane (Fig. 6) [35]; however, CD99 expression is not specific to ES, as it is also detected in synovial sarcoma [36], lymphoblastic leukemia, lymphoma, and other tumors [4]. Atypical ES, a variant of ES composed of large cells, has also been reported [37, 38]. In addition, ES composed of spindle-shaped and adamantinoma-like cells, as well as other variants have also been reported [39].

**Fusion gene analysis**

In recent years, molecular techniques have been commonly used to diagnose ES because it often exhibits specific chromosomal translocations. Reverse transcription polymerase chain reaction (RT-PCR) and fluorescent in situ hybridization (FISH) are very useful methods for detecting fusion genes (Fig. 7). Table 2 shows the most common chromosomal translocations found in ES. The EWS-FLI1 fusion gene, which is caused by the t(11;22)(q24;q12) translocation, is the most common type of fusion gene: 85% of ES tumors that exhibit the EWS gene rearrangement were found to possess this type of translocation [4, 5, 26].

**EWS-ERG**, which is caused by the t(21;22)(q22;q12) translocation, is observed in 10% of cases [40, 41]. Other rare fusion genes include: EWS-ETVI, which is caused by the t(7;22)(q22;q12) translocation [42]; EWS-ETV4, which is caused by the t(17;22)(q21;q12) translocation [43, 44]; and EWS-FEV, which is caused by the t(2;22)(q35;q12) translocation [45]. These fusion products encode chimeric proteins that function as aberrant oncogenic transcription factors. Other cytogenetic abnormalities have also been reported [33, 46]. Subjecting bone marrow aspiration samples to RT-PCR might be useful for detecting fusion genes in the bone marrow of ES patients. Kunisada et al. [47] reported that 2 of 5 patients without radiologically detectable metastasis (M0) possessed fusion genes in their bone marrow.

**Table 2** Most common types of translocations found in Ewing sarcoma

| Translocation       | Fusion gene    | % of tumors exhibiting EWS gene rearrangement |
|---------------------|---------------|---------------------------------------------|
| t(11;22)(q24;q12)   | EWSR1-FLI1    | 85                                          |
| t(21;22)(q22;q12)   | EWSR1-ERG     | 10                                          |
| t(7;22)(q22;q12)    | EWSR1-ETVI    | rare                                        |
| t(17;22)(q21;q12)   | EWSR1-ETV4    | rare                                        |
| t(2;22)(q35;q12)    | EWSR1-FEV     | rare                                        |

![Fig. 6](image_url) Membranous expression of CD99, a product of the MIC2 gene, is observed in ES cells.
The most common fusion gene involves the in frame fusion of exon 7 of the EWS gene with exon 6 of the FLI1 gene (the type 1 fusion gene). When the prognosis of 147 ES patients was examined according to fusion gene type in the Cooperative ES Study (CESS), patients with the type 1 fusion gene were reported to have a better prognosis than patients with other types of fusion gene [48]. In addition, in a study by the Memorial Sloan Kettering Cancer Center the 64 patients with the type 1 fusion gene exhibited a better prognosis than the 35 patients with other types of fusion gene [49]. However, in 1999 Ginsberg examined 136 cases of ES and found that patients with the EWS-FLI1 and EWS-ERG fusion genes had similar clinical courses [50]. In a recent prospective study (the European Ewing Tumor Working Initiative National Groups 99 study; the Euro-EWING 99 study), which examined 565 patients with primary ES tumors (1999–2007), including 296 patients with type 1 fusion genes and 269 patients with other types of fusion genes, a prospective evaluation did not find that the type 1 fusion gene confers a prognostic benefit [51]. In ES, the accumulation of genetic aberrations involving several genes on different chromosomes seems to have a greater influence than fusion gene type on the biological and clinical behavior of ES.

**Treatment**

Radiotherapy had been the standard treatment for ES, and until the 1960s radiotherapy or surgery were the only treatments for ES [15]. ES is currently treated in a multidisciplinary manner involving chemotherapy, surgery, and radiotherapy. If a tumor is considered to be difficult to excise with an adequate margin, preoperative radiotherapy involving 36–55 Gy is administered. Similarly, postoperative radiotherapy is performed if the margin achieved by surgery is inadequate for local control.

According to the bone tumor registry developed by the JOA [27], 173 of 188 patients with ES of the bone received treatments including chemotherapy, including 65 patients who underwent chemotherapy and surgery; 50 patients who received chemotherapy and radiotherapy; and 32 patients who were treated with chemotherapy, surgery, and radiotherapy (Fig. 8).

In the 1960s, a maximum of 10 % of ES patients survived [15], and VCR (a vinca alkaloid), ACT-D (an antitumor antibiotic), CPM (an alkylating agent), and DOX (an antitumor antibiotic) started to be included in treatment protocols for ES. After the 1980s, IFO (an alkylating agent) and ETO (a vinca alkaloid) were added to such protocols [15]. Currently, the 5-year overall survival rate of ES patients is approximately 60 % [10, 11, 14, 50, 52].

The purpose of preoperative chemotherapy is (1) to eradicate any micrometastases that exist at the time of diagnosis, (2) to reduce the volume of the tumor in order to facilitate its excision, and (3) to provide information that will aid the selection of anti-tumor drugs for postoperative chemotherapy. In the USA, the Memorial Sloan-Kettering Cancer Center has developed a few treatment protocols for ES [7]. In addition, Rosen et al. [7] described an effective chemotherapy regimen called T-11.

IESS-I (the Intergroup ES Study), which included 331 patients, compared the prognosis of patients that were treated with the VAC regimen (VCR, ACT-D, and CPM) and that of patients that were administered the VAC + DOX (VACD) regimen [8] (Table 3). As a result, it was found that the addition of DOX had a beneficial effect on patient survival. Patients treated with the VAC regimen alone, the VAC regimen and whole lung irradiation, or the VACD regimen alone exhibited 5-year disease-free survival rates of 24, 44, and 60 %, respectively. IESS-II, which included 293 patients, reported that patients that were treated with an intensified VACD regimen displayed a 5-year disease-free survival rate of 68 %, whereas that of the patients treated with a moderate dose VACD regimen was 48 % [9]. NCI INT-0091 (1988–1992) was a prospective randomized trial of a single VDC-containing regimen (VCR, DOX, and CPM) versus the administration of VDC and the IE regimen (IFO + ETO) [10]. The 5-year disease-free survival rate was 54 % in the VDC group and 69 % in the VDC + IE group; thus, VDC + IE had a significantly positive effective on patient survival in localized cases compared with VDC. The main concept behind this regimen was adopted by the Japanese Ewing Sarcoma Study (JESS) 04 protocol.

In recent years, the results of the AEWS0031 study performed by the Children’s Oncology Group, which included
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587 patients, were reported [11]. The latter study prospectively compared the effects of VDC + IE between regimens involving administration intervals of 3 and 2 weeks. The 5-year disease-free survival rate was 65 % in the 3-week interval group and 73 % in the 2-week interval group ($p = 0.048$), and there was no difference in the incidence of toxicities between the 2 groups. At present, the administration of VDC + IE using a short administration interval is regarded as the standard chemotherapy regimen for treating ES in the USA.

In the CESS-86 study, which included 301 patients, the VACD regimen was used to treat patients with tumor volumes of <100 ml, and the VAIID regimen, in which the CPM included in the VACD regimen was replaced with IFO, was administered to patients with tumor volumes of $\geq 100$ ml [13]. The 10-year disease-free survival rate was 52 % in the standard risk group treated with VACD and 51 % in the high risk group administered VAIID. Thus, the VAIID regimen was effective at increasing the survival of high risk patients. In the EICESS-92 study, which included 647 patients, patients with tumor volumes of $<$100 ml were randomly assigned to receive either the VAIID or VACD regimen, and patients with tumor volumes of $\geq 100$ ml with/without metastasis (including skip metastasis) were randomly assigned to receive either the VAIID or EVAID regimen.
regimen [14]. In the standard risk group, the 5-year disease-free survival rate was 68% in the VAID group and 67% in the VACD group. Therefore, in the standard risk group CPM had a similar effect on event-free survival to IFO; however, it was also associated with increased toxicity. In the high risk group, the 5-year disease-free survival rate was 44% in the VAID group, and adding ETO to the VAID regimen resulted in an increase in the survival rate to 52% in the EV AID group. Therefore, it was confirmed that ETO had a beneficial effect among high risk patients. In recent years, the Euro-EWING 99 study examined the utility of induction treatment with the VIDE regimen and one postoperative cycle of the VAI regimen [16]. Patients with localized disease or lung metastasis were classified into the R1 or R2 arm. The patients in the R1 group were randomly assigned to receive the VAC or VAI regimen, and the patients in the R2 group were randomly assigned to receive the VAI regimen or busulfan and melphanal after one postoperative cycle of VAI. In the R1 group, which contained 856 patients, it was found that there was no difference in survival between the VAC and VAI groups.

On the other hand, Obata et al. [52] conducted a Japanese study involving 243 patients from 29 institutions who exhibited a mean follow-up period of 66 months. Of the 243 patients, 183 underwent definitive surgery as the primary local treatment. The treatment protocols included many different regimens such as the T-11 and modified T-11 regimens in 47 patients, V(A)CD + IE-based regimens in 41 patients [10, 53, 54], the VAID/EVAID regimen in 22/3 patients [13, 14], and VACD-based regimens in 22 patients [9, 12], etc. In addition, high-dose chemotherapy with hematopoietic stem cell rescue was performed in 51 patients. In patients with localized disease (M0), the 5-year overall survival rate was 55%, and the event-free survival rate was 47%. In patients with metastatic disease (M1), the 5-year overall survival rate was 13%, and the event-free survival rate was 7%. The following characteristics were found to be associated with a poor prognosis: age ≥16 years, M1 disease, and a tumor located in the trunk [52]. The Japanese ES Study (JESS) group has not published the final results of the JESS04 study; however, satisfactory results have been obtained in similarly large studies conducted in the USA and Europe.

### Intensive treatment

Meyers et al. [55] reported the results of intensive treatment in 32 patients with bone or bone marrow metastasis from ES. If a good response was obtained after 5 cycles of induction chemotherapy composed of a 3-drug regimen (CPM, DOX, and VCR) alone or the same 3-drug regimen combined with an additional 2-drug regimen (IFO and ETO), consolidation therapy including high-dose melphalan, ETO, and whole body irradiation was performed followed by stem-cell support. The event-free 2-year survival rate of all 32 cases was 20%, and that of the 23 cases that received stem-cell support was 24%; i.e., the latter regimen failed to improve the survival of high risk patients.

The treatment results for primary disseminated multifocal ES, excluding single pulmonary metastases that were present at diagnosis, were also reported in the Euro-EWING 99 trial [56]. In this group, 6 cycles of the VIDE regimen were administered preoperatively and then local therapy involving surgery and/or radiotherapy was performed. After one postoperative cycle of the VAI regimen had been administered, high-dose busulfan-melphanal was administered followed by an autologous stem cell transplantation (HDT/SCT). The median follow-up period was 3.8 years, and the 3-year disease-free survival rate was 27%.

Patients with pulmonary metastasis are administered chemotherapy based on the first-line regimens for patients without metastasis. Single pulmonary metastases can be controlled with intensive chemotherapy; however, the prognosis of patients with bone or bone marrow metastasis remains poor.

### Local treatment: radiotherapy and tumor excision

As ES is sensitive to radiotherapy, radiotherapy was performed as a local treatment before the introduction of chemotherapy. It was reported that ES is usually treated with radiation doses ranging from 36 to 60 Gy [12, 14, 57]. Two irradiation techniques are commonly used to treat ES. Definitive radiotherapy aims to destroy all viable tumor cells and is used to treat centrally located lesions, such as those located in the spinal column (Fig. 9). On the other hand, pre- or postoperative adjuvant radiotherapy is administered in cases in which the risk of local relapse is considered to be high, e.g., because an insufficient margin was acquired or it is considered that a safe margin would be difficult to obtain. In the CESS86 study [57], 46 Gy were delivered to patients with positive surgical margins, and 60 Gy were delivered to the non-surgical group. There was no significant difference in the treatment results of the two groups; thus, 60 Gy successfully obtained local control of ES.

Several studies have detected higher local relapse rates after radiotherapy alone than after combined therapy involving surgery and radiotherapy. In the CESS studies, the local control rate obtained in the patients who received definitive radiotherapy was significantly worse than that achieved in the patients who underwent surgery with/without additional radiotherapy [58]. Bacci et al. [59] reported that the local
Control rate of ES was 100% in patients who underwent surgery and radiotherapy and 67% in patients that were treated with radiotherapy alone. Wilkins et al. [60] found that the 5-year survival rate of patients that received radiotherapy alone as a local treatment was 27%, whereas that of the patients treated with radiation and surgery was 72%. In patients with ES, surgery improves the safety of local control. As for safe surgical margins, it has been suggested that tumors must be excised together with 2 cm of normal tissue [61]. In other sarcomas, membranous structures around the tumor can function as a barrier against tumor extension; however, the barrier function of such structures seems to be insufficient to prevent growth in ES.

In 2003, based on the results of the CESS and EICESS trials, Schuck et al. [62] reported that postoperative radiotherapy improves local control in poor responders to chemotherapy, even after wide resection. Currently, the standard treatment strategy for surgically accessible primary lesions is to surgically resect the tumor as much as possible together with a safe margin, although radiotherapy might be selected depending on the surgical margin and the histological effects of chemotherapy. If a tumor is inoperable, radiotherapy alone is employed as a local treatment. After radiotherapy, it might be possible to surgically excise previously inoperable tumors together with a safe margin.

The author thinks that radiotherapy is not necessary after adequate wide excision in cases involving patients that respond well to preoperative chemotherapy. However, the author considers that radiotherapy should be added after inadequate excision and in cases involving poor responders to chemotherapy or excessively narrow surgical margins.

Among patients who exhibited pulmonary metastasis at diagnosis, the patients who received total lung irradiation were found to have a better prognosis than those who did not undergo such treatment [63, 64]. A dose of 14–18 Gy is recommended for total lung irradiation [63]. However, clinicians should be aware that more than 50% of ES patients have functional lung abnormalities [64].

In recent years, carbon ion beam treatment has prevailed in Japan [65], and it is often used to achieve local control of surgically inaccessible tumors due to anatomical reasons. However, when a tumor can be surgically excised without
causing a reduction in function or quality of life, surgery should be selected.

**Reconstructive surgery**

It is very important to prevent surgical site infections in ES patients: if an infection occurs, postoperative chemotherapy must be postponed until the infection has been completely eradicated. In recent years, the dose intensity of chemotherapy has been increasing, which could lead to an increase in the infection rate. Orthopedic surgeons should not select reconstruction methods that are associated with high infection rates. In recent years, liquid nitrogen-treated recycled bone has been developed and has since been used frequently [66]. This method is reported to induce a cryo-immunological response [67] so it might be expected to result in a higher survival rate than other reconstruction methods.

The pelvis is the most frequent site for ES and patients with pelvic ES have a poor prognosis [68]. Fibula strut grafts are available for pelvic reconstruction after iliac excision (P1). Non-vascularized fibula grafts seem to be sufficient for pelvic reconstruction because bone union can be expected to occur within a few months after their implantation [69]. The author is currently examining the utility of hip joint transposition in cases involving large tumors of the iliac wing that affect the acetabulum [70, 71], and so far no postoperative surgical site infections have occurred in any patient. In a study of cases in which local control of pelvic ES was obtained using internal hemipelvectomy, the patients reported that they had a good postoperative quality of life [72].

The prompt administration of intensive chemotherapy is important in ES. Most ES patients are aged between 10 and 20 years of age. Although the reconstruction of skeletal defects using tumor prostheses might be an established treatment after tumor excision, if available biological reconstruction methods seem to be more suitable than tumor prostheses for cases involving children.

**Metastasis and secondary malignancies**

A total of 34% of ES patients exhibit metastasis at diagnosis [27]. Patients with lung metastasis alone, display a better prognosis than patients with bone or bone marrow metastases. As the survival rate of ES has increased, cases of late relapse, e.g., relapses that occur more than 10 years after treatment, are being reported (Fig. 10). No standard treatment strategy for relapsed ES has been established.

![Fig. 10](image)

**Fig. 10** A 10-year-old boy with ES of the right humerus. He had a pain in his right upper arm. A plain X-ray showed a limited periosteal reaction. **a** T1-weighted MRI depicted an area of heterogeneous low signal intensity in the humerus. **b** A bone scan showed abnormally high isotope uptake in the right humerus. After the diagnosis of ES had been confirmed by open biopsy, preoperative chemotherapy composed of DOX, CPM, methotrexate, VCR, IFO, and ACT-D was administered. **c** After the preoperative chemotherapy, the patient underwent wide excision of the tumor in his right humerus. A sling procedure involving a vascularized fibula graft was performed for reconstruction, and postoperative chemotherapy was initiated. At 13 years after surgery, he visited our hospital due to dyspnea and coughing. A chest X-ray showed a white region in his right lung, and **d** CT depicted a large amount of pleural effusion and atelectasis due to the pulmonary metastasis of ES.
There have been several trials of the ICE regimen (IFO, carboplatin, and ETO) [73], topotecan + CPM [74], and the irinotecan (CPT-11) plus temozolomide regimen [75].

In the EICESS92 study, which examined 647 cases, the frequency of secondary malignancies was 0.9% among all cases and 1.2% among patients that were with treated with ETO. On the other hand, none of the patients that were treated without ETO developed secondary malignancies [76]. In the Italian Sarcoma Group Experience study (1983–2006), which involved 543 ES patients that exhibited a median follow-up period of 86 months, secondary malignancies developed in 15 patients (3%). Among the latter patients, the median interval between the diagnosis of the primary and secondary malignancies was 84 months. In another study, the cumulative frequency of secondary malignancies was 3.4% after 10 years, 4.7% after 20 years, and 5% after 25 years [77].

Further improving the cure rate

Increasing the dose intensity of anti-tumor drugs, e.g., via their bi-weekly administration, might lead to improvements in patient prognosis. New drugs such as pazopanib [78], eribulin [79], and trabectedin [80, 81] are becoming available and might lead to further increases in patient survival. Of course, controlling treatment complications and the early detection and prevention of secondary malignancies are mandatory. In Japan, single institutional trials are not sufficient for producing scientific evidence, as they would involve too few patients; however, the multi-institutional study being conducted by the JESS group is expected to produce high quality data.

Summary

The prognosis of ES patients has improved in recent years. To diagnose ES, molecular techniques that aim to detect characteristic fusion genes are commonly used in

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**Fig. 11**  A 1-year-old boy suddenly suffered a pain in his right lower leg without any obvious cause.  

a A plain X-ray showed a radiolucent lesion and widening of the diaphysis of his right tibia. A periosteal reaction was also observed.  
b T2-weighted imaging demonstrated an area of high signal intensity in the tibia. An open biopsy resulted in a diagnosis of ES of the tibia. After preoperative chemotherapy composed of 6 courses of VIDE according to the protocol outlined in the Euro-EWING 99 study, radiotherapy involving 55.8 Gy was performed as a local therapy. After the radiotherapy, one course of the VAI regimen and 7 courses of the VAC regimen were administered. When the patient was 9.5 years old, CT detected lymph node swelling in his neck. A biopsy of the lymph node demonstrated metastasis from papillary thyroid cancer. The patient underwent excision of his right thyroid lobe and the swollen lymph node.  

He displayed a 5-cm leg length discrepancy at 10 years after the local therapy.
combination with conventional histological and immunohistochemical techniques. As for chemotherapy, several new lines of evidence have been obtained in large-scale studies conducted in Europe and North America. The use of multidisciplinary treatment teams composed of specialists from various fields such as pediatric oncologists, medical oncologists, radiation oncologists, and orthopedic surgeons is necessary to further improve patient prognosis. After treatment, ES patients must be carefully followed up for tumor relapses, growth-related musculoskeletal complications, and secondary malignancies.

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