Case Description
A 15 year old boy complains of pain in his right thigh. Pain is independent of activity and sometimes even occurs at night. Physical examination shows a slight swelling. Radiographs demonstrate an osteolytic lesion in the femoral diaphysis, MRI shows a medullary tumour with penetration of the cortex and surrounding soft tissue involvement. Chest CT scan, whole body technetium bone scintigraphy, and iliac crest bone marrow biopsy exclude metastases. Diagnostic biopsy of the femoral lesion shows a malignant (grade III), small-round-blue cell tumour; immunohistochemistry (CD99 positivity) and molecular biology (translocation t(11;22)(q24;q12)) confirm the diagnosis of a Ewing tumour. He is started on alkylator- and doxorubicin- based treatment in the framework of a multinational trial (Euro-E.W.I.N.G. 99). After six courses, his tumour is completely resected, an endoprosthesis is implanted. After an additional 8 courses of chemotherapy he finishes treatment and enters long term follow-up.

Epidemiology
Ewing tumours (ET) are the second most common primary bone malignancies in childhood and adolescence with an annual incidence of 3 per million in the Caucasian population, the male:femal ratio is 1.5:1. The median age at presentation is 15 years, but ET are observed observed in all age groups. Pelvic bones, the femur, the thoracic skeleton, tibia, fibula and spine are the bones most commonly affected, but other sites including purely soft tissue tumours do occur. 25% of cases present with metastases at diagnosis in lungs, bones or bone marrow, other metastatic sites like lymph nodes, central nervous system or liver are very uncommon.\[1,2\]

Diagnosis
Pain is the presenting symptom in most cases, later followed by tenderness, swelling, and loss of function. As most patients are in the second decade of life, sport injuries are often recalled and may falsely delay proper diagnostic measures. Thus, pain lasting for more than 4 weeks, or pain independent of activity, should prompt imaging studies even if a “trauma” is recalled. The conventional radiograph demonstrates an aggressive osteolytic lesion, typically penetrating the periosseous, leading to “spiculae” and “onion skin” phenomena. Magnetic resonance imaging (MRI) reveals a medullary tumour with an often massive extrasosseous soft tissue mass. Imaging must include the whole involved bone with both adjacent joint in order to detect “skip metastases”. Screening for metastases must include chest computed tomography (CT) and whole body technetium bone scan – or, where available, 16-fluorodesoxyglucose positron emission tomography (16-FDG PET), as well as bone marrow aspirate and biopsy (taken at a site distant from the primary tumour, e.g. iliac crest). The definitive diagnosis must be made as soon as possible by biopsy. The biopsy should be performed by a team experienced in the management of malignant bone tumours, as the biopsy channel has to be regarded as tumour contaminated and must later on be included in the definitive local treatment. The biopsy specimen must be saved both as fixed tissue and as fresh (frozen) material in order to allow for sufficient diagnostic testing. This should be performed by an experienced bone pathologist and molecular biologist: Small, blue, round tumour cells are found at light microscopy, CD 99 (mic-2 antigen) is commonly positive. Definitive diagnosis today includes RT-PCR demonstration of a rearrangement of the EWS (Ewing’s sarcoma) gene on chromosome 22,
most often as translocation t(11;22)(q24;q12). This genetic alteration is found both in Ewing’s sarcomas and the so-called malignant peripheral neuroectodermal tumours (PNET) including Askin tumours of the chest wall. Today, all these tumours are denoted “Ewing tumours” or “Ewing family of tumours”. [3-9]

As both the correct choice of surgical approach, and proper preparation and processing of the biopsy specimen are demanding, the patient should ideally be transferred to a specialised centre for the biopsy procedure.

Treatment

Chemotherapy

In 1921, James Ewing realised these tumours were radio-responsive. However, all of his first series of patients died within two years from distant metastases. [10] This situation changed only when in the 1970s the application of cytostatic drugs in addition to local therapy was introduced. Since the early studies of Rosen and others [11-13], three to five drug regimens based on alkylating agents like cyclophosphamide (CYC) or ifosfamide (IFO), doxorubicin (DOX), vincristine (VCR), topoisomerase inhibitors like etoposide (ETO), and actinomycin D (ACT) have become standard. In the IESS studies, it could be demonstrated, that the addition of DOX significantly enhanced the efficacy of a VCR, ACT, CYC schedule. [14,15] The second COG-CCG study indicated that the addition of IFO and ETO to the above mentioned four drugs increased survival in paediatric patients with localised disease. Most important, all patients with this rare disease should be treated in the existing large intergroup trials, e.g. in the Euro-E.W.I.N.G. 99 study framework. In this European-American cooperative project, as an example of a modern ET therapy, all patients – paediatric or adult – receive six course of VCR, IFO, DOX, ETO (VIDE) followed by local therapy – wherever feasible complete surgery – and further consolidation therapy. This consolidation therapy is stratified and randomised in four treatment arms, depending on initial stage of disease, histological response, and local therapy applied. With this trial, two conventional regimens are compared for standard risk patients, while for high-risk patients conventional treatment is compared to high-dose therapy with stem cell rescue. [17]

Local therapy

There has been a long debate over the optimum choice of local therapy: Surgery or radiotherapy. Nowadays, surgery is recommended wherever feasible, with radiotherapy applied to patients in whom surgery is not feasible, or where surgery was incomplete, and/or where in the surgical specimen, a poor response to induction chemotherapy is demonstrated. [19]

Prognostic Factors

The most important predictor of outcome is the stage of disease at diagnosis: In localised disease, 10-year survival is about 65%, while in patients with metastases at diagnosis, only 15-35% survival can be achieved, depending on the sites involved – patients with lung metastases fare better than those with bone, bone marrow or other metastases. Second to “stage”, the histological response to induction chemotherapy is of most significance in predicting outcome, followed by other less indicative factors like tumour size, or patient age. Of note, patients who cannot undergo surgery are at a higher risk of local relapse and of a fatal outcome. [19]

Outlook

The unique feature of a defined chromosomal rearrangement leading to a specific tumour has initiated efforts to identify potential therapeutic targets, but so far no major breakthrough has been achieved. For the time being, optimising therapeutic schedules and drug combinations, and testing of newer drugs in vitro and possibly in vivo are the next steps to take. Moreover, tailoring treatment to individual prognostic features in order to avoid both over- and undertreatment is a matter of research in current trials.

Conclusion

Early and appropriate use of imaging techniques, immediate patient transfer to an experienced bone tumour centre, proper biopsy, and qualified histopathological and molecular biological diagnosis are the most important steps to early diagnosis. Once the diagnosis of an Ewing tumour is established, patients with this rare disease should be treated within cooperative clinical trials in order to define risk pattern, tailor treatment to individual risks, optimise treatment schedules, and test new drugs for their
therapeutic potential. Moreover, large trial frameworks assure optimal and qualified treatment and help to avoid undue adverse effects of treatment. When these aspects are observed, the majority of Ewing tumour patients may be cured today.

References