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Editorial Comment

Soft tissue sarcoma of high grade — a primary systemic disease?

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Soft tissue sarcoma is a very heterogenous disease. The incidence is rather low (1–2 cases per 100 000 population) and large databases are required to enable homogenous analysis. Major sources for data, although not population-based, are run by the EORTC Soft Tissue and Bone Sarcoma Group, the Memorial Hospital at New York (MSKCC), the French Sarcoma Group and the Scandinavian Sarcoma Group (SSG). The latter has the advantage of having collected data prospectively and derived from a uniform treatment regimen which is applied throughout Scandinavia as well as relying on centralised pathology for more than 15 years [1].

Chemotherapeutic regimens and radiotherapy can easily be standardised, however, it is difficult to compare surgical procedures. How wide is wide when performing a 'wide excision' and how 'compartmental' is a resection for an extracompartmental lesion? Surgery is always mentioned as the key modality to yield treatment results providing survival free from both local and systemic relapse. In limb sarcoma, two trials of amputation versus limb-sparing treatment did not result in improved survival rates [2,3]. Due to advances in surgical techniques, limb-saving treatment has increasingly become possible [4]. However, the rate of local recurrences is higher after limb-preserving therapy, particularly in high grade lesions, and it is matter of discussion whether this influences the overall survival of patients.

An evaluation of the AJCC (American Joint Committee on Cancer) staging system revealed that 43/100 patients developing locally recurrent sarcoma subsequently died from their disease [5]. Several major reports clearly demonstrated that operative procedures with resections margins that are not tumour-free (R1/2-resection) will be followed by local recurrence in the overwhelming majority of patients [6,7]. Does inadequate surgery compromise survival? Early reports have to be interpreted with some caution as they are influenced by retrospective sampling and inconsistent management of patients (for example, +/− radiotherapy, or chemotherapy as an adjuvant measure).

The paper by Trovik and colleagues in this issue (pp. 710–716) evaluated the metastasis-free survival of 559 patients with soft tissue sarcoma of the trunk wall and extremities. All patients had been treated with surgery only and the median follow-up was 7.4 years (range: 0.1–12.5 years). The rate of local recurrences was 18% and using a Cox regression model local recurrence was analysed as a time-dependent variable.

As expected, high histopathological grade (relative risk (RR) 3.0; 95% confidence interval (CI) 1.5–6.3) and an inadequate surgical margin (RR 2.9; 95% CI 1.8–4.6) were shown to be the main risk factors for local recurrence. High grade was also the main factor associated with metastasis (RR 3.3; 95% CI 1.8–6.3) and tumour size >7 cm was the next major contributing factor (RR 2.3; 95% CI 1.6–3.3). Surgical margin was not a risk factor for metastasis (RR 1.3; 95% CI 0.9–2). If the Cox model was carried out incorporating local recurrence as a time-dependent variable, this was shown to be the highest contributing factor (RR 4.4; 95% CI 2.9–6.8) overriding even the effect of histological grade. The authors conclude that the commonly proven association between local recurrence and metastasis must be interpreted as likely to be non-causal.

This study is of value as adjuvant radiotherapy after inadequate margins was not used and, therefore, the relationship of local recurrence and subsequent metastasis could be studied. However, there might be some bias as approximately one fourth of the patients of the original data basis were excluded from analysis due to inadequate margins and probably had high-grade lesions.

The SSG data are contradictory to an analysis at MSKCC. The study reported by Pisters suggested a contribution of positive surgical margins to tumour-specific mortality [6]. However, a subsequent study by Lewis showed that local recurrence was an independent

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predictor of both metastasis and tumour-specific survival [7], in terms of a biological marker but not based on causal relationship. However, both analyses are hampered by the fact that primary tumours and recurrences were summarised and patients had undergone adjuvant treatment.

1. What do we have to learn from the analysis by the SSG?

Residual disease after initial excision of soft tissue sarcoma should be treated by re-excision to obtain clear margins if technically possible. Tumour remnants can be found in approximately 45% of the cases [8,9].

Local recurrences develop due to inadequate surgery. However, locally recurrent disease after adequate margins clearly indicates aggressive sarcoma biology. High-grade and large (usually deeply located and/or extracompartmental, UICC/AJCC stage III) soft tissue sarcomas are at considerable risk for local and systemic relapse even if excised with clear margins. These tumours should be considered as a primary systemic disease and require combined modality therapy as the initial treatment.

Fig. 1 shows a schematic representing the potential influence of treatment-related factors (surgery, margins and adjuvant measures) and tumour biological factors

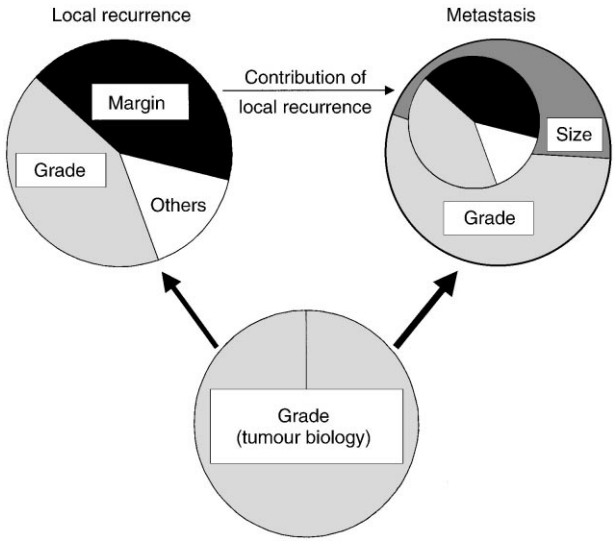

Fig.1. A model of the influence of tumour biology/grade on the development of local recurrence and metastasis in high grade sarcoma. Grade as well as margin contribute to local recurrence. Local recurrence is a factor for metastasis in the Cox analysis. Due to the fact that tumour grade and size also contribute, the effect of the surgical margin is no longer a significant factor but is overridden by tumour biology (grade) and tumour load (size).

in high-grade lesions on local recurrence and metastasis. According to the paper by Trovik and colleagues, grade and surgical margin contribute evenly to local recurrence. Grade and size contribute fairly evenly to metastasis-free survival. However, local recurrence contributes to metastasis-free survival but the surgical margin does not. Grading/tumour biology must be the underlying factor influencing both local recurrence and metastasis and thereby potentiating the effect of grade but minimising the effect of the margins. For surgical efforts in high grade lesions the message is: recurrence is at least as much tumour-driven as related to the surgical procedure.

2. What are the consequences for research work?

Presently, necrosis, mitosis, and dedifferentiation form the basis upon which the pathologist decides the grading of sarcomas [10]. Nevertheless, further markers of tumour progression and metastasis are being evaluated such as MIB-1, S phase fraction and Ki-S11 [11].

Furthermore, molecular approaches associated with DNA amplification could improve the definition of 'sarcoma of aggressive biological behaviour', for example, the *GLI* gene [12].

Detection of residual disease in sarcoma after primary treatment is of the utmost importance. In Ewing's sarcoma, karyotypic aberrations in blood-borne tumour cells (chimeric transcripts, for example, fusion products of *EWS-fli1*) were detected by RT-PCR [13]. In soft tissue sarcomas, genetic aberrations were also found but circulating tumour cells as an indicator of systemic disease are waiting to be detected. In this way, a better rationale for adjuvant and neoadjuvant therapy could be provided. The meta-analysis published in the *Lancet* in 1997 provides some evidence on the efficacy of adjuvant chemotherapy but is hampered by the fact it summarises a number of small trials [14]. Entry criteria to trials could be based on molecular tumour characteristics in the near future.

Until then the main effort of clinicians and researchers will be to perform first-line treatment at experienced centres only, applying the broad spectrum of resective surgery, as well as reconstructive procedures [4,15], to minimise the influence of surgery on the development of recurrence. Studies on systemic therapy (for example, the EORTC 62931 trial on adjuvant chemotherapy, the 62961 trial on neoadjuvant hyperthermia + chemotherapy and the 62933 trial on preoperative chemotherapy for lung metastases) should be performed as intergroup trials using the transatlantic connections of the Connective Tissue Oncology Society (CTOS).

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