Prognostic factors and late effects of treatment in localised high grade extremity osteosarcoma
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chapter 8

General Discussion and Future Perspectives
8.1 Increased survival, possibilities of reconstruction in limb saving surgery, and investment by the patient

High grade Osteosarcoma is the most common primary malignant bone tumor. It is rare with an incidence of about 3 per million, with a peak in the second decade of life(1,2).

Before the 1970’s, surgery was the only therapeutic option for patients, mainly, in 90% of cases, involving amputation of the inflicted limb. Survival was poor, about 10 to 15%(3-5). After the introduction of adjuvant chemotherapy in the early 1970’s, survival increased to around 50%. Since the 1980’s, the combination of pre-operative, neo-adjuvant chemotherapy, surgery, and postoperative chemotherapy, results in a survival rate of around 70%(6-11).

This improvement of survival is generally attributed to the effect of chemotherapy. For the choice of the pre-operative chemotherapy regimen, patients are stratified in different risk groups, depending on the stage of the disease at diagnose. After assessment of chemotherapy response, determined in the resected tumor, stratification is repeated, and chemotherapy regimen post-operatively is, if necessary, changed(6,12).

Apart from improving survival, pre-operative chemotherapy also proved to be of use in down-staging of the tumor; If the tumor reacts on chemotherapy, it decreases in volume in a number of cases. This facilitates the resection, or even makes this first possible.

Another aspect that has chanced in the last decennia is the development of imaging techniques. First computed tomography, and especially later magnetic resonance imaging, has facilitated pre-operative planning of the resection(13,14).

With all this, the surgical therapy has changed from predominantly ablative to predominantly limb saving. In about 90% of cases the limb can nowadays be preserved(6,8,9). After resection, a deficit of bone, and usually also muscles and tendons, results. Reconstruction methods have greatly improved. There now is a spectrum of possibilities for reconstruction, from biological, with bone lengthening or vascularized autografts, to complete endoprosthetic replacements. Occasionally, amputation or rotationplasty still is necessary. Each of these reconstruction methods has advantages and disadvantages(15,16). A complete biological reconstruction with, for instance, replacement of the resected bone with a vascularized fibular graft, knows on the long run excellent results with vital bone. This allows the patient eventually to lead a normal life with little or no restrictions concerning the limb(17,18). The investment for the patient, however, is high. A long period of non
weight bearing, up to 18 months postoperatively, is often required, as are sometimes re-operations (19;20). The same goes for segmental bone transport after resection. On the other end of the spectrum, reconstruction with a cemented endoprosthesis allows the patient to mobilize fully weight bearing quickly, usually already after 1 or 2 weeks. On the long run however the patient has to always take into account that he is walking with an endoprosthesis. Risk of peri-prosthetic fracture, infection, and eventually loosening is always there and will hamper the patient more or less for the rest of his life (15;21;22).

8.2 Increased number of survivors and late effects of treatment

The increase in survival of high grade osteosarcoma has resulted in a growing number of long term survivors (23). More and more is reported about long term health effects these survivors may encounter as a result of the intensive treatment they had, especially if they were children at the time of treatment. Late effects may concern secondary tumors, cardiac, neurologic or bone marrow problems, which can be invalidating or even life threatening. They can also consist of auditory, metabolic, fertility, psychological or musculoskeletal impairments, which can have a moderate, but sometimes severe impact on quality of life (24;25).

8.3 The importance of individual prognostication

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 possible realistic chance of survival, combined with the best possible functional result after surgery, giving the least possible late adverse effects of treatment.

In order to make these considerations optimally, adequate information about the survival chance of the individual patient is essential. Accurate estimation of the survival chance could improve stratification in risk groups, and ideally should be possible early in treatment, allowing early and more adequate assignment of patients to the best chemotherapy schedule.

Surgery needs to be tailored to the patient, and should be planned taking into account the expected survival chance of the patient. It is well worth motivating a patient with a high survival chance to have a biological reconstruction done, and bear with a long and intensive rehabilitation period. On the long run the result will be rewarding.
On the other hand, someone with a low chance of survival should be enabled to have a good quality of life on the short term, and should not be hindered by an unnecessary long and intensive rehabilitation. More knowledge about the relation of type and cumulative dose of chemotherapy, and of the followed surgical strategy, with late adverse effects of treatment, could lead to a more integrated decision about the total treatment, which is optimizing survival chance and minimizing late adverse effects.

### 8.4 General aim and scope of the thesis

Prognostication for individual patients remains difficult. Many prognostic factors have been reported in literature, but most of these reports do not meet the standard of modern evidence based medicine, and the value of different factors for the individual patient is not clear\(^{(26;27)}\). 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 type of treatment patients underwent.

It was decided to limit the scope of the thesis to patients with high grade, non metastatic osteosarcoma of an extremity. The reason for this was to enable studying homogeneous patient populations and rule out bias by treatment variations, allowing a proper comparison of groups regarding prognostic factors and late adverse effects. Patients, who present with metastasis, were excluded because they often are treated in a non standardized way, from a curative to sometimes only palliative perspective. For the same reason, we focused on patients with an extremity osteosarcoma. Axial osteosarcoma behaves differently, and also is treated variably. Because both chemotherapy and surgery are considered essential in the treatment of osteosarcoma, only patients were included who completed the full treatment, consisting of chemotherapy and surgery.
8.5 Discussion of the chapters of the thesis

Systematic review of the literature

Chapter 2 presents a systematic review of the literature concerning prognostic factors in high grade osteosarcoma. We tried to identify evidence-based prognostic factors in the literature since 1992 and to establish pooled relative risks of factors. Factors that were already known, and regarded a poor sign for survival, such as more proximal location and large tumors, appear to be inconsistently reported (7-9;11;28-41). Chemotherapy response, the only proven independent factor in an earlier review (26), is reported to predict outcome by most, but not all authors (28;30;42-45). Newly reported factors are mostly “indirect” factors. Most promising among these seem to be the high expression of p-glycoprotein (46-52), expression of the human epidermal growth factor receptor 2 (HER2) (28;53-56), expression of vascular endothelial growth factor (VEGF) (42;57-59), and loss of heterogeneity of the Rb-gene (60).

These factors may be of true predictive value, but it is important to keep in mind that the majority of the studies had methodological flaws (61). Because of this, simply counting the papers with a supposed predictive value is dangerous. Valid conclusions can not yet be drawn from this part of the literature.

Only 7 papers were of sufficient quality to use in a meta-analysis. Poor chemotherapy response, large tumor volume and ablative surgery could be used in a meta analysis and appear to be predictors of a bad outcome. For absence of an adequate surgical margin, although proven to be an independent factor in 2 studies (8;9), there was vast heterogeneity, so no pooling could be performed. This heterogeneity of studies and of reported data is a major problem in comprehending the literature. Different cut off points for various factors may make pooled results less reliable. Authors report on different sets of factors in their multivariate analyses, making pooling of results less valuable. Because of the relatively small sample sizes in most studies, even very powerful prognostic factors may not have become significant (62), and may have been left unreported. If the non-significant results would have been available, and could have been pooled, more precise estimates of the effect might have been possible. Moreover, usually the actual figures about prognostic factors only were published if they were significant, thus, the pooled relative risks that are calculated from these publications might be overestimated (outcome bias).

From the available information in the literature one may assume that chemotherapy response is an independent prognostic factor, a poor response increasing the risk for dying of the disease probably approximately 2.4 times. Further factors that are presumably independently predicting a worse outcome are large tumors, inadequate
excision margin, ablative surgery, age under 14 years, male gender, high alkaline phosphatase, local recurrence, p-Glycoprotein expression, and absent Erb2 expression.

We concluded that there is a need for methodologically high quality studies with more uniform study design and reporting. All results should be reported, whether significant or not. It would be most useful if raw data could be made available on line or in collaborative databases.

**Survival, prognostic factors, and late effects of treatment in the paediatric cohort, treated in the Emma Children's Hospital/AMC Amsterdam** Chapter 3 evaluates survival, prognostic factors for survival, and the occurrence of 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. The 5 year survival rate was 75%. This seems slightly higher than what is reported in other series(8;9;63). The explanation for this might be that we only included patients with localised extremity osteosarcoma, who were treated completely with pre-operative chemotherapy, resection, and post-operative chemotherapy. This was decided to allow proper comparison of prognostic factors, unhindered by treatment variations. Patients with metastatic disease or axial osteosarcoma are very often treated in a non-standardized way(64;65). Tumor size and chemotherapy response were the only factors found to independently predict overall survival, which is in accordance with earlier literature on prognostic factors(27).

All patients but one, surviving more than 5 years after the end of treatment, had one or more adverse effect. This is a high proportion compared to earlier literature, which mentions adverse effects in approximately two-thirds of patients in survivors of childhood cancer in general(23;24). Other publications, however, show that survivors of bone tumors are at higher risk for late health effects than survivors of other cancers(25;66;67) In 2 patients the adverse effect was fatal. Apart from the 2 fatal effects, which were cardiac and bone marrow related, the musculoskeletal ones were the most frequent and the most severe. No less than 95% of survivors suffered from a musculoskeletal adverse effect, and in 70% this concerned a grade 4 (disabling) effect. This is the inevitable result of the treatment strategy, in which adequate tumor resection is obligatory. In the studied period a relatively large proportion of patients underwent rotationplasty. In the CTCAE classification, absence of a limb is defined as a grade 4 event. Although it seems reasonable to score rotationplasty as such, there are studies which show comparable functional results of rotationplasty in comparison with endoprosthetic replacement, and better than after amputation(68;69). More recently, reconstruction methods have improved considerably. Over 90% of patients can be treated with limb saving surgery(15). This
will doubtlessly have a favourable effect on long term outcome and will decrease burden of long term effects.

The second most frequently found type of adverse long term effect was auditory. This is not surprising, because all of the used chemotherapy regimen contained cisplatin, which is known for its ototoxicity, especially in young children(70-73). Although mostly mild or moderate, some patients suffer severe hearing loss in speech frequencies, which can be socially invalidating.

Cardiac effects occurred in 20% of patients. These mostly were mild or moderate, but 1 patient died of cardiomyopathy, even as long as 18 years after the end of treatment. Late cardiac toxicity has been reported before, and, although uncommon, is known to have a high mortality(74). Usually, this is attributed to the use of anthracyclines. Alkylating agents, such as ifosfamide, seem to add to this effect(25;74). This is confirmed in our study; patients with ifosfamide in the treatment regimen had significantly more cardiac adverse effects. Prevention of toxicity should be aimed for if possible by lowering the cumulative dose, or by the use of cardio protective agents. Long term follow-up and alertness, should allow early detection and treatment(75-77). The myelodysplastic syndrome, which was fatal in 1 patient, long (11 years) after the end of treatment, is another effect which, although rare, justifies long term alertness.

Large scale prospective evaluation is necessary to evaluate possible prognostic factors, and for the development of more accurate ones. Attention should also be directed at adverse effects in survivors, especially at the long term results of surgical procedures. Better prognostication, for survival and for adverse effects, should lead to a more individually planned treatment strategy in order to improve both oncologic outcome and long term health status of survivors.

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. The percentage of tumor necrosis after chemotherapy still is the most consistently reported independent predictor of survival(27), but can only be assessed in the resection specimen after resection of the tumor when this can be pathologically evaluated. Chemotherapy response is an important factor in planning further therapeutic strategy after preoperative chemotherapy, both in planning of type and timing of surgery, and in further chemotherapy treatment. Earlier, pre-surgical, prediction of histological response would have obvious advantages. Clinical and conventional radiological methods, including conventional MRI, have proven not to be reliable in predicting chemotherapy response(78;79). The value of skeletscintigraphy remains controversial(80-82).
Dynamic MRI does seem to enable accurate prediction response after completion of chemotherapy (83-86). Reports about dynamic Thalium-scintigraphy and Positron Emission Tomography are promising (87-92).

A disadvantage of the above-mentioned methods is that they are time-consuming, more or less invasive, and requiring patient compliance. Therefore they are not particularly suitable for children, for whom a simple and short procedure, non-invasive, is desirable.

Color Doppler ultrasound (CDUS) is such a non-invasive, short procedure (93).

The ultrasound system used in our study is available in most modern hospitals. The procedure is simple and lasts at the most 20 minutes; there is no need for the patient to lie still. Because of the short duration of the procedure and the availability of the equipment, logistic planning is easy. These are clear advantages of the CDUS method compared to dynamic MRI. A conventional MRI will still have to be carried out pre-operatively as well, to establish extent of the tumor and relation to surrounding tissues after chemotherapy. For prediction of chemotherapy response however, CDUS would be much shorter and less invasive than a dynamic MRI. Apart from this, it is less costly. In circumstances where one has no, or little, access to dynamic MRI, CDUS could possibly be of use even more.

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.

A possible explanation for this could be the fact that CDUS, similar to other methods, does not detect small amounts of remaining viable tumor cells, because these have no effect on the vascularity of the tumor or of the afflicted limb. These small amounts of viable cells could also be the reason that chemotherapy response, although until now the most powerful prognostic factor, is not in all cases predictive.

CDUS is a relatively simple procedure, predicting chemotherapy response before surgery is carried out. The method is suitable for patients, especially children, with an extremity osteosarcoma. CDUS is widely available and not costly. It could be a useful tool for therapeutic considerations pre-operatively, and should be used more routinely in assessment of chemotherapy response.

The value of serum alkaline phosphatase for predicting chemotherapy response and survival

Even more than CDUS, alkaline phosphatase (AP) is easily assessable and cheap. Earlier reports on prognostic factors in osteosarcoma mention the predictive value of this enzyme (40;94;95), but only of the serum alkaline phosphatase measured before chemotherapy. Strange enough, no authors have established its predictive value for survival after chemotherapy, although the
biological status of the tumor after chemotherapy seems the most important factor for survival. In our study 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\cite{96,97}. The serum level of it, however, is also influenced when fractures occur, and by bone growth. Both of these cause serum alkaline phosphatase to rise considerably, regardless of the tumor activity. For this reason, in our study only patients were included, aged 18 years or older, and patients with pathological fractures were excluded.

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%. This is in accordance with other studies, addressing pre-treatment AP levels\cite{40,94,98,99}. The AP level after chemotherapy, but before surgery, seems to be even more useful. This has not been reported before\cite{100}. 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.

We concluded that 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. This factor is cheap and easy to determine and could, together with other factors, play a role in individual prognostication.

Alkaline phosphatase before and after chemotherapy should be determined routinely in adults, and further evaluated for its prognostic value in children.

**The influence of pathological fracture on surgical management, local recurrence and survival**

A pathological fracture through a bony sarcoma is thought to decrease the survival chance by spreading tumor via the fracture haematoma, or by spreading micro-metastases. It can also lead to joint involvement. The literature is unclear about the implications of a pathologic fracture on the outcome for patients with bony sarcomas\cite{101-106}. The aim of the current study was to establish whether a pathological fracture had any influence on surgical management, local recurrence or survival in patients treated for a localised high grade extremity sarcoma of bone. Apart from osteosarcoma, this was investigated for Ewing’s and high grade osteosarcoma.
Chondrosarcoma. Alongside pathological fracture, other prognostic factors were analyzed. 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). Moreover, in osteosarcomas, the fracture group had a higher proportion of telangiectatic subtypes, and in chondrosarcomas the fracture group showed a tendency towards more dedifferentiated subtypes. This is not surprising, because if bone defects are located proximally in a limb, especially in the lower limb, the risk of fracture seems higher(107). Also, telangiectatic osteosarcomas are usually more destructive to the cortical bone than other types(108).

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 revealed no difference in local recurrence either.

In a univariate analysis, survival in the fracture group was lower than in the control group for osteosarcoma and chondrosarcoma, but not for Ewing’s. In a multivariate analysis, fracture remained a significant predictor of survival for osteosarcoma, but not for chondrosarcoma, where dedifferentiated subtype appeared to be decisive.

For osteosarcoma, the literature on implications of pathological fracture is inconsistent. Glasser and Scully report worse survival for patients with a fracture, but in the study of Scully, a considerable part of the patients did not receive pre-operative chemotherapy so these results are biased(11;109). Bacci(103) found no difference in survival, neither did Abudu(101). The latter found a higher chance of local recurrence in fracture patients that were treated with limb saving surgery, but this difference disappeared after correction for surgical margin. Both Scully and Abudu compared oncological outcome for limb saving and ablative therapy and found no difference. Our findings are in accordance with this. It seems that it is not spreading of tumor cells in the fracture hematoma that leads to a worse prognosis, but rather that fracture is a symptom of a more aggressive osteosarcoma.

In chondrosarcoma, the importance of adequate resection is stressed by several authors(110-115). In a large study concerning pathological fracture in chondrosarcoma no influence of fracture on the oncologic outcome was found(102). Surgical margin and tumor grade did correlate with survival. In our patients the importance of tumor grade was confirmed. Survival was less in patients with a fracture, but in the multivariate analysis only grade appeared to be an independent prognostic factor.
For Ewing’s sarcoma our study seems consistent with earlier literature, in which authors find no difference in oncologic outcome between patients with or without a fracture\cite{106,116}. None of the studies compares ablative and limb saving surgery in fractured Ewing’s sarcoma patients, which in our study does not reveal a difference. The explanation why Ewing’s sarcoma does not show a difference in overall survival between fracture and no-fracture group, could be that Ewing’s sarcoma generally is more chemotherapy -sensitive\cite{117}. This idea is strengthened by our finding that in osteosarcoma, good chemotherapy responders do not show a difference in survival between fracture and control group.

Unfortunately we did not have sufficient information about tumor volume in the three studied patient groups to establish the influence of tumor volume. This factor might influence both survival and the chance of pathological fracture. Earlier reports about volume and pathological fracture in regard to survival, regrettably are very much contradictory \cite{8,102,106,109}.

We conclude that a pathological fracture in a bony sarcoma 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. Probably it is not the fracture in itself that causes the lower survival. It is rather a symptom of a more aggressive tumor. The influence of tumor volume should be further studied. 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.

We recommend that patients with a pathological fracture through a bony sarcoma be treated by non-operative stabilisation of the fracture (e.g. by means of a splint) and appropriate analgesia, followed by chemotherapy according to the standard protocol. After this, resection of the tumor should, as usual, be done with wide margins.

8.6 General remarks and future perspectives

Both in our literature review as in our own research it appears that the identification of prognostic factors is hampered by the rareness of the disease, resulting in relatively small patient groups in single institutions, and even in multicentered trials. Pooling of results of different research groups is hardly possible because of the lack of raw data. Even the actual numbers of non-significant factors are often not made available. Another problem is the inconsistent methodology and reporting of studies.
Possible prognostic factors may thus remain undiscovered. Pakos et al succeeded in gathering raw retrospective data from 10 large centres, treating osteosarcoma (63). This has clarified the value of several prognostic factors. Missing information however made it impossible in this large retrospective review to identify other factors. Large cooperative prospective studies as those of the European Osteosarcoma Intergroup (EOI), the Cooperative Osteosarcoma Study group (COSS), and the European and American Osteosarcoma Study Group (EURAMOS), will hopefully improve this situation. Joining forces, also in experimental research, or at least sharing the raw data of results, could greatly improve our knowledge and bring about new factors, which are more reliable for individual prognostication. Eventually it should be possible to design a nomogram, in which a number of reliable factors are combined, which can give a reliable prediction of survival chance for the individual patient. This nomogram should have the possibility to include treatment factors. With such a nomogram, treatment, chemotherapeutic as well as surgical, could be tailored to the individual patient, taking survival chance, rehabilitation time, and the chance of late effects of treatment into account. Thus an optimal combination of therapies could be offered to each single patient.
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