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Διδακτορική Διατριβή

" EWING ΣΑΡΚΩΜΑ ΤΗΣ ΠΥΕΛΟΥ "

υπό

ΑΣΤΕΡΙΟΥ ΔΡΑΜΗ

Ειδικευμένος Ορθοπαιδικός Χειρουργός

Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διδακτορικού Διπλώματος

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“EWING SARCOMA OF THE PELVIS”

BY

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A thesis submitted to the Faculty of Medicine, School of Health Sciences

of the University of Thessaly for the degree of

DOCTORATE OF MEDICINE

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Synopsis

We are reporting our experience on patients with pelvic Ewing's Sarcoma treated in the Royal Orthopaedic Oncology Unit. We retrospectively reviewed a series of patients with non-metastatic pelvic Ewing's sarcoma treated between 1977 and 2009. Patients were classified into three groups according to the local treatment received: Group 1: Radiotherapy-chemotherapy; Group 2: Surgery-chemotherapy and Group 3: Radiotherapy-surgery-chemotherapy. Recurrence free and overall survival rates were calculated using the Kaplan-Meier method. Influence of various factors (age at diagnosis, gender, tumour site and size, chemotherapy response, surgical margins and type of treatment) on survival was assessed with a logistic regression model. A total of 85 patients were treated with a mean follow-up of 65.8 months and mean tumour volume of 435ml. The 5-year survival for all patients was 40.7% decreased to 36.2% at 10 years. A significant prognostic factor identified was chemotherapy response only. There was a trend for improved survival and local control rates for patients who had chemotherapy and surgery and the results were apparent for all tumours irrespective of size but not statistically significant. Currently, the optimal management of pelvic Ewing's sarcoma is controversial but our study shows a trend for improved survival for patients treated with chemotherapy and surgery.

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Chapter 1

**Overview of the epidemiology, aetiology, pathology, clinical features,
diagnosis, management and prognosis of Ewing's sarcoma of bone**

1.1 Introduction

Ewing sarcoma (EWS) was named after James R. Ewing, an eminent American pathologist at Cornell who described the first cases in 1921. Dr Ewing reported in the Proceedings of the New York Pathological Society several cases of a new bone cancer he called “diffuse endothelioma of bone,” which ultimately became his eponym [1]. He described the tumours as slow growing, vascular and fluctuating in size. On radiographs, he distinguished his series from osteosarcoma: “A large portion or the whole of the shaft is involved, but the ends are generally spared, contrary to the rule with osteogenic sarcoma. The shaft is slightly widened, but the main alteration is a gradual diffuse fading of the bone structure. Bone production has been entirely absent. . . The radiograph is therefore rather specific.” Based on Ewing’s publication, a few years later the noted Boston surgeon, Ernest Codman, referred to this new entity as Ewing sarcoma [2].

1.2 Epidemiology

Ewing’s sarcoma is the second most common type of primary bone malignancy in children and young adults, and age of onset is most often in the second decade, with a slight male predominance [3]. It accounted for 6% of primary malignant tumours at the Mayo clinic [4], and 10% of primary malignant tumours in a Swedish study [5]. About a quarter of Ewing’s sarcomas arise in soft tissues rather than bone, and about a quarter of patients have detectable metastases at diagnosis. The lungs are the most common site for metastases (50%), followed by bone (25%) and bone marrow (20%) [6]. The mean annual incidence of Ewing’s sarcomas per million population is 0.6 in England and 0.8 in Sweden.

1.3 Natural History

Patients with Ewing's sarcoma have had a dismal prognosis in the past with more than 90% of patients dying with disseminated disease [7]. With the use of multimodal therapy that combines chemotherapy, radiotherapy and surgery, the long-term survival has increased from 10% to 65% [8].

1.4 Aetiology

Genetic factors have been implicated because of the racial distribution and a high incidence of second malignancies but no specific predisposing factors have been identified. However, Ewing's sarcoma has been reported to affect three pairs of female siblings [9].

Furthermore, data from the Intergroup Ewing's Sarcoma Study on 204 patients [10] and 43 patients by Holly et al [11], found significant association between paternal agricultural occupation and EWS but the mechanism of influence of environmental factors remains unknown.

1.5 Pathology

1.5.1 Cell of Origin

The origin of Ewing's sarcoma is a controversial topic [12]. Histologically, Ewing's sarcoma has a certain resemblance to primitive neuroectodermal cells, and it was once widely believed that the tumour arose from such cells. In all cases of the disease, there is a characteristic reciprocal chromosomal translocation (11;22) (Fig. 1.1), which leads to an in-

frame fusion between the *EWS* gene and one of the *ETS* family gene members [13]. Many now believe that EWS arises from a mesenchymal stem cell (MSC) [14]. Expression of the *EWS-FLI1* fusion gene in MSCs changes cell morphology to resemble Ewing's sarcoma and induces expression of neuroectodermal markers. In murine cells, transformation to sarcomas can occur. In knockdown experiments, Ewing's sarcoma cells develop characteristics of MSCs and the ability to differentiate into mesodermal lineages. However more research is needed before definite conclusions are made.

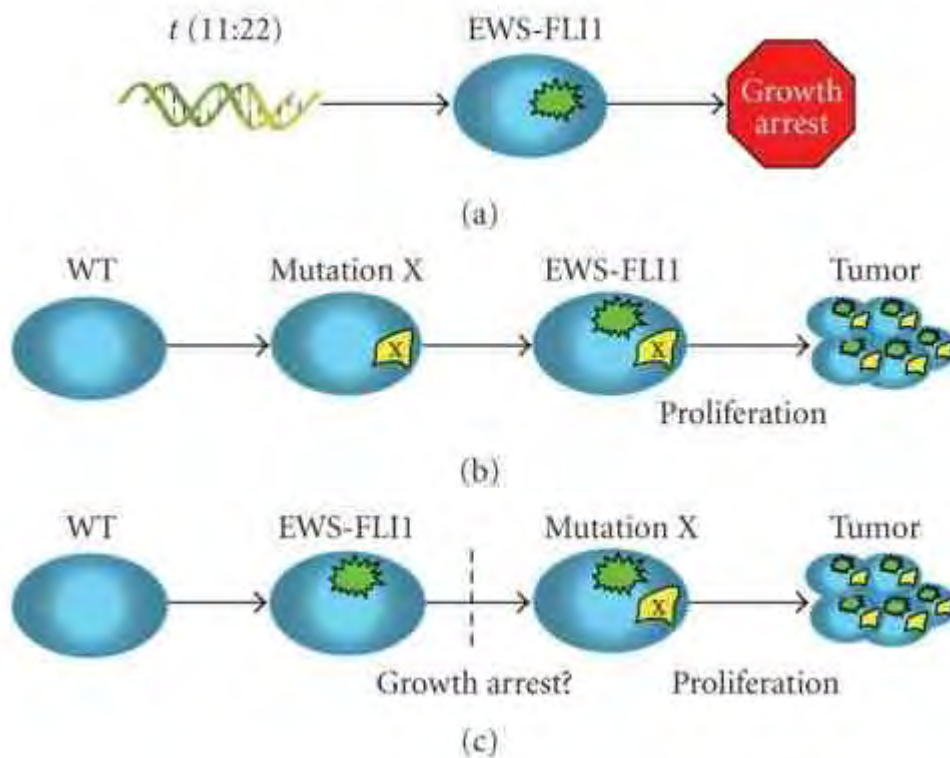


Figure 1.1 Cooperative mutations in the development in Ewing's sarcoma. (a) A $t(11;22)$ reciprocal translocation produces the EWS-FLI1 gene, but this tends to cause growth arrest in normal cells. (b) A mutation randomly occurring prior to the $t(11;22)$ translocation might cooperate with EWS-FLI1 to permit escape from growth arrest (or even promote cell proliferation) and subsequent transformation to Ewing's sarcoma. (c) The cooperative mutation may occur after the $t(11;22)$ translocation; this would necessarily imply a mechanism for continued cell growth after EWS-FLI1 is expressed (adapted from Lin et al. [14])

1.5.2 Gross Pathologic Features

Solid masses of viable tumour are characteristically grey-white, moist, glistening and sometimes translucent. The tumour frequently invades bone beyond the limits indicated on the radiograph. Zones of necrosis, haemorrhage and even cyst formation are common. The neoplastic tissue is often admixed with proliferating bony and fibrous tissue in the periosseous regions (Fig. 1.2). The medullary cavity seems to be the site of origin of nearly all these tumours [15].

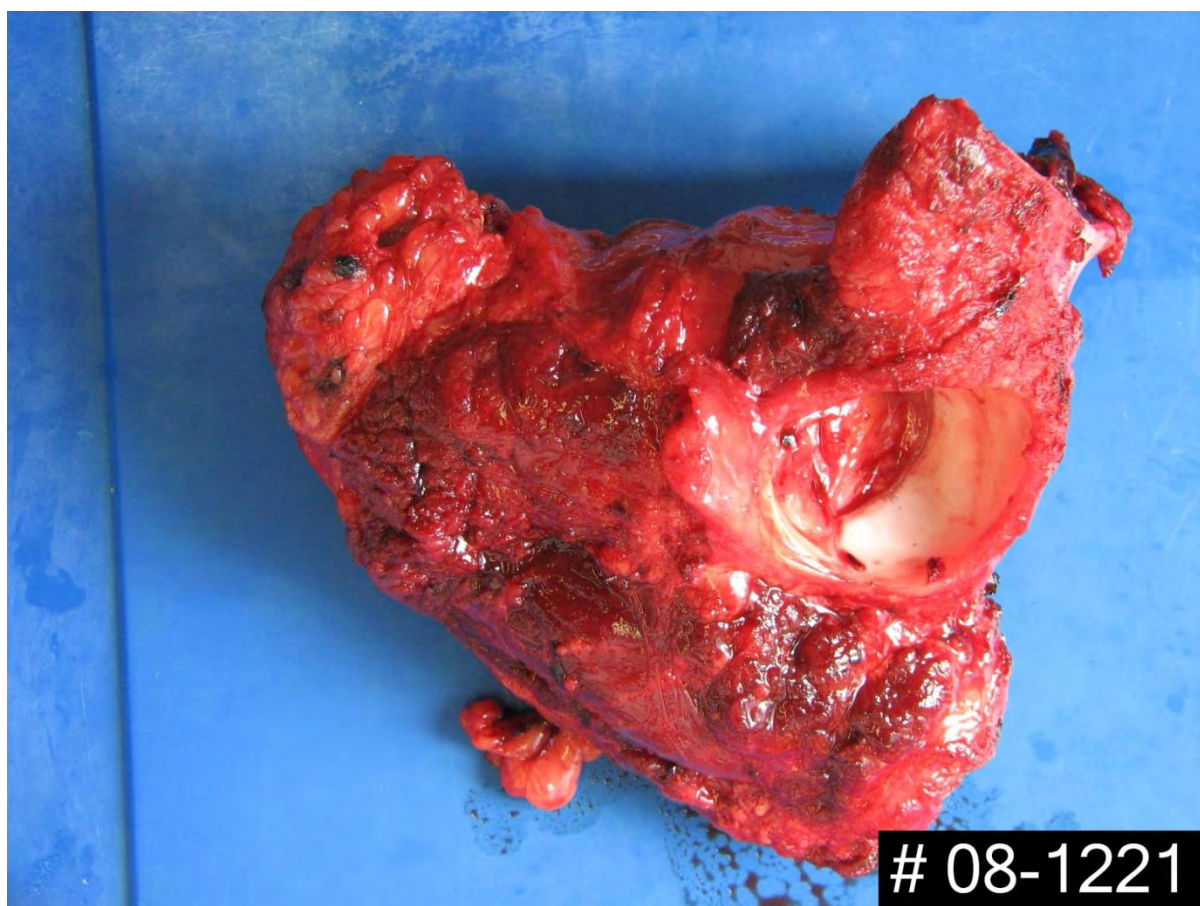


Figure 1.2. Photograph of a gross specimen of a Ewing's sarcoma of the pelvis.

1.5.3 Histopathological Features

Classic Ewing's sarcoma, as first described by James Ewing in 1921, is composed of a monotonous population of small round cells with high nuclear to cytoplasmic ratios arrayed in sheets (Fig. 1.3 & 1.4). The cells have scant, faintly eosinophilic to amphophilic cytoplasm, indistinct cytoplasmic borders, and round nuclei with evenly distributed, finely granular chromatin and inconspicuous nucleoli. Mitotic activity is usually low. Frequently areas of necrosis are present due to tumour outgrowing the blood supply. Often, viable cells are found in cords or masses about blood vessels with necrosis in more remote areas.

A diagnosis of Ewing's sarcoma is generally made by excluding other round cell tumours that occur in bone. Cytoplasmic glycogen, which appears as periodic acid-Schiff-positive diastase-digestible granules, is usually present. Strong expression of the cell-surface glycoprotein p30/32MIC2 (CD99) is characteristic of Ewing's sarcoma and strong, diffuse membrane staining in a "chain-mail pattern" is present in 95%-100% of Ewing's sarcoma with one or more of the monoclonal antibodies to this antigen, including O13, 12E7, and HBA71 [16]. In addition, Ewing's sarcoma is immunoreactive for vimentin [17,18]. More differentiated Ewing's sarcomas (peripheral primitive neuroectodermal tumours [pPNETs]) may also show immunohistochemical evidence of neural differentiation, staining for neuron-specific enolase (NSE), S-100 protein, Leu-7, and/or PgP 9.5 [19]. Ewing's sarcoma is immunoreactive for cytokeratins in up to 20% of cases, with diffuse immunoreactivity for cytokeratins noted in up to 10% of cases [20].

The tumours that must be differentiated from Ewing's sarcoma both clinically and pathologically include primary lymphoma of bone, embryonal rhabdomyosarcoma, metastatic neuroblastoma, small cell osteogenic sarcoma and mesenchymal

chondrosarcoma [4]. Most primary lymphomas of bone are common leucocyte antigen positive, distinguishing them from Ewing's sarcomas which are negative. Metastatic embryonal rhabdomyosarcoma can be differentiated from Ewing's sarcoma by immunocytochemistry which reveals the presence of muscle markers such as actin, desmin and myoglobin. Electron microscopy shows cytoplasmic filaments and occasionally Z-band formation in rhabdomyosarcoma but not in Ewing's sarcoma. Finally, osteomyelitis which can occur concurrently with Ewing's sarcoma and Langerhan's cell histiocytosis also fall into the differential diagnosis.

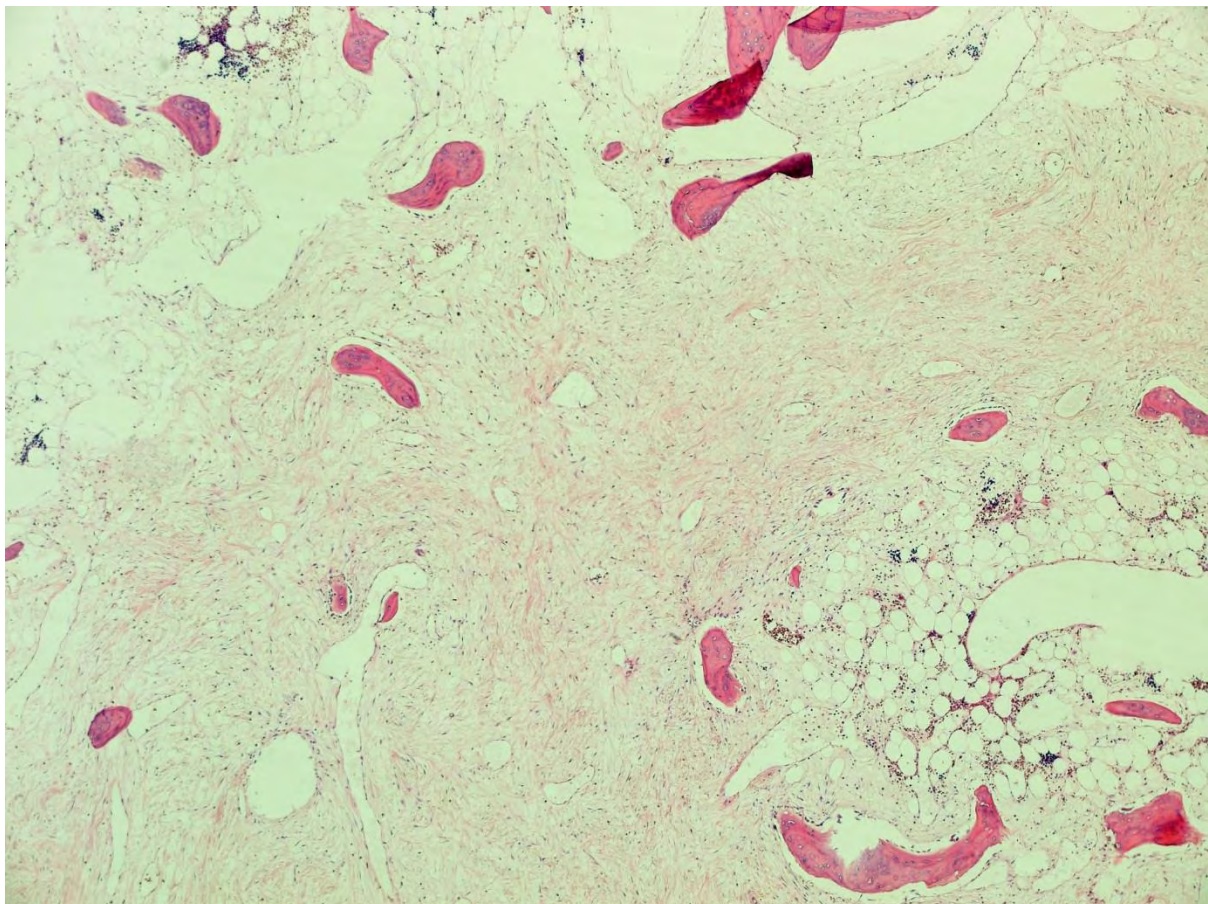


Figure 1.3. A low magnification photomicrograph of a Ewing's sarcoma.

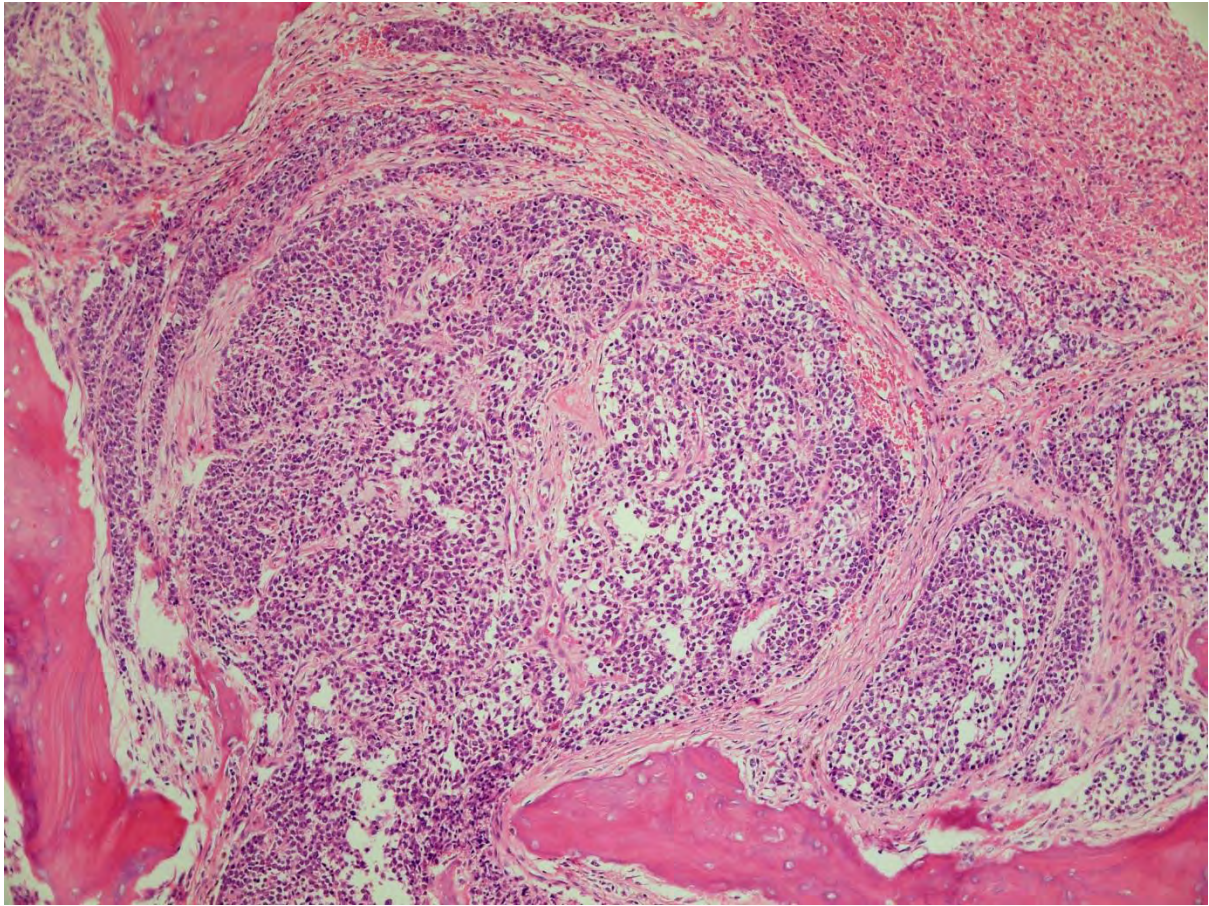
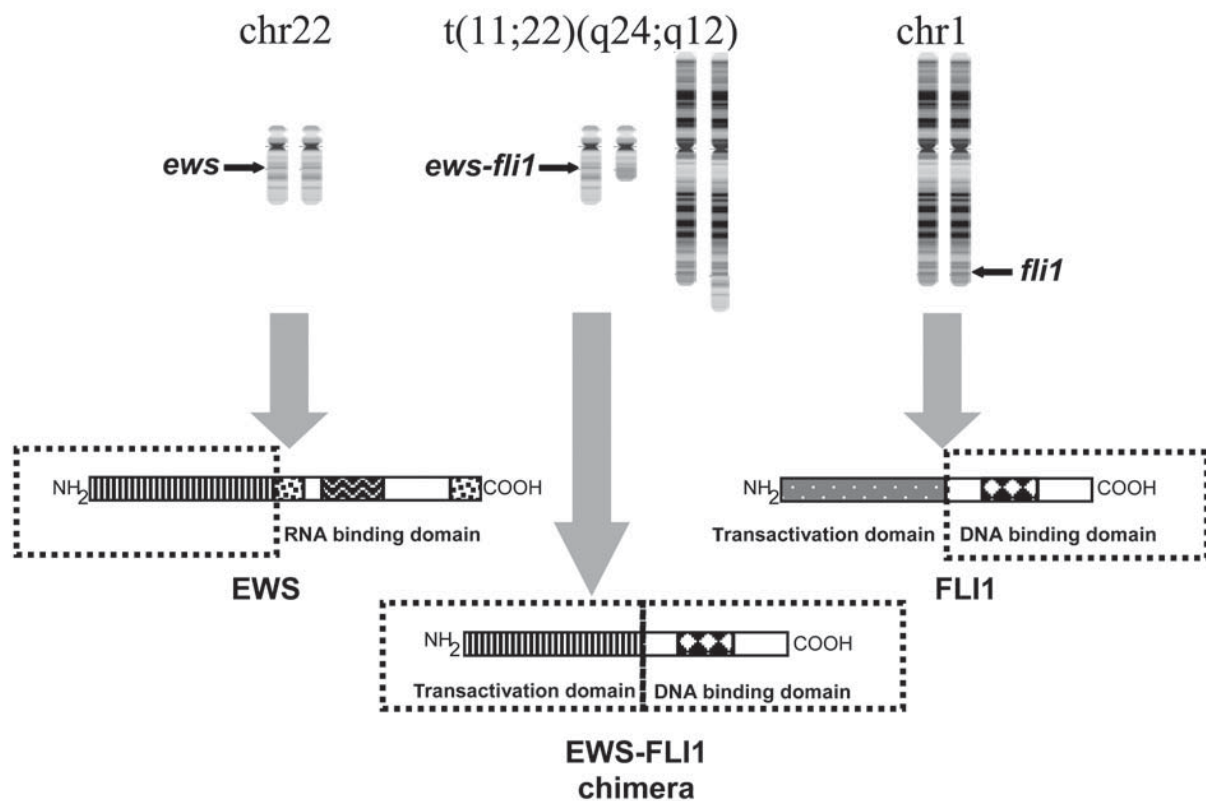


Figure 1.4. A high magnification photomicrograph of a Ewing's sarcoma.

1.5.4 Molecular Pathology

Ewing's sarcoma is characterized by a relatively simple karyotype with only a few numerical and structural aberrations. A reciprocal chromosomal translocation between chromosomes 11 and 22, the $t(11;22)(q24;q12)$, is present in about 85% of these tumours [21] and is therefore considered pathognomonic for the disease. In most of the remaining cases, variant translocations are observed always involving chromosomes 22q12 and either 21q22 (10% of Ewing's sarcomas) or 7p22, 17q12, and 2q36 (<1% of Ewing's sarcomas each). These variant translocations frequently occur as either complex or interstitial chromosomal rearrangements and are therefore difficult to diagnose by conventional cytogenetics. Additional structural changes affect chromosomes 1 and 16 in about 20% of tumours, most frequently leading to a gain of 1q and a loss of 16q and the formation of a derivative chromosome $der(1;16)$. Among numerical chromosome changes, trisomy 8 and/or 12 are observed in half and one third of cases, respectively [22]. Deletion of the chromosomal region 9p21 housing the *ink4A* gene, which has been shown to be homozygously lost in about 25% of Ewing's sarcoma, remains cytogenetically cryptic in most patients [23]. Loss of heterozygosity at 17p13 with mutation of the remaining p53 tumour suppressor allele is rare (<10% of cases) but, together with homozygous deletions of the *ink4A* gene, constitutes an unfavourable prognostic factor in this disease [24]. Among recurrent cytogenetic aberrations, the molecular equivalent has been best characterized for the $t(11;22)(q24;q12)$ [25]. The rearrangement results in the translocation of the 3' portion of the friend leukaemia virus integration site 1 (*fli1*) gene from chromosome 11 to the 5' portion of the Ewing's sarcoma gene *ews* on chromosome 22 (Fig. 1.5).



*Figure 1.5. The reciprocal translocation between chromosomes 11 and 22 results in the formation of an *ews-flt1* fusion gene on the abnormal chromosome 22 that codes for a chimeric transcription factor with the N-terminal transcriptional regulatory domain deriving from *ews* and the *ets*-specific DNA-binding domain derived from *flt1* (adapted from Bernstein et al.[26])*

1.6 Clinical Features

The peak incidence of Ewing's sarcoma (65% of cases) occurs in the second decade of life [4,27,28]. The disease is uncommon before age of 5 and after age of 30 but can occur at any age (Fig. 1.6).

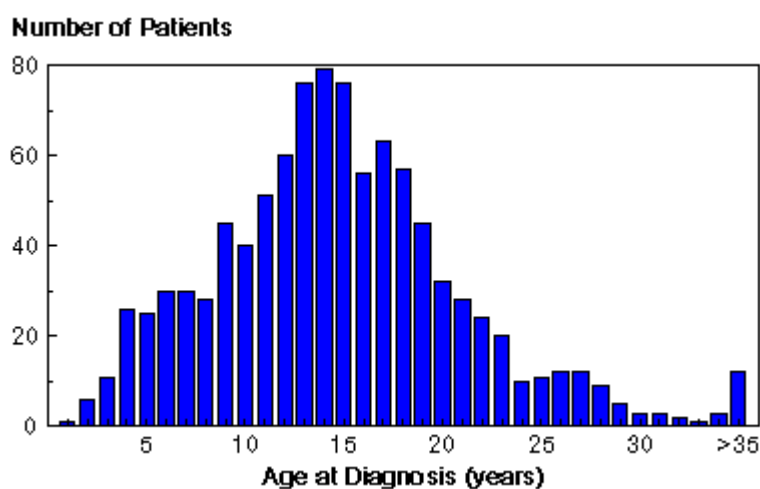


Figure 1.6. The figure above shows the age distribution for over 900 people with Ewing's sarcoma of bone registered with clinical trial groups in Germany and the UK (adapted from <http://www.cancerindex.org/ccw/faq/ewings.htm> [29])

It is slightly more common in males than females (ratio 1.6:1) and rarely occurs in the black population (less than 2%) [30]. Ewing's sarcoma most commonly involves the pelvis and the long bones (Fig. 1.7) and unlike osteosarcomas, it tends to arise from the diaphyseal rather than the metaphyseal portion. In a review of the Mayo clinic, 59.6% of the tumours occurred in the lower extremities and the pelvic girdle with the pelvis being the most

common bone involved (24.7%) followed by the femur (21.4%), the humerus (9.1%) and the tibia (8.1%) [15].

In 167 cases studied at Memorial Hospital [31], the most common site of involvement was the distal femoral metaphysis and diaphysis followed by the pelvis, tibia, fibula, humerus and less often the ribs, scapula, vertebral and small bones of the hands and feet.

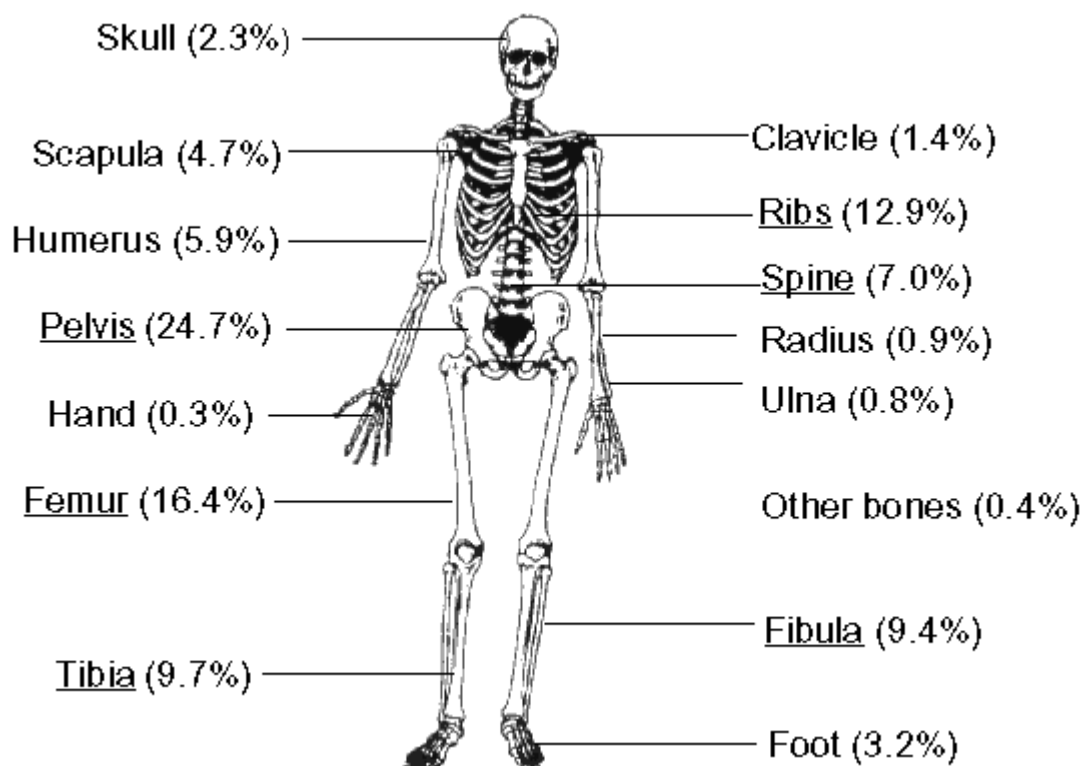


Figure 1.7. The figure above gives a summary of primary tumour site in a series of over 900 people diagnosed with Ewing's sarcoma of bone (adapted from <http://www.cancerindex.org/ccw/faq/ewings.htm> [32])

The most common presenting symptom is pain, which is found at 90% of patients, followed by swelling which occurs in about 70% [27,33].

Pain can be intermittent and variable in intensity. Pain often does not completely disappear during the night [34]. As the majority of Ewing's sarcoma patients are in their second decade of life and physically active, pain is often mistaken for "bone growth" or injuries resulting from sport or everyday activities. Pain may be accompanied by paraesthesia in some cases. Pain as the initial symptom may be followed by a palpable mass. The duration of symptoms prior to the definitive diagnosis can be weeks to months, rarely even years, with a median of 3-9 months [34,35]. Approximately one-fifth of the cases present with a fever, which may lead to the mistaken diagnosis of osteomyelitis. Pathological fractures at the site of the tumour have been reported at presentation in about 5 to 10 percent of patients.

Approximately half of the patients with Ewing's sarcoma of the spine present with a neurological deficit which may initially be misdiagnosed as a lumbar disc herniation [36].

Finally, no blood, serum, or urine test can specifically identify Ewing's sarcoma. Nonspecific signs of tumour or inflammation may be noted, such as an elevated erythrocyte sedimentation rate, moderate anaemia, or leukocytosis. Elevated levels of serum lactate dehydrogenase correlate with tumour burden and, for this reason, with inferior outcome.

1.7 Radiographic Features

Ewing's sarcoma tends to be extensive, sometimes involving the entire shaft of a long bone. Lytic destruction is the most common finding but there may be regions of density due to stimulation of new bone formation (Fig 1.8). As the tumour bursts through the cortex, which may show only minimal radiographic changes, it often elevates the periosteum gradually. This elevation the characteristic multiple layers of subperiosteal reactive new bone, which produces the 'onionskin' appearance of Ewing's sarcoma (Fig. 1.9). Radiating spicules from the cortex of an affected bone are not uncommon and occasionally it expands the affected bone and may even superficially resemble a cyst. A few tumours are almost completely in a juxtaosseous position and show little cortical destruction and very rarely a tumour may have little or no medullary component.

There are several tumours that can produce similar radiographic feature such as osteomyelitis, metastatic carcinoma, malignant lymphoma and osteosarcoma. Modern imaging techniques such as computerized tomography (CT) and magnetic resonance imaging (MRI) do not produce images that are diagnostic of Ewing's sarcoma but are very helpful in defining the extend of the disease, both intramedullary and in the soft tissues (Fig 1.10). There are also very helpful in establishing the relationship of the tumour with the neurovascular bundle, giving information which is critical for surgical planning.



Figure 1.8. Ewing's sarcoma extensively involving the radius in an 8-year-old boy. The lesion has a permeative pattern of bone destruction (adapted from Dahlin & Unni 2010 [15])



Figure 1.9. Ewing' sarcoma involving the proximal humerus in a 15-year-old boy. Pronounced periosteal new bone formation produces an "onionskin" appearance (adapted from Dahlin & Unni 2010 [15])

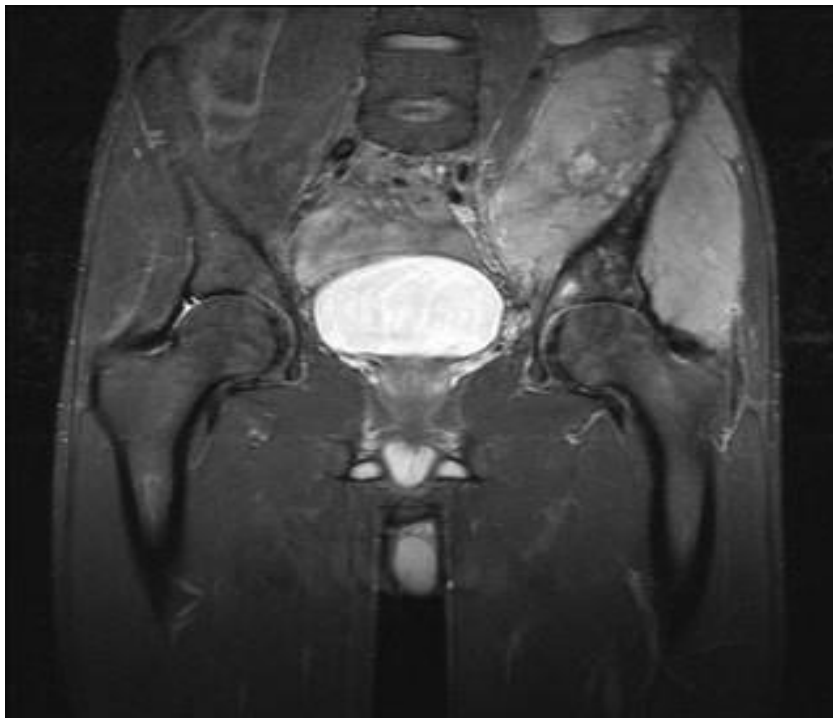
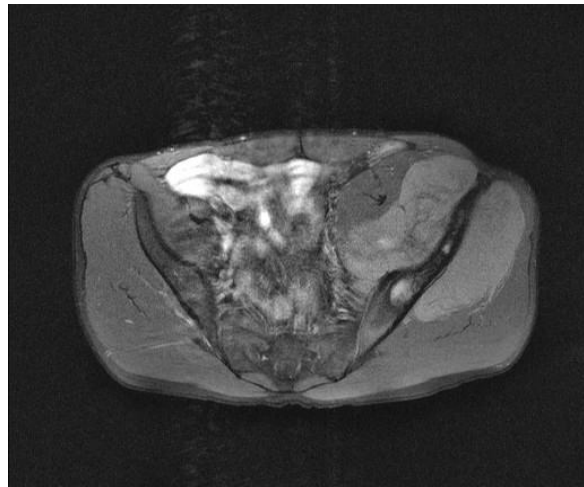


Figure 1.10. Ewing's sarcoma involving the pelvis. The plain radiograph shows a lytic mass involving the left ilium. The magnetic resonance imaging more clearly shows the massive size of the tumour with the associated large soft-tissue mass.

1.8 Clinical Staging

Staging systems may be useful for developing evaluation strategies, planning treatment, and predicting prognosis. For musculoskeletal lesions, the staging systems of the Musculoskeletal Tumor Society (also called the Enneking system) and the American Joint Commission on Cancer (AJCC system) are the most popular. In the Enneking system, there are two separate systems for benign and malignant lesions. For malignant lesions, the system is based on knowing the histologic grade of the lesion (low or high), the anatomic features (intracompartmental or extracompartmental), and the absence (M0) or presence (M1) of metastases. The Enneking staging system can be synthesized into six distinct stages (Table 1.1).

Stage	GTM	Description
IA	G ₁ T ₁ M ₀	Low grade Intracompartmental No metastases
IB	G ₁ T ₂ M ₀	Low grade Extracompartmental No metastases
IIA	G ₂ T ₁ M ₀	High grade Intracompartmental No metastases

Stage	GTM	Description
IIB	G ₂ T ₂ M ₀	High grade Extracompartmental No metastases
IIIA	G _{1/2} T ₁ M ₁	Any grade Intracompartmental With metastases
IIIB	G _{1/2} T ₂ M ₁	Any grade Extracompartmental With metastases

Grade system (G): Low grade (G₁) and high grade (G₂). High-grade lesions are intermediate between low-grade, well-differentiated tumors and high-grade, undifferentiated tumors.

Tumor size (T): The size of the tumor is determined by using specialized procedures, including radiography, tomography, nuclear studies, computed tomography (CT), and magnetic resonance imaging (MRI). Compartments are used to describe the tumor site. These compartments are usually easily defined based on fascial borders in the extremities. Of note, the skin and subcutaneous tissues are classified as a compartment, and the potential periosseous space between cortical bone and muscle is often considered a compartment as well. T₀ lesions are confined within the capsule and within its compartment of origin. T₁ tumors have extracapsular extension into the reactive zone around it, but both the tumor and the reactive zone are confined within the compartment of origin. T₂ lesions extend beyond the anatomic compartment of origin by direct extension or some other means (e.g., trauma, surgical seeding). Tumors that involve major neurovascular bundles are almost always classified as T₂ lesions.

Metastases (M): Both regional and distal metastases have ominous prognoses; therefore, the distinction is simply between no metastases (M₀) and the presence of metastases (M₁).

Table 1.1. Staging system of the Musculoskeletal Tumor Society (ENNEKING SYSTEM) (adapted from Frassica et al. 2008 [37])

The most recent edition of the AJCC system has become more popular among medical oncologists and many orthopaedic oncologists. A working knowledge of both systems is necessary for examinations. To use this system, one must know the grade, the size, the presence or absence of discontinuous tumor (skip metastases), and the absence or presence of systemic metastases. The various stages are shown in Table 1.2. One should remember the order of importance for the variables of the AJCC staging system: stage (takes into account all factors), presence of metastases, discontinuous tumour, grade, and size.

Stage	Tumour	Lymph Node	Metastases	Grade
IA	T1	N0	M0	G1 or G2
IB	T2	N0	M0	G1 or G2
IIA	T1	N0	M0	G3 or G4
IIB	T2	N0	M0	G3 or G4
III	T3	N0	M0	Any G
IVA	Any T	N0	M1a	Any G
IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

Tx = primary tumor cannot be assessed; T0 = no evidence of primary tumor; T1 = tumor 8 cm or less in greatest dimension; T2 = tumor more than 8 cm in greatest dimension; T3 = discontinuous tumors in the primary bone; Nx = regional lymph nodes not assessed; N0 = no regional lymph node metastases; N1 = regional lymph node metastasis; Mx = distant metastasis cannot be assessed; M0 = no distant metastasis; M1 = distant metastasis; M1a = lung; M1b = other distant sites; Gx = grade cannot be assessed; G1 = well differentiated (low grade); G2 = moderately differentiated (low grade); G3 = poorly differentiated (high grade); G4 = undifferentiated (high grade).

Table 1.2. American Joint Committee on Cancer Staging System for Primary Malignant Tumors of Bone for those tumors diagnosed on or after January 1, 2003 (adapted from Greene et al. 2002 [38])

Grading can be difficult and is based on nuclear anaplasia (degree of loss of structural differentiation), pleomorphism (variations in size and shape), and nuclear hyperchromasia (increased nuclear staining). Grading of tumours requires a morphologic range. Most grading systems are based on three grades: grade I, well differentiated; grade II, moderately differentiated; and grade III, poorly differentiated. The grade of the tumour most strongly correlates with the potential for metastasis: grade I (low grade), less than 10%; grade 2 (intermediate grade), 10-30%; and grade III (high grade), greater than 50%. Most malignant lesions are high grade (G2); low-grade malignant (G1) lesions are less common.

Patients with suspected Ewing's sarcoma should have diagnostic imaging at presentation which must include appropriate search and staging for metastases, which are detected in about 25% of patients (Table 1.3).

Investigation	Primary tumour site	Staging for metastases
Radiograph in two planes: whole bone with adjacent joints	+	At suspicious sites
MRI and/or CT: affected bone(s) and adjacent joints	+	At suspicious sites
Biopsy: material for histology and molecular biology	+	At suspicious sites
Thoracic CT (lung window)		+
Bone marrow biopsy and aspirates: microscopy (molecular biology still investigational)	+	
Whole body 99m-technetium bone scan	+	+
FDG-PET	+ ²	+ ²

Abbreviations: CT, computed tomography; FDG-PET, fluorine-18 fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; +, mandatory; +², indicated, if available.

Table 1.3. Staging investigations at diagnosis (adapted from Bernstein et al. 2006 [26])

Patients should be staged for both local and metastatic disease. Local disease is evaluated with a plain radiograph of the bone as well as MRI imaging of the site involved. The MRI is more sensitive than the CT scan in assessing soft tissue involvement and bone marrow spread. The MRI is repeated after several cycles of chemotherapy to assess the response to chemotherapy better and to help plan surgical treatment of the primary site.

Metastatic disease is evaluated at the time of presentation with chest radiographs and a chest CT, looking for pulmonary metastases. A bone scan is used to look for bone metastases. The lungs and bones are the most common sites for metastases in patients with Ewing's sarcoma though any organ can be affected (including pleura, lymph nodes, dura and/or meninges and central nervous system) and metastases frequently present at multiple site [39]. Microscopically detectable bone marrow metastases occur in <10% of patients and are associated with a poor prognosis [40]. As tumour cells may be focally distributed in bone marrow, bone marrow samples should be harvested from multiple sites, conventionally both posterior iliac crests. Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) has recently been proven to be a highly sensitive screening method for the detection of bone metastases in Ewing's sarcoma, although its exact role in the management of Ewing's sarcoma remains to be defined. In detecting bone metastases, FDG-PET may be even more sensitive than whole-body MRI scans [41].

All patients pre-chemotherapy should have routine haematological (full blood count, clotting studies) and biochemistry investigations including renal, bone and liver profile. Cardiac function is evaluated with an echocardiogram (some chemotherapy agents can cause cardiotoxicity) and finally lactate dehydrogenase levels are also measured because

elevated levels have been associated with a poor prognosis and metastatic disease in others [33].

1.9 Biopsy of Malignant Bone Tumours

A biopsy is intended to confirm the radiological diagnosis in patients with malignant bone tumours. The biopsy is done to confirm the initial diagnostic impression and to permit accurate grading of the lesion. Biopsy is generally performed after complete evaluation of the patient. Biopsy is best performed in a centre which specialises in the diagnosis and management of musculoskeletal tumours. This is mainly for the following reasons:

- a) additional imaging may be required prior to surgery
- b) a musculoskeletal pathologist should be available when the biopsy is taken for accurate interpretation of the material retrieved
- c) the quality of the biopsy, incision and technique may profoundly affect the treatment and prognosis of the patient. More specifically, a study by members of the Musculoskeletal Tumour Society have shown that errors, complications, and changes in the course and outcome were two to twelve times greater when the biopsy was done in a referring institution instead of in a treatment centre [42].

There are several surgical principles that the clinician must follow [37]:

- a) The orientation and location of the biopsy tract are critical. If the lesion proves to be malignant, the entire biopsy tract must be removed with the underlying lesion.

Transverse incisions should be avoided (Fig. 1.11).

- b) The surgeon must maintain meticulous haemostasis to prevent hematoma formation and subcutaneous haemorrhage. When possible, biopsies are done through muscles so that the muscle layer can be closed tightly. Haematoma may lead to contamination of local tissues and should be avoided. A compression dressing is routinely used on the extremities.
- c) Before biopsy, the surgeon should review the radiographs to plan the biopsy site. When possible, the soft tissue component rather than the bony component should be sampled.
- d) All biopsy samples should be submitted for bacteriologic analysis. Antibiotics should not be delivered until the cultures are obtained.
- e) Needle biopsy is an excellent method for achieving a tissue diagnosis and providing minimum tissue disruption. Careful correlation of the small tissue sample with the radiographs will often yield the correct diagnosis. When the nature of the lesion is obvious based on the radiographic features and when adequate tissue can be obtained with needle biopsy, the needle biopsy technique is safe to use. The pathologist must be experienced and comfortable with the small sample of tissue. When the diagnoses of needle biopsy and imaging studies are not concordant, an open biopsy should be done to establish the diagnosis. Open biopsy is often necessary in low-grade tumours and when the needle biopsy does not provide a definitive diagnosis.

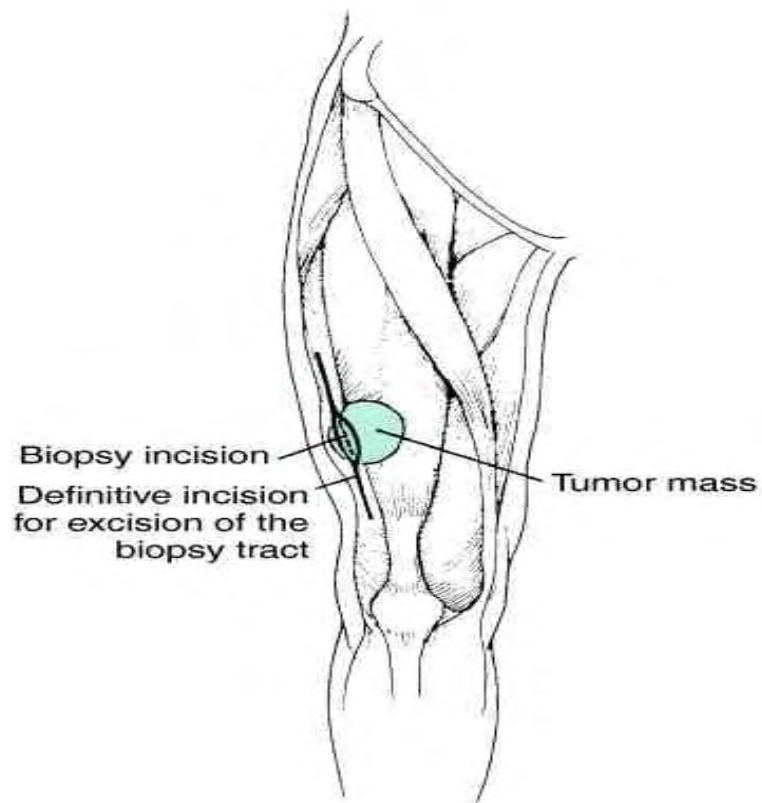


Figure 1.11. Lesion in the lateral aspect of the quadriceps mechanism. A short longitudinal incision is made over the lesion. Before the skin incision, a second incision line should be drawn to demonstrate how the biopsy tract can be removed at the time of the definitive surgery (adapted from Sim et al. 1994 [43])

1.9.1 Techniques of Biopsy

Biopsy of a suspected Ewing's sarcoma can be performed by open or closed technique.

Closed Biopsy

Closed biopsy can be achieved by fine needle aspiration (FNA) or core needle biopsy. Both techniques produce limited amount of tissue and therefore require an experienced pathologist [44]. The advantages include minimal risk of tumour spillage, fewer skin complications and it requires less time and cost [44,45]. However, sampling errors and insufficient biopsy occur up to 33% [45]. With increasing experience and the use of CT-guided biopsy, it is possible to reduce sampling error to less than 10% [46].

Open Biopsy

This method allows the surgeon to obtain relatively large amount of tissue which makes the diagnosis easier particularly for the inexperienced pathologist. The disadvantages include wound complications, haematoma, tumour spillage and in cases where the cortex is breached, pathological fractures may occur [47].

With increasing experience, it is likely that closed biopsy of musculoskeletal tumours will supplant open biopsy in most instances.

1.10 Treatment Principles

Modern treatment of patients diagnosed with Ewing's sarcoma of bone involves a multidisciplinary approach. Treatment involves the orthopaedic oncology surgeons, medical and clinical oncologists, histopathologists, specialist nursing staff, physiotherapists, psychologists, social workers and other supporting staff. Accurate diagnosis and full local and systemic staging are essential before any treatment is commenced. Systemic spread of the disease is controlled by aggressive multiagent chemotherapy. Local disease is controlled by surgery, radiotherapy or both. The treatment should be guided on an individual basis with the aim of providing the best therapeutic and functional outcome.

1.10.1 Chemotherapy

The discovery of effective chemotherapy has been one of the most dramatic advances in the management of patients with Ewing's sarcoma of bone over the last 20 years. Earlier treatment consisted of local radiation therapy or surgery alone but only 10% of the patients survived with the rest succumbing to local and systemic dissemination of the disease [48,49].

The first reports of drug treatment of Ewing's sarcoma stem from the 1960s. In 1964, the American National Cancer Institute and St. Jude Children Hospital started to study the effects of certain combination chemotherapy and reported improved results [50,51,52].

Following Hustu's et al [50] publication on the combination of cyclophosphamide, vincristine, and radiotherapy that resulted in sustained responses in five patients, the era of modern multimodality treatment of Ewing's sarcoma began.

In brief, in 1974, Rosen et al [53] from the Memorial Sloan-Kettering Cancer Centre published the first results of a trial of radiotherapy given with a four-drug regimen consisting of vincristine, actinomycin D, cyclophosphamide, and doxorubicin used in combination rather than sequentially (the VACD scheme), leading to long-term survival in 12 patients with Ewing's sarcoma.

The first North American randomised study (Intergroup Ewing's Sarcoma Study [IESS-I]; 1973–78) showed that VAC plus doxorubicin was better than VAC plus chest irradiation, which in turn was better than VAC alone for patients with localised, non-pelvic primary tumours [54]. In the second IESS study (IESS-II, 1978–82) higher doses of doxorubicin earlier in therapy improved on the IESS-I regimen (overall survival 77% vs 56%) [55]. The subsequent Children's Cancer Group-Paediatric Oncology Group (CCG-POG) cooperative study (INT-0091, 1988–92) showed that ifosfamide and etoposide (IE), alternating with the standard regimen of vincristine, doxorubicin, cyclophosphamide (VDC), and dactinomycin markedly improved both overall and event-free survival (69% vs 54%, and 72% vs 61%, respectively) for patients with localised tumours [56]. There was a marked decrease in local (rather than metastatic) relapse that led to the improvement in outcome. Most recently, a Children's Oncology Group (COG) study (AEWS0031, 2001-2005) compared VDC–IE treatment every 2 weeks with VDC–IE treatment every 3 weeks for patients with localised disease, with 14 cycles and equal cumulative doses in each group. Interval compression provided a 25% increase in dose intensity of all agents without an increase in toxicity. Overall and event-free survivals were both improved in the interval-compressed group (event-free survival 79% vs 70% at 4 years) [57]. Therefore, the regimen of alternating VDC–IE every 2 weeks has become standard for North American patients with Ewing's sarcoma.

A different approach evolved among the European cooperative groups, through independent single-group studies by the UK Children's Cancer Study Group (UKCCSG) and the German–Dutch–Swiss Cooperative Ewing's Sarcoma Studies (CESS). Both the CESS and UKCCSG adopted a chemotherapy design in which four drugs are given at once, and this evolved from VACA (vincristine–doxorubicin–cyclophosphamide– actinomycin), to VAIA (substituting ifosfamide for cyclophosphamide), to EVAIA (adding etoposide), to the current VIDE (omitting actinomycin). The only randomised controlled trial in this series, EICESS-92, found no difference between VACA and VAIA for standard risk patients with Ewing's sarcoma, and a slight advantage (although statistically insignificant) for EVAIA over VAIA in patients with high-risk localised or metastatic tumours [58]. The current Euro-EWING-99 study uses VIDE as initial chemotherapy for all patients. In a complex scheme, it compares VAC (vincristine-actinomycin-cyclophosphamide) with VAI as continuing chemotherapy for patients with good histological responses to VIDE, or small (<200 mL) tumours treated with radiation. For patients with poor histological responses, or large tumours treated with radiation or lung metastases, it compares VAI with busulfan–melphalan megatherapy [59]. Outcome data are not yet available from this on-going trial.

1.10.2 Radiotherapy

Despite surgical resection playing a more dominant role in recent years, radiation therapy is still an important modality in treating Ewing's sarcoma locally. This is especially true for anatomic sites where surgical resection is difficult, such as pelvis and the spine. In a recent analysis of 1,058 patients with localized Ewing's sarcoma treated in the EICESS trials, 266 patients had radiotherapy alone. Local or combined local and systemic failures in this

subgroup occurred in 26% of patients [60,61], which was worse than the recurrence rate following surgery with or without radiotherapy (4%-10%). Therefore, they recommended that when marginal or wide resection is possible, surgery should be performed. Definitive radiotherapy is indicated when only an intralesional resection is possible. In the EICESS trials, patients who had an intralesional resection followed by radiotherapy had the same local control rate as patients who had radiotherapy alone [60,61].

In order to control Ewing's sarcomas, a radiation dose above 40 Gy is necessary. In the St. Jude's Children's Research Hospital experience with the use of lower radiation doses, a high rate of local recurrence was observed [62]. A clear dose-response correlation at doses above 40 Gy has not yet been established. For definitive radiotherapy, doses between 55 Gy and 60 Gy, most frequently not exceeding 55.8 Gy, are usually given. When surgery precedes or follows radiotherapy, the doses range between 45 Gy and 55 Gy depending on the individual risk factors (i.e., resection margins and response) [26].

The risks of radiotherapy include radiation induced sarcoma, increased risk of pathological fracture and retarded growth potential in skeletally immature patients. The risk of secondary malignancy is high in patients who received doses of radiation greater than or equal to 60 Gy, with one study reporting a 40-fold increase risk at that dose [63]. Strong et al [64] estimated that the cumulative risk of developing secondary malignancy after 10 years is 35%. In a review from Mayo Clinic of 17 patients with Ewing's sarcoma of the proximal femur treated with radiotherapy, reported a pathological fracture rate of 65% [65]. Finally in order to avoid growth disturbances in skeletally immature patients is to shield the growth plate during radiation and to limit the radiation dose to 45 Gy [66].

1.11 Principles of Surgical Treatment for Local Control

The general philosophy is to give intense multiagent neoadjuvant chemotherapy which decreases the size of the primary tumour followed by wide *en bloc* excision [67]. The roll of *en bloc* excision of the primary tumour has expanded in an attempt to minimise the risk of local recurrence which is frequently chemotherapy resistant and leads to distant metastases [31]. Radiotherapy is added postoperatively if it is found that the postoperative margin is intralesional or marginal. In certain anatomic sites such as the pelvis or spine where *en bloc* excision is very difficult, radiotherapy may be used preoperatively in order to allow a closer margin of resection.

The principles of surgical management are:

- Complete excision of the tumour
- Preservation of function
- Limb preservation surgery and adequate reconstruction (if limb salvage surgery leads to an unsatisfactory orthopaedic result then amputation is warranted)
- Provision of a durable reconstruction
- Radical or wide excision margins as defined by Enneking [68] (Table 1.4 & Fig. 1.12)

Intralesional resection - Tumour opened during surgery, or surgical field contaminated, or microscopic or macroscopic residual disease.

Marginal resection - Tumour removed en bloc; however, resection through the pseudocapsule of the tumour; microscopic residual disease likely.

Wide resection - Tumour and its pseudocapsule removed en bloc, surrounded by healthy tissue, within the tumour bearing compartment.

Radical resection - The whole tumour-bearing compartment removed en bloc (e.g., above-the-knee amputation for a lower-leg tumour)

Table 1.4. Enneking classification of surgical intervention (adapted from Enneking et al. 1980 [68])

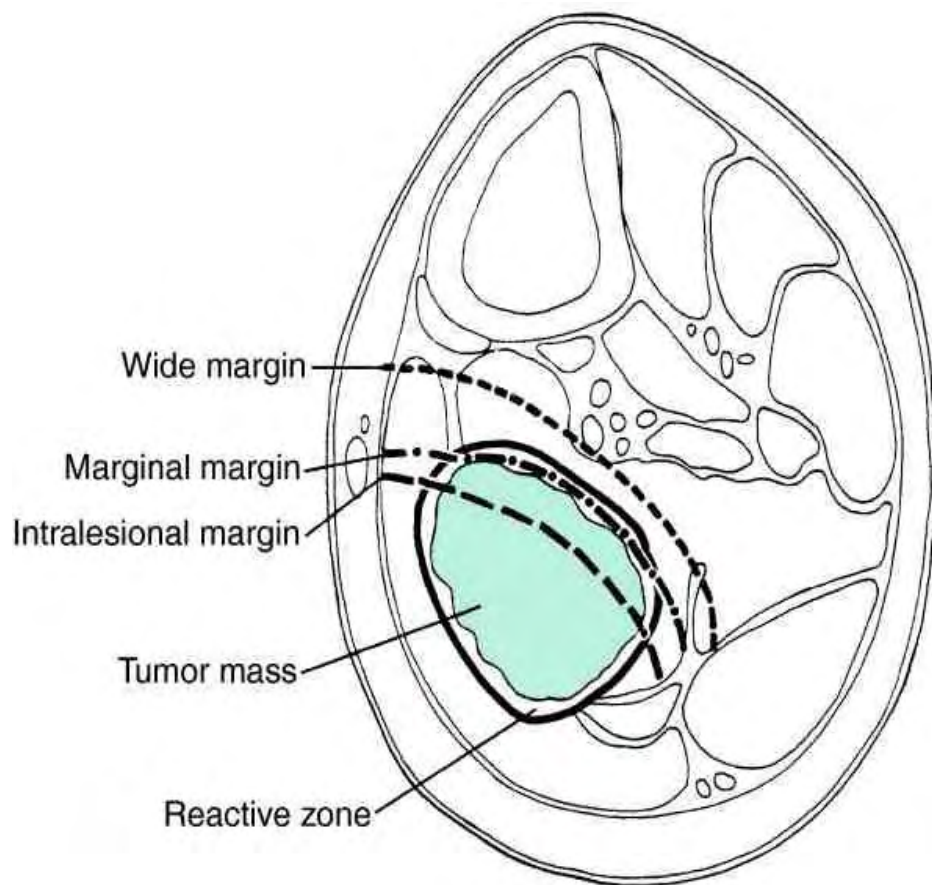


Figure 1.12. Types of surgical margins. An intralesional line of resection enters the substance of the tumour. A marginal line of resection travels through the reactive zone of the tumour. A wide surgical margin removes the tumour with a cuff of normal tissue (adapted from Sim et al. 1994 [43])

The surgical options include limb salvage surgery and amputations. The advent of chemotherapy induced tumour shrinkage and better implant design has resulted in more limb preservation procedures in the surgical management of patients with Ewing's sarcoma. The social, psychological and economical cost associated with amputations has made this a less favourable option whenever limb salvage is possible. The disease-free interval and overall survival of patients treated by limb salvage surgery are similar to those treated by amputations if adequate excision margins can be achieved [69,70]. The advantages of limb salvage surgery is the ability to maintain body image and preserve function, however the excision margins must not be compromised by an attempt to preserve the limb. The options for limb salvage surgery in patients with Ewing's sarcoma include:

- Simple excision without reconstruction
- Excision and reconstruction with allograft or autograft
- Excision and prostheses
- Rotationplasty

Simple excision is useful for cases where the tumours are located in expandable bones such as fibula. Autologous grafts are ideal but their limited sources compared to the large defects that are often encountered following excision of tumours limit their use. However, they are of great use in the reconstruction of supra-acetabular and periacetabular defects [71]. In certain instances the tumour contacting the bone can be sterilized and re-implanted with a good outcome [72].

Allografts allow reconstruction of ligaments, accurate matching of the graft to the defect and incorporation of the graft to the host bone. They are associated though with high incidence of infections, graft failure, non-union and fractures [73].

Custom made prostheses are very popular and allow early return of function but the drawbacks include implant loosening, infection and breakage. In children, the use of extensible prostheses allows maintenance of limb length [74].

Rotationplasty is used in the treatment of tumours around the knee joint which involves en bloc excision of the thigh and knee joint and the joint of the tibia to the upper femur with the foot pointing backwards. The advantages are no phantom pain and good functional results but some patients develop psychological disorders after treatment [75].

The final decision regarding surgical reconstruction techniques depends on the location and extent of the tumour and the preference of the surgeon and the patient.

1.12 Principles of Surgery for Pelvic Ewing's Sarcoma

The treatment of pelvic sarcomas is difficult in terms of local control because of the complexity of pelvic anatomy, which increases the difficulty of resection and reconstruction [76,77]. Before the 1970s, most tumours in the bony pelvis were surgically treated with hindquarter amputation. Currently, improved techniques for clinical staging, adjuvant treatments, evolutions in metallurgy, and development of new techniques in oncologic reconstruction make limb-salvage surgery and reconstruction at the pelvis possible as alternatives to hemipelvectomy and resection arthrodesis [78,79].

Major pelvic resections have been classified by the Musculoskeletal Tumor Society into 3 resection types: type I (iliac), type II (periacetabular), and type III (obturator) [80].

Resections involving the sacrum are type IV resections. Pelvic resections that include the femoral head have been designated as type H and are classified into 3 types: type H1 (femoral head), type H2 (peritrochanteric area), and type H3 (subtrochanteric area) (Figure 1.13) [80].

Major spinopelvic resections have been classified into 4 types: type 1 (total sacrectomy), type 2 (hemisacrectomy), and type 3 and 4 (partial and total sacrectomies in conjunction with external hemipelvectomy) [81].



Figure 1.13. Types of pelvic and proximal femoral resections (adapted from Mavrogenis et al. 2012 [82])

The specific type of pelvic resection to be performed depends on the area involved and the extent of the tumour. The following alternatives are available for reconstruction of the pelvis or reattachment of the extremity following pelvic resections:

- flail hip
- pseudarthrosis
- arthrodesis
- megaprosthesis, or allograft reconstruction
- excision, extracorporeal irradiation and re-implantation

1.12.1 Reconstructions for Type I and III Resections

The bony defect in type I resections can be reconstructed with autograft fibula, cortical or pelvic allograft, bone cement or excision, extracorporeal irradiation and re-implantation (Fig 1.14). The advantages of replacing the resected bone are pelvic stability and maintenance of limb length. The disadvantages are the increased risks of infection and failure of the reconstruction [83]. No formal reconstruction is required for type III resections.

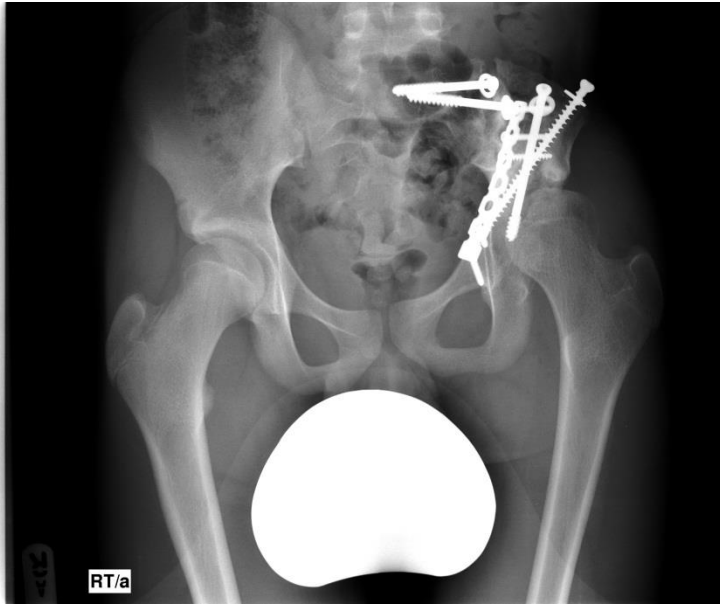


Figure 1.14. AP radiograph of the pelvis showing a type I resection, extracorporeal irradiation and re-implantation

1.12.2 Reconstructions for Type II Resections

Defects can be reconstructed with a pseudarthrosis (Fig.1.15) or arthrodesis allografts, iliac allograft composites with a hip arthroplasty and custom made metallic pelvic prostheses (Fig. 1.16) [84,85]. Each reconstruction option has its own advantages and disadvantages, and most studies report a high failure rate; it is generally best to do the easiest reconstruction possible.

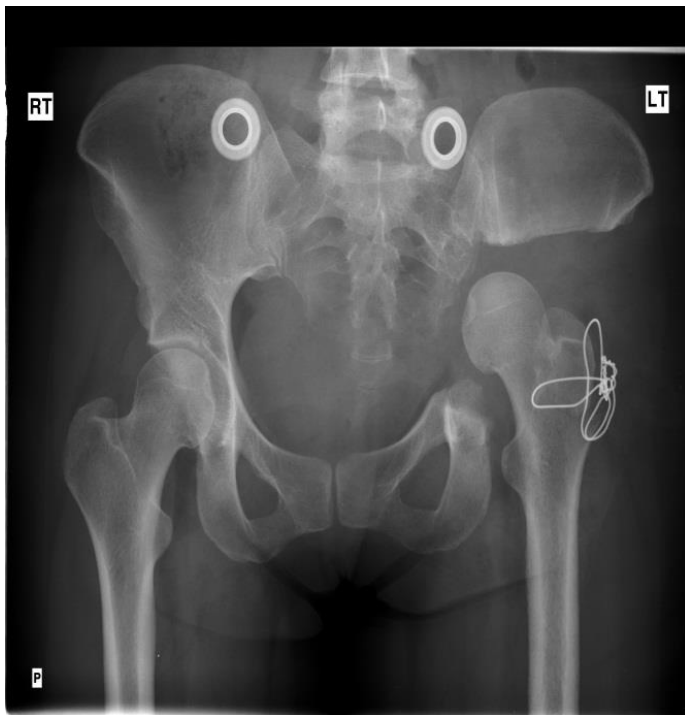


Figure 1.15. AP radiograph of the pelvis showing a type II resection and a flail hip.

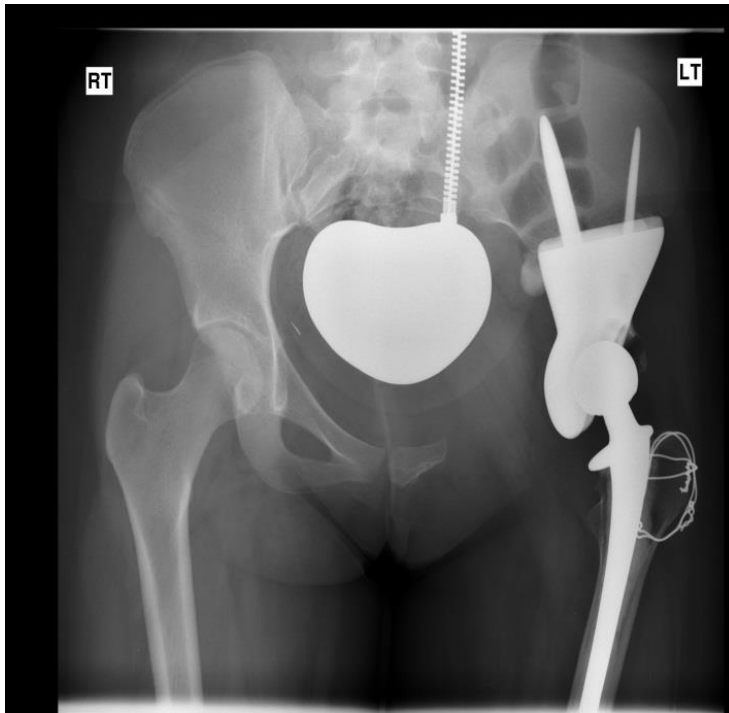


Figure 1.16. AP radiograph of the pelvis showing a type II resection and an endoprosthetic pelvic replacement

Pseudarthrosis and arthrodesis involve establishment of a fibrous or solid union, respectively, between the proximal femur and the remaining pelvis (iliofemoral, ischiofemoral, or sacrofemoral) using a plate or similar implant, cables, cerclage wires, or screws [86,87]. Disadvantages of arthrodesis include loss of the functioning hip joint, which is not recommended in younger patients, shortening of the leg, lack of mobility, and long consolidation times, which means longer periods of rehabilitation and the use of gait support [88,89].

Endoprosthetic pelvic replacements are recommended when adequate ilium is present. They are expensive but provide good cosmetic result and limb-length equality. The acetabular component should be symmetric with the contralateral side in height, lateral distance, and orientation [90]. However, the eccentric position of the new hip centre reduces the range of motion, and loosening, lateral shift, or dislocation of the prosthesis is common [91].

1.12.3 Reconstructions for Type IV Resections

Sacral resections below S1 are structurally stable and very rarely require reconstruction. Stability is preserved because the common S2-S3 partial sacrectomy does not disrupt the sacroiliac articulations and lumbopelvic structure. In the contrary, sacral tumours at the S1 level alter the biomechanics at the lumbosacral junction, and therefore may require stabilization. [92,93]. Spinopelvic stabilization after major spinopelvic resections has been attempted using various constructs with combinations of screws, wires, bars, and plates but the current instrumentation used in spinopelvic reconstruction is the pedicle screw–rod construct with a strut graft [94].

1.12.4 Hemipelvectomies

Hemipelvectomies include resection of the hemipelvis with (external hemipelvectomy) or without amputation of the limb (internal hemipelvectomy) [83]. When someone decides whether to proceed to an internal rather than an external hemipelvectomy, the internal hemipelvectomy should at least lead to the same tumour-free margins and provide a superior functional outcome with acceptable morbidity [70,95]. However, the incidence of complications is lower and the patient recovers more quickly after an external hemipelvectomy. External hemipelvectomy is recommended in recurrent sarcomas when there is sacral involvement and extension of the tumour across the sacroiliac joint and into the sciatic notch [83]. This type of surgery though results in a large defect with subsequent destabilization of the spinopelvic segment and therefore, reconstruction is necessary for spinopelvic stability and function [96].

1.13 Treatment of Metastases and Local Recurrence

About 25% of patients with Ewing's sarcoma present with metastases at the time of diagnosis [26] with a disappointing hope of cure. Survival data reported by Cangir et al [97] from the IESS-I and IESS-II studies showed that the 5 year rate was 30% at best with bone metastases did worse than lung metastases. First-line therapy for metastatic Ewing's sarcoma is similar to that for localized disease and utilizes the same chemotherapy backbone with adequate local control to both primary and metastatic sites. While this strategy often results in complete or partial responses, overall survival rates remain dismal at 20% [98]. Attempts to improve outcomes through changes in chemotherapy regimens have been largely unsuccessful. Currently, upfront whole-lung irradiation is often used in patients with lung metastases, regardless of radiographic response following neoadjuvant chemotherapy. The strongest evidence for this comes from the European Intergroup Cooperative Ewing Sarcoma Study (EICES) group, which reported an event free survival rate of 38% (versus 27% in non-irradiated patients) using 15 to 18Gy whole lung irradiation in patients with isolated lung metastases [99]. Unlike osteosarcoma, there is little role for pulmonary metastasectomy in these patients. Finally, the role for high-dose myeloablative chemotherapy with autologous stem cell rescue in patients with metastatic Ewing's sarcoma at initial diagnosis remains controversial due to the lack of prospective, randomized trials [100].

Despite the superior multimodal therapeutic regimes, 30%-40% of patients still experience recurrent disease either locally, distantly, or combined, and have a dismal prognosis. Patients with primary metastatic disease have a higher risk for relapse than those with localized disease [101]. The likelihood of long-term survival after recurrence is less than

20%-25% [102,103]. There is no established treatment regimen for these patients. Salvage treatment includes multiagent chemotherapy, local control measures with radiotherapy and surgery, or a combination of these as appropriate. Patients with local recurrence are usually treated with surgery and further chemotherapy [104]. Recurrent distant disease involving the lungs or bones occurs in more than 50% of patients presenting with local recurrence and mandates further chemotherapy [40,99,105,106,107]. Patients with a single pulmonary nodule appear to benefit from additional whole-lung irradiation and have better outcomes, especially if the recurrence is late, longer than 2 years following the primary diagnosis [99].

1.14 Prognostic Factors in Ewing's Sarcoma

Many studies have provided an insight into some factors that affect the outcome of Ewing's sarcoma. These factors allow us to categorise patients to different risk groups. The treatment of the patients may then be tailored according to risk and different protocols may be compared more meaningfully. The following are considered as prognostic factors in Ewing's sarcoma:

1.14.1 Metastases

The presence of metastases at diagnosis is an ominous sign in patients suffering from Ewing's sarcoma. Data from IESS-I and IESS-II showed a 5-year survival of over 60% in patients with localised disease compared to 30% in those with metastases at diagnosis [55,97]. Those with isolated pulmonary metastases have a slightly better outcome (approximately 30% survive) than those with bone or bone marrow metastases at initial diagnosis (20% or less) [101,108].

1.14.2 Anatomical site of tumour

Patients with Ewing's sarcoma of distal sites, such as bones of the hands and feet, have a better prognosis than patients with central lesions, such as those of the pelvis or sacrum. Bacci et al [109] in a review of 144 patients with localised Ewing's sarcoma found a survival rate of 23% for pelvic tumours and 46% for other locations at a minimum follow up of 5 years. The IESS-I study reported 5-year survival of 57% for non-pelvic tumours compared to 34% for pelvic tumours. These studies however did not take into account the tumour volume and the different forms of local therapy. But Sailer et al [110] in a retrospective

multivariate analysis of 46 patients with Ewing sarcoma found non-pelvic sites to be an important prognostic factor irrespective of whether the volume was less or greater than 500mls.

1.14.3 Tumour volume

The CESS 81 studied 93 patients and identified the survival of patients with small volume tumour (<100ml) to be better than those with large volume tumours (≥100ml). In the study, the 5-year survival of small volume tumours was 65% compared to 32% for large volume tumours and was independent of site [111].

1.14.4 Response to chemotherapy

Response to chemotherapy can be assessed by measuring the degree of clinical regression of tumour volume or chemotherapy induced necrosis. Necrosis in a malignant bone tumour provides only an indirect measure of histologic response to chemotherapy. Salzer-Kuntschik et al [112] published a morphological system of necrosis in osteosarcoma and correlated this to necrosis. The Cooperative European Ewing Sarcoma trial subsequently graded those in grades 1 to 3 as having less than 90% necrosis with grades 4-6 having 90% or more necrosis. These were termed 'poor responders' and 'good responders' respectively and analysis showed that 79% of the good responders were free of disease at 3 years compared to 31% of the poor responders [107]. Furthermore, Picci et al [113] in a review of 68 patients with non-metastatic Ewing's sarcoma of the extremities, showed that patients who demonstrated grade III response (no identifiable viable tumour nodules present) had

improved 5-year disease-free survival rates as compared with patients with grade II (microscopic nodes present) and grade I responses (macroscopic nodules present).

1.14.5 Age

The IESS-I study of 342 patients found a more favourable prognosis in patients younger than 10 years [54]. But Wilkins et al [33] and Bacci et al [109], after reviewing 140 and 144 patients respectively found age and sex to have no prognostic value.

1.14.6 Haematological and Biochemical parameters

Raised erythrocyte sedimentation rate, white cell count and systemic symptoms have been implicated as prognostic factors in Ewing's sarcoma. Hayes et al [114] and Lichtestein & Jaffree [115] found increased leucocyte count to be associated with fever and poorer prognosis. Wilkins et al [33] found erythrocyte sedimentation rate of greater than 33mm/hr to be associated with a poor outcome. Furthermore, in a study by Bacci et al [116] of 618 patients with Ewing's sarcoma of the extremities, the authors found that elevated serum lactic dehydrogenase levels to be associated with poor prognosis and metastatic disease. These parameters are non-specific and may indicate the presence of microscopic systemic dissemination of the tumour, which are not detectable by radiological imaging scans because of their small sizes.

Chapter 2

Aims of the present study

2.1 Aims

The present study is a retrospective review of a prospective series of patients with pelvic Ewing's sarcoma (EWS) treated at a single centre (Department of Orthopaedic Oncology, Royal Orthopaedic Hospital, Birmingham, UK). The period of the study included all patients which were referred to our centre between 1977 and 2009.

The main aims of this study were as follows:

1. To determine the overall survival and recurrence free survival of patients with non-metastatic pelvic EWS
2. To identify possible prognostic factors which may influence the prognosis and management of patients with non-metastatic pelvic EWS

2.2 Relevance of the present study to clinical practice

The importance of the present study to clinical practice lies in the fact that it may allow the grouping of patients with Ewing's sarcoma of the pelvis according to risk factors and prognosis. This will provide a rationale for the determination of the treatment options according to expected course of the disease and prognosis. Currently, treatment of patients with pelvic EWS remains controversial. Treatment recommendations based on the available literature are limited by selection bias, small study size and mixed results. This study contains one of the largest numbers worldwide of patients with pelvic EWS treated at a single institution by the same team of surgeons, radiotherapists and oncologists. Therefore, this grants a uniformity of treatment, especially as regards local control. We anticipate this study to further update the literature regarding management of patients with pelvic EWS.

Chapter 3

Oncologic Outcomes and Prognostic Factors of Non-Metastatic Ewing's Sarcoma of the Pelvis

3.1 Introduction

Ewing's sarcoma is a poorly differentiated, malignant, small round cell tumour that can occur in the bone or soft tissues [6]. It is the second most common primary malignant bone tumour of children and the fourth most common malignant tumour of bone overall [27].

They most frequently occur in the long bones and pelvis. In a review of the Mayo clinic, 59.6% of the tumours occurred in the lower extremities and the pelvic girdle with the pelvis being the most common bone involved (24.7%) followed by the femur (21.4%), the humerus (9.1%) and the tibia (8.1%) [15]. Prior to the introduction of effective chemotherapy, more than 90% of patients died with disseminated disease [7]. Following the development of effective multiagent chemotherapy over the past 20 years, the 5-year survival has increased to about 70% [55,117,118,119].

Despite this, patients with Ewing's sarcoma of the pelvis still have a poor prognosis, significantly worse than that of tumors located outside the pelvis [120,121]. This is probably due to the difficulty of achieving local control in the pelvis [118] and the distant relapses occurring in many patients [122]. Pelvic tumours also tend to present larger, which further connotes a poor prognosis [62,118].

Ewing's sarcoma has been traditionally treated with chemotherapy and radiotherapy, and surgery also plays an important role. There has never been a randomized trial of surgery versus RT for local control for pelvic lesions, and this is unlikely to change. These analyses are subject to bias because of the patient characteristics that led to selection of a particular modality, such as location within pelvis, tumour size, response to chemotherapy and surgical resectability, which are also related to risk for subsequent disease progression.

Many studies fail to reach statistical significance but show a trend favouring surgery in pelvic lesions [120,123,124,125].

The aim of our study is to retrospectively review a prospectively registered case series of patients with non-metastatic pelvic EWS, to determine the overall and recurrence free survival, to assess the influence of type of treatment on survival and to identify possible prognostic factors.

3.2 Patients and Methods

One hundred forty six patients were referred to our unit between 1977 and 2009 (Table 3.1). Forty one patients presented with lung and/or bone metastases and 14 patients were referred for an opinion without follow up data available. There were 6 pelvic soft tissue Ewing's tumours. Thus, 85 patients with non-metastatic skeletal pelvic EWS were eligible for evaluation of possible prognostic factors at diagnosis.

Of the 85 patients, 45 were male and 40 female with a mean age of 18 years (range, 5 – 60). The mean follow up time was 65.8 months (range, 5-343). The mean tumour volume was 435 mL (range, 2.5-2593). According to Enneking classification the tumour site was as follows: 44 (P1-iliac bone); 4 (P2-periacetabulum); 20 (P3-pubic bone); 5 (P4-hemisacrum); 4 (P23-peri-acetabulum & pubic); 7 (P14-sacroiliac); 1 (P123-hemipelvis).

The 85 patients with data available for evaluation (Table 3.2), were divided into three groups according to the local treatment received: Group 1: radiotherapy-chemotherapy (54 patients); Group 2: surgery-chemotherapy (21 patients) and Group 3: radiotherapy-surgery-chemotherapy (10 patients).

Sixteen patients underwent limb-sparing surgery, 10 patients had an endoprosthesis replacement and in 5 patients data was not available.

All patients received neo adjuvant and adjuvant chemotherapy as per the existing national protocol and reflected the most up to date chemotherapeutic regimens.

Local treatment consisted of radiotherapy only, surgery only and surgery followed by radiotherapy. Surgical margins were classified according to Enneking et al [126] as intralesional, marginal, wide and radical. All resected specimens had a histological assessment of the effectiveness of chemotherapy and surgical margins. More than 90% necrosis was classified as good response. Radiotherapy was added to surgery for close margins or poor necrosis.

Measurement of the volume of the tumour was independent and blind, without any knowledge of the outcome of the patients and was performed by the first author. Assessment of the intra- and extra osseous component for each patient was made from the extension of the tumour in the longitudinal, lateral and anteroposterior planes. The calculations were as recommended by the CESS depending on whether the soft-tissue component of the tumour was large or discrete [111]. The CT or MRI scans taken before biopsy, were used to measure the volume of the tumour (Fig. 3.1).

Evaluation included history, clinical examination, routine haematological studies, immunohistochemistry tests and bone marrow aspiration/biopsy. All patients had histopathological diagnosis of Ewing's tumour proven and confirmed by at least two pathologists. Radiological assessment used included plain radiographs of pelvis and chest, bone scan (Tc MDP), CT of chest and pelvis and MRI of the pelvis. Systemic and local control

of the disease was monitored by routine clinical examination, and appropriate radiographic studies. These tests were carried out every 3 months for the first 2 years, every 6 months for the following 2 years and yearly thereafter for a total of 10 years.

Statistical analysis

Overall survival and recurrence free survival curves were estimated according to the Kaplan–Meier method. The logistic regression model was used to analyze possible factors influencing prognosis. The results of the logistic regression analyses were expressed as odds ratio (OR) and p values of less than 0.05 were considered to be statistically significant. All statistical analyses were carried out using the IBM SPSS 20 package (Armonk, New York, USA).

Gender	Age at Diagnosis	Site of Tumour	Mets at Diagnosis	Treatment	Margins	Histologic Response	Tumour Volume (cc)	Time Alive (months)	Time to LR	Time to Mets	Status
F	15	sacro-iliac	None	ct + rt				13	12	13	DOD
F	13	iliac crest	None	ct + rt			493.92	158	0	0	NED
F	13	pubis	None	ct + surgery	W	Poor		35	0	0	DOD
M	18	ilium	Lung	ct + rt			1323	23	0	0	DOD
F	26		None	ct + surgery + rt	I		158.02	185	0	0	NED
M	13	ilium	Lung	ct + rt				23	0	0	DOD
F	6	ilium	None	ct + rt				154	0	0	NED
M	10	pubis	None	ct + surgery	W	Good	9.08	157	0	0	NED
M	19	ilium	None	ct + rt				54	0	0	DOD
M	19	ilium	Lung	ct + rt				24	0	18	DOD
M	13	ilium	None	ct + rt				19	0	13	DOD
F	16	pubic ramus	None	ct + surgery	W			187	0	0	NED
F	32	pubis	Lung	ct + surgery	W	Good		192	0	21	DOD
F	10	ilium	None	ct				12	9	0	DOD
M	24	ilium	None	ct + rt			308.7	219	0	0	NED
M	8	ilium	None	ct + surgery	W		411.6	222	0	0	NED
M	31	ilium	None	ct				7	0	0	DOD
M	15	ilium	None	ct + rt				16	0	14	DOD
F	20	sacrum/ coccyx	None	ct + rt				22	16	15	DOD
F	18	paraspinal muscles	None	ct + surgery	W			14	0	11	DOD
M	6	ilium	None	ct				20	0	0	DOD
F	52	ilium	None	ct + rt				13	0	0	DOD
M	9	ilium	None	ct + rt			323.4	213	0	0	NED
M	36	ilium	None	ct + rt			238.88	206	0	0	DOD
F	15	iliac crest	None	ct + rt			452.76	242	0	0	NED
F	16	ilium	None	ct + rt			646.8	240	0	0	NED
M	13	ilium	None	ct + surgery	M	Good		257	0	0	NED
F	27	ilium	None	ct + rt				55	0	8	AWD
M	20	ilium	Lung	ct + surgery	W	Good	1997	59	0	0	NED
F	15	ileum/acetabulum/femur	Bone	ct + rt					0	0	NED
M	34	ilium	None	ct				5	0	0	DOD
M	8	ilium	None	ct + surgery + rt	W	Good	205.8	58	0	0	NED
M	26	ilium	Lung	ct + rt				13	0	0	DOD
M		hemi pelvis	None						0	0	NED
F	14	ilium	None	ct + rt			22.05		0	0	NED
M	24	pubic ramus	None	ct + surgery	W	Good	10.89	62	0	0	NED
F	13	ilium	Bone	ct + rt			376.32	6	0	0	DOD
F	11	pubic ramus	None	ct + surgery + rt	M	Poor	26.46	21	0	14	DOD

M	24	pubis	Lung	ct + surgery + rt	W	Good	898.56	38	24	0	DOD
F	16	ilium	None	ct + rt			1102.5	30	0	18	DOD
M	12	pubis/ischium/acetabulum	Multiple	ct			1234.8	9	0	0	DOD
F	39	sacrum/ilium	None	ct + rt					0	0	NED
F	11	sacrum	None	ct + surgery		Good			0	0	NED
M	30	ramus	Lung	ct					0	0	DOD
M	24	sacrum	None	ct				3	0	0	DOD
F	8	hemi pelvis	Bone	ct + rt			291.06	21	0	0	DOD
F	21	ilium	None	ct + rt				25	0	22	DOD
M	17	sciatic notch	None	ct + surgery	W			10	0	0	DOD
M	30	iliac fossa	None	ct + surgery + rt	M	Good	352.8	30	15	15	DOD
F	10	ilium	Lung	ct + rt			88.2	37	0	15	DOD
F	13	pubic ramus	None	ct + surgery	W	Good	288.12	75	0	51	AWD
M	19	ilium	Bone + Lung	ct + rt			1852.2	32	0	0	DOD
M	16	sacrum	Lung	ct + rt			452.76	77	0	0	NED
F	2	ilium	Lung	ct + rt			588	12	0	4	DOD
F	18	pubic ramus	Lung + Bone	ct + rt					0	0	DOD
F	36	ilium	None	ct + rt			477.75	25	0	20	DOD
M		ilium	None	ct + rt					0	0	NED
F	16	ischium	None	ct + rt			588	30	19	19	DOD
F	9	iliac crest	Lung	ct + rt			367.5	11	0	11	DOD
F	19	ilium/sacrum	None	ct + rt				12	0	12	DOD
M	15	ilium	None	ct + rt			88.2	20	20	20	DOD
F	17	ilium	None	ct + rt			1203.93	18	17	18	DOD
F	23	ilium	None	ct + rt				338	0	0	NED
M	22	pubic ramus	Lung	ct + rt			2205	8	0	0	DOD
F	16	ilium	Lung	ct + rt			1543.5	16	0	0	DOD
F	23	acetabulum/pubic ramus	None	ct + rt			83.2	111	0	0	NED
M	25	ilium	None	ct + rt			220.5	14	0	0	DOD
M	21	ilium	None	ct + rt			776.16	16	0	11	DOD
M	16	ilium	None	ct + rt			572	24	0	16	DOD
M	19	sacrum/ileum	None	ct + rt				12	0	0	DOD
F	15	pubis	None	ct + surgery + rt	I	Good	152.88	110	0	78	AWD
M	16	periacetabulum	None	ct + rt			327.6	5	0	2	DOD
F	17	ilium	None	ct + rt			212.16	21	19	0	DOD
M	10	ilium	Bone	ct + rt				7	0	0	DOD
F	14	ilium	None	ct + rt			1146.6	26	20	21	DOD
F	12	ilium	None	ct + rt			514.5	118	0	0	NED
M	20	ilium	None	ct + rt			898.56	111	0	0	NED
F	16	ilium	Lung	ct + rt			463.05	12	0	8	DOD
M	10	ileum	None	ct + rt			220.78	15	13	0	DOD
M	12	psoas	None	ct + rt			277.83	61	0	0	NED
M	15	ilium	None	ct + surgery	M	Poor	780	63	42	42	DOD
F	49	ischium	Lung	ct + rt			128.63	30	0	0	DOD

M	60	sacroiliac	None	ct + rt		183.75	87	0	0	DOD	
F	19	ischium	None	ct + rt		764.4	66	0	49	DOD	
M	18	pubis	None	ct + rt			343	0	0	NED	
M	14	ilium	Lung	ct + rt			22	19	19	DOD	
F	25	ilium	Bone	ct + rt			16	13	12	DOD	
M	9	ilium	Lung	ct + rt			21	15	14	DOD	
F	17	pubis	None	ct + surgery + rt	W	Poor	25	15	14	DOD	
F	27	ilium	None	ct + surgery	W	Poor	40	20	35	DOD	
M	19	ilium	None	ct + surgery		Poor	13	0	10	DOD	
M	26	ischium	None	ct + rt			14	0	0	DOD	
F	18	ischium	None	ct + surgery	W		9	0	9	DOD	
M	19	pubis	None	ct + rt			12	0	8	DOD	
M	30	ilium	None	ct				0	0	DOD	
F	5	pubis	None	ct + surgery + rt	I		88.2	196	0	0	NED
F	21	ilium	None	ct + surgery	W	Poor	67	0	44	DOD	
F	20	ilium	Lung	ct + surgery + rt	M	Good	34	0	15	DOD	
M	13	pubis	None	ct + surgery	W	Good	295.15	16	13	14	DOD
M	19	ilium	Lung	ct + rt			22	0	0	DOD	
M	19	ilium	None	ct + rt			11	0	2	DOD	
M	10	ilium	None	ct + surgery + rt	I	Poor	58.8	21	19	0	DOD
M	17	pubis	None	ct + surgery	M	Poor	351	33	20	20	DOD
F	24	ilium	Lung	ct + rt			17	0	0	DOD	
F	39	acetabulum	None	ct + rt			14	10	10	DOD	
M	11	iliac crest	None	ct + surgery	W	Good	42	0	25	DOD	
F	16	pubis	None	ct + rt			9	4	7	DOD	
M	17	acetabulum	None	ct + rt			20	0	18	DOD	
F	12	ilium/sacrum	None	ct + rt			20	16	20	DOD	
F	20	ischium	Lung	ct + rt			11	0	0	DOD	
M	13	pubis/ischium	None	ct + surgery	M	Good	67	0	46	DOD	
M	16	acetabulum/ischium/pubis	None	ct + surgery	W	Good	46.31	33	0	0	NED
M	17	sacro iliac notch	None	ct + rt				0	0	NED	
F	24	ilium	None	ct + rt			735	49	49	0	AWD
F	15	ilium/sacrum	None	ct + rt				0	0	NED	
M	15	iliac crest	Bone	ct + rt			793.8	12	0	0	NED
F	18	ilium/ischium	Lung	ct + rt			1433.25	21	0	10	DOD
M	16	pubic ramus/acetabulum	None	ct + surgery + rt	W	Good	235.2	15	0	13	DOD
M	14	iliac wing	None	ct + rt			376.32	23	0	0	NED
M	7	sacrum	None	ct + rt				0	0	NED	
F	30	acetabulum/pubis	Lung	ct + rt			705.6	9	0	0	DOD
F	10	ilium	None	ct + surgery	W	Good	11.76	16	0	0	NED
M	13	acetabulum	None	ct + rt				0	0	NED	
M	27	ilium	Lung	ct + rt			374	6	0	0	DOD

F	13	ilium	Lung	ct + rt			546	28	0	0	NED
M	29	ilium	None	ct + surgery + rt	W	Poor	2593.08	10	0	10	DOD
M	13	ilium	Bone	ct + rt				6	0	0	DOD
F	11	ischium	Lung	ct + surgery	W	Good	17.79	23	0	0	NED
F	11	ilium	None	ct					0	0	NED
M	25	ilium	None	ct + rt			735	14	0	8	DOD
M	8	pubis acetabulum	None	ct + surgery	W	Good	2.48	8	0	0	NED
M	13	ilium	Lung	ct + rt				17	0	0	NED
M	21		None	ct + surgery	I	Poor	1142.99	13	13	13	DOD
M	21	pubic ramus	None	ct + rt				24	0	12	AWD
M	15	sacrum	None	ct + rt			654.88	19	0	0	NED
M	13	acetabulum/pubis	None	ct					0	0	NED
M	36	psoas	None	ct + surgery			659.3	16	0	0	DOD
M	13	sacrum	None	ct + rt				22	20	0	AWD
F	13	pubis/ilium	None	ct + surgery + rt	W	Poor	52.41	11	10	10	DOD
M	24	pelvis/bilateral femur	Bone	ct + rt					0	0	NED
M	24	ilium	None	ct + rt			721.18	11	0	0	NED
M	8	ilium	Lung	ct + surgery	W	Good	514.8	5	0	0	NED
F	13	ilium/acetabulum/hip	Bone	ct + rt			1070.1	5	0	0	NED
F	15	iliac crest/sacrum	None	ct + rt			267.23		0	0	NED
M	44		None	ct + surgery + rt	M	Poor	780	10	0	0	NED
F	14	pubic ramus	Bone	ct + rt			844.5		0	0	NED

M: male; F: female; Mets: metastases; LR: local recurrence; ct: chemotherapy; rt: radiotherapy; W: wide; M: marginal; I: intralesional; DOD: died of disease; NED: no evidence of disease; AWD: alive with disease
(Blank spaces means that data was unavailable)

Table 3.1 Characteristics of the 146 patients with Pelvic EWS

Gender	Number of cases
Male	45
Female	40
Site (Enneking classification)	
P1	44
P2	4
P3	20
P4	5
P14	7
P23	4
P123	1
Tumour volume ^a	
<100ml	12
≥100ml	37
Local treatment	
Surgery	31
No surgery	54
Histologic response ^b	
Good	16
Poor	11

Surgical margin ^c	
Intralesional	3
Marginal	6
Wide	20
Radical	0
Local recurrence	
Yes	21
No	64
Metastases	
Yes	42
No	43

^aThirty six cases missing for tumour volume

^bFour cases missing for histologic response

^cTwo cases missing for surgical margins

Table 3.2 Characteristics of the 85 patients with non-metastatic Pelvic EWS

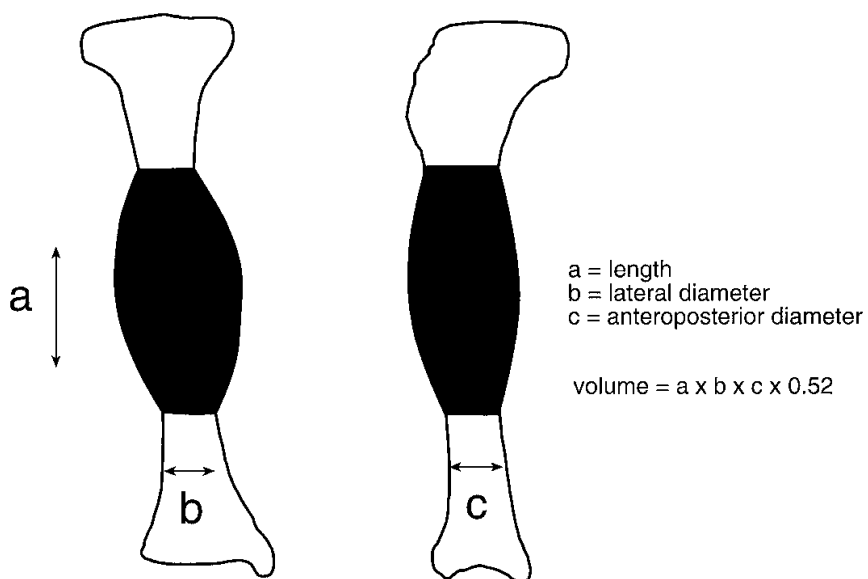
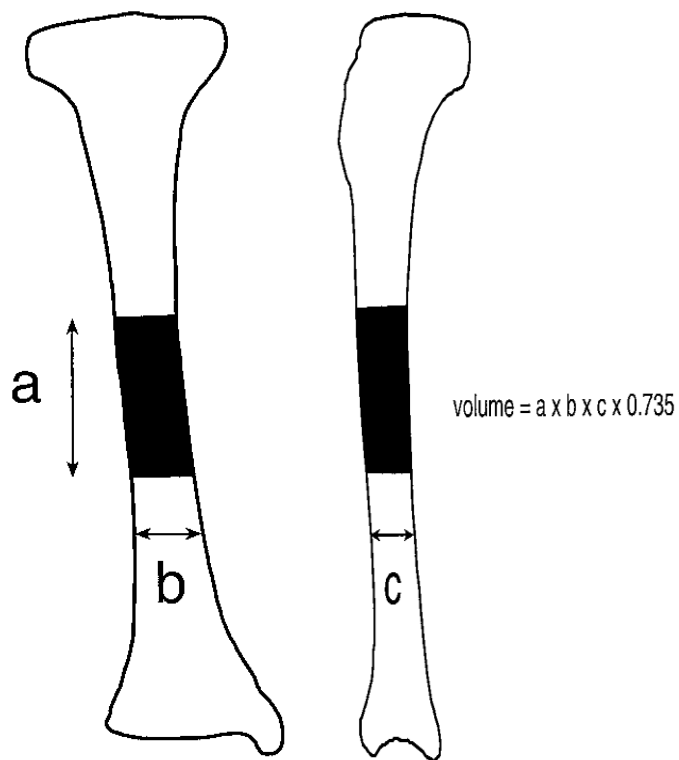


Figure 3.1. Diagram of the measurement of the volume of tumours with a) a discrete soft-tissue component and b) a large soft-tissue component

3.3 Results

Fifty one died of the disease, 6 are alive with the disease, 20 are disease free and in 8 no relevant data was available. The 5-year survival for all patients was 40.7%, decreased to 36.2% at 10 years (Fig.3.2). In our series, the 5-year survival of the patients who had surgical resection was 44.7% and at 10 years 31.3%.

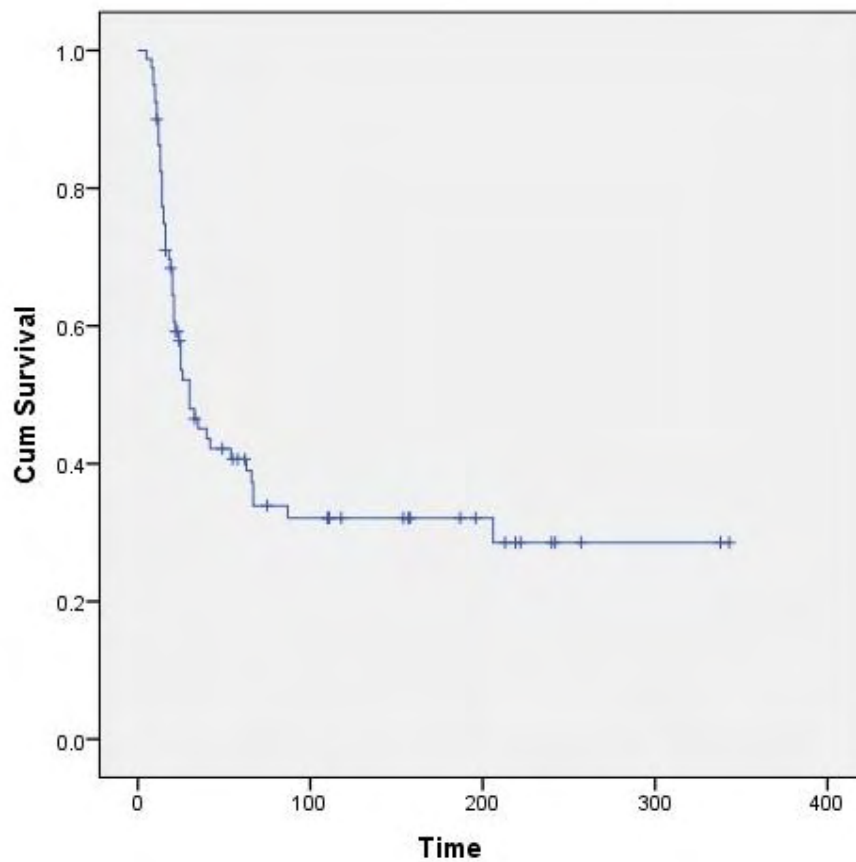


Figure 3.2 Kaplan-Meier survival curve for all patients

In patients free of local and distant recurrences the 5-year survival was 74% and the 10-year survival 70%. The 5-year local recurrence free survival was 51.8% and at 10 years it was 42.7%.

Regarding overall survival in terms of treatment group, there was a trend for improved survival in the group of chemotherapy and surgery but it was not statistically significant (OR: 0.87, 95% CI 0.27-1.75, $p = 0.75$) (Fig. 3.3).

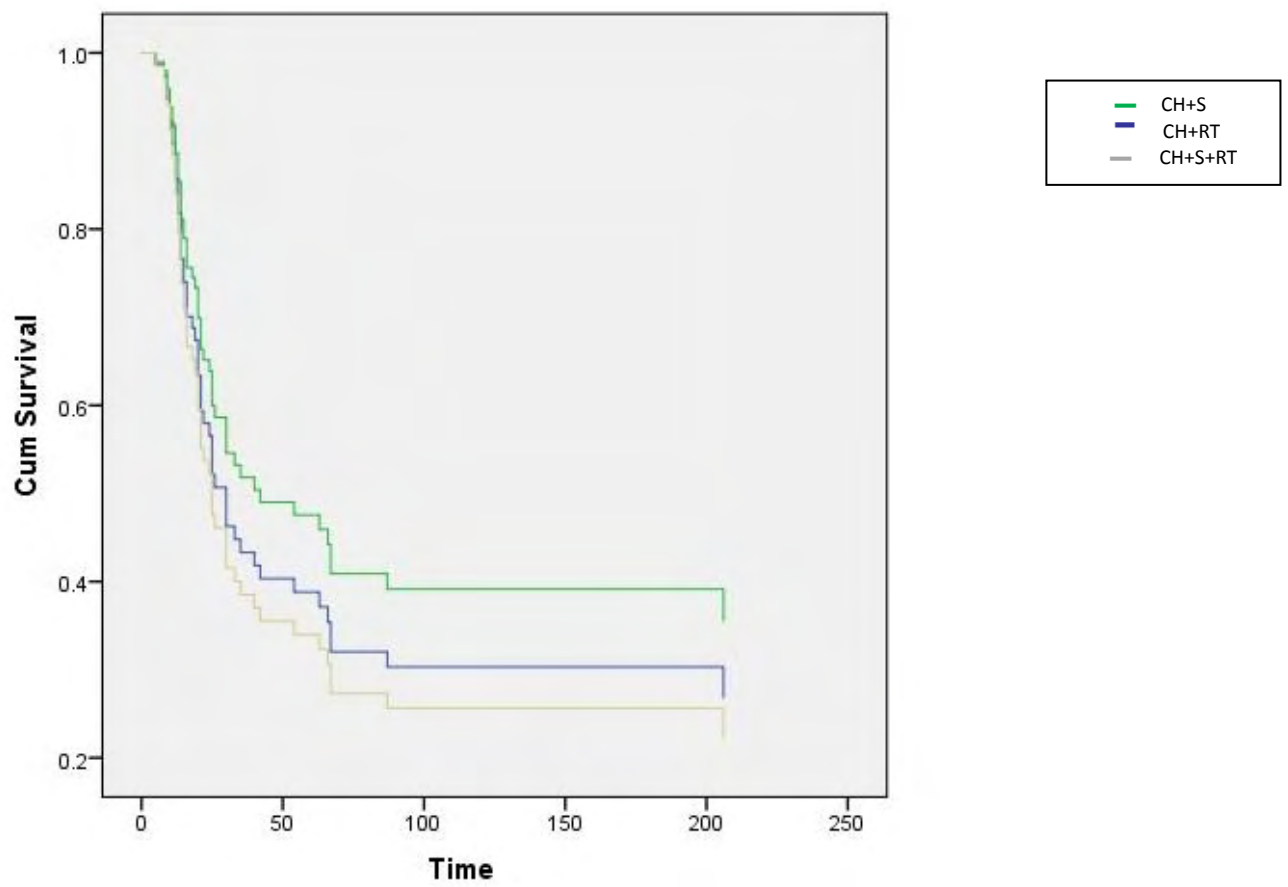


Figure 3.3 Kaplan-Meier survival curve according to treatment group for all patients

For small tumours that received chemotherapy and surgery, there was a trend for improved survival although not statistically significant (OR: 2.43, 95% CI 0.2-28.9, $p = 0.48$). There was true for large tumours as well (Fig. 3.4) (OR: 0.81, 95% CI 0.23-2.82, $p = 0.74$).

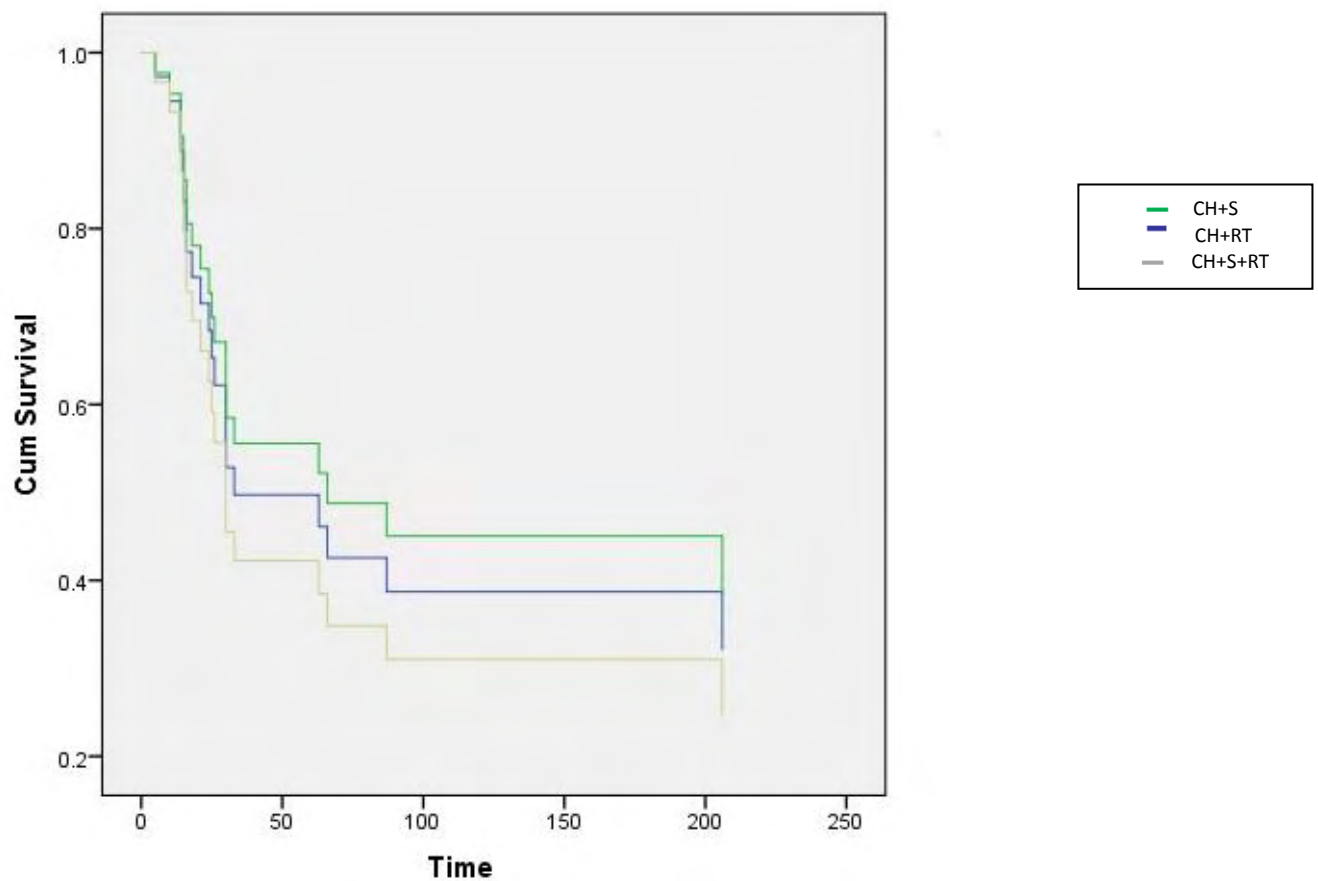


Figure 3.4 Kaplan-Meier survival curve for large tumours according to treatment group

Of the 21 patients in the surgery only group, 15 wide and 4 marginal surgical margins were achieved. All small tumours were removed with wide margins. Four local recurrences developed in 2 tumours removed with wide margins and in 2 tumours removed with marginal margins.

Twenty six patients developed metastases only, 21 patients had a local recurrence and 16 patients developed both local and distant relapses. Eight patients who had surgery developed local recurrence. Of those patients, 4 had wide, 3 marginal and 1 intralesional surgical margins.

Among patients with small tumours only 3 developed local recurrences, compared with 18 local recurrences within patients with tumors larger than 100 ml. Patients with recurrence had a worst prognosis as expected (Fig. 3.5).

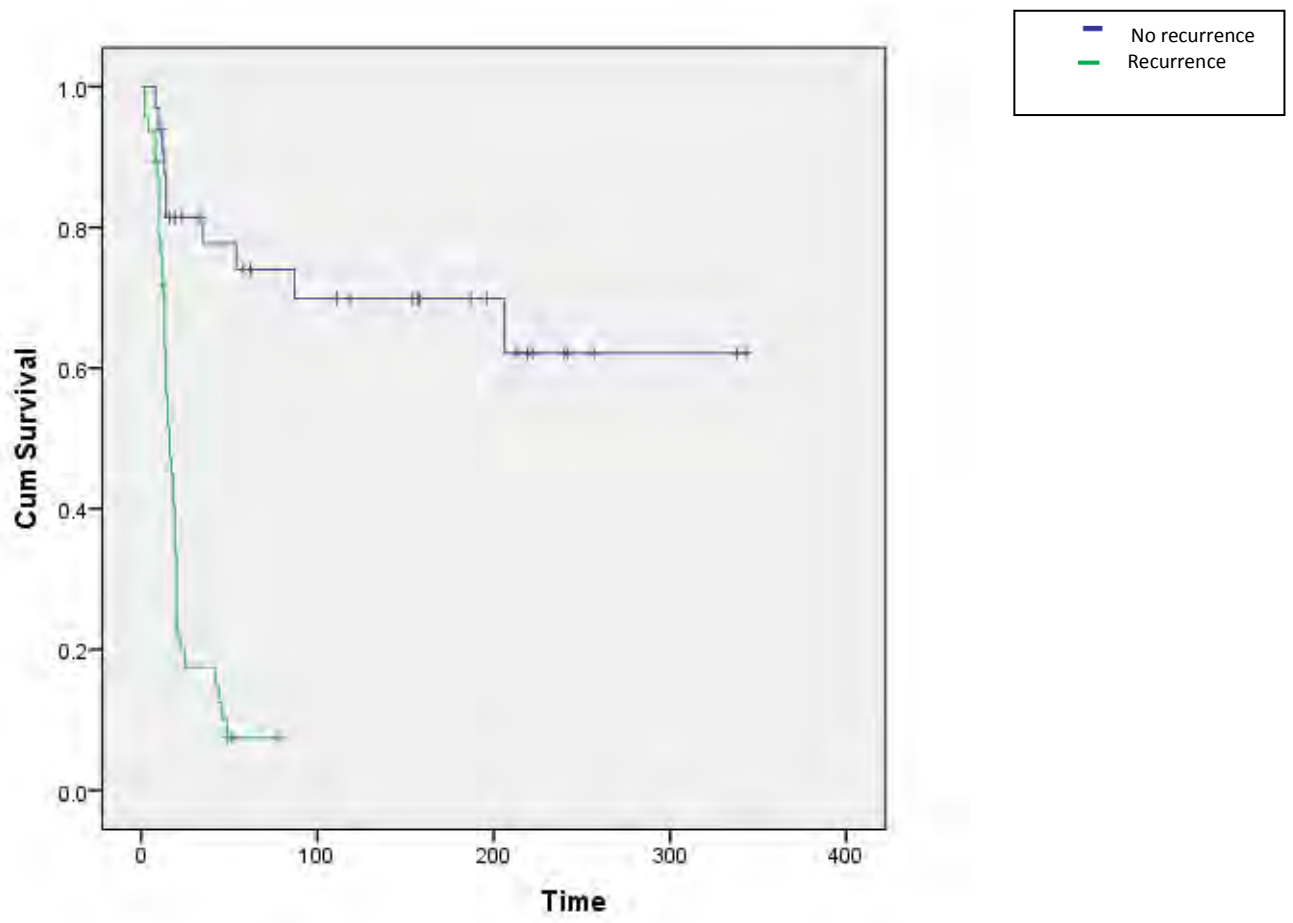


Figure 3.5 Kaplan-Meier survival curve for all patients according to recurrence

Logistic regression analysis was performed on those 85 patients. Age, gender, tumour location tumour volume, treatment type and surgical margins were not found to be significant (Table 3.3). The only significant factor identified was adequate response to chemotherapy (necrosis > 90%) (OR: 0.06, p = 0.01).

Variable	p value	Odds ratio
Tumour volume	0.16	1.0
Chemotherapy response	0.01	0.06
Gender	0.37	0.67
Age	0.06	2.35
Tumour site	0.5	1.01
Treatment type	0.65	1.15
Surgical margins	0.79	1.15

Table 3.3 Logistic regression analysis

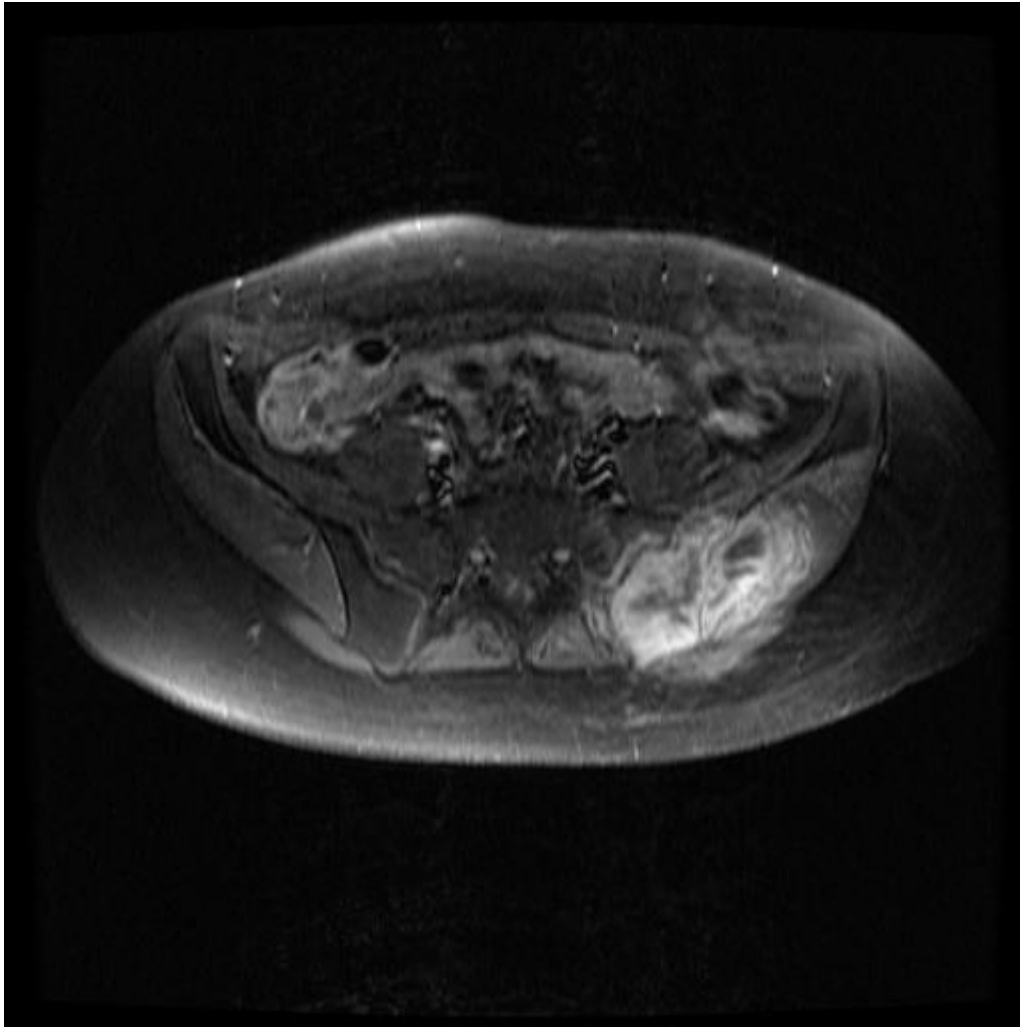


Figure 3.6a. Axial view of a MRI scan of a pelvis showing a tumour affecting left ilium before chemotherapy treatment

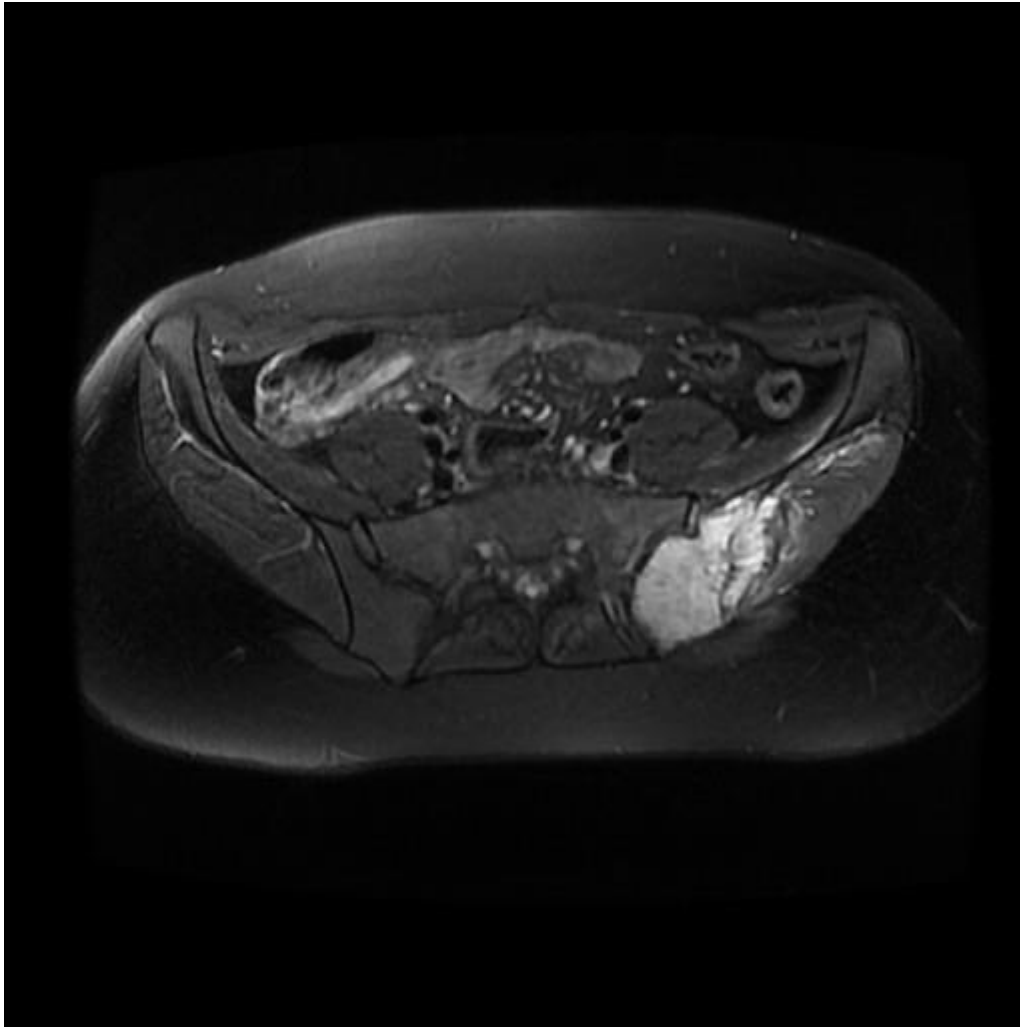


Figure 3.6b. An axial view of a MRI scan showing shrinkage of the tumour following chemotherapy treatment

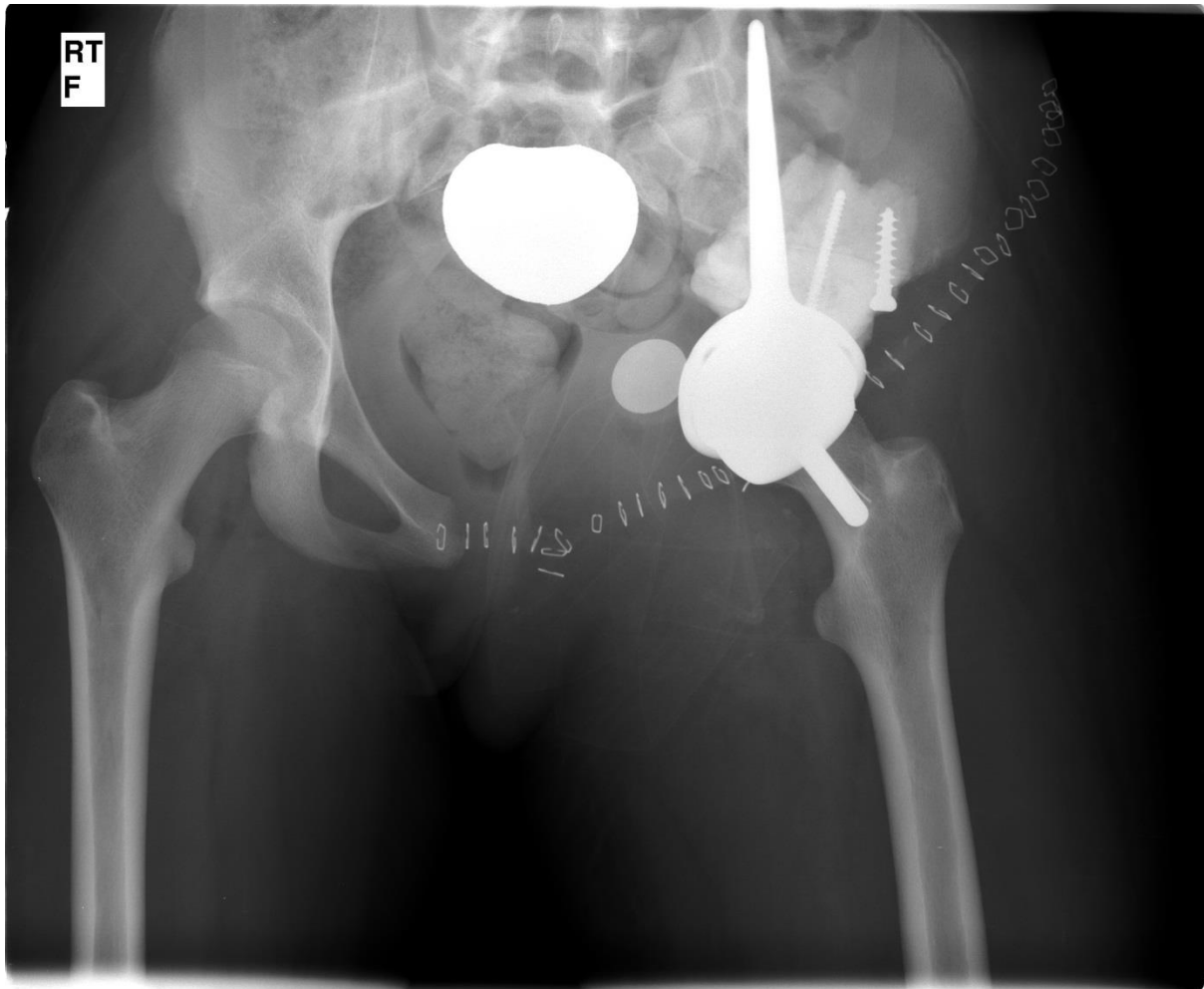


Figure 3.7. An AP radiograph of pelvis showing an endoprosthesis replacement of pelvis for type II/III tumour

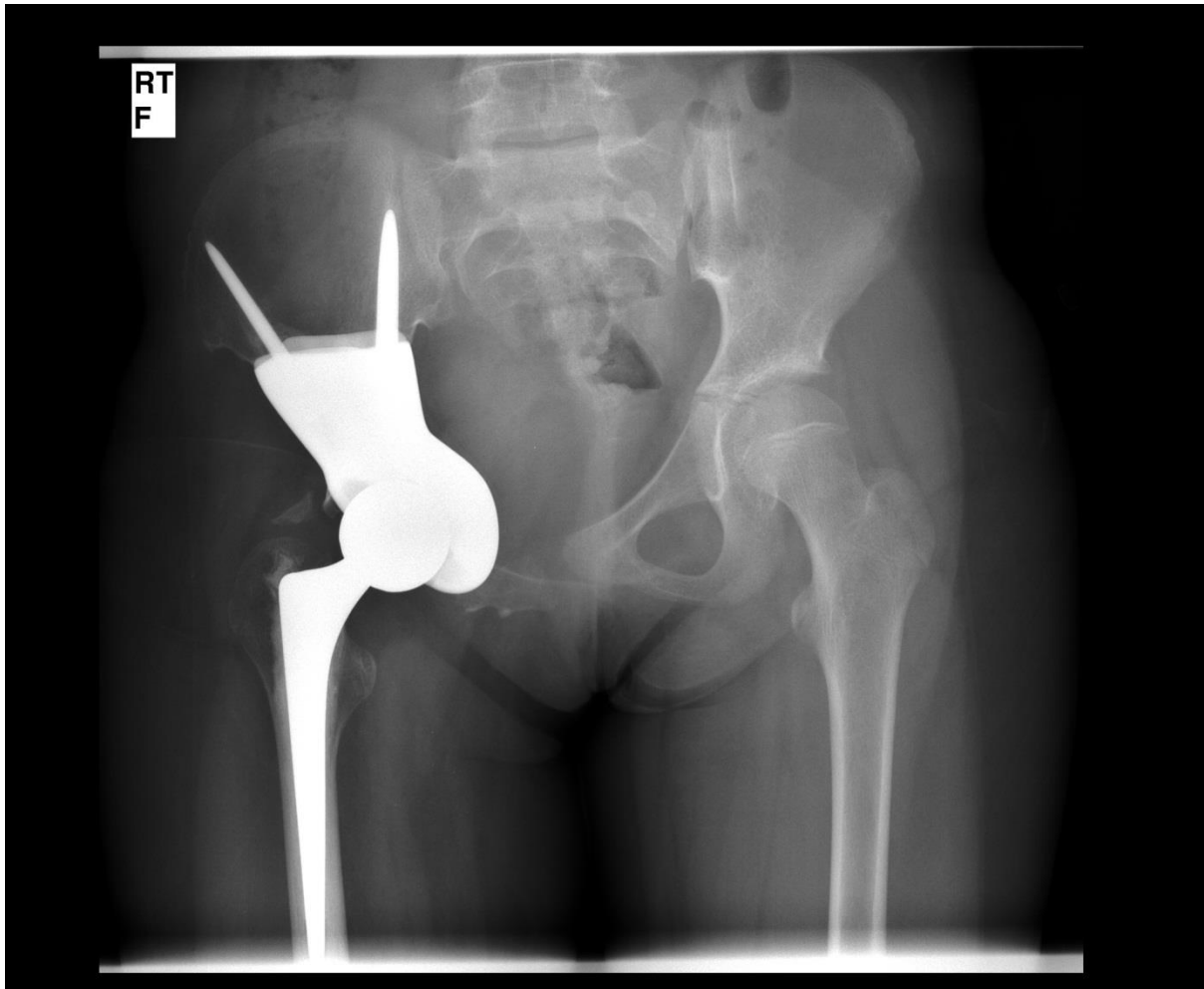


Figure 3.8. An AP radiograph of pelvis showing an endoprosthetic replacement for a type II tumour

3.4 Discussion

Ewing sarcoma of the pelvis requires particular attention because this site is the second most common primary site and is also associated with a particularly unfavorable prognosis [123,54,127].

In our series the 5-year survival for all patients with non-metastatic pelvic EWS was 40.7%, decreased to 36.2% at 10 years. In recurrence free patients, the 5-year survival was 74% and the 10-year survival 70%. Hoffman et al [124] in their large retrospective study have shown that the overall and event free survival rates for patients without metastases at diagnosis were 45% and 39%, respectively.

Evans et al [128] reported a 63% 5-year survival in the IESS-II study, Sucato et al [125] 51.3%, and Rodl et al [129] 49%. Furthermore, Bacci et al [130] showed that 5 and 10-year event-free survival rates were 45% and 44% respectively, and the 5 and 10-year overall survival rates were 48% and 44%.

When we look at the overall survival for our patients who had a surgical resection, that was 44.7% at 5 years. Puri et al [131] showed an overall survival of 72% at 5 years and Carrie et al [120] an overall survival of 72% in patients with non-metastatic pelvic EWS treated with surgery.

The decision about the selection of the most appropriate local treatment was made combining both aims of the complete local control, associated with the need to retain the highest level of function. Retrospectively, we do not know the exact basis for each decision. The decision about the local treatment was based on careful consideration of patients' characteristics (age, tumour site and size, resect ability, chemotherapy response, and

surgical margins) and after discussion with surgeons, oncologists and histopathologists. In general, patients with small tumours had chemotherapy and surgery, as did those with peri-acetabular and pubic tumours. Iliac tumours extending near to acetabulum were usually treated with chemotherapy and radiotherapy. Thirty one of 85 cases (36%) of non-metastatic Ewing's sarcoma of the pelvis underwent surgical resection at our institute. Furthermore, patients with close surgical margins received radiotherapy and therefore they had the worst survival results.

Although several papers seem to indicate a trend of better local control and a higher rate of cure for patients treated surgically [101,110,128,132,133,134] it is difficult to assess fully the usefulness of surgical treatment. The treatment outcome of pelvic EWS depends on many factors and many of these studies were not randomised, so selection bias might have played an important role in the evaluation of prognostic factors and the assessment of different local treatments. Studies on local control in pelvic EWS are quite rare and usually include a small number of patients. In our series we showed a trend for improved survival for patients treated surgically but it was not statistically significant. Furthermore, we have shown that there was a trend for improved survival for patients treated surgically for all tumours irrespective of size.

In this retrospective evaluation we also tried to identify possible prognostic factors which could help determining possible treatment strategies. We identified positive response to chemotherapy as the only significant prognostic factor.

Hoffman et al [124] showed the only variables that appeared to be statistically relevant were tumour volume and histologic response to initial chemotherapy. Jawad et al [135] also

showed tumour volume as a significant prognostic factor whereas Zang et al [136] showed resection margin and metastatic disease as independent prognostic factors.

One of the main strengths of our study was the large number of patients treated at a single institution by the same team of surgeons, radiotherapists and oncologists. This grants a uniformity of treatment, especially as regards local control. On the other hand the main weakness was that this was a retrospective study of patients over a 30-year period in which many changes in the chemotherapy protocols, radiation therapy and imaging studies have occurred and influenced the diagnostic approach and treatment of patients with EWS.

In our unit we tended to operate on the patients with smaller tumours who had a good response to chemotherapy and hence that could have accounted for the improved survival. Also, patients with poor surgical margins went over to the surgery plus radiotherapy group.

This could have had some selection bias in our study. The iliac bone was the most frequent involved site and this is the reason most of our patients were treated non-surgically. We did not use a proxy for assessing the response - such as reduction in tumour volume - in those patients who did not have surgery. In a study by Abudu et al [137], the authors showed that change in volume of the tumour is a good predictor of necrosis induced by chemotherapy but they did not show the percentage of tumour volume reduction needed to be labelled as good response to chemotherapy. Therefore, we thought that no valuable information could have be drawn if we had attempted to assess the volume response to chemotherapy to those patients who did not have surgery. This though, could be another limitation to our study.

Furthermore, some of the data was unavailable; this could have contributed to some of the results being not statistically significant. It could also further explain that the recurrence free survival of our patients was 70% at 10 years, as someone could speculate that some of these patients either died of the disease (but this information never reached our database) or died from other causes.

3.5 Conclusion

In conclusion, pelvic Ewing's sarcoma remains a challenge and current available literature stresses the need for a multinational prospective randomised study that would decide on the best local treatment strategy. However, the favorable results obtained with surgical treatment are encouraging and suggest that a further extension of this strategy might be worthwhile.

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