



Pathologie Bochum



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Sarkome

Pathologie und Molekularpathologie

Ingo Stricker

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Weichteiltumoren

Epidemiologie

Inzidenz: ca. 1,5-2 pro 100.000 Einwohner

1% aller malignen Tumoren des Erwachsenen

ca. 15% kindlicher/juveniler Tumoren.

Lokalisation:

60% Extremitäten

20-35% retro-/intraperitoneal (einschl. GIST)

15-20% Körperstamm



Weichteiltumoren

Übersicht benigne / maligne

Ursprung	Benigne	Maligne
Muskeln	Rhabdomyom	Rhabdomyosarkom
Fett	Lipom	Liposarkom
Bindegewebe	Fibrom	Fibrosarkom
	Aggressive Fibromatose	
Glatte Muskeln	Leiomyom	Leiomyosarkom
Gefäße	Hämangiom	Angiosarkom

Sarkome

Übersicht Tumorentitäten nach WHO

lipogen	Liposarkom lipomähnlich (ALT)	myxoid / rundzellig dedifferenziert, pleomorph
(myo-) fibroblastisch	Fibrosarkom (adult) Myxofibrosarkom Low grade fibromyxoid Sarkom	
undifferenziert	Undifferenzierte Sarkome	pleomorph, spindelzellig, Riesenzell-haltig, rundzellig
glatt-muskulär	Leiomyosarkom	
skelett-muskulär	Rhabdomyosarkom	embryonal pleomorph, alveolär
vaskulär	Hämangioendotheliom Angiosarkom	epitheloid
chondro-ossär	Extraskellettales Osteosarkom Mesenchymales Chondrosarkom	
„uncertain“	Epitheloides Sarkom Synoviales Sarkom PNET	



Sarkome

Häufigkeiten der Entitäten

Liposarkome	15-25%
Leiomyosarkome	10-15%
undifferenzierte Sarkome (früher MFH, NOS)	15-25%
Synovialsarkome	6-10%
GIST	3-5%
Maligne periphere Nervenscheidentumoren (MPNST)	3-5%
Fibrosarkome	2-3%
Angiosarkome	2-3%

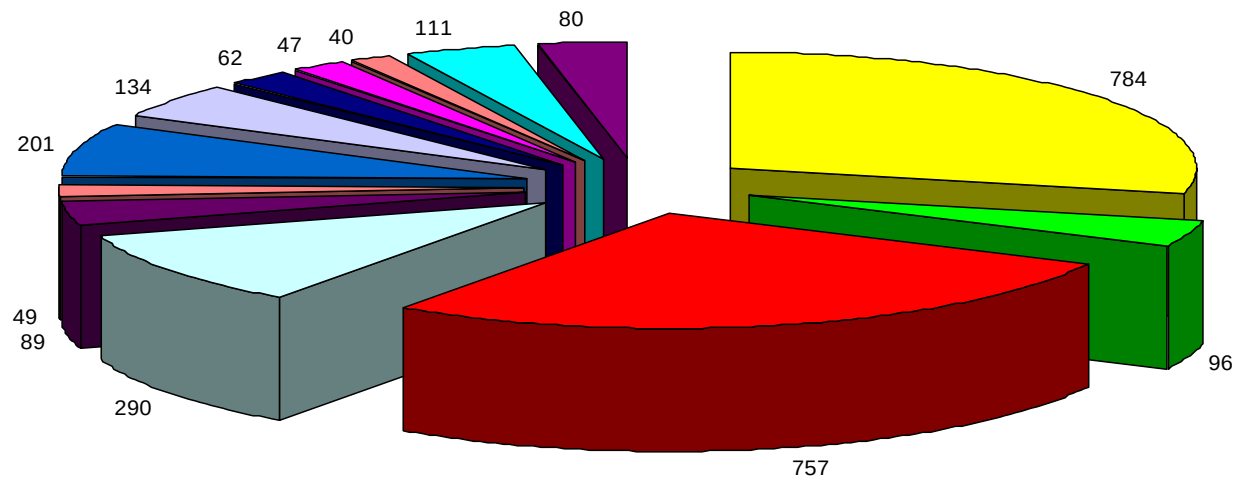


Sarkome

Häufigkeiten der Entitäten

Weichteil-Sarkome

Datenauszug aus dem Weichteiltumorregister des Instituts für Pathologie Bochum
Stand Mitte 2012, Gesamtsumme n=3011



- MFH
- Leiomyosarkom
- Synovialsarkom
- Extraskellettales Ewing- Sarkom / PNET
- DFSP

- Fibrosarkom
- Rhabdomyosarkom
- MPNST
- Klarzellsarkom

- Liposarkom
- Angiosarkom
- Epitheloides Sarkom
- spindelzelliges Sarkom



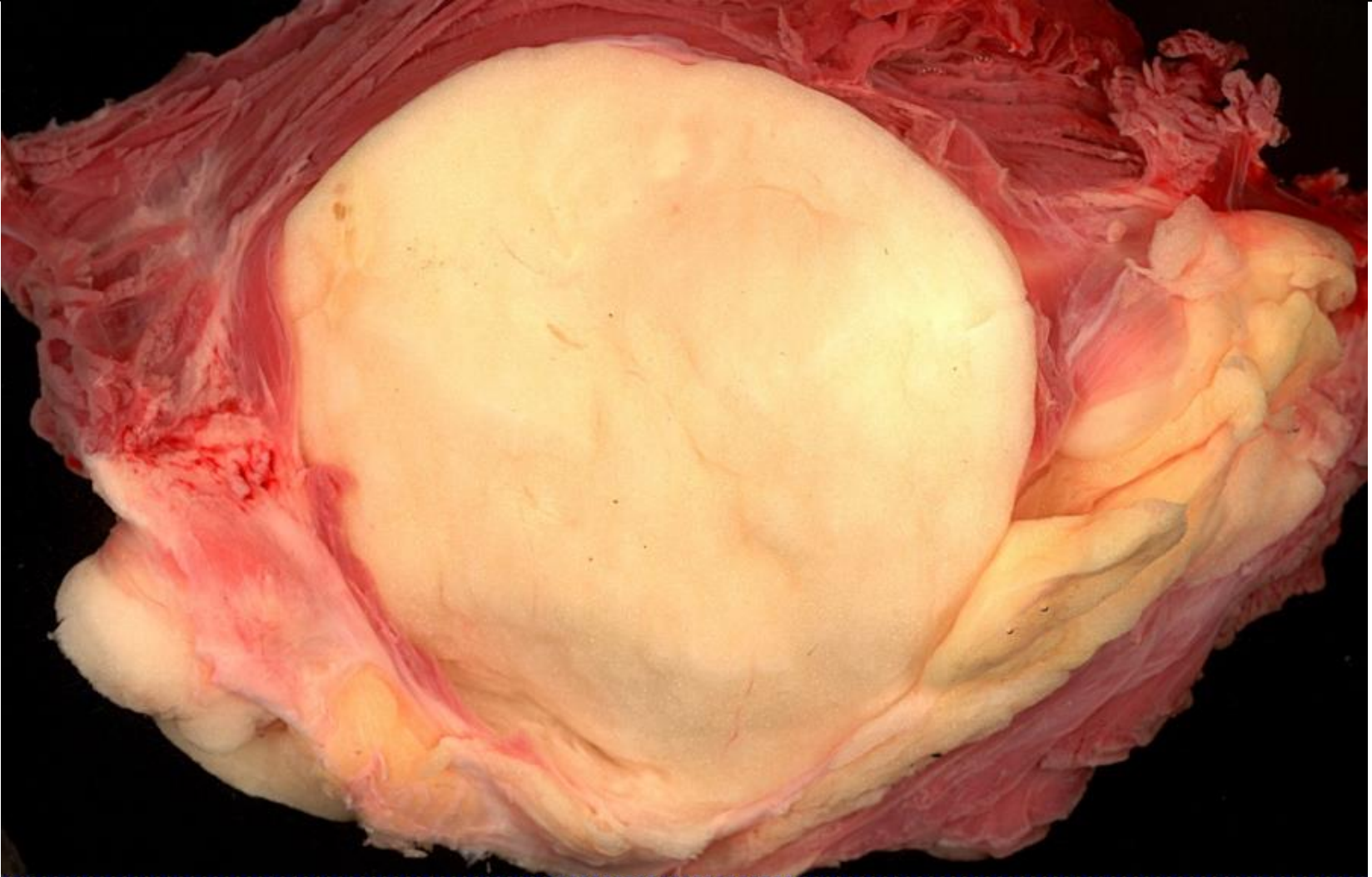
„Liposarkom“

Atypischer lipomatöser Tumor - ALT
(Gut differenziertes lipomähnliches Liposarkom)



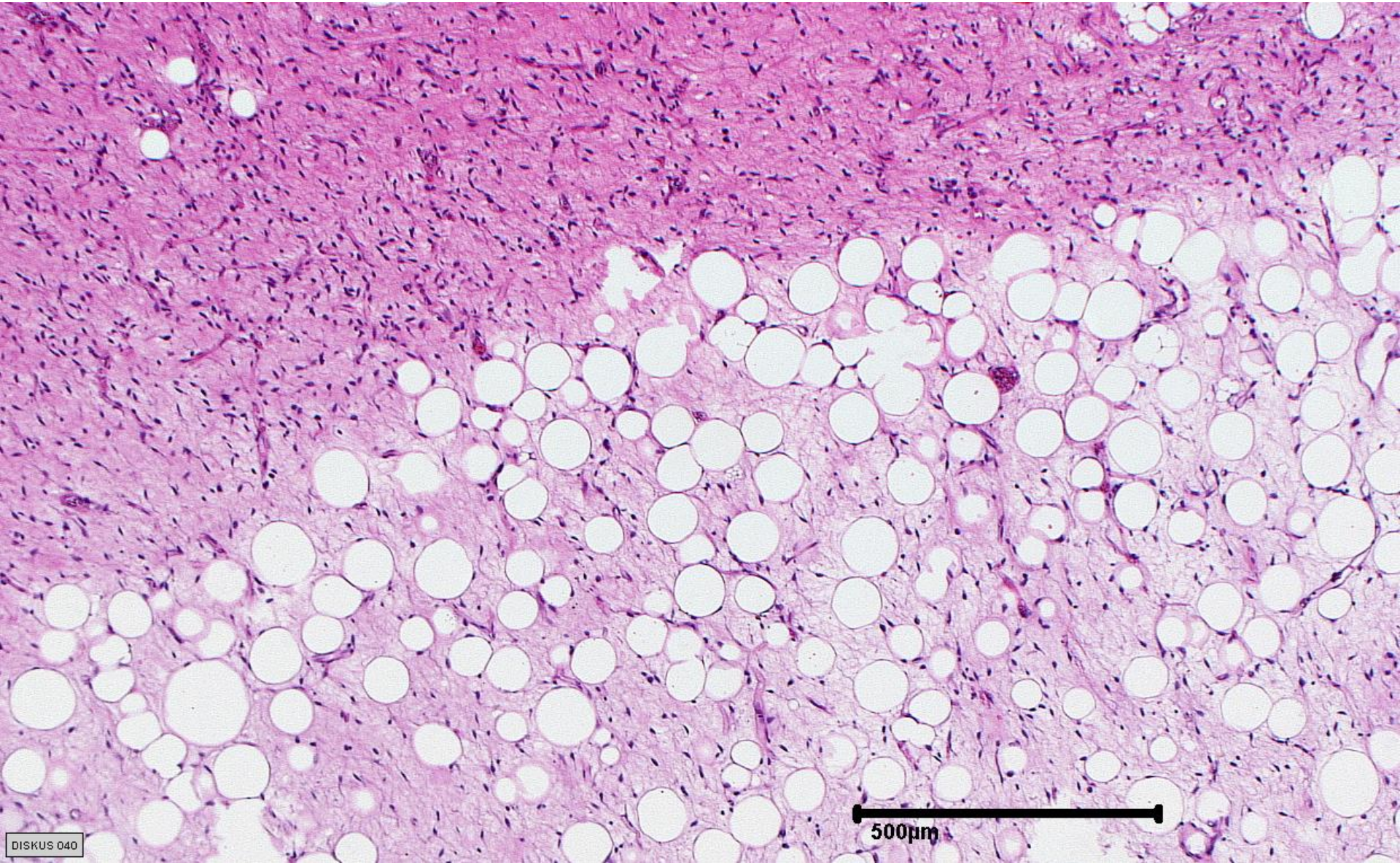
„Liposarkom“

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„Liposarkom“

Atypischer lipomatöser Tumor - ALT

(Gut differenziertes lipomähnliches Liposarkom)

Atypical lipomatous tumour

A.P. Dei Tos
F. Pedetour

Definition

Atypical lipomatous tumour (ALT) is a locally aggressive mesenchymal neoplasm composed either entirely or partly of a mature adipocytic proliferation showing significant variation in cell size and at least focal nuclear atypia in both adipocytes and stromal cells. The presence of scattered hyperchromatic, often multinucleate, stromal cells and a varying number of monovacuolated or multivacuolated lipoblasts (defined by the presence of single or multiple sharply margined cytoplasmic vacuoles scalloping an enlarged hyperchromatic nucleus) may contribute to the morphological diagnosis. Use of the term "atypical lipomatous tumour" is determined principally by tumour location and resectability.

Terminology in clinical practice

The fact that a well-differentiated liposarcoma shows no potential for metastasis unless it undergoes dedifferentiation led, in the late 1970s, to the introduction of terms such as "atypical lipoma" or "atypical lipomatous tumour" (791) for lesions arising at surgically amenable locations in the limbs and on the trunk. At these sites, complete excision is usually curative and hence the designation "sarcoma" is not warranted. However, the variable, sometimes controversial, application of this new terminology has represented a source of potential diagnostic confusion (782,1419, 2933). ALT and well-differentiated liposarcoma are synonyms describing lesions that are identical

morphologically and karyotypically (see below), and in terms of biological potential. The choice of terminology is therefore best determined by the degree of reciprocal comprehension between surgeon and pathologist to prevent inappropriate treatment (622). Most often, the term "well-differentiated liposarcoma" is not appropriate for lesions in somatic soft tissue. However, in sites such as retroperitoneum and mediastinum, it is commonly impossible to obtain a wide excision margin and, in such cases, local recurrence (often repeated and ultimately uncontrolled) is almost inevitable and often leads to death, even in the absence of dedifferentiation and metastasis. Hence, at these sites, retention of the term "well-differentiated liposarcoma" can readily be justified. The same applies for spermatic cord lesions, which often relapse in retroperitoneum.

ICD-O code

Atypical lipomatous tumour 8850/1

Synonyms

Atypical lipoma; well-differentiated liposarcoma; adipocytic liposarcoma; lipoma-like liposarcoma; sclerosing liposarcoma; spindle cell liposarcoma; inflammatory liposarcoma

Epidemiology

ALTs account for about 40–45% of all liposarcomas and therefore represent the largest subgroup of aggressive adipocytic

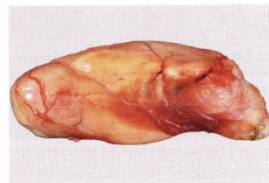


Fig. 2.22 Atypical lipomatous tumour. Surgical specimen showing a well-circumscribed, lobulated mass.

neoplasms. These lesions mostly occur in middle-aged adults with peak incidence in the sixth decade. Convincing examples in childhood are extremely rare, but may be associated with Li-Fraumeni syndrome. Males and females are equally affected, with the obvious exception of those lesions affecting the spermatic cord (758, 860,2930).

Sites of involvement

ALT occurs most frequently in deep soft tissue of the limbs, especially the thigh, followed by the retroperitoneum, the paratesticular area and the mediastinum (758,859,1076, 2929). The head and neck region is also affected (2005). These lesions may also arise in subcutaneous tissue and, very rarely, in skin.

Clinical features

ALT usually presents as a deep-seated, painless enlarging mass that can slowly

Keine Metastasen (wenn nicht dedifferenziert)

Terminologie anhand der Tumorlokalisation und Resektabilität:

Klassische Extremitätenlokalisation ist für gewöhnlich resektabel und hat einen guten Verlauf / Prognose → ALT

Retroperitoneum / Samenstrang / Mediastinum ist die Resektabilität eingeschränkt, der Eingriff unwesentlich größer für den Patienten und führt häufig zum Tode, auch ohne Dedifferenzierung / Metastasen, sodass hier der Begriff „gut differenziertes Liposarkom“ gerechtfertigt erscheint.

Aber

8850/1

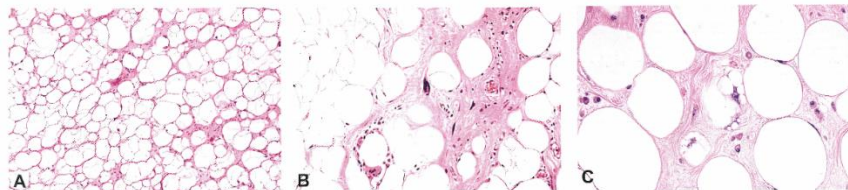
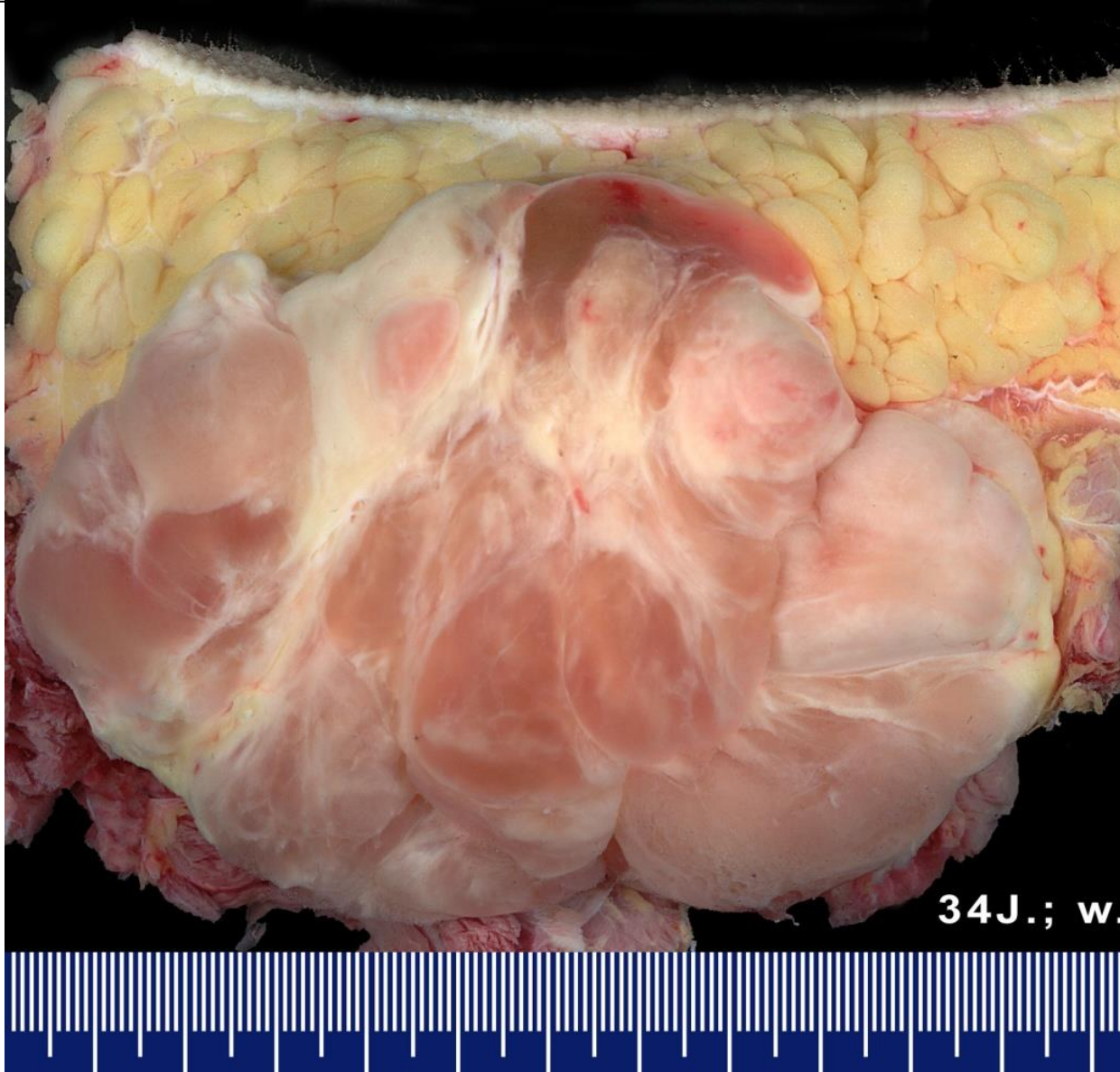


Fig. 2.21 Atypical lipomatous tumour. A Marked variation in adipocyte size is one of the most important diagnostic clues. B The presence of atypical, hyperchromatic stromal cells represents a common finding. C A varying number of lipoblasts can be seen in well-differentiated liposarcoma, but their presence neither makes nor is required for a diagnosis of liposarcoma.

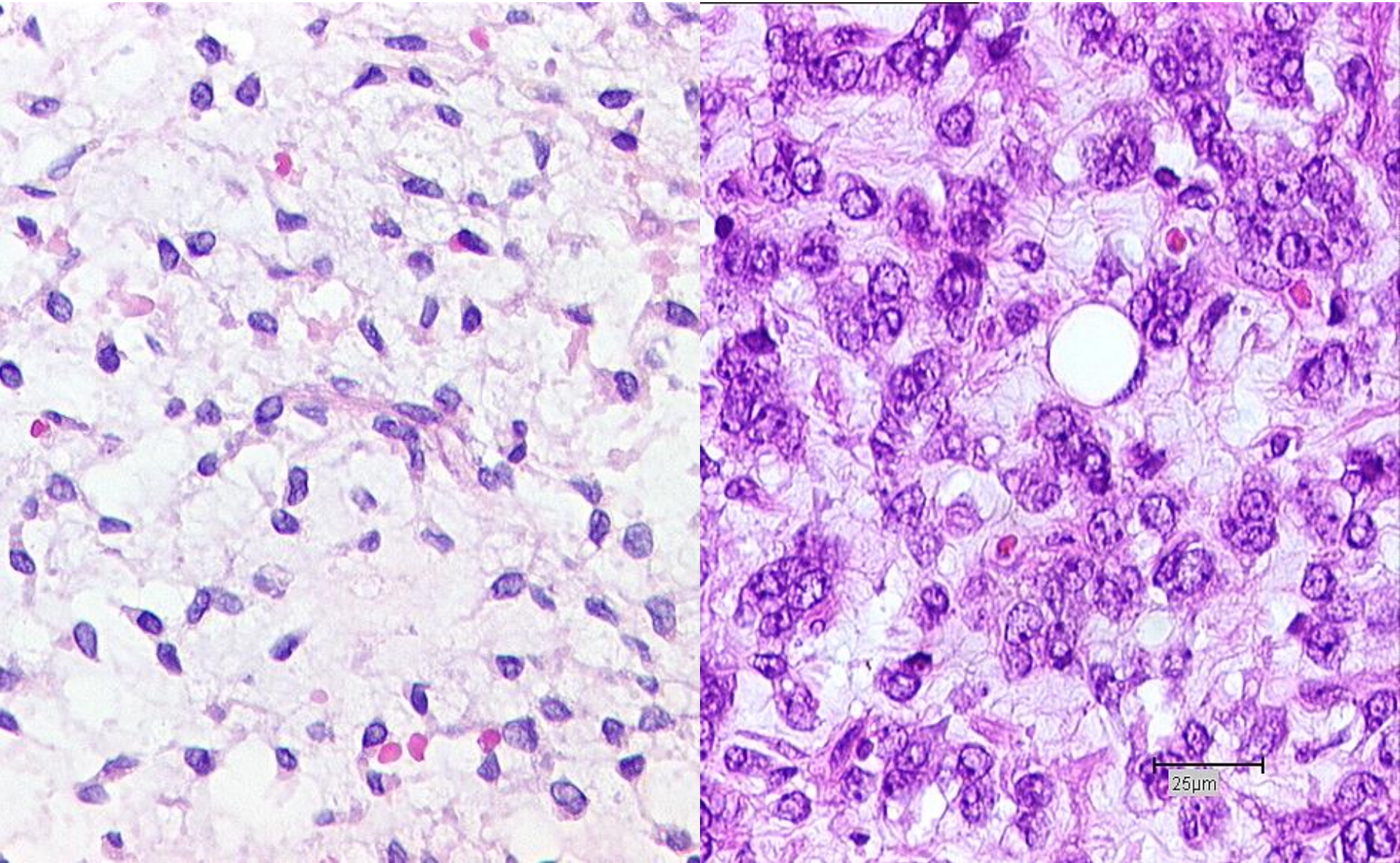
Liposarkom

Myxoides / Rundzelliges Liposarkom



Liposarkom

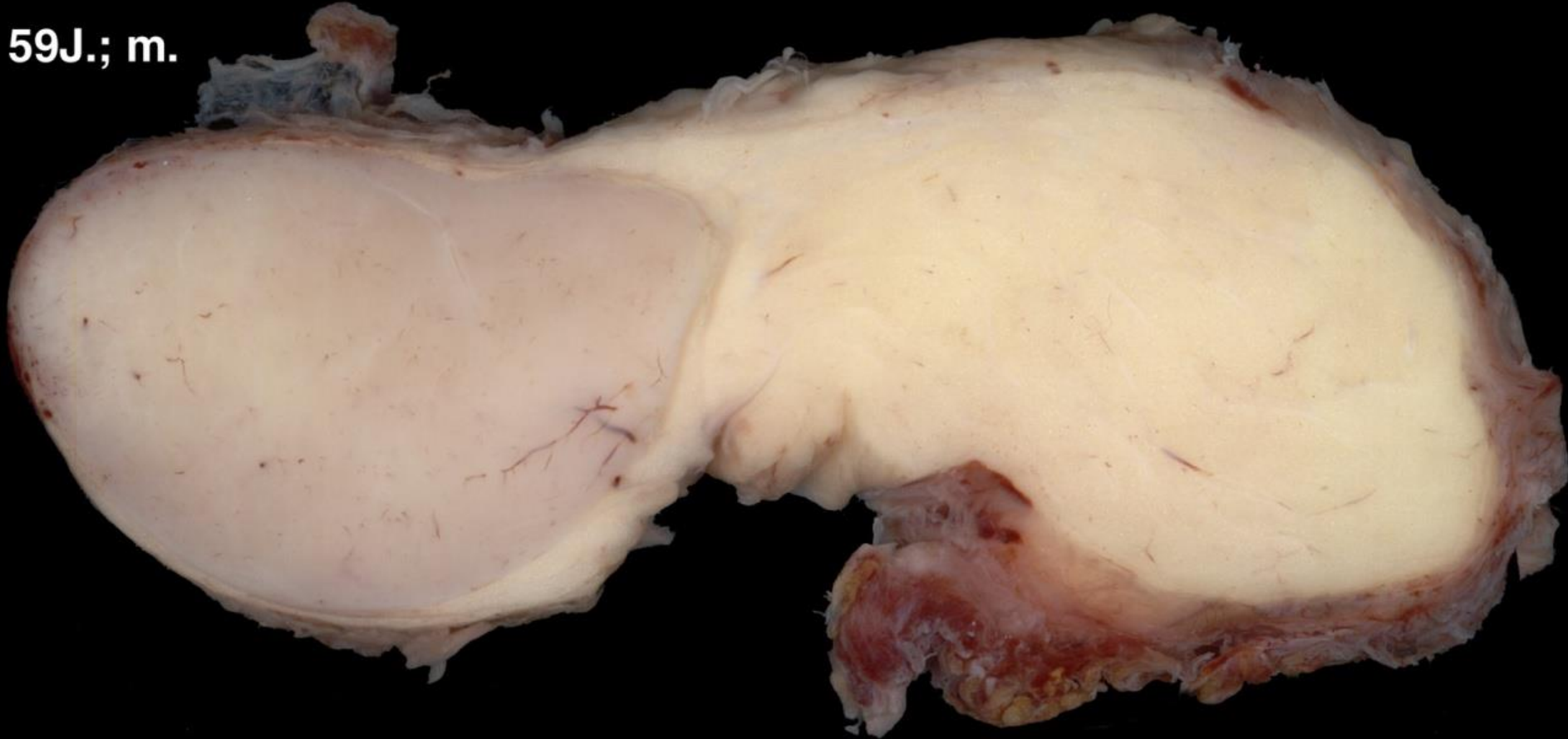
Myxoides / Rundzelliges Liposarkom



Liposarkom

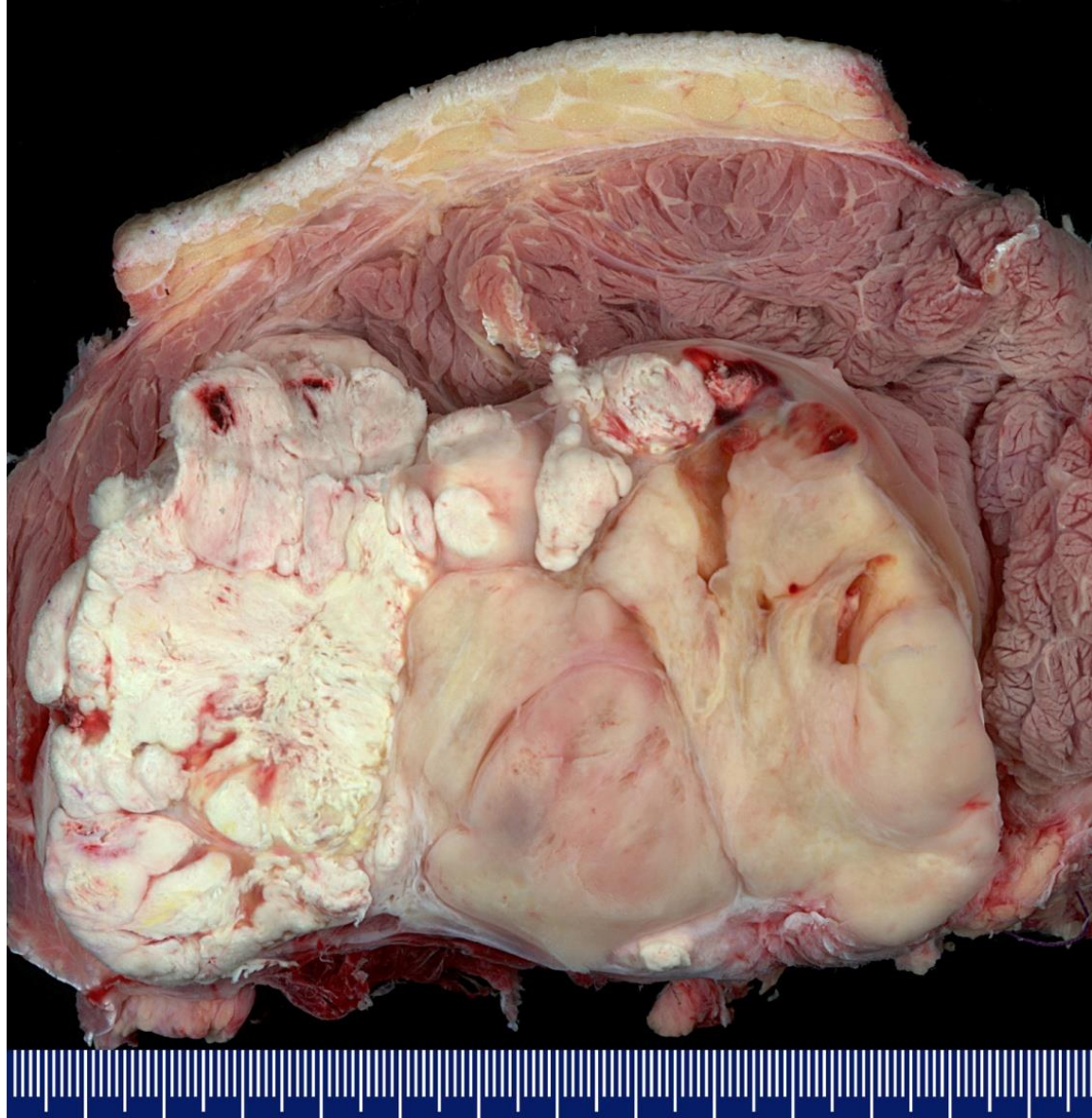
Dedifferenziertes Liposarkom

59J.; m.



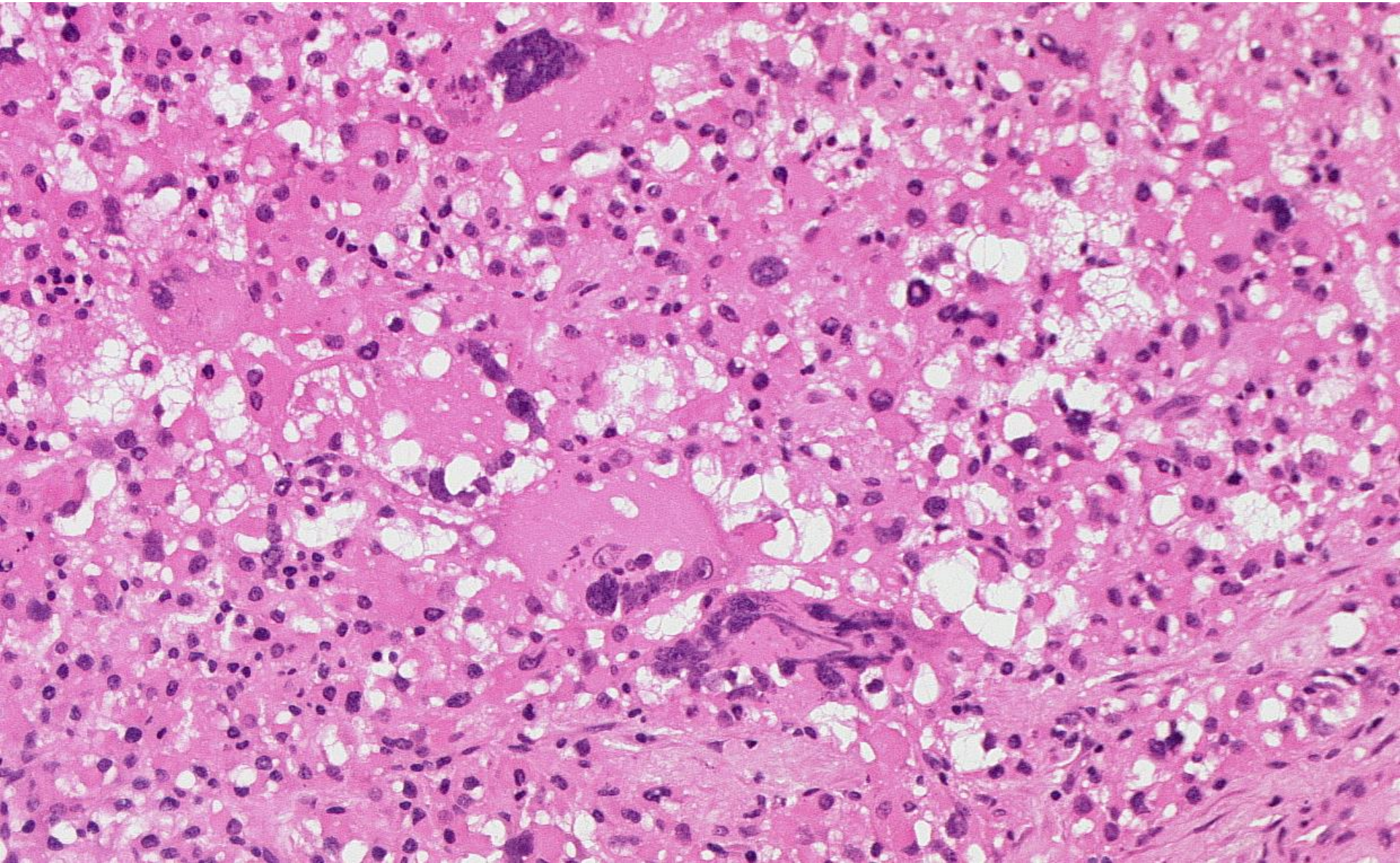
Liposarkom

Pleomorphes Liposarkom



Liposarkom

Pleomorphes Liposarkom



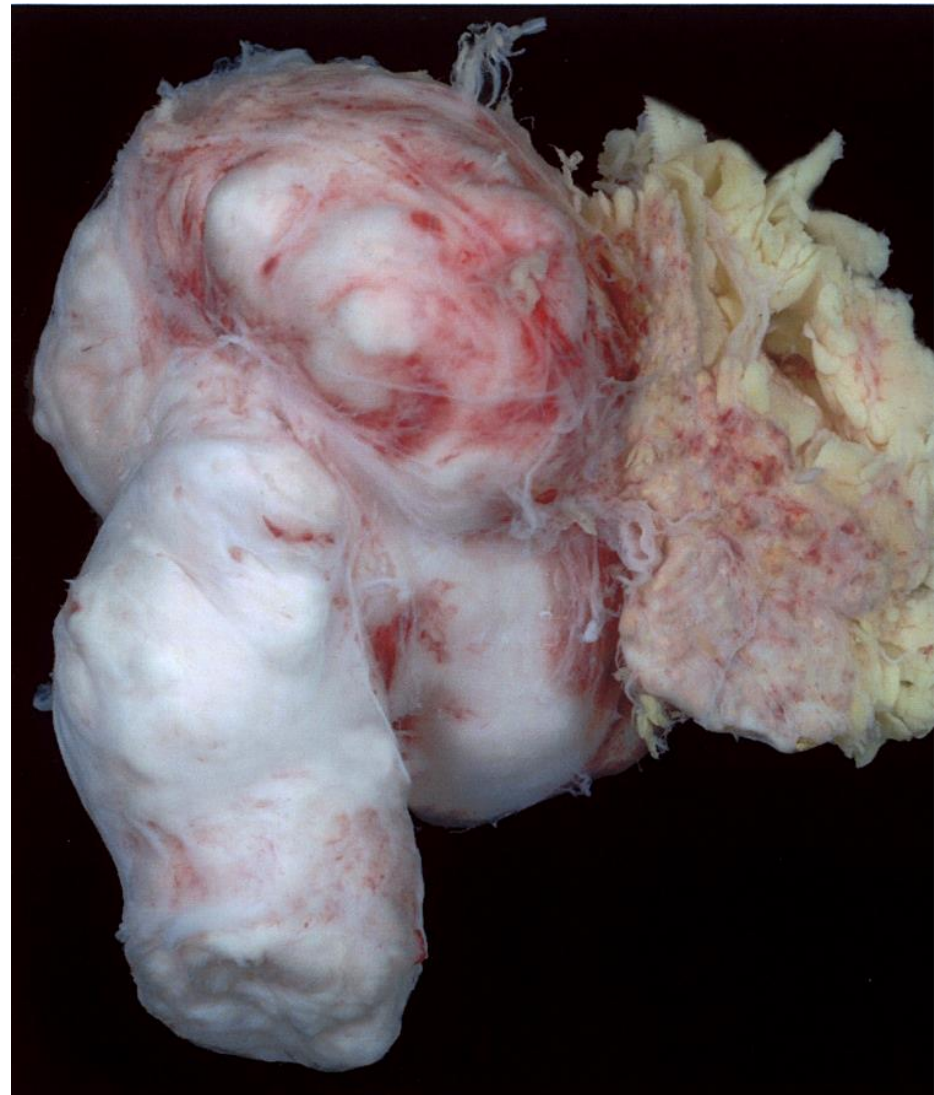
Leiomyosarkom

Makroskopie



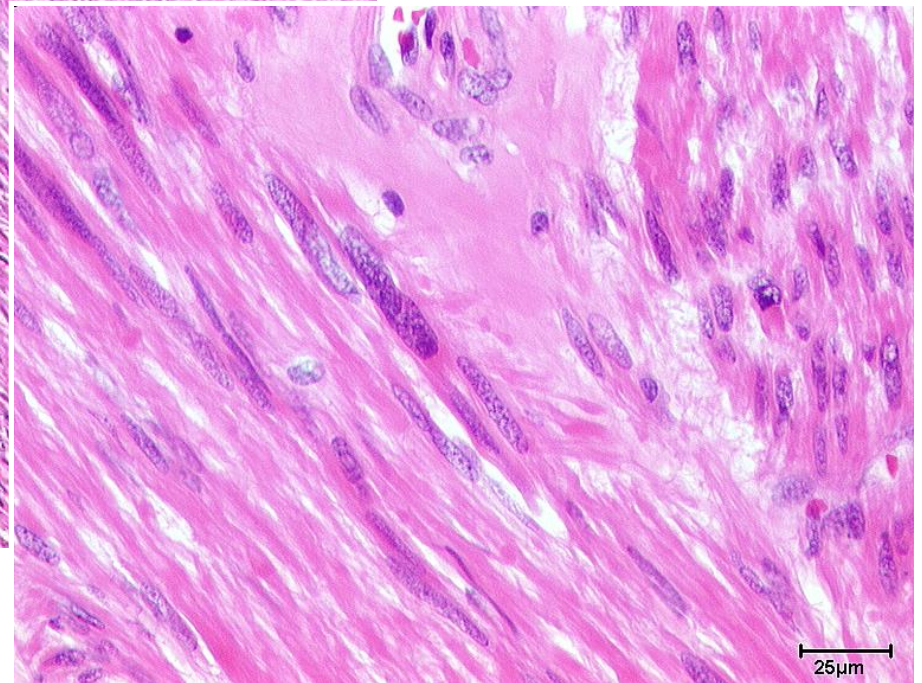
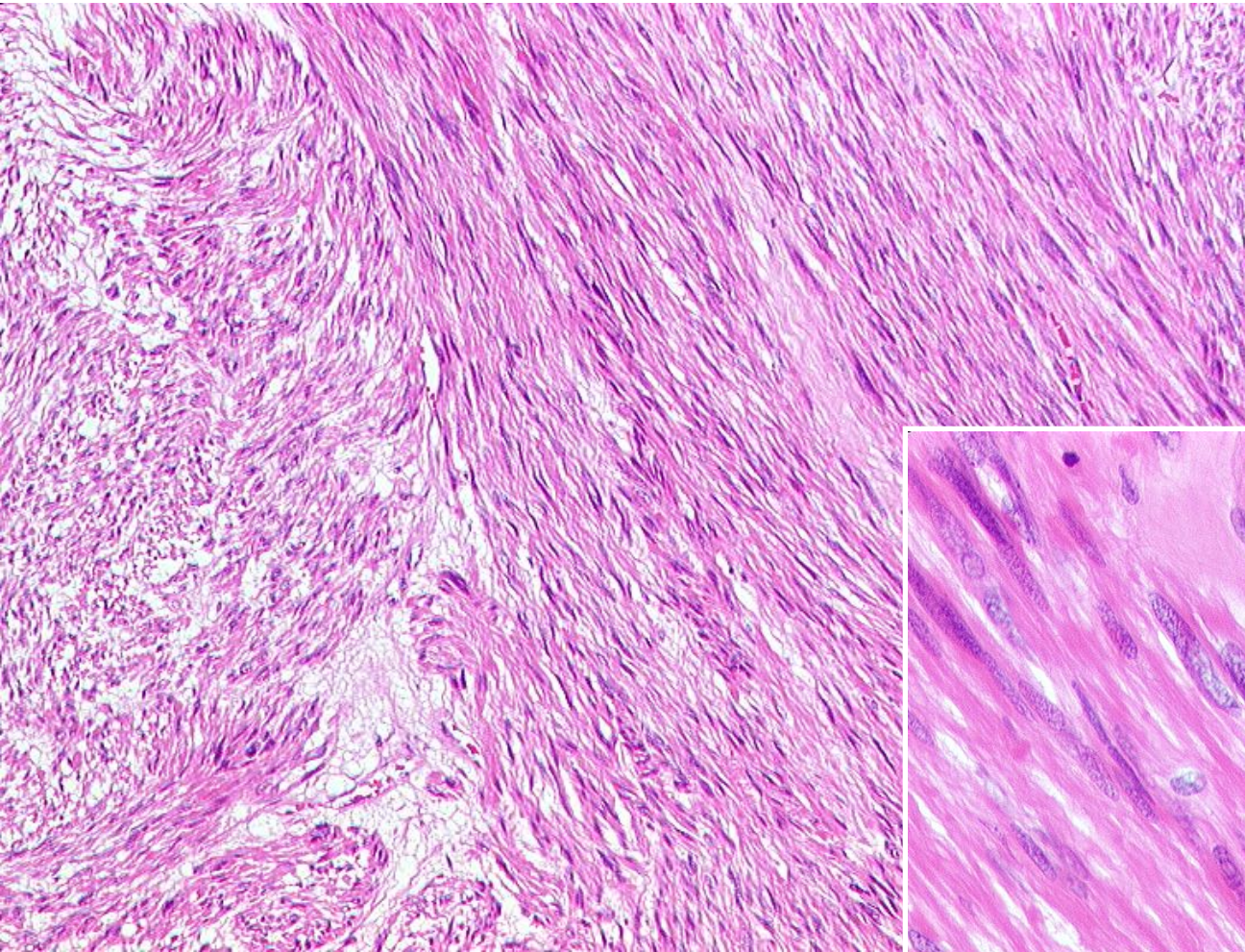
Leiomyosarkom

Makroskopie - Sonderform vaskuläres Leiomyosarkom - Vena cava inferior



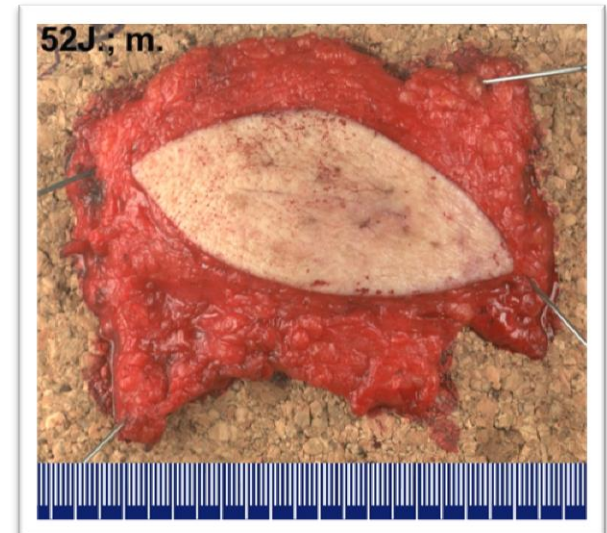
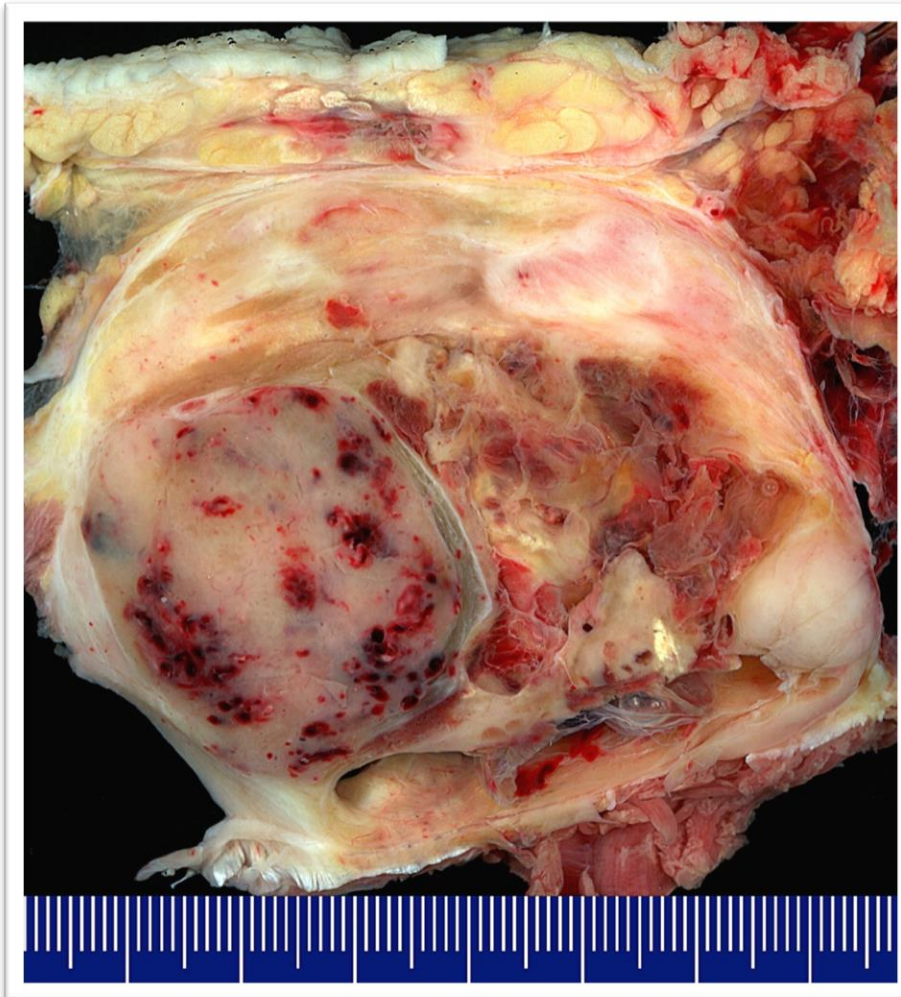
Leiomyosarkom

Mikroskopie



Undifferenziertes pleomorphes Sarkom

Sarkom früher MFH



Undifferenziertes pleomorphes Sarkom

MFH: Malignes Fibröses Histiozytom

**= Pleomorphes Sarkom NOS
(Not Otherwise Specified), sog. MFH**

- (Noch) Häufigstes Sarkom im Erwachsenenalter (ca. 20%)
- Höheres Lebensalter: 6., 7. Lebensdekade
- Histologie: Storiforme („bastmattenartige“) und pleomorphe Anteile



Undifferenziertes pleomorphes Sarkom

MFH

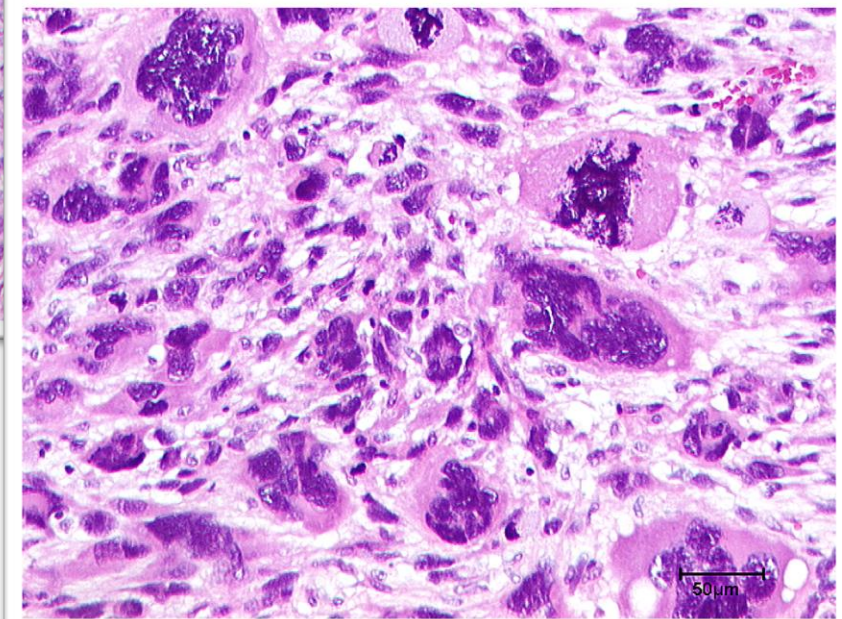
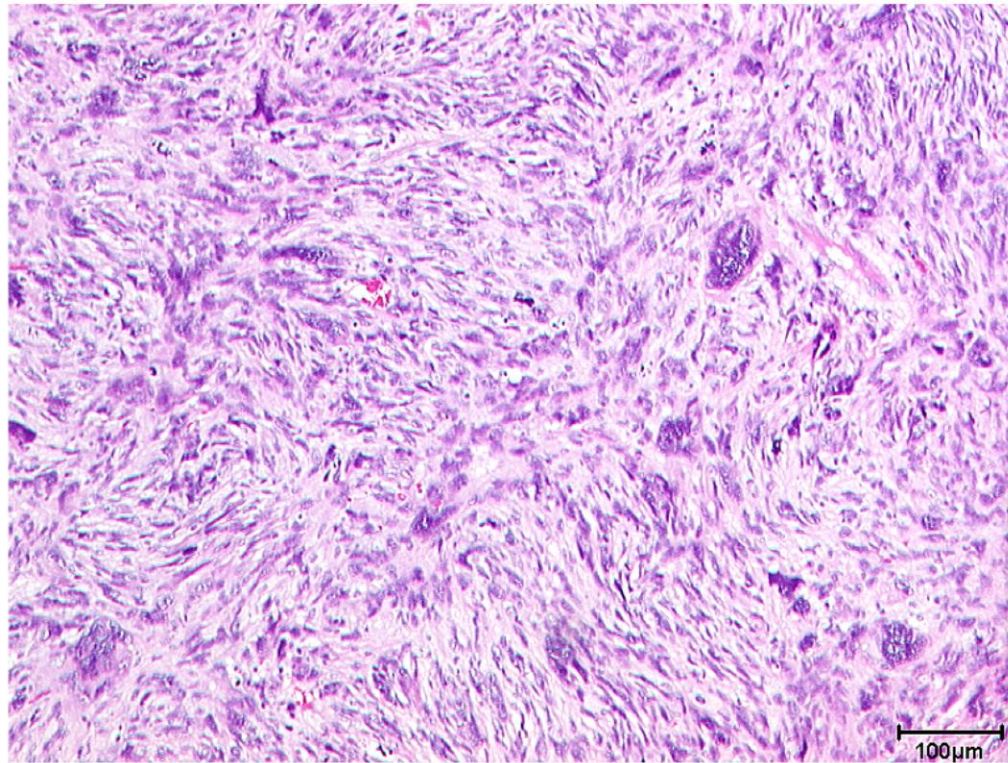
Prototyp eines undifferenzierten pleomorphen Sarkoms.

Keine histiozytäre, sondern undifferenzierte mesenchymale (fibroblastische) Differenzierung!

⇒ „Sarkom NOS (Not Otherwise Specified), sog. MFH“



Undifferenziertes pleomorphes Sarkom



**Storiform-pleomorphes
Sarkom**

Definition

A soft tissue sarcoma showing no identifiable line of differentiation when analysed by presently available technology. At present, this is a heterogeneous group and a diagnosis of exclusion, although genetic subgroups are emerging. Not included are dedifferentiated types of specific soft tissue sarcoma, in which the dedifferentiated component is commonly undifferentiated.

ICD-O codes

Undifferentiated round cell sarcoma	8803/3
Undifferentiated spindle cell sarcoma	8801/3
Undifferentiated pleomorphic sarcoma	8802/3
Undifferentiated epithelioid sarcoma	8804/3
Undifferentiated sarcoma, not otherwise specified	8805/3

Epidemiology

Undifferentiated soft tissue sarcomas (USTS) are uncommon mesenchymal neoplasms that are anatomically ubiquitous and occur at all ages with no difference between the sexes. USTS account for up to 20% of all soft tissue sarcomas. Those with round cell morphology are most frequent in young patients and may ultimately prove to be specific entities; those that are pleomorphic (often known as pleomorphic malignant fibrous histiocytoma in the past) occur mostly in older adults.

Etiology

The etiology of most USTS is unknown. However, at least 25% of radiation-associated soft tissue sarcomas are undifferentiated [987,1555].

Sites of involvement

USTS may be found at any location. Published data are limited but, overall, it seems that these lesions are most common in somatic soft tissue.

Clinical features

USTS has no characteristic clinical features that would distinguish it from other types of sarcoma, other than a frequently rapid growth rate.

Macroscopy

USTSs are a heterogeneous group and thus have no distinctive macroscopic features, other than the frequent presence of necrosis.

Histopathology

USTS may be broadly divided into pleomorphic, spindle cell, round cell and epithelioid subsets, but none have specific defining features other than their lack of an identifiable line of differentiation [861]. Pleomorphic USTS closely resembles other specific types of pleomorphic sarcoma and is often patternless, with frequent bizarre multinucleate tumour giant cells.

Spindle cell USTS most often shows a fascicular architecture with variably amphophilic or palely eosinophilic cytoplasm and tapering nuclei. Round cell USTS consist of relatively uniform rounded or ovoid cells with a high nuclear to cytoplasmic ratio and most often closely resembles other specific types of round cell sarcoma, especially Ewing sarcoma. USTS with epithelioid morphology has been little studied as yet [2421], but is probably not rare. Morphologically these lesions closely resemble metastatic carcinoma or melanoma, but generally lack nesting and have amphophilic or palely eosinophilic cytoplasm and large vesicular nuclei. Importantly, genomic profiling may reveal that some seemingly undifferentiated sarcomas can be classified more specifically [379,496,498,1904].

Immunophenotype

As defined, USTS shows no reproducible immunophenotype, nor any pattern of protein expression that would allow more specific subclassification. However, USTS may often show small numbers of cells that may express keratin, actin, desmin or EMA and there may be patchy positivity for CD99 in round cell neoplasms. Vimentin and CD34 may be positive, but have no discriminatory value.

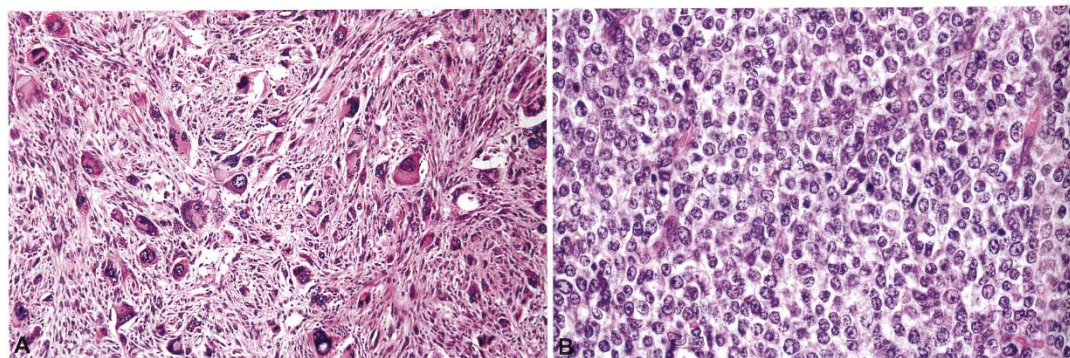


Fig. 13.1 Undifferentiated sarcoma. A Pleomorphic morphology. B Round cell morphology.

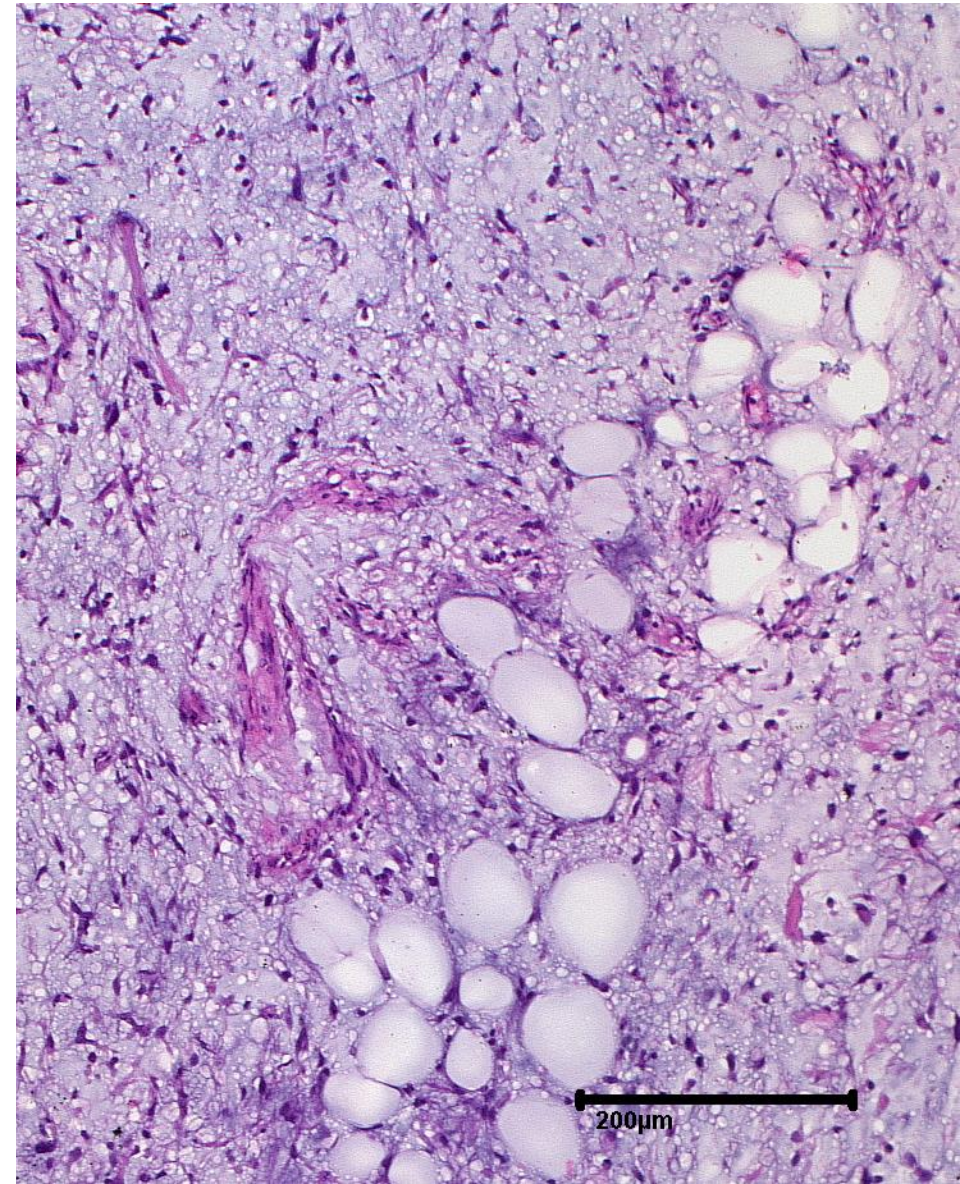
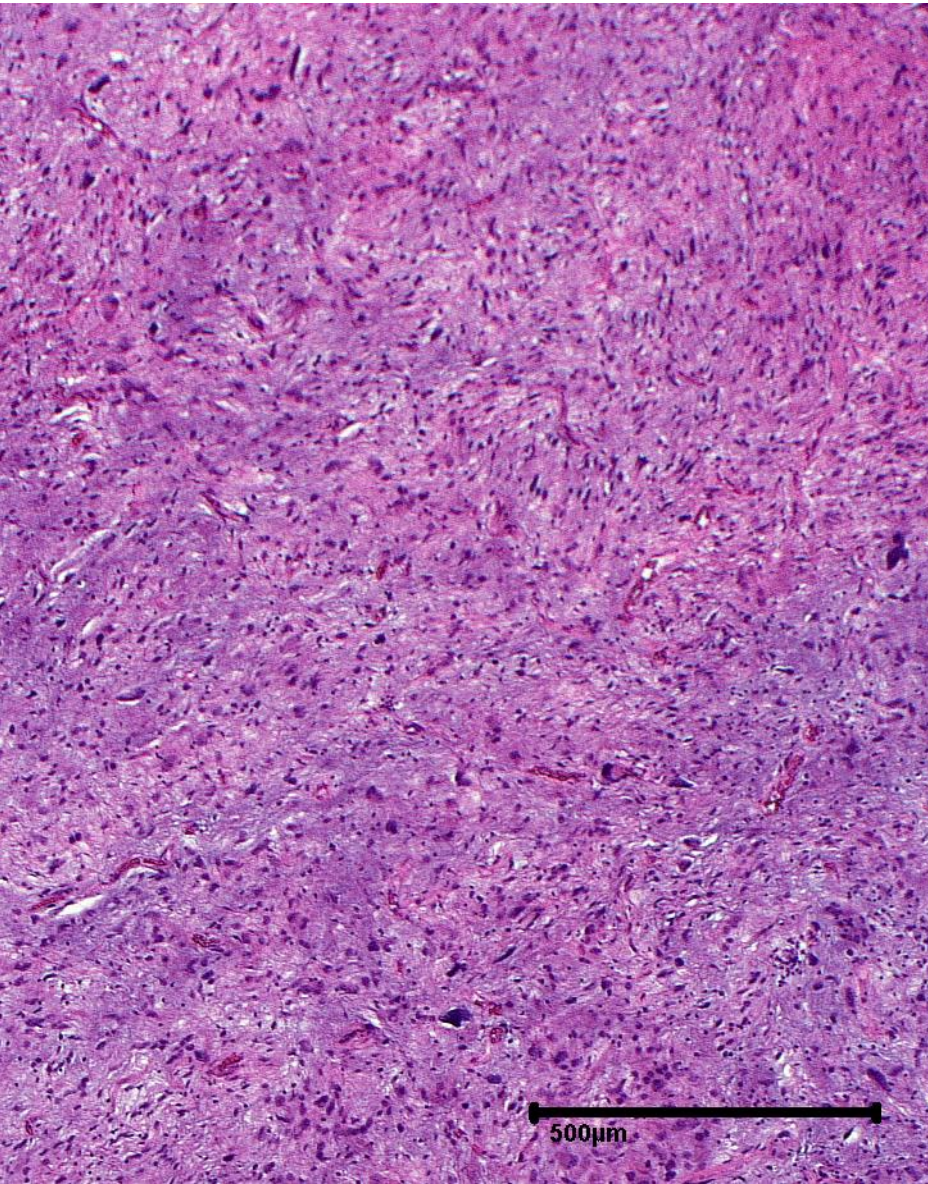
Welche Möglichkeiten der Diagnostik gibt es über die konventionelle Histologie hinaus?



Differentialdiagnose - Myxoides Sarkom

Myxofibrosarkom

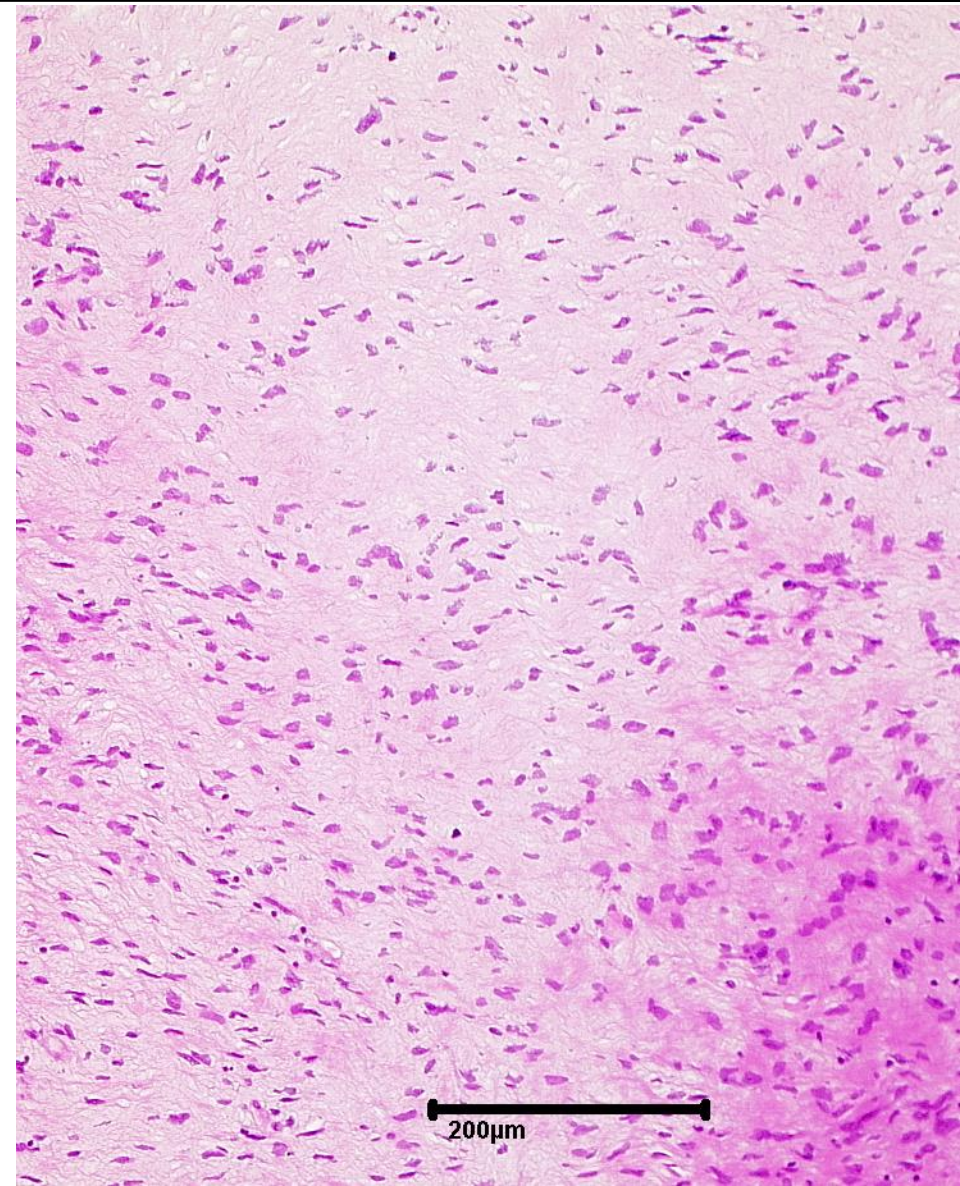
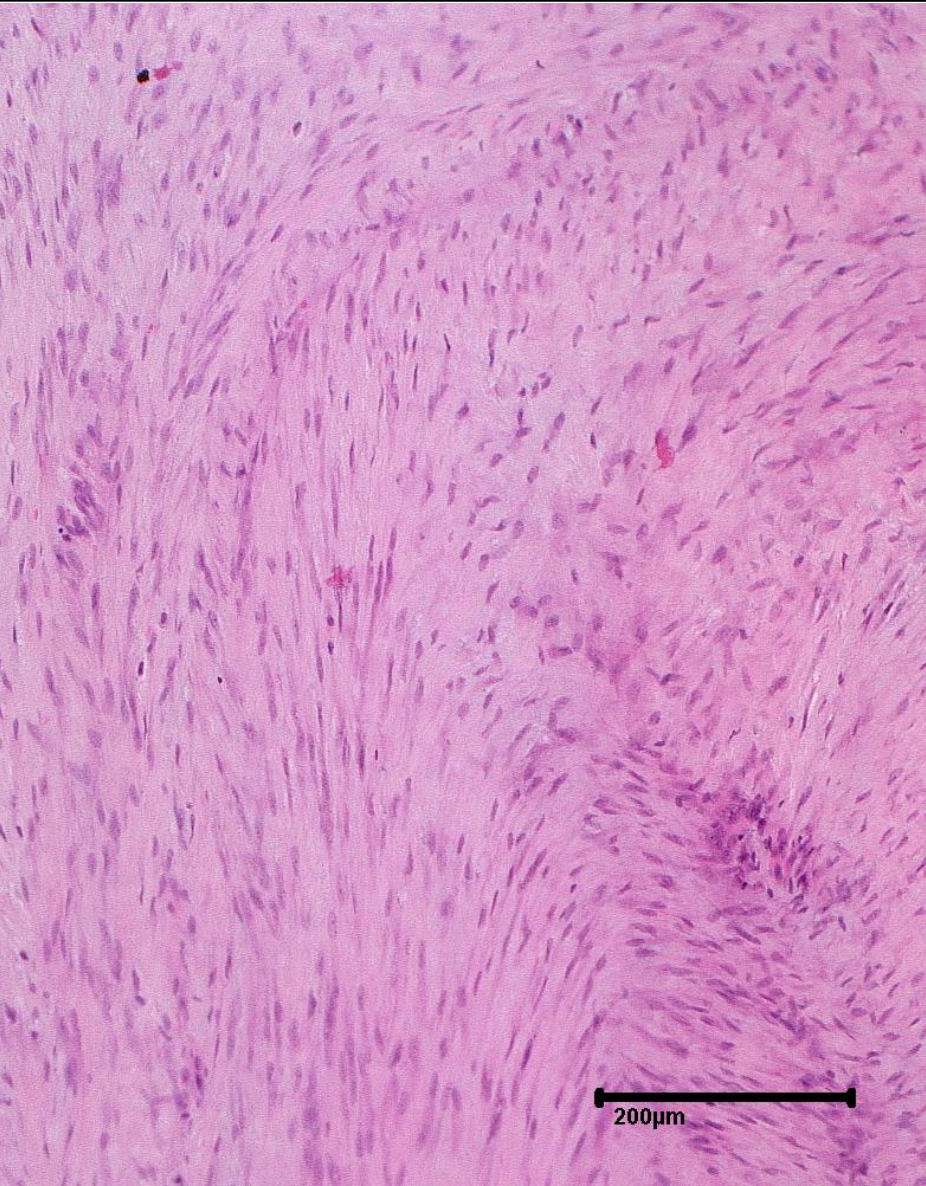
Myxoides Liposarkom



Differentialdiagnose - Spindelzelliger Tumor

Aggressive Fibromatose

(Myo-) fibroblastisches Sarkom



Immunhistochemie

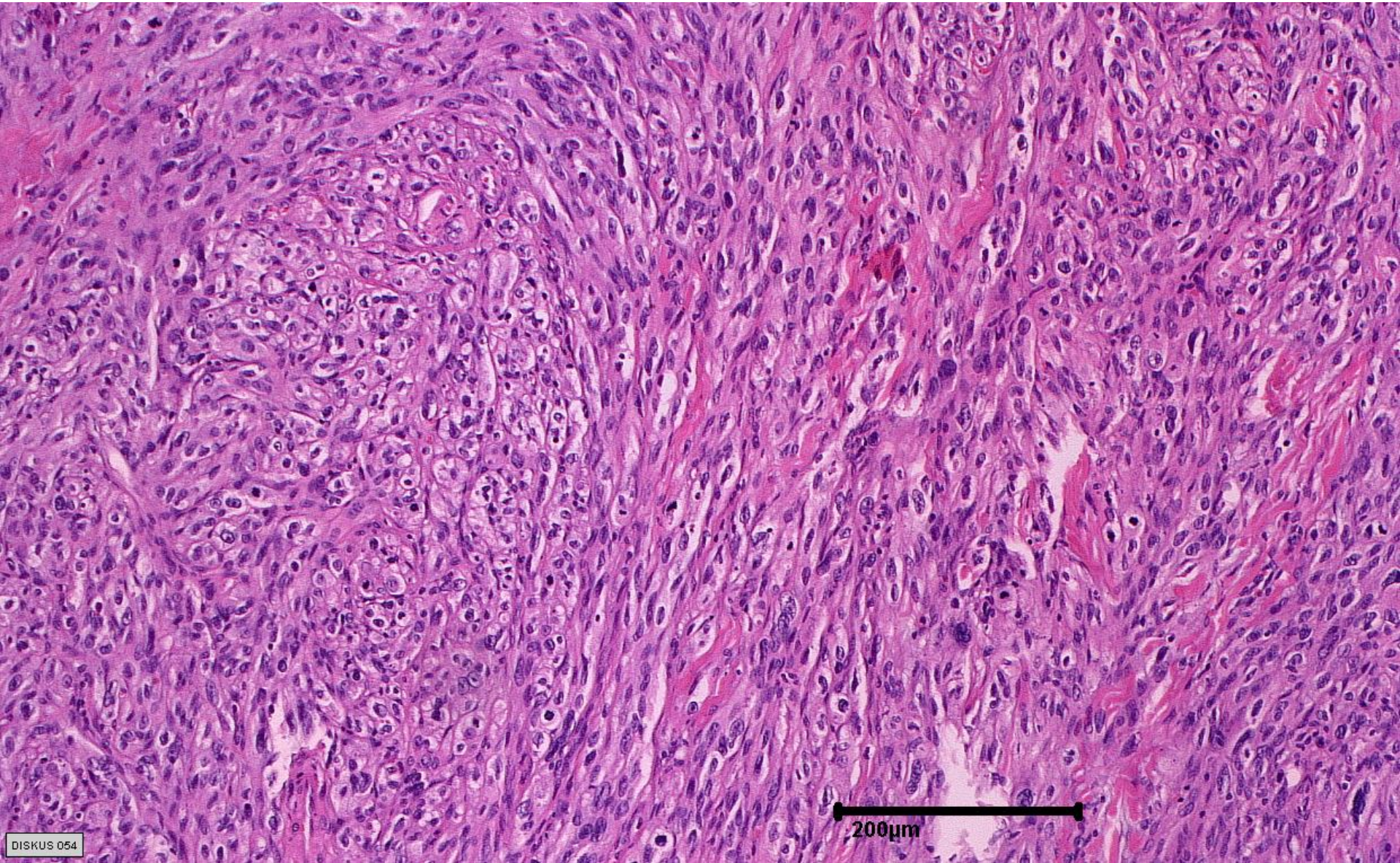
Ausgewählte Antikörper

Antikörper	exprimiert bei folgenden Tumoren
Zytokeratine	Karzinome, Epitheloide Sarkome, Synoviale Sarkome, MPNST
Desmin	Tumoren der glatten Muskulatur und Skelettmuskel (benigne+maligne)
glattes Aktin	glattmuskuläre / myofibroblastische Tumoren (benigne+maligne)
S100	Melanom, MPNST, Chondrogene Tumoren, Fettgewebstumoren
CD34	vaskuläre Tumoren, SFT, DFSP
CD99	Ewing Sarkom / PNET, Synoviale Sarkome, einige Osteosarkome
MDM2/CDK4	Atypische Lipomatöse Tumoren und dedifferenzierte Liposarkome
bcl-2	Synoviale Sarkome, SFT, andere Spindelzelltumoren



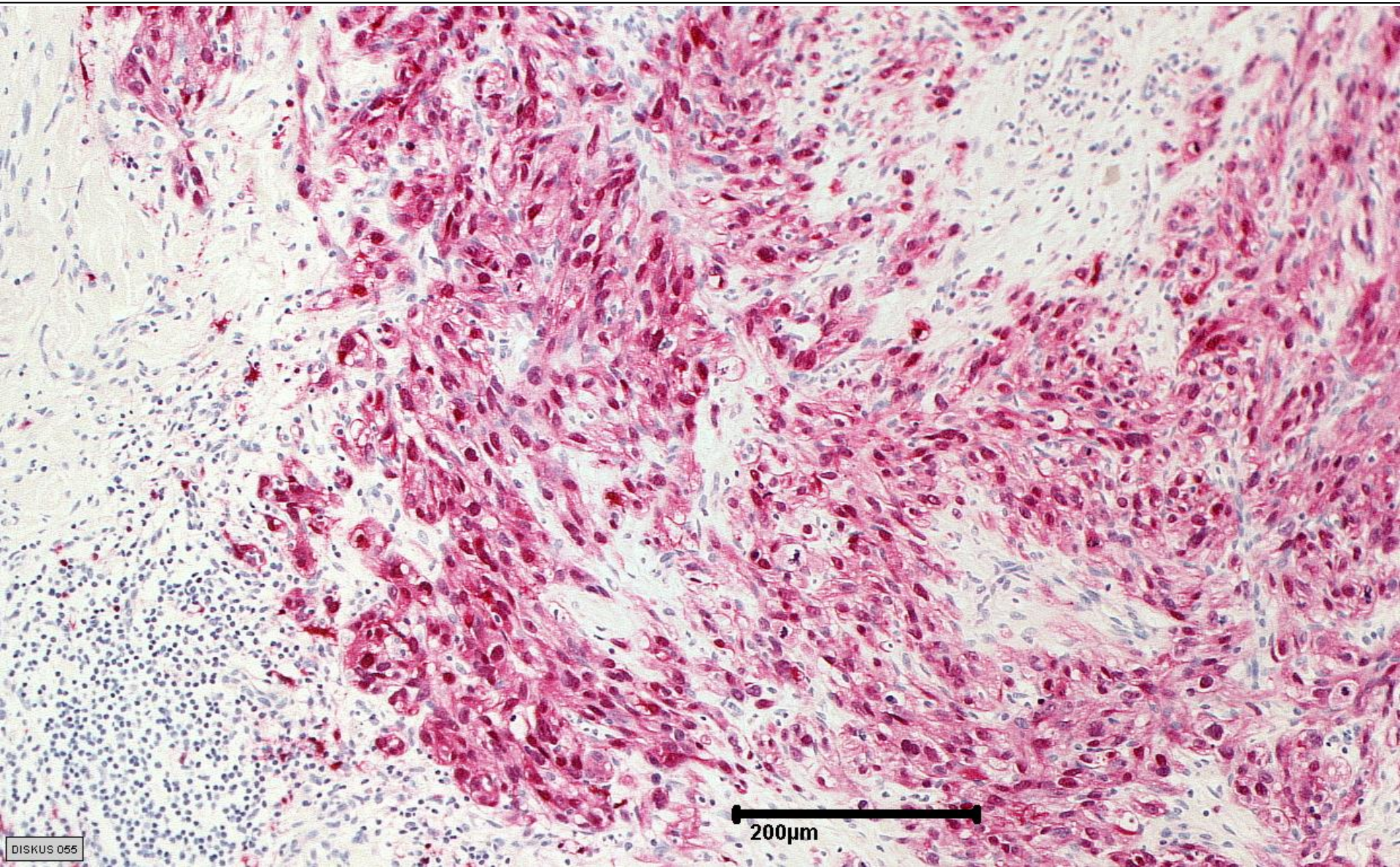
MPNST

HE / konventionelle Histologie



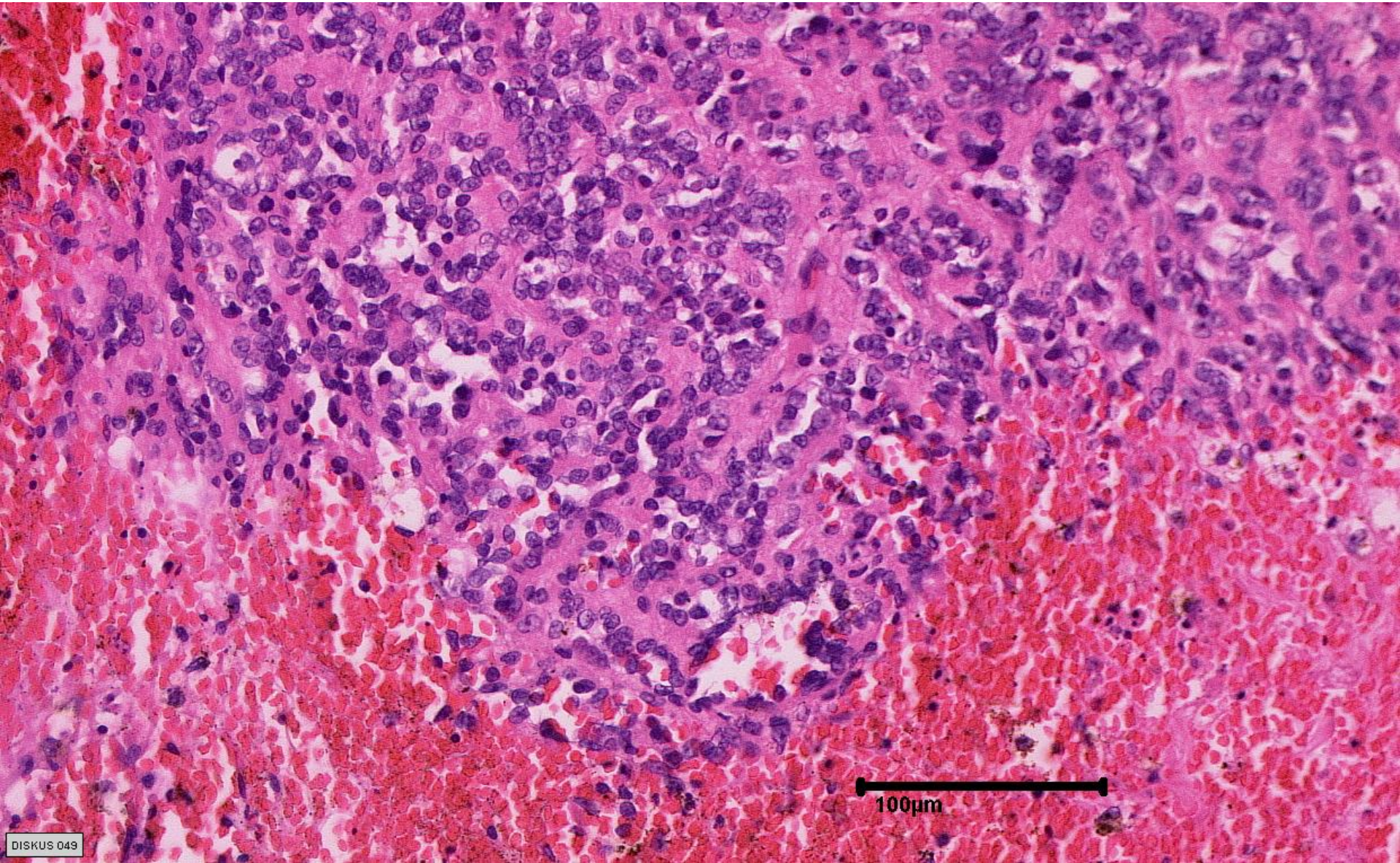
MPNST

Immunhistochemie S100



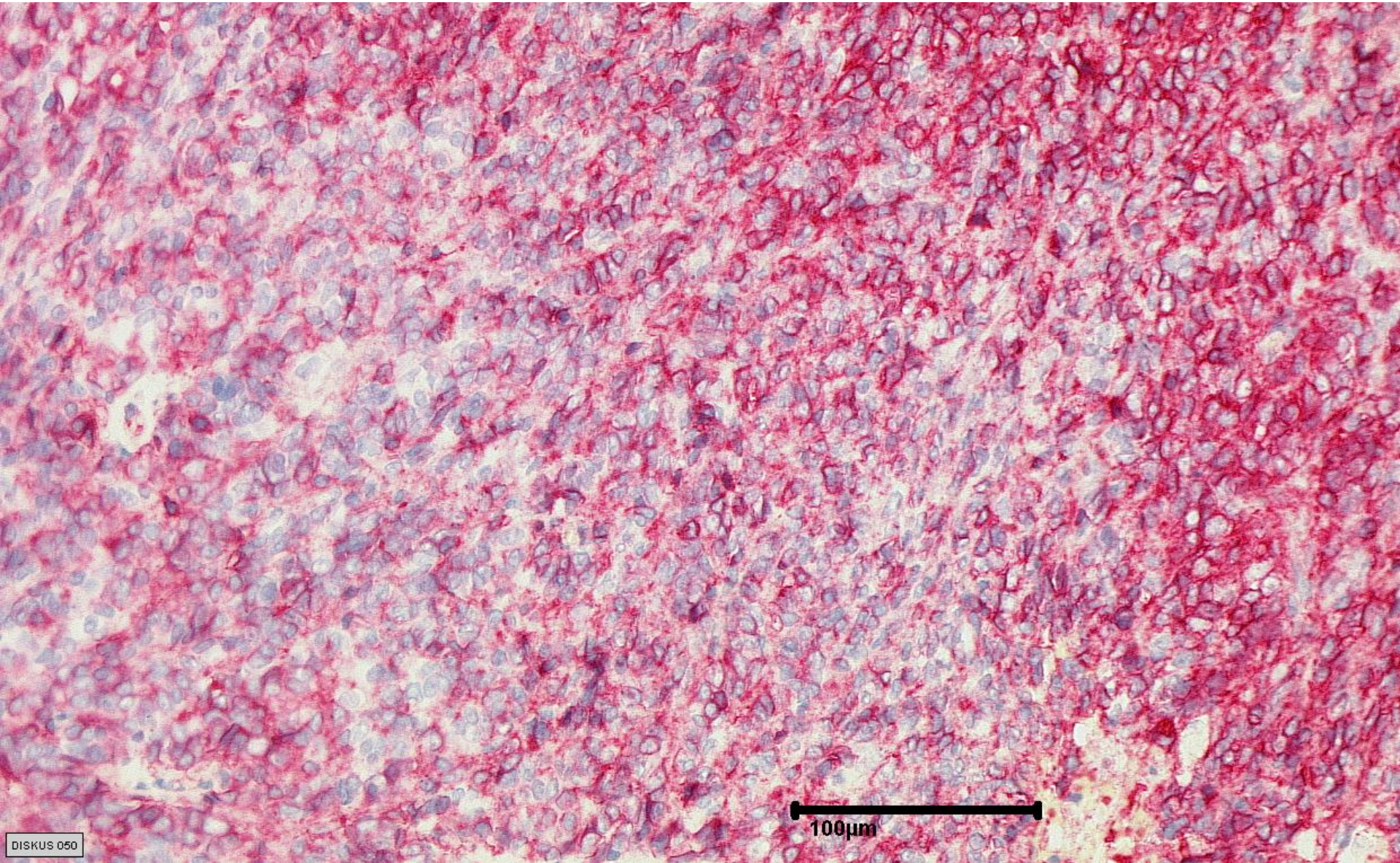
Angiosarkom

Konventionelle Histologie (HE)



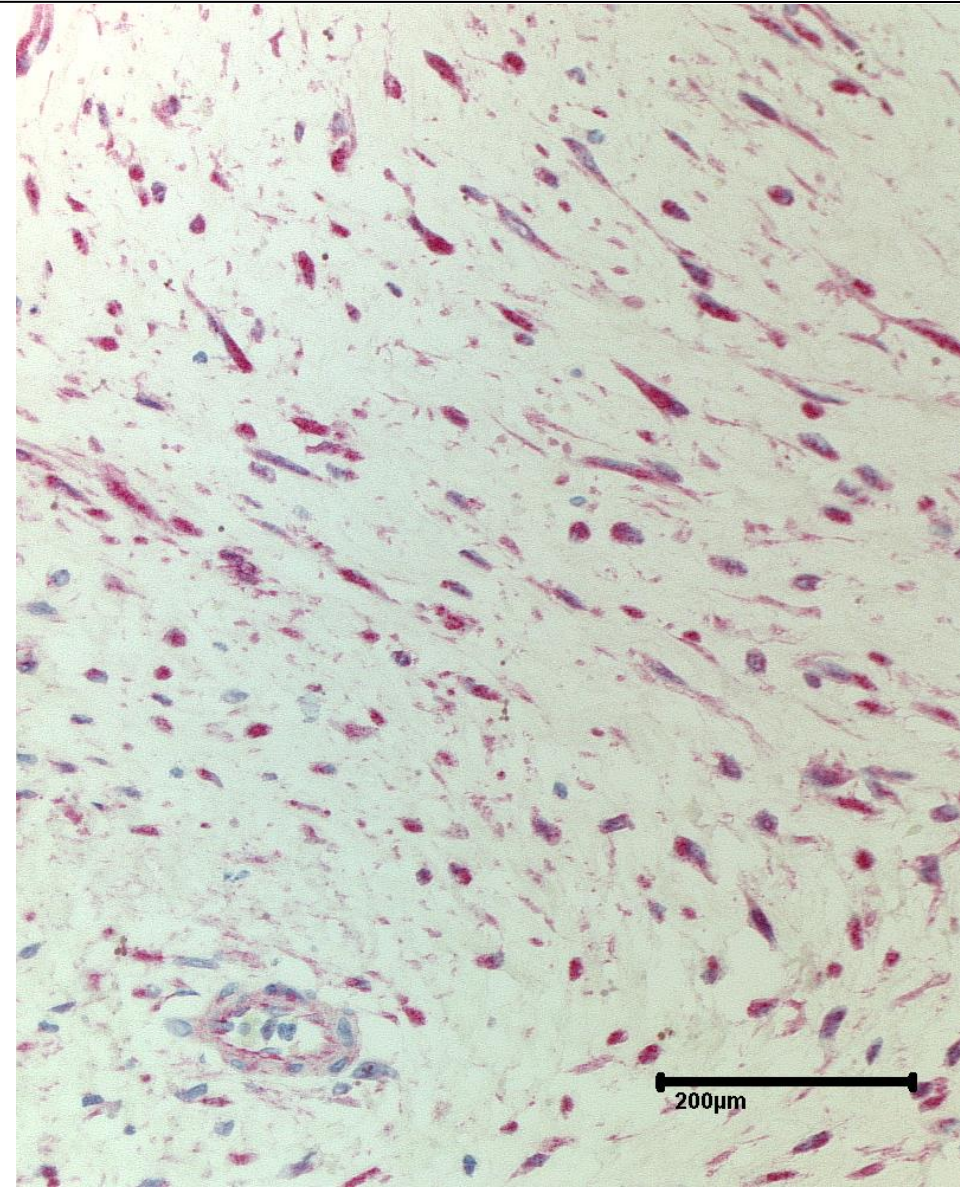
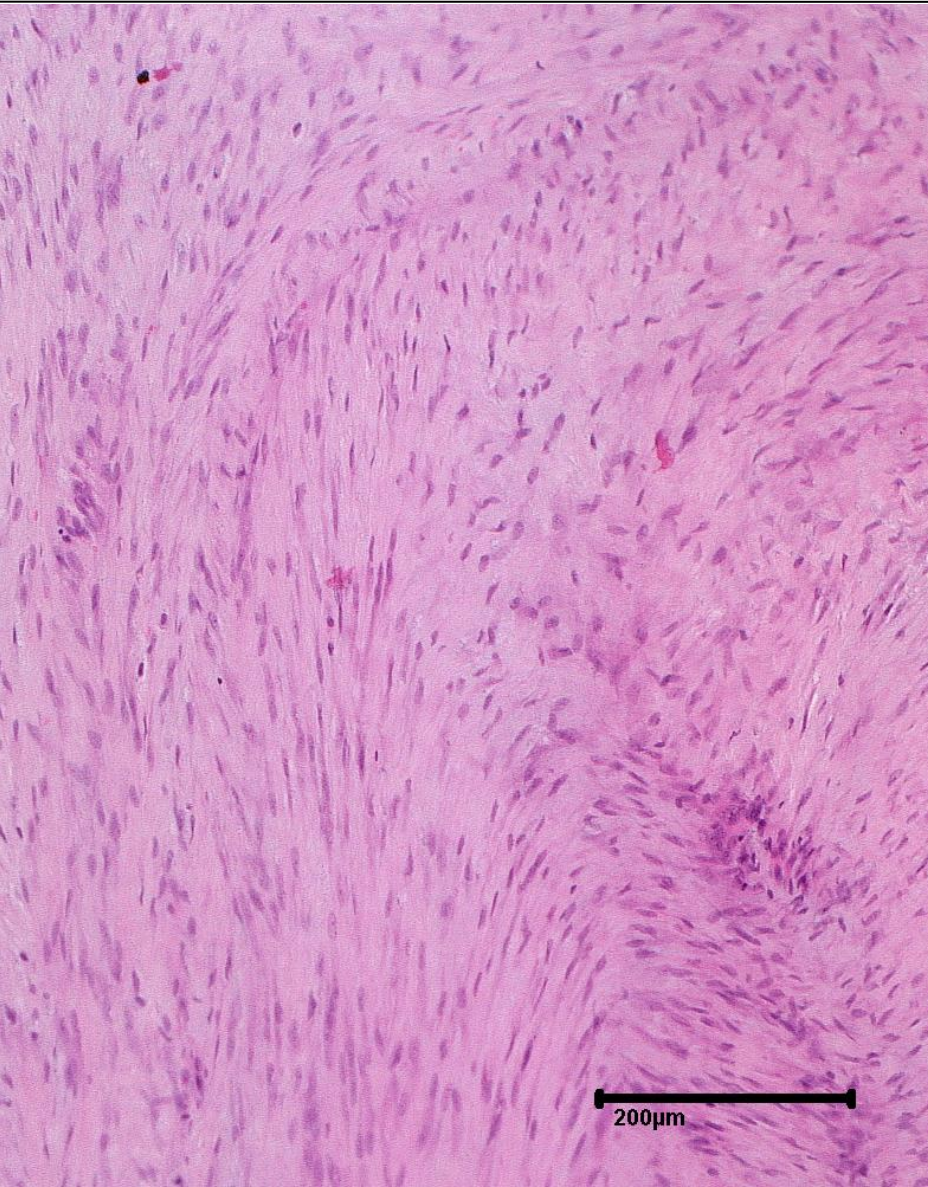
Angiosarkom

Immunhistochemie CD31



Aggressive Fibromatose / Immunhistochemie

Nukleär positive Reaktion: Beta Catenin



Aggressive Fibromatose / Desmoidfibromatose

Makroskopischer Aspekt



TABLE 4-1 RECURRENT CHROMOSOMAL TRANSLOCATIONS IN BENIGN AND MALIGNANT SOFT TISSUE TUMORS

Soft tissue tumor	Translocation	Gene fusion	Approximate prevalence ¹
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	<i>PAX3-FKHR</i>	65%
	t(1;13)(p36;q14)	<i>PAX7-FKHR</i>	15%
Angiomatoid fibrous histiocytoma	t(2;22)(q33;q12)	<i>EWS-CREB1</i>	*
	t(12;22)(q13;q12)	<i>EWS-ATF1</i>	*
	t(12;16)(q13;p11)	<i>FUS-ATF1</i>	*
Alveolar soft part sarcoma	t(X;17)(p11;q25) ²	<i>ASPL-TFE3</i>	>95%
Clear cell sarcoma	t(12;22)(q13;q12)	<i>EWS-ATF1</i>	>90%
	t(2;22)(q33;q12)	<i>EWS-CREB1</i>	*
Dermatofibrosarcoma protuberans/giant cell fibroblastoma	t(17;22)(q21;q13) ³	<i>COL1A1-PDGFB</i>	>90%
Desmoplastic fibroblastoma	t(2;11)(q31;q12)	Unknown	*
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	<i>EWS-WT1</i>	>95%
Epithelioid hemangioendothelioma	t(1;3)(p36.3;q25)	Unknown	*
Extraskelatal myxoid chondrosarcoma	t(9;22)(q22-q3;q12)	<i>EWS-NR4A3</i>	75%
	t(9;17)(q22;q11)	<i>TAF15-NR4A3</i>	25%
Ewing sarcoma/PNET	t(11;22)(q24;q12)	<i>EWS-FLI1</i>	90%
	t(21;22)(q22;q12)	<i>EWS-ERG</i>	5%
	t(7;22)(p22;q12)	<i>EWS-ETV1</i>	<1%
	t(2;22)(q33;q12)	<i>EWS-FEV</i>	<1%
	t(17;22)(q12;q12)	<i>EWS-E1AF</i>	<1%
	t(16;21)(p11;q22)	<i>FUS-ERG</i>	<1%
Fibromyxoid sarcoma (low-grade)	t(7;16)(q33;p11.2)	<i>FUS-CREB3L2</i>	>95%
	t(11;16)(p13;p11.2)	<i>FUS-CREB3L1</i>	<5%
Giant cell tumor of tendon sheath	t(1;2)(p13;q37)	<i>CSF1-COL6A3</i>	*
Infantile fibrosarcoma	t(12;15)(p13;q26)	<i>ETV6-NTRK3</i>	>95%
Inflammatory myofibroblastic tumor	t with 2p23	<i>ALK</i> fusions	>50%
Lipoblastoma	t with 8q12	<i>PLAG1</i> fusions	*
Lipoma, ordinary	t with 12q15	<i>HMGA2</i> fusions	*
	t with 6p21	<i>HMGA1</i> rearrangements ⁴	*
Myxoid/round cell liposarcoma	t(12;16)(q13;p11)	<i>FUS-CHOP</i>	>95%
	t(12;22)(q13;q11)	<i>EWS-CHOP</i>	<5%
Pericytoma	t(7;12)(p2;q13)	<i>ACTB-GLI</i>	*
Synovial sarcoma	t(X;18)(p11.2;q11.2)	<i>SYT-SSX1</i>	65%
		<i>SYT-SSX2</i>	35%
		<i>SYT-SSX4</i>	<1%

¹Insufficient data to estimate prevalence.²Translocation usually present in unbalanced form as der(X) only (see text for details).³Translocation usually present and amplified as ring chromosome (see text for details).⁴*HMGA1* rearrangements usually do not result in fusion transcripts (see text for details).

Tumorspezifische Translokationen / Amplifikationen / Genumlagerungen

Tumortyp und involvierte Gene

Ewing-Sarkom/PNET

EWS-FLI1, EWS-ERG, EWS-ETV1

Desmoplastic small round
cell tumor

EWS-WT1

Klarzellsarkom

EWS-ATF1

myxoides Chondrosarkom

EWS-TEC

alv. Rhabdomyosarkom

PAX3-FKHR, PAX7-FKHR

Myxoides Liposarkom

CHOP-TLS, CHOP-EWS

Synovialsarkom

SYT-SSX

DFSP

PDGFB-COL1A1

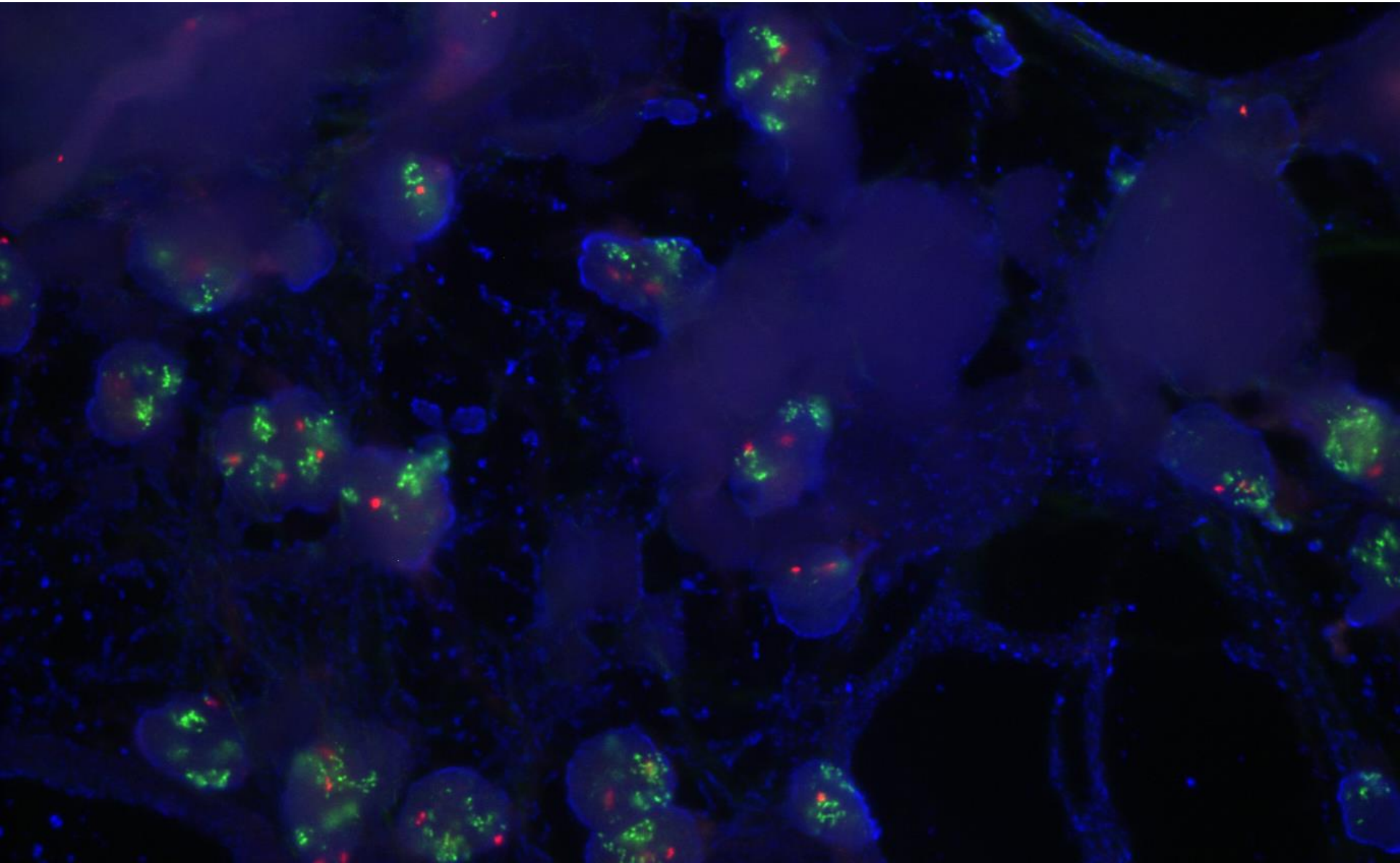
ALT / Liposarkom

MDM2 / CDK4 Amplifikation



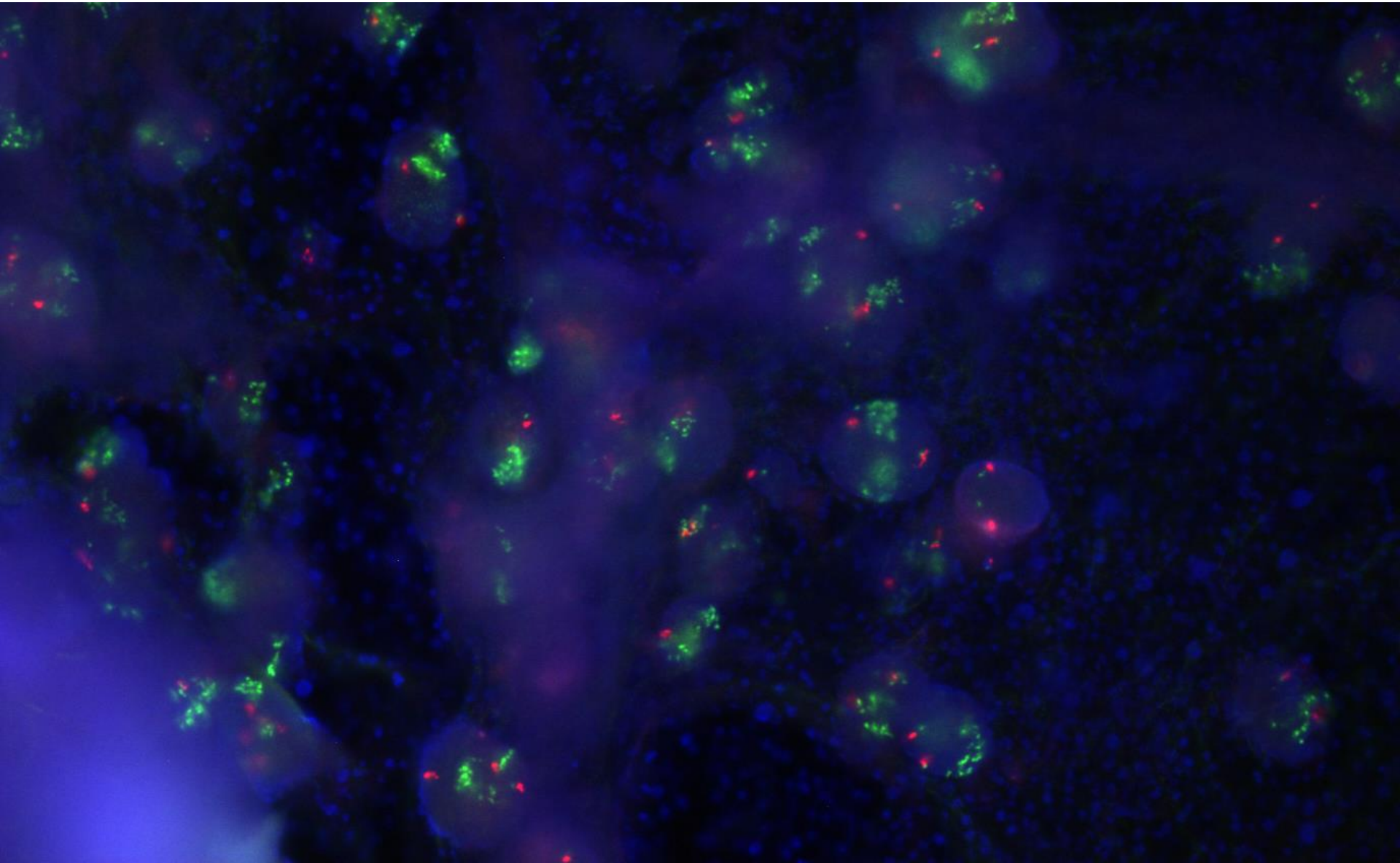
Fluoreszenz in situ Hybridisierung (FISH)

MDM2 Amplifikation bei einem atypischen lipomatösen Tumor (ALT)



Fluoreszenz in situ Hybridisierung (FISH)

MDM2 Amplifikation bei einem atypischen lipomatösen Tumor (ALT)



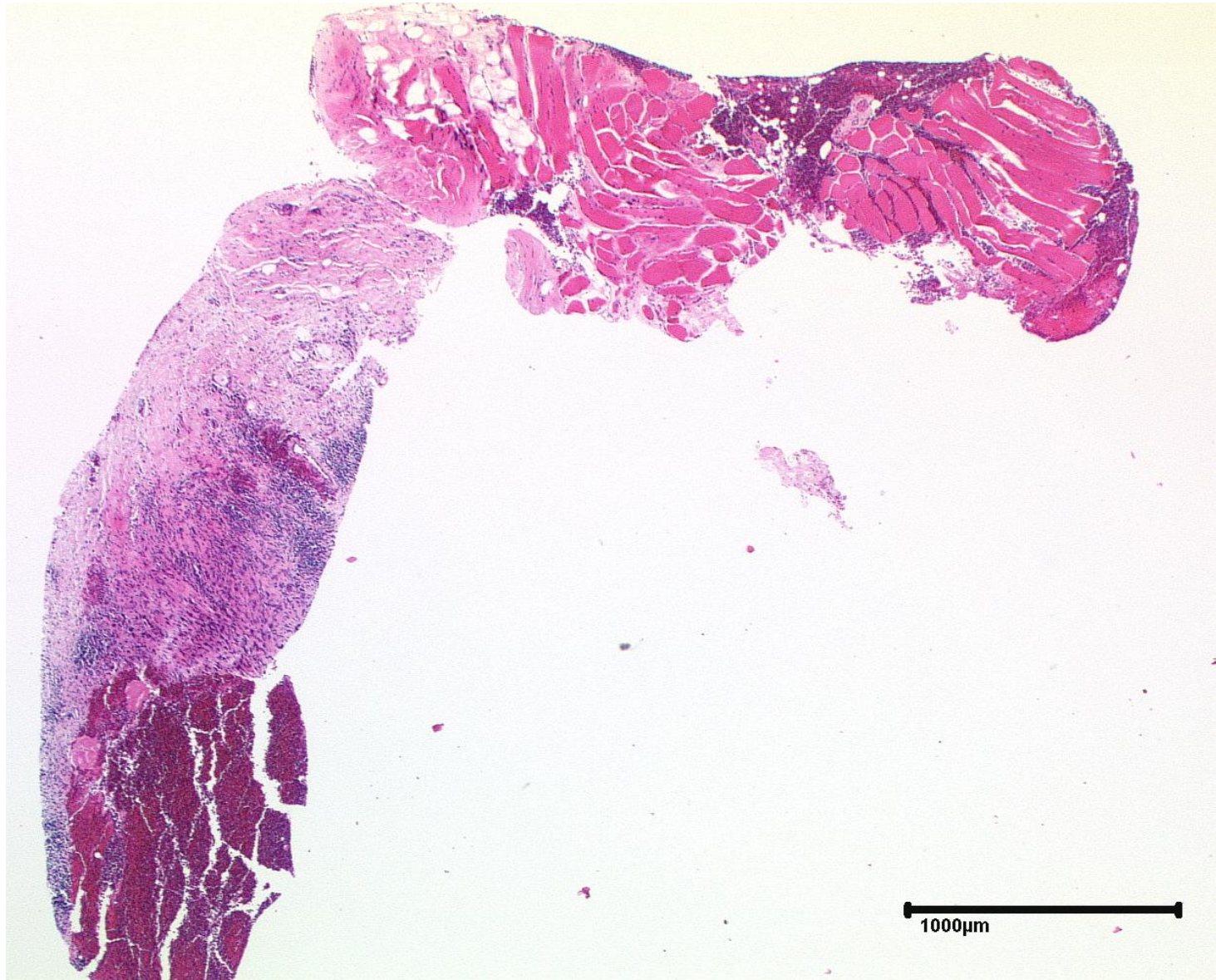


Pathologe als Partner des Kliniklers

Stanzbiopsie, CT-gesteuert

Klinisch hochgradiger Verdacht auf ein Sarkom des M. deltoideus rechts

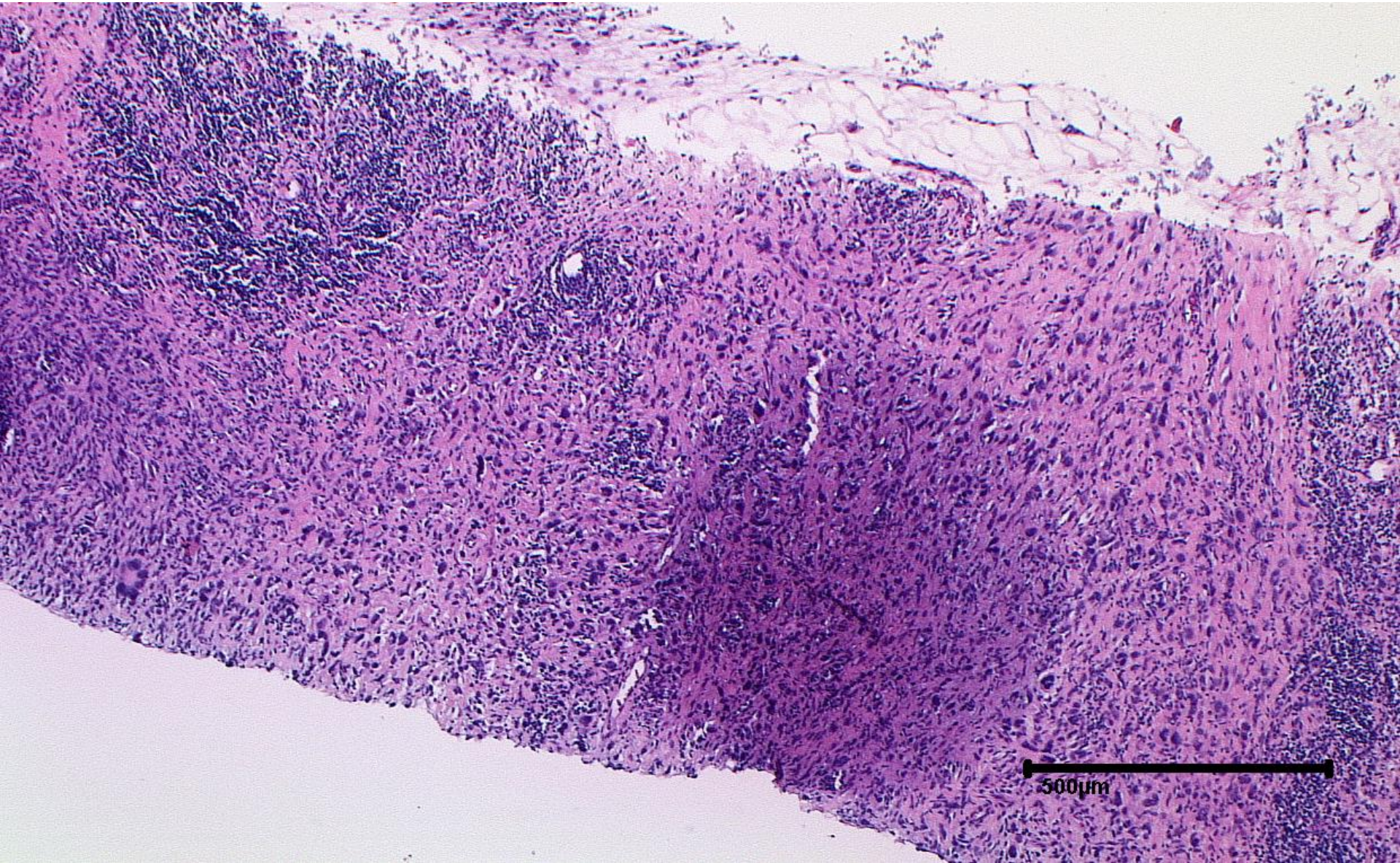
Befund: Kein Tumornachweis, regelrechte Muskulatur, Entzündung



Stanzbiopsie, Rebiopsie

Verdacht auf ein Sarkom des M. deltoideus rechts

Befund: pleomorphes Sarkom als Rezidiv eines pleomorphen Liposarkoms

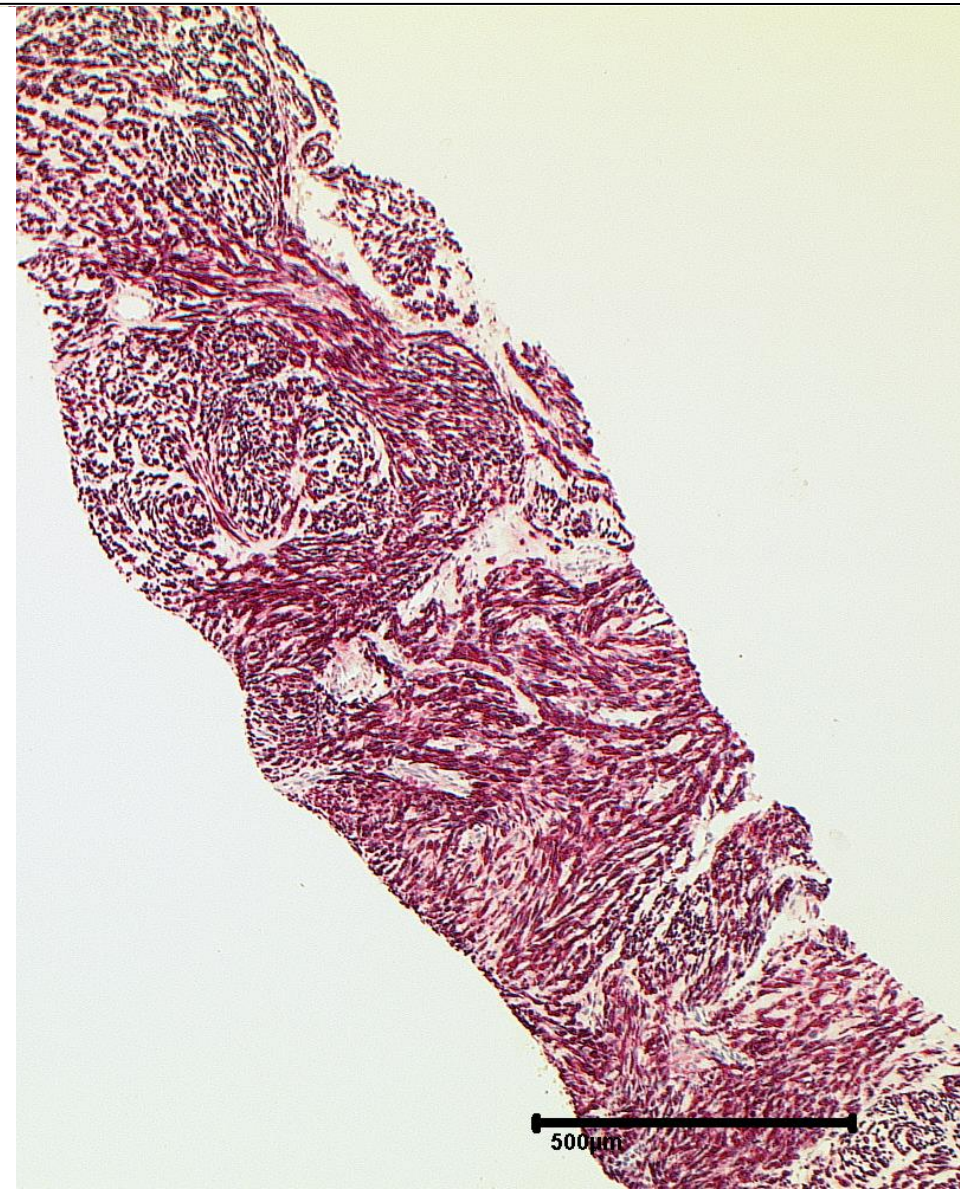
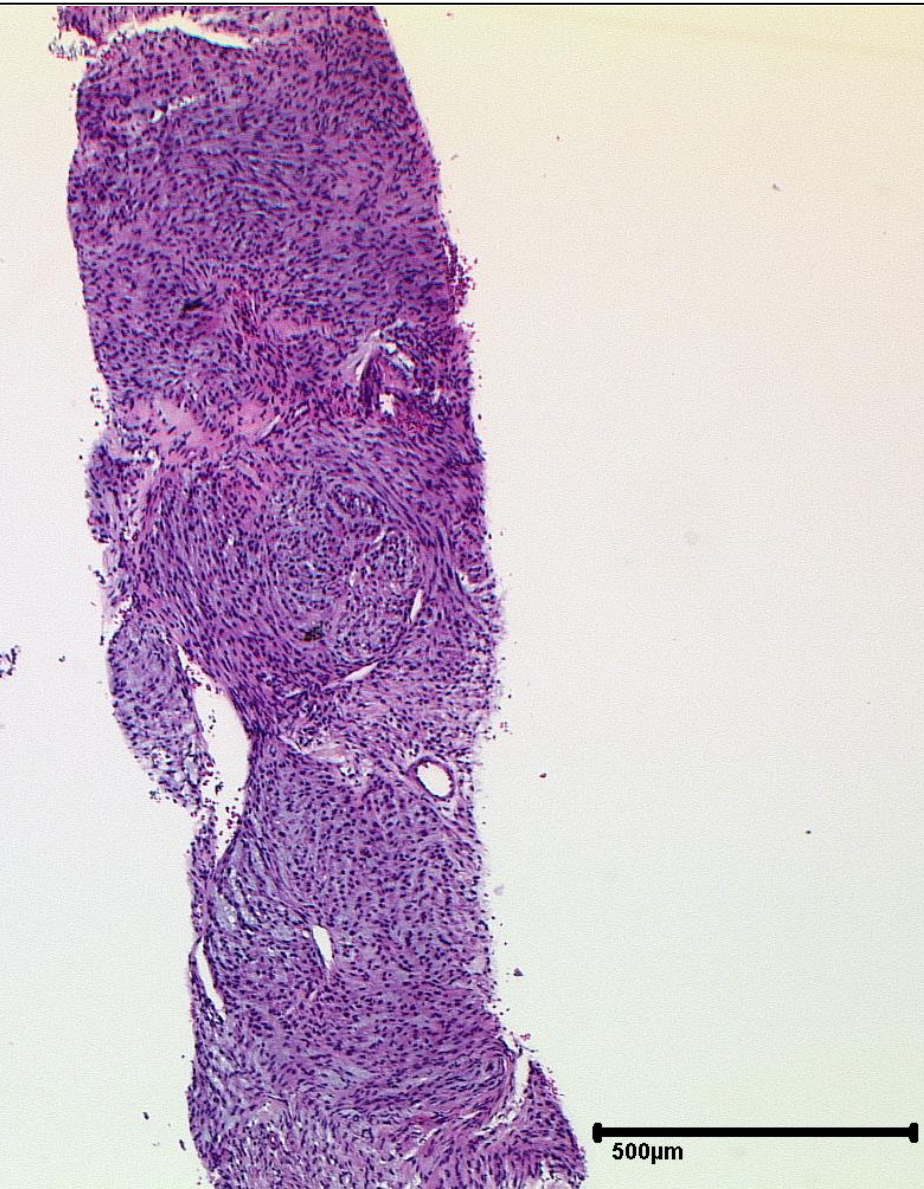


Stanzbiopsie, CT-gesteuert

Rezidiv eines bekannten Leiomyosarkoms

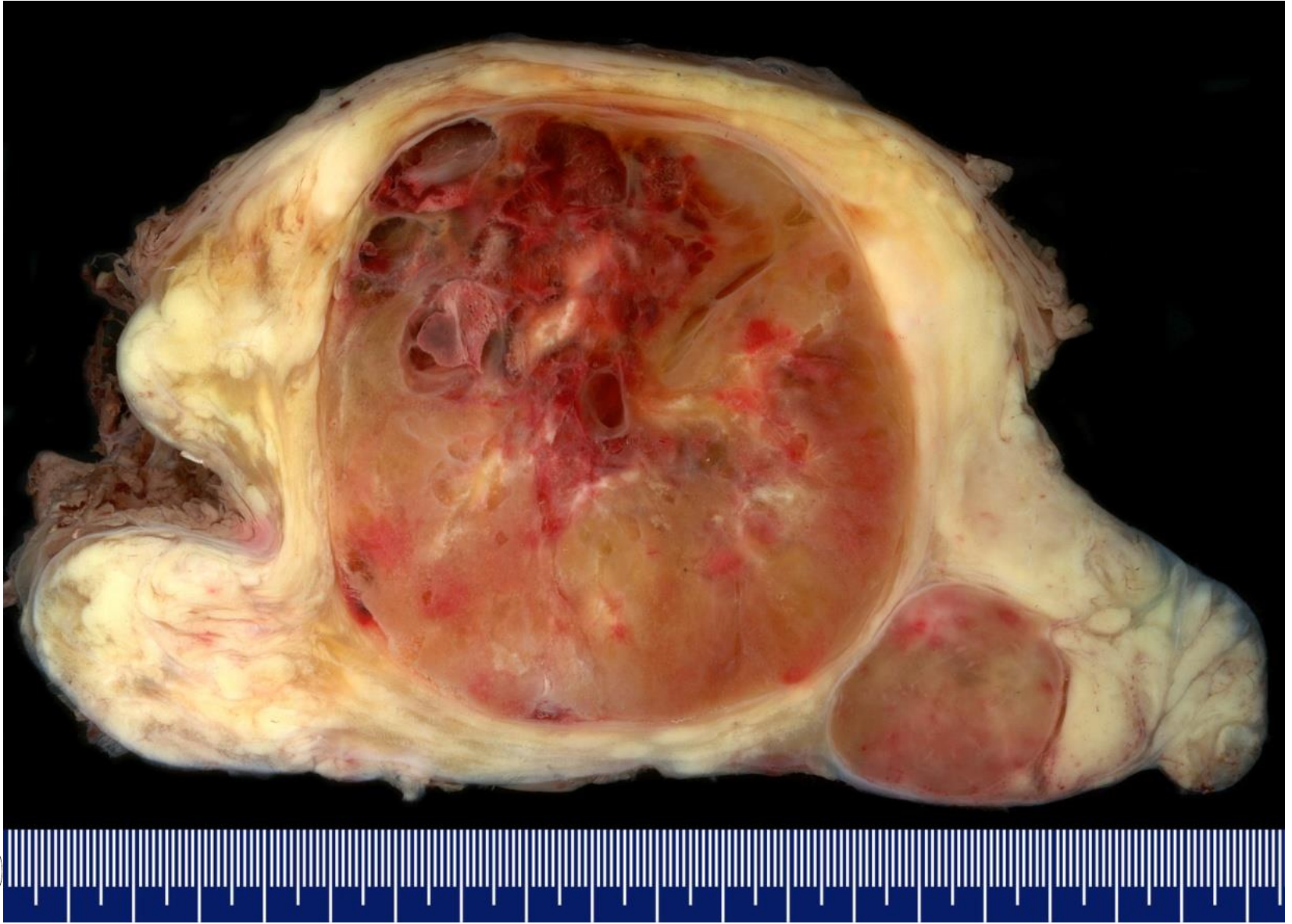
HE

Desmin (Immunhistochemie)



Liposarkom

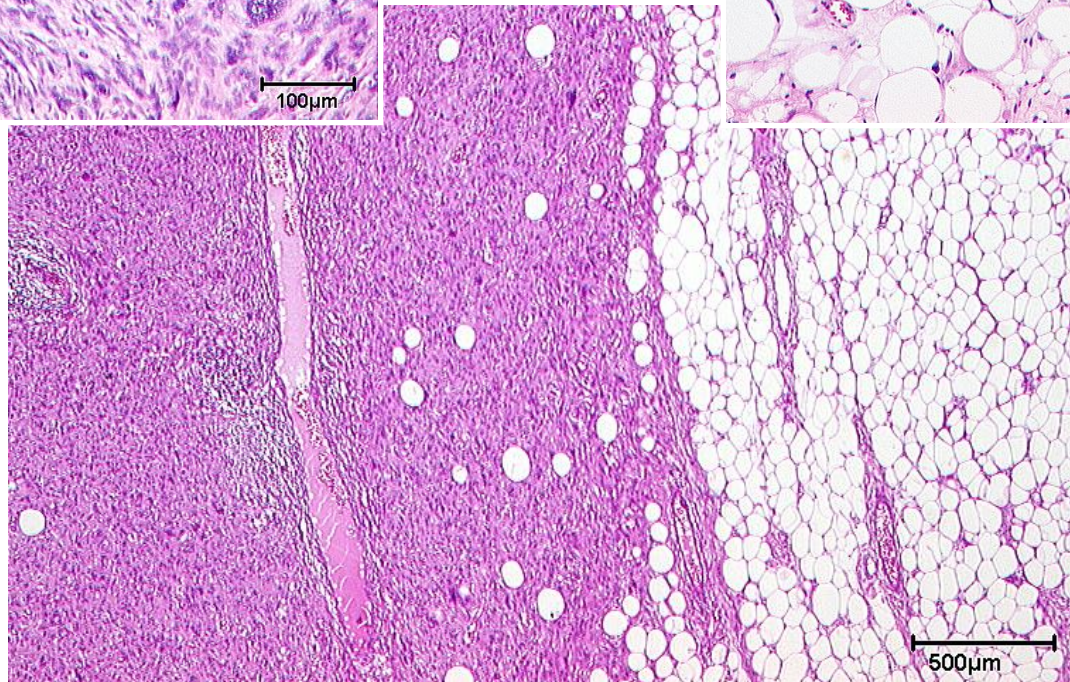
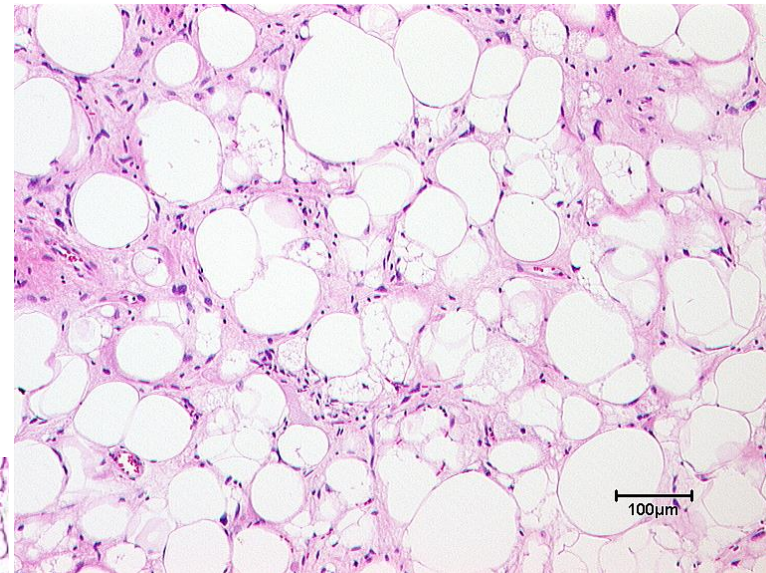
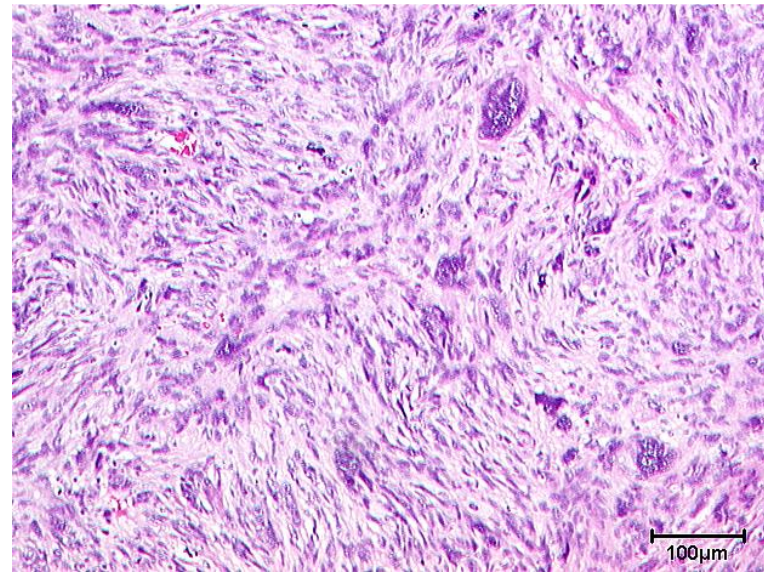
Dedifferenziertes Liposarkom



Liposarkom

Dedifferenziertes Liposarkom

„Nebeneinander“ von undifferenzierter und gut differenzierter Komponente



Grading von Weichgewebssarkomen

Histologischer Differenzierungsgrad

	Dreistufiges Gradingssystem (FNCLCC)	Vierstufiges Gradingssystem (UICC)
niedriggradig	Grad 1	Grad 1
	-	Grad 2
hochgradig	Grad 2	Grad 3
	Grad 3	Grad 4



Grading von Weichgewebssarkomen

Grading Parameter des FNCLCC – Systems

Histological parameter	Definition
Tumour differentiation (see Table 1.2)	- Score 1: Sarcomas closely resembling normal adult mesenchymal tissue and potentially difficult to distinguish from the counterpart benign tumour (e.g. well-differentiated liposarcoma, well-differentiated leiomyosarcoma) - Score 2: Sarcomas for which histological typing is certain (e.g. myxoid liposarcoma, myxofibrosarcoma) - Score 3: Embryonal and undifferentiated sarcomas, synovial sarcomas, sarcomas of doubtful type
Mitotic count (established on the basis of 10 HPF; 1 HPF measures 0.1734 mm ²)	- Score 1: 0–9 mitoses per 10 HPF - Score 2: 10–19 mitoses per 10 HPF - Score 3: > 19 mitoses per 10 HPF
Tumour necrosis	- Score 0: no necrosis - Score 1: < 50% tumour necrosis - Score 2: ≥ 50% tumour necrosis
Histological grade	- Grade 1: total score 2, 3 - Grade 2: total score 4, 5 - Grade 3: total score 6, 7, 8

FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; HPF, high-power field
 Modified from {494}

Histological type	Differentiation score
Well-differentiated liposarcoma	1
Well-differentiated leiomyosarcoma	1
Malignant neurofibroma	1
Well-differentiated fibrosarcoma	1
Myxoid liposarcoma	2
Conventional leiomyosarcoma	2
Conventional MPNST	2
Conventional fibrosarcoma	2
Myxofibrosarcoma	2
Myxoid chondrosarcoma	2
Conventional angiosarcoma	2
High-grade myxoid (round cell) liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3
Rhabdomyosarcoma	3
Poorly differentiated/pleomorphic leiomyosarcoma	3
Poorly differentiated/epithelioid angiosarcoma	3
Poorly differentiated MPNST	3
Malignant Triton tumour	3
Synovial sarcoma	3
Extraskeletal osteosarcoma	3
Extraskeletal Ewing sarcoma	3
Mesenchymal chondrosarcoma	3
Clear cell sarcoma	3
Epithelioid sarcoma	3
Alveolar soft part sarcoma	3
Malignant rhabdoid tumour	3
Undifferentiated (spindle cell and pleomorphic) sarcoma	3
FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; MPNST, malignant peripheral nerve sheath tumour	
Modified from {494}	



Grading von Weichgewebssarkomen

Limitationen eines Gradings

- **Per definitionem high grade sind:**
 - PNET / Ewingsarkome
 - Angiosarkome (bis auf kutane „low grade“ Variante)
 - Pleomorphe Liposarkome
 - Rhabdomyosarkome
 - Desmoplastic small round cell tumor
- **Per definitionem low grade sind:**
 - ALT / gut differenziertes lipomähnliches Liposarkom
 - Infantile Fibrosarkome
 - Dermatofibrosarkoma protuberans
- **Tumoren mit Grading ohne wesentliche prognostische Bedeutung**
 - Klarzellsarkome
 - Epitheloide Sarkome
 - Synovialsarkome
 - „low grade“ fibromyxoides Sarkom



