The impact of neoadjuvant systemic therapy on the surgical management of soft tissue sarcoma

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Appendices

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Summary

Soft tissue sarcomas (STS) are rare malignancies of mesenchymal origin that can develop in any part of the body. The annual incidence is approximately five cases per 100.000 people, and they account for 1–2% of all adult malignancies. Gastrointestinal stromal tumors (GIST), a subtype originating in the gastrointestinal tract, represent about one-third of all STS. Surgery is the cornerstone of treatment, complemented by radiotherapy in selected cases. Neoadjuvant systemic therapy, which includes targeted therapy for GIST and chemotherapy for other STS subtypes, has shown value as an additional treatment in specific scenarios. In this thesis, the impact of neoadjuvant systemic therapy on response evaluation, survival, and the surgical approach in patients with STS is discussed.

In **chapter 1**, a general introduction to STS and the treatment options is provided. **Chapter 2** displays the results of a survey completed by 111 members of the Soft Tissue and Bone Sarcoma Group within the European Organization for Research and Treatment of Cancer (EORTC). The results of the survey reveal differences in neoadjuvant treatment strategies within the EORTC. These regional differences highlight the need for further research to optimize care.

Chapter 3 evaluates the value of an ^{18}F-fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography ([^{18}F]FDG PET/CT) before the start of NACT and as an early evaluation method during NACT in a retrospective study including 42 patients. Multiple associations were found between baseline or evaluation PET parameters and pathological response or recurrences. These findings underscore the potential utility of [^{18}F]FDG PET/CT in selecting patients likely to respond to NACT and in aiding decisions on whether NACT should be continued after the first cycles of chemotherapy.

The main topic of **chapter 4** is the prognostic value of radiological and pathological response for patients with RPS treated with NACT. A total of 141 patients from the prospectively maintained REtroperitoneal SArcoma Registry (RESAR) were included. No significant association was found between radiological response after NACT and survival, but a linear relationship was observed between tumor growth and increased mortality. In contrast to radiological response, progressive disease on early evaluation after a median of two cycles was associated with worse overall survival. In addition, an association between partial response and pathological response defined as >20% fibrosis/hyalinization was observed. These findings warrant confirmation in larger cohorts and further evaluation of the relationship between radiological response and survival.

In **chapter 5**, the survival benefit after NACT for radiotherapy-associated angiosarcoma (RAAS) of the breast is discussed. A total of 35 patients treated between 1994 and 2024 were retrospectively included, of whom 37% received NACT and 63% did not. A complete pathological response was achieved in 69% of the NACT group, and recurrence occurred in only one patient after 6.5 years. Oncological outcomes favored the NACT group, with improved 3-year local recurrence-free survival (100% vs. 63.9%), distant metastasis-free survival (100% vs. 47.5%), and overall survival (100% vs. 56.1%). These results suggest that NACT is effective for RAAS of the breast.

The effect of neoadjuvant systemic treatment on the surgical approach is addressed in **chapter 6**. In this study, the anticipated surgical plan was analyzed in 113 patients with large or locally advanced GIST treated with neoadjuvant imatinib. Tumor size decreased in 88% of patients and the anticipated surgical extensiveness decreased in 51%. Examples of decreased surgical extensiveness were change from a multivisceral to a monovisceral resection, or from partial gastrectomy to wedge resection. These results demonstrate that in more than half of the included patients, neoadjuvant imatinib reduced the anticipated surgical extensiveness, confirming its effectiveness in this setting.

Chapter 7 describes a multicenter study of 385 patients with gastric GIST treated between 2009 and 2022 evaluating the use of minimally invasive surgery (MIS). MIS was associated with significantly fewer postoperative complications, shorter hospital stay, and shorter operating times, while perioperative tumor rupture rates remained consistently low. No direct association was found between the use of neoadjuvant imatinib and increased use of MIS, but smaller tumor size was associated with more frequent MIS, suggesting an indirect association through tumor downsizing.

In certain cases, tumor size decreases to the extent that the lesions become difficult to locate. **Chapter 8** therefore describes a solution for this problem. The feasibility of magnetic seed localization (MSL) was evaluated in 68 surgeries for 76 lesions using Sirius Pintuition for non-palpable melanoma, Merkel cell carcinoma (MCC), and STS lesions. All lesions were successfully localized and resected, with no seed migration observed. These findings suggest that MSL is a reliable and safe technique for localizing and resecting non-palpable lesions.

In the final part, **chapter 9**, all results are discussed with a focus on response evaluation, survival, and the change in surgical approach.