Prognostic factors in soft tissue sarcoma

Population-based studies on comorbidity, biomarkers, and methodological aspects

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PREFACE

The PhD thesis is based on studies carried out during my employment at the Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark.

The thesis is based on the following five papers:

I. Maretty-Nielsen K, Aggerholm-Pedersen N, Keller J, Safwat A, Baerentzen S, Pedersen AB. Population-based Aarhus Sarcoma Registry: validity, completeness, and incidence of bone and soft tissue sarcomas in western Denmark. Clinical Epidemiology 2013; 5: 45–56

II. Maretty-Nielsen K, Aggerholm-Pedersen N, Safwat A, Jørgensen PH, Hansen BH, Baerentzen S, Pedersen AB, Keller J. Prognostic factors for local recurrence and mortality in adult soft tissue sarcoma of the extremities and trunk wall: a population-based cohort study of 922 consecutive patients. Acta Orthopaedica 2014; 85(3): 323-32

III. Maretty-Nielsen K, Aggerholm-Pedersen N, Safwat A, Baerentzen S, Pedersen AB, Keller J. Prevalence and prognostic impact of comorbidity in soft tissue sarcoma: a population-based cohort study. Acta Oncologica 2014; 53(9): 1188-96

IV. Maretty-Nielsen K, Aggerholm-Pedersen N, Keller J, Pedersen AB, Baerentzen S, Safwat A. Pretreatment biomarkers as prognosticators for survival in adult patients with non-metastatic soft tissue sarcoma: Does adjustment for comorbidity change the picture? Submitted

V. Maretty-Nielsen K, Aggerholm-Pedersen N, Keller J, Safwat A, Baerentzen S, Pedersen AB. Relative mortality in soft tissue sarcoma patients: a Danish population-based cohort study. BMC Cancer 2014; 14: 682

ABBREVIATIONS

ASR	Aarhus Sarcoma Registry
CDR	Danish Cause of Death Registry
CI	Confidence interval
COD	Cause of death
CPR	Civil personal registration
CRP	C-reactive protein
CT	Computed tomography
DAG	Directed acyclic graph
DCR	Danish Cancer Registry
GIST	Gastrointestinal stromal tumor
Gy	Gray
HR	Hazard ratio
ICD	International Classification of Diseases
ICD-O	ICD for Oncology
IR	Incidence rate
IRR	Incidence rate ratio
MFH	Malignant fibrous histiocytoma
MR	Mortality rate
MRI	Magnetic resonance imaging
MRR	Mortality rate ratio
NLR	Neutrophil to lymphocyte ratio
NPR	National Patient Registry
NPU	Nomenclature, Properties and Units
RM	Relative mortality
RMR	Relative mortality rate
STS	Soft tissue sarcoma
WHO	World Health Organization

INTRODUCTION

Soft tissue sarcomas (STS) are rare tumors accounting for less than 1% of all cancers, corresponding to approximately 200 new cases in Denmark annually.[1]

They comprise a heterogenic group of malignancies arising from the embryonic mesoderm, and are classified according to their presumed tissue of origin, or their morphological appearance, into more than 50 histological subtypes. The most common subtypes include pleomorphic sarcoma (previously named malignant fibrous histiocytoma), liposarcoma, and leiomyosarcoma. STS can occur at any age, but is most commonly seen, except for a few histological subtypes, in middle-aged adults. Although they can arise in any anatomical location or organ in the body, the majority occurs in the muscle groups of the extremities and trunk wall. Most sarcoma arise *de novo* without identifiable etiology, even though previous irradiation and predisposing genetic mutations have been shown to be associated with certain histological subtypes.

The treatment of STS in the extremity and trunk wall consists primarily of surgical excision with a margin of surrounding tissue. This is usually combined with different regimes of radiotherapy, administered either pre- or postoperatively, according to depth, grade, margin, and local preferences. The use of adjuvant chemotherapy as part of the standard treatment is, except for certain histological subtypes, still controversial. While meta-analyses have suggested increased survival in high-risk patients, this has not been confirmed in randomized controlled trials.[2-4]

Even though the diagnostic tools, treatment possibilities, etc. have changed significantly during the last decades, no apparent change in the prognosis for patients with non-metastatic STS has been seen. Approximately 20% develop local recurrence, while 30% develop distant metastasis, most frequently to the lungs. The majority of patients with metastatic disease will die of their STS. Thus, in order to identify patients who might benefit from more intensive treatment, studies of prognostic factors are crucial.

Studies of STS are often complicated by the rarity of the disease, rendering it difficult to conduct high evidence research such as randomized controlled trials. Thus the majority of studies are based on retrospectively collected data from major tertiary sarcoma units. These data are often compiled into clinical databases, which ensure large sample sizes, long follow-up periods, and high external validity. However, when clinical databases are used, validation of data is either not reported or not done, although it is a crucial factor in determining the quality and value of the results reported.

Hence the aim of this thesis was to identify prognostic factors in STS using population-based, validated data.

BACKGROUND

The main focus of this thesis is the prognosis of patients with STS located in the extremities or trunk wall. Prognosis is generally used to denote a prediction of the course of a disease following its onset and can be a description of either the natural course of the disease (i.e. without any treatment) or the clinical course (i.e. with medical treatment).

METHODOLOGICAL PROBLEMS IN STUDYING SOFT TISSUE SARCOMA (STS)

In general, prognostic studies of STS patients are limited by the rarity of the disease and thus the low number of patients. In order to conduct research with a high level of evidence, randomized controlled trials are usually preferred over observational studies, which suffer from the problem of unmeasured confounding. However, the large number of patients needed, the relatively short follow-up periods, as well as the expensive set up make this type of study difficult to perform. Therefore, most studies on prognosis in STS are based on data from major tertiary centers, clinical databases, or large registries.

The use of clinical databases and registries has a number of apparent advantages, including a large number of patients, prospective collection of data independently of specific studies, as well as low costs. However, the use of databases and registries entails some crucial limitations that are important to properly address. One of the major issues is the quality of the database or registry used, i.e., the completeness and correctness of registered data. The validation of data used in studies is a very fundamental issue that determines the quality and value of the reported results. Yet, in most of the published material, data validation is either not done or not reported.

Additionally, the majority of the few existing STS databases are based on data collected from individual centers with major tertiary referral practices or pooled from different centers. Studies from these databases might, suffer from selection bias due to including a higher proportion of complicated cases. Therefore, another possibility is to use population-based databases or registries, i.e., which include all patients in a well-defined geographical region, limiting the risk of bias due to selection.

To assess whether a database is in fact population-based, validation against another data source, e.g., a national cancer registry, is needed in order to determine the completeness of the patient registration. One of the existing population-based registries, the SSG Register, which has registered STS patients prospectively in Norway and Sweden since 1986, reports more than 90% completeness of patient registration when compared with the National Cancer Registries.[5,6] However, it is difficult to determine whether the analyses of completeness were based on individual or group levels. A comparison on the group level is problematic and may result in misleading estimates.

PROGNOSTIC FACTORS

A prognostic factor is a variable that estimates the risk of an outcome of interest at a specific time. Prognostic factors are used not only to inform patients about the expected prognosis, but also to determine diagnostic procedures, treatments, and follow-up regimens. In this thesis we focus on factors for non-metastatic STS in the extremity and trunk wall that are relevant at the time of diagnosis and prognostic for local recurrence and mortality. In order to separate biological and treatment factors, prognostic factors are often divided into three types: patient-related, tumor-related, and treatment-related factors. Patient-related factors include age, sex, duration of symptoms, and calendar year at diagnosis. Tumor-related factors include anatomical location, depth, compartmentalization, size, and grade. Treatment-related factors include unplanned surgery, type of surgery, surgical margin, radiotherapy, and chemotherapy.

LITERATURE ON PROGNOSTIC FACTORS

Patient-, tumor-, and treatment-related factors have been studied numerous times in STS. In order to outline the existing literature, we used the following query in Medline: ("sarcoma"[MeSH] OR soft tissue sarcoma") AND ("prognosis"[MeSH] OR "prognosis" OR "prognostic factor") AND ("survival"[MeSH] OR "survival" OR "mortality"[MeSH] OR "mortality" OR "local recurrence" OR "recurrence-free" OR "local failure"). This resulted in 8184 hits. To exclude studies not studying STS, we repeated the search without including the "sarcoma" [MeSH]. This resulted in 1190 hits. After reviewing the titles of these, 214 papers were selected. Based on a preliminary review of these 214 papers and the data available in the ASR, we decided to investigate the following prognostic factors: age, duration of symptoms, size, depth, compartmentalization, location, grade, surgical margin, and radiotherapy and their impact on local recurrence and disease-specific mortality. Studies that did not investigate these factors, which did not report local recurrence or disease-specific mortality, or which included less than 100 STS patients were excluded, leaving 58 relevant studies. Since no studies investigated the correlation between duration of symptoms and disease-specific mortality, studies investigating the correlation between duration of symptoms and overall mortality were included. Finally, the reference lists of the most recent studies were reviewed, revealing 17 additional papers. The summarized results of the studies regarding the prognostic value of

each of the factors on local recurrence and mortality are shown in Table 1. Descriptive data on the studies, including number, study period, and study population, are presented in Appendix I.

In summary, the prognostic role of **age** has not been clearly established. While the majority of studies found a significant impact on disease-specific mortality[7-11], but not on local recurrence[12-22], some studies with a significant number of STS patients report the opposite.[7,8,20,23-25] This might be explained by the manner in which age has been analyzed. All but two studies[20,26] analyze age as a continuous linear or categorical variable, usually dichotomized. Gronchi et al. analyzed age as a continuous non-linear variable and reported that it had no independent impact on either local or disease-specific mortality, while Biau et al. found that age had a significant impact on local recurrence.[20,26]

The impact of **duration of symptoms** on local recurrence and disease-specific mortality has, to our knowledge, not previously been investigated. The impact on overall mortality after adjustment for important confounders has only been investigated in few studies, and their results have been highly contradictory.[27-33] Some studies reported no prognostic impact of duration of symptoms, while others reported that a short duration of symptoms was associated with increased mortality, and finally others reported that a short duration of symptoms was associated with decreased mortality.[27-33] All of these studies analyzed duration of symptoms as a categorical variable, which might explain the contradicting results.

Tumor size is defined as the largest diameter of the tumor, determined either on the unfixed pathological specimen or the diagnostic imaging. However, the majority of studies do not report their method of determining the size. Tumor size is one of the most consistently reported prognostic factors for mortality, with the vast majority of studies showing that mortality increases with tumor size.[7-9,11,20,23-25,34-37] The prognostic impact for local recurrence is still controversial, with some larger studies reporting an impact[7,8,21,22,35,38], while others report no impact.[12,13,20,24,26,36,37,39,40] Most studies analyze tumor size as a categorical variable, often with different cut-off values, which might explain the difference in impact on local recurrence. This is supported by Zagars et al., who report that there is a significant impact on mortality when 5 cm is used as a cut-off value, but not when 10 cm is used.[8]

The tumor **depth** is defined in relation to the deep fascia, subcutaneous tumors being considered superficial and tumors below the deep fascia being considered deep. The literature regarding the prognostic value of depth on local recurrence and mortality varies substantially. In contrast to the majority of the published studies, a recent study comparing the 6th and the 7th version of the staging system of American Joint Committee on Cancer (where depth is no longer included) found no significant difference, supporting that depth is not an independent prognostic factor.[7,9,11,20,23,36-39,41] However since deep tumors tend to be larger than superficial ones, adjusting sufficiently for tumor size is essential in order to properly address the independent prognostic impact of depth, and some authors argue that the prognostic impact of depth is explained by the close correlation with tumor size.[42]

Compartmentalization is defined as whether or not the tumor is located in a well-defined fascial compartment, e.g., the anterior compartment in the thigh. Tumors growing infiltratively into more than one compartment or also involving superficial tissue are considered extracompartmental. The literature regarding compartmentalization as a prognostic factor is limited and consists of a few, older studies with small numbers of patients. Overall, the impact on both local recurrence and disease-specific mortality varies. The two largest studies by Rydholm et al.[34] and Gaynor et al.[43] reported a significant impact; however, other studies found no impact.[16,17,44-46]

Tumor **location** is often categorized into upper, lower, and trunk locations. In studies not limited to tumors located in the extremity and trunk wall, tumors in retroperitoneum, abdomen, genitalia, and head and neck are often analyzed as separate categories. Most larger studies show that location is an important prognostic factor for mortality[8-11,23,25,35], but not local recurrence[7,23,38,47], even though some show the contrary.[7,8,21,35,40] These differences might be caused by exclusions of different anatomical locations in the populations studied.

Histological grade is, along with tumor size and surgical margin, the most well-established prognostic factor. The overall purpose of grading systems is, based on the histological parameters, to evaluate the degree of malignancy and thus identify patients at greater risk of dying. Histological grade was first introduced by Broders in 1920 in a study that analyzed the impact of histological grade on patient outcome in carcinomas of the lip.[48] Since then, many grading systems have been developed and validated for STS.[21,49-53] Most of these grading systems are based on the same principles, i.e., mitotic count, cellularity, and differentiation, grading patients into 2 to 4 categories. The two most widely used grading systems are the National Cancer Institute (NCI) system and the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) system.[52,53] Even though different factors and different cut-off values are used in the different grading systems, all systems have proven to correlate with the risk of mortality in patients. Virtually all studies have reported histological grade as a significant prognostic factor for mortality and most have reported the same for local recurrence.[7-9,23-26,35-41,47] Contrary to this, Biau et al. reported only a minor prognostic impact of grade on local recurrence in a cohort of 1668 STS with non-metastatic disease, when analyzed in a competing risk setting.[39]

Standard treatment of STS involves surgical excision with a **margin** of surrounding tissue. Overall, no clear consensus on the adequate margin exists and the interpretation of the existing literature is complicated further by the use of different definitions, which are not always clearly described. The most widely used definitions include Enneking's as well as the R classification from the AJCC and UICC.[92,93] According to Enneking's definitions a excision is defined as intralesional if the incision is within the tumor; as marginal if the incision is within the pseudocapsule; as wide if the tumor is surrounded by a cuff of normal tissue; or as radical if the tumor is surrounded by a complete muscle compartment.[94] The R classification denotes the presence or absence of residual tumor after treatment and categorizes patients into: no residual tumor, microscopic residual tumor, macroscopic residual tumor, or presence of residual tumor cannot be assessed.[92,93] Other terms such as "positive" or "negative" margins are used, even though the definition of these terms is seldom elaborated on. The surgical margin has been shown to be closely correlated with the risk of local recurrence, as well as the disease-specific mortality,[7,8,20,23-26,35-39,89] even though one study of 911 adult STS patients with tumors in the extremities found no correlation with disease-specific mortality.[20]

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Table 1. Studies on prognostic factors for local recurrence and disease-specific mortality

	Local recurrence		Disease-specific mortality	
Factor	**Impact**	**No impact**	**Impact**	**No impact**
Age	Berlin[54], Biau[26], Brooks[55], Cahlon[56], Collin[57], Eilber[47], Gaynor[43], Jebsen[38], Koea[24], LeVay[58], Lewis[40], Liu[59], Pisters[23], Rydholm[34], Weitz[7], Zagars[8]	Alektiar[60], Alho[14], Alkis[18], Bell[44], Coindre[61], Dagan[19], Felderhof[62], Gronchi[20], Guillou[22], Gustafson[21], Heslin[63], Kim[64], Lintz[17], Matsubara[65], McGee[66], McKee[67], Novais[68], Ravaud[69], Rööser[70], Saddegh[16], Sampo[71], Stefanovski[72], Stoeckle[73], Stotter[15], Trovik[13], Wilson[74]	Berlin[54], Gadgeel[75], Gaynor[43], Gutierrez[10], Kattan[9], Koea[24], Le Doussal[76], Maki[11], McGee[66], Parsons[41], Pisters[23], Rydholm[34], Weitz[7], Zagars[8]	Alkis[18], Brooks[55], Gronchi[20], Heslin[63], Kolovich[77], Lahat[25], LeVay[58], Lintz[17], Liu[59], Merimsky[78], Peabody[45], Rööser[70], Saddegh[16], Stotter[15]
Duration of symptoms	None	None	* Nakamura[31], Urakawa[29], Saithna[28]	* Rougraff[30], Rougraff[32], Tomita[33], Ueda[27]
Tumor size	Alho[14], DeLaney[79], Guillou[22], Gustafson[21], Ipach[80], Jebsen[38], Matsubara[65], McKee[67], Pisters[23], Stojadinovic[35], Weitz[7], Zagars[8]	Alamanda[81], Alektiar[60], Alkis[18], Bell[44], Biau[26], Biau[39], Brooks[55], Coindre[61], Dagan[19], Dinges[82], Eilber[47], Felderhof[62], Gaynor[43], Gronchi[20], Gronchi[36], Heslin[63], Khanfir[83], Kim[64], Koea[24], LeVay[58], Lewis[40], Lintz[17], Liu[59], Mandard[84], Novais[68], Ravaud[69], Rööser[70], Saddegh[16], Sampo[71], Singer[85], Stefanovski[72], Stoeckle[73], Stojadinovic[37], Stotter[15], Trovik[13], Wilson[74]	Alkis[18], Brooks[55], Dagan[19], Dinges[82], Gadgeel[75], Gaynor[43], Gronchi[20], Gronchi[36], Kattan[9], Koea[24], Kolovich[77], Lahat[25], Le Doussal[76], LeVay[58], Liu[59], Maki[11], Parsons[41], Peabody[45], Pisters[23], Rougraff[30], Rydholm[34], Rööser[70], Saddegh[16], Sampo[86], Stojadinovic[37], Stojadinovic[35], Stotter[15], Weitz[7], Zagars (5 cm)[8]	Heslin[63], Lintz[17], Zagars (10 cm)[8]
Depth	Biau[26], Biau[39], Coindre[61], DeLaney[79], Gaynor[43], Guillou[22], Liu[59]	Alamanda[81], Alektiar[60], Alho[14], Bell[44], Collin[57], Felderhof[62], Gronchi[20], Gronchi[36], Gustafson[21], Jebsen[38], Khanfir[83], Koea[24], Lewis[40], Lintz[17], Mandard[84], McKee[67], Pisters[23], Ravaud[69], Rööser[70], Stoeckle[73], Stojadinovic[37], Stotter[15], Trovik[13], Weitz[7]	Gaynor[43], Gronchi[20], Gronchi[36], Kattan[9], Koea[24], Le Doussal[76], Liu[59], Pisters[23], Sampo[86], Stojadinovic[37], Weitz[7]	Lintz[17], Maki[11], Merimsky[78], Parsons[41], Peabody[45], Rööser[70], Stotter[15]
Compartmentalization	Gaynor[43], Mandard[84], Rydholm[34], Rööser[70]	Bell[44], Saddegh[16], Lintz[17]	Gaynor[43], Rydholm[34]	Lintz[17], Peabody[45], Rööser[70], Saddegh[16]
Location	Alektiar[60], DeLaney[79], Felderhof[62], Guillou[22], Gustafson[21], Lewis[40], Stojadinovic[35], Zagars[8]	Alamanda[81], Alkis[18], Brooks[55], Cahlon[56], Coindre[61], Collin[57], Dagan[19], Dinges[82], Eilber[47], Gaynor[43], Jebsen[38], Karakousis[87], Kim[64], LeVay[58], Lintz[17], McKee[67], Pisters[23], Ravaud[69], Saddegh[16], Stefanovski[72], Stoeckle[73], Stotter[15], Trovik[13], Weitz[7], Wilson[74]	Dinges[82], Gutierrez[10], Kattan[9], Lahat[25], LeVay[58], Maki[11], Pisters[23], Sampo[86], Stojadinovic[35], Zagars[8]	Alkis[18], Brooks[55], Gaynor[43], Kolovich[77], Lintz[17], Merimsky[78], Saddegh[16], Stotter[15], Weitz[7]
Grade	Biau[26], Biau[39], Coindre[61], Collin[57], Delaney[79], Dinges[82], Eilber[47], Gronchi[36], Guillou[22], Jebsen[38], Kim[64], LeVay[58], Lewis[40], Stefanovski[72], Stoeckle[73], Stojadinovic[37], Stojadinovic[35], Trovik[13], Zagars[8]	Alamanda[81], Alho[14], Alkis[18], Bell[44], Brooks[55], Felderhof[62], Gaynor[43], Gronchi[20], Gronchi[36], Gustafson[21], Karakousis[87], Khanfir[83], Koea[24], Lintz[17], Liu[59], McKee[67], Novais[68], Pisters[23], Ravaud[69], Rööser[70], Singer[85], Stotter[15], Weitz[7]	Alkis[18], Berlin[54], Brooks[55], Dagan[19], Dinges[82], Gadgeel[75], Gaynor[43], Gronchi[20], Gronchi[36], Ipach[80], Kattan[9], Koea[24], Lahat[25], Le Doussal[76], LeVay[58], Lintz[17], Liu[59], Maki[11], Merimsky[78], Parsons[41], Peabody[45], Pisters[23], Rydholm[34], Rööser[70], Saddegh[16], Sampo[86], Stojadinovic[37], Stojadinovic[35], Stotter[15], Weitz[7], Zagars[8]	None
Margin	Alamanda[81], Bell[44], Berlin[54], Biau[26], Biau[39], Coindre[61], Collin[57], Dagan[19], DeLaney[79], Dickinson[88], Gaynor[43], Gronchi[20], Gronchi[36], Gronchi[89], Gustafson[21], Heslin[63], Jebsen[38], Koea[24], Le Doussal[76], LeVay[58], Lintz[17], Liu[59], Mandard[84], McKee[67], Novais[68], Pisters[23], Ravaud[69], Rydholm[34], Rööser[70], Saddegh[16], Sampo[71], Singer[85], Stefanovski[72], Stoeckle[73], Stojadinovic[37], Stojadinovic[35], Stotter[15], Trovik[13], Ueda[27], Weitz[7], Wilson[74], Zagars[8]	Alho[14], Brooks[55], Eilber[47], Felderhof[62], Khanfir[83], Kim[64], McGee[66]	Berlin[54], Brooks[55], Gadgeel[75], Gaynor[43], Gronchi[36], Heslin[63], Koea[24], Lahat[25], Le Doussal[76], Lintz[17], Liu[59], McGee[66], Merimsky[78], Peabody[45], Pisters[23], Rydholm[34], Rööser[70], Stojadinovic[37], Stojadinovic[35], Weitz[7], Zagars[8]	Alho[14], Dagan[19], Gronchi[20], Kolovich[77], LeVay[58], Stotter[15]
Radiotherapy	Alektiar[60], Alkis[18], Biau[26], Biau[39], Coindre[61], Gronchi[20], Gronchi[36], Ipach[80], Jebsen[38], Khanfir[83], Le Doussal[76], Lewis[40], Stotter[15], Wilson[74], Yang[90]	Heslin[63], LeVay[58], McKee[67], Novais[68], Rööser[70], Weitz[7]	Gadgeel[75], Gronchi[20], Gutierrez[10], Schreiber (> 5 cm)[91], Stotter[15]	Alkis[18], Gronchi[36], Heslin[63], Kolovich[77], LeVay[58], Parsons[41], Rööser[70], Schreiber(all patients)[91], Weitz[7], Yang[90]

from the AJCC and UICC.[92,93] According to Enneking's definitions a excision is defined as intralesional if the incision is within the tumor; as marginal if the incision is within the pseudocapsule; as wide if the tumor is surrounded by a cuff of normal tissue; or as radical if the tumor is surrounded by a complete muscle compartment.[94] The R classification denotes the presence or absence of residual tumor after treatment and categorizes patients into: no residual tumor, microscopic residual tumor, macroscopic residual tumor, or presence of residual tumor cannot be assessed.[92,93] Other terms such as "positive" or "negative" margins are used, even though the definition of these terms is seldom elaborated on. The surgical margin has been shown to be closely correlated with the risk of local recurrence, as well as the disease-specific mortality,[7,8,20,23-26,35-39,89] even though one study of 911 adult STS patients with tumors in the extremities found no correlation with disease-specific mortality.[20]

The primary purpose of **radiotherapy** is to kill microscopic extensions of the tumor, allowing for surgery with narrower margins, thus improving local control with less aggressive resections. The use of radiotherapy has increased significantly during the previous decades and is now a common adjunct in the surgical management of STS. In accordance with this, most studies have reported that radiotherapy reduces the local recurrence significantly.[12,20,26,36,38,39,95,96] Only a few studies have investigated the effect of radiotherapy on disease-specific mortality.[7,10,20,41,75] Gronchi et al. reported a significant association between radiotherapy and disease-specific mortality in a cohort of 911 non-metastatic extremity STSs, while Weitz et al. reported no associa-

tion in a cohort of 1261 non-metastatic extremity STSs treated with complete resections.[7,20]

LIMITATIONS OF THE LITERATURE

Even though several of the selected prognostic factors in this thesis have been studied numerous times and the prognostic value of some factors is generally accepted, the value of others is still uncertain.

Several of the studies are based on few patients, because the rarity of STS makes obtaining a sufficient sample size challenging. These studies may not have sufficient power to identify prognostic factors in an adjusted setting, or they may find associations due to chance, making their results less reliable. In addition to this, different inclusion and exclusion criteria are often used, causing great heterogeneity of study populations and low generalizability. This selection of patients might result in biased estimates, especially since studies often are from major tertiary centers with a greater proportion of large, high-grade, recurrent, or otherwise complicated STSs.

Another limitation of the existing studies is the adaptation of continuous factors such as age, duration of symptoms, and tumor size. The majority of studies analyze these either categorically with one cut-off value or continuously linearly; however, this results in loss of information, residual confounding, or incorrect assumptions, and is rarely a good approach.[97] Furthermore, since no clear consensus on the cut-off value exists, several different values are used, rendering the comparability difficult. Different methods to select these cut-off values exist, including medians, receiver operating characteristic (ROC) curves, or the "optimal" cut point method; however, these are seldom reported or lead to over-optimized and irreproducible estimates.[98] A more appropriate method is to analyze the variables in flexible regression models such as cubic splines or fractional polynomials.[99-101]

In order to get as reliable results as possible, analyzing the prognostic factors in an adjusted setting is preferable. However, when selecting which possible confounders to adjust for, different methods are used: forward selection, where only significant variables in a crude analysis are included; backward selection, where all variables are included in an adjusted analysis and then excluded based on their p-values; combinations of forward selection and backward elimination included in statistical software; or inclusion of all possible confounders. However, these methods can result in biased estimates as well as too narrow confidence intervals and too low p-values. Another method, which, to our knowledge, has not been used in STS studies, is to select possible confounding factors using directed acyclic graphs where causal relations are depicted.[102-105] This method relies on an *a priori* hypothesis of causal relations and has been used mostly in epidemiological research.

All the reported studies, except those on duration of symptoms, used local recurrence or disease-specific mortality as outcomes; however, the majority of studies censored patients if they died or if they died of other causes than sarcoma, respectively. A crucial assumption in the Kaplan-Meier method of survival analyses is that censoring is independent, i.e., that patients have the same risk of experiencing an event before and after the censoring. This is, however, not the case when we have competing risks, i.e., more than one mutually exclusive event, and thus the results obtained from a study in which patients are censored reflects the risk of getting the event (e.g. local recurrence) in a hypothetical situation in which patients cannot experience the competing event (e.g. dying). This leads to an overestimation of the outcome if a failure measure is used, depending on how frequent the competing event is. Furthermore, not using a competing risk model might result in biased estimates if the frequency of the competing event is not the same in the compared groups.

COMORBIDITY

Comorbidity is defined as diseases which coexist with the diagnosis of interest (index disease, i.e., STS).[106] In this thesis comorbidity relates to diseases diagnosed prior to or at the time of STS diagnosis. Any diseases occurring after the STS diagnosis can be caused by the STS or the treatment, and are therefore not included.

The incidence of STS increases with age, and since a demographic shift in the age distribution of the general population is anticipated in the future, resulting in more elderly patients, more STS patients with comorbidity are expected.[107] Comorbidity might affect mortality in STS patients in several ways: as an independent cause of death; by delaying diagnosis, which could result in a more advanced stage at diagnosis; causing complications of treatment; and being the reason for less aggressive treatment of the STS.

In order to study the effect of multimorbidity and generate appropriate statistical power, comorbidity is often studied as an index instead of as individual diseases. Several comorbidity indices exist, with the most widely used being the Charlson Comorbidity Index.[108] The Charlson Comorbidity Index was originally developed in 1984 to predict 1-year mortality in a cohort of 559 medical patients, and was later validated for 10-year mortality in 685 breast cancer patients. The index includes 19 diseases, which are weighted from 1 to 6 points according to their risk of mortality (Table 2). These points are added up to form a final score corresponding to the level of comorbidity.[108]

Table 2. The Charlson Comorbidity Index

Disease	Points
Myocardial Infarct	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes	1
Hemiplegia	2
Moderate/severe renal disease	2
Diabetes with end organ damage	2
Any tumor	2
Leukemia	2
Lymphoma	2
Moderate/severe liver disease	3
Metastatic solid tumor	6
AIDS	6

The Charlson Comorbidity Index was originally based on medical records, but has since been adapted and validated for ICD-based hospital discharge data in various cancer types.[109] Other comorbidity indices, including adaptations of the Charlson Index, have been developed, such as Klabunde's adaptation, the Elixhauser method, the Cumulative Illness Rating Scale, and the Index of Coexisting Disease.[110-113] So far, comparisons of these have not revealed that any one is superior to the other, except for minor advantages in some situations.[114-116] Disease-specific comorbidity indices have been developed for other cancer types, such as head and neck cancer; however, to our knowledge no sarcoma-specific index exists.[117,118]

LITERATURE ON COMORBIDITY

Comorbidity has proven to be an important prognostic factor for mortality in other cancer types, even after adjusting for other significant factors such as age, disease stage, and treatment.[119-124]

To identify studies investigating the correlation between comorbidity and mortality in STS, we used the following query in Medline: ("comorbidity"[MeSH] OR "comorbidity") AND ("sarcoma"[MeSH] OR "sarcoma" OR "soft tissue sarcoma") AND ("Mortality"[MeSH] OR "Mortality" OR "Survival"[MeSH] OR "Survival"). This query resulted in 324 hits and after reading the titles, the abstracts of nine papers were collected and reviewed. Of these nine papers, five investigated comorbidity in STS patients; however, four of these only included descriptive data on the level of comorbidity or used treatments as outcomes, and only one investigated the impact of comorbidity on survival.[125-129] The reference lists of the five relevant papers were reviewed and revealed no additional papers. However, during the review of the literature on prognostic factors, one additional paper was discovered. Gadgeel et al. investigated the impact of comorbidity on survival in 345 adult STS patients with tumors in the extremity or trunk, whereas Nakamura et al. included 322 adult STS patients with primary, non-metastatic high-grade disease.[75,129] Neither of these found a prognostic impact of comorbidity on survival.

LIMITATIONS OF THE LITERATURE

Thus, the literature on comorbidity and survival in STS is limited. Indeed, to our knowledge only two studies exist and these studies have some limitations. The study by Nakamura et al. was based on a small sample of patients from a single center with major tertiary referral practices, which might cause biased estimates due to selection. In addition, the follow-up periods in both studies were relatively short, with a median of only 28.4 months (range 1–101) and a maximum of 47 months, respectively. Furthermore, comorbidity was analyzed as a continuously linear variable as well as a binomial categorical variable, which might cause loss of information. The studies used forward selection to select variables in their adjusted analyses, and comorbidity was therefore only analyzed as crude estimates, rendering the results less reliable when no adjustment for confounding were included.

BIOMARKERS

A biomarker is defined as a "characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".[130] Many of these are taken routinely prior to treatment in order to screen for undiscovered diseases or abnormalities that could be contraindications for treatment or require additional treatment. In order to use biomarker levels as prognostic markers, we are interested in the level at diagnosis; therefore, the results from any blood sample taken at or up to 30 days prior to the STS diagnosis were included. In order to eliminate any changes in biomarker levels caused by the treatment for the STS, results from blood samples taken after treatment had begun were not included. Based on the standard blood samples taken prior to treatment at the Aarhus Sarcoma Center and a literature search, the following biomarkers were selected: albumin, C-reactive protein (CRP), hemoglobin, neutrophil to lymphocyte ratio (NLR), and sodium.

The correlation between biomarker levels and cancer is assumed to be multifactorial. Circulating cytokines, especially interleukin 1 and 6 (IL-1 and IL-6), are thought to play an important role. A high level of IL-1 and IL-6 induces the synthesis of acute phase proteins and hepcidin in the liver while inhibiting the synthesis of albumin.[131-134] Hepcidin is an iron-regulating hormone, which inhibits the utilization of iron, causing anemia. The causes of hyponatremia in cancer patients are not clearly established, but possibly related to the syndrome of inappropriate antidiuretic hormone secretion by some tumors, tumor lysis syndrome, or the anorexia and cachexia commonly seen in cancer patients, though admittedly rare in STS patients.

LITERATURE ON BIOMARKERS

Albumin, CRP, hemoglobin, NLR, and sodium have been identified as prognostic factors in other cancers, such as urological and gastrointestinal cancer.[135-147] To identify studies investigating the correlation between these biomarkers and survival in STS patients, a systematic search using the following query was performed in Medline: ("sarcoma"[MeSH] OR "soft tissue sarcoma") AND ("mortality"[MeSH] OR "mortality" OR "survival" OR "survival"[MeSH]) AND (("albumin" OR "hypoalbuminemia"[MeSH] OR "hypoalbuminemia" OR "hypoalbuminaemia") OR ("c-reactive protein"[MeSH] OR "c-reactive protein" OR "c reactive protein" OR CRP) OR ("haemoglobin" OR "hemoglobins"[MeSH] OR "hemoglobin") OR ("anaemia" OR "anemia"[MeSH] OR "anemia") OR ("neutrophils"[MeSH] OR "neutrophil" OR "lymphocytes"[MeSH] OR "lymphocyte") OR ("sodium" OR "sodium"[MeSH] OR "hyponatremia"[MeSH] OR "hyponatremia")). This resulted in 881 hits. After reading the titles of these publications, 29 relevant studies were identified, including one comment. Of these, 16 studies were excluded after reviewing the abstract. Finally, the reference lists of the remaining 13 studies were reviewed, revealing 1 additional study. In total, 14 papers were found to be relevant (Table 3).

In summary, the most studied biomarkers have been inflammatory, e.g., CRP and NLR, even though the number of studies are limited. The majority of studies found significant associations with the outcomes of interest, even though some studies report the opposite.[146,148-156] Albumin has previously been investigated in only one study, where a significant impact on overall, but not disease-specific, survival was found.[157] Studies regarding hemoglobin identified pretreatment anemia as a prognostic factor for event-free, disease-specific, as well as overall survival.[145,158] Hyponatremia has never been investigated as a prognosticator in non-metastatic STS, even though a study of advanced gastrointestinal stromal tumors showed poorer overall survival in patients with hyponatremia than in patients with normonatremia.[159]

LIMITATIONS OF THE LITERATURE

Biomarkers in STS patients have recently received increasing attention, but the existing literature is still limited. Most of the studies are based on a few hundred patients, with the attendant risk of insufficient statistical power or unreliable results due to chance. Furthermore, all studies are based on selected patients from single institutions with major tertiary referral practices, which might induce selection bias. Additionally, most of the studies only had short follow up-periods. None of the existing studies adjusted their analyses for comorbidity, which, since other diseases are known to cause changes in biomarkers, is considered an important confounder. When adjustment for important confounders is not performed, estimates are likely to be biased. Furthermore, none of the studies that use disease-specific outcomes, e.g., recurrence-free, disease-specific survival, analyzed their results taking competing risks into account. Since the

Table 3. Studies of the impact of biomarkers on survival in STS patients

Author, year	N	Period	Study population	Biomarkers, cut off value	Outcome of interest	Results and comments
Aggerholm-Pedersen, 2011[159]	80	2001–2009	Unresectable or metastatic gastrointestinal stromal tumors.	Sodium, 135 mmol/L; Neutrophil, 7.0 10^9/L; Hemoglobin, 7.4 mmol/L	Time to progression and overall survival.	13% of the patients had hyponatremia. Hyponatremia was significantly associated with poorer overall survival in the adjusted analysis (HR = 0.3, p = 0.04), while anemia was not (HR = 0.7, p = 0.29). Neutrophils were not significant in the crude analysis of overall survival and were not analyzed adjusted. None of the biomarkers were significant in the analyses of time to progression.
Barreto-Andrade, 2009[157]	61	1986–2006	Primary, adult STS, including metastatic cases and all anatomical locations.	Albumin, 3.5 mg/dL	Overall and disease-specific survival.	Proportion of abnormal values not reported. Hypoalbuminemia was independently associated with decreased overall survival (RR 5.0 [95% CI: 2.1–9.4]). No impact was seen on disease-specific survival when analyzed univariately
Idowu, 2012[149]	223	2002–2009	Non-metastatic benign (n=140) and malignant (n=83) soft tissue tumors in the extremity and trunk.	NLR, 5.0	Recurrence-free and overall survival.	Mean NLR in benign tumors were 2.8 compared to 4.1 in malignant tumors, p<0.001. Elevated NLR was seen in 24.1% of malignant tumors. Elevated NLR was an independent prognostic factor for overall survival (HR = 5.13 [95% CI: 1.25–21.09]), but not recurrence-free survival.
Nakamura, 2012[151]	102	2003–2009	Primary, non-metastatic STS.	CRP, 0.3 mg/dL	Overall and disease-free survival.	Elevated levels were seen in 17.6%. The overall 5-year survival was 81.3% in patients with normal CRP and 53.8% in patients with elevated CRP, p = 0.01. No significant difference was found in the adjusted analysis. Normal CRP was a positive prognostic factor for disease-free survival (HR = 0.36 [95% CI: 0.16–0.84]).
Nakamura, 2013[129]	332	2003–2010	Primary, non-metastatic, high-grade STS, excluding patients with inadequate surgical treatment before referral and patients with incomplete clinical history or laboratory data.	CRP, 10 mg/dL	Disease-specific survival and local control.	Elevated levels were seen in 46%. Normal CRP levels were significantly associated with higher disease-specific survival (HR = 0.25 [95% 0.14–0.45]) and local control (HR = 0.45 [95% CI: 0.21–0.98]) in adjusted analyses.
Nakamura, 2013[152]	142	1995–2010	Primary, adult STS, excluding patients with inadequate surgical treatment before referral and patients with incomplete clinical history or laboratory data. Metastatic cases included.	NLR, 2.3 (median) and CRP, 0.3 mg/dL	Metastasis-free and disease-specific survival.	49% of the patients had both normal CRP and NLR, 20% had both elevated CRP and NLR, and 32% had either an elevated CRP or NLR. Neither CRP, NLR, nor a combination was significant in the analyses of metastasis-free survival. In the adjusted analysis of disease-specific survival, a combination of both elevated CRP and NLR was significant, while elevated values in only one was not (HR = 2.79 [95% CI: 1.04–7.48] and HR = 1.34 [95% CI: 0.52–3.49]).
Nakamura, 2013[158]	376	2003–2010	Primary, non-metastatic adult STS, excluding patients with inadequate surgical treatment before referral and patients with incomplete clinical history or laboratory data. 3 patients with anemia due to obvious renal failure were excluded.	Hemoglobin, 13 g/dL for males and 12 g/dL for females.	Event-free rate and disease-specific survival.	Pretreatment anemia was observed in 30%. The median value was 13.4 g/dL. Levels of CRP were correlated with levels of hemoglobin. Normal levels of hemoglobin were independently associated with both event-free and disease-specific survival (HR = 0.50 [95% CI: 0.35–0.73] and HR = 0.47 [95% CI: 0.29–0.76]). NOTE: CRP was excluded from the prognostic analyses because of the correlation with hemoglobin.
Nakanishi, 2002[154]	46	1990–2001	Primary, non-metastatic MFH, excluding patients without laboratory data.	CRP, 1 mg/dL	Metastasis-free and overall survival	Elevated levels were seen in 65%. Elevated CRP was correlated with poorer metastasis-free and overall survival in the crude analyses, but not in the adjusted.
Perez, 2013[156]	271	1995–2010	Primary, non-metastatic GIST, excluding patients treated with Imatinib and patient with incomplete blood values.	NLR, 2.7	Recurrence-free survival	Elevated NLR levels were seen in 49%. High NLR was significantly associated with recurrence-free survival, in the crude, but not adjusted analyses.
Ruka, 2001[172]	145	1997–1999	Both recurrent and metastatic STS at diagnosis, excluding patients with prior radiochemotherapy treatment.	Hemoglobin, 11.0 g/dL; Neutrophil, 2.3 10^9/L; Lymphocyte, 0.1 10^9/L	Overall survival	Increased neutrophil and decreased lymphocyte were significantly associated with overall survival in the crude, but not adjusted analyses. No association between hemoglobin and overall survival was found.
Stefanovski, 2002[72]	395	1985–1997	Primary STS, excluding patients with uterine sarcoma and insufficient data.	Hemoglobin, 12 g/dL	Local recurrence, overall survival, distant recurrence, and post-metastasis survival	26.8% had low hemoglobin. Normal levels of hemoglobin was significantly associated with increased overall survival in adjusted analyses (HR = 0.52 [95% 0.28–0.98]). Only investigated crudely for the remaining outcomes, where no association was found.
Szkandera, 2013[155]	304	1998–2010	STS patients. No exclusion criteria mentioned.	CRP, 6.9 mg/L	Disease-specific, disease-free, and overall survival	The median CRP level was 3.3 mg/L (IQR 1–11.5). Increased CRP levels were significantly associated with a poor outcome for disease-specific, disease-free, and overall survival. NOTE: Cut off value was determined by a ROC curve. Different HRs were reported in the abstract and tables for the disease-specific and the disease-free survival.
Szkandera, 2013[173]	260	1998–2010	STS patients treated with curative surgical resection. No further description. Metastatic cases included.	NLR, 3.45 for time to recurrence and 3.58 for overall survival	Time to recurrence and overall survival	Increased NLR was independently associated with both decreased time to recurrence and overall survival (HR = 1.98 [95% CI: 1.05–3.71] and HR = 1.88 [95% CI: 1.14–3.12], respectively). NOTE: Cut off value determined by ROC curves.

NOTES: Abbreviations: STS, soft tissue sarcoma; CRP, c-reactive protein; NLR, neutrophil to lymphocyte ratio; HR, hazard ratio; CI, confidence interval; IQR, interquartile range; ROC, receiver operative characteristic; MFH, malignant fibrous histiocytoma; GIST, gastrointestinal stromal tumors.

frequency of the competing events, i.e., death and death from causes other than sarcoma, is likely to be different in the patients with normal biomarkers compared to patients with abnormal biomarkers, not taking the competing event into account might cause biased results.

MORTALITY IN SOFT TISSUE SARCOMA (STS)

The outcome in studies of prognosis can vary; however, in this thesis we focus on local recurrence and death. The prognosis regarding death of STS patients has been studied extensively; however, the definitions and methodology differ.

Overall mortality, i.e., death by any cause, is generally considered a reliable and unbiased outcome. However, it not only covers death due to the STS, but also death due to other causes, rendering it less informative when the focus of interest is to study the impact of STS on mortality.

Therefore, disease-specific estimates, i.e., disease-specific mortality or survival, are often used as outcomes since these are expected to better reflect the "true" mortality caused by the STS. However, using disease-specific estimates entails two potential problems: misclassification of the underlying cause of death (COD), and no consensus on which CODs are related to the disease. Assessing disease-specific mortality relies on precise and correct data on the COD; however, such data can be difficult to achieve. Previously, most patients dying at hospitals were autopsied in order to determine the correct COD; however, like most other countries the autopsy rate in Denmark has declined rapidly.[160-162] At present, the COD is often registered by the physicians attending the patient at the time of death, and the validity of the registered COD is thus dependent on the physicians' preceding knowledge of the patient. Previous studies have concluded that CODs registered on this basis are inaccurate and vary substantially according to cancer type, age at death, and time period.[160,163-168] Another problem when using disease-specific estimates is the issue of which CODs are "due" to the STS. Even in cases where the correct immediate COD is known, the contribution of the STS as part of the underlying cause can be impossible to determine; therefore, assigning death as either disease-specific or not can be problematic and ambiguous.[169]

Another method to obtain the "true" mortality caused by the STS is by using relative estimates as outcomes, i.e., the mortality in cancer patients compared with the mortality in a general population.[170] The mortality in the general population can be determined using either national life tables or a matched general comparison cohort; however, in either case, the general population from which the data is acquired is assumed to be free of STS. The main prerequisite for relative mortality is the assumption of internal comparability between STS patients and the general comparison cohort, and violation of this can result in possible bias.[171]

LITERATURE ON RELATIVE MORTALITY

Traditionally, but unwarranted, relative estimates have primarily been used in epidemiological research, while the disease-specific estimate has been preferred in clinical trials. Thus, most studies on prognosis in STS use either overall or disease-specific mortality as outcomes. To identify studies on the prognosis in STS assessed as relative mortality, we used the following query in Medline/PubMed: (("relative" AND ("mortality"[MeSH] OR "mortality" OR "survival" OR "survival"[MeSH])) OR "excess mortality" OR ("life tables"[MeSH] OR "life tables") OR ("Survival Rate"[MeSH] AND "epidemiology")) AND ("sarcoma"[MeSH] OR "soft tissue sarcoma"). This resulted in 837 hits, limited to studies in humans, written in English. After reviewing the titles 36 studies were selected for review of abstracts. Based on this, six studies were reviewed and all were found relevant. One additional paper was included after review of the reference lists. An overview of the papers is shown in Table 4.

In summary, all seven studies were based on data from large cancer registries. All, except Guadagnolo et al., investigated 5-year relative survival estimates both overall as well as according to different subgroups, e.g., age, sex, histological subtype, and calendar year.[174-180] In general the relative survival decreased with age, and no significant difference in relative survival was found between males and females. Some of the studies reported an increase in relative survival over the study period, while others reported no difference. As opposed to the other studies, Guadagnolo et al. investigated a subgroup of patients previously cured for STS without any relapse in order to determine whether the aggressive treatment impacted survival.[177] Female patients, patients older than 50 years, patients with non-extremity tumors, and patients with follow-up more than 10 years all had significantly increased standardized mortality rates.[177]

LIMITATIONS OF THE LITERATURE

The majority of the previous studies on relative mortality are all characterized by a large number of patients. However, most of these are international projects, with data derived from individual national cancer registries in which the level of data validation is unclear. Furthermore, since few of the countries have the possibility to conduct population-based studies with linkage of data on an individual level, the results from these might be biased by selection. Additionally, most of these studies used national life tables to obtain survival of the general population, which might be problematic, since data used to construct these also include STS patients. Another limitation of using national life tables is the lack of the possibility to assess whether the internal comparability is sufficient, i.e., to compare basic characteristics of the STS patients with the general population.

AIMS AND HYPOTHESES OF THESIS

The aims and hypotheses of this thesis were:

I. To examine the validity of the Aarhus Sarcoma Registry (ASR), including the completeness of patient registration and the quality of the registered data, and to examine the incidence of sarcomas in western Denmark during the period from 1979 to 2008 (Study I).
Hypothesis: The ASR is a population-based valid data source. The actual incidence of STS has increased over time.

II. To identify prognostic factors for local recurrence and disease-specific mortality in adult non-metastatic STS using an improved statistical approach with DAGs and cubic splines in a competing risk setting (Study II).
Hypothesis: Improved statistical methods are feasible. Patient-, tumor- and treatment-related factors have an impact of local recurrence and mortality in STS patients.

III. To assess and describe the prevalence of comorbidity in STS patients as well as to investigate the impact of comorbidity on overall and disease-specific mortality (Study III).

Table 4. Studies of relative survival in soft tissue sarcoma patients

Author, year	N	Period	Study population	Population mortality source	Results and comments
Bray, 2010[174]	4,203	1964–2003	Danish STS patients registered with the ICD-10 codes: C49 and C46.1.	National life tables	No overall estimate. No changes in 5-year RS over the study period, neither for male or female. The 5-year RS decreased with increasing age for both male and female. NOTE: STS is often classified under other ICD-10 codes.
Guadagnolo, 2008[177]	629	1960–2000	Patients who previously had been treated and cured for a non-metastatic STS with surgery and radiotherapy and have never experienced any relapse, excluding patients with treatment before referral, patients with other cancers at diagnosis and patients with desmoid tumors, angiosarcoma, Kaposi sarcoma, dermatofibrosarcoma, or cystosarcoma.	Person year method	Overall comparable survival between study population and the general population. Females (SMR = 1.48 [95% CI: 1.15–1.88]), patients over 50 years (SMR = 1.46 [95% CI: 1.06–1.95]), patients with nonextremity tumors (SMR = 1.57 [95% CI: 1.15–2.08]), and patients with more than 10 years of follow up (SMR = 1.36 [95% CI: 1.10–1.66]) had increased mortality compared with the general population.
Levi, 1999[178]	645	1974–1994	Patients registered with STS in the Vaud Cancer Registry. All cases were histologically confirmed and reclassified.	National life tables	5-year RS was 45% (41% in males and 50% in females). Highest RS was seen in patients with liposarcoma and fibrosarcoma.
Ng, 2013[176]	26,739	1975–2004	Patients registered in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database. 28% of the national population.	National life tables	No overall estimation. Results reported according to histological type, grade and stage. Patients with localized MFH, liposarcoma, and leiomyosarcoma had 5-year relative survivals of 80%, 76%, and 90%, respectively, while the corresponding mortalities in patients with metastatic disease were 11%, 12%, and 26%, respectively. The 5-year RS decreased with increasing age.
Sant, 2009[180]	13,901	1995–1999	89 European cancer registries included in the EUROCARE IV database. Detailed description of inclusion criteria not reported.	National life tables	The 1-year RS was 80.4% (95% CI: 79.4–81.4) and the 5-year RS was 59.5% (95% CI: 58.4–60.8). The RS decreased with increasing age. No difference in RS was observed between male and females. NOTE: the study included data from the Danish Cancer Registry.
Stiller, 2013[175]	12,693	2000–2002	89 European cancer registries included in the project "Surveillance of rare cancer in Europe" (RARECARE). Patients registered with ICD O-3 M codes 8800–8935, 8910, 8920, 8940, 8950–8959, 8963–8964, 8990–8991, 9020–9044, 9120–9133, 9150, 9170, 9180, 9231, 9240, 9251, 9260, 9364–9372, 9540 combined with all ICD 0-3 T codes, codes except C40.0–41.9.	National life tables	1-year RS: 77.1%, 1-year observed survival: 75.1%, 5-year RS: 57.8% and 5-year observed survival: 50.4% when including all anatomical locations. 5-year RS in patients with extremity tumors: 68.0%. 5-year RS in patients with tumors in superficial trunk: 44.1%. NOTE: the study included data from the Danish Cancer Registry.
Storm, 1998[179]	2,151	1985–1989	45 European cancer registries included in the extended EUROCARE II database. STS and bone cancers were identified in the EUROCARE database using the ICD-O. Patients over 15 years registered with the ICD-O code 171 were included.	National life tables	1-year RS was 78% (95% CI: 75–81) for male and 79% (95% CI: 76–82) for females, the corresponding 5-years RS was 59% (95% CI: 53–65) and 59% (95% CI: 55–63), respectively. The 5-year RS increased from 55% in the first part of the study period to 59% in the last. NOTE: the study included data from the Danish Cancer Registry.

NOTES: Abbreviations: STS, soft tissue sarcoma; RS, relative survival; SMR, standardized mortality rate; CI, confidence interval; ICD, international classification of diseases; ICD-O, international classification of diseases for oncology; MFH, malignant fibrous histiocytoma.

Hypothesis: Improved statistical methods are feasible. Patient-, tumor- and treatment-related factors have an impact of local recurrence and mortality in STS patients.

IV. To assess and describe the prevalence of comorbidity in STS patients as well as to investigate the impact of comorbidity on overall and disease-specific mortality (Study III).
Hypothesis: Comorbidity has an impact on mortality in STS patients.

V. To determine the prognostic value of pretreatment biomarkers for overall and disease-specific mortality in non-metastatic STS patients (Study IV).
Hypothesis: Pretreatment biomarkers have an impact on mortality in STS patients.

VI. To estimate the relative mortality in STS patients, and compare relative and disease-specific mortality based on death certificates (Study V).
Hypothesis: STS patients have increased mortality compared to the general population. Relative mortality is similar to disease-specific mortality

MATERIAL AND METHODS

SETTING

All five studies were conducted in western Denmark within a population of approximately 2.5 million.[181] The public health care system in Denmark is tax-funded and free of charge, allowing free access to hospital care for all citizens. The national health insurance is universal (covers all citizens) and covers treatment in the primary health care sector and by specialists outside the hospitals after referral.

All residents in Denmark are assigned a unique 10-digit registration number, the CPR number. This provides information about date of birth and sex, and is used throughout Danish society including the health care system. The CPR number allows for linkage on an individual level between clinical and national population-based registries.

LOCAL PRACTICES AT THE AARHUS SARCOMA CENTER

There are approximately 200 new cases of STS annually in Denmark. To ensure sufficient quality of treatment, sarcomas in Denmark are treated at two specialized sarcoma centers, with all

patients in western Denmark being treated at the Sarcoma Center at Aarhus University Hospital since 1979.

Patients referred to the center go through a diagnostic program, according to Danish and international guidelines, including clinical examination, diagnostic imaging, biopsy, and histopathological evaluation conducted by an experienced multidisciplinary team.[182,183] The primary treatment is surgery, aiming for a wide margin, defined as a surrounding cuff of normal tissue.[94] Standard treatment for low-grade tumors is marginal or wide margins, while deep intermediate and high-grade tumors are treated with wide or radical margins and postoperative radiotherapy. Radiotherapy is administered in fractions of 2 Gray (Gy) to a total dose of 50–60 Gy, depending on the margin.

Patients are followed for a minimum of 5 years after last treatment, with intervals ranging from 3 to 6 months. At follow-up visits patients are examined clinically, supplemented with chest x-rays for intermediate- and high-grade tumors, as well as MRI scans for patients with deep-seated tumors.

DATA SOURCES

The Civil Registration System

The Danish Civil Registration System was established in 1968 and contains information on all persons living in Denmark. The system encompasses both historical and current data, including CPR number, municipality of residence, vital status, as well as date of birth, emigration, and/or death. The vital status is registered continuously and is updated on a daily basis.[184,185]

Medical records

In Denmark it is mandated by law to keep medical records that document information, diagnostic procedures, and treatments of patients by any authorized health professional. These records must be kept for at least 10 years after the last note. Medical records from both the Department of Orthopedic Surgery and Department of Oncology, for all sarcoma patients treated at the Aarhus Sarcoma Center between January 1, 1979 and December 31, 2008, as well all patients registered in the ASR, were retrieved.

The Aarhus Sarcoma Registry (ASR)

Since 1979, the treatment of patients with sarcoma in western Denmark has been carried out at the Sarcoma Center of Aarhus University Hospital, which resulted in the development of the ASR. All patients treated for STS, bone sarcoma, and some borderline and benign tumors have been registered in the ASR. The ASR collects basic patient data, including CPR number, sex, county of residence, date of diagnosis; specific data on tumor characteristics and treatment, including tumor size, location, histological type, tumor grade, stage of diagnosis, date and type of treatment; as well as data on follow-up examinations, local recurrence, distant metastases, and death. From 1993, data were registered prospectively.

The Danish Cancer Registry (DCR)

Since 1943, all incident cases of cancers in Denmark have been registered in the DCR. Until 1987, reporting to DCR was voluntary; but after 1987, reporting became mandatory for medical doctors at hospital departments as well as private medical specialists.[186] Until 2004, cases were manually reviewed, and incomplete or incorrect registrations were corrected by the reporting doctor. After 2004 the registration has been done electronically, and the completeness of patient registration and validation of data is ensured by cross-referencing data from DCR with data from three national registries: the National Patient Registry (NPR), the Danish Pathology Registry, and the Danish Cause of Death Registry (CDR). The main data in the DCR are CPR number, diagnosis, date of diagnosis, clinical stage, initial treatment, topography codes according to ICD-8 and IDC-10, and morphology codes according to ICD-O-1 and ICD-O-3.

StatBank Denmark

StatBank Denmark is a national database, administered by Statistics Denmark, containing detailed statistical information on Danish society.[181] Data are free of charge, anonymized, and fully accessible. It includes information about numerous fields, e.g., population, education, economic, social conditions, environment, national accounts, and can be used in various research areas. The population data contain the number of citizens for every year, per January 1, classified by age, sex, and place of residence.

The National Patient Registry (NPR)

The NPR contains information on all patients admitted to Danish hospitals since 1977, including outpatient visits since 1995.[187-189] Recording is mandatory, and the registry covers more than 99% of Danish hospital admissions in the period.[189] The registered data are used for administrative purposes, as well as to monitor health care. For each contact to a hospital or outpatient clinic, CPR number, dates of admission and discharge, treatment, as well as up to 20 discharge diagnoses according to ICD-8 (before 1994) and ICD-10 are registered. The discharge diagnoses are coded by physicians and include both main and secondary diagnoses.

The Danish Cause of Death Registry (CDR)

The completion of death certificates for any death occurring in Denmark is mandatory, and data regarding the COD has been registered in the CDR since 1875.[190] The CDR contains data on CPR number, date of death, as well as the immediate, contributing, and underlying CODs, according to the ICD-8 and ICD-10. Data in the registry are based on the diagnosis from the death certificates completed by physicians, either the deceased's general practitioner or hospital doctors.

The Clinical Laboratory Information System

The clinical laboratory information system is used to order tests and display results. Virtually all results from tests performed at hospitals, outpatient clinics, and general practitioners are included (excluding some results, e.g., blood glucose, hemoglobin and CRP, from small and rapid point-of-care devices used by patients or in general practices). Test results are entered immediately after analysis into a computer-based laboratory information system at each clinical chemistry department and recorded uniformly according to the international Nomenclature, Properties and Units (NPU) coding system.[191] The registered data includes CPR number, date and time of test, test name and code, as well as test result and unit. Additionally, test results from all patients in the northern (since 1997) and central (since 2000) regions of western Denmark are transferred to a regional research database, the LABKA research database.[192] The LABKA research database is updated once a year.

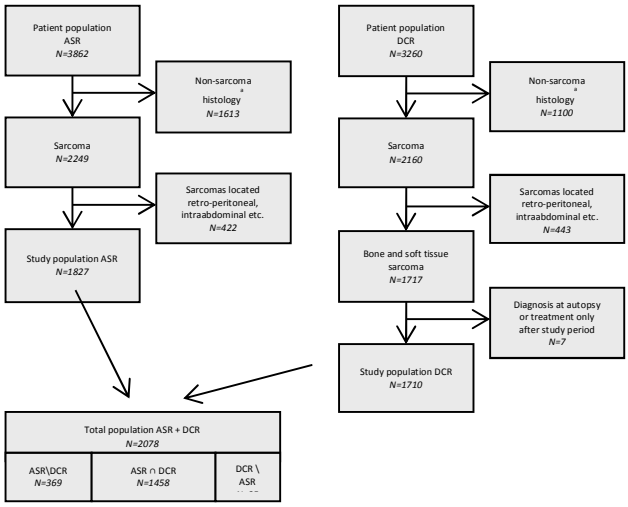
STUDY DESIGN

All studies included in this thesis were designed as population-based cohort studies.

STUDY POPULATION

Study I included all sarcoma patients in western Denmark between January 1, 1979 and December 31, 2008, treated at the Sarcoma Center of Aarhus University Hospital or registered in the ASR (Figure 1). We included adult STS patient with non-metastatic disease in the extremities or trunk wall recorded in the ASR from January 1, 1979 (study II) and from January 1, 1994 (study IV) to December 31, 2008. Studies III and V included STS patients with both metastatic and non-metastatic disease in the extremities or trunk wall recorded in the ASR between January 1, 1979 and December 31, 2008. Study III included only adult patients, while study V included all ages. Study V also included an age- and sex-matched comparison cohort comprised of individuals who lived in the same geographical area, had not previously been diagnosed with a sarcoma, and were alive at the date of sarcoma diagnosis.

Figure 1. *Flow chart for patients registered in the ASR and DCR in the period 1979–2008.*



NOTES: Abbreviations: ASR, Aarhus Sarcoma Registry; DCR, Danish Cancer Registry; WHO, World Health Organization; ASR\DCR, patients only registered in the ASR; DCR\ASR, patients only registered in the DCR; ASR∩DCR, patients registered in both registries. [a] Based on the WHO ICD-03 codes. Non-sarcoma pathology includes benign, borderline and some malignant tumors. This population is not complete.

DEFINITION OF VARIABLES

Validation of the Aarhus Sarcoma Registry (ASR)

The validation of ASR consisted of three parts: revision of the variables registered and the registration forms used in the ASR, review of medical records for all patients registered in ASR, and review of medical records for patients treated at the Sarcoma Center of Aarhus University Hospital in the study period but not yet registered in the ASR. Initially, a random sample was selected using the first two digits of the CPR numbers, indicating the day of birth, and choosing the 100 patients with the lowest numbers. Based on a revision of these patients and a review of the literature regarding prognostic factors, standardized registration forms were designed in cooperation with a surgeon, an oncologist, and a pathologist with expertise in sarcoma (Appendix II). All medical records were reviewed by two independent researchers not involved in treatment, using the standardized forms. Based on medical records from both the Department of Orthopedic Surgery and the Department of Oncology, data which were missing or incorrect in the ASR were added or corrected. All uncertain cases were discussed with the same team of sarcoma experts, and a consensus was reached.

The medical records were considered the gold standard in the analyses of validity, and the DCR was the gold standard in the analyses of completeness of patient registration. The outcomes assessed in study I were the validity of data registered in the ASR, completeness of patient registration in the ASR, as well as the incidence of STS in western Denmark.

Prognostic factors

The exposures in study II were patient-, tumor-, and treatment-related factors, selected prior to data analyses based on a literature search. Based on the number of events in the study (i.e. in order to have sufficient statistical power), the following factors were included: age at diagnosis, duration of symptoms, tumor size, location, depth, compartmentalization, grade, surgical margin, and radiotherapy. Tumor size was recorded as the largest diameter, based on the fixed pathological specimen. However, if patients were not treated surgically, or if the pathology-report was insufficient, diagnostic imaging was used. Tumors located in the shoulder and gluteal area were classified as trunk tumors. STS patients were classified into three grades based on cellularity, necrosis, anaplasia, and number of mitoses using the grading system described by Jensen et al.[51] Margins were defined, based on the pathological specimen, as intralesional/marginal if the incision was within the tumor or the pseudocapsule, or as wide/radical if the tumor was surrounded by a cuff of normal tissue or muscle compartment.[94]

Comorbidity

The level of comorbidity at the time of sarcoma diagnosis was considered an exposure in study III and a confounding covariate in studies IV and V. The level of comorbidity was assessed using the Charlson Comorbidity Index, which has been adapted and validated for ICD-based hospital discharge data in various cancer types.[108,109] The ICD codes included in the index are shown in the Appendix III.

Data from the ASR and NPR were linked through the CPR number, and for each of the STS patients identified in the ASR, all discharge diagnoses registered in the NPR between January 1, 1977 and the date of the sarcoma diagnosis were extracted. Based on these discharge diagnoses, a Charlson Comorbidity Index score for each patient was computed. To eliminate nonspecific symptoms or hospital admissions related to the sarcoma, all discharge diagnoses within 30 days, and all cancer diagnoses within 90 days prior to the sarcoma diagnosis were excluded. In studies III and V the level of comorbidity was categorized into four groups: no (score 0), mild (score 1), moderate (score 2), and severe (score ≥ 3) comorbidity. Moderate and severe comorbidity was collapsed into one group in study IV.

Biomarkers

The exposures in study IV were albumin, CRP, hemoglobin, NLR, and sodium, which are all measured routinely before treatment for STS. In study IV, biomarkers were analyzed as dichotomized categorical variables. The cut-off values were chosen prior to the data analyses based on the reference values used at Aarhus University Hospital for all biomarkers except NLR.[193] Albumin was recorded in both g/L and µmol/L, and hypoalbuminemia was defined as albumin levels < 36 g/L and < 542 µmol/L. CRP was recorded in mg/L and nmol/L, and an elevated CRP was defined as values ≥ 8 mg/L and ≥ 75 nmol/L. Hemoglobin was recorded in mmol/L and anemia was defined as a hemoglobin level <7.3

mmol/L in females and <8.3 mmol/L in males. Since there is no local standard reference value of NLR, a cut-off value was chosen based on the reference values for neutrophil (7.0 109/L) and lymphocyte (1.3 109/L), and thus an elevated NLR was defined as levels > 5.3. Sodium was recorded as mmol/l and hyponatremia was defined as a sodium level < 137 mmol/L.

Prognostic outcomes

The outcomes in study II were local recurrence and disease-specific mortality. Overall and disease-specific mortality were used as outcomes in studies III and IV, while relative and disease-specific mortality were used in study V. Patients were followed from the date of their last primary treatment for local recurrence analyses and the date of diagnosis for mortality analyses to the date of outcome, emigration, or end of the study period. Local recurrence was defined as a recurrence in the same location as the primary tumor, either histopathologically verified or as a multidisciplinary consensus diagnosis based on clinical examination and diagnostic imaging. Disease-specific mortality was defined as death by sarcoma or death with metastatic disease. Relative mortality was computed as one minus the relative survival (S_r), where the relative survival[170] was defined as the ratio of the observed overall survival of STS patients (S_o) and the expected survival in an age- and sex-matched general comparison cohort (S_e):

$$S_r = \frac{S_o}{S_e}$$

The random general comparison cohort was sampled from the general population by individual matching using the Civil Registration System.[184] For each STS patient registered in the ASR, 5 age- and sex-matched individuals from the general population were found who were alive at the date of sarcoma diagnosis (index date), had not previously been diagnosed with a sarcoma, and lived in the same geographical area as the STS patient. Death from all causes and death by causes other than sarcoma were considered competing events in the analyses of local recurrence and disease-specific mortality, respectively.

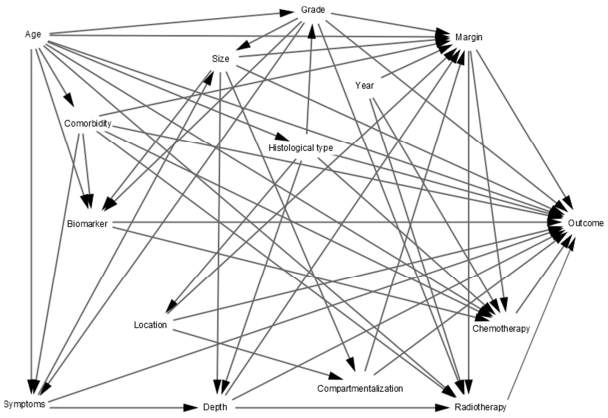
Confounders

As potential confounders, we considered covariates associated with the outcome, but not on the causal path, which are likely unevenly distributed between exposure groups. Confounding can be limited or controlled for in the design of the study, i.e., by matching or randomization, or in the data analyses, e.g., by stratification or adjustment.[103,194] Based on our study design and the number of patients, confounding was controlled for by adjustment. Possible confounders to include in the adjusted analyses, in order to minimize bias, were selected based on DAGs (Figure 2) and the principles described by Shrier and Platt for studies II and IV, and an a priori literature search for study III.[105] These principles consist of the following six steps, where covariates are the variables chosen to minimize bias:

I. The covariates should not be caused by the exposure (i.e. descendants).
II. Delete variables that do not cause the exposure, do not cause the outcome, and do not cause the covariates (i.e. non-ancestors)
III. Delete all lines emanating from the exposure.
IV. Connect any two variables that both cause a third covariate.
V. Remove all arrowheads
VI. Delete all lines between the covariates and the variables.

In study II, comorbidity and biomarkers were unobserved covariates. The ASR was used to obtain information on age, calendar year at diagnosis, as well as possible tumor- and treatment-related confounders in studies II, III, and IV. Information regarding comorbidity (possible confounder in study IV) was obtained from the NPR.

***Figure 2**. Directed acyclic graph of possible causal relations between prognostic factors, comorbidity, biomarkers, outcome, and confounding covariates in STS patients with non-metastatic disease.*



STATISTICAL ANALYSES

Characteristics

In all five studies demographic, tumor, and treatment characteristics were summarized as medians and ranges or interquartile ranges (IQRs) for continuous variables, and numbers and percentages for categorical variables. Baseline characteristics were assessed according to calendar year at diagnosis (study II), level of comorbidity (study III), and level of biomarkers (study IV) using the Pearson's chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables.

Validity of the Aarhus Sarcoma Registry (ASR)

In study I, we assessed the validity of the ASR by calculating the correctness and completeness of the data. Correctness of the data was defined as the amount of registered data unchanged during the validation divided by the number of registered data before validation. Completeness of data was defined as the amount of registered data divided by the number of registered patients.

Completeness of patient registration

In study I we estimated the completeness of patient registration in the ASR (*P*) as the number of the patients registered in both the ASR and the DCR (*ASR* ∩ *DCR*), divided by the total number of patients registered in the DCR (*DCR*):

$$P = \frac{ASR \cap DCR}{DCR}$$

Differences in completeness according to sex, age, region, and 5-year periods were examined.

Incidence

Incidence was calculated as IR per 100,000 inhabitants per year with 95% CIs. Crude and age-standardized incidence rates using

the WHO standard population were calculated.[195] The changes in age-standardized 5-year incidence rate for age and sex were assessed as IRR with 95% CIs using Poisson regression.

Absolute risks
Absolute risks were presented as cumulative incidence functions with 95% CIs, both crude and confounder adjusted. Local recurrence and disease-specific mortality (studies II–V) were estimated using the pseudo-value approach, treating death of all causes and death due to causes other than sarcoma as competing events. Overall mortality (studies III–V) was analyzed using the Kaplan-Meier method estimating 5- and 10-year overall mortality. Risk was presented as overall risk, as well as according to location, compartmentalization, grade, margin, and radiotherapy (study II), level of comorbidity (study III), albumin, CRP, hemoglobin, NLR, sodium (study IV), as well as grade and stage at diagnosis (study V).

Cox proportional hazard regression
The Cox proportional hazard regression was used to compute hazard ratios with 95% CIs in studies II–V. Both crude- and confounder-adjusted analyses were performed. In study II no adjustment was performed in the analyses of age; duration of symptoms was adjusted for age and grade; tumor size was adjusted for duration of symptoms and grade; location was adjusted for histological subtype; depth was adjusted for duration of symptoms, size, and histological subtype; compartmentalization was adjusted for size and location; grade was adjusted for age and histological subtype; margin was adjusted for age, size, depth, location, compartmentalization, grade, and year of diagnosis; and radiotherapy was adjusted for age, depth, grade, margin, and year of diagnosis. Comorbidity (study III) was adjusted for age, sex, stage at diagnosis, tumor size, depth, grade, surgical margin, radiotherapy, and chemotherapy. In study IV, biomarkers were adjusted for age and calendar year at diagnosis, level of comorbidity, size, grade, histological type, surgical margin, and chemotherapy. In study V, the hazard ratio was used as an estimate for mortality rate ratios (MRRs), which compare the mortality of the STS patients with the age- and sex-matched comparison cohort, adjusting for the level of comorbidity. Age, tumor size, and duration of symptoms were analyzed as continuous non-linear variables using cubic spline regression.

The assumption behind the regression model, i.e., proportional hazard, was checked graphically for all the included variables, both crude and adjusted, using log-minus-log plots. Based on this, no contradictions were found in studies II–IV; however, the assumption was not met in study V and data were analyzed separately from 0 to 5 years and from 5 to 10 years. No contradictions to the assumption were found within these follow-up periods.

Stratified analysis
In studies III and V both crude and adjusted analyses were stratified by certain covariates. These analyses, which are also referred to as subgroup analyses, were performed to evaluate whether the association between exposure and outcome varied according to subgroups, i.e., if effect modification was present. In both study III and study V, stratified analyses according to age and sex were performed. Additionally, analyses were stratified by calendar year in study III and level of comorbidity as well as follow-up period in study V.

Missing data
In study IV, data on tumor size, margin, and biomarkers were missing in up to 11% of the patients. The risk of bias from missing data depends on why the data is missing.[196] Excluding patients with missing data might introduce bias if they were not missing completely at random; however, in most cases the probability of data being missing depends on other characteristics, i.e., missing at random, but not completely at random. When data are missing at random, a complete case approach (excluding patients with missing data in any of the included variables) will most likely cause selection bias. Several methods to handle missing data are available, including multiple imputation.[196-198]

Multiple imputation consist of two steps. Firstly, a number of copies of the dataset are created, and in each dataset the missing values are replaced by imputed values generated based on the remaining characteristics. Secondly, the model of interest is fitted using standard statistical methods on each dataset, and the results are averaged into a final estimation.[198] We imputed size, margin, and biomarkers in study IV using multiple imputation by chained equations (MICE) in patients in whom at least one of the biomarkers was observed. The imputation dataset was considered our main dataset; however, the results of the complete case approach were compared to the results of the main dataset in order to assess the impact of the missing data.

RESULTS

STUDY I
We identified 1827 patients with a extremity or trunk wall sarcoma treated at the Sarcoma Center of Aarhus University Hospital in the period 1979–2008, of which 1275 had STS. The median age was 53 years (range 0–95) and 56% were males. The validation of the ASR increased the number of patients from 1442 to 1827 (26.7%). The completeness and correctness of the data registered in the ASR are shown in Table 5.

The overall completeness of patient registration in the ASR was 85.3% (95% CI: 83.5–86.9). The completeness of registration was significantly higher after 1994, in patients < 60 years, and in patients from the northern and central part of western Denmark, as seen in Table 6. The crude and WHO-age standardized incidence of STS in western Denmark was 1.8 (95% CI: 1.7–1.9) and 1.4 (95% CI: 1.3–1.5), respectively.

The incidence increased significantly over the study period, with an IRR of 2.08 (95% CI: 1.65–2.62) in 2004–2008 compared with 1979–1984.

STUDY II
Study II included 922 adult patients with non-metastatic STS in the extremity or trunk wall. The median age was 60 years (range 15–95) and 52% were males. The most frequent tumor types were malignant fibrous histiocytoma (30%), liposarcoma (20%), and leiomyosarcoma (18%). In total, 97% (*n* = 894) were treated surgically, with 95% (*n* = 879) being macroscopically disease-free after primary treatment. During the study period, the amputation rate decreased from 24% to 8%. The median follow-up was 7.1 years (range 0.0–34.2). The 5-year local recurrence and disease-specific mortality were 16% and 24%, respectively. As seen in Table 7, important prognostic factors for both local recurrence and disease-specific mortality were grade, margin, and radiotherapy, while anatomical and compartmental location was prognostic for disease-specific mortality. Depth was not prognostic for either local recurrence or disease-specific mortality. Age, duration

Table 5. Completeness and correctness of data by selected variables in the Aarhus Sarcoma Registry

	Data completeness % (95% CI) N						Correct data % (95% CI) N		
Variables	**Pre-validation**			**Post-validation**			**Pre-validation**		
Date of admission	81.8	(79.7–83.8)	1180/1442	100.0	(99.8–100.0)	1827/1827	43.2	(40.4–46.1)	510/1180
Duration of symptoms	88.1	(86.3–89.7)	1270/1442	95.9	(94.9–96.8)	1752/1827	50.2	(47.4–53.0)	638/1270
Cause for referral	81.1	(78.9–83.1)	1169/1442	100.0	(99.8–100.0)	1827/1827	93.7	(92.1–95.0)	1095/1169
Tumor size	79.1	(76.9–81.2)	1141/1442	95.5	(94.4–96.4)	1744/1827	42.7	(39.8–45.6)	487/1141
Location									
Soft tissue sarcoma	81.8	(79.4–84.1)	877/1072	100.0	(99.7–100.0)	1275/1275	86.1	(83.6–88.3)	755/877
Bone sarcoma	77.6	(72.3–81.7)	287/370	100.0	(99.3–100.0)	552/552	94.1	(90.7–96.5)	270/287
Compartment	79.3	(77.1–81.3)	1143/1442	100.0	(99.8–100.0)	1827/1827	73.0	(70.3–75.5)	834/1143
Histological subtype									
Soft tissue sarcoma	81.0	(78.5–83.3)	868/1072	100.0	(99.7–100.0)	1275/1275	79.4	(76.5–82.0)	868/868
Bone sarcoma	77.8	(73.3–82.0)	288/370	100.0	(99.3–100.0)	552/552	64.2	(58.4–69.8)	185/288
Grade	95.6	(94.4–96.6)	1378/1442	100.0	(99.8–100.0)	1827/1827	53.4	(50.7–56.1)	736/1378
Surgery [a]									
Date	68.1	(65.5–70.6)	895/1315	100.0	(99.8–100.0)	1564/1564	25.3	(22.4–28.2)	226/895
Type	80.7	(78.4–82.8)	1061/1315	100.0	(99.8–100.0)	1564/1564	97.7	(96.7–98.5)	1037/1061
Margin	79.9	(77.7–82.1)	1051/1315	99.9	(99.6–100.0)	1563/1564	76.0	(73.3–78.6)	799/1051
Radiotherapy [b]	95.6	(94.4–96.6)	1379/1442	100.0	(99.8–100.0)	1827/1827	90.5	(88.8–92.0)	1248/1379
Chemotherapy [b]	95.6	(94.4–96.6)	1379/1442	100.0	(99.8–100.0)	1827/1827	95.9	(94.8–96.9)	1323/1379

NOTES: [a] Subgroup only includes patients treated with surgery (pre N=1315, post N=1564). [b] Data on whether the patient was treated with radiotherapy and chemotherapy or not.

Table 6. Completeness of patient registration in the Aarhus Sarcoma Registry by sex, age, regions, and calendar year

	%	(95% CI)	N	P-value [a]
Sex				
Male	84.5	(82.1–86.7)	829/981	
Female	86.3	(83.6–88.7)	629/729	0.31
Age (years)				
< 20	90.2	(85.3–93.9)	184/204	
20–39	90.5	(86.5–93.6)	266/294	
40–59	89.6	(86.4–92.3)	396/442	
> 60	79.5	(76.5–82.3)	612/770	<0.0001
Region				
South	76.9	(73.2–80.4)	423/550	
Central	94.2	(92.2–95.8)	634/673	
North	82.3	(78.7–85.6)	401/487	<0.0001
Calendar year				
1979–1983	68.0	(61.5–73.9)	157/231	
1984–1988	76.8	(70.9–81.9)	185/241	
1989–1993	77.4	(71.9–82.3)	206/266	
1994–1998	89.8	(85.7–93.1)	255/284	
1999–2003	95.9	(93.1–97.8)	305/318	
2004–2008	94.6	(91.8–96.7)	350/370	<0.0001
Total	85.3	(83.5–86.9)	1458/1710	

of symptoms, and tumor size were significantly associated with both local recurrence and disease-specific mortality, when analyzed continuously (Figure 3).

STUDY III

In study III, we included 1210 adult patients with STS in the extremities or trunk. At diagnosis, 88% presented with a non-metastatic primary tumor. The median follow-up in live patients was 13.1 years (range 2.8–34.2). The overall prevalence of comorbidity was 25% (*n* = 299). The prevalence according to age and calendar year at diagnosis is shown in Figure 4. Comorbidity was significantly associated with stage at diagnosis, histological grade, and treatment. After adjusting for possible confounders, comorbidity was independently associated with an increased overall and disease-specific mortality (Table 8). Moderate and severe comorbidity was not associated with an additionally increased risk compared to mild comorbidity ($p = 0.79$ and $p = 0.17$, respectively)

STUDY IV

In study IV, we included 614 STS patients with non-metastatic STS diagnosed between 1994 and 2008. The level of biomarkers was significantly associated with adverse prognostic factors, such as older age and larger, deep-seated, high-grade tumors. Albumin, hemoglobin, and NLR were independently associated with both overall mortality and disease-specific mortality, while CRP and sodium were only associated with overall mortality (Table 9). Comorbidity was an important confounder and biased the correlation between albumin, CRP, hemoglobin, sodium, and disease-specific mortality away from the null, ranging from 0.05 to 0.25. The prognostic effect of the biomarker score including albumin, CRP, hemoglobin, NLR, and sodium for overall mortality, and albumin, hemoglobin, and NLR for disease-specific mortality is shown in Figure 5. Patients with abnormal values in all biomarkers had a significant additional risk of dying, both in general and from sarcoma, compared to patients with only some abnormal values (overall mortality: HR = 2.62 [95% CI: 1.13–6.07] and disease-specific mortality: HR = 3.91 [95% CI: 1.68–9.10]).

Table 7. Cumulative incidence (%) and confounder adjusted Cox proportional hazard analyses of possible prognostic factors for local recurrence and disease-specific mortality in adult patients with non-metastatic soft tissue sarcoma in the extremities or trunk wall.

		Local recurrence		Disease-specific mortality		
Factor	**N (%) [a]**	**5-y**	**HR (95% CI) [b]**	**5-y**	**10-y**	**HR (95% CI) [b]**
Anatomical location						
Upper extremity	152 (16)	19	1	18	25	1
Trunk	275 (30)	20	1.18 (0.76-1.82)	29	33	1.72 (1.18-2.52)
Lower extremity	495 (54)	12	0.89 (0.58-1.36)	23	28	1.49 (1.03-2.14)
Tumor depth						
Subcutaneous/superficial	262 (28)	14	1	11	14	1
Deep/subfascial	660 (72)	17	0.80 (0.53-1.21)	29	35	1.31 (0.88-1.97)
Compartmentalization						
Intra	340 (37)	11	1	16	19	1
Extra	582 (63)	19	1.35 (0.94-1.94)	29	35	2.15 (1.62-2.86)
Grade						
1	147 (16)	9	1	3	3	1
2	142 (15)	15	1.61 (0.85-3.03)	9	17	7.23 (2.51-20.79)
3	617 (67)	18	2.00 (1.16-3.44)	32	37	15.75 (5.78-42.93)
Unclassifiable	16 (2)	8	1.76 (0.39-7.86)	50	57	30.60 (9.20-101.78)
Surgery [c]						
Wide/radical	636 (72)	12	1	20	25	1
Intralesional/marginal	245 (28)	25	2.01 (1.41-2.85)	29	34	1.05 (0.80-1.40)
Radiotherapy						
No	626 (68)	17	1	22	27	1
Yes	296 (32)	14	0.47 (0.32-0.71)	28	34	0.64 (0.48-0.86)
Year of diagnosis						
1979-1988	214 (23)	19	1	26	33	1
1989-1998	295 (32)	14	0.86 (0.57-1.28)	22	27	0.93 (0.68-1.26)
1999-2008	413 (45)	15	0.85 (0.58-1.24)	24	29	0.93 (0.69-1.25)

NOTES: Abbreviations: LR, local recurrence; HR, hazard ratio; CI, confidence interval. [a] 43 patients not macroscopically tumor-free after primary treatment excluded in the analyses of local recurrence. [b] Confounding variables were selected based on the directed acyclic graph depicted in figure 2; location was adjusted for histological type; depth was adjusted for duration of symptoms, size, and histological type; compartmentalization was adjusted for size and location; grade was adjusted for age and histological type; margin was adjusted for age, size, depth, location, compartmentalization, grade, and year of diagnosis; radiotherapy was adjusted for age, depth, grade, margin, and year of diagnosis; no adjustments were included in the analysis of year at diagnosis. [c] Only patients treated with surgery (N=876) included. 3 missing values.

Figure 3. *Adjusted hazard ratios (HR [solid line]) with 95% confidence intervals (dashed line) for local recurrence (a, c, e) and disease-specific mortality (b, d, f) according to age, duration of symptoms, and tumor size, based on Cox proportional hazard analyses.*

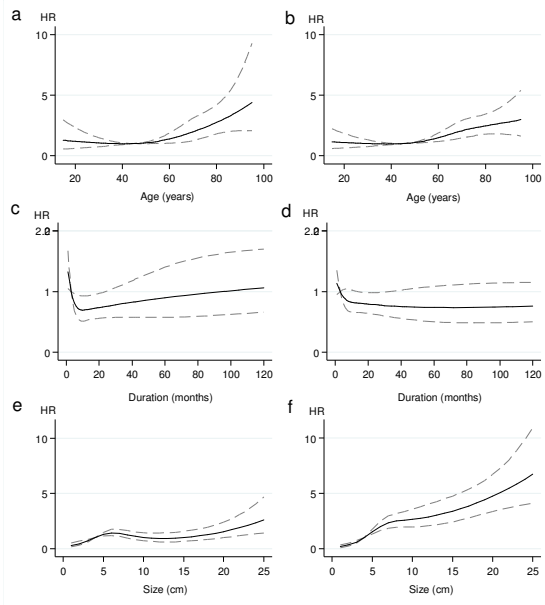


Figure 4. *Prevalence of comorbidity as percentage by age (a) and calendar year of diagnosis (b) in adult soft tissue sarcoma patient.*

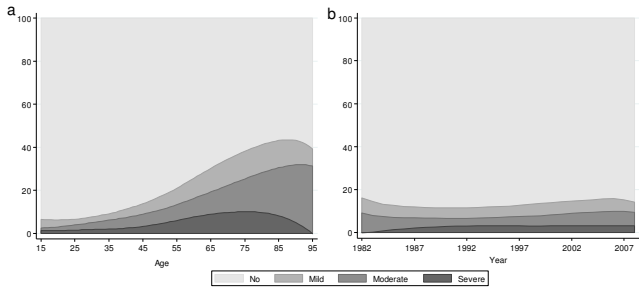


Table 8. Cumulative incidences (%) and adjusted Cox proportional hazard analyses for the effect of comorbidity on overall and disease-specific mortality in 1210 adult soft tissue sarcoma patients by age-groups.

		Overall mortality		Disease-specific mortality	
	N	5-year	HR (95% CI) [a]	5-year	HR (95% CI) [a]
Overall					
No	911	35	1	26	1
Mild	106	52	1.56 (1.20–2.02)	33	1.46 (1.01–2.10)
Moderate	107	62	1.55 (1.20–2.00)	41	1.55 (1.10–2.19)
Severe	86	69	2.05 (1.56–2.70)	44	2.04 (1.39–2.99)
15–49 years					
No	386	24	1	22	1
Mild	12	33	1.21 (0.52–2.84)	33	1.43 (0.60–3.44)
Moderate	17	59	2.99 (1.53–5.84)	59	3.20 (1.57–6.54)
Severe	8	40	8.77 (2.57–29.87)	38	10.77 (2.30–50.35)
50–69 years					
No	322	33	1	27	1
Mild	41	39	1.86 (1.18–2.91)	29	1.63 (0.85–3.11)
Moderate	36	50	1.72 (1.04–2.87)	44	1.15 (0.57–2.33)
Severe	31	65	2.01 (1.27–3.19)	48	1.65 (0.92–2.96)
≥ 70 years					
No	203	59	1	35	1
Mild	53	66	1.46 (1.02–2.10)	36	1.19 (0.68–2.07)
Moderate	54	70	1.18 (0.84–1.66)	33	0.90 (0.54–1.53)
Severe	47	77	1.97 (1.37–2.85)	43	1.93 (1.11–3.37)

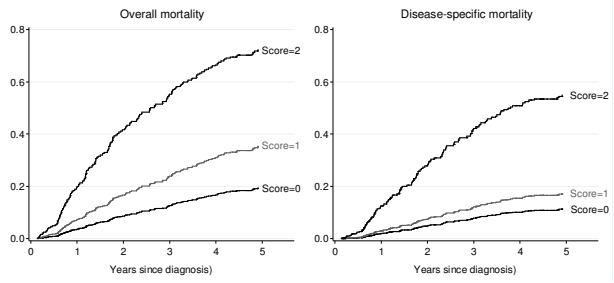
NOTES: Abbreviations: HR, hazard ratio; CI, confidence interval. [a] Analyses adjusted for age, sex, stage at diagnosis, tumor size, depth, grade, surgical margin, radiotherapy, and chemotherapy.

Table 9. Cox proportional hazard analyses of the importance of biomarkers for overall and disease-specific mortality in soft tissue sarcoma patients with and without adjustment for comorbidity. (N=614)

	No. of patients	No. of deaths	HR (95% CI) [a] w/ comorbidity	HR (95% CI) [a] w/o comorbidity
Overall mortality				
Albumin				
Normal	537	227	1	1
Low	61	54	1.67 (1.18-2.35)	1.62 (1.15-2.30)
CRP				
Normal	406	151	1	1
High	139	100	1.53 (1.15-2.04)	1.57 (1.18-2.10)
Hemoglobin				
Normal	517	207	1	1
Low	90	76	1.70 (1.26-2.30)	1.81 (1.34-2.44)
NLR				
Normal	525	224	1	1
High	68	52	2.00 (1.43-2.79)	1.98 (1.44-2.73)
Sodium				
Normal	556	249	1	1
Low	49	33	1.55 (1.06-2.26)	1.60 (1.10-2.34)
Disease-specific mortality				
Albumin				
Normal	537	124	1	1
Low	61	28	1.82 (1.12-2.94)	1.97 (1.20-3.21)
CRP				
Normal	406	77	1	1
High	139	57	1.44 (0.97-2.12)	1.55 (1.06-2.27)
Hemoglobin				
Normal	517	114	1	1
Low	90	38	1.66 (1.07-2.56)	1.91 (1.25-2.93)
NLR				
Normal	525	120	1	1
High	68	28	1.76 (1.12-2.75)	1.68 (1.09-2.59)
Sodium				
Normal	556	135	1	1
Low	49	16	1.47 (0.85-2.55)	1.52 (0.88-2.64)

NOTES: Abbreviations: HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; NLR, Neutrophil to lymphocyte ratio. [a] Analyses adjusted for age, tumor size, grade, histological type, surgical margin, chemotherapy, and calendar year at diagnosis.

Figure 5. *Cumulative incidence of overall and disease-specific mortality according to biomarker scores adjusted for age, comorbidity, size, grade, histological type, surgical margin, chemotherapy, and calendar year. Score 0: normal values for all markers. Score 1: abnormal value for at least one, but not all, markers. Score 2: abnormal values for all markers.*



STUDY V

Study V included 1246 STS patients and a general comparison cohort of 6230 individuals. The prevalence of comorbidity was comparable, except for the conditions 'any tumor' and 'metastatic solid tumor', where STS patients had a higher prevalence. The median follow up period was 6.6 years (IQR 1.7–13.7) for STS patients and 11.2 years (IQR 6.8–17.7) for the general comparison cohort. The 5- and 10-year MRRs according to sex, age, and level of comorbidity are shown in Table 10. The overall risk of dying was 4.4 times (95% CI: 3.9–4.9) higher for the STS patients within the first 5 years after diagnosis, compared with the general comparison cohort, while 'only' 1.6 times (95% CI: 1.3–2.0) higher within the subsequent 5 years. The 5- and 10-year relative mortalities for STS were 32.8% (95% CI: 29.8–36.0) and 36.0% (95% CI: 32.3–39.8) compared to disease-specific mortalities of 29.7% (95% CI: 27.2–32.2) and 34.1% (95% CI: 31.5–36.8), respectively (Figure 6). The largest discrepancy between the relative and

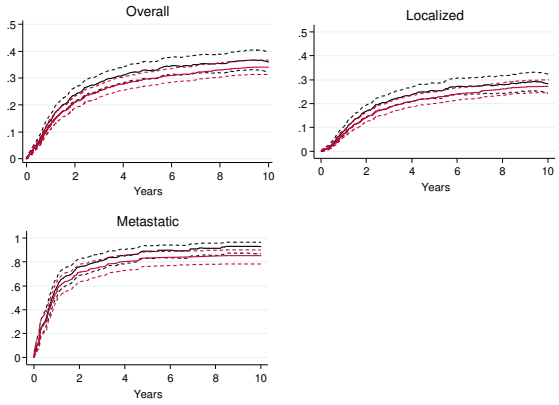
disease-specific mortality was observed in patients with metastatic disease, where the 5- and 10-year disease-specific mortality underestimated the "true mortality" by 5.7 (95% CI: -1.5–12.9, p = 0.06) and 7.8 percentage points (95% CI: 1.1–14.5, p = 0.013), respectively.

Table 10. Relative mortality rates and mortality rate ratios by sex and age at diagnosis/index date for soft tissue sarcoma patients and the general comparison cohort.

	STS patient mortality %	General mortality %	Adjusted MRR [a]
0 to 5 years			
Gender			
Female	40.2 (36.4-44.3)	10.7 (9.7-11.9)	4.7 (3.9-5.6)
Male	41.6 (37.9-45.5)	13.5 (12.4-14.7)	4.2 (3.6-4.9)
Age (years)			
0-39	27.2 (22.5-32.7)	0.3 (0.1-0.7)	110.8 (40.5-303.0)
40-59	24.4 (20.3-29.2)	2.4 (1.8-3.3)	11.0 (7.6-15.8)
60-79	53.9 (49.5-58.5)	16.5 (15.1-18.1)	4.4 (3.7-5.1)
≥ 80	72.2 (64.3-79.6)	51.2 (47.4-55.1)	1.9 (1.5-2.4)
Comorbidity			
None	34.9 (31.9-38.0)	7.0 (6.3-7.8)	6.6 (5.7-7.7)
Low	52.3 (43.3-62.0)	24.3 (21.2-27.8)	3.0 (2.2-4.1)
Moderate	60.6 (51.5-69.7)	34.2 (29.7-39.2)	2.8 (2.1-3.8)
High	68.7 (58.8-78.2)	48.9 (43.0-55.3)	2 (1.4-2.7)
Total	41.0 (38.3-43.7)	12.2 (11.4-13.0)	4.4 (3.9-4.9)
5 to 10 years			
Gender			
Female	49.8 (45.7-54.0)	21.2 (19.7-22.8)	1.8 (1.3-2.5)
Male	52.8 (49.0-56.8)	26.6 (25.1-28.3)	1.5 (1.2-2.0)
Age (years)			
0-39	33.2 (28.0-38.9)	1.0 (0.6-1.8)	11.1 (5.0-24.6)
40-59	33.8 (29.0-39.0)	6.7 (5.6-8.1)	2.9 (1.8-4.4)
60-79	67.0 (62.5-71.5)	36.8 (34.8-39.0)	1.2 (0.9-1.6)
≥ 80	88.9 (82.2-93.9)	82.4 (79.0-85.6)	1.1 (0.7-1.7)
Comorbidity			
None	43.8 (40.6-47.1)	16.8 (15.7-17.9)	1.5 (1.2-2.0)
Low	72.0 (61.9-81.4)	46.0 (42.0-50.3)	1.6 (0.9-2.8)
Moderate	78.3 (69.7-85.8)	51.8 (46.5-57.4)	2.8 (1.6-4.9)
High	79.0 (70.0-87.1)	77.5 (70.7-83.7)	0.9 (0.4-2.0)
Total	51.4 (48.6-54.3)	24 (23.0-25.2)	1.6 (1.3-2.0)

NOTES: Abbreviations: STS, soft tissue sarcoma; MRR, mortality rate ratio; CI, confidence interval. Numbers in parenthesis correspond to 95% CI. [a] Adjusted for age, gender, and level of comorbidity

Figure 6. *Relative (black lines) and disease-specific mortality (red lines) for soft tissue patients, overall as well as stratified by stage at diagnosis with 95% confidence intervals.*

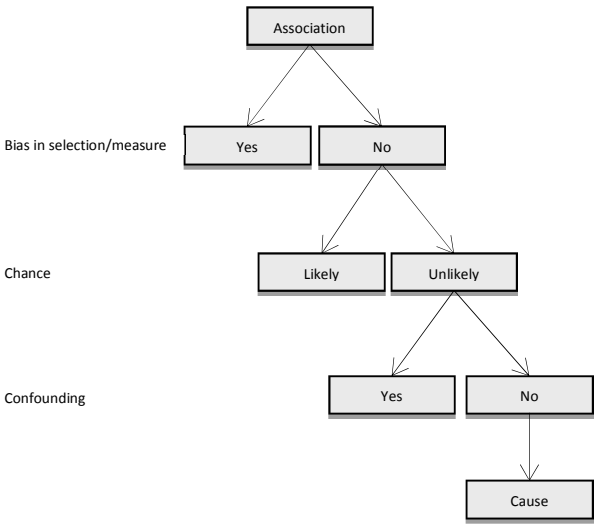


DISCUSSION

METHODOLOGICAL CONSIDERATIONS

The overall methodological objective is to obtain precise and valid estimates of the association between an exposure and an outcome, with a high level of external generalizability. In observational studies, a number of systematic errors may affect the validity of the findings, i.e., selection bias, information bias, statistical imprecision, and confounding (Figure 7).

Figure 7. *The relationship between association and cause. Modified from "Clinical Epidemiology: The Essentials" by Fletcher et al.*[199]



Selection bias

Selection bias is usually defined as the systematic error arising from the differences between included and non-included patients, in which the association between the exposure and the outcome is different. The cohort in all five studies included nearly all incident STS patients in western Denmark between 1979 and 2008 for studies I–III and V, and between 1994 and 2008 for study IV. Additionally, the Danish CPR number allows for individual linkage, enabling complete follow-up on all STS patients, as well the comparison cohort in study V. Based on this, no bias due to selection is expected. In study IV, 41 patients were excluded due to irretrievable blood sample results. Exclusion of these patients might cause bias if these blood samples were not missing completely at random. The majority of these patients had small, subcutaneous tumors, which were removed at an outpatient visit, at which blood samples are not taken routinely. However, selection of patients to the outpatient clinic is primarily based on the expected complexity and length of the surgery and not on the biomarker level; therefore, we expect that possible selection bias on this basis is minor.

Information bias

Information bias is defined as a systematic error that occurs because data on the exposure, confounder, and/or outcome are misclassified. Misclassification can be divided into two types: non-differential misclassification, where the misclassification of the exposure is independent of the outcome, or vice versa; and differential misclassification, where the misclassification of the exposure is dependent upon the outcome, or vice versa. Non-differential misclassification causes bias of an association toward the null, i.e., no difference between the compared groups, while differential bias can cause bias of the association in either direction.

Medical files were used to validate data in the ASR. The risk of information bias in studies I and II is considered low, given that the medical files were systematically reviewed by only two persons in close collaboration, using standardized forms as well as a manual with definitions of all variables. Furthermore, all uncer-

tain cases were discussed by a multidisciplinary team, and a consensus was reached. There is a possibility that correct data in the ASR were replaced by incorrect data from the medical files; however, this is considered very unlikely given the fact that medical files are generally dictated immediately after the consultation, whereas registration in the ASR is often done later. Additionally, since data in the medical files are registered prospectively, and thus independently of the outcomes, any misclassification is non-differential.

The WHO classification, which was used to classify STS in this study, has recently been updated, resulting in the change of some histological subtypes, e.g., MFH, renamed as undifferentiated pleomorphic sarcoma, and fibrosarcoma, becoming increasingly rare due to classification as other more specific types.[200,201] The pathology of the STS patients reported in this study has not been reviewed, which might cause misclassification, when compared to the new WHO classification. However, a histopathological evaluation according to the, at that time, relevant classification, was performed at the time of diagnosis, by an experienced sarcoma pathologist, for all patients referred to or diagnosed/ treated at the Aarhus Sarcoma Center. Furthermore, during the study period only 2-3 pathologists have performed these evaluations, ensuring that the classification is consistent throughout the study period. Due to this, misclassification is expected to be minor and of no significance to our studies where several histological types are considered together.

In studies III and IV, data on comorbidity were obtained from the NPR, and misclassification could have arisen due to incorrect coding of diseases included in the Charlson Comorbidity Index. Misclassifications occur to some extent; however, in this case the comorbidity occurred before the sarcoma diagnosis, and any misclassification is therefore expected to be unrelated to the sarcoma, i.e., non-differential. NPR has previously been validated as a data source for the Charlson Comorbidity Index and showed a high positive predictive value.[202] Based on this as well as the prospective registration of data in the NPR, which was independent of the aim of our study, the potential information bias is considered low.

In study V, the coding of biomarkers in the LABKA database is expected to be both accurate and complete. Since test results are entered immediately after analysis into a computer-based laboratory information system at each clinical chemistry department, we expect the potential information bias to be insignificant.

Regarding misclassification of the outcome, the Central Registration System was used to obtain information on vital status, and is expected to be virtually without coding errors; therefore, misclassification of overall mortality (studies III–V), and thus relative mortality, is not expected. Local recurrence was defined as either the date on which a biopsy showed recurrence, or the date a multidisciplinary consensus decision was made. No significant misclassification of the histopathologically diagnosed local recurrence is expected; however, there is a risk of misclassification of the local recurrence diagnosed only by clinical examination and diagnostic imaging. If this misclassification is unrelated to the patient-, tumor-, and treatment-related factors, the bias is typically in the direction of underestimation of the prognostic value of the factor. However, if the misclassification is related to the prognostic factor - e.g., a high-grade primary tumor increases the risk of (falsely) being diagnosed with local recurrence - this will lead to an overestimation of the prognostic value. Either way, any potential bias is expected to be minor since the majority of patients with local recurrence are biopsied or treated surgically.

Data regarding the COD were obtained from both the ASR and the DCR. Data on the COD were retrieved from the ASR in the majority of the cases, as the information in the ASR is suspected to be more correct. Data on the COD in the CDR is registered by physicians, either the deceased's general practitioner or hospital doctors, and the validity of the registered causes are thus dependent upon the physicians' knowledge of preceding diseases. If the risk of stating the cancer as COD is suspected to be higher in patients with adverse prognostic factors - e.g., high-grade, insufficient treatment, or advanced stage - this might cause a differential misclassification. However, we suspect that the increased risk might merely be due to the fact that the patients had a cancer in general, and not the specific prognostic factors (i.e. exposures) used in this study.

Statistical imprecision

Statistical precision is reported as 95% CIs throughout this thesis. The width of the CIs indicates the degree of random error in estimates. Based on the number of patients included, as well as the number of events recorded, we expect chance to play a minimal role in the overall analyses, which the width of the CIs supports. Some of the subgroup analyses included a limited number of patients with wide confidence intervals, and thus these results should be interpreted with caution.

Confounding

Confounding is, as previously mentioned, an important issue when conducting observational studies. In order for a factor to be a confounder, the common definition is that a factor should: be associated with both the exposure and the outcome; be unevenly distributed between exposure groups; and not lie on the causal path between the exposure and the outcome. Unlike selection and information bias which can only be prevented in the study design, confounding can be counteracted in the statistical analyses of the study. However, adjustment or stratification in the analyses presupposes that all important confounders have been measured. Unmeasured confounding is a core issue in observational studies, as opposed to randomized controlled studies where both measured and unmeasured confounders are (if the randomization is successful) evenly distributed and therefore do not bias the association.

Another issue is which factors to include as covariates in the adjusted analyses in order to minimize bias of the estimates due to confounding. The traditional approach has been that all factors that meet the above-mentioned definition should be included. However, recent advances in epidemiology have shown that this approach, rather than minimizing bias, might actually introduce it. In order to assess whether adjustment for a factor minimizes or introduces bias, DAGs depicting causal relations can be used. Previous studies describing the use of DAGs have been limited by their use of very simply causal structures, which rarely reflects reality where numerous factors interact in multiple ways. However, the simple six-step approach described by Shrier et al., as well as recent developments of computer software, such as the DAGitty, has made the use of DAGs feasible.[105,203,204]

Potential confounders were included in the statistical analyses as adjustments in studies II–V and as strata in study III and V. Covariates were selected based on the DAG approach in studies II and IV and the "traditional" approach in study III.

In studies II and IV we limited our analyses to patients with non-metastatic disease to reduce confounding due to the stage of the disease. In study III, we adjusted our analyses for age, sex, stage at diagnosis, size, depth, grade, margin, radiotherapy, and

chemotherapy, which were selected prior to our data analyses. As seen in Figure 2, adjusting for these variables decreased the bias of the direct association between comorbidity and mortality; therefore, using the "traditional approach" did not introduce bias in this case. However, based on a DAG (with the additional inclusion of stage at diagnosis), adjustment for compartmentalization, location, histological type, and duration of symptoms should have been included in order to assess the direct association between comorbidity and mortality. In study IV, we adjusted the analyses for both factors, which might affect the biomarker level (i.e., age and comorbidity) as well as factors related to the treatments. The importance of adjusting for comorbidity is stressed by the changes seen in Table 9.

There are some unmeasured factors that might have affected our results. In study II, the level of comorbidity was unmeasured, which might have biased the total association between duration of symptoms, margin, and radiotherapy. In studies III and IV, factors such as body mass index, socioeconomic status, smoking, and alcohol intake were unmeasured. These factors might be correlated with both comorbidity and biomarkers, but the impact of these factors in STS has not been established. Socioeconomic status has been shown to be related to both stage at diagnosis as well as survival in other cancer types.[205-209] However, based on the structure of the Danish health care system, with free access for all residents, the impact of socioeconomic status might be less important than in other countries. Additionally, since these factors are expected to be related to the comorbidity status, at least some of the confounding caused by these is expected to be captured by adjusting for comorbidity in study IV.

COMPARISON WITH THE LITERATURE

Validation of databases

Accurate registration and validation of data is crucial when registries are used as data sources. However, available information on the level of validation is limited for the majority of the few existing STS databases and studies including data from large cancer registries. The completeness of patient registration in the ASR of 85.3% appears to be in overall agreement with the completeness reported for the few other sarcoma registries.[5,6,10] The Scandinavian Sarcoma Group Register, which includes sarcoma patients from Sweden, Norway, and Finland, reports a completeness of > 90%, while the SEER database reports a completeness of 100%.[5,6,210] However, it was not possible to determine, for either of these, whether the analyses of patient completeness were based on individual or group levels. Furthermore, when studies on STS are based on large cancer registries, the ICD and ICD-O-codes included are essential in order to assess whether all cases are included, and since STS arises anywhere in the body, selection based on these codes might not capture all cases. Data from the DCR have been included in large European studies combining cancer registries from multiple countries, such as the EUROCARE studies, which benefit from a large number of patients. Previous studies have shown a high quality of the data in the DCR; however, our results showed that the DCR was not a perfect reference for STS, and validation of the STS data in the DCR should be standard.

Prognostic factors

Previously, there have been numerous studies investigating the impact of patient-, tumor-, and treatment-related factors in STS. However, except for factors such as tumor, size, histological grade, and surgical margin, the prognostic impact of most of these are still debatable because studies show contradictory results. These differences might be explained by the low number of patients, the heterogeneity within study populations, as well as biased results.

Our study demonstrated the important effect of age on disease-specific mortality when analyzed as a continuously non-linear variable, which has not previously been reported. Two recent studies have investigated the prognostic value of age when analyzed using cubic splines. Biau et al.[26] reported that age was significantly associated with local recurrence, while Gronchi et al.[20] reported no association with either local recurrence or disease-specific mortality. Our findings are supported by studies analyzing age as a binomial variable.[7-11,23,24,38,40,47]

To our knowledge, no study has previously analyzed the impact of symptom duration as a continuously non-linear variable in a confounder-adjusted setting. We showed that the duration was important for both local recurrence and disease-specific mortality, and that short and long durations were associated with the highest risks. Our findings are ironically supported by the seemingly disparate result of previous studies, where some found no prognostic impact, while others found decreased risks for either short or long duration.[27-31] These contractions, as well as the findings of Maguire et al., namely that the effect of duration of symptoms on survival was not linear, support that the correlation between duration of symptoms and mortality is "J" shaped, as an expression of the rapid growth of high-grade tumors, while low-grade tumors grow slowly and later de-differentiate into higher grades.[211]

We found that tumor size, grade, and margin were all important prognostic factors for both local recurrence and disease-specific mortality, and the majority of these findings are supported by the existing literature.[7-9,11,20,23-26,35-39,41,47] However, some studies did not find any impact of tumor size on local recurrence.[12,13,20,24,26,36,37,39,40] Contrary to studies in which tumor size is analyzed as a categorical or continuous linear variable, we analyzed tumor size as a continuous non-linear variable. This revealed that increasing tumor size was associated with an increased risk of local recurrence for tumors < 5 cm or > 15 cm, whereas no increase in risk was seen in tumors between 5 and 15 cm. This finding accentuates the importance of analyzing continuous variables as such, and might explain the impact on local recurrence.

Our finding that compartmentalization impacted disease-specific mortality, but not local recurrence, is supported by some of the few existing studies.[16,34,42-44] However, all of these are based on a small number of patients included before our study period, and no newer studies of the prognostic impact of compartmentalization exist.

The anatomical location of the tumor was significantly associated with disease-specific mortality, but not local recurrence, which the majority of studies[7-11,23,25,35,38,47], but not all[7,8,21,35,40], support. In contrast to the majority of the published studies, we found that depth impacted neither local recurrence nor disease-specific mortality.[7,9,20,23,24,26,36,37,39] Our finding is supported by a recent study comparing the 6th and the 7th version of the American Joint Committee on Cancer's staging system (where depth is no longer included), which found no significant difference between the versions.[11] These differences in the impact of depth might, as previously mentioned, be caused by residual confounding due to insufficient adjustment for tumor size.[42,212]

We found that treatment with radiotherapy was associated with both decreased local recurrence and disease-specific mortality. The impact on local recurrence is in accordance with most

studies[12,20,26,36,38,39,95,96], whereas the impact on disease-specific mortality has only been investigated in few studies, with contradictory results.[7,10,20,41,75] Two of these included a significant number of patients with non-metastatic STS in the extremities; however, all patients in the study that found no association were treated with complete resection, which might explain the difference.[7,20] Subgroup analyses were not obtainable in our study due to the low number of patients in certain groups, e.g., low-grade tumors treated with radiotherapy, but the existing literature regarding which patients benefit from radiotherapy varies.[12,38,95]

Comorbidity

We found a prevalence of comorbidity that is in overall agreement with the prevalence of 20% that was reported in a study investigating comorbidity in 322 high-grade non-metastatic STS patients.[129] Another study by van Herk-Sukel et al. investigated the prevalence of medical conditions in 533 STS patients separately, and reported that 33% had cardiovascular disease, 10% had respiratory disease, and 6–7% had diabetes, anemia, or depression.[128] The higher prevalence of these conditions compared to our results might be explained by the differences in inclusion of diagnostic codes, e.g., van Herk-Sukel et al. included hypertension in cardiovascular disease.[128]

Contrary to our result that showed comorbidity as an important prognostic factor, the only two previous studies investigating comorbidity in STS found no correlation with mortality.[75,129] Comorbidity was assessed as both dichotomized and continuously linear; however, since comorbidity was not significant in either of the crude analyses, adjusted analyses were not performed.[129] As previously discussed in this thesis, neither of these approaches of analyzing continuous variables is optimal. The crude analyses of disease-specific mortality in our study showed that moderate and severe comorbidity were statistically significant, while mild was not. Thus, this difference in results may simply be explained by the different categorization of comorbidity. Additionally, the low number of patients included makes the results less reliable.

Biomarkers

Overall, the existing literature on the prognostic role of biomarkers in STS is still limited. Our study adds to the previous research by providing validated population-based data with complete follow-up on a significantly larger number of patients, as well as by including an adjustment for comorbidity, which none of the published studies did.

We found that hypoalbuminemia was associated with overall mortality, which is supported by a small study of STS patients.[157] Contrary to our results, Barreto-Andrade et al. found no significant association with disease-specific mortality; however, the association was only studied univariately in a small number of patients, making their results less reliable.[157] Our finding that anemia was an important prognostic factor corroborates the findings in a study of 376 adult STS patients with non-metastatic disease that showed that anemia was independently associated with poorer event-free and disease-specific mortality.[158] Contrary to our findings, studies investigating the prognostic role of CRP in STS patient have found CRP to be significantly associated with both a poorer overall and disease-specific mortality.[129,151,152,154] However, none of the published studies on CRP in STS adjusted their analyses for comorbidity. Without adjustment for comorbidity we found a stronger, and significant, association between CRP and mortality, indicating that comorbidity biases the association. The prognostic role of NLR has previously been investigated in non-metastatic STS patients.[149,152,156,173] Two recent studies concluded that an elevated NLR was significantly associated with poorer mortality, in accordance with our findings, while a third study concluded that only a combination of elevated CRP and elevated NLR was significant. The impact of hyponatremia on mortality in non-metastatic STS patients has, to our knowledge, not been investigated previously. However, hyponatremia has been found to be an important prognostic factor in cancer patients with metastatic disease and the inappropriate antidiuretic hormone secretion syndrome. [135,138,141,144,159,213]

Relative mortality

The 5-year relative mortality of 33% estimated in our study is relatively low compared with the few published studies of STS patients, which have reported 5-year relative mortalities between 40% and 55%.[175,176,178-180] Previously, relative mortality has primarily been studied in large international studies combining data from national cancer registries. Similar to our findings, these showed that the relative mortality increased with age and that there was no significant difference between males and females.[176,179,180] Ng et al. reported 5-year relative mortalities varying from 5% to 15% in low-grade MFH, liposarcoma, and leiomyosarcoma, i.e., the three most frequent subtypes in our study, whereas the 5-year mortality was 1.2% in our study.[176]

Relative mortality has not previously been compared with disease-specific mortality obtained through death certificates in STS. Our results indicate, surprisingly, that there is a tendency toward underestimating sarcoma as the COD. The correlation between relative and disease-specific mortality has been investigated in other cancer types, and these studies have shown both under- and overestimations depending on age, stage at diagnosis, as well as the type of cancer.[214-221] Hu et al. studied breast, colorectal, lung, skin, prostate, and pancreatic cancer in 338,445 patients and reported an overall tendency toward underestimation of the disease-specific mortality, albeit small.[221] Contrary to this, Johnson et al. reported an overall overestimation regarding all cancer types using population-based registries in California, Colorado, and Idaho covering the period from 1993 to 1995.[220]

CONCLUSION

STUDY I

We found that the systematic validation process significantly improved the data quality of the ASR. The ASR is now considered a population-based, validated, and valuable data source for epidemiological research and prognostic studies of STS. Documented validation of registries should be required before they are used as data sources.

STUDY II

We showed that more advanced statistical methods, including DAGs, cubic splines, and a competing risk model, are feasible. Using these improved statistical methods on a large, validated dataset we found that age, duration of symptoms, tumor size, grade, margin, and radiotherapy were important prognostic factors for both local recurrence and disease-specific mortality, while anatomical and compartmental location were prognostic for disease-specific mortality.

STUDY III
We found that 25% of STS patients had comorbidity and that the presence of comorbidity was associated with a higher degree of negative prognostic factors, such as metastatic disease at diagnosis, high grade, and less aggressive treatment. Patients with comorbidity had significantly increased overall and disease-specific mortality compared to patients without comorbidity, even after adjustment for important prognostic factors including age. Moderate and severe comorbidity was not associated with an additionally increased risk compared to mild comorbidity.

STUDY IV
We identified hypoalbuminemia, anemia, and an elevated NLR as independently associated with both overall and disease-specific mortality. Hyponatremia and an elevated CRP were independent negative prognostic factors for overall, but not disease-specific mortality. We showed that adjusting analyses of biomarkers for comorbidity is important in order to minimize bias. A biomarker score can be used as an additional tool to identify patients with a higher risk of death that could be candidates for possible intensive therapy.

STUDY V
We showed that a tendency toward underestimating mortality due to sarcoma was seen when disease-specific mortality based on death certificates was used. This underestimation varied, with the largest discrepancy observed in patients with metastatic disease. Relative mortality provided an accurate method to differentiate between cancer-specific and non-cancer-specific deaths.

PERSPECTIVES
Detailed data on the prognosis of STS is important for accurately predicting the prognosis of individual patients, selecting the most optimal treatment strategy, improving the quality of treatment, as well as for health policy and research purposes. The studies represented in this thesis add to the knowledge of the prognosis of STS, as well as raise important methodological issues. The unique possibility of conducting clinical epidemiological research on STS patients, through the use of Danish databases and registries, allows for population-based data with complete follow up. This thesis demonstrated that the ASR comprises an important data source, which may be used to improve the knowledge of prognosis in STS and specifically address some of the following issues in the future.

In order to obtain a more detailed understanding of the correlation between comorbidity and STS, future studies should investigate which diseases are associated with the increased mortality in STS patients and attempt to develop a more sensitive measure of the comorbidity. The measure should focus not only on the severity and temporal relations between comorbidity and STS, but also aim at identifying specific interactions resulting in fatality. Improved knowledge and awareness of these interactions might prevent complications and thereby contribute to reduced morbidity and mortality.

This knowledge is important for physicians, not only in order to select the most optimal treatment strategy for each patient, but also in order to most accurately inform patients of the expected prognosis. This is also important from a health care/societal perspective, where primary prevention of comorbidity may reduce the mortality associated with STS. Even though STS is rare and might not have a significant socioeconomic impact, this is counterbalanced by STS patients being younger than in other cancer types, with a subsequently larger decrease in life expectancy in the event of death.

Since a significant aging of the population is expected in the future, consideration of the role of age as a prognostic factor is warranted. Even though the majority of studies have found age to be an important prognostic factor, none have adjusted their results with regard to comorbidity. Thus, the important question is whether age alone has an adverse effect or if it is merely contributing to the higher prevalence of comorbidity.

We found that the abnormal levels of some pretreatment biomarkers were independently associated with a poorer prognosis. The use of these as a future standardized diagnostic tool is promising, especially when combined into a score which more accurately reflects a patient's risk of dying. A first step to further study the role of a biomarker score as a prognostic marker for disease-specific mortality is the necessary validation of these results in another, independent dataset. This validation should not only aim at validating the results, but also address the issues of selecting the optimal cut-off value in order to identify high risk patients who are more likely to benefit from more aggressive treatment.

SUMMARY
Despite major advances in the knowledge of soft tissue sarcoma (STS) during the last decades, no significant improvement in survival has been observed. Detailed data on the prognosis of STS are crucial in order to identify patients who might benefit from more aggressive treatment. Such data can be obtained from properly designed databases; however, the validation of data is crucial in order to obtain valid, reliable results. Furthermore, the majority of prognostic studies in STS have been limited by potential selection bias, low power, and biased estimates due to the statistical methods used, e.g., dichotomizing continuous variables, censoring competing events, as well as not adjusting for important confounders. The overall aim of this thesis was to investigate the prognosis of STS patients using data from the Aarhus Sarcoma Registry (ASR), covering western Denmark in the period from 1979 to 2008.

In study I, we systematically validated data in the ASR and evaluated the validity, including completeness of patient registration and accuracy of data. In study II, we investigated the prognostic impact of patient-, tumor-, and treatment-related factors on local recurrence and disease-specific mortality. These were analyzed in a competing risk model in which continuous variables were included as cubic splines and possible confounders were selected based on directed acyclic graphs. In study III, we examined the impact of comorbidity on overall and disease-specific mortality. In study IV, we compared mortality in patients with abnormal biomarkers to those with normal values, assessed the significance of adjusting for comorbidity, as well as constructed a prognostic biomarker score. In study V, we described the relative mortality, i.e., the mortality in STS patients compared with the mortality in a general population, and compared relative and disease-specific estimates. The mortality in the general population was determined using an individually age- and sex-matched comparison cohort.

All five studies were conducted in western Denmark within a population of approximately 2.5 million. Individual linkage between the ASR and national registries was made possible by the unique Danish civil registration number. The National Patient Registry and the LABKA research database were used to obtain

data on comorbidity and biomarkers. In studies II to V we used a time-to-event-analysis approach that included cumulative incidence functions as well as crude and confounder adjusted Cox proportional hazard regression.

In study I, we established that the overall validity of data in the ASR, after validation, was satisfactory and that the ASR included 85.3% of sarcoma patients from western Denmark between 1979 and 2008. In study II, we found a 5-year local recurrence and disease-specific mortality of 16% and 24%, respectively. We excluded depth as a prognostic factor, and established that age, duration of symptoms, tumor size, anatomical and compartmental location, as well as radiotherapy were important prognostic factors for disease-specific mortality. In study III, we found that the level of comorbidity before or at diagnosis was an independent prognostic factor for both overall and disease-specific mortality, even after adjustment for age. In study IV, we showed that pretreatment levels of albumin, hemoglobin, and neutrophil to lymphocyte ratios were independently correlated with disease-specific mortality, and that adjusting for comorbidity was significant. In study V, we found 5- and 10-year relative mortalities of 32.8% and 36.0%, respectively. The mortality in patients with low-grade STS was not significantly increased compared with the general population. The 5- and 10-year disease-specific mortalities were underestimated by 3.1 and 1.9 percentage points compared to the relative mortality, respectively. We showed that relative mortality provided an accurate method to differentiate between cancer-specific and non-cancer-specific deaths.

In conclusion, we showed that the ASR is a valid source of population-based data on STS. Improving the statistical methods used in prognostic studies of STS is important in order to obtain unbiased and reliable results. The level of comorbidity and biomarkers were important prognostic factors and should be used to identify high-risk STS patients who might benefit from more aggressive treatment.

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APPENDIX

APPENDIX 1: OVERVIEW OF PROGNOSTIC PAPERS

Author, year	Period	N	Study population	Results	Follow up
Alamanda, 2012[75]	2000–2006	278	Adult patients with extremity STS, excluding patients with adequate medical records and tumors with a good prognosis or borderline malignancies, e.g., dermatofibrosarcoma protuberans.	Adjusted	Median: 3.1 years
Alektiar, 2000[54]	1982–1997	110	Primary, adult, high-grade, extremity STS treated with limb-sparing surgery and a positive microscopic margin.	Crude and adjusted	Median: 41 months (range 3–186)
Alho, 1989[14]	1981–1986	240	Primary non-metastatic, adult, grade III and IV, extremity STS, excluding patients with other malignancies and patients with contradictions to treatment with Doxorubicin.	Crude and adjusted	Survivors, median: 47 months (range 23–85)
Alkis, 2011[18]	1996–2002	294	Primary, adult STS excluding patients with incomplete data.	Crude	Median: 41 months (range 2–84)
Bell, 1989[44]	1976–1982	100	Primary, non-metastatic, adult, extremity STS treated with local resection and adjuvant RT, excluding patients not macroscopic disease-free after surgery, patients with concurrent malignant disease, and patients with incomplete data.	Adjusted	Median: 14 months (rage: 4–52)
Berlin, 1990[48]	1956–1976	137	Non-metastatic, adult, extremity STS treated with surgery, excluding patients with adjunctive treatment.	Adjusted	Minimum: 6 years
Biau, 2011[26]	1989–2008	2385	Adult, extremity and trunk STS treated with surgery, excluding rhabdomyosarcoma and intraabdominal/retroperitoneal tumors.	Adjusted	Median: 32 months (IQR: 12–85)
Biau, 2012[39]	1989–2010	1668	Non-metastatic, extremity, and trunk STS, excluding patients with well-differentiated liposarcoma, dermatofibrosarcoma, and patients who developed metastasis before definitive treatment.	Adjusted	Median: 38 months (IQR: 15–84)
Brooks, 1998[49]	1982–1996	215	Primary, adult, superficial, extremity STS.	Crude and adjusted	Median: 45 months (range 0.07–151)
Cahlon, 2008[50]	1982–2002	200	Primary, non-metastatic, adult, extremity STS treated with limb-sparing surgery, excluding patients with desmoid tumors or dermatofibrosarcoma and patients treated with adjuvant RT.	Crude and adjusted	Median: 82 months (range 1–289)
Coindre, 1996[55]	1980–1989	546	Primary, non-metastatic, adult STS macroscopically disease-free after primary treatment.	Crude and adjusted	Survivors, median: 5.1 years (range 0.3–12.6)
Collin, 1987[222]	1968–1978	423	Non-metastatic, adult, extremity STS treated with resection.	Adjusted	Median: 8.2 years
Dagan, 2012[19]	1980–2008	317	Primary, non-metastatic, adult, extremity STS treated with preoperative RT and minimum 1 year of follow-up, excluding patients with trunk involvement, patients treated with postoperative RT, patients not treated with limb-sparing intent, and certain histological subtypes.	Crude and adjusted	Median: 4.7 years (range 0.1–25.9)
DeLaney, 2007[73]	1971–2001	154	Consecutive STS treated with surgery with a positive margin and adjuvant curatively RT, excluding desmoid, dermatofibrosarcoma protuberans, rhabdomyosarcoma, and PNET.	Crude and adjusted	Median: 75 months (range 3–371)
Dickinson, 2006[82]	1987–2002	279	Primary, non-metastatic STS treated surgically, excluding patients with giant cell or angiomatoid MFH.	Crude	Median: 40 months (range 1.7–187)

APPENDIX 1: OVERVIEW OF PROGNOSTIC PAPERS, CONTINUED

Author, year	Period	N	Study population	Results	Follow up
Dinges, 1994[76]	1974–1990	102	Non-metastatic, adult STS treated curatively with surgery and RT.	Adjusted	Median: 48.5 months
Eilber, 2003[47]	1975–1997	607	Primary, non-metastatic, intermediate- and high-grade, extremity STS.	Crude and adjusted	Survivors, median: 88 months
Felderhof, 2012[56]	1995–2010	118	Non-metastatic extremity STS treated with curatively limb-sparing surgery and adjuvant RT, excluding patients with Kaposi sarcoma and desmoid-type fibromatosis.	Crude	Median: 93.4 months (range 9–192)
Gadgeel, 2009[69]	2002	345	Adult, extremity STS patients, excluding patients diagnosed at autopsy or with a prior cancer diagnosis.	Crude	Maximum: 47 months
Gaynor, 1992[43]	1968–1978	423	Non-metastatic, adult, extremity STS.	Crude and adjusted	Survivors, median: 8.7 years
Gronchi, 2005[20]	1980–2000	911	Non-metastatic extremity STS treated with curative intent, excluding patients without complete resection and patients with dermatofibrosarcoma protuberans.	Adjusted	Median: 107 months (IQR: 58–1309
Gronchi, 2010[36]	1985–2005	997	Primary, non-metastatic, adult, extremity STS treated surgically with curative intent.	Adjusted	Median:85 months (IQR: 51–121)
Gronchi, 2013[83]	2002–2007	252	Non-metastatic, high risk (high-grade, deep, size>5 cm) extremity and trunk STS treated with conservative surgery, chemotherapy, and radiotherapy.	Crude	Median: 60 months (IQR: 45–74)
Guillou, 1997[22]	1980–1989	410	Primary, non-metastatic, adult STS.	Crude	Median: 74.8 month (range 2.2–155.4)
Gustafson, 1994[21]	1964–1989	471	Adult, non-metastatic STS treated with surgery, excluding patients with Kaposi, dermatofibrosarcoma protuberans, post-irradiation, desmoid, strictly dermal tumors or Mb. Recklinghausen or Stewart-Treves syndrome.	Adjusted	Median 5 years (range 0.8–28)
Gutierrez, 2007[10]	1981–2004	8249	Primary cases of fibrosarcoma, MFH, liposarcoma, or leiomyosarcoma/GIST.	Adjusted	N/R
Heslin, 1996[57]	1983–1989	168	Primary, non-metastatic, high risk (high-grade, large size, deep), extremity STS.	Crude and adjusted	Survivors, median: 48.
Ipach, 2012[74]	1990–2008	118	Extremity and trunk STS with minimum 12 months follow up and meaningful data. Metastatic cases included.	Adjusted	Median: 58 months
Jebsen, 2008[38]	1986–2005	1093	Primary, non-metastatic, adult, extremity, and trunk STS not surgically treated before referral, excluding patients with Kaposi, dermatofibrosarcoma protuberans, mesothelioma, myxoid chondrosarcoma, Ewing/PNET, and low-grade liposarcoma.	Adjusted	Survivors, median: 5.0 years (range 0.1–20.0)
Karakousis, 1999[81]	1977–1994	194	Extremity STS.	Crude	Median: 58 months
Kattan, 2002[9]	1982–2000	2136	Primary, non-metastatic, adult STS, excluding patients with skin tumors and patients with incomplete data.	Adjusted	Median: 3.2 years
Khanfir, 2003[77]	1975–1996	133	Primary, non-metastatic, adult, extremity STS treated with wide *en-bloc* resection, excluding patients with R1/R2, uncertain or <1 mm margin, patients treated with preoperative chemotherapy, or patients with osteosarcoma, Ewing/PNET, rhabdomyosarcoma, dermatofibrosarcoma, or fibromatosis.	Crude and adjusted	Median: 10 years (range 3–25)
Kim, 2008[58]	1980–2003	150	Non-metastatic, extremity, and trunk STS treated with surgery and adjuvant RT, excluding patients with histological types not in the AJCC system, patients treated with palliative or preoperative RT, and patients with residual tumor after surgery.	Crude	Median: 48 months
Koea, 2003[24]	1982–1998	951	Primary, non-metastatic, adult, extremity STS, excluding patients with desmoid tumors or patients treated before referral.	Adjusted	Median: 35 months (range 2–201)
Kolovich, 2012[71]	2002–2010	118	High-grade STS treated with surgery, excluding patients with incomplete data or treatment of primary tumor before referral.	Adjusted	N/R
Lahat, 2008[25]	1996–2007	1091	Primary, non-metastatic, adult STS treated with complete total resection, excluding patients with desmoid or dermatofibrosarcoma histology or uncertain pathologies.	Crude and adjusted	Survivors, median: 53.3 months
Le Doussal, 1996[70]	1980–1989	216	Primary, non-metastatic, adult MFH, excluding atypical fibroxanthoma and angiomatoid subtype.	Crude and adjusted	Median 3.5 years (range 45 days-12 years)
LeVay, 1993[52]	1980–1988	389	Adult, extremity, head, neck, and torso STS treated with surgery, excluding retroperitoneal tumors.	Adjusted	Survivors, mean: 6.7 years (range 3.3–10.1)
Lewis, 1997[40]	1982–1995	911	Primary, non-metastatic, adult STS.	Crude and adjusted	Median: 3.0 years
Lintz, 2012[17]	2000–2007	105	Adult, extremity, and trunk STS treated with curative intent, excluding patients with low-grade liposarcoma, patients treated with palliative surgery, and patients not treated according to the standards.	Crude and adjusted	Median: 42 months (IQR: 24–60)
Liu, 2010[53]	1997–2007	181	Primary, non-metastatic, adult, extremity STS.	Adjusted	Median: 43 months
Maki, 2013[11]	1982–2010	8647	Consecutive STS, no exclusions mentioned. Metastatic cases and all anatomical locations included.	Adjusted	N/R
Mandard, 1989[78]	1972–1984	109	Non-metastatic, adult, extremity, trunk wall, head, and neck STS.	Adjusted	N/R
Matsubara, 2013[59]	1999–2009	170	Extremity and trunk STS, excluding patients with small superficial or low-grade tumors and patients treated with amputation.	Adjusted	Mean: 47 months (range 3–131)
McGee, 2012[60]	1970–2008	173	Non-metastatic extremity STS treated with postoperative RT, excluding patients treated with preoperative RT or previous RT to the site.	Adjusted	Median: 10.4 years (range 0.3–32.1)
McKee, 2004[61]	1979–1988	111	Primary, non-metastatic, extremity and trunk STS treated curatively with complete resection, excluding patients with incomplete follow up.	Adjusted	Median: 45 months
Merimsky, 2005[72]	1994–2002	133	Adult, intermediate- and high-grade, extremity STS treated with limb-sparing surgery and post-operative RT.	Crude	Median 4 years
Nakamura, 2011[31]	2001–2009	100	Primary STS, excluding patients with well-differentiated liposarcoma and dermatofibrosarcoma protuberans.	Adjusted	Median 29 months (range 1–97)
Novais, 2010[62]	1995–2008	248	Primary, non-metastatic, adult, deep, intermediate- and high-grade, extremity STS treated with surgery, excluding patients treated before referral, patients with secondary sarcoma, and patients with axial, pelvic, or retroperitoneal sarcoma.	Crude	Median: 4.4 years (range 0.4–13)
Parsons, 2011[41]	1991–2006	6215	Non-metastatic, adult, extremity STS treated surgically, excluding patients with prior malignant disease, patients with Kaposi, Ewing, or dermatofibrosarcoma protuberans histology, and patients with incomplete data or from certain areas and time.	Adjusted	N/R
Peabody, 1993[45]	1975–1990	172	Extremity STS.	Adjusted	Median 36 months
Pisters, 1996[23]	1982–1994	1041	Non-metastatic, adult, extremity STS.	Crude and adjusted	Survivors, median: 3.95 years
Ravaud, 1992[63]	1975–1988	144	Primary, non-metastatic, adult STS treated with surgery, excluding patients with visceral tumors and patients treated with chemotherapy.	Crude and adjusted	Median: 57.6 months (range 11–168)

APPENDIX 1: OVERVIEW OF PROGNOSTIC PAPERS, *CONTINUED*

Author, year	Period	N	Study population	Results	Follow up
Rougraff, 2007[30]	1992–2003	382	High-grade, extremity, and flank STS. No exclusions mentioned. Metastatic cases included.	Crude and adjusted	Mean: 57 months (range 4–154)
Rougraff, 2012[32]	1992–2007	381	High-grade, extremity, and flank STS. No exclusions mentioned.	Crude and adjusted	Survivors, median: 59 months (range 1–201)
Rydholm, 1984[34]	1964–1978	237	Non-metastatic STS in the locomotor system treated with surgery, excluding patients with Kaposi, dermatofibrosarcoma, strictly dermal, and post-irradiation sarcomas.	Adjusted	3–18 years
Rööser, 1987[64]	1964–1978	144	Non-metastatic, high-grade STS in the locomotor system surgically treated, excluding patients with incomplete data.	Crude and adjusted	6–21 years
Saddegh, 1992[16]	1972–1984	137	Non-metastatic STS treated with surgery.	Adjusted	Mean: 10 years
Saithna, 2008[28]	25-year period	1508	Primary STS, excluding patients with previous malignancy.	Crude	N/R
Sampo, 2008[65]	1987–1997	270	Non-metastatic, extremity, and trunk STS treated with surgery.	Adjusted	Median: 6.6 years
Sampo, 2012[80]	1987–2002	294	Non-metastatic extremity and trunk STS, excluding patient treated with preoperative radiotherapy patients treated with chemotherapy and certain histological subtypes.	Adjusted	Survivors, median: 7.2 years (range 0.3–17.5)
Schreiber, 2012[85]	1988–2006	983	Adult, high-grade, extremity STS treated with radical limb-sparing surgery, excluding patients coded as "local excision", patients treated with preoperative RT, patients with incomplete data, and patients who died within 3 months post-surgery.	Crude	Median: 34 months (range 4–225)
Singer, 1994[79]	1970–1992	182	Adult, extremity STS treated with surgery.	Adjusted	Median: 105 months (range 1–321)
Stefanovski, 2002[66]	1985–1997	395	Primary STS, excluding patients with uterine tumors and incomplete data.	Crude and adjusted	Median: 35 months
Stoeckle, 2006[67]	1996–2002	205	Primary, adult extremity, and trunk STS treated with surgery, excluding patients with Kaposi sarcoma or desmoid tumors.	Crude and adjusted	Survivors, median: 53 months (range 5–107)
Stojadinovic, 2002[37]	1982–1999	2123	Primary, non-metastatic, adult STS completely resected.	Adjusted	>2 years for 80% of the patients
Stojadinovic, 2002[35]	1982–2000	2084	Primary, non-metastatic, adult STS. All anatomical locations included.	Adjusted	Median: 50 months
Stotter, 1990[15]	1982–1987	175	Extremity and trunk wall STS, excluding patients where the primary tumor was not established and patients who died before treatment.	Adjusted	Survivors, median: 42 months (range 5–348)
Tomita, 1994[33]	1962–1989	190	Non-metastatic, adult, extremity, and trunk STS.	Crude	Median: 45 months (range 1–297)
Trovik, 2000[13]	1986–1991	559	Primary, non-metastatic, adult, extremity, and trunk STS treated with surgery as single therapy.	Adjusted	Survivors, median 7.4 years (range 0.1–12.5)
Ueda, 1988[27]	1964–1986	163	Non-metastatic, extremity, and trunk STS treated with complete resection, excluding infantile fibrosarcoma, dermatofibrosarcoma, and patients with incomplete data.	Crude	Survivors, median: 34 months (range 1–176)
Urakawa, 2013[29]	2001–2011	152	Primary, extremity, and trunk STS, excluding patients with neurofibromatosis 1, well-differentiated liposarcoma, dermatofibrosarcoma protuberans, patients with symptoms less than a month, and patients with incomplete data.	Adjusted	Median: 38.5 months (range 1.5–110.4)
Weitz, 2003[7]	1982–2001	1261	Non-metastatic, adult, extremity fibrosarcoma, liposarcoma, MFH, leiomyosarcoma and synovial sarcoma treated with complete macroscopic resection.	Crude and adjusted	Median: 55 months (IQR: 23–103)
Wilson, 1999[68]	1972–1992	119	Non-metastatic, adult, extremity STS, excluding patients with a second cancer within 5 years of diagnosis and Kaposi sarcoma.	Crude	Mean: 9.3 years
Yang, 1998[84]	1983–1991	141	Non-metastatic, extremity STS treated with limb-sparing surgery, excluding patients with a history of a second malignancy or contradictions to receive RT or chemotherapy.	Crude	Median: 9.6 years (range 4.3–12.3)
Zagars, 2003[8]	1960–1999	1225	Non-metastatic STS treated with conservative, macroscopic, total tumor resection, excluding Kaposi, cystosarcoma, angiosarcoma, dermatofibrosarcoma, and desmoid tumors.	Adjusted	Survivors, median: 9.5 years

NOTES: Abbreviations: STS, soft tissue sarcoma; IQR, interquartile range; RT, radiotherapy; PNET, primitive neuroectodermal tumor; MFH, malignant fibrous histiocytoma.

APPENDIX II: REGISTRATION FORMS USED IN THE ASR

SARCOMA REGISTRATION – 1st admission

Name
CPR-number

County |__|
1 Aarhus
2 Others

Retrospective:

DATE for 1st contact |__|__|__|__|__|__|

Duration of symptoms |__|__|__| months

Treatment before referral |__|
1 None
2 Biopsy
3 Resection |__|__|__|__|__|__|
4 Amputation |__|__|__|__|__|__|
5 Completed primary treatment |__|__|__|__|__|__|

Reason for admission |__|
1 Primary diagnostic
2 Local recurrence
3 Metastases

Diagnostic procedures
(1 Normal, 2 Tumor, 3 Not performed)

Lungs X-ray |__|
CT-scan |__|

Bones W-ray |__|
Scintigraphy |__|

Other metastases Present |__|

Specify_____

Primary tumor X-ray |__|
CT-scan |__|
MRI |__|
Biopsy |__|__|
(Biopsy, 2nd digit: 1 Needle, 2 Open)

TUMOR largest diametre |__|__|__| cm

Treatment Surgery |__|
(0 No, 1 Yes.) Chemoth. |__|
Radioth. |__|

Compartmentalization |__|
(1 Intra, 2 Extra, 3 Unknown)

DATE OF SURGERY |__|__|__|__|__|__|

Type |__|__|__|

1st ciffer: 1 Resection, 2 Amputation
2nd ciffer: 0 None, 1 autotransplant, 2 allograft, 3 arthroplasty, 4 cement, 5 skintransplant, 6 tubed flap, 7 free flap, 8 rotationplasty, 9 knoglesubstitut, 10 bone bridging, 11 atrodesis, 12 bone transport, 13 prolene net
3rd ciffer, amputation: 1 toe, 2 crus, 3 knee exartic.,4 femur, 5 hip exartic., 6 hemipelvectomi, 7 finger, 8 forearm, 9 upper arm, 10 shoulder exartic., 11 interthoracoscapular

Surgical margin |__|

1 Intralesional, 2 Marginal, 3 Wide, 4 Radical

Wound complications|__|
(1 Yes, 2 No)
Specify: _____

Histological grade: |__|

0 Benign, 1 Grad I, 2 Grad II, 3 Grad IIIA, 4 Grad IIIB, 5 Malignant, unclassifiable, 6 Grad III, 7 Malignant, obs. pro

Disease-free after treatment |__|
(1 Yes, 2 No)

TUMOR LOCATION

STS |__|__|		BS |__|__|	
1 Head/neck	10 Thigh		1 Cranium	9 Hand
2 Thorax	11 Knee		2 Vertebra	10 Sacrum.
3 Abd/Lumbar	12 Crus		3 Clavicle	11 Pelvis
4 Shoulder	13 Foot/ankle		4 Scapula	12 Femur
5 Upper arm	14 Others		5 Costae	13 Tibia
6 Elbow	15 Intraabdominal		6 Humerus	14 Fibula
7 Lower arm	16 Retroperitonal		7 Ulna	15 Foot
8 Hand, wrist	17 Mamma		8 Radius	16 Others
9 Gluteal	18 Genitalia			

Region |__|
1 Proksimal, condyle
2 Middle, diaphysis
3 Distal, condyle

Fracture |__|
(1 Yes, 2 No)

EXTENSION:

STS |__|	BS |__|
1 Cutaneous	1 Intraosseous
2 Subcutaneous	2 Cortikal growth
3 Subfacial	3 Soft tissue

HISTOPATHOLOGICAL TYPE:

STS |__|__|	BS |__|__|
Malignant	Malignant
1 Chondrosarcoma, extraosseous	1 Ewing sarcoma
2 Dermatofibrosarcoma	2 Chondrosarc., classic
3 Fibrosarcoma	4 Giant cell tumor
4 Leiomyosarcoma	5 Osteosarcoma, classic
5 Liposarcoma	7 Malignant lymphoma
6 Malignant lymphoma	8 Myelomatosis
7 MPNST	9 Chordoma
8 MFH	10 Others
9 Osteosarcoma, extraosseous	11 Unclassifiable
10 Rhabdomyosarcoma	30 Ademantinoma
11 Synovial sarcoma	31 Angiosarcoma
13 Others	32 Dediff. chondrosarc.
14 Unclassifiable	33 Juxtacort. chondrosar
15 Aggressive fibromatosis	34 Fibrosarcoma
30 Alveolar sarcoma	35 Udiff. pleom. or MFH
31 Angiosarcoma	36 Chondroblast. osteo.
32 Malignant hemangiopericytoma	37 Teleangiektat. osteo.
33 Clear cell sarcoma	38 Fibroblastic osteo.
34 Desmoplastic small round cell	39 Parosteal osteo.
35 Epithelioid sarcoma	40 Periostal osteo.
36 Infantile fibrosarcoma	41 Small cell osteo.
37 Solitary fibrous tumor	
38 GIST	
39 Kaposi sarcoma	
40 PNET	
Benign	Benign
21 Desmoid	21 Aneurysm. bone cyst
22 Hemangioma	22 Chondrogenetic
23 Lipoma	23 Eosinoph. granuloma
24 Myxoma	24 Giant cell tumor
25 Neurilemmoma	25 Non-ossifiic. fibroma
26 Nodular fasciitis	26 Osteogenetic
27 Others	27 Simple bone cyst
	28 Other
80 Metastases, non-STS	80 Metastases, non-BS
90 Other disease	90 Other disease
Specify: _____	Specify: _____

APPENDIX II: REGISTRATION FORMS USED IN THE ASR, CONTINUED

SARCOMA REGISTRATION -Radiotherapy

Name
CPR-number Primary/relapse treatment

Treatment intension |__|
1. Adjuvant
2. Curative
3. Palliative

START DATE |__|__|__|__|__|__|
END DATE |__|__|__|__|__|__|

Relation to surgery |__|
1. Preoperative
2. Postoperative

Dose |__|
Number of fractions |__|

CT guided dose plan |__|
(1 Yes, 2 No)

Photons |__|
(1 Yes, 2 No)

Boost |__|
(1 Yes, 2 No)

Margin of radiation field |__|

Electrons |__|
(1 Yes, 2 No)

Radiation energy |_____|

Complications |__|
(1 Yes, 2 No)
Specify: _____

Best treatment response:
MRI |__| 1. CR
Histology |__| 2. PR
Other methods |__| 3. NC
4. PD
5. Unclassifiable
Other methods, specify: _____

SARCOMA REGISTRATION -Chemotherapy

Name
CPR-number Primary/relapse treatment

Treatment intension |__|
1. Adjuvant
2. Curative
3. Palliative

START DATE |__|__|__|__|__|__|
END DATE |__|__|__|__|__|__|

Protocol |__|
(1 Yes, 2 No) Number:_____

Number of drugs |__|

Number of treatment series |__|

Drugs used:
Doxorubicin (Dox) |__|
Imatinib (Gleevec) |__|
Gemcitabin (Gem) |__|
Vincristin (Vinc) |__|
Methotrexat (MTX) |__|
Cisplatin (Cis) |__|
Taxotere (Tax) |__|
Ifosfamid (Ifos) |__|
Etoposid (Eto) |__|
Actinomycin D (Act D) |__|
Cyklofosfamid |__|

Complications |__|
(1 Yes, 2 No) Specify:_____

Best treatment response:
MRI |__| 1. CR
Histology |__| 2. PR
Other methods |__| 3. NC
4. PD
5. Unclassifiable
Other methods, specify: _____

SARCOMA REGISTRATION -Relapse

Name
CPR-number

DATE OF RECURRENCE |__|__|__|__|__|__|

TREATMENT STRATEGY:

1. No treatment |__|
1. Tumor resistant to chemo/radiotherapy
2. Inoperable due to extension/location of tumor
3. Poor general condition/comorbidity

4. Advanced age
5. Other reasons. Specify:_____

OR

2. Treatment intension |__|
0. Palliative
1. Curative

Treatment Surgery |__|
(0 No, 1 Yes.) Chemotherapy |__|
Radiotherapy |__|

DATE OF SURGERY Local recurrence |__|__|__|__|__|__|

Type |__|
1 Resection, 2 Amputation

Surgical margin |__|
1 Intralesional, 2 Marginal, 3 Wide, 4 Radical

Wound complications |__|
(1 Yes, 2 No)
Specify: _____

DATE OF SURGERY Lung metastases |__|__|__|__|__|__|

DATE OF SURGERY Other metastases |__|__|__|__|__|__|

Histology |__|
1. Same as primary tumor
2. Increased malignancy
3. Unknown

Disease-free after treatment |__|
(1 Yes, 2 No, 3 Unknown)

TYPE OF RELAPSE: Local recurrence |__|
(1 Yes, 2 No) Lung metastases |__|
Specify: _____
Other metastases |__|
Specify: _____

APPENDIX III: ICD CODES INCLUDED IN THE CHARLSON COMORBIDITY INDEX

Condition	**ICD-8**	**ICD-10**
Myocardial Infarct	410	I21; I22; I23
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440–445	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	430–438	I60–I69; G45; G46
Dementia	290.09–290.19; 293.09	F00–F03; F05.1; G30
Chronic pulmonary disease	490–493; 515–518	J40–J47; J60–J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	135.99; 446; 712; 716; 734	M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86
Ulcer disease	530.91; 530.98; 531–534	K22.1; K25–K28
Mild liver disease	571; 573.01; 573.04	B18; K70.0–K70.3; K70.9; K71; K73; K74; K76.0
Diabetes	249.00; 249.06; 249.07; 249.09; 250.00; 250.06; 250.07; 250.09	E10.0, E10.1; E10.9; E11.0; E11.1; E11.9
Hemiplegia	344	G81; G82
Moderate/severe renal disease	403; 404; 580–583; 584; 590.09; 593.19; 753.10–753.19; 792	I12; I13; N00–N05; N07; N11; N14; N17–N19; Q61
Diabetes with end organ damage	249.01–249.05; 249.08; 250.01–250.05; 250.08	E10.2–E10.8; E11.2–E11.8
Any tumor *	140–169; 172–192.48; 193–194	C00–C39; C42–C46; C48; C50–C75
Leukemia	204–207	C91–C95
Lymphoma	200–203; 275.59	C81–C85; C88; C90; C96
Moderate/severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 456.00–456.09; 573.00	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumor	195–199	C76–C80
AIDS	079.83	B21–B24