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

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Chapter 1

General introduction and outline of this thesis

The term ‘sarcoma’ is derived from the Greek words σάρξ (sárx), meaning ‘flesh’ or ‘meat’, and όμα (óma), meaning ‘mass’ or ‘tumor’, so combined, sarcoma translates to ‘mass of flesh’. Nowadays, it is known that sarcomas can indeed arise from muscular tissue, but also from e.g. connective tissue, blood vessels, adipose tissue, cartilage, or bones. These types of tissue are derived from mesenchymal stem cells, originating from the embryonic mesoderm (1). The mesoderm develops into many different types of cells, resulting in the current distinction of more than one hundred histologic subtypes of sarcoma (2).

Due to its origin, a sarcoma can arise at any anatomical site in the body and affect individuals across all age groups. This diversity leads to a wide range of symptoms, clinical courses, and treatment approaches. Based on these characteristics, sarcomas are broadly categorized into two groups: soft tissue sarcomas (STS) and bone sarcomas (BS)(2). Among the STS group are gastrointestinal stromal tumors (GIST), which arise in the gastrointestinal tract. GIST are distinct from STS due to their unique gastrointestinal origin and their own clinical characteristics and type of treatments. Consequently, GIST are often treated as a separate entity. Both worldwide and in the Netherlands, approximately 86% of all sarcomas are classified as STS, with one-third of these being a GIST, while BS account for the remaining 14% (3, 4). This thesis will solely focus on STS and GIST.

Soft tissue sarcoma

STS is a rare malignancy with an incidence of approximately 5 per 100.000 patients annually in Europe (5). Together, all STS account for only 1-2% of all malignancies in adults and they can arise at any age. Young adults are less frequently affected and the incidence increases drastically after the age of 50, resulting in a mean age of onset of 58 years. At presentation, nine out of ten patients have localized disease while the tenth patient presents with a metastasis (4). The most common location for a STS in the Netherlands is the extremities (42%), followed by the trunk wall (32%), head & neck (15%) and retroperitoneum & mediastinum (11%) (3). Worldwide, the percentage of STS in the retroperitoneal cavity is higher with approximately 20% (6).

Besides location, there are multiple other tumor characteristics to differentiate between STS. One of these characteristics is the Federation Nationale des Centers de Lutte Contre le Cancer (FNCLCC) grading system (7, 8). This grading is based on three aspects; tumor differentiation, mitotic count and tumor necrosis. The FNCLCC outcome differentiates between high-grade (FNCLCC grade II and III) and low-grade (FNCLCC I). This grading system has proven itself as one of the best predictors of prognosis for STS (9-11), and therefore aids in making treatment decisions.

Other prognostic factors are tumor size, the depth of the tumor, especially in extremity and trunk wall STS, and the histologic subtype (12). When taking all STS into account, the most common ones in the Netherlands are liposarcoma (LPS)(21%), followed by leiomyosarcoma (LMS)(11%). Liposarcomas are often divided in in well-differentiated LPS (WDLPS) and dedifferentiated LPS (DDLPS). When focusing solely on high-grade (FNCLCC grade II and III) STS, the most frequently found subtypes are sarcoma not otherwise specified (NOS) (23%), LPS (19%), myxofibrosarcoma (11%), angiosarcoma (11%), and LMS (9%) (3). The most frequently seen histologic subtypes in retroperitoneal cavity are WDLPS, DDLPS and leiomyosarcoma (13).

The combination of the rarity and heterogeneity of STS often results in a long diagnostic pathway (14). The symptoms at first presentation vary greatly for every STS. It happens often that a sarcoma is present for months or years before symptoms, such as feeling a lump, are noticed. This often delays a visit to their general practitioner (GP). The referral from GP to a peripheral hospital, and from the peripheral hospital to a sarcoma expert center, is often delayed due to unfamiliarity with the disease. Even in an expert center, obtaining a definitive diagnosis can take longer due to the complexity and rarity of the tumor. The longer the diagnostic pathway, the longer before the patient receives treatment. Meanwhile, the STS can grow in size, increasing the difficulty of complete resection and the chance of metastasis, which consequently has an impact on survival (12).

Although dependent on many factors, the overall survival for STS is low. The five-year survival rate is between 60% and 66% (15, 16), with significant variability depending on tumor subtype. In the United states of America, the 5-year cause-specific survival ranged from 53.8% to 99.2% for angiosarcoma and dermatofibrosarcoma, respectively (17). Approximately half of the patients with high-grade STS will eventually develop incurable disease (10), and for patients with metastatic disease, the median overall survival is only 12 to 20 months (18). In the Netherlands, the five-year survival rates for low-grade and high-grade STS are 81% and 46%, respectively (3). The current survival numbers underscore the urgent need for advancements in the treatment and care for STS patients.

GIST

Gastrointestinal stromal tumors (GIST) originate from the interstitial cells of Cajal, often referred to as the ‘pacemaker’ cells of the gastrointestinal tract due to their role in regulating peristaltic movement (19). As previously mentioned, GIST are typically treated as a distinct entity because of their unique origin and the relatively high proportion of STS cases that they represent (33%). Despite being the most prevalent subtype of STS, with an annual incidence of 1–1.5 cases per 100.000 individuals, GISTs account for less than 2% of all gastrointestinal tumors (20, 21). GIST can develop throughout the whole gastrointestinal tract, however,

they predominantly arise in the stomach (60%) and the small intestine (35%), with the remaining 5% arising in the colon, rectum, or esophagus (22).

In the Netherlands, the median age at diagnosis is 67 years and in 90% of the cases patients do not have metastases (3). Globally, the percentage of localized disease at diagnosis is less with 68-75% (23, 24). Reasons for a patient with a GIST to visit a doctor usually are abdominal pain or obstipation, though GIST can also present as a gastrointestinal bleeding. Approximately 80% of patients present with symptoms, while in the remaining 20%, the tumor is discovered incidentally and while being asymptomatic (25).

When diagnosed, GIST are categorized according to the Miettinen criteria. Where the FNCLCC grading system for STS differentiates based on tumor differentiation, mitotic rate and necrosis, Miettinnen et al. differentiates based on mitotic rate, tumor size and location (22, 24). The Miettinen outcome prediction is based on the 5-year risk of recurrence and is categorized as very low risk, low risk, intermediate risk and high risk. The risk category has a prognostic value and also aids in making treatment decisions. Another tumor characteristic influencing the choice of treatment is mutational status. Up to 80% of all GIST harbor a mutation in the KIT-oncogene and another 15% in the PDGFR- oncogene (19).

Nowadays, independent of the GIST being localized disease at diagnosis, around 33% of the patients with GIST eventually develop metastases (26). Most common locations for these metastases are the liver and the peritoneum (27). The median survival for metastasized patients is approximately 62 months (28). Altogether, the 5-year overall survival for GIST patients, including localized and metastasized disease, is 74-77% (3).

Angiosarcoma

Six chapters in this thesis focus on different types of STS or a GIST, except for **chapter 5**. All patients discussed in that chapter had an angiosarcoma, which is a histologic subtype comprising 2-4% of all STS. The underlying cause of angiosarcoma remains largely unclear; however, these tumors are categorized into primary and secondary forms (29). Secondary angiosarcomas are further divided into subtypes linked to ultraviolet exposure, chronic lymphedema (Stewart-Treves syndrome), or prior radiotherapy treatment (30, 31). Due to extensive use of radiotherapy as treatment for breast cancer, the most common location for radiation associated angiosarcoma is the breast. **Chapter 5** will focus on this subtype of sarcoma on that specific location, which is known for the low chance of survival, with a 5-year overall survival varying from 28% to 54% (29, 32, 33).

Treatment

In 'The Emperor of All Maladies: A Biography of Cancer', a book written by Siddhartha Mukherjee, the history of cancer treatment is summarized. The first description of cancer comes from an ancient Egyptian text from 2500 BC, where tumors of the breast were described. In the thousands of years to follow, resection of the tumor became and remained the only cure for cancer. In the 1890s, William Halsted, an American surgeon, introduced the radical mastectomy for breast cancer, arguing that not only the cancer should be removed, but also as much surrounding tissue as possible. Around the same time, the first reports of radiotherapy as cancer treatment were published, and in the 1920s, the radiation techniques became more refined and were increasingly adopted in clinical practice. The next breakthrough was the discovery of chemotherapy around 1940 by Sidney Farber, who is now called the "father of modern chemotherapy". He developed Aminopterin causing remission in pediatric leukemia patients, which paved the way for the development of other chemotherapy types. The following practice changing discovery occurred in the 1990s, when the first targeted therapy was developed for chronic myeloid leukemia. The Times magazine announced the development of these new drugs as 'the new ammunition against cancer'. Targeted therapy precisely identifies and attacks specific molecules involved in cancer growth and progression, unlike chemotherapy, which generally affects rapidly dividing cells, including both cancerous and healthy cells.

Mukherjee describes that chemotherapy first was used in the metastatic setting only, but its potential as additional treatment to surgery for primary tumors became clearer in the 1970s. The first large trial proving the value of adjuvant chemotherapy in treating cancer was the National Surgical Adjuvant Breast and Bowel Project (NSABBP) trial (34), which was open for inclusion for patients with breast cancer between 1972 and 1974. Adjuvant chemotherapy aims to treat potential micrometastases at an early stage, thereby improving overall survival. A decade later, the first studies describing the use of neoadjuvant chemotherapy (NACT) were conducted, including patients with osteogenic sarcomas (35, 36). The benefit of neoadjuvant compared with adjuvant was the potential downsizing of the tumor resulting in less extensive resections and higher chances of clear resection margins, plus the opportunity to do response evaluation (37). Since then, the role of (neo)adjuvant chemotherapy or radiotherapy, and later targeted therapy, has been studied for many different types of cancer, including soft tissue sarcoma.

Currently, the cornerstone of treatment for extremity and trunk wall STS is surgery with clear margins. Neoadjuvant RT (NART) and/or NACT is considered in specific cases. Targeted therapy does not have a role in the treatment of STS, except for GIST (38). Treatment of extremity and trunk wall STS are discussed in one chapter in

the ESMO guidelines, although extremity STS are better represented in the practice changing trials.

The additional value of adjuvant RT in terms of local control for FNCLCC grade II-III STS has been proven by trials initiated in the 1980s (39, 40). Subsequent studies found no significant difference in oncological outcomes between adjuvant radiotherapy and NART. However, the advantages of NART, including reduced long-term morbidity and occasional tumor downsizing before surgery which facilitates achieving clear margins, have led to its adoption as the preferred approach (41, 42).

The role of (neo)adjuvant chemotherapy in primary extremity and trunk wall STS has been subject to greater debate compared to the role of NART. Following the publication of the NSABBP trial in the 1980s (34), which established the role of adjuvant chemotherapy, 18 subsequent studies have investigated its efficacy in STS. In 2008, Pervaiz et al. conducted a meta-analysis of these studies, demonstrating that adjuvant chemotherapy provided a survival benefit for STS patients (43). However, four years later, the EORTC 62931 trial, the largest study of its kind at the time, failed to show significant improvements in relapse-free or overall survival (44). The lack of statistical significance in this trial was attributed to its broad inclusion criteria, raising the possibility that adjuvant chemotherapy may be more effective in larger, grade III extremity sarcomas. Again four years later, in 2016, Gronchi et al. demonstrated the non-inferiority of three neoadjuvant cycles of chemotherapy to three neoadjuvant and two adjuvant cycles of chemotherapy (45). Since then, chemotherapy in the neoadjuvant setting is considered for STS, but the actual survival benefit was still not established. In 2020, Gronchi et al. published ISG-STS 1001 trial, demonstrating no difference between histology-tailored neoadjuvant chemotherapy or anthracycline plus ifosfamide neoadjuvant chemotherapy for patients with localized high-risk STS (46).

In 2017 and 2018, the PERSARC (47) and Sarculator (48) nomograms were introduced, respectively. Both tools predict local recurrence, distant metastasis, and overall survival for extremity STS based on factors such as tumor size, grade, histology, and patient age. In 2021, Pasquali et al. published a post hoc analysis of the ISG-STS 1001 trial, stratifying patients according to survival predictions generated by the Sarculator and assessing the impact of NACT within these subgroups (49). The analysis revealed a significant survival benefit for patients with a predicted 10-year overall survival below 60%. Acem et al. conducted a comparable study and observed improved survival among patients receiving NACT who had a predicted 5-year survival below 66% based on the PERSARC (50). While these findings are based on post hoc analyses, the use of nomograms in selecting patients for NACT is currently included in the guidelines (38).

For primary retroperitoneal sarcomas (RPS), the same multimodality treatment is considered, meaning that resection is the mainstay treatment, and that NART and NACT are only used in specific cases. Three meta-analyses demonstrated the positive effect of (neo)adjuvant RT for RPS in terms of local control and survival, but the level of evidence of the included studies was low (51-53). Within these studies, no clear oncologic superiority of neoadjuvant or adjuvant RT was observed. However, NART was preferred due to reduced toxicity, improved target volume delineation, and lower risk of severe late fibrosis (54). Based on that information, the STRASS trial was initiated, randomizing patients with resectable primary retroperitoneal LPS and LMS between surgery versus surgery and NART (55). Initial analysis after 3 years of follow-up did not show a significant improvement in abdominal recurrence-free survival in patient who received NART. However, after pooling patients from the STRASS trial and patients with the same types of RPS, but treated outside the trial (the STREXIT cohort), a propensity-score matched analysis demonstrated significantly improved abdominal recurrence-free survival in patients with WDLPS and low-grade DDLPS who received NART (56).

The role of NACT in RPS is even less defined than in extremity STS, primarily due to the lack of trials focused exclusively on this location of STS. Patients with RPS were included in some before mentioned studies on NACT for STS, but they often represented only a small part of the total study population. Multiple retrospective studies evaluated (neo)adjuvant chemotherapy but the results are contradicting (57). Currently, the STRASS 2 trial is open, which is a randomized phase III trial comparing surgery versus surgery and neoadjuvant chemotherapy for retroperitoneal LMS or high-grade DDLPS (58). This is the first NACT trial including only RPS. The results will be suspected by the end of the 2020s.

While surgery is also the standard treatment for GIST, radiotherapy and chemotherapy are no part of the treatment in the primary setting. For GIST the additional treatment modality to surgery is targeted therapy in the form of imatinib. Especially GIST with a KIT mutation, representing 80% of all GIST, are sensitive to imatinib. While imatinib was first used in the metastatic setting (59, 60), Dematteo et al. (61) and Joensuu et al. (62) demonstrated a survival benefit in patients receiving adjuvant imatinib for high-risk GIST. High-risk is defined based on mitotic count, location and tumor size according to Miettinen (22, 24). Based on these results, 3-year adjuvant imatinib is given on patients with a 5-year risk of recurrence above 50%. Imatinib in the neoadjuvant setting has not been proven to have an impact on survival, but it is recommended to give in case of suspected unresectability or in case of an extensive and/or multivisceral resection (63). In addition, neoadjuvant imatinib may reduce the risk of tumor rupture, which is an independent predictor of recurrence, by downsizing the tumor and inducing hyalinization (64).

Difficulty of phase III randomized trials

While the role of NART for STS is established through large phase III randomized trials, the holy grail of medical research, clear comparable evidence is lacking for neoadjuvant systemic treatment. This limitation arises mainly from the rarity of STS, which results in a significant barrier to conducting sufficiently powered trials. For instance, although recent knowledge suggests that high-risk extremity STS might benefit from NACT, the incidence of high-risk sarcomas according nomograms is so low that it would take many years and many centers to complete a trial capable of demonstrating a survival benefit in this subgroup.

Another difficulty in conducting a randomized phase III trials on NACT is the heterogeneity of STS. For instance, the STRASS 2 trial focuses solely on retroperitoneal LMS and high-grade DDLPS, aiming to provide insights into whether NACT improves survival in these specific subtypes. If a significant result will be found, this approach leaves unanswered questions regarding other histologic subtypes, such as retroperitoneal FNCLCC grade II DDLPS, synovial sarcomas, malignant peripheral nerve sheath tumors, or sarcoma not otherwise specified (NOS). However, restricting the trial to LMS and high-grade DDLPS is well-justified, as including other histologic subtypes could reduce the impact of findings by making it unclear which subtype is driving the results. This exemplifies the dilemma in designing randomized phase III trials for STS.

A third challenge in designing these trials is the ethical consideration. For example, the efficacy of neoadjuvant imatinib for large GIST with specific mutations, or NACT for high-risk extremity sarcomas, is supported by such substantial evidence that randomizing patients to a group not receiving these treatments would raise ethical concerns. These three challenges (rarity, heterogeneity, and ethical constraints) create the current situation where the evidence for NACT or neoadjuvant imatinib in specific situations remains insufficient to convince all clinicians, but at the same time, the prospect of conducting additional large phase III randomized trials in the near future appears unlikely.

Outline of the thesis

Since NAST for STS is already used in clinical practice for specific cases, new research questions and topics for debate arise. To answer these new questions, observational cohort studies are of increasing importance due to the difficulty of initiating a randomized phase III trial on these topics. In this thesis, we aim to attribute to the following three topics concerning NAST for STS:

1. Response evaluation
2. Patient selection for improving survival outcomes
3. The surgical approach

In **Chapter 2**, all three topics are discussed through a survey on current practices in the neoadjuvant treatment of extremity STS across Europe. The following two chapters focus on response evaluation. **Chapter 3** describes the role of [^{18}F]FDG PET/CT in patient selection and early response evaluation in patients with STS who receive NACT. In **chapter 4,** the prognostic value of radiologic and pathologic response in RPS is discussed. The next chapter, **Chapter 5,** describes the survival benefit of NACT in a specific subtype of STS; radiation associated angiosarcoma of the breast. The last three chapters discuss changes in the surgical approach. **Chapter 6** describes the change in the planned surgical strategy after neoadjuvant imatinib for patients with a GIST. **Chapter 7** describes the influence of the increased use of minimal invasive surgery in patients with a GIST, of which a substantial part is treated with neoadjuvant imatinib. **Chapter 8** discusses the feasibility of magnetic seed localization in STS lesions that are pretreated with NACT or an isolated limb perfusion.

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