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Review Article

Diagnosis and Treatment of Ewing's Sarcoma

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Ewing's sarcoma is a small round-cell tumor typically arising in the bones, rarely in soft tissues, of children and adolescents. Ewing's sarcoma has retained the most unfavorable prognosis of all primary musculoskeletal tumors. Prior to the use of multi-drug chemotherapy, long-term survival was less than 10%. The development of multi-disciplinary therapy with chemotherapy, irradiation, and surgery has increased current long-term survival rates in most clinical centers to greater than 50%. In addition, the preferred method of tumor resection has changed; limb salvage has nearly replaced amputation of the affected limb. Limb salvage procedures can be performed in place of amputation without compromising patient survival rates. Recent studies have revealed that the pathognomonic translocations involving the *EWS* gene on chromosome 22 and an *ETS*-type gene, which is most commonly the *Fli*1 gene on chromosome 11, are implicated in more than 95% of Ewing's sarcomas, primitive neuroectodermal tumors and Askin's tumors. Therefore, these lesions have become regarded as a single entity, dubbed the Ewing's family of tumors. RT-PCR to detect *EWS–ETS* gene arrangements is widely used to confirm the diagnosis of Ewing's family of tumors. Experimental results suggest that inhibition of the signaling pathway downstream of the *EWS–ETS* gene may lead to the development of molecularly targeted therapy in the future.

Key words: Ewing's sarcoma – diagnosis – treatment

INTRODUCTION

Recent years have seen a remarkable change in the perception of the histogenesis and the relationship between skeletal and extra-skeletal Ewing's sarcoma and primitive neuroectodermal tumor (PNET) (1). In 1918, Stout reported a case with an ulnar nerve tumor composed of undifferentiated round cells that form rosettes, subsequently defined as PNET of soft tissue (2). In 1921, James Ewing reported a case of round cell tumor in the radius of a 14-year-old girl as a 'diffuse endothelioma of bone', proposing an endothelial derivation (Ewing's sarcoma) (3). It was in 1975 that Angervall and Enzinger reported the first case of an Ewing's sarcoma arising in soft tissue (extra-skeletal Ewing's sarcoma) (4). In 1979, Askin *et al.* reported a 'malignant small-cell tumor of the thoracopulmonary region' (Askin tumor) with similar histologic features as PNET (5). In 1984, Jaffe *et al.* described a small round-cell tumor of bone, calling it a neuroectodermal tumor of bone (PNET of bone) (6). Recent clinicopathological studies have revealed that these lesions have overlapping features, supporting a common histogenesis. Identification of a common translocation t(11;22)(q24;q12) (7,8) that results in the formation of the *EWS–ETS* fusion gene (9) in cases of Ewing's sarcoma, PNET and Askin's tumor strongly supported the hypothesis that these tumors are related. Therefore, all these lesions are now included in the same classification, the Ewing's sarcoma family of tumors (EFTs).

Thanks to the development of novel methods for diagnosis and treatment, the prognosis of EFTs has improved greatly. This review overviews the updated diagnostic and treatment methods for management of EFTs.

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FREQUENCY

According to data of Bone Tumor Registry Japan, Ewing's sarcoma is the third most frequent primary sarcoma of bone

after osteosarcoma and chondrosarcoma (10). It is the second most frequent bone sarcoma after osteosarcoma in patients younger than 20 years of age. It remains an infrequent neoplasm, however; only approximately 20 new cases are registered per year. Caucasians are much more frequently affected by Ewing's sarcoma than Asians, while Africans and African-Americans rarely suffer from this disease. In the Surveillance, Epidemiology, and End Results (SEER) program series in the USA between 1973 and 1985, only three of 650 cases of Ewing's sarcoma occurred in black patients. In North America, 225 patients younger than 20 years old are diagnosed per year with this disease (11).

SEX AND AGE

Ewing's sarcoma has a predilection for the male sex (male/female ratio, 1.3–1.5:1). Ewing's sarcoma occurs in a wide range of ages from infants to the elderly, although approximately 80% of patients afflicted are younger than 20 years of age. Peak incidence is during the second decade of life, although 20–30% of cases are diagnosed in the first decade (Fig. 1). The age of the patient is important diagnostically. When confronted with patients older than 30 years, the clinician must first eliminate other small round-cell tumors, including small-cell carcinoma and large-cell lymphoma, before making a diagnosis of Ewing's sarcoma. In patients younger than 5 years, the possibility of metastatic neuroblastoma or acute leukemia needs to be ruled out.

LOCALIZATION

Ewing's sarcoma demonstrates a predilection for the trunk and long bones. In the truncal skeleton, the pelvis predominates, followed by the scapula, vertebral column, ribs and clavicle (Fig. 1). Of the long bones, the most common site is the femur, followed by the humerus, tibia and bones of forearm in that order. As opposed to osteosarcoma, Ewing's sarcoma of the long bones tends to arise from the diaphysis rather than the metaphysis.

Ewing's sarcoma has a strong potential to metastasize. Metastases most commonly occur in the lungs and bone. More than 10% of patients present with multiple bone metastases at initial diagnosis. While metastases in the lungs, bone, bone marrow, or a combination thereof are detectable in approximately 25% of patients, metastases to lymph nodes are rare.

Ewing's sarcoma primarily occurs in bones, with rare occurrences in soft tissues. Most extra-skeletal Ewing's sarcomas affect patients between 10 and 30 years of age, with a peak incidence at approximately 20 years old. The most common sites are the chest wall, para-vertebral muscles, extremities, buttocks and retro-peritoneal space. Extra-skeletal Ewing's sarcomas present with rapid growth and frequent distant metastases, similarly to Ewing's sarcoma of bone.

SYMPTOMS

Ewing's sarcoma typically progresses quite rapidly. Skeletal lesions typically progress to large tumors that form in soft tissues within a few weeks.

The earliest symptom is pain. At first, the pain can be intermittent and mild, but rapidly progresses to the point at which it becomes so intense as to require the use of analgesic drugs. When the tumor is vertebral or pelvic in origin, the pain may be accompanied by paresthesia and treated by irradiation. As pain can precede definitive diagnosis for weeks or months and years in some cases, patients with bone pain without defined trauma should undergo prompt imaging studies.

Tumor growth eventually leads to a visible or palpable swelling of the affected site. This swelling is tense, elastic, hard, tender, rapidly increasing and accompanied by local heat. The tumor bulk, however, may be indiscernible for a long period of time in the cases of pelvic, spinal, or femoral tumors that are not palpable as these tumors are deep-seated

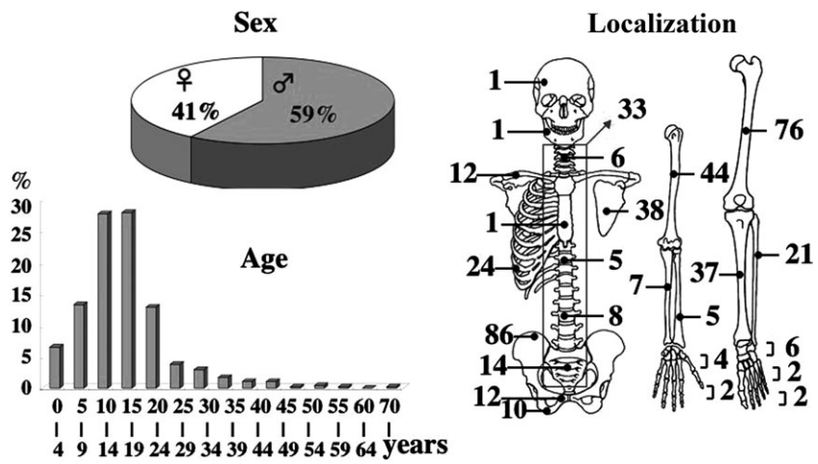

Figure 1. Sex, age and localization of Ewing's sarcoma in Japan (1972–2003) (11) (please note that a colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org).

or cases in which the Ewing's sarcoma extends only into the cancellous bone or along the medullary canal of long bones without expanding outside the cortex (Fig. 2A).

Other common symptoms include fever, anemia, and non-specific signs of inflammation, such as increases in sedimentation rate, moderate leukocytosis and an increase in serum LDH. Conventional blood, serum and urine tests cannot specifically identify Ewing's sarcoma. Unlike neuroblastoma, serum and urine catecholamine levels remain normal. However, de Alava *et al.* reported that the *EWS–Fli*1 fusion gene is frequently detected in peripheral blood samples from patients with Ewing's sarcoma (12). In advanced cases, the symptoms listed above are frequent; the majority of patients experience loss of appetite and weight.

DIAGNOSTIC IMAGING

Plain Radiograph

The initial imaging investigation of a suspected bone tumor is a radiograph in two planes. Tumor-related osteolysis and periosteal reactions suggest a diagnosis of primary malignant tumor. Periosteal reactions, the reactive osteogenesis of the periosteum, are caused by extra-osseous extension of the tumor. Several types of periosteal reactions have been observed: (i) an 'onion skin' or 'onion-peel appearance' is a prominent multi-layered reaction, (ii) a 'sunburst' or 'spiculae' pattern is a perpendicular reaction, while (iii) 'Codman's triangle' is a triangular lifting of the periosteum from the bone at the site of detachment. Typically, Ewing's sarcoma appears as an ill-defined, permeative, or focally moth-eaten, destructive intramedullary lesion accompanied by a periosteal reaction ('onion skin') that affects the diaphyses of long bones (Figs. 2A, 3A). The sunburst type of periosteal reactions can present, but is less common in comparison with its occurrence in osteosarcoma.

MRI

The most precise definition of the local extent of bone tumors, including the degree of expansion into the intramedullary portion and the relationship of the lesion to adjacent blood vessels and nerves, is provided by MRI (Figs. 2B, 3B). When malignant bone tumors are suspected, MRI is routinely performed for staging and surgical planning. MRI is particularly important in the imaging of Ewing's sarcoma

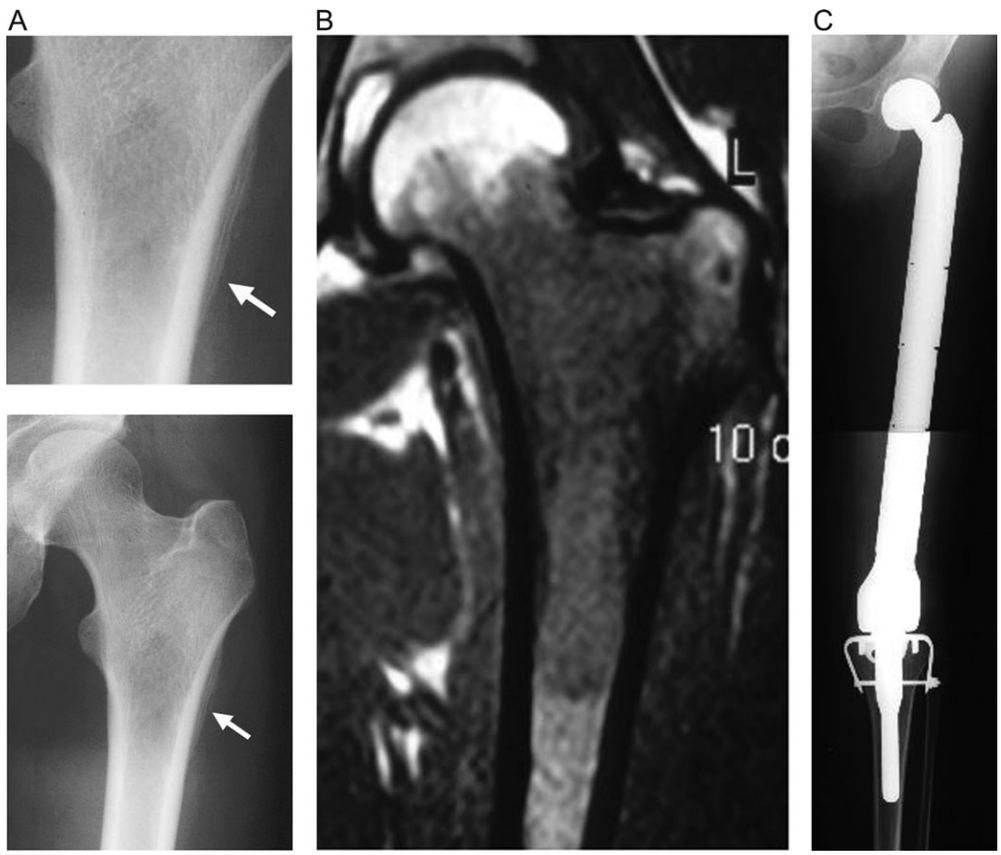

Figure 2. Ewing's sarcoma of the femur. (A) Plain roentgenogram displays a permeative lesion of the proximal femoral shaft associated with an 'onion skin' periosteal reaction (*Arrow*). *Insert* is a magnification of 'onion skin' periosteal reaction (*Arrow*). (B) A coronal T1-weighted MR image displays a low-signal intramedullary tumor involving the long segment of the femoral shaft that extends into the femoral neck. Note that the involvement detected by MRI extends beyond the anticipated area seen on plain roentgenogram. (C) After resection with wide margins, the affected limb was reconstructed with endoprosthesis.

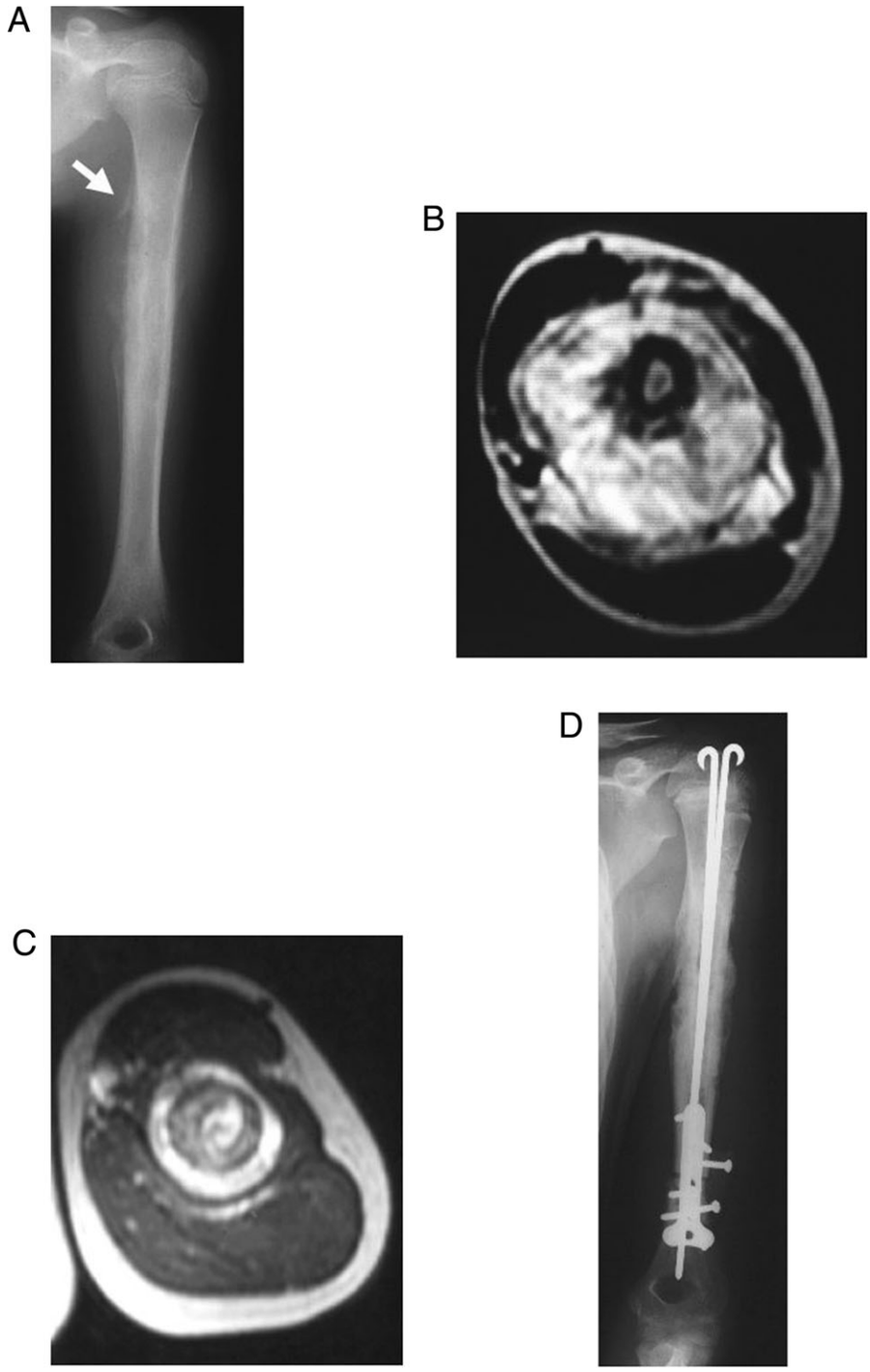

Figure 3. Ewing's sarcoma of the humerus. (A) Plain roentgenogram shows an osteolytic lesion of the humeral shaft associated with the periosteal reactions of 'Codman's triangle' (*Arrow*). (B) Transverse T2-weighted MR image displays a high-signal large tumor extending into the soft tissues. (C) After preoperative adjuvant treatment, including multi-drug chemotherapy and irradiation, the size of the soft tissue tumor was dramatically reduced. (D) After resection with wide margins, the affected bone was transplanted after autoclaving.

as this tumor is ill-defined on plain radiographs or by computed tomography (CT). MRI typically demonstrates lesions that involve large segments of the intramedullary cavity, which extend beyond the area indicated by plain radiographs. MRI can also evaluate the extent of soft tissue masses, which can be quite large.

MRI is widely used to assess responses to neoadjuvant chemotherapy or irradiation, because regression of the extra-

skeletal tumor mass can be precisely defined (Fig. 3B, C). Currently, MRI is the standard imaging method for such evaluation. Recent studies have demonstrated, however, that PET, thallium-201 scintiography and dynamic MRI provide more valuable information than MRI for assessment of therapeutic responses (13).

STAGING

Enneking *et al.* created a staging system for both benign and malignant musculoskeletal tumors to support decision making in treatment and to allow meaningful comparison between treatment methods (14). The system, based on the histological grade of the tumor, local extent, and the presence or absence of metastasis, incorporates the most significant prognostic factors into a set of progressive stages that can help to guide surgical and adjuvant treatments. High-grade lesions, such as Ewing's sarcomas, are designated as stage II tumors, which can be subdivided according to the extent of local growth. While stage IIA lesions are contained within well-defined anatomical compartments, stage IIB lesions extend beyond their compartment of origin. Stage III includes any lesion that has metastasized, regardless of the size or grade of the primary tumor. Almost all Ewing's sarcomas fall into stages IIB or III. Many oncologists stage malignant bone tumors according to the American Joint Committee on Cancer (AJCC) system, which is similar to Enneking's system (15).

Diagnostic staging should include a CT scan of the chest to determine pulmonary metastases and a technetium-99 m whole-body radionucleotide bone scan to identify skeletal metastases. Fluorine-18 fluorodeoxyglucose position emission tomography (FDG-PET) was recently reported to increase the sensitivity of detection for both skeletal metastases and therapeutic responses (16). The exact role for this modality in the management of Ewing's sarcoma, however, remains to be defined.

PATHOLOGY

The definitive diagnostic method is biopsy. Although tumor sampling can be performed by fine needle aspiration biopsy or core needle biopsy, sampling is most adequately achieved by incisional open biopsy. Open biopsy is best performed by an experienced orthopedic oncologist to avoid violation of tissue flap planes and neovascular structures. Appropriate biopsy can thus facilitate eventual complete excision and limb salvage.

Histologically, Ewing's sarcoma is composed of a homogeneous population of small round cells with high nuclear to cytoplasmic ratios that are arrayed in sheets (Fig. 4A). There is scant cytoplasms, which is pale, vacuolated and characterized by faded boundaries. In contrast, the nuclei are clearly visualized by their intense color. Mitotic activity is typically low. Cytoplasmic glycogen, which appears as periodic acid-Schiff-positive diastase-positive digestive granules, is also usually present.

Cytogenetic or immunohistochemical studies are often required to differentiate Ewing's sarcoma from other small round-cell tumors. The t(11;22)(q24;q12) translocation, the most common translocation diagnostic for Ewing's sarcoma, is present in more than 85% of cases. Other diagnostic

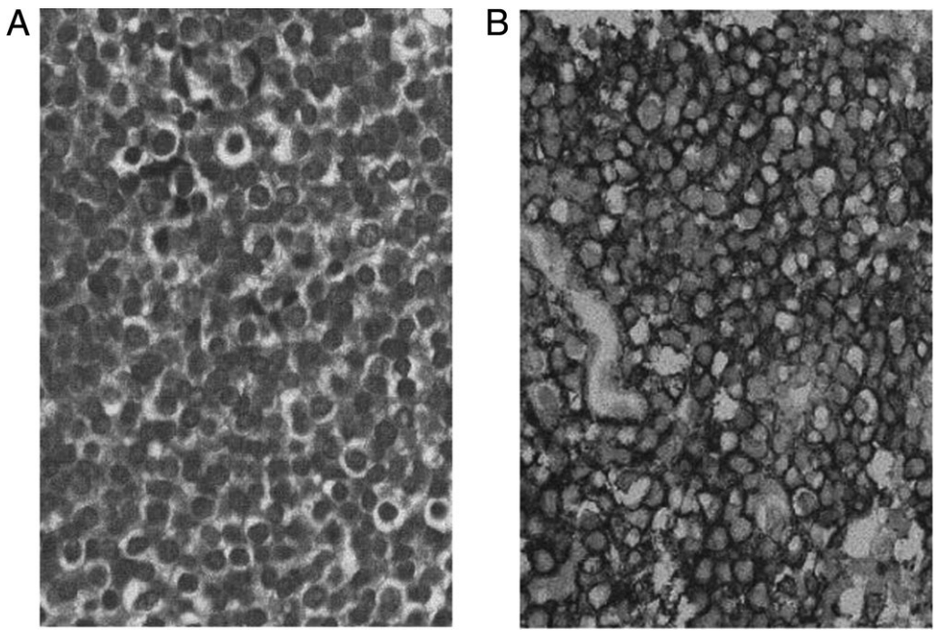

Figure 4. Microscopic features of Ewing's sarcoma. (A) Hematoxylin-eosin specimens demonstrate a uniform population of small round cells with a high nuclear to cytoplasmic ratio. (B) Immunohistochemical staining for the MIC2 is positive (please note that a colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org).

translocations involving the *EWS* locus on chromosome 22, including t(21;22)(q22;q12) and t(7;22)(p22;q12), have also been identified. Immunohistochemical staining for the *MIC*2 gene product was reported to be positive in 90% of Ewing's sarcomas (Fig. 4B). In addition, Ewing's sarcomas are often PAS-positive (owing to intracellular glycogen) and reticulin-negative; in contrast, lymphomas are PAS-negative and reticulin-positive. Lymphocyte-derived tumors also stain positive for leukocyte common antigen and other T and B cell markers. Embryonal rhabdomyosarcoma stains positive for desmin, myoglobin and muscle-specific actins. Hemangiopericytomas stain with antibodies against factor VIII, while small-cell metastatic carcinomas and melanomas express detectable cytokeratin.

Some of the more differentiated Ewing's sarcomas (primitive neuroectodermal tumors, PNET) may exhibit neural differentiation by light microscopy (Homer Wright rosettes in more than 20% of tumor tissue) and immunohistochemical staining for neuron-specific enolase (NSE), S-100 protein, Leu-7, and PgP9.5. In addition, neuroendocrine differentiation can be observed by ultrastructural studies visualizing the presence of neurosecretary granules. In 1979, Askin *et al.* described a small round-cell tumor of the thoracopulmonary region that affected children (5). In the original report, the authors postulated that this lesion had a pathogenesis different from Ewing's sarcoma and PNET, but was microscopically indistinguishable. The pathological distinction of PNET and Askin's tumor from Ewing's sarcoma had previously been important, as the prognoses of these lesions were reported to be significantly different from Ewing's sarcoma (17). More recent studies, however, have failed to demonstrate any significant differences in outcomes among these tumors (18), most likely as a result of the recent development of intensive chemotherapy. Recent studies revealed that pathognomonic translocation between the *EWS* gene on chromosome 22 and an *ETS*-type gene, most commonly the *Fli*1 gene on chromosome 11, is implicated in more than 95% of Ewing's sarcomas, PNETs and Askin's tumors. Therefore, these lesions have currently been grouped as the same entity, dubbed the Ewing's family of tumors (EFTs).

CYTOGENETIC AND MOLECULAR GENETIC INFORMATION

The t(11;22)(q24;q12) translocation, a chromosomal abnormality specific to the Ewing's family of tumors (EFTs), is detected in approximately 85% of cases (11,12). This translocation results in the formation of the *EWS-Fli*1 fusion gene, which includes the 5′ half of the *EWS* gene from chromosome 22 fused to the 3′ half of the *Fli*1 gene from chromosome 11. In the more rare variant translocations, *EWS* is fused to genes closely related to *Fli*1, such as *ERG*, *ELA*F/*ETV*4/*PEA*3, *ETV*/*ER*81, or *FEV*. The rearrangements of *EWS* with *Fli*1 or *Fli*1-related genes comprises greater than 95% of all EFTs. Thus, at the genetic level, EFTs are defined by the presence of *EWS–ETS* gene arrangements (13,19,20). This discovery has led to the application of RT-PCR assays both for the initial differential diagnosis and the detection of minimal residual disease, circulating tumor cells and occult marrow disease (Fig. 5). While recent studies have indicated the potential of these fusion products to act as aberrant transforming factors (21–24), the biological significance of *EWS–ETS* gene arrangements remains unclear. We reported that the suppression of *EWS–Fli*1 expression using antisense oligonucleotides arrested the growth of Ewing's sarcoma cells at the G0–G1 phase of the cell cycle. G1 cyclins, including cyclin D1 and cyclin E, were upregulated by *EWS–Fli*1 expression, while the CDK inhibitors p21 and p27 were downregulated (25,26) (Fig. 6). As these molecules function upstream of the retinoblastoma tumor suppressor (Rb), the *EWS–Fli*1 fusion may affect the Rb pathway in Ewing's sarcoma cells, promoting tumorigenesis. Abnormalities in the p53 pathway, however, have not been well analyzed in Ewing's sarcoma. We investigated the effects of *EWS–Fli*1 on the p53 pathway, focusing on the induction of apoptosis in Ewing's sarcoma cells. The expression of p21, a target of p53, was inhibited by *EWS–Fli*1 via suppression of p21 gene promoter activity (27). Histone deacetylase inhibitors, which induce p21 expression in cancer cells, inhibited the growth of Ewing's sarcoma cells via induction of p21 expression both *in vitro* and *in vivo* (27,28). Introduction of an expression vector encoding p27 markedly inhibited the growth of EFT cells (29). Transfection of E2F-decoy oligonucleotides into EFT cells markedly inhibited the growth of the cells (30). We also reported that small interfering RNAs (siRNA) against the breakpoint of *EWS–Fli*1 mRNA might be very efficient agent to inhibit the expression of *EWS–Fli*1 and the growth of EFT cells, and that *EWS–Fli*1 might have functions that prevent the induction of senescence in cells through the promotion of Skp-2-mediated and 26S proteasome-dependent degradation of p27 protein (31). These results suggest that inhibition of signaling pathway

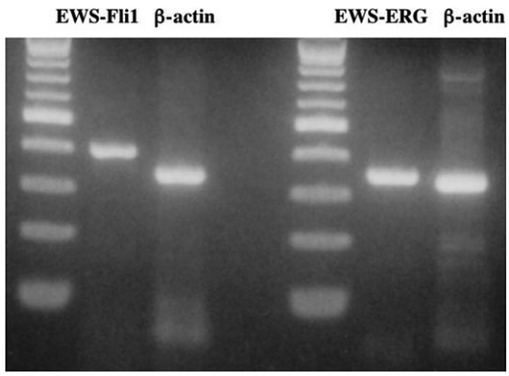

Figure 5. RT-PCR assay for the detection of *EWS–ETS* gene arrangements. *EWS–Fli*1 (left) and *EWS–ERG* fusion gene (right) transcripts were detected in the biopsy specimens of different patients with Ewing's sarcoma.

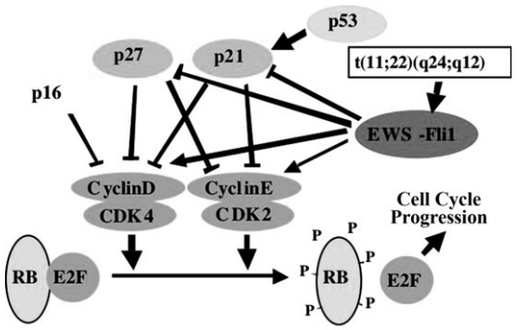

Figure 6. Oncogenesis of Ewing's sarcoma. The t(11;22)(q24;q12) translocation is a specific chromosomal abnormality detected in Ewing's sarcoma. This translocation results in the formation of the *EWS–Fli*1 gene fusion that acts as an oncogene. The *EWS–Fli*1 fusion gene product is thought to affect the expression of cell cycle-regulatory molecules involved in the control of the G1-S transition. G1 cyclins, including cyclin D1 and cyclin E, are upregulated by *EWS–Fli*1, while CDK inhibitors of the G1-S transition, p21 and p27, are downregulated. An imbalance between the G1 cyclin-CDK complex components and p21 and/or p27 in Ewing's sarcoma may be responsible for uncontrolled proliferation, leading to transformation. The tumor suppressor genes, Rb and p53, function by blocking entry of cells into DNA synthesis (S) phase of the cell cycle. Cyclin-CDK complex and CDK inhibitors are located upstream of the Rb tumor suppressor gene. Therefore, *EWS–Fli*1 may affect the Rb pathway, leading to oncogenesis. As p21 is one of the target genes of p53, the p53 pathway is also indirectly affected by *EWS–Fli*1 (please note that a colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org).

downstream of *EWS–Fli*1 may lead to the molecular target therapy of Ewing's sarcoma in the future.

PROGNOSTIC FACTORS

The most unfavorable prognostic factor in Ewing's sarcoma is the presence of distant metastasis at diagnosis. Even with aggressive treatment, patients with metastases have only an approximately 20% chance of long-term survival. Patients with bone or bone marrow metastasis at the time of initial diagnosis have a worse prognosis than those with isolated pulmonary metastases (less than 20 versus 30%). Other unfavorable prognostic factors include an age older than 10 years, a size larger than 200 ml, more central lesions (as in the pelvis or spine), and poor response to chemotherapy. Patients with such lesions have a reduced chance of survival (32,33). The histological grade is of no prognostic significance, however, as all Ewing's sarcomas are of high grade. Fever, anemia, and elevation of the number and values of WBC, ESR, and LDH have been reported to indicate more extensive disease and a poorer prognosis. Recently, it has been reported that the type of *EWS/Fli*1 fusion transcript is prognostically relevant, as patients with the type1 *EWS/Fli*1 fusion transcript appear to have increased disease-free survival over that of patients with other fusion transcript types (34). Ginsburg *et al.*, however, could not identify any significant clinical differences between tumors with *EWS/Fli*1 and *EWS/ERG* fusion transcripts (35).

CHEMOTHERAPY (TABLE 1)

Treatment of Ewing's sarcoma should include chemotherapy to treat distant metastases regardless of their identification at initial staging. Prior to the use of multi-agent chemotherapy, the long-term survival of Ewing's sarcoma was less than 10%. Currently, most clinical centers performing intensive chemotherapy are reporting long-term survival rates between 60 and 70%, suggesting that Ewing's sarcoma is sensitive to anti-cancer agents. Current anti-cancer drugs proven effective for the treatment of Ewing's sarcomas are doxorubicin (DXR), cyclophsophamide (CPA), vincristine (VCR), actinomycin-D (ACT), ifosfamide (IFM), and etoposide (VP16).

In 1962, Sutow and Pinkel independently reported experiences of chemotherapy using cyclophosphamide for Ewing's sarcoma (36,37). In 1968, Hustu *et al.* reported that the combination of cyclophosphamide, vincristine and radiotherapy resulted in sustained responses in five patients with Ewing's sarcoma. These reports marked the start of the modern multimodality treatment of Ewing's sarcoma (38).

In 1974, Rosen *et al.* reported that the combination of VACD four-drug regimen (vincristine, actinomycin-D, cyclophsphamide and doxorubicin) with radiotherapy led to the long-term survival of 12 patients with Ewing's sarcoma (39). The effectiveness of DXR was proven by the first Intergroup Ewing's Sarcoma Study (IESS-1) beginning in 1973. Long-term follow-up of this study demonstrated the superiority of the VACD regimen over a three-drug VAC regimen lacking doxorubicin in terms of local control (96 versus 86%) and event-free survival (60 versus 24%) (40). The effect of dose intensity of DXR was then investigated in the IESS II study, which indicated the superiority of escalated doses of DXR plus VAC over conventional doses of DXR plus VAC in 5-year relapse-free survival of non-metastatic Ewing's sarcoma (73 versus 56%) (41). In Europe, the effect of the VACD four-drug regimen was also investigated in the Cooperative Ewing's Sarcoma Study (CESS). In CESS-81, the 5-year relapse-free survival of patients with non-metastatic Ewing' sarcoma after the VACD regimen was 55% (42). These clinical trials lead to the adoption of the VACD scheme as the standard therapy in many clinical trails. In the CESS-86 study, IFM was substituted for DXR in the treatment of large Ewing's sarcoma. DXR plus VAC was used for tumor with a volume less than 100 ml, while IFM plus VAC was used for those greater than 100 ml in volume. The 10-year event-free survival was 51% for the former and 52% for the latter, suggesting the usefulness of VAC plus IFM as well as VACD in the treatment of Ewing's sarcoma (32).

Excellent phase II results achieved with the combination of IFM and etoposide (IE) prompted patients to be randomized to receive either VACD alone or VACD-IE in the Pediatric Oncology Group–Children's Cancer Group (POG–CCG) study INT-0091 (43,44). In patients with localized Ewing's sarcoma, the VACD arm achieved a 5-year

Table 1. Summary of treatment results in Ewing's sarcoma

Study	Period	Patients	Regimen	Results (5-year DFS)	Reference
IESS-I	1973–1978	342	VAC	24	40
			VAC + WLI	44	
			VACD	60	
IESS-II	1978–1982	214	VACD-HD	73	
			VACD-MD	56	
CESS-81	1981–1985	93	VACD	Tumor size < 100 ml	41
				80% (3 years)	
				Tumor size > 100 ml	
				31% (3 years)	
CESS-86	1986–1991	301	SR: VACD	52%	32
			HR: VAID	51% (10 years)	
INT-0091	1988–1992 (non-metastatic)	398	VACD	54%	33
			VACD-IE	69%	

DFS, disease free survival; WLI, whole lung irradiation; HD, high-dose; MD, moderate-dose; SR, standard risk; HR, high risk; VAC, vincristine, actinomycin D, cyclophosphamide; VACD, vincristine, actinomycin D, cyclophosphamide, doxorubicin; VACD-IE, vincristine, actinomycin D, cyclophosphamide, doxorubicin, ifosfamide, etoposide; VAID, vincristine, actinomycin D, ifosfamide, doxorubicin.

event-free survival rate of 54%, while the VACD-IE arm achieved a rate of 69% (33). Therefore, the VACD-IE regimen was adopted as standard therapy for localized Ewing's sarcoma.

To achieve treatment intensification in Ewing's sarcoma, high-dose chemotherapy with autologous hematopoetic stem cell rescue (HDT) was attempted. In most studies, HDTs were reserved for high-risk patients, typically those with metastases or recurrence, because of the considerable toxicity of this approach. There has not been a controlled randomized clinical study, however, that was able to prove the superiority of HDT (45–48).

LOCAL TREATMENT; SURGERY AND/OR IRRADIATION?

Local treatment of the primary lesion remains controversial. Previous reports demonstrated a decrease in the rate of local recurrence (<10%) and an increase in the rate of overall survival with wide resection of the primary tumor. In addition, retrospective analyses by several groups provide the impression that local control is preferable when surgery is possible (49,50). However, there have not been any randomized trials comparing local therapy modalities; there may also be a selection bias favoring a subset of patients for whom surgery is applicable. Therefore, the choice between surgery and irradiation as a method for control of the primary lesion should be made on an individual basis.

If pre-operative imaging suggests that it will likely be possible to resect the lesion with wide margins, wide resection without irradiation is the treatment of choice for primary lesions. If the possibility of achievement of adequate surgical margins is uncertain, pre-operative radiotherapy should be added. As Ewing's sarcomas are sensitive to both chemotherapy and irradiation, even questionable candidates for limb salvage may be eligible after neoadjuvant chemotherapy with or without irradiation. If the surgical margins are found to be inadequate after surgery, postoperative radiotherapy may also be added. When surgical margins are certain to be inadequate at preoperative imaging, amputation may be the only surgical option available. Central, large, unresectable primary tumors are sometimes treated with radiation alone. A debulking intralesional procedure does not improve local control; in the CESS and EICESS trials, patients who had an intralesional resection followed by radiotherapy displayed the same local control rate as those who were treated with radiotherapy alone (49).

SURGICAL MARGIN

The current standard treatment schedules for resectable Ewing's sarcoma begin with neoadjuvant chemotherapy, followed by limb salvage procedure and post-operative adjuvant chemotherapy. Although amputation had been the only surgical method for several decades, limb salvage procedures, which include local resection and reconstruction, are currently performed in almost all the cases of Ewing's sarcomas. Limb salvage procedures can be performed without compromising survival rates (49–51).

When describing a surgical procedure, it is imperative that the surgical margin be appropriately defined. The terms 'amputation' and 'resection' mean little without a modifier describing the margins, especially when evaluating surgical procedures and outcomes in the literature. In orthopaedic oncology, surgical margins can be described by one of four terms: intralesional, marginal, wide, or radical (52). An intralesional margin is one in which the plane of surgical dissection is within the tumor, which is often called 'debulking', because it leaves gross residual tumor behind. A marginal margin is achieved when the closest plane of dissection passes through the pseudocapsule of the tumor. The pseudocapsule, however, often contains microscopic tumor foci. Marginal resection often leads to local recurrence if the remaining tumor cells do not respond to adjuvant chemotherapy or radiation therapy. Wide margins are achieved when the plane of dissection is in normal tissue. Wide margins are the goal for most procedures, especially with high-grade malignancies such as Ewing's sarcoma. Radical margins are achieved when all compartments that contain tumor are removed en bloc.

RECONSTRUCTION (FIGS. 2 AND 3)

After resection of Ewing's sarcomas, large bone defects should be reconstructed to restore the function of the affected limbs. The main options for reconstruction include autogenous bone grafts, allogeneic bone grafts and endoprosthesis.

Autogeneous bone grafts may be vascularized; vascularized bone autograft operations are now performed widely as a result of the development of microsurgery. As blood flow can be preserved and the cells in the grafted bone remain alive, bone formation and bone fusion are vigorous. This technique has generated remarkable improvement in therapeutic success rates (53). Because of the limited amounts of bone that can be collected, however, it is sometimes difficult to repair large bone defects; in such cases, allogeneic bone grafts or endoprosthesis is indicated.

Allografts are a form of reconstruction utilizing dead bone. Frozen or freeze-dried bone allografts have been widely used for limb salvage procedures in western countries. Although fracture and non-union of the grafts can reduce success rates, acceptable functional limbs can be recreated with allografts (54). Allografts can be difficult to obtain in some Asian countries, especially Japan and Korea, for socio-religious reasons (55,56). Therefore, recycling of affected bone has been adopted in Japan. Several methods have been developed to allow re-use of resected bones for reconstruction, including irradiation (57), autoclaving (58) (Fig. 3D), pasteurization (59), and treatment with liquid nitrogen (60).

Endoprosthetic replacement after excision of the tumor can provide excellent results more rapidly than other methods (Fig. 2C). Therefore, the most popular reconstruction method after resection of malignant bone tumors is prosthetic replacement (61). The late complications of this method, such as a loosening, infection and fracture of the prosthesis after replacement, have not been solved. More successful methods for reconstruction than those in existence need to be explored in the future.

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Conflict of interest statement

None declared.

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