Prognostic factors and late effects of treatment in localised high grade extremity osteosarcoma
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chapter 7

Summary
7.1 Summary of introduction and general aim of the thesis

Before the 1970’s, surgery was the sole available therapy for high grade extremity osteosarcoma, in 90% of cases involving amputation of the inflicted limb. Survival was only 10 to 15%(1-3). This has changed with the introduction of chemotherapy in the 1970’s, and since the 1980’s, the combination of pre-operative chemotherapy, surgery, and postoperative chemotherapy, results in a survival rate of around 70%(4-9). Down-staging of the tumor, decreasing in volume if reacting on chemotherapy, facilitates the resection. The development of imaging techniques, especially magnetic resonance imaging, has facilitated pre-operative planning (10;11). Nowadays, surgery can be limb saving in about 90% of cases (4;6;7). Reconstruction methods after resection have improved, and range from biological to complete endoprosthetic replacements. Each of these has advantages and disadvantages(12;13). A complete biological reconstruction, knows on the long run good results with vital bone, allowing a normal life with little restrictions concerning the limb(14;15). A long period of non weight bearing, however, up to 18 months postoperatively, is often required, as are sometimes re-operations(16;17). On the other hand, reconstruction with a cemented endoprosthesis allows the patient full weight bearing quickly, usually after 1 or 2 weeks. On the long run, however, there is always a risk of peri-prosthetic fracture, infection, and eventually loosening (12;18;19).

The increased survival has resulted in a growing number of long term survivors(20). These may experience long term health effects of treatment, especially if they were children at the time of treatment. Late effects sometimes are mild, but may have a severe impact on quality of life or even be fatal (21;22).

The combination of factors mentioned above is leading in decision making for osteosarcoma patients. In each patient the optimal treatment has to be chosen, with the highest chance of survival, and the least possible late adverse effects of treatment. The surgical treatment should be planned balancing expected rehabilitation time and chance of survival.

Adequate estimation of the survival chance of the individual patient is essential for making these considerations. This should ideally be possible early in treatment, allowing early assignment to the best chemotherapeutic and surgical treatment. Unfortunately, prognostication for individual patients remains difficult. Many prognostic factors have been reported, but the value of different factors for the
individual patient is not clear. Extend, importance, and etiology of late effects of treatment need to be further clarified.

**General aim of this thesis** was to establish the available prognostic factors predicting survival chance after treatment of high grade osteosarcoma, and to assess the value of these for the individual patient. Special focus was on factors which can be assessed before, or in an early stage of treatment and which are easy to assess. Furthermore, it was investigated which adverse late effects of treatment occurred in patients who were treated for high grade osteosarcoma in childhood, and who survived more then 5 years after the end of treatment. The impact of these effects was established as well as the relation of the effects with the sort of treatment patients underwent.

### 7.2 Summary of chapters 2 to 6

**Chapter 2: A systematic review of the literature** In chapter 2 a systematic review of the literature concerning prognostic factors in high grade osteosarcoma is presented, trying to identify evidence-based prognostic factors in the literature since 1992 and to establish pooled relative risks of factors. Of 1777 “hits”, 93 papers were studied in depth. Only 7 papers were of sufficient quality to use in a meta-analysis. Poor chemotherapy response (pooled RR = 2.37), large tumor volume (pooled RR = 1.36) and ablative surgery (pooled RR= 2.18) were independent predictors of a bad outcome. Further factors that are presumably predicting a worse outcome, but could not be pooled, are inadequate excision margin, age under 14 years, male gender, high alkaline phosphatase, local recurrence, p-Glycoprotein expression, and absence of Erb2 expression.

Conclusion: Poor chemotherapy response, large tumor volume and ablative surgery were independent predictors of a bad outcome. The literature is abundant but only few papers are of sufficient quality to allow hard conclusions. Because of heterogeneity of the studies pooling results is hardly possible. Because of the relatively small sample sizes in most studies, even very powerful prognostic factors may not have become significant and may have been left unreported.

**Chapter 3: Survival, prognostic factors, and late effects of treatment in children** Chapter 3 evaluates survival, prognostic factors, and late effects of treatment in children, treated for non-metastatic high grade extremity osteosarcoma, in our institute, the Emma Children’s Hospital (EKZ)/Academic Medical Centre in Amsterdam.
For the analysis of survival and prognostic factors a retrospective survey was performed on all consecutive patients, treated between 1985 and 2006, who were younger than 18 years of age at the time of diagnosis. For the assessment of late effects of treatment, patients who survived more than 5 years after the end of treatment, were seen at an especially established outpatient clinic. Adverse effects were graded according to the Common terminology Criteria for Adverse Events version 3.0 (CTCAE) from grade 1 (mild) to grade 5 (fatal).

Seventy patients were included. The 5 year survival was 75%. Tumor size and chemotherapy response were the only factors found to independently predict overall survival. Thirty-nine of the 40 patients, surviving more then 5 years after the end of treatment had one or more adverse effect. In 2 patients this was fatal (1 cardiac and 1 bone marrow related effect). Musculoskeletal adverse effects were found in 95% of survivors, and in 70% this concerned a grade 4 (disabling) effect. This was the result of the treatment strategy, with obligatory adequate tumour resection. In the studied period a large proportion of patients underwent rotationplasty, a grade 4 event.

The second most frequently found type of adverse long term effect was auditory (in 35% of patients). This was mostly mild or moderate; some patients however suffered from severe hearing loss in speech frequencies.

Cardiac effects occurred in 20% of patients. These also mostly were mild or moderate, but 1 patient died of cardiomyopathy, 18 years after the end of treatment. Patients with ifosfamide in the treatment regimen, had significantly more cardiac adverse effects. One patient died of a myelodysplastic syndrome, 11 years after the end of treatment. Other types of adverse effects were rare and mostly not very important.

Conclusion: Survival was good (75%) in this patient group. Chemotherapy response and tumor size were of prognostic value. Late adverse effects were common, quit often disabling, and mainly musculoskeletal.

Chapter 4: The value of Colour Doppler Ultrasound for predicting chemotherapy response and survival

In chapter 4 it was investigated whether chemotherapy response and survival could be predicted with Colour Doppler Ultrasound (CDUS) after chemotherapy, but before resection of the tumor. Color Doppler ultrasound (CDUS) is a non-invasive, short procedure (24). The ultrasound system used in our study is available in most modern hospitals. CDUS was performed in 21 consecutive patients, treated in our institution for a high grade extremity osteosarcoma, before and after pre-operative chemotherapy. The Peak Systolic Velocity (PSV) in the soft tissue component of the tumor and the Quotient of Resistive Index of the feeding artery and contra lateral control (QRI) were assessed. After surgery, a pathologist,
unaware of CDUS results, assessed histological response to chemotherapy in the resection specimen. QRI-change after chemotherapy was significantly higher in histological responders compared to non-responders. There was no significant difference in PSV-change comparing any of the subgroups, and neither QRI nor PSV were directly predictive for survival.

Conclusion: CDUS appeared useful in predicting chemotherapy response (sensitivity 83%, specificity 86%), especially for negative response (predictive value for poor response 92%), but not for survival.

Chapter 5: The predictive value of serum alkaline phosphatase for predicting chemotherapy response and survival

Alkaline phosphatase (AP) is easily assessable and cheap. We aimed to determine the value of alkaline phosphatase for predicting chemotherapy response, local recurrence, and survival in patients with high grade osteosarcoma. Alkaline phosphatase is directly produced by osteosarcoma cells but the serum level of it is also influenced by the occurrence of fractures and by bone growth. For this reason patients aged under 18 years and patients with pathological fractures were excluded. A retrospective study was performed in 132 consecutive adult patients, treated for high grade, non metastatic osteosarcoma in the Royal Orthopaedic Hospital (Birmingham, UK) between 1983 and 1999.

Alkaline phosphatase levels were recorded before chemotherapy (pre-ct AP), after chemotherapy but before surgery (post-ct AP), and the change in the level of alkaline phosphatase before and after chemotherapy was recorded. The alkaline phosphatase values were divided into 3 categories: Normal (below the upper normal limit), High (raised, but less then twice the upper limit), and Very High (raised more than twice the upper limit).

We found that elevated pre-treatment AP over twice the upper normal level (“Very High”) was predictive of a worse survival. Moreover, the predictive value of a Very High pre-treatment AP for a poor chemotherapy response was 80%. The AP level after chemotherapy, but before surgery, seems to be even more useful. Survival decreased stepwise with post-ct AP values being normal, moderately raised or severely raised. The predictive value of any elevated post-ct AP for a poor chemotherapy response was 100%. A decrease of AP levels after chemotherapy appeared not to correlate with improved survival unless AP returned to normal, in which case survival was the same as in patients with a normal AP at diagnosis. We did not find a significant relationship between AP levels at any stage and local recurrence.
Conclusion: Alkaline phosphatase, measured before chemotherapy, after chemotherapy, and the change of alkaline phosphatase after chemotherapy are valuable factors in predicting chemotherapy response and survival in high grade osteosarcoma in adults.

Chapter 6: The influence of pathological fracture on surgical management, local recurrence and survival

This was established in a retrospective review of 770 patients with a high grade, non metastasized bony sarcoma of an extremity. It concerned 484 patients with an osteosarcoma, 130 patients with a chondrosarcoma, and 156 with a Ewing’s sarcoma.

Alongside pathological fracture, other prognostic factors that were analyzed were proximity of the tumor, subtype (for osteosarcoma and chondrosarcoma), chemotherapy response (for osteosarcoma and Ewing’s sarcoma), surgery type and achieved surgical margin.

Fracture occurred in 12 % of osteosarcoma patients, in 25% of chondrosarcoma patients, and in 10 % of patients with a Ewing’s sarcoma. The groups of patients with or without a fracture were in all 3 tumors comparable for sex, age at diagnose, and treatment, including achieved surgical margin. For all 3 tumors however, the fracture groups had more proximally located tumors (significantly so in osteo- and Ewing’s sarcoma). In osteosarcomas, the fracture group had a higher proportion of telangiectatic subtypes, and in chondrosarcomas the fracture showed a tendency towards more dedifferentiated subtypes. Limb salvage was done in 79% of patients with a fracture compared to 84% of patients without (p=0.17). No difference in local recurrence was found between fracture and control group in any of the 3 tumors. Comparing the group of patients where limb saving surgery was done with those who were treated with ablative surgery no difference in local recurrence was found either.

In a univariate analysis, survival in the fracture group was lower than in the control group for osteosarcoma (34% versus 58%, p<0.01) and chondrosarcoma (35% versus 63%, p=0.04), but not for Ewing’s (75% versus 64%, p=0.80). In a multivariate analysis, fracture remained a significant predictor of survival for osteosarcoma, but not for chondrosarcoma, where dedifferentiated subtype appeared to be decisive.

Of the other tested prognostic factors in the osteosarcoma patients, proximity of the tumor, surgery type, surgical margin and chemotherapy response, showed an independent predictive value for survival in the multivariate analysis. In chondrosarcoma only histological grade was independently predictive for survival, and in Ewing’s sarcoma none of the tested prognostic factors showed correlation with survival.
Conclusion: A pathological fracture in the studied bony sarcomas does not increase the chance of local recurrence. Overall survival is worse in patients with a fracture in osteo- or chondrosarcoma, but not in Ewing’s sarcoma. Fracture is an independent predictor of survival in osteosarcoma only. Limb saving surgery in fractured patients does not seem to have an influence on local recurrence or survival and therefore is thought to be safe, as long as adequate margins can be obtained.
Reference List


