Clinical features of Ewing and chondrosarcoma

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Chapter 1

General introduction

Sarcoma

For the last couple of years cancer has become the number one cause of death in Europe [1]. The most common form of cancer is carcinoma, which means that the cancer arises in epithelial tissues. A rarer form of cancer is sarcoma, this cancer arises in tissues of mesenchymal origin. Sarcoma can be divided in 2 subtypes, namely bone sarcoma such as Ewing sarcoma, chondrosarcoma, and osteosarcoma, and soft-tissue sarcoma for example rhabdomyosarcoma and liposarcoma. Soft tissue sarcoma is the most common form accounting for 76% of sarcomas. Of all new diagnosed cancers 1% is a sarcoma which calculates to 15,000 new cases a year in the United States [2] and almost 28,000 in Europe [3]. In the Netherlands a total of 973 new cases were reported in 2015 (www.cijfersoverkanker.nl).

Ewing sarcoma

Ewing sarcoma (ES) is the third most common primary malignant bone tumor after osteosarcoma and chondrosarcoma, however it is still rare with approximately 500 new diagnoses in Europe each year. It affects mostly children and adolescents with a peak

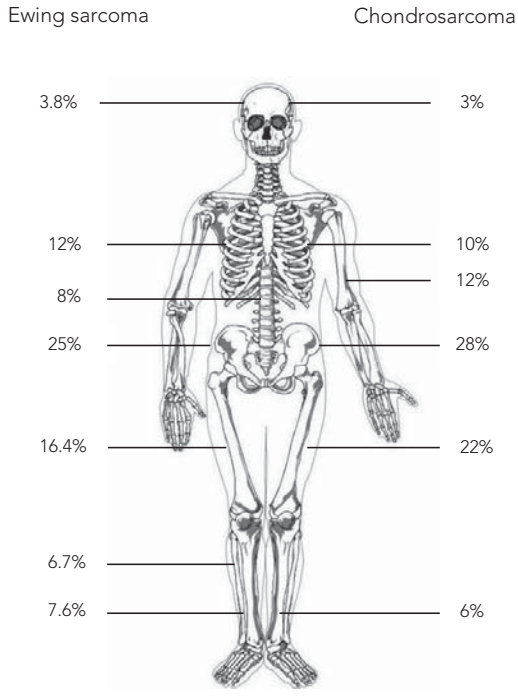

Figure 1.1 Most commonly diagnosed locations for Ewing sarcoma and chondrosarcoma.

incidence at age 15. ES is diagnostically defined by a reciprocal translocation, causing a fusion of the EWSR1-gene on chromosome 22 with a member of the ETS family of transcription factors. The most common translocation (85%) is the t(11;22)(q24;q12), fusing EWSR1 to FLI1. An example of the histology ES cells is shown in Figure 1.2. ES is most commonly diagnosed in the pelvis, femur, humerus, ribs and clavicle (Figure 1.1), an example of a typical radiological presentation is shown in Figure 1.2. With current treatment options including surgery, conventional chemotherapy, radiotherapy and high dose chemotherapy and peripheral blood stem cell transplant (PBSCT), the 5 year survival for local disease is 60%. However, for patients that present with metastatic disease the 5-year survival decreases to only 20% and the outcome for patients with relapsed or refractory Ewing sarcoma is even worse with a 5-year survival of no more than 10% [4]. During the last four decades, patient outcome has been improved significantly in patients with localized disease, by dose intensification of conventional therapeutics and the use of multidisciplinary treatments, such as chemotherapy (including Vincristine, Doxorubicin, Cyclophosphamide, Ifosfamide and Etoposide), surgery and radiation therapy. However, advances in the treatment of ES patients with metastatic or relapsed disease have not been made and their outcome is still poor.

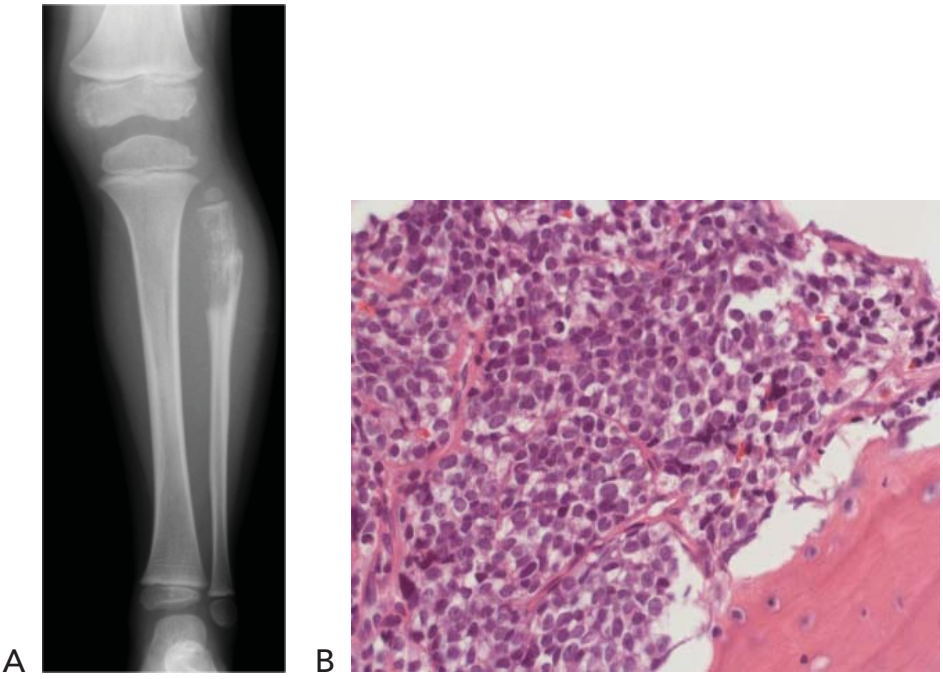

Figure 1.2 X-ray of a typical radiological presentation for ES (A) with a lytic lesion in the proximal fibula of the right leg and an example of Haematoxylin and eosin staining on ES (B) showing small round blue cells without any differentiation.

Chondrosarcoma

Chondrosarcoma is the second most common primary bone cancer. It is an orphan disease and accounts for 20% of all the new primary bone malignancies [5]. It is a heterogeneous group that have in common the production of chondroid matrix. Chondrosarcoma affects adults mostly over 40 years of age with an incidence that is gradually increasing and no difference of occurrence between sex and race. It mostly affects the pelvis, femur and humerus (Figure 1.1), a typical radiological presentation is shown in Figure 1.3. Chondrosarcoma consist of different subtypes with conventional chondrosarcoma being the most common (75%), more rare subtypes include dedifferentiated, clear cell and mesenchymal chondrosarcoma. Histologically, conventional chondrosarcoma can be subdivided in grade 1 (now called "atypical cartilaginous tumour"), grade 2 and grade 3 according to the nuclear size, matrix composition, mitotic activity and degree of cellularity. An example of histology of Haematoxylin and eosin staining of chondrosarcoma cells is shown in Figure 1.3. The grade of the tumour is one of the most important predictors of outcome [6, 7]. From two benign cartilaginous lesions it is known that they can progress to chondrosarcoma. The first is osteochondroma which is a cartilage-capped bony projection arising on the external surface of a bone. It can arise as a single lesion or as an inherited condition within the genetic disorder multiple osteochondromas (previously called

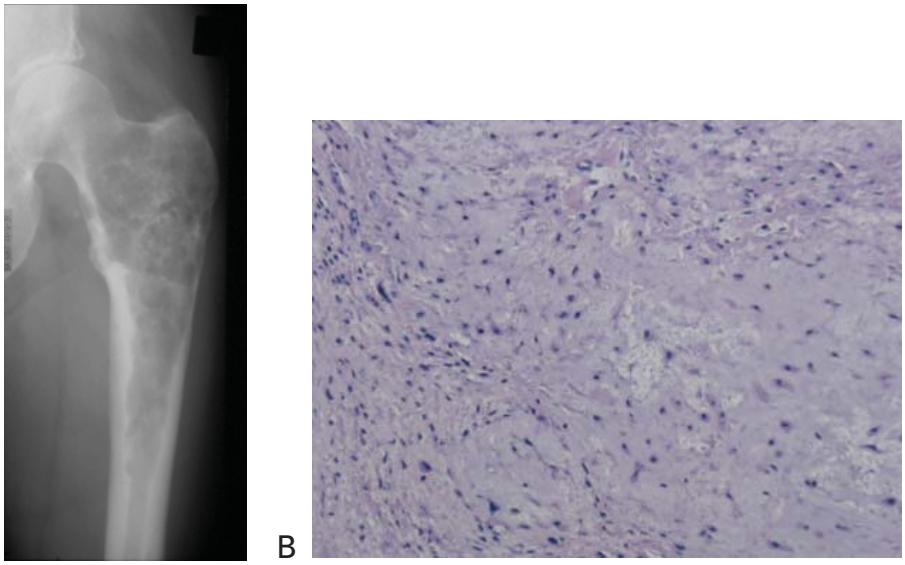

Figure 1.3 X-ray of a typical radiological presentation for chondrosarcoma (A) with ill-defined lytic bone lesion with calcifications of the right proximal femur and an example of Haematoxylin and eosin staining on chondrosarcoma cells (B) showing tumour cells displaying chondrogenic differentiation by depositing cartilaginous of extracellular matrix.

"hereditary multiple exostoses"). Malignant transformation occurs in 1 percent of patients with a solitary and 2 till 6 percent of patients with multiple osteochondromas [8-15]. The average time between initial diagnosis and malignant transformation was 9.8 years [8]. All chondrosarcoma arising in the setting of an osteochondroma are secondary peripheral tumors. The other precursor lesion for chondrosarcoma is enchondroma which is a benign cartilaginous tumor that develops in the medulla (marrow cavity) of bone. Enchondromas can occur in a non-hereditary syndrome of which the most common forms are Ollier disease and Maffucci syndrome. The risk of malignant transformation in these forms is up to 50 percent, depending on the location of the tumors [16-21].

Grade 1 chondrosarcoma / atypical cartilaginous tumours are slowly growing and metastasize rarely with a 10 years survival rate of ~80% [22]. In contrast, grade 3 chondrosarcomas have a high metastatic rate and a 10 year survival of ~38% [7]. For the grade 2 and 3 chondrosarcomas the most important treatment option is surgery and it is considered to be the only chance for cure. Most subtypes of chondrosarcoma have always been considered chemotherapy resistant and it was assumed that patients would not benefit from non-surgical treatment options.

Several studies were conducted to investigate new treatment options for patients diagnosed with chondrosarcoma. Recent preclinical and retrospective studies show that patients may benefit from non-cytotoxic, chemo- and radiotherapy. These studies enrolled only small numbers of patients because of the orphan state of the disease. Because of the rarity of chondrosarcoma and especially the grade 2 and 3 tumours this is difficult to assess with few reported series consisting mostly of small numbers of patients [23, 24].

In the last decades pre-clinical and clinical studies have been conducted including patients diagnosed with local or advanced ES or chondrosarcoma. Because both ES and chondrosarcoma are orphan diseases with few new patients diagnosed each year most studies can enrol only small numbers of patients and the conclusions from these studies are limited. There are no uniform treatment regimens for patients with advanced disease and the treatment options in different countries vary greatly. Systemic analysis of the available pre-clinical and clinical data is needed to identify the most optimal treatment regimen and collaborations between countries need to be formed to conduct clinical studies based on pre-clinical work.

Aim and outline of this thesis

The aim of this thesis was to categorise the clinical studies executed for Ewing sarcoma and chondrosarcoma patients in the past, to determine the outcome for unresectable Ewing and chondrosarcoma patients and to find new treatment options based on pre-clinical studies on molecular pathways for the future.

In the last twenty years the outcome for patients with metastasized bone sarcoma shows no major improvement. To identify which clinical studies have been conducted **chapter 2** is a literature search of published phase I/II clinical trials which included Ewing sarcoma patients between 1990 and 2010.

Several new treatment options are being tested in a preclinical or clinical setting for patients diagnosed with Ewing sarcoma. Two interesting pathways for potential targeted therapy are the IGF-1R and PARP pathway. **Chapter 3** summarises the preclinical data available of these pathways and the results of the clinical studies conducted so far.

There are limited treatment options for patients diagnosed with unresectable Ewing sarcoma. Several sarcoma centres in Europe treat these patients with the combination of etoposide and either cisplatin or carboplatin. **Chapter 4** shows the outcome for patients treated with this combination and several possible prognostic factors were tested.

Gene transcription is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs) which modulates chromatin and thereby influences the wrapping of eukaryotic DNA. HDACs prevent gene transcription and upregulation is associated with silencing of tumour suppressor genes and oncogenesis. Panobinostat is a HDAC inhibitor, **chapter 5** describes one of the first Ewing sarcoma patients treated with panobinostat monotherapy.

Chapter 6 gives an overview of the published prospective and retrospective studies with systemic therapies for chondrosarcoma patients between 2000 and 2013. The results on outcome are compared and promising therapies are emphasized.

Overall survival for patients who are diagnosed with unresectable chondrosarcoma remains poor. To gain insight, **chapter 7** gives the retrospective overall survival data from all patients diagnosed with unresectable conventional chondrosarcoma between 1980 and 2011 in two major European bone sarcoma centres.

The effect of systemic therapy of patients diagnosed with unresectable chondrosarcoma, per subtype, is shown in **chapter 8**.

Chapter 9 gives a general discussion of this thesis with future perspectives.

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