



**Karolinska  
Institutet**

**Institutionen för molekylär medicin och kirurgi**

## **Markers for clinical outcome and therapy response in soft tissue sarcomas**

**AKADEMISK AVHANDLING**

som för avläggande av medicine doktorsexamen vid Karolinska  
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## ABSTRACT

Soft-tissue sarcomas (STSs) constitute a heterogeneous group of rare but aggressive tumors that originate from mesenchymal cells in almost any part of the body. Gastrointestinal stromal tumor (GIST), located in the gastrointestinal tract, is the most common type of STS. The aim of this thesis was to evaluate markers for development of progressive disease in highly malignant STS; moreover to assess the impact of adverse drug reactions and surgical margins on outcome for patients with GIST.

**Paper I.** We evaluated 101 patients with high-grade STS for known and suggested prognostic markers, particularly the insulin-like growth factor type 1 receptor (IGF-1R). A significant association was seen between high expression of IGF-1R and favorable outcome. Furthermore, large tumor size, occurrence of necrosis, high mitotic count, intralesional surgery, deep location and microvessel density were all significantly associated with poor outcome, whereas no association with outcome was found for either malignancy grade 3 or 4, infiltrative growth pattern, vascular invasion or any of the remaining immunohistochemical markers Ki67, p53, p27 or Bcl-2.

**Paper II.** In 50 patients with highly malignant STS from the same series as *Paper I* we evaluated the prognostic role of ezrin, a protein involved in metastatic spread of cancer cells. Positive expression of ezrin by immunohistochemistry was found in half of the cases and this finding was significantly associated to death from or with disease as well as to development of metastasis.

**Paper III.** The application of surgery and the tyrosine kinase inhibitor imatinib in the treatment of GIST has led to dramatically prolonged survival. However, imatinib is associated with frequent side-effects of variable severity. In a retrospective review of medical records from 75 patients who had received imatinib, we correlate side-effects to outcome, and found that moderate to severe or life-threatening toxic reactions were registered in 30 patients. Most of the side-effects occurred early. For the 34 patients with metastatic or recurrent GIST, presence of side-effects and female gender were associated with longer recurrence-free survival.

**Paper IV.** Surgery is the main and only curative treatment for GIST. Complete surgical resection with microscopically negative margin (R0) is widely regarded as a prerequisite for intended curative treatment. We divided the patients on the basis of the surgical resection margin, as with other STSs, into wide, marginal or intralesional margin at surgery or referral and retrospectively correlated this to outcome. Local/peritoneal recurrence was diagnosed in 2 of 40 GISTs with wide margins, in 7 of 24 GISTs with marginal margins, and in 13 of 19 GISTs with intralesional surgery. Cox regression analysis showed that a wide surgical margin is of significant prognostic importance independently of size and site. Furthermore, we analyzed the incidence of infiltrative growth pattern and its correlation to surgery and outcome. We found that 64% of GISTs had infiltrative growth and that this was significantly correlated to recurrent disease. However, there were no correlations to surgical margins.

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