Prognostic factors in bone sarcomas

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Among the bone sarcomas, prognostic factors have been most extensively studied for osteosarcoma and Ewing's sarcoma, as these are usually tumours of high-grade malignancy that carry 80-95% mortality in the absence of chemotherapy. Other tumours are either too rare for systematic prognostication (malignant fibrous histiocytomas, fibrosarcomas), or they have a good prognosis with surgical treatment alone (chondrosarcomas). This short review will therefore concentrate on high-grade osteosarcoma and Ewing's sarcoma, and as they share several of the known prognostic factors, the two will be considered together under each heading.

Age

In both tumour forms, the median age at diagnosis is 14–16 years. In osteosarcoma, some reports have indicated that patients <10–12 years at diagnosis have a worse prognosis [1–3]. Also, for patients over 30–40 years of age, the prognosis in osteosarcoma is poor, both due to an inability to tolerate adequate treatment and a tendency towards non-extremity tumour sites [2, 4]. However, the importance of age as a prognostic factor in osteosarcoma is difficult to assess, as most multivariate analyses do not include patients over 30 years of age.

In Ewing's sarcoma it has been indicated that prognosis improves with decreasing age, and in one study, age <15 years remained a significant favourable prognostic factor in a multivariate analysis [5]. Whether this is a reflection of true differences in tumour biology with age, or due to more aggressive treatment in the young, remains unknown.

Sex

Some previous studies have indicated male sex to be an adverse factor in osteosarcoma [3], whereas others have not [2, 3]. One study found male sex to be an independently significant factor in multivariate analysis of overall survival [6]. This is in accordance with an analysis of all patients treated in the Scandinavian Sarcoma group (SSG) II and SSG VIII protocols, where male sex was the strongest independent prognostic factor for metastasis-free survival (Figure 1).

In Ewing's sarcoma, sex has not been found to be of prognostic significance.

Stage

For both tumours, the detection of metastases at diagnosis is of important prognostic significance. In osteosarcoma, metastatic patients only have a 20–30% long term survival, even following aggressive chemotherapy and removal of all macroscopic pulmonary disease [7]. Also, patients with metastases at diagnosis tend to have a histological response inferior to that of patients with localized disease.

In Ewing's sarcoma the situation is analogous, with 15–20% survival for patients with detectable metastases at diagnosis. Recently, the introduction of high dose therapy with stem cell rescue has indicated improvement for these patients, but the reported series are small, have short follow-up, and are heterogenous both with regard to patient selection and treatment [8].

Tumour site

For both osteosarcoma and Ewing's sarcoma, non-extremity localisation is associated with poor prognosis. In osteosarcoma (Figure 2), this is both due to a reduced possibility to perform adequate surgery and to an association between non-extremity site and higher age, prohibiting adequate chemotherapy [4]. In Ewing's sarcoma, the surgical difficulty is to some degree alleviated by the radiosensitivity of the tumour,

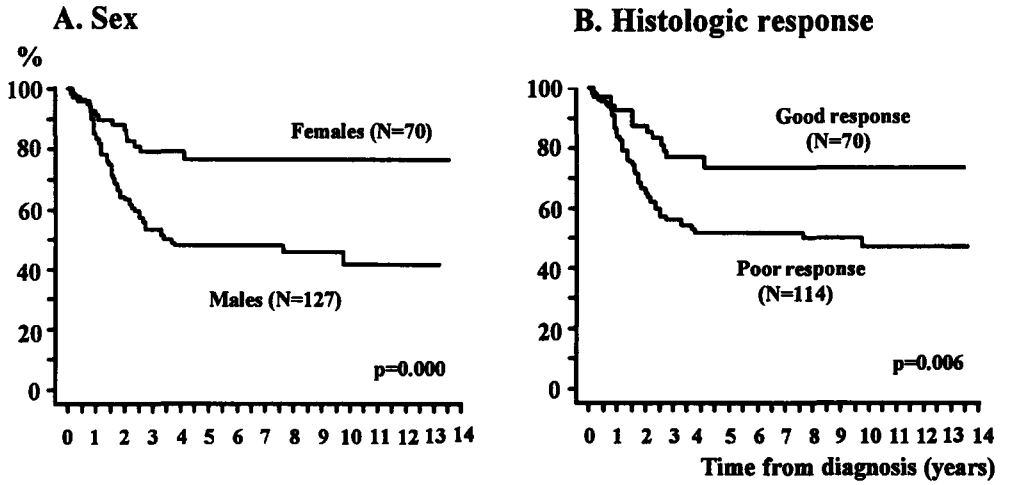

Figure 1. Combined results of Scandinavian Sarcoma Group osteosarcoma studies SSG II and SSG VIII; the two independent prognostic factors for metastasis-free survival (multivariate analysis).
Patients were divided into poor (grade I-II) and good (grade III-IV) responders according to the classification of Huvos [36].

making radiotherapy a valuable alternative or supplement to surgery [9]. However, non-extremity sites, and particularly pelvic tumours, are associated with large tumour volumes, which is an important prognostic factor (see below).

For extremity osteosarcomas, patients with tumours in the femur or humerus have been reported to have worse prognosis than more distal tumours [1, 2], but the type of extremity localisation has not been a significant factor in multivariate analyses [3].

Tumour size

Tumour volume or the largest tumour diameter are some of the most important factors in both diseases. In osteosarcoma, a recent study from the COSS group has shown that following treatment with one of three different chemotherapy protocols, only 4/53 patients with an absolute tumour volume below 150 cm^3 developed metastases, whereas for the group with larger tumours, relapse rate was 40–60%. The importance of tumour volume as a prognostic factor was maintained in a multivariate analysis [10]. In Ewing's sarcoma, a tumour diameter over 8–10 cm is a well established poor prognostic sign, irrespective of tumour localisation [11, 12].

Histological subtypes

Among the subtypes of high-grade osteosarcomas, telangiectatic tumours have been reported to have a somewhat better prognosis than the osteoblastic or chondroblastic types [1, 13]. However, histologic subtype has not been reported to be independent factors in multivariate analyses. In the Ewing family of tumours, no certain difference in outcome has been noted between Ewing's sarcoma, PNET or undifferentiated variants [14].

Primary tumour response

In patients with localized osteosarcoma or Ewing's sarcoma, histologic response in the primary tumour to pre-operative chemotherapy is probably the single most important prognostic factor for long term outcome (Figures 1 and 3) [3, 5, 10, 12, 15–17]. Thus it is appearent that the effect of pre-operative chemotherapy on the primary tumour to a significant degree mirrors the effect on the micrometastatic disease. This has recently been substantiated by a study at the Rizzoli institute, where a strong correlation was found in osteosarcoma between the response in the primary tumour and in simultanously resected pulmonary metastases [18].

Drug resistance

Tumour cell expression of the multidrug resistance (MDR) gene has recently been identified as a strong adverse prognostic factor in osteosarcoma [19]. Thus, P-glycoprotein-mediated general resistance to chemotherapeutic agents may offer an explanation to why the post-operative switch to novel agents in poor histologic responders ("salvage chemotherapy") has generally been unsuccessful [15, 20–22]. However, it should be noted that in the Bologna study, no relationship was found between P-glycoprotein expression and histologic tumour response, and that they both remained significant independent predictors of event-free survival [19].

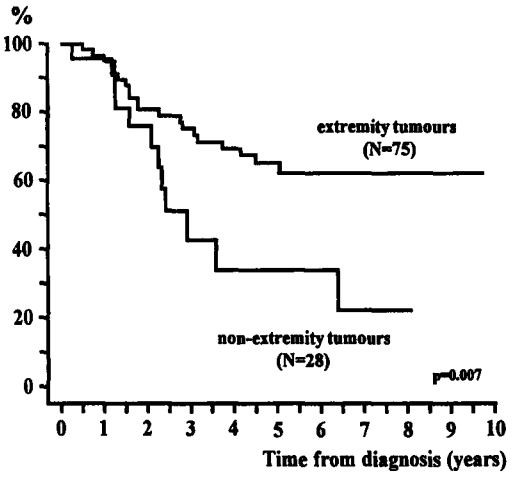

Figure 2. Overall survival in patients with high-grade osteosarcoma treated at the Norwegian Radium Hospital from 1981 to 1995 by tumour localisation. From [4].

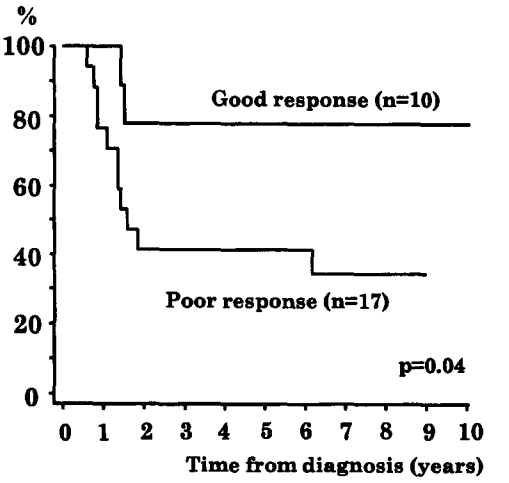

Figure 3. Overall survival according to histologic response in Ewing's sarcoma study SSG IV. Good response, Huvos grade III-IV; Poor response, Huvos grade I-II [36].

In Ewing's sarcoma MDR expression has been associated with poor response to chemotherapy, but its relationship to long term outcome remains unclear [23, 24].

Individual patient pharmacokinetics

Following high-dose methotrexate (HDMTX) treatment for osteosarcoma, serum MTX levels variy considerably between patients having received an identical dose/m^2, and there are also large variations from course to course within the same patient. Such variations may be related to age or to constitutional differences in e.g. renal MTX excretion, but are also influenced by factors such as MTX infusion time, hydration volume and diuresis [15, 25, 26]. As serum MTX levels have been positively correlated to both tumour response and survival, it follows that pharmacokinetic characteristics of individual patients may be of prognostic importance. In this context it is of interest to note that in the SSG experience, osteosarcoma histologic response is more strongly correlated to the serum MTX levels at 24 and 48 hours than to the peak end-of-infusion level, indicating that in addition to MTX dose, the rate of MTX excretion is of importance for outcome [22].

There is no reason to believe that the relationships between MTX pharmacokinetics and outcome parameters in osteosarcoma are unique to this drug, and similar studies should be done for other cytostatic agents. In this manner, one may be able to individualize chemotherapy for each patient on the basis of the patient's pharmacokinetic profile for individual agents.

Other factors

In osteosarcoma, elevated levels of serum alkaline phosphatase (ALP) has been associated with poor prognosis [27]. However, the real importance of this marker is difficult to assess, as there is inadequate methodology for age-dependent standardization of normal levels. In Ewing's sarcoma, elevated serum LDH levels and aneuploid DNA content have been implicated as unfavourable factors [24, 28], but their real importance remains poorly defined.

Summary

Based on a literature review and the SSG experience, the most important prognostic factors in high-grade *osteosarcoma* appear to be the presence of detectable metastases at diagnosis, tumour volume, old age, sex, histologic response, and possibly tumoral P-glycoprotein expression. However, for an adolescent patient with non-metastatic extremity disease, there is no consensus regarding prognostic factors at initial presentation, and currently there is thus no established method for dividing them into high- and low risk groups for the purpose of treatment differentiation. It should also be remembered that available prognostic factors have been identified only in a retrospective manner, following aggressive treatment of all patients. Thus patients in "favourable" prognostic groups may simply be patients who have had a good effect from aggressive treatment, and how they would have done with reduced treatment remains to be shown. Obviously the best method for prognostication would be the direct demonstration of micrometa-

static disease in the lungs or in peripheral blood. In the relatively near future, this may become possible with immunoscintigrapy or immunohistochemistry utilizing monoclonal antibodies [29–31].

In *Ewing's sarcoma*, the most powerful factors indicating poor prognosis are metastases at diagnosis, poor histologic response, large tumour size and possibly pelvic localisation. There appears to be a somewhat better international consensus regarding prognostic factors in Ewing's sarcoma than in osteosarcoma. Although several studies have implemented intensified treatment for poor prognostic groups [8, 32], the role (if any) of high-dose treatment with stem cell rescue remains to be proven. The same factors are prognostic both for the development of metastases and local recurrence, but in addition, surgical treatment as opposed to radiotherapy appears to reduce local failure rate [12, 17, 33, 34]. As in osteosarcoma, the near future offers promise regarding the detection and quantification of micrometastatses and minimal residual disease, by means of PCR techniques recognizing specific genetic changes in the Ewing family of tumours [35].

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