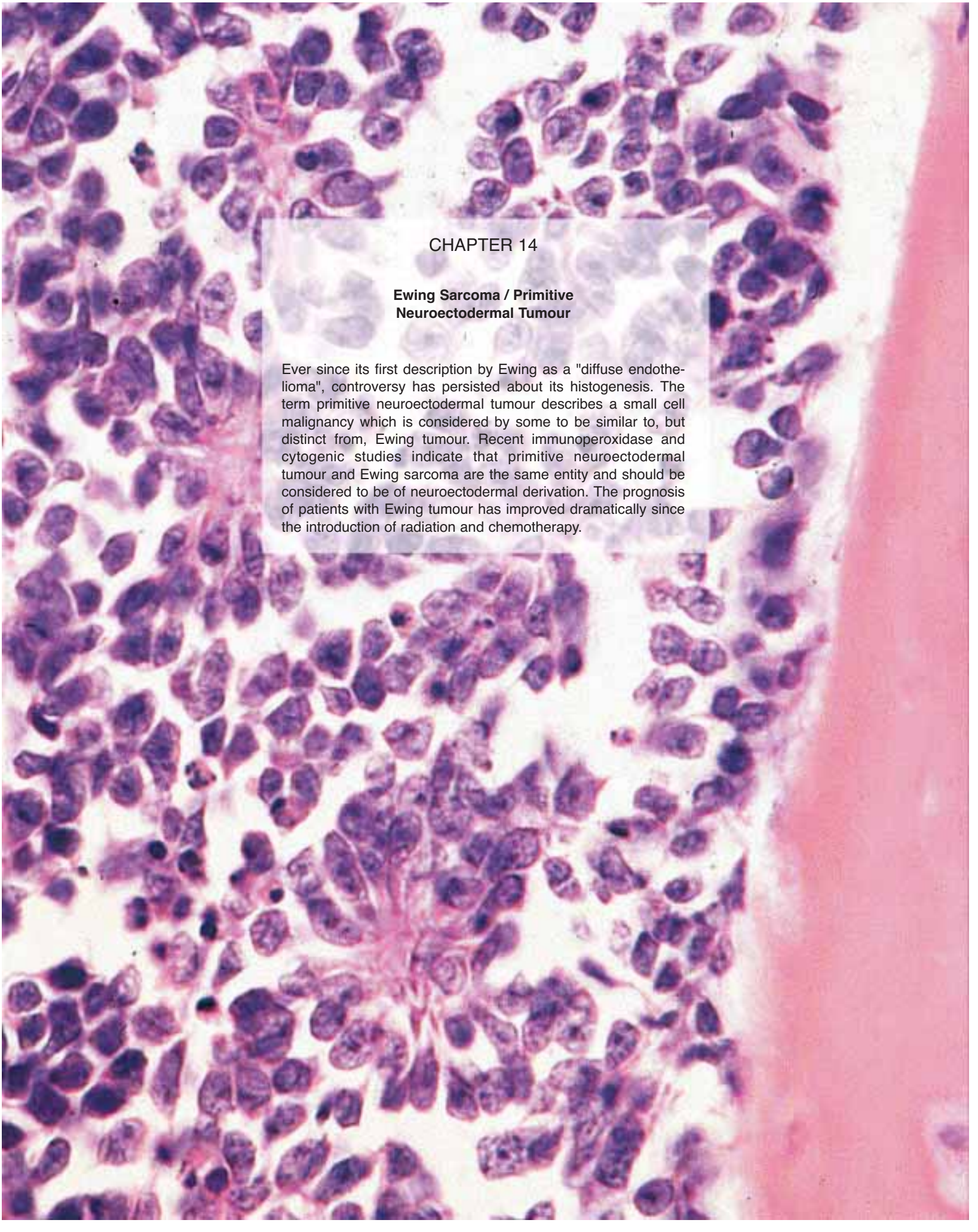

CHAPTER 14

## Ewing Sarcoma / Primitive Neuroectodermal Tumour

Ever since its first description by Ewing as a "diffuse endothelioma", controversy has persisted about its histogenesis. The term primitive neuroectodermal tumour describes a small cell malignancy which is considered by some to be similar to, but distinct from, Ewing tumour. Recent immunoperoxidase and cytogenic studies indicate that primitive neuroectodermal tumour and Ewing sarcoma are the same entity and should be considered to be of neuroectodermal derivation. The prognosis of patients with Ewing tumour has improved dramatically since the introduction of radiation and chemotherapy.

# Ewing sarcoma / Primitive neuroectodermal tumour (PNET)

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## Definition

Ewing sarcoma and PNET are defined as round cell sarcomas that show varying degrees of neuroectodermal differentiation. The term Ewing sarcoma has been used for those tumours that lack evidence of neuroectodermal differentiation as assessed by light microscopy, immunohistochemistry, and electron microscopy, whereas, the term PNET has been employed for tumours that demonstrate neuroectodermal features as evaluated by one or more of these modalities.

## ICD-O codes

| | |
|---|---|
| Ewing sarcoma | 9260/3 |
| PNET | 9364/3 |
| Askin tumour | 9365/3 |

## Synonyms

Ewing tumour, peripheral neuroepithelioma, peripheral neuroblastoma, Askin tumour.

## Epidemiology

Ewing sarcoma / PNET is relatively uncommon accounting for 6-8% of primary malignant bone tumours and is less common than myeloma, osteosarcoma and chondrosarcoma. It is the second most common sarcoma in bone and soft tissue in children. Ewing sarcoma / PNET shows a predilection for males with the ratio of 1.4 to 1. Nearly 80% of patients are younger than 20 years, and the peak age incidence is during the second decade of life. Patients older than 30 are extremely uncommon. Ewing sarcoma / PNET rarely arises in Blacks.

## Sites of involvement

Ewing sarcoma / PNET tends to arise in the diaphysis or metaphyseal-diaphyseal portion of long bones. The pelvis and ribs are also common locations. The skull, vertebra, scapula, and short tubular bones of hands and feet are rarely involved.

## Clinical features / Imaging

Pain and a mass in the involved area are the most common clinical symptoms. Fever (remittent, about 38°C), anaemia, leukocytosis and increase in sedimentation rate are often seen. Pathological fracture is an uncommon complication.
Radiographically, an ill defined osteolytic lesion involving the diaphysis of a long tubular bone or flat bone is the most common feature. Permeative or moth-eaten bone destruction often associated with "onion-skin" like multilayered periosteal reaction is characteristic. The cortex overlying the tumour is irregularly thinned or thickened. A large, ill-defined soft tissue mass is a frequent association in Ewing tumour. Expansile bone destruction with soap-bubble appearance might be seen.
MRI and CT study help demonstrate the extent of the tumour in the bone and soft tissue.

## Macroscopy

The tumour in bone and soft tissue is tan–grey and often necrotic and haemorrhagic. Necrotic yellowish and semi-fluid tissue obtained from intramedullary or subperiosteal lesion at open biopsy might grossly be erroneously interpreted as pus by surgeons. Some soft tissue tumours may be associated with a large peripheral nerve.

## Histopathology

The morphology of the tumour is variable. Most cases are composed of uniform small round cells with round nuclei containing fine chromatin, scanty clear or eosinophilic cytoplasm, and indistinct cytoplasmic membranes, whereas in others, the tumour cells are larger, have prominent nucleoli, and irregular contours {1540}. The cytoplasm of the tumour cells frequently contains PAS positive glycogen. In soft tissue tumours, the tumour cells rarely have a spindle cell morphology. In some cases Homer–Wright rosettes are present {2161}. Necrosis is common with viable

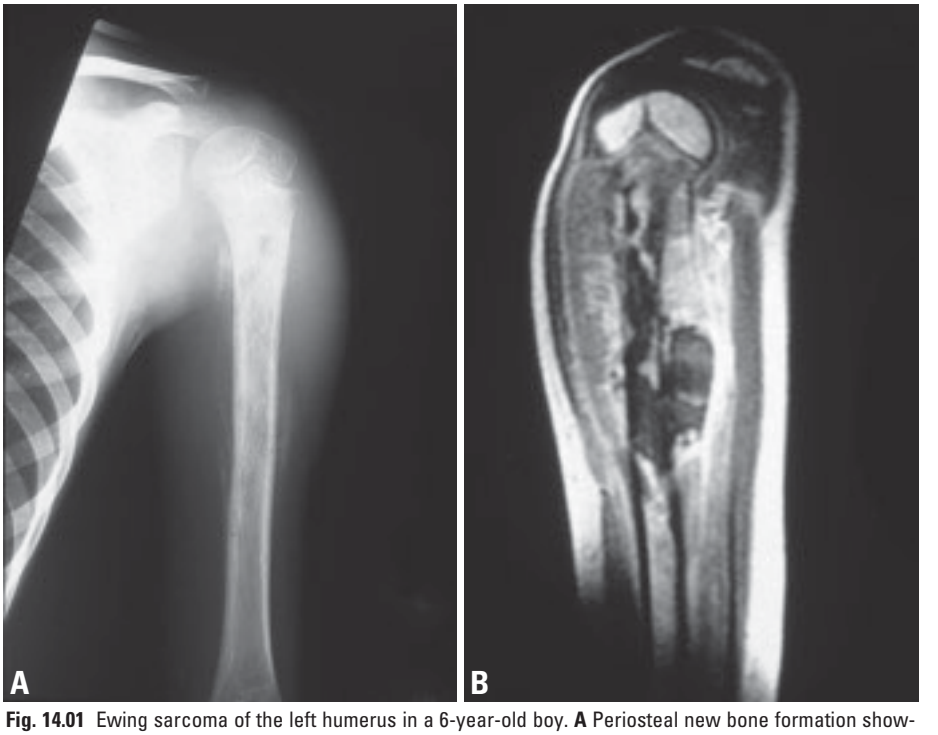


**Fig. 14.01** Ewing sarcoma of the left humerus in a 6-year-old boy. **A** Periosteal new bone formation showing "onion-skin" appearance. **B** Axial T1-weighted MRI of the same lesion. Both intraosseous and extraosseous tumours are more clearly demonstrated than on plain X-ray.

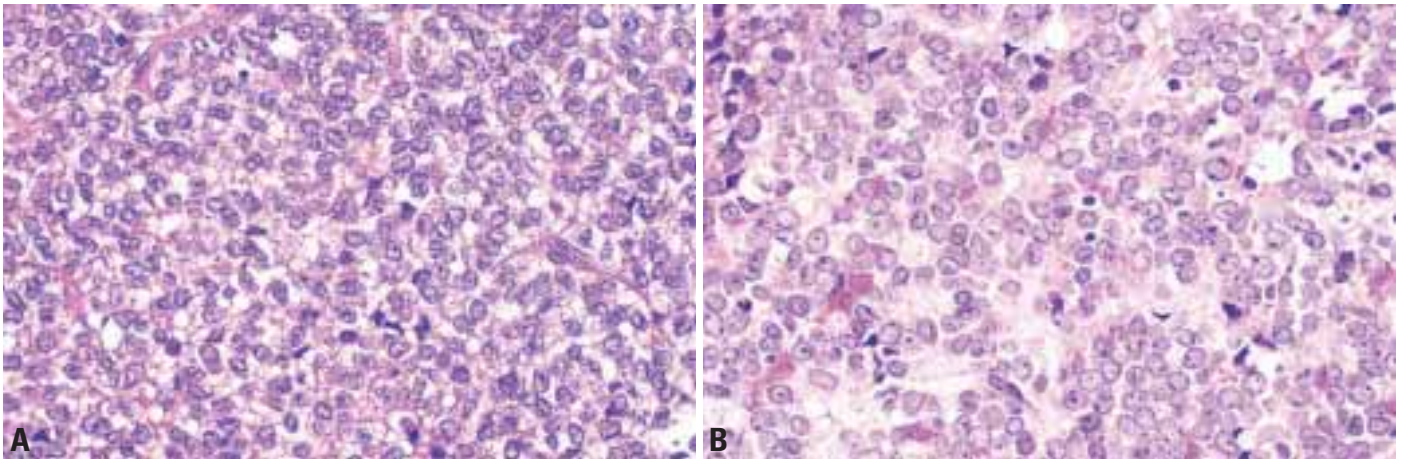


**Fig. 14.02** Ewing sarcoma. **A** Uniform round cells with uniform round nuclei. **B** Histology of Ewing tumour / PNET predominantly composed of rosettes of small round cells and luminal fibrillary processes.

cells frequently perivascular in distribution.

### Immunophenotype

CD99 is expressed in almost all cases in a characteristic membranous fashion, though it is not specific. Vimentin stains most tumour cells and neural markers such as neuron specific enolase (NSE), are frequently expressed. Ewing sarcoma / PNET has also been shown to stain with keratin in some cases.

### Ultrastructure

Ewing sarcoma / PNET is composed of primitive round to oval tumour cells often with glycogen aggregates in the cytoplasm. Fine cytoplasmic processes are often observed. Primitive intercellular junctions are often seen. Neurosecretory granules (100-150 nm) and microtubules may be present.

### Genetics

The Ewing family of tumours (EFT) is characterized by a recurrent t(11;22)(q24;q12) chromosomal translocation, detectable in approximately 85% of the cases {96,2146,2257}. Secondary chromosomal aberrations, notably gains of chromosome arm 1q and chromosomes 8 and 12 occur in more than half of the cases. Molecular cloning of the t(11;22) breakpoints revealed an in-frame fusion between the 5' end of the *EWS* gene from chromosome band 22q12 with the 3' portion of the 11q24 *FLI1* gene, a member of the ETS family of transcription factors {497,1360}. It was subsequently found that another 10-15% of cases have a variant t(21;22)(q22;q12) translocation fusing *EWS* to a closely related ETS gene, *ERG* from chromosome band 21q22 {790,1995,2351}. In 1% or less of EFT cases, t(7;22), t(17;22), and t(2;22) translocations and inv(22) have been described that give rise to fusions between *EWS* and the *ETS* genes *ETV1*, *E1AF*, *FEV*, and *ZSG*, respectively {1038,1060,1693,2159}. Therefore, virtually all EFTs appear to express some form of *EWS/ETS* gene fusion {496}.

Chimeric transcripts analysed to date all encode the N-terminal transcriptional activation domain of EWS fused to the C-terminal DNA binding domain of the ETS partner (reviewed in {89}). EWS/FLI1 has potent oncogenic activity {1360}, and many studies have suggested that it and other EWS/ETS chimeric proteins function as aberrant transcription factors binding to ETS target genes {111,1242, 1361,1598}. In this regard, a number of up-regulated genes have been identified in EWS/FLI1 expressing cells {88, 248, 1359, 2110}. One target is suggested by the observation that EWS/ETS proteins down-regulate expression of the TGF-β type II receptor (TGFBR2), a putative tumour suppressor {865,1003}. TGF-β signalling induces apoptosis in many cell types, and, therefore, repression of TGFBR2 may provide EFT cells with a mechanism to avoid programmed cell death. Inactivation of the INK4a locus encoding the CDKN2A cell cycle inhibitor is the second most common genetic alteration in EFTs {1162}. The significance of this finding is underscored by the recent observation that loss of CDKN2A stabilises the EWS/FLI1 onco-

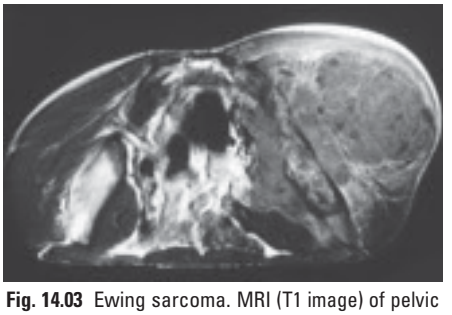

**Fig. 14.03** Ewing sarcoma. MRI (T1 image) of pelvic tumour showing a huge soft tissue mass outside and inside the iliac wing.

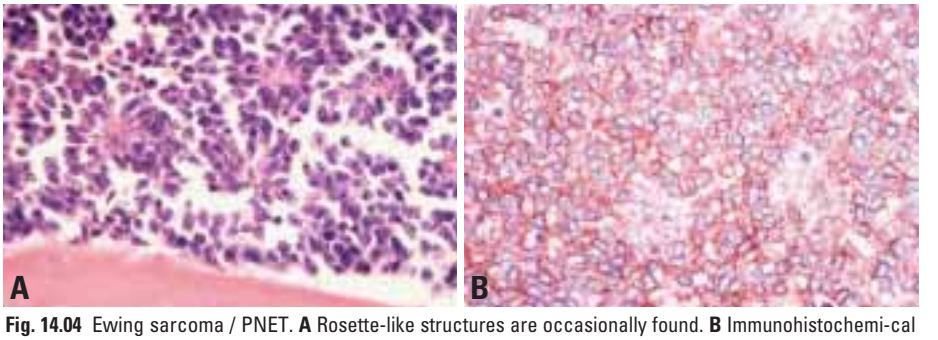


**Fig. 14.04** Ewing sarcoma / PNET. **A** Rosette-like structures are occasionally found. **B** Immunohistochemi-cal expression of CD99 showing characteristic reactivity on the cell membranes.

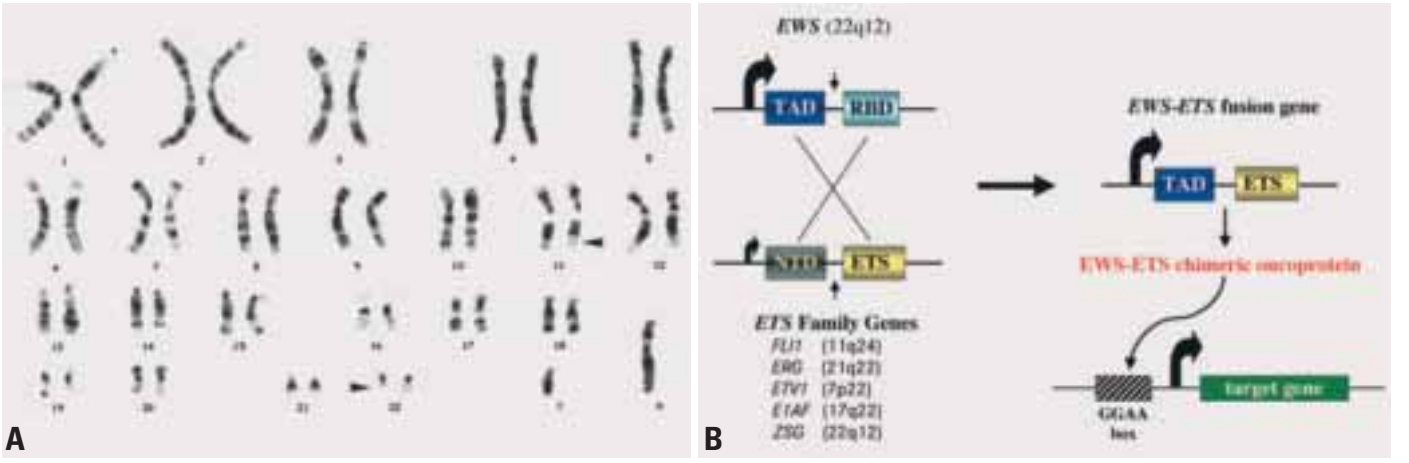


**Fig. 14.05** Ewing sarcoma. **A** Karyotype showing the most common rearrangement, a translocation t(11;22)(q24;q12). Arrowheads indicate breakpoints. **B** Schematic diagram of *EWS-ETS* gene fusions in Ewing family of tumours.

protein {501}, and that *CDKN2A* mutations may be associated with poor outcome in EFTs {2228}.

Genetic diagnostic approaches include chromosome banding analysis, interphase fluorescence in situ hybridisation, RT-PCR assays, and Southern blotting. It is advisable to have available more than one diagnostic modality, to be able to confirm unexpected or discrepant results {126,549,1181,1204,1380,1694,1996}.

Detection of fusion transcripts in peripheral blood or bone marrow is a sensitive marker of minimal residual disease {462, 2252,2348}, although the clinical significance of such a finding remains to be determined {94,1380}

### Prognostic factors

The prognosis in Ewing sarcoma / PNET has improved in the modern era of treatment and current survival rate is estimated to be 41%. Important prognostic features include the stage, anatomic location and the size of the tumour. Tumours, that are metastatic at the time of diagnosis, arise in the pelvis, and are large tend to do poorly. In addition to its diagnostic utility, *EWS/ETS* fusion status also provides prognostic information. Further diversity of these rearrangements is conferred by different combinations of exons from *EWS* and its partner genes giving rise to variably sized chimeric proteins {2351}. Among loco-regional tumours with *EWS/FLI1* gene fusions, the most common so-called type 1 gene fusion (in which *EWS* exon 7 is fused to *FLI1* exon 6) has been reported to be associated with a better prognosis than cases with larger, less common, fusion types {460}.