Current diagnostics and treatment of fibrosarcoma – perspectives for future therapeutic targets and strategies

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Fibrosarcoma is characterized by its low sensitivity towards radio- and chemotherapy as well as by its high rate of tumour recurrences. Thus it is important to identify new methods to improve treatment of this tumour entity. We discuss some promising new directions in fibrosarcoma research, specifically focusing on more effective targeting of the tumour microenvironment. Communication between tumour cells and their surrounding stromal tissue play a crucial role in cancer progression, invasion, metastasis and chemosensitivity. The therapeutic potential of targeting the tumour microenvironment is addressed.
纤维肉瘤的特点是对放疗和化疗的敏感性低以及肿瘤复发率高。因此，重要的是确定新的方法来改善这种肿瘤实体的治疗。我们讨论了纤维肉瘤研究中一些有前途的新方向，特别关注更有效地靶向肿瘤微环境。肿瘤细胞与其周围基质组织之间的通讯在癌症进展、侵袭、转移和化学敏感性中起着至关重要的作用。解决了靶向肿瘤微环境的治疗潜力。

The diagnosis of fibrosarcoma is by one of exclusion [10]. Using immunhistochemical and molecular techniques, it is possible to further subdivide the various subtypes of fibrosarcoma which can be very similar in their morphology, tumour genetics and clinical manifestation. These include Low-Grade fibromyxoid sarcoma (LGFMS, Evans tumour), sclerosing epitheloid fibrosarcoma and myxofibrosarcoma. Moreover, other spindle-type tumours such as the monophasic fibrous synovial sarcoma, malignant peripheral nerve sheath tumour (MPNST), solitary fibrous tumour (SFT), aggressive fibromatosis as well as spindle-cell types of angiosarcoma, rhabdomyosarcoma, leiomyosarcoma and epitheloid sarcoma should be distinguished from fibrosarcoma [6, 5, 11, 8] Fibrosarcoma can occur near the skin surface. In these cases, spindle-cell malignant melanoma and sarcomatoid carcinoma should be excluded. The diagnosis of fibrosarcomas which arise secondarily in dermatofibrosarcoma protuberans (DFSP) is important, as they may respond to imatinib mesylate therapies [12–14]. Therefore, the diagnostic procedures should be thoroughly performed by all involved specialists.

Anamnesis and a complete clinical examination should always precede imaging, histopathologic, immunhistochemic and moleculargenetic investigations. The best current therapy of fibrosarcomas is generous surgical removal [15].Even though the response rate of fibrosarcoma towards radio- and chemotherapy is very low, they are broadly used as a neoadjuvant and/or adjuvant tumour treatment. In this context, doxorubicin in combination with other chemotherapeutic agents is the major drug applied to patients.
纤维肉瘤的诊断是通过排除之一[10]。**使用免疫组织化学和分子技术，可以进一步细分在形态、肿瘤遗传学和临床表现上非常相似的各种纤维肉瘤亚型。**这些包括低级别纤维粘液样肉瘤（LGFMS，埃文斯瘤）、硬化性上皮样纤维肉瘤和粘液纤维肉瘤。此外，其他梭形肿瘤如单相纤维滑膜肉瘤、恶性外周神经鞘瘤（MPNST）、孤立性纤维瘤（SFT）、侵袭性纤维瘤病以及梭形细胞型血管肉瘤、横纹肌肉瘤、平滑肌肉瘤和上皮样肉瘤应与纤维肉瘤相鉴别 [6, 5, 11, 8] 纤维肉瘤可发生在皮肤表面附近。在这些情况下，应排除梭形细胞恶性黑色素瘤和肉瘤样癌。继发于隆突性皮肤纤维肉瘤 (DFSP) 的纤维肉瘤的诊断很重要，因为它们可能对甲磺酸伊马替尼治疗有反应 [12-14]。因此，诊断程序应由所有相关专家彻底执行。病史和完整的临床检查应始终先于影像学、组织病理学、免疫组化和分子遗传学研究。纤维肉瘤目前最好的治疗方法是大手术切除 [15]。尽管纤维肉瘤对放化疗的反应率非常低，但它们被广泛用作新辅助和/或辅助肿瘤治疗。在这种情况下，多柔比星联合其他化疗药物是应用于患者的主要药物

诊断：
Patients with unclear and potentially malignant soft tissue masses should be thoroughly examined for information about its location, size, shape, consistency and relationship to the surrounding tissue. Determination of the range of motion of nearby joints, a complete neurovascular examination as well as palpation of regional lymph nodes in view of tumour metastasis should be part of the physical examination [19, 20].
应彻底检查具有不明确和潜在恶性软组织肿块的患者，了解其位置、大小、形状、一致性和与周围组织的关系。确定附近关节的活动范围、完整的神经血管检查以及针对肿瘤转移的区域淋巴结触诊应该是体格检查的一部分 [19, 20]。

Imaging diagnostics

If the anamnesis and physical examination suggest a potential soft tissue tumour, radiological imaging (Table 1) is the next step. Radiological imaging plays an important role in confirming a diagnosis,

in assessing the tumour`s extent, in guiding biopsy and in determining the stage of disease [21] (Table 2). A multi-disciplinary evaluation of the images by oncologists, radiologists and pathologists is highly recommended. The procedure of choice in imaging soft tissue tumours of the extremities, the pelvis or the trunk, is the magnetic resonance imaging (MRI) [21, 22], **accompanied by the application of contrast medium to assess vascularisation and necrosis(**造影剂在评估血管形成和坏死中的应用). Soft structures including muscle, fat, nerves and vessels as well as necrotic, haemorrhagic and oedematous degenerations are additionally demonstrated by MRI. The tumour's growth and size, its margin, the signal density, homogeneity and the distribution of contrast accumulation can be determined.

如果病史和体格检查提示潜在的软组织肿瘤，放射成像（表（表1）1）是下一步。放射成像在确诊、评估肿瘤范围、指导活检和确定疾病分期方面发挥着重要作用[21]（表（表2）.2）。强烈建议肿瘤科医生、放射科医生和病理学家对图像进行多学科评估。对四肢、骨盆或躯干的软组织肿瘤进行成像的首选程序是磁共振成像 (MRI) [21, 22]，同时应用对比剂来评估血管形成和坏死。 MRI 还显示了软结构，包括肌肉、脂肪、神经和血管以及坏死、出血和水肿性变性。可以确定肿瘤的生长和大小、其边缘、信号密度、均匀性和对比剂积累的分布。

Table 2

TNM Staging system for adult soft tissue sarcomas UICC/AJCC* (2010) [105]

Stage	Grade of differentiation (FNCLCC)	Primary tumour	Local lymph nodes	Distant metastasis
IA	G1, GX	T1a	N0	M0
		T1b	N0	M0
IB	G1, GX	T2a	N0	M0
		T2b	N0	M0
IIA	G2, G3	T1a	N0	M0
		T1b	N0	M0

IIB	G2	T2a	N0	M0
		T2b	N0	M0
III	G3	T2a	N0	M0
		T2b	N1	M0
	Any G	any T	N1	M0
IV	Any G	any T	Any N	M1

[a] the tumour is exclusively located above the superficial fascia without invading the fascia

肿瘤仅位于浅筋膜上方而不侵犯筋膜

[b] the tumour is exclusively located underneath the fascia/ the tumour is located superficially with invasion of or through the fascia/ the tumour is located both superficial yet beneath the fascia

[*] International Union against Cancer (UICC)/American Joint Committee on Cancer (AJCC)

肿瘤仅位于筋膜下方/肿瘤位于浅表并侵入或穿过筋膜/肿瘤位于浅表但位于筋膜下方

TNM Staging system for adult soft tissue sarcomas UICC/AJCC [*] (2010), Histologic grade (G), GX: grade cannot be assessed; G1: low-grade; G2, G3: high-grade, Primary Tumour (T), TX: primary tumour cannot be assessed; T0: no evidence of primary tumour; T1: size > 5 cm; T1a: superficial tumoura; T1b: deep tumourb, T2 size < 5 cm; T2a: superficial tumoura ; T2b: deep tumourb, Regional lymph nodes (N), NX: regional lymph nodes cannot be assessed; N0: no regional lymph node metastasis; N1: regional lymph node metastasis, Distant metastasis (M), M0: no lymph node metastasis; M1: regional lymph node metastasis.

成人软组织肉瘤 TNM 分期系统 UICC/AJCC * (2010)，组织学分级 (G)，GX：分级无法评估； G1：低档； G2、G3：高级别，原发性肿瘤（T），TX：无法评估原发性肿瘤； T0：没有原发肿瘤的证据； T1：尺寸 > 5 厘米； T1a：浅表肿瘤； T1b：深部肿瘤，T2 大小 < 5 cm； T2a：浅表肿瘤； T2b：深部肿瘤，区域淋巴结（N），NX：无法评估区域淋巴结； N0：无区域淋巴结转移； N1：区域淋巴结转移，远处转移（M），M0：无淋巴结转移； M1：区域淋巴结转移。

Alternatively, computed tomography (CT) or X-ray can help detect bone involvement. CT of the chest and abdomen/pelvis or an MRT of the whole body or positron emission tomography (PET)-CT can assist in the detection of distant metastases. CT is also recommended for retroperitoneal located tumours.[21, 22], More rarely ultrasound can be used to help distinguish between benign, cystic and malignant, rather than solid tumour formations, and should always be followed by MRI or CT [22

或者，计算机断层扫描 (CT) 或 X 射线可以帮助检测骨骼受累。胸部和腹部/骨盆的 CT 或全身 MRT 或正电子发射断层扫描 (PET)-CT 可以帮助检测远处转移。 CT 也被推荐用于腹膜后定位的肿瘤。[21, 22]，更

罕见的是，超声可用于帮助区分良性、囊性和恶性，而不是实体瘤形成，应始终进行 MRI 或 CT [22]

In radiological imaging, fibrosarcomas appear as unspecific, often intramuscular localized, ovoid lesions. Its margins are slightly irregular.[11] A fibrosarcoma`s growth is characterized by displacing the surrounding tissue. Consequently, the impression of so-called pseudocapsules is created in the sectional view [21].
在放射成像中，纤维肉瘤表现为非特异性的，通常是肌肉内局部的卵圆形病变。它的边缘有点不规则。 [11]纤维肉瘤的生长特征在于置换周围组织。因此，在剖视图中产生了所谓的假胶囊的印象[21]。

活检：Biopsy

There are different biopsy procedures for soft tissue sarcomas. It can be done by incisional or excisional biopsies conducted via open surgery. A minimal invasive procedure such as fine needle aspiration (FNA) biopsy or the core needle biopsy can be used [23–25]. The advantages of minimal invasive biopsies over open biopsies include a low rate of perioperative complications and reduced risk of tumour cell contamination. **However, an accurate diagnosis can only be made if the tissue samples derive from distinct areas within the tumour, and if the material removed is sufficient for histological typing and grading**
软组织肉瘤有不同的活检程序。它可以通过开放手术进行的切开或切除活检来完成。可以使用微创手术，例如细针抽吸 (FNA) 活检或核心针活检 [23-25]。微创活检优于开放活检的优点包括围手术期并发症发生率低和肿瘤细胞污染风险降低。然而，只有当组织样本来自肿瘤内的不同区域，并且去除的材料足以进行组织学分型和分级时，才能做出准确的诊断

Due to the often insufficient amount of tissue obtained, FNA biopsies have been criticized and are often thought to be unsuitable as a diagnostic device. FNA biopsy in fibrosarcoma diagnostics is only recommended if the cytological finding, which should be interpreted by an experienced pathologist, is compared with prior clinical and imaging findings [26].
由于获得的组织数量通常不足，FNA 活检受到批评，并且通常被认为不适合作为诊断设备。仅当应由经验丰富的病理学家解释的细胞学发现与先前的临床和影像学发现进行比较时，才建议在纤维肉瘤诊断中进行 FNA 活检 [26]。

In Oncological Centres, for example, where interdisciplinary communication and expertise can be provided, the sensitivity of FNA is about 95% [27]. The sensitivity of core needle (tru-cut) biopsies is even higher [24].
例如，在可以提供跨学科交流和专业知识的肿瘤中心，FNA 的敏感性约为 95% [27]。核心针 (tru-cut) 活检的敏感性更高 [24]

While FNA biopsies play a limited role in the primary sarcoma diagnosis, it can be used to confirm tumour recurrences and nodal metastases. **In contrast to FNA, the amount of tissue obtained by core-needle biopsies is generally sufficient which makes CT-guided core-needle biopsy a robust diagnostic procedure**.[22] If the tumour exceeds the size of 3 cm and/or if minimal invasive methods have failed, surgical biopsies are indicated. Soft tissue tumours ranging between 3 and 5 cm in size should be biopsied via excisional biopsy. If the tumours exceed the size of 5cm, incisional biopsies can be conducted where only a part of the tumour is resected [19, 21]. The material obtained forms the basis for determination of the histological type and grade (Table (Table3)3) and subsequent immunohistochemical investigation.

Table 3

Histopathologic grading of fibrosarcoma

Score 1	**Score 2**	**Score 3**		
Score A Tumour differentiation score		Sarcomas closely resembling normal adult mesenchymal tissue Well differentiated fibrosarcoma	Sarcomas for which histological typing is certain: Classical fibrosarcoma	Embryonal and undifferentiate sarcomas: Poorly differentiated fibrosarcoma
Score B Mitotic activity score		0–9 mitoses* per 10 HPF	10–19 mitoses per 10 HPF	≥ 20 mitoses per 10 HPF
Score C Tumour necrosis score	no necrosis	≤ 50% necrosis	> 50% necrosis	
Final grade Grade1 (G1): Well differentiated, Low grade	Score A + score B + score C = 2 or 3			
Grade 2 (G2):	Score A + score B + score C = 4 or 5			

Moderately differentiated, Intermediate grade	
Grade 3 (G3): Poorly differentiated, High grade	Score A + score B + score C = 6,7 or 8

A determination of the tumour`s malignancy is made by determining its degree of differentiation. The most widely recommended grading system is that of the French Federation of Cancer Centers Sarcoma Group (FNCLCC) [24, 98]. Three prognostically relevant factors, the tumour cell differentiation, mitotic index and the amount of necrosis, are scored independently. Finally, those scores are summed up and the grade of the tumour is assessed. The lower the combined score, the lower the grade, the less aggressive the tumour and the better a patient`s prognosis. There are four grades for sarcoma: GX (the grade cannot be evaluated), G1, G2 and G3. G1 tumours are considered low-grade. G2 and G3 are considered high-grade. [99] About 80% of fibrosarcomas are high-grade reflecting its overall aggressive character. [4, 30, 34].

* HPF (high-power field): 1 HPF = 0.1734 mm^2

通过确定其分化程度来确定肿瘤的恶性程度。最广泛推荐的分级系统是法国癌症中心肉瘤组织联合会 (FNCLCC) [24, 98]。三个与预后相关的因素，肿瘤细胞分化、有丝分裂指数和坏死量，独立评分。最后，总结这些分数并评估肿瘤的等级。综合评分越低，等级越低，肿瘤侵袭性越小，患者预后越好。肉瘤有四个等级：GX（等级无法评估）、G1、G2和G3。 G1 肿瘤被认为是低级别的。 G2和G3被认为是高档的。 [99] 大约 80% 的纤维肉瘤是高级别的，反映了其整体侵袭性特征。 [4, 30, 34]。

虽然 FNA 活检在原发性肉瘤诊断中的作用有限，但它可用于确认肿瘤复发和淋巴结转移。与 FNA 相比，通过芯针活检获得的组织数量通常足够，这使得 CT 引导的芯针活检成为一种可靠的诊断程序。 [22]如果肿瘤超过 3 cm 和/或微创方法失败，则需要进行手术活检。大小在 3 到 5 厘米之间的软组织肿瘤应通过切除活检进行活检。如果肿瘤大小超过 5 厘米，则可以在仅切除部分肿瘤的情况下进行切口活检 [19, 21]。获得的材料构成了确定组织学类型和等级（表（表3）3）和随后的免疫组织化学研究的基础。

Immunohistochemic (IHC) marker

Histopathology alone is not sufficient for a clear distinction between fibrosarcoma and other spindle-cell neoplasms. Immunohistochemistry (IHC) is applied in the diagnostics of fibrosarcoma where specific antibody reagents allow the detection of differential diagnostically important tumor markers [10, 6, 34–36], Tumour markers are molecules such as cell surface antigens, oncofetal antigens, enzymes, receptors, hormones, oncogenes or cytoplasmatic proteins. They are either overly expressed by the malignant cells themselves, or by the body's reaction to the tumour.[37] They may be detected on the tumour cell surface, in the surrounding tumour microenvironment, in blood or urine. Tumour markers are used as part of therapy monitoring, process control and monitoring for tumour recurrence. The use of IHC markers is crucial for the differential diagnosis of fibrosarcoma [5, 8, 38–40].

免疫组化 (IHC) 标记：

单独的组织病理学不足以明确区分纤维肉瘤和其他梭形细胞肿瘤。免疫组织化学 (IHC) 应用于纤维肉瘤的诊断，其中特异性抗体试剂允许检测鉴别诊断上重要的肿瘤标志物 [10, 6, 34-36]，肿瘤标志物是分子，如细胞表面抗原、癌胚抗原、酶、受体、激素、致癌基因或细胞质蛋白。它们要么被恶性细胞本身过度表达，要么被身体对肿瘤的反应过度表达。 [37]它们可以在肿瘤细胞表面、周围肿瘤微环境、血液或尿液中检测到。肿瘤标志物用作治疗监测、过程控制和肿瘤复发监测的一部分。 IHC 标志物的使用对于纤维肉瘤的鉴别诊断至关重要 [5, 8, 38-40]。

The positive staining of vimentin demonstrates the mesenchymal origin of fibrosarcoma. Desmin, alpha smooth muscle actin (α-SMA) and muscle specific actin (MSA) belong to the most common myogenic markers. The S-100 protein is a neuronal marker that serves to exclude malignant peripheral nerve sheath tumors (MPNST). Positive CD 31, CD34 and factor VIII (von Willebrand factor) immunostains point to vascular malignancies e.g. spindle-cell angiosarcomas. Epithelial markers such as the epithelial membrane antigen (EMA), and cytokeratins can be helpful in the differential diagnosis of sarcomatoid carcinomas [35, 10]. In some mesenchymal tumours a differentiation of malignant cells into epithelial tissue can be observed during tumorigenesis. This phenomenon is called mesenchymal to epithelial transition (MET). Increased levels of E-cadherin and β-cadherin are associated with MET and are used to diagnose synovial sarcoma, epitheloid sarcoma and leiomyosarcoma, but not fibrosarcoma [41]. Cytokeratin expression can also be helpful in the differential diagnosis of synovial- and epitheloid sarcomas, which mostly expresscytokeratins 7, 8, 18 and 19 [36, 42]. Considered alone, immunohistochemical results are somewhat inconclusive as tumours usually express a number and variety of tumour cell- and tissue markers. Consequently, there is generally no individual immunohistochemical marker which is monospecific for a tumour type [36].

波形蛋白的阳性染色表明纤维肉瘤的间充质起源。结蛋白、α 平滑肌肌动蛋白 (α-SMA) 和肌肉特异性肌动蛋白 (MSA) 属于最常见的肌源性标志物。 S-100 蛋白是一种用于排除恶性周围神经鞘瘤 (MPNST) 的神经元标志物。 CD 31、CD34 和 VIII 因子（von Willebrand 因子）免疫染色阳性表明血管恶性肿瘤，例如梭形细胞血管肉瘤。上皮标志物如上皮膜抗原 (EMA) 和细胞角蛋白有助于肉瘤样癌的鉴别诊断 [35, 10]。在一些间充质肿瘤中，在肿瘤发生过程中可以观察到恶性细胞分化为上皮组织。这种现象称为间质上皮转化（MET）。 E-cadherin 和 β-cadherin 水平升高与 MET 相关，用于诊断滑膜肉瘤、上皮样肉瘤和平滑肌肉瘤，但不用于诊断纤维肉瘤 [41]。细胞角蛋白表达也有助于滑膜和上皮样肉瘤的鉴别诊断，滑膜肉瘤和上皮样肉瘤主要表达细胞角蛋白 7、8、18 和 19 [36, 42]。单独考虑，免疫组织化学结果有些不确定，因为肿瘤通常表达许多和多种肿瘤细胞和组织标志物。因此，通常没有针对某一肿瘤类型具有单特异性的个体免疫组化标志物 [36]。

In fibrosarcoma, vimentin, is often the only positively stained marker [10, 34, 35, 3]. Sometimes muscle specific antigen (MSA) and/or smooth muscle actin (SMA) can be detected as a sign of myofibroblastic differentiation [10, 3]. In those fibrosarcomas which arise secondarily from either solitary fibrous tumour (SFT) or dermatofibrosarcoma, CD34 can sometimes be detected.

Ki-67, a cell cycle–associated nuclear antigen, is also used as a diagnostic marker for fibrosarcoma [2, 43, 44]. It is stained with anti-ki-67 antibodies such as MIB-1 which allow assessment of the so-called ki-67/MIB1 labelling index.[45]

在纤维肉瘤中，波形蛋白通常是唯一阳性染色的标志物 [10, 34, 35, 3]。有时可以将肌肉特异性抗原 (MSA) 和/或平滑肌肌动蛋白 (SMA) 检测为肌成纤维细胞分化的标志 [10, 3]。在那些继发于孤立性纤维瘤 (SFT) 或皮肤纤维肉瘤的纤维肉瘤中，有时可以检测到 CD34。 Ki-67 是一种细胞周期相关的核抗原，也可用作纤维肉瘤的诊断标志物 [2, 43, 44]。它用 MIB-1 等抗 ki-67 抗体染色，可以评估所谓的 ki-67/MIB1 标记指数。 [45]

MicroRNAs- diagnostic markers

The lack of specifity of IHC markers has driven the search for additional biomarkers. In this context, microRNAs (miRNAs) have recently gained importance. Micro RNAs (miRNAs) are a class of small noncoding RNAs that bind to the 3′ untranslated regions (UTRs) of messenger RNA (mRNA), where they negatively regulate translation. It has been suggested that more than 60% of all mRNAs are controlled by miRNAs suggesting that they are major players in the posttranscriptional gene regulation.[46] Malignant cells aberrantly express specific miRNAs which may influence tumour proliferation, cell cycle control, apoptosis, differentiation and invasion. The miRNA expression profile appears to be cancer-type specific. To this end, (Table 4) it can also be used to distinguish fibrosarcoma from other spindle-cell sarcomas [47–49].

IHC 标志物缺乏特异性推动了对其他生物标志物的寻找。在这种情况下，microRNAs (miRNAs) 最近变得越来越重要。微小 RNA (miRNA) 是一类小的非编码 RNA，它们与信使 RNA (mRNA) 的 3' 非翻译区 (UTR) 结合，在那里它们负调控翻译。有人提出，超过 60% 的 mRNA 受 miRNA 控制，这表明它们是转录后基因调控的主要参与者。 [46]恶性细胞异常表达可能影响肿瘤增殖、细胞周期控制、细胞凋亡、分化和侵袭的特定miRNA。 miRNA 表达谱似乎是癌症类型特异性的。为此，（表（表4）4）它也可用于区分纤维肉瘤与其他梭形细胞肉瘤[47-49]。

Prognosis of fibrosarcoma

纤维肉瘤的预后

Fibrosarcomas and soft tissue sarcomas are prognostically evaluated by taking into account the age of the patient, the tumour size, depth and malignancy, the involvement of nerves, vessels, bone, the collagen density, as well as the metastatic potential and the formation of tumour recurrences [3, 8, 26, 21]. Prognostically unfavourable factors of fibrosarcoma include: (i) high histologic grade, (ii) large amount of tissue necrosis (> 50%), (iii) a high number of mitotic figures (> 20/10 hpf), (iv) a decrease of collagen fibres in favour of an increased cellularity, (v) deeply localized tumours, (vi) and tumours exceeding the 5 cm [8, 24]. Histopathological grading is considered to be the most important prognostic indicator, [26, 30]. High-grade fibrosarcoma patients with great risks for metastases will most likely benefit from adjuvant therapy [24]. 80% of adult-type fibrosarcomas are found to be high-grade malignancies [34]. Regardless of grade, the overall 5-year survival rate is about 40–60 % [8, 24, 34]. The ten year survival rate is 60% for low-grade, and 30% for high-grade tumours respectively [10]. Depending on the tumour grade, the patient`s age and the histology of the tumour margin, the recurrence rate lies between 12 and 79%, averaging in the 40% to 50% range need to be esbablished. In 10–20% of patients whose tumours had been adequately resected, recurrences occur within 5 years [8]. Haematologically spread metastases have been described in 9–63% of patients with adult-type fibrosarcoma [3]. In this context, the lungs and bones of the axial skeleton are the major site of metastatic spread. In a fewer number of cases, lymph node involvement is also seen [4, 3].

纤维肉瘤和软组织肉瘤通过考虑患者的年龄、肿瘤大小、深度和恶性程度、神经、血管、骨的受累情况、胶原密度以及转移潜力和肿瘤形成来进行预后评估复发 [3, 8, 26, 21]。纤维肉瘤的预后不利因素包括：（i）高组织学分级，（ii）大量组织坏死（> 50%），（iii）大量有丝分裂象（> 20/10 hpf），（iv）减少胶原纤维有利于增加细胞结构，(v) 深度定位的肿瘤，(vi) 和超过 5 厘米的肿瘤 [8, 24]。组织病理学分级被

认为是最重要的预后指标 [26, 30]。具有很大转移风险的高级别纤维肉瘤患者最有可能从辅助治疗中受益[24]。 80% 的成人型纤维肉瘤被发现是高级别恶性肿瘤 [34]。无论等级如何，总体 5 年生存率约为 40-60% [8, 24, 34]。低级别肿瘤的十年生存率分别为 60% ，高级别的生存率是30% 。根据肿瘤分级、患者年龄和肿瘤边缘组织学，复发率介于 12% 至 79% 之间，平均需要确定在 40% 至 50% 范围内。在 10-20% 的肿瘤已充分切除的患者中，5 年内复发 [8]。 9-63% 的成人型纤维肉瘤患者出现血液学扩散转移[3]。在这种情况下，中轴骨骼的肺和骨骼是转移扩散的主要部位。在少数病例中，也可见淋巴结受累 [4, 3]。

治疗：

Therapy：

Surgical intervention

Surgery represents the standard therapy of localized soft tissue sarcomas [22]. The surgical procedure depends on the tumour localization, its size and grade of malignancy [21]. In case of intramuscular localized soft tissue tumours, the affected muscle compartment should be resected en-bloc as part of the so-called compartment resection. In those cases, adjuvant radiation therapy is not indicated [22]. If on the other hand the tumours do not reach the muscle origin, and its insertion, or in case of an extracompartmental growth, a wide resection should be performed. If possible an R0, tumour margin-free, resection should be achieved in order to minimize the risk of local recurrences. This means that not only the tumour tissue itself, but also part of the adjacent healthy tissue has to be removed due to the infiltrative growth of fibrosarcoma. Even though a 2 cm margin is sometimes recommended, [21] a generally valid safety margin has not yet been determined. The reason lies in the patient-dependent involvement of anatomical critical structures such as nerves and vessels. In case of deep, high-grade, </> 5 cm large tumours, radiation therapy after an R0 resection is highly recommended. In case of other constellations of tumour grade, size and localization, the necessity of adjuvant radiation therapy in an R0 situation should be discussed in a multi-disciplinary fashion [22]. In case of R1/R2 situations, a reoperation should be performed if possible.

手术是局部软组织肉瘤的标准治疗方法 [22]。手术程序取决于肿瘤的定位、大小和恶性程度[21]。在肌内局部软组织肿瘤的情况下，受影响

的肌肉隔室应作为所谓的隔室切除术的一部分整块切除。在这些情况下，不需要辅助放射治疗 [22]。另一方面，如果肿瘤没有到达肌肉起源，并且它的插入，或者在室外生长的情况下，应该进行广泛切除。如果可能，应实现 R0 无肿瘤边缘切除，以尽量减少局部复发的风险。这意味着不仅肿瘤组织本身，而且由于纤维肉瘤的浸润性生长，必须切除部分邻近的健康组织。尽管有时建议使用 2 厘米的裕度，[21] 尚未确定普遍有效的安全裕度。原因在于患者依赖的解剖关键结构（例如神经和血管）的参与。如果是深部、高级别、</> 5 cm 大肿瘤，强烈建议在 R0 切除后进行放射治疗。对于其他肿瘤分级、大小和定位的情况，应以多学科的方式讨论 R0 情况下辅助放射治疗的必要性 [22]。在 R1/R2 情况下，如果可能，应进行重新手术。

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R0 corresponds to resection for cure or complete
remission. R1 to microscopic residual tumor, R2 to
macroscopic residual tumor. The R classification
takes into account clinical and pathological
findings. A reliable classification requires the
pathological examination of resection margins.
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Chemotherapy

In addition to surgery, radiotherapy and/or hyperthermia therapy, chemotherapy is a major category of treatment. By targeting and killing rapidly dividing and proliferating cells, such as malignant tumour cells, chemotherapeutical agents are broadly used to stabilize disease and for tumour remission. Adjuvant chemotherapeutic therapy in soft tissue sarcomas is very controversial, [22, 21] and is therefore not a standard treatment in these tumours. Patients with advanced cancers are the most likely to show some benefit. Generally, the number of poor/non-responders among fibrosarcoma patients is very high. This is in large part due to the pronounced drug resistance of the tumour. Human fibrosarcoma cells have been shown to establish co-resistances against vincristine, actinomcin D, vinblastine and etoposid when treated with the first-line chemotherapeutic agent doxorubicin.[50] This phenomenon of acquired multi-resistance is known under the term multidrug resistance (MDR).

化疗：

除了手术、放射疗法和/或热疗之外，化学疗法是主要的治疗类别。通过靶向和杀死快速分裂和增殖的细胞，例如恶性肿瘤细胞，化学治疗剂被广泛用于稳定疾病和缓解肿瘤。软组织肉瘤的辅助化疗是非常有争议的，[22, 21] 因此不是这些肿瘤的标准治疗。晚期癌症患者最有可能表现出一些益处。一般来说，纤维肉瘤患者中不良/无反应者的数量

非常多。这在很大程度上是由于肿瘤的显着耐药性。当用一线化疗药物多柔比星治疗时，人类纤维肉瘤细胞已显示对长春新碱、放线菌素 D、长春碱和依托泊苷产生共抗性。 [50]这种获得性多重耐药性现象在术语多药耐药性 (MDR) 下为人所知。

Chemotherapy in patients with advanced stage fibrosarcomas is based on anthracyclines as the first-line treatment. In this context, doxorubicin is the most widely applied drug. Besides doxorubicin, response rates above 15% can be reached by actinomycin D and ifosfamide [51, 52]. A number of phase III studies have been conducted in order to assess the effect of adjuvant chemotherapy on the rate of local recurrences, on the rate of distant metastases, the disease-free-survival rate, and on the overall survival rate. An improvement of the overall survival has been detected in only 4–11% of sarcoma patients treated with chemotherapy.

晚期纤维肉瘤患者的化疗以蒽环类药物为一线治疗。在这种情况下，阿霉素是应用最广泛的药物。除多柔比星外，放线菌素 D 和异环磷酰胺的反应率可达到 15% 以上 [51, 52]。为了评估辅助化疗对局部复发率、远处转移率、无病生存率和总生存率的影响，已经进行了许多 III 期研究。在接受化疗的肉瘤患者中，只有 4-11% 的患者总生存期有所改善。

In contrast to adjuvant chemotherapy, neoadjuvant treatment has been shown to be more effective. Patients with high-grade fibrosarcomas can benefit from a presurgical MAID (mesna, doxorubicin, ifosfamide, dacarbazine) treatment [53].

与辅助化疗相比，新辅助治疗已被证明更有效。高级别纤维肉瘤患者可受益于术前 MAID（美司钠、多柔比星、异环磷酰胺、达卡巴嗪）治疗 [53]。

Current therapeutic focus – the tumour microenvironment

To this end, the tumour surrounding tissue, or stroma, has been the focus of new therapy approaches. The tumour microenvironment consists of two main components, the cellular component comprising tumor associated fibroblasts, smooth muscle cells, adipocytes, endothelial cells and immune cells. The second component is the extracellular matrix (ECM) which fills the intercellular space. The ECM consists mainly of proteoglycans, fibrous proteins, adhesion molecules and proteases, and is characterized by being high dynamic [54]. The interactions between the tumour cells and their microenvironment is important to cancer progression, invasion and metastasis. The following sections discuss fibrosarcoma microenvironments in which are thought to have a high

therapeutic potential for the control tumour growth and the enhancement of chemosensitivity.
为此，肿瘤周围组织或基质一直是新治疗方法的重点。**肿瘤微环境由两个主要成分组成**，细胞成分包括肿瘤相关成纤维细胞、平滑肌细胞、脂肪细胞、内皮细胞和免疫细胞。第二个成分是填充细胞间隙的细胞外基质 (ECM)。 ECM 主要由蛋白多糖、纤维蛋白、粘附分子和蛋白酶组成，具有高动态性 [54] 的特点。肿瘤细胞与其微环境之间的相互作用对癌症的进展、侵袭和转移很重要。以下部分讨论了纤维肉瘤微环境，其中被认为具有控制肿瘤生长和增强化学敏感性的高治疗潜力。

Matrix metalloproteinases (MMPs) and their inhibitors

//基质金属蛋白酶 (MMP) 及其抑制剂

So there is a general positive correlation between the amount of MMPs present and tumour progression. The higher the MMP concentration, the more advanced the cancer - the poorer the prognosis and overall survival. Controlling MMP activity within the tumour microenvironment is one way to locally control fibrosarcoma growth and metastasis.

因此，存在的 MMP 数量与肿瘤进展之间存在普遍的正相关关系。MMP 浓度越高，癌症越晚期 - 预后和总生存期越差。控制肿瘤微环境中的 MMP 活性是局部控制纤维肉瘤生长和转移的一种方法。

Specific inhibitors of MMPs

MMPs的特异性抑制剂

As a means to control ECM degradation and tumour progression, a series of broad spectrum MMPs inhibitors such as batimastat (BB-94), marimastat (BB-2516), GM 6001, CT1746, KB-R7787, prinomastat (AG3340), BMS275291, BAY 12-9566, CGS 27023A were developed. However, due to the high levels of side effects such as the musculoskeletal syndrome, most clinical phase III studies had to prematurely be curtailed [65, 66]. As an additional problem , therapeutic plasma levels often could not been reached. Thus to date, the synthetic broad spectrum inhibitors could not be shown to improve the survival rate. In fact, rather the opposite occurred. In some cases the unspecific inhibition of MMPs led to an acceleration of tumour progression which was thought to be due to the existence of “tumour-protective” MMPs. Their inhibition led to increased tumour growth. MMPs 3, 9, 11 and 19 possess both –tumour-progressive and protective characteristics. MMPs 8, 12 and 26 are largely protective proteases [67, 68]. The broad-spectrum inhibitors are also seen as less effective for

the treatment of more advanced tumour diseases [65]. Due to the disappointing results of the broad spectrum inhibitors, the research has increasingly focused on the development of new inhibitors with a low side effect profile, and the exclusive inhibition of MMPs with tumour-progressive characteristics.

作为控制 ECM 降解和肿瘤进展的一种手段，一系列广谱 MMPs 抑制剂如 batimastat (BB-94)、marimastat (BB-2516)、GM 6001、CT1746、KB-R7787、prinostat (AG3340)、BMS275291、开发了 BAY 12-9566、CGS 27023A。然而，由于肌肉骨骼综合征等高水平的副作用，大多数临床 III 期研究不得不过早地缩减 [65, 66]。另一个问题是，治疗性血浆水平通常无法达到。因此，迄今为止，合成广谱抑制剂不能提高存活率。事实上，恰恰相反。在某些情况下，MMPs 的非特异性抑制导致肿瘤进展加速，这被认为是由于“肿瘤保护性”MMPs 的存在。它们的抑制导致肿瘤生长增加。 MMP 3、9、11 和 19 具有肿瘤进展和保护特性。 MMP 8、12 和 26 主要是保护性蛋白酶 [67, 68]。广谱抑制剂也被认为对治疗更晚期的肿瘤疾病效果较差[65]。由于广谱抑制剂的结果令人失望，研究越来越集中于开发具有低副作用的新抑制剂，以及对具有肿瘤进展特征的 MMP 的独家抑制。

The MMPs expression profile is generally tumour-specific. Human fibrosarcoma cells express extracellular MMPs 1, 2, 3, 7 and 9 as well as the membrane type MMPs 14, 15, 16 [69, 63], MMPs 1, 2, 3, 9 and 14 in particular are thought to play a key role in tumor invasion, metastasis and angiogenesis [55]. N-Biphenylsulfonyl-*N*-Isopropoxy-Aminoacetohydroxamic (ARP 101) selectively inhibits MMP2 activity which is strongly increased in fibrosarcoma. *In vitro*, ARP 101 resulted in a decrease of tumour invasion [70]. Selective inhibitors of tumour type-specific MMPs may show less side effects but this remains to be seen.

MMPs 表达谱通常是肿瘤特异性的。人纤维肉瘤细胞表达细胞外基质金属蛋白酶 1、2、3、7 和 9 以及膜型基质金属蛋白酶 14、15、16 [69、63]，特别是基质金属蛋白酶 1、2、3、9 和 14 被认为是在肿瘤侵袭、转移和血管生成中起关键作用[55]。 N-Biphenylsulfonyl-N-Isopropoxy-Aminoacetohydroxamic (ARP 101) 选择性抑制 MMP2 活性，该活性在纤维肉瘤中强烈增加。在体外，ARP 101 导致肿瘤侵袭减少 [70]。肿瘤类型特异性 MMP 的选择性抑制剂可能表现出较少的副作用，但这仍有待观察。

Intratumoural injection of TIMP-1-GPI

TIMP-1-GPI瘤内注射

Because these enzymes play such central roles in tissue homeostasis, pronounced side effects are seen with systemically applied MMPs-inhibitors (MMPI) [65]. **To help address this, a recent approach in**

sarcoma research is to locally increase MMPI concentration by injecting inhibitors directly into the tumour tissue. The normal surrounding tissue is largely uninfluenced and the systemic side effects are decreased. An intratumoral change in MMP activity status has been shown to lead to reduced primary tumour growth. In this context, TIMP-1, a broad spectrum MMPI with low toxicity has been evaluated .[71] Its systemic application showed disadvantages including low bioavailability, short half-life and the high amount of protein required for minimum effective doses (MED) [72]. A more recent approach is to i**ncrease the TIMP-1 concentration within the tumour tissue**. **One method to do this involves engineering the tumor tissue with expression vectors to enhance TIMP-1 production. [73, 74] Our group has developed a means of locally increasing the intratumoral TIMP-1 concentration by using a method called cell surface engineering. The principle involves the engineering of recombinant TIMP-1 protein to include a glycophosphatidylinositol-anchor (GPI-anchor). This lipid structure leads to efficient protein incorporation into cell membranes [75]. The particularly strong effect of TIMP-GPI-fusion proteins on tissue homeostasis and cell proliferation has been demonstrated in pathological wound healing specifically on hyperproliferating fibroblasts where an increase in apoptotic sensitivity and inhibition of cell proliferation was seen.** [76, 77] TIMP-1-GPI was subsequently investigated as a therapeutic agent for the treatment of experimental fibrosarcoma [72]. Intratumoral injections of TIMP-1-GPI into fibrosarcoma-bearing mice led to a significant decrease in the tumour mass. The *in vitro* treatment of human fibrosarcoma cells with TIMP-1-GPI showed an inhibition of cell proliferation and migration as well as in an increased cell apoptosis and enhanced sensitivity to chemotherapy agents [72].

由于这些酶在组织稳态中发挥着如此重要的作用，因此全身应用的 MMPs 抑制剂 (MMPI) 会出现明显的副作用 [65]。为了帮助解决这个问题，最近肉瘤研究的一种方法是通过将抑制剂直接注射到肿瘤组织中来局部增加 MMPI 浓度。正常周围组织基本不受影响，全身副作用减少。已显示 MMP 活性状态的瘤内变化导致原发性肿瘤生长减少。在这种情况下，TIMP-1 是一种低毒性的广谱 MMPI。[71] 其全身应用显示出缺点，包括生物利用度低、半衰期短以及最小有效剂量 (MED) 所需的大量蛋白质 [72]。最近的一种方法是增加肿瘤组织内的 TIMP-1 浓度。一种方法是使用表达载体对肿瘤组织进行工程改造，以增强 TIMP-1 的产生。 [73, 74] 我们小组开发了一种通过使用称为细胞表面工程的方法局部增加肿瘤内 TIMP-1 浓度的方法。该原理涉及重组 TIMP-1 蛋白的工程化，以包括糖磷脂酰肌醇锚 (GPI-锚)。这种脂质结构导致蛋白质有效地掺入细胞膜[75]。 TIMP-GPI 融合蛋白对组织稳态和细胞增殖的特别强的影响已在病理性伤口愈合中得到证实，特别是

对过度增殖的成纤维细胞，其中观察到凋亡敏感性增加和细胞增殖抑制。 [76, 77] 随后研究了 TIMP-1-GPI 作为治疗实验性纤维肉瘤的治疗剂 [72]。将 TIMP-1-GPI 瘤内注射到携带纤维肉瘤的小鼠中导致肿瘤块显着减少。用 TIMP-1-GPI 对人纤维肉瘤细胞的体外治疗显示出对细胞增殖和迁移的抑制作用以及细胞凋亡增加和对化疗药物的敏感性增强 [72]。

Approaches to increase chemosensitivity

Fibrosarcoma shows pronounced resistance towards apoptosis inducing chemotherapeutic agents [52]. **An increase in tumour chemosensitivity represents an important direction in fibrosarcoma research**. **There are several approaches that have been found to improve chemosensitivity, these include: (i) TIMP-1-GPI application, [72] (ii) suppressing potential chemoresistant cancer stem cells (CMCs) such as the side population (SP) cells e.g. via TIMP-1-GPI [72], and (iii) interrupting CAM-DR[78] by either homotrimeric collagen type I degradation or inhibiting the PI3K-Akt signalling pathway**.

增加化学敏感性的方法：

纤维肉瘤对诱导细胞凋亡的化学治疗剂表现出明显的抗性 [52]。肿瘤化学敏感性的增加代表了纤维肉瘤研究的一个重要方向。已经发现有几种方法可以提高化学敏感性，包括：(i) TIMP-1-GPI 应用，[72] (ii) 抑制潜在的化学抗性癌症干细胞 (CMC)，例如侧群 (SP) 细胞，例如通过 TIMP-1-GPI [72]，以及 (iii) 通过同源三聚体 I 型胶原蛋白降解或抑制 PI3K-Akt 信号通路中断 CAM-DR[78]。

Homotrimeric collagen type I – a promoter of CAM-DR

The reduced fibrosarcoma response towards therapeutic agents is linked in part to interactions between the tumour cells and their microenvironment [79]. This phenomenon, called environment mediated drug resistance (EMDR), describes a *de novo* development of drug resistance [80]. It is in contrast to acquired drug resistances where chemotherapy-induced genetic changes result in an increased extracellular transfer of drugs by enhanced expression of efflux pumps [81]. The EMDR is further subdivided into soluble factor mediated drug resistance (SFM-DR) or cell adhesion mediated drug resistance (CAM-DR) [78]. The autocrine and/or paracrine stimulation of tumour cells by growth factors, cytokines or chemokines leads to intracellular

changes in chemotherapy-associated signal pathways and consequently decreases the therapeutic response rate. This is what is meant by the term SFM-DR. CAM-DR is mediated by adhesion between the tumour cells and components of the ECM. Integrins on the tumour cell surface moderate adhesion to ECM proteins such as collagens, fibronectins, laminins or stromal cell ligands. The activation integrin-mediated signal pathways, such as the PI3K-Akt pathway, results in enhanced drug resistance [82].

纤维肉瘤对治疗剂的反应降低部分与肿瘤细胞与其微环境之间的相互作用有关[79]。这种现象称为环境介导的耐药性 (EMDR)，描述了耐药性的从头发展 [80]。与获得性耐药形成对比的是，化疗诱导的基因变化通过增强外排泵的表达导致药物的细胞外转移增加[81]。 EMDR 进一步细分为可溶性因子介导的耐药性 (SFM-DR) 或细胞粘附介导的耐药性 (CAM-DR) [78]。生长因子、细胞因子或趋化因子对肿瘤细胞的自分泌和/或旁分泌刺激导致化疗相关信号通路的细胞内变化，从而降低治疗反应率。这就是术语 SFM-DR 的含义。 CAM-DR 由肿瘤细胞和 ECM 成分之间的粘附介导。肿瘤细胞表面的整联蛋白适度粘附到 ECM 蛋白，如胶原蛋白、纤连蛋白、层粘连蛋白或基质细胞配体。激活整合素介导的信号通路，如 PI3K-Akt 通路，导致耐药性增强 [82]。
Collagen type I plays an important role in CAM-DR in fibrosarcomas. Two type I collagens have been found within the tumour tissue [83]. The heterotrimeric collagen type I is composed of two α1(I) and one α2(I)-chains. Homotrimeric isoforms are also expressed by tumour cells. These isoforms are largely resistant to MMP degredation [84]. In fibrosarcoma, homotrimeric collagen fibres can represent up to 50% of collagen type I present [83]. The autocrine interaction between homotrimeric collagen molecules and the tumour cells promotes CAM-DR and enhances tumour proliferation and migration, [85, 86]. The PI3K-akt signalling pathway is thought to play a central role in this biology [82]. Thus methods that help promote the degradation of the type I collagen isoforms may improve the efficiency of chemotherapeutic drugs. Because homotrimeric type I collagen is only seen in fetal and pathological tissue, its detection may help in the identification of residual tumour cells during surgery.
I型胶原蛋白在纤维肉瘤的CAM-DR中起重要作用。在肿瘤组织中发现了两种 I 型胶原蛋白 [83]。 I 型异三聚体胶原蛋白由两条 α1(I) 和一条 α2(I) 链组成。同源三聚体同工型也由肿瘤细胞表达。这些亚型在很大程度上抵抗 MMP 降解 [84]。在纤维肉瘤中，同型三聚体胶原纤维可代

表高达 50% 的 I 型胶原 [83]。同源三聚体胶原分子与肿瘤细胞之间的自分泌相互作用促进 CAM-DR 并增强肿瘤增殖和迁移，[85, 86]。PI3K-akt 信号通路被认为在该生物学中发挥核心作用 [82]。因此，有助于促进 I 型胶原同种型降解的方法可以提高化疗药物的效率。由于同源三聚体 I 型胶原蛋白仅见于胎儿和病理组织中，因此其检测可能有助于识别手术过程中残留的肿瘤细胞。

The role of cancer stem cells (CSCs) in tumour initiation, proliferation and chemoresistancy

癌症干细胞 (CSC) 在肿瘤起始、增殖和化疗耐药中的作用

Recently the 'cancer stem cell hypothesis' has gained importance in cancer research [87, 88], It postulates the existence of a hierarchy within the tumour tissue where a small subpopulation of cells possess self-renewal, and stem cell-like characteristics. These cancer stem cells (CSC) are thought to be responsible for the initiation and regulation of tumour growth and have been called the roots of cancer [89]. CSCs are thought to have their own microenvironment referred to as the CSC niche [89].
最近，“癌症干细胞假说”在癌症研究中变得越来越重要[87, 88]，它假设在肿瘤组织中存在一个等级，其中一小部分细胞具有自我更新和干细胞样特征。这些癌症干细胞 (CSC) 被认为负责肿瘤生长的启动和调节，被称为癌症的根源 [89]。 CSC 被认为有自己的微环境，称为 CSC 生态位 [89]。
CSCs are proposed to retain their ability to self-renew and to give rise to stem cell-derived cancer progenitor cells. Their environment helps protect the CSC from chemotherapeutic toxicity. Reports have suggested the existence of such a CSC niche in sarcomas [90]. CSCs are linked to the high recurrence rate of fibrosarcoma and its pronounced chemoresistancy and for this reason represent important targets for new treatment strategies for fibrosarcoma [91].
建议 CSC 保留其自我更新的能力并产生干细胞衍生的癌症祖细胞。他们的环境有助于保护 CSC 免受化疗毒性。报告表明肉瘤中存在这样的 CSC 生态位 [90]。 CSC 与纤维肉瘤的高复发率及其显着的化疗耐药性有关，因此代表了纤维肉瘤新治疗策略的重要目标 [91]。
A specific fibrosarcoma stem cell marker has not yet been identified. In general CSCs are described to have the following characteristics: (i) they possess sphere formation ability, (ii) a high self-renewal potential, (iii) they behave invasively, (iv) they

can be chemoresistant, (v) they possess tumour initiating potential, and (vi) they express the embryonic stem-cell related genes; Nanog, Oct3/4, Sox2, and Sox10. [92; 89] Hoechst staining is often used for the identification and isolation of a distinct subpopulation of CSC called side population (SP) cells [87].
尚未确定特定的纤维肉瘤干细胞标志物。一般来说，CSCs 被描述为具有以下特征：（i）它们具有球体形成能力，（ii）高自我更新潜力，（iii）它们具有侵入性，（iv）它们可以是化学抗性的，（v）它们具有肿瘤起始潜能，和 (vi) 它们表达胚胎干细胞相关基因； Nanog、Oct3/4、Sox2 和 Sox10。 [92; 89] Hoechst 染色通常用于识别和分离称为侧群 (SP) 细胞的不同 CSC 亚群 [87]。

SP are characterized by their expression of transmembrane efflux pumps which makes them highly resistant towards chemotherapy [93–95]. Some CSCs are also characterized by their upregulation of drug detoxifying enzymes such as the aldehyd dehydrogenases (ALDH) [87]. Fluorescent staining of ALDH allows the selection of ALDH positive cells which often possesses typical stem cell-like characteristics. Due to the fact that neither SP cells nor ALDH positive cells represent the total amount of CSC, it is necessary to combine both methods in addition to CSC markers for a more accurate characterization of the cells. The surface antigens CD24, CD90 and CD133 are thought to represent fibrosarcoma stem cell markers [92, 87, 96]. In the human fibrosarcoma cell line HT1080, 9% of cells were found to be ALDH-positive, 3.4–8.4% of the cells were CD133-positive, whereas only 0.3–0.54% belong to the SP, [92, 90, 96].
P 的特点是表达跨膜外排泵，这使得它们对化疗具有高度抵抗力 [93-95]。一些 CSC 的特征还在于它们上调药物解毒酶，例如醛脱氢酶 (ALDH) [87]。 ALDH 的荧光染色允许选择通常具有典型干细胞样特征的 ALDH 阳性细胞。由于 SP 细胞和 ALDH 阳性细胞都不代表 CSC 的总量，因此除了 CSC 标记外，有必要将这两种方法结合起来，以更准确地表征细胞。表面抗原 CD24、CD90 和 CD133 被认为代表纤维肉瘤干细胞标志物 [92, 87, 96]。在人纤维肉瘤细胞系 HT1080 中，发现 9% 的细胞为 ALDH 阳性，3.4-8.4% 的细胞为 CD133 阳性，而只有 0.3-0.54% 属于 SP，[92,90,96].

Current clinical trials for soft-tissue sarcoma

The tumour microenvironment raises hopes for new sarcoma treatments [97]. This is confirmed by ongoing clinical trials. The therapeutic effect of olaratumab in combination with doxorubicin is

currently being evaluated in a phase III clinical trial (ANNOUNCE) in patients with advanced or metastatic soft-tissue sarcoma [98]. Olaratumab is a platelet-derived growth factor (PDGF) receptor-alpha-blocking monoclonal antibody which blocks PDGF ligands from binding. Due to the positive results of the phase II trial, the combination of olaratumab and doxorubicin has been approved in the United States as a first-line therapy for patients with advanced soft-tissue sarcoma responding to anthracycline therapy. The trial completion is expected in 2020 [99–101].

The phase III placebo-controlled clinical trial of Anlotinib, a multi-target tyrosine kinase inhibitor, is another example of a clinical trial in progress to find a more effective treatment of advanced soft-tissue sarcoma by targeting the tumour microenvironment [102–104].

//2020年的试验，可能在2022年有重大突破，需要阅读最新的论文

肿瘤微环境为新的肉瘤治疗带来了希望[97]。正在进行的临床试验证实了这一点。 olaratumab 联合阿霉素的治疗效果目前正在晚期或转移性软组织肉瘤患者的 III 期临床试验 (ANNOUNCE) 中进行评估 [98]。Olaratumab 是一种血小板衍生生长因子 (PDGF) 受体-α-阻断单克隆抗体，可阻断 PDGF 配体结合。由于 II 期试验的积极结果，奥拉单抗和阿霉素的组合已在美国被批准作为对蒽环类药物治疗有反应的晚期软组织肉瘤患者的一线治疗。试验预计在 2020 年完成 [99-101]。 多靶点酪氨酸激酶抑制剂安罗替尼的 III 期安慰剂对照临床试验是另一个正在进行的临床试验，旨在通过靶向肿瘤微环境寻找更有效的晚期软组织肉瘤治疗方法 [102–104] .

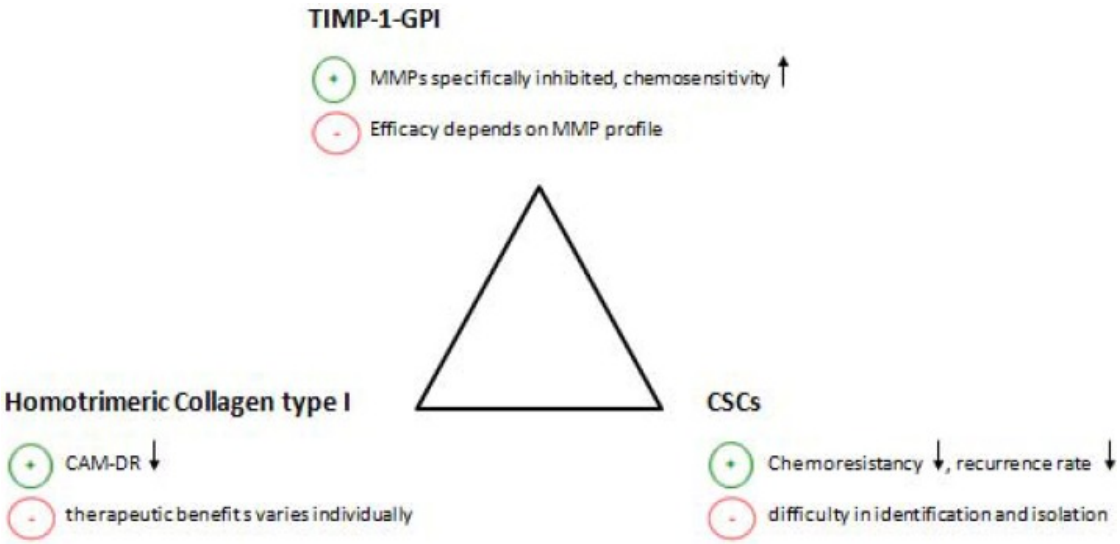
CONCLUSIONS

A tumour`s proliferation and migration significantly correlates with the composition of the surrounding ECM components. The high concentration of MMPs within the tumour tissue results in a highly increased degradation of the ECM which consequently facilitates tumour growth as well as its spread to distant sites. In this context, intratumoral injections especially of the recently developed TIMP-1-GPI fusion protein [72] may represent a promising new treatment strategy. In addition, modulating the mechanisms which lead to CAM-DR may show benefit [78]. Homotrimeric isoforms of collagen type I [83] have been shown to play an important role in the acquirement of drug resistances. 肿瘤的增殖和迁移与周围 ECM 成分的组成显着相关。肿瘤组织内高浓度的 MMP 导致 ECM 的降解高度增加，从而促进肿瘤生长以及扩散到

远处部位。在这种情况下，肿瘤内注射，尤其是最近开发的 TIMP-1-GPI 融合蛋白 [72] 可能代表一种有前途的新治疗策略。此外，调节导致 CAM-DR 的机制可能会显示出益处 [78]。 I 型胶原蛋白的同三聚体异构体 [83] 已被证明在获得耐药性中起重要作用。

Similar to other treatment strategies the ones discussed above have their pros and cons (Figure 2). Hence the local application of TIMP-1-GPI inhibits specific MMPs and leads to a better chemosensitivity. However, the treatment efficacy is likely to depend on the MMP profile within the tumour tissue. Therefore, patients with fibrosarcoma may respond differently to TIMP-1-GPI treatment. The degradation of homotrimeric collagen I is an approach to decrease the cell adhesion mediated drug resistance (CAM-DR). However, the efficiency of this approach depends on the amount of homotrimeric collagen type I within the tumour tissue. Thus supposably not all the patients will benefit from this approach. Last but not least, the therapeutic potential of targeting the cancer stem cells lies in the decrease of chemoresistancy as well as in a lower recurrence rate. The challenge of this approach is to selectively identify and isolate those cells.

与其他治疗策略类似，上面讨论的策略各有利弊（图（图2）.2）。因此，局部应用 TIMP-1-GPI 会抑制特定的 MMP 并导致更好的化学敏感性。然而，治疗效果可能取决于肿瘤组织内的 MMP 谱。因此，纤维肉瘤患者对 TIMP-1-GPI 治疗的反应可能不同。同型三聚体胶原蛋白 I 的降解是一种降低细胞粘附介导的耐药性 (CAM-DR) 的方法。然而，这种方法的效率取决于肿瘤组织内 I 型同源三聚体胶原蛋白的数量。因此，据推测，并非所有患者都会从这种方法中受益。最后但同样重要的是，靶向癌症干细胞的治疗潜力在于降低化疗耐药性以及降低复发率。这种方法的挑战是选择性地识别和分离这些细胞。



The figure shows three different approaches to improve the chemosensitivity of fibrosarcoma

This includes the application of TIMP-1-GPI, the suppression of potential chemoresistant cancer stem cells (CMCs) and the interruption of CAM-DR by homotrimeric collagen type I degradation. The above figure further summarizes the pros (+) and cons (−) of each approach. CAM-DR (cell adhesion mediated drug resistance), CSCs (cancer stem cells), ↓ (reduction),↑(increase).

该图显示了提高纤维肉瘤化疗敏感性的三种不同方法 这包括应用 TIMP-1-GPI、抑制潜在的化学抗性癌症干细胞 (CMC) 以及通过 I 型同源三聚体胶原蛋白降解中断 CAM-DR。上图进一步总结了每种方法的优点（+）和缺点（-）。 CAM-DR（细胞粘附介导的耐药性），CSCs（癌症干细胞），↓（减少），↑（增加）。

It should also be kept in mind that all the approaches mentioned in this article are pieces of the puzzle. The complexity of cancer is multidimensional. Therefore, the tumour microenvironment is only one dimension in the treatment of fibrosarcoma.

Targeting the tumour initiating cancer stem cells may be an important step in the treatment of fibrosarcoma. At present fibrosarcoma stem cell markers, even in combination, still fail to identify all CSC present in a sample. Further work in this field is urgently needed.

还应该记住，本文中提到的所有方法都是拼图的一部分。癌症的复杂性是多维的。因此，肿瘤微环境只是治疗纤维肉瘤的一个维度。 靶向启动肿瘤的癌症干细胞可能是治疗纤维肉瘤的重要一步。目前，纤维肉瘤干细胞标记物，即使结合使用，仍然无法识别样品中存在的所有 CSC。迫切需要在该领域开展进一步的工作。