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German Guideline Program in Oncology (GGPO)

Evidence-based Guidelines: Soft Tissue Sarcoma

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Guideline (Long Version)

DKG KREBSGESELLSCHAFT
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Important Updates

Amendment (März 2022, Version 1.1)

The guideline underwent an amendment in March 2022 resulting in version 1.1.
In chapter 10.1.4 (Clinical Management of metastatic GIST) a recommendation on the use of ripretinib was added.

English Version

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1.1. Editors

Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (AWMF), Deutschen Krebsgesellschaft e. V. (DKG) und der Stiftung Deutsche Krebshilfe (DKH).

1.2. Leading Scientific Societies

Arbeitsgemeinschaft internistische Onkologie der Deutschen Krebsgesellschaft e. V. (AIO)

Deutsche Krebsgesellschaft (DKG) vertreten durch IhrevArbeitsgemeinschaften

German Interdisciplinary Sarcoma Group (GISG)

1.3. Funding of the Guideline

This guideline was supported by the German Cancer Aid within the framework of the guideline program oncology.

1.4. Contact

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1.5. How to cite

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1.6. Previous Changes

March 2022, Version 1.02: Addition of a recommendation on ripretinib (see Recommendation 10.28.).

1.7. Special Comment

Medicine is subject to a continuous development process, so that all information, in particular on diagnostic and therapeutic procedures, can only correspond to the state of knowledge at the time of printing of the guideline. The greatest possible care has been taken with regard to the recommendations given for therapy and the selection and dosage of medications. Nevertheless, users are urged to consult the manufacturers' package inserts and expert information for verification and, in case of doubt, to consult a specialist. In the general interest, any discrepancies should be reported to the OL editorial office.

The user himself remains responsible for any diagnostic and therapeutic application, medication and dosage.

In this guideline, registered trademarks (protected trade names) are not specially marked. It can therefore not be concluded from the absence of a corresponding reference that it is a free trade name.

1.8. Objectives of the Guideline Program for Oncology

The Association of the Scientific Medical Societies in Germany (AWMF), the German Cancer Society (DKG) and the German Cancer Aid Foundation (Stiftung Deutsche Krebshilfe) have set themselves the goal of jointly promoting and supporting the development, updating and use of scientifically based and practicable guidelines in oncology with the German Guideline Program in Oncology (OL). The basis of this program is based on the medical-scientific findings of the professional societies and the DKG, the consensus of medical experts, users and patients, as well as on the set of rules for guideline development of the AWMF and the professional support and funding by the German Cancer Aid. In order to reflect the current state of medical knowledge and to take medical progress into account, guidelines must be regularly reviewed and updated. The application of the AWMF regulations should be the basis for the development of high-quality oncological guidelines. Since guidelines are an important instrument of quality assurance and quality management in oncology, they should be introduced into everyday care in a targeted and sustainable manner. Thus, active implementation measures and also evaluation programs are an important part of the promotion of the German Guideline Program in Oncology. The aim of the program is to create professional and medium-term financially secure conditions for the development and provision of high-quality guidelines in Germany. This is because these high-quality guidelines not only serve the structured transfer of knowledge, but can also find their place in shaping the structures of the healthcare system. Mention should be made here of evidence-based guidelines as a basis for creating and updating disease management programs or the use of quality indicators extracted from guidelines as part of the certification of organ tumor centers.

1.9. Additional Documents relating to this Guideline

This document is the long version of the S3 guideline „Adult soft tissue sarcomas“. In addition to the long version, there will be the following supplementary documents to this guideline:

- Guideline report on the guideline development process.
- Document with extraction tables for the guideline
- Evidence report
- Short version of the guideline
- Patient guideline (lay version)

The guideline is also included in the Guideline Program Oncology app.

For more information, visit: https://www.leitlinienprogramm-onkologie.de/app/

This guideline and all supplementary documents can be accessed via the following sites.

- AWMF (http://www.awmf.org/leitlinien/aktuelle-leitlinien.html)
- German Guideline Program in Oncology (https://www.leitlinienprogramm-onkologie.de/leitlinien/adulte-weichgewebesarkome/)
- Guidelines International Network (https://g-i-n.net/)

1.10. Composition of the Guideline Group

1.10.1. Guideline Coordination

The coordinators were appointed by the lead professional society (GISG). The composition and distribution of tasks of the guideline steering group were determined by them as follows:

Coordinators	Prof. Dr. med. Peter Hohenberger; Mannheim Prof. Dr. med. Bernd Kasper; Mannheim Prof. Dr. med. Viktor Grünwald; Essen
Editors	Dr. rer. nat. Vlada Kogosov; Mannheim

The tasks of the steering group included contacting and feeding back to the participating professional societies and organizations, implementation of the methodological specifications, preparation of a project plan, management of the financial resources, support of the content-related work of the experts, compilation and editing of the texts prepared by the experts and working groups, and documentation of a guideline report.

Steering Group

Prof. Dr. med. Hans Roland Dürr; München
Prof. Dr. med. Viktor Grünwald; Essen
Prof. Dr. med. Peter Hohenberger; Mannheim
Prof. Dr. med. Bernd Kasper; Mannheim
PD Dr. med. Peter Reichardt; Berlin
Prof. Dr. med. Eva Wardelmann; Münster

Scientific Advice

Physicians from the Competence Center Oncology of the GKV-Spitzenverband and the MDK Association were involved in an advisory capacity in the development of this S3 guideline on individual aspects with sociomedical relevance.

They did not participate in the voting on the individual recommendations and are not responsible for the content of this guideline.

1.10.2. Involved Professional Societies and Organisations

Table 1: Involved Professional Societies and Organisations

Participating professional associations and organizations (alphabetical)	Representative(s)
Arbeitsgemeinschaft Bildgebung in der Onkologie der DKG (ABO)	Prof. Dr. Benedikt Schaarschmidt
Arbeitsgemeinschaft Dermatologische Onkologie der DKG und DDG (ADO)	Prof. Dr. Selma Ugurel Dr. Carsten Weishaupt (1)
Arbeitsgemeinschaft erbliche Tumorerkrankungen in der DKG (AET)	Prof. Dr. Jens Chemnitz
Arbeitsgemeinschaft für Psychoonkologie in der DKG (PSO)	Dipl.-Psych. Beate Hornemann Dipl.-Psych. Leopold Hentschel (1)
Arbeitsgemeinschaft Gynäkologische Onkologie der DGGG und DKG (AGO)	Prof. Dr. Ingolf Juhasz-Böss
Arbeitsgemeinschaft Internistische Onkologie in der DKG (AIO)	Prof. Dr. med. Sebastian Bauer
Arbeitsgemeinschaft onkologische Pathologie in der DKG (AOP)	Prof. Dr. med. Eva Wardelmann
Arbeitsgemeinschaft Onkologische Rehabilitation und Sozialmedizin (AGORS)	Dr. med. Mario Schubert
Arbeitsgemeinschaft Pädiatrische Onkologie (APO)	PD Dr. med. Simone Hettmer

Participating professional associations and organizations (alphabetical)	Representative(s)
Arbeitsgemeinschaft Palliativmedizin in der DKG (APM)	Dr. Anne Flörcken Prof. Dr. Anne Letsch (1)
Arbeitsgemeinschaft Prävention und integrative Medizin in der Onkologie in der DKG (PRIO)	Prof. Dr. med. Jörg Thomas Hartmann
Arbeitsgemeinschaft Radioonkologie in der DKG (ARO)	Dr. med. Christina Jentsch Dr. med. Anna Simeonova-Chergou (1)
Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie (AGSMO)	Prof. Dr. med. Gerlinde Egerer
Arbeitsgemeinschaft Urologische Onkologie der Deutschen Krebsgesellschaft e. V. (AUO)	Prof. Dr. Jens Bedke
Arbeitsgemeischaft Onkologische Thoraxchirurgie in der DKG (AOT)	Prof. Dr. med. Thomas Graeter
Berufsverband der Deutschen Chirurgen e.V. (BDC)	Prof. Dr. Wolfram Trudo Knoefel Dr. med. Hany Ashmawy (1)
Berufsverband der Niedergelassenen Hämatologen und Onkologen e.V. (BNHO)	Prof. Dr. med. Joachim Schütte
Berufsverband Deutscher Strahlentherapeuten e.V. (BVDST)	Prof. Dr. Oliver Micke
Berufsverband für Orthopädie und Unfallchirurgie e.V. (BVOU)	Prof. Dr. med. Hanns-Peter Scharf (3) PD. Dr. med. Dimosthenis Andreou (4)
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Beteiligte Fachexperten ohne Stimmrecht	PD Dr. med. Sylke Zeißig Prof. Dr. med. Anja Hermann
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Participating professional associations and organizations (alphabetical)	Representative(s)
Deutsche Gesellschaft für Allgemein- u. Viszeralchirurgie (DGAV)	Prof. Dr. med. Robert Grützmann
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Deutsche Gesellschaft für Interventionelle Radiologie und minimal-invasive Therapie (DeGIR)	Prof. Dr. Andreas Mahnken
Deutsche Gesellschaft für Mund-, Kiefer- und Gesichtschirurgie (DGMKG)	Prof. Dr. Dr Jürgen Hoffmann PD Dr. Dr. Falk Birkenfeld Prof. Dr. Dr. Benedicta Beck-Broichsitter (5)
Deutsche Gesellschaft für Neurochirurgie e.V. (DGNC)	Prof. Dr. med. Cordula Matthies PD Dr. med. Rezvan Ahmadi (1)
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Deutsche Gesellschaft für Unfallchirurgie e.V. (DGU)	Prof. Dr. Thomas Gösling
Deutsche Röntgengesellschaft e.V. (DRG)	Prof. Dr. med. Rolf Janka
Deutsche Sarkom-Stiftung	Markus Wartenberg
German Interdisciplinary Sarcoma Group (GISG)	PD Dr. med. Peter Reichardt

Participating professional associations and organizations (alphabetical)	Representative(s)
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Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO)	Prof. Dr. Jalid Sehouli Prof. Dr. Alexander Mustea (1)

1: substitute, 2: subsitute: Dipl.-Psych. Leopold Hentschel, 3: 2017-2019, 4: seit 2019, 5: substitute for Prof. Hoffmann

In addition, the following professional societies were contacted for the guideline process:

- DGU (German Society of Urology); however, this society did not respond to the request and did not nominate any representatives.
- ATO (Arbeitsgemeinschaft Tumorklassifikation in der Onkologie in der DKG); does not participate in the guideline development due to lack of resources.
- KOK (Konferenz onkologischer Kranken- und Kinderkrankenpflege in der DKG); does not participate in the guideline development due to lack of resources.
- ZVK (Deutscher Verband für Physiotherapie e.V.); does not participate in the guideline development due to lack of resources.

Table 2: Composition of Guideline Workgroups

Workgroup	Composition of Workgroup
WG 3: Epidemiology, Risk factors, and Prevention	**Directorship: PD Dr. med. Simone Hettmer** Prof. Dr. med. Abbas Agaimy Prof. Dr. Jens Chemnitz Prof.Dr. Jaild Sehouli Prof. Dr. med. Eva Wardelmann PD Dr. med. Sylke Zeißig
WG 4: Diagnosis, Prognostic markers and scores	**Directorship: Prof. Dr. med. Eva Wardelmann** Prof. Dr. med. Abbas Agaimy Prof. Dr. Moritz Felcht Prof. Dr. med. Florian Haller Prof. Dr. med. Rolf Janka PD Dr. med. Burkhard Lehner Prof. Dr. Andreas Mahnken Prof. Dr. Benedikt Schaarschmidt Prof. Dr. med. Klemens Scheidhauer Prof. Dr. Philipp Ströbel
WG 5: Therapy of localized soft tissue tumors	**Directorship: Prof. Dr. Peter Hohenberger** Prof. Dr. Wilfried Budach Prof. Dominik Denschlag Prof. Dr. Hans Roland Dürr Prof. Dr. Thomas Gösling Prof. Dr. med. Thomas Graeter Prof. Dr. med. Robert Grützmann Prof. Dr. med. Jens Jakob Prof. Dr. Ingolf Juhasz-Böss PD Dr. med. Burkhard Lehner Prof. Dr. Marcus Lehnhardt Prof. Dr. med. Lars Lindner

Workgroup	Composition of Workgroup
	PD Dr. med. Peter Reichardt Prof. Dr. Selma Ugurel PD Dr. med. Johannes Veit
WG 6: Therapy of local recurrence	**Directorship: Prof. Dr. Wilfried Budach** PD. Dr. med. Dimosthenis Andreou Prof. Dr. Jens Bedke Prof. Dr. Dr Jürgen Hoffmann Dr. med. Christina Jentsch Prof. Dr. Wolfram Trudo Knoefel Prof. Dr. med. Cordula Matthies Prof. Dr. Oliver Micke
WG 7: Systemic therapy	**Directorship: Prof. Dr. med. Bernd Kasper** Prof. Dr. med. Sebastian Bauer Prof. Dr. med. Uta Dirksen Prof. Dr. med. Uta Dirksen, Essen PD Dr. med. Steffen Frese Prof. Dr. Viktor Grünwald Dr. med. Christina Jentsch Prof. Dr. med. Lars Lindner Prof. Dr. Andreas Mahnken PD Dr. med. Peter Reichardt Prof. Dr. med. Joachim Schütte Markus Wartenberg
WG 8: Rehabilitation and Aftercare	**Directorship: Dr. med. Mario Schubert** Prof. Dr. Hans Roland Dürr Prof. Dr. med. Gerlinde Egerer Susanne Gutermuth Prof. Dr. med. Jörg Thomas Hartmann Prof. Dr. med. Rolf Janka Prof. Dr. Marcus Lehnhardt
WG 9: Psychooncology, psychosocial and palliative issues	**Directorship: Dr. med. Ulrike Schneider** Prof. Dr. med. Anja Hermann Dipl.-Psych. Beate Hornemann Prof. Dr. Karin Oechsle Markus Wartenberg
WG 10: Quality Indicators	PD. Dr. med. Dimosthenis Andreou Prof. Dr. Peter Hohenberger Prof. Dr. med. Jens Jakob Prof. Dr. med. Bernd Kasper PD Dr. med. Sylke Zeißig
WG 11: Specifics of sarcoma subtypes and localizations	**Directorship: Prof. Dr. med. Sebastian Bauer** Prof. Dr. Peter Hohenberger Prof. Dr. med. Eva Wardelmann

1.10.3. Patient Involvement

Two representatives of the German Sarcoma Foundation, Ms. Susanne Gutermuth and Mr. Markus Wartenberg, are actively integrated into the guideline development process with voting rights in order to adequately consider the patients' perspective. Both

are represented in the working groups and are involved in the process of drafting recommendations and background texts. The mandate holders are involved in the design and final approval of the patient guideline.

1.10.4. Methodological Support

By the German Guideline Program in Oncology:

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- Dr. Monika Nothacker, MPH (AWMF-Institut für Medizinisches Wissensmanagement)
- Dr. Markus Follmann, MPH, MSc (Office des Leitlinienprogramms Onkologie c/o Deutsche Krebsgesellschaft e.V.)
- Dipl.-Soz. Wiss. Thomas Langer (Office des Leitlinienprogramms Onkologie c/o Deutsche Krebsgesellschaft e.V.)
- Dipl. Biologe Gregor Wenzel (Office des Leitlinienprogramms Onkologie c/o Deutsche Krebsgesellschaft e.V.)

1.11. Abbreviations Used

Table 3: Abbreviations Used

Abbreviation	Explanation
5-HT3-RA	5-hydroxytryptamine-3 receptor antagonist
ACS-NSQIP	American College of Surgeons National Surgical Quality Improvement Program
AFIP	Armed Forces Institute of Pathology
AFX	atypical fibroxanthoma
AGIHO	Working Group on Infections in Haematology and Oncology
AHB	Follow-up treatment
AIO	Working Group on Internal Oncology of the DKG
AJCC	American Joint Committee on Cancer
ALT	atypical lipomatous tumour
AML	Acute myeloid leukaemia
AR	Follow-up rehabilitation measure
ARMS	Alveolar rhabdomyosarcoma
ASORS	Working Group on Supportive Measures in Oncology, Rehabilitation and Social Medicine
AWMF	Working Group of the Scientific Medical Societies

Abbreviation	Explanation
BAR	Federal Working Group for Rehabilitation
bzw.	respectively
C-Kit	Tyrosine Protein Kinase Kit, Tyrosine Kinase
CCSS	Childhood Cancer Survivor Study
CD	Cluster of Differentiation
CDC	Centres for Disease Control
CI	Confidence interval
CoI	Conflict of Interest
COSMIC	Catalogue Of Somatic Mutations In Cancer
CR	Complete remission
CT	Computed tomography
CTV	Clinical target volume
CTX	Chemotherapy
CWS	Cooperative Soft Tissue Sarcoma Study Group
DFS	disease-free survival
DFSP	Dermatofibrosacoma protuberans
DKG	German Cancer Society
DKH	German Cancer Aid Foundation
DNA	Deoxyribonucleic acid
DRV	German Pension Insurance
DSA	Digital subtraction angiography
DSS	Disease-specific survival
DTIC	Dacarbazine
EBV	Epstein-Barr virus
e. g.	for example

Abbreviation	Explanation
EHE	Epithelioid haemangioendothelioma
EIA	Etoposide, ifosfamide, adriamycin
EK	Expert consensus
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society of Medical Oncology
FAP	familial adenomatous polyposis coli
FDA	Food and Drug Administration
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
FISH	Flourescence in situ hybridisation
FNCLCC	Fédération Nationale des Centres de Lutte Contre le Cancer
FSG	French Sarcoma Group
G-CSF	Granulocyte colony-stimulating factor
G-BA	Federal Joint Committee
GI	gastrointestinal
GIN	Guidelines International Network
GISG	German Interdisciplinary Sarcoma Group e.V.
GIST	Gastrointestinal Stromatutmor
GKV	Statutory Health Insurance
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GTV	Macroscopic tumour volume (gross tumour volume)
HG-ESS	High-grade endometrial stromal sarcoma
HIV	Human immunodeficiency virus
HPF	High-power field (high-resolution field of view)
HR	Hazard ratio

Abbreviation	Explanation
HT	Hyperthermia
i.v.	intravenous
ICD-10	International Statistical Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
ICF	International Classification of Functioning, Disability and Health
IFOM	Institute for Research in Operative Medicine
IGRT	Image-guided radiation therapy
ILP	Isolated Limb Perfusion (ISP)
IMRT	Intensity modulated radiotherapy
IMT	Inflammatory myofibroblastic tumour
INKA	Information network for cancer patients and relatives
IOERT	Intraoperative electron radiation therapy
IORT	Intraoperative radiotherapy
IRLM	International Registry of Lung Metastases
ISG	Italian Sarcoma Group
ISKS	International Sarcoma Kindred Study
KIT	KIT protooncogene
KM	Contrast agent
LDH	Lactate dehydrogenase
LG-ESS	Low-grade endometrial stromal sarcoma
LGFMS	Low-grade fibromyxoid sarcoma
LK	Lymph node
LMS	Leiomyosarcoma
LPFS	Local progression-free survival
LPS	Liposarcoma

Abbreviation	Explanation
LR	Local recurrence
LRFS	Local recurrence-free survival
MASCC	Multinational Association of Supportive Care in Cancer
MDK	Medical service of the health insurance
MFH	Malignant fibrous histiocytoma
MFS	metastasis-free survival
mg	Milligram
mm	Millimetre
MPNST	Malignant peripheral nerve sheath tumour
MRT	Magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
nb	Not determinable
NCDB	National Cancer Database (USA)
NCI	National Cancer Institute
NF1	Neurofibromatosis type 1
NGS	Next-Generation Sequencing
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NK1-RA	Neurokinin-1 receptor antagonist
NOCCA	Nordic Occupational Cancer
NOS	Not otherwise specified
OL	Office of the Guideline Programme in Oncology (DKG)
OP	Surgery
OR	Odds Ratio
OS	Overall survival

Abbreviation	Explanation
PCR	Polymerase chain reaction
PD	Progressive Disease
PDGFR	Platelet derived growth factor receptor
PDS	Pleomorphic dermal sarcoma
PEOPSA	Psychosocial initial counselling of oncological patients by social work in in-patient care
PET	Positron emission tomography
PFS	Progression-free survival
PICO	Population Intervention Comparison Outcome
PNET	Primitive neuroectodermal tumour
PR	Partial remission, partial remission
PTV	Planning target volume
QoL	Quality of life
RFA	Radiofrequency ablation
RHT	Regional deep hyperthermia
RNA	Ribonucleic acid
RPS	Retroperitoneal sarcoma
RR	Risk ratio (relative risk)
RT-PCR	Reverse transcriptase-polymerase chain reaction
RTOG	Radiation Therapy Oncology Group
RTX	Radiotherapy
s.u.	see below
SDH	Succinate dehydrogenase
SEER	Surveillance, Epidemiology, and End Results (USA)
SEF	Sclerosing epithelioid fibrosarcoma
SFT	Solitary fibrous tumour

Abbreviation	Explanation
SGB	Social Code
SGHT	Systemic whole-body hyperthermia
SIRS	Systemic inflammatory response syndrome
SIRT	Selective internal radiotherapy
SLNB	sentinel lymph node biopsy
SPV	Specialised palliative care
SS	Synovial sarcoma
STS	Soft tissue sarcoma
TACE	Transarterial chemoembolisation
TARPSWG	Trans-Atlantic Retroperitoneal Sarcoma Working Group
TNF	Tumour necrosis factor
TNM-Klassifikation	Classification according to T=tumour, N=nodes, lymph nodes and M=metastases (tumour-nodes-metastases)
TRK	Tropomyosin receptor kinase
UESL	Undifferentiated embryonal sarcoma of the liver
UICC	UICC (Union internationale contre le cancer) classification
UPS	Undifferentiated pleomorphic sarcoma
UUS	Undifferentiated uterine sarcoma
VAC	Vacuum therapy (vacuum assisted closure-therapy)
VMAT	Volumetric modulated arc therapy (VMAT)
vs.	versus
WHO	World Health Organization
WT	Wild-type
Abbreviation	Explanation
5-HT3-RA	5-hydroxytryptamine-3 receptor antagonist

2. Introduction

2.1. Scope and Purpose

2.1.1. Objective and Key Questions

The primary goal of the present S3 guideline „Adult soft tissue sarcomas“ is to develop recommendations for evidence-based diagnostics and therapy depending on histology and tumor stage. This applies to adequate imaging, histological confirmation, surgical primary therapy, drug treatment, including the use and timing of different modalities and combinations in the different stages of the disease, and follow-up needs of individual tumour sub-types.. The treatment of rare subtypes as well as hereditary variants will also be addressed. The aim is to prolong the overall survival of patients and improve their quality of life. So far, there are expert recommendations for optimal treatment in German-speaking countries and in Europe; however, a guideline supported by the professional societies and other organizations involved in care is not available.

The development of the S3-guideline „Adult soft tissue sarcoma“ is intended to improve the quality and standardization of procedures for adult soft tissue sarcoma and to standardize the necessary and required diagnostic measures, surgical and medical or other local therapy measures. In particular, the histopathological and molecular biological workup of the tumors must be standardized for the best possible therapy. Furthermore, it is necessary to provide uniform therapy and to use quality specifications. The different available components of therapy and their best possible combination will be comparatively evaluated.

Some treatment procedures are almost exclusively available for soft tissue sarcoma patients, such as isolated limb perfusion with recombinant human tumor necrosis factor alpha, regional deep hyperthermia or liposomal cytostatics. It is the aim of the guidelines to describe the significance of these procedures and to formulate recommendations for their use or non-use. For patients with soft tissue sarcoma, this should result in optimized comprehensive care. Another specific goal of this guideline is to report and rate the postoperative mortality of different treatment options in patients with retroperitoneal sarcoma (RPS).

By implementing the S3-guideline „Adult Soft Tissue Sarcoma“ a better quality oriented care for patients, also considering health economic aspects, should be achieved.

This S3 guideline examines the following clinical questions:

Epidemiology, risk factors and prevention.

- How frequently does soft tissue sarcoma occur in Germany, broken down by gender?
- What is the frequency distribution in relation to age?
- What is the frequency of the different subtypes of soft tissue sarcoma?
- What is the proportion of secondary sarcomas after another malignancy, especially after radiotherapy?
- Are there validated risk factors for the occurrence of soft tissue sarcoma? Does this pertain to specific histologic subtypes?

- Which hereditary tumor syndromes are associated with an increased risk of soft tissue sarcoma occurrence?
- Are there validated measures (regarding diet, addictive habits, exercise) that prevent the occurrence of soft tissue sarcoma?

Diagnostics, prognostic markers and scores

- Which imaging techniques should be used for diagnosis?
- In which cases should a biopsy be performed (recommended procedure, technique)?
- Which histopathological diagnostic procedures are necessary to confirm the diagnosis (minimum requirements for accurate findings)?
- Are there clinical parameters that influence the prognosis of the disease?
- Are there validated clinical prognosis scores?
- Which molecular markers are identified as prognostic or predictive markers, depending on the histological subtype? (Significance in clinical practice)

Therapy of the localized soft tissue tumor

- What is the standard procedure for surgery of localized soft tissue sarcomas (e.g., extremities, trunk, retroperitoneal, visceral, etc.)?
- What are the standards to be followed prior for histopathologic evaluation?
- What standards apply to resection margins?
- What plastic/reconstructive measures, if any, are required in the treatment of localized disease?
- What is the value of radiotherapy in localized soft tissue sarcoma?
- Which radiation dose and which radiation field are indicated depending on tumor type and localization (neoadjuvant, intraoperative, adjuvant)?
- What is the importance of neoadjuvant/adjuvant systemic therapy?
- What is the value of hyperthermia and isolated limb perfusion?
- Patient education

Therapy of isolated local recurrence

- What is the incidence and prognosis of local recurrence?
- What is the value of systemic therapy?
- What is the procedure for patients who have undergone surgery alone?
- What measures apply if radiotherapy has already been performed?

Therapy of metastatic disease

- What first-line/second-line agents are available for the treatment of metastatic soft tissue sarcoma?
- Are there recommended therapy sequences or therapy combinations?
- What is the value, depending on the different metastatic sites, of local ablative procedures (surgery, radiotherapy, RFA, SIRT, etc.)? Which techniques should be used?
- What supportive measures are useful in the context of therapy for metastatic soft tissue sarcoma?

Rehabilitation and aftercare

- What is the role of physiotherapy and rehabilitation in completing therapy for patients?
- What long-term toxicities (e.g., cardiovascular toxicity) need to be considered and how are they treated/controlled?

- At what intervals and over how many years should follow-up be performed in the localized stage?
- At what intervals should follow-up be performed in the metastatic stage?
- What measures are included in follow-up (localized/metastatic)? What imaging should be performed (CT, MRI)? How often is imaging indicated?

Psycho-oncological, psychosocial and palliative medical aspects

- What psycho-oncological services should be available to a patient with soft tissue sarcoma?

Gastrointestinal stromal tumors

- What are the diagnostic requirements for GIST?
- What are the requirements for pathological diagnostics?
- What is the significance of the imatinib-sensitive mutation?
- What is the standard procedure for gastrointestinal stromal tumor surgery?
- What standards apply to resection margins?
- What is the value of adjuvant imatinib therapy (400 mg/day) in GIST?
- What agents are available in first-line/second-line/third-line and for specific GIST subtypes to treat the metastatic setting?

2.1.2. Target Audience

Primary addressees of the guideline are physicians and members of other health care professions involved in the diagnosis, therapy and follow-up of patients with soft tissue sarcoma (all stages; outpatient and inpatient care as well as rehabilitation). Here, surgeons/surgical oncologists, medical oncologists, hematologists, pathologists, orthopedists/tumor orthopedists, radiologists, nuclear medicine specialists, psycho-oncologists, radiation oncologists, and internists should be mentioned.

In its form as a patient guideline, the guideline is intended to reach both patients and self-help groups. These include primarily the German Sarcoma Foundation (represented in the guideline group by Markus Wartenberg and Susanne Gutermuth) but also organizations that are not specifically focused on sarcomas such as the Cancer Information Service, INKA, and others.

The guideline group is composed of an interdisciplinary committee of experts. Thus, all health care providers involved in the provision of care, as well as their patient representatives, were considered in contributing to the content of the guideline. The guideline serves as information for physicians in primary care, physiotherapists and nursing staff.

Further addressees of the guideline are:

- Medical-scientific societies and professional associations
- Health policy institutions and decision-makers at federal and state level
- Patient information and counseling organizations
- Hospitals
- Health insurance companies and contract managers of integrated care contracts
- Quality assurance institutions and projects at federal and state level

2.1.3. Validity and Update Process

The S3 guideline is valid until the next update, the validity period is estimated to be a maximum of 5 years. Regular updates are planned; in case of urgent need for changes, these will be published separately. Comments and suggestions for the update process are explicitly welcome and can be sent to the following address: weichgewebesarkome@leitlinienprogramm-onkologie.de

2.2. Methodology

The methodological procedure for the preparation of the guideline is described in the guideline report. This is freely available on the Internet, e.g., on the pages of the Guideline Program in Oncology(http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html) and the pages of the AWMF(http://www.awmf.org/).

2.2.1. Levels of Evidence (LoE)

To grade the studies analyzed in the external search, the system developed by the GRADE Working Group (http://www.gradeworkinggroup.org) was used in this guideline.

For this purpose, the endpoints for the individual PICO questions were first prioritized by the WG leaders. The quality assessment of the evidence included the end points considered important and relevant to patients (so-called critical end points), for each of which (end point-specific) confidence in the underlying evidence is determined by means of the GRADE system. The system provides for a structured and transparent downgrading and upgrading of the level of evidence depending on relevant factors for the certainty of results of an effect estimator.

The following study or quality characteristics led to the devaluation of the level of evidence [1]:

- A non-randomized study design [1]
- A potentially high risk of bias in the underlying body of evidence [2]
- Heterogeneity or inconsistency of an outcome parameter across the individual studies considered [3]
- An outcome value that is indirectly attributable to the target population or outcome parameter studied [4]
- An imprecisely estimated effect with a wide confidence interval [5]
- An indication of publication bias [6]

The following characteristics lead to upgrading the quality of the underlying body of evidence [1], [7]:

- A very pronounced effect
- A dose-response relationship
- Residual confounding

Downgrading and upgrading of evidence grades are shown in the extraction tables (there with +/- symbolism). The GRADE system provides a four-level scheme of evidence quality (see table below, which is indicated in the recommendation boxes for all evidence-based statements and recommendations in each case by endpoint.

Table 4: Grading of evidence according to GRADE (http://www.gradeworkinggroup.org).

Quality of evidence	Description	Symbol
High quality	We are very confident that the true effect lies close to that of the estimate of the effect. „We are very confident that the true effect lies close to that of the estimate of the effect“	⊕⊕⊕⊕
Moderate quality	We are moderately confident in the effect estimator: the true effect is probably close to the effect estimator, but there is a possibility that it is relevantly different. „We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different“	⊕⊕⊕⊖
Low quality	Our confidence in the effect estimator is limited: The true effect may well be relevantly different from the effect estimate. „Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect“	⊕⊕⊖⊖
Very low quality	We have very little confidence in the effect estimate: The true effect is likely to be relevantly different from the estimate of the effect. „We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect“	⊕⊖⊖⊖

2.2.2. Grades of Recommendation (GoR)

The methodology of the guideline program oncology provides for the assignment of grades of recommendation by the guideline authors within the framework of a formal consensus process. Accordingly, moderated nominal group processes or structured consensus conferences were conducted by the AWMF [8]. Within these processes, the recommendations were formally voted on by the voting mandate holders (see Participating Professional Societies and Organizations). The results of the respective votes (consensus strength) are assigned to the recommendations according to the categories in Table Consensus strength.

In the guideline, the quality of the evidence according to GRADE (see Chapter 2.2.1) and, in the case of recommendations, the strength of the recommendation (degree of recommendation) are shown for all evidence-based statements and recommendations. With regard to the strength of the recommendation, three grades of

recommendation are distinguished in this guideline (see Table: Scheme of recommendation grading), which are also reflected in the wording of the recommendations in each case.

Table 5: Scheme of recommendation grading

Grade of recommendation	Description	Expression
A	Strong recommendation	shall
B	Recommendation	should
0	Recommendation open	Can/may

Table 6: Consensus strength

Consensus strength	Percentage consensus
Strong consensus	> 95% of those voting
Consensus	> 75 – 95 % of those entitled to vote
Majority consensus	50 – 75 % of those entitled to vote
Dissent	< 50 % of those entitled to vote

The decision criteria for determining the grades of recommendation are explained in the guideline report (see section 5.3.2 there) for this guideline.

Recommendations

Recommendations are thematically related action guiding core principles of the guideline, which are developed by the guideline group and agreed upon in formal consensus procedures.

2.2.3. Statements

Statements are presentations or explanations of specific facts or issues without an immediate call to action. They are adopted in accordance with the procedure for recommendations as part of a formal consensus process and can be based either on study results or on expert opinions.

2.2.4. Expert Consensus (EC)

Statements/recommendations for which editing was decided on the basis of expert consensus of the guideline group are shown as expert consensus. No systematic literature search was performed for these recommendations (studies cited in the background texts, where applicable, were selected by the participating subject matter

experts). For recommendations based on expert consensus, no symbols or letters are used to represent the strength of recommendation and quality of evidence. The strength of the recommendation is determined here solely by the wording used (should/should/could) according to the gradation in Table Scheme of Grading of Recommendations.

2.2.5. Independence and Disclosure of Possible Conflicts of Interest

German Cancer Aid provided the financial resources through the Guidelines Program in Oncology (OL). These funds were used for personnel costs, office supplies, literature procurement, and the consensus conferences (room rentals, technology, catering, moderator fees, travel expenses of participants). The guideline was developed editorially independent from the funding organization.

Obtaining declarations of interest

Declarations of interest were obtained from all guideline group members (coordinators, mandate holders, authors, subject matter experts) at the beginning of the guideline project. For this purpose, the applicable template of the AWMF „Declaration of Interests“, beta version for practice test, as of June 29, 2016, was used. The disclosed information is listed in the guideline report (see Chapter 12) for this guideline(http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html). Statements from all eligible voters were complete by the first consensus conference (06/28/2018). They are located in the Guideline Secretariat. In cases of a change of mandate by the professional society or a subsequent nomination of a subject matter expert with voting rights, the required conflict of interest declaration was submitted in a timely manner. Third-party funding from industry and advisory boards, as well as owner interests (shareholdings, patents) should be declared. The company name (third-party funds) should be mentioned. In the case of third-party funding, it should also be made transparent from which company it originates and what it was spent on.

Dealing with conflicts of interest

The guideline group members for whom a conflict of interest (CoI, any financial ties to industry) was identified after review of a summary of the declarations of interest on the part of the OL Office were informed of this prior to the first consensus conference (for details, see Guideline Report Chapter 8). During the first consensus conference, the procedure for dealing with conflicts of interest was discussed and it was unanimously agreed that persons entitled to vote with identified CoI should be identified in votes with a corresponding topic reference and counted as abstentions. However, double voting should be done in these cases. One vote with all persons eligible to vote and one vote with abstention of those with conflicts of interest. Control evaluations should be performed (result of the entire group vs. group of persons without CoI). In this case, the result of the group of persons without CoI was decisive.

We would like to point out that possible undue influence by conflicts of interest was reduced by the fact that the evidence-based search, selection, evaluation, and assessment of the literature was performed by IFOM staff. Formal consensus building with external, independent facilitation, interdisciplinary development of the guideline, and public peer review of the guideline provide additional means for reducing bias.

At this point, we would like to thank all participants for their exclusively voluntary contribution to the project.

3. Epidemiology, risk factors and prevention

3.1. Epidemiology

Soft tissue sarcomas, as a whole, represent a very heterogeneous and rare group of malignancies with a diverse pathologic and clinical presentation, an occurrence in virtually any anatomic location, and accounting for 7 % of childhood cancers but less than 1 % of all adult malignancies [10], [9].

3.1.1. Incidence and histological distribution

Internationally, incidences of soft tissue sarcomas are reported to range from 1.8 to 5.0 per 100,000 persons per year [11], [12]. Regional differences in incidence rates are based on differences in ethnic composition of the population, new Kaposi-sarcoma incidence rates, classification systems used, and diagnostic capabilities, among other factors.

Incidence estimates for soft tissue tumors from the Center for Cancer Registry Data at the Robert Koch Institute summarize tumors according to ICD-10 C46-C49. Thus, approximately 16% also include tumors that occur in these localizations but are not sarcomas. In addition, organ-specific sarcomas are not included in these registry codes, since, for example, sarcomas in the lung are coded with C34 in cancer registries, or the relatively frequent leiomyosarcomas and carcinosarcomas/Müllerian mixed tumors of women are coded with C54 [13]. Gastrointestinal stromal tumors as the most common sub-entity of soft tissue tumors are classified nonspecifically („unspecified") as C15.9 (esophagus), C16.9 (stomach, C17.9 (duodenum, small intestine), C18.9 (colon), and C20.9 (rectum), and possibly also as C52 (spatium recto-vaginale), depending on the organ. For Germany, this underestimates the specific new case rate of soft tissue sarcomas when compared with routine reporting in some other countries.

In a specific analysis of Germany-wide cancer registry data (excluding Baden-Württemberg) for the diagnosis year 2013 with identification of sarcomas by histology and inclusion of all new cases of persons aged 15 years and older, including gastrointestinal stromal tumors (GIST)- 3,048 new cases were registered in men and 3,140 diagnoses of soft tissue sarcomas in women. This represents an incidence of 6.3 per 100,000 in men and 5.7 per 100,000 in women. The median age of onset was approximately 69 years in both sexes. For GIST, 1,353 cases were reported, corresponding to an age-standardized incidence of 1.5 per 100,000 men and 1.1 per 100,000 women [14].

Rhabdomyosarcomas and synovial sarcomas account for approximately one-third of soft tissue sarcoma diagnoses in young adults [15]. In contrast, the most common diagnoses in older adults are sarcomas with undifferentiated histology, complex neoplasms, leiomyosarcomas, liposarcomas, fibrosarcomas, and pleomorphic sarcomas [14], [16]. Table 7 shows the breakdown by histological subtype in the pooled data set of the German cancer registries for the diagnosis year 2013 [14].

Table 7: Relative frequency of different subtypes of adult soft tissue and bone tumors (all sarcomas except ICD-10 C40 and C41) in Germany* (%), year of diagnosis 2013

Histological subtype	N	Percentage
Gastrointestinal stromal tumors	1.353	21,9
Sarcomas, not further specified (NOS)	1060	17,1
Complex neoplasms (excluding synovial sarcomas)	761	12,3
Leiomyosarcomas	710	11,5
Liposarcomas	639	10,3
Angiosarcomas	399	6,5
Fibrosarcomas (except pleomorphic sarcomas, dermatofibrosarcomas)	299	4,8
Pleomorphic sarcomas (formerly malignant fibrous histiocytomas (MFH))	271	4,4
Dermatofibrosarcomas	192	3,1
Synovial sarcomas	124	2,0
Malignant peripheral nerve sheath tumors (MPNST)**	112	1,8
Rhabdomyosarcomas	87	1,4
Ewing sarcomas	76	1,2
Phylloides tumors	56	0,9
Chondrosarcomas	31	0,5
Chordoma	12	0,2
Osteosarcomas	5	0,1

Histological subtype	N	Percentage
Tenosynovial giant cell tumors	1	0,0
Total	6.188	100

* Pooled data set of the Center for Cancer Registry Data (without Baden-Württemberg); only disease cases aged 15 years and older.
** incl. 10 malignant neurinomas

modified according to [14]

The increasing incidence of soft tissue sarcomas worldwide over the years [10], [14], [17] can be explained by improved diagnostics and documentation, as well as the significant increase in the incidence of Kaposi's sarcoma during the HIV/AIDS epidemic of the late 1980s/early 1990s [18]. For Germany, the incidence of soft tissue sarcoma (excluding GIST) decreased significantly in women after 2009, while it remained constant in men over the period from 2004 to 2013. For GIST, the German data also confirmed a significant increase in incidence in both sexes over the aforementioned 10-year period [14]. The significant increase in the incidence of GIST at the beginning of this century can be explained by the establishment of the entity in 1998 through detection of its driver mutations [19]. The routine use of markers such as CD 117 and DOG1 has increased the reliability of diagnosis, and the disease has also increasingly come into the view of physicians making diagnoses [20], [21].

3.1.2. Mortality and survival

Data on mortality and death rates of patients with soft tissue tumors in Germany have the same limitation as the incidence estimate in routine health reporting: a presentation is made summarized according to ICD-10 C46-C49 as a group of soft tissue including Kaposi's sarcoma (C46) and malignant neoplasms of the peripheral nerves and autonomic nervous system (C47). For 2015, the cause-of-death statistics of the Federal Statistical Office for Germany document a total of 1,770 deaths for this group (men 843, women 927). The age-standardized mortality rate was thus 1.4 per 100,000 for men and 1.3 per 100,000 for women.

For C46-C49 in 2013 and 2014, the Center for Cancer Registry Data reports relative 5-year survival rates of 64 % for men and 49 % for women. The absolute 5-year survival rates are correspondingly slightly lower at 55 % (men) and 44 % (women) [13]. For Europe as a whole, the RARECARE project reported 5-year relative survival for soft tissue sarcomas to be 58 % on average. The survival rates of individual soft tissue sarcomas vary. Sarcomas of the skin (mainly dermatofibrosarcoma protuberans) range from 90 % and higher, while soft tissue sarcomas of the mediastinum or heart have survival rates below 15 % [12]. In addition to the histological subtype, the degree of differentiation is decisive for the prognosis [17], [22].

3.2. Modifiable risk factors

The risk potential of numerous environmental factors has been investigated with regard to the development of soft tissue sarcomas. However, the majority of the corresponding studies are small, subject to considerable bias, and must be interpreted with caution [9].

3.2.1. Infections

3.1	Consensus-based Recommendation
EC	When a soft tissue tumor is diagnosed in a patient with congenital or acquired immunodeficiency, the presence of an EBV-associated soft tissue tumor should be considered and Epstein-Barr virus-encoded RNA-1 (EBER-1) in situ hybridization should be performed. If an EBV-associated soft tissue tumor is diagnosed and Epstein-Barr virus-encoded RNA-1 (EBER-1) is detected in the tumor cells, the presence of a causative immune deficiency should be investigated.
	Strong Consensus

Background

An increased risk of soft tissue sarcoma has been documented in people with immune deficiency. A survey by the U.S. Centers for Disease Control (CDC) showed that between 1983 and 1986, Kaposi's sarcoma rates in HIV patients ranged from 14.2% to 30.9% [23]. In addition, a systematic literature search revealed 176 cases of published non-Kaposi soft tissue sarcomas in immunosuppressed patients; 75 cases were diagnosed in HIV/AIDS patients and 101 cases in transplant patients. Soft tissue sarcoma diagnoses included leiomyosarcomas (n=101), angiosarcomas (n=23) and fibrohistiocytic tumors (n=17), rhabdomyosarcomas (n=8), GISTs (n=6), liposarcomas (n=4), Interdigitating dendritic cell sarcomas (n=3), fibrosarcomas (n=3), nerve sheath tumors (n=2), Ewing sarcomas (n=2), synovial sarcomas (n=1), osteosarcomas (n=1), carcinosarcomas (n=1), and other sarcomas (n=4) [24].

The development of soft tissue sarcomas in immunosuppressed patients has been causally associated with viral infections. Human herpes virus 8 can be detected in > 90 % of all Kaposi's sarcomas, regardless of whether the affected individuals have HIV or are immunosuppressed [25], [26].

Furthermore, 85-88 % of leiomyomas and leiomyosarcomas diagnosed in immunocompromised patients contain Epstein Barr virus (EBV) [24], [27], whereas leiomyomas and leiomyosarcomas in immunocompetent patients are EBV negative [28]. The incidence of leiomyosarcoma in the general population is 0.81–1.23 cases per year per 100,000 people [11]. The incidence of EBV-associated soft tissue tumors after solid organ transplantation is reported to be 0.7 per 1000 patient-years [29]. After heart transplantation in childhood, the incidence is 2.6 per 1000 patient-years [29]. Numerous case reports also demonstrate that individuals with congenital cellular immunodeficiencies are at increased risk of developing EBV-associated soft tissue tumors [27], [30], [31]. Causal treatment of the immunodeficiency is often associated with spontaneous remission of EBV-associated soft tissue tumors.

3.2.2. Iatrogenic risk factors

3.2	Consensus-based Recommendation
EC	There is an increased risk of developing soft tissue sarcoma after chemotherapy and/or radiotherapy. As part of the follow-up after radiotherapy, the increased risk of soft tissue sarcoma occurring in the former radiation field should be communicated, especially to younger patients.
	Consensus

Background

There is an increased risk of developing soft tissue sarcoma after radiotherapy. Rubino et al followed 6,597 patients with breast cancer for an average of 8.3 years and identified 14 sarcomas (4 angiosarcomas, 4 malignant fibrous histiocytomas, 5 fibrosarcomas, and 1 osteosarcoma) in a retrospective case-control study. Each patient who developed a secondary sarcoma was matched with 7 other patients from the total cohort and compared with the incidence of sarcomas in the French general population. The study found a 7-fold increased risk of sarcoma for the former breast cancer patients. The sarcomas all occurred in or in close proximity to the former radiation field. All 14 sarcomas developed in sites that had received at least 11.8 Gy. There was a significant correlation between dose and effect ($p < 0.001$) [32]. Virtanen et al. used the Finnish Cancer Registry to study the sarcoma risk of 295,712 cancer patients. Sarcoma risk within 10 years of diagnosis was 3.2-fold increased after radiotherapy, 4.9-fold increased after chemotherapy, and 3.4-fold increased after radiotherapy and chemotherapy. Sarcoma risk after radiotherapy was higher for patients younger than 55 years [33].

Menu-Branthomme et al followed 4,400 patients from France and the United Kingdom with childhood solid tumors for an average of 15 years and identified 16 soft tissue sarcomas in a retrospective case-control study. Each patient who developed a secondary sarcoma was matched with 5 other patients from the overall cohort and compared with the incidence of sarcomas in the Danish cancer registry. The Danish registry was chosen because French cancer registries did not cover the relevant time period and other European cancer registries were too small for patients younger than 45 years. Soft tissue sarcoma risk was 19-fold increased after radiotherapy, 28-fold increased after chemotherapy, and 113-fold increased after radiotherapy and chemotherapy [34]. A British study showed that the risk of developing soft tissue sarcoma was increased 38-fold after radiotherapy with a dose > 30Gy in childhood [35].

When sarcomas occur as secondary malignancies after prior tumor treatment, the presence of tumor predisposition should always be considered. Patients with cancer predisposing germline defects are more likely to develop secondary malignancies [36] (see Chapter 3.3).

Chronic lymphedema of the extremities, for example after therapy for breast carcinoma, is associated with the occurrence of secondary cutaneous angiosarcomas (Stewart-Treves syndrome) [37], [38].

The X-ray contrast agent Thorotrast was used for angiographic studies in Europe, Japan, and the United States from 1930 to 1960. An estimated 100,000 people were

exposed. Thorotrast was first associated with angiosarcomas of the liver in 1947. There is also an association with cholangiocarcinomas and hepatocellular carcinomas. Tumors occur between 16 and over 45 years of age after thorotrast exposure [39]. In 2014, a case was published in which hepatic angiosarcoma occurred 65 years after thorotrast exposure [40].

3.2.3. Other risk factors

Occupational exposures associated with increased soft tissue sarcoma risk have been investigated in several population studies. The Nordic Occupational Cancer (NOCCA) Project in Scandinavia showed a slightly increased soft tissue sarcoma risk among men for janitors (SIR 1.30, 95%, CI 1.08-1.56) and military personnel (SIR 1.27, 95% CI 1.01 - 1.59) [41]. In the US Selected Cancers Study, there was some correlation between soft tissue sarcoma incidence and contact with chlorophenol (adjusted OR 1.79, 95 % CI 1.10 – 2.88) and cutting oils (adjusted OR 1.65, 95 % CI 1.04 – 2.61) [42]. The association between occupational exposure to vinyl chloride and the occurrence of angiosarcoma of the liver is considered established [43].

Published studies regarding a possible association between alcohol or tobacco use and the occurrence of soft tissue sarcomas yielded conflicting results, so that ultimately no conclusion can be drawn [44], [45].

No association was observed between differences in birth weight, growth/development in adolescence, age at menopause, number of births and incidence of soft tissue sarcomas [9].

3.3. Non-modifiable risk factors and genetic risk factors.

The probability of the presence of a genetic predisposition to tumors in people with soft tissue sarcomas is between 6 and 14% [46], [47]. More likely to be affected are younger people, people with more than one malignant diagnosis or a cluster of malignancies in the family, people with malformations or other rare conditions in addition to a sarcoma diagnosis, and people with specific, usually atypical manifestations of sarcoma [48].

3.3.1. Inclusion criteria for genetic counseling

3.3	Consensus-based Recommendation
EC	Genetic testing (TP53) shall be offered if the Chompret criteria for clinical diagnosis of Li-Fraumeni syndrome are met: • Diagnosis of soft tissue sarcoma before age 46 & Diagnosis of a Li-Fraumeni tumor (soft tissue sarcoma, osteosarcoma, brain tumor, choroid plexus tumor, premenopausal breast cancer, adrenocortical carcinoma, leukemia, bronchial carcinoma) in a first or second degree relative before age 56. • Diagnosis of soft tissue sarcoma in an individual who has had at least one other Li-Fraumeni tumor prior to age 46.
	Strong Consensus

GISTs can occur in people who carry germline mutations in the SDH genes SDH A/B/C/D, NF1, C-KIT, or PDGFRA. Therefore, the following recommendation applies.

3.4	Consensus-based Recommendation
EC	Genetic testing (SDH A/B/C/D) should be offered upon diagnosis of wild-type (WT) GIST without evidence of KIT or PDGFRA mutation and with immunohistochemical SDHB loss in the tumor. When a wild-type (WT) GIST is diagnosed, it should be evaluated whether the clinical criteria for the diagnosis of neurofibromatosis type 1 (NF1) are met. If a diagnosis of wild-type (WT) GIST is made, genetic testing (NF1) may be offered.
	Strong Consensus

3.5	Consensus-based Recommendation
EC	When a diagnosis of malignant peripheral nerve sheath tumor (MPNST) or plexiform neurofibroma is made, it should be determined whether the clinical criteria for the diagnosis of neurofibromatosis type 1 are met. If a malignant peripheral nerve sheath tumor or plexiform neurofibroma is diagnosed, genetic testing (NF1) may be offered.
	Consensus

3.6	Consensus-based Recommendation
EC	Genetic testing may be offered in the presence of any of the following risk diagnoses: • Anaplastic sarcoma of the kidney (DICER1). • Desmoid tumor/aggressive fibromatosis without CTNNB1 mutation (APC) • Embryonal rhabdomyosarcoma of the cervix (DICER1) • Angiomyolipoma, PEComa (TSC1, TSC2) • Chordoma (TBXT gene)
	Strong Consensus

Background

Li-Fraumeni syndrome is a hereditary tumor predisposition syndrome caused by a germline mutation in the TP53 gene in at least 70 % of cases [47], [48]. CDKN2A germline mutations were found in 8 of 667 families with Li-Fraumeni like syndrome [46].

Soft tissue sarcomas occur in 12-21% of people with Li-Fraumeni syndrome [48], and account for 15%-25% of all cancers associated with Li-Fraumeni syndrome [47], [49], [50]. Soft tissue sarcomas associated with Li-Fraumeni syndrome occur at a younger

age than sporadic soft tissue sarcomas [49]. In a study of 475 tumors in 91 families with TP53 germline mutations, rhabdomyosarcomas (55 %), fibrosarcomas (13 %), and undifferentiated pleomorphic sarcomas (10 %) were shown to be the most common soft tissue sarcomas associated with a TP53 germline mutation [51].

In rhabdomyosarcomas, TP53 germline mutations are found in 1-4% of all affected individuals [52], [53]. In rhabdomyosarcomas with a diagnosis age less than 3 years, the TP53 germline mutation rate increases to 23% [54]. In children with anaplastic rhabdomyosarcomas, the frequency of TP53 germline mutations is 73 % [55].

Familial polyposis adenomatosis coli (FAP) is an autosomal dominant hereditary cancer predisposition syndrome caused by germline mutations in the APC gene. Familial polyposis adenomatosis coli predisposes affected individuals to early formation of colorectal polyps, which typically develop into colon carcinomas by age 25 to 40 years.

Gardner syndrome is an FAP variant characterized by extracolonic manifestations [48]. This includes the development of desmoid fibromatosis in 7.5-16% of affected individuals [48]. In case series, FAP germline mutations have been found in people with desmoid fibromatoses in 0-16% of affected individuals. The germline mutation rate in children with desmoids was 16% [56], [57], [58].

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder that is the most common known tumor predisposition syndrome with an incidence of 1/3000 live births. A positive family history is present in approximately 50 % of cases. The clinical diagnosis of NF1 is made when two of the following seven criteria are met: (1) ≥ 6 café au lait spots of the skin (at least 5 mm in diameter in prepubertal and at least 15 mm in diameter in postpubertal individuals), (2) ≥ 2 neurofibromas or a plexiform neurofibroma, (3) freckling in the axilla or groin, (4) ≥ 2 Lisch nodules (iris hamartomas), (5) diagnosis of optic glioma, (6) dysplasia of the long bones with or without pseudarthrosis, (7) neurofibromatosis in a first-degree relative. NF1 is caused by loss-of-function mutations in the NF1 gene that lead to activation of the MAPK pathway.

People with NF1 have an 8-13% risk of developing a malignant peripheral nerve sheath tumor [59], [60], [61] and a 7% risk of developing a GIST during their lifetime [59]. There is also an increased risk of rhabdomyosarcoma [62].

Carney-Stratakis syndrome is an autosomal dominant hereditary tumor predisposition syndrome associated with gastrointestinal stromal tumors (GIST) and paragangliomas. Carney-Stratakis syndrome is caused by germline mutations in the SDH gene subunits (SDHA, SDHB, SDHC, SDHD) [48], [63]. Boikos et al identified SDHX germline mutations in 31 people with wild-type (WT) GIST. The associated tumors did not carry KIT or PDGFRA mutations, and SDHB expression was undetectable by immunohistochemistry [64], [65]. A proportion of WT GISTs were associated with neurofibromatosis type 1 [63], [66].

KIT-mutated GISTs can occur in people with KIT germline mutations, associated with dysphagia with or without hyperpigmentation and various manifestations of mastocytosis [63]. PDGFRA-mutated GISTs may occur in people with PDGFRA germline mutations, associated with lipomas, intestinal fibromas, and large hands [63].

People who had hereditary retinoblastoma as children are more likely to develop soft tissue sarcomas. Soft tissue sarcomas occur both in the former radiation field and outside the radiation field 67, reaching a 60-year incidence of 9.3% (95% CI 7.0-11.7%)

in the head and neck region. In contrast, sarcomas of the extremities do not cluster after adolescence [67]. In 7 of 525 women with hereditary retinoblastomas, uterine leiomyosarcomas were diagnosed later [68].

Finally, in case series, the following soft tissue sarcoma histotypes were associated with germline mutations in specific cancer-related genes: DICER1 germline mutations were found in 4 of 9 patients with anaplastic renal sarcomas [69]; the latter were also detected in patients with embryonal rhabdomyosarcoma of the cervix [70]. Germline mutations in the TBXT gene (brachyuria) were identified in 4 families with chordomas [71].

In addition to Li-Fraumeni syndrome, Dicer1 syndrome and neurofibromatosis type 1, embryonal rhabdomyosarcomas are associated in rare cases with Bloom syndrome, mismatch repair deficiency syndrome, Costello syndrome (HRAS germline mutations), Gorlin syndrome (PTCH1), Nijmegen breakage syndrome, Noonan syndrome (PTPN11), Rubinstein Taybi syndrome and Werner syndrome [59], [72], [73].

Angiomyolipomas and PEComas occur in people with tuberous sclerosis and are associated with TSC1 or TSC2 germline mutations [59].

3.3.2. Risk Communication

The following section is adapted from the S3 Guideline Breast Cancer (S3 Guideline Early Detection, Diagnosis, Therapy and Follow-up of Breast Cancer, Version 4.3, 2020 AWMF Registry Number: 032-045OL, http://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/) [74].

3.7	**Consensus-based Recommendation**
EC	Counseling shall enable participatory decision-making. This requires comprehensive information for the patients concerned and clarification and inclusion of their preferences in the decision-making processes. Risk counseling prior to genetic testing should consider the following content in particular: • Probability of the presence of a germline mutation • risks of disease in case of a positive result • benefits and harms of preventive and therapeutic options, including the option of doing nothing • Possibility of false negative findings • Importance of genetic testing for family members After receiving the genetic findings, the following content should be explored in depth during risk counseling before offering preventive measures: • Implications for disease progression and risk of associated tumors depending on genetic findings, age, and concomitant diseases. • Benefits and risks of preventive options • Probability of false positive and false negative results of preventive measures • Psycho-oncological counseling services
	Strong Consensus

Background

The desire of women and men for detailed information and shared decision-making about prevention and treatment options has been repeatedly documented. In a survey of 1200 participants in the International Sarcoma Kindred Study (ISKS), 60% of soft tissue sarcoma patients interviewed reported a positive attitude toward genetic diagnosis to detect hereditary predispositions [75].

The results of the case-control study showed that 638 patients (55%) had a significantly increased rate of pathologic germline abnormalities (OR 1·43, 95% CI 1·24–1·64, p<0·0001) [76]. All pathogenic variants were associated with earlier onset of cancer. In addition to the known TP53, ATM, ATR, and BRCA2 alterations, pathogenic variants of ERCC2 were also found with disproportionate frequency. These findings have implications for risk management as well as current treatment.

Consensus-based recommendation 3.7. was adapted from recommendations 3.31. and 3.32. of the S3 guideline Breast Cancer.

3.3.3. Early detection

3.8	Consensus-based Recommendation
EC	For TP53 mutation carriers, the screening program according to the Toronto Protocol should be applied. Regardless of age, the Toronto Protocol includes the recommendation to perform an annual whole-body MRI scan.
	Strong Consensus

Background

Prospective studies have shown that the use of a screening program in TP53 germline mutation carriers in childhood and adulthood, including annual whole-body MRI examinations, resulted in early detection of tumors and improved survival in 40 affected individuals (89% at 5 years, compared with 60 % in the control group) [77], [78]. In another study, baseline whole-body MRI was performed in 578 TP53 germline mutation carriers; 42 malignancies were found in 39 affected individuals, of whom 35 were treated with curative intent [79]. The Toronto Protocol provides for the following screenings:

For children, adolescents, and adults:

- Complete physical examination every four months, including blood pressure, neurological examination, and for children, growth and pubertal signs.
- Laboratory tests every four months: BB/diff, LDH, ESR, 17-OH-progesterone, testosterone, DHEA-S, androstenedione.
- Cortisol level in 24h collection urine every four months.
- Ultrasound of abdomen and pelvis every four months.
- Cranial MRI once a year.
- Whole body MRI once a year.

Additionally, for adults over 18 years of age:

- Women: Breast self-exam once a month, physician breast exam every six months, breast MRI once a year starting at age 20-25 or 5-10 years before earliest family diagnosis of breast cancer.
- Colonoscopy/gastroscopy every 2-5 years starting at age 25, or 10 years prior to first colon cancer in family.
- Dermatological examination once a year.

3.3.4. Therapy

3.3.4.1. Therapy of soft tissue sarcomas occurring in the context of a genetic tumor predisposition

3.9	Consensus-based Recommendation
EC	Soft tissue sarcomas occurring in TP53 mutation carriers should be treated according to general treatment recommendations. However, the indication for radiation and/or chemotherapy should be carefully considered because of the increased risk of secondary malignancy.
	Consensus

Background

Technological advances and the rapid gain in knowledge in the field of tumor genetics make it likely that evidence of a genetic predisposition to tumors will be found in an increasing number of patients with soft tissue sarcomas in the coming years. However, the direct impact of many sarcoma-related germline gene defects on treatment response and treatment risks is still unclear, and systematic programs for early tumor detection are costly, burdensome, and in many places unavailable in clinical practice. Implementing the claim of people with a sarcoma predisposition to individual counseling, diagnosis, therapy and screening is a major challenge for the coming years.

4. Diagnostics, prognostic markers and scores

4.1. Diagnostics

Guidelines are of particular importance ifor sarcoma diagnosis. This applies in particular to the histological iagnosis, which has a considerable influence on prognosis. Due to their rarity, soft tissue tumors often cause diagnostic difficulties for the pathologist. Therefore, a reference pathological second opinion is encouraged and is expected to take place more frequently than in other tumor entities. The integration of different disciplines with specialist expertise into sarcoma centers is increasingly recognized as a necessity in order to provide optimal care. A consensus on the differences between typical (<6/100,000) and ultra-rare (<2/100,000) sarcomas has been adopted by an expert group [80].

4.1	Consensus-based Recommendation
EC	The diagnosis and therapy of soft tissue sarcoma shall be performed by or in coordination with a certified sarcoma center or associated cooperation partner.
	Strong Consensus

4.2	Consensus-based Recommendation
EC	The planning of sarcoma treatment shall take place pre-therapeutically in the interdisciplinary tumor board. At least one surgical discipline with a focus on soft tissue sarcomas, as well as hematology/oncology, pathology, radiology, and radiation oncology shall be represented. Location-specific expertise should be consulted on a case-by-case basis.
	Strong Consensus

4.1.1. Imaging

4.1.1.1. Primary imaging at initial diagnosis

Sonography is the method of choice for primary imaging of a superficial or extremity tumor. An experienced examiner can classify a palpated mass primarily as either non-tumor-specific lesions such as lipomas, cysts, abscesses, or hematomas or as tumor-specific findings. The localization and delineation of the tumor by ultrasound can also be used for a targeted core biopsy.

4.3	Consensus-based Statement
EC	When a malignant soft tissue tumor is suspected, contrast-enhanced magnetic resonance imaging is the primary imaging modality of choice.
	Strong Consensus

4.4	Consensus-based Recommendation
EC	If an image-guided biopsy is performed, the region(s) with the lowest degree of differentiation according to radiological criteria should be selected.
	Strong Consensus

Background

When a malignant soft tissue tumor is suspected, contrast-enhanced magnetic resonance imaging (MRI) is favored as the primary imaging modality because it provides the best visualization of tumor margins and differentiation of fatty tumors as well as cystic and necrotic and non-necrotic tumor components.

Soft tissue tumors often have a heterogeneous structure, with the most aggressive tumor portion usually being the least differentiated (i.e., having the highest grading) and therefore determining the biological behavior of the tumor. These are often regions of highest tumor cell density, highest vascularization, and therefore highest glucose uptake. Imaging prior to biopsy should primarily be performed with MRI including intravenous (i.v.) contrast and diffusion weighting to optimise assessment of tumor margins. If there are contraindications to i.v. contrast, i.v. (and if necessary, enteral) contrast-enhanced CT or PET-CT with i.v. contrast should be performed as an alternative.

In MRI, the axial plane is the most important for determining the tumor boundary. The MRI protocol should include at least one T1w sequence (SE or TSE) in a long axis (coronary or sagittal), two T2w sequences in axial and long axis planes, and two T1w sequences after i.v. contrast agent in the axial slice and a long axis plane. A T1w sequence without fat saturation should be measured before and after contrast administration with identical acquisition parameters to detect “true“ contrast uptake. The spatial resolution should be approximately 0.5 x 0.5 mm in the slice direction, and the slice thickness should be 3 to 5 mm. An axial T2 sequence without fat saturation is obligatory. A DIXON sequence is acceptable as an alternative if the spatial resolution is appropriate.

In addition to the above sequences, a diffusion-weighted sequence should be performed. This is useful for determining diagnosis, highest cell density to guide biopsy, and differentiation from hematoma.

A conventional radiograph or native CT can be performed to detect calcification, bony involvement, or to estimate fracture risk. The calcific component of a soft tissue tumor may be underestimated or undetectable by MRI.

In retroperitoneal tumors, CT with i.v. contrast may be equal to MRI for local staging and can be used as an alternative. CT can distinguish between well-differentiated and poorly differentiated sarcomas relatively well [84]. However, MRI is more suitable for delineating sarcomas from neurovascular bundles and for identification of marrow infiltration, [82], [83], [81].

4.1.1.2. Other imaging before histological diagnosis confirmation

4.5	Consensus-based Recommendation
EC	Staging shall be performed prior to therapy for soft tissue sarcoma.
	Strong Consensus

Background

Early staging of soft tissue tumors suspected of malignancy can in some cases facilitate interdisciplinary diagnosis and contribute to assessing whether a malignant lesion is present when metastatic disease has already been detected. This allows prompt treatment planning and the initiation of further diagnostic/molecular investigations (e.g. mutation analysis in metastatic gastrointestinal stromal tumor).

4.1.2. Biopsy

The technique employed plays a central role in the diagnosis of soft tissue tumors. If sarcoma is clinically suspected, the first tissue biopsy should always be performed in a specialized center. The gold-standard technique for biopsy is multiple percutaneous core biopsies (preferably ≥16G) or open incisional biopsy [85], [86], [87]. If this is not possible or does not yield a result, an open excisional biopsy may be performed for superficial lesions [86]. The biopsy sampling site should be determined by the multidisciplinary team and should be performed in the least differentiated, non-necrotic tumor portion defined by imaging. The access route should be chosen to ensure complete co-excision of the biopsy channel or sampling site/scar during the subsequent resection.

4.1.2.1. Bioptic histology acquisition by fine needle biopsy

4.6	Consensus-based Recommendation
EC	Fine needle biopsy for initial diagnosis of soft tissue sarcoma shall not be performed.
	Strong Consensus

Background

Due to the increasing demands on the number and complexity of diagnostic techniques to be performed on a biopsy sample, the regular use of a fine needle biopsy for initial diagnosis is discouraged. Fine needle biopsy also limits reference pathological second opinions due to limited material. Reliable grading of sarcomas is usually not possible on fine needle biopsy, especially in highly differentiated lesions or spindle cell sarcomas with low proliferative activity [88]. Although fine needle biopsy is more successful for the diagnosis of high-grade sarcomas, „accuracy“ remains limited to 91 % [89]. If neoadjuvant therapy is planned, an exclusively fine-needle biopsy diagnosis is not recommended. By using higher caliber core biopsies, significantly more diagnostic material can be obtained, which is then also available for immunohistochemical and molecular pathological investigations.

Although fine-needle aspiration biopsy may have significant limitations in definitive histologic assignment, it is capable of separating malignant from benign lesions with high sensitivity and specificity [90]. Fine needle aspiration biopsy can therefore be considered for histological confirmation of local recurrence or metastases of previously histologically confirmed soft tissue sarcomas.

4.1.2.2. Bioptic histology acquisition by punch cylinder biopsy

4.7	Consensus-based Recommendation
EC	For histological confirmation of a soft tissue sarcoma, a core needle biopsy or an incisional biopsy shall be performed. The decisive factor for the choice of procedure is experience in performing it and in processing and examining the tissue obtained.
	Strong Consensus

4.8	Consensus-based Recommendation
EC	If an image-guided core needle biopsy is performed to confirm the diagnosis of a soft tissue tumor, it should be performed using the coaxial technique with ≥16G punches. Multiple cores cylinders should be obtained.
	Strong Consensus

4.9	Consensus-based Recommendation
EC	The biopsy route should be selected so that it can be removed with the definitive resection without widening the resection access. In the case of an incisional biopsy, the biopsy route should always be removed en bloc with the specimen.
	Strong Consensus

Background

The access route should be determined by an interdisciplinary discussion prior to biopsy.

Core needle biopsy is now a frequently recommended procedure in guidelines for obtaining samples from soft tissue tumors. Studies have shown that this technique is comparable [91] or at most slightly inferior to open biopsy in terms of diagnostic accuracy in experienced hands [92]. Percutaneous core biopsies require a smaller access route than open biopsies, which facilitates resection of the puncture tract during subsequent definitive surgery [93], [94], [95]. Multiple core biopsies are typically performed through one access point. This is relevant because tumor cell metastases can be found in the biopsy tract during both open biopsy and percutaneous biopsy. It has been shown that cell metastases are significantly more likely to be present in the biopsy tract after open biopsy than after percutaneous biopsy [96]. As a consequence, core biopsy in combination with optimal imaging is favoured to guide diagnosis [97], [98]. A systematic review with meta-analysis proved that core biopsy has a high accuracy for soft tissue tumor diagnosis and subtyping. The lower complication rates associated with core biopsies also contributes to its use as the first-line biopsy technique [99].

For an adequate histological diagnosis, biopsy specimens must meet minimum standards. Smaller lesions often pose a technical challenge for biopsy. Core biopsy is applicable for lesions from about 1 cm in diameter, but for lesions < 2 cm diagnostic accuracy decreases [100]. Another important influential factor is the length and, in particular, the number of specimens. It has been shown that a plateau in diagnostic accuracy is reached for soft tissue tumors when the number of specimens exceeds 4 [101]. Existing recommendations suggest that needles of at least 16G diameter should be used [85].

4.1.2.3. Biopsy histology acquisition by incisional or excisional biopsy.

4.10	Consensus-based Recommendation
EC	A biopsy should be taken at a specialized center, by or in consultation with the subsequent surgeon.
	Consensus

4.11	Consensus-based Recommendation
EC	Drainage close to the access site shall be applied together with a compression bandage to avoid hematoma formation.
	Consensus

4.12	Consensus-based Recommendation
EC	Excisional biopsy may be considered for superficial tumors smaller than 3 cm, provided that safe removal of the tumor in healthy tissue is assured.
	Consensus

Background

Incisional biopsy usually yields the largest diagnostically useful volume of tissue and thus the highest diagnostic certainty. The incision should be chosen in such a way that no healthy structures, especially nerves and vessels, are contaminated. The access must be completely removed at subsequent resection. The incision should be made as longitudinally as possible. ADrainage through the incision or led out directly in extension of the incision together with a dressing should minimise hematoma formation.

Excisional biopsy as an initial diagnostic measure may be considered for superficial, well circumscribed lesions less than 3 cm in diameter, provided that safe removal of the tumor in healthy tissue is assured [86]. British surgeons analyzed data from 3018 patients with primary benign (52 %) and malignant soft tissue tumors in a hierarchical analysis, finding the threshold between benign/malignant in the size region between 3 and 5cm. An analysis according to the Bayesain model indicated the practically relevant tumor size, above which a malignancy could be assumed with a high probability [102]. Consequently, a golf ball was sent to all British surgeons with the text „If your lump is bigger than a golf ball and growing, think Sarcoma“.

4.1.2.4. Relevance of frozen section examination

4.13	Consensus-based Recommendation
EC	Frozen section examination shall not be used for assessment of malignancy and subtyping of soft tissue tumors.
	Strong Consensus

Background

Frozen section examinations are not suitable for diagnosis, subtyping or grading of soft tissue tumors. In individual cases, frozen section examination may help in the assessment of narrow resection margins. This does not apply to differentiated lipomatous tumors, however.

4.1.2.5. Biopsy shipment to pathology

4.14	Consensus-based Recommendation
EC	Biopsy material shall be sent to pathology in buffered, 4% formalin.
	Strong Consensus

Background

If possible, core biopsies should be fixed in sufficient 4% buffered formalin for at least 6 hours before pathological processing. Non fixed samples are not recommended as material dries out quickly. Dispatch in NaCl is strongly discouraged, as this has a very unfavorable effect on the morphology of the tissue. Substitution of formalin by alcohol is also not indicated, as this hardens tissue and makes further processing considerably more difficult. Special fixatives such as Bouin's solution are strongly discouraged, as this interferes with DNA extraction for any additional molecular pathology studies that may be required. Electron microscopy now plays only a very minor role in sarcoma diagnostics, so that preservation of tumor tissue in appropriate special fixative is generally not envisaged. Preservation of tumor tissue for later RNA extraction (e.g., RNA-later) is usually reserved for research studies.

4.1.3. Sending the tumor resection specimen to the pathology department

4.15	Consensus-based Recommendation
EC	As a minimum requirement, the surgeon shall mark the surgically removed resection specimen with thread markings in such a way that three-dimensional orientation is possible for the pathologist. If necessary, a schematic drawing of the orientation should be included.
	Strong Consensus

4.16	Consensus-based Recommendation
EC	In the case of macroscopically close resection, if detected or suspected intraoperatively, the margins of deposition shall be marked on the resection specimen.
	Strong Consensus

4.17	Consensus-based Recommendation
EC	The provision of radiological images or body diagrams (electronic/digital or printout/X-ray) should be discussed with the pathologist.
	Strong Consensus

4.18	Consensus-based Recommendation
EC	If logistically possible, the tumor on the resection specimen should be transferred directly to the pathology department in its native, unfixed state to enable immediate and optimal further processing. Otherwise, the specimen shall be transferred to pathology in a sufficient amount of 4% buffered formalin as quickly as possible.
	Consensus

Background

Before sending tumor resected specimens to pathology, relevant anatomical structures or incision margins must be marked by the surgeon in such a way that a clear three-dimensional orientation is possible. Particularly important resection structures (e.g. fascia, periosteum, vessels) should be specially marked, e.g. with thread markings. Ideally, the position of the specimen should be drawn in a corresponding body diagram and, if necessary, imaging should be provided. Incision of the specimen by the surgeon must be avoided at all costs, as this can significantly hinder the assessment of the resection margins.

Native transmission of the on the resection specimen under frozen section conditions is encouraged, as this allows the collection of native material (impression preparations, tissue samples for a biobank). If possible, a blood sample should also be sent to pathology in addition to the specimen, provided that the technical requirements for its further processing and storage are available there. Due to the increasingly necessary additional molecular examinations, the presence of normal DNA/RNA for comparison with the tumor sample is very helpful. In this context, general patient consent must be obtained.

If native submission is not possible in a reasonable time frame, the preparation must be fixed in a sufficient amount (tissue to formalin 1:4) of 4% buffered formalin. When the specimen is fixed in this way it can be stored and transported at room temperature. Cooling is not necessary.

4.1.4. Processing of the tumor resection specimen

4.1.4.1. Macroscopic workup

4.19	Consensus-based Recommendation
EC	Tumor resection specimen sent in native form shall be viewed by a specialist soft tissue pathologist immediately after its arrival in the pathology department. In the case of fixed specimens, the pathologist shall check that sufficient formalin is added and, if necessary, cut the specimen several times to achieve better fixation.
	Strong Consensus

4.20	Consensus-based Recommendation
EC	Macroscopic description of soft tissue specimen shall include tumor heterogeneity, extent of necrosis, and previous tissue removal.
	Strong Consensus

4.21	Consensus-based Recommendation
EC	The minimum distances to relevant resection margins and critical structures shall be specified in the histopathological findings. R0 status is defined as „no tumor on ink“.
	Strong Consensus

Background

The specimen received in the pathology department should - if sent native/unfixed - be immediately or - if fixed - promptly inspected by a qualified pathologist and photographically documented. Before collecting native specimens, the specimen should be measured and weighed. The site of collection of native specimens should be marked appropriately so as not to compromise subsequent evaluation of resection margins. In the case of larger specimens, these should be incised several times before further detailed processing to ensure adequate penetration of the formalin into the tissue. After sufficient fixation (usually overnight), macroscopic workup should be performed according to EORTC recommendations [103].

This includes, after appropriate color marking of the various resection margins, lamination into approximately 1 cm wide slices and photo documentation of these lamellae. The corresponding photos can be used to mark where samples were taken. The rule of thumb is to collect one kerosene block per cm of tumor diameter plus separately collect tumor samples related to the resection margins. The extent of necrosis and infarct zones should be described macroscopically and quantified approximately in %. Particular attention should be paid to the minimum distances to relevant resection margins and critical anatomical as well as clinically separately identified

structures. Resection margins close to the tumor are stained to facilitate assessment of tumor infiltration. R0 resection is defined as no tumor manifestation on the stained resection margin („no tumor on ink“) [104], [105]. If neoadjuvant therapy has preceded, workup should be performed according to the suggestions of the EORTC-STBSG guidance [103].

4.1.4.2. Microscopic processing of the tissue

All collected samples are automatically dehydrated (mostly overnight), embedded in kerosene and cast according to standard protocols after sufficient fixation in 4% buffered formalin. Sections 2 to 4 µm thick are then made from the kerosene blocks. These are stained with a hematoxylin-eosin stain (H&E). General recommendations for further histochemical staining do not exist.

4.22	Consensus-based Recommendation
EC	Context-dependent immunohistochemical antibody panels should be used in the diagnosis of soft tissue sarcomas.
	Strong Consensus

4.23	Consensus-based Recommendation
EC	The immunohistochemical antibodies used shall be validated with regard to their suitability by internal quality controls. An on-slide control is recommended for each antibody used.
	Strong Consensus

4.24	Consensus-based Recommendation
EC	Regular participation in external certified interlaboratory comparisons as external quality control shall be performed.
	Strong Consensus

Background

The classification of soft tissue sarcomas is based on the recognition of specific growth patterns (e.g., spindle cell, small-blue round cell, biphasic), the vascular pattern, and, if applicable, the accompanying inflammatory infiltrate, and on the detection of a lineage-specific differentiation (e.g., lipomatous, muscular, neuronal, etc.).e.g. lipomatous, muscular, neuronal, etc.), or the detection of a specific genotype, so that immunohistochemical and, if necessary, molecular investigations play a key role in the diagnosis of soft tissue sarcomas [106]. In addition, sarcomas must be differentiated from other tumors with similar morphology, such as sarcomatoid carcinomas, malignant melanomas, mesotheliomas, germ cell tumors, or even hematologic neoplasms. Many of the antibodies used (e.g., CD34, S100) are not entity-specific and must be interpreted and weighted differently for diagnosis depending on the

context. For these reasons, extensive immunohistochemical analyses (so-called antibody panels) are often necessary in primary diagnostics and are now preferably used in automated systems.

For the basic diagnosis of soft tissue tumors, the following antibodies, among others, have proven successful: Broad spectrum keratins, EMA, Ki67, S100, CD45/PanLeu, CD21, CD23, SOX10, MelanA, HMB45, ER/PR, CD10, smooth muscle actin, desmin, caldesmon or calponin, myogenin, WT1, calretinin, BAP1, podoplanin/D2-40, CD34, ERG, CD117, DOG1, NSE, synaptophysin, chromogranin, CD56, CD99.

A number of relatively specific markers exist for advanced immunohistochemical diagnosis, some of which can be used to screen for underlying genetic alterations. This ever-expanding group includes beta-catenin (e.g. Desmoid fibromatosis), MDM2/CDK4 (highly differentiated/de-differentiated liposarcoma), BRAF V600E (malignant melanoma), TLE1 (synovial sarcoma), STAT6 (solitary fibrous tumor, SFT) [104], MUC4 (low grade fibromyxoid sarcoma, sclerosing epithelioid fibrosarcoma) [108], TFE3 (alveolar soft tissue sarcoma), SDHB (SDH-mutated gastrointestinal stromal tumors, GIST), HHV8 (Kaposi's sarcoma), c-MYC (radiation-induced sarcomas, especially angiosarcomas), CAMTA1 (epithelioid hemangioendothelioma), FOSB (pseudomyogenic hemangioendothelioma, epithelioid hemangioma), INI-1 (malignant rhabdoid tumor, epithelioid sarcoma, epithelioid malignant nerve sheath tumor), H3K27me (malignant peripheral nerve sheath tumor) [107], brachyury (chordoma), ALK (inflammatory myofibroblastic tumor), NKX2.2 (Ewing sarcoma), WT1/ETV4 (CIC-rearranged small cell sarcoma), BCOR (BCOR-rearranged small cell sarcoma) [108], [109]. If preceded by neoadjuvant therapy, the workup should be performed according to the suggestions of the EORTC-STBSG [103].

4.1.4.3. Histopathologic subtyping and grading of soft tissue tumors.

4.25	Consensus-based Recommendation
EC	Histopathological subtyping shall be performed according to the currently valid WHO classification. The tumor shall be classified into the diagnostic groups benign, intermediate (locally aggressive), intermediate (rarely metastatic) or malignant. The ICD-O coding (if available) shall be added as additional information.
	Strong Consensus

4.26	Consensus-based Recommendation
EC	The current TNM classification should be applied.
	Strong Consensus

4.27	Consensus-based Recommendation
EC	The grading of sarcomas should be entity-dependent using the European preferred FNCLCC system (Fédération Nationale des Centres de Lutte Contre le Cancer) or according to the NCI system (National Cancer Institute). The three parameters relevant for this, degree of differentiation, mitotic count per 10 HPFs and extent of necrosis, should be taken from the findings.
	Strong Consensus

Background

Tumor grading has less prognostic value than histopathologic subtype for some tumor entities (including angiosarcomas, dedifferentiated and myxoid round cell liposarcomas, rhabdomyosarcomas, Ewing sarcomas, alveolar soft tissue sarcomas, epithelioid sarcomas, clear cell sarcomas) and should not be used for tumors in the intermediate dignity group (eg.E.g., dermatofibrosarcoma protuberans, solitary fibrous tumor, inflammatory myofibroblastic tumor, and others) should not be used [110], [111], [112]. For the diagnostic groups „intermediate – locally aggressive“ and „intermediate – rarely metastatic“, these terms should instead be explained in the assessment in terms of their biological meaning. Thus, if grading is not performed, the reason should be clearly explained. TNM classification is also generally not used for intermediate diagnostic groups with the exception of gastrointestinal stromal tumors).

Table 8: FNCLCC Grading System: Definition of Parameters*

Tumor differentiation (see next table)	
Score 1	Sarcomas closely resembling normal adult mesenchymal tissue (eg, well-differentiated liposarcoma)
Score 2	Sarcomas for which histologic typing is certain (eg, myxoid liposarcoma)
Score 3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, osteosarcomas, PNET
Mitotic count	
Score 1	0-9 mitoses per 10 HPF**
Score 2	10-19 mitoses per 10 HPF
Score 3	≥20 mitoses per 10 HPF
Tumor necrosis	
Score 0	No necrosis
Score 1	<50% tumor necrosis
Score 2	≥50% tumor necrosis
Histologic grade	
Grade 1	Total score 2, 3
Grade 2	Total score 4, 5
Grade 3	Total score 6, 7, 8

* Modified from Trojani et al. [113]. FNCLCC indicates Fédération Nationale des Centres de Lutte Contre le Cancer; PNET, primitive neuroectodermal tumor.

** A high-power field (HPF) measures 0.1734 mm2.

Table 9: FNCLCC Grading System: Tumor Differentiation Score According to Histologic Type*.

Histologic Type	Tumor Differentiation Score
Atypical lipomatous tumor/Well-differentiated liposarcoma	1
Well-differentiated leiomyosarcoma	1
Myxoid liposarcoma	2
Conventional leiomyosarcoma	2
Myxofibrosarcoma	2
High-grade myxoid (round cell) liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3
Poorly-differentiated fibrosarcoma	3
Pleomorphic rhabdomyosarcoma	3
Poorly-differentiated/pleomorphic leiomyosarcoma	3
Biphasic/monophasic/poorly differentiated synovial sarcoma	3
Mesenchymal chondrosarcoma	3
Extraskeletal osteosarcoma	3
Extraskeletal Ewing sarcoma	3
Malignant rhabdoid tumor	3
Undifferentiated pleomorphic sarcoma	3
Undifferentiated sarcoma, not otherwise specified	3

* Modified from Guillou et al. [114]. FNCLCC indicates Fédération Nationale des Centres de Lutte Contre le Cancer

For some tumor entities, alternative classifications for risk assessment exist instead, such as the AFIP classification by Miettinen et al. 2006 [115] or the nomograms by Joensuu et al. [116] (see Figure 3) for gastrointestinal stromal tumors (see Chapter 10.1). For PEComes, prognostic factors have been proposed by Folpe et al. and by Doyle et al. including parameters such as mitotic count, necrosis, infiltrative tumor growth, and tumor size [117], [118].

It is noted that a reported grading on core biopsy material may not be representative and may be too low, as necrosis and higher grade tumor areas may not be included. This is especially true for entities with frequent heterogeneity such as lipomatous tumors and myxofibrosarcomas. There are usually insufficient fields of view for a representative count of mitoses. The extent of necrosis cannot be adequately estimated. Imaging, which is certainly helpful in this context, is mostly not available to the pathologist (even though this should be urgently sought). The extent to which consideration of the results of radiological imaging can influence and improve grading in the future has not yet been investigated in larger prospective case series.

4.1.5. Molecular pathology of soft tissue tumors

4.1.5.1. Molecular pathological workup of soft tissue tumors

4.28	Consensus-based Recommendation
EC	For entities with recurrent genetic aberration, confirmation of the diagnosis should be made by molecular pathological detection of the respective alteration.
	Strong Consensus

4.29	Consensus-based Recommendation
EC	Evidence of a diagnostically relevant translocation can be obtained using an appropriate FISH probe that shows a break for one of the two gene loci involved in the translocation.
	Strong Consensus

4.30	Consensus-based Recommendation
EC	Detection of predictive gene fusions shall be performed using an appropriate next-generation sequencing (NGS) panel, which will identify the exact gene fusion variant.
	Strong Consensus

4.31	Consensus-based Recommendation
EC	For cases with inconclusive assignment to a known entity by morphology and immunohistochemistry, investigation with an NGS panel covering the known common gene fusions and driver alterations of soft tissue sarcomas shall be sought.
	Strong Consensus

Background

The number of identified molecular pathologic aberrations is steadily increasing in soft tissue tumors [119], [120], [121], [122], [123]. These are chromosomal translocations, amplifications or specific mutations. Next-generation sequencing (NGS) technology has identified recurrent gene fusions or other genetic alterations for numerous entities in recent years. The detection of a recurrent genetic alteration can be used diagnostically, and in some cases has predictive significance [122], [123], [124]. In tumors with reciprocal chromosomal translocation or gene fusion, in the vast majority of entities, only one specific gene fusion is present that is characteristic of that entity. Rarely, the same gene fusions may be detectable in different tumor entities; more common is the involvement of one gene (e.g., EWSR1) in different gene fusions in different entities. For an overview of gene fusions, see the Mitelman database(https://mitelmandatabase.isb-cgc.org/) [125] and the COSMIC database(https://cancer.sanger.ac.uk/cosmic/fusion) [126]. The most common translocation types and genetic aberrations in soft tissue tumors are listed in Table „Selected diagnostically relevant recurrent gene fusions and driver alterations“ [119]. For each genetic aberration, different detection options are indicated (e.g., immunohistochemistry, RT-PCR, FISH, NGS).

In non-pleomorphic sarcomas, there are clustered translocations whose detection may have therapeutic consequences (e.g., NTRK). NTRK gene fusions occur in some tumor subtypes e.g. in inflammatory myofibroblastic tumor (IMT) in max. 1 %. This alteration, which can be used very well therapeutically, should be searched for in a targeted manner according to defined algorithms [127], [128].

If diagnostic evidence for NTRK fusions is secured, approved agents are available for metastatic/non-operable stage patients with larotrectinib and entrectinib.

In non-pleomorphic sarcomas, translocations are frequent and their detection may have therapeutic consequences (NTRK). NTRK gene fusions occur in some tumor subtypes, e.g. in inflammatory myofibroblastic tumor (IMT) in max. 1 %.

Table 10: Selected diagnostically relevant recurrent gene fusions and driver changes [119].

Tumor entity	Recurrent gene alteration	Detection methods
Atypical lipomatous tumor (ALT) / highly differentiated liposarcoma	*MDM2/ CDK4* Amplification	MDM2/ CDK4 immunohistochemistry, *MDM2/ CDK4* FISH, *MDM2/ CDK4* CISH
Dedifferentiated liposarcoma	*MDM2/ CDK4* Amplification	MDM2/ CDK4 immunohistochemistry, *MDM2/ CDK4* FISH, *MDM2/ CDK4* CISH
Myxoid liposarcoma	*FUS-DDIT3/ EWSR1-DDIT3* gene fusion	*DDIT3* FISH, NGS
Dermatofibrosarcoma protuberans (DFSP)	*COL1A1-PDGFB* gene fusion	*COL1A1*-PDGFB FISH, NGS
Solitary fibrous tumor (SFT)	*NAB2*-STAT6 gene fusion	STAT6 immunohistochemistry, NGS
Infantile fibrosarcoma	*ETV6-NTRK3* gene fusion	*ETV6* FISH, panTRK immunohistochemistry
Low-grade fibromyxoid sarcoma (LGFMS)	*FUS-CREB3L2* gene fusion, more rarely *EWSR1-CREB3L1* gene fusion	MUC4 immunohistochemistry, NGS
Sclerosing epithelioid fibrosarcoma (SEF)	*EWSR1-CREB3L1* gene fusion, *EWSR1-CREB3L2* gene fusion	MUC4 immunohistochemistry, *EWSR1-FISH*, NGS.
Inflammatory myofibroblastic tumor (IMT)	*ALK* gene fusion, less frequently *ROS1* gene fusion	ALK immunohistochemistry, *ALK* FISH, *ROS1* FISH, NGS
Alveolar rhabdomyosarcoma (ARMS)	*PAX3*-FOXO1 gene fusion, *PAX7-FOXO1* gene fusion	*PAX3* FISH, *PAX7* FISH, *FOXO1* FISH, NGS
Synovial sarcoma (SS)	*SS18*-SSX1/ *SS18-SSX2/ SS18-SSX4* gene fusion	*SS18* FISH, NGS
Alveolar soft tissue sarcoma	*ASPSCR1-TFE3* gene fusion	*TFE3* FISH, TFE3 Immunohistochemistry, NGS
Clear cell sarcoma	*EWSR1-CREB1/ EWSR1-ATF1* gene fusion	*EWSR1* FISH, NGS
Extraskeletal myxoid chondrosarcoma	*EWSR1-NR4A3/ TAF15-NR4A3* gene fusion	*NR4A3* FISH, *EWSR1* FISH, NGS
Desmoplastic small-blue round cell tumor	*EWSR1*-WT1 gene fusion	*WT1* FISH, WT1 (c-terminus) immunohistochemistry, NGS

Tumor entity	Recurrent gene alteration	Detection methods
Ewing sarcoma	*WSR1*-ERG/ *EWSR1-ETV1/ EWSR1-ETV4/ EWSR1-FEV/ EWSR1-FLI1* gene fusion	*EWSR1* FISH, NGS
Undifferentiated/unclassified sarcoma with *BCOR-CCNB3* gene fusion	*BCOR*-CCNB3 gene fusion	CCNB3 immunohistochemistry, BCOR immunohistochemistry, NGS
Epithelioid hemangioendothelioma (EHE)	*WWTR1-CAMTA1* gene fusion, *YAP1-TFE3* gene fusion	CAMTA1 immunohistochemistry, TFE3 immunohistochemistry, NGS
Pseudomyogenic hemangioendothelioma	*SERPINE1-FOSB* gene fusion	FOSB immunohistochemistry, NGS
Undifferentiated/unclassified sarcoma with *CIC-DUX4* gene fusion	*CIC-DUX4* gene fusion	WT1 immunohistochemistry, ETV4 immunohistochemistry, NGS (not all assays suitable)

4.1.5.2. Molecular pathological methods

4.32	Consensus-based Recommendation
EC	The detection method used for the detection of a gene fusion or other genetic driver alteration shall have sufficient sensitivity and specificity for the intended purpose and shall be validated for suitability by internal and, if possible, external quality controls.
	Strong Consensus

Background

There are several methods to detect specific gene fusions and driver alterations, which have different sensitivity and specificity [129], [130].

Hybridization-based detection (fluorescence in situ hybridization, FISH):

In FISH, detection of a translocation or gene amplification is performed by using gene-specific probes at the DNA level. Depending on the probe combination used, one or both genes involved in a translocation can be detected by split signals (e.g. EWSR1 break-apart probe) or fusion signals (e.g. COL1A1-PDGFB fusion probe). Focal amplification of a gene locus (e.g. MDM2) is detected by using a gene locus-specific probe in combination with a centromere control probe.

Advantages of FISH testing include ease of performance, low cost, high sensitivity and specificity for the corresponding break event, and a short time to result (approximately 2 working days). Disadvantages are that usually only one translocation partner is examined (e.g., EWSR1), which may lead to misinterpretation due to the involvement of this translocation partner in different, entity-specific translocations, and the lack of breadth of the procedure. Unknown or unanticipated translocations are not indicated. False-positive results, due to coexisting genetic defects (such as false-positive EWSR1-FISH for INI1-deletions, etc.), may also occur.

Sequencing-based detection (RT-PCR, NGS):

In sequencing-based detection of translocation events, detection can in principle be performed at the DNA or RNA level; however, due to the sometimes very large intronic sequences in which translocation events occur, RNA-based detection is usually used, as the examination of exonic regions is sufficient here. The enrichment of the gene fusion segments to be examined can be either PCR-based (RT-PCR, amplification-based NGS method) or via sequence-specific enrichment (hybrid capture-based NGS method). In the former, only already known gene fusions can be detected, since both translocation partners and the exact breakpoints must be known and covered by appropriate primers. With the latter method, previously unknown gene fusions can in principle also be detected via the use of gene-specific enrichment methods, if at least one of the two genes involved is appropriately covered in the enrichment approach.

The advantage of RT-PCR is the high specificity and sensitivity for the respective fusion event and the low cost. The major disadvantage is that, on the one hand, if the partner gene is previously unknown and not covered, the test is negative, and on the other hand, as with FISH testing, only known and expected fusions can be tested. The former disadvantage also applies to amplification-based NGS methods. Advantage of hybrid capture-based NGS methodology is that also previously unknown gene fusions

can be detected if at least one of the partner genes is included in the assay, as well as the possibility – with appropriate panel size - to detect fusion events/entities not previously suspected in the differential diagnosis. Disadvantages of NGS methods are the higher costs, the longer processing time and the sometimes very complex validation.

4.1.6. Reference pathological second opinion for soft tissue tumors

4.33	Consensus-based Recommendation
EC	For tumors with defined genetic alterations, the diagnosis should be confirmed by molecular biological detection of the respective alteration. In cases where this is not possible at the institution or there is insufficient experience with the method, a reference assessment should be performed in a specialized laboratory.
	Strong Consensus

4.34	Consensus-based Recommendation
EC	For soft tissue tumors with uncertain diagnostic assignment to a defined entity or with unexpected genetic findings, a histopathologic second opinion shall be obtained at a specialized reference center.
	Strong Consensus

Background

The classification of soft tissue sarcomas is complex and must take into account epidemiologic, clinical, anatomic, and histopathologic aspects including immunohistochemical and molecular pathologic findings. Sufficient specific experience in the use of the methods employed is required for the evaluation and weighting of these different components.

In recent years, several European sarcoma groups have shown that the number of misdiagnoses or diagnostic discrepancies between local and centralized pathology was as high as 30% [131], [132]. In some cases not only the subtype but also the diagnosis was different. It should be recognized that a histopathological second opinion and treatment in a specialized center improves outcomes of patients [133].

4.2. Prognosis scores for sarcomas and GISTs

4.35	Consensus-based Recommendation
EC	Molecular estimation of individual risk of recurrence in sarcomas shall not be performed as standard practice.
	Strong Consensus

Background

The prognosis of soft tissue sarcomas is predominantly determined by tumor size, location (limb vs. trunk and epifascial vs. subfascial), histologic tumor type, and most importantly, grading (see Recommendation 4.27. and Table 8). Accumulation of these factors with resection status (R0 vs. R1 and R2) may indicate a particularly unfavorable prognosis [134], [135]. In contrast to other tumor entities such as lung carcinomas [136], the TNM categories (according to UICC and AJCC) for sarcomas are hardly able to delineate survival time differences by stagingclassifications [134, 135]. This is mainly due to the different influence of the many different sarcoma subtypes.

The definition of ‚high-risk' sarcoma for inclusion in therapeutic trials is highly relevant. For this purpose, tumor size (>5cm, in some papers also >8cm), subfascially located tumor and a grading 2 or 3 according to FNCLCC are usually used. These factors do not adequately define the high-risk patient group, as patients after marginal R0 or R1 resection, for example, benefit most from adjuvant chemotherapy [137].

Nomograms were therefore developed to predict overallsurvival at 12 years based on the MSKCC data [138]. This nomogram has been validated at two other sarcoma centers and the NCDB [139]. The main limitation of this nomogram is the use of histological subtypes that no longer exist today. In the following years histology-typical nomograms, e.g. for synovial sarcomas [140] with regard to systemic chemotherapy and retroperitoneal sarcomas [141] were published.

For adult patients following resection of extremity sarcomas, overall survival as well as the risk for the occurrence of distant metastases after R0 resection can be calculated using the ‚Sarculator' nomogram, which is available as an app [142]. The prognostic tool was developed on a database of 7926 patients and validated on over 4600 patients (primary tumor surgery 1994-2013) from four centers (Milan, Paris, Toronto, London) [143]. For the two nomograms, age, maximum tumor size, grading by FNCLCC, and 9 different histological subtypes are assessed. Tumor size was assessed dichotomously in the nomogram ≤5cm vs. >5cm which is an approach that has been open to criticism. It is important to recognize that the data are valid only for therapy in sarcoma centers [142].

Thus, molecular characteristics beyond those necessary for correct diagnosis do not play a role in the assessment of the prognosis of patients with sarcomas to date. In this respect, commercially offered (and not validated) ‚molecular tests' are also not suitable to provide meaningful guidance for prognosis assessment of prognosis.

4.36	Consensus-based Recommendation
EC	For the assessment of the individual risk of recurrence, a risk classification shall be used that includes tumor rupture in addition to primary site, absolute mitotic count/5mm² and tumor size. Here, the modified consensus criteria and contour maps have proven most useful. The TNM classification for GIST has no added clinical value.
	Strong Consensus

4.37	Consensus-based Recommendation
EC	An assessment of individual recurrence risk shall be performed on the resected primary localized GIST without evidence of distant metastases (cM0) to assess the indication for adjuvant imatinib therapy.
	Strong Consensus

4.38	Consensus-based Recommendation
EC	For every intermediate/high risk GIST as well as for every metastatic GIST, a mutation analysis of at least the KIT (exon 9, 11) and PDGFRA (exon 18) genes shall be performed. If no mutation can be detected in these three loci, further hot spot regions shall be investigated by molecular pathology or the case should be sent to a reference laboratory.
	Strong Consensus

Background

to recommendation 4.36.:

For more detailed information, see also chapter Chapter 10.1.1.1.1.1 " Minimal requirements reports" in the chapter of pathological diagnosis of GIST.

Regarding recommendation 4.37.:

For more detailed information, see chapter Chapter 10.1.1.3 „Risk classification of localized tumors" in the chapter of pathological diagnosis of GIST and chapter 10.1.3 „Adjuvant drug therapy of localized, R0 resected GIST".

Regarding recommendation 4.38.:

For complete background text, see chapter Chapter 10.1.1.2 „Molecular Diagnostics" in the chapter of pathologic diagnosis of GIST.

5. Treatment of localized soft tissue tumor

5.1. Surgical therapy

General recommendations for primary therapy

5.1	Consensus-based Recommendation
EC	When there is clinical suspicion and/or imaging suspicion of soft tissue sarcoma, this shall be confirmed on histology.
	Strong Consensus

5.2	Consensus-based Recommendation
EC	The planning of the treatment of sarcomas shall take place in the interdisciplinary tumor board before treatment is instigated. At least one surgical discipline with a focus on soft tissue sarcomas, as well as hematology/oncology, pathology, radiology, and radiation oncology shall be represented in the tumor board. Site-specific surgical expertise shall be obtained on a case-by-case basis for sarcomas arising at certain anatomical locations.
	Strong Consensus

5.3	Consensus-based Recommendation
EC	In cases of clinical suspicion and/or imaging suspicion of soft tissue sarcoma that is smaller than 3 cm in diameter and superficially located, primary R0 resection may be performed.
	Strong Consensus

General aspects

Surgical resection with tumor-free resection margins (R0 resection) represents the core therapeutic element for patients with adult localized soft tissue sarcoma of all sites. En bloc resection of both tumor and biopsy access should be undertaken [144]. The assessment of whether a tumor is resectable with an R0 margin can only be made by a surgeon with experience in this area. Accordingly, the tumor stage, anatomic location, comorbidities, and expected functional limitation of the patient must be considered in this context.

For resection of extremity sarcomas, the term ‚compartment resection' was coined by Enneking and later applied as a treatment concept. The surgical technique was developed for the treatment of osteosarcoma [145]. It meant resecting the bone tumor together with the surrounding muscles, thereby preserving the tumorcoverage. Compartmental resection according to Enneking involved the co-resection of the attachment and origin of the muscles.

A compartment (lat. ‚compartimentum', German ‚Loge') refers to functionally related skeletal muscles that are surrounded by a common aponeurosis. However, there are relatively few anatomically defined compartments in the extremities. Examples include in the thigh the adductor muscles, the quadriceps, the hamstring compartment on the dorsal thigh, and in the lower leg, the anterior lunge and the flexor and fibular lunge. In the arm, there are biceps or triceps compartments on the upper arm and extensor and flexor compartments on the forearm.

From the point of view of resection of soft tissue sarcomas, a radical compartment resection is not always required unless the tumor is located in the area of attachment and origin of muscles. If the origin and attachment of the muscle are far from the tumor, they may be preserved. This avoids unnecessary morbidity (cushioning of joints by muscle preserved components) and functionality (extension of the radiation field to the entire surgical area) [146]. For resection of soft tissue sarcomas growing centrally within a compartment, these should be resected with portions of the surrounding muscles. A complete compartmental resection is not necessary, provided that the resection of a portion of muscle can completely cover the tumor (wide resection). Preservation of muscle portions, whether longitudinal or transverse, reduces the morbidity of the surgery.

The terms for the width of the resection margins can be described analogously to Enneking [145]:

- **Intralesional:** Resection margin passes through tumor and leaves tumor behind.
- **Marginal:** Resection margin goes along the pseudocapsule (reactive zone).
- **Wide resection:** tumor remains covered on all sides by a layer of healthy tissue.
- **Compartment resection:** complete resection of the tumor-bearing muscle compartment including the origin and attachment of the muscles.

The quality of the resection margins is not to be measured only by metric safety distance [104]. Through different research groups the concept of barrier has been propagated, i.e. the anatomical boundary layer of non-tumor affected tissue (fascia, periosteum etc.), is also of great importance [147].

5.1.1. Sarcomas of the extremities

Surgical resection / amputation

Historically, amputation of the extremity for soft tissue sarcoma was frequently advised. A comparative cohort study of patients with lower extremity sarcomas by Shiu et al. [148] suggested that local recurrence risk was lower after amputation than after monobloc resection, with a RR of 0.62 (CI 0.39-0.98). Overall survival at 10 years was not significantly more favorable after amputation (RR 4.11, CI 0.85-19.76). It should be noted that this cohort included patients with rhabdomyosarcomas and angiosarcomas and did not receive any additional drug or radiotherapy treatment. Also, nearly half of the patients underwent surgery for tumor recurrence.

A 2:1 randomized trial of extremitypreserving sarcoma resection combined with adjuvant chemotherapy and radiotherapy vs amputation and adjuvant chemotherapy failed to demonstrate a survival advantage for amputation. Patients with R0 resection had a significantly lower local recurrence rate ($p<0.0001$). Based on this study, the recommendation for extremity-preserving sarcoma resection [149].

However, amputation may be indicated when there is infiltration of neurovascular bundles, when trhere is life-threatening hemorrhage, for tumors with extensive ulceration or when, after conserving surgery, it is expected that the patient will not be able to return to a living situation that is manageable for him. In a cohort of patients over 15 years of 1597 patients with sarcomas, 2.3 % underwent major amputation (hemipelvectomy, thoraco-scapular) [150]. The authors report a high rate of complications, short survival, and most severe impairment of quality of life.

In a cohort study of 413 patients, 6% underwent primary amputation [151]. This group of patients had significantly larger tumors, were of older age, and had a higher risk of metastasis. However, multivariate analysis showed no effect on systemic metastasis, which was determined by tumor size and grading.

5.4	Consensus-based Recommendation
EC	The diagnosis and therapy of soft tissue sarcoma of the extremities shall be performed by or in coordination with a certified sarcoma center or associated cooperation partner.
	Strong Consensus

5.5	Consensus-based Recommendation
EC	If a soft tissue sarcoma of the extremities is detected, the primary approach shall be limb preservation.
	Strong Consensus

5.6	Evidence-based Recommendation
GoR **A**	Resection of primary soft tissue sarcoma of the extremities shall be performed as a wide resection. The goal is an R0 resection.
LoE ⊕⊕⊕⊖ ⊕⊕⊕⊕ ⊕⊕⊕⊖	[152]; [153]; [154]; [155]; [156]; [157]; [158]; [159]; [160]; [161]; [162] ⊕⊕⊕⊖: Local recurrence ⊕⊕⊕⊕: Overall survival ⊕⊕⊕⊖: Metastasis-free survival
	Consensus

Background

R0 resection is a positive predictive factor for local recurrence-free and overall survival. In a Scandinavian Sarcoma Group analysis of 559 patients with sarcoma (median tumor size 7 cm) and a median follow-up of 88 months, there was a highly significant lower risk of developing tumor recurrence after adequate tumorresection than after

intralesional or marginal resection (RR 2.9 [1.8-4.6]. p<0.001). Patients did not undergo adjuvant therapy [161].

A later analysis on 426 patients who had received adjuvant radiation after sarcoma resection confirmed that patients with wide resection had more favorable local recurrence-free survival than after marginal resection (HR 1.62 [0.62-4.20], p<0.001) [156].

For the liposarcoma subgroup, the same study group reported 237 patients who had either wide resection or marginal resection [153]. Wide resection resulted in a significantly lower risk of local recurrence (RR 0.36 [0.23-0.56], p<0.001) at a median follow-up of 8 years. Similar results for liposarcomas have been reported previously. In a multivariate analysis, according to grading and tumor size, resection distance with adequate safety margin versus marginal resection was associated with a lower local recurrence rate [164].

A database analysis of the National Cancer Data Base from 2003-2012 on 27,969 patients, 79.3% of whom had been treated with R0 resection (12.4 % R1 resection, 8.5% R2 resection) demonstrated that R0 resection was associated with improved survival over R1 resection (HR 1.1438, CI 1.024-1.1869, p<0.001) [154].

Regardless of clinical outcome, the need for reoperation after R1 resection also results in a substantial additional financial burden [165].

In an analysis of 687 patients with highly malignant sarcoma of the extremities from 4 tertiary referral centers [163], it could be shown that surgical safety distance had a favorable effect against the occurrence of local recurrence with a HR of 0.61 (95% CI 0.33-1.12) for a distance of 0-2 mm, and a HR of 0.16 (95% CI 0.07-0.41) for a distance greater than 2 mm.

An exception to this is the atypical lipomatous tumor (liposarcoma G1 of the extremities). Here, due to the rather benign behavior with extremely rare dedifferentiation and metastasis, complete but marginal resection is possible in primary and recurrent cases. This also applies under the aspect of a very frequent inclusion of vital structures in the tumor [166].

5.1.1.1. Resection

5.7	Consensus-based Recommendation
EC	The wound should be closed without tension.
	Strong Consensus

5.8	Consensus-based Recommendation
EC	If primary tension-free wound closure is not possible, the aim shall be to cover the wound with plastic reconstructive measures.
	Strong Consensus

5.9	Consensus-based Recommendation
EC	If a sarcoma grows to bony structures or is suspected, the periosteum of the affected bone section should also be resected.
	Strong Consensus

5.10	Consensus-based Recommendation
EC	In cases of urgent suspicion of infiltration of bone structures by a sarcoma, co-resection of the affected bone section shall be generously indicated.
	Strong Consensus

5.11	Consensus-based Recommendation
EC	If infiltration of blood vessels by sarcoma is suspected, preoperative vascular imaging shall be performed by appropriate imaging e.g. CT angiography, MR angiography, DSA.
	Strong Consensus

5.12	Consensus-based Recommendation
EC	If there is evidence of blood vessel infiltration by sarcoma, the affected vessels should be segmentally resected and reconstructed.
	Consensus

5.13	Consensus-based Statement
EC	If infiltration of functionally relevant nerves is detected, the corresponding nerves should be resected. Infiltration of such a nerve alone does not constitute an indication for amputation.
	Strong Consensus

Background

Tumor resection should include the access route of an incisional biopsy by en bloc excision of a skin ellipse. For punch biopsies, this approach is not clearly supported by data.

It is important that wound closure is performed in a tension-free fashion so that adjuvant radiotherapy, for example, can be performed without problems. Local displacement flaps are suitable for this purpose. If a tension-free wound closure is not possible, a sterile wound closure should be performed via a VAC suction system, if necessary. The histological findings of the resection margins should be awaited before definitive wound closure. Mesh graft coverage does not constitute a wound closure suitable for irradiation.

If there is a resulting larger skin defect after surgical resection there should be a low threshold for considering plastic surgical reconstructive coverage by regional pedicled flaps aor by free flap transfer.

R0 resection is a positive predictive factor for local recurrence-free and overall survival. In contrast, infiltration of neurovascular bundle and bone by sarcoma are negative predictive factors for local recurrence-free survival [164]. These situations require special attention to avoid an R1 resection. R1 resection is also a highly significant negative predictive factor for local recurrence-free and overall survival.

In special cases, e.g. favorable tumor biology (liposarcoma) or after preoperative measures resulting in a less viable sarcoma (radiation, limb perfusion), a tissue layer such as perineurium, fascia, adventitia or periosteum may be sufficient to allow complete tumor resection.

If the soft tissue sarcoma is adjacent to the bone without infiltrating it, the extent of resection must be determined on an interdisciplinary basis [167]. In radiation-sensitive lesions, neoadjuvant RTX may allow avoidance of bony resection. However, this is an individualized case-by-case decision based on tumor size, grade, histological subtyper and patient status. The periosteum must be removed as well in these cases, as it must be considered infiltrated. Due to the deperiosis and the radiation therapy, an increasing biomechanical weakening of the bone can be assumed as a long term consequence of treatment. Therefore, in order to avoid a usually poorly healing insufficiency fracture, intramedullary prophylactic stabilization after completion of tumor therapy may be a treatment option [168].

A risk of insufficiency fractures also exists after isolated limb perfusion when during the tumor resection there is stripping of the periosteum and subsequent radiation [169].

Close association with bone by soft tissue sarcoma affects about 5-6 % of patients, of which only a few (less than 1 %) have true infiltration [170]. It is often difficult to decide preoperatively whether true bone infiltration is present. Frequently, co-resection of the bone adjacent to the sarcoma is necessary to avoid exposing the tumour surface in the tumor bearing muscle area. Often the periosteum is sufficient for this in terms of the ‚Barrier' concept [147], although occasionally a bone lamella has to be resected as well. Complete resection of the bone and reconstruction should be considered if the bone is encased by the sarcoma or if there is true tumor infiltration of the bone.

For sarcomas with infiltration into blood vessels, venous or arterial vascular resection and reconstruction is often required to safely ensure R0 resection. Typically, these are highly malignant stage III sarcomas that require multimodality therapy. The exception is primary vascular sarcomas, which are often grade 1 but also require vascular resection and reconstruction.

Sarcomas can affect vessels in a number of ways including simple displacement, direct infiltration, encasement but is still in itself, not an indication for amputation. or compression [171].

Vascular resection and reconstruction requires complex surgical planning involving vascular surgeons [172]. With adequate surgical expertise, treatment outcomes are no less favorable than after sarcoma resection of the extremities without vascular involvement [173], [174]. Amputation cannot be inferred from vascular infiltration alone.

When sarcomas infiltrate neurovascular bundles, nerves are often involved as well. Analogous to the classification of the anatomic relation of vessels to sarcomas, a classification regarding the relation to nerves has also been established [175]. The previous universal indication for amputation because of involvement of a major nerve in eg resection of the sciatic nerve cannot be maintained [176], [177]. In the evaluation of walking ability after sciatic nerve resection using the MSTS Rating Scale, half of the patients had a score of 25 or more points (out of a possible 30), indicating unimpaired function of the limb. No amputation indication per se can be inferred from the need to resect the sciatic nerve.

Resection of the femoral nerve is the far less favorable constellation for leg function due to the loss of innervation of the quadriceps muscle but is still in itself, not an indication for amputation.

Functionality, mobility

5.14	**Consensus-based Recommendation**
EC	In the case of macroscopically close resection, if detected or suspected intraoperatively, the suspected close margins shall be marked on the resection specimen.
	Strong Consensus

Background

If the tumor is located close to critical vessels or nerves, these do not need to be routinely removed as long as there is no direct infiltration. Resection of the adventitia or perineurium may be sufficient, taking into account the the histologic tumor subtype (most likely in liposarcomas) and the grade (most likely in grade 1).

Resection with a microscopically tumor-affected sedimentation margin (R1 resection) is an important negative predictor of local recurrence in STS [178], [179]. Microscopically positive resection margins are associated with both a higher rate of local recurrence and a shorter disease-free interval (DFS) in STS [178], [180]. In a cohort study (N=1668) of patients with STS of the extremities and trunk, which examined the main predictors of local recurrence in patients with STS, there was a significantly higher rate of local recurrence after a 10-year follow-up for patients with tumor-involved settling margins ($p < 0.001$) [179].

If resection with microscopically positive resection margins is anticipated, they should be marked intraoperatively for subsequent radiotherapy boost. Close collaboration between surgeons, pathologists, and radiation therapists is required for optimal treatment outcomes. After consideration of treatment alternatives, expected functional postoperative limitation, and comorbidity, a less aggressive surgical approach may also be reasonable, even if it is expected preoperatively that the microscopic deposition margins are not certainly tumor-free [181].

See also chapter Chapter 5.7.1 „Planned marginal resection“ and acceptance of minimal safety margins [105].

Stage-dependent treatment:

5.15	**Consensus-based Statement**
EC	Following resection of a primary sarcoma and histologic findings of R1 resection (other than ALT), presentation to a sarcoma center for consideration of resection shall be made.
	Strong Consensus

5.16	**Consensus-based Recommendation**
EC	Patients with stage III soft tissue sarcoma shall be offered multimodality therapy preoperatively as part of an interdisciplinary sarcoma board.
	Strong Consensus

Background

Stage I: T1 G1 = *stage IA*, tumor <5cm

Stage IB: T2a G1, Tu >5<10cm

Complete resection is the primary treatment goal in stage IA patients, tumor-free margins of deposition with a wide safety margin should be aimed for [182]. Adjuvant therapy is usually not indicated.

In stage IB (T2a G1), depending on tumor location and tumor size, a circumferential safety margin (previously required 1 cm) is sometimes not achievable. If the final histology shows a marginal resection, a further resection or adjuvant RTX may be necessary [183]. For Atypical Lipomatous Tumors (ALT), marginal resection is sufficient to achieve long-term local control [184].

Stage II: T1 G2/3

For stage II sarcomas, complete R0 resection of the tumor should be aimed for. It may be that a surgical approach alone may be an option for patients with small tumors that can be removed with a very wide safety margin. Adjuvant radiotherapy even after R0 resection should be considered in all cases.

In a phase II trial (RTOG 9514) in 66 patients with highly malignant sarcoma and a tumor size of ≥8 cm, the combination of preoperative radiotherapy of 44 Gy combined with chemotherapy of doxorubicin/DTIC/ifosfamide yielded R0 resection in 88% of patients [185]. After 7 years, the local recurrence rate and metastasis rate were both 22 %. However, this approach resulted in grade 3 and grade 4 morbidity in 97% of patients and mortality of 4.7 %.

A randomized phase II/III EORTC trial with this question failed to show a survival gain for these patients compared with surgery alone. There was no benefit in recurrence-free survival in 134 phase II patients. The phase III trial planned for survival analysis was not conducted because of slow recruitment [186]. Patients with tumors larger than 8 cm are at increased risk for local recurrence or the development of distant metastases. There is also evidence that a surgical approach alone may be adequate in selected patients with high-grade lesions. Here, a prospective study showed in the long-term results that acceptable local control and good long-term survival can be achieved if an R0 situation is achieved [187]. Here, local recurrence rates at 5 and 10 years were 7.9% and 10.6% for patients with an R0 resection. In another analysis of 242 patients, the local recurrence rate was found to be significantly increased when there was a safety margin of less than 1 cm from the resection margin [188]. In this regard, a surgical approach followed by radiotherapy should always be considered in stage II [189]. Preoperative radiotherapy may also be an option in this case.

Plastic reconstruction procedures using artificial tissue to stabilize the chest wall but also with myo-cutaneous muscle plasty may be necessary. (see chapter Chapter 5.2)

Stage III: T2G2/3 = *Stage IIIA*, T3/4 (Tu > 10 or >15cm G2/3)

Even in stage III, complete R0 resection of the tumor should be aimed for, but this is often difficult due to the size of the tumor and its aggressive growth.

Table 11: Staging - extremities and superficial trunk, retroperitoneum (UICC/AJCC 2017 [190])

Stage	T	N	M	Grading three-stage	Grading two-level
IA	T1	N0	M0	G1	low grade
IB	T2, T3	N0	M0	G1, GX	low grade
II	T1	N0	M0	G2, G3	high grade
IIIA	T2	N0	M0	G2, G3	high grade
IIIB	T3, T4	N0	M0	G2, G3	highly malignant
IIIC	any T	N1	M0	any	
IV	each T	each N	M1	each	

No stages are currently recommended for tumors of the head and neck and the viscera of the thorax and abdomen.

5.1.1.2. Management of the regional lymph nodes

5.17	Consensus-based Recommendation
EC	In particular, rhabdomyosarcomas, clear cell sarcomas, epithelioid sarcomas, and synovial sarcomas may metastasize lymphogenically. Staging studies for these tumor types should include the lymphatic drainage pathways.
	Strong Consensus

Background

The majority of sarcoma subtypes metastasize preferentially hematogenously. Therefore, systematic lymph node removal is not recommended. However, there are sarcoma entities in which this rule does not apply.

In a recent series by Keung et al, lymph node (LN) metastases (pN1 and cN1) were found in 3.5% of sarcoma patients, and in 6.1% of angiosarcomas, 13.1% of epithelioid sarcomas, 15.9% of clear cell sarcomas, and 19.1% of undifferentiated small cell sarcomas [191]. Other research groups have come to similar conclusions (e.g., Daigeler et al. 2009 [192]).

The frequency of lymph node metastases in other sarcoma subtypes is less than 10 %, such as in rhabdomyosarcomas and synovial sarcomas (4.2 % in the work of Jacobs et al. who found lymph node metastases diagnosed in 5.3 % of 15,525 patients with

sarcomas in the SEER database [193]. It is important to consider which age cohorts are being studied. In the work of Jacobs et al. the high rates of LK metastases for rhabdomyosarcomas are explained by the high proportion of pediatric patients in the studied collective with a median age of 35 years.

Not infrequently, other distant metastases exist in addition to LN metastases, so the question of local resection of lymph nodes must be answered in the context of the other staging results. LN metastases are prognostically relevant only in the localized tumor stage. In general, LN metastases occur less frequently in sarcomas of the trunk and extremities than, for example, in sarcomas of the head and neck, thorax, or abdomen.

5.18	**Consensus-based Recommendation**
EC	Histological confirmation of lymph node metastases shall be performed if this results in therapeutic consequences.
	Strong Consensus

5.19	**Consensus-based Recommendation**
EC	Routinely, sentinel lymph node biopsy should not be performed in patients with soft tissue sarcomas.
	Strong Consensus

5.20	**Consensus-based Recommendation**
EC	In the absence of evidence of lymphogenic metastasis, lymphadenectomy should not be performed as part of the primary tumor resection.
	Consensus

5.21	**Consensus-based Recommendation**
EC	Lymphadenectomy may be considered for locoregional lymph node involvement without systemic metastasis.
	Strong Consensus

5.22	**Consensus-based Recommendation**
EC	For cutaneous sarcomas, sentinel lymph node biopsy (SLNB) shall not be performed.
	Strong Consensus

5.1.1.2.1. Lymphadenectomy

5.23	Consensus-based Recommendation
EC	Lymph node dissection shall not be performed as a standard procedure during resection of soft tissue sarcoma.
	Strong Consensus

5.24	Consensus-based Recommendation
EC	Depending on resectability and histology, radical lymphadenectomy should be considered as resection therapy in cases of locoregional lymph node involvement of a corresponding sarcoma subtype.
	Strong Consensus

Background

Lymph node metastases represent a route of spread in sarcomas only for certain tumor subtypes (see Chapter Chapter 5.1.1.2), predominantly clear cell sarcomas, rhabdomyosarcomas, epithelioid sarcomas, and myxoid round cell sarcomas. Thus, lymphadenectomy is not a standard of surgical primary therapy. However, for patients with locoregional lymph node involvement, radical lymphadenectomy may be a treatment option. Analysis of a database of 1772 patients between 1982 and 1991 showed that when patients with radical lymphadenectomy were compared with patients without, median survival increased from 4.3 to 16.3 months [194]. For those patients with radical lymphadenectomy and lymph node involvement, the 5-year survival was 46%.

Detection of lymph node metastases can be performed by sentinel node biopsy in individual cases. It might be helpful also to exclude non tumor-related LN enlargement caused by atypical lymphatic drainag in large primary tumors. Detection of tumor involvement by sentinel node biopsy was successful in a workup of 62 consecutive patients in 2 of 42 patients with synovial sarcoma and 6 of 12 patients with clear cell sarcoma [195]. Thus, a general indication for SN biopsy cannot be derived from this data.

5.1.2. Trunk / Thorax

Primary soft tissue sarcomas of the trunk and thorax are rare. Therefore, only few studies exist, especially hardly any prospective and randomized studies. Thereby, the clinical behavior of adult soft tissue sarcomas of the body trunk/thorax is to be evaluated similarly to that of sarcomas of the extremities [144]. Therefore, for this chapter, findings from studies involving both patients with STS of the extremities and body trunk were included, as well as those studies that evaluated results in patients with involvement of the extremities only. Radiation-induced sarcomas after multimodality therapy for breast carcinoma are a speciasl case. In sarcomas of the thoracic wall, the reconstruction is a very important part of therapeutic planning.

5.1.2.1. Resection

The treatment principles for sarcomas of the trunk/thorax are identical to those for sarcomas of the extremities (see Chapter Chapter 5.1.1).

5.25	Consensus-based Recommendation
EC	Patients with stage III soft tissue sarcoma of the trunk or thorax shall be offered multimodality therapy preoperatively as part of an interdisciplinary sarcoma board.
	Strong Consensus

Background

Surgical resection with tumor-free resection margins (R0 resection) also represents the core therapeutic element for patients with adult localized soft tissue sarcoma on the body trunk and thorax. The assessment of whether a tumor is R0 resectable can only be performed by a surgeon experienced in this topic. Accordingly, the tumor stage, anatomic location, comorbidities, and expected functional limitation of the patient must be considered in this context.

In patients with localized STS, resection with tumor-free resection margins (R0 resection) should be aimed for. Soft tissue sarcomas of the chest wall can be well controlled with complete surgical resection with wide margins [144]. En bloc resection of both the tumor and the incisional biopsy approach should be aimed for.

5.1.2.2. Re-resection

5.26	Consensus-based Recommendation
EC	Following resection of a primary sarcoma and histologic findings of R1 resection, presentation to a sarcoma center for consideration of resection shall be made.
	Strong Consensus

Background

If the margins of the resection specimen histologically show tumor cells (R1 resection), a further resection should be considered. Macroscopic as well as microscopic residual tumor imply a worse prognosis, and local control cannot be safely achieved with additive radiotherapy either [196]. In an analysis of 666 patients with localized STS and a surgical approach, resection was necessary in 295 patients with residual tumor. Among these, after 5, 10, and 15 years, 85%, 85%, and 82% of patients with resection were without local recurrence. In patients who did not receive resection, the local recurrence-free rate was 78%, 73% and 73%, respectively (p=0.03). R0 re--resection was a significant predictor of local tumor control [197].

5.1.2.3. Neoadjuvant/adjuvant therapy

If the tumor is only borderline resectable due to size or location, there is the option of neoadjuvant treatment by means of systemic therapy and/or radiotherapy (see chapter Chapter 5.6) [198]. This decision is influenced by the expected probability of response to systemic treatment, the histology of the tumor, as well as the general condition of the patient.

Surgically, resection should again be performed by wide, local resection if possible with a margin of healthy tissue (see also Section Chapter 5.4 and Chapter 5.6). When performing the resection after neoadjuvant pretreatment, wide resections with small safety margins may also be appropriate (e.g., safety margin < 2 mm), depending on the response of the tumor.

5.1.3. Head and neck

5.1.3.1. Surgical therapy of the primary tumor

Surgical „wide resection“ in healthy tissue represents the primary curative therapeutic pillar for soft tissue sarcomas of the head and neck [199], [200], [201], [202], [203], [204], [205], [206]. Wide resection in the first attempt - along with tumor size and tumor stage at initial diagnosis [200], [201], [205], [207], [208], [209], [210], [211] - is the most important prognostic factor for local tumor control, recurrence-free survival, and overall survival [200], [204], [205], [206], [212], [213], [214], [215]. Wide resection corresponds to a complete removal of the tumor surrounded on all sides by healthy tissue including any possible puncture channel from a core biopsy or In- or excisional biopsy scar. Regarding safety distances and definitions (‚Marginal resection‘) or “a layer of non-tumor infiltrated tissue“ especially after preoperative multimodal therapy, please refer to chapter Chapter 5.1 “Surgical therapy - General aspects“ and chapter Chapter 5.7.1 „Planned marginal resection“.

Macroscopic incomplete resection (R2) has the most unfavorable prognosis compared to microscopic incomplete resection (R1), close margin resection or resection in healthy tissue (R0). Individual cohort studies critically discuss the benefit of resection in healthy tissue for survival and could not show a clear survival benefit of in-sano resection in retrospective analyses [199], [203], [209], [210], [216], [217], [218], [219]. Tumor invasion into adjacent structures such as bone or blood vessels was identified as an independent negative risk factor [199], [211], [218].

In the head and neck region, there is a high spatial density of critical and essential structures is present, such as the extracranial cranial nerves, the carotid artery, the orbitals, or the skull base. In addition, the integrity of function and aesthetics in the head and facial region represents an essential requirement for quality of life. The preservation or restoration of the aforementioned structures or functions cannot always be guaranteed with radical surgical therapeutic approaches. Modification of radical surgical procedures due to the aforementioned complex and vital structures in the head and neck region results in incomplete resection rates of 8-42 % [200], [205], [211], [214], [215], [218], [220] in published cohort studies. Therefore, it is critical to openly and thoroughly discuss the expected surgical morbidity or radicality with each patient in advance.

In the head and neck region, the concepts of „wide resection developed elsewhere“ do not apply in simple analogy to, for example, the criteria in the extremities because of the close anatomic relationship to important functional structures.

In case of curative therapy approach (localized primary tumor, locoregional resectable neck lymph node and resectable distant metastases), the surgical indication for the head and neck region has to be discussed in the interdisciplinary sarcoma board considering functional and aesthetic aspects. Also for the head and neck region, resection of the tumor in healthy tissue with the biopsy scar without compromising the tumor tissue and the pseudocapsule (R0) should be aimed for [221].

5.1.3.2. Cervical Lymph Node Management

In contrast to squamous cell carcinomas of the head and neck, soft tissue sarcomas rarely have lymph node metastases (3-15%); however, when these are detected, the prognosis is less favorable, corresponding to distant metastasis [199], [214], [218]. Since soft tissue sarcomas are a very heterogeneous group of malignancies, a general recommendation for neck dissection cannot be made. Thus, neck dissection in cases of clinical and radiological suspicion of neck lymph node metastases should be performed only after presentation to the interdisciplinary tumor board. B-mode sonography represents the primary diagnostic modality, but this is supplemented by cross-sectional imaging in cases of suspected sarcoma. Lymph nodes in the head and neck region should be considered suspicious if they are 10-12 mm or larger in diameter, if they are not rounded, if they form conglomerates, or if there is no hilar sign. Pathologic contrast uptake or necrosis may represent a malignancy sign [199], [206], [214], [218].

5.27	Consensus-based Recommendation
EC	During resection of soft tissue sarcomas or recurrences, clinically and/or radiologically conspicuous lymph nodes should be removed in the sense of a modified radical neck dissection mono-bloc, if possible after histological confirmation. This is especially true for sarcoma subtypes that preferentially metastasize to lymph nodes (e.g., rhabdomyosarcoma*, clear cell sarcoma, epithelioid sarcoma, myxoid round cell sarcoma). For subtypes such as rhabdomyosarcoma, the recommendations of the Cooperative Soft Tissue Sarcoma Study Group (CWS) are used. * This applies to adults only, not ARMS and ERMS.
	Consensus

5.1.3.3. Reconstructive procedures

5.28	Consensus-based Statement
EC	Plastic reconstructive, especially microvascular, surgery is an essential therapeutic pillar for maintaining or restoring quality of life in soft tissue sarcomas of the head and neck.
	Strong Consensus

Background

Because of tissue loss due to tumor resection, the use of plastic reconstructive procedures in the head and neck region is often warranted. In addition to local flaps, vessel-pedicled flaps (e.g., latissimus dorsi flap, pectoralis major flap) are important options. In addition, microvascular free tissue transfer such as the forearm flap, latissimus dorsi flap, or antero-lateral thigh flap are frequently used [222], [223], [224]. If the maxilla or mandible is involved, the microvascular scapula flap, microvascular crista-iliaca graft, or fibularis graft are most commonly used [200], [225].

In addition to surgical reconstructive procedures, epithetics and prosthetics have an important role in restoring function and aesthetics. Epithetic procedures can also be combined with surgical reconstructive procedures or used as a temporary or permanent approach [226], [227]. This may be particularly the case in patients with multiple co-morbidities who are not able to tolerate multiple lengthy procedures and multiple anesthetics.

5.1.4. Skin

The following chapter refers to primary cutaneous soft tissue sarcomas that do not show clinical or imaging evidence of metastasis at diagnosis. This is a very heterogeneous group of tumors of the dermis and subcutis. The most common primary cutaneous soft tissue sarcomas are dermatofibrosarcoma protuberans (DFSP), atypical fibroxanthoma (AFX), dermal undifferentiated pleomorphic sarcoma (UPS), and leiomyosarcoma.

5.1.4.1. Surgical therapy of the primary tumor

5.29	Consensus-based Recommendation
EC	For primary cutaneous soft tissue sarcomas without the presence of metastasis, surgical resection in healthy (R0) shall be performed.
	Strong Consensus

5.30	Consensus-based Recommendation
EC	Depending on the entity, tumor grading, and local recurrence rate, specific safety distances should be observed for cutaneous sarcomas.
	Strong Consensus

5.31	Consensus-based Recommendation
EC	For cutaneous sarcomas, sentinel lymph node biopsy (SLNB) shall not be performed.
	Strong Consensus

Background

Surgical resection in healthy tissue (R0) is the treatment of choice for primary cutaneous sarcoma without evidence of metastasis. In cases of histopathologically close (close margin) or non-in-sane resection (R1, R2), resection should be performed whenever possible to achieve R0 status.

Depending on sarcoma severity, grading, and histopathologic workup, different final safety margins are recommended for resection/post-resection (see Table 12). For dermatofibrosarcoma (DFSP), according to S1 guideline of the ADO, a safety distance of 2 cm is recommended when conventional histologic section margin control is used; when three-dimensional micrographic section margin control is used, a safety distance of 1 cm is considered sufficient [228]. Three-dimensional micrographic incision margin control should be performed on paraffin embedded sections and not on the frozen sections and should be distinguished from Mohs surgery. For cutaneous angiosarcoma, a wide safety margin is considered desirable according to S1 guideline of the ADO, but without exact size specification [229]. This is different for cutaneous Kaposi's sarcoma, where tight safety margins are considered sufficient for surgery of the primary tumor due to its frequent multilfocal recurrence and good treatment alternatives, such as primary radiotherapy [229]. For rarer entities, there are no guideline-based recommendations. However, a choice of safety margin adapted to tumor grading and local recurrence propensity is generally considered reasonable. For atypical fibroxanthoma (AFX) with a high propensity for local recurrence, a three-dimensional, micrographic incision margin or a safety distance of 1-2 cm is recommended. For dermal superficial undifferentiated pleomorphic sarcoma (UPS) not associated with actinic damage, wide resection with three-dimensional, micrographic incision margin control is recommended. For pleomorphic dermal sarcomas (PDS) in actinically damaged skin with p53 mutation, evidence of a better prognosis was found, so

a safety margin of 1 cm with three-dimensional, micrographic incision margin control is recommended here [230]. For cutaneous leiomyosarcoma, a wide resection with three-dimensional, micrographic incision margin control is recommended [231]. The safety margins suggested in Table 12 are based on case series, retrospective studies, and expert opinion.

Table 12: Safety distances cutaneous soft tissue sarcomas

Entity	Safety distance (SA)	Alternative method	Reference
Dermatofibrosarcoma protuberans (DFSP)	1 cm + DMS* DMS alone, if SA not possible	2 cm	[232] [233] (n=5249, retrospective) [234] (n=70, prospective)
Fibrosarcoma transformed DFSP	wide resection** + DMS, 2 cm should be aimed for		[235] (n=13, case series)
Pleomorphic dermal sarcoma, superficial, assoc. with actinic damage and p53 mutations Undifferentiated pleomorphic sarcoma, superficial, not in actinically damaged skin	1 cm + wide resection** + DMS, 2 cm should be aimed for		[236], [237], [238], [239]
Atypical fribroxanthoma	DMS		[240] (n=91, retrospective) [237] (n=907, retrospective)
Leiomyosarcoma, cutaneous location	1 cm + DMS		[241] (n=71, retrospective) [242]
Leiomyosarcoma, subcutaneous location	wide resection** + DMS, 2 cm should be aimed for		[242]
Liposarcoma	wide resection** + DMS		no studies, case series
Angiosarcoma	wide resection** + DMS		
Kaposi's sarcoma	scarce SA		

* DMS: Three-dimensional, micrographic incision margin control; this should be performed on the kerosene section and not on the cryosection and should be distinguished from Mohs surgery.
** Wide resection: complete removal of the tumor surrounded on all sides by healthy tissue including a possible puncture channel or biopsy scar. If wide resection is not possible or prognostic, function-preserving surgery should be performed with the goal of R0 resection.

There are no reliable data on sentinel lymph node diagnostics (SLNB) for cutaneous sarcomas; therefore, it is not recommended.

Highly malignant cutaneous sarcomas, especially angiosarcomas, are treated according to the same adjuvant principles as other sarcomas, e.g. with regard to radiotherapy [243].

Radiation-associated angiosarcomas following therapy for breast carcinoma present a special problem. These tumors are always highly malignant and have a high rate of locoregional and distant metastases. Prospective study data are not currently available. A German prospective study is evaluating pazopanib and paclitaxel (GISG-06, EVA study, NCT02212015).

The risk in women with breast carcinoma and radiation of developing angiosarcoma is 26 times higher than with therapy without radiation. Even when tumors appear localized, field cancerization is almost always present. Accordingly, achieving R0 resection in these tumors is not associated with a lower rate of distant metastases or more favorable survival [244]. Mastectomy as the first therapeutic step is therefore usually not effective and followed by a recurrence rate of 55%. In contrast, preoperative or perioperative chemotherapy could achieve improved local control [244].

5.1.5. Retroperitoneum

5.1.5.1. Presentation and specific problem

Retroperitoneal sarcomas (RPS, C48.0 by ICD-10) account for approximately 12 % of all soft tissue sarcomas [245]. The tumors often present with only mild symptoms of abdominal girth gain and malaise over a prolonged period of time. Rapid tumor growth is also suggestive of a higher grade malignant tumor in RPS, e.g. Rhabdomyosarcoma. Through international cooperation (Transatlantic Retroperitoneal Sarcoma Group, TARPSWG), a large database has been generated in recent years, better allowing the development of prognostic criteria [246], [247], [248], but also providing the basis for randomized trials [249].

At diagnosis, RPS have a median diameter of about 20 cm [247]. The tumor size alone and its close relationship to surrounding organs often necessitate a complex surgical approach. According to a 2017 survey of German surgical clinics, there are large divergences between clinics with less and more experience in dealing with these tumors, especially regarding biopsy, targeted safety margins, extent of resection, or lymphadenectomy [250].

Histologic subtyping and therapeutic implications.

The distribution of histologic subtypes of sarcomas in the retroperitoneum differs significantly from sarcomas of the extremities and trunk.

Most common subtypes in the retroperitoneum are dedifferentiated liposarcomas (36 %), well-differentiated liposarcomas (26 %), and leiomyosarcomas (19%). Solitary fibrous tumors (SFT), undifferentiated pleomorphic sarcomas, and malignant peripheral nerve sheath tumors (MPNST) occur with lower frequency [247], [251]. For dedifferentiated and well-differentiated liposarcomas, cluster amplification of MDM2 and mostly also of CDK4 on chromosome 12q13-15 can be detected.

Differential diagnoses include rhabdomyosarcomas, malignant lymphomas, germ cell tumors, carcinosarcomas, desmoid fibromatoses, gastrointestinal stromal tumors, and benign tumors such as leiomyomas and schwannomas [252]. These differential diagnoses have considerable consequences for therapy (e.g., systemic therapy instead of surgery, watch and wait for desmoids). Therefore, histological clarification is mandatory before resection. Primary surgery without diagnosis of the tumor may represent a mistreatment.

5.1.5.2. Diagnostics and biopsy

5.32	Consensus-based Recommendation
EC	If RPS is suspected, cross-sectional imaging of the abdomen and pelvis, with contrast administration, if possible, shall be performed before biopsy and therapeutic measures.
	Strong Consensus

5.33	Consensus-based Recommendation
EC	Histologic confirmation of soft tissue tumors of the retroperitoneum shall be performed preoperatively.
	Strong Consensus

Background

Prior to any therapeutic intervention, cross-sectional imaging with contrast administration of the thorax, abdomen, and pelvis is required to assess tumor extent (diaphragm, bladder, ureter, vessels), vasculature, and vascularization of the sarcoma, and to rule out metastasis. Sagittal and coronal reconstruction are helpful in addition to transverse imaging. The area with the highest contrast uptake should be targeted as the biopsy site, as this is where the best perfusion and highest proliferation (most representative of grading) can be assumed.

The extent of resection, i.e., the eventual acceptability of marginal resection, and the indication for preoperative radiotherapy or chemotherapy, all depend on the histologic subtype [253]. The time required for a CT-guided percutaneous core biopsy and its histologic evaluation is not significant given the history of the disease, that often goes back a long time. Even when patients displays compressive symptoms attributable to the tumour, there is usually no indication for rapid surgery or even emergency intervention. Percutaneous core biopsy has no negative consequences in terms of local recurrence risk [254], [255].

An exception with regard to biopsy are at most homogeneous lipomatous tumors without focal contrast enhancement or central necrosis areas, in which an experienced team of radiologist and surgeon can assume with high probability a low-malignant liposarcoma without dedifferentiation.

5.1.5.3. Resection treatment

5.34	Consensus-based Recommendation
EC	Complete surgical resection (R0) shall be performed as standard therapy of retroperitoneal soft tissue sarcomas. Even without evidence of histologic infiltration of adjacent organs, (portions of) adjacent organs should be removed as part of an en bloc resection.
	Strong Consensus

5.35	Consensus-based Recommendation
EC	Surgical treatment of retroperitoneal sarcoma shall be performed in a sarcoma center with special expertise in surgery of RPS.
	Strong Consensus

Background

Complete macroscopic resection of the tumor results in the best chance of long-term tumor-free survival. Therefore, optimal planning of surgical therapy is the crucial aspect for treatment. With regard to the surgical goal in terms of resection, a distinction must be made between a marginal resection and a compartment-oriented approach.

Anatomically, the retroperitoneal space is not really a compartment analogous to the muscle groups of the extremities. However, its 3-dimensional boundaries can be defined. These are ventrally the peritoneum and ipsilateral mesentery/mesocolon and colon. Cranially, it is bounded on the left by the pancreatic tail and spleen. Posteriorly and laterally, muscles (transversus abdominis muscle, iliopsoas muscle, and quadratus lumborum muscle) border the retroperitoneal space, and cranially, the diaphragm borders it on both sides.

Most RPS have minimal distance from surroundingorgans, i.e., kidney, colon, pancreas, diaphragm, aorta, v. cava, ureter, psoas muscle, femoral nerve, and adrenal gland are almost always in direct contact with the tumor. It is often mistakenly assumed that RPS represent encapsulated tumors, which is factually incorrect. Due to the growth pressure of the tumor, the surrounding tissue is stretched out and regularly shows tumor infiltration.

In the past, peeling operations were predominantly performed leaving the structures adjacent to the tumor. Resection within these limits results in recurrence rates as high as 63% [256], and 80 % of these patients die from local recurrence. Resection of the sarcoma together with its surrounding structures and organs (compartment-oriented resection) has resulted in dramatically reduced local recurrence rates, lower rates of distant metastases, and improved survival [257], [258], [259].

International recommendations consider en bloc resection with co-resection of adjacent organs and tissues covering the tumor to be the standard of care (primary multivisceral resection). The organs do not necessarily have to be tumor infiltrated, but they form the tissue layer covering the sarcoma. The strategy follows the principles of sarcoma surgery at the extremities: where adequate resection distance is possible

with low morbidity (co-resection of the colon and mesocolon), organ resection is performed; where induced morbidity is significant (e.g., additional pancreatectomy), focal-marginal resection is planned rather. This has implications relating to the application of preoperative radiation (see below).

Thus, depending on tumor location, a compartment-oriented resection in the right-sided retroperitoneum typically includes the right hemicolon, the right kidney, if applicable, adrenal gland and diaphragm, and the transversus abdominis muscle as well as the fascia or portions of the psoas muscle. On the left side, the left hemicolon, transversus abdominis muscle, fascia or portions of the psoas muscle, pancreascorpus/tail and spleen, and diaphragm, if any, bordering the tumor are part of the resectate [252], [259].

Historically, the prognosis of RPS has been poor, with 5-year survival rates of 50-55 % [257]. With adoption of the surgical approach described above, 5-year survival rates of 65-70 % are achievable [246], [258], [259].

Data from the TARPSWG group [247], [260] underscore the critical role of pretherapeutic workup for RPS and histology-adapted surgeryplanning. Analysis of a patient group of 586 patients with a median follow-up of 6.5 years showed that, in addition to infiltration of adjacent organs by the sarcoma, performance of surgery by a specialized center was the most important prognostic parameter for local recurrence rate and overall survival [253]. In this regard, performing such surgery in a specialized center and avoiding incomplete resections turn out to be the two most important prognostic factors for RPS. It could be shown that these improvements in diagnostics and therapy also have a significant positive impact on the long-term prognosis of patients [261]. Comparing three 5-year periods from 2002 to 2017, analysis of 1942 patient histories showed that the 5-year OLR improved from 61.2% to 67% to 71.9% in the most recent period evidence. At the same time, the rate of incomplete (R2) resections decreased from 7.1% to 4.7%.

Under such conditions, severe perioperative morbidity (Clavien-Dindo 3) affected 16.8% of patients and 30-day mortality was 1.8% [262]. The 90-day mortality improved from 4.3% to 2.3% between 2002 and 2017 [260]. A median of one unit of blood was transfused, and half of patients managed without transfusion. Only procedures including pancreatico duodenectomy or large vessel replacement had higher morbidity, with an odds ratio of 1.5.

Data from a recently published systematic review are higher, with a morbidity of 23% and a mortality of 3% [263]. However, it should be noted that half of the patients in this database analysis (SEER, NCDB, ACS-NSQIP) had undergone surgery before 2000.

5.1.5.4. Preoperative therapy

5.36	Consensus-based Recommendation
EC	Neoadjuvant multimodality therapy should be discussed in the interdisciplinary sarcoma board for retroperitoneal sarcomas.
	Strong Consensus

Background

The same therapeutic principles apply to RPS as to sarcomas at other sites, i.e., in highly malignant sarcomas there is an indication to consider neoadjuvant therapy and an indication for adjuvant radiotherapy after R0 resection. However, some special problems arise:

- Given the size of the tumors, a biopsy is often not representative, so that highly malignant tumor components are not detected preoperatively.
- Adjuvant postoperative radiotherapy is usually not feasible because the small bowel loops occupy the former space of the tumor. The limited tolerance of the small bowel almost always prevents application of the necessary radiation dose.
- The size and complexity of the resection specimen significantly limit the pathologist's ability to review the resection margins with respect to R0 resection.

Under these aspects, it seems obvious to try to perform any postoperative adjuvant therapy as neoadjuvant treatment. Neither radiotherapy nor chemotherapy currently has sufficient evidence of long-term improvement in treatmentoutcome.

Data from the only randomized phase III trial of 266 patients (EORTC 62092-22092, NCT01344018, STRASS) failed to demonstrate superiority of preoperative radiotherapy [264]. The study included 266 patients with 1:1 randomization from 31 centers with expert status from Europe and the United States. Patients in the radiation arm received 50.4 Gy in 28 fractions of 1.8 Gy as 3D conformal radiotherapy or intensity-modulated radiation therapy (IMRT) according to EORTC Radiation Oncology Group (ROG) quality standards.

The primary endpoint of the study was the ‚intra-abdominal recurrence-free interval (IARFS)'. With a median follow-up of 43.1 months, median recurrence-free survival was not significantly different in the surgery alone group at 5 years (95 % CI 3.4-nb) versus the preoperative radiotherapy group at 4.5 years (95 % CI 3.9-nb). This was true for all subtypes (well-differentiated liposarcoma, dedifferentiated liposarcoma, leiomyosarcoma). In the subgroup with well-differentiated liposarcoma, a post-hoc analysis at 3 years showed that IARFS tended to be more favorable (HR 0.62, 95% CI 0.38–1.02) in the arm ‚radiation+surgery' with 75.7 % (95 % CI 65.6-83.2) compared to the arm ‚surgery alone' with 65.2 % (95 % CI 54.5-74.0).

From these data, no general indication for radiotherapy before surgery for RPS can be derived. In this respect, a discussion of the indication for preoperative radiotherapy in RPS depends on the individual tumor situation.

Just as in previous smaller studies that used radiotherapy alone or in combination with e.g. antiangiogenic therapy, the results show good tolerability and no relevant interaction with surgery [265], [266]. In two interim safety analyses after 66 and 132 patients, respectively, the STRASS study had not shown a significantly different rate of reoperation. Only 3 % of patients in the radiation arm could not be operated on at the scheduled time due to adverse events. The perioperative complication rate was 37% in the radiation arm versus 27% in the surgery-only patient group, which was within the range of morbidity reported by the TARPS group in over 1000 patients operated on [262]. The need for blood transfusion affected 19% of the surgery-only versus 29% of the preirradiated patients. In both treatment arms, 2 patients died postoperatively.

The extent to which it is necessary to irradiate the entire tumor volume was discussed. Recurrence after adequate primary surgery typically occurs dorsally paravertebrally or along the diaphragm or the costal process. In this respect, irradiation of the ventral tumor circumference, which is well controlled surgically, may be unnecessary and can be replaced by a so-called ‚banana field' perivertebral or an IORT [267], [268].

RPS were also included in the neoadjuvant trial comparing systemic anthracycline-containing chemotherapy +/- regional deep-wave hyperthermia [269]. A subgroup analysis of 149 patients with abdominal or retroperitoneal sarcoma showed an analogous result to the overall study, with a long-term advantage for patients with hyperthermia. The study also proves that preoperative systemic chemotherapy, even in combination with deep hyperthermia, does not affect the surgical procedure and perioperative morbidity [269].

5.1.5.5. Preoperative measures

5.37	Consensus-based Recommendation
EC	Patients in whom multivisceral resection of RPS is planned shall be evaluated preoperatively with side-separated renal function clearance.
	Strong Consensus

Background

When compartment-oriented resection is the goal, side-separated renal function testing is mandatory preoperatively to ensure that a unilateral nephrectomy can be performed without compromising the patient's overall renal function.

Stentting of the ureter is optional depending on tumor location.

If it is apparent preoperatively that resection of the spleen is required, vaccination should be given according to the recommendations of the Robert Koch Institute against asplenia (pneumococci, Haemophilus influenzae type B, and meningococci) [270].

5.1.5.6. Procedure for R1 resection

5.38	Consensus-based Recommendation
EC	If R1 resection of soft tissue sarcoma of the retroperitoneum is found, re-resection should not be performed.
	Strong Consensus

5.39	Consensus-based Recommendation
EC	After R1 or R2 resection of a primary RPS, presentation to a sarcoma center shall be made for consideration of further therapeutic modalities.
	Strong Consensus

Background

After multivisceral resection of an RPS, determination of R status is particularly difficult. Workup of the entire circumference of the specimen is neither goal-directed nor efficiently performed by the pathologist. If the surgeon has marked a possible area of R1 resection or sent resection margin biopsies separately, the pathologist has a higher chance of confirming R1 resection histologically.

From a pragmatic point of view, R0 and R1 resection are combined internationally – in contrast to sarcomas of the extremities and trunk. However, it must be ensured that the tumor is macroscopically completely removed and that there is no R2 resection.

Especially in well-differentiated liposarcoma (G1), the clinical course is such that even after R1 resection, tumor recurrence is often detectable only after many months.

A subsequent resection to achieve improved resection margins in relation to the surgical intervention already performed is usually not useful.

If an inadequate resection (e.g., enucleation, resection in multiple tumor parts) was performed during the initial intervention, a re-resection is generally not the first choice. If enucleation is performed, there is a small chance that the tumor is nevertheless completely removed. Depending on the age of the patient and histological subtype of the RPS, the further procedure must be discussed. In G1 liposarcoma, a wait-and-see approach is justified. In patients in whom the tumor was removed in multiple parts, it is reasonable to wait and see at which site a tumor recurrence occurs or whether a multifocal recurrence develops. Under the conditions described, preoperative irradiation of the tumor recurrence is then almost always indicated in order to achieve devitalization of the tumor parts in the surgical area.

5.1.6. Visceral

GIST are the most common soft tissue sarcomas of the digestive tract, accounting for about 90%. In addition, leiomyosarcomas occur in significant frequency, especially in the esophagus and stomach. In addition, solitary fibrous tumors (SFT), PEComas, de-differentiated liposarcomas, and malignant lymphomas should also be considered for differential diagnosis.

5.1.6.1. Biopsy

5.40	Consensus-based Recommendation
EC	Histologic confirmation of soft tissue tumors (non-GIST) of the digestive tract shall be performed for locally advanced tumors that can be removed only by complete resection of the affected organ or by multivisceral resection.
	Strong Consensus

5.41	Evidence-based Recommendation
GoR A	Complete surgical resection (R0) shall be undertaken as the standard treatment of localized soft tissue sarcomas (not GIST) of the digestive tract. In case of infiltration of adjacent organs, R0 resection shall be aimed at by en bloc resection including parts of adjacent organs.
LoE ⊕⊕⊕⊖ ⊕⊕⊕⊕ ⊕⊕⊕⊖	[152]; [153]; [154]; [155]; [156]; [157]; [158]; [159]; [160]; [161]; [162]; [163] ⊕⊕⊕⊖: Local recurrence ⊕⊕⊕⊕: Overall survival ⊕⊕⊕⊖: Metastasis-free survival
	Strong Consensus

5.42	Consensus-based Recommendation
EC	In R1 resection of soft tissue sarcoma of the visceral organs/abdomen, resection should be pursued if it can be done specifically with knowledge of the site of incomplete resection and with reasonable morbidity.
	Strong Consensus

5.43	Consensus-based Recommendation
EC	If follow-up resection cannot be performed after R1 resection of soft tissue sarcoma of the visceral organs/abdomen, the option of additive radiotherapy shall be explored.
	Strong Consensus

Background

When there is a high radiological suspicion of a GIST and a primary resection could be performed without loss of organ function, biopsy may be omitted. For all other tumors that must be considered for differential diagnosis (leiomyosarcoma, SFT, PEComa, desmoid, dedifferentiated liposarcoma), histologic confirmation is mandatory. The therapy of the tumors is very different depending on the histological subtype. Above all, the exclusion of lymphoma, carcinoid or non-malignant tumors (desmoid) is required. Analogous to the recommendations for sarcomas of the extremities, a limit for performing a biopsy of approximately 3 cm is reasonable, depending on the localization. Histologic confirmation should be sought for all locally advanced tumors that can be removed only by organ resection (gastrectomy, rectal extirpation) and those tumors whose resection results in functional changes of the GI tract (esophago-cardiac junction, duodenum, lower rectum).

For non-GIST soft tissue sarcomas, the same criteria apply with regard to the assessment of prognosis as for tumor localizations outside the abdomen (grading and tumor size). The indication for neoadjuvant and postoperative adjuvant therapies such as chemotherapy and/or radiotherapy follows the same considerations as for sarcomas of the extremities or retroperitoneum, i.e., they are predominantly indicated in TNM stage III.

Regarding the extent of resection, safety distances analogous to extra-abdominal tumors should be aimed for: metrically 1-2 cm, anatomically: at least one layer of non-tumor infiltrated tissue (e.g. diaphragm, fascia, etc).

In soft tissue sarcomas that do not originate from the hollow organs of the stomach and small intestine, R0 resection can often only be achieved by taking along adjacent structures such as the abdominal wall, diaphragm, or organs such as the liver and bladder. If this is foreseeable preoperatively, preoperative radiotherapy and/ or chemotherapy may improve the treatment outcome [271].

If R1 resection of the tumor has been performed without prior therapy (chemotherapy, radiotherapy), the extent to which the area of R1 resection can be identified must be considered. If this can be assumed with sufficient certainty by the surgeon and the findings on the resection specimen, it must be determined whether an R0 resection can be achieved by postoperative resection with acceptable morbidity and potential loss of function of abdominal structures and organs. In particular, the results of postoperative radiation are better after R0 resection than after R1 resection. It should also be taken into account that especially the abdominal structures can very often only be covered to a limited extent by external beam radiotherapy with the desired target dose.

Adjuvant chemotherapy data for high-malignant sarcomas show that prognosis in patients with R1 resection can be improved by postoperative chemotherapy [137], [272]. Due to the relatively small proportion of patients with abdominal soft tissue sarcomas in the respective studies, these data cannot be readily transferred. Furthermore, it should be noted that the studies were undertaken at a time when GIST was not yet established as a distinct tumor entity and thus GIST patients were also recruited into these studies. This further limits the transferability of the results.

5.1.7. Gynecology - Uterine Sarcomas

This chapter contains recommendations for the surgical treatment of uterine sarcomas. For further information, please refer to the S2k guideline „Uterine Sarcomas", 2019 AWMF Registry Number: 015-074, https://www.awmf.org/leitlinien/detail/ll/015-074.html [273]. Carcinosarcomas of the uterus (malignant mixed müllerian tumors), which were previously classified as uterine sarcomas, behave biologically like endometrial carcinomas according to new findings and are therefore dealt with in the corresponding S3 guideline (AWMF 032/034-OL) [274].

Uterine sarcomas refer to a heterogeneous group of overall rare malignancies of the uterine musculature, endometrial stroma, or uterine connective tissue. They account for 3-9 % of all malignancies of the uterus. The incidence is approximately 1.5 (Caucasian) - 3 (African-American) / 100,000 population [275].

Tumor typing is according to the WHO, and staging is according to the FIGO or TNM classification [276]. The WHO classification lists the following entities as malignant mesenchymal tumors [277], [278]:

- Leiomyosarcomas (LMS).
- Low-grade endometrial stromal sarcomas (LG-ESS)
- High-grade endometrial stromal sarcomas (HG-ESS)
- Undifferentiated uterine sarcomas (UUS)

Surgical management will be presented below for these more common entities, with HG-ESS and UUS addressed together in one chapter due to their comparable tumor biology.

5.1.7.1. Leiomyosarcomas

5.44	Consensus-based Recommendation
EC	In leiomyosarcoma confined to the uterus, complete removal of the uterus shall be performed without morcellement or uterine injury.
	Consensus

5.45	Consensus-based Recommendation
EC	In leiomyosarcoma, systematic pelvic and para-aortic lymphadenectomy shall not be performed if the lymph nodes are diagnostically unremarkable.
	Consensus

Background

Removal of the uterus in total is the gold standard of surgical management. The indication for adnexal extirpation is optional depending on menopausal status. In premenopausal women with tumors confined to the uterus, the ovaries can be preserved [279], [280], [281]. Intraperitoneal morcellement leads to a worsening of prognosis; therefore, dismembering procedures such as laparoscopic supracervical

hysterectomy or else laparoscopic uterus-preserving procedure with intraperitoneal morcellement for suspected sarcoma should be discouraged [282], [283].

The incidence of primary pelvic and para-aortic lymph node metastases is very low in LMS. If the lymph nodes – are affected, often already conspicuous intraoperatively, there is usually already a hematogenous metastasis. In this respect, systematic pelvic and para-aortic lymphadenectomy is not associated with an improved prognosis and is generally not recommended [284]. Lymph nodes that are suspicious for involvement should still be removed at surgery but without recourse to a formal lymphadenectomy. Very limited data are available regarding a fertility-preserving approach, so this cannot be recommended.

In case of extensive, advanced findings and symptoms, surgical tumor reduction should be attempted [279]. The recommendation to forgo systematic pelvic and para-aortic lymphadenectomy differs from the recommendation in the S2k guideline „Uterine Sarcomas“, in which it is a „should recommendation“, i.e., a weak recommendation. The guideline panel felt that a stronger recommendation was appropriate.

5.1.7.2. Low-grade endometrial stromal sarcomas.

5.46	Consensus-based Recommendation
EC	In low-grade endometrial stromal sarcoma, complete removal of the uterus shall be performed without morcellement or uterine injury.
	Strong Consensus

5.47	Consensus-based Recommendation
EC	In low-grade endometrial stromal sarcoma, systematic pelvic and para-aortic lymphadenectomy should not be performed if the lymph nodes are diagnostically unremarkable.
	Strong Consensus

Background

The treatment of choice is total hysterectomy (without morcellement) with removal of both adnexa [285].

The endocrine dependence of LG-ESS is well established. For example, a retrospective analysis of 153 LG-ESS patients showed a significantly increased recurrence rate when the ovaries were left in premenopausal patients. However, both in this analysis and in two other evaluations of the SEER database, there was no negative impact on overall survival. In this respect, the benefits of ovarian preservation in young patients should be carefully weighed against the risk of higher recurrence probability and discussed in detail with patients [286], [287], [288], [289], [290].

Lymph node involvement is rare and does not seem to have an impact on prognosis. In this respect, no prolonged survival can be expected from a systematic

lymphadenectomy, as well as from adjuvant therapy options based on it, so that lymphadenectomy cannot be recommended as a standard overall [289], [291], [292].

Whether cytoreduction has an impact on patient survival in advanced tumors is unclear [293]. The indication for this results – if necessary in palliative intention – from the clinical symptoms of the patient.

5.1.7.3. High-grade endometrial stromal sarcomas and undifferentiated uterine sarcomas.

5.48	Consensus-based Recommendation
EC	In high-grade endometrial stromal sarcoma confined to the uterus, complete removal of the uterus shall be performed without morcellement or uterine injury.
	Strong Consensus

5.49	Consensus-based Recommendation
EC	In high-grade endometrial stromal sarcoma, systematic pelvic and para-aortic lymphadenectomy shall not be performed if the lymph nodes are diagnostically unremarkable.
	Strong Consensus

Background

Again, the treatment of choice is total hysterectomy (without morcellement) [294]. It is unclear whether the adnexa can be left in the premenopausal period. According to a 1998-2013 National Cancer Database (NCDB) analysis of 3797 patients, R0 resection plays a relevant role in survival for resection of HG-ESS [158]. Patients with R1 resection have a 5-year survival rate of 14.2% compared to 41.8% when R0 resection is achieved.

Although positive pelvic and/or para-aortic lymph nodes are associated with a less favorable prognosis, there is no evidence that surgical resection and subsequent adjuvant therapy options improve this limited prognosis [295], [296], [297], [298], [299]. The recommendation to forgo systematic pelvic and para-aortic lymphadenectomy differs from the recommendation in the S2k guideline „Uterine Sarcomas“, in which it is a „should recommendation“, i.e., a weak recommendation. The guideline panel felt that a stronger recommendation was appropriate.

Whether cytoreduction has an impact on patient survival in advanced tumors is unclear. However, a multicenter retrospective analysis was able to demonstrate a positive effect of cytoreduction on survival in this regard, in contrast to low-grade ESS [293].

5.2. Plastic reconstructive therapy

Reconstruction after surgical removal of a soft tissue sarcoma always represents an individual decision that can vary greatly from case to case.

5.50	Consensus-based Recommendation
EC	When deciding to reconstruct, the following three types of reconstruction shall be considered: • functional reconstruction • bony and soft tissue reconstruction • pure defect coverage
	Consensus

5.51	Consensus-based Statement
EC	Oncology-compatible en bloc resection of the sarcoma (primary tumor or recurrence) in healthy tissue represents the basis of any successful reconstructive therapy.
	Strong Consensus

5.52	Consensus-based Recommendation
EC	In the case of tension-free primary closure after tumor resection, this shall be aimed for while avoiding cavities.
	Strong Consensus

5.53	Consensus-based Recommendation
EC	If a drain is applied, it shall be discharged close to the wound edge.
	Strong Consensus

5.54	Consensus-based Statement
EC	Larger soft tissue defects involving multiple tissue layers such as subcutaneous fat, fascia, and muscle that cannot be closed by tension-free primary closure shall be covered by adequate soft tissue replacement.
	Strong Consensus

5.55	Consensus-based Statement
EC	Neoadjuvant/preoperative radiotherapy is not a contraindication to performing microsurgery.
	Strong Consensus

5.56	Consensus-based Statement
EC	Functional restoration can be single or double sided.
	Strong Consensus

5.57	Consensus-based Recommendation
EC	If blood vessel reconstruction is indicated, close coordination with radiation oncologists and surgeons shall occur.
	Strong Consensus

5.58	Consensus-based Recommendation
EC	The decision to amputate shall be a case-by-case decision after interdisciplinary discussion and consideration of all limb preservation options, including CTX, ILP, RHT, and HT.
	Consensus

5.59	Consensus-based Recommendation
EC	The planning of resection and plastic reconstruction shall be made as an interdisciplinary therapeutic decision.
	Strong Consensus

Background

Functional reconstruction (e.g. motor function replacement surgery), bony and soft tissue reconstruction (especially flap surgery) and pure defect coverage (e.g. split skin grafting) have to be differentiated.

The following aspects should be considered when deciding on the respective reconstruction:

- resection status/probability of recurrence

- curative/palliative approach
- adequate soft tissue reconstruction (e.g. special requirements of the sole of the foot)
- safe coverage of reconstructed/exposed vessels, nerves, tendons
- optimal time to perform functional reconstructions (one-time/multi-time)
- Consideration of possible consequences of adjuvant therapy and here in particular radiation consequences, since adjuvant radiation therapy can impair healing of the reconstructed tissue (e.g. nerve and vessel interposition) (see recommendations 5.56 and 5.57)
- prophylaxis of the formation of a seroma cavity
- Primary wound healing (delay adjuvant treatment).

For this purpose, simple mobilization of the wound edges, which is performed subfascially to ensure blood supply to the extremities (so-called advancement flap), can be used. In the majority of cases, this is sufficient for secure wound closure, for example, at the most common site, the thigh. On the abdomen, mobilization of the wound edges can also be performed in the plane of Scarpa's fascia (fascia abdominalis superficialis).

Drains should be drained close to the wound edge so that, in the event of a necessary resection, the former drainage channel can be removed as well without extensive skin excision. Drains should be inserted into the former tumor bed to prevent the formation of a seroma cavity, and care should be taken to ensure consistent hemostasis during the surgical procedure. Sufficient compression therapy should also be ensured during postoperative treatment.

For reconstruction of the resected soft tissue, all techniques from split skin grafting to free, microsurgically anastomosed flapplasty are generally suitable. When choosing the appropriate technique, the postoperative procedure should be considered in addition to tumor-specific and patient-related factors. Functionally, in the plantar region, split skin may be better than flap-based reconstruction, which is too bulky. Conversely, in the gluteal region, split skin does not provide enough soft tissue cushion to allow pain-free sitting [300]. In the scalp area, most defects can be covered by split skin or rotational flaps. Deeper defects down to the skull bone can be safely covered by free flap reconstruction.

In principle, despite the more complex technique, free or pedicled flap reconstruction is preferable to split skin grafting because it results in an all-layer soft tissuereconstruction and creates a stable skin-soft tissue mantle. Split-thickness skin grafting is not sufficient to achieve permanent wound closure, especially when postoperative radiotherapy is used [301]. Postoperative wound healing disorders are particularly common after adjuvant radiatio [302], [303].

Soft tissue reconstruction must also consider the issue of possible recurrence: while classic myocutaneous flap reconstruction, such as the latissimus flap, maintain their blood supply through the pedicle for life, a modern perforator flap randomizes within 3 months. Thus, in the case of recurrence, incision can be made longitudinally or transversely through the flap without threat of loss of blood flow [146], [301], [304].

Functional restoration, for example, of the extensor function of the hand after proximal resection of the radial nerve by means of radial artery arthroplasty, can be performed one-stage (as part of the tumor operation) or two-stage. Often, the one-stage approach offers a shortening of the surgical procedure and the start of oncologic follow-up and also improves the functional outcome [146].

Conversely, after adjuvant radiotherapy, it is important to consider the effect of radiation on the tissue, which often provides poor conditions for motor replacement surgery, whereas irradiation of a replacement surgery that has already been performed tends to be well tolerated [146].

In particular, the indication for reconstruction of vessels requires close coordination with radiation therapists and vascular surgeons. Thus, irradiation of a vascular graft is associated with a significantly increased rate of thrombosis [303]. However, adjuvant irradiation 6 weeks before surgery appears to be safe and does not affect the flow of microvascular anastomoses, for example [305].

Amputation of an affected limb should always be considered in terms of reconstructive surgery. Advanced or exulcerating recurrent tumors, extensive infiltration of functionally important nerves and joints may represent indications for amputation, but the decision to do so should always be a case-by-case decision and patient-specific. The indication for amputation should be made in the interdisciplinary tumor conference of a sarcoma center, where all limb-preserving options should be explored beforehand.

With modern arthroplasty, even advanced tumors with bony infiltration can often be operated on while preserving the limb [306]. Localised infiltration of major nerves is also not a primary indication for amputation. After intensive physiotherapeutic follow-up, patients with soft tissue sarcomas and resection of the sciatic nerve showed a good functional outcome [177].

If amputation is indicated, it can be performed in the surgical department of the sarcoma center or a hospital close to home, which will then also initiate further prosthetic treatment.

5.3. Standards before histopathological evaluation of the resection specimen

5.3.1. Marking the resectate

5.60	Consensus-based Recommendation
EC	As a minimum requirement, the surgeon shall mark the surgically removed resectate with thread markings in such a way that three-dimensional orientation is possible for the pathologist. If necessary, a schematic drawing of the removal localization shall be included.
	Strong Consensus

5.61	Consensus-based Recommendation
EC	The sending of the surgically removed resection specimen should be accompanied by appropriate radiological imaging with which the sent resection specimen can be correlated. This not only facilitates orientation for the pathologist, but also the macroscopic percentage estimation of the extent of necrosis necessary for grading.
	Strong Consensus

Background

Adequate workup of a localized soft tissue/bone tumor requires that the pathologist can orient the ex situ specimen sent by the surgeon in three dimensions. Optimally, the resection specimen should be sent with appropriate imaging with intraoperative digital photographs and radiological images. In practice, this will often not be guaranteed. The minimum requirement is therefore to send the specimen with an appropriately prepared standardized schematic drawing in which the resection specimen is drawn. This should then also explain the corresponding markings of the surgeon, ideally according to an interdisciplinary consensus standard (e.g., for suture markings long-lateral, short-cranial, etc.).

5.3.2. Transfer of the resection specimen to the pathology lab

5.62	Consensus-based Recommendation
EC	The immediate transmission of the surgically removed resection specimen shall be sought, ideally in a fresh, unfixed state. Written consent from the patient shall be obtained in advance for the removal of fresh tissue.
	Strong Consensus

5.63	Consensus-based Recommendation
EC	If unfixed transmission of the surgically removed resectate in the fresh state is not possible for local reasons, fixation in a sufficient amount of buffered 4% formalin shall be performed.
	Strong Consensus

Background

The surgically removed specimen should be transferred to pathology as soon as possible. The unfixed immediate transfer allows the collection of fresh tissue samples for the biobank, which is of considerable advantage for further analysis and research purposes. The preservation of fresh tissue for the biobank requires appropriate written consent from the patient, which, depending on local regulations, should be obtained either at the time of admission (e.g., in the admission contract) or preoperatively together with the surgical information.

If, due to local conditions, immediate transmission of the resectate in the unfixed state is not possible, fixation of the material in a sufficient quantity of buffered 4% formalin must be ensured (sufficient means that the preparation is sent in such a quantity of formalin that the preparation floats in a sufficiently large vessel).

5.3.3. Reconditioning

5.64	Consensus-based Recommendation
EC	Before tissue is removed from the surgical resection specimen, the resection margins shall be color-marked so that the R status can be determined later.
	Strong Consensus

Background

Upon arrival of the unfixed or fixed specimen, it should be immediately inspected in the pathology department by a pathologist familiar with soft tissue/bone tumor sectioning. At this time, the type of further processing is determined. In the case of fresh tissue, the immediate removal of tumor and normal tissue and the immediate transfer of the specimens to the biobank. For fixed material, the amount of formalin should

be checked and modified if necessary. In the case of large specimens, it may be useful to incise them several times according to the institute's internal standards before further fixation to ensure adequate fixation. A prerequisite for this is that the anatomical orientation of the resected specimen is possible through the attached markings and the imaging sent along with the specimen. Before incising the specimen, the corresponding resection margins should be marked in color beforehand so as not to jeopardize the assessment of the resection margins during subsequent processing.

During further processing after adequate fixation (usually overnight), systematic color marking of the clinically relevant resection margins is mandatory. Subsequently, the specimen is lamellated into uniform slices approximately 1 to 1.5 cm thick according to the axis guidance of the attached imaging. This allows correlation of imaging and pathology. Subsequently, photodocumentation of the resulting tumor slices is performed before further systematic embedding takes place. The rule of thumb for the minimum amount of specimens to be embedded is to take at least one block per centimeter of maximum tumor diameter. In addition, the relationships of the tumor to relevant resection margins and clinically marked relevant anatomical structures should be documented by tissue sampling. Also, the extent of tumor necrosis in percent shall be recorded during sectioning.

5.3.4. Workup after preoperative pretherapy

After preoperative radiotherapy and/or chemotherapy, correlation of the resection specimen with imaging is of particular importance, as this is the only way to ensure that the extent of response to therapy can be adequately documented. This is especially true for tumors with bone involvement, where preparation radiography - ideally in pathology - plays a particularly important role. The most precise possible estimation of the percentage of vital residual tumor (e.g., according to Salzer-Kuntschik [307]) is of utmost importance for the prognosis and therapy planning of bone tumors and requires systematic preparation of the specimen. For soft tissue tumors, standards of specimen workup and tumor response assessment have also been proposed by the EORTC-STBSG 2016 [103], in which the percentage of stainable residual tumor cells is estimated. The prognostic and predictive significance of this score remains to be tested in prospective clinical trials.

5.4. Radiotherapy: sarcomas of the extremities and trunk of the body

5.4.1. Radiosensitivity of soft tissue sarcomas.

Contrary to the still widely held belief that soft tissue sarcomas are radioresistant, experimental and clinical data indicate that the radiosensitivity of sarcomas is approximately equivalent to that of HPV-negative squamous cell carcinomas [308], [309], [310]. Soft tissue sarcomas can therefore be controlled locally in the long term with high-dose radiotherapy alone (> 66 Gy), especially in tumors < 10 cm in maximal diameter [311]. However, soft tissue sarcomas shrink very slowly after radiotherapy and residual space-occupying lesions may remain detectable for years. Therefore, tumor shrinkage rarely occurs after preoperative irradiation, although histologically high levels of necrosis are often induced [312], [313]. Differences in radiosensitivity of different histologic subtypes have not been reproducibly demonstrated. Clinical data indicate a lower than average radiosensitivity of malignant peripheral nerve sheath tumors [134] and a higher than average sensitivity of synovial sarcomas. Myxoid liposarcoma is also particularly radiosensitive [314]. For this histotype, neoadjuvant radiotherapy should be considered preferentially. Malignancy grade does not correlate with radiosensitivity.

5.4.2. Postoperative radiotherapy (extremities, trunk, non-retroperitoneal)

5.65	Consensus-based Recommendation
EC	In well-differentiated (G1) soft tissue sarcomas resected with healthy tissue on all sides, postoperative radiotherapy should be avoided.
	Consensus

5.66	Evidence-based Recommendation
GoR A	For G2 and G3 soft tissue sarcomas, preoperative or postoperative radiotherapy shall be given.
LoE ⊕⊕⊕⊖ ⊕⊕⊕⊖ ⊕⊕⊕⊖ ⊕⊕⊕⊖ ⊕⊕⊕⊖ ⊕⊕⊖⊖ ⊕⊕⊕⊖	[315]; [316]; [317]; [318] ⊕⊕⊕⊖: Overall survival (follow-up: 16 months) ⊕⊕⊕⊖: Disease-specific survival (follow-up: 76 months). ⊕⊕⊕⊖: Overall survival low-grade STS (follow-up: 67 months). ⊕⊕⊕⊖: Local recurrence (follow-up: 76 months) ⊕⊕⊕⊖: Free of distant metastases (follow-up: 76 months) ⊕⊕⊖⊖: Overall survival (follow-up: 240 months) ⊕⊕⊕⊖: Local recurrence (follow-up: 232.7 months)
	Strong Consensus

5.67	Consensus-based Statement
EC	In the case of unplanned R1 or R2 resection, irradiation does not replace a definitive re-resection.
	Strong Consensus

5.68	Consensus-based Statement
EC	Regardless of the outcome of a re-resection, postoperative radiotherapy shall be given for G2 and G3 soft tissue sarcomas if preoperative radiotherapy has not been given.
	Strong Consensus

5.69	Consensus-based Statement
EC	Postoperative percutaneous radiotherapy should begin within 3-6 weeks after surgery or after completion of adjuvant chemotherapy. In case of postoperative brachytherapy, it should be started 5 days after surgery.
	Strong Consensus

Background

In randomized trials treating predominantly R0 (86%) resected soft tissue sarcomas, Yang et al. [189] with adjuvant percutaneous radiotherapy (45 Gy/1.8 Gy single dose + 18 Gy/1.8 Gy single dose boost) and Pisters et al. [316] with adjuvant brachytherapy (45 Gy low dose rate) demonstrated that local recurrence rate can be highly significantly reduced by radiotherapy. In the latter study, in patients with G2/G3 sarcomas, the local control rate with brachytherapy was 89% versus 66% without brachytherapy (p=0.0025). However, radiation had no effect in G1 sarcomas (p=0.49) [316].

No other randomized trials addressing this question have been performed. Analyses from large prospective databases have confirmed the clear effect of adjuvant radiotherapy on local recurrence rate [155]. Only in small (T1), subcutaneous tissue tumors of low grade resected with wide margin, no significant improvement in local tumor control was observed. In a meta-analysis of 3,155 patients predominantly from cohort analyses (only 4.5% randomized), Albertsmeier et al. [319] showed that adjuvant radiotherapy) halved the local recurrence rate (odds ratio 0.49 [95% CI 0.31–0.77]).

A statistically significant survival benefit was not demonstrated in the randomized trials. However, the case numbers in the trials were also too small to demonstrate a survival benefit. There was also no statistically significant survival benefit in the large databases and their meta-analysis [319]. A possible reason for the lack of survival benefit, despite significantly improved local tumor control, could be the so-called „prescription bias“, i.e. the tendency in non-randomized comparisons to use radiotherapy more frequently in patients at high risk of relapse. Qu et al. [320] stratified the available studies according to the „risk of bias“ by quantifying the „risk of bias“ from the rates of R1 resections and G3 tumors in the treatment arms compared with the control arms of the studies. A total of 5 studies with available hazard ratios and a very low „risk of bias“ (0.9–1.1) were identified. For these studies with low bias (n = 2,294), there was a significant survival benefit in favor of adjuvant radiotherapy (hazard ratio 0.65 [95% CI 0.52–0.82], p < 0.001).

In the case of R1 resection, the local recurrence rate is increased by approximately a factor of 2-3 after adjuvant radiotherapy compared with R0 resection, in association with worse overall survival [134]. Therefore, if R1 resection is predictable, neoadjuvant treatment concepts should be discussed on a multidisciplinary basis. A resection is considered reasonable if it is surgically possible with acceptable morbidity. If resection is only possible with significant loss of function, e.g. amputation, risk and benefit should be weighed against each other. After R1 resections in the extremities, local recurrence rates between 15% – 35% are reported, despite additive radiotherapy. DeLaney et al. [321] were able to show in a retrospective evaluation that radiation doses of > 64 Gy after R1 resection reduce the local relapse rate from 29 % to 13 % (p < 0.01).

The subgroup of atypical lipomatous tumors (G1 liposarcoma) represents a special case. The French Sarcoma Group (FSG) retrospectively analyzed 283 patients of whom 132 had received adjuvant radiotherapy [322]. When the entity was localized to the extremities, adjuvant radiotherapy after R0 resection did not significantly reduce the local recurrence rate (HR 1). In contrast, after marginal resection, additive radiotherapy significantly reduced the local recurrence rate (HR 6.49 (1.89–22.25), p<0.003). For localization to the body trunk, the cohort was too small (n=25) to conduct a valid analysis.

The time interval between resection and start of postoperative radiotherapy ranged from 3 weeks to 2 months in the majority of patients registered in the studies and databases. Because residual tumor cells may continue to proliferate postoperatively, a timely start of postoperative radiotherapy is desirable. However, wound healing should be completed to the greatest extent possible, meaning that radiotherapy can begin at the earliest 3 weeks after surgery.

In contrast to other tumor entities, such as breast carcinoma [323] and head and neck tumors [324], the negative effect of a long interval between surgery and the start of radiotherapy is not well established scientifically. This is mainly because this association has only been studied in small cohorts [325], [326], [327], in which few patients had a long interval between surgery and radiotherapy. Given the clear data in other tumor entities and in the absence of a plausible reason why residual soft tissue sarcomas cells should not proliferate postoperatively, prompt initiation of radiotherapy within 6 weeks of resection, if possible, is recommended. Adjuvant brachytherapy was started 5 days after surgery in the randomized trial by Pisters et al. [317]. Earlier initiation was associated with an increased acute complication rate.

5.4.3. Preoperative radiotherapy (extremities, trunk, non-retroperitoneal)

5.70	Evidence-based Statement
LoE ⊕⊕⊕⊖ ⊕⊕⊖⊖	There is evidence that preoperative or postoperative radiotherapy is associated with improved overall survival. There are hints, but no proof, that the survival benefit is greater with preoperative radiotherapy than with postoperative radiotherapy.
	[328] ⊕⊕⊕⊖: Overall survival (follow-up: 39.6 months) ⊕⊕⊖⊖: Local recurrence (follow-up: 39.6 months)
	Strong Consensus

5.71	Evidence-based Statement
LoE ⊕⊕⊕⊖ ⊕⊕⊖⊖	Sarcomas of the extremities: preoperative radiotherapy (50 Gy/25 fractions) reduces the local recurrence rate as effectively as higher-dose postoperative radiotherapy (66 Gy/ 33 fractions) despite a lower total dose.
	[328] ⊕⊕⊕⊖: Overall survival (follow-up: 39.6 months) ⊕⊕⊖⊖: Local recurrence (follow-up: 39.6 months)
	Strong Consensus

5.72	Consensus-based Recommendation
EC	Surgical resection after preoperative radiotherapy shall be performed after the acute radiation response has resolved (no earlier than 3 weeks) and should be performed no later than 8 weeks after completion of radiotherapy.
	Strong Consensus

Background

Preoperative radiotherapy with or without additional chemotherapy was originally used for large, unresectable or borderline resectable soft tissue sarcomas in case series and phase II trials. In most of the soft tissue sarcomas, necrosis zones occurred in > 90% of the tumor volume. In a smaller proportion of sarcomas, no viablel tumor cells are detectable histopathologically. Studies with additional chemotherapy or 2x daily radiation reported higher average necrosis rates than after conventional fractionated radiotherapy alone [312], [313]. Myxoid liposarcoma in particular often shows a good response to neoadjuvant radiotherapy with significant tumor regression: currently, preoperative radiotherapy with only 36 Gy is being tested in a

prospective study (NCT02106312). These observations were the starting point to test preoperative radiotherapy also in well resectable soft tissue sarcomas.

O'Sullivan et al. [328], [329] randomized patients (n = 188) with resectable soft tissue sarcomas of the extremities to either preoperative radiotherapy with 50 Gy in 25 fractions or postoperative radiotherapy with 64 Gy in 32 fractions. Despite the preoperative dose being just over 20% lower, local tumor control and distant metastasis rates were the same. Overall survival was significantly better in the preoperative arm. This was due to lower mortality from non-sarcoma-related deaths. After preoperative radiotherapy, wound healing problems occurred twice as often as in the control arm (35% vs. 17%, $p < 0.001$). However, this predominantly affected only patients with soft tissue sarcomas of the lower extremity. Grade III–IV late sequelae of radiotherapy (edema, limitation of joint mobility, or subcutaneous fibrosis) occurred less frequently in the preoperative arm, probably as a consequence of the lower radiation dose and significantly smaller radiation fields due to the preoperatively more definable target volume [330].

Sampath et al. [331] performed a multivariable analysis of a group of 816 well-documented sarcoma patients from several large centers with respect to the effect of pre versus postoperative radiotherapy (50.4 Gy vs. 60 Gy in 1.8 Gy–2.0 Gy single dose). Preoperative radiotherapy was associated with significantly better distant metastasis-free and overall survival with the same effect on local recurrence rate. Gingrich et al. [154] analyzed data on patients with sarcomas of the extremity from the National Cancer Database (USA). 14,263 patients were treated surgically only. Radiotherapy was given preoperatively in 3,309 patients and postoperatively in 10,397. The rate of R0 resection after preoperative radiotherapy was significantly higher than after postoperative radiotherapy (90.1% vs. 74.9%, $p < 0.001$). The higher rate of R0 resection was associated with significantly better overall survival, as was the use of radiotherapy.

In a meta-analysis based on a series of cohort studies and a randomized trial [319], preoperative radiotherapy was associated with a significantly lower local recurrence rate (n=1663, odds ratio: 0.67, 95% CI 0.49–0.92) and significantly improved overall survival [n = 1486, odds ratio: 0.67, 95% CI 0.47–0.94] compared with postoperative radiotherapy. However, the rate of postoperative wound healing disorders was increased [odds ratio: 2.92, 95 % CI 1.74–4.88]. In summary, evidence from the large data bases suggests that preoperative radiotherapy results in better oncologic outcomes than postoperative radiotherapy, although the data available to date are predominantly for sarcomas greater than 5 cm in diameter with a high malignancy grade. In these tumors, preoperative radiotherapy is a reasonable option.

5.73	**Consensus-based Recommendation**
EC	In the case of a preoperatively probable or intraoperatively proven R1/R2 resection, intraoperative radiation therapy (IORT) may be considered as a boost.
	Strong Consensus

Background

If R1 resection is performed despite preoperative radiotherapy, it is scientifically uncertain whether postoperative dose boost improves the therapeutic outcome. Since

there is a chance that the remaining residual microscopic tumor cells may still die postmitotically as a result of preoperative radiotherapy, R1 resection after preoperative radiation is not associated with a very high local recurrence risk.

Dagan et al. [332] observed only one local recurrence in a group of 17 patients after preoperative radiotherapy (50 Gy/25 foci) and subsequent R1 resection, which occurred after almost 9 years. Al Yami et al. [333] compared both approaches in a retrospective study of 93 patients with R1 resection after preoperative radiotherapy with 50 Gy in 15 fractions. The local recurrence rate at 7 years was 34% when a boost of 16 Gy was applied (n = 41) and 19% when no boost was given (n = 52, p = 0.13). Known risk factors for local recurrence were approximately equally distributed in both groups. Even assuming a selection bias to the disadvantage of the group treated with a boost, the data do not suggest a benefit from a postoperative boost. R1 resection after preoperative radiation is not associated with a significantly increased local recurrence rate, in contrast to postoperative radiation therapy.

Based on the available data and radiobiologic considerations, a boost cannot be routinely recommended. Intraoperative radiotherapy or brachytherapy starting a few days after surgery is theoretically more effective because of the high local dose and the short time interval from preoperative radiotherapy. However, the available evidence [334] is too limited to prove a clinical advantage.

5.4.4. Radiotherapy for soft tissue sarcomas of the trunk (non-retroperitoneal/visceral).

5.74	Consensus-based Recommendation
EC	For soft tissue sarcomas of the trunk (non-RPS), radiotherapy shall be used similarly as for soft tissue sarcomas of the extremities.
	Strong Consensus

Background

Randomized studies on the value of pre- or postoperative radiotherapy are not available for soft tissue sarcomas in this location. In the larger prospective case series [155] and a meta-analysis [319] of these case series, the results for soft tissue sarcomas of the trunk were combined with those of the extremities because no different effects were found for the effect of radiotherapy. As with soft tissue sarcomas of the extremities, preoperative or postoperative radiotherapy halved the local recurrence rate. Available data are not adequate to assess a possible effect on overall survival. No significantly increased rate of wound healing complications is described after preoperative radiotherapy [335]. It is considered likely that the effects of additional radiotherapy are not relevantly different from those in the treatment of soft tissue sarcomas of the extremity.

5.4.5. Radiotherapy for unresectable tumors or after R2 resection.

5.75	Consensus-based Statement
EC	For primary tumors after R2 resection or tumors that are not resectable with acceptable morbidity after neoadjuvant therapy, local radiotherapy alone or in combination with simultaneous chemotherapy and/or hyperthermia should be discussed on an interdisciplinary basis.
	Strong Consensus

Background

For non-resectable soft tissue sarcomas or after R2 resection, radiotherapy has also been used in some case series with in a high-dose curative intention. In the largest case series [311] consisting of 112 patients, it was shown that durable local tumor control can be achieved with radiotherapy alone in a significant proportion of patients. If these patients are not eligible for neoadjuvant therapy or if resection with acceptable morbidity is not deemed possible even after neoadjuvant therapy, radiotherapy alone or in combination with chemotherapy and/or local hyperthermia can be successfully used as locally definitive therapy [336], [337], [338].

5.4.6. Preoperative radiotherapy in combination with systemic therapy for primarily unresectable or marginally resectable tumors.

The value of neoadjuvant chemotherapy simultaneously or sequentially with preoperative radiotherapy has been investigated in a total of 17 phase I-II studies and case series for locally advanced soft tissue sarcomas or sarcomas that are not considered completely resectable upfront (for review: [339]). On average, higher necrosis rates were reported than in case series with radiotherapy alone. Local recurrence rates and overall survival were favorable compared with historical controls without radiotherapy. In some case series, these therapies were also combined with deep hyperthermia sometimes with high necrosis rates and better outcomes in indirect comparison to radiotherapy or radiation chemotherapy without hyperthermia [336], [340], [341], [342], [343], [344]. However, in the absence of randomized trials, the superiority of any of the above therapies cannot be clearly demonstrated. The best studied are adriamycin (doxorubicin) and ifosfamide in combination as monosubstances or in combination with dacarbazine. A treatment regimen that can be considered standard therapy has not been established to date. For high grade (G2-G3) soft tissue sarcomas (G2-G3) of approximately > 5cm or larger, these preoperative therapeutic strategies should be discussed within the context of a multidisciplinary tumor board, especially if the soft tissue sarcoma crosses a compartmental boundary, extends to involve larger vessels or nerves, or infiltrates bone or organs.

5.4.7. Radiotherapy for retroperitoneal soft tissue sarcoma (RPS).

Soft tissue sarcomas of the retroperitoneum are often diagnosed only at tumor diameters of > 15 cm, because clinical symptoms develop late. Liposarcomas represent by far the most common entity. Retroperitoneal liposarcomas are characterized by local size growth and metastasize to the lung less frequently than other soft tissue sarcomas. The value of preoperative or postoperative radiotherapy for retroperitoneal soft

tissue sarcomas can be assessed from the results of a randomized trial and retrospective and prospective case collections [345], [346], [347], [264].

In the case of retroperitoneal tumors, which are often very large, it is sometimes not possible to apply a sufficiently effective radiation dose postoperatively with acceptable risk while maintaining the radiation tolerance of the adjacent organs, especially the small intestine. This is particularly relevant to patients who have already undergone resection of their primary RPS, with resultant fixation of the small intestine in the potential irradiation area. The application of new radiation techniques, especially intensity-modulated radiotherapy, has brought improvements in this regard, but has not really solved the problem.

Postoperative radiation of RPS (adjuvant or additive indication) usually results in complex concave target volumes, with difficulty in defining the target volume in relation to the bowel and mesentery, due to the commonly massive changes in anatomy resulting from surgery. The target volume can be much better defined preoperatively. A bowel-sparing radiotherapy plan is typically possible, since the tumor often displaces the bowel to a large extent from the target volume by forming a convexity. More conformal target volume acquisitions can therefore be achieved than with postoperative radiotherapy [348]. Increased wound healing disturbances after preoperative radiotherapy of retroperitoneal soft tissue sarcomas have not been reported in retrospective comparisons [334], [349] and could not be found as a significant difference in the prospectively randomized STRASS study (see also the presentation of the results of the STRASS study on page 92. Together with the results of prospectively accrued case series, it can be considered proven that if radiotherapy is indicated for RPS (tumor recurrence, expected R2 resection) preoperative radiotherapy can lead to a reduction of the local intra-abdominal recurrence rate with low toxicity.

Direct comparisons with other preoperative therapies such as chemotherapy combined with deep hyperthermia (subset of a phase III trial [271] or combined radiochemotherapy (case series, single-arm phase II trials [350], [351]) are not available. It should be noted that only high grade (G2, G3) soft tissue sarcomas could be included in the treatment protocols with chemotherapy, so that only for well-differentiated (G1) soft tissue sarcomas are robust data on preoperative radiotherapy alone available. Whether and which neoadjuvant therapy should be performed for RPS remains a matter that should be determined in the context of a multidisciplinary tumor board.

5.4.8. Technique of radiotherapy

5.76	Consensus-based Recommendation
EC	Percutaneous, postoperative radiotherapy shall be as conformal as possible. The use of IMRT/VMAT techniques also with integrated boost should be preferred for better conformality.
	Strong Consensus

5.77	Consensus-based Recommendation
EC	Radiation therapy shall meet defined requirements in terms of target volume, dosage, and safety margins.
	Strong Consensus

Background

Pre- or postoperative radiotherapy should usually be delivered as intensity-modulated (IMRT) or volume-adapted radiotherapy (VMAT). In most cases, 3D-planned therapy results in inferior dose distributions even for convex target volumes. IORT or brachytherapy via a multicatheter technique is also used in some institutions. Proton therapy should also be considered for tumors that are not completely resectable. Only therapy with photons will be discussed.

According to the recommendations of the RTOG consensus panel [352], the clinical target volume (CTV) postoperatively comprises the surgical bed. In the case of preoperative irradiation, it comprises the macroscopic tumor (gross tumor volume=GTV) in the extent of the T1 weighting on preoperative MRI with contrast medium with a safety margin of 3 cm in the direction of the muscle fiber course (usually longitudinal) and of 1.5 cm in the transverse direction of the muscle fiber course (usually axial). If postoperative irradiation is performed, the sometimes considerable modifications of the anatomy caused by the resection of the tumor and possible reconstructive measures must be taken into account, which may lead to uncertainties in the definition of the CTV in the case of large tumors. Therefore, the CTV is usually larger postoperatively than it would have been with preoperative therapy, where the CTV is clearly definable.

The longitudinal safety margins of up to 10 cm previously proposed for high grade (G2-G3) soft tissue sarcomas are no longer appropriate in the era of routine, accurate preoperative cross-sectional imaging. No consensus exists as to whether the peritumoral edema zone seen in many patinets on T2 weighted images should be included in the CTV. If the increase in target volume is not expected to significantly increase radiotherapy morbidity, it should be included in the CTV. In the RTOG-0630 trial (phase II), reduced safety margins were prospectively investigated for preoperative radiotherapy with 50 Gy in 25 fractions [353]: For G2-G3 soft tissue sarcomas less than 8 cm in diameter and all G1 sarcomas, safety margins for CTV were reduced to 2 cm longitudinally and 1 cm axially. For G2-G3 tumors > 8 cm in diameter, 3 cm longitudinal and 1.5 cm axial safety margins were used. For Planning Target Volume (PTV), a 5 mm safety margin was used assuming the use of image-guided radiotherapy.

After a follow-up period of 4 years, 5 local recurrences (all in G3 tumors) were observed. All recurrences were within the 95% isodose, 3 after R1 resection. This study demonstrates that reduced safety margins should be considered safe for preoperative therapy and should be used clinically. Reported late adverse events were significantly lower than expected.

Clinical target volume (CTV) for postoperative radiotherapy.

The CTV for postoperative percutaneous radiotherapy [352] for high grade (G2-G3) soft tissue sarcomas includes the surgical bed with a 3 cm distance longitudinally from the muscle fiber direction and 1.5 cm axially from the muscle fiber direction. Adaptations to anatomy like bony structures or thick fascia should be considered. Any edema zones present on preoperative MRI should be included in the CTV. In the case of very large edema zones, a clinical decision must be made as to whether the additional morbidity due to expansion of the CTV is in reasonable proportion to the potential benefit.

For low grade (G1) soft tissue sarcomas, safety margins around the surgical bed of 2 cm longitudinally and 1 cm axially are sufficient.

The „Boost"-CTV includes the former tumor region as appreciated on the preoperative MRI, with 1.5 - 2 cm longitudinal and 1.0 - 1.5 cm axial anatomically reasonable modified safety margins.

The additional safety margins for the planning target volume (PTV) depend on the possibility of immobilization of the region to be irradiated in the individual patient and on the availability of imaging available within the linear accelerators. As a rule, distances of 5-10 mm are sufficient. For regions that move with respiration, an ITV concept should be considered, as well as the possibility of respiratory-triggered radiotherapy to minimize PTV.

For postoperative brachytherapy, CTV includes the surgical tumor bed with 2 cm longitudinal (in muscle fiber direction) and 1.5 cm axial safety margins [316], [317]. An additional safety margin for the PTV with good catheter fixation is usually not necessary.

To avoid increased wound healing complications, brachytherapy should not be initiated until postoperative day 5 [316], [317].

Dosage in postoperative radiotherapy

In the postoperative situation after R0 resection, total doses of 60 to 64 Gy (1.8-2.0 Gy single dose) should be considered standard for percutaneous radiotherapy [189], with 45-50.4 Gy given initially with the safety margins described above, followed by a boost of 10-14 Gy with isotropic safety margins of 1.0-1.5 cm with respect to the former tumor extent. The recommended doses with the above safety margins are often not achievable, especially in retroperitoneal soft tissue sarcomas, due to necessary dose restrictions by surrounding organs at risk. Whether significantly reduced safety margins or total doses reduced to 45-50.4 Gy will still impact the local recurrence risk in this situation is not well established from studies and case series. Since the dose-response relationships for adjuvant radiotherapy could be assumed to be relatively flat, one might expect it be effective with the lowered doses after R0 resection. In the case of R1 resection, the total dose should be increased to 66 Gy if possible. Dose

compromise after R1 resection has been shown [321] to result in a significantly higher local recurrence rate.

For postoperative brachytherapy, either 45 Gy in „low dose rate“ or 36 Gy in „high dose rate“ (10 fractions) was applied within 4-6 days in the studies [317], see also Chapter Chapter 5.4.2.

Clinical target volume (CTV) for preoperative radiotherapy.

For preoperative radiotherapy, the macroscopic tumor (GTV) based on the extent of cross-sectional imaging (MRI with contrast agent is recommended first, see recommendation 4.3). Because of possible differences in rotation that are difficult to compensate, it is useful to also perform the planning CT with contrast medium, especially on the upper extremity.

The CTV for preoperative percutaneous radiotherapy includes the GTV with a distance of 3 cm longitudinally to the muscle fiber direction and 1.5 cm axially to the muscle fiber direction for highly malignant soft tissue sarcomas (G2-3) with ≥8 cm extension. For soft tissue sarcomas less than 8 cm in extent and all G2 soft tissue sarcomas, the CTV surrounds the GTV with a distance of 2 cm longitudinally to the muscle fiber direction and of 1 cm axially to the muscle fiber direction. Anatomic modifications due to bony structures or large fascial courses should be considered. Any edema zones present on preoperative MRI should be included in the CTV [353]. In the case of very large edema zones, a clinical decision must be made as to whether the additional morbidity caused by extending the CTV is in reasonable proportion to the potential benefit.

The same recommendations apply to PTV as to postoperative percutaneous radiotherapy (see recommendations 5.69. and 5.76).

Caveat: In approximately 20 % of cases, especially in soft tissue sarcomas larger than 10 cm, significant tumor volume increase occurs during preoperative radiotherapy. Therefore, at least weekly conebeam CT checks a should be performed at least once per week nd, if necessary, adaptation of the target volumes undertaken. This edema-related increase in size is not to be considered as tumor progression.

Dosage during preoperative radiotherapy

For preoperative percutaneous radiotherapy, total doses of 45-50.4 Gy (1.8-2.0 Gy single dose) were predominantly used in the clinical case series. Surgery was performed between 4-8 weeks after preoperative radiotherapy in the studies, which is why other intervals are not recommended. Imaging after completion of radiotherapy to assess the effect of therapy is useful after 3-4 weeks at the earliest [328].

5.5. Additional therapy modalities

5.5.1. Hyperthermia

In these guidelines, hyperthermia is understood to be the application of whole-body-hyperthermia or regional deep-wave hyperthermia in combination with cytostatic chemotherapy and intratumoral temperature measurement. For other forms of hyperthermia, there is no reviewed evidence for use in soft tissue sarcomas.

5.5.1.1. Systemic whole body hyperthermia

5.78	Consensus-based Recommendation
EC	Systemic whole-body hyperthermia has no place in the treatment of patients with soft tissue sarcomas and shall not be used outside of trials.
	Strong Consensus

Background

In systemic whole-body hyperthermia (SBHT), the entire patient is heated. There are two forms of hyperthermia: moderate SBHT with temperatures of 40.5 °C and extreme SBHT with 41.8 °C. They pursue the goal of the stimulating the immune system and are mainly in use in complementary medicine approaches. Heating is performed by whole-body infrared irradiation under sedation and intensive monitoring conditions. To date, there are no controlled clinical studies that justify the use of SBHT for patients with soft tissue sarcomas.

5.5.1.2. Regional deep hyperthermia

Technique

Regional deep(-wave) hyperthermia (RHT) involves non-invasive heating of the tumor as well as the surrounding tissue to temperatures of 40-43 °C for 60 minutes by irradiation of electromagnetic waves. It is used in addition to standard therapies because of its chemo- and radiosensitizing properties, but not as the sole treatment method, due to chemo- and radiosensitizing properties. In addition, an immune effect is postulated [354]. RHT is suitable for tumors of the pelvis and abdomen as well as for trunk or extremity tumors. The electromagnetic waves are emitted in the frequency range from 27 MHz to about 120 MHz via antennas arranged in a ring around the patient. To avoid reflections on the body surface, a water bolus is placed between the antennas and the patient. This additionally fulfills the function of cooling the skin surface. The electromagnetic waves can be focused within the target area. Temperature monitoring plays a central role. If possible, it is performed directly by temperature probes inserted into the tumor (CT- or sonography-guided) or, in the case of pelvic tumors, approximately via probes in the rectum, bladder or vagina. Due to the development of hyperthermia systems with integrated MRI imaging (MRI deep hyperthermia hybrid system), non-invasive thermometry via temperature-sensitive MR sequences is increasingly possible.

For patients, RHT represents a form of therapy with few side effects and is generally well tolerated. Possible adverse effects include a sensation of pressure and tightness triggered by the water bolus, as well as local insensations caused by the irradiation of

the radio waves. Thermal tissue damage occurs only very rarely in the form of slight skin burns or fatty tissue necrosis. Patients with pacemakers or metal implants in the treatment area cannot be treated with RHT.

Radiative RHT in combination with neo-adjuvant chemotherapy has been evaluated within a randomized phase III trial for the use of locally advanced high-risk soft tissue sarcomas (see below). For the capacitive hyperthermia systems, which are also used for local tumor therapy, there is insufficient experience regarding the temperatures reached in the tumor, so that they cannot be recommended for the therapy of soft tissue sarcomas outside of studies.

Clinical studies

5.79	Evidence-based Recommendation
GoR **B/0**	Neo-adjuvant chemotherapy for patients with soft tissue sarcomas of the pelvis, abdomen, and extremities should/can be combined with deep hyperthermia.
LoE ⊕⊕⊕⊖ ⊕⊕⊖⊖ ⊕⊕⊖⊖ ⊕⊕⊕⊖ ⊕⊕⊕⊖ ⊕⊕⊕⊖	[269]; [271]; [355] ⊕⊕⊕⊖: Overall survival (follow-up: 98.4 months) ⊕⊕⊖⊖: DFS (median follow-up: 99 months) ⊕⊕⊖⊖: LPFS (median follow-up: 99 months) ⊕⊕⊕⊖: Survival (Follow up: 135.6 months) IT experience ⊕⊕⊕⊖: LPFS (follow-up: 135.6 months) ⊕⊕⊕⊖: DFS (follow-up: 135.6 months)
	Consensus

Background

Due to the limited availability of regional deep hyperthermia at only a few specialized hospitals as well as the changed chemotherapy standard (AI vs. EIA) compared to the hyperthermia study, no consensus for a „should“ recommendation was reached despite the positive phase 3 study with a survival benefit in the context of the vote. The compromise proposal „should/can“ on the other hand in the sense of „use of regional deep hyperthermia in the context of neo-adjuvant chemotherapy concepts if available“ found a broad majority.

The value of RHT in combination with systemic chemotherapy was investigated in a randomized phase III trial (EORTC 62961 / ESHO RHT-95) in patients with high-risk soft tissue sarcomas. Patients received 4 neoadjuvant cycles of EIA chemotherapy consisting of etoposide (250 mg/m2), ifosfamide (6 g/m2), and doxorubicin (50 mg/m2) followed by surgery and, if possible, radiation, and 4 adjuvant cycles of EIA chemotherapy. In the experimental arm, patients received 2 RHT treatments in parallel with each cycle of EIA chemotherapy (total maximum of 16 RHT). There were 341 patients randomized to either the hyperthermia arm or the chemotherapy alone arm (1:1). Inclusion criterion was the presence of high-risk soft tissue sarcoma (FNCLCC grade 2–3, tumor diameter > 5 cm, deep location in relation to superficial fascia) or

its recurrence. Of note, the study included a large number of patients with retroperitoneal or intra-abdominal soft tissue sarcomas (n=192).

After a median observation period of 34 months, the addition of hyperthermia to neoadjuvant and adjuvant chemotherapy showed a significant improvement in local progression-free survival (LPFS; hazard ratio 0.58; 95 % CI 0.41-0.83; p=0.003), disease-free survival (DFS; hazard ratio 0.70; 95 % CI 0.54-0.92; p=0.011), and a doubling of treatment response (28.8 % vs. 12.7 %). The risk of progression with preoperative chemotherapy was also significantly reduced in the hyperthermia arm (6.8 % vs. 20.6 %) [354]. For patients with retroperitoneal and visceral sarcomas (N=149) with macroscopically complete tumor resection, the benefit in LPFS and DFS with the addition of RHT was also present [269]. After long-term follow-up with a median observation time of 11.3 years, survival was also significantly prolonged for patients additionally treated with RHT (hazard ratio 0.73; 95% CI 0.54-0.98; p=0.04) [355].

The current therapeutic regimen for high-risk soft tissue sarcomas at centers with deep hyperthermia facilities is guided by this study. Due to the risk of developing secondary AML due to etoposide and the expected low priority in the treatment of adults with soft tissue sarcomas, EIA chemotherapy is no longer used and instead doxorubicin and ifosfamide (AI) are combined with RHT.

5.5.2. Isolated limb perfusion

The treatment goal of isolated limb perfusion (ILP) is local tumor control and limb preservation in locally advanced soft tissue sarcomas. There is a different starting point for the indication of limb perfusion (see below). As an alternative to limb perfusion, other multimodal therapies or amputation may be considered. Management is highly dependent on patient and tumor factors as well as previous therapies.

5.5.2.1. Isolated Limb Perfusion (ILP) Technique

Isolated limb perfusion is an approved standard treatment [356], [357]. The technically complex procedure involves surgical, vascular isolation of the limb with establishment of a separate circuit under general anesthesia and full heparinization to target. Within the perfusion circuit, mild tissue hyperthermia of 38-39.5 °C is induced and nuclear medicine procedures are used to ensure that there is no leakage to the systemic circuit. In the perfusion circuit, 3-4 mg rhTNFα-1a („recombinant human necrosis factor α-1a“, Tasonermin) combined with 10 mg melphalan/liter perfused limb-volume is applied over 90 minutes. Other substances are used only in individual cases.

Postoperative complications such as redness, hyperthermia, blistering, and desquamation of the cornea are typical. Rhabdomyolysis up to compartment syndrome as well as cardiac stress with application of rhTNF-α may occur [358]. The toxicity of the procedure is classified according to Wieberdink [359].

5.5.2.2. Recombinant human tumor necrosis factor α

Tumor necrosis factor alpha (TNFα) is a multifunctional cytokine that plays an important role in innate and acquired immunity. TNFα binds to two different receptors and leads to hemodynamic and antitumor effects [360]. Clinical studies in patients with solid tumors have so far failed to demonstrate that effective tumor control can be achieved by systemic administration. The route of administration induces a vital threat to patients from systemic inflammatory response syndrome (SIRS) [361], [362].

Administration of rhTNF-α during ILP avoids the hemodynamic effects and shows a strong synergistic antitumor effect with chemotherapeutic agents in melanoma and sarcoma patients [363]. In the setting of ILP, rhTNF-α has two potentially synergistic antitumor properties: increased uptake of melphalan and selective destruction of tumor vascularization [364].

Limb perfusion without rhTNF-α, is significantly inferior to TNF-ILP in terms of tumor response [365], [366]. ILP with rhTNF-α may only be performed at accredited centers. Tasonermin (Beromun®) is dispensed by the manufacturer only after verification of logistical, technical, and medical competence. Extremity perfusions without rhTNF-α are therefore performed exclusively in clinics where the drug is not available. Therefore, a data comparison of ILP cohorts with or without rhTNF-α cannot be performed because of selection bias.

5.5.2.3. Indication for isolated limb perfusion

The approval of rhTNF-α followed a European multicenter study in 186 patients with locally advanced soft tissue sarcomas (107 primary tumors, 79 local recurrences, median tumor diameter 16 cm, 42/186 multifocal tumors) [367]. Inclusion criterion of the study was the presence of an extremity-threatening tumor or already established amputation indication. Tumor response was observed in 82 % of patients, allowing extremity-preserving resection. Treatment outcome showed 33 complete remissions (CR) (18 %), 106 partial remissions (PR) (57 %), no change (NC) in 42 patients (22 %) and progressive disease (PD) in five cases (3 %). With a median follow-up of 22 (6-58) months, amputation was also avoided in the long term in 82 % of patients. In 23/25 patients with metastatic disease when ILP was indicated, the limb was successfully preserved. Therefore, in patients with locally advanced soft tissue sarcoma, regardless of the status of metastasis, the indication for limb perfusion should be considered when no other effective therapeutic option is available.

Cohort studies after approval of tasonermin reported limbpreservation of 76 to 96 % in locally advanced tumors [365], [368], [369], [370], [371], [372], [373]. Pathologic tumor response rates (vital tumor remnant less than 10 % or [Bonvalot, S. et al. 2011]. Treating institutions have a treatment preference depending on the availability of ILP [375]. Randomization between treatment alternatives is also difficult to justify from the patient's perspective.

5.80	Consensus-based Recommendation
EC	In isolated limb perfusion for therapy of locally advanced soft tissue sarcomas, recombinant human tumor necrosis factor-α in combination with melphalan shall be applied as effective substances.
	Strong Consensus

5.81	Consensus-based Recommendation
EC	Before performing an amputation, the indication for isolated limb perfusion shall be reviewed in the interdisciplinary sarcoma board.
	Strong Consensus

5.82	Consensus-based Recommendation
EC	Extremity perfusion may be indicated in locally advanced primary tumors or local recurrences of soft tissue sarcomas as a preoperative therapy with the goal of tumor revitalization and avoidance of mutilating and severely function-restricting procedures.
	Strong Consensus

5.83	Consensus-based Recommendation
EC	Extremity perfusion may be indicated as a palliative measure regardless of tumor stage with the goal of local tumor control.
	Strong Consensus

5.6. Chemotherapy

5.6.1. Neoadjuvant chemotherapy

5.84	Consensus-based Recommendation
EC	Soft tissue sarcomas smaller than 5 cm (T1) shall not receive neoadjuvant chemotherapy regardless of grading and location. This recommendation does not apply to extraosseous Ewing sarcomas and embryonal rhabdomyosarcomas.
	Consensus

5.85	Evidence-based Recommendation
GoR **0**	For soft tissue sarcomas at high risk of recurrence (> 5cm, deep-seated, G2/3) and chemosensitive subtype, neoadjuvant chemotherapy may be offered regardless of location.
LoE ⊕⊕⊖⊖ ⊕⊕⊖⊖	[186] ⊕⊕⊖⊖: Overall survival (median follow-up: 7.3 years) ⊕⊕⊖⊖: DFS (median follow-up: 7.3 years)
	Strong Consensus

5.86	Evidence-based Recommendation
GoR **B**	Neoadjuvant chemotherapy should be anthracycline-based combination therapy.
LoE ⊕⊕⊕⊖ ⊕⊕⊕⊖	[376] ⊕⊕⊕⊖: Overall survival (median follow-up: 12.3 months) ⊕⊕⊕⊖: DFS (median follow-up: 12.3 months)
	Strong Consensus

Background

In individual cases, preoperative chemotherapy may be considered as part of a multimodal therapy concept if this, in combination with marginal resection at critical resection margins (nerves, vessels, etc.), enables function-preserving surgery.

Patients with locally advanced high-risk soft tissue sarcoma (FNCLCC grade 2-3, tumor diameter ≥ 5 cm, deep location) have a high risk of dying from local recurrence or the appearance of distant metastases despite the best possible local therapy, consisting of surgery and, in most cases, additional radiotherapy. The 5-year survival rates are approximately 50-80 % for extremities and 40-60 % for retroperitoneal

sarcomas, depending on the location. Nomograms now exist for both soft tissue sarcomas in the extremities [142] and retroperitoneal sarcomas [141], which allow a relatively accurate estimation of the risk of recurrence and, in addition to localization and grading, also take into account the patient's age and histological subtype and, in the case of retroperitoneal sarcomas, any multifocality [377].

Neoadjuvant chemotherapy aims both to shrink the primary tumor and thus improve the surgical outcome and to treat radiologically undetectable micrometastases. Surgery is usually performed within 3-4 weeks after completion of chemotherapy. Response rates described to date for this situation range from 16 to 34 % [186], [355], [376], [378], [379].

Results are available for preoperative chemotherapy alone (3 cycles of Adriamycin 50 mg/m2 and ifosfamide 5 g/m2) compared with immediate resection without neoadjuvant chemotherapy from a randomized EORTC phase II trial of 134 patients with resectable soft tissue sarcoma (≥ 8 cm, grade I-III or < 8 cm, grade II/III; or recurrence grade II/III) [186]. The objective tumor response rate to preoperative chemotherapy was 29 % (CR 8 %, PR 21 %) in 49 evaluable patients in the experimental arm. 18 % of patients showed tumor progression during preoperative chemotherapy. This study was stopped early due to insufficient recruitment. Furthermore, due to the open inclusion criteria also for patients with stage IB and IIA and the lack of statistical power due to only 67 evaluable patients per arm, published results on 5-year disease-free survival in both arms (56 % vs. 52 %, n.s.) are not interpretable for the evaluation of preoperative chemotherapy.

After an Italian Sarcoma Group (ISG) study of adjuvant chemotherapy in high-risk patients (104 participants) initially showed a significant survival benefit [380], a follow-up study compared the administration of 3 preoperative cycles with the additional administration of 2 postoperative cycles versus 3 cycles of preoperative chemotherapy alone because of the declining dose intensity in the adjuvant trial for cycles 4-5 and because of the potential benefit of neoadjuvant chemotherapy. The final analysis showed non-inferiority of preoperative chemotherapy alone with a 10-year survival of 64 vs 59 % [381], [382]. The survival curve here resembles that of adjuvant-only patients from the first study, making this study further evidence of the efficacy of neo-/adjuvant chemotherapy.

A randomized phase III trial (ISG-STS 1001) that tested different histology-specific chemotherapy regimens in the neoadjuvant setting in patients with high-risk soft tissue sarcoma of the extremities or trunk versus the standard anthracycline in combination with ifosfamide showed a significant survival advantage for patients treated with three preoperative cycles of epirubicin and ifosfamide within the control arm.

Contrary to the original assumption of the study initiators, superiority for treatment with gemcitabine/docetaxel in undifferentiated pleomorphic sarcomas (UPS), trabectedin in myxoid liposarcomas, high-dose ifosfamide in synovial sarcomas, etoposide/ifosfamide in malignant peripheral nerve sheath tumors (MPNST), and gemcitabine/dacarbazine in leiomyosarcomas, the study had to be stopped early due to the significant superiority of the control arm. For standard therapy, disease-free survival at 46 months was 62 % and overall survival was 89 % versus 38 % and 64 %, respectively, for patients treated with histology-specific therapy. Trabectedin was noninferior in high-grade myxoid liposarcoma in primary therapy, so this study arm will still continue [376]. The results of this study reinforce the recommendation for neoadjuvant chemotherapy consisting of a combination of an anthracycline with ifosfamide in patients with high-risk soft tissue sarcomas.

The addition of regional deep wave hyperthermia to anthracycline-based neoadjuvant chemotherapy resulted in a significant survival benefit in high-risk patients with extremity and retroperitoneal or abdominal soft tissue sarcomas [271] (see Section Chapter 5.5.1). The current therapeutic approach at centers with deep hyperthermia facilities is guided by this study.

5.6.2. Adjuvant chemotherapy

5.87	Consensus-based Recommendation
EC	Soft tissue sarcomas smaller than 5 cm (T1) shall not receive adjuvant chemotherapy regardless of grading and location. This recommendation does not apply to extraosseous Ewing sarcomas and embryonal rhabdomyosarcomas.
	Consensus

5.88	Consensus-based Recommendation
EC	For soft tissue sarcomas at high risk of recurrence (> 5cm, deep-seated, G2/3) and chemosensitive subtype, adjuvant chemotherapy may be offered regardless of location.
	Strong Consensus

5.89	Evidence-based Recommendation
GoR B	Adjuvant chemotherapy should be anthracycline-based combination therapy.
LoE ⊕⊕⊕⊖ ⊕⊕⊕⊖	[383]; [384]; [385]; [386]; [387]; [388]; [389]; [390]; [391]; [392]; [393] ⊕⊕⊕⊖: Overall survival (follow-up: 8.1-96 months) ⊕⊕⊕⊖: DFS (Follow-up: 8.1-84 months).
	Strong Consensus

Background

Recommendation 5.87. is subject to adequate histopathological staging. For individual case exceptions see above under chapter Chapter 5.6.1.

Until the end of the 1990s, 14 randomized studies on adjuvant chemotherapy in patients with soft tissue sarcomas were published. These were mostly smaller studies with small numbers of cases. Regarding the inclusion criteria, patients with sarcomas of all localizations and with different grading, i.e. not exclusively high-risk patients from today's point of view, were generally included. The therapeutic regimens used consisted of doxorubicin mono [383], [384], [386], [387], [388], [389], [390], [391], [394], as well as different combinations that today would no longer find use in advanced soft tissue sarcoma [395], [396].

Because of the divergent results and mostly small case numbers, a meta-analysis of all 14 studies published up to that time was performed in 1997. For local relapse-free survival, metastasis-free survival, and overall relapse-free survival, there was a significant improvement with chemotherapy with an absolute advantage of 6-10 %. For overall survival, there was a nonsignificant absolute benefit of 4 % at 10 years. However, it is noteworthy that for the subgroup of patients with extremity sarcomas there was a significant benefit also for overall survival [397].

Based on positive data on ifosfamide-containing combinations in the treatment of advanced soft tissue sarcomas in adults, further studies on adjuvant therapy with corresponding combination therapies were subsequently conducted [385].

In a study of the Italian Sarcoma Group (ISG), only high-risk patients with G3 sarcomas of the extremities were included. It reviewed full-dose adjuvant chemotherapy with 5 cycles of epirubicin 120 mg/m2 and ifosfamide 9 g/m2 versus follow-up alone. The first interim analysis showed a significant survival benefit of 13 % at 2 years and 19 % at 4 years, so the study was stopped early [380]. However, at a median follow-up of 89.6 months, the significance was lost again, so that in conclusion the study could not show a convincing survival benefit. Only per-protocol analysis continued to show a significant survival benefit (5-year survival 66 % vs. 46 %) [398].

In 2008, another meta-analysis was published with now 18 studies [272]. This showed a significant advantage for patients who had received adjuvant chemotherapy in terms of local recurrence-free and metastasis-free survival. For overall survival, significant superiority was found for the subgroup of patients who had received combination therapy with doxorubicin and ifosfamide, with an absolute advantage of 11 % and a „number needed to treat“ of 17 to prevent one death.

The importance of grading was further supported by a retrospective study from France. Thus, for patients with G3 tumors, a highly significant impact on overall survival was found, corresponding to an absolute risk reduction of dying from soft tissue sarcoma of 13 %. In G2 tumors, however, adjuvant chemotherapy did not improve overall survival [399].

Not yet included in the meta-analyses were the results of a large randomized trial by the EORTC Soft Tissue and Bone Sarcoma Group [393]. This included patients with sarcomas of all sites, any size, and grading 2 and 3. Overall, there was no significant difference in 5-year relapse-free survival or overall survival (66.5% for the chemotherapy group vs. 67.8 % for the control group). Of note is the unexpectedly high value for 5-year overall survival, which reflects the patient population. The chemotherapy used, with doxorubicin 75 mg/m² plus ifosfamide 5 g/m², does not appear optimal with regard to ifosfamide dosing.

Thus, overall, adjuvant chemotherapy after resection of localized soft tissue sarcoma should not be considered standard. Possible indications for adjuvant combination chemotherapy are in patients at high risk of recurrence (grade 3, deep-seated, >5 cm) and in retroperitoneal sarcomas in which an increased local recurrence rate must be expected due to limited options for follow-up radiation. Usually, an anthracycline-containing combination therapy should be used. The indication must be made individually in informed consensus together with the patient [400].

5.7. Planning of multimodal therapy concepts

5.7.1. Planned marginal resection/lower recurrence rate.

5.90	Consensus-based Statement
EC	A marginal resection is a surgical procedure in which resection is performed along the outer tumor border. This shall be communicated to the pathologist.
	Strong Consensus

5.91	Consensus-based Recommendation
EC	Considering morbidity, complications, and functional failure, marginal resection may be performed at critical sites in low-grade sarcomas. This shall be discussed preoperatively in the interdisciplinary sarcoma board.
	Strong Consensus

5.92	Consensus-based Recommendation
EC	The atypical lipomatous soft tissue tumor can be resected marginally without a multimodality therapeutic approach.
	Strong Consensus

Background

In the literature, different terms are used within studies to describe the resection procedure and the outcome of tumor resection.

The R-classification is a standardized part of the pathological report of resection within the TNM system. The R-classification describes the surgical result with regard to the achieved completeness of tumor resection and the safety distance to the margin of the specimen according to R0, R1 and R2.

Studies focused on surgical technique for tumor resection often use terms such as intralesional, marginal, wide, and radical resection.

Different definitions of marginal resection are used in the literature. For example, a minimum distance of 2 mm from the tumor is required for a marginal resection, but also only a narrowest margin of healthy tissue („no tumor on ink“). In a retrospective study with 643 patients, the patients were divided into 3 groups according to their resection margin: less than 1 mm (“no tumor on ink“), 1-5 mm, >5mm. No difference could be found regarding local recurrence-free (LRFS), disease-specific (DSS), and metastasis-free survival (MFS) [104].

In other retrospective studies, a minimal resection margin of 2 mm is required [401]. Gundle et al. studied 2,217 patients with high-grade sarcoma regarding the effect of

surgical resection margin on local recurrence rates at 5 and 10 years. The highest rate of local recurrence was found in the R2 group, followed by the R1 group („tumor on ink“) and the R0 group („no tumor on ink“). The authors formed a subgroup R+1mm in the R0 group, significant that <there was 1 mm safety distance between the tumor and the ink mark. In some studies, a status of R+1mm is not considered R0 but R1. In Gundle's study, the local recurrence rate was lower in the R+1mm group than in the R1 group and similar to the R0 group [105].

It is important to distinguish between a vital tumor that grows progressively into the surrounding area and a tumor that has devitalized after preoperative therapy with regard to the evaluation of the aforementioned R categories.

Some soft tissue tumors of the extremities grow preferentially in a longitudinal direction. In the literature it is mentioned in many places that tissue such as periosteum, fascia, adventitia or perineurium forms a safer margin with regard to the development of a local recurrence [105], [147]. There is no prospectively evaluated evidence on this. In the presence of a tumor not pretreated with neoadjuvant, the histologic subtype and grading play a crucial role. Liposarcomas usually do not infiltrate the aforementioned structures, allowing them to serve as a safe dissection layer. Synovial sarcomas or leiomyosarcomas do infiltrate surrounding structures, so marginal resection is not expected to provide local tumor control. MPNST originate from a nerve (e.g., femoral nerve, sciatic nerve) that must be resected as well.

This problem is particularly common in large atypical lipomatous tumors (ALT, equivalent to G1 liposarcoma). The incidence of distant metastasis in ALT is very low. The incidence of local recurrence is high, often occurring after many years. Only in rare cases are patients vitally threatened by this.

Several case series exist regarding resection of ALT [166], [402], [403], [404], [405]. The largest case series with 151 patients compares the procedure of two different reference centers in Italy [403]. In one center patients underwent marginal R0 resection, in the second center marginal (R1) resection. The 10-year LRFS was 82 %. Margin-forming resection resulted in an increased recurrence rate. No case of dedifferentiation into high-grade sarcoma was detected in 16 local recurrences in this patient population. Similar results are shown by a German single-center study reporting no recurrence after wide resection and a 7.5 % recurrence rate after marginal resection. None of the 3 patients with recurrence experienced tumor dedifferentiation [166]. A single-center study from Japan with 41 patients showed no recurrence with wide resection of an ALT, and a recurrence rate of 10 % with marginal resection. Among the 3 recurrences, dedifferentiation occurred in one case [404]. In one study with 25 recurrences, one recurrent tumor showed dedifferentiation [405]. In both studies, there was no metastasis in the patients with dedifferentiation during the observation period.

For highly malignant sarcomas (grading 2 and 3), the local recurrence risk is much higher than for G1 sarcomas. These sarcomas require at least adjuvant radiotherapy anyway. In this constellation, consideration of neoadjuvant therapy is indicated (see Section Chapter 5.6.1). In the case of tumor localization at critical sites with expected high functional morbidity, it may be possible to perform a marginal resection with curative (R0) intention in the case of a sarcoma devitalized by neoadjuvant therapy.

With marginal resection, there is a risk of failing to remove tumor cells via the fate of the reactive zone [105], [145], [406]. The reactive zone is characterized by signal enhancement on T2-weighted MRI images and mostly by contrast enhancement on

contrast-enhanced T1-weighted images. It is also described as a pseudocapsule and may extend to several centimeters beyond the tumor. It typically consists of surrounding tissue compressed by the expansion pressure of the growing tumor. Tumor cells are detected in this reactive zone up to 4 cm away from the macroscopic sarcoma borders [407].

Grabellus et al. investigated the quality of the pseudocapsule after neoadjuvant therapy. Histologic „improvement“ (fibrosis and widening) of the pseudocapsule was seen with all neoadjuvant therapies, most pronounced after ILP and radio-chemotherapy. The improved capsular integrity of the sarcoma resulted in a lower rate of LR [408]. Without (neo-) adjuvant therapy, marginal resection leads to a higher rate of local recurrence [105], [178]. However, marginal resection shows a similar LR rate to wide resection in the multimodal therapy concept. In particular, the positive effect of radiotherapy in marginal resection on LR rate has been demonstrated in several studies [104], [105]. Analyses of adjuvant chemotherapy trials that included patients with marginal resection (e.g., EORTC 62931 „removal of all grossly visible tumor“) describe a positive effect of adjuvant chemotherapy on LR rate [137]. The addition of hyperthermia to systemic chemotherapy after marginal resection (S3 group in the EORTC 62961-ESHO 95 trial) resulted in improved local recurrence-free and overall survival [271], [355].

5.7.2. Survival improvement

Patients with high-risk soft tissue sarcomas (see also chapter Chapter 4.2) have a high risk of developing metastases in the course of local therapy alone and thus ultimately dying from their disease. From the point of view of improving overall survival, systemic therapy with the aim of treating occult metastases at an early stage is therefore of primary importance. Under this objective, systemic therapy can be given both preoperatively, i.e. neoadjuvant, and postoperatively, adjuvant.

For neoadjuvant therapy, data are available from two randomized phase III trials [355], [376]. From ISG-STS 1001, there is evidence regarding improved survival with standard anthracycline plus ifosfamide therapy versus histology-matched chemotherapy. From EORTC 62961-ESHO 95, evidence regarding improved survival even after 10-year follow-up results from combination chemotherapy with regional deep hyperthermia versus chemotherapy alone [271] (see Section Chapter 5.5.1.2).

For adjuvant chemotherapy, the data situation is much more complex, as positive results regarding survival from phase III trials are lacking. However, retrospective analyses [272], [397] provide evidence that combination chemotherapy of anthracyclines and ifosfamide can improve overall survival in clearly defined risk groups (G3 vs. G2) with a hazard ratio of 0.86 (CI 0.75-0.97).

For the largest adjuvant chemotherapy trial, EORTC 62931 a reanalysis was performed using Sarculator [409] (see also chapter Chapter 4.2). It showed that chemotherapy halved survival and risk of recurrence in the patient group with the most prognostically unfavorable value (HR = 0.46, 95 % CI 0.24-0.89), whereas no benefit was demonstrated in the other prognostic groups.

Overall, therefore, both a revised evidence base, and a more comprehensible definition of patients with high-risk soft tissue sarcomas now exist to recommend individualized education regarding the data and shared treatment decision-making in „informed consent“. The data situation for neoadjuvant therapy (randomized phase III trial [271], remission rate of the doxorubicin+ifosfamide arm in the EORTC 62012

trial [410] and in the ISG1001 trial [376] neoadjuvant phase II trial for therapy with trabectedin [411] is thereby broader than that for the meta-analyses [272] or Re-analyses based on a new prognostic parameter of the EORTC 62931 study [409] so that here there tends to be more in favor of preoperative therapy (see recommendations 5.85 and 5.86).

5.7.3. Patient education

The text including the literature references is adapted from the S3 guidelines

„Diagnostics, therapy and follow-up of malignant ovarian tumors“, version 4.0, March 2020 [412] and „Early detection. Diagnosis, Therapy, and Follow-up of Breast Carcinoma“, version 4.4, September 2021 [74].

Due to the increasing need of patients for information and co-determination in the treatment of their disease, knowledge transfer and patient education play an important role. Their importance for the doctor-patient relationship, the course of the disease and the achievement of the therapeutic goal has been proven by numerous studies [413], [414]. Open-ended patient education with the goal of shared (participatory) decision-making enables sufficient medical action.

Two ethical principles are at work in these interactions: the patient's self-determination (autonomy) and the physician's care [415].

The patient's autonomy is of the highest importance. A patient's decision is always voluntary and binds medical action. Patients can speak out for or against medical measures in diagnostics and therapy or also decide in favor of a „I do not want to know“. In order for patients to be able to make a decision in the sense of effective consent („informed consent“), existing information deficits must be compensated for by the physician as best as possible. The personal discussion between patient and physician is of particular importance as the basis for a trusting and respectful understanding. Participatory decision-making is of great importance („shared decision making“). This applies in particular when the outcome of a possible therapy cannot be well estimated.

Of course, these considerations also apply to patients with soft tissue sarcomas, for whom, however, specific problems must be taken into account. For example, minor differences in tumor location and tumor grading may have significant therapeutic and prognostic implications that require particularly detailed clarification (e.g., functional impairment).

The following recommendation has been adapted from the S3 guideline „Diagnostics, therapy and follow-up of malignant ovarian tumors“, version 4.0, March 2020, AWMF register number 032/035OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/ovarialkarzinom/ [412].

5.93	Consensus-based Recommendation
EC	Medical education of the patient shall include: • information about the disease • the results of the examination • the course of treatment so far • diagnosis and discussed differential diagnoses • treatment options including expected side effects and late effects as well as • assessments of the associated prognoses and the impact on the patient's life planning and quality of life.
	Strong Consensus

5.94	Consensus-based Recommendation
EC	All patients with adult soft tissue sarcoma shall be informed about networking opportunities in self-help/patient groups, due to the rarity of the disease with special consideration also of internet-based information and communication opportunities (see chapter 0).
	Consensus

5.95	Consensus-based Recommendation
EC	The patient's attention should be drawn to the patient guideline on the diagnosis, treatment and follow-up of patients with adult soft tissue sarcomas (see Chapter 9).
	Strong Consensus

Background

The information provided by the physician should be comprehensive, truthful, complete with regard to the type of measure, purpose, benefits and risks and, in particular, comprehensible (including information on frequencies instead of relative percentages) [416], [417]. The hope for healing or alleviation should not be blocked. The physician providing the information must ensure that the information is provided in accordance with the course of treatment.

The patient's individual somatic, psychological and social situation, gender, age and comorbidities must be taken into account when conducting the discussion. In this context, the patient's fears and concerns, specific burdens, and in particular his or her need for information, treatment expectations, and preferences are to be addressed directly by the physician [418], [419], [420], [421]. The patient's wish to have

the conversation or further conversations together with a trusted person must be complied with.

The prerequisite for this is the patient-centered conversation. According to the following basic principles the switching of information and the clearing-up of the patient are to take place [422], [423], [424], [425], [426]:

- Expression of empathy and active listening.
- Addressing difficult issues directly and empathetically
- If possible, avoidance of medical vocabulary, explanation of technical terms if necessary
- Strategies to improve understanding (repetition, summarizing important information, use of graphics, etc.)
- Encouragement to ask questions
- Request to write down questions that arise later and bring them to the next meeting
- Permission and encouragement to express feelings, especially fears and anxieties
- Offering further help (see chapter 9.1 Psychooncology)
- Offer further help by involving the oncology nurse (or advanced practice nurse)

General information about the treatment

The educating physician should explain the recommendations for a form of treatment, especially if there is a patient-centered and consensus-based treatment recommendation from an interdisciplinary conference, and present the principles of treatment, its benefits and risks. Alternative forms of treatment that may be considered for the patient as part of participation in a clinical trial shall be explained. During the discussion, implications for the patient's lifestyle and quality of life should be discussed. This includes informing patients about „normal and unremarkable“ examination results and the course of treatment (reassurance) and providing prognostic information (life planning) [427], [428], [429].

Specific aspects of information for soft tissue tumors

In any case, the following points should be considered as contents of a therapy clarification discussion:

Surgical therapy:

- Explanation of the extent of muscle resections and their consequence for the function of limbs, joints and organs (control of knee joint function after (partial) resection of the quadriceps muscle, internal rotation of the leg after resection of the obturator nerve.
- Changes in respiratory function and body image after resection on the body cavities (e.g. thoracic wall, abdominal wall relaxation after retroperitoneal resection).
- Information about rehabilitation measures (e.g. functional gait training, muscle building) and provision of assistive devices
- Information about foreseeable limitations in the profession practiced as a result of surgical measures (joint mobility, reduction in gross strength, loss of surface and depth sensitivity)

Multimodal therapies:

- Education about effects of neoadjuvant therapies (e.g., radiation therapy and wound healing, consequences of isolated limb perfusion such as lymphedema, systemic chemotherapy combined with deep hyperthermia)
- For neoadjuvant therapies, in particular, the intended benefit compared with the primary surgical approach should be explained and weighed against the loss of time until definitive surgery.
- Principles and treatment goals of any adjuvant therapy, duration and implementation of the treatment, its side effects and possible late effects, as well as treatment options for side effects

Radiotherapy:

- Advantages and disadvantages of radiotherapy when given before or after surgery (irradiation field smaller preoperatively, irradiation dose larger postoperatively, delay to surgery by radiotherapy of about 8-12 weeks, effects on joint mobility and lymphedema by radiation dose and irradiation field.

General aspects of therapy:

- Participation in clinical trials: principles and treatment goals sought, explanation especially of development status of new drugs (phase I, II, III) and sponsor of trial (investigator initiated, academic research group, industrial client).
- Duration and implementation of the therapy as a whole: effects and side effects known so far, late effects, special features (monitoring, additional measures, participation, data storage and processing)
- Others: possibilities of prophylaxis and treatment of therapy-related side effects (e.g. premature menopause, vomiting, neurotoxicity, lymphedema, skin changes during radiotherapy, etc.), necessity of follow-up care,
- Possibilities of psycho-oncological support as well as services of self-help groups, aspects of personal responsibility and participation (e.g., communication of symptoms and problems, therapy compliance) [430], [431], [432].
- Clarification of a genetic risk
- Possibility of special nursing support for prophylaxis and complementary nursing measures in case of side effects of the therapy by the Oncological Specialist Nursing (or Advanced Practice Nurse).

6. Therapy of isolated local recurrence

6.1. Frequency and prognosis

6.1	Consensus-based Statement
EC	Local recurrences of soft tissue sarcomas are associated with a higher risk of further local recurrence and distant metastasis compared with primary tumors.
	Strong Consensus

6.2	Consensus-based Statement
EC	There are no prospective randomized studies on local therapy of local recurrences of soft tissue sarcomas.
	Strong Consensus

Background

The incidence of local recurrence is best documented for sarcomas of the extremities. In specialized centers, this is usually below 15 % in series treated after 1995 [155]. Higher local recurrence rates are reported for localization to the trunk or retroperitoneum [321]. Local recurrences are most frequently observed in the first 2 years after completion of primary therapy. According to Eilber et al [433] 65 % of all local recurrences occur during this period and within 4 years approximately 90 %. Consistently, the highest risk of local recurrence is after marginal and intralesional resections according to the results of multivariate analyses from several databases [134], [155], [316], [434]. In contrast, tumor size, grading, and tumor location (for extremity sarcomas) were significant risk factors in these databases only in univariate analysis.

In the MSKCC database, age older than 50 years, history of local recurrence, and histologic subtype of MPNST were also associated with an increased risk of local recurrence on multivariate analysis [134]. The prognosis of patients with local recurrence is not significantly worse than after therapy for the primary tumor in all databases. In the multivariate analyses, the rates of distant metastasis after local recurrence were shown to be only slightly increased. Data from the Scandinavian Sarcoma Group demonstrate that although there is a statistical correlation, a causal relationship cannot be established because other prognostic factors for metastasis such as initial tumor size and, most importantly, grading play a decisive role [161]. Short intervals (<2 years) until local recurrence are associated with a less favorable prognosis [435]. Therefore, consistent local therapy is as important in isolated local recurrence as in primary therapy.

6.2. Local recurrences pretreated by surgery alone

6.2.1. Surgical therapy

6.3	Consensus-based Recommendation
EC	If no preoperative or postoperative radiotherapy or medical tumor therapy has been given during primary treatment, local recurrences of soft tissue sarcomas shall be treated diagnostically and surgically according to the same recommendations as for primary therapy.
	Strong Consensus

Background

The criteria for surgical treatment of local recurrence do not differ from those in primary treatment. In some cases, however, a more complex local situation is present after previous plastic-reconstructive surgery. Accordingly, the rate of recurrence of local recurrence even after achieving R0 resection is somewhat higher than in primary therapy [134], [434].

As with initial surgery, the prognosis of patients with local recurrence is much better if R0 resection is achieved [435], [436]. Therefore, the goal of surgery for isolated local recurrence is to achieve R0 resection, just as in the primary setting. If a complete resection is not achievable despite neoadjuvant therapies (see next paragraph), amputation may also be useful in the case of unfavorably located recurrences in the extremities.

6.2.2. Preoperative / neoadjuvant therapies (without previous therapy)

6.4	Consensus-based Recommendation
EC	In local recurrences of soft tissue sarcomas not pretreated with neoadjuvant or adjuvant therapy, a multimodal therapy concept shall be defined in an interdisciplinary sarcoma board.
	Strong Consensus

Background

For marginally resectable primary tumors and highly malignant local recurrences, the value of neoadjuvant therapies has not been systematically studied (radiotherapy, chemotherapy +/- hyperthermia, isolated limb perfusion). Some of the studies addressing these questions have included small numbers of cases not previously treated with neoadjuvant or adjuvant therapy with local recurrences after surgery alone [271], [328], [376]. The benefit of neoadjuvant chemotherapy in combination with hyperthermia compared with neoadjuvant chemotherapy alone was as great in the local recurrence subgroup in terms of DFS and overall survival as with primary therapy [271], [376]. In Gronchi et al. [376] (neoadjuvant chemotherapy) and O'Sullivan et al. [328] (preoperative radiotherapy), local recurrence outcomes were not reported separately.

Since local recurrences are associated with an increased risk of further local and distant recurrence and are less frequently R0-resectable than primary cases, it seems plausible to assume that the benefit of neoadjuvant therapeutic procedures for local recurrence is, if anything, even higher than in the primary situation. The possibility of multimodal therapy should therefore be reviewed in the interdisciplinary sarcoma board.

For hyperthermic isolated extremityperfusion (TN-ILP) with rhTNF-alpha and melphalan, available in accredited centers, response rates of up to 85 % (defined as more than 90 % tumor necrosis in the resected tumor) could be achieved in case series of up to 208 patients [373], [437]. In patients with recurrences completely resectable only by amputation in most cases, the amputation rate after 5 years was about 20 %, which was higher than in patients with the same treatment for the primary tumor [356]. Clearly, the results of TNF-ILP are less favorable in patients with recurrent tumor [437]. It is particularly important to consider that efficacy and toxicity are negatively influenced by previous radiotherapy [438], [439]. Relevant acute toxicities have been reported in approximately 10 % of patients after TNF-ILP. Late toxicities depend on the extent of surgery. In particular, the fracture risk associated with periosteal stripping during resection surgery is relevant [169]. The rate and extent of lymphedema is also influenced by the additive toxicity of TNF-ILP (lymphodynamic insufficiency) and postoperative adjuvant radiotherapy.

6.2.3. Radiotherapy (without previous radiotherapy)

6.5	Consensus-based Recommendation
EC	Preoperative or postoperative radiotherapy shall be given for local recurrences of poorly differentiated (G2-3) or >5 cm soft tissue sarcomas in tissues of the extremities or trunk that have not been preirradiated.
	Strong Consensus

6.6	Consensus-based Recommendation
EC	Preoperative radiation therapy may be given for local recurrences of retroperitoneally located liposarcomas.
	Strong Consensus

Background

The effects of preoperative or postoperative radiotherapy have not been explicitly tested in randomized trials for local recurrences compared with surgery alone. However, randomized trials of the effect of preoperative or postoperative percutaneous radiotherapy [189], [328], [330] and postoperative brachytherapy [316] in primary therapy also included smaller numbers of patients with local recurrence after surgery alone as primary treatment. The results for patients treated for local recurrence have not been published separately, even as a subgroup analysis. There is no reason to assume that in the absence of pre-irradiation, the beneficial effect of radiotherapy for local recurrence is different from that in primary treatment. If radiotherapy has not

been given at primary treatment, it should be used for local recurrences in the extremities and trunk. Because of the demonstrated increased risk [134], [434] of local recurrence compared with primary treatment, the indication for postoperative radiotherapy of even well-differentiated (G1) soft tissue sarcomas <5 cm should be more generous than in the primary situation.

For local recurrences of non-preirradiated retroperitoneal soft tissue sarcomas, the data are extremely limited. However, well-differentiated liposarcomas may benefit from preoperative radiotherapy (50.4 Gy in 28 fractions as IMRT) given the results of the STRASS trial [264]. However, it must be taken into account that due to the possibility that scarred small bowel loops may be fixed in the former surgical area, the side effects rate of preoperative radiotherapy may be higher. For the surgical procedure, this means a higher risk of complications after possible bowel resection in the irradiated area, since the irradiation dose is less distributed to mobile bowel loops.

6.2.4. Adjuvant chemotherapy (without prior chemotherapy)

In the trials of adjuvant chemotherapy, series also included patients with local recurrences that had been pretreated only surgically [272]. Subgroup analyses in this regard are not available from most trials. However, it seems plausible to assume at least the same (small) benefit in terms of overall survival for adjuvant chemotherapy in the relapse setting. Therefore, it is advisable to inform patients with large, highly malignant recurrences in the extremities about the potential benefit of adjuvant chemotherapy.

6.3. Therapy after preoperative/neoadjuvant or adjuvant therapy.

6.7	Consensus-based Statement
EC	The following factors argue for repeat external beam radiation therapy of previously irradiated tissues: • Interval until recurrence >2 years • Minor late sequelae of previous radiotherapy (fibrosis, atrophy, limitation of movement). • Highly malignant sarcoma (grading 2-3) • Small resection margins or R1/R2 resection or expected small resection margins or R1/R2 resection.
	Strong Consensus

6.8	Consensus-based Recommendation
EC	Conformal irradiation techniques should be used for re-irradiation: • Brachytherapy (intraoperative insertion of catheters). • Intraoperative radiation therapy with electrons (IOERT) • External beam: IMRT or VMAT with IGRT
	Strong Consensus

6.9	Consensus-based Recommendation
EC	Local recurrences in oligometastatic patients should be treated according to the same recommendations as nonmetastatic patients, provided that all distant metastases can be treated surgically or with local ablative procedures.
	Strong Consensus

Background

After neoadjuvant treatment (limb perfusion, radiation, chemotherapy with hyperthermia) or adjuvant treatment (radio- or chemotherapy) the initial conditions for resection of local recurrences are often much less favorable than for primary therapy. Higher local complication rates after repeat surgery are typical in these cases [436]. Only the results of smaller, heterogeneously treated case collections are available [256], [435], [436], [438], [439], [440], [441], [442], [443], [444], [445], [446], [447], [448], [449], [450], [451], [452].

There is consensus among the authors that surgical treatment with the goal of R0 resection should be pursued even for recurrences not treated by surgery alone. The rate of R0 resection is significantly lower than in primary treatment, and the incidence of

recurrence of local recurrence despite R0 resection is also significantly higher. Reported recurrence rates of local recurrence range from 15% to over 50% even after R0 resection, although the majority of patients also received additional neoadjuvant or adjuvant therapies (radiotherapy, chemotherapy +/- hyperthermia) and/or intraoperative radiotherapy or brachytherapy. Contributing to this is the fact that local recurrence predominantly occurs in G2/G3 sarcomas, which in any case have a less favorable tumor biology. Studies on the aforementioned therapeutic procedures in combination with surgery or on resection alone are either completely lacking or not usable due to bias that cannot be assessed.

Repeat pre- or postoperative percutaneous radiotherapy for local recurrence is not associated with an increased risk of acute radiation side effects, but the risks of wound healing complications after preoperative radiotherapy and grade III-IV late toxicities, such as fibrosis and necrosis, are increased with reported rates of 20 - 50 % [435], [443], [444]. However, experimental and clinical data are available that tolerance of irradiated tissues to re-irradiation 1-2 years after 1st radiotherapy returns to 50 - 90% of tolerance of unirradiated tissues [453]. In particular, if the first radiotherapy has not left any serious late sequelae and was performed more than 1 year ago, and the pre-irradiated area has been resected, a new radiotherapy can therefore be performed with only a slightly increased risk of complications. Since it is known from therapy in the primary situation that preoperative radiotherapy with 50 Gy in 25 fractions is equivalent to postoperative 66 Gy in 33 fractions, it makes sense in the case of planned re-irradiation to perform it preoperatively, especially since with preoperative irradiation the irradiated volume can also be kept smaller [328], [329]. Especially at the lower extremity, however, wound healing disorders occur more frequently after preoperative radiotherapy.

In smaller case series, intraoperative radiotherapy has been used additionally or alone, especially for regions where only marginal (R1) surgical resection was expected prior to the surgical proicedure or documented intraoperatively. Because of the small volume of irradiation, toxicity is relatively low. However, increased rates of wound infection, seroma, and, with direct irradiation of larger nerves, nerve damage have also been reported [440], [448].

More reports are available on adjuvant brachytherapy using intraoperative insertion of afterloading catheters. In experienced hands, highly conformal dose distributions can be achieved. Toxicity is also increased compared with that of primary treatment, with reports of increased rates of wound healing problems and infections [440], [441], [446], [447].

In patients with local recurrence who have received radiotherapy as a sole treatment besides surgery, neoadjuvant chemotherapy can also be given in combination with hyperthermia without significantly increased acute toxicity compared with primary treatment. The few very small case series indicate an increased complication rate of subsequent surgery [454], [455].

The combination of neoadjuvant chemotherapy with hyperthermia and re-irradiation is also applicable according to the results in a few small patient series with an increased but acceptable toxicity compared to primary treatment [336], [337], [338], [456].

Which of the described procedures should be applied depends on the individual situation, availability and experience at the centers and should be discussed in the multidisciplinary sarcoma board.

Synchronous or previous distant metastasis is found in up to 30% of patients with local recurrences [452]. In the presence of oligometastasis, a curative chance still exists for a smaller proportion of patients [457]. Therefore, it seems reasonable to treat local recurrences in patients according to the same principles as in non-metastatic patients.

In some patients, the local recurrences are so unfavorable or so extensive that, regardless of the previous therapy, a complete resection with acceptable morbidity or surgical risk is not possible. Smaller case series have shown that a good palliative effect can be achieved even without resection or in rare cases even after incomplete resection with conservative therapies (radiotherapy, system therapies, chemotherapy or radiotherapy +/- hyperthermia). In the subgroup of smaller recurrences (<5-10 cm in diameter), this approach can also achieve long-term local tumor control [336], [337], [338]. In patients with multiple distant metastases, local treatment of an additional (symptomatic) local recurrence may help, especially if local complications are imminent. The aforementioned therapeutic options can usefully complement palliative medical care and be discussed in an interdisciplinary manner.

6.3.1. Preoperative chemotherapy

6.10	Consensus-based Recommendation
EC	In resectable, isolated local recurrence of high-risk (G2/3) sarcoma not pretreated with chemotherapy according to guidelines and with a chemosensitive subtype, preoperative chemotherapy may be given.
	Strong Consensus

6.11	Consensus-based Recommendation
EC	In resectable, isolated local recurrence of sarcoma pretreated with chemotherapy according to guidelines, no additional preoperative chemotherapy should be given.
	Strong Consensus

6.12	Consensus-based Recommendation
EC	In isolated and non-resectable local recurrence, a multidisciplinary therapeutic decision shall be made.
	Strong Consensus

6.13	Consensus-based Recommendation
EC	If systemic therapy is used for isolated and non-resectable local recurrence, anthracycline-based combination therapy should be used if the subtype is chemosensitive and resectability is expected in the case of tumor shrinkage or to relieve local symptoms. Otherwise, the choice of chemotherapeutic agents is analogous to the metastatic situation.
	Strong Consensus

Background

When isolated local recurrence occurs, the approach differs between local recurrence judged to be R0 resectable and non-R0 resectable. In resectable local recurrence, there is no proven benefit to the use of systemic therapy in addition to tumor resection. This is true in both the preoperative and postoperative settings. Studies on the value of systemic therapy in localized soft tissue sarcoma are only available for primary tumors (see Chapter Chapter 5.6). Accordingly, the use of preoperative chemotherapy can be considered as a case-by-case decision in the case of local recurrence not previously treated with chemotherapy and meeting the high-risk criteria (T2, G2/3). In all other cases, only resection of the local recurrence is recommended [86] with or without the use of radiotherapy as discussed in Chapter 5.4. A retrospective study by Gustafson et al. in 1993 describes metastasis-free long-term survival after resection and radiotherapy alone for an isolated local recurrence, but refers mainly to patients with smaller low-grade tumors [458].

Patients with local recurrence are at increased risk of distant metastases and therefore require close follow-up [459]. In the case of non-resectable local recurrence, the therapeutic principles are based on the procedure for metastatic soft tissue sarcoma (see chapter Chapter 7.1).

6.3.2. Additive chemotherapy

6.14	Consensus-based Recommendation
EC	Additive chemotherapy may be given after complete resection of an isolated high-risk local recurrence that has not been pretreated with chemotherapy according to guidelines.
	Strong Consensus

6.15	Consensus-based Recommendation
EC	After incomplete resection of an isolated local recurrence, whether pretreated with chemotherapy according to guidelines or not, a multidisciplinary therapeutic decision shall be made.
	Strong Consensus

7. Therapy of metastatic disease

The heterogeneity of soft tissue sarcomas underscores the need for selection from available drug agents. Table 13 details those soft tissue sarcomas that can be treated with conventional chemotherapy, those for which a targeted therapy is appropriate and those for which no treatment can currently be recommended.

Table 13: Sarcoma subgroups considered to be sensitive to chemotherapy, unless otherwise stated

Sarcoma group	Sarcoma subtype	ICDO code	Remarks
Vascular tumors	Epithelioid hemangio-endothelioma	9133/3	No standard chemother-apy, see subtype-specific treatment
	Angiosarcoma	9120/3	
Gastrointestinal stromal tumors		8936/3	Subtype-specific treat-ment (see chapter 10.1)
Nerve sheath tumors	MPNST	9540/3	
	Malignant Triton tumor	9561/3	
Tumors of unclear differentiation	Synovial sarcoma	9040/3	
	Epithelioid sarcoma	8804/3	No standard chemother-apy, see subtype-specific treatment
	Extraskeletal myxoid chondrosarcoma	9231/3	No standard chemother-apy, see subtype-specific treatment
	Extraskeletal Ewing sar-coma	9364/3	Analogous to therapy for osseous Ewing sarcoma
	Desmoplastic small and round cell tumor	8806/3	No standard chemother-apy, see subtype-specific treatment
Undifferentiated / non-classified sar-comas	Undifferentiated spindle cell sarcoma	8801/3	
	Undifferentiated pleo-morphic sarcoma	8802/3	
	Undifferentiated round cell sarcoma	8803/3	
	Undifferentiated epitheli-oid sarcoma	8804/3	
	Undifferentiated sar-coma NOS	8805/3	
Adipocytic sarcoma	Dedifferentiated liposar-coma	8858/3	

Sarcoma group	Sarcoma subtype	ICDO code	Remarks
	Myxoid liposarcoma	8852/3	
	Pleomorphic liposarcoma	8854/3	
Fibroblastic / Myofibroblastic sarcomas	Malignant solitary fibrous tumors	8815/3	No standard chemotherapy, see subtype-specific treatment
	Adult fibrosarcoma	8810/3	Distinct from infantile fibrosarcoma, where *NTRK fusion* is frequent
	Myxofibrosarcoma	8811/3	
Tumors of the smooth musculature	Leiomyosarcoma	8890/3	
Tumors with skeletal-muscular differentiation	Embryonal rhabdomyosarcoma	8910/3	analogous to pediatric RMS protocol
	Pleomorphic rhabdomyosarcoma	8901/3	analogous to pediatric RMS protocol, there is discussion whether this subtype does not beong to the group of adult STS an is not particularly sensitive to chemotherapy

A number of approved and non-approved substances are currently available for clinical use in the treatment of these entities. Table 14 lists the substances alphabetically as well as their approvals.

Table 14: List of recommended substances for drug therapy of soft tissue sarcomas according to approval and clinical use.

Substance	Clinical use	Approval	Benefit assessment
Dacarbazine (DTIC)	Pretreated patients*	Soft tissue sarcoma	-
Docetaxel	Only in combination	-	-
Doxorubicin	First-line	Soft tissue sarcoma	-
Liposomal Doxorubicin	First-line	-	-
Eribulin	Pretreated patients	Liposarcoma after anthracycline	Evidence of substantial additional benefit[1]
Gemcitabine	Pretreated patients	-	-
Ifosfamide	Pretreated patients*	Soft tissue sarcoma	-
Pazopanib	Pretreated patients	Non-adipocytic soft tissue sarcoma after anthracycline	-
Trabectedin	Pretreated patients	Soft tissue sarcomas after anthracycline +/- ifosfamide	-

* Suitable as a combination partner for first-line therapy.
1 For patients for whom dacarbazine is a suitable therapeutic option. For other patients: an additional benefit is not proven (BAnz AT 27.12.2016 B2). [460]

7.1. Systemic therapy

7.1	Consensus-based Recommendation
EC	Patients with locally untreatable, localized, or metastatic disease should receive guideline-based systemic therapy.
	Strong Consensus

7.2. Objective of drug therapy

7.2.1. First-line therapy

7.2	Consensus-based Recommendation
EC	The choice of systemic therapy shall be doxorubicin monotherapy or anthracycline-containing combination therapy, taking into account toxicity and goals.
	Strong Consensus

The selection of the appropriate system therapy for locally advanced or metastatic soft tissue sarcoma is subject to the individual therapeutic situation. In the first-line setting, several anthracycline-based options are available and should be selected based on their advantages or disadvantages for the appropriate patient population. Figure 1 shows an overview of the available options as single or combination therapy. Details on the different regimens can be found in the background text.

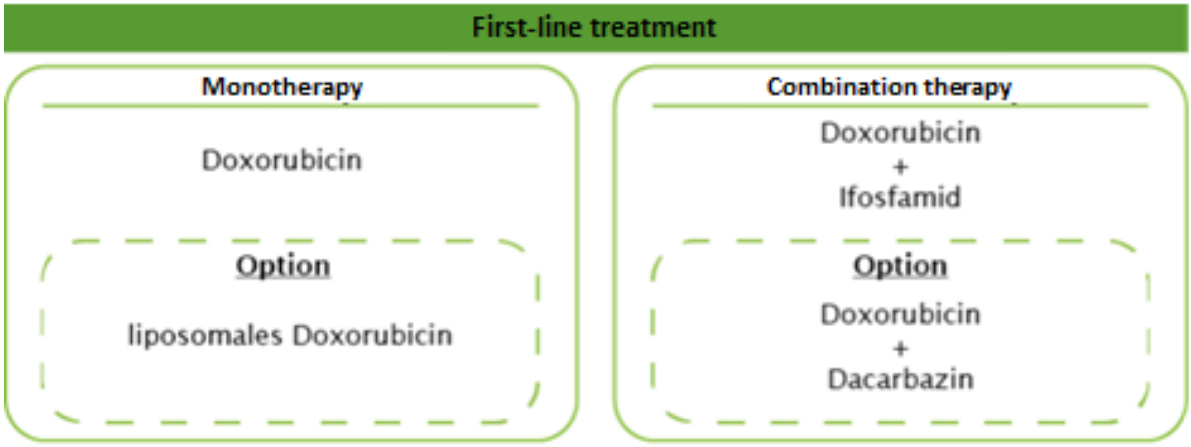

Figure 1: Overview of available options as monotherapy or combination therapy

After failure of the first-line therapy, a follow-up therapy should be offered. Currently, different follow-up therapies are available, which are shown in Figure 2. A specific sequence cannot be defined, so that the selection of the appropriate therapy can be selected according to patient-specific factors (Table 15 and Table 16).

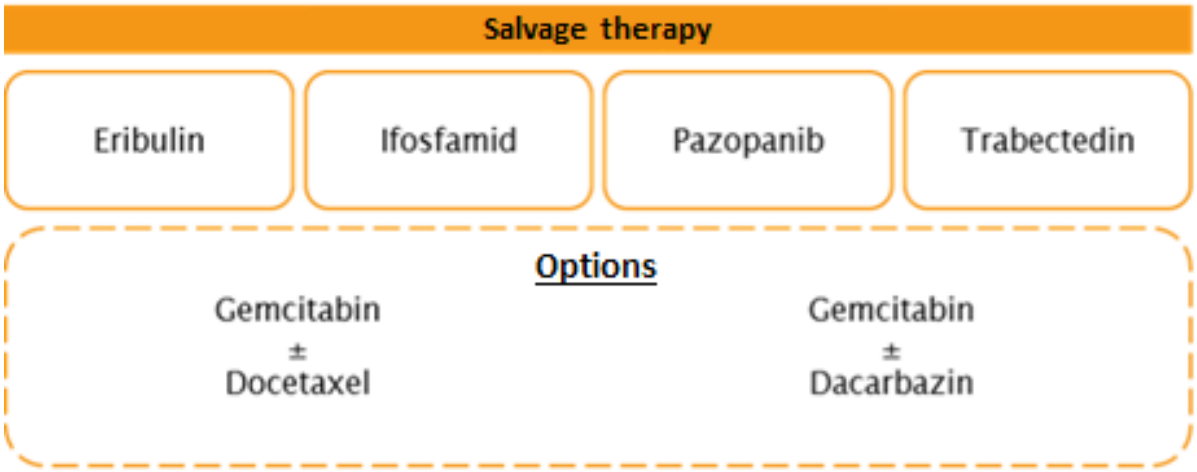

Figure 2: Follow-up therapy in advanced or metastatic soft tissue sarcoma.

Table 15: Approved substances for drug therapy and their mechanisms of action (as of 2021)

Substance	Mechanism of action
Dacarbazine (DTIC)	Inhibition of DNA synthesis by alkylating effect
Doxorubicin	Inhibitor of topoisomerase II
Epirubicin	Inhibitor of topoisomerase II, also doing damage to DNA and RNA polymerase via free radical mechanisms, close analogue to doxorubicin
Entrectinib	Inhibitor of tropomyosin receptor kinases (TRK)
Eribulin	Prevention of tumor cell replication by binding to tubulins
Ifosfamide	DNA alkylation: prevention of cell replication
Larotrectinib	Inhibitor of tropomyosin receptor kinases (TRK)
Pazopanib	Inhibitor of multiple tyrosine kinases
Trabectedin	Blocking transcription factor-DNA binding, inhibiting transcription and interfering with DNA repair mechanisms

Table 16: Approved substances, indication and assessment of added benefit by the G-BA [460], [461], [462]

Substance	Indication	Added benefit
Entrectinib	Adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, in whom locally advanced or metastatic disease is present or disease, for which surgical resection is likely to result in severe morbidity and who have not previously received an NTRK inhibitor inhibitor and for whom no satisfactory satisfactory treatment options are available. available.	An additional benefit is not proven.
Eribulin	Treatment of adult patients with advanced or metastatic liposarcoma previously treated with anthracycline-containing chemotherapy (if appropriate).	Evidence of substantial added benefit compared with dacarbazine in a clinical trial For other therapy options: No additional benefit proven
Larotrectinib	Adult and pediatric patients with solid tumors with a neurotrophic tyrosine receptor kinase (NTRK) gene fusion who have locally advanced or metastatic disease, or disease for which surgical resection is likely to result in severe morbidity, and for whom there are no satisfactory satisfactory treatment options are available. are available.	No additional benefit has been demonstrated.

7.2.1.1. Monotherapy

7.3	Evidence-based Recommendation
GoR **A**	Patients with an indication for monotherapy shall be treated with doxorubicin.
LoE ⊕⊕⊕⊖ ⊕⊕⊕⊖	[410]; [463]; [464]; [465]; [466]; [467]; [468]; [469] ⊕⊕⊕⊖: Overall survival (median follow-up: 8.6 months) ⊕⊕⊕⊖: Progression-free survival (re-analysis, median follow-up: 6.2 months)
	Strong Consensus

Background

To date, no improvement in efficacy or overall survival has been achieved by the addition of other chemotherapeutic agents in histology-agnostic studies [410], [463], [464], [465], [466], [467], [468] [469], [470].

No other chemotherapeutic agent has been shown to be superior to doxorubicin [471], [472], [473], [474], [475]. Doxorubicin is furthermore equivalent to the gemcitabine/docetaxel combination in grade 2/3 sarcomas in a randomized trial and more favorable in terms of toxicity [476].

In a non-comparative randomized phase II trial, liposomal doxorubicin demonstrated comparable efficacy to doxorubicin in terms of remission rate and progression-free survival (PFS) and appears warranted as an alternative. The study was too small to draw a conclusion regarding overall survival (OS) [477].

Epirubicin was randomized in two papers and showed comparable efficacy data (overall survival, progression-free survival) and toxicity profiles compared with doxorubicin [478], [479]. Epirubicin thus represents an alternative to doxorubicin.

For aldoxorubicin, a randomized phase II trial suggested a PFS advantage over doxorubicin (8.3 vs. 4.6 months) [480], but the phase III trial that followed it, but compared pretreated patients vs. „Physician‘s Choice“, did not confirm this advantage [481].

Olaratumab was randomized in combination with doxorubicin (experimental arm) in a phase II trial compared against doxorubicin as monotherapy. There was a significant overall survival benefit for patients in the experimental arm of 26.5 vs. 14.7 months [482]. In the study, rare sarcoma subgroups were partially included in only one study arm. No significant difference was found in remission rate or progression-free survival. The combination was associated with an increased risk of °IV adverse events (42% vs. 31%). Based on the exceptional significant survival benefit, conditional approval of olaratumab was granted [483]. However, the subsequent phase III trial (ANNOUNCE) failed to meet the primary endpoint of prolonging overall survival in either the overall population or the leiomyosarcoma subpopulation [484]. The marketing authorization for olaratumab as the active ingredient in the drug Lartruvo® was revoked by the European Commission on July 19, 2019, due to proven inefficacy.

When diagnostic evidence for NTRK fusions is established, approved agents larotrectinib and entrectinib are available for metastatic/non-operable stage patients.

7.2.1.2. Combination therapy

7.4	Consensus-based Recommendation
EC	Patients for combination chemotherapy (high treatment pressure with rapid progression or symptomatic disease) shall receive anthracycline-based chemotherapy combination.
	Strong Consensus

7.5	Consensus-based Recommendation
EC	In patients with leiomyosarcomas or liposarcomas, combination therapy with doxorubicin and dacarbazine may be administered.
	Strong Consensus

Background

The EORTC 62012 trial [485] which compared doxorubicin plus ifosfamide with single agent docorubicin showed a highly significant advantage of the combination over monotherapy in terms of objective remission rate (26% vs. 14%; p < 0.0006) and improved PFS (HR 0.74, 95% CI 0.60-0.90; p = 0.003) in a range of histologic sarcoma subtypes studied. Therefore, combination therapy should be offered to patients likely to benefit symptomatically from tumor shrinkage or those with rapid disease progression, subject to the usual considerations of toxicity, such as frailty etc.. This is also true for patients with potential resectability (only one organ system affected) of metastases.

A subgroup analysis based on local and central pathology review, central review data suggested that patients with undifferentiated sarcomas (UPS), had a survival benefit with combination regardless of the extent of metastasis (OR 9.90, 95 % CI 1.93-50.7 Combi vs HR 0.44, 95 % CI 0.26-0.79 Mono).). Although there was a higher response rate with combination therapy in all subgroups studied with the exception of liposarcoma, this was only statistically significant in the case of UPS. This may have been due to small numbers in the subgroups.

Subgroup analysis of a retrospective EORTC study [486] suggests a benefit of adding dacarbazine to doxorubicin treatment for objective remission rate in patients with leiomyosarcoma (55% doxo + DTIC vs 20% doxo mono, p = 0.04). A retrospective analysis of 22 patients each with leiomyosarcoma and liposarcoma showed similar results, which were published as an abstract in 2011 [487]. A direct randomized comparison with a doxorubicin/ifosfamide combination has not been performed to date. An EORTC retrospective study did not show an improvement in objective remission rate in leiomyosarcoma and liposarcoma with the addition of ifosfamide [488].

7.2.2. Second-line therapy

7.6	Consensus-based Recommendation
EC	Selection of follow-up therapy should be individualized based on indications for treatment, histologic subtype, and patient preference.
	Strong Consensus

7.7	Evidence-based Recommendation
GoR **A**	In patients who have received chemotherapy according to the guidelines, follow-up therapy with pazopanib, trabectedin or eribulin shall be offered. Pazopanib is not approved for liposarcoma and shall therefore not be used in this setting. Eribulin is only approved in liposarcoma and therefore shall only be used there.
LoE ⊕⊕⊕⊖ ⊕⊕⊕⊕ ⊕⊕⊕⊖ ⊕⊕⊕⊖ ⊕⊕⊖⊖ ⊕⊕⊖⊖ ⊕⊕⊕⊖ ⊕⊕⊕⊖ ⊕⊕⊖⊖ ⊕⊕⊕⊖	[489]; [490]; [491]; [492]; [493]; [494] ⊕⊕⊕⊖: Overall survival (pazopanib) ⊕⊕⊕⊕: Progression-free survival (pazopanib) ⊕⊕⊕⊖: Health-related QoL (pazopanib). ⊕⊕⊕⊖: Overall survival (trabectedin)*. ⊕⊕⊖⊖: Progression-free survival (trabectedin)*. ⊕⊕⊖⊖: Overall survival (trabectedin)** ⊕⊕⊕⊖: Progression-free survival (trabectedin)** ⊕⊕⊕⊖: Overall survival (eribulin) ⊕⊕⊖⊖: Progression-free survival (eribulin) ⊕⊕⊕⊖: Global health status QoL (eribulin)
	Consensus

7.8	Evidence-based Recommendation
GoR **0**	Gemcitabine can be used as monotherapy or combination with docetaxel or dacarbazine in pretreated patients.
LoE ⊕⊕⊖⊖ ⊕⊕⊖⊖	[495]; [496]; [497] ⊕⊕⊖⊖: Overall survival ⊕⊕⊖⊖: Progression-free survival
	Strong Consensus

Background

The heterogeneity of the disease and the different approved drugs require an individual assessment of the therapy situation. The therapeutic landscape is heterogeneous and the level of evidence for individual therapies varies enormously. The spectrum of side effects, treatment indications, histologic subtype, and patient preference should all factor into drug selection.

A number of drug therapies have been evaluated in pretreated patients with soft tissue sarcoma in randomized trials versus placebo, best-supportive-care, or single agent therapy. Comparative trials between multiple treatment options do not exist, so selection of agents is based on contraindications, histological subtype or patient preference.

Trabectedin was approved in the EU in September 2009 based on a randomized dose comparison study (1.5 mg/m2 vs. 1.2 mg/m2) in 270 patients [498]. The 2016 US pivotal trial demonstrated a significant improvement in PFS compared with active therapy with DTIC in patients with leiomyosarcoma and liposarcoma not further subtyped (HR 0.55; moderate strength of evidence) [493]. However, there was only a trend for OS (HR 0.87; low strength of evidence).

A Japanese study compared trabectedin with best supportive care in patients with previously treated translocation-associated sarcomas (including myxoid liposarcomas, synovial sarcomas, mesenchymal chondrosarcomas, and alveolar soft part sarcomas). This showed significantly improved OS – (CI 12.8 months - not reached) vs. 8 months (CI 7.0 – not reached); HR: 0.42; p = 0.04) in addition to significantly improved PFS (from 0.9 to 5.6 months, HR: 0.07; p < 0.0001). Within randomized trials, the range of different sarcoma subgroups was limited and efficacy data exist almost exclusively from retrospective analyses.

Eribulin was also compared to dacarbazine therapy in a patient population restricted to leiomyosarcomas and liposarcomas. This showed an improvement in OS over dacarbazine (HR 0.77, moderate evidence) [489], while PFS was largely unaffected (HR 0.88). A subgroup analysis for patients with liposarcomas showed a highly significant overall survival benefit for eribulin over dacarbazine (15.6 vs. 8.4 months; HR 0.51; 95% CI 0.35-0.75; p < 0.001). There was also a moderate but also significant benefit in PFS (2.9 vs. 1.7 months, HR 0.52; 95 % CI 0.35-0.78; p=0.0015). A quality of life analysis for this study showed a significant improvement in health-associated quality of life throughout the study period as well as at the time of progression. In particular, dacarbazine patients showed more pronounced symptoms such as nausea, vomiting, insomnia and loss of appetite [494]. Based on the above data, approval was granted only for patients with liposarcoma.

Pazopanib was compared to placebo therapy in 369 patients in a 2:1 randomized phase III trial (PALETTE) including most sarcoma subgroups (except liposarcoma which were excluded due to inadequate efficacy in phase II). Pazopanib improved PFS (4.6 vs. 1.5 months, HR 0.31, p=0.0001) and patient QoL, while overall survival was not significantly imprved (11.9 vs. 10.4 months, HR 0.86, p=0.17) [491], [492]. As a result, follow-up therapy should be offered. A large number of different sarcoma subtypess were treated with only small numbers of cases each, so that no reliable efficacy data can be derived from the study.

In summary, pazopanib is suitable for all subgroups except liposarcomas (PFS advantage). Trabectedin (with PFS advantage in the overall LMS/LPS group) is only

optionally recommended for LPS due to available alternatives, but is preferred for LMS. For all other subtypes, the agent is also suitable. Eribulin should only be used in liposarcoma. Here, the drug showed advantages in PFS, OS, and QoL and is thus preferred for this subgroup of soft tissue sarcomas.

The data on comparisons of gemcitabine as single agent compared with the combination of gemcitabine + docetaxel are conflicting. In one study gemcitabine-docetaxel failed to improve PFS (uLMS: HR 1.15; others 0.93) or OS compared to gemcitabine alone, but with an overall low level of evidence [495]. The addition of bevacizumab has no effect, however the study confirmed the principle efficacy of the combination of gemcitabine and docetaxel [497]. It should be noted that this study was first-line data. In another first-line study, the gemcitabine/taxotere combination offered no advantage over monotherapy with doxorubicin [476] (see Chapter 7.2.1.1). In another study, the gemcitabine and docetaxel combination was superior to gemcitabine monotherapy in terms of PFS (HR 0.67), but an overall survival advantage could not be shown [496]. The combination is associated with greater toxicity and should only be used after careful consideration.

Gemcitabine in combination with dacarbazine was superior to dacarbazine alone in a randomized phase II trial [499]. A total of 113 patients with different histologies were randomized, with leiomyosarcomas and undifferentiated pleomorphic sarcomas predominating. Combination therapy was shown to result in an improvement in PFS from 2.0 to 4.2 months and was associated with a survival benefit (16.8 vs. 8.2 months; p=0.014). Again, an increase in toxicity was reported with combination therapy, so use should be assessed individually in each case.

7.2.3. Follow-up therapy

7.9	Consensus-based Recommendation
EC	Patients with progression after failure of second-line therapy may receive re-chemotherapy with drugs not yet used.
	Strong Consensus

Background

When making a decision about follow-up therapy considerations are the patient's general condition and organ functions and the patient's wishes. Drugs described in Chapter 7.2.2 can be used. A specific sequence has not been established.

7.3. Metastatic surgery

7.10	Consensus-based Recommendation
EC	The indication for local therapy of metastases shall be multidisciplinary.
	Strong Consensus

7.11	Consensus-based Recommendation
EC	Surgical resection of pulmonary metastases shall be performed only under the following conditions: • expected R0 removal of all pulmonary metastases • no evidence of local recurrence that cannot be controlled • previous pulmonary metastasectomies are not a contraindication In the presence of extrapulmonary metastases, resection shall be performed only after an interdisciplinary case-by-case decision. Predictive factors for improved survival are a time interval after primary treatment of > 12 months and the radicality of the procedure. Resection of pulmonary metastases with palliative intent is generally not recommended and should be reserved for exceptional cases with severe symptoms.
	Strong Consensus

7.12	Consensus-based Recommendation
EC	No additive chemotherapy shall be given for metachronous resected lung metastases.
	Strong Consensus

7.13	Consensus-based Recommendation
EC	Surgical resection of liver metastases shall only be performed following an interdisciplinary case-by-case decision if the following conditions are met: • expected R0 removal of all liver metastases • No evidence of local recurrence that cannot be controlled. Predictive factors for improved survival are a time interval after primary treatment of > 24 months and the radicality of the procedure. Resection of liver metastases with palliative intent is not recommended.
	Strong Consensus

7.14	Consensus-based Recommendation
EC	Metastases from other sites may be surgically removed on a case-by-case basis.
	Strong Consensus

Background

The decision to resect metastases is often a difficult decision because, firstly, no results from randomized prospective studies are available. Secondly, the decision strongly depends on the subjective assessment and experience of the treating surgeon regarding the extent and radicality of the intervention. Thirdly, under certain conditions, such as in the case of recurrent surgery or when the patient's general condition is significantly impaired, other locally ablative procedures (see Chapter 7.4) should also be considered in addition to a surgical procedure. Therefore, the indication for metastatic surgery should be made on a multidisciplinary basis within the framework of the tumor conference.

20-25% of all patients with soft tissue sarcoma develop pulmonary metastases during the course of the disease, with the frequency of occurrence of pulmonary metastases depending on the grading (G3: 40-60%). The lung represents the organ most commonly affected by soft tissue sarcoma metastases, accounting for 65-80%, and most lung metastases occur within the first two years after resection of the primary tumor [500], [501], [502].

The evidence in favour of resection of pulmonary metastases in metastatic soft tissue sarcoma has been limited to a few large retrospective multicenter studies and a number of smaller observational studies. In 1997, the International Registry of Lung Metastases (IRLM) published a study of 5206 patients after pulmonary metastatic resections. In this cohort, 2173 patients had a diagnosis of sarcoma (soft tissue and osteosarcoma combined). The risk of the pulmonary metastasectomy procedure was acceptable, with a perioperative mortality of 1%. Subgroup analysis from this first large registry study identified incomplete resection (R1), a disease-free interval of less than 36 months from primary diagnosis to the appearance of pulmonary metastases, and an increased number of metastases (>3) as risk factors for less favorable survival in these patients [503].

Subsequent retrospective single enter studies essentially confirmed the above findings and were able to demonstrate a disease-free interval of >12 months from primary diagnosis to the appearance of pulmonary metastases, radicality of surgery (R0), a low number of pulmonary metastases, and extrapulmonary tumor control as predictive factors for improved survival [504], [505], [506], [507], [508], [509], [510], [511], [512], [513], [514].

The best evidence to date, but indirect, that resection of pulmonary metastases provides a survival benefit for patients with metastatic soft tissue sarcoma comes from the French Sarcoma Group METASARC trial, published in 2017. Analysis of 1619 patients with metastatic soft tissue sarcoma only showed a significant increase in survival for patients who had metastases of different sites treated surgically [502]. Since pulmonary metastases were by far the most common metastatic site in this cohort at

65%, these results suggest improved survival for pulmonary metastasectomy for soft tissue sarcoma.

Regarding the surgical procedure, few and hardly robust data exist for a minimally invasive approach to pulmonary metastasectomy [503], [515], [516]. Therefore, the gold standard should still be the open procedure with manual palpation of the entire lung parenchyma. Whether the use of laser technology and mediastinal lymphadenectomy in pulmonary metastasectomy provide benefits for patient survival remains controversial [517], in contrast to renal cell carcinoma, for example, in which the metastatic pathway is via the mediastinal lymph nodes. This is only true for sarcomas in exceptional cases. In contrast, a clear recommendation can be made for pulmonary re-metastasectomies, as surgical treatment of pulmonary recurrence has been shown in several studies to confer a survival benefit for these patients [503], [512], [513], [518], [519].

In 1995, Choong et al postulated that adjuvant chemotherapy after resection of pulmonary metastases was a negative predictive factor for survival [520]. Subsequent studies failed to demonstrate a significant impact of adjuvant chemotherapy on survival in these patients [521], [522]. The French Sarcoma Group registry study of 281 patients with oligometastatic soft tissue and osteosarcoma showed a significant survival benefit for surgical treatment of metastases; however, this was independent of whether chemotherapy was also administered [519].

The liver is the second most commonly affected organ by metastases in soft tissue sarcoma, accounting for 19%. The 5-year survival of these patients is significantly less favorable compared with patients with lung metastases (15% vs. 66%) [502]. Retrospective studies investigated whether resection of liver metastases improves survival in these patients. 5-year survival rates of 27-49% were reported [523], [524], [525], [526], [527]. Prognostic positive factors were defined as a disease-free interval of more than 24 months, calculated from the primary tumor to the appearance of liver metastases, [526], [527], and the radicality of the procedure [525], [527]. However, a problem with these studies is that approximately half of the included patients underwent surgery for liver metastases from GIST. Because drug therapy is highly successful for GIST compared with other soft tissue sarcomas, these survival rates are false positives, and the overall survival of the cohort without GIST is only about 20% [523], [528]. Therefore, only a weak recommendation can be made for resection of liver metastases.

Isolated soft tissue metastases, bone or brain metastases can be resected surgically in terms of individual case decisions. In this case, symptomatic metastases should be considered as the primary indication. In addition to a surgical approach, however, radiotherapy and other locally ablative and less invasive procedures (see Chapter 7.4) should also be considered. Data on improved survival do not exist regarding these indications.

7.4. Locoregional and ablative procedures

7.15	Consensus-based Recommendation
EC	When surgical therapy of metastases is not an option, local ablative procedures may be used as an interdisciplinary case-by-case decision.
	Strong Consensus

7.16	Consensus-based Recommendation
EC	The use of SIRT or TACE to control liver metastases is a case-by-case decision to be coordinated on an interdisciplinary basis and should be limited to patients with disseminated metastases in the liver with concomitant low extrahepatic tumor volume.
	Strong Consensus

Background

In the French Sarcoma Group METASARC observational study, 42 patients were treated with radiofrequency ablation out of a total of 1054 patients with locoregional treatment. The data showed a significant positive impact on overall survival in these patients, although the study did not indicate which localizations were treated with radiofrequency ablation [502]. For radiofrequency ablation of lung metastases, positive results have also been reported by other groups, with 3-year survival of 47% and 85%, respectively [529], [530]. This was different in the case of liver metastases; here, the retrospective study by Pawlik et al. showed that radiofrequency ablation as sole therapy or in combination with a surgical approach had a negative impact on overall survival [524].

In contrast to the small number of patients treated with radiofrequency ablation, 254 patients were treated with local radiotherapy in the METASARC study. Despite the larger number of patients with local ablative radiotherapy, there was only a positive trend regarding the impact on survival [502]. In other studies, stereotactic irradiation of pulmonary sarcoma metastases yielded good local control and 2-year survival rates of 85% and 66% with low toxicity [531], [532]. Positive results for sarcoma patients have also been shown for irradiation of spinal metastases [533], irradiation of brain metastases [534], and postradiation of surgically removed brain metastases [535], so radiotherapy can be considered for local control of metastases when surgery is not an option.

The use of transarterial radioembolization (SIRT) [536], [537] and chemoembolization (TACE) for disseminated liver metastases and at the same time low extrahepatic tumor volume, or extrahepatic tumor control, applies to only a few patients but should be considered as an option in such a case. Evidence for this comes from a few retrospective studies in which eradication of liver metastases from soft tissue sarcoma was performed using TACE or SIRT. Patients treated in this way showed a median overall survival of 21-30 months with good tolerability of the method [538]. More favorable results are reported when performing SIRT for liver metastases in GIST with a median overall survival of 29.8 months and a hepatic PFS of 15.9 months [537].

7.5. Supportive measures

Regarding supportive therapy, reference is made to the S3 guidelines „Supportive therapy in oncological patients“, version 1.3, 2020, AWMF registry number: 032/054OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/supportive-therapie/ [539] and „Early detection, diagnosis, therapy and follow-up of breast carcinoma“, version 4.3, 2020 AWMF registry number: 032-045OL, http://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/ [74]. These are illustrated there in detail.

Special features of supportive therapy in the treatment of soft tissue sarcomas are discussed below.

Addition to moderate emetogenic drug tumor therapy:

Carboplatin, which is only occasionally used to treat soft tissue sarcomas, is among the most potent agents in the moderately emetogenic risk group. Several studies have shown the benefit of 3-fold antiemesis with 5-HT3-RA / NK1-RA / dexamethasone [540], [541], [542]. The updated MASCC/ESMO guidelines [543] therefore recommend prophylaxis with an additional NK1-RA during carboplatin-containing chemotherapy.

7.5.1. Supportive therapy for trabectedin therapy

Trabectedin [498], approved by the EMA since 2007 as a 24-hour infusion (1.5 mg/m2 body surface area), is mainly metabolized hepatically, involving the cytochrome 3A4 system. Therefore, parallel use of potential inhibitors of this enzyme complex (e.g., aprepitant, ritonavir) or cytochrome 3A4 inducers (e.g., rifampicin, phenobarbital, or St. John's wort) should be avoided, as this may lead to additional hepatotoxicity [544], [545]. Studies included patients with renal insufficiency (creatinine clearance < 30 ml/min for monotherapy and < 60 ml/min for combination therapy). Based on pharmacokinetic characteristics, renal elimination of trabectedin plays a minor role, which is why patients on hemodialysis can also be treated with trabectedin [546].

Jordan et al. [547] comprehensively describe supportive strategies in the management of trabectedin.

7.5.1.1. Hepatotoxicity

7.17	Consensus-based Recommendation
EC	With trabectedin, special attention should be paid to concomitant medications.
	Strong Consensus

Background

Phase II studies have reported that trabectedin treatment is regularly associated with an increase in transaminases as well as bilirubin and alkaline phosphatase [548], [549]. The elevation of liver enzymes is usually reversible and not associated with clinically relevant liver dysfunction [550]. Clinical data suggest that pretreatment with

high-dose dexamethasone does not affect trabectedin efficacy, but may protect against trabectedin-induced liver toxicity [551]. According to the EMA approval [552], [553], it is recommended that all patients receive 20 mg of dexamethasone intravenously 30 minutes prior to trabectedin administration.

7.5.1.2. Neutropenia

One of the main side effects of trabectedin during clinical trials is myelosuppression, especially neutropenia. The incidence of all grades of neutropenia varies from 24 to 100 % [551], [554]. The risk of febrile neutropenia varies from 6 to 9 %. According to the national guidelines of the AGIHO (Working Group on Infections in Hematology and Oncology) [555], prophylactic use of G-CSF is recommended only at a risk of febrile neutropenia > 20 %, which is why prophylactic use is not routinely part of the supportive treatment plan in trabectedin monotherapy [554].

7.5.1.3. Nausea and vomiting

Until now, trabectedin is not classified within the emetic risk groups by the national and international guidelines [74], [539], [543]. The incidence of grade III / IV emesis was 9 % in the study by Le Cesne [548]. Because antiemetic prophylaxis is given in most studies, antiemetic risk classification is complicated because it should be done without the use of antiemesis [556]. To date, trabectedin is considered to be moderately emetogenic. Since dexamethasone is already used by default to prevent hepatotoxicity, it is recommended to administer 20 mg of dexamethasone 30 minutes before administration of trabectedin. To prevent the delayed phase of nausea and vomiting, 8 mg of dexamethasone should be given on each of days 2 and 3, according to the guidelines [74], [539], [557]. A 5HT3 receptor antagonist may be used alternatively.

The antiemetic aprepitant, an NK1 receptor antagonist, is metabolized by cytochrome P450 (ZYP 3A4) [558]. The drug represents a moderate inhibitor and inducer of ZYP 3A4 and should be used very cautiously in patients receiving trabectedin for soft tissue sarcoma therapy.

7.5.1.4. Extravasate

After reviewing the guidelines, trabectedin is classified as „Vesican“ according to the national guideline [539] and ASORS expert recommendations [559]. Trabectedin must be administered through a CVC to reduce the risk of extravasation. If extravasation occurs, the infusion must be stopped, aspiration should occur, followed by removal of the cannula [559]. A specific antidote does not exist. The use of sodium thiosulfate is controversial [559], if necessary, a surgeon should be consulted early, especially if there is pain at the extravasation site.

7.5.2. Prophylaxis of ifosfamide-induced encephalopathy.

Ifosfamide-induced encephalopathy is a significant problem in patients receiving high doses of the drug alone or in combination [560], [561]. Ifosfamide represents one of the active agents for the treatment of soft tissue sarcoma. In 10-50% of cases treated with ifosfamide, symptoms such as fatigue, somnolence, tremor, aphasia, auditory or visual hallucinations, and epileptic seizures occur [562]. In 1994, methylene blue was first published for the prophylaxis and treatment of ifosfamide-induced encephalopathy by Küpfer et al. [562]. In 2004, Kasper et al. [563] published the successful prophylaxis of ifosfamide-induced encephalopathy with methylene blue. This was an off-label use. Already on the day before, 50 mg of methylene blue were to be

administered i.v. once, on the days of the ifosfamide treatment then 3 x daily. Accompanying thiamine (3 x 100 mg i.v.) was administered and hydration was done with 3 l of a 5% glucose solution [564].

8. Rehabilitation and aftercare

8.1. Follow-up in localized and metastatic stage

8.1	Consensus-based Recommendation
EC	The follow-up plan for soft tissue sarcoma patients shall be determined by or in coordination with a certified sarcoma center or associated cooperation partner*. * For specific subgroups such as DFSP/angiosarcoma/Kaposi's sarcoma, reference shall be made to the guidelines of the professional societies.
	Consensus

Background

This strong recommendation for the follow-up of soft tissue sarcoma patients resulted from the review of the criteria of the Evidence to Decision (EtD) frameworks. The outcome of the review justifies the level of recommendation and sets out the balance of benefits and harms. The required decision making is structured and transparent.

Soft tissue sarcomas are rare diseases. The expertise to follow up patients is available at a certified sarcoma center. Sarcoma center certification has only been in place since 2018, so evidence in this area is not yet available and is the content of current research.

The benefit of follow-up per se and follow-up at or in coordination with the certified sarcoma center is for early detection of recurrence or metastases. Professional expertise is very high in all diagnostic and therapeutic areas.

Reactions from patients from Das Lebenshaus (now the German Sarcoma Foundation) show that they feel better off at a center. An uncontrolled follow-up close to home, especially if the sarcoma center is far away, leads to uncertainty for patients with such a rare disease.

The resource requirements are the same as for risk-adapted follow-up of other cancers. A long journey is accepted by the patients. It is cost-efficient, since imaging is evaluated on-site and, if necessary, further diagnostic/therapeutic measures can be agreed immediately in a personal discussion with the patient. Travel costs have a limited impact. Incorrect evaluation of radiological or clinical findings can lead to misjudgments, delays in therapy, or require diagnostic/therapeutic measures which would otherwise be unnecessary. This leads to a higher consumption of resources.

Therefore, the follow-up plan for soft tissue sarcoma patients should be determined by or in coordination with a certified sarcoma center or associated cooperation partner.

8.1.1. Timing of the follow-up examinations

8.2	Consensus-based Statement
EC	During follow-up after local therapy of highly malignant sarcomas, frequent control intervals (3 months) should be observed in the first 2 years after completion of therapy, since the probability of recurrence or metastasis is highest during this period.
	Strong Consensus

Background

The evidence base regarding the implementation and design of follow-up for soft tissue sarcomas is insufficient. Accordingly, there is a significant heterogeneity between the follow-up strategies in clinical practice [565], [566]. Regular follow-up examinations following a successful tumor resection serve to detect local recurrences and/or metastases at an early stage in order to deliver necessary therapy to improve the overall prognosis [567], [568], [569].

Tumor entity, tumor size and localization, and histologic grading have a major impact on the local recurrence rate and metastatic behavior of soft tissue sarcomas, especially when combined. In this regard, histologic grading is of major importance in the vast majority of different entities [112], [134], [135], [567], [570]. This should be taken into account when planning follow-up.

The wide diversity of tumor entities is problematic for establishing a general recommendation [567]. Local recurrences typically occur within the first two years after tumor resection, but in certain tumor entities (Atypical lipomatous tumor /G1 liposarcoma) it may occur even after >5 years. Retrospective analyses suggest a limitation of the follow-up period to 10 years, but late recurrences/metastases may also be observed after more than 15 years in individual entities [571], [572].

Adaptations are also required with regard to the body regions to be monitored. Thus, myxoid liposarcomas tend to osseous and soft tissue metastases. Accordingly, in addition to an MRI of the affected region, an MRI examination of the neighboring regions, especially in the lymphatic drainage area should be performed [573].

Besides a few retrospective studies, only one prospective randomized study is available. However, this study could not prove the non-inferiority of planned follow-up examinations at an interval of 6 months compared to 3 months in the first 2 years after surgical resection therapy [574].

Table 17: Well differentiated sarcomas (low-grade according to FNCLCC [113])

Year 1and 2	Year 3 to 5	From year 6
Interval: 3-6 months Physical examination Imaging: Tumor region (kmMRI) Lung (low-dose CT)	Interval: 6 months Physical examination Imaging: Tumor region (kmMRI) Lung (low-dose CT)	Interval: 12 months Physical examination Imaging: Tumor region (kmMRI) Lung (low-dose CT)

Table 18: Poorly differentiated sarcomas (high grade according to FNCLCC [113])

Year 1 and 2	Year 3 to 5	From year 6
Interval: 3 months Physical examination Imaging: Tumor region (kmMRI) Lung (low-dose CT)	Interval: 6 months Physical examination Imaging: Tumor region (kmMRI) Lung (low-dose CT)	Interval: 12 months Physical examination Imaging: Tumor region (kmMRI) Lung (low-dose CT)

8.1.1.1. Retroperitoneal sarcomas

8.3	Consensus-based Recommendation
EC	For G2 and G3 retroperitoneal soft tissue sarcomas, follow-up should be every 3 months for the first 2 years as for other highly malignant sarcomas. For G1 liposarcomas, intervals of 6 months are recommended because of the more favorable tumor biology.
	Strong Consensus

8.4	Consensus-based Recommendation
EC	In cases of retroperitoneal sarcoma, anticipated artifacts in the study area, or if there are reasons not to undergo MRI, contrast-enhanced CT should be performed.
	Strong Consensus

Background

Follow-up of retroperitoneal sarcomas should follow the plan of high-grade sarcomas regardless of their grading [247]. In retroperitoneal sarcomas, the main focus is on the detection of locoregional recurrence and, in dedifferentiated liposarcomas, on the detection of a de novo second tumor. Because of the anatomic changes that occur as a result of multivisceral resection, abdominal MRI is the best possible technique for

delineating anatomic structures. If artifacts are expected in the study area (e.g., after prosthesis implantation), or if there are reasons not to perform MRI, contrast-enhanced computed tomography should be performed [575], [576]. A condition after nephrectomy in the context of the preceding tumor resection can become problematic here. If CT can be performed despite this, oral contrast is indicated not with i.v.

For the detection of local recurrences after surgical therapy of RPS, the patient's self-perception plays a lesser role. However, descriptions of newly occurring disturbances in sensitivity, e.g. in the femoral nerve region, could raise suspicion.

8.1.2. Clinical examination and instrumental diagnostics

8.1.2.1. Medical history and physical examination

8.5	Consensus-based Recommendation
EC	For the detection of local recurrences after surgical therapy of extremity sarcomas, self-awareness of the patients plays a special role. Patients with these tumor localizations should therefore be advised to perform self-examination and taught what to look for.
	Strong Consensus

Background

In addition to the assessment of the general condition, the detailed questioning of the patient's memory should particularly look for signs of recurrent tumor growth or indications of metastases. Descriptions of nonspecific musculoskeletal complaints, or in special cases circumscribed disturbances of motor function or sensibility, may raise suspicion [568], [569].

Local physical examination in the area of the original primary tumor should identify newly occurring space-occupying processes. Here, attention must also be paid to possible consequences of radiation therapy. Also, the draining lymphatic nodes should be examined for abnormalities.

Retrospective studies showed that the vast majority of tumor recurrences were first detected by the patient themself, between scheduled follow-up appointments, as a newly occurring mass [567], [574].

8.1.2.2. Imaging examinations

8.6	Consensus-based Statement
EC	In the follow-up of soft tissue sarcomas of the extremities, contrast-enhanced magnetic resonance imaging is the method of choice.
	Strong Consensus

8.7	Consensus-based Recommendation
EC	In the detection of pulmonary metastases after primary therapy of sarcomas, clinical symptoms do not play a relevant role. Therefore, patients at significant risk for pulmonary metastasis shall undergo image-based follow-up (CT or chest X-ray).
	Consensus

Background

In the diagnosis of soft tissue sarcomas of the extremities, contrast-enhanced magnetic resonance imaging is considered the method of choice [575], [576] and in follow-up imaging is valid in differentiating postoperative conditions from tumor regrowth [569], [574]. MR tomographic imaging allows differentiation between scarring and tumor recurrence in follow-up and coarse assessment when the previous findings are known and therapies performed are included [577]. In nonmyxoid tumors, diffusion weighting can improve the detection of tumor recurrence [578].

Regular imaging of the lung, as the primary metastatic site of soft tissue sarcomas, is mandatory. There is no clear recommendation on the preference of CT examination over conventional X-ray radiography in two planes. However, if CT provides additional information, the higher radiation exposure must be put into perspective [574]. Various working groups were able to show in individual retrospective observations that conventional imaging is not inferior to CT diagnostics and can be evaluated as adequate considering the costs, the false-positive findings and also the radiation exposure in the follow-up [567], [569], [579], [580]. Also the only available prospective study on follow-up by Puri et al. from 2014 with 500 included patients could not prove an advantage of CT over conventional chest imaging [574]. With significantly reduced radiation exposure and yet comprehensive image information, low-dose CT of the thorax offers the preferred alternative to conventional X-ray examination in the overall context.

8.1.2.3. Laboratory diagnostics

8.8	Consensus-based Recommendation
EC	Standardized laboratory chemistry testing during follow-up shall not be performed.
	Strong Consensus

8.9	Consensus-based Recommendation
EC	If chemotherapies have been used, laboratory chemistry tests should be performed during follow-up (see S3 Guideline Supportive Therapy in Oncology Patients, Chapters 3+4).
	Strong Consensus

Background

However, in the case of neoadjuvant or adjuvant chemotherapies, extended follow-up should look for signs of organ toxicity and consequent dysfunction (see also S3 guideline Supportive Therapy in Oncology Patients, https://www.leitlinienprogramm-onkologie.de/leitlinien/supportive-therapie/ [539].

8.1.3. Follow-up in the metastasized stage

8.10	Consensus-based Recommendation
EC	In the metastatic, or locally recurrent stage, after R0/1 resection, the follow-up strategy should be the same as that in the localized stage.
	Strong Consensus

8.11	Consensus-based Recommendation
EC	Follow-up of patients with metastatic soft tissue sarcomas who cannot be treated with curative therapy should be based on the detection of tumor progression and the indication for further local or drug therapies or supportive therapy (see also section 9.3).
	Strong Consensus

Background

In this context, the resection of the metastasis/recurrence should be compared with the initial diagnosis or the first complete resection of the primary tumor when planning the examination intervals.

Patients should be included in palliative care with the goal of symptom control according to the extended S3 guideline „Palliative care for patients with non-curable cancer“, version 2.2, 2020, AWMF registry number: 128/001OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin [581]).

Regarding supportive therapy, reference is made to the S3 guidelines „Supportive therapy in oncology patients“, version 1.3, 2020, AWMF Registry Number: 032/054OL.

8.2. Medical rehabilitation

Medical rehabilitation serves the treatment of disease and therapy-related secondary disorders in order to regain an active lifestyle and professional, private and social participation. In addition to targeted multimodal approaches for individual sequelae, the aim is to improve the patients' quality of life, their ability to cope with the disease and the acceptance of possible permanent limitations is to be supported.

8.12	Consensus-based Recommendation
EC	After completion of primary therapy, follow-up rehabilitation shall be offered to all patients capable of rehabilitation.
	Consensus

8.13	Consensus-based Recommendation
EC	Medical rehabilitation should be performed in an oncological rehabilitation facility, taking into account functional disorder with any orthopedic focus (e.g., after resection of an extremity sarcoma).
	Consensus

8.14	Consensus-based Recommendation
EC	If symptoms persist, patients should be informed about the possibility of further rehabilitation measures.
	Strong Consensus

Background

Oncological patients are entitled to medical rehabilitation services as stipulated in Book IX of the Social Code (SGB IX). These measures aim to promote the patients' self-determination and their equal participation in life and society, to avoid disadvantages or to counteract them [582].

The need for rehabilitation services always exists when there is a tumor- or therapy-related functional restriction that is a permanent impairment in daily life. The patient is considered fit for rehabilitation if his or her physical and mental condition (e.g., ability to cope with stress, motivation or motivability) is sufficient for participation in a rehabilitation service.

Rehabilitation services can be provided as follow-up rehabilitation directly after completion of inpatient or outpatient primary treatment. In this case, follow-up rehabilitation is initiated by the last treating physician or social service of the last treating clinic; follow-up rehabilitation is carried out in special rehabilitation facilities suitable for this purpose [583]. If serious functional disorders persist, further rehabilitation services can be claimed. For this purpose, an application must be submitted to the responsible cost unit.

The cost units for oncological rehabilitation are, in addition to the German Pension Insurance, also health insurance funds, employers' liability insurance associations or other social insurance providers. The legal basis for this can be found in the SGB V in the case of the GKV or in the SGB VI in the case of the DRV.

Requirements for the structural, process and outcome quality of oncological rehabilitation have been formulated by the Federal Working Group for Rehabilitation (BAR) and the German Pension Insurance (DRV) and are regularly monitored in an elaborate external quality management process [584], [585], [586].

The requirement profiles for rehabilitation facilities are sensibly based on the more common cancers (breast, colon, prostate, lung cancer). Patients with soft tissue sarcomas are typically not addressed with specific rehabilitation offers. In order to address the special sarcoma problems, it may be necessary to deviate from the usual routines of assigning patients to rehabilitation clinics.

Due to the very complex and variable pattern of limitations in patients with adult soft tissue sarcoma, an interdisciplinary and multimodal approach to rehabilitation is essential. For example, in cases of specific orthopedic dysfunction which may be an outcome for patients with extremity sarcoma, the selection of a suitable oncology clinic with an additional orthopedic focus may be appropriate. A study of 728 patients with extremity sarcoma showed that early functional rehabilitation resulted in significantly improved oncologic outcome (OR 0.5, CI 0.3-0.9) [587].

According to current framework agreements, medical rehabilitation must always be oriented to a comprehensive bio-psychosocial model of disease, which is based on the International Classification of Functioning, Disability and Health (ICF) of the World Health Organization (WHO) [588]. In this model, a patient is viewed as an individual, recognising contextual factors, and the disease, as well as its consequences. These are understood together with mutually influencing somatic, psychological and social factors.

In addition to the individual rehabilitation goals based on the criteria of the ICF, the objectives of oncological rehabilitation in patients with adult soft tissue sarcoma generally include the following:

- Diagnosis and treatment of disease and therapy-related sequelae.
- Preservation or restoration of physical and mental capacity
- Preservation or re-enablement of participation in normal social life and,
- if the patient is still at work, maintenance or restoration of earning capacity.

Patients with adult soft tissue sarcoma have limitations, depending on tumor location and type of primary intervention, predominantly due to musculo-skeletal problems. For example, patients with extremity sarcoma have significantly reduced physical activity compared with their age cohort, even in the long term, as shown in a systematic review by Kwong et. al. [589. Authors of a data analysis of the Childhood Cancer Survivor Study (CCSS) [590] concluded that there is a need for rehabilitation services and, in particular, exercise-based therapy services.

A review by Gerrand and Furtado shows that a relevant proportion of sarcoma patients also suffer from various other sequelae in addition to musculoskeletal limitations: 28 % of patients report severe tumor-associated exhaustion (fatigue), almost all patients report pain (9.5 % of it severe), about one third suffers from lymphedema; a large proportion of up to 77 % of patients show long-term psychosocial problems such as depression, social withdrawal or sexual dysfunction, which also results in a need for rehabilitation. The authors conclude that ICF-based multidisciplinary rehabilitation enables patients to achieve normalization of physical and psychosocial function, as well as participation, and should therefore be started early [591].

Medical rehabilitation in patients with adult soft tissue sarcoma

8.15	Evidence-based Recommendation
GoR **B**	Patients with soft tissue sarcoma should be offered early systematic exercise therapy.
LoE ⊕⊖⊖⊖ ⊕⊖⊖⊖ ⊕⊖⊖⊖	⊕⊖⊖⊖: Overall survival (median follow-up: 140 months SRAS, 40 months ERAS). ⊕⊖⊖⊖: Risk of local recurrence (median follow-up: 140 months SRAS, 40 months ERAS). ⊕⊖⊖⊖: Overall morbidity (median follow-up: 140 months SRAS, 40 months ERAS).
	Strong Consensus

Background

A comparative study by Michot et al. demonstrated the benefit of early systematic exercise therapy and rehabilitation treatment on wound healing, number of hospital days, and functional outcome for patients with adult soft tissue sarcoma [592].

Unfortunately, further systematic evidence on the effect of rehabilitation treatment is not available for this small patient population.

However, a general literature search on oncological rehabilitation, or on individual therapeutic modalities used in rehabilitation, such as exercise and sports therapy, shows overarching positive effects, or positive effects proven for other oncological entities, from which a benefit of rehabilitation can also be at least inferred for patients with soft tissue sarcoma. Thus, it has been shown that oncological patients benefit from physical training at every stage of therapy in terms of quality of life, function, and activity, and sequelae such as tumor-related fatigue symptoms could be improved [593], [594], [595]. For patients with osteosarcoma, it has been shown that their subjective quality of life depends less on the surgical approach and more on the functional outcome achieved [596] and that functional improvements can be achieved by rehabilitation treatment [597], [598], [599].

9. Psychooncological and psychosocial aspects, palliative care

9.1. Psycho-oncological aspects

The following recommendation was adopted from the S3 guideline „Psycho-oncological diagnosis, counseling and treatment of adult cancer patients", https://www.leitlinienprogramm-onkologie.de/leitlinien/psychoonkologie/ [600]:

9.1	Consensus-based Recommendation
EC	All patients shall receive screening for psychosocial distress. Psycho-oncological screening should be performed as early as possible at appropriate intervals, when clinically indicated, or repeated during the course of the disease if a patient's disease status changes (e.g., recurrence or progression of the disease).
	Consensus

9.2	Consensus-based Recommendation
EC	Regardless of the reported psychosocial distress, psychological, social, and spiritual needs shall be assessed in all patients with adult soft tissue sarcoma.
	Consensus

9.3	Consensus-based Recommendation
EC	Patients with adult soft tissue sarcoma and their relatives shall be informed about inpatient and outpatient psychosocial and psychotherapeutic services regarding content, scope and access at the primary treating oncology center.
	Strong Consensus

9.4	Consensus-based Recommendation
EC	There should be regular exchange between medical therapists and psycho-oncologists in the multidisciplinary team.
	Consensus

Background

The use of a psycho-oncological screening instrument should be performed as early as possible and repeated at appropriate intervals if clinically indicated or if the disease status of the patients changes (e.g. recurrence or progression of the disease).

Standardized and validated screening procedures should be used [601] (cf. S3 Guideline Psycho-oncology, Chapter 7.3.1). In case of a positive result of a screening and/or patient request, a diagnostic interview to clarify psychosocial stress and psychological comorbidity should take place.

Psychological, social and spiritual aspects and their impact on patient function, are summarized in the term quality of life. The recording of quality of life as a patient-relevant outcome parameter is becoming increasingly important in medical and health science care and research [602], [603], [604]. The EORTC recommends a complementary survey of quality of life [605]: generic instruments, entity-specific instruments, and, if necessary, supplementary individual items (e.g., from the EORTC Item Library) [606] for symptom domains not previously mapped. Generic aspects can be collected using FACT-G or EORTC QLQ-C30.

For sarcoma diseases, no entity-specific survey instrument exists so far, which makes a valid quality-of-life measurement in care as well as an endpoint in scientific activities very difficult. A sarcoma-specific quality of life module for complementary use with the EORTC QLQ-C30 is currently being developed in a collaboration between the EORTC Quality of Life Group and the Soft Tissue and Bone Sarcoma Group.

Every patient must be offered the possibility of counseling by social services and psycho-oncology in all phases of the disease in a local and timely manner, proof is required. In the survey form „Sarcoma Center - Module in the Oncological Center of the German Cancer Society" [607] it is referred with regard to psycho-oncology under 1.4.1 and social work under 1.5.1 that the „requirements of the survey form Oncological Centers" are to be fulfilled. For social work, the expert standard "Psychosocial initial counseling of oncological patients by social work in inpatient care (PEOPSA)" [608], [609] should be applied as soon as it is adopted. Preparing outpatient follow-up care by outpatient psycho-oncology service providers is stated under 1.4.7 in the task profile of psycho-oncology in the survey form for Oncology Centers of Excellence and Oncology Centers [610].

The special situation of patients in and after treatment for soft tissue sarcoma is characterized in detail in Recommendation 9.6. The background text on psychosocial counseling must be taken into account when describing outpatient psychosocial and psychotherapeutic services at the center.

Because of the rarity of the disease, patients with adult soft tissue sarcomas often experience delayed initiation of treatment, mismanagement of diagnosis, or primary mistreatment [611], [612]. At the same time, it is often difficult for them - even in the medical system - to obtain adequate information. The feelings of uncertainty, helplessness or mistrust that may result from this can make it difficult to build relationships between patients and therapists in centers. This should be given special consideration by medical therapists and reflected in interdisciplinary exchange with psycho-oncologists.

9.2. Psychosocial aspects

9.5	Consensus-based Recommendation
EC	All patients with high psychosocial distress and adult soft tissue sarcoma shall have the option of psychosocial support during their treatment.
	Strong Consensus

9.6	Consensus-based Recommendation
EC	Patients with high psychosocial stress shall have access to continuous outpatient psychotherapeutic support and treatment close to home, even during long courses of the disease. This should include exchange of information with the in-patient therapists in the oncology center.
	Consensus

9.7	Consensus-based Recommendation
EC	All patients with adult soft tissue sarcoma shall be informed about networking opportunities in self-help/patient groups. Due to the rarity of the disease there should be special consideration of internet-based information and support opportunities.
	Consensus

Background

The rarity of the disease dictates that primary treatment of patients is either local with subsequent presentation to a sarcoma center or primary at a specialized center. These are often located far from the patient's home. Although psychosocial distress tends to be highest at the time of diagnosis and primary treatment, a similar proportion of patients show relevant signs of psychosocial distress such as depression, (progression) anxiety, and distress even after a long disease-free survival [591], [611], [612], [613], [614], [615], [616], [617]. After therapeutic measures that are typically very intrusive and can be functionally restrictive for patients with soft tissue sarcoma, reintegration into everyday life and the limitations experienced due to disease and therapy consequences, can also threaten self-esteem and confidence. [618]. Serious problems with body image and mobility limitations, especially after sarcomas localized to the extremities (about 70% of cases), can lead to avoidant coping strategies and to social isolation with negative effects on quality of life [619].

Therefore, even after the primary treatment in the specialized center - which offers psychosocial services - patients under great stress should be able to receive outpatient psychotherapeutic treatment close to home. This can address the protracted problems mentioned above and provide help in finding personal solutions. The same applies to any problems in family relationships that may become apparent in this phase of the disease.

In the case of repeated treatment following tumor recurrence, a familiar contact person close to home is helpful ensuring sufficient support for the considerable stresses and strains then experienced and the process of adjustment that is once again required.

Due to the rarity of their diagnoses, patients with „Rare Cancer“ often rely heavily on additional support. Here, contact with a patient/self-help group can be very helpful. The organizations active in Germany (e.g. German Sarcoma Foundation (formerly Das Lebenshaus), SOS Desmoid and others) are well connected with certified sarcoma centers and associated cooperation partners. Additionally, there are often connections to patient organizations in other countries.

Patient/self-help groups usually offer free counseling as well as information and assistance to affected persons, carers and companions (relatives).

These groups can help patients find their way to specialized centers as early as possible and help them better understand their disease and treatment options. Knowledge about available clinical studies and special therapy options can also be conveyed, using plain language information rather than medical terms. Often, contact with a patient/self-help group also facilitates open discussion with other affected individuals and the solidarity from such association gives the important feeling of not being alone with a rare disease.

However, experience has shown that the use of non-quality-assured services (online groups, websites, forums, chats, etc.) can also lead to greater uncertainty and spreads disinformation among patients. Therefore, only references to quality-assured self-help/networking offers should be given.

Two essential offers for sarcoma patients in Germany should be emphasized here:

GIST/Sarcoma - www.sarkome.de - the non-profit German Sarcoma Foundation.

The „patient range“ of the Foundation is the successor of Das Lebenshaus, formed in 2003 as the registered association for GIST/Sarkome. The German Sarcoma Foundation is „a Mitmach organization“, in which patients, and all professions involved in the diagnostics and therapy co-operate. The Foundation also has a focus on sarcoma research, which has received too little funding to date, and it is committed to improving the quality of care/treatment.

Desmoide - www.sos-desmoid.de - The self-help organization „sos-desmoid e. V.“

offers people with a desmoid (aggressive fibromatosis) and their relatives support and guidance during the course of the disease, as well as information about desmoids to anyone interested.

Both organizations are members of the international network of all GIST/sarcoma and desmoid patient organizations - Sarcoma Patients EuroNet e.V. (www.sarcoma-patients.eu), founded in 2009.

9.3. Palliative care

9.8	Consensus-based Recommendation
EC	All patients with metastatic adult soft tissue sarcoma shall have easy access to information about palliative care, regardless of disease stage.
	Strong Consensus

The following recommendation is adapted from the expanded S3 guideline „Palliative Care for Patients with Noncurable Cancer" Version 2.2, September 2020, https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/ [581]:

9.9	Evidence-based Recommendation
GoR A	All patients shall be offered palliative care after a diagnosis of non-curable cancer, regardless of whether tumor-specific therapy is used.
LoE 1-	[581]
	Consensus

Background

To date, no entity-specific data are available on the palliative care of patients with metastatic adult soft tissue sarcoma. Therefore, for patients with non-curable adult soft tissue sarcoma, the basic recommendations for palliative care of patients with non-curable cancer should apply.

In principle, early co-care by general or specialized forms of palliative care integrated into the daily routine of care of oncologic patients can be helpful and effective for patients [620], [621], [622], [623], [624], [625], [626], [627].

The goals here are to inform patients and their relatives about the possibilities and accessibility of specialized palliative care, to integrate physical and/or psychosocial needs not previously identified or considered into the treatment concept, even in preparation for the developing course of the disease. The complexity of the situation should be repeatedly assessed and take into account both patient and family needs using validated multidimensional assessment tools, the patients' functional status, and the phase of illness. Patients more complex needs should receive specialized palliative care (SPV) [620], [621], [622], [623], [624], [625], [626], [627].

10. Specific sarcoma subtypes and localizations.

10.1. Gastrointestinal stromal tumors (GIST)

Surgical therapy

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. Surgical resection in healthy individuals represents the primary curative treatment [628]. R0 resection corresponds to a complete removal of the tumor surrounded on all sides by healthy tissue including a possible puncture channel or biopsy site.

Biopsy

10.1	Consensus-based Recommendation
EC	Preoperative histological confirmation of tumors of the digestive tract with suspected GIST shall be performed for locally advanced tumors that can only be removed by complete resection of the affected organ or by multivisceral resection. In the case of biopsy evidence of locally advanced GIST, the mutational status shall be assessed in light of the predictive value of neoadjunt therapy.
	Strong Consensus

10.2	Consensus-based Recommendation
EC	In locally advanced GIST and evidence of an imatinib-sensitive mutation, neoadjuvant drug therapy with imatinib should be undertaken with the goal of reducing the extent of surgery.
	Strong Consensus

Background

In cases of high level suspicion of GIST and primary resectability without loss of organ function, biopsy need not be mandated. Analogous to the recommendations for sarcomas of the extremities, a tumor size of approximately 3 cm can be applied as a threshold for biopsy, depending on the location.

Histological confirmation is required for tumors with differential diagnosis, e.g., to malignant lymphoma, leiomyosarcoma, or desmoid [629]. Histological confirmation should also be sought in all locally advanced tumors that can only be removed by organ resection (gastrectomy, rectumextirpation) and those tumors whose resection results in functional changes of the GI tract (esophagocardial junction, duodenum, deep rectum).

Despite the fact that GIST are often very soft, fragile tumors that can easily rupture if not managed properly, biopsy backup for advanced GIST has not had a negative impact on patient prognosis [630].

For GIST that can only be removed by organ resection or for which functional changes of the GI tract are foreseeable during resection, preoperative therapy with imatinib should be considered [631]. This is especially true for tumors that require multivisceral resection for resection. In the presence of an imatinib-sensitive mutation, a 6- to 12-month pretreatment can significantly reduce the extent of surgery in almost all patients.

With imatinib-sensitive mutation, tumor regression is usually detectable by CT or MRI after 2-3 months. When tumor response is analyzed by PET, a highly significant reduction in tumor metabolism can be detected as early as 48 hours [632]. Neoadjuvant therapy is typically continued until no further tumor remission can be achieved, meaning that the extent of surgery cannot be further minimized.

A positive side effect of drug pretreatment is that the strong vascularization of GIST disappears. Otherwise, this often necessitates multivisceral resection in order to operate in regions with less blood supply. Gastric loss in particular should be avoided for patients with locoregionally advanced GIST, as adjuvant therapy is compromised by this. Patients with gastrectomy have significantly lower blood levels of imatinib, which may then be in the subtherapeutic range [633]. Limited resection can also be achieved with neoadjuvant therapy in patients with GIST of the Oesophago-gastric junction or rectum and Recto-vaginal septum [634], [635], [636].

GIST of the rectum and spatium rectovaginale

10.3	Consensus-based Recommendation
EC	If neoadjuvant treatment could reduce perioperative morbidity, imatinib shall be pretreated in the case of an imatinib-sensitive mutation.
	Strong Consensus

10.4	Evidence-based Recommendation
GoR **A**	When resecting a primary GIST, an R0 resection shall be achieved. The extent of the safety margin can be less than a 1cm as long as an R0 resection is achieved.
LoE ⊕⊕⊕⊖	[152] ⊕⊕⊕⊖: Local recurrence
	Strong Consensus

10.5	Consensus-based Recommendation
EC	If the location is favorable (stomach, small intestine) and expertise is available, GIST can also be removed minimally invasively. The oncological principles shall be applied in the same way as in conventional open surgery.
	Strong Consensus

10.6	Consensus-based Recommendation
EC	Systematic lymphadenectomy shall not be performed because of the low frequency of lymph node metastases. This excludes patients with SDH-deficient GIST who have clinical suspicion of lymph node involvement.
	Strong Consensus

10.7	Consensus-based Recommendation
EC	Tumor rupture during preparation or retrieval of the specimen shall be avoided.
	Strong Consensus

10.8	Consensus-based Recommendation
EC	In case of R1 resection of GIST and a very low to low risk of tumor recurrence, a „wait-and-see“ strategy can be discussed with the patient.
	Strong Consensus

10.9	Consensus-based Recommendation
EC	GIST of the stomach less than 2 cm in diameter may be monitored regularly by endoscopic ultrasound.
	Strong Consensus

Background

Rectal GIST and GIST of the recto-vaginal septum represent approximately 5 % of all GIST. GIST of the colon outside the rectum are extremely rare. Therefore, therapy should be performed on a case-by-case basis analogous to the therapeutic principles of GIST outlined above [20]. While GIST of the rectum were often radically operated in the era before imatinib, local and function-preserving resections are almost always

possible today after neoadjuvan therapy with imatinib. Single smaller retrospective studies could show a positive effect of neoadjuvant therapy. Prospective randomized data are not available for this rare tumor. The study by Cavnar et al. showed that even with positive resection margins after local function-preserving resection, no local recurrences occurred if perioperative therapy with imatinib was given [637], [638].

Resection is indicated for GIST with tumor size of 2 cm or more (with the exception of the rectum, where smaller GIST even below 2 cm should be removed), as these tumors are at higher risk for metastasis. However, subsequent growth cannot be ruled out even for small GIST. Therefore, even for smaller GIST, resection may be weighed against long-term follow-up. It should be noted that there is only high or low risk in GIST of the rectum. In the AFIP classification based on 111 GIST of the rectum, only tumors less than 5 cm with less than 5 mitoses/5 mm2 have a risk of metastasis of 8.5 %, All other tumors (>5 cm or any tumor size with > 5 mitoses/5 mm2) have a risk of recurrence of 52 % - 71 % [115].

The principle of resection treatment of GIST is guided by achieving tumor-free resection margins (R0). Prospective randomized data on the extent of the safety margin are not available. Complete monobloc R0 resection of GIST is the standard procedure. Because GIST mostly do not show lymphatic or vascular or perineural spread, safety margins of 1 cm in the longitudinal direction are considered sufficient. An analysis by the Scandinavian Sarcoma Group demonstrated that resection with tumor-involved resection margins resulted in significantly less favorable survival (RR 2.4[1.1-4.3], p=0.02) [152].

Any GIST, regardless of tumor size, is potentially malignant. The risk for malignant behavior is influenced by factors such as mitotic rate/5 mm² and mutational status, data that are often not available at primary tumor resection. In this respect, oncologic resection should always be performed.

Enucleation of the tumor has significantly higher recurrence rates. In particular, endoscopic resection in multiple parts leads to R1 resection and high recurrence rates. In such cases, laparoscopic resection is often the procedure more likely to result in R0 resection.

For gastric GIST, wedge resection or segmental resection is the treatment of choice; GIST of the small bowel are adequately treated by segmental resection.

Especially for gastric GIST and those of the small bowel, minimally invasive approaches (laparoscopy, robotic-assisted) can also be considered for resection. There are many reports, including comparative studies, on laparoscopic resection, especially of GIST of the stomach. The studies all show a very favorable perioperative course and R0 resection rates comparable to access by laparotomy. However, few long-term data are available for the mostly small tumors in the published series [639], [640].

Laparoscopic resection is not recommended for larger tumors with the risk of tumor rupture.

Systematic lymphadenectomy is not necessary due to the low frequency of lymph node metastases (less than 1%). Only in the rare SDH-deficient GIST, which occurs mainly in pediatric patients and young adults with Carney-Stratakis syndrome or a familial mutation, is the lymph node metastasis rate higher [641]. Lymph node dissection should then be discussed and also performed if the lymph nodes are abnormal.

R0 resection during primary surgery is the most important prognostic factor for local tumor control - besides mitotic index, tumor size, tumor location (gastric vs. non-gastric) and tumor rupture [116], [642]. Macroscopic incomplete resection (R2) of a GIST primary tumor has the least favorable prognosis. Intraoperative tumor rupture with contamination of the abdominal cavity by vital tumor cells also falls into this category. Without drug therapy, almost all patients suffer tumor recurrence [643], [644]. Patients with tumour rupture should be treated as for metastatic disease, i.e. continuous drug therapy depending on the mutation status.

In the risk classification of Joensuu [116], which best reflects the tumor biological aspects, but also in the classification of Rutkowski [643], tumor rupture is represented with its own risk classification. Therefore, intraoperative tumor rupture should be avoided under all circumstances. This necessitates the use of a salvage bag in minimally invasive resection. Conversion of a minimally surgically initiated procedure to an open procedure for safe specimen salvage should be generously considered.

Regarding microscopic incmplete resection (R1), close margins resection, or resection in healthy tissue (R0), there are no clear prospective data for GIST. In large adjuvant therapy trials, R1 resection rates have ranged from 6.5 % [645], 7.3 % [646], and 19 % [647]. Metastasis-free survival is not affected by R0 resection.

In an analysis of 410 patients, including 47 R1 resections and 52 tumor perforations, R1 resection had no unfavorable effect on recurrence-free survival, which was highly significantly negatively affected by tumor rupture [642].

If an R1 situation is found in the frozen section or in the final histology, a re-resection should be performed whenever possible. After R1 resection in the final histology (marginal resection with margin-forming tumor cells), re-resection can be considered if no major functional limitations are expected from the re-resection.“ In the case of R1 resection of a very low to low risk tumor, a wait-and-see „strategy should also be advocated and discussed with the patient [648].

In an analysis of patients with an R1 resection from the US adjuvant Z9001 trial [645] (1 year imatinib vs. placebo), there was no significant difference in recurrence-free survival in the treatment arm with a HR of 1.095 (95% CI 0.66-1.82, p=0.73) and in the placebo arm with a HR of 1.51 (95% CI 0.76-2.99, p=0.24). A systematic review on the impact of R1 resection demonstrated that R1 compared with R0 resection negatively influenced disease-free survival (HR 1.596, 95 % CI 1.128-2.258; I2 = 37.5 %, p = 0.091) [649]. However, an impact on overall survival could not be demonstrated (HR 1.430, 95 % CI 0.608-3.363; I2 = 60.8 %, p = 0.013). It should be taken into account that adjuvant therapy naturally attenuates the recurrence rate.

In this respect, individual consideration is required for re-intervention, as these operations are not always easily performed and the prognostic impact of R1 resection has not been established.

GIST of the stomach with a diameter smaller than 2 cm are very often incidental findings in the course of endoscopy for other reasons, or they are discovered intraoperatively by chance, e.g., in the course of bariatric or gynecologic surgery.

In all risk classifications, these tumors have a minimal risk of metastasis. Small GIST of the stomach can be safely followed up by endoscopic ultrasound at 6-monthly intervals and at annual intervals if the findings are consistent. A biopsy is required if the tumors are continuously growing. A punch biopsy or fine needlebiopsy under

endoscopic control is the method of choice. If the limit of 2 cm is exceeded, resection is the appropriate treatment.

For intraoperative incidental findings of small GIST of the small bowel, resection in healthy tissue is the treatment of choice. Risk classification is based not only on tumor size but also on mitotic rate per 5 mm2. In most cases, this cannot be determined with certainty on a biopsy. Since GIST of the small bowel cannot be reliably monitored by ultrasound or CT with regard to their size progression, they should be resected intraoperatively by an appropriately experienced physician [650].

10.1.1. Pathological diagnostics of GIST

10.1.1.1. Minimum requirements reports

10.10	Consensus-based Recommendation
EC	The diagnosis of gastrointestinal stromal tumor should be established with an immunohistochemical antibody panel in addition to morphologic diagnosis (minimum: CD117, CD34, DOG1, Ki67, SDHB).
	Strong Consensus

10.11	Consensus-based Recommendation
EC	When diagnosing GIST on a resected tumor, R status, primary location, tumor size (largest longitudinal diameter), number of mitoses per 5 mm², and a determination of whether tumor rupture is present shall be included in the pathology report.
	Strong Consensus

Background

More than 90 % of GIST diagnoses can be made when immunohistochemical methods are used [651], [652], [653], [654]. If there is doubt about the diagnosis, further immunohistochemical testing may be necessary to differentiate it from other mesenchymal tumors (e.g., desmin, MDM2, S-100 protein, Sox-10, Melan A). In addition, for the rare equivocal findings, molecular confirmation of findings should be sought or reference pathologic co-evaluation should be performed.

For patients with localized GIST, the location, size, and number of mitoses / 5 mm² represent the most important independent risk factors [115], [655]. There is a consensus that mitoses are counted in 5 mm² instead of 50 HPF. In modern microscopes, this corresponds to about 20 fields of view at 400x magnification (high power fields /HPF).

Complete documentation of risk factors in the pathology report is a prerequisite for correct risk classification using risk tables and contour maps [116], [115], [655]. The first risk classifications used a dichotomous division of mitotic count (≤5 vs. >5 mitoses). This may lead to an overestimation of the risk of metastasis, especially in tumors with mitoses just above 5 per 5 mm², and thus may also cause overtreatment.

The proportion of GIST with mitoses between 6 and 10 mitoses per 5 mm² is about 10 %. Therefore, newer classifications use further gradations, which is why the exact number of mitoses per 5 mm² should always be used for pathological reports and not only the indication of > 5 mitoses.

10.1.1.2. Molecular diagnostics

10.12	Consensus-based Recommendation
EC	Molecular pathologic analysis shall be performed for all GISTs that are at least intermediate risk or for which drug therapy is being considered.
	Strong Consensus

Background

Genotype should be available in all patients, whether localized or metastatic, prior to initiation of drug therapy. This influences dose selection in KIT-mutated GIST [656] and may be a predictor of primary therapy resistance (e.g., PDGFRα D842V mutations or some rare primary exon 17 mutations of KIT) [657], [658], [659]. Exons 9, 11, 13, and 17 of the KIT gene and exons 12, 14, and 18 of the PDGFRA gene will be sequenced. Exon 14 of the KIT gene may also be affected if the tumor has become resistant to therapy [658], [660].

Mutation analyses can also be performed sequentially according to the frequency of affected exons, however, increasingly most GIST are investigated simultaneously in these gene segments using deepsequencing. In typical cases of sporadic GIST without KIT or PDGFRA mutation at initial diagnosis and without evidence of genetic predisposition and (older age of the patient at disease onset, no neurofibromatosis), diagnosis should therefore be performed by deep sequencing to detect mutations with lower allelic frequency. Here, the expertise of reference centers is helpful.

10.13	Consensus-based Recommendation
EC	For patients who do not show mutations in the KIT or PDGFRA gene, further molecular analysis shall be performed to rule out the presence of genetic alterations relevant for treatment.
	Strong Consensus

Background

Patients without evidence of a *KIT* or *PDGFRA mutation* have long been grouped together as „wild-type“ GIST. This term should no longer be used, as it has (incorrectly) subsumed quite different genotypes that are actually well characterized [661].

In cases without evidence of *KIT* or *PDGFRA mutation*, the presence of SDH deficiency, *NF1 mut*ation, *BRAF mut*ation or rare gene fusions must be investigated. There may be a tumorpredisposition syndrome (Carney-Stratakis syndrome, neurofibromatosis, germline mutation in *KIT* or *PDGFRA)* or primary imatinib resistance. In these cases,

referral to specialized reference centers for diagnostics and / or clinical consultation should be made.

10.14	Consensus-based Recommendation
EC	Familial GISTs are diagnosed, among other things, as part of the diagnostic workup for iron deficiency anemia. In people with Carney-Stratakis syndrome, GIST screening can be performed using blood counts at annual intervals.
	Strong Consensus

Background

If SDH deficiency is detected, the possibility of heredity (risk of Carney-Stratakis syndrome) must be considered. This is also true if an NF1 mutation is present (neurofibromatosis) or if other family members have GIST and have an identical genotype.

Intestinal bleeding with development of symptomatic anemia is among the most common symptoms leading to the diagnosis of GIST. Therefore, in individuals with familial GIST syndromes, annual screening by blood counts is performed by individual centers. The value of regular cross-sectional imaging (whole-body MRI) or even gastroscopy must be weighed against the lifetime risk of GIST together with human geneticists and patients [662], [652][663]. Again, linking affected individuals to specialized GIST centers is recommended.

10.1.1.3. Risk classification of localized tumors

10.15	Consensus-based Recommendation
EC	For the treatment decision on postoperative adjuvant therapy with imatinib, a risk classification should be used that includes tumor rupture in addition to primary site, absolute mitotic count/5 mm² and tumor size. In this regard, the modified consensus criteria and contour maps have proven most useful. The TNM classification for GIST has no added clinical value.
	Strong Consensus

Background

For patients with localized tumors, a determination of the risk for metastasis postoperatively should be made during histological examination of the primary tumor. The AFIP classification allows an accurate assignment of a percentage risk of recurrence [663]. However, the dichotomous division of mitotic rates leads to artificial jumps in recurrence risk for mitotic counts around 5/5 mm². The modified criteria of the contour maps with continuous assessment of the mitotic rate have proven useful for discussion with the patient [116]. In addition to a finer division of mitoses, the high prognostic value of tumor rupture is also taken into account. The use of TNM classification cannot be recommended for GIST because the classification is not based on validated data.

To date, mutation status has not been integrated into risk classifications. Nevertheless, distinct natural histories are found in some genotypes. Especially in patients

without KIT or PDGFRA mutations, the peculiar clinical courses (multiple primary tumors, very late metastasis, indolent course) should be considered for patient counseling.

In patients with GIST of the stomach, mutations in exon 11 of KIT leading to deletion of amino acids 557 and 558 appear to be associated with an increased risk of relapse [664], [665], [666].

Table 1 Rates of metastases or tumor related death in GISTs of stomach and small intestine by tumors grouped by mitotic rate and tumor size*

	Tumor parameters		% of patients with progressive disease during long-term follow up and characterization of risk for metastasis			
Group	Size	Mitotic rate	Gastric GISTs	Jejunal and ileal GISTs	Duodenal GISTs	Rectal GISTs
1	≤2 cm	≤5 per 50 HPFs	0 none	0 none	0 none	0 none
2	>2 ≤ 5 cm	≤5 per 50 HPFs	1.9 very low	4.3 low	8.3 low	8.5% low
3a	>5 ≤ 10 cm	≤5 per 50 HPFs	3.6 low	24 moderate		
3b	>10 cm	≤5 per 50 HPFs	12 moderate	52 high	34 high‡	57† high‡
4	≤2 cm	>5 per 50 HPFs	0†	50†	§	54 high
5	>2 ≤ 5 cm	>5 per 50 HPFs	16 moderate	73 high	50 high	52 high
6a	>5 ≤ 10 cm	>5 per 50 HPFs	55 high	85 high		
6b	>10 cm	>5 per 50 HPFs	86 high	90 high	86 high‡	71 high‡

*Based on previously published long-term follow-up studies on 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs.[12,15,18,30]
†Denotes tumor categories with very small numbers of cases.
‡Groups 3a and 3b or 6a and 6b are combined in duodenal and rectal GISTs because of small number of cases.
§No tumors of such category were included in the study. Note that small intestinal and other intestinal GISTs show a markedly worse prognosis in many mitosis and size categories than gastric GISTs.

Figure 3: Risk of metastases and tumor-associated deaths as a function of tumor size, mitotic rate, and location (Miettinen and Lasota [115])

The reference to 50HPF no longer corresponds to today's recommended mitotic rate of 5mm2. For citation reasons, the original data are shown.

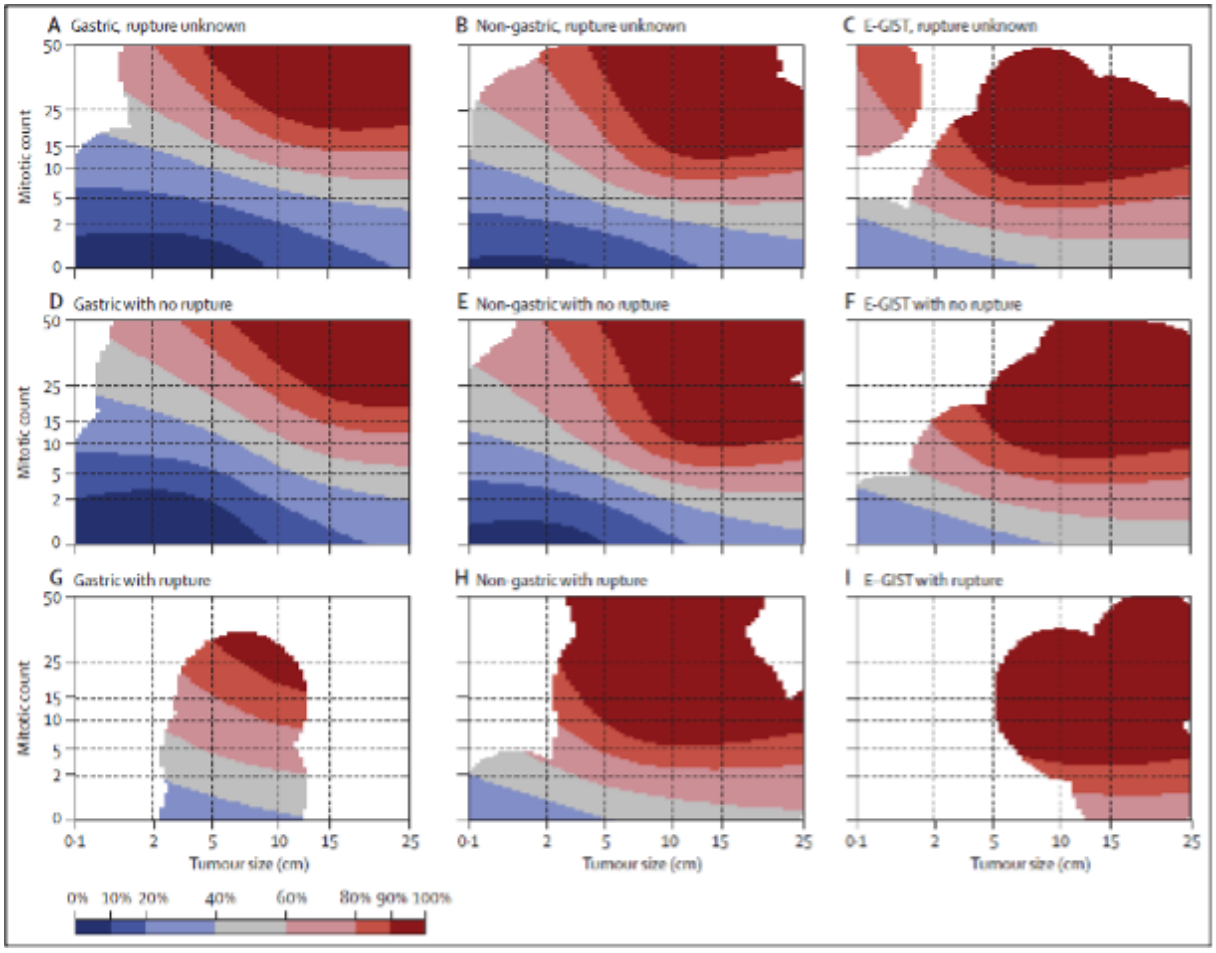

Figure 4: Contour maps to estimate the risk of GIST recurrence after surgery [116]

Top row maps are used when tumor rupture status is unknown (A,B,C), middle row maps when tumor is not ruptured (D,E,F), and bottom row maps when tumor rupture has occurred (G,H,I). Red areas represent high risk, blue areas represent low risk, and white areas indicate missing data. The percentages associated with each color (key) indicate the probability of GIST recurrence within the first 10 years of follow-up after surgery. For example, the middle map left column (D) shows that the 10-year risk of GIST recurrence in a patient diagnosed with a 10-cm gastric GIST with five mitoses per 50 HPFs of microscope and no rupture is 20-40 %. The 10-year risk associated with a similar tumor when the mitotic count is ten per 50 HPF increases to 40-60 %.

E-GIST = GIST arising outside the gastrointestinal tract.

10.1.2. Staging

10.16	Consensus-based Recommendation
EC	For staging GIST of the stomach, small bowel, and rectum, contrast-enhanced CT abdomen or contrast-enhanced MRI abdomen with imaging of the pelvis should be performed. For GIST of the esophagus, a contrast-enhanced CT thorax should also be performed. For GIST of the rectum, additional MRI of the pelvis should be performed for more accurate assessment of local disease extent.
	Strong Consensus

Background

For the diagnosis of spread in GIST, the particular pattern of metastasis should be used as a rationale for the choice of diagnosis. For GIST of the stomach and small bowel, virtually only peritoneal or hepatic metastases are found when metastasis is synchronous at the time of diagnosis. Therefore, contrast-enhanced CT of the abdomen or, as an alternative, MRI of the abdomen are the staging modality of choice. Chest CT may be performed once as part of the diagnosis; however, pulmonary metastases are rare at diagnosis with the exception of rectal GIST. For rectal GIST, MRI should be performed preoperatively to assess operability.

10.1.3. Adjuvant drug therapy of localized, R0 resected GIST.

10.17	Evidence-based Recommendation
GoR A	Patients at significant risk of relapse after primary tumor resection who have an imatinib-sensitive *KIT* or *PDGFRA mutation* in their tumor shall receive adjuvant therapy with imatinib for 3 years.
LoE ⊕⊕⊕⊕ ⊕⊕⊕⊕	[647]; [667] ⊕⊕⊕⊕: Survival (median follow-up: 54 months) ⊕⊕⊕⊕: Recurrence-free survival (median follow-up: 54 months)
	Strong Consensus

10.18	Evidence-based Statement
LoE ⊕⊖⊖⊖ ⊕⊕⊖⊖ ⊕⊕⊖⊖ ⊕⊕⊖⊖ ⊕⊕⊖⊖ ⊕⊕⊖⊖	Patients receiving only year or two years of adjuvant treatment with imatinib after resection of a primary GIST have a benefit only uring the treatment period. No significant impact on overall survival could be demonstrated.
	[645]; [668]; [669]; [670] ⊕⊖⊖⊖: Overall survival (median follow-up: NR) ⊕⊕⊖⊖: Overall survival (median follow-up: 19.7 months) (ACOSOG Z9001 study). ⊕⊕⊖⊖: Overall survival (median follow-up: 74 months) (ACOSOG Z9001 study). ⊕⊕⊖⊖: Recurrence-free survival (median follow-up: 19.7 months) (ACOSOG Z9001 study). ⊕⊕⊖⊖: Recurrence-free survival (median follow-up: 74 months) (ACOSOG Z9001 study). ⊕⊕⊖⊖: Recurrence-free survival (median follow-up: 14 months)
	Strong Consensus

Background

Three randomized trials evaluated the value of adjuvant therapy with imatinib in completely resected GIST. In the Z9001 trial, 359 patients were randomized in a double-blind fashion between 1 year of therapy with imatinib 400 mg and placebo control after complete resection of a GIST 3 cm in diameter or larger [645]. Recurrence-free survival of patients in the treatment arm was significantly improved (HR 0.6, CI 0.43-0.75) while overall survival showed no significant difference.

In the EORTC 62024 trial, 908 patients at intermediate or high risk of relapse were randomized between adjuvant therapy with imatinib 400 mg daily for 24 months versus no therapy, according to NIH Consensus [651]. Recurrence-free survival was found to be significantly better in the treatment arm than in the control group (RR

0.75, CI 0.62-0.91) with a median follow-up of 56.4 months [668]. However, overall survival of patients in the two groups was not significantly different (RR 1.14, CI 0.7-1.84). Considering the two risk groups ‚intermediate' and ‚high', a non-significant trend for better survival was detectable only in the high-risk group.

In the SSG XXVIII-AIO study, 400 patients who were classified in the high-risk group according to NIH Consensus and were macroscopically tumor-free intraoperatively after primary tumor resection were randomized between 1 year of imatinib 400 mg therapy and 3 years of treatment [647]. Significantly better relapse-free survival (HR, 0.46; 95 % CI 0.32-0.65; p<0.001; 5-year RFS, 65.6 % vs. 47.9 %), as well as significantly better overall survival (HR, 0.45; 95 % CI 0.22-0.89; p=0.02; 5-year OS, 92.0 % vs. 81.7 %), were demonstrated in the 3-year treatment arm. The significant survival benefit was also confirmed after a median follow-up of 10 years after randomization [671].

A prerequisite for successful adjuvant therapy is the detection of an imatinib-sensitive mutation in the primary tumor.

Patients with imatinib-sensitive KIT or PDGFRA mutations and a high risk of relapse should receive adjuvant therapy at 400 mg for 3 years. For patients with a KIT exon 9 mutation in the tumor, some centers use a dose of 800 mg/d in analogy to the treatment in the metastatic setting. However, the benefit of higher dosing has not been prospectively demonstrated for adjuvant therapy.

A therapeutic benefit for adjuvant therapy with imatinib has not been demonstrated for patients with SDH-deficient, NF1-mutated, or BRAF-mutated GIST or those without evidence of a mutation and is therefore not indicated.

10.1.4. Clinical management of metastatic GIST

10.19	Evidence-based Statement
LoE ⊕⊕⊖⊖ ⊕⊕⊖⊖	Patients with metastatic GIST and patients with metastasis occurring after completion of adjuvant imatinib therapy should be treated with imatinib. The genotype of the tumor should be available for indication and dosing.
	[672] ⊕⊕⊖⊖: Overall survival (follow-up: 24 months) ⊕⊕⊖⊖: Progression-free survival (follow-up: 24 months)
	Strong Consensus

10.20	Consensus-based Recommendation
EC	Patients with metastatic or unresectable GIST harboring a D842V mutation in the PDGFRA gene should receive therapy with avapritinib at the recommended daily dose of 300 mg.
	Consensus

Background 10.19 and 10.20

Gastrointestinal stromal tumors were often classified as gastrointestinal leiomyomas or leiomyosarcomas until the late 1990s based on immunohistochemical similarities and were also treated with chemotherapy in clinical trials. Retrospective analyses in this regard identify GIST as refractory to classical chemotherapies [673]. Until the introduction of imatinib, there was no effective therapy and the median survival of patients with locally advanced or metastatic disease was 12-18 months [674]. Because of the dramatic clinical benefit of imatinib in phase II trials, a placebo-controlled randomized phase III trial had been omitted. In historical comparisons, median overall patient survival more than tripled with the use of imatinib [675]. The two confirmatory phase III trials therefore compared only two different doses (400 mg vs. 800 mg daily) [675], [676]. A joint analysis of the two trials (META-GIST analysis) showed a median progression-free survival of 1.6 to 2.0 years (p= 0.04) and a median survival in both dose arms of 4 years. Genotype analysis showed a significant benefit for progression-free survival as well as a trend for better overall survival in favor of the 800 mg/d treatment arm only in patients who had a primary mutation in exon 9 of the *KIT gene*.

Therefore, for patients with metastatic GIST without pretreatment or with tumor recurrence after completion of adjuvant therapy, imatinib at a daily dose of 400 mg/d is the standard of care. In the presence of a *KIT* exon 9 mutation, a higher dose (800 mg/d) should be considered.

Given the background of primary imatinib resistance in patients with primary *KIT* exon 17 mutations as well as certain mutations of the *PDGFRA* gene, the results of genotype determination should be available before initiating therapy to avoid ineffective treatment [658], [677]. In cases of urgent treatment indicatio, initiation of therapy without the presence of the genotype may be warranted.

Avapritinib has been approved by the FDA and EMA for patients with a PDGFRA-D842V mutation [678], [679]. All previously approved tyrosine kinase inhibitors are ineffective in this mutation type and thus not indicated. Avapritinib was specifically designed to target the D842V mutation and steric alteration of the PDGFRA receptor and thus is currentlc unique. Patients with a D842V mutation in the primary tumor often have a benign course without metastases. Patients who develop metastasis usually have rapid disease progression and with an urgent need for treatment. Therapy with avapritinib has an objective remission rate of 88% (95 % CI 76-95), with long remission duration, so the median progression-free survival in the NAVIGATOR study has not yet been reached even with a follow-up of 19 months. Of 56 patients, 37 (66 %) were still on therapy [678]. The recommended daily treatment dose is 300mg, and the maximum tolerated daily dose was 400mg. Treatment-associated grade 3-4 toxicity developed in 57% of patients, including anemia (17 %).

Cognitive side effects (cognitive impairment) occur with avapritinib - a first for approved GIST therapies. These patients require close, sensitive, and dedicated side effect management.

To date, only nilotinib has been randomized versus imatinib in first-line treatment. The trial, which was designed to show superiority of nilotinib over imatinib, failed to demonstrate an advantage (median PFS of 26 versus 30 months for imatinib). Nilotinib was ineffective in patients with primary KIT exon 9 mutation; in patients with exon 11 mutation, there was comparable effect to imatinib. The side effect profile for both drugs was similarly favorable. In patients with primary exon 11 mutation and

rare imatinib intolerance, nilotinib represents a treatment alternative. The compound is approved for the treatment of CML (off-label use for GIST).

10.21	Consensus-based Recommendation
EC	Patients with metastatic GIST without a drug-sensitive mutation in the *KIT* or *PDGFRA* gene shall be treated in cooperation with a GIST-experienced center.
	Strong Consensus

Background 10.21

Patients in whom no mutations in the *KIT* or *PDGFRA gene* can be detected require intensive molecular pathological clarification, as many therapeutic implications arise. Here, patients should be treated in cooperation with GIST-experienced centers (centers with high study activity and molecular pathology that has comprehensive diagnostics available).

Different mutations even within the same exon (e.g., *KIT* exon 17 or *PDGFRA* exon 18) can result in resistance to imatinib as well as be imatinib sensitive [658], [677]. Therefore, for the therapeutic decision in these cases, a molecularly adjusted classification of the mutation must be performed, if necessary by a molecular tumor board.

Patients with SDH-deficient GIST not infrequently show an indolent disease course so that a wait-and-see approach regarding active therapy should also be considered initially until clear evidence of progression. The therapeutic benefit of imatinib is also unclear, as imatinib is a moderately potent inhibitor of wild-type KIT, but on the other hand, the oncogenic dependence on KIT seems to be lower in this molecular subgroup [65], [680]. Remissions on imatinib are virtually never observed. Therefore, many centers favor primary treatment with sunitinib when there is a systemic treatment indication.

In very rare cases, typical BRAF mutations (so far exclusively pV600E) are found as the major driver mutation *(KIT* and *PDGFRA* are not mutated). This mutation is predictive of primary imatinib resistance, which is why imatinib is not indicated either in the adjuvant or metastatic setting. Due to the uncoupling of the oncogenic mutation from the KIT receptor, it is also not possible to derive a rationale for other specific KIT inhibitors. A treatment response has been described for a single patient on regorafenib. This is most likely explained by the broad inhibitory profile of regorafenib, which also has activity against BRAF and mutant BRAF. However, because of its high entity-independent efficacy, therapy with a BRAF inhibitor in combination with a MEK inhibitor should primarily be considered here [681], [682]. In other disease entities, the combination results not only in better efficacy but also in better tolerability.

Patients with GIST who have *NTRK fusion* have also been reported. Again, no activating mutation of KIT or the PDGF receptor is then found. In this case, NTRK inhibitors (larotrectinib, entrectinib) should primarily be used according to the licence indication [661], [683].

10.22	Consensus-based Recommendation
EC	To evaluate the response to systemic therapy in patients with GIST, the change in contrast uptake on CT or MRI should be determined in addition to the size of the metastases to detect possible pseudoprogression.
	Strong Consensus

Background 10.22

Patients with hepatic metastatic GIST not infrequently have a similar density in the margins of the metastases as the liver tissue itself. In response to therapy, this may result in demarcation of previously liver-isodense foci, which can be misinterpreted as progression [684], [685]. This pseudoprogression can usually be easily classified as such by a clear decrease in density.

To ensure maximum comparability, changes in diagnostic modalities (from CT to MRI and vice versa) should be avoided.

Positron emission tomography (PET) is a highly sensitive method for assessing response to imatinib [684], however, assessment by CT or MRI is sufficient in the vast majority of cases. In addition, genotype is usually sufficient to predict treatment response (in the first line of therapy).

10.23	Consensus-based Recommendation
EC	A daily dose of 800 mg imatinib should be used in patients with a *KIT* exon 9 mutation.
	Strong Consensus

Background 10.23

Patients with a KIT exon 9 mutation have significantly better progression-free survival (Relative Risk Reduction: 42 %, p=0.017, Wald test) and a significantly higher remission rate (47 % vs. 21 %, p=0.0037) when dosed at 800 mg/d [656]. The META-GIST analysis, which evaluated both phase III trials together, also showed a trend for better overall survival, but statistical significance was not demonstrated. A daily dose of 800 mg is therefore considered the standard for this genotype. Most centers start with a dose of 400 mg and increase to 800 mg imatinib within the first 4-6 weeks because of better tolerability. In case of unacceptable toxicity, the dose can be titrated in 100 mg increments to a dose acceptable to the patient.

10.24	Consensus-based Recommendation
EC	Patients with metastatic disease shall receive therapy with imatinib continuously until progression or development of intolerance.
	Strong Consensus

Background 10.24

The BFR14 trial randomized patients with metastatic GIST on ongoing imatinib therapy (stable disease) to interruption of therapy at one, three, and five years [686]. This demonstrated that regardless of remission status and duration of prior therapy, interruption of imatinib treatment is associated with a very high risk of disease progression. In particular, rapid progression after discontinuation of therapy is associated with poor progression-free survival after resumption of therapy. Therefore, imatinib therapy should be maintained continuously until progression or intolerance develops. Therapy breaks should be kept to a minimum [687].

10.25	Consensus-based Recommendation
EC	In patients with metastatic disease, resection of regressed, residual tumor on imatinib therapy may be offered if macroscopic tumor resection can be achieved with acceptable surgical morbidity. The decision and surgery shall be performed exclusively at GIST-experienced centers.
	Strong Consensus

Background 10.25

A prospective study to test the value of metastasectomy has not yet been successful due to lack of recruitment. Nevertheless, a number of retrospective studies are available that suggest a clinical benefit of resection is likely, but more importantly, also suggest no evidence of harm. Particularly for patients who can be completely resected macroscopically (R0/R1) at the time of treatment response (without evidence of progression), very long progression-free courses can be observed in some cases. Compared with patients who did not undergo surgery, significant survival advantages are found [688], [689], [690], [691]. However, due to the retrospective nature, the influence of selection bias cannot be excluded here, as patients with non-resectable disease may have an increased tumor burden and thus a worse prognosis anyway [692], [693].

The optimal time window for resection is considered to be 6 to 12 months after initiation of therapy with imatinib [688], [694]. In principle, however, the risks of surgery y must be weighed against the patients' chance of achieving long-term tumor control without surgery. Even if a surgically complete resection is achieved, continuation of imatinib treatment postoperatively is required.

Radical surgery in patients with progressive disease should be considered very cautiously [688], [690], [691], [694], [695]. Here, most centers set the goal of symptom relief as a prerequisite for surgery – a prognostic improvement is not expected according to the data available. In the case of focal progression, resection can be considered; a number of cases have been described in which imatinib could be continued for long periods without further evidence of progression [694], [696].

The decision and surgery should be performed at sarcoma centers that have proven GIST experience (regular participation in studies, experience in the sarcoma board, surgical experience).

10.26	Evidence-based Recommendation
GoR A	Patients who do not respond or no longer respond to therapy with imatinib shall receive therapy with sunitinib.
LoE ⊕⊕⊖⊖ ⊕⊕⊖⊖ ⊕⊕⊕⊖ ⊕⊕⊖⊖	[697]; [698] ⊕⊕⊖⊖: Overall survival (median follow-up: 41.7 months) ⊕⊕⊖⊖: Progression-free survival (median follow-up: 41.7 months) ⊕⊕⊕⊖: Overall survival (median follow-up: NR) ⊕⊕⊖⊖: Progression-free survival (Follow up: NR)
	Strong Consensus

Background 10.26

In case of evidence of progression or the rare case of imatinib intolerance, the tyrosine kinase inhibitor sunitinib represents the approved standard therapy. Imatinib intolerance may only be assumed if intensified side effect management has occurred and dose modifications have been made, possibly including plasma level determinations, therapy trial with nilotinib (see above). For these cases, linkage to centers with specialized GIST consultations is also recommended.

In a a phase III trial using a daily dose of 50 mg in a 6-week treatment cycle (4 weeks of therapy followed by 2 weeks off) [697] sunitinib demonstrated a nearly 5-month improvement over placebo, with a median progression-free survival of 6.2 months. There was no survival benefit; however, patients were also allowed to crossover to the treatment arm.

Mucosal and skin toxicity and arterial hypertension represent common and distressing side effects for patients. Although no formal comparative study has been conducted, continuous therapy with 37.5mg sunitinib daily (without pause) appears to have comparable efficacy but is associated with a more favorable side effect profile [699]. This regimen can therefore be used as an alternative option on an individual basis. For sunitinib, maximum utilization of supportive therapy measures and individualized dosing and regimens, should be used to achieve the best possible tolerability. However, daily doses below 25 mg usually have no therapeutic benefit.

Sunitinib appears to be particularly active against resistance mutations in exon 13 and 14 of the KIT gene, whereas secondary mutations in exon 17 and 18 are barely inhibited [700], [701], [702]. However, the clinical utility of determining resistance mutations (by tumor biopsy or plasma sequencing) has not been prospectively studied to date and should not influence the order of second- or third-line therapy outside of clinical trials.

10.27	Evidence-based Recommendation
GoR A	Patients who do not respond or no longer respond to therapy with sunitinib shall receive therapy with regorafenib.
LoE ⊕⊕⊖⊖ ⊕⊕⊕⊖ ⊕⊕⊖⊖	[703]; [704] ⊕⊕⊖⊖: Overall survival (median follow-up: NR) ⊕⊕⊕⊖: Progression-free survival (median follow-up: NR) ⊕⊕⊖⊖: QoL (EQ-5D, during treatment)
	Strong Consensus

Background 10.27

In third-line therapy, regorafenib is the therapy of choice after clear progression or unacceptable toxicity with sunitinib. The approval of regorafenib is based on data from the GRID trial, which compared regorafenib (160 mg daily, 3 weeks of therapy, 1 week off) with placebo therapy [704]. Regorafenib had a median progression-free survival of 4.8 months vs. 0.9 months for placebo (HR 0.27; p<0.0001). Regorafenib, like sunitinib, inhibits a broad spectrum of tyrosine kinases; both were originally developed as potent VEGFR inhibitors. Therefore, in contrast to more specific KIT inhibitors such as imatinib and nilotinib, higher-grade side effects such as arterial hypertension and also severe hand-foot syndrome and mucositis with gastrointestinal symptoms are found much more frequently. Here, in analogy to sunitinib, close monitoring of patients as well as intensive side effect management must be pursued, especially at the beginning of therapy.

The VOYAGER study, a phase III trial, evaluated the efficacy and safety of avapritinib vs. regorafenib as a third-line or later treatment in patients with unresectable or metastatic GIST. The primary endpoint was not met. There was no significant difference in median progression-free survival between avapritinib and regorafenib in patients with molecularly unselected late-stage GIST.

10.28	Evidence-based Recommendation	new 2022
GoR A	Patients who fail or no longer respond to therapy with three or more kinase inhibitors, including imatinib, shall receive therapy with ripretinib at the recommended daily dose of 150mg.	
LoE ⊕⊕⊖⊖ ⊕⊕⊕⊖ ⊕⊕⊖⊖ ⊕⊕⊖⊖	[705] ⊕⊕⊖⊖: Overall survival ⊕⊕⊕⊖: Progression-free survival ⊕⊕⊖⊖: QoL (EQ-5D VAS) ⊕⊕⊖⊖: EORTC QLQ-C30 (Physical Function, Role Function)	
	Strong Consensus	

Background 10.28

In the case of tumor progression during treatment with three or more tyrosine kinase inhibitors, including imatinib, the switch-pocket inhibitor ripretinib was approved by the EMA for fourth-line treatment. The INVICTUS trial, a double-blind, randomized phase III study, evaluated ripretinib versus placebo in patients after failure or intolerance to imatinib, sunitinib and regorafenib [705]. A total of 129 patients in 12 countries were enrolled in the trial and randomized to ripretinib (n=85) or placebo (n=44). 64% of patients had 3 prior therapies, and 36% of patients had 4-7 prior therapies. There was a highly significant improvement in progression-free survival in the ripretinib arm (6 months vs. 1 month; p<0.0001 according to independent central review). Median survival was 15 months in the treatment arm and 7 months in the placebo arm, which could not be formally tested for statistical significance due to the hierarchical test design. In an analysis of the impact of genomic heterogeneities on treatment outcome, neither the primary mutation (exon 9 vs. 11) nor the various secondarymutations significantly affected the efficacy of ripretinib [706]. The most common (in ≥20% of patients) treatment-related side effects of ripretinib included alopecia, myalgia, nausea, fatigue, hand-foot syndrome, and diarrhea. Treatmentassociated adverse events with grade 3 or 4 in the ripretinib group included lipase elevation (5%), hypertension (4%), fatigue (2%), and hypophosphatemia (2%).

10.29	Consensus-based Recommendation
EC	In patients with metastatic disease who no longer respond to available drugs and in whom only individual metastases show progression, local therapy may be offered. The decision shall be made at centers experienced in GIST.
	Strong

Background 10.29

Resection of metastases at the time of progression to first-, second-, or third-line drug therapy are usually associated with a very short progression-free time and often short median survival in retrospective series [635], [707]. This is particularly true for multifocal progression. In contrast, in patients with only isolated progressive foci (e.g. „nodules within a mass“ [708]), continuation of e.g. imatinib therapy can be achieved by isolated resection or even a local ablative procedure.

Non-surgical procedures include thermoablation (radiofrequency or microwave ablation), but also selective internal radiation therapy (radioembolization with Y-90 microspheres) [537], [709], [710], [711], [712], [713], [714].

In any case, a careful risk-benefit assessment must be made here, preferably in consultation with centers experienced in GIST.

10.30	Evidence-based Recommendation
GoR **0**	Patients with metastatic disease who no longer respond to multiple tyrosine kinase inhibitors can be offered therapy with imatinib again. Decisions shall be made at GIST-experienced centers.
LoE ⊕⊕⊖⊖ ⊕⊕⊕⊕ ⊕⊕⊖⊖	[715]; [716] ⊕⊕⊖⊖: Overall survival (median follow-up: 5.2 months) ⊕⊕⊕⊕: Progression-free survival (median follow-up: 5.2 months) ⊕⊕⊖⊖: QoL (EORTC QLQ-C30, general health status, 8 weeks after treatment).
	Strong Consensus

Background 10.30

In particular, the INVICTUS trial has very powerfully demonstrated that discontinuation of TKI therapy in a late line of treatment leads to rapid progression and is associated with a very unfavorable survival prognosis. Resistance development in GIST is generally clonal [717], [718], [719]. That is, at the time of progression, there is a coexistence of metastases that still respond to therapy and those that are resistant due to secondary mutation. Discontinuation of any therapy therefore often leads to a global growth spurt („tumor flare"), which is why TKI treatment beyond progression should always be favored. If possible, therapy should be given in the setting of clinical trials.

Alternatively, inhibitors that have been given before can be used („Rechallenge"). In the RIGHT trial, after failure of imatinib and sunitinib (but not regorafenib), a rechallenge with imatinib was studied compared to placebo. This showed a small but significant benefit (1.8 months vs. 0.9 months) of imatinib over placebo [715], [716].

Prospectively, a placebo-controlled trial in 81 patients compared the efficacy of pazopanib versus placebo (PAZOGIST, [720]). Inclusion criteria for the study were progression or intolerance to imatinib and sunitinib. Pazopanib significantly improved progression-free survival compared with placebo (HR 0.59, CI 0.37-0.96) [720]. There was no improvement in overall survival. Pazopanib is approved for second-line metastatic sarcoma therapy, but not for GIST therapy.

A randomized phase III trial evaluating nilotinib after imatinib and sunitinib failure showed no advantage over best-supportive care in progression-free or overall survival and therefore cannot be recommended [721].

10.1.5. Follow-up

10.31	Consensus-based Recommendation
EC	Patients after resection of localized GIST should have risk-adapted follow-up.
	Strong Consensus

Background

There is no prospective study on the benefit of routine follow-up. However, metastases in GIST patients usually lead to clinical symptoms late. In turn, a high tumor burden represents an unfavorable prognostic factor in the metastatic setting.

Tumor recurrences occur almost exclusively in the liver and/or peritoneum, which is why cross-sectional imaging of the abdomen is sufficient for most patients.

For patients with very low risk of recurrence (very low risk according to NIH or AFIP), many centers do not perform regular follow-up.

For patients at low to intermediate risk, a follow-up interval of (6-)12 months for 5 years is appropriate, although in individual cases follow-up up to 10 years is acceptable.

Most patients at high risk of relapse receive adjuvant therapy with imatinib. Under ongoing therapy, if compliance is good and a KIT exon 11 mutation is present, follow-up can be every 6 months (CT or MRI abdomen). As data from the SSG XVIII trial have shown, the risk of recurrence after the end of adjuvant therapy is highest in the first 2-3 years [722]. Therefore, follow-up intervals of 3-4 months in the first two years after the end of adjuvant therapy seem reasonable. Thereafter, the interval can be stretched to 6 months for a total of 5 years and then annually for another 5 years [723].

10.2. Epithelioid sarcomas

This sarcoma subtype occurs predominantly in young (including pediatric) patients on the extremities. A distal (hand, foot) and a proximal type are distinguished, up to 20 % of tumors are primarily multifocal (skip lesions) and up to 30 % metastasize to lymph nodes with a high tendency to recur [724].

Loss of integrase interactor 1 (SMARC1/INI1) function occurs in nearly 90 % of cases and is a consequence of biallelic deletion of the SMARCB1 gene or epigenetic dysregulation [725]. This results in EZH2 becoming an oncogenic driver in tumor cells.

Data on doxorubicin-based combination chemotherapy show a response rate of 22 % with a median PFS of 6 months [726].

As of January 2020, tazemetostat, a selective oral EZH inhibitor has been FDA approved for therapy in advanced epithelioid sarcoma. In a multicenter study in patients with proven INI-1 loss, the ORR for the 62 patients was 15 % (95 % CI: 7 %, 26 %), with complete remission of 1.6 % and partial remission of 13 %; 67 % of these patients showed a continued response over a time frame of more than 6 months [727].

10.3. Solitary fibrous tumors (SFT)

Solitary fibrous tumors (SFT) and hemangiopericytomas (HPC) are now grouped together as distinct forms of a spectrum of mesenchymal tumors with fibroblastic or myofibroblastic differentiation [728]. SFTs can occur ubiquitously. Pedunculated tumors of the visceral pleura are a particular localization and usually require surgical resection.

Solitary fibrous tumors exhibit recurrent gene fusion of NAB2 and STAT6, which cause upregulation of the oncogenic EGR-1 gene. The NAB2-STAT-6 fusion variants correlate with the anatomic localization of the tumors and their morphology. Nuclear overexpression of STAT6 on immunohistochemistry is a diagnostic landmark.

SFTs may be associated with hypoglycemia (Doege-Potter syndrome, insulin receptor activation) or with hypertrophic osteoarthropathies (Pierre-Marie-Bamberg syndrome) as paraneoplastic syndromes.

The proportion of malignant SFT has been described as high as 20 % with a higher proportion in extrapulmonary tumors. The four variables patient age >55 years, tumor size, mitotic count/10HPF and tumor necrosis (> 10 %) allowed discrimination between patients at low, intermediate and high risk for metastasis-free survival (p = 0.0005 [729]).

SFT rarely respond to systemic chemotherapy, so radiotherapy may be considered if neoadjuvant intent is considered. There is no standard ‚therapy' in the metastatic setting. Remissions are rarely reported for classical cytostatic agents. For sunitinib tumor stabilizations (according to RECIST) in 18 of 35 patients and up to 45 % partial remissions according to Choi criteria (14/29 pat.) with a median PFS of 6 months have been described [730]. In addition, long-lasting disease stabilizations are sometimes found under anti-VEGFA antibody bevacizumab in combination with temozolomide [731].

10.4. Angiosarcomas

Angiosarcomas are classified as malignant vascular tumors and represent approximately 2% of all soft tissue sarcomas. Epithelioid hemangioendotheliomas are also classified as malignant vascular tumors in the current WHO classification.

Cytogenetically, complex aberrations are found. In the majority, VEGF(-A) and VEGFR expression are detectable. Radiation-induced angiosarcomas of the breast almost always show MYC and FLT4 (VEGFR-3) overexpression [732].

Angiosarcomas show a higher than average incidence of lymphatic and hematogenous (usually pulmonary) metastasis and can manifest multifocally,, especially when occurring after prior radiotherapy. They can occur at all body sites. Cerebral metastasis is also found more frequently.

Epithelioid hemangioendotheliomas (see below) are commonly found in the liver or lung and are characterized by specific translocations (WWTR1-CAMTA1 or YAP1-TFE3).

The 5-year survival rates are less favorable than for other sarcoma subtypes and are usually < 40% [733].

Anthracyclines and taxanes show high efficacy with remission rates of 30-70% for doxorubicin and approximately 20-80% for taxanes [734]. Angiosarcomas of the scalp

show a particularly high response rate to paclitaxel [735]. In a retrospective analysis of the EORTC-STBSG database, combination therapy with adriamycin plus ifosfamide was superior to monotherapy in terms of PFS (HR 0.53; p = 0.010) and overall survival (HR 0.53; p = 0.018) [736]. For gemcitabine, a long-lasting treatment response has been shown in several phase II trials. Pazopanib represents another therapeutic option [737], possibly in combination with taxanes (6-month PFS of 46 % in the overall group and 61.1 % for cutaneous angiosarcomas [738]). In scalp angiosarcomas, remissions with immune checkpoint inhibitors have been described [739].

10.5. Clear cell sarcomas

Clear cell sarcomas were previously also referred to as malignant melanoma of the soft tissues, but can be clearly separated by molecular pathology. The tumors develop in the deep soft tissues with relation to tendons and aponeuroses. Younger adults are usually affected and lymph node metastases occur in up to 40 % of patients.

Clear cell sarcoma is usually characterized by a reciprocal translocation t(12;22) resulting in rearrangement of the EWSR1 gene with-ATF1, with consequent MET overexpression.

Clear cell sarcomas are frequently refractory to cytostatic chemotherapy, and even aggressive therapies such as doxorubicin+ifosfamide induce only low remission rates [740]. Targeted (‚targeted'-) therapy also does not exist, in MET-positive clear cell sarcomas the response rate with crizotinib was only 3.8 % [741]. In this respect, surgical measures also come to the fore in the metastatic situation.

10.6. Alveolar soft tissue sarcomas

Alveolar soft-part sarcoma (ASPS) occurs predominantly in young adults (median age 25 years) at the extremities. Characteristically, in addition to lung and liver metastases, there is (often primary) cerebral metastasis, making MRI of the skull obligatory for staging. Even in the metastatic stage, the course is often indolent.

The tumors are characterized by a translocation, t(X;17) (p11.2;q25) resulting in a fusion gene ASPSCR1-TFE3. The ASPL-TFE3 fusion protein activates MET transcription among other c-MET gene transcription. Alveolar soft tissue sarcomas usually show a slow progression tendency.

Alveolar soft tissue sarcomas are considered refractory to conventional chemotherapy. In a double-blind, placebo-controlled study, the VEGFR inhibitor cediranib resulted in a median PFS of 10.1 months (IQR 5.3-19.0) versus 4.9 months (IQR 1.9-20.0) with placebo (p=0.001) was described with the VEGF inhibitor cediranib [742]. Unfortunately, the compound is not available for therapy. The results of therapy with pazopanib or sunitinib have been reported retrospectively [743], however, clinical benefit is also regularly observed.

A study with axitinib plus the immune checkpoint inhibitor pembrolizumab showed a 3-month PFS of 72.7 % (95 % CI 37.1-90.3) in ASPS patients [744], final study results are currently not available. Activity against ASPS has also been reported in other clinical trials involving immune checkpoint inhibitors e.g. sunitinib plus nivolumab (Martin-Broto et al. Journal for ImmunoTherapy of Cancer 2020;8:e001561. doi:10.1136/jitc-2020-001561)

10.7. Inflammatory myofibroblastic tumors.

Inflammatory myofibroblastic tumors (IMT) are rare soft tissue tumors of ubiquitous localization in children and younger adults. The tumors tend to be locally invasive, may have an indolent course, and rarely metastasize.

In more than 50 % of IMT there is a genetic rearrangement of the anaplastic lymphoma kinase (ALK) on chromosome 2p.23.13. Another group of the tumors shows ROS1 translocations.

In a retrospective analysis of different chemotherapies in 38 patients from 9 sarcoma centers, surprisingly good remission rates of 47.6 % are reported with a median PFS of 6.3 months for doxorubicin-based therapy [745].

Data from the CWS study group showed remission in 3 of 11 pediatric patients with a treatment protocol for rhabdomyosarcoma [746].

In the prospective EORTC CREATE [747] study with central histologic review, half of ALK-positive IMT developed partial remission with crizotinib therapy. The disease control rate was 100 % (85.7 % in ALK-negative tumors). At one year, 73.3 % of patients (95% CI 37.9-90.6) were progression-free. Crizotinib is currently not approved for the treatment of the disease in Germany.

10.8. PEComa

Tumors of perivascular epithelioid cells (PEC) (PEComas) express melanocytic (HMB-45, melan A) and smooth muscle markers (actin, desmin). The group of PEComas includes pulmonary lymphangioleiomyomatosis in young women, as well as angiomyolipomas, most commonly located perirenally but also found in subcutaneous tissue. PEComas occur ubiquitously and 70-80 % are found in women.

There is an association with mutations in one of the tuberous sclerosis complex genes, *TSC1* or *TSC2*. This results in activation of mTORC1 [748], [749].

Metastasis is found in about 7 % of patients at diagnosis, usually pulmonary, hepatic, bone or cerebral. Effective cytostatic chemotherapy does not exist.

mTOR activation suggests the value of therapy with antagonists such as sirolimus, temsirolimus, or everolimus. Indeed, 18 of 25 patients had tumor regression of 53.2 % [750] after 1 year of therapy with sirolimus. However, tumor regrowth to 86 % of baseline size occurred after treatment discontinuation. This may open options for preoperative therapy in locoregionally advanced PEComa.

10.9. Epithelioid hemangioendotheliomas (EHE)

Epithelioid hemangioendotheliomas (EHE) are extremely rare malignant tumors with an incidence < 0.1/100,000 population for which there is no good evidence for therapy and mainly retrospective data have been published. The entity was not delineated until the 1980s. The tumors show vascular differentiation and are a low-grade malignancy [756]. At the time of diagnosis, the tumors may be unifocal, multifocal (multiple lesions in one organ or compartment), or multicentric (mainly in lung/liver/bone). Therefore, whole-body CT or MRI (in case of bone involvement) is required for staging.

EHE are commonly found in liver or lung but also in deep soft tissues, bone [751] and pleura. In visceral organs, they often appear multifocal or metastatic at diagnosis [752]. However, very indolent courses often occur even in metastatic stages. Spontaneous remissions have also been described for pulmonary EHE [753].

In half of the cases, a relation to the blood vessels can be established and angiocentric EHE often become symptomatic due to deep vein thrombosis. The tumors are characterized by specific translocations t(1;3)(p36.3;q25) with a WWTR1-CAMTA1 fusion gene or, in in tumors lacking the typical translocation, a YAP1-TFE3 fusion gene [754]. Detection of the translocation allows the tumors to be distinguished from other hemangioendotheliomas such as the pseudomyogenic or retiform subtype with more favorable biology. The definitive diagnosis should be made only after reference pathology has been performed. Regarding older literature reports, it must be kept in mind that patients were often included without a confirmed diagnosis. Liver transplantation outcomes have been linked to the diagnostic criterion of detection of factor VIII-associated antigen [755] and traced back to the early 1980s [756]. Histopathologically, high-risk tumors for aggressive behavior are those with primary tumor size of >3cm and >3 mitoses/10mm2 [757].

According to recently published data from MSKCC, two groups of EHE can be delineated [752]. One is patients with single lesions of the soft tissues or multifocally in the lung, who may have a relatively indolent course, and in whom R0 resection may be curative. Indolent courses also occur in patients with EHE of the liver, so that therapeutic waiting is more warranted in the recurrence situation. In a series of 10 patients, six patients with diffuse involvement and slow growth could be treated without surgical intervention with a 5-year survival rate of 67 % [758] (see also Section Chapter 10.10). On the other hand, patients with pleural involvement or lymph node metastases often have a very aggressive course. For EHE of soft tissues, metastasis can be expected in about 20 % of patients [757].

The options for locoregional treatment are highly dependent on localization and multifocality. In general, unifocal, resectable EHE should be resected after an observation period indicating disease progression, R0 if necessary. For EHE of bone and soft tissue, the principles of sarcoma surgery apply. Unifocal tumors of the liver can be resected by segmental liver resection and treated with e.g. radiofrequency or microwaveablation for multiple lesions - also as a bridge to rarely indicated liver transplantation. The results of liver transplantation report 5-year survival rates of more than 50% [759], [760]. In the European Transplant Registry, 10-year survival in 149 patients is 74.4 % with the above limitations.

EHE are considered radiosensitive, so that after R1 resection additional radiotherapy (60 Gy) is recommended. If surgical therapy is feasible only with unacceptable morbidity or loss of function, ablative procedures, such as definitive radiotherapy (60 Gy), may be considered [761]. For palliative purposes, doses of 40 Gy [762] may also be used. According to a literature compilation of published individual cases, this also applies to skeletal EHE [763].

In the metastatic setting, anthracycline-based chemotherapies are ineffective. A prospective phase II study with sorafenib reported a response rate of 13 % with a median PFS of 6 months and a 2-year survival rate of 24 % [764]. Recently published results from 38 patients with a molecularly confirmed diagnosis of EHE and progressive disease who received therapy with sirolimus show disease stabilization in 86% with a median PFS of 13 months and median survival of 18.8 months [765].

There are very well established and networked patient support groups in the UK (www.ehercc.org.uk) and the USA (www.fightehe.org). A consensus recommendation on therapy for EHE, agreed with patient representatives, has been published in June 2021 [766].

10.10. Sarcomas of the liver

Due to the relatively low proportion of mesenchymal cells, the liver is rarely a localization for primary sarcomas, but much more frequently a metastatic site of GIST or abdominal leiomyosarcomas. However, the liver offers specific treatment options for some tumors (local ablative procedures, transplantation) that deserve special consideration in the treatment concept of sarcoma therapy. The incidence of autochthonous sarcomas of the liver in adults is low, with 30 patients reported in a 25-year period at MSKCC [758]. The authors conclude that histologic subtype is the primary factor influencing treatment outcome.

The principles of sarcoma therapy also apply to mesenchymal malignancies that are obviously not metastases of other primary tumors, i.e., biopsy verification first. Given the many subtypes and rarity of sarcomas, it is important to delineate tumors for which there is established therapy (see Table 12) as:

- Kaposi sarcoma (most common tumor of the liver in HIV patients),
- extraskeletal Ewing sarcoma (primary systemic therapy analogous to Ewing protocol),
- Rhabdomyosarcoma (primary systemic therapy analogous to RMS protocol),
- Epstein-Barr virus associated follicular dendritic sarcoma (FDCS, extremely rare entity between sarcoma and lymphoma which may respond to CHOP chemotherapy [767], if the disease is not resectable [768]).

A primary surgical approach is indicated especially for low grade (G1) leiomyosarcomas, which may arise from the retrohepatic vena cava, for example. G3 leiomyosarcomas should rather be treated by preoperative systemic chemotherapy (e.g. doxorubicin + dacarbazine (see also chapter Chapter 7.1). Solitary fibrous tumors of the liver that are already very large at diagnosis are also an indication for primary surgical therapy, as neoadjuvant treatment is unlikely to result in tumor shrinkage [769].

Angiosarcomas represent a special subgroup, which frequently occur in the liver secondary to radiation and are always highly malignant (G3). Causes historically were the alpha emitter thorium dioxide which was used as an X-ray contrast agent (thorotrast) until about 1950 [770], [771]. Currently, whole-body radiotherapy as a myelo-ablative procedure prior to allogeneic stem celltransplantation is considered causative [772]. Angiosarcomas are almost always multifocal, accordingly the results after resection alone are rather disappointing (4/9 patients still alive after 15.5 months [773]. In angiosarcomas, rupture risk is described because of the high vascularization [714], however, transarterial chemoembolization resulted in a median survival of only 19 days in 3 patients.

In the pediatric setting, hepatoblastomas, undifferentiated embryonal sarcomas (UESL), and embryonal rhabdomyosarcoma of the bile ducts are delineated malignancies [774]. Unfortunately, these are often grouped together with adult sarcomas in reviews, leading to misinterpretations regarding tumor rupture risk, lymphatic metastasis, jaundice, or Kasabach-Merritt syndrome. However, UESL also occurs in adulthood [775]. After R0 resection and adjuvant chemotherapy, median survival was 29 months.

10.11. Sarcomas of the spermatic cord/groin

The groin represents a special localization for sarcomas. In women, the ligamentum teres (or rotundum) uteri, which is inserted here, is the connection to the angle of the tube and can, in extremely rare cases, serve as the origin of a leiomyosarcoma [776].

Much more often in men, under the suspected diagnosis of inguinal hernia [777] or hydrocele testis, a soft tissue tumor of the scrotum or spermatic cord is resected, which usually corresponds to a lipoma, in 20-30% of cases histologically is a malignancy. The tumors may arise from the tunica vaginalis testis, the spermatic cord, or the epididymis, are also grouped together as paratesticular sarcomas [778] (C63.0-C63.8), and are reported to have an incidence of 0.3/1 million population [779]. Clinically, there is usually a unilateral, slowly enlarging mass in the inguinal canal or scrotum.

In an analysis of 4741 orchiectomy specimens, 31 rhabdomyosarcomas were found in younger patients (median age 18 years) [780], this patient groupoe also develops lymph node metastases and should be treated similarly to pediatric rhabdomyosarcoma protocols.

In the 6th and 7th decades of life, G1 liposarcomas are predominant histologically, but dedifferentiated liposarcomas [781], leiomyosarcomas, and pleomorphic (G3) sarcomas are also present [782]. Highly malignant (G3) tumors are reported in up to 50 % of cases [783], [784]. Lymph node metastases in this group are very rare.

In most cases, the tumors are not diagnosed as sarcoma preoperatively and hence resections are unlikely to be R0. Accordingly, the local recurrence rate is high [785]. When technically feasible, there is an indication for radical R0 resection [786]. In an analysis of 72 patients treated between 1981 and 2011 (67 % liposarcomas, 19 % leiomyosarcomas, 61 % high-grade tumors), 48 patients could be R0 re-resected by high orchiectomy with placement of the spermatic cord at the inguinal junction and had a good chance of recurrence-free survival. It did not matter whether the resection was performed within 5 months of the initial surgery or later [786]. Data from two European centers (Milan and Birmingham) with 82 patients followed up also confirm the importance of R0 resection for liposarcomas while for subgroups such as leiomyosarcoma and rhabdomyosarcoma distant metastasis has a greater impact on survival [784].

Liposarcomas are characterized by a slowly enlarging, painless tumor with suspected inguinal hernia. In two papers with a total of 42 and 25 patients, respectively [781], [787] with dedifferentiated liposarcomas, about half of whom underwent additional radiotherapy, multivariate analysis found no prognostic factors for local recurrence. In R1 resection, high recurrence rates have been reported despite additive radiation [783], [784]. The role of radiotherapy is inconsistently assessed in the literature [788]. Because of the high likelihood of local recurrence, adjuvant radiotherapy with a typical dose of 60-65 Gy should be given after R0 resection, usually resulting in a low local recurrence rate [788], [789]. In case of R1 resection and unclear localization of incomplete resection, especially in liposarcomas, it may be possible to wait for the development of local recurrence and then perform neoadjuvant irradiation.

For tumors infiltrating beyond the spermatic cord into the surrounding area, a co-resection of the abdominal wall, re-resection of the spermatic cord up to the inner inguinal ring and reconstruction may be necessary. If infiltration of the scrotum occurs,

hemiscrotectomy may be necessary. Simple resection is not sufficient [783], [785], as residual tumor is found in 27%-33% of cases.

For patients with leiomyosarcomas of the spermatic cord, a European multicenter study of 23 patients showed that testis-preserving procedures were possible without recurrence in tumor sizes of median 12 mm. In all patients, however, a tumor was suspected preoperatively and clarified by ultrasound and CT. In the orchiectomized patients, whose tumors had a median size of 3 cm, recurrences occurred in 50% of the cases [790].

Prognostically, a 5-year disease-specific survival rate of 92% was found in the analysis of 82 patients treated from 1992-2013, with a local recurrence rate of 26% and a distant metastasis rate of 24%. Patients with sarcomas of the spermatic cord should be followed up long-term, as late recurrences can occur in up to 42% at 15-year follow-up [782], [788].

11. Quality indicators

Quality indicators are measured variables whose collection serves to assess the quality of the underlying structures, processes or results. Quality indicators are an important management tool. The aim of their use is the continuous improvement of care by presenting outcomes, critically reflecting on them and, if necessary, improving them. The present selection of quality indicators was defined according to the methodology of the guideline program oncology [791]. For the definition process, a „working group Quality Indicators“ (AG QI) was constituted. This created the final set of quality indicators based on the strong recommendations („should“) of the newly developed guideline and the results of the search for existing national and international quality indicators. The exact procedure and composition of the WG QI are presented in the guideline report.

After two online meetings of this WG, the final set of 14 quality indicators was adopted.

In addition, the WG makes as a recommendation that local disease-free survival (DFS), metastasis-free survival, and overall survival (OS) are provided by cancer registries, both for the guideline group updating the S3 guideline Adult Soft Tissue Sarcomas and for the individual certified sarcoma center.

Table 19: Quality Indicators

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
QI 1: Pre-therapeutic presentation in the tumor board (initial diagnosis of soft tissue sarcoma)		
Enumerator Patients of the denominator presented in the pre-therapeutic tumor board. **Denominator** All patients with initial diagnosis of soft tissue sarcoma Participants Tumor Board: surgical discipline with treatment focus on soft tissue sarcomas, hematology/oncology, pathology, radiology and radiation oncology.	**4.2** The planning of the therapy of sarcomas shall take place pre-therapeutically in the interdisciplinary tumor board. At least one surgical discipline with a focus on soft tissue sarcomas, as well as hematology/oncology, pathology, radiology and radiation oncology shall be represented. Localization-specific expertise shall be consulted on a case-by-case basis.	EC Quality objective: Pretherapeutic presentation of patients with first diagnosis soft tissue sarcoma in the interdisciplinary tumor board as often as possible

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
QI 2: Treatment in the certified sarcoma center		
Enumerator Patients of the denominator with care in certified sarcoma center **Denominator** All patients with soft tissue sarcoma	**4.1** The diagnosis and therapy of soft tissue sarcoma shall be performed by or in coordination with a certified sarcoma center or associated cooperation partner.	EC Quality objective: Treatment of as many patients with soft tissue sarcoma as possible in certified sarcoma centers
QI 3: Complete report of findings after resection of soft tissue sarcoma		
Enumerator Patients of the denominator with report of findings indicating: Grading according to FNCLCC; Minimum distances to relevant resection margins and critical structures; WHO classification; Dignity group-ICD-O **Denominator** All patients with initial diagnosis of soft tissue sarcoma and resection. Dignity groups: benign, intermediate (locally aggressive), intermediate (rarely metastatic) or malignant. FNCLCC: see in chapter 4.1.4.3, table "FNCLCC Grading System: Definition of Parameters" and table "FNCLCC Grading System: Tumor Differentiation Score According to Histologic Type".	**4.21** The minimum distances to relevant resection margins and critical structures shall be specified in the histopathological findings. R0 status is defined as „no tumor on ink“. **4.25** Histopathological subtyping shall be performed according to the currently valid WHO classification. The tumor shall be classified into the dignity groups benign, intermediate (locally aggressive), intermediate (rarely metastatic) or malignant. The ICD-O coding (if available) should be added as additional information.	4.19: EK; 4.20: EK; 4.24: EK Quality objective: Complete report of findings after resection of a soft tissue sarcoma as often as possible.

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
QI 4: Risk assessment GIST		
Enumerator Patients of the denominator with risk assessment of GIST. **Denominator** All patients with initial diagnosis of localized GIST, M0 and resection.	**4.37** An assessment of individual recurrence risk shall be performed on the resected primary localized GIST without evidence of distant metastases (cM0) to assess the indication for adjuvant imatinib therapy.	EC Quality objective: To assess the risk of recurrence after resection of a GIST, M0, as frequently as possible.
QI 5: Mutation analysis GIST		
Enumerator Patients of the denominator with mutation analysis of the genes KIT (exon 9, 11) and PDGFRA (exon 18). **Denominator** All patients with initial diagnosis of intermediate/high risk GIST and/or M1. Risk classification GIST: see chapter 10.1.1.3 of the guideline.	**4.38** For every intermediate/high risk GIST as well as for every metastatic GIST, a mutation analysis of at least the KIT (exon 9, 11) and PDGFRA (exon 18) genes shall be performed. If no mutation can be detected in these three loci, further hot spot regions shall be investigated by molecular pathology or the case should be sent to a reference laboratory.	EC Quality Objective: To perform mutation analysis as frequently as possible in intermediate/high risk GIST and/or M1.
QI 6: Primary histological confirmation of soft tissue sarcomas		
Enumerator Patients of the denominator with pre-therapeutic histologic backup. **Denominator** All patients with soft tissue sarcoma and therapy, except superficial soft tissue sarcomas ≤3cm.	**5.1** In cases of clinical suspicion and/or imaging suspicion of soft tissue sarcoma, this shall be primarily confirmed histologically. **5.3** In cases of clinical suspicion and/or imaging suspicion of soft tissue sarcoma that is smaller than 3 cm in diameter and superficially located, primary R0 resection may be performed.	5.1: EK; 5.3: EK Quality objective: Histological confirmation of soft tissue sarcomas, except for superficial soft tissue sarcomas ≤3cm, as often as possible before therapy.

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
Therapy: surgery, radiation, chemotherapy, hyperthermia, isolated limb perfusion.		
QI 7: R0 resection for soft tissue sarcoma		
Enumerator Patients of the denominator with R0 resection **Denominator** All patients with initial diagnosis of soft tissue sarcoma and resection.	**5.6** Resection of primary soft tissue sarcoma of the extremities shall be performed as a wide resection. The goal is R0 resection.	GRADE: moderate-high Quality objective: R0 resection of primary soft tissue sarcomas as often as possible (except planned R1 resections).
QI 8: Hysterectomy without morcellement for sarcoma confined to the uterus.		
Enumerator Patients of the denominator with hysterectomy without morcellation. **Denominator** All patients with sarcoma confined to the uterus (ICD-O T C54, C55 iVm morphology codes chapter 13.1), M0 with hysterectomy.	**5.44** In leiomyosarcoma confined to the uterus, complete removal of the uterus shall be performed without morcellation or uterine injury. **5.48** In high-grade endometrial stromal sarcoma confined to the uterus, complete removal of the uterus shall be performed without morcellation or uterine injury.	5.44: EK; 5.48: EK Quality objective: Hysterectomy without morcellation for sarcoma confined to the uterus as frequently as possible.
QI 9: Pre/postoperative radiotherapy for soft tissue sarcoma.		
Enumerator Patients of the denominator with preoperative or postoperative radiotherapy. **Denominator** All patients with initial diagnosis of soft tissue sarcoma of extremities or trunk (excluding cutaneous sarcomas ICD-0 T C44), G2 or G3, M0	**5.66** For G2 and G3 soft tissue sarcomas, pre-operative or post-operative radiotherapy shall be given.	GoR: A; GRADE: low-moderate Quality objective: To provide pre-operative or post-operative radiotherapy as frequently as possible for soft tissue sarcomas of the extremities or trunk (G2 or G3, M0).

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
and resection. ICD-O topography extremities or trunk: C47.1 - C47.8, C48.0, C49.1 – C49.8		
QI 10: Pre-therapeutic presentation in the tumor board (recurrence and/or secondary distant metastasis of a soft tissue sarcoma).		
Enumerator Patients of the denominator with pre-therapeutic presentation in the tumor board **Denominator** All patients with local recurrence and/or newly diagnosed secondary distant metastases of soft tissue sarcoma. Participants Tumor Board: surgical discipline with treatment focus on soft tissue sarcomas, hematology/oncology, pathology, radiology and radiation oncology.	**6.4** In local recurrences of soft tissue sarcomas not pretreated with neoadjuvant or adjuvant therapy, a multimodal therapy concept shall be defined in an interdisciplinary sarcoma board. **7.10** The indication for local therapy of metastases shall be multidisciplinary.	6.4: EK; 7.10: EK Quality objective: Pretherapeutic presentation of recurrences and/or secondary distant metastasis of soft tissue sarcomas in the interdisciplinary tumor board as often as possible.
QI 11: Post-operative presentation to the tumor board (local recurrence and R1/R2 resection of soft tissue sarcoma).		
Enumerator Patients of the denominator who presented postoperatively to the tumor board **Denominator** All patients with local recurrence soft tissue sarcoma and R1/R2 resection. Participants Tumor Board: surgical discipline with treatment focus on soft tissue sarcomas, hematology/oncology, pathology, radiology and radiation oncology.	**6.15** After incomplete resection of an isolated local recurrence, whether pretreated with chemotherapy according to guidelines or not, a multidisciplinary therapeutic decision shall be made.	EC Quality objective: Post-operative presentation of R1-/R2-resected local recurrences of soft tissue sarcomas in the interdisciplinary tumor board as often as possible.

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
QI 12: First-line chemotherapy for soft tissue sarcoma		
Enumerator Patients of the denominator with doxorubicin monotherapy or anthracycline-containing combination therapy. **Denominator** All patients with soft tissue sarcoma and first-line chemotherapy.	**7.2** The choice of systemic therapy shall be doxorubicin monotherapy or anthracycline-containing combination therapy, taking into account toxicity and goals.	EC Quality objective: To use doxorubicin monotherapy or anthracycline-containing combination therapy as frequently as possible in first-line chemotherapy.
QI 13: Complete report of findings after resection GIST		
Enumerator Patients of the denominator with reports of findings indicating: R status; Primary location; Number of mitoses per 5mm²; Tumor rupture **Denominator** All patients with initial diagnosis of GIST and resection.	**10.11** When diagnosing GIST on resectate, R status, primary location, tumor size (largest longitudinal diameter), number of mitoses per 5 mm², and a determination of whether tumor rupture is present shall be included in the pathology report.	EC Quality objective: Complete report of findings after resection of a GIST as often as possible.
QI 14: Postoperative mortality in retroperitoneal sarcoma.		
Enumerator Patients of the denominator who died within 30d post-operatively. **Denominator** All patients with initial diagnosis of retroperitoneal sarcoma (RPS) (ICD-10 C48.0 or C48.8) and tumor resection.		As a result of the discussion of the international QI, the LL defines as a specific objective that post-operative mortality should be collected for patients with retroperitoneal sarcoma (RPS). Since the basis is the existing international QI, its population is also adopted. Source wording: *QPI 11a - 30 Day Mortality*

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
		Following Curative Oncological Treatment. *30-day mortality following curative treatment for extremity and retroperitoneal sarcoma.* *Numerator: Number of patients with extremity or retroperitoneal sarcoma who receive oncological treatment with curative intent who die within 30 days of treatment.* *Denominator: All patients with extremity or retroperitoneal sarcoma who receive curative oncological treatment.* *Exclusions: No exclusions.* *Source: Sarcoma National Managed Clinical Network, N., South East and West of Scotland Cancer Networks Audit Report Sarcoma Quality Performance Indicators. Clinical Audit Data: 01 April 2014 to 31 March 2015. 2016.*

12. Research questions

The guideline group sees a need for research in some areas of the diagnosis and therapy of soft tissue sarcoma. Listed here are those issues that directly affect the guideline itself or topics discussed in the guideline.

12.1. Health Services Research

It is necessary to review the extent to which the guideline contents are applied and what influence this has on patient care.

The guideline group therefore strongly advocates the establishment of evaluationprograms of guideline application. What barriers can be identified to the establishment of the S3 guideline? In particular, the members of the steering group and patient representatives are happy to provide advice on the design of evaluation studies. This includes health economic analyses of the various primary therapy procedures.

There is a need for research on the care of geriatric patients, especially with regard to the offer of therapy standards and time delays in treatment, e.g., due to limited mobility for coordination or implementation of therapy. The possibilities of video communication should be evaluated in this partly also vulnerable patient group. The guideline group also sees a need for research in the analysis of treatment indications, since this patient group is usually excluded from registration studies.

12.2. Pathomorphological examinations

The guideline group advocates studies to ensure the evaluation of biopsies (size, number, localization in the tumor of punch biopsies).

Histologic markers to assess the aggressiveness of sarcomas in relation to clinical parameters (e.g., sarculator) could be an important pillar for indicationsto adjuvant systemic therapies, see also below in other contexts.

In particular, the value of early application of a next generation sequencing panel (NGS) versus staged (immuno)histologic diagnostics represents an important concern, including both temporal relation to therapy as well as economic and availability aspects.

12.3. Diagnosis and therapy of locally limited and locally advanced soft tissue sarcoma

The guideline group sees a therapeutic need for research especially in neoadjuvant therapy with regard to the question of the value of neoadjuvant chemotherapy and the combination of chemotherapy and surgery also in the metastatic situation.

There is an urgent need for research in better defining patients who are at high risk for systemic tumor recurrence and thus may benefit from adjuvant systemic (chemo)therapy. This includes both a validation of prognostic nomograms in Germany (e.g. Sarculator) but also of significantly improved follow-up data from clinical cancer registries.

12.4. Diagnostics and therapy of tumor recurrence

There is a need for research to clarify the extent to which molecular prognostic markers can be defined for sarcomas or even individual subgroups. In particular, this also concerns the analysis of cDNA findings to define tumor recurrence and to verify to what extent such findings can be used for early detection of tumor recurrence before manifestation in imaging. Given the relatively high frequency of immune phenomena in the vicinity of sarcomas, sarcoma-specific immune markers need to be better explored to improve the diagnosis of tumor recurrence, if necessary.

12.5. Diagnosis and therapy of metastatic soft tissue sarcoma

Soft tissue sarcoma therapy has been able to expand its portfolio in recent years. However, the development of different chemotherapy regimens could not lead to a prognostic leap in these entities. The lack of specific therapies clearly underlines the need for new forms of treatment. The transition of differential molecular diagnostics to specific therapies is a relevant focus of clinical research and should be expanded.

Consequently, there is a need for research in improving first-line therapy in metastatic soft tissue sarcoma. In second-line and follow-up therapy, it is important to investigate and optimize the sequencing of these therapies. In addition, sarcoma type-specific therapies can be further differentiated to develop new therapies.

12.6. Tumorigenesis and risk factors

There is a need for research in clarifying the development of sarcomas, both through genetic conditions (neurofibromatosis, Li-Fraumeni syndrome – see Australian KINDRED study). The rate of clarification of genetic risk factors to date is not yet within the desirable range.

Also iatrogenic factors (postradiogenic angiosarcoma after breast carcinoma, visceral sarcoma after whole body radiotherapy) have not yet been sufficiently investigated with regard to frequency and mechanisms of development, e.g. on the combined influence of chemotherapy and radiotherapy.

There is also a need for research on the problem of field carcinogenesis of dedifferentiated liposarcomas of the retroperitoneum, for which environmental influences in the development are also conceivable (e.g. lipotrophic chemicals).

12.7. Follow-up: length and intensity of follow-up.

Data on patient follow-up are scarce. Distinguishing different clinical scenarios for a differentiated recommendation in the study sequence is a data gap. Studies to model risk-adapted follow-up concepts are therefore necessary.

13. Appendix

13.1. List of morphology codes

Table 20: List of morphology codes

Histological group	Subgroups	Morphology code according to WHO Blue Book 2020
Soft tissue tumors		
Adipocytic tumors	Atypical lipomatous tumor/	8850/1
	highly differentiated liposarcoma	8850/3
	Dedifferentiated liposarcoma	8858/3
	Myxoid liposarcoma	8852/3
	Round cell liposarcoma	8853/3
	Pleomorphic liposarcoma	8854/3
	Myxoid pleomorphic liposarcoma	8859/3
	Liposarcoma, NOS	8850/3
	Desmoid fibromatosis	8821/1
	Giant cell fibroblastoma	8834/1
	Dermatofibrosarcoma protuberans	8832/1
	Fibrosarcomatous DFSP	8832/3
	Pigmented DFSP	8833/1
	Solitary fibrous tumor	8815/1
	malignant	8815/3
	Low grade myofibroblastic sarcoma	8825/3
	Low grade fibromyxoid sarcoma	8840/3
	Sclerosing epithelioid fibrosarcoma	8840/3
	Myxoinflammatory fibroblastic sarcoma/atypical	8811/1
	myxoinflammatory fibroblastic tumor	
	Infantile fibrosarcoma	8814/3
	Adult fibrosarcoma	8810/3
	Myxofibrosarcoma	8811/3
Fibrohistiocytic tumors	Plexiform fibrohistiocytic tumor	8835/1
	tenosynovial giant cell tumor, diffuse type	9252/1
	Tenosynovial giant cell tumor, malignant	9252/3
	Giant cell tumor of soft tissue	9251/1
	Malignant fibrous histiocytoma	8830/3

Histological group	Subgroups	Morphology code according to WHO Blue Book 2020
Smooth muscle tumors	Leiomyosarcoma/Uterine Leiomyosarcoma	8890/3
	Inflammatory leiomyosarcoma	
Pericytic tumors	Malignant glomus tumor	8711/3
Skeletal muscle tumors	Embryonal rhabdomyosarcoma	8910/3
	(incl. botryoid, anaplastic)	
	Alveolar rhabdomyosarcoma	8920/3
	(also solid, anaplastic)	
	Spindle cell/sclerosing rhabdomyosarcoma.	8912/3
	Pleomorphic rhabdomyosarcoma	8901/3
Vascular tumors	Kaposiform and composite hemangioendothelioma	9130/1
	Retiform hemangioendothelioma	9136/1
	Papillary intralymphatic angioendothelioma	9135/1
	Pseudomyogenous (epithelioid sarcoma-like) hemangioendothelioma.	9136/1
	Kaposi's Sarcoma	9140/3
	Epithelioid hemangioendothelioma	9133/3
	Angiosarcoma	9120/3
Tumors with uncertain differentiation	Angiomatoid fibrous histiocytoma	8836/1
	Parachordom	9373/1
	Myoepithelioma	8982/0
	Myoepithelial carcinoma	8982/3
	Mixed tumor	8940/0
	Mixed tumor malignant	8940/3
	Synovial Sarcoma	9040/3
	Spindle cell	9041/3
	biphasic	9043/3
	Epithelioid sarcoma	8804/3
	Alveolar soft tissue sarcoma	9581/3
	Clear cell sarcoma	9044/3
	Extraskeletal myxoid chondrosarcoma	9231/3
	extraskeletal Ewing's sarcoma	

Histological group	Subgroups	Morphology code according to WHO Blue Book 2020
	PNET (peripheral neuroectodermal tumor).	9364/3
	Desmoplastic small round cell sarcoma (DSRCT).	8806/3
	Extrarenal rhabdoid tumor	8963/3
	Malignant mesenchymoma	8990/3
	PECom (myomelanocytic tumors)	No digits
	[new WHO code for malignant PECome.]	[8714/3]
	Intimal Sarcoma	No specific Digit
	[new WHO code]	[9137/3]
	Extraskeletal osteosarcoma	9180/3
	Extraskeletal mesenchymal chondrosarcoma	9240/3
Nerve sheath tumors	Malignant peripheral nerve sheath tumor	9540/3
	Epithelioid malignant peripheral nerve sheath tumor	9542/3
	Malignant triton tumor	9561/3
	Malignant granular cell tumor	9580/3
Undifferentiated/unclassifiable sarcomas	Undifferentiated spindle cell sarcoma	8801/3
	Undifferentiated pleomorphic sarcoma	8802/3
	Undifferentiated round cell sarcoma	8803/3
	Undifferentiated epithelioid cell sarcoma	8804/3
	Undifferentiated sarcoma, NOS	8805/3
	Adamantinoma	9261/3
Gastrointestinal stromal tumors		
GIST	Stromasarcoma o.n.a.	8931/3
	Gastrointestinal stromal tumor with uncertain malignant potential	8936/1
	Malignant gastrointestinal stromal tumor	8936/3
Uterine sarcomas		
Uterine sarcomas	High grade endometrial stromal sarcoma	8930/3
	Low grade endometrial stromal sarcoma	8931/3
	Undifferentiated uterine sarcoma	8805/3
	Smooth muscle tumor of uncertain malignant potential (STUMP).	8897/1

Histological group	Subgroups	Morphology code according to WHO Blue Book 2020
	Diffuse/intravenous leiomyomatosis	8890/1
	Metatasizing leiomyoma	8898/1
	Uterine leiomyosarcoma	8890/3
	Epithelioid leiomyosarcoma	8891/3
	Myxoid leiomyosarcoma	8896/3
	Uterine rhabdomyosarcoma	8900/3
	Uterine malignant PECom	8714/3

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