Faculty of Medicine
University of Helsinki

# ONCOVASCULAR RECONSTRUCTIONS IN SOFT TISSUE SARCOMAS –

# MYXOID AND RETROPERITONEAL LIPOSARCOMAS

**Pauliina Homsy**

DOCTORAL DISSERTATION

To be presented for public discussion with the permission of the Faculty of Medicine of the University of Helsinki, in Niilo Hallman Sali, Puistosairaala, on the 31st of March 2023 at 12 o'clock.

Helsinki 2023

**Supervised by:**

MD PhD, Docent Erkki Tukiainen
Department of Plastic Surgery
Helsinki University Hospital and University of Helsinki
Helsinki, Finland

and

MD PhD, Docent Carl Blomqvist
Department of Oncology
Helsinki University Hospital and University of Helsinki
Helsinki, Finland

**Reviewed by:**

MD PhD, Docent Ilkka Koskivuo
Department of Plastic and General Surgery
Turku University Hospital and University of Turku
Turku, Finland

and

MD PhD, Docent Matti Pokela
Department of Surgery
Oulu University Hospital and University of Oulu

**Opponent:**

MBBS FRCS(Glasg) FRCS(Plast) Maniram Ragbir
Department of Plastic Surgery
Newcastle upon Tyne NHS Foundation trust
President of British Association of Plastic Reconstructive and Aesthetic Surgeons

ISBN 978-951-51-8956-1 (pbk.)
ISBN 978-951-51-8957-8 (PDF)

Unigrafia
Helsinki 2023

To those who inspire me

# CONTENTS

# 1. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I **Homsy P**, Böhling T, Seitsonen A, Sampo M, Tukiainen E, Blomqvist C. Patterns of metastatic recurrence of genetically confirmed myxoid liposarcoma. Ann Surg Oncol. Online ahead of print. doi: 10.1245/s10434-023-13312-x

II **Homsy P**, Heiskanen I, Sampo M, Rönty M, Tukiainen E, Blomqvist C. Single center 30-year experience in treating retroperitoneal liposarcomas. J Surg Oncol. 2020 Nov;122(6):1163-1172. doi: 10.1002/jso.26118

III **Homsy P**, Blomqvist C, Heiskanen I, Vikatmaa L, Tukiainen E, Numminen K, Sampo M, Leppäniemi A, Albäck A, Kantonen I, Vikatmaa P. Multidisciplinary oncovascular surgery is safe and effective in the treatment of intra-abdominal and retroperitoneal sarcomas; a retrospective single center cohort study and a comprehensive review of literature. Eur J Vasc Endovasc Surg. 2020 Nov;60(5):752-763. doi: 10.1016/j.ejvs.2020.05.029

IV **Homsy P**, Kantonen I, Salo J, Albäck A, Tukiainen E. Reconstruction of the superficial femoral vessels with muscle flap coverage for soft tissue sarcomas of the proximal thigh. Microsurgery. 2022 Sep;42(6):568-576. doi: 10.1002/micr.30932

The publications are referred to in the text by their roman numerals. The articles have been reprinted with the permission of their copyright holders.

# 2. ABBREVIATIONS

| | |
|---|---|
| AJCC/UICC | American Joint Committee on Cancer/International Union against Cancer |
| CI | Confidence interval |
| CT | Computer tomography |
| DFA | Deep femoral artery |
| DFV | Deep femoral vein |
| ePTFE | Expanded polytetrafluoroethylene |
| EIA | External iliac artery |
| EIV | External iliac vein |
| FNCLCC | The French Federation Nationale des Centers de Lutte Contre le Cancer |
| HDU | High dependency unit |
| HPF | High power field |
| HR | Hazard ratio |
| IVC | Inferior vena cava |
| IQR | Inter-quartile range |
| L | Left |
| LD | Latissimus dorsi microvascular musculocutaneous flap |
| MLS | Myxoid liposarcoma |
| MRI | Magnetic resonance imaging |
| PET | Positron emission tomography |
| PNET | Primitive neuroectodermal tumor |
| POD | Postoperative day |
| PTA | Percutaneous transluminal angioplasty |
| PTFE | Polytetrafluoroethylene |
| R | Right |
| SFA | Superficial femoral artery |
| SFV | Superficial femoral vein |
| UPS | Undifferentiated pleomorphic sarcoma |
| USA | the United States of America |

# 3. ABSTRACT


**Background**

Soft tissue sarcomas are rare malignancies of mesenchymal origin, often occurring in the extremities or the retroperitoneum. Radical resection of the tumor with a healthy tissue margin is the key to controlling local disease and reducing the risk of a systematic relapse. Liposarcomas are the most common histological subtype, accounting for approximately 20% of the tumors. Around 30% of liposarcomas are of the myxoid subtype and have a unique propensity to metastasize to extrapulmonary locations. The exact pattern of the metastases is less clear, and the patients are, at present, followed-up using the standard soft tissue sarcoma protocol. Another challenging group of liposarcomas is those occurring in the abdomen, including the retroperitoneum, as achieving radical resection can be difficult due to the adjacent viscera. In addition, the benefits of adjuvant treatments for these tumors are less clear than for soft tissue sarcomas elsewhere.

Oncovascular surgery, with blood vessels resected and reconstructed during the resection of the tumor, has emerged as a surgical option for patients with retroperitoneal soft tissue sarcomas. A similar approach of vascular reconstructions following tumor surgery has been adopted for tumors of the proximal thigh, enabling limb preservation. Long-term patency of the vascular grafts has not been established. The functional outcomes achieved with the limb preservation have not been studied in detail.

**Patients and methods**

Four retrospective cohort studies were performed. Study I consisted of 32 patients with genetically confirmed myxoid liposarcoma, treated between 1987 and 2017. For study II, all 107 patients treated for intra-abdominal or retroperitoneal liposarcomas between 1987 and 2017 were included. Study III consisted of 17 patients with retroperitoneal soft tissue sarcoma who required vascular reconstructions to enable resection of the tumor, treated consecutively between 2010 and 2018. Study IV consisted of eight consecutive patients treated between 2014 and 2020 for soft tissue sarcomas of the proximal thigh or inguinal region who required vascular reconstructions in conjunction with the tumor resection.

For all studies, hospital records were analyzed for oncological outcomes. For studies III and IV, the perioperative morbidity and the long-term patency of the vascular grafts were also evaluated. For study IV, the functional outcomes were also assessed. Comprehensive reviews of literature were done to establish the distribution of first metastases in myxoid liposarcoma and to evaluate the long-term patency of the vascular grafts in retroperitoneal reconstructions.

**Results**

Study I

Gene translocation analysis confirmed 32 patients with myxoid liposarcoma. During a median follow-up of 7.6 (range 2.1 to 16.7) years, seven patients (22%) developed metastatic disease. Five of the first metastases were in the abdomen and one in the lungs. The comprehensive review included 14 series with 1853 patients, 348 (19%) of whom had metastases. Abdomen was the most common anatomical region of first metastases (26%), although soft tissues around the body were, overall, most prevalent (32%). Lungs and pleura (24%) and bone (17%) were also frequently affected.

Study II

Altogether 107 patients were treated for intra-abdominal liposarcoma. Tumor resection with microscopically negative margins was achieved in 79% of the 96 patients operated with curative intent. Local recurrence developed in 72% and metastases in 15% during median follow-up of 5.4 (IQR 2.2 to 8.8) years. The five-year disease-free survival was 31% and disease-specific survival 66%. Multifactorial analysis revealed histological type and grade as predictors of disease-specific survival ($p<0.01$), while multifocality carried a poor prognosis for local recurrence ($p=0.02$) and higher histological grade for metastases ($p<0.01$).

Study III

Sixteen patients with retroperitoneal soft tissue sarcoma and one patient with a suspected tumor recurrence underwent vascular reconstructions, eleven of whom arterial. Three patients required a reoperation during the early perioperative period and two patients suffered major organ dysfunction. The perioperative mortality was zero. Early graft thrombosis occurred in two venous and one arterial reconstructions. Late thrombosis, after the 30-day perioperative period, was detected in three (18%). The median follow-up time was 27 (range 0 to 82) months. Of the patients with sarcoma resections five (31%) died of sarcoma and further four (25%) developed local recurrence or new distant metastases. The comprehensive review of literature identified 37 articles with 110 patients, 89 of whom had IVC reconstruction only. The follow-up was 0-181 months, during which 57% remained disease free and 7% died of sarcoma. Only eight arterial reconstructions were described. Late graft thrombosis occurred in 14%.

Study IV

Eight patients had reconstruction of at least the superficial femoral artery and vein during the resection of a soft tissue sarcoma. A microvascular latissimus dorsi flap was used to cover the vessels in five patients and a pedicled muscle flap in three. At median follow-up of 48 (range 1 to 76) months, the arterial graft was patent in six and the vein graft in two patients. The gait was normal in five of the six patients assessed. The reconstructed limbs had a degree of functional impairment on formal assessment, but the patients reported near normal function.

**Conclusions**

Myxoid liposarcomas metastasize often to the abdomen and soft tissues around the body. Thus, whole-body imaging may be indicated during the initial assessment and follow-up of these patients. Primary intra-abdominal and retroperitoneal liposarcomas tend to recur locally. For tumors that have been resected with macroscopically clear margins, histological type and grade are significant predictors of survival. Vascular reconstructions enable radical resection of advanced intra-abdominal and retroperitoneal tumors, with an acceptable rate of postoperative complications. Future studies are needed on the long-term performance of the grafts. With femoral vessels, vascular reconstructions combined with soft tissue reconstruction can enable limb-sparing surgery. Although the surgery is associated with significant early morbidity, the long-term functional outcomes are good.

# 4. SUOMENKIELINEN TIIVISTELMÄ

**Tausta**

Pehmytkudossarkoomat ovat harvinaisia mesekymaalisia tuumoreita, jotka tyypillisesti esiintyvät raajoissa tai vatsaontelon takaosassa, retroperitoneumissa. Taudin uusiutumisen estämiseksi kasvain tulisi poistaa puhtaalla marginaalilla. Liposarkoomat ovat tavallisin pehmytkudossarkooman alatyyppi ja muodostavat arviolta 20% tautitapauksista. Noin 30% liposarkoomista on myksoidista alatyyppiä. Muista pehmytkudossarkoomista poiketen, ne metastasoivat usein muualle kuin keuhkoihin. Näiden etäpesäkkeiden esiintymistodennäköisyys eri kudoksissa ei ole täysin tiedossa ja potilaita seurataan uusiutumisen varalta käyttäen tavanomaista pehmytkudossarkoomien seurantaa, jossa kuvataan leikkausalue ja keuhkot. Toinen haastava liposarkoomaryhmä on vatsaontelossa ja retroperitoneumissa sijaitsevat kasvaimet, sillä puhtaiden kudosmarginaalien saavuttaminen näiden kasvainten poistossa on usein vaikeaa, koska monet tärkeät rakenteet ja elimet sijaitsevat hyvin lähellä tai kiinni kasvaimessa.

Onkovaskulaarinen kirurgia tarkoittaa sitä, että kasvaimen poiston yhteydessä poistetaan tärkeitä verisuonia, jotka korjataan samassa leikkauksessa. Tämä tuo kirurgisen hoidon piiriin myös sellaisia retroperitoneumin kasvaimia, joita aikaisemmin ei voitu poistaa kirurgisesti. Reiden ja nivusaluen kasvaimissa onkovaskulaarinen kirurgia voi mahdollistaa raajan säästävän leikkaushoidon. Verisuonirekonstruktioiden pitkäaikaista toimivuutta ei sarkoomapotilailla ole selvitetty. Myöskään toiminnallisia tuloksia raajan säästävän kirurgian jälkeen ei ole tarkkaan arvioitu.

**Potilaat ja menetelmät**

Väitöskirjaan sisältyy neljä retrospektiivistä kohorttitutkimusta. I tutkimuksessa oli 32 potilasta, joilla hoidettiin geneettisesti myksoidiksi alatyypiksi vahvistettua liposarkoomaa vuosina 1987-2017. II tutkimus sisälsi kaikki 107 intra-abdominaalisen tai retroperitoneaalisen liposarkooman vuoksi hoidettua potilasta, jotka oli leikattu vuosina 1987-2017. III tutkimus sisälsi 17 vuosina 2010-2018 leikattua potilasta, joille oli tehty verisuonirekonstrutio retroperitoneaalisen pehmytkudossarkooman poiston yhteydessä. IV tutkimus sisälsi kahdeksan vuosina 2014-2020 leikattua potilasta, joille oli tehty verisuonirekonstruktio nivusalueen tai yläreiden pehmytkudossarkooman poiston yhteydessä.

Kaikkia tutkimuksia varten tiedot potilaiden hoitotuloksista kerättiin potilaskertomuksista. III ja IV tutkimuksia varten tutkittiin myös potilaiden leikkaukseen liittyvät ja sen jälkeen esiintyvät oireet sekä verisuoni-

rekonstruktioiden auki pysyminen seurannan aikana. IV tutkimusta varten arvioitiin lisäksi potilaiden alaraajojen toimintakyky leikkauksen jälkeen. Myksoidi liposarkooman primäärimetastaasien sijaintia sekä retroperitoneaalisten verisuoni-rekonstruktioiden pitkäaikaista aukipysyvyyttä arvioitiin kattavan kirjallisuus-katsauksen avulla.

**Tulokset**

Tutkimus I

Geenitranslokaatioanalyysi vahvisti myksoidisen liposarkooman diagnooosin 32 potilaalla. Potilaiden mediaani seuranta-aika oli 7.6 (vaihteluväli 2.1-16.7) vuotta. Seitsemälle potilaalle (22%) kehittyi etäpesäkkeitä. Ensimmäisistä metastaaseista viisi oli vatsaontelossa ja yksi keuhkoissa. Kirjallisuuskatsaus sisälsi 14 potilassarjaa, yhteensä 1853 potilasta, joista 348 (19%) potilaalla oli metastasoinut tauti. Vatsaontelo oli tavallisin ensimmäisten metastaasien ilmaantumispaikka (26%), vaikkakin pehmytkudosmetastaasit kehon muissa osissa olivat yhteensä yleisempiä (32%). Ensimmäisiä metastaaseja havaittiin myös keuhkoissa ja pleurassa (24%) sekä luissa (17%).

Tutkimus II

Kaikkiaan 107 potilasta hoidettiin vatsaontelon sisäisen liposarkooman vuoksi. Heistä 96 leikattiin tavoitellen kasvaimen täydellistä poistoa. Mikroskooppisesti kasvaimesta puhtaat marginaalit saavutettiin 79% leikatuista potilaista. Mediaaniseurata-aika oli 5.4 vuotta (IQR 2.2-8.8 vuotta). Taudin paikallinen uusiutuma kehittyi 72% ja metastaasit 15% potilaista. Viiden vuoden kohdalla 31% potilaista oli taudista vapaita ja viiden vuoden tautikohtainen elossa olo-osuus oli 66%. Monimuuttuja-analyysissä kasvaimen histologinen alatyyppi ja gradus ennustivat tautikohtaista selviämistä ($p<0.01$), primääritaudin multifokaalisuus paikallista uusimista ($p=0.02$) ja korkeampi histologinen gradus metastaattisen taudin kehittymistä ($p<0.01$).

Tutkimus III

Verisuonirekonstruktioita tehtiin kuudelletoista potilaalle, joilla oli retroperitoneaalinen pehmytkudossarkooma ja yhdelle potilaalle, jolla epäiltiin uusinutta kasvainta alueella. Arteriarekonstruktioita tehtiin yhdelletoista potilaalle. Kolmella potilaalla todettiin uusintaleikkauksen vaatinut komplikaatio varhaisen postoperatiivisen jakson aikana. Kahdelle potilaalle kehittyi pääte-elinvaurio. Varhainen verisuonigraftin tukos todettiin kahdessa laskimo- ja yhdessä arteriarekonstruktiossa. Myöhäinen tukos, 30 perioperatiivisen päivän jälkeen,

todettiin kolmessa graftissa (18%). Mediaani seuranta-aika oli 27 kuukautta (vaihteluväli 0-82 kuukautta). Potilaista, joille tehtiin sarkoomaresektio, viisi (31%) menehtyi sarkoomaan ja neljälle muulle (25%) kehittyi paikallinen uusiutuminen tai metastaaseja. Kirjallisuuskatsaus sisälsi 37 artikkelia ja 110 potilasta, joista 89:llä oli tehty ainoastaan alaonttolaskimon rekonstruktio. Seuranta-aika potilaille oli 0-181 kuukautta, jona aikana 57% pysyi remissiossa ja 7% kuoli sarkoomaan. Vain kahdeksan valtimokonstruktiota kuvattiin potilassarjoissa. Myöhäinen graftitukos raportoitiin 14% rekonstruktioista.

Tutkimus IV

Kahdeksalle potilaalle tehtiin reisivaltimon ja -laskimon rekonstruktio pehmytkudos-sarkooman poiston yhteydessä. Rekonstruoidut suonet peitettiin mikro-vaskulaarisella latissimus dorsi kielekeellä viidellä potilaalla ja paikallisella lihaskielekkeellä kolmella potilaalla. Valtimorekonstruktio todettiin avoimeksi kuudella potilaalla ja laskimorekonstruktio kahdella potilaalla 48 kuukauden mediaaniseurannan kohdalla (vaihteluväli 1-76 kuukautta). Kävely oli normaalia viidellä kuudesta arvioidusta potilaasta. Rekonstruoidussa raajoissa todettiin lievä toiminnan vajaus standardoiduilla testeillä, mutta potilaat raportoivat lähes normaalin toiminnan.

**Johtopäätökset**

Myksoidiset liposarkoomat metastasoivat usein ja tyypillisesti pehmytkudoksiin kehon eri osissa. Näin ollen, koko kehdon kuvantaminen metastaasien havaitsemiseksi saattaa olla aiheellista näiden potilaiden diagnoosivaiheessa ja seurannassa. Vatsaontelon sisällä ja retroperitoneaalitilassa olevat liposarkoomat uusivat usein paikallisesti. Makroskooppisesti puhtain marginaalein resekoitujen kasvainten kohdalla histologinen alatyyppi ja gradus ovat merkittäviä tautikohtaisen kuolleisuuden ennustetekijöitä. Verisuonirekonstruktiot mahdollistavat paikallisesti edenneiden vatsaontelon sisäisten ja retroperitoneaalisten kasvainten kirurginen poiston ja tähän liittyvät leikkausriskit ovat hyväksyttäviä. Verisuonigraftien toimintaa tulee jatkossa arvioida pidemmällä seuranta-ajalla. Reiden ja nivusalueen sarkoomissa verisuonirekonstruktio yhdistettynä pehmytkudosten rekonstruktioon tuo raajaa säästävän leikkaushoidon piiriin sellaisia potilaita, joita aikaisemmin ei voitu operoida ilman amputaatiota. Leikkauksiin liittyvät varhaisvaiheen haittavaikutukset ovat merkittäviä, mutta pitkä-aikaiset toiminnalliset tulokset ovat rohkaisevia.

# 5. INTRODUCTION

Soft tissue sarcomas are tumors of mesenchymal origin with an estimated incidence of 4-5 per 100 000 in Europe.(Gatta et al. 2017) They are classified according to the cell type the tumor cells most closely resemble.(Board 2020) Around 40% of the primary tumors occur in the extremities, 38% in the retroperitoneum or the viscera, and the rest elsewhere in the body.(Brennan et al. 2014) The distribution of the tumors vary by the histological subtype. For example, while myxoid and pleomorphic liposarcomas and undifferentiated pleomorphic sarcomas are common in the periphery, leiomyosarcomas frequently occur in the retroperitoneum.(Lewis et al. 1998, Brennan et al. 2014, Toulmonde et al. 2014)

Radical resection with tumor free margin is the key in controlling local disease and improving survival.(Sampo et al. 2008, Brennan et al. 2014) The role of chemo- and radiotherapy is more limited.(Jones et al. 2005, Bonvalot et al. 2020) As soft tissue sarcomas are relatively rare tumors, the Scandinavian Sarcoma group recommends that their treatment is based in high volume centers.(Bauer et al. 2001) The Helsinki University multidisciplinary sarcoma team evaluates approximately 80 new patients each year.

Myxoid liposarcomas (MLS) account for around 10% of soft tissue sarcomas and 30% of liposarcomas.(Dei Tos 2000) MLS is characterized by a relatively early peak age of presentation, early in the fifth decade, and a strong tendency to metastasize. Additionally, MLS frequently metastasizes to extrapulmonary locations, a feature atypical for soft tissue sarcomas. (Estourgie et al. 2002, Haniball et al. 2011, Moreau et al. 2012, Muratori et al. 2018) The pattern of extrapulmonary metastases is less well established. Understanding the distribution of the metastases is important as currently the metastases are not routinely imaged for, during follow-up, in any other location than lungs.

Retroperitoneal liposarcomas present a surgical challenge as their proximity to vital organs and major blood vessels can limit the extend of feasible resection. Thus, retroperitoneal location is associated with worse local disease control and survival.(Vos et al. 2019) The benefit of adjuvant radiotherapy is also less clear than in other primary tumor locations, and the role of chemotherapy is also limited.(Almond et al. 2018, Bonvalot et al. 2020) With the absence of strong data to base treatment guidelines on, local treatment protocols for retroperitoneal liposarcomas vary, encouraging sharing of treatment outcomes.

Retroperitoneal or intra-abdominal soft tissue sarcomas often present late due to their concealed location.(Lewis et al. 1998, Toulmonde et al. 2014) When growing near major blood vessels, the tumors often surround the vessels or infiltrate the vessel walls. These patients have traditionally been considered poor candidates for surgery as, in order to achieve clear margins with the resection, the blood vessels need to be resected with the tumor. Advancements in oncological treatments and

increasing experience in the reconstruction of these vessels has led to more patients with advanced disease offered surgery. Provided clear margins are achieve with the resection, the need for vascular reconstruction is not associated with worse prognosis.(Schwarzbach et al. 2006) However, the surgery is demanding and involves significant perioperative morbidity. In addition, the long-term patency rates of the reconstructed vessels have not yet been fully established.

Oncovascular surgery has become the standard of care also for soft tissue sarcomas of the proximal thigh and groin, involving the femoral or iliac vessels. While previously subjected to proximal thigh amputation of hip disarticulation, limb-sparing surgery is now possible for the majority of these patients.(Davis et al. 2017, Fujiki et al. 2020) These operations are, however, associated with high perioperative morbidity, wound complications and reoperations, while the long-term functional outcomes and graft survival are sparsely reported.(Ghert et al. 2005, Schwarzbach et al. 2005, Poultsides et al. 2015, Davis et al. 2017, Okamoto et al. 2018, Fujiki et al. 2020)

# 6. REVIEW OF THE LITERATURE

## 6.1 SOFT TISSUE SARCOMAS

### 6.1.1 HISTOLOGICAL CLASSIFICATION OF SOFT TISSUE SARCOMAS

Soft tissue sarcomas arise from cells of mesenchymal origin. The classification is based on morphological, immunohistochemical and molecular features of the tumor. The World Health Organization Classification of Tumors specifies around 80 types of soft tissue sarcoma, the exact number changing each revision.(Sbaraglia et al. 2020) Histological subtype is an important predictor of outcome with only about half of soft tissue sarcomas commonly developing systemic disease, with the rest being locally aggressive but with limited metastatic potential.

A single-institute review from New York of 10 000 soft tissue sarcoma patients identified liposarcoma as the most common histological type (20%), followed by leiomyosarcoma (14%), undifferentiated pleomorphic sarcoma (14%), gastrointestinal stromal tumor (9%), synovial sarcoma (5%), myxofibrosarcoma (5%), fibrosarcoma (3%) and malignant peripheral nerve sheet tumor (2%), with the remaining 28% being rare varieties.(Brennan et al. 2014) A study on 1851 patients form the Scandinavian Sarcoma Group Register reported undifferentiated pleomorphic sarcoma (45%) and liposarcoma (14%) as the most common histological types.(Bauer et al. 2001)

#### *6.1.1.1 Liposarcomas*

Five subtypes of liposarcoma have been identified: well differentiated liposarcoma, dedifferentiated, myxoid (MLS), pleomorphic and myxoid pleomorphic.(Board 2020, Sbaraglia et al. 2020) The subtypes differ in their histological appearance, genetics and disease course.(Dei Tos 2000, Lee et al. 2018, Board 2020, Tyler et al. 2020)

**Well differentiated liposarcoma** is the most common subtype, representing 40-45 % of all liposarcomas. In the periphery, these tumors are often referred to as atypical lipomatous tumors. The age of peak incidence is 50-60 years. It is slowly growing and locally aggressive, but has little to no metastatic potential. It typically occurs in the limbs and the retroperitoneum, and is occasionally encountered also in the spermatic cord and the mediastinum. Under 15% of the tumors recur locally and the disease-specific mortality is close to zero.(Olson et al. 2021) Both the disease recurrence and the mortality are strongly influenced by the tumor location, with up to 90% of retroperitoneal tumors recurring and often dedifferentiating.(Weiss and Rao 1992) Three histological subtypes exist. Lipoma-like liposarcomas are composed mainly of mature adipocytes with marked variation in cell size and a varying degree of nuclear atypia. Lipoblasts may be present. Sclerosing liposarcomas contain a large fibrous collagen component with stromal cells and few multivacuolated lipoblasts. Inflammatory liposarcomas are characterized by a prominent, typically B-cell predominant lymphocytic infiltrate. An amplification of the chromosome segment 12q13-15 is present in all well differentiated liposarcomas, typically containing the genes MDM2, that acts as a negative regulator of the tumor suppressor gene p53, and cyclin dependent kinase 4, a cell cycle facilitator.

**Dedifferentiated liposarcomas** account for 15-20% of liposarcomas. The age of peak incidence is 50-60 years. It often coexists with well differentiated liposarcoma, with around 10% of the well differentiated tumors undergoing dedifferentiation. The core genetic profile of is similar to well differentiated liposarcomas, supporting a theory of dedifferentiation through accumulation of additional chromosomal abnormalities. Retroperitoneum is the most common location for dedifferentiated liposarcoma, but it can occur in the extremities and elsewhere in the body. Typically high grade and aggressive tumors, approximately 10% of dedifferentiated liposarcomas recur locally and 15-20% metastasize.(Board 2020) The tumors are relatively insensitive to chemotherapy.(Jones et al. 2005) The disease-specific mortality is under 30%.(Henricks et al. 1997)

**Myxoid liposarcoma** is the second most common subtype of liposarcomas, accounting for around a third. The peak age of presentation is about a decade earlier than for other liposarcomas, early in the fifth decade. Histologically, myxoid liposarcomas have myxoid stroma and an arborating capillary network. Two pathognomonic gene translocations have been identified, the more common *FUS::DDIT3* fusion from t(12;16)(q13;11.2) translocation and the *EWSR1::DDIT3* fusion from t(12;22) (q13;q12) translocation.(Turc-Carel et al. 1986, Sreekantaiah et al. 1992, Crozat et al. 1993, Rabbitts et al. 1993, Panagopoulos et al. 1996, Dal Cin et

al. 1997, Antonescu et al. 2000) The presence of the fused DDIT3 protein has been suggested to inhibit adipocyte differentiation.(Kuroda et al. 1997) The specific translocation type does not appear to predict any aspect of the disease course.(Antonescu et al. 2001) The primary tumor is often located in the thigh but can occur anywhere in the extremities, the trunk or the head and neck region. Primary retroperitoneal myxoid liposarcomas are rare or nonexistent.(de Vreeze et al. 2009, Setsu et al. 2016) The tumors are highly sensitive to radiotherapy, uniquely for liposarcomas.(Pitson et al. 2004) The radiosensitivity of the tumor is linked to excellent local disease control rates with up to 98% 5-year local recurrence-free survival rates reported.(Guadagnolo et al. 2008, Chung et al. 2009) The response rate to first-line chemotherapy is also higher than for other types of liposarcomas.(Jones et al. 2005) However, distant metastases are common, with a 5-year metastases-free survival of 15-44%.(Guadagnolo et al. 2008, Haniball et al. 2011, Muratori et al. 2018, Gouin et al. 2019) Unlike for other soft tissue sarcomas, the metastases are typically extrapulmonary.(Estourgie et al. 2002, Haniball et al. 2011, Moreau et al. 2012, Muratori et al. 2018) However, the pattern of extrapulmonary metastases is less well established. The reported 10-year disease-specific survival is 56-87%.(Zagars et al. 1996, ten Heuvel et al. 2007, Guadagnolo et al. 2008, Haniball et al. 2011, Hoffman et al. 2013, Muratori et al. 2018)

**Pleomorphic liposarcomas** are rare, accounting for around 5% of all liposarcomas. The peak incidence is in the early seventh decade. The histological appearance varies, with some tumors containing multivacuolated lipoblasts and a UPS-like appearance while others are highly cellular with sheets of pleomorphic or spindle cells and lipoblasts. The genetic profile is mixed, characterized by several chromosomal rearrangements without any pathognomonic mutations. The primary tumor is typically in the limbs. Pleomorphic liposarcomas are high grade and aggressive, both recurring locally and metastasizing. The reported 5-year local recurrence-free survival is 37-81% and metastases-free survival 41-79%. The 5-year disease-specific survival reports range 48-81%.(Zagars et al. 1996, Gebhard et al. 2002, Hornick et al. 2004, Fiore et al. 2007)

**Myxoid pleomorphic liposarcoma** is a recently identified, aggressive subtype of liposarcoma, occurring preferentially in the mediastinum of children and adolescents.(Alaggio et al. 2009) Histologically it contains areas resembling both myxoid and pleomorphic liposarcomas, but genetically it lacks the characteristic translocation of myxoid liposarcomas, bearing some similarity to the genetic profile of pleomorphic liposarcomas.(Creytens et al. 2021)

### 6.1.2 GRADING OF SOFT TISSUE SARCOMAS

Histologic grade is the most important prognostic factor for soft tissue sarcomas and the best predictor of metastatic risk.(Bjerkehagen B 2009, Brennan et al. 2014, Board 2020) Two grading systems exist, a four-tire system historically preferred in Scandinavia, and a three-tire system by the French Federation Nationale des Centers de Lutte Contre le Cancer (FNCLCC).(Coindre 2006, Bjerkehagen B 2009) The FNCLCC system is used more commonly nowadays, and has also been applied in the present study. Details of the grading are displayed in table 1.

The histological diagnosis and the grade are closely linked for many soft tissue sarcomas. For example, all well-differentiated liposarcomas are grade 1 and all pleomorphic liposarcomas are grade 3. For myxoid liposarcomas, while most of the tumors are grade 2, the round cell variants are always grade 3. Excluded from the grading system is the gastrointestinal stromal tumor, which is not graded but characterized by size and mitotic rate.

**Table 1. Histological grading of sarcomas according to the FNCLCC grading system. The scores for tumor differentiation, mitotic count and tumor necroses are summated to determine the histological grade. UPS = undifferentiated pleomorphic sarcoma. HPF = high power field. PNET = primitive neuroectodermal tumor. Adapted from Coindre 2006.**

| | | |
|---|---|---|
| **Tumor differentiation** | | |
| | Score 1 | Sarcoma closely resembling normal adult mesenchymal tissue |
| | | Well-differentiated liposarcoma |
| | | Well-differentiated fibrosarcoma |
| | | Well-differentiated leiomyosarcoma |
| | Score 2 | Sarcoma for which histologic typing is certain |
| | | Myxoid liposarcoma |
| | | Conventional fibrosarcoma |
| | | Myxofibrosarcoma |
| | | Pleomorphic UPS with storiform pattern |
| | | Conventional leiomyosarcoma |
| | | Well-differentiated angiosarcoma |
| | Score 3 | Embryonal and undifferentiated sarcomas, sarcomas of doubtful type |
| | | Round cell liposarcoma |
| | | Pleomorphic liposarcoma |
| | | Poorly-differentiated fibrosarcoma |
| | | Pleomorphic UPS with no storiform pattern |
| | | Giant cell UPS |
| | | Poorly-differentiated/ pleomorphic/ epithelioid leiomyosarcoma |
| | | Embryonal/ alveolar/ pleomorphic rhabdomyosarcoma |
| | | Mesenchymal chondrosarcoma |
| | | Osteosarcoma |
| | | PNET |
| | | Malignant triton tumor |
| | | Synovial sarcoma |
| | | Poorly-differentiate/ epithelioid angiosarcoma |
| | | Epithelioid sarcoma |
| | | Clear cell sarcoma |
| **Mitotic count** | | |
| | Score 1 | 0-9 mitoses per 10 high-power field |
| | Score 2 | 10-19 mitoses per 10 high-power field |
| | Score 3 | ≥20 mitoses per 10 high-power field |
| **Tumor necrosis** | | |
| | Score 0 | No necrosis |
| | Score 1 | < 50% tumor necrosis |
| | Score 2 | > 50% tumor necrosis |
| **Histologic grade** | | |
| | Grade 1 | Total score: 2 or 3 |
| | Grade 2 | Total score: 4 or 5 |
| | Grade 3 | Total score: 6 to 8 |

### 6.1.3 STAGING OF SOFT TISSUE SARCOMAS

Staging of tumors is used to predict prognosis. For soft tissue sarcomas, three staging systems have been used.

The Surgical Staging System of the Musculoskeletal Tumor Society contains three stages that take into account the histological malignancy grade (rated as low grade or high grade), the local extent of the disease (intracompartmental or not), and the presence of metastases.(Enneking et al. 1980) All low grade tumors are stage I, with intracompartmental being stage IA and extracompartmental stage IB. High grade tumors are stage II with the same subdivision based on the local extent. Stage III is metastatic disease.

The Memorial Sloan Kettering Cancer Center staging system includes evaluation of the tumor size (≤ 5 cm or larger), site relative to deep fascia (superficial or deep), histologic grade (low or high), and the presence of metastases.(Hajdu et al. 1988) The number of unfavourable characteristics is added to produce a stage on a 0-IV scale, where stage III is a tumor larger than 5 cm, deep to fascia and of high histological grade, and stage IV is metastatic disease.

The most commonly used staging system is the American Joint Committee on Cancer/International Union against Cancer (AJCC/UICC) unified staging system, currently at its eight edition.(Amin et al. 2017, Blay et al. 2017) It takes into account the size of the tumor, regional lymph node status, presence of distant metastases (all in table 2) and the FNCLCC histologic grade (table 1) to produce the stage (table 3). The stage groups for retroperitoneal soft tissue sarcomas are slightly different (table 4).(Amin et al. 2017, Tanaka and Ozaki 2018) The eight edition differs from its predecessors in having two additional size classifications in lieu of tumor depth for soft tissue sarcomas of the extremities or trunk, and in grouping lymph node metastases with distant metastases. These changes have, however, been argued to decrease the prognostic power of the staging system for advanced tumors.(Cates 2018)

The evaluation of the staging systems in terms of their ability to accurate predict the patients who are likely to develop a disease recurrence is difficult due to the heterogenicity of the tumor group. For localized extremity soft tissue sarcomas, for example, the tumor depth, grade and size appear to be independent prognostic factors predictive of systemic relapse, and the Surgical Staging System has been proposed to perform worse at outcome prediction than the other two staging systems.(Wunder et al. 2000) Several complex personalized prognostic models, or nomograms, have been developed for a range of soft tissue sarcomas, some even with smartphone applications.(Callegaro et al. 2017) However, their usefulness in guiding day-to-day clinical practice is markedly user-dependent.

**Table 2. Definition of primary tumor (T), regional lymph node (N) and distant metastases (M). Adapted from Amin et al. 2017.**

| T Category | T Criteria |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Tumor 5 cm or less in greatest dimension |
| T2 | Tumor more than 5 cm and ≤10cm in greatest dimension |
| T3 | Tumor more than 10 cm and ≤15 cm in greatest dimension |
| T4 | Tumor more than 15 cm in greatest dimension |

| N Category | N Criteria |
|---|---|
| N0 | No regional lymph node metastasis or unknown lymph node status |
| N1 | Regional lymph node metastasis |

| M Category | M Criteria |
|---|---|
| M0 | No distant metastases |
| M1 | Distant metastases |

**Table 3. AJCC stage groups for soft tissue sarcoma of the trunk and extremity. Adapted from Amin et al. 2017.**

| Stage | Primary tumor (T) | Regional lymph node (N) | Distant metastases (M) | Histologic Grade (G) |
|---|---|---|---|---|
| IA | T1 | N0 | M0 | G1, Gx |
| IB | T2, T3, T4 | N0 | M0 | G1, Gx |
| II | T1 | N0 | M0 | G2, G3 |
| IIA | T2 | N0 | M0 | G2, G3 |
| IIB | T3, T4 | N0 | M0 | G2, G3 |
| IV | Any T | N1 | M0 | Any G |
| | Any T | Any N | M1 | Any G |

**Table 4. AJCC stage groups for soft tissue sarcoma of the retroperitoneum. Adapted from Amin et al. 2017.**

| Stage | Primary tumor (T) | Regional lymph node (N) | Distant metastases (M) | Histologic Grade (G) |
|---|---|---|---|---|
| IA | T1 | N0 | M0 | G1, Gx |
| IB | T2, T3, T4 | N0 | M0 | G1, Gx |
| II | T1 | N0 | M0 | G2, G3 |
| IIA | T2 | N0 | M0 | G2, G3 |
| IIB | T3, T4 | N0 | M0 | G2, G3 |
| | Any T | N1 | M0 | Any G |
| IV | Any T | Any N | M1 | Any G |

## 6.2 DIAGNOSIS OF SOFT TISSUE SARCOMAS

Presentation of the primary soft tissue sarcoma tumor vary. However, a growing, painful mass over 5 cm in size and deep to the muscle fascia, is the most typical presentation.(Johnson et al. 2001) The Scandinavian Sarcoma Group guidelines state that deep tumors of any size, subcutaneous tumors larger than 5 cm and all other tumors, suspected of being malignant, should be referred to a tumor center without prior biopsy.(Alvegård et al. 2009) If a biopsy or excision has resulted in a soft tissue sarcoma diagnosis, the patient should be referred before any further surgery. The early referral is key to avoiding delays in diagnosis and treatment.

The best imaging modality for soft tissue tumors of the extremities, trunk and pelvis is magnetic resonance imaging (MRI).(Kind et al. 2009) For abdominal tumors, however, computer tomography (CT) performs equally well.(Gronchi et al. 2021) The differentiation between a benign lipoma and a liposarcoma on MRI can be challenging.(Jones et al. 2012) Features suggesting malignancy are decreased fat composition and swirling or nodularity, irregularly thickened septae and associated non-adipose tissue.(Kransdorf et al. 2002)

If the imaging of a soft tissue tumor raises the possibility of a malignancy, core biopsies of the tumor are taken. The biopsy approach is designed in a way that enables the resection of the biopsy route with the tumor. In the case of retroperitoneal tumors, the biopsy is performed through a posterior approach to avoid contamination of the peritoneal cavity. For small superficial tumors only a few centimeters across, an excisional biopsy is also an option.

Testing for specific gene translocations is recommended when the histological diagnosis is unclear or the clinical presentation is atypical for the histological diagnosis.(Gronchi et al. 2021) In addition, some of tumors have pathognomonic translocations, such as the common *FUS::DDIT3* fusion in myxoid liposarcomas. Although not yet part of international guidelines, many centers run confirmatory testing for these translocations, often in the form of next generation sequencing translocation panels. Archer FusionPlex Sarcoma panel, that assesses 148 locations, has recently become part of routine soft tissue sarcoma diagnostics in Helsinki University Hospital.(Invitae)

## 6.3 TREATMENT OF SOFT TISSUE SARCOMAS

Multidisciplinary management in specialized referral centers has been shown to increase the survival of soft tissue sarcoma patients and is recommended by the European Society for Medical Oncology and the Scandinavian Sarcoma Group.(Bauer et al. 2001, Blay et al. 2017, Gronchi et al. 2021) The Helsinki University Central Hospital soft tissue sarcoma group was founded in 1987 and meets weekly to evaluate new referrals, review diagnoses and plan treatments. The group consists of oncologists, plastic surgeons, gastrointestinal surgeons, pathologists, and

radiologists. When indicated, soft tissue sarcoma patients are also evaluated by the oncovascular group that includes vascular, plastic, gastrointestinal, endocrinological and cardiothoracic surgeons, urologists, oncologists, pathologists and radiologists.

### 6.3.1 SURGICAL TREATMENT

#### *6.3.1.1 Oncological goals of the surgery*

Radical surgery with tumor-free margins is the most effective way to reduce local recurrence and improve overall survival in soft tissue sarcomas.(Sampo et al. 2008, Brennan et al. 2014)

Enneking devised a margin classification for musculoskeletal sarcomas in 1980.(Enneking et al. 1980) Four categories exist in the classification; radical, wide, marginal and intralesional. Radical excision entails the removal of the entire tissue compartment containing an intracompartmental tumor. In wide excision, the tumor is removed with a cuff of normal tissue within the compartment, aiming to remove the reactive zone surrounding the tumor. Marginal excision removes the tumor along the surrounding pseudocapsule, through the reactive zone. Intralesional excision has tumor at the edge of the specimen.

The R classification of margins, in its current form, was first published by the International Union Against Cancer in 1987, and has since been adopted into the American Joint Committee on Cancer staging.(Hermanek 1987, Blay et al. 2017) It contains four R categories. Rx: The presence of residual tumor cannot be assessed. R0: No residual tumor. R1: Microscopic residual tumor. R2 Macroscopic residual tumor.

The definition of a sufficient surgical margin, however, remains under debate. Tumor-free margins as small as 1 mm have been proposed sufficient for overall disease control by some, at least in the context of tumors with well-contoured proliferation at the borders.(Lintz et al. 2012, Gundle et al. 2018) It has even been suggested that, in a situation where the tumor comes to contact with critical structures, such as major nerves or blood vessels, planned positive surgical margins sparing the involved structures and adjuvant treatment may not hinder the local recurrence free survival to a clinically significant extent.(O'Donnell et al. 2014) Other cohorts, however, demonstrate an improvement in all survival parameters with surgical margins over 10 mm.(Liu et al. 2010) A study on 270 soft tissue sarcoma patients treated in Helsinki University Central Hospital between 1987 and 1997 demonstrated that a 2.5 cm tumor-free surgical margin resulted in superior local recurrence-free survival rate than a smaller margin compared with radiotherapy.(Sampo et al. 2008)

Resection of soft tissue sarcoma metastases is not considered first line treatment, although retrospective series have suggested a medium-term survival benefit from

R0 metastectomy from various soft tissue locations and liver.(Marudanayagam et al. 2011, Wigge et al. 2018, Gronchi et al. 2021) An exception is the resection of pulmonary metastases with tumor-free margins, that has been suggested potentially curative.(Nevala et al. 2019) The surgery is an option for patients with sufficient performance status, no active disease at the primary tumor site. In addition, the metastatic nodules need to be confined to the lung parenchyma, and be either singular or distributed in a manner that enables complete surgical resection. The presence of a single metastatic lesion is associated with improved survival.(Chudgar et al. 2017, Nakamura et al. 2021) Incomplete surgical removal of pulmonary metastases does not convey better disease-free survival than chemotherapy.(Nevala et al. 2019, Nakamura et al. 2021)

Treatment of soft tissue sarcomas at high volume centers has been associated with fewer operations and a better local recurrence-free survival compared with other hospitals in a nationwide Finnish study, as well as elsewhere.(Gutierrez et al. 2007, Sampo et al. 2012) In Helsinki, the surgery is planned either as a compartmental excision or with a 5 cm macroscopic margin to achieve a histological tumor-free margin of at least 2.5 cm. If one of these criteria is not met, but the resection margins are free of tumor, the excision is considered marginal, and a postoperative course of radiotherapy is recommended. With intralesional margins, a re-excision is recommended, if considered feasible.(Sampo et al. 2008)

#### *6.3.1.2 Reconstruction of the soft tissue defect*

The wound closure after resection of the tumor can, at its simplest, be done through direct apposition of the resection cavity walls and suture of the wound edges. However, if a significant amount of skin, muscle, or both, has been removed so that the cavity cannot be closed directly, a more complex solution is needed. For large skin resections without an underlying soft tissue defect, a partial thickness skin graft can be used. A tissue flap coverage is needed for the defect when blood vessels, nerves or bone cannot be covered with direct opposition of the surrounding tissues. With soft tissues sarcoma resections, the resulting defect is typically cavernous. A local skin flap, typically, does not contain sufficient volume to fill the defect. Thus, a muscle flap is often preferred.

Local muscle transposition flaps involve the release of a muscle from its insertion, origin, or both, and placing the muscle to an adjacent defect, without severing the vascular pedicle or causing significant morbidity. Examples in the thigh, and thus relevant to study III, include the sartorius flap, suitable for covering small defects in the region of the femoral triangle, and the gracilis flap, that can provide a larger muscle bulk to fill defects in the proximal thigh or pelvis. The wound can be closed primarily over the muscle flaps, or a partial thickness skin graft can be used. Additionally, a vertical rectus abdominis flap can be raised with a skin island and used to cover defects in the inguinal region.

When a large tissue defect has been created, and in areas where no local options are available for transposition, a microvascular flap can be employed for wound closure. Microvascular reconstruction of the soft tissue defect to enable limb salvation after resection of a lower limb soft tissue sarcomas, for example, has been found safe with a 95% flap success and 82% five-year local recurrence-free survival in a series with 73 patients from our institute.(Barner-Rasmussen et al. 2009) The local recurrence-free survival is similar to that observed in the lower limb soft tissue sarcoma population as a whole.(Popov et al. 2000) The choice of the flap depends on the defect size, the availability of suitable donor regions, functional goals for the reconstruction, and the preference of the operating surgeon.(Slump et al. 2018, Lucattelli et al. 2021, Samà et al. 2022) The two most frequently used flaps in our unit are, currently, latissimus dorsi and anterolateral thigh flap.(Barner-Rasmussen et al. 2009, Barner-Rasmussen et al. 2010)

Latissimus dorsi is a thin, fan-shaped muscle that acts to extend, adduct and medially rotate the shoulder joint. Its main blood supply is the thoracodorsal branch of the subscapular artery, on which the entire muscle can be transferred to a recipient site. The muscle often has good bulk that can be used to fill a resection cavity. A secondary blood supply from the lumbar perforators enables harvesting of only a part of the muscle, in cases where less volume is needed and the preservation of the muscle action is desired. The skin overlying the muscle can be included in the flap, taken in a horizontal or a vertical ellipse for direct closure of the donor site with skin islands up to 7-10 cm in width. In rare cases, the thoracodorsal nerve can be anastomosed, in an attempt to gain function at the recipient site.(Doi et al. 1999, Innocenti et al. 2009, Muramatsu et al. 2011, Grinsell et al. 2012) The flap can be used also in a pedicle manner, for reconstruction of defect is the upper arm, chest wall or neck.

Anterolateral thigh flap is a perforator flap, based on the descending branch of the lateral femoral circumflex artery. Typically a fasciocutaneous flap, it can be designed to contain a section of the muscle for additional bulk, either along the course of the perforator or as a chimeric flap on a second perforator. Suprafascial of fascial flaps are possible, but less frequently used in sarcoma surgery.(Lee et al. 2009, Momeni et al. 2011, Weichman et al. 2015) The advantages of the anterolateral thigh flap include its predictable anatomy, long and sizeable pedicle, and the harvest position with the patient on their back.(Chen and Tang 2003)

### 6.3.2 VASCULAR RECONSTRUCTIONS

In cases where no clear tissue margin between the tumor and the associated blood vessels is evident on imaging, and the tumor cannot be dissected off the vessels, radical excision of the tumor requires sacrifice of the involved vessels. Major vessels, such as the aorta or iliac vessels in the case of retroperitoneal tumors, or the superficial femoral vessels with lower limb tumors, need to be reconstructed in order to salvage the implicated structures. Provided clear margins are achieved with the resection, the need for vascular resection is not associated with worse oncological

prognosis.(Fortner et al. 1977, Imparato et al. 1978, Karakousis et al. 1996, Bonardelli et al. 2000, Ghert et al. 2005, Schwarzbach et al. 2005, Schwarzbach et al. 2006, Song et al. 2009, Poultsides et al. 2015, Davis et al. 2017, Okamoto et al. 2018, Fujiki et al. 2020)

The aim of the arterial reconstruction is to secure sufficient blood flow to the structures supplied by the resected vessel. Thus, the decision to reconstruct any major vessel is conceptually straightforward. The necessity of reconstructing the resected veins has, on the other hand, been questioned, for both retroperitoneal and peripheral veins.(Hollenbeck et al. 2003, Daylami et al. 2010, Goel et al. 2022, Hauguel et al. 2022, Palacios et al. 2022) Some authors describe ligation of the IVC an option in patients where the vessel is already thrombosed pre-operatively.(Hardwigsen et al. 2005, Schwarzbach et al. 2006) In patients with lower limb soft tissue sarcoma resections, studies comparing postoperative limb oedema, infections and functional scores detected no difference between patients with arterial reconstructions, with or without venous reconstructions.(Adelani et al. 2007, Tsukushi et al. 2008) However, the studies included only 14 and 25 patients in total. Some authors propose that resection of the superficial femoral vein without reconstruction is adequate provided the saphenous vein is intact.(Hohenberger et al. 1999, Schwarzbach et al. 2005) However, reports from most centers describe reconstruction of the resected veins, at least in patients without significant collateral venous circulation, to decrease the likelihood of edema development in the early postoperative weeks.(Fujiki et al. 2020)

Oncovascular procedures have become an established approach for a range of malignancies, including head and neck tumors, renal and adrenal tumors, gynaecological tumors, pancreatic tumors and liver tumors, in addition to sarcomas.(Baláž et al. 2022) However, the reported rates of in-hospital morbidity, wound complications and reoperations are high, with around 60-80% of patients experiencing some postoperative complication (Ghert et al. 2005, Schwarzbach et al. 2005, Poultsides et al. 2015, Davis et al. 2017, Okamoto et al. 2018) In addition, most publications of venous and arterial reconstructions in patients with intra-abdominal or retroperitoneal sarcomas are case reports or small series from single institutes, with short follow-up and a range of reconstruction materials used. The long-term graft survival and functional outcomes for lower limb reconstructions are also sparsely described.(Fujiki et al. 2020)

#### *6.3.2.1 Autologous venous grafts*

Autogenous vein has long been the material of choice for revascularization surgery and has, when practicable, been adopted to reconstructive surgery. The saphenous vein is the longest vein available for grafting, and it is easy to harvest from the subcutis in in the lower limb. Thus, saphenous vein grafts are frequently used in a range of arterial and venous reconstructions, across surgical fields. It is, however, relatively narrow. When a larger diameter graft is needed, a cylinder with the desired

diameter can be created through splitting the vein longitudinally, and suturing the vein wall in a spiral fashion or in vertical panels.(Chiu 1998, van Zitteren et al. 2011, Ketenciler et al. 2018)

When the saphenous vein is unavailable, the cephalic or the basilic vein from the upper arm can be used.(Arvela et al. 2010) Another alternative is the superficial femoral vein, although it is more invasive to harvest.(Schulman et al. 1987, Clagett et al. 1993) For long reconstructions, such as those involving a segment of aorta and the iliac vessels, the use of autologous veins for graft construction is impractical.

#### *6.3.2.2 Allografts in vascular reconstruction*

Vascular allografts were introduced as a reconstructive option in the context of aortic infections and contaminated surgical fields where the likelihood of a synthetic graft getting infected is judged high.(Harlander-Locke et al. 2014, Cananzi et al. 2021) Cryopreserved aortic allografts were the first to gain popularity, replacing like with like.(Noel et al. 2002) The cryopreserved aortic allografts have a better resistance to dilatation than fresh allografts.(Kieffer et al. 2004) However, the at times poor long-term durability of the arterial grafts, and their propensity for thrombosis, led to cryopreserved venous allografts being evaluated for use in supra-inguinal arterial reconstruction.(Heinola et al. 2019)

Most experience of the use of allografts in vascular reconstructions is in the context of infections of either a native aorta or infection of an artificial graft in the aortic position. Thrombotic occlusion of the cryopreserved allografts in aortic or aortoiliac reconstructions has been reported in 4-11% of the grafts. The grafts are durable, with both aneurysms and pseudo-aneurysms reported to occur in 0-10 % of patients in most centres. When the graft is used in an infected area, a persistent infection is associated with an increased rate of graft degradation. In addition, potentially fatal graft rupture, typically at the site of the anastomosis, remains a significant problem with rates of 3-24% reported.(Harlander-Locke et al. 2014, Touma et al. 2014, Lejay et al. 2017, Ben Ahmed et al. 2018, Couture et al. 2021, Weiss et al. 2021) Circumferential reinforcement of the anastomosis has been recommended to reduce the likelihood of anastomotic dilatations.(Lejay et al. 2017, Heinola et al. 2019)

Reports of the use of allografts in IVC reconstruction are sparce and show an obstruction rate of up to 50% on long-term follow-up.(Fiore et al. 2012)

Helsinki University Children's Hospital Homograft Bank has cryopreserved venous allografts harvested from multiorgan donors since 2012. Large caliber veins with a diameter over 6 mm are used. After treatment with antibiotic decontamination medium, the grafts can be stored for up to five years. Prior to use, the venous grafts are cleaned off perigraft tissue, and the valves are removed.(Heinola et al. 2019) The allografts are used in reconstruction of long sections of medium to large vessels, such as the femoral vessels, vena cava and aorta.

#### 6.3.2.3 Xenografts in vascular reconstruction

Bovine pericardium can be used as a patch to repair non-circumferential defects in vascular walls when primary closure could lead to lumen narrowing, both from the defect and intimal hyperplasia stimulated by the closure. Its use is well-established in cardiovascular surgery and in the repair of endarterectomies. The product is commercially available in an acellular form, with no bovine DNA or proteins. While not providing an improved patency, when compared with autologous vein patches, it is easy to handle, has less suture bleeding, and saves the harvest of an autologous vein.(Li et al. 2011)

Bovine pericadium can also be used to form a tubular graft for arterial reconstruction and has been used as an alternative to allografts in the replacement of infected aorta.(Yamamoto et al. 2009) The reported durability of the graft in aortic reconstruction is high and rate of thrombosis low. However, the largest series to date contains only 35 patients with a median follow-up of four year, while the other series are notably smaller and with shorter follow-up.(Czerny et al. 2011, Kubota et al. 2015, Anibueze et al. 2017, Lutz et al. 2017, Weiss et al. 2017, Kreibich et al. 2018, Rojas et al. 2019) No series have been published on the use of these grafts in venous reconstructions.

#### 6.3.2.4 Artificial vascular grafts

Polyethylene and polytetrafluoroethylene (PTFE) are old, but most commonly used, synthetic vascular graft materials.(Desai 2011) Several modifications have been made to polyethylene and PTFE in an attempt to improve graft patency. Early on, polyethylene grafts were replaced with knitted polyethylene, coated with gelatine, albumin, or collagen to improve handling and suturing qualities, and to reduce thrombogenicity. These modifications have replaced simple polyethylene since the 1980's. External support in the form of firmer outer rings or spirals surrounding a thin graft wall in expanded PTFE (ePTFE) graft is conceived beneficial in extra-anatomic or below knee grafts, preventing graft lumen closure. Meta-analysis on peripheral artery disease studies suggests that compared with autologous vein grafts, above the knee femoral prosthetic graft bypasses are more likely to occlude.(Ambler and Twine 2018)

More recently, heparin coating has been used with both materials to improve biocompatibility, with retrospective series suggesting better long-term patency.(Devine et al. 2001, Bosiers et al. 2006, Samson et al. 2016) Non-randomized studies have suggested performance of heparin-coated PTFE similar to autologous vein grafts, but randomized controlled studies have yet to be performed.(Daenens et al. 2009) The PTFE grafts used in nowadays Helsinki University Central Hospital are heparin-coated.

Two randomized trials comparing polyethylene and PTFE in aortoiliac reconstruction demonstrated no difference in long-term patency rates or perioperative complications.(Polterauer et al. 1992, Prager et al. 2001) No difference in patency rates was observed between the two materials in femoropopliteal bypass grafts either.(Abbott et al. 1997, Robinson et al. 1999)

Artificial vascular grafts are in risk of bacterial colonisation and are not recommended for use in infected fields. For infected artificial grafts, the gold standard of treatment is removal of the graft and debridement of the area, followed by either an extra-anatomic reconstruction outside the infected field or the use of a biological graft.(Chakfé et al. 2020)

## 6.4 RADIOTHERAPY IN THE TREATMENT OF SOFT TISSUE SARCOMAS

The Scandinavian Sarcoma Group recommends postoperative radiotherapy in high-grade, deep-seated soft tissue sarcomas regardless of surgical margin, following marginal surgery in all high-grade soft tissue sarcomas irrespective of tumor depth and following intralesional surgery irrespective of malignancy grade.(Group 2015) The benefit of radiotherapy is considered negligible for patients with grade 1 liposarcoma, dermatofibrosarcoma protuberans or chondrosarcoma.(Jebsen et al. 2008) The evidence supporting the use of adjuvant radiotherapy is derived from several retrospective patient series and register studies with sparse randomized controlled trials on the topic.(Pisters et al. 1996, Yang et al. 1998)

Radiotherapy is associated with both a reduced local recurrence rate and an improved overall survival in patients with high grade extremity soft tissue sarcomas.(Jacobs et al. 2015) In patients with extremity or trunk wall soft tissue sarcomas, postoperative radiotherapy has been found to reduce the risk of local recurrence regardless of the surgical margin.(Jebsen et al. 2008)

The use of adjuvant radiotherapy in the treatment of retroperitoneal soft tissue sarcomas is widely adopted but the benefits are less well-established. Large retrospective studies have observed a benefit of radiotherapy in both local disease control and overall survival. (Nussbaum et al. 2016, Haas et al. 2019) However, the effect was not significant in multivariate analysis the treatment center, patient age, patient sex, tumor size and grading, completeness of surgical resection, multifocality, intraoperative tumor rupture, and administration of chemotherapy.(Haas et al. 2019) The first randomized, multicenter trial assessing the effectiveness of radiotherapy in retroperitoneal soft tissue sarcomas failed to show an effect of preoperative radiotherapy on the abdominal progression free survival with three years of follow-up.(Bonvalot et al. 2020) The study included 266 patients randomized to either preoperative radiotherapy or no radiotherapy. Notably, for patients with liposarcoma, that formed 75% of the 266 patients included, subgroup analyses

suggested a potential benefit of preoperative radiotherapy in this patient group in reducing the likelihood of abdominal disease progression.

Whether the radiotherapy is given pre- or postoperatively appears to convey no difference to local control, disease-free nor disease-specific survival.(Zagars et al. 2003) Pre- or postoperative radiotherapy is also not a contraindication for microvascular reconstructions.(Spierer et al. 2003, Tseng et al. 2006)

In Helsinki University Hospital, the use of adjuvant radiotherapy pre- or postoperatively is decided on individual bases at the multidisciplinary sarcoma meetings.(Sampo et al. 2012) In general, preoperative radiotherapy is offered to high grade tumors for which resection is predicted to result in macroscopically or microscopically positive margins. Postoperative radiotherapy is used in peripheral soft tissue sarcomas after intralesional or marginal resection. For retroperitoneal sarcomas, postoperative radiotherapy is used only for residual macroscopic disease as the radiotherapy field required to target the borders of a marginally resected tumor is deemed too extensive. Tumors of low malignancy such as grade 1 liposarcomas are treated operatively with no adjuvant treatment. The practice is, in general, in line with recommendations of the Scandinavian Sarcoma group and the European Society for Medical Oncology.(Group 2015, Gronchi et al. 2021)

## 6.5 CHEMOTHERAPY IN THE TREATMENT OF SOFT TISSUE SARCOMAS

Exact prediction of which soft tissue sarcoma patients are likely to benefit from chemotherapy is difficult. During primary presentation with a single disease focus, chemotherapy might be used preoperatively for tumor shrinkage when otherwise achievable surgical resection margins would be insufficient, and data for a long-term survival benefit for any histological subtype is sparce.(Pasquali and Gronchi 2017) Adjuvant chemotherapy is indicated for tumors with high risk features to improve local recurrence and distal recurrence and overall recurrence-free survival.(Collaboration 1997, Pervaiz et al. 2008, Gronchi et al. 2016) For disease recurrence, the role of chemotherapy is palliative.(Gronchi et al. 2021)

Anthracyclines, such as doxorubicin, are regarded as standard first line therapy, with ifosfamide as the most commonly used adjunct.(Patrikidou et al. 2011) The use of combination therapy, in comparison with doxorubicin alone, may not bring an overall survival advantage.(Bramwell et al. 2003) Several systemic agents have shown activity in selected soft tissue sarcoma types, and are mainly recommended as second line agents in systemic disease.(Gronchi et al. 2021) For example, gastrointestinal stromal tumors, characteristically bear a mutation in the proto-oncogene c-KIT, coding for a transmembrane receptor tyrosine kinase, which can be inhibited with imatinib.(Joensuu et al. 2012) Myxoid liposarcoma has a unique targeted treatment, accepted in Europe for use as a second line option due to its

hematologic and hepatologic toxicity. The chemotherapeutic agent trabectedin blocks DNA-binding of the oncogenic transcription factor FUS-CHOP fusion protein, has been shown effective in the treatment of advanced myxoid liposarcoma in both localized and metastatic disease.(Di Giandomenico et al. 2014, Assi et al. 2019)

In Helsinki University Hospital, adjuvant chemotherapy is recommended for patients with tumors that fulfill at least two of the following criteria: size greater than 8 cm (5 cm in synovial sarcomas), necrosis or vascular invasion. Sufficient performance status and age generally less than 70 years are additional criteria. The treatment regime varies but is doxorubicin-based.(Sampo et al. 2012) Like for radiotherapy, the use of chemotherapy is, in general, in line with recommendations of the Scandinavian Sarcoma group and the European Society for Medical Oncology.(Group 2015, Gronchi et al. 2021)

## 6.6 FOLLOW-UP OF SOFT TISSUE SARCOMAS

All soft tissue sarcoma patients are reviewed at the multidisciplinary meeting after the surgery to plan potential further treatments and follow-up. The primary aim of the follow-up is to detect a potentially curable disease recurrence, either locally at the primary tumor site or as a metastatic focus suitable for resection. The follow-up consists of chest X-rays or chest CT scans, designed to detect metastatic disease, and physical examination and an MRI, or rarely CT, of the primary tumor site, designed to detect local disease recurrence. Guidelines of the recommended imaging frequency are limited by the lack of studies assessing the optimal follow-up pattern.(Rothermundt et al. 2014, Puri et al. 2018, Gronchi et al. 2021, Baia et al. 2022)

In Helsinki University hospital, for low-grade sarcomas, a chest X-ray is performed every four months during the first two years, twice a year up to four years, yearly up to seven years, and every 18 months up to ten years. A physical examination and an MRI of the primary tumor site are performed yearly for seven years, and every 18 months up to ten years.

For high-grade sarcomas, a chest X-ray is performed every two months during the first two years and every four months up to five years. A physical examination and an MRI of the primary tumor site are performed every six months during the first two years and annually up to five years.

## 6.7 FOLLOW-UP OF ONCOVASCULAR RECONSTRUCTIONS

No international guidelines exist on the follow-up of the vascular reconstructions done in patients operated on for malignancy. The absence of guidelines is explained by the range of disease burden and the complexity of reconstructions in this

relatively small group of patients. In Helsinki University Hospital, the patency of the vascular grafts is typically assessed at three months postoperatively, using MRA or CT imaging for retroperitoneal grafts, duplex ultrasound assessment for the lower limb grafts and physical exam at the vascular surgery outpatient clinic for all patients. The aim is to pick up not only issues with the vascular reconstructions but also any potential insufficiently treated symptoms, such as lower limb swelling or gait disturbance. Subsequent evaluation of the grafts is synchronised with the imaging done for local disease control, with the vascular surgeon annually assessing the graft patency in the MRA or CT images. The patient is invited for a follow-up appointment only if an issue with the reconstructions is identified in the images, sparing them the travel to the quaternary centre.

An acute obstruction of the arterial graft, more common in the early postoperative period, leads to ischemia and risks the loss of the limb. Thrombectomy is indicated, possibly with fasciotomies of the affected limb, followed by an increase in the thromboprophylaxis. Stenosis of the arterial graft may lead to claudication and necessitate angioplasty. Vein grafts, on the other hand, can obstruct with few or no symptoms. In the early postoperative period, thrombectomy and stenting may be required for the obstructed vein graft, while often no intervention is required for late thrombosis.

# 7. AIMS OF THE STUDY

The aim of this project was to evaluate the treatment results and prognostic factors of patients with rare presentations of soft tissue sarcomas. The specific aims of the studies were:

I To assess the metastatic pattern of myxoid liposarcomas to obtain information on the appropriate imaging approach for their detection.

II To examine the prognostic factors for patients with intra-abdominal or retroperitoneal liposarcomas.

III To evaluate the safety of oncovascular surgery in the treatment of intra-abdominal and retroperitoneal soft tissue sarcomas.

IV To appraise reconstructive outcomes of oncovascular surgery for soft tissue sarcomas of the inguinal region and proximal thigh.

# 8. PATIENTS AND METHODS

The studies were approved by the Helsinki University research ethics committee, license number 270/12/03/2011, and the Finnish institute for health and welfare, license number THL/1303/5.05.00/2011, and conducted in accordance with the Helsinki Declaration.

## 8.1 PATIENTS

The study was carried out in Helsinki University Hospital. The patients were operated on in the Helsinki University Hospital Department of Plastic Surgery (Study I, Study IV), Department of Gastrointestinal Surgery (Study II) and Department of Vascular Surgery (Study III). Study I consisted of 32 patients with myxoid liposarcoma who had been treated between 1987 and 2017 and for whom tissue samples of the tumor confirmed the diagnosis. Study II consisted of all the 107 patients treated for retroperitoneal liposarcomas between 1987 and 2017. Study III consisted of 17 patients with retroperitoneal soft tissue sarcoma who required vascular reconstructions to enable resection of the tumor, treated consecutively between 2010 and 2018. Study IV consisted of eight consecutive patients treated between 2014 and 2020 for soft tissue sarcomas of the proximal thigh or inguinal region who required vascular reconstructions in conjunction with tumor resection.

*Study I*

A review of the prospectively maintained sarcoma database and a pathology database was used to identify myxoid liposarcoma patients for the study. Based on histological review, 46 patients were classified as myxoid liposarcomas and subjected to genetic analysis.

Genetic analysis of the tumor samples was done in collaboration with the HUS Diagnostics Center. The presence of the most common gene translocation pathognomonic of myoxid liposarcoma, t(12; 16)(q13;p11.2) producing the *FUS::DDIT3* fusion was evaluated with fluorescent in situ hybridization (FISH) using FUS (16p11.2) dual-color break-apart probe according to the manufacturer's protocol.(Vysis) Tumors that did not have the index translocation detectable on FISH were further analyzed with Archer FusionPlex Sarcoma panel that assesses 148 locations using next generation sequencing.(Invitae) Only tumors that displayed either the *FUS::DDIT3* fusion or the *ESWR1::DDIT3* fusion from t(12;22)(q13;q12) translocation were included in the final study population.

Of the 46 patients identified in the databases and classified as myxoid liposarcomas in the histology review, 26 had a *FUS::DDIT3* fusion identified though FISH analysis. No translocation was identified in eleven samples and nine of the FISH analysis produced no result. The NGS Sarcoma panel was run on these twenty samples and

revealed four *FUS::DDIT3* fusions and two *ESWRT1::DDIT3* fusions. No result was obtained in six of the samples and eight of the samples did not reveal either one of the interest translocations. Two of these patients revealed other translocations: *NAB2::STAT6* fusion and *COL1A1::PDGFB* fusion, suggestive of solitary fibrous tumor and dermatofibrosarcoma protuberans, respectively.(Simon et al. 1997, Chmielecki et al. 2013) Thus, the final study population was 32 patients with genetically confirmed MLS.

The patient records were reviewed for patient demographics, tumor size and resection margins, adjuvant treatments, and follow-up details.

*Study II*

A total of 107 patients treated for intra-abdominal or retroperitoneal liposarcoma between 1987 and 2017, and for whom patient records were obtainable, were included in the study. The patients were identified using the Helsinki University Hospital sarcoma database and the pathology database. The patient records were reviewed for demographic details, tumor histopathology and resection margins, adjuvant treatments and oncological follow-up details.

*Study III*

The study included 17 consecutive treated patients with retroperitoneal sarcoma who underwent tumor resection and vascular reconstruction between 2010 and 2018. The patients were identified through reviewing all patients with retroperitoneal sarcoma operated on by members of the oncovascular surgical team in the time period. The patient records were reviewed for demographic details, tumor histopathology, surgical details including the resected vessels and vascular reconstructions, perioperative complications, adjuvant treatments, oncological follow-up results, and patency of the vascular reconstructions on follow-up. Local recurrence-, metastases-free and disease-specific survival were assessed.

*Study IV*

Eight patients with soft tissue sarcoma of the proximal thigh or inguinal region who required vascular reconstruction following tumor resection were treated between 2014 and 2020. The patient records were reviewed for demographic details, tumor histopathology, surgical details including the resected vessels and vascular reconstructions, perioperative complications, adjuvant treatments and oncological follow-up results.

## 8.2 SURGERY

The treatment of all patients newly diagnosed with a soft tissue sarcoma is planned by a multidisciplinary soft tissue sarcoma team. The team, founded in 1987, consists of surgeons, oncologists, radiologists and pathologists, and meets weekly. A multidisciplinary oncovascular team was established in 2015 to plan the treatment of tumors invading or growing near large vessels. Meeting every two weeks, the team includes vascular surgeons, gastrointestinal surgeons, endocrinological surgeons, urologists, cardiothoracic surgeons and radiologists.

*Study I*

Thirty (94%) of the patients had a sheated needle biopsy of the tumor before surgery, with the two without a biopsy having been treated over 30 years ago. All patients had the primary tumor resected, the approach depending on the tumor location.

*Study II*

A core needle biopsy was done to confirm the diagnosis preoperatively in the 40% of the patients considered preoperative adjuvant treatment. A sheated needle and a posterior approach were used to avoid contamination of the peritoneal cavity in patients considered for preoperative adjuvant treatment.

The tumors were removed through laparotomy with an aim to achieve an excision without any compromise to the tumor pseudocapsule. Due to the challenging anatomical location, a tumor-free margin of 2.5 cm, that is generally considered desirable in soft-tissue sarcoma excision, was often not practicable.

Resection of one or more visceral organs was done in 61% of the patients, in order to achieve wider resection margins. Five patients (5%) required vascular reconstructions in conjunction with the resection.

*Study III*

A total of seventeen patients were operated on, ten for primary soft tissue sarcoma, six for a recurrent tumor and one for a suspected tumor recurrence. Seven of the ten patients with primary tumor had the pathological diagnosis confirmed preoperatively with a sheathed needle through a posterior approach.

All the operations were laparotomies, and no concurrent thoracotomy was required. Eleven patients (65%) had one or more visceral organs resected to improve resection margins.

One or more arterial reconstructions were performed in 11 (65%) of the operations, combined with a venous reconstruction in 8 (47%). The IVC was the only vessel

reconstructed in two (14%), and altogether nine (64%) IVC reconstructions were performed. Temporary extra-anatomical bypass from the axillary artery to the kidneys or other viscera was used in three patients, to maintain end organ perfusion during clamping of the aorta.(Heinola et al. 2016) Details of the reconstructions are listed in table 5. The median operation duration was 7.02 (3.62-13.16) hours. Median blood loss was 3700 (550 -13300) ml.

*Study IV*

Eight patients had soft tissue sarcomas resections that involved sacrifice of some of the major vessels in the proximal thigh. The superficial femoral artery and vein were reconstructed in all patients. The reconstruction included the external iliac vessels in three patients, one of whom had also the deep femoral vessels reconstructed (Table 6). Smaller branches of the deep femoral artery were reconstructed when assessed beneficial.

All reconstructions were done with either autologous vein (6 grafts in four patients) or allograft (10 grafts in six patients). The preferred autograft was the saphenous vein, while the cephalic vein was used when the saphenous vein was insufficient or unavailable.

Pedicular muscle flaps with sartorius and gracilis were used for soft tissue coverage in three of the primary operations and microvascular LD in three. In two patients, no flap was initially used but the free flap reconstructions were performed on postoperative days 64 and 105 to solve wound healing problems.

The median operative time was 7.9 (4.3 – 9.1) hours (Table 7). The median blood loss during surgery was 1565 (92 – 5000) ml, and 1 (0 - 14) units of red blood cells were transfused during the day of the surgery.

The thromboprophylaxis regime included perioperative intravenous heparin at a dose of 100 IU/kg and long-term acetylsalicylic acid 100 mg once daily. Low molecular weight heparin was used postoperatively for up to three months. A double platelet inhibition with the addition of clopidogrel was introduced for three months after balloon angioplasty for graft stenosis.

**Table 5. Details of the vascular reconstructions of the 17 patients included in Study III.**

| | Age (y)/ Sex | Tumour type | Vessels resected | Vessel reconstruction | Operative details |
|---|---|---|---|---|---|
| Patient 1 | 59 F | Leiomyosarcoma G2 T2bN0M0 | Infrarenal Aorta and IVC | Aorta with polyethylene prosthesis, IVC with bovine pericardium patch | Temporary axillo-birenal bypass. |
| Patient 2 | 62 F | Leiomyosarcoma G2 T2bN0M1 | Aorta, IVC, L renal vein | Aorta with polyethylene Y-graft, IVC and L renal vein with homocraft vein | R kidney resected. |
| Patient 3 | 56 F | Leiomyosarcoma G2 T2bN0M0 | L iliac vein | Autologous vein graft | Preoperative embolisation of the arteries feeding the tumour. Sigma, L kidney and ureter resected. |
| Patient 4 | 26 M | Leiomyosarcoma G3 T1bN0M0 | Aorta, SMA, hepatic artery and R renal artery | Polyethylene | Temporary bypass from axillary artery to hepatica communis, SMA, right renal artery. Pancreas, spleen and L kindery resected. |
| Patient 5 | 58 F | Leiomyosarcoma G3 T2bN0M0 | IVC | Homograft vein | |
| Patient 6 | 46 M | Leiomyosarcoma G3 T2bN0M1 | IVC | Autologous vein graft | R kidney resected. |
| Patient 7 | 68 F | Leiomyosarcoma G3 T1bN0M0 | IVC and L renal vein | Autologous vein graft | R kidney resected. |
| Patient 8 | 61 F | Leiomyosarcoma G3 T2bN0M0 | IVC and L renal vein | IVC with homograft vein, renal vein with autologous vein graft | R kidney resected. |
| Patient 9 | 40 F | Leiomyosarcoma G3 T1bN0M0 | L internal iliac artery and external iliac vein | Artery with PTFE, vein with autologus vein graft | |
| Patient 10 | 64 F | Undifferentiated pleomorphic sarcoma G3 T2bN0M0 | Aorta, IVC, L renal artery and vein | Arteries with polyethylene, veins with autologous vein graft | Temporary axillo-renal bypass. Gallbladder and R kidney resected. |
| Patient 11 | 59 F | Sclerosing liposarcoma G2 T2bN0M0 | Iliaca interna and externa artery and vein | Homocraft vein | Uterus resected. |
| Patient 12 | 70 M | Myxoid liposarcoma G3 T2bN0M0 | Common iliac artery and vein | Artery with polyethylene, vena with autologous vein graft | |
| Patient 13 | 50 F | Dedifferentiated liposarcoma G2 T2bN0M0 | L renal vein | Autologous vein patch | |
| Patient 14 | 63 F | Dedifferentiated liposarcoma G2 T2bN0M0 | Hepatic artery | Autologous vein graft | Pancreaticoduodenectomy and R hemicolon resected. |
| Patient 15 | 60 F | Dedifferentiated liposarcoma G3 T2bN0M0 | Aorta and IVC | Aorta with polyehtylene, IVC Homograft vein | R kidney resected. |
| Patient 16 | 32 M | Angiosarcoma epithelioides G3 T2bN0M0 | Aorta, IVC patch, coeliac trunc | Aorta, coeliac trunc, SMA, left renal vein and both internal iliac arteries with polyethylene prosthesis, IVC with bovine pericardium patch | Temporary axillo-renal bypass. R kidney resected. |
| Patient 17 | 30 F | Thrombosis, lung metastases | Aorta | Polyethylene | |

**Table 6. Reconstruction details for the patients in study IV. *Synthetic mesh / **composite mesh used for inguinal ligament reconstruction and abdominal wall support.**

| ID | Artery resection | Vein resection | Arterial graft material | Vein graft material | Soft tissue reconstruction | Later revision | Graft complications |
|---|---|---|---|---|---|---|---|
| Patient 1 | EIA - SFA & DFA | EIV - SFV & DFV | Autologous vein | Autologous vein | Pedicular sartorius | Revision and pedicular gracilis due to infection on POD 22. | |
| Patient 2 | EIA - SFA | EIV – SFV | Allograft | Allograft | Direct closure* | Revision due to skin necrosis on POD 21. Prolonged lymphatic leak. LD on POD 64. Tendon transfers for knee extension at 36 months. | |
| Patient 3 | SFA | SFV | Autologous vein | Allograft | Pedicular gracilis | Revision for seroma infection on POD 15. | New SFA graft with autologous vein at 19 months. |
| Patient 4 | SFA | SFV | Allograft | Allograft | LD | | |
| Patient 5 | SFA | SFV | Allograft | Allograft | Skin graft | LD on POD 105 due to an infected seroma. | PTA and stent to proximal arterial stenosis 7 months, 8 times thereafter. |
| Patient 6 | SFA | SFV | Autologous vein | Allograft | Pedicular Sartorius* | Seroma drainage on POD 13. | |
| Patient 7 | SFA | SFV | Autologous vein | Autologous vein | LD | Hematoma evacuation on POD 23. | |
| Patient 8 | EIA - SFA | EIV – SFV | Allograft | Allograft | LD** | LD harvest site hematoma evacuation on POD 34. Ureter compression requiring pyelostoma on POD 41. | Vein graft thrombectomies on POD 2 and 13. Thrombus on POD 33, treated conservatively. |

**Table 7. Perioperative details for patients with soft tissue sarcoma who underwent tumor removal and vascular reconstruction in study IV. *Within 30 days of surgery.**

| ID | Duration of operation (h) | Blood volume loss during surgery (ml) | Units of red blood cells transfused (n) | Days in HDU | Days in hospital | Perioperative complications* (Clavien-Dindo class) |
|---|---|---|---|---|---|---|
| Patient 1 | 8.9 | NA | NA | 1 | 11 | 3b |
| Patient 2 | 8.1 | 860 | 2 | 1 | 24 | 3b |
| Patient 3 | 4.3 | 1565 | 1 | 0 | 9 | 3b |
| Patient 4 | 8.8 | 2035 | 2 | 1 | 10 | none |
| Patient 5 | 5.3 | 1735 | 2 | 0 | 10 | none |
| Patient 6 | 7.1 | 92 | 0 | 1 | 8 | 3a |
| Patient 7 | 7.7 | 1300 | 2 | 0 | 8 | 3b |
| Patient 8 | 9.1 | 5000 | 14 | 2 | 54 | 3b |

## 8.3 ADJUVANT TREATMENTS

Adjuvant treatments were decided by the multidisciplinary Helsinki University Hospital sarcoma team, following the local guidelines. Preoperative radiotherapy was offered to patients with high grade tumors for which resection was predicted to result in macroscopically or microscopically positive margins. Postoperative radiotherapy was recommended generally after marginal or intralesional surgery. However, for intra-abdominal or retroperitoneal tumors, postoperative radiotherapy is reserved for residual macroscopic tumors as the radiotherapy field required to target borders of a marginally resected tumor was assessed too extensive. The criteria for radiotherapy have remained unchanged during the 30 years covered in these studies. Chemotherapy is recommended for patients with good performance status and high-grade tumors fulfilling at least two of the following criteria: size larger than 8 cm, necrosis or vascular invasion. A combination of doxorubicin and ifosfamide has been used since 1998 in adjuvant treatments and is generally also as the first line chemotherapy regime.

Study I

Twenty (63%) patients had radiotherapy for their primary tumor, all postoperatively. Four of them (13% of all patients) had chemotherapy in addition to radiotherapy.

Study II

Grade 1 liposarcomas were treated operatively with no adjuvant treatments. Preoperative radiotherapy was given to seven (7%) patients and postoperative radiotherapy to 5 (5%) during the treatment of the primary tumor. One patient received chemotherapy before and nine (9%) after surgery. In addition, three (3%) patients were given both radio- and chemotherapy.

Two patients who did not have the tumor removed were treated with chemo- and radiotherapy and two with radiotherapy alone.

Study III

Ten (63%) of the patients with tumor surgery received no adjuvant treatments. Five of these patients were treated for the primary presentation of the tumor. Six (38%) patients received preoperative radiotherapy, two of whom also received preoperative chemotherapy. One patient received only postoperative chemotherapy.

Study IV

Six (75%) of the patients had radiotherapy to the primary or recurrent tumor that was operated on, three preoperatively and three postoperatively. None of the patients received chemotherapy for the index presentation.

## 8.4 SYSTEMATIC REVIEW OF LITERATURE

Study I

A comprehensive review of literature following PRISMA guidelines was done to assess the pattern of myxoid liposarcoma metastases locations.(Moher et al. 2009) A systematic literature search was performed on 22 June 2022 on databases Medline, Web of Science and Scopus, using the search terms shown in table 8. Articles including at least 10 patients with myxoid liposarcoma metastases were assessed for eligibility and those reporting the locations and sequence of metastases in the patients were included (Figure 1).

Location of the first metastases was recorded for each of the patients in the included series. The locations were classified as pulmonary, intra-abdominal, soft tissue, bone or multiple. Abdominal solid organ metastases and retroperitoneal metastases were included in the intra-abdominal group, lymph node metastases in the soft tissue group.

**Table 8. Search terms for the literature review run on June 24th 2022.**

| Database | Search terms |
|---|---|
| Medline | (liposarcoma myxoid) AND ((neoplasm metastasis) OR metastasis) |
| Web of Science Core Collection | **TOPIC:** (myxoid* near/1 liposarcoma*) *AND* **TOPIC:** (metasta*) |
| Scopus | TITLE-ABS-KEY (liposarcoma myxoid) AND ((neoplasm metastasis) OR metastasis) AND NOT INDEX (medline) |

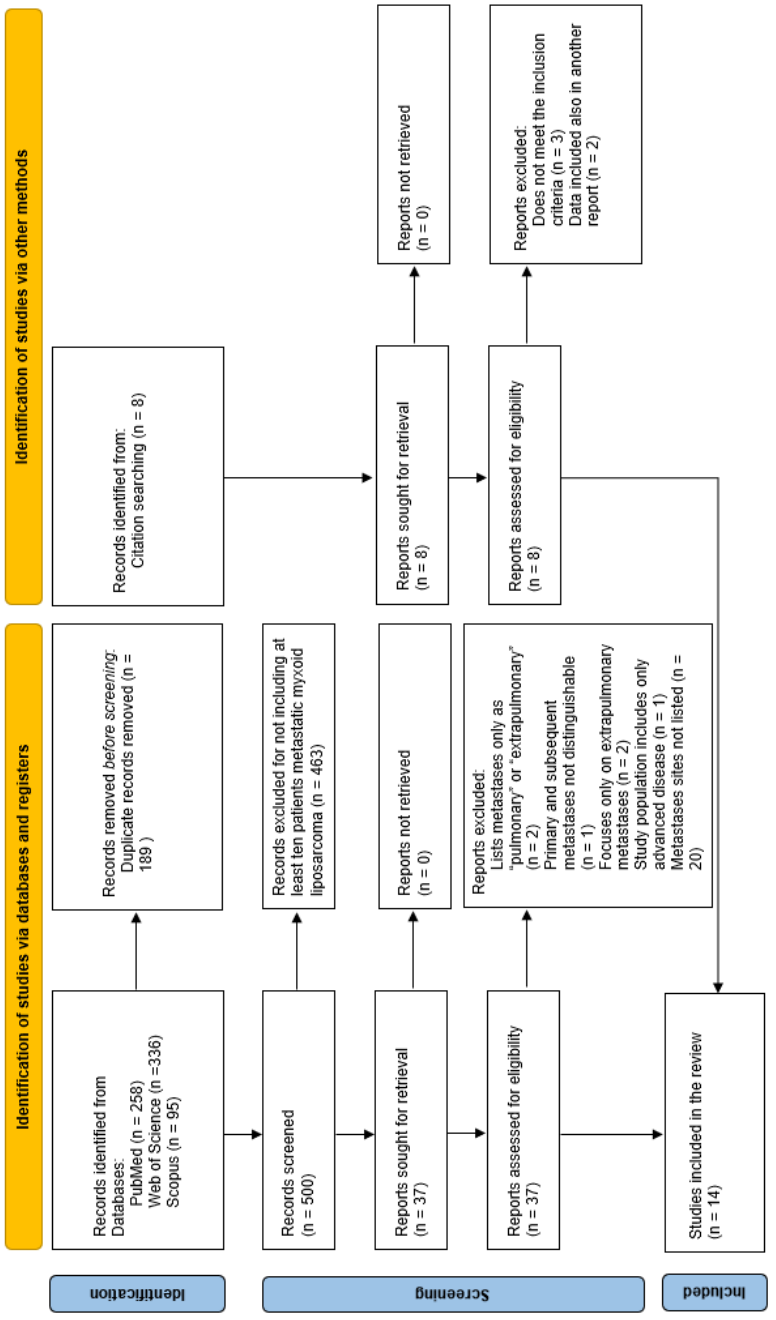



**Figure 1. PRISMA flow diagram of the systematic review for locations of myoxid liposarcoma metastases. Chart based on Moher et al. 2009.**

Study III

A comprehensive literature review was performed to identify reports of patients with intra-abdominal or retroperitoneal sarcomas who had a vascular reconstruction during the resection of the tumor. The systematic literature search was performed on databases World of Science, MEDLINE, and SCOPUS on 27.1.2020 with terms shown in table 9. PRISMA guidelines were followed in the article selection (Figure 2).(Moher et al. 2009) Thirty-seven articles with 110 patients were identified for inclusion.

**Table 9. Search terms for the comprehensive review of literature in Study III.**

| Search engine | Search terms |
|---|---|
| PubMed | ((vascular reconstruction) AND (((intra-abdominal) OR intra abdominal) OR retroperitoneal)) AND (((neoplasm) OR cancer) OR tumor) |
| Web of Science | **TOPIC:** (intra* near/2 abdominal* OR retroperitoneal*) *AND* **TOPIC:** (cancer* OR neoplasm* OR tumor* or tumour*) *AND* **TOPIC:** (vascular AND reconstruct*) |
| MEDLINE | 1. (intra* adj2 abdominal*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] |
| | 2. retroperiton*.mp. |
| | 3. 1 or 2 |
| | 4. neoplasm*.mp. |
| | 5. exp NEOPLASMS/ |
| | 6. cancer*.mp. |
| | 7. (tumor* or tumour*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] |
| | 8. 4 or 5 or 6 or 7 |
| | 9. (vascular* adj3 reconst*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] |
| | 10. 3 and 8 and 9 |
| SCOPUS | ( TITLE-ABS-KEY ( intra* W/2 abdominal* OR retroperitoneal* ) AND TITLE-ABS-KEY ( neoplasm* OR tumor* OR tumour* OR cancer* ) AND TITLE-ABS-KEY ( vascular* AND reconstruct* ) ) AND NOT INDEX ( medline ) |

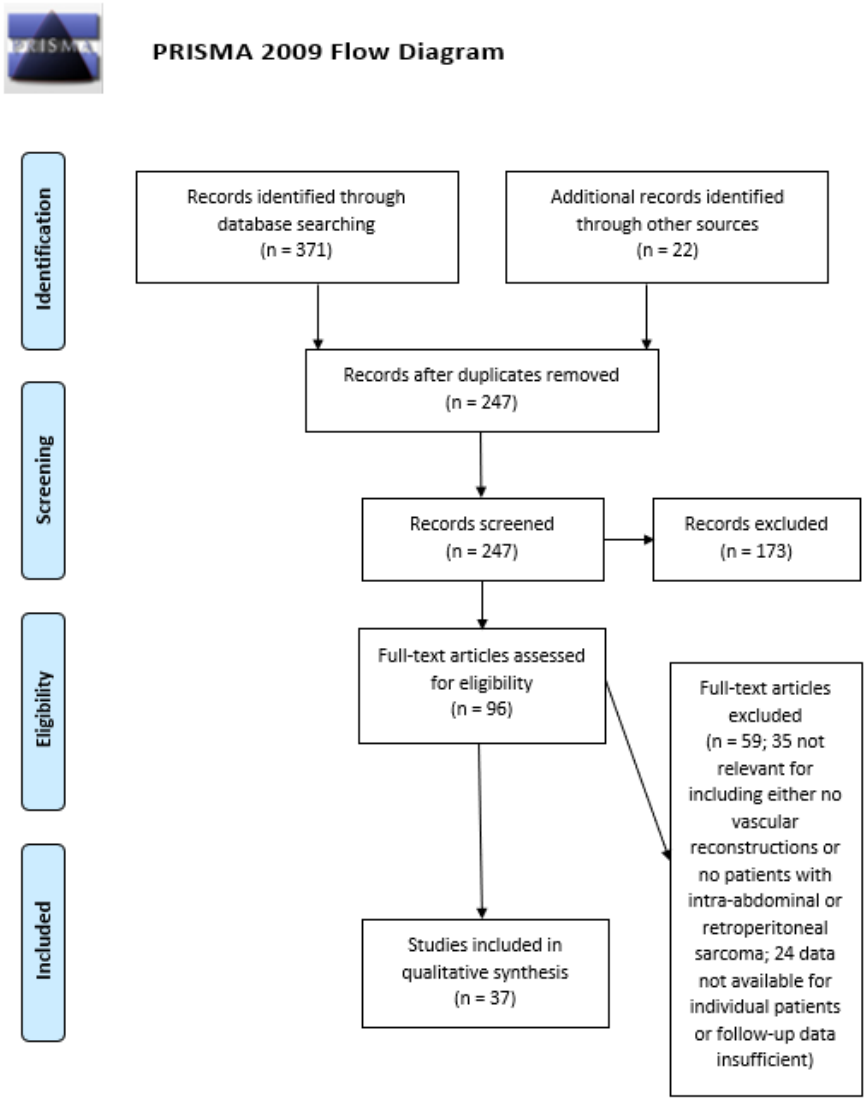



**Figure 2. Steps followed in the identification of articles for the comprehensive literature review in Study III. Chart based on Moher et al. 2009.**

## 8.5 FOLLOW-UP

The patients in studies I-IV were followed up for cancer recurrence according to the Helsinki University sarcoma protocol outlined in section 6. The follow-up of the vascular grafts was designed for each patient on a case-by-case bases.

In patients of Study IV who attended the vascular follow-up clinic, the patency of the vascular grafts was assessed with duplex ultrasound and lymphoedema of the operated leg was evaluated using the truncated cone method (Brorson et al. 2015). Function of the operated leg was evaluated with the Musculoskeletal Tumor Society (MSTS) 1993 score which comprises of functional assessment of the affected limb, completed by a physician (Davis et al. 1996, Kask et al. 2019), and the patient-reported outcomes instrument Toronto extremity salvage score (TESS) (Enneking et al. 1993, Kask et al. 2020).

## 8.6 STATISTICAL METHODS

IBM SPSS Statistics software, versions 26 and 27, was used for all the analysis.(IBM 2017)

Study I

Local progression-free, metastases-free and disease-specific survival were assessed with Kaplan-Meier analysis for the patients treated in Helsinki University Hospital.

The fraction of the metastases in pulmonary, intra-abdominal, soft tissue, bone or multiple location was calculated and the Clopper-Pearson exact with 95% confidence intervals were estimated using Epitools.(Epitools 2022)

Study II

Local recurrence-free survival, metastases-free survival and disease-specific survival were calculated with Kaplan-Meier analysis for each tumor type and grade as well as age at diagnosis, sex, tumor size over 20 cm, tumor multifocality, resection margins, radiotherapy and chemotherapy. The results were compared using Log-Rank method and a result with $p < 0.05$ was taken as a significant difference. Cox multiple regression was done with variables found significant in univariate analysis. All tests were two-sided. IBM SPSS software was used for all the analysis.

Study III

Estimates of survival or times to recurrence were calculated with Kaplan-Meier analysis using IBM SPSS software and reported as median (range) or proportion event-free at three years.

Study IV

All the results are presented as medians and ranges

# 9. RESULTS

## 9.1 STUDY I

The final study group included 32 patients with myxoid liposarcoma, 21 men and eleven women. The median age at diagnosis was 47.7 years (rage 22.7 to 82.7 years). The median follow-up time was 7.6 (2.1 to 16.7) years. The location of the primary tumor was the lower limb in 29, and the upper limb, the head and the trunk wall for one patient each.

### 9.1.1 HISTOPATHOLOGY

The maximum diameter of the tumor was over 10 cm in 17 (53%) patients and smaller in 14 (44%). The size was not retrieved for one of the tumors. Twenty-one (66%) of the tumors were grade 2 and eleven (34%) grade 3. The resection margins were R0 in 8 (25%), R1 in 19 (59%) and R2 in three (9%) patients. Data on resection margins was not available for two of the patients.

### 9.1.2 TREATMENT RESULTS

Six (19%) of the patients developed a local recurrence during the follow-up. Four of the local recurrences were in the lower limb, one in the upper limb and one in the trunk wall. The five-year local progression-free survival was 84 ± 7% (Figure 3).

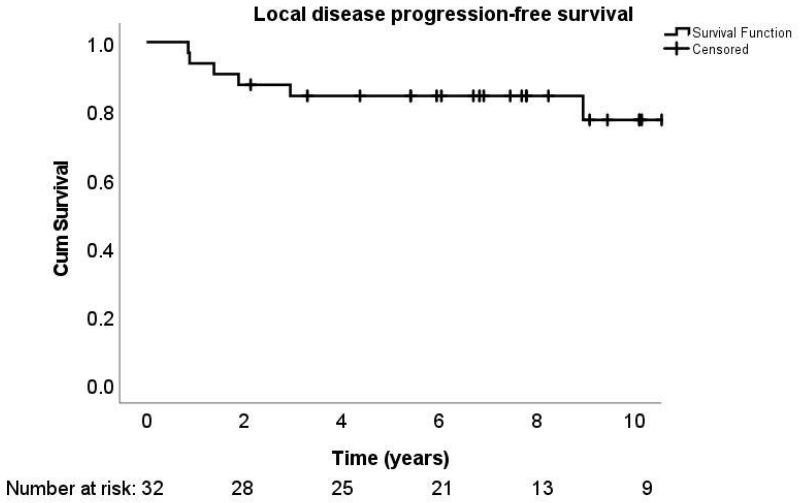



**Figure 3. Local progression-free survival of patients with myxoid liposarcoma.**

Metastases were detected in seven patients (22%), including two of the patients (6%) presenting primarily with metastatic disease. The five-year metastases-free survival was 78 ± 7% (Figure 4). Each of the patients had initially a single metastatic tumor in each location. Locations of the metastases were: Patient 1) lungs and pleura, recurring later in the same location, patient 2) first intra-abdominal and a supraclavicular lymph node, then subcutaneous, further intra-abdominal, lungs and spine, patient 3) intra-abdominal, patient 4) first intra-abdominal, then further intra-abdominal and subcutaneous around the scar, patient 5) the brain, patient 6) intra-abdominal and contralateral thigh soft tissue, patient 7) first intra-abdominal, then bone. Four of these patients developed also local disease recurrence.

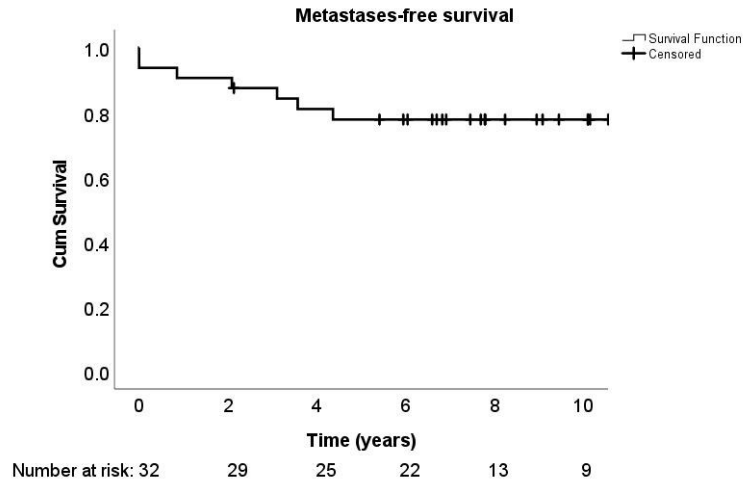



**Figure 4. Metastases-free survival of patients with myxoid liposarcoma.**

Overall, nine patients had a local recurrence or metastases during follow-up with a five-year disease-free survival of 75 ± 8% (Figure 5). Six patients died of myxoid liposarcoma during follow-up with a 5-year disease-specific survival of 87 ± 6% (Figure 6).

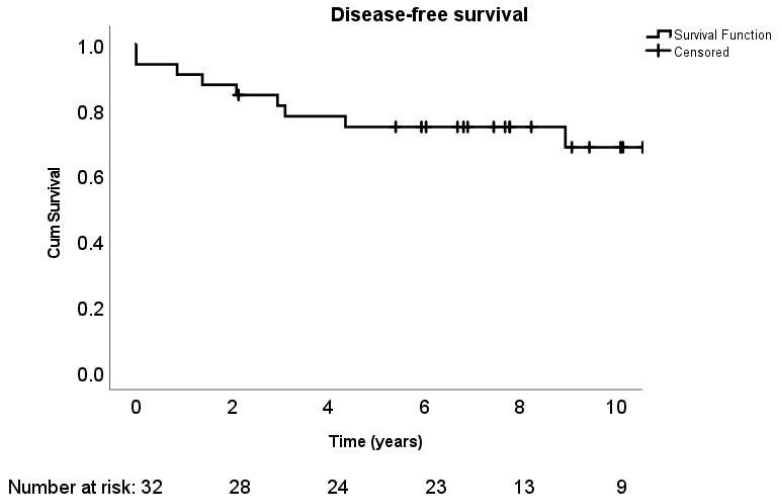



**Figure 5. Disease-free survival of patients with myxoid liposarcoma.**

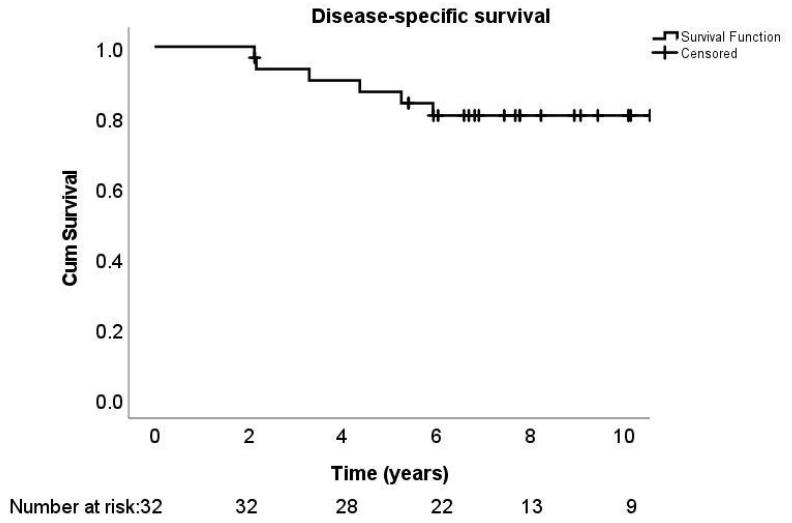



**Figure 6. Disease-specific survival of patients with myxoid liposarcoma.**

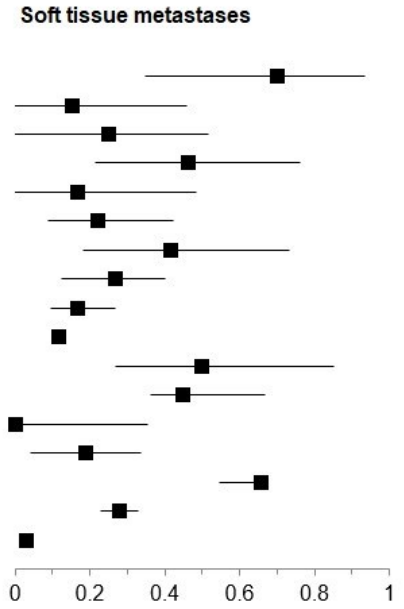
### 9.1.3 SYSTEMATIC REVIEW OF LITERATURE

Fourteen articles describing unique patient series with at least ten patients with metastatic myxoid liposarcoma were identified for the analysis. The series included a total of 1853 patients with myxoid liposarcoma, 348 (19%) of whom had metastatic disease (Table 10).

**Table 10. Series of patients with myxoid liposarcoma metastases included in the meta-analysis. *Time for all types of liposarcoma included in the article. **Average follow-up time.**

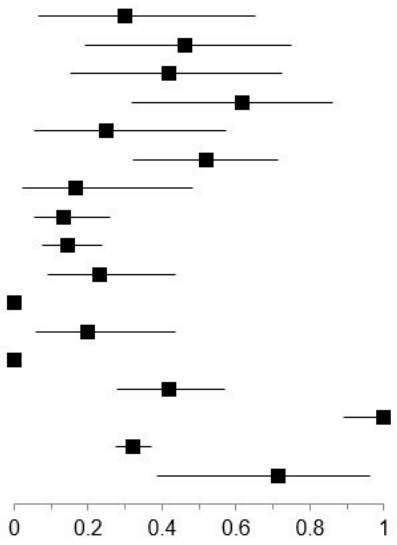
| Author | Publication year | City | Time period | Number of patients with MLS | Number of patients with metastases | Follow-up time (months, median) |
|---|---|---|---|---|---|---|
| Smith *et al.* | 1996 | Cleveland, USA | 1961-1992 | 29 | 10 | 72 |
| Zagars *et al.* | 1996 | Houston, USA | 1964-1992 | 71 | 13 | 109* |
| Spillane *et al.* | 1999 | London, UK | 1988-1998 | 50 | 12 | 43 |
| ten Heuvel *et al.* | 2007 | Groningen, Holland | 1977-2004 | 49 | 13 | 101 |
| Sheah *et al.* | 2008 | Massachusetts, USA | 1999-2007 | 112 | 12 | Not reported |
| Guadagnolo *et al.* | 2008 | Houston, USA | 1960-2003 | 127 | 27 | 109 |
| Chung *et al.* | 2009 | Toronto, Canada | 1986-2004 | 88 | 12 | 86 |
| Haniball *et al.* | 2011 | Birmingham, USA | 1987-2005 | 160 | 52 | 55 |
| Moreau *et al.* | 2012 | Montreal, Canada | 1977-2008 | 418 | 83 | 62 |
| Hoffman *et al.* | 2012 | Houston, USA | 1990-2010 | 207 | 26 | 68 |
| Baxter *et al.* | 2015 | Atlanta, USA | 2000-2010 | 75 | 10 | 60 |
| Muratori *et al.* | 2018 | Firenze, Italy | 1994-2015 | 148 | 20 | 63** |
| Gouin *et al.* | 2019 | Lyon, France | 2006-2011 | 45 | 10 | 43 |
| Shinoda *et al.* | 2020 | Tokyo, Japan | 2001-2015 | 274 | 48 | 47 |

The overall prevalence of metastatic disease was 19%. Soft tissue metastases were most common with a 32% prevalence (95% CI 28-38%; Figure 7), followed by intra-abdominal at 26% (95% CI 21-31%; Figure 8), followed by pulmonary at 24% (95% CI 19-29%; Figure 9) and bone metastases at 17% (95% CI 13-22%; Figure 10). Of note, for twelve of the series, pulmonary and pleural metastases were reported together, or the potential inclusion of pleural metastases in the lung metastases counts was not disclosed. Primary metastases were detected at multiple locations in 26% (95% CI 22-31%; Figure 11).



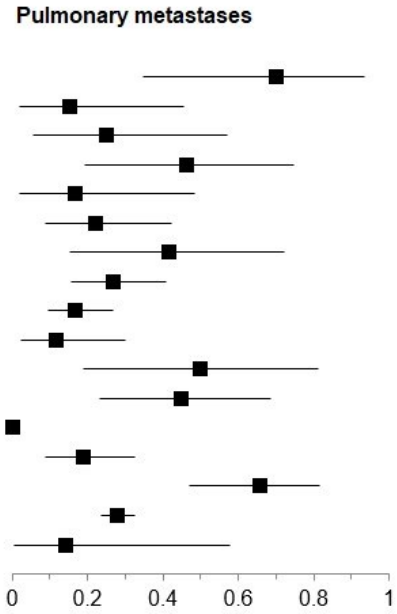

| Publication | Prevalence | (95% CI) |
|---|---|---|
| Smith 1996 | 0.7 | 0.35 - 0.93 |
| Zagars 1996 | 0.31 | 0.09 - 0.61 |
| Spillane 1999 | 0.58 | 0.28 - 0.85 |
| ten Heuvel 2007 | 0.38 | 0.14 - 0.68 |
| Sheah 2008 | 0.33 | 0.1 - 0.65 |
| Guadagnolo 2008 | 0.22 | 0.09 - 0.42 |
| Chung 2009 | 0.33 | 0.1 - 0.65 |
| Haniball 2011 | 0.62 | 0.47 - 0.75 |
| Moreau 2012 | 0.17 | 0.1 - 0.27 |
| Hoffman 2013 | 0 | 0 - 0 |
| Baxter 2015 | 0.3 | 0.07 - 0.65 |
| Muratori 2018 | 0.1 | 0.01 - 0.32 |
| Gouin 2019 | 0.2 | 0.03 - 0.56 |
| Shinoda 2020 | 0.48 | 0.33 - 0.63 |
| Visgauss 2021 | 1 | 0.89 - 1 |
| **Overall** | **0.38** | **0.33 - 0.43** |
| Current series | 0 | 0 - 0 |

**Figure 7. First metastatic recurrence in soft tissues in myxoid liposarcoma patients.**



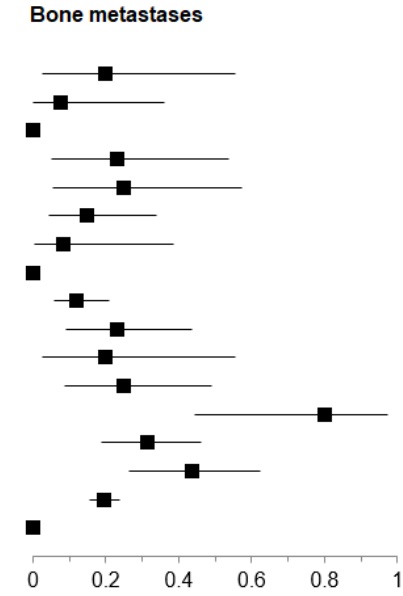

| Publication | Prevalence | (95% CI) |
|---|---|---|
| Smith 1996 | 0.3 | 0.07 - 0.65 |
| Zagars 1996 | 0.46 | 0.19 - 0.75 |
| Spillane 1999 | 0.42 | 0.15 - 0.72 |
| ten Heuvel 2007 | 0.62 | 0.32 - 0.86 |
| Sheah 2008 | 0.25 | 0.05 - 0.57 |
| Guadagnolo 2008 | 0.52 | 0.32 - 0.71 |
| Chung 2009 | 0.17 | 0.02 - 0.48 |
| Haniball 2011 | 0.13 | 0.06 - 0.26 |
| Moreau 2012 | 0.14 | 0.08 - 0.24 |
| Hoffman 2013 | 0.23 | 0.09 - 0.44 |
| Baxter 2015 | 0 | 0 - 0 |
| Muratori 2018 | 0.2 | 0.06 - 0.44 |
| Gouin 2019 | 0 | 0 - 0 |
| Shinoda 2020 | 0.42 | 0.28 - 0.57 |
| Visgauss 2021 | 1 | 0.89 - 1 |
| **Overall** | **0.32** | **0.27 - 0.37** |
| Current series | 0.71 | 0.29-0.96 |

**Figure 8. First metastatic recurrence in the abdomen in myxoid liposarcoma patients.**



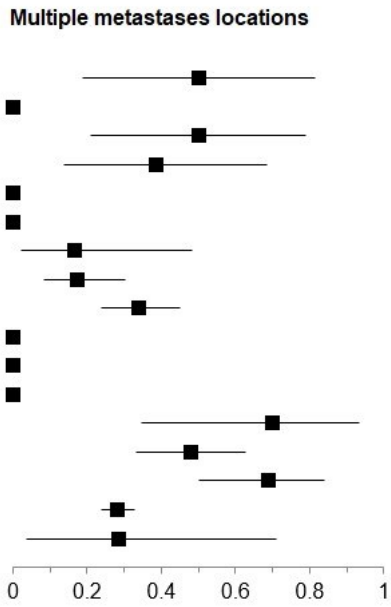

| Publication | Prevalence | (95% CI) |
|---|---|---|
| Smith 1996 | 0.7 | 0.35 - 0.93 |
| Zagars 1996 | 0.15 | 0.02 - 0.45 |
| Spillane 1999 | 0.25 | 0.05 - 0.57 |
| ten Heuvel 2007 | 0.46 | 0.19 - 0.75 |
| Sheah 2008 | 0.17 | 0.02 - 0.48 |
| Guadagnolo 2008 | 0.22 | 0.09 - 0.42 |
| Chung 2009 | 0.42 | 0.15 - 0.72 |
| Haniball 2011 | 0.27 | 0.16 - 0.41 |
| Moreau 2012 | 0.17 | 0.1 - 0.27 |
| Hoffman 2013 | 0.12 | 0.02 - 0.3 |
| Baxter 2015 | 0.5 | 0.19 - 0.81 |
| Muratori 2018 | 0.45 | 0.23 - 0.68 |
| Gouin 2019 | 0 | 0 - 0 |
| Shinoda 2020 | 0.19 | 0.09 - 0.33 |
| Visgauss 2021 | 0.66 | 0.47 - 0.81 |
| **Overall** | **0.28** | **0.23 - 0.33** |
| Current series | 0.14 | 0 - 0.58 |

**Figure 9. First metastatic recurrence in the lungs in myxoid liposarcoma patients.**




| Publication | Prevalence | (95% CI) |
|---|---|---|
| Smith 1996 | 0.2 | 0.03 - 0.56 |
| Zagars 1996 | 0.08 | 0 - 0.36 |
| Spillane 1999 | 0 | 0 - 0 |
| ten Heuvel 2007 | 0.23 | 0.05 - 0.54 |
| Sheah 2008 | 0.25 | 0.05 - 0.57 |
| Guadagnolo 2008 | 0.15 | 0.04 - 0.34 |
| Chung 2009 | 0.08 | 0 - 0.38 |
| Haniball 2011 | 0 | 0 - 0 |
| Moreau 2012 | 0.12 | 0.06 - 0.21 |
| Hoffman 2013 | 0.23 | 0.09 - 0.44 |
| Baxter 2015 | 0.2 | 0.03 - 0.56 |
| Muratori 2018 | 0.25 | 0.09 - 0.49 |
| Gouin 2019 | 0.8 | 0.44 - 0.97 |
| Shinoda 2020 | 0.31 | 0.19 - 0.46 |
| Visgauss 2021 | 0.44 | 0.26 - 0.62 |
| **Overall** | **0.19** | **0.16 - 0.24** |
| Current series | 0 | 0 - 0 |

**Figure 10. First metastatic recurrence in bone in myxoid liposarcoma patients.**




| Publication | Prevalence | (95% CI) |
|---|---|---|
| Smith 1996 | 0.5 | 0.19 - 0.81 |
| Zagars 1996 | 0 | 0 - 0 |
| Spillane 1999 | 0.5 | 0.21 - 0.79 |
| ten Heuvel 2007 | 0.38 | 0.14 - 0.68 |
| Sheah 2008 | 0 | 0 - 0 |
| Guadagnolo 2008 | 0 | 0 - 0 |
| Chung 2009 | 0.17 | 0.02 - 0.48 |
| Haniball 2011 | 0.17 | 0.08 - 0.3 |
| Moreau 2012 | 0.34 | 0.24 - 0.45 |
| Hoffman 2013 | 0 | 0 - 0 |
| Baxter 2015 | 0 | 0 - 0 |
| Muratori 2018 | 0 | 0 - 0 |
| Gouin 2019 | 0.7 | 0.35 - 0.93 |
| Shinoda 2020 | 0.48 | 0.33 - 0.63 |
| Visgauss 2021 | 0.69 | 0.5 - 0.84 |
| **Overall** | **0.28** | **0.24 - 0.33** |
| Current series | 0.29 | 0.04 - 0.71 |

**Figure 11. First metastatic recurrence in multiple locations in myxoid liposarcoma patients.**

## 9.2 STUDY II

Altogether 107 patients with intra-abdominal or retroperitoneal liposarcoma were included in the study, The median age at diagnosis was 62 years (interquartile range (IQR) 52 to 73 years). Sixty-two (58 %) patients were female.

### 9.2.1 HISTOPATHOLOGICAL DIAGNOSIS

There were 28 (26 %) lipoma-like liposarcomas, 18 (17 %) dedifferentiated liposarcomas, 3 (3 %) myxoid liposarcomas, 15 (14 %) pleomorphic liposarcomas and 43 (40 %) not specified liposarcomas. Twenty (19 %) tumors were multifocal at presentation. Thirty (28%) tumors were histological grade 1, 31 (29%) grade 2, and 46 (43%) grade 3. Nine patients (8%) had metastatic disease at time of presentation. (Table 11)

Tumor resection with microscopically negative margins was achieved in 84 (79%) patients. The resection was intralesional in eleven (10%) patients. No resection or only incomplete resection was done in eleven (10%) patients.

**Table 11. Details of the 107 retroperitoneal liposarcomas included in the analysis.**

| | | Tumor type | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Lipoma-like liposarcoma | | Dedifferentiated | | Myxoid | | Pleomorphic | | Not specified | |
| | | Count | % | Count | % | Count | % | Count | % | Count | % |
| Tumor gradus | Grade 1 | 20 | 74% | 0 | 0% | 0 | 0% | 0 | 0% | 10 | 23% |
| | Grade 2 | 5 | 19% | 7 | 39% | 3 | 100% | 1 | 7% | 15 | 34% |
| | Grade 3 | 2 | 7% | 11 | 61% | 0 | 0% | 14 | 93% | 19 | 43% |
| Tumor size | < 20 cm | 14 | 52% | 12 | 67% | 2 | 67% | 6 | 40% | 11 | 25% |
| | > 20 cm | 12 | 44% | 6 | 33% | 1 | 33% | 8 | 53% | 33 | 75% |
| Resection | R0 | 22 | 81% | 14 | 78% | 2 | 67% | 7 | 47% | 40 | 91% |
| margins | R1 | 3 | 11% | 1 | 6% | 0 | 0% | 4 | 27% | 3 | 7% |
| | R2 or no resection | 2 | 7% | 1 | 6% | 1 | 33% | 4 | 27% | 1 | 2% |
| Metastases at | No | 23 | 85% | 13 | 72% | 1 | 33% | 10 | 67% | 34 | 77% |
| presentation | Yes | 4 | 15% | 5 | 28% | 2 | 67% | 5 | 33% | 10 | 23% |
| Radiotherapy | No | 20 | 74% | 17 | 94% | 2 | 67% | 13 | 87% | 39 | 89% |
| for primary | Yes | 7 | 26% | 1 | 6% | 1 | 33% | 1 | 7% | 5 | 11% |
| presentation | | | | | | | | | | | |
| Chemotherapy | No | 22 | 81% | 17 | 94% | 3 | 100% | 13 | 87% | 35 | 80% |
| for primary | Yes | 5 | 19% | 1 | 6% | 0 | 0% | 1 | 7% | 9 | 20% |
| presentation | | | | | | | | | | | |

### 9.2.2 PERIOPERATIVE COMPLICATIONS

Information on postoperative complications was available for 89 patients. Of these, ten (11 %) patients had complications within 30 days of surgery. There were two Clavien-Dindo class 1 complications, two class 2, one class 3a, three class 3b and two class 5.(Dindo et al. 2004)

The complications were: Pneumonia, pulmonary embolus, pneumothorax, one abdomen left open for later closure due to challenging hemostasis after heparinization due to clamping of the aorta, one wound dehiscence, one patient requiring to relaparotomies for postoperative bleed and poor stoma perfusion, and two patients experiencing leg weakness due to spinal ischemia and nerve damage. The two deaths were a patient who was found to have disseminated disease on laparotomy and a patient who presented with an intestinal obstruction related to a locally advanced tumor.

### 9.2.3 TREATMENT RESULTS

The five-year local recurrence-free survival was 37 ± 5 % in the 96 patients who had a macroscopically complete resection of a primary liposarcoma. Sixty-nine of the patients (72%) developed a local recurrence with a median time of 3.1 years (95% CI 2.1 to 4.2 years). While tumor type ($p = 0.04$, Figure 12) and grade ($p < 0.01$, Figure 13) were predictive of local recurrence in univariate analysis, multifocality of the tumor was the only factor that remained prognostic of local recurrence in multivariate analysis ($p = 0.02$, Figure 14). (Table 12)

Local recurrence was surgically removed in 58 (84%) patients of whom 14 (24%) received also adjuvant treatment. Four (6%) patients received only chemo- or radiotherapy. The treatment for a local recurrence was considered successful in 53 (77%) patients of whom 45 (85%) developed one or more further recurrences during the follow-up. The histological grade of the tumor increased during one or more of the recurrences in 17 (25%) patients.

The five-year metastases-free survival was 81 ± 4%. Nine patients (8%) had metastatic disease at the time of liposarcoma diagnosis and further 17 (16%) developed metastases during follow-up. Both local recurrence and metastases developed in fourteen (15%) patients.

Tumor type ($p = 0.01$), grade ($p < 0.01$, Figure 15), surgical resection margins ($p = 0.03$), radiotherapy ($p < 0.01$) and chemotherapy ($p < 0.01$) were predictive of metastasis free survival. Histological grade and chemotherapy remained predictive factors in Cox multiple regression analysis. (Table 13)

The overall five-year disease-specific survival was 65 ± 5%. Fifty-five patients (51%) died of liposarcoma during follow-up. The median disease-specific survival from diagnosis was 8.7 years (95% CI 5.7 to 11.8 years). Tumor type ($p < 0.01$, Figure 16), grade ($p < 0.01$, Figure 17) resection margins ($p < 0.01$, Figure 18), age ($p = 0.02$), radiotherapy ($p = 0.02$), chemotherapy ($p < 0.01$) and metastases at time of diagnosis ($p < 0.01$) were prognostic of disease-specific survival on univariate analysis. Histological subtype and grade, and resection margins remained predictive factors in Cox multiple regression analysis. (Table 14)

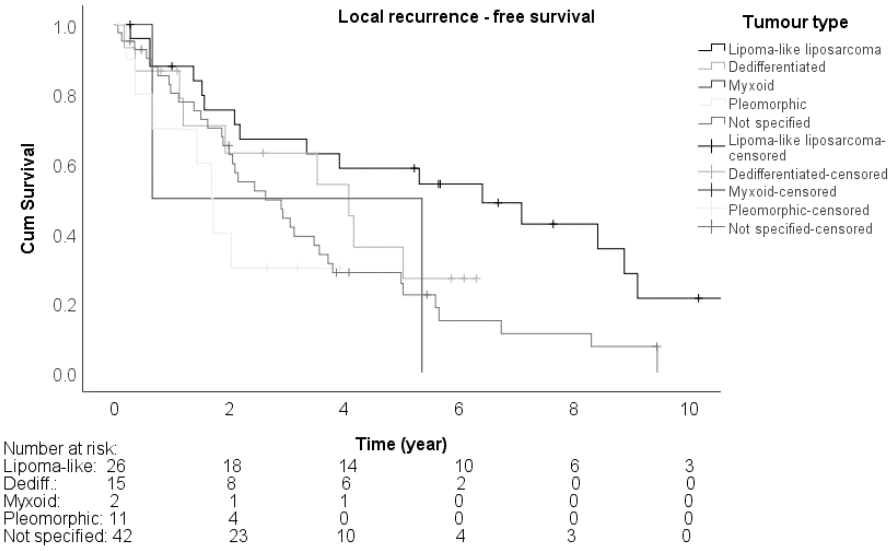



**Figure 12. Local recurrence-free survival by tumor type in 96 patients with retroperitoneal liposarcoma who had the tumor resected with curative intent.**

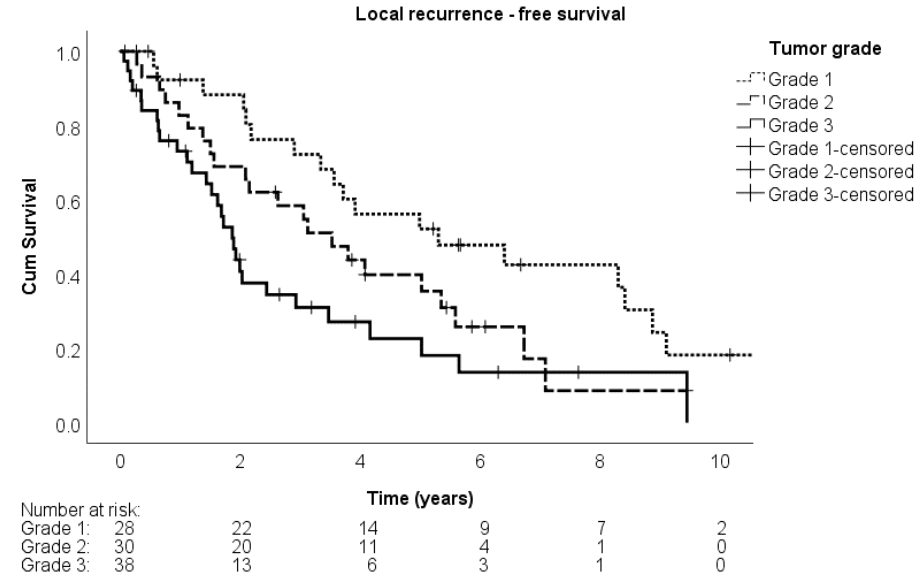



**Figure 13. Local recurrence-free survival by tumor grade in 96 patients with retroperitoneal liposarcoma who had the tumor resected with curative intent.**

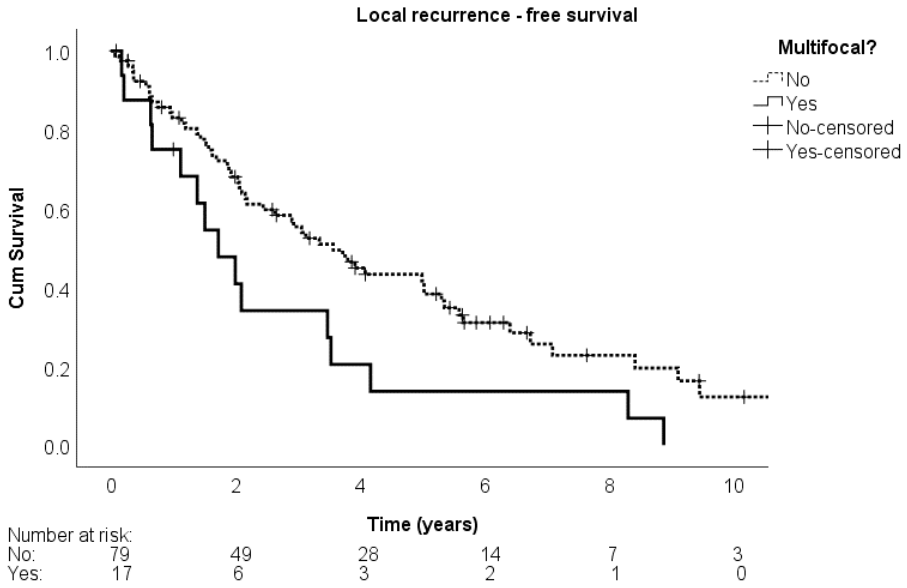



**Figure 14. Local recurrence-free survival by tumor multifocality in 96 patients with retroperitoneal liposarcoma who had the tumor resected with curative intent.**

**Table 12. Local recurrence-free survival for 96 patients after retroperitoneal liposarcoma was resected with curative intent.**

| | | 5-year local recurrence-free survival | Hazard Ratio | 95% CI | p |
|---|---|---|---|---|---|
| **Histological subtype** | | | | | 0.37 |
| | Lipoma-like | 0.59 | 1 | | |
| | De-differentiated | 0.36 | 0.98 | 0.36 to 2.65 | 0.97 |
| | Myxoid | 0.50 | 2.50 | 0.51 to 12.35 | 0.26 |
| | Pleomorphic | 0.30 | 1.84 | 0.61 to 5.45 | 0.28 |
| | Not specified | 0.26 | 1.64 | 0.80 to 3.37 | 0.18 |
| **Histological grade** | | | | | 0.08 |
| | Grade 1 | 0.52 | 1 | | |
| | Grade 2 | 0.40 | 1.47 | 0.67 to 3.19 | 0.33 |
| | Grade 3 | 0.23 | 2.29 | 1.07 to 4.90 | 0.03 |
| **Multifocality** | | | | | 0.02 |
| | No | 0.14 | 1 | | |
| | Yes | 0.42 | 2.08 | 1.14 to 3.80 | |

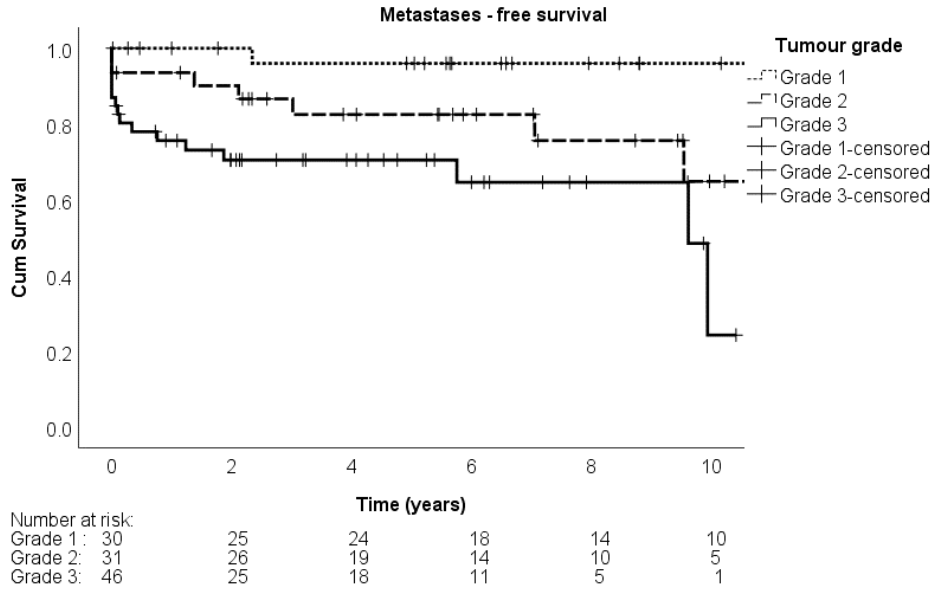



**Figure 15. Metastases-free survival by tumor grade in 107 patients with retroperitoneal liposarcoma.**

**Table 13. Metastases-free survival in 107 patients with retroperitoneal liposarcoma.**

| | | 5-year metastases-free survival | Hazard Ratio | 95% CI | p |
|---|---|---|---|---|---|
| **Histological subtype** | | | | | 0.18 |
| | Lipoma-like | 0.86 | 1 | | |
| | De-differentiated | 0.82 | 0.27 | 0.05 to 1.48 | 0.27 |
| | Myxoid | 0.33 | 2.28 | 0.28 to 18.38 | 0.44 |
| | Pleomorphic | 0.73 | 0.41 | 0.08 to 1.17 | 0.29 |
| | Not specified | 0.83 | 0.3 | 0.08 to 1.12 | 0.09 |
| **Histological grade** | | | | | 0.02 |
| | Grade 1 | 0.96 | 1 | | |
| | Grade 2 | 0.83 | 4.30 | 0.67 to 27.47 | 0.12 |
| | Grade 3 | 0.71 | 16.47 | 2.23 to 121.7 | <0.01 |
| **Resection margins** | | | | | 0.02 |
| | R0 | 0.83 | 1 | | |
| | R1 | 0.89 | 0.45 | 0.09 to 2.34 | 0.34 |
| | R2 or no resection | 0.64 | 1.61 | 0.44 to 5.89 | 0.48 |
| **Radiotherapy** | | | | | |
| | No | 0.86 | 1 | | |
| | Yes | 0.51 | 1.95 | 0.67 to 5.65 | 0.22 |
| **Chemotherapy** | | | | | |
| | No | 0.88 | 1 | | |
| | Yes | 0.41 | 3.03 | 1.15 to 7.98 | 0.03 |

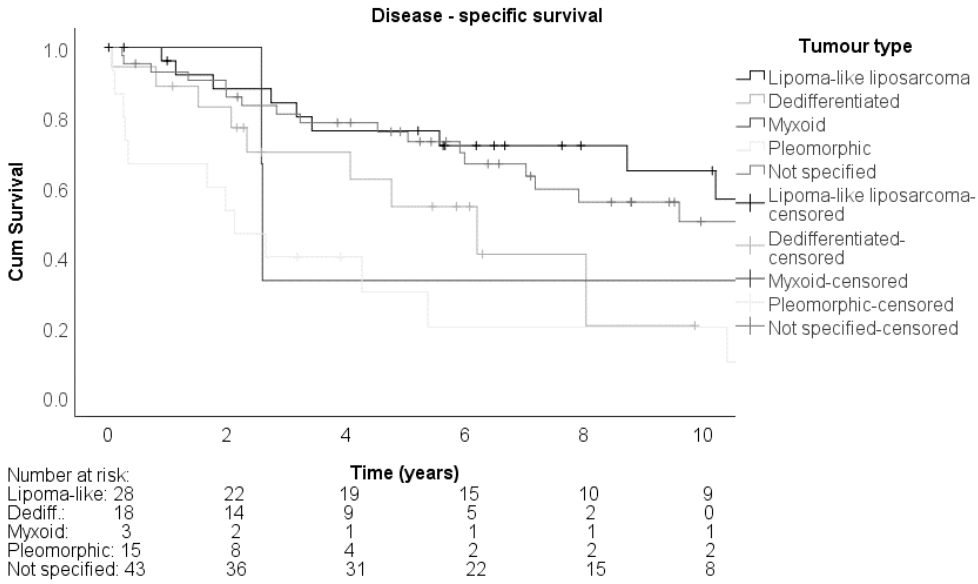



**Figure 16. Disease-specific survival by histological tumor type in 107 patients with retroperitoneal liposarcoma.**

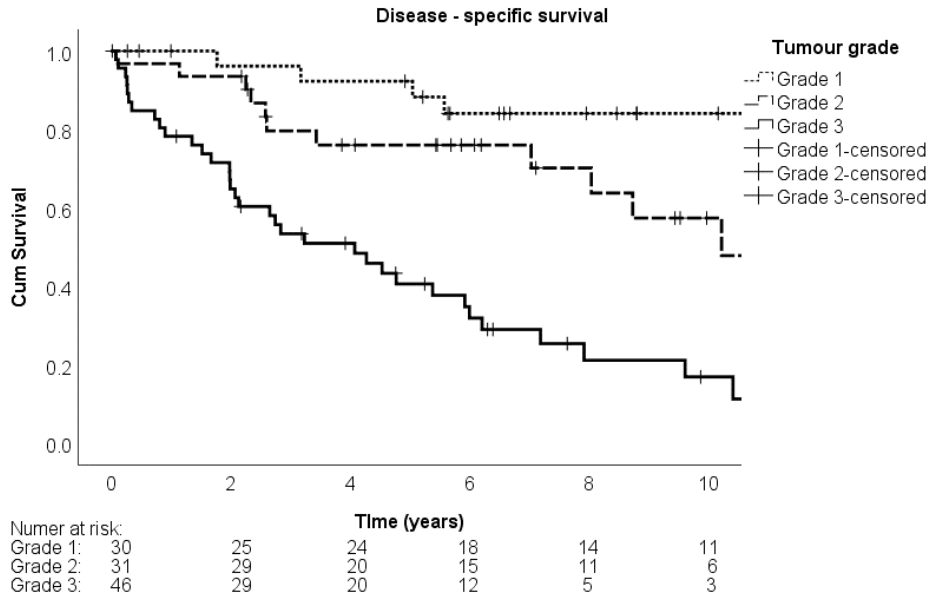



**Figure 17. Disease-specific survival by tumor grade in 107 patients with retroperitoneal liposarcoma.**

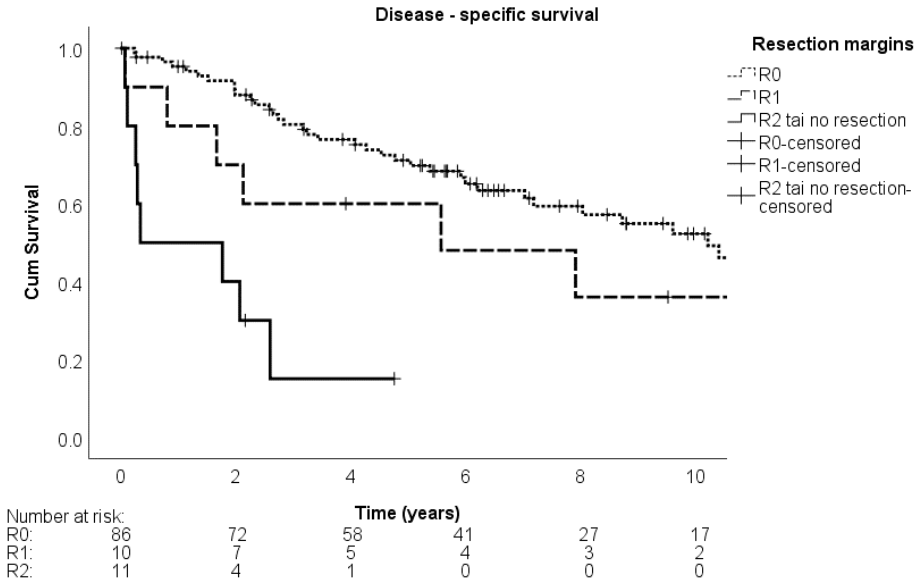



**Figure 18. Disease-specific survival by resection margins in 107 patients with retroperitoneal liposarcoma.**

**Table 14. Disease-specific survival in 107 patients with retroperitoneal liposarcoma.**

| | | 5-year disease - specific survival | Hazard Ratio | 95% CI | p |
|---|---|---|---|---|---|
| **Histological subtype** | | | | | 0.04 |
| | Lipoma-like | 0.76 | 1 | | |
| | De-differentiated | 0.55 | 0.26 | 0.08 to 0.82 | 0.02 |
| | Myxoid | 0.33 | 0.39 | 0.07 to 2.39 | 0.31 |
| | Pleomorphic | 0.30 | 0.44 | 0.14 to 1.40 | 0.16 |
| | Not specified | 0.76 | 0.23 | 0.09 to 0.63 | <0.01 |
| **Histological grade** | | | | | <0.01 |
| | Grade 1 | 0.92 | 1 | | |
| | Grade 2 | 0.76 | 9.13 | 2.38 to 35.07 | <0.01 |
| | Grade 3 | 0.41 | 29.42 | 6.68 to 129.6 | <0.01 |
| **Resection margins** | | | | | <0.01 |
| | R0 | 0.71 | 1 | | |
| | R1 | 0.60 | 1.82 | 0.74 to 4.45 | 0.19 |
| | R2 or no resection | 0.15 | 4.17 | 1.69 to 10.31 | <0.01 |
| **Radiotherapy** | | | | | |
| | No | 0.70 | 1 | | |
| | Yes | 0.40 | 1.16 | 0.50 to 2.69 | 0.73 |
| **Chemotherapy** | | | | | |
| | No | 0.74 | 1 | | |
| | Yes | 0.16 | 1.71 | 0.74 to 5.93 | 0.17 |
| **Metastases at diagnosis** | | | | | |
| | No | 0.70 | 1 | | |
| | Yes | 0.13 | 1.70 | 0.62 to 4.65 | 0.30 |
| **Age** | | | 1.02 | 1.00 to 1.05 | 0.08 |

## 9.3 STUDY III

Ten patients with primary presentation of a retroperitoneal soft tissue sarcoma, six patients with a disease recurrence and one patient with a suspected disease recurrence were included. The median age at operation was 59 (26-70) years. Details of the patients and tumors are in table 5. The median follow-up time was 27 (0-82) months.

### 9.3.1 HISTOPATHOLOGY

Ten patients had leiomyosarcoma, five had liposarcoma, one had undifferentiated pleomorphic sarcoma, and one had an epithelioid angiosarcoma. One patient with resection of a leiomyosarcoma two years earlier was operated on for a suspected intravascular recurrence in the inferior vena cava (IVC), but only thrombosis and scar tissue were found in the histological examination.

A wide resection margin, defined as a tumor-free margin of at least 2.5 cm or marginal margin was achieved in 14 (86% of the patients with a tumor).

### 9.3.2 PERIOPERATIVE COMPLICATIONS

All but one patient were treated in the intensive care unit for three (0-9) days postoperatively.

Two patients had minor, Clavien-Dindo class 1 and 2 complications while five patients had complications of higher class (Table 15). Patient 1 had transient chylous leak and a urinary tract infection. Patient 2 underwent thrombectomy for IVC homograft, had acute kidney injury requiring dialysis, and had melaena with no bleeding visible on gastro- or colonoscopy. Patient 3 had thrombectomy and stenting of iliac vein autologous vein graft. Patient 10 underwent relaparotomy for haemorrhage on the eighth post-operative day. Patient 15 had spinal ischaemia resulting in paraparesis that had not resolved by the discharge from hospital. Patient 16 had transient chylous leak as well as persistent diarrhoea attributed to disturbed enteral nervous system function. Patient 17, who had aortic reconstruction with polyethylene, underwent thrombectomy and embolectomies combined with bilateral lower leg fasciotomies due to early thrombosis. This patient was known to have resistance to activated protein C.

The perioperative 30-day mortality was zero. Two patients were lost to follow-up after being transferred for further care and follow-up at their local hospital on the seventh postoperative day. However, they both were alive according to the Finnish population register at the time of data collection, two and seven years after the operation.

### 9.3.3 VASCULAR COMPLICATIONS ON FOLLOW-UP

Two of the nine patients with IVC reconstruction had late IVC thrombosis with minor symptoms and no intervention was required. Two further patients had IVC obstruction caused by local tumor recurrence. Patient 17 who had aortic graft thrombosis in the early post-operative period had further graft thrombosis 19 months after the operation. Embolectomy and stenting were performed, and the graft remained open for the remainder of the follow up. Three of the patients did not have imaging studies to assess graft patency on follow-up. (Table 15)

**Table 15. Surgical outcomes, vascular complications on follow-up and oncological outcomes for retroperitoneal sarcoma resections and vascular reconstructions.**

| | Resection margins | Vascular invasion | Vascular complication on follow-up | Follow-up time (months) | State at the end of follow-up |
|---|---|---|---|---|---|
| Patient 1 | M | Yes | IVC thrombosis, minor sympoms. | 41 | Free |
| Patient 2 | M | No | IVC thrombosis, thrombectoy on 1st postoperative day. | 10 | Living with |
| Patient 3 | M | No | Iliac thrombosis, thrombectomy and stent on 5th postoperative day. | 22 | Dead of |
| Patient 4 | M | Yes | | 11 | Free |
| Patient 5 | M | Yes | | 54 | Free |
| Patient 6 | M | Arises from IVC | Graft thrombosis, minor sympoms | 1 | Living with |
| Patient 7 | IL | No | | 0.2 | Free |
| Patient 8 | M | Yes | | 54 | Living with |
| Patient 9 | W | No | | 15 | Free |
| Patient 10 | M | Arises from IVC | | 72 | Free |
| Patient 11 | M | Not specified on PAD | | 12 | Dead of |
| Patient 12 | M | No | | 43 | Dead of |
| Patient 13 | M | No | | 45 | Living with |
| Patient 14 | W | No | | 66 | Dead of |
| Patient 15 | M | No invasion into aorta; IVC not specified on PAD | | 0.2 | Free |
| Patient 16 | M | Arises from aorta | | 16 | Free |
| Patient 17 | Not applicable | Not applicable | IVC thrombosis, thrombectomy and lower leg fasciotomies on 1st postoperative day. | 10 | Living with |

### 9.3.4 TREATMENT RESULTS

In the patients with sarcoma resection, local recurrence developed in six patients with an estimated median local relapse-free time of 43 months. The three-year local-relapse-free survival rate was 61% (Figure 19). Metastases were present at the time of surgery in three patients and four additional patients developed metastases during follow-up. Estimated median and 3-year metastasis-free survival were 48 (20-76) months and 68%, respectively (Figure 20).

The estimated median and three-year disease-free survival time for the sarcoma resection patients were 35 (0-74) months and 46%, respectively (Figure 21). Two patients had the metastases resected in a later operation and remained disease free thereafter. Patient 5 with leiomyosarcoma grade 3 had liver metastases resected at 47 months and was disease free at 54 months while patient 10 with undifferentiated pleomorphic sarcoma G3 was disease free at 72 months after having pulmonary metastases resected at 10 months. At the end of the follow-up, eight (47%) patients were disease free, four (24%) were living with sarcoma and five (29%) had died of the disease.

The three-year survival was 80%, and the estimated median survival 66 months. All deaths during follow-up were due to sarcoma. The five patients who died had local recurrence, with three having had the vascular reconstruction as part of a resection of an already recurrent tumor. One of the patients dying with recurrent disease also had metastases at time of surgery and one developed metastases during follow-up.

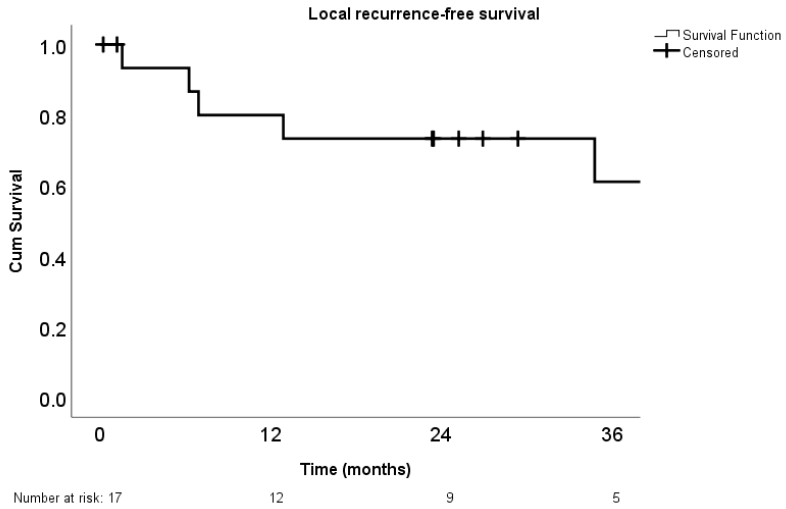



**Figure 19. Local recurrence-free survival for patients with intra-abdominal or retroperitoneal sarcoma following oncovascular surgery.**

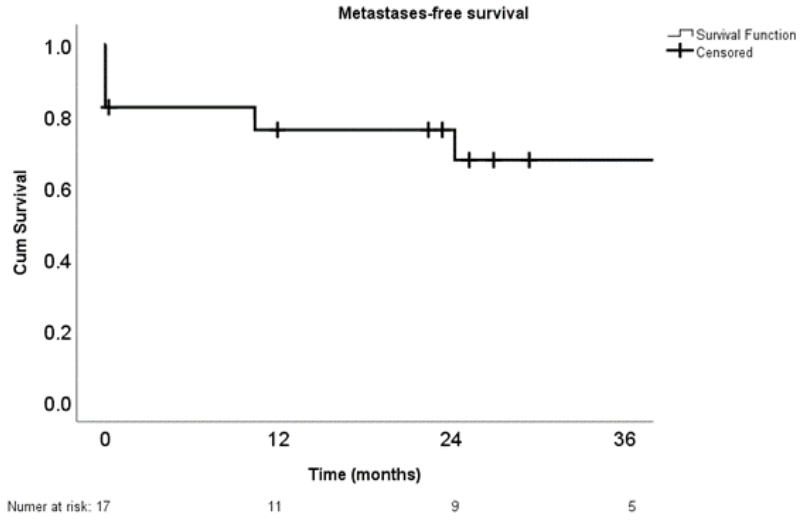



**Figure 20. Metastases-free survival for patients with intra-abdominal or retroperitoneal sarcoma following oncovascular surgery.**

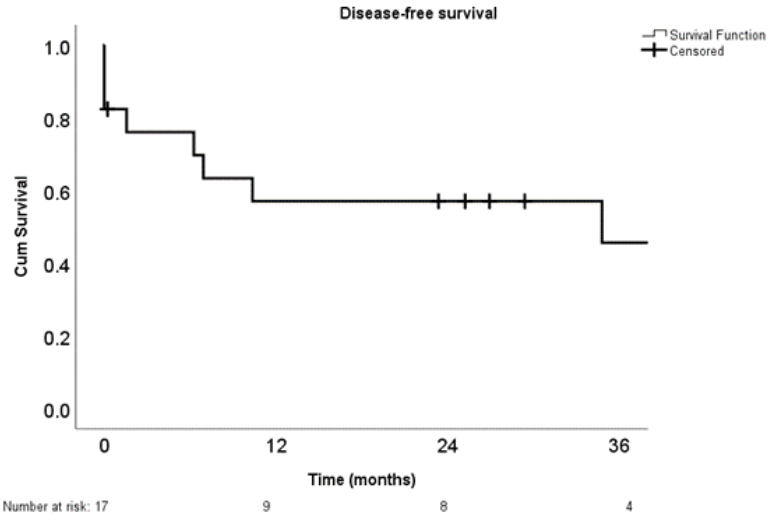



**Figure 21. Disease-free survival for patients with intra-abdominal or retroperitoneal sarcoma following oncovascular surgery.**

### 9.3.5 SYSTEMATIC REVIEW OF LITERATURE

Thirty-seven articles were included in the systematic review on vascular reconstructions in patients with retroperitoneal sarcoma (Table 16). The median number of eligible patients per article was 2 (1-17) and 19 (51%) articles included only one eligible patient. Fifteen patients (14%) had other vessel reconstructions in conjunction with the IVC reconstruction. Five of these patients had aortic reconstructions while the others had one or both renal veins reconstructed. Details of the tumor type, histological margins, and perioperative complications are in table 17.

The majority of patients (58%) remained disease free during a follow-up of 0 to 181 months. Local recurrence or metastases were reported in 47 (43%) of patients. The time of disease recurrence was not reported with sufficient consistency to allow for formal survival analysis. Eight (7%) patients died of sarcoma. The estimated three-year overall survival was 94%.

Graft occlusion was reported in 14 (13%) patients. No graft patency data was reported for 20 patients. The estimated three-year patency for the grafts was 82%.

#### *9.3.5.1 IVC reconstructions*

IVC was the most common vessel reconstructed with 103 reconstructions reported. The reconstruction was done with an interposition graft in 90 (87%) patients. Polytetrafluoroethylene (PTFE) was the most common graft material, either ring-reinforced (46 patients (45%)) or without support (22 patients (21%)). Polyethylene terephthalate grafts (10 patients (10%)), homograft (10 patients (10%)) and grafts fashioned from autologous vein (2 patients (2%)) were less frequent. Patch reconstruction was used in 13 (13%) patients.

The range of follow-up for all patients with IVC reconstructions was 0 to 181 months. Data on graft patency was reported for 73 patients (71%), including patients in whom the assessment of graft patency relied on clinical status alone. The range grafts were reported open was 0 to 72 months. Twelve (16%) graft occlusions were identified during follow-up. These included one ring expanded PTFE graft that occluded in the presence of infection 16 days postoperatively following a duodenal leak. In addition, partial graft occlusion was reported in two patients with PTFE grafts, one of which was reinforced.

The number of patients included in this review is too small to allow for comparison of occlusion rates in the various graft types. Further, the absence of imaging data during follow-up may have resulted in underreporting of asymptomatic occlusions. Data on IVC patency was available for 11 (85%) of patch repaired IVC. Only one IVC, patch repaired with polyethylene, occluded during follow-up. One partial IVC stenosis related to patch repair with peritoneum was also reported. (Table 18)

**Table 16. Articles included in the systematic review on vascular reconstructions in patients with retroperitoneal sarcoma.**

| Authors | Year | City | Number of patients total | Number of patients with sarcoma | Time period for the patients | Follow up (months, median (range)) |
|---|---|---|---|---|---|---|
| Alkhalili et al | 2016 | New Mexico | 2 | 2 | 2013-2016 | 18 (1-36) |
| Anaya-Ayala et al | 2011 | Houston | 1 | 1 | 2011 | 2 |
| Angiletta et al | 2001 | Bari, Italy | 1 | 1 | not stated | 36 |
| Arii et al | 2003 | Tokyo | 11 | 1 | 1990-2001 | 11 |
| Bower et al | 2000 | Washington, USA | 29 | 17 | 1990-1999 | 31 (0-72) |
| Brown et al | 2015 | Sydney, Australia | 1 | 1 | not stated | 5 |
| Caldarelli et al | 2002 | Pisa, Italy | 7 | 3 | 1991-2001 | 24 (12-28) |
| Caso et al | 2008 | Tampa, Florida, USA | 18 | 1 | 1999-2008 | 6 |
| Cho et al | 2008 | Pittsburgh, USA | 9 | 3 | 1990-2008 | 30 (12-181) |
| Coppa et al | 2013 | Milan, Italy | 5 | 1 | 2005-2011 | 50 |
| Coubeau et al | 2017 | Brussels, Belgium | 4 | 3 | 2015 | 4 (4-4) |
| DuBay et al | 2009 | Toronto, Canada | 1 | 1 | not stated | 3 |
| Fiore et al | 2012 | Milan, Italy | 15 | 11 | 2004-2011 | 20 (2-62) |
| Gage et al | 2012 | New York, USA | 1 | 1 | not stated | 15 |
| Grimaldi et al | 2019 | Rome, Italy | 4 | 1 | 2009-2017 | 74 |
| Guerrero et al | 2007 | Houston, USA | 1 | 1 | not stated | 14 |
| Hardwigsen et al | 2005 | Marseille, France | 5 | 4 | 1995-2000 | 41 (20-52) |
| Hardwigsen et al | 2001 | Marseille, France | 14 | 2 | 1992-1998 | 20 (20-20) |
| Hirohashi et al | 2002 | Oska, Japan | 1 | 1 | 1996 | 69 |
| Ito et al | 1998 | Nagoya, Japan | 1 | 1 | not stated | 18 |
| Kato et al | 2013 | Sapporo, Japan | 23 | 1 | 1984-2011 | 9 |
| Kraybill et al | 1997 | Washington, USA | 3 | 3 | 1993-1994 | 19 (1-26) |
| Kwon et al | 2003 | Seoul, Korea | 4 | 4 | 1999-2002 | 24 (61) |
| Kyriazi et al | 2010 | Athens, Greece | 2 | 1 | not stated | 36 |
| Liu et al | 2018 | Peking, China | 10 | 8 | 2009-2017 | 46 (10-67) |
| Mann et al | 2012 | Washington, USA | 17 | 8 | 1984-2009 | 50 (18-125) |
| Nayyar et al | 2010 | New Delhi | 2 | 2 | not stated | 8 (6-9) |
| Ohman et al | 2013 | Houston, USA | 1 | 1 | not stated | 0 |
| Sarkar et al | 1998 | Los Angeles, USA | 10 | 7 | 1993-1997 | 18 (7-48) |
| Stauffer et al | 2008 | Jacksonville, USA | 1 | 1 | not stated | 12 |
| Suzman et al | 2000 | New York, USA | 1 | 1 | not stated | 1 |
| Tameo et al | 2010 | Philadelphia, USA | 2 | 2 | not stated | 10 (4-16) |
| Teixeira et al | 2017 | Sao Paulo, Brazil | 7 | 4 | 2007-2013 | 48 (38-57) |
| Teo et al | 2005 | Singapore | 4 | 1 | 2002 | 18 |
| Wachtel et al | 2015 | Philadelphia, USA | 6 | 6 | 2005-2013 | 43 (12-108) |
| Wang et al | 2012 | Changchun, China | 2 | 2 | not stated | 18 (9-27) |
| Wise et al | 2012 | Rochester, USA | 1 | 1 | not stated | 0 |

**Table 17. Tumor type, resection margins and perioperative complications in previously published patients who had undergone vascular reconstruction during resection of a retroperitoneal soft tissue sarcoma.**

| | | Number of patients (%) |
|---|---|---|
| **Histological type** | Leiomyosarcoma | 95 (87) |
| | Liposarcoma | 8 (7) |
| | Rhabdomyosarcoma | 3 (3) |
| | Fibrosarcoma | 1 (1) |
| | Malignant fibrous histiocytoma | 1 (1) |
| | Synovial sarcoma | 1 (1) |
| **Resection margin** | Negative | 62 (56) |
| | Positive | 11 (10) |
| | Not stated | 37 (34) |
| **Clavien-Dindo class** | None | 59 (54) |
| | 1 | 4 (4) |
| | 2 | 9 (8) |
| | 3 | 15 (14) |
| | 4 | 3 (3) |
| | 5 | 1 (1) |
| | Not stated | 19 (17) |

**Table 18. Details of IVC reconstructions in review patients.**

| Graft type | n (%) | Follow-up (months, range) | Patency info available (n) | Graft occlusion n (% of those for whom info available) | Graft reported patent until (months, range) |
|---|---|---|---|---|---|
| **All** | 103 (100) | 0-181 | 84 | 13 (15) | 0-106 |
| ***Grafts*** | | | | | |
| PTFE, ringed | 46 (45) | 0-72 | 38 | 4 (11) | 0-72 |
| PTFE | 22 (21) | 1-85 | 15 | 2 (14) | 1-67 |
| Polyethylene | 10 (10) | 12-181 | 8 | 3 (38) | 3-57 |
| Homograft | 10 (10) | 2-62 | 10 | 3 (30) | 2-62 |
| Autologous vein | 2 (2) | 3-5 | 2 | 0 | 3-5 |
| ***Patches*** | | | | | |
| PTFE | 2 (2) | 13-36 | 1 | 0 | 13 |
| Polyethylene | 1 (1) | 9 | 1 | 1 (100) | 0 |
| Autologous vein | 2 (2) | 106-125 | 1 | 0 | 106 |
| Peritoneum | 4 (4) | 1-4 | 4 | 0 | 1-4 |
| Bovine pericardium | 4 (4) | 2-51 | 4 | 0 | 0-51 |

#### *9.3.5.2 Aortic reconstructions*

Reconstruction of the aorta was reported for six patients with polyethylene as the most common (83%) graft material (Table 19). Two of the reconstructions were from suprarenal level down to bifurcation while the other four were infrarenal. No superior mesenteric artery or renal artery reconstructions were done in these patients. Five of the reconstructions were done in conjunction with IVC reconstructions.

No perioperative complications were reported for four of the patients. One patient had persistent left chylothorax, which was treated with a pleurovenous shunt, as well as persistent diarrhea. One had persistent diarrhea. No graft occlusions were reported. The follow-up range was 0 to 26 months.

#### *9.3.5.3 Renal vein reconstructions*

Renal vein reconstruction was reported for ten patients in six publications (Table 19). Nine of these were done in conjunction with IVC reconstruction. Various materials were used and material for the repair done without concomitant IVC reconstruction was not specified.

One occlusion of a PTFE graft at 24 months was reported. No perioperative complications were reported for six of the patients. Three patients had relaparotomies for hemorrhage. One patient had a Clavien-Dindo class 2 complication, not further specified. The follow-up range was 4 to 66 months.

#### *9.3.5.4 Iliac artery and vein reconstructions*

Iliac vessel reconstruction without IVC reconstruction was reported for four patients in two publications (Table 19*)*. No other vascular reconstructions were done for these patients. One series included three patients in whom ring reinforced PTFE grafts were used. Spiral autologous vein was used in the fourth patient.

One of the patients had postoperative ileus that resolved with conservative management. No other perioperative complications were reported. The follow-up range was 5 to 28 months. Two of the three PTFE grafts occluded, at 6 and 10 months.

#### *9.3.5.5 Other reconstructions*

Reconstruction of the superior mesenteric vein and the portal vein with an autologous vein patch was reported in one patient with leiomyosarcoma of the splenic vein. A 15-month follow-up was reported for this patient, but no details of the vein patency or oncological outcome were specified.(Gage et al. 2012) Notably,

no reconstructions of other visceral arteries, such as the superior mesenteric artery or the renal arteries, were described.

## 9.4 STUDY IV

Eight patients with soft tissue sarcoma resection in the thigh necessitating vascular reconstructions were included in the study. The median age at operation was 59 (19-77) years (Table 19).

### 9.4.1 HISTOPATHOLOGY

Six patients were treated for a primary tumor; three leiomyosarcomas, one myxoid liposarcoma, one myoepithelioma and one alveolar soft tissue sarcoma (Table 19). The patient number 4 had a recurrent leiomyosarcoma treated three years earlier with marginal excision and postoperative radiotherapy. The patient number 8 was now operated on for synovial sarcoma metastases after having had the primary tumor, located then at the distal thigh, treated with wide excision already 35 years ago. No local recurrence had been detected but inguinal lymph node metastases have been resected 29 years ago and again 8 months prior to this presentation. The patient number 3 had small, stable lung metastases at time of surgery while the other patients had local disease.

The histological resection margin was wide or marginal in seven patients and intralesional in one. In addition, surgical site contamination with the tumor occurred during the operation on the patient number 8.

### 9.4.2 PERIOPERATIVE COMPLICATIONS

Five of the patients required a second operation within the 30-day perioperative period and four patients later on for postoperative complications. Three of the patients required more than one additional operation. (Table 6)

An additional flap was done in three patients, two for complications related to lymphatic collections and one in the context of a surgical site infection. This included the patient number 5 who did not have a flap as part of the primary operation. The patient number 8 required repeat thrombectomies to the graft vein without long-term patency, despite the use of venous compression devices and high dose low molecular weight heparin.

**Table 19. Patient demographics, treatment and follow-up details of lower limb soft tissue sarcoma patients treated with vascular and soft tissue reconstructions by Helsinki University sarcoma team from 2014 to 2020. F = female; M = male. *Time of metastases detection reported in brackets. **Postoperative chemotherapy was not given due to delayed wound healing.**

| ID | Age (years) sex | Tumor | Resection margins | Adjuvant treatment | Length of follow-up (months) | Status at the end of follow-up* |
|---|---|---|---|---|---|---|
| Patient 1 | 77 M | Leiomyosarcoma G3 T2N0M0 | Intralesional | Preoperative radiotherapy | 73 | Alive with metastases (24 months) |
| Patient 2 | 58 F | Leiomyosarcoma G3 T1N0M0 | Marginal | Preoperative radiotherapy** | 48 | Alive with metastases (37 months) |
| Patient 3 | 59 M | Leiomyosarcoma G3 T2N0M1 | Marginal | Postoperative radiotherapy | 43 | Alive with metastases |
| Patient 4 | 53 F | Leiomyosarcoma G3 recurrence T1N0M0 | Marginal | None | 36 | Death from metastatic disease (13 months). Local recurrence resected at 13 months. |
| Patient 5 | 29 M | Myoepithelioma GX T3N0M0 | Marginal | Postoperative radiotherapy | 44 | Alive, no evidence of disease |
| Patient 6 | 67 M | Myxoid liposarcoma G2 T2N0M0 | Marginal | Preoperative radiotherapy | 30 | Alive, no evidence of disease |
| Patient 7 | 19 M | Alveolar soft tissue sarcoma GX T2N0M0 | Wide | None | 6 | Alive, no evidence of disease |
| Patient 8 | 75 M | Synovial sarcoma metastases | Marginal | Postoperative radiotherapy | 2 | Alive, no evidence of disease |

### 9.4.3 PATENCY OF VASCULAR GRAFTS ON FOLLOW-UP

Assessment of femoral or iliac graft patency with duplex ultrasound was available for seven patients out of eight, with a follow up of 48 (2 – 76) months (Table 20). Five (71%) of the vein grafts had thrombosed. These included both of the autologous vein grafts and three of the five allografts. The twelve-month patency rate for the venous grafts was 50 ± 18%.

Five of the arterial grafts remained patent during follow-up. The arterialized autologous vein graft of patient 3 had obstructed at 19 months, and, after an unsuccessful angioplasty, a new arterial bypass graft was done. The new graft was found obstructed with sufficient collateral circulation to maintain leg vitality at 23 months. At the 48-month follow-up, he reported a claudication distance of 40 meters. The patient number 5 had several angioplasties for the arterial allograft

starting at 7 months. At 48 months the graft was again found stenosed and an angioplasty was programmed. With the above interventions, the achieved twelve-month patency rate for the arterial grafts was 100% and 24-month patency rate 83 ± 15%.

### 9.4.4 FUNCTIONAL OUTCOMES

The postoperative functional outcome was assessed clinically for six patients at 48 (6 – 76) months (Table 20). Three of the patients had oedema with more than 10 % volume increase in comparison with the non-operated leg, one despite appropriate use of compression garments. Reflecting an acceptable functional outcome, the median MSTS score was 70 (43 – 87)% and TESS 90 (75 – 100)%. Only patient 2 had an abnormal gait and used a crutch.

**Table 20. Graft patency and functional outcomes for patients with soft tissue sarcoma who underwent tumor removal and vascular reconstruction *Volume difference in comparison with the non-operated side. **Lost to follow-up. ***Only discharged from hospital at time of writing. Venous graft obstructed on postoperative day 33, artery patent.**

| ID | Time from surgery (months) | Graft patency | Edema* | Compressive sock use / Appropriate | MSTS | TESS | Gait |
|---|---|---|---|---|---|---|---|
| Patient 1 | 76 | Artery patent, vein obstructed at 4 months | 14 % | Yes / No | 80 % | 85 % | Normal |
| Patient 2 | 52 | Artery patent, vein obstructed at 23 months | 13 % | Yes / Yes | 43 % | 75 % | Unsteady, uses a crutch |
| Patient 3 | 48 | Artery obstructed at 21 months, vein patent | 2 % | No / No | 70 % | 89 % | Normal. Claudication at 40 m |
| Patient 4 ** | | | | | | | |
| Patient 5 | 48 | Artery stenosed, vein obstructed at 6 months | 144 % | Yes / Yes | 70 % | 90 % | Normal |
| Patient 6 | 33 | Artery and vein patent | 23 % | Yes / No | 70 % | 100 % | Normal |
| Patient 7 | 6 | Artery patent, vein obstructed since last assessment | 3 % | No / No | 87 % | 91 % | Normal |
| Patient 8 *** | | | | | | | |

# 10. DISCUSSION

## 10.1 METASTATIC PATTERN OF MYXOID LIPOSARCOMAS AND ITS IMPLICATIONS FOR IMAGING DURING DISEASE STAGING AND FOLLOW-UP

The metastatic disease is more common in MLS than other types of liposarcoma, with 15-44% of patients been diagnosed with metastatic disease by five years from diagnosis.(Guadagnolo et al. 2008, Haniball et al. 2011, Muratori et al. 2018, Gouin et al. 2019) While the disease has, overall, a fairly good prognosis with 10-year disease-specific survival of 56-87%, the development of metastases is associated with a significantly reduced prognosis. (Zagars et al. 1996, Spillane et al. 1999, ten Heuvel et al. 2007, Guadagnolo et al. 2008, Haniball et al. 2011, Hoffman et al. 2013, Muratori et al. 2018)

The metastatic pattern of MLS is particularly interesting as, unlike for other liposarcomas and most soft tissue sarcomas, extrapulmonary metastases are common in MLS.(Estourgie et al. 2002, Pitson et al. 2004, Guadagnolo et al. 2008, Chung et al. 2009) In our patient population, uniquely containing only patients with confirmed pathognomonic gene translocation, seven (22%) of the patients developed metastatic disease. Five of them, 16% of all patients, had abdomen as the first location of metastases with only one patient having lung metastases combined with pleural disease. This distribution of metastases is in line with the pattern observed in the 1835 MLS patients included in the systematic review, except for our patients having a larger portion of the metastases intra-abdominally. It is, however, possible that the stringent inclusion criteria applied to our patient series resulted in an inappropriate exclusion of some MLS patients with degraded tumor samples or gene fusion variants not detected by the sequencing probes, thus impacting the distribution of metastases observed in our population. In the present review patients, metastases were first detected in the soft tissues in 32%, intra-abdominally, including the retroperitoneum, in 26% and in bone in 17%. Several metastases were discovered simultaneously in 26%.(Smith et al. 1996, Zagars et al. 1996, Spillane et al. 1999, ten Heuvel et al. 2007, Guadagnolo et al. 2008, Sheah et al. 2008, Chung et al. 2009, Haniball et al. 2011, Moreau et al. 2012, Hoffman et al. 2013, Baxter et al. 2015, Gouin et al. 2019, Shinoda et al. 2020, Visgauss et al. 2021) No association was observed between the location of the primary tumor and the first metastases in our patients or the review series, pointing to likely hematologic spread, independent of vascular anatomy.(Smith et al. 1996, Spillane et al. 1999, ten Heuvel et al. 2007, Sheah et al. 2008)

Lungs or pleura were the single first site of metastases in only 24% of the review patients, with most of the series not specifying whether the metastases were in fact in the lungs or pleura. The distinction is important as resection of pulmonary

metastases with tumor-free margins is potentially curative in patients with soft tissue sarcoma.(Nevala et al. 2019) Incomplete surgical removal, on the other hand, does not convey better disease-free survival than chemotherapy.(Nevala et al. 2019, Nakamura et al. 2021) The surgery can be considered for patients with sufficient performance status and no active disease at the primary tumor site. In addition, the metastatic nodules need to be confined to the lung parenchyma, and be either singular or distributed in a manner that enables complete surgical resection. The presence of a single metastatic pulmonary lesion is associated with improved survival.(Chudgar et al. 2017, Nakamura et al. 2021) For our patient with primary metastases in the lungs and pleura, surgery was thus not an option.

Chest X-rays, or chest CT scans, are recommended during follow-up of soft tissue sarcomas, including MLS.(Gronchi et al. 2021) The aim of the follow-up is to detect treatable disease recurrence. For soft tissue sarcomas that tend to metastasize to lungs, the benefits of chest imaging are straightforward as it is likely to lead to the detection of metastatic disease. For MLS, chest imaging is used to detect resectable, and potentially curable metastatic disease. The benefit of early detection of extrapulmonary metastases remains under debate, as resection of the metastases, or adjuvant treatments, is not considered curative. However, patient series containing a range of soft tissue sarcomas, radical resection of extrapulmonary metastases has resulted in encouraging medium-term disease control.(Marudanayagam et al. 2011, Wigge et al. 2018, Gronchi et al. 2021)

With abdomen being the most common anatomical region of metastases in MLS, Inclusion of abdominal CT scans in the staging and follow-up imaging of patients with myxoid liposarcoma has been proposed.(Estourgie et al. 2002, Chung et al. 2009) However, conventional abdominal CT scans involve a significant radiation exposure. In addition, abdominal scans do not capture the, also frequent, soft tissue metastases in the limbs, the chest and the head and neck region.

Bone metastases of MLS present another challenge to imaging. Up to 90% of MLS metastases are not sclerotic, and thus difficult to detect with CT. (Visgauss et al. 2021) Bone scan and PET-CT have also been suggested to have a negative predictive power of only 88% and 85%, respectively, at detecting spinal metastases.(Schwab et al. 2007)

Whole-body MRI imaging has been proposed as a suitable imaging modality in the follow-up of MLS patients, detecting capturing soft tissue, visceral and bone metastases.(Schwab et al. 2007, Gorelik et al. 2018, Visgauss et al. 2021) However, no studies have yet demonstrated an improved disease-specific survival from the earlier detection of the metastases that whole-body MRI might bring. In addition, no consensus has been reached on the potentially beneficial frequency of the whole-body MRI. The literature review identified two centers that routinely use whole-body MRI in the standard follow-up of MLS patients.(Gouin et al. 2019, Visgauss et al. 2021) Most centers, including ours, have used MRI only in imaging of the primary tumor site for local recurrence.

Overall, more studies are needed on the potential overall and disease-free survival that early detection and treatment of MSL metastases might bring. Currently, the available data are insufficient to justify recommending the inclusion of abdominal or whole-body imaging to the routine follow-up of MLS patients. However, whole-body imaging may have a place during the staging of these patients.

## 10.2 PROGNOSTIC FACTORS FOR PATIENTS WITH INTRA-ABDOMINAL OR RETROPERITONEAL LIPOSARCOMA

Often intimately surrounded by abdominal viscera or retroperitoneal structures, abdominal and retroperitoneal, hereafter referred to as retroperitoneal, liposarcomas are particularly challenging to treat. Due to the location, the tumors often present late, having reached a size large enough to cause symptoms. In our patient population, 91% of the patients presented with symptoms and 57% of the tumors were over 20 cm in diameter. In addition, 9% of the tumors had invaded surrounding viscera.

For many retroperitoneal liposarcomas, radical resection of the tumor is not possible without the resection of affected viscera or major blood vessels. This presents a challenge as radical resection of the primary tumor is key to disease control in liposarcomas.(Lewis et al. 1998, Sampo et al. 2008, Bonvalot et al. 2009, Brennan et al. 2014, Toulmonde et al. 2014) In our series, microscopically negative margins were achieved in 79% of patients, with contiguous resection of one or more visceral organs in 61% of patients. Oncovascular reconstruction was done in 5%. The resection margins were predictive of disease-specific survival, with the actuarial five-year survival for patients who had not been operated on or had the tumor removed intralesionally 15%, a marked difference to 92% for patients with negative resection margins. The overall disease-specific survival, 65%, is similar to that reported by other large centers. centers.(Singer et al. 2003, Hassan et al. 2004, Vos et al. 2019) Microscopically positive resection margins, a situation where the all of the tumor had been macroscopically removed, were not associated with a worse disease-specific or local recurrence-free survival. Similar finding has been previously reported in a series involving a range of retroperitoneal soft tissue sarcomas.(Hassan et al. 2004) These findings support a surgical approach aiming at gross complete removal of the tumor, if the location of the tumor does not enable inclusion of boarder margins without damage to adjacent structures.

Radiotherapy is given preoperatively in our institute for gradus 2 or higher tumors to increase the likelihood of radical resection, and postoperatively for high grade tumors that have been resected intralesionally or with a narrow tumor-free margin. Overall, 9% of our patients received radiotherapy. The benefits of preoperative radiotherapy on disease-specific and local recurrence-free survival have been debated, with two large collaborative studies demonstrating no survival advantage from the treatment compared to surgery alone.(Lee et al. 2016, Chouliaras et al.

2019, Haas et al. 2019) However, a randomized multicenter, open-label trial suggested that, although radiotherapy does not convey survival advantage in most retroperitoneal sarcomas, the local recurrence of liposarcomas may be reduced with the treatment.(Bonvalot et al. 2020)

Histological grade was a second factor predictive of disease-specific survival in our population. The actuarial five-year disease-specific survival was 92% for grade 1 tumors, 76% for grade 2 tumors and 41% for grade 3 tumors. This is in line with previous reports identifying grade as a predictor of survival in retroperitoneal soft tissue sarcomas.(Lewis et al. 1998, Chouliaras et al. 2019) Univariate analysis suggested that higher grade is associated with a greater likelihood of local recurrence. The effect was not maintained in a multivariate analysis including also the histological subtype and multifocality. Of the 69 patients that developed one or more local recurrences, tumor dedifferentiation to a higher grade was observed in 17 (25%), in line with a previous report of 33% dedifferentiation rate observed in lipoma-like liposarcomas.(Fabre-Guillevin et al. 2006) Histological grade was additionally predictive of metastatic disease, with grade 3 tumors having a 16-fold higher risk of developing metastases than grade 1 tumors. A trend of higher grade retroperitoneal liposarcomas metastasizing more frequently has been observed also in other institutes.(Chouliaras et al. 2019)

Histological subtype was a third factor predictive of disease-specific survival in our population, a finding observed also in larger series of retroperitoneal soft tissue sarcomas.(Singer et al. 2003, Hassan et al. 2004) (Tan et al. 2016) It was also predictive of local recurrence on univariate analysis, but failed to reach significance in multivariate analysis that included tumor grade and multifocality. Histological subtypes of retroperitoneal liposarcoma have also been suggested to have different metastatic potential but we did not observe this. (Singer et al. 2003, Bonvalot et al. 2009, Chouliaras et al. 2019) Altogether, metastases in our patient group were rare, with a five-year metastases-free survival of 80%. In addition, our analysis of the effect of histological subtype was based on the original pathology reports and hindered by 40% of the tumors not having a subgroup specified in the report. Compared with most series, well-differentiated liposarcomas were underrepresented in our patients, with only 26% of the tumors classified in that, typically least aggressive, category. Three myxoid liposarcomas were included in the series, none of which were included in study I due to failure of the tissue samples to produce any result, positive or negative, on the gene analyses.

Multifocality of the tumor at time of diagnosis was the only factor predictive of local recurrence-free survival on multivariable analysis and was associated with two-fold increase in risk of recurrence. Of those who had the recurrence resected, 85% developed one or more further recurrences. This is similar to rates reported previously (60-84%) and supports the idea that development of multifocal disease in the peritoneum renders the disease poorly controllable with repeat surgeries. (Lewis

et al. 1998, Ikoma et al. 2018) Early surgery, in these situations, may not be the best treatment strategy.

## 10.3 SAFETY OF ONCOVASCULAR SURGERY IN THE TREATMENT OF SOFT TISSUE SARCOMAS

Emergence of oncovascular surgery has enabled surgical treatment of soft tissue sarcoma patients with involvement of retroperitoneal vessels and limb sparing surgery in patients with invasion of the common or superficial femoral vessels.(Fortner et al. 1977, Imparato et al. 1978, Schwarzbach et al. 2006) . Provided clear margins are achieved with the resection, the need for vascular resection is not associated with worse oncological prognosis.(Schwarzbach et al. 2006) Despite the first case reports of vascular reconstructions during soft tissue sarcoma resections being over thirty years old, the surgery is infrequent and most published series are small. The perioperative morbidity and mortality, and long-term patency rates of the vascular grafts have not been fully established.

The operations are long and undertaken by members of the oncovascular team, including a vascular surgeon with a gastrointestinal surgeon, in the case of retroperitoneal tumors, or with a plastic surgeon during lower limb surgery. The median operative time for retroperitoneal tumors was seven hours. The median blood loss during the operation was 3700 ml, with one patient losing over 13 l. All but one of the patients require postoperative care at the intensive care unit, for a median three days. For lower limb tumors, the median length of the operation was eight hours and the median blood loss 1565 ml. Typically the patients spent the first postoperative night at the intensive care unit.

The rate of postoperative complications observed in our patients was high. For the 17 patients undergoing retroperitoneal surgery, postoperative complications occurred in 41%. Two patients (12%) suffered major organ dysfunction with one requiring dialysis for acute kidney injury and another one developing paraparesis from spinal ischemia. Additional operations were done in 24% during the 30-day postoperative period. For 18% of the patients, the reason for additional surgery was graft occlusion. In the review population, postoperative complications occurred in 30%, reoperations were done in 3% and graft occlusion was detected in 14%, respectively.(Kraybill et al. 1997, Sarkar et al. 1998, Bower et al. 2000, Suzman et al. 2000, Hardwigsen et al. 2001, Hirohashi et al. 2002, Kwon et al. 2003, Hardwigsen et al. 2005, Guerrero et al. 2007, Cho et al. 2008, DuBay et al. 2009, Kyriazi et al. 2010, Nayyar et al. 2010, Tameo et al. 2010, Anaya-Ayala et al. 2011, Angiletta et al. 2011, Fiore et al. 2012, Wang et al. 2012, Wise et al. 2012, Kato et al. 2013, Ohman et al. 2013, Brown et al. 2015, Wachtel et al. 2015, Alkhalili et al. 2016, Coubeau et al. 2017, Teixeira et al. 2017, Liu et al. 2018) The perioperative mortality was, however, low with none of our patients and only one of the 110 review patients dying. These data suggest that even though oncovascular surgery in patients with retroperitoneal

sarcomas is associated with significant perioperative morbidity, many of the complications can be managed conservatively or with non-complicated reoperations.

Complications requiring surgery were common in our patients with sarcomas resected in the proximal thigh, all related directly to the surgical site. However, the limb salvage was successful in all eight patients. This is in line with the combined limb-salvage rate of 94 % reported in a recent review including 18 studies and 271 sarcoma patients with lower limb vascular reconstructions.(Fujiki et al. 2020) Five (63%) patients required a second operation during the 30-day postoperative period. Three of the re-operations were done for surgical site infection, two of these in the context of an infected seroma. Notably, the only two patients in whom a muscle flap coverage for the grafts was not judged necessary at the primary operation, developed sustained seroma collections at the resection cavity and underwent seroma revisions with muscle flap reconstructions after 64 and 105 days. No microvascular flap loss or partial necrosis was detected in our population, possibly reflecting the small number of patients included in the series, use of the reliable LD-flap, and the experience of the surgeons and the medical team in microvascular surgery.

The observation of increased wound healing issues, and reports of prolonged lymphatic collection despite meticulous ligation of the lymphatic vessels during the surgery, have shaped our practice to favor immediate flap reconstruction in the limbs, involving a pedicled or a microvascular flap is used to cover the vessel grafts and to fill the created cavity.(Ghert et al. 2005, Davis et al. 2017) The flaps are employed in primary surgery unless the grafts can be covered directly with surrounding muscles. When no pedicled flap of sufficient volume is available in the thigh, or preoperative radiotherapy has rendered the local flap less reliable, musculocutaneous LD is our preferred choice. The arterial inflow to the flap is often connected to the arterial graft, but a native vein is preferred for the venous outflow to minimize the circulatory compromise an obstructed venous graft would inflict on the microvascular flap.

Long-term patency of the vascular grafts has previously been poorly described and no consensus exists on the recommended frequency and modality of the imaging used for the grafts following oncovascular surgery. In the 110 patients with retroperitoneal vascular reconstructions included in the present review, patency of the graft at follow-up was reported for 90%. The combined estimated three-year patency for the grafts was 82%. Comparisons between graft materials were not possible due to the small number of patients and occlusions. Homografts have, however, been found to be associated with higher rates of occlusion.(Fiore et al. 2012, Ferraris et al. 2019) In line with this, three of the ten homografts in the review population occluded during follow-up. Our series had a relatively high number of homografts as they are the graft material of choice for contaminated clean field, in our unit and elsewhere.(Quinones-Baldrich et al. 2012, Brennan et al. 2014, Poultsides et al. 2015) In our patients, one of the five homografts occluded on day one and underwent thrombectomy with a sustained result. No late homograft

occlusions were observed. Two late IVC thrombosis were detected, one in an autologous vein graft and one following a bovine patch repair. One late thrombosis of an aortic graft was observed, in a patient who had aortic graft thrombosis treated for the first time already in early postoperative period. Analysis of factors influencing the risk of graft infection was not possible either, as only one infection was reported in the review population, and none occurred in our cohort.

The patency of the vascular grafts was assessed in seven of our patients with superficial femoral vessel reconstructions. The median follow-up, 48 months, was too short for assessment of a three-year patency. The two-year patency for the arterial grafts was 83%, including one patient who required repeat angioplasties for graft stenosis. The occlusion rate was higher for the vein grafts, with only two of the grafts patent at two years. The twelve-month patency rate for the venous grafts was 50%. Notably, six of the vein reconstructions were homografts, two of which remained patent on follow-up. The arterial graft patency rates we observed were similar to, but the venous graft rates worse than, those reported elsewhere for sarcoma patients.(Adelani et al. 2007, Nishinari et al. 2015, Poultsides et al. 2015, Okamoto et al. 2018, Fujiki et al. 2020, Berner et al. 2021) The risk factors for graft occlusion have not, to my knowledge, been studied in the context of sarcoma reconstruction, and our population was too small for any informative analysis on that. With arterial bypass grafts for arteriosclerosis, the graft patency is dependent on the distal vasculature, not properties of the graft.(Albäck et al. 1998) In addition, the long-term patency of venous grafts for arterial bypass in the femoral region supersedes that for PTFE grafts, supporting our preference for autologous grafts and homografts.(Klinkert et al. 2004)

At least mild limb edema was present in four out of our six patients evaluated. The presence or extent of edema is inconsistently reported in the literature for this patient group, with some series observing a degree of edema in all patients while others report edema only as a transient postoperative issue, minimized by venous reconstruction.(Ghert et al. 2005, Baxter et al. 2007, Umezawa et al. 2013, Nishinari et al. 2015, Berner et al. 2021) The etiology of the edema is likely to be multifactorial. Graft obstruction, or the decision not to reconstruct the vein, is likely to be a contributor in the early postoperative period, the impact dissipating if and when sufficient collateral circulation develops.(Adelani et al. 2007, Tsukushi et al. 2008, Fujiki et al. 2020) A second contributor is the disruption of the lymphatic pathways caused by the resection. One method proposed to enhance lymph flow recovery following tissue reconstruction is the placement of the flap in an orientation where pre-mapped lymphatic channels in the skin align axially with the lymphatic flow present at the defect site prior to resection, either with or without a lymphaticovenous anastomosis. (Yamamoto et al. 2018, Pereira et al. 2021, Scaglioni et al. 2021, Yamamoto et al. 2021, Scaglioni et al. 2022) While the microvascular flaps with a skin island are typically aligned in an orientation reflecting the likely path of the lymphatics, no preoperative lymphatic mapping or lymphaticovenous anastomosis are done in our practice.

The functional outcomes achieved with the vascular and soft tissue reconstructions in our patients with proximal thigh soft tissue sarcoma resections were good. Our patients scored high, median 90%, on the self-reported TESS that assesses the ability to perform tasks of daily living, suggesting that the patients did not feel limited by their leg function. The physician-assessed MSTS median score 70% reflected a slight impairment in the strength and mobility of the limb. The MSTS scores were slightly lower than previously reported scores, 83% and 85%, for patients with lower limb sarcomas requiring oncovascular surgery.(Emori et al. 2012, Davis et al. 2017)

The oncological outcomes of the resections were encouraging. For the patients with retroperitoneal tumors, resection with wide or marginal margins was achieved in 88% of our patients, in line with the 85% radical resection rate reported for the review patients. The three-year disease-free survival of our patients was 46%, with 35% developing a local recurrence during follow-up, and the sarcoma-related mortality was 29%. The oncovascular approach enabling radical resection is likely to have improved the disease-free survival in these patients, particularly since the benefits of radio- and chemotherapy are limited in this patient group. (Lewis et al. 1998, Sampo et al. 2008, Brennan et al. 2014, Toulmonde et al. 2014)

Of the eight patients with femoral tumors, resection with wide or marginal margins was achieved in seven. One local recurrence was detected at twelve months. One of the patients had metastatic disease already at the time of the operation and further three developed metastatic disease during follow-up. The median disease-free survival was 37 months. The patient with a local recurrence died with metastatic disease at 36 months. The median follow-up duration for the others was 30 (range 2 to 73) months. While the patient group is too small for comparison with previously published series, the disease course observed in these patients with advanced disease at time of surgery, together with the good performance status of the salvaged limb, imply a successful surgical strategy.

# 11. CONCLUSIONS

Study I

The single most frequent anatomical location for first metastases in MLS is the abdomen, in prevalence preceded by soft tissues around the body. Lungs are the first location in less than third of patients. Thus, imaging of only the primary tumor site and lungs is insufficient at detecting majority of the metastases and, as such, inadequate for primary staging.

Study II

Intra-abdominal or retroperitoneal liposarcomas tend to recur locally. Histological subtype and grade are significant predictors of survival for tumors resected with macroscopically clear margins. Multifocality is associated with poor survival.

Study III

Vascular reconstructions enable radical resection of advanced intra-abdominal and retroperitoneal tumors. The level of postoperative complications is acceptable. While longer follow-up data are needed to assess the long-term performance of the vascular reconstructions, oncovascular surgery enables operative treatment of these patients who were previously considered inoperable.

Study IV

Vascular reconstructions combined with microvascular reconstructions enable limb-sparing surgery in patients with soft tissue sarcoma involving the femoral vessels. The functional outcomes achieved for the reconstructed limb are good to excellent, justifying the complex surgery and early high morbidity.

# 12. ACKNOWLEDGEMENTS

There are several people who have been instrumental during the process of composing this dissertation.

My supervisor, professor emeritus Erkki Tukiainen, who offered me the research opportunity more years ago than I care to admit, and has been a source of inspiration and support ever since. Erkki's warm and considerate approach to his patients is one I aspire to emulate.

My supervisor, professor emeritus Carl Blomqvist, whose insight and constructive criticism have helped me improve my work tremendously. Carl's attention to detail has set the standard for my future scientific work.

My examiners, docent Ilkka Koskivuo and docent Matti Pokela, whose guidance on my dissertation led to an enhanced literature review and helped me to prepare for the public examination.

Professor Tom Böhling who, with awe-inspiring patience, introduced me to the world of liposarcomas. Tom's dedication to teaching, coupled with his kindness to his students is exemplary.

Docent Pirkka Vikatmaa, the senior author of the first published article contributing to this dissertation, whose proactive style and rapid feedback gave this project the impetus it desperately needed for completion. Pirkka's fortright attitude is one I aim to adopt with my students.

My other coauthors, who have advanced the care of the patients included in the studies: Plastic surgeon Dr. Juho Salo; vascular surgeons docent Ilkka Kantonen and docent Anders Albäck; gastrointestinal surgeons Dr. Ilkka Heiskanen and professor emeritus Ari Leppäniemi; anaesthesiologist docent Leena Vikatmaa; radiologist D. Kirsti Numminen; geneticist Dr. Anne Seitsonen; pathologists docent Mika Sampo and docent Mikko Rönty.

Professor Virve Koljonen, whose encouragement and focus helped me to complete this project.

Leena Caravitis, who, in addition to helping with the assessment of patients in study IV, has been irreplaceable in the progress of my research projects outside the scope of this dissertation. Outi Malkavaara, who located the patient files from around the country for me. Jaana Jäppinen, without whose help I would have struggled to start any of the research projects.

Docent Patrik Lassus, Dr. Tuija Ylä-Kotola, docent Andrew Lindford, Dr. Ian Barner-Rasmussen and Dr. Atte Manninen, who have welcomed me to the head and neck reconstruction team and who create a fun and inspiring work environment. They have also supported my research aspirations, providing opportunities and guidance.

Docent Tiina Jahkola and docent Susanna Kauhanen, who supported me throughout the training and who have been tremendously helpful in expanding my research and teaching skills.

Docent Jussi Repo, who introduced me to the world of patient-reported outcome instruments. Arguably, this dissertation might have reached completion quicker without the unrelated research projects, but much fun would have been missed!

My colleagues at the Department of plastic surgery, who, with their passion for their work, repeatedly remind me how great our specialty is.

Aleksi and Aleksander, who have shared my love for dancing. Aino, whose friendship I have cherished for over twenty years.

My parents Tuulikki and Kari, and my siblings Anniina and Valtteri, who have supported me throughout my various career decisions and remind me that there is much life outside medicine.

My husband Olivier: In the acknowledgements of my Cambridge PhD dissertation, I thanked him for treating me like a princess. Much has changed in the past twelve years, but not that.

# 13. REFERENCES


Abbott, WM, RM Green, T Matsumoto, JR Wheeler, N Miller, FJ Veith, WD Suggs, L Hollier, S Money and HE Garrett (1997). "Prosthetic above-knee femoropopliteal bypass grafting: results of a multicenter randomized prospective trial. Above-Knee Femoropopliteal Study Group." J Vasc Surg 25(1): 19-28.

Adelani, MA, GE Holt, RS Dittus, MA Passman and HS Schwartz (2007). "Revascularization after segmental resection of lower extremity soft tissue sarcomas." Journal of Surgical Oncology 95(6): 455-460.

Alaggio, R, CM Coffin, SW Weiss, JA Bridge, J Issakov, AM Oliveira and AL Folpe (2009). "Liposarcomas in Young Patients: A Study of 82 Cases Occurring in Patients Younger Than 22 Years of Age." The American Journal of Surgical Pathology 33(5): 645-658.

Albäck, A, F Biancari, O Saarinen and M Lepäntalo (1998). "Prediction of the immediate outcome of femoropopliteal saphenous vein bypass by angiographic runoff score." European Journal of Vascular and Endovascular Surgery 15(3): 220-224.

Alkhalili, E, A Greenbaum, M Langsfeld, J Marek, MA Rana, R Glew and I Nir (2016). "Leiomyosarcoma of the Inferior Vena Cava: A Case Series and Review of the Literature." Ann Vasc Surg 33: 245-251.

Almond, LM, A Gronchi, D Strauss, M Jafri, S Ford and A Desai (2018). "Neoadjuvant and adjuvant strategies in retroperitoneal sarcoma." Eur J Surg Oncol 44(5): 571-579.

Alvegård, T, KS Hall, H Bauer and A Rydholm (2009). "The Scandinavian Sarcoma Group." Acta Orthopaedica 80(sup334): 1-104.

Ambler, GK and CP Twine (2018). "Graft type for femoro-popliteal bypass surgery." Cochrane Database Syst Rev 2(2): Cd001487.

Amin, MB, S Edge, F Greene, D Byrd, RK Brookland, MK Washington, JE Gershenwald, CC Compton, KR Hess, DC Sullivan, JM Jessup, JD Brierley, LE Gaspar, RL Schilsky, CM Balch, DP Winchester, EA Asare, M Madera, DM Gress and LR Meyer (2017). "AJCC Cancer Staging Manual."

Anaya-Ayala, JE, ZF Cheema, MG Davies, AB Lumsden and MJ Reardon (2011). "Concomitant reconstruction of infrarenal aorta and inferior vena cava after en bloc resection of retroperitoneal rhabdomyosarcoma." Vasc Endovascular Surg 45(8): 769-772.

Angiletta, D, M Fullone, L Greco, D Marinazzo, P Frontino and G Regina (2011). "Leiomyosarcoma of the Inferior Vena Cava: Resection and Vascular Reconstruction Using a Dacron Graft and an Adam De Weese Clip 2014;Three-Year Follow-Up." Ann Vasc Surg 25(4): 557.e555-557.e559.

Anibueze, C, V Sankaran, U Sadat, K Tan, YG Wilson, RE Brightwell, MS Delbridge and PW Stather (2017). "Neoaortic Xenoprosthetic Grafts for Treatment of Mycotic Aneurysms and Infected Aortic Grafts." Annals of Vascular Surgery 44: 419.e411-419.e412.

Antonescu, CR, A Elahi, M Humphrey, MY Lui, JH Healey, MF Brennan, JM Woodruff, SC Jhanwar and M Ladanyi (2000). "Specificity of TLS-CHOP Rearrangement for Classic Myxoid/Round Cell Liposarcoma: Absence in Predominantly Myxoid Well-Differentiated Liposarcomas." J Mol Diagn 2(3): 132-138.

Antonescu, CR, SJ Tschernyavsky, R Decuseara, DH Leung, JM Woodruff, MF Brennan, JA Bridge, JR Neff, JR Goldblum and M Ladanyi (2001). "Prognostic impact of P53 status, TLS-CHOP fusion transcript structure, and histological grade in myxoid liposarcoma: a molecular and clinicopathologic study of 82 cases." Clin Cancer Res 7(12): 3977-3987.

Arii, S, K Teramoto, T Kawamura, S Takamatsu, E Sato, N Nakamura, T Iwai, A Mori, J Tanaka and M Imamura (2003). "Significance of hepatic resection combined with inferior vena cava resection and its reconstruction with expanded polytetrafluoroethylene for treatment of liver tumors." J Am Coll Surg 196(2): 243-249.

Arvela, E, M Söderström, A Albäck, P-S Aho, M Venermo and M Lepäntalo (2010). "Arm vein conduit vs prosthetic graft in infrainguinal revascularization for critical leg ischemia." Journal of Vascular Surgery 52(3): 616-623.

Assi, T, J Kattan, E El Rassy, C Honore, S Dumont, O Mir and A Le Cesne (2019). "A comprehensive review of the current evidence for trabectedin in advanced myxoid liposarcoma." Cancer Treatment Reviews 72: 37-44.

Baia, M, SJ Ford, S Dumitra, L Samà, DN Naumann, G Spolverato and D Callegaro (2022). "Follow-up of patients with retroperitoneal sarcoma." Eur J Surg Oncol.

Baláž, P, P Vikatmaa, M Björck, M Venermo, K Mani and A Whitley (2022). "Oncovascular Surgery: The Current Situation and Future Perspectives in Europe." European Journal of Vascular and Endovascular Surgery 63(2): 350-351.

Barner-Rasmussen, I, P Popov, T Böhling, C Blomqvist and E Tukiainen (2010). "Microvascular reconstructions after extensive soft tissue sarcoma resections in the upper limb." Eur J Surg Oncol 36(1): 78-83.

Barner-Rasmussen, I, P Popov, T Böhling, M Tarkkanen, M Sampo and E Tukiainen (2009). "Microvascular reconstruction after resection of soft tissue sarcoma of the leg." Br J Surg 96(5): 482-489.

Bauer, HC, CS Trovik, TA Alvegård, O Berlin, M Erlanson, P Gustafson, R Klepp, TR Möller, A Rydholm, G Saeter, O Wahlström and T Wiklund (2001). "Monitoring referral and treatment in soft tissue sarcoma: study based on 1,851 patients from the Scandinavian Sarcoma Group Register." Acta orthopaedica Scandinavica 72(2): 150-159.

Baxter, BT, C Mahoney, PJ Johnson, KM Selmer, II Pipinos, J Rose and JR Neff (2007). "Concomitant Arterial and Venous Reconstruction with Resection of Lower Extremity Sarcomas." Annals of Vascular Surgery 21(3): 272-279.

Baxter, KJ, N Govsyeyev, JP Namm, RJ Gonzalez, KK Roggin and K Cardona (2015). "Is multimodality therapy necessary for the management of pure myxoid liposarcomas? A multi-institutional series of pure myxoid liposarcomas of the extremities and torso." J Surg Oncol 111(2): 146-151.

Ben Ahmed, S, A Louvancourt, G Daniel, P Combe, A Duprey, J-N Albertini, J-P Favre and E Rosset (2018). "Cryopreserved arterial allografts for in situ reconstruction of abdominal aortic native or secondary graft infection." Journal of Vascular Surgery 67(2): 468-477.

Berner, JE, A Dearden, AA Magdum, TP Crowley, K Rankin, MJ Clarke and M Ragbir (2021). "Safety of limb-salvaging surgery for sarcomas compromising major vessels: A 15-year single-centre outcomes study." Journal of Plastic, Reconstructive & Aesthetic Surgery 74(9): 2076-2084.

Bjerkehagen B, WJ, Hansson M, Domanski H, Bohling T (2009). "SSG pathology review experiences and histological grading of malignancy in sarcomas." Acta Orthop Scand 80 Suppl 334: 31-36.

Blay, JY, P Soibinet, N Penel, E Bompas, F Duffaud, E Stoeckle, O Mir, J Adam, C Chevreau, S Bonvalot, M Rios, P Kerbrat, D Cupissol, P Anract, F Gouin, JE Kurtz, C Lebbe, N Isambert, F Bertucci, M Toumonde, A Thyss, S Piperno-Neumann, P Dubray-Longeras, P Meeus, F Ducimetière, A Giraud, JM Coindre, I Ray-Coquard, A Italiano and A Le Cesne (2017). "Improved survival using specialized multidisciplinary board in sarcoma patients." Ann Oncol 28(11): 2852-2859.

Board, WCoTE (2020). WHO Classification of Tumours, 5th Edition. France, Inernational Agency for Research on Cancer.

Bonardelli, S, F Nodari, R Maffeis, V Ippolito, M Saccalani, L Lussardi and S Giulini (2000). "Limb salvage in lower-extremity sarcomas and technical details about vascular reconstruction." J Orthop Sci 5(6): 555-560.

Bonvalot, S, A Gronchi, C Le Péchoux, CJ Swallow, D Strauss, P Meeus, F van Coevorden, S Stoldt, E Stoeckle, P Rutkowski, M Rastrelli, CP Raut, D Hompes, A De Paoli, C Sangalli, C Honoré, P Chung, A Miah, JY Blay, M Fiore, J-J Stelmes, AP Dei Tos, EH Baldini, S Litière, S Marreaud, H Gelderblom and RL Haas (2020). "Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial." The Lancet Oncology 21(10): 1366-1377.

Bonvalot, S, M Rivoire, M Castaing, E Stoeckle, AL Cesne, JY Blay and A Laplanche (2009). "Primary Retroperitoneal Sarcomas: A Multivariate Analysis of Surgical Factors Associated With Local Control." J Clin Oncol 27(1): 31-37.

Bosiers, M, K Deloose, J Verbist, H Schroë, G Lauwers, W Lansink and P Peeters (2006). "Heparin-bonded expanded polytetrafluoroethylene vascular graft for femoropopliteal and femorocrural bypass grafting: 1-year results." Journal of Vascular Surgery 43(2): 313-318.

Bower, TC, DM Nagorney, KJ Cherry, Jr., BJ Toomey, JW Hallett, JM Panneton and P Gloviczki (2000). "Replacement of the inferior vena cava for malignancy: An update." J Vasc Surg 31(2): 270-281.

Bramwell, VH, D Anderson and ML Charette (2003). "Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma." Cochrane Database Syst Rev 2003(3): Cd003293.

Brennan, MF, CR Antonescu, N Moraco and S Singer (2014). "Lessons learned from the study of 10,000 patients with soft tissue sarcoma." Ann Surg 260(3): 416-422.

Brorson, H, B Svensson and K Ohlin (2015). Volume Measurements and Follow-Up. Lymphedema: Presentation, Diagnosis, and Treatment. A. K. Greene, S. A. Slavin and H. Brorson. Cham, Springer International Publishing: 115-122.

Brown, KG, CE Koh, MJ Solomon, IC Choy and S Dubenec (2015). "Spiral saphenous vein graft for major pelvic vessel reconstruction during exenteration surgery." Ann Vasc Surg 29(6): 1323-1326.

Caldarelli, G, A Minervini, M Guerra, G Bonari, C Caldarelli and R Minervini (2002). "Prosthetic replacement of the inferior vena cava and the iliofemoral vein for urologically related malignancies." BJU Int 90(4): 368-374.

Callegaro, D, R Miceli, L Mariani, CP Raut and A Gronchi (2017). "Soft tissue sarcoma nomograms and their incorporation into practice." Cancer 123(15): 2802-2820.

Cananzi, FCM, L Ruspi, M Fiore, F Sicoli, V Quagliuolo and A Gronchi (2021). "Major vascular resection in retroperitoneal sarcoma surgery." Surgery 170(3): 848-856.

Caso, J, J Seigne, M Back, PE Spiess, J Pow-Sang and WJ Sexton (2009). "Circumferential resection of the inferior vena cava for primary and recurrent malignant tumors." J Urol 182(3): 887-893.

Cates, JMM (2018). "The AJCC 8th Edition Staging System for Soft Tissue Sarcoma of the Extremities or Trunk: A Cohort Study of the SEER Database." J Natl Compr Canc Netw 16(2): 144-152.

Chakfé, N, H Diener, A Lejay, O Assadian, X Berard, J Caillon, I Fourneau, AWJM Glaudemans, I Koncar, J Lindholt, G Melissano, BR Saleem, E Senneville, RHJA Slart, Z Szeberin, M Venermo, F Vermassen, TR Wyss, EG Committee, GJ de Borst, F Bastos Gonçalves, SK Kakkos, P Kolh, R Tulamo, M Vega de Ceniga, R Document, RS von Allmen, JC van den Berg, ES Debus, MJW Koelemay, JP Linares-Palomino, GL Moneta, J-B Ricco and A Wanhainen (2020). "Editor's Choice – European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Vascular Graft and Endograft Infections." European Journal of Vascular and Endovascular Surgery 59(3): 339-384.

Chen, H-c and Y-b Tang (2003). "Anterolateral thigh flap: an ideal soft tissue flap." Clinics in Plastic Surgery 30(3): 383-401.

Chiu, RC (1998). "Spiral vein graft: a historical vignette." Can J Surg 41(1): 8-9.

Chmielecki, J, AM Crago, M Rosenberg, R O'Connor, SR Walker, L Ambrogio, D Auclair, A McKenna, MC Heinrich, DA Frank and M Meyerson (2013). "Whole-exome sequencing identifies a recurrent NAB2-STAT6 fusion in solitary fibrous tumors." Nat Genet 45(2): 131-132.

Cho, SW, JW Marsh, DA Geller, M Holtzman, H Zeh III, DL Bartlett and TC Gamblin (2008). "Surgical Management of Leiomyosarcoma of the Inferior Vena Cava." J Gastrointest Surg 12(12): 2141-2148.

Chouliaras, K, R Senehi, CG Ethun, G Poultsides, V Grignol, CN Clarke, KK Roggin, RC Fields, PB Schwartz, SM Ronnekleiv-Kelly, R D'Agostino, Jr., EN Johnson, EA Levine, K Cardona and KI Votanopoulos (2019). "Role of radiation therapy for retroperitoneal sarcomas: An eight-institution study from the US Sarcoma Collaborative." J Surg Oncol 120(7): 1227-1234.

Chouliaras, K, R Senehi, CG Ethun, G Poultsides, T Tran, V Grignol, TC Gamblin, KK Roggin, J Tseng, RC Fields, SM Weber, GB Russell, EA Levine, K Cardona and K Votanopoulos (2019). "Recurrence patterns after resection of retroperitoneal sarcomas: An eight-institution study from the US Sarcoma Collaborative." J Surg Oncol 120(3): 340-347.

Chudgar, NP, MF Brennan, RR Munhoz, PR Bucciarelli, KS Tan, SP D'Angelo, MS Bains, M Bott, J Huang, BJ Park, VW Rusch, PS Adusumilli, WD Tap, S Singer and DR Jones (2017).

"Pulmonary metastasectomy with therapeutic intent for soft-tissue sarcoma." J Thorac Cardiovasc Surg 154(1): 319-330.e311.

Chung, PWM, BM Deheshi, PC Ferguson, JS Wunder, AM Griffin, CN Catton, RS Bell, LM White, RA Kandel and B O'Sullivan (2009). "Radiosensitivity translates into excellent local control in extremity myxoid liposarcoma." Cancer 115(14): 3254-3261.

Clagett, GP, BL Bowers, MA Lopez-Viego, MB Rossi, RJ Valentine, SI Myers and A Chervu (1993). "Creation of a neo-aortoiliac system from lower extremity deep and superficial veins." Ann Surg 218(3): 239-248; discussion 248-239.

Coindre, J-M (2006). "Grading of Soft Tissue Sarcomas: Review and Update." Archives of Pathology & Laboratory Medicine 130(10): 1448-1453.

Collaboration, SM-a (1997). "Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. ." Lancet 350(9092): 1647-1654.

Coppa, J, D Citterio, C Cotsoglou, A Germini, F Piccioni, C Sposito and V Mazzaferro (2013). "Transhepatic anterior approach to the inferior vena cava in large retroperitoneal tumors resected en bloc with the right liver lobe." Surgery 154(5): 1061-1068.

Coubeau, L, JMR Juri, O Ciccarelli, N Jabbour and J Lerut (2017). "The Use of Autologous Peritoneum for Complete Caval Replacement Following Resection of Major Intra-abdominal Malignancies." World J Surg 41(4): 1005-1011.

Couture, T, J Gaudric, ST Du Montcel, J Jayet, D Verscheure, JM Davaine, M Jarraya, L Chiche and F Koskas (2021). "Short and Mid Term Outcomes of Cryopreserved Abdominal Aortic Allografts Used as a Substitute for Infected Prosthetic Grafts in 200 Patients." European Journal of Vascular and Endovascular Surgery 62(1): 89-97.

Creytens, D, AL Folpe, C Koelsche, T Mentzel, L Ferdinande, JM van Gorp, M Van der Linden, L Raman, B Menten, K Fritchie, A von Deimling, J Van Dorpe and U Flucke (2021). "Myxoid pleomorphic liposarcoma—a clinicopathologic, immunohistochemical, molecular genetic and epigenetic study of 12 cases, suggesting a possible relationship with conventional pleomorphic liposarcoma." Modern Pathology 34(11): 2043-2049.

Crozat, A, P Åman, N Mandahl and D Ron (1993). "Fusion of CHOP to a novel RNA-binding protein in human myxoid liposarcoma." Nature 363(6430): 640-644.

Czerny, M, R von Allmen, P Opfermann, G Sodeck, F Dick, A Stellmes, V Makaloski, R Bühlmann, U Derungs, MK Widmer, T Carrel and J Schmidli (2011). "Self-made pericardial tube graft: a new surgical concept for treatment of graft infections after thoracic and abdominal aortic procedures." Ann Thorac Surg 92(5): 1657-1662.

Daenens, K, S Schepers, I Fourneau, S Houthoofd and A Nevelsteen (2009). "Heparin-bonded ePTFE grafts compared with vein grafts in femoropopliteal and femorocrural bypasses: 1- and 2-year results." Journal of Vascular Surgery 49(5): 1210-1216.

Dal Cin, P, R Sciot, I Panagopoulos, P Åman, I Samson, N Mandahl, F Mitelman, H Van Den Berghe and CDM Fletcher (1997). "Additional evidence of a variant translocation t(12;22) with EWS/CHOP fusion in myxoid liposarcoma: clinicopathological features." J. Pathol 182(4): 437-441.

Davis, AM, JG Wright, JI Williams, C Bombardier, A Griffin and RS Bell (1996). "Development of a measure of physical function for patients with bone and soft tissue sarcoma." Quality of Life Research 5(5): 508-516.

Davis, LA, F Dandachli, R Turcotte and OK Steinmetz (2017). "Limb-sparing surgery with vascular reconstruction for malignant lower extremity soft tissue sarcoma." J Vasc Surg 65(1): 151-156.

Daylami, R, A Amiri, B Goldsmith, C Troppmann, PD Schneider and VP Khatri (2010). "Inferior Vena Cava Leiomyosarcoma: Is Reconstruction Necessary after Resection?" Journal of the American College of Surgeons 210(2): 185-190.

de Vreeze, RSA, D de Jong, IHG Tielen, HJ Ruijter, PM Nederlof, RL Haas and F van Coevorden (2009). "Primary retroperitoneal myxoid/round cell liposarcoma is a nonexisting disease: an immunohistochemical and molecular biological analysis." Mod Pathol 22(2): 223-231.

Dei Tos, AP (2000). "Liposarcoma: New entities and evolving concepts." Ann Diagn Pathol 4(4): 252-266.

Desai, MH, G. (2011). Graft Materials Past and Future. Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists. R. T. Fit´ridge, M. Adelaide (AU), University of Adelaide Press.

Devine, C, BA Hons and C McCollum (2001). "Heparin-bonded Dacron or polytetrafluoroethylene for femoropopliteal bypass grafting: A multicenter trial." Journal of Vascular Surgery 33(3): 533-539.

Di Giandomenico, S, R Frapolli, E Bello, S Uboldi, SA Licandro, S Marchini, L Beltrame, S Brich, V Mauro, E Tamborini, S Pilotti, PG Casali, F Grosso, R Sanfilippo, A Gronchi, R Mantovani, R Gatta, CM Galmarini, JMF Sousa-Faro and M D'Incalci (2014). "Mode of action of trabectedin in myxoid liposarcomas." Oncogene 33(44): 5201-5210.

Dindo, D, N Demartines and P-A Clavien (2004). "Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey." Annals of surgery 240(2): 205-213.

Doi, K, N Kuwata, F Kawakami, Y Hattori, K Otsuka and K Ihara (1999). "Limb-Sparing Surgery with Reinnervated FreeMuscle Transfer following Radical Excision of Soft-Tissue Sarcoma in the Extremity." Plastic and Reconstructive Surgery 104(6): 1679-1687.

DuBay, DA, T Lindsay, C Swallow and I McGilvray (2009). "A cylindrical femoral vein panel graft for caval reconstructions." J Vasc Surg 49(1): 255-259.

Emori, M, K Hamada, S Omori, S Joyama, Y Tomita, N Hashimoto, H Takami, N Naka, H Yoshikawa and N Araki (2012). "Surgery With Vascular Reconstruction for Soft-Tissue Sarcomas in the Inguinal Region: Oncologic and Functional Outcomes." Annals of Vascular Surgery 26(5): 693-699.

Enneking, WF, W Dunham, MC Gebhardt, M Malawar and DJ Pritchard (1993). "A system for the functional evaluation of reconstructive procedures after surgical treatment of tumors of the musculoskeletal system." Clin Orthop Relat Res(286): 241-246.

Enneking, WF, SS Spanier and MA Goodman (1980). "A system for the surgical staging of musculoskeletal sarcoma." Clin Orthop Relat Res(153): 106-120.

Epitools. (2022). "epitools.ausvet.com.au/ciproportion." Epitools Retrieved 11.9.2022.

Estourgie, SH, GP Nielsen and MJ Ott (2002). "Metastatic patterns of extremity myxoid liposarcoma and their outcome." J Surg Oncol 80(2): 89-93.

Fabre-Guillevin, E, J-M Coindre, NdSA Somerhausen, F Bonichon, E Stoeckle and NB Bui (2006). "Retroperitoneal liposarcomas: Follow-up analysis of dedifferentiation after clinicopathologic reexamination of 86 liposarcomas and malignant fibrous histiocytomas." Cancer 106(12): 2725-2733.

Ferraris, M, D Callegaro, F Barretta, M Fiore, S Radaelli, S Stacchiotti, R Miceli, AM Socrate, P Locati and A Gronchi (2019). "Outcome of iliocaval resection and reconstruction for retroperitoneal sarcoma." J Vasc Surg 7(4): 547-556.

Fiore, M, C Colombo, P Locati, M Berselli, S Radaelli, C Morosi, PG Casali and A Gronchi (2012). "Surgical technique, morbidity, and outcome of primary retroperitoneal sarcoma involving inferior vena cava." Ann Surg Oncol 19(2): 511-518.

Fiore, M, F Grosso, S Lo Vullo, E Pennacchioli, S Stacchiotti, A Ferrari, P Collini, L Lozza, L Mariani, PG Casali and A Gronchi (2007). "Myxoid/round cell and pleomorphic liposarcomas: prognostic factors and survival in a series of patients treated at a single institution." Cancer 109(12): 2522-2531.

Fortner, JG, DK Kim and MH Shiu (1977). "Limb-Preserving Vascular Surgery for Malignant Tumors of the Lower Extremity." Archives of Surgery 112(4): 391-394.

Fujiki, M, T Kimura and A Takushima (2020). "Limb-salvage surgery with vascular reconstruction after lower extremity sarcoma resection: A systematic review and meta-analysis." Microsurgery 40(3): 404-413.

Gage, MJ, E Newman, TS Maldonado and CH Hajdu (2012). "Leiomyosarcoma of the splenic vein." J Vasc Surg 55(5): 1485-1487.

Gatta, G, R Capocaccia, L Botta, S Mallone, R De Angelis, E Ardanaz, H Comber, N Dimitrova, MK Leinonen, S Siesling, JM van der Zwan, L Van Eycken, O Visser, MP Žakelj, LA Anderson, F Bella, I Kaire, R Otter, CA Stiller and A Trama (2017). "Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study." Lancet Oncol 18(8): 1022-1039.

Gebhard, S, J-M Coindre, J-J Michels, P Terrier, G Bertrand, M Trassard, S Taylor, M-C Château, B Marquès, V Picot and L Guillou (2002). "Pleomorphic Liposarcoma: Clinicopathologic, Immunohistochemical, and Follow-up Analysis of 63 Cases: A Study From the French Federation of Cancer Centers Sarcoma Group." The American Journal of Surgical Pathology 26(5): 601-616.

Ghert, MA, AM Davis, AM Griffin, AH Alyami, L White, RA Kandel, P Ferguson, B O'Sullivan, CN Catton, T Lindsay, B Rubin, RS Bell and JS Wunder (2005). "The surgical and functional outcome of limb-salvage surgery with vascular reconstruction for soft tissue sarcoma of the extremity." Annals of Surgical Oncology 12(12): 1102-1110.

Goel, M, A Mohan, S Patkar, K Gala, N Shetty, S Kulkarni and J Dhareshwar (2022). "Leiomyosarcoma of inferior vena cava (IVC): do we really need to reconstruct IVC post resection? Single institution experience." Langenbeck's Archives of Surgery 407(3): 1209-1216.

Gorelik, N, SMV Reddy, RE Turcotte, K Goulding, S Jung, T Alcindor and TI Powell (2018). "Early detection of metastases using whole-body MRI for initial staging and routine follow-up of myxoid liposarcoma." Skeletal Radiol 47(3): 369-379.

Gouin, F, A Renault, A Bertrand-Vasseur, L Bouilleau, V Crenn, P Rosset, M Tallegas, R Samargandi and L-R Le Nail (2019). "Early detection of multiple bone and extra-skeletal metastases by body magnetic resonance imaging (BMRI) after treatment of Myxoid/Round-Cell Liposarcoma (MRCLS)." Eur J Surg Oncol 45(12): 2431-2436.

Grinsell, D, C Di Bella and PFM Choong (2012). "Functional Reconstruction of Sarcoma Defects Utilising Innervated Free Flaps." Sarcoma 2012: 315190.

Grimaldi, C, A Bertocchini, A Crocoli, J de Ville de Goyet, A Castellano, A Serra, M Spada and A Inserra (2019). "Caval replacement strategy in pediatric retroperitoneal tumors encasing the vena cava: a single-center experience and review of literature." J Pediatr Surg 54(3): 557-561.

Gronchi, A, AB Miah, AP Dei Tos, N Abecassis, J Bajpai, S Bauer, R Biagini, S Bielack, JY Blay, S Bolle, S Bonvalot, I Boukovinas, J Bovee, K Boye, B Brennan, T Brodowicz, A Buonadonna, E De Álava, XG Del Muro, A Dufresne, M Eriksson, F Fagioli, A Fedenko, V Ferraresi, A Ferrari, AM Frezza, S Gasperoni, H Gelderblom, F Gouin, G Grignani, R Haas, AB Hassan, S Hecker-Nolting, N Hindi, P Hohenberger, H Joensuu, RL Jones, C Jungels, P Jutte, L Kager, B Kasper, A Kawai, K Kopeckova, DA Krákorová, A Le Cesne, F Le Grange, E Legius, A Leithner, A Lopez-Pousa, J Martin-Broto, O Merimsky, C Messiou, O Mir, M Montemurro, B Morland, C Morosi, E Palmerini, MA Pantaleo, R Piana, S Piperno-Neumann, P Reichardt, P Rutkowski, AA Safwat, C Sangalli, M Sbaraglia, S Scheipl, P Schöffski, S Sleijfer, D Strauss, S Strauss, K Sundby Hall, A Trama, M Unk, MAJ van de Sande, WTA van der Graaf, WJ van Houdt, T Frebourg, PG Casali and S Stacchiotti (2021). "Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up(☆)." Ann Oncol 32(11): 1348-1365.

Gronchi, A, DC Strauss, R Miceli, S Bonvalot, CJ Swallow, P Hohenberger, F Van Coevorden, P Rutkowski, D Callegaro, AJ Hayes, C Honoré, M Fairweather, A Cannell, J Jakob, RL Haas, M Szacht, M Fiore, PG Casali, RE Pollock and CP Raut (2016). "Variability in Patterns of Recurrence After Resection of Primary Retroperitoneal Sarcoma (RPS): A Report on 1007 Patients From the Multi-institutional Collaborative RPS Working Group." Annals of Surgery 263(5): 1002-1009.

Group, SS. (2015). "SSG XXIV Recommendations for radiotherapy in bone- and soft tissue sarcoma." Retrieved 4.12.2020, 2020.

Guadagnolo, BA, GK Zagars, MT Ballo, SR Patel, VO Lewis, RS Benjamin and RE Pollock (2008). "Excellent local control rates and distinctive patterns of failure in myxoid liposarcoma treated with conservation surgery and radiotherapy." Int J Radiat Oncol Biol Phys 70(3): 760-765.

Guerrero, MA, CA Cross, PH Lin, TE Keane and AB Lumsden (2007). "Inferior vena cava reconstruction using fresh inferior vena cava allograft following caval resection for leiomyosarcoma: Midterm results." J Vasc Surg 46(1): 140-143.

Gundle, KR, L Kafchinski, S Gupta, AM Griffin, BC Dickson, PW Chung, CN Catton, B O'Sullivan, JS Wunder and PC Ferguson (2018). "Analysis of Margin Classification Systems for Assessing the Risk of Local Recurrence After Soft Tissue Sarcoma Resection." Journal of Clinical Oncology 36(7): 704-709.

Gutierrez, JC, EA Perez, FL Moffat, AS Livingstone, D Franceschi and LG Koniaris (2007). "Should soft tissue sarcomas be treated at high-volume centers? An analysis of 4205 patients." Ann Surg 245(6): 952-958.

Haas, RLM, S Bonvalot, R Miceli, DC Strauss, CJ Swallow, P Hohenberger, F van Coevorden, P Rutkowski, D Callegaro, AJ Hayes, C Honoré, M Fairweather, R Gladdy, J Jakob, M Szacht, M Fiore, PW Chung, WJ van Houdt, CP Raut and A Gronchi (2019). "Radiotherapy for retroperitoneal liposarcoma: A report from the Transatlantic Retroperitoneal Sarcoma Working Group." Cancer 125(8): 1290-1300.

Hajdu, SI, MH Shiu and MF Brennan (1988). "The role of the pathologist in the management of soft tissue sarcomas." World J Surg 12(3): 326-331.

Haniball, J, VP Sumathi, LG Kindblom, A Abudu, SR Carter, RM Tillman, L Jeys, D Spooner, D Peake and RJ Grimer (2011). "Prognostic factors and metastatic patterns in primary myxoid/round-cell liposarcoma." Sarcoma 2011: 538085.

Hardwigsen, J, P Balandraud, P Ananian, J Saïsse and YP Le Treut (2005). "Leiomyosarcoma of the retrohepatic portion of the inferior vena cava: Clinical presentation and surgical management in five patients." J Am Coll Surg 200(1): 57-63.

Hardwigsen, J, P Baqué, B Crespy, V Moutardier, JR Delpero and YP Le Treut (2001). "Resection of the inferior vena cava for neoplasms with or without prosthetic replacement: a 14-patient series." Ann surg 233(2): 242-249.

Harlander-Locke, MP, LK Harmon, PF Lawrence, GS Oderich, RA McCready, MD Morasch and RJ Feezor (2014). "The use of cryopreserved aortoiliac allograft for aortic reconstruction in the United States." Journal of Vascular Surgery 59(3): 669-674.e661.

Hassan, I, SZ Park, JH Donohue, DM Nagorney, PA Kay, AG Nasciemento, CD Schleck and DM Ilstrup (2004). "Operative management of primary retroperitoneal sarcomas: a reappraisal of an institutional experience." Annals of surgery 239(2): 244-250.

Hauguel, A, Y Goueffic, D Tzanis, T Bouhadiba, J Perlbarg-Samson, S Bonvalot and B Boura (2022). "Arterial reconstruction for en-bloc resection of soft tissue sarcoma: a single tertiary center experience." Annals of Vascular Surgery.

Heinola, I, K Halmesmäki, I Kantonen, P Vikatmaa, P Aho, M Lepäntalo and M Venermo (2016). "Temporary Axillorenal Bypass in Complex Aorto-Renal Surgery." Annals of Vascular Surgery 31: 239-245.

Heinola, I, I Kantonen, I Mattila, A Albäck and M Venermo (2019). "Cryopreserved Venous Allografts in Supra-inguinal Reconstructions: A Single Centre Experience." European Journal of Vascular and Endovascular Surgery 58(6): 912-919.

Henricks, WH, YC Chu, JR Goldblum and SW Weiss (1997). "Dedifferentiated Liposarcoma: A Clinicopathological Analysis of 155 Cases with a Proposal for an Expanded Definition of Dedifferentiation." The American Journal of Surgical Pathology 31(3): 271-281.

Hermanek, PS, L.H. (1987). TNM Classification of Malignant Tumours. Heidelberg, Springer Berlin.

Hirohashi, K, T Shuto, S Kubo, H Tanaka, T Tsukamoto, T Shibata, T Yamamoto, A Kanazawa, T Fukui, S Suehiro and H Kinoshita (2002). "Asymptomatic Thrombosis as a Late Complication

of a Retrohepatic Vena Caval Graft Performed for Primary Leiomyosarcoma of the Inferior Vena Cava: Report of a Case." Surg Today 32(11): 1012-1015.

Hoffman, A, MP Ghadimi, EG Demicco, CJ Creighton, K Torres, C Colombo, T Peng, K Lusby, D Ingram, JL Hornick, WL Wang, V Ravi, AJ Lazar, D Lev and RE Pollock (2013). "Localized and metastatic myxoid/round cell liposarcoma: clinical and molecular observations." Cancer 119(10): 1868-1877.

Hohenberger, P, JR Allenberg, PM Schlag and P Reichardt (1999). "Results of surgery and multimodal therapy for patients with soft tissue sarcoma invading to vascular structures." Cancer 85(2): 396-408.

Hollenbeck, ST, SR Grobmyer, CK Kent and MF Brennan (2003). "Surgical Treatment and Outcomes of Patients with Primary Inferior Vena Cava Leiomyosarcoma." Journal of the American College of Surgeons 197(4): 575-579.

Hornick, JL, MW Bosenberg, T Mentzel, ME McMenamin, AM Oliveira and CDM Fletcher (2004). "Pleomorphic Liposarcoma: Clinicopathologic Analysis of 57 Cases." The American Journal of Surgical Pathology 28(10): 1257-1267.

IBM (2017). IBM SPSS Statistics for Windows. Armonk, NY, IBM Corp.

Ikoma, N, CL Roland, KE Torres, Y-J Chiang, W-L Wang, N Somaiah, GN Mann, KK Hunt, JN Cormier and BW Feig (2018). "Salvage Surgery for Recurrent Retroperitoneal Well-Differentiated Liposarcoma: Early Reoperation may not Provide Benefit." Annals of surgical oncology 25(8): 2193-2200.

Imparato, AM, DF Roses, KC Francis and MM Lewis (1978). "Major vascular reconstruction for limb salvage in patients with soft tissue and skeletal sarcomas of the extremities." Surg Gynecol Obstet 147(6): 891-896.

Innocenti, M, YY Abed, G Beltrami, L Delcroix, A Balatri and R Capanna (2009). "Quadriceps muscle reconstruction with free functioning latissimus dorsi muscle flap after oncological resection." Microsurgery 29(3): 189-198.

Invitae, C. Boulder, Colorado, U.S.A.

Ito, F, Y Watanabe, T Harada, H Ando, T Seo, K Kaneko, Y Ishiguro and T Sakurai (1998). "Combined resection of abdominal aorta and inferior vena cava for retroperitoneal rhabdomyosarcoma invading the aortoiliac bifurcation." J Pediatr Surg 33(10): 1566-1568.

Jacobs, AJ, R Michels, J Stein and AS Levin (2015). "Improvement in Overall Survival from Extremity Soft Tissue Sarcoma over Twenty Years." Sarcoma 2015: 279601.

Jebsen, NL, CS Trovik, HCF Bauer, A Rydholm, OR Monge, KS Hall, T Alvegård and ØS Bruland (2008). "Radiotherapy to Improve Local Control Regardless of Surgical Margin and Malignancy Grade in Extremity and Trunk Wall Soft Tissue Sarcoma: A Scandinavian Sarcoma Group Study." International Journal of Radiation Oncology*Biology*Physics 71(4): 1196-1203.

Joensuu, H, M Eriksson, K Sundby Hall, JT Hartmann, D Pink, J Schütte, G Ramadori, P Hohenberger, J Duyster, SE Al-Batran, M Schlemmer, S Bauer, E Wardelmann, M Sarlomo-Rikala, B Nilsson, H Sihto, OR Monge, P Bono, R Kallio, A Vehtari, M Leinonen, T Alvegård and P Reichardt (2012). "One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial." Jama 307(12): 1265-1272.

Johnson, CJ, PB Pynsent and RJ Grimer (2001). "Clinical features of soft tissue sarcomas." Ann R Coll Surg Engl 83(3): 203-205.

Jones, AP, CJ Lewis, P Dildey, G Hide and M Ragbir (2012). "Lipoma or liposarcoma? A cautionary case report." J Plast Reconstr Aesthet Surg 65(1): e11-14.

Jones, RL, C Fisher, O Al-Muderis and IR Judson (2005). "Differential sensitivity of liposarcoma subtypes to chemotherapy." European Journal of Cancer 41(18): 2853-2860.

Karakousis, CP, C Karmpaliotis and DL Driscoll (1996). "Major vessel resection during limb-preserving surgery for soft tissue sarcomas." World J Surg 20(3): 345-349; discussion 350.

Kask, G, I Barner-Rasmussen, J Repo, C Blomqvist and E Tukiainen (2019). "Functional Outcome After Lower Extremity Soft Tissue Sarcoma Treatment: A Pilot Study Based on Translated and Culturally Adapted Measures." Scand J Surg 108(2): 164-171.

Kask, G, MM Uimonen, I Barner-Rasmussen, EJ Tukiainen, C Blomqvist and JP Repo (2020). "Further validation of the Toronto extremity salvage score for lower extremity soft tissue sarcoma based on Finnish patients." Journal of Plastic, Reconstructive & Aesthetic Surgery.

Kato, S, T Tanaka, H Kitamura, N Masumori, T Ito, N Kawaharada and T Tsukamoto (2013). "Resection of the inferior vena cava for urological malignancies: single-center experience." Int J Clin Oncol 18(5): 905-909.

Ketenciler, S, K Boyacıoğlu, İ Akdemir, G Kömürcü and A Polat (2018). "Autologous Saphenous Vein Panel Graft for Vascular Reconstruction." Annals of Vascular Surgery 53: 117-122.

Kieffer, E, D Gomes, L Chiche, MH Fléron, F Koskas and A Bahnini (2004). "Allograft replacement for infrarenal aortic graft infection: Early and late results in 179 patients." Journal of Vascular Surgery 39(5): 1009-1017.

Kind, M, N Stock and JM Coindre (2009). "Histology and imaging of soft tissue sarcomas." European Journal of Radiology 72(1): 6-15.

Klinkert, P, PN Post, PJ Breslau and JH van Bockel (2004). "Saphenous vein versus PTFE for above-knee femoropopliteal bypass. A review of the literature." Eur J Vasc Endovasc Surg 27(4): 357-362.

Kransdorf, MJ, LW Bancroft, JJ Peterson, MD Murphey, WC Foster and HT Temple (2002). "Imaging of Fatty Tumors: Distinction of Lipoma and Well-differentiated Liposarcoma." Radiology 224(1): 99-104.

Kraybill, WG, MP Callery, JP Heiken and MW Flye (1997). "Radical resection of tumors of the inferior vena cava with vascular reconstruction and kidney autotransplantation." Surgery 121(1): 31-36.

Kreibich, M, M Siepe, J Morlock, F Beyersdorf, S Kondov, J Scheumann, FA Kari, T Berger, H Schröfel, B Rylski and M Czerny (2018). "Surgical Treatment of Native and Prosthetic Aortic Infection With Xenopericardial Tube Grafts." The Annals of Thoracic Surgery 106(2): 498-504.

Kubota, H, H Endo, M Noma, H Ishii, H Tsuchiya, A Yoshimoto, Y Takahashi, Y Inaba, Y Nishino, M Nunokawa, Y Hosoi, T Ikezoe, M Nemoto, Y Makino, Y Nemoto, M Matsukura, M Sugiyama, N Abe, H Takeuchi, G Nagao, E Kondo, O Yanagida, H Yoshino and K Sudo (2015). "Xenopericardial roll graft replacement for infectious pseudoaneurysms and graft infections of the aorta." Journal of Cardiothoracic Surgery 10(1).

Kuroda, M, T Ishida, M Takanashi, M Satoh, R Machinami and T Watanabe (1997). "Oncogenic transformation and inhibition of adipocytic conversion of preadipocytes by TLS/FUS-CHOP type II chimeric protein." The American journal of pathology 151(3): 735-744.

Kwon, TW, KB Sung, YP Cho, DK Kim, SM Yang, JY Ro and GE Kim (2003). "Pararenal leiomyosarcoma of the inferior vena cava." J Korean Med Sci 18(3): 355-359.

Kyriazi, MA, VK Stafyla, I Chatzinikolaou, A Koureas, A Chatziioannou, A Kondi-Paphiti, N Arkadopoulos and V Smyrniotis (2010). "Surgical challenges in the treatment of leiomyosarcoma of the inferior vena cava: analysis of two cases and brief review of the literature." Ann Vasc Surg 24(6): 826.e813-827.

Lee, ATJ, K Thway, PH Huang and RL Jones (2018). "Clinical and Molecular Spectrum of Liposarcoma." Journal of Clinical Oncology 36(2): 151-159.

Lee, HS, JI Yu, DH Lim and SJ Kim (2016). "Retroperitoneal liposarcoma: the role of adjuvant radiation therapy and the prognostic factors." Radiation oncology journal 34(3): 216-222.

Lee, N, S Roh, K Yang and J Kim (2009). "Reconstruction of hand and forearm after sarcoma resection using anterolateral thigh free flap." Journal of Plastic, Reconstructive & Aesthetic Surgery 62(12): e584-e586.

Lejay, A, C Delay, E Girsowicz, B Chenesseau, E Bonnin, M-Z Ghariani, F Thaveau, Y Georg, B Geny and N Chakfe (2017). "Cryopreserved Cadaveric Arterial Allograft for Arterial Reconstruction in Patients with Prosthetic Infection." European Journal of Vascular and Endovascular Surgery 54(5): 636-644.

Lewis, JJ, D Leung, JM Woodruff and MF Brennan (1998). "Retroperitoneal soft-tissue sarcoma: analysis of 500 patients treated and followed at a single institution." Ann Surg 228(3): 355-365.

Li, X, Y Guo, KR Ziegler, LS Model, SD Eghbalieh, RA Brenes, ST Kim, C Shu and A Dardik (2011). "Current usage and future directions for the bovine pericardial patch." Ann Vasc Surg 25(4): 561-568.

Lintz, F, A Moreau, GA Odri, D Waast, O Maillard and F Gouin (2012). "Critical study of resection margins in adult soft-tissue sarcoma surgery." Orthopaedics & Traumatology: Surgery & Research 98(4, Supplement): S9-S18.

Liu, C-Y, C-C Yen, W-M Chen, T-H Chen, PC-H Chen, H-TH Wu, C-Y Shiau, Y-C Wu, C-L Liu and C-H Tzeng (2010). "Soft Tissue Sarcoma of Extremities: The Prognostic Significance of Adequate Surgical Margins in Primary Operation and Reoperation After Recurrence." Annals of Surgical Oncology 17(8): 2102-2111.

Liu, D, HL Ren, B Liu, J Shao, YX Chen, XJ Song, ZL Liu, Y Chen, YJ Li, CW Liu and YH Zheng (2018). "Renal Function Preservation in Surgical Resection of Primary Inferior Vena Cava Leiomyosarcoma Involving the Renal Veins." Eur J Vasc Endovasc Surg 55(2): 229-239.

Lucattelli, E, IL Lusetti, F Cipriani, A Innocenti, G De Santis and M Innocenti (2021). "Reconstruction of upper limb soft-tissue defects after sarcoma resection with free flaps: A systematic review." Journal of Plastic, Reconstructive & Aesthetic Surgery 74(4): 755-767.

Lutz, B, C Reeps, G Biro, C Knappich, A Zimmermann and H-H Eckstein (2017). "Bovine Pericardium as New Technical Option for In Situ Reconstruction of Aortic Graft Infection." Annals of Vascular Surgery 41: 118-126.

Mann, GN, LV Mann, EA Levine and P Shen (2012). "Primary leiomyosarcoma of the inferior vena cava: A 2-institution analysis of outcomes." Surgery 151(2): 261-267.

Marudanayagam, R, B Sandhu, MTPR Perera, SR Bramhall, D Mayer, JAC Buckels and DF Mirza (2011). "Liver resection for metastatic soft tissue sarcoma: An analysis of prognostic factors." European Journal of Surgical Oncology (EJSO) 37(1): 87-92.

Moher, D, A Liberati, J Tetzlaff and DG Altman (2009). "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement." BMJ 339: b2535.

Momeni, A, Z Kalash, GB Stark and H Bannasch (2011). "The use of the anterolateral thigh flap for microsurgical reconstruction of distal extremities after oncosurgical resection of soft-tissue sarcomas." Journal of Plastic, Reconstructive & Aesthetic Surgery 64(5): 643-648.

Moreau, LC, R Turcotte, P Ferguson, J Wunder, P Clarkson, B Masri, M Isler, N Dion, J Werier, M Ghert and B Deheshi (2012). "Myxoid\round cell liposarcoma (MRCLS) revisited: an analysis of 418 primarily managed cases." Ann Surg Oncol 19(4): 1081-1088.

Muramatsu, K, K Ihara, T Miyoshi, K Yoshida, T Hashimoto and T Taguchi (2011). "Transfer of latissimus dorsi muscle for the functional reconstruction of quadriceps femoris muscle following oncological resection of sarcoma in the thigh." Journal of Plastic, Reconstructive & Aesthetic Surgery 64(8): 1068-1074.

Muratori, F, L Bettini, F Frenos, N Mondanelli, D Greto, L Livi, A Franchi, G Roselli, M Scorianz, R Capanna and D Campanacci (2018). "Myxoid Liposarcoma: Prognostic Factors and Metastatic Pattern in a Series of 148 Patients Treated at a Single Institution." Int J Surg Oncol 2018: 8928706.

Muratori, F, F Frenos, L Bettini, D Matera, N Mondanelli, M Scorianz, P Cuomo, G Scoccianti, G Beltrami, D Greto, L Livi, G Baldi, G Roselli, R Capanna and DA Campanacci (2018). "Liposarcoma: Clinico-pathological analysis, prognostic factors and survival in a series of 307 patients treated at a single institution." J Orthop Sci 23(6): 1038-1044.

Nakamura, T, K Asanuma, M Takao, T Yamanaka, H Koike, TF Chen-Yoshikawa, S Tsukushi, H Kuroda, E Kozawa, M Sano, H Aiba, R Nakanishi, A Nagano, K Yamada, Y Shido, K Kawanami, Y Izubuchi, A Sudo and Y Nishida (2021). "Clinical Outcome in Soft Tissue Sarcoma Patients with Lung Metastasis Who Received Metastasectomy and/or Radiofrequency Ablation: Tokai Musculoskeletal Oncology Consortium Study." Cancer Manag Res 13: 8473-8480.

Nayyar, R, S Panda, A Saini, A Seth and SK Chaudhary (2010). "Leiomyosarcoma of inferior vena cava involving bilateral renal veins: Surgical challenges and reconstruction with upfront saphenous vein interposition graft for left renal vein outflow." IJU 26(3): 438-440.

Nevala, R, S Jäämaa, E Tukiainen, M Tarkkanen, J Räsänen, C Blomqvist and M Sampo (2019). "Long-term results of surgical resection of lung metastases from soft tissue sarcoma: A single center experience." J Surg Oncol 120(2): 168-175.

Nishinari, K, M Krutman, S Aguiar Junior, BS Pignataro, G Yazbek, GA Zottele Bomfim, MP Teivelis and N Wolosker (2015). "Surgical outcomes of vascular reconstruction in soft tissue sarcomas of the lower extremities." Journal of Vascular Surgery 62(1): 143-149.

Noel, AA, P Gloviczki, KJ Cherry, H Safi, J Goldstone, MD Morasch and KH Johansen (2002). "Abdominal aortic reconstruction in infected fields: Early results of the United States cryopreserved aortic allograft registry." Journal of Vascular Surgery 35(5): 847-852.

Nussbaum, DP, CN Rushing, WO Lane, DM Cardona, DG Kirsch, BL Peterson and DG Blazer, 3rd (2016). "Preoperative or postoperative radiotherapy versus surgery alone for retroperitoneal sarcoma: a case-control, propensity score-matched analysis of a nationwide clinical oncology database." The Lancet Oncology 17(7): 966-975.

O'Donnell, PW, AM Griffin, WC Eward, A Sternheim, CN Catton, PW Chung, B O'Sullivan, PC Ferguson and JS Wunder (2014). "The effect of the setting of a positive surgical margin in soft tissue sarcoma." Cancer 120(18): 2866-2875.

Ohman, JW, V Chandra, G Poultsides and EJ Harris (2013). "Iliocaval and aortoiliac reconstruction following en bloc retroperitoneal leiomyosarcoma resection." J Vasc Surg 57(3): 850.

Okamoto, K, A Koga, H Tazume, R Noguchi, S Kumamoto, H Satoh, T Sueyoshi and T Fukui (2018). "Early and Mid-Term Outcomes after Vascular Reconstruction for Patients with Lower-Extremity Soft-Tissue Malignant Tumors." Ann Vasc Dis 11(2): 228-232.

Olson, CR, LP Suarez-Kelly, CG Ethun, RD Shelby, PY Yu, TM Hughes, M Palettas, TB Tran, G Poultsides, J Tseng, KK Roggin, K Chouliaras, K Votanopoulos, BA Krasnick, RC Fields, DM King, M Bedi, RE Pollock, VP Grignol, K Cardona and JH Howard (2021). "Resection Status Does Not Impact Recurrence in Well-Differentiated Liposarcoma of the Extremity." The American Surgeon 87(11): 1752-1759.

Palacios, AR, BN Schmeusser, E Midenberg, D Patil, L Xie, R Nabavizadeh, K Ogan, K Cardona, SK Maithel and VA Master (2022). "Resection of retroperitoneal tumors with inferior vena cava involvement without caval reconstruction." Journal of Surgical Oncology 126(7): 1306-1315.

Panagopoulos, I, M Höglund, F Mertens, N Mandahl, F Mitelman and P Aman (1996). "Fusion of the EWS and CHOP genes in myxoid liposarcoma." Oncogene 12(3): 489-494.

Pasquali, S and A Gronchi (2017). "Neoadjuvant chemotherapy in soft tissue sarcomas: latest evidence and clinical implications." Therapeutic Advances in Medical Oncology 9(6): 415-429.

Patrikidou, A, J Domont, A Cioffi and A Le Cesne (2011). "Treating soft tissue sarcomas with adjuvant chemotherapy." Curr Treat Options Oncol 12(1): 21-31.

Pereira, N, Á Cambara, M Kufeke and R Roa (2021). "Prevention and Treatment of Posttraumatic Lymphedema by Soft Tissue Reconstruction With Lymphatic Vessels Free Flap: An Observational Study." Annals of Plastic Surgery 86(4): 434-439.

Pervaiz, N, N Colterjohn, F Farrokhyar, R Tozer, A Figueredo and M Ghert (2008). "A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma." Cancer 113(3): 573-581.

Pisters, PW, LB Harrison, DH Leung, JM Woodruff, ES Casper and MF Brennan (1996). "Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma." Journal of Clinical Oncology 14(3): 859-868.

Pitson, G, P Robinson, D Wilke, RA Kandel, L White, AM Griffin, RS Bell, CN Catton, JS Wunder and B O'Sullivan (2004). "Radiation response: An additional unique signature of myxoid liposarcoma." Int J Radiat Oncol Biol Phys 60(2): 522-526.

Polterauer, P, M Prager, T Hölzenbein, J Karner, G Kretschmer and M Schemper (1992). "Dacron versus polytetrafluoroethylene for Y-aortic bifurcation grafts: a six-year prospective, randomized trial." Surgery 111(6): 626-633.

Popov, P, E Tukiainen, S Asko-Seljaavaara, R Huuhtanen, M Virolainen, P Virkkunen and C Blomqvist (2000). "Soft tissue sarcomas of the lower extremity: surgical treatment and outcome." European Journal of Surgical Oncology 26(7): 679-685.

Poultsides, GA, TB Tran, E Zambrano, L Janson, DG Mohler, MW Mell, RS Avedian, BC Visser, JT Lee, K Ganjoo, EJ Harris and JA Norton (2015). "Sarcoma Resection With and Without Vascular Reconstruction: A Matched Case-control Study." Ann Surg 262(4): 632-640.

Prager, M, P Polterauer, H-J Böhmig, O Wagner, A Fügl, G Kretschmer, M Plohner, J Nanobashvili and I Huk (2001). "Collagen versus gelatin-coated Dacron versus stretch polytetrafluoroethylene in abdominal aortic bifurcation graft surgery: Results of a seven-year prospective, randomized multicenter trial." Surgery 130(3): 408-414.

Puri, A, P Ranganathan, A Gulia, S Crasto, R Hawaldar and RA Badwe (2018). "Does a less intensive surveillance protocol affect the survival of patients after treatment of a sarcoma of the limb?" The Bone & Joint Journal 100-B(2): 262-268.

Quinones-Baldrich, W, A Alktaifi, F Eilber and F Eilber (2012). "Inferior vena cava resection and reconstruction for retroperitoneal tumor excision." J Vasc Surg 55(5): 1386-1393; discussion 1393.

Rabbitts, TH, A Forster, R Larson and P Nathan (1993). "Fusion of the dominant negative transcription regulator CHOP with a novel gene FUS by translocation t(12;16) in malignant liposarcoma." Nat Genet 4(2): 175-180.

Robinson, BI, JP Fletcher, P Tomlinson, RDM Allen, SJ Hazelton, AJ Richardson and K Stuchbery (1999). "A prospective randomized multicentre comparison of expanded polytetrafluoroethylene and gelatin-sealed knitted Dacron grafts for femoropopliteal bypass." Cardiovascular Surgery 7(2): 214-218.

Rojas, M, O Stehno, P Stadler and V P. (2019). "Biointegrated xenograft in management of aortofemoral vascular graft infections." Austin J Surg 6(27): 1236.

Rothermundt, C, JS Whelan, P Dileo, SJ Strauss, J Coleman, TW Briggs, SR Haile and BM Seddon (2014). "What is the role of routine follow-up for localised limb soft tissue sarcomas? A retrospective analysis of 174 patients." British Journal of Cancer 110(10): 2420-2426.

Samà, L, JP Binder, L Darrigues, B Couturaud, B Boura, S Helfre, L Chiche, N Nicolas, D Tzanis, T Bouhadiba, D Gentile, J Perlbarg-Samson and S Bonvalot (2022). "Safe-margin surgery by plastic reconstruction in extremities or parietal trunk soft tissue sarcoma: A tertiary single centre experience." European Journal of Surgical Oncology 48(3): 526-532.

Sampo, M, M Tarkkanen, R Huuhtanen, E Tukiainen, T Böhling and C Blomqvist (2008). "Impact of the smallest surgical margin on local control in soft tissue sarcoma." BJS 95(2): 237-243.

Sampo, MM, M Rönty, M Tarkkanen, EJ Tukiainen, TO Böhling and CP Blomqvist (2012). "Soft tissue sarcoma - a population-based, nationwide study with special emphasis on local control." Acta Oncol 51(6): 706-712.

Samson, RH, R Morales, DP Showalter, MR Lepore, Jr. and DG Nair (2016). "Heparin-bonded expanded polytetrafluoroethylene femoropopliteal bypass grafts outperform expanded polytetrafluoroethylene grafts without heparin in a long-term comparison." Journal of Vascular Surgery 64(3): 638-647.

Sarkar, R, FR Eilber, HA Gelabert and WJ Quinones-Baldrich (1998). "Prosthetic replacement of the inferior vena cava for malignancy." J Vasc Surg 28(1): 75-81; discussion 82-73.

Sbaraglia, M, E Bellan and AP Dei Tos (2020). "The 2020 WHO Classification of Soft Tissue Tumours: news and perspectives." Pathologica - Journal of the Italian Society of Anatomic Pathology and Diagnostic Cytopathology 113(2): 70-84.

Scaglioni, MF, M Meroni, E Fritsche and B Fuchs (2021). "Combined pedicled superficial circumflex iliac artery perforator (SCIP) flap with lymphatic tissue preservation and lymphovenous anastomosis (LVA) for defect reconstruction and lymphedema–lymphocele prevention in thigh sarcoma surgery: Preliminary results." Journal of Surgical Oncology 123(1): 96-103.

Scaglioni, MF, M Meroni, E Fritsche and B Fuchs (2022). "Combined double superficial circumflex iliac artery perforator flap with lymphatic tissue preservation and lymphovenous anastomosis for lymphatic sequelae prevention in thigh defect reconstruction: A case report." Microsurgery 42(3): 265-270.

Schulman, ML, MR Badhey and R Yatco (1987). "Superficial femoral—popliteal veins and reversed saphenous veins as primary femoropopliteal bypass grafts: A randomized comparative study." Journal of Vascular Surgery 6(1): 1-10.

Schwab, JH, PJ Boland, C Antonescu, MH Bilsky and JH Healey (2007). "Spinal metastases from myxoid liposarcoma warrant screening with magnetic resonance imaging." Cancer 110(8): 1815-1822.

Schwarzbach, MH, Y Hormann, U Hinz, L Bernd, F Willeke, G Mechtersheimer, D Böckler, H Schumacher, C Herfarth, MW Büchler and JR Allenberg (2005). "Results of limb-sparing surgery with vascular replacement for soft tissue sarcoma in the lower extremity." J Vasc Surg 42(1): 88-97.

Schwarzbach, MHM, Y Hormann, U Hinz, C Leowardi, D Bockler, G Mechtersheimer, H Friess, MW Buchler and JR Allenberg (2006). "Clinical results of surgery for retroperitoneal sarcoma with major blood vessel involvement." J Vasc Surg 44(1): 46-55.

Setsu, N, M Miyake, S Wakai, F Nakatani, E Kobayashi, H Chuman, N Hiraoka, A Kawai and A Yoshida (2016). "Primary Retroperitoneal Myxoid Liposarcomas." Am J Surg Pathol 40(9): 1286-1290.

Sheah, K, HA Ouellette, M Torriani, GP Nielsen, S Kattapuram and MA Bredella (2008). "Metastatic myxoid liposarcomas: imaging and histopathologic findings." Skeletal Radiol 37(3): 251-258.

Shinoda, Y, E Kobayashi, H Kobayashi, T Mori, N Asano, R Nakayama, H Morioka, S Iwata, T Yonemoto, T Ishii, T Hiruma, A Kawai and H Kawano (2020). "Prognostic factors of metastatic myxoid liposarcoma." BMC Cancer 20(1): 883.

Simon, MP, F Pedeutour, N Sirvent, J Grosgeorge, F Minoletti, JM Coindre, MJ Terrier-Lacombe, N Mandahl, RD Craver, N Blin, G Sozzi, C Turc-Carel, KP O'Brien, D Kedra, I Fransson, C Guilbaud and JP Dumanski (1997). "Deregulation of the platelet-derived growth factor B-chain gene via fusion with collagen gene COL1A1 in dermatofibrosarcoma protuberans and giant-cell fibroblastoma." Nat Genet 15(1): 95-98.

Singer, S, CR Antonescu, E Riedel and MF Brennan (2003). "Histologic subtype and margin of resection predict pattern of recurrence and survival for retroperitoneal liposarcoma." Annals of surgery 238(3): 358-371.

Slump, J, SOP Hofer, PC Ferguson, JS Wunder, AM Griffin, HJ Hoekstra, E Bastiaannet and AC O'Neill (2018). "Flap choice does not affect complication rates or functional outcomes following extremity soft tissue sarcoma reconstruction." Journal of Plastic, Reconstructive & Aesthetic Surgery 71(7): 989-996.

Smith, TA, KA Easley and JR Goldblum (1996). "Myxoid/round cell liposarcoma of the extremities. A clinicopathologic study of 29 cases with particular attention to extent of round cell liposarcoma." Am J Surg Pathol 20(2): 171-180.

Song, TK, EJ Harris, Jr., S Raghavan and JA Norton (2009). "Major blood vessel reconstruction during sarcoma surgery." Arch Surg 144(9): 817-822.

Spierer, MM, KM Alektiar, MJ Zelefsky, MF Brennan and PG Cordiero (2003). "Tolerance of tissue transfers to adjuvant radiation therapy in primary soft tissue sarcoma of the extremity." Int J Radiat Oncol Biol Phys 56(4): 1112-1116.

Spillane, AJ, C Fisher and JM Thomas (1999). "Myxoid liposarcoma--the frequency and the natural history of nonpulmonary soft tissue metastases." Ann Surg Oncol 6(4): 389-394.

Sreekantaiah, C, CP Karakousis, SP Leong and AA Sandberg (1992). "Cytogenetic findings in liposarcoma correlate with histopathologic subtypes." Cancer 69(10): 2484-2495.

Stauffer, JA, GP Fakhre, MK Dougherty, RE Nakhleh, WJ Maples and JH Nguyen (2009). "Pancreatic and multiorgan resection with inferior vena cava reconstruction for retroperitoneal leiomyosarcoma." World J Surg Oncol 7: 3.

Suzman, MS, AJ Smith and MF Brennan (2000). "Fascio-peritoneal patch repair of the IVC: a workhorse in search of work?" J Am Coll Surg 191(2): 218-220.

Tameo, MN, KD Calligaro, L Antin and MJ Dougherty (2010). "Primary leiomyosarcoma of the inferior vena cava: Reports of infrarenal and suprahepatic caval involvement." Journal of Vascular Surgery 51(1): 221-224.

Tan, MCB, MF Brennan, D Kuk, NP Agaram, CR Antonescu, L-X Qin, N Moraco, AM Crago and S Singer (2016). "Histology-based Classification Predicts Pattern of Recurrence and Improves Risk Stratification in Primary Retroperitoneal Sarcoma." Annals of surgery 263(3): 593-600.

Tanaka, K and T Ozaki (2018). "New TNM classification (AJCC eighth edition) of bone and soft tissue sarcomas: JCOG Bone and Soft Tissue Tumor Study Group." Japanese Journal of Clinical Oncology 49(2): 103-107.

Teixeira, FJ, SDD Netto, ALD Perina, FCM Torricelli, LR Teixeira, AE Zerati, FD Ferreira, EH Akaishi, WC Nahas and EM Utiyama (2017). "Leiomyosarcoma of the inferior vena cava: Survival rate following radical resection." Onc Let 14(4): 3909-3916.

ten Heuvel, SE, HJ Hoekstra, RJ van Ginkel, E Bastiaannet and AJH Suurmeijer (2007). "Clinicopathologic Prognostic Factors in Myxoid Liposarcoma: A Retrospective Study of 49 Patients With Long-Term Follow-Up." Ann Surg Oncol 14(1): 222-229.

Teo, MC, PK Chow and KC Soo (2005). "Surgery for retroperitoneal sarcoma requiring major vascular resection and reconstruction." Asian J Surg 28(4): 312-315.

Toulmonde, M, S Bonvalot, P Méeus, E Stoeckle, O Riou, N Isambert, E Bompas, M Jafari, C Delcambre-Lair, E Saada, A Le Cesne, C Le Péchoux, JY Blay, S Piperno-Neumann, C Chevreau, JO Bay, V Brouste, P Terrier, D Ranchère-Vince, A Neuville, A Italiano and G French Sarcoma (2014). "Retroperitoneal sarcomas: patterns of care at diagnosis, prognostic factors and focus on main histological subtypes: a multicenter analysis of the French Sarcoma Group." Ann Onc 25(3): 735-742.

Touma, J, F Cochennec, J Parisot, A Fialaire Legendre, JP Becquemin and P Desgranges (2014). "In Situ Reconstruction in Native and Prosthetic Aortic Infections Using Cryopreserved Arterial Allografts." European Journal of Vascular and Endovascular Surgery 48(3): 292-299.

Tseng, JF, MT Ballo, HN Langstein, JD Wayne, JN Cormier, KK Hunt, BW Feig, AW Yasko, VO Lewis, PP Lin, CP Cannon, GK Zagars, RE Pollock and PWT Pisters (2006). "The Effect of Preoperative Radiotherapy and Reconstructive Surgery on Wound Complications after Resection of Extremity Soft-Tissue Sarcomas." Annals of Surgical Oncology 13(9): 1209-1215.

Tsukushi, S, Y Nishida, H Sugiura, H Nakashima and N Ishiguro (2008). "Results of limb-salvage surgery with vascular reconstruction for soft tissue sarcoma in the lower extremity: Comparison between only arterial and arterovenous reconstruction." Journal of Surgical Oncology 97(3): 216-220.

Turc-Carel, C, J Limon, P Dal Cin, U Rao, C Karakousis and AA Sandberg (1986). "Cytogenetic studies of adipose tissue tumors. II. Recurrent reciprocal translocation t(12;16)(q13;p11) in myxoid liposarcomas." Cancer Genetics and Cytogenetics 23(4): 291-299.

Tyler, R, K Wanigasooriya, P Taniere, M Almond, S Ford, A Desai and A Beggs (2020). "A review of retroperitoneal liposarcoma genomics." Cancer Treat Rev 86.

Umezawa, H, M Sakuraba, S Miyamoto, S Nagamatsu, S Kayano and M Taji (2013). "Analysis of immediate vascular reconstruction for lower-limb salvage in patients with lower-limb bone and soft-tissue sarcoma." J Plast Reconstr Aesthet Surg 66(5): 608-616.

van Zitteren, M, TJ van der Steenhoven, DHC Burger, DP van Berge Henegouwen, JMM Heyligers and PWHE Vriens (2011). "Spiral Vein Reconstruction of the Infected Abdominal Aorta Using the Greater Saphenous Vein: Preliminary Results of the Tilburg Experience." European Journal of Vascular and Endovascular Surgery 41(5): 637-646.

Visgauss, JD, DA Wilson, DL Perrin, R Colglazier, R French, J-C Mattei, AM Griffin, JS Wunder and PC Ferguson (2021). "Staging and Surveillance of Myxoid Liposarcoma: Follow-up Assessment and the Metastatic Pattern of 169 Patients Suggests Inadequacy of Current Practice Standards." Ann Surg Oncol.

Vos, M, WC Boeve, TM van Ginhoven, S Sleijfer, C Verhoef and DJ Grünhagen (2019). "Impact of primary tumor location on outcome of liposarcoma patients, a retrospective cohort study." Eur J Surg Oncol 45(12): 2437-2442.

Vysis. M. I. Abbott. Abbott Park, Illinois, U.S.A.

Wachtel, H, BM Jackson, EK Bartlett, GC Karakousis, RE Roses, JE Bavaria and DL Fraker (2015). "Resection of primary leiomyosarcoma of the inferior vena cava (IVC) with reconstruction: a case series and review of the literature." J Surg Oncol 111(3): 328-333.

Wang, Q, J Jiang, C Wang, G Lian, MS Jin and X Cao (2012). "Leiomyosarcoma of the inferior vena cava level II involvement: curative resection and reconstruction of renal veins." World J Surg Oncol 10: 120.

Weichman, K, RJ Allen, Jr., V Thanik, E Matros and BJ Mehrara (2015). "Adipofascial Anterolateral Thigh Free Flaps for Oncologic Hand and Foot Reconstruction." J Reconstr Microsurg 31(9): 684-687.

Weiss, S, B Bachofen, MK Widmer, V Makaloski, J Schmidli and TR Wyss (2021). "Long-term results of cryopreserved allografts in aortoiliac graft infections." Journal of Vascular Surgery 74(1): 268-275.

Weiss, S, E-L Tobler, H von Tengg-Kobligk, V Makaloski, D Becker, TP Carrel, J Schmidli and TR Wyss (2017). "Self Made Xeno-pericardial Aortic Tubes to Treat Native and Aortic Graft Infections." European Journal of Vascular and Endovascular Surgery 54(5): 646-652.

Weiss, SW and VK Rao (1992). "Well-Differentiated Liposarcoma (Atypical Lipoma) of Deep Soft Tissue of the Extremities, Retroperitoneum, and Miscellaneous Sites: A Follow-up Study of 92 Cases with Analysis of the Incidence of “Dedifferentiation”." The American Journal of Surgical Pathology 16: 1051-1058.

Wigge, S, K Heißner, V Steger, R Ladurner, F Traub, B Sipos, H Bösmüller, L Kanz, F Mayer and HG Kopp (2018). "Impact of surgery in patients with metastatic soft tissue sarcoma: A monocentric retrospective analysis." J Surg Oncol 118(1): 167-176.

Wise, KB, SM Said, CJ Clark, SH Okuno, SS Shah, SJ Park, DM Nagorney and P Gloviczki (2012). "Resection of a giant primary synovial sarcoma of the inferior vena cava extending into the right atrium with caval reconstruction under cardiopulmonary bypass and circulatory arrest." Perspect Vasc Surg Endovasc Ther 24(2): 95-101.

Wunder, JS, JH Healey, AM Davis and MF Brennan (2000). "A comparison of staging systems for localized extremity soft tissue sarcoma." Cancer 88(12): 2721-2730.

Yamamoto, H, F Yamamoto, K Ishibashi and M Motokawa (2009). "In situ replacement with equine pericardial roll grafts for ruptured infected aneurysms of the abdominal aorta." Journal of Vascular Surgery 49(4): 1041-1045.

Yamamoto, T, T Iida, H Yoshimatsu, Y Fuse, A Hayashi and N Yamamoto (2018). "Lymph Flow Restoration after Tissue Replantation and Transfer: Importance of Lymph Axiality and Possibility of Lymph Flow Reconstruction without Lymph Node Transfer or Lymphatic Anastomosis." Plastic and Reconstructive Surgery 142(3): 796-804.

Yamamoto, T, N Yamamoto, T Kageyama, H Sakai, Y Fuse and R Tsukuura (2021). "Lymph-interpositional-flap transfer (LIFT) based on lymph-axiality concept: Simultaneous soft tissue and lymphatic reconstruction without lymph node transfer or lymphatic anastomosis." Journal of Plastic, Reconstructive & Aesthetic Surgery 74(10): 2604-2612.

Yang, JC, AE Chang, AR Baker, WF Sindelar, DN Danforth, SL Topalian, T DeLaney, E Glatstein, SM Steinberg, MJ Merino and SA Rosenberg (1998). "Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity." Journal of Clinical Oncology 16(1): 197-203.

Zagars, GK, MT Ballo, PW Pisters, RE Pollock, SR Patel and RS Benjamin (2003). "Preoperative vs. postoperative radiation therapy for soft tissue sarcoma: a retrospective comparative evaluation of disease outcome." Int J Radiat Oncol Biol Phys 56(2): 482-488.

Zagars, GK, MS Goswitz and A Pollack (1996). "Liposarcoma: Outcome and prognostic factors following conservation surgery and radiation therapy." Int J Radiat Oncol Biol Phys 36(2): 311-319.