Prognostic factors and late effects of treatment in localised high grade extremity osteosarcoma
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General Introduction and Outline of the Thesis
1.1 A short history of survival in osteosarcoma

An often cited remark is that of a famous surgeon in the beginning of the last century who summarized a scientific meeting on bone sarcomas in the 1920’s by acknowledging: “If you do not operate, they die; if you do operate, they die just the same. Gentlemen, this meeting should be concluded with prayers”(1).

High grade osteosarcoma is the most common malignant, primary, non-hematopoietic, bone tumour. It still is a rare disease with an incidence of around 3 per million(2), with a peak in the second decade of life. The incidence in children under 18 years of age is found to be 6.9 per million in the Dutch population(3). Males are about 1.5 times more affected than females. Before the 1970’s, treatment of high grade osteosarcoma was limited to surgery. In the majority of extremity osteosarcoma patients, amputation was carried out. Survival was only 15-20%(4-6).

In the early 1970’s, adjuvant, postoperative, chemotherapy treatment was introduced. In combination with surgery, this treatment resulted in survival rates of about 50%. In the late seventies, neoadjuvant; pre-operative chemotherapy was added to this. Standard treatment nowadays consists of “sandwich therapy” with pre-operative induction chemotherapy, followed by resection of the tumor, after which post-operative chemotherapy is given. Chemotherapy usually concerns combinations of doxorubicin, cisplatin, high dose methotrexate, and ifosfamide. The aim of surgery is resection of the tumor with adequate margins. Most patients in Europe and America are treated within one of the multicentered trials like those of the European Osteosarcoma Intergroup (EOI)(7;8), the Cooperative Osteosarcoma Study Group (COSS), the Italian Sarcoma Group / Scandinavian Sarcoma Group or lately the European and American Osteosarcoma Study (EurAmos) , and EUROBOSS (European Bone Over 40 Sarcoma Study)(9;10).

With these changing therapeutical modalities, survival in patients with high grade osteosarcoma has improved from 15-20% to 60-70%(7;11-15), and has even been reported to be 93% in one population(16).

1.2 Changing challenges in osteosarcoma treatment

The success of chemotherapy, with increasing survival and the possibility of downsizing the tumour with pre-operative chemotherapy, has led to a change from predominantly ablative surgery to limb saving surgery in about 90% of patients nowadays(7;12;13). The development of imaging techniques and reconstruction materials has contributed to this change as well. First Computer Tomography (CT), and especially later the Magnetic Resonance Imaging (MRI) techniques have proven
to be very helpful in planning surgical procedures. This way, adequate margins could be achieved with closer resections, leading to less mutilation and better possibilities for reconstruction(17-19). Biomedical engineering has led to the development of more successful implants for reconstruction of defects after resection. Tumour prosthesis have shown good functional results and reasonable long term prosthetic survival(20-26). Because the majority of osteosarcoma patients are children, and the majority of tumours are located in the meta- and epiphyseal region, the growth plate often has to be sacrificed. Especially in young children this poses the problem of progressive leg length discrepancy. One solution for this is rotationplasty, of which the functional results were reported to superior, or at least comparable, to those of amputation and endoprosthetic replacement(27-32). Cosmetically, rotationplasty is less desirable compared to these other possibilities, although differences in quality of life or self esteem could not be objectified(33-36). Later, extendable, “growing” prostheses for reconstruction of long bone defects in children were successfully implanted as well(37-41). A promising new development is the non invasive growing prosthesis, which can be lengthened from outside the body, without the need for re-operations(42-44). Tumour prostheses, however, are still associated with late loosening, infects, and peri-prosthetic fractures and other complications(45-47), with a reported revision rate of 42%(20). Allografts possibly allow better fixation of soft tissue and partly fuse with the patient’s remaining bone, but infections and allograft fracture pose problems(48;49). Preferably, a defect in a long bone would be replaced by biological material, if possible living bone. Reconstruction of bone defects with a vascularised fibula autograft or callus distraction results, if successful, in living bone. This allows the patient a more normal and more physically active life. The risk of infection is lower, and if a fracture occurs, it has a healing potential(50;51). Combinations of allografts with prosthesis or with a vascularised fibula graft are other possibilities for reconstruction. Both have their advantages and disadvantages(19;52-57). On rare occasions, amputation or rotationplasty still is the best option. The challenge is to choose the right surgical strategy for each individual patient.

Another challenge in modern osteosarcoma treatment is the management of long term effects of treatment. Because of the current survival rate of 60 to 70%, there is a growing number of adults, who were treated for osteosarcoma in their youth(58). They have to live with the consequences of this treatment(59-62). Living with an amputation, rotationplasty, or with a large endoprosthesis, can compromise quality of life. Long term effects of chemotherapy can occur on the basis of cardiotoxicity(63), ototoxicity(64;65), infertility, renal failure(66;67), or psychosocial disturbance(68). Chemotherapy can be also the cause of secondary malignancies(69-71).
1.3 The importance of individual prognostication and prognostic factors

With the diversity of reconstructive possibilities, chemotherapy, and early and late consequences of treatment, decision making in osteosarcoma patients has become multifactorial. The first priority is always to achieve the best possible oncological result for each patient. Within the oncological optimal frame, the best possible functional result should be aimed at. Therapeutic choices have become very much individualized. The choice of reconstruction method from the variety of possibilities obviously does have implications for the patient. Some (especially biological) reconstruction methods, have excellent long term results but require a long (up to 2 year) rehabilitation time (53-55), whereas others, such as endo-prosthetic replacements, allow early mobilization but can lead to problems on the long run (19;35;45) (see table 1.1).

In spite of the dramatic improvement of survival in osteosarcoma patients, up to 40% of them still die of the disease. To counsel patients and their parents adequately, it would be helpful if an accurate estimation of survival chances could be made, if possible early in the course of treatment. Choice of chemotherapy and of surgical approach could be tailored to the patient. Furthermore, if reaction on chemotherapy could be predicted early, the chemotherapy regimen could be changed accordingly.

Individual prognostication in osteosarcoma remains difficult. Many prognostic factors have been reported, but only few seem to be independently predictive in a multivariate analysis. The literature is abundant, but very divers. Most consistently reported as valid factor is chemotherapy response (11-13;15;72). A number of literature reviews were published on specific factors (73-76), but reviews covering a “complete set” of factors for predicting survival are rare. In 1997 Saeter gave an narrative overview about most known predictive factors in which stage at diagnose was considered the most important, followed by chemotherapy response, tumor volume, age, sex, and possibly p-glycoprotein expression (77).

In 1994, Davis et al published a systematic review of the literature until 1992 (72), analyzing age, sex, tumor location, tumor size and necrosis after chemotherapy. The authors concluded that chemotherapy response was the only proven independent factor predicting survival.

This response however, can only be established after neo-adjuvant chemotherapy and resection are carried out. Ideally, a prognostic factor would be assessable before, or early in the course of treatment. Furthermore, factors should be easy to assess, and practical in clinical use.
1.4 Outline of the thesis and research questions

Aim of the thesis was to establish practical and reliable prognostic factors predicting survival in patients with extremity osteosarcoma. It was chosen to focus on patients without metastatic disease at the time of diagnosis, because treatment in non-metastatic high grade osteosarcoma nowadays is very uniform, and mostly embedded in one of the abovementioned research protocols. This is not so for patients with metastatic disease at the time the osteosarcoma is first diagnosed. Some of those patients are still treated with a curative prospective; some are only palliated, with treatment, directed at quality of life, and sometimes no treatment at all is given. This makes comparing prognostic factors in this group virtually impossible.

In chapter 2 a systematic review is presented on prognostic factors in non metastatic osteosarcoma. The aim was to identify new independent predictive factors, reported in the recent literature. Furthermore an attempt was made to perform a meta-analysis, in order to try and establish pooled estimates of the risk ratio of specific predictive factors.

Chapter 3 discusses the treatment and outcome of the patients, treated in the Emma Children’s Hospital at the Academic Medical Centre Amsterdam. Aim is to compare the oncological results with those in literature and to evaluate known prognostic factors in this population. Furthermore the late effects of treatment are studied in patients surviving more than 5 years after the end of treatment. Second malignancies, organ or psychosocial dysfunction and cognitive problems have been reported. Incidence of these late complications is established in our patient group alongside the burden on patients and the relation with the treatment.

In Chapter 4 the value of Colour Doppler Ultrasound (CDUS) for predicting chemotherapy response and survival in paediatric osteosarcoma is evaluated. CDUS
is widely available, non-invasive, and easy to assess. Our hypothesis was that CDUS could predict chemotherapy response before resection of the tumour is carried out, and survival in high grade extremity osteosarcoma.

Although pre-chemotherapy alkaline phosphatase serum level was already recognised as a predictive factor, and chemotherapy response as the most consistent one, the value of post-chemotherapy alkaline phosphatase was never before established. In Chapter 5 the value of Pre- and post-chemotherapy alkaline phosphatase levels as prognostic indicators in adults with localised osteosarcoma is established in the larger population of the Royal Orthopaedic Hospital, Birmingham, United Kingdom. The hypothesis was that post-chemotherapy alkaline phosphatise level could predict chemotherapy response and survival in adults with localised high grade osteosarcoma.

Chapter 6 deals with the relevance of pathological fractures in bony sarcomas. The literature is contradictive about this. It is suggested that the occurrence of a pathological fracture worsens the prognosis because of tumour spread in the fracture hematoma. To clarify this more, a study was done in the patient populations which were treated for high grade chondrosarcoma, osteosarcoma, and Ewing´s sarcoma in the Royal Orthopaedic Hospital, Birmingham, United Kingdom. The hypothesis was that the presence of pathological fracture influenced and predicted survival and local recurrence rate in patients with high grade chondrosarcoma, osteosarcoma, and Ewing´s sarcoma.

Chapter 7 summarizes the thesis. In chapter 8 (general discussion and future perspectives) an attempt is made to put all of the above in perspective with modern osteosarcoma treatment. Chapter 9 presents our recommendations for clinical practice and future research. Chapter 10, finally, gives summary and recommendations in Dutch.
Reference List


