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REVIEW

Cutaneous soft tissue sarcomas: survival-related factors

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Abstract

Cutaneous sarcomas are a heterogeneous group of rare mesenchymal neoplasms representing less than 1% of malignant tumors. Histology report remains the cornerstone for the diagnosis of these tumors. The most important clinicopathologic parameters related to prognosis include larger tumor size, high mitotic index, head and neck location, p53 mutations, depth of infiltration and histological grade, vascular and perineural invasion as well as the surgical margins status. Applying advanced biopsy techniques might offer more precise assessment of surgical margins, which constitutes a significant precondition for the management of these tumors. The management of cutaneous soft tissue sarcomas requires a multidisciplinary approach. Surgery remains the standard treatment, nonetheless adjuvant therapy may be required, consisting of radiotherapy, chemotherapy, and molecular targeted therapies to improve treatment outcomes. The role of molecular profiling in the treatment of uncontrolled disease is promising, but it may be offered to a relatively small proportion of patients and its use is still considered experimental in this setting. Due to the rarity of the disease, there is a need for knowledge and experience to be shared, pooled, organized and rationalized so that recent developments in medical science can have a major impact on the disease course. Multicenter clinical trials are needed to improve the care of patients with cutaneous sarcomas.

Keywords Cutaneous · Sarcomas · Factors · Biopsy · Treatment · Survival · Recurrence

Abbreviations

DFSP	Dermatofibrosarcoma protuberans
LMS	Leiomyosarcoma
PDS	Pleomorphic dermal sarcoma
AFX	Atypical fibroxanthoma
RMS	Rhabdomyosarcoma
CA	Cutaneous angiosarcoma
KS	Kaposi sarcoma
RT	Radiotherapy
PDGFRB	Platelet-derived growth factor receptor
VEGFR3	Vascular endothelial growth factor receptor 3
HAART	Highly active antiretroviral treatment
MR	Magnetic resonance
WLE	Wide local excision
MMS	Mohs micrographic surgery

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Introduction

Cutaneous soft tissue sarcomas constitute a rare group of mesenchymal spindle cell neoplasms of the dermis and subcutis with large pathogenetic heterogeneity and represent less than 1% of malignant tumors [1]. DermatofibrosarcomaProtuberans (DFSP) constitutes the most common entity while other primary cutaneous neoplasms include Leiomyosarcoma (LMS), Malignant Undifferentiated Sarcomas (older term Malignant Fibrous Histiocytoma-MFH), Pleomorphic Dermal Sarcoma (PDS) (also known as Atypical Fibroxanthoma-AFX), Rhabdomyosarcoma (RMS), Liposarcoma, Vascular Sarcomas (Cutaneous Angiosarcoma-CA) and Kaposi Sarcoma (KS), as well as some rare modalities, such as Myxoinflammatory Fibroblastic Sarcoma and Myxofibrosarcoma [2].

Histology remains the keystone for the diagnosis of these tumors. It should be noted that the exclusion of other dermal neoplasms such as melanoma is of exceptional importance, due to their possibly aggressive and malignant course. Genetics and molecular biology have revealed crucial

aberrations in the natural history of these tumors. Thus, targeted therapies have been added to the therapeutic armamentarium of the clinicians dealing with cutaneous sarcomas [3].

Surgical excision ensuring negative surgical margins remains the mainstay of local disease treatment. In the case of local recurrence or subtotal excision and when re-excision is not an option, radiotherapy (RT) and systemic chemotherapy can be employed. However, the ideal treatment algorithm in case of metastatic and/or recurrent disease is not defined in detail in the major treatment guidelines (European society for medical oncology—ESMO, National Comprehensive Cancer Network-NCCN) for the majority of these sarcomas.

Methods

A systematic literature review was performed based on database search in PubMed/MEDLINE and included articles up to July 2020. The terms used for the search were 'Cutaneous', 'sarcomas' and synonyms combined with one or more of the following: 'factors', 'biopsy', 'chemotherapy', 'treatment', 'survival', 'recurrence' and synonyms. Pre-clinical, clinical phase I, II, randomized phase III and IV studies, reviews, meta-analyses and abstracts of important meetings were analyzed. Articles published in English were included.

Results

Epidemiology, histopathologic profile and immunohistochemistry

While the vast majority of cutaneous sarcomas usually affects elderly patients with their peak incidence in the 6th to 8th decade, DFSP is more likely to occur in early and middle adulthood [3]. Clinical presentation usually consists of a painless tumor, mostly observed in the trunk and proximal extremities [4]. Histological examination of DFSP reveals a proliferation of uniform spindle tumor cells incorporated into fibrous stroma that have minimal cytoplasm, indistinct margin and present minimal mitotic activity [5, 6]. The growth pattern of these tumor cells is characterized by asymmetry and a characteristic infiltration of subcutaneous fat, which resembles a honeycomb pattern [7]. Except for cutaneous and subcutaneous fat, the fascia, muscle, and bone may be also infiltrated by these tumors with lateral margins being distinctly larger than clinical in most of the cases [8]. Concerning the immunohistochemistry of these tumors, it should be mentioned that they exhibit positivity for CD34 and negativity for Factor XIIIa, which may be useful for the differentiation from other cutaneous sarcomas [9, 10]. DFSP is considered as a low malignant type, with a propensity to recur locally after resection. However, the prognosis is good with a 5-year relative survival rate up to 99% while its metastatic profile is fortunately very low [11]. Although there is no staging system for the prediction of clinical outcomes, some clinicopathologic parameters are more likely to predict the recurrence incidence and affect survival rates [5, 12]. Indeed, older age, male gender, larger tumor size, high mitotic index, head and neck location and p53 mutations seem to be associated with worse prognosis affecting both recurrence and survival. Identification of the translocation t(17;22) (q22;q13), which results in the formation of a fusion gene between beta-type platelet-derived growth factor receptor (PDGFRB) gene and the collagen type 1 alpha1 (COL1A1) gene, is pathognomonic for this tumor type. Furthermore, it reveals that the activation of PDGFRB signaling pathway is crucial for the pathogenesis of DFSP. This molecular finding has offered the option of targeted therapies (imatinib) and potentially innovative immunotherapy approaches.

Similar to DFSP, Cutaneous Leiomyosarcoma (LMS) represents a rare dermal sarcoma accounting for less than 3% of dermal sarcomas that grow slowly [13]. In contrast to deep LMS, superficial ones are found in the dermis or subcutaneous tissue and present a lower metastatic rate, not exceeding 15% [13]. Given the more favorable prognosis for dermal LMS, it is worth mentioning that infiltration depth and histological grade may constitute prognostic factors for these tumors [14]. Cutaneous LMS is exhibited with an infiltrative growth pattern consisting of atypical spindle cells with eosinophilic cytoplasm, nuclear atypia and multiple mitoses [14]. The diagnosis depends on findings of hemorrhagic and necrotic regions, atypical smooth muscle cells and the expression of the vimentin, α-smooth muscle actin, and desmin, that is observed in 60% of cases [17, 18]. With regard to their immuno-histochemical profile, these tumors present positivity for SMA, desmin, and h-caldesmon [19, 20]. Cutaneous LMS presents a locally aggressive behavior with estimated recurrence and survival rates after excision as high as 60% and 92%, respectively [21]. Indeed, researchers have noticed recurrences even after adequate resections with wide margins, of about 5 mm [22]. Except for the depth of infiltration and histological grade, other factors are considered to be important, including mitotic rate, necrosis, vascular invasion as well as tumor size [23]. In particular, it has been illustrated that tumors with size up to 2 cm compared to those larger than 5 cm exhibit survival rates of approximately 95% versus 30%, respectively [24].

Undifferentiated Sarcomas constitute approximately one-fifth of cutaneous soft tissue sarcomas when KS cases are not incorporated [15]. These tumors mostly occur in elderly males, in the head and neck region and extremities [25]. The histological profile of Undifferentiated Sarcoma includes short and ovoid spindle cells with a great number of mostly

atypical mitoses. There is usually observed a great variety of cells (inflammatory, giants, macrophages) and regions with characteristic necrosis. With regard to immunohistochemistry, the majority of cases present positivity for XIIIa, SMA and CD68 and express the molecular markers desmin and CD34 [26]. Similar to other cutaneous sarcomas, undifferentiated sarcomas present locally aggressive behavior, which explains both the high recurrence rates, estimated between 30 and 71%, as well as their metastatic behavior that reaches approximately 40% of reported cases [27].

Regarding vascular sarcomas, Kaposi Sarcoma (KS) is the most frequent type of soft tissue sarcoma, accounting for approximately 70% of cases in the United States [21]. It is a locally aggressive tumor, strongly associated with the Human Herpes Virus 8 infection [28]. KS is commonly found in patients with immunodeficiency diseases, such as AIDS, affecting either lymph nodes or organs. Additionally, it mainly affects males and children in African countries where there is a significant association between morbidity and mortality [29]. The cellular nature of KS remains indistinguishable. The histopathological findings include spindle-shaped cells, vascular proliferation, erythrocytes blood cells and lymphoplasmacytic infiltration of these lesions [30]. Several markers are found positive in the immunochemistry, which are expressed by almost all of these spindle cells. Concerning the fact that both the lymphatic and vascular endothelium compose the spindle cells, both endothelial markers, such as CD31, CD34, ERG, FLI-1, and markers of lymphatic endothelium, such as vascular endothelial growth factor receptor 3 (VEGFR3) and D2-40, are being expressed [31, 32]. However, it is noteworthy that there is still no effective therapy for the disease. Indeed, although highly active antiretroviral treatment (HAART) has led to the reduction of the Kaposi Sarcoma incidence, no total regression has been observed yet [33]. RT, surgery and chemotherapy may complete the therapeutic approach of KS, while molecular targeted therapies are currently investigated.

Cutaneous Angiosarcomas (CA) constitute aggressive vascular tumors representing 2% of soft tissue sarcomas mostly found in the head and neck region of elderly individuals [34]. They are detected more frequently in males and the etiologic risk factors include history of prior radiation, chronic lymphedema after mastectomy in women and chronic skin exposure to ultraviolet light [35, 36]. CA are tumors composed of spindle cells with various differentiations [14]. Vascular channels with atypical endothelium are usually observed in well-differentiated tumors while lesions with increased mitoses and absence of erythrocytes are characteristics in high-grade tumors [37, 38]. The immuno-histochemical findings that are helpful in the diagnosis of CA include the expression of the markers CD31, CD34, ERG FLI-1 and cytokeratins [39]. Unlike other superficial sarcomas, CA has a poorer prognosis because of their propensity for early metastases through the blood stream to lungs, bone, liver or brain [40]. Studies have noted that the 5-year survival rate ranges from 20 to 45% [41]. Factors related to a poor prognosis include older age, tumor size larger than 45 mm, depth of invasion greater than 3 mm, higher mitotic rate, the anatomic region of the tumor (location on the head and neck have more favorable prognosis) as well as failure to achieve clear surgical margins [42]. Due to the presence of positive surgical margins in approximately 80–90% of reported cases, a generally high local recurrence rate is reported in the literature that exceeds 70% or even 80% [43].

Rare histologic subtypes of cutaneous sarcomas have also been described. Pleomorphic Dermal Sarcomas (PDS) are rare neoplasms mainly observed in the sun-exposed skin of the elderly [16]. The histological profile of PDS is characterized by pleomorphic, epithelioid, atypical spindle cells, combined with giant multinucleated tumor cells presenting frequent and atypical mitoses, including abnormal forms [14, 44]. PDS has a nodular, exophytic growth and despite the fact that they are often presented within the dermis, findings of subcutis or vascular invasion can be observed, indicating more aggressive tumor behavior [45]. Regarding the immuno-histochemical profile, most of the cases present positive reactions to CD34 and less frequently to SMA and EMA [46]. Although these tumors have a low metastatic profile, which is estimated lower than 5%, the presence of some factors, such as deep infiltration, necrosis, vascular and perineural invasion, is significantly associated with higher local recurrence and metastatic rates [47].

Lastly, other rare tumor types include Myxoinflammatory Fibroblastic Sarcoma and Myxofibrosarcoma. The former mostly appears in middle-aged individuals and presents high local recurrence rates [48]. The latter is a rare tumor which also has recurrence rates of 50–60%, regardless of histological grade. Additionally, those tumors with a more aggressive histological grade, are related to an increased metastatic profile ranging from 20 to 35% [49].

The role of histological examination

Improved histological examination constitutes a precondition for the enhanced management of these tumors. Fine-needle aspiration, core biopsy, incisional and excisional biopsy, are reliable biopsy techniques [50]. However, before the biopsy, several demographic and tumor-related factors, such as patient age and sex, tumor size and location, the subclinical extent of the tumor, the number of required surgical excisions for the achievement of clear surgical margins, as well as the depth of invasion and the esthetic outcome should be evaluated by clinicians [50].

The number of re-excisions and tumor growth pattern might predict tumor aggressiveness [51]. Several factors should be assessed through the examination of hematoxylin

and eosin–stained sections with microscope. Characteristically, the tumor growth pattern, cellularity, cells' appearance, amount and type of matrix formation, tumor and adjacent tissue interfaces, vascularity, tumor necrosis, and mitotic activity should be evaluated [50]. Excisional biopsies are usually required for the confirmation of smaller lesions and punch biopsies for larger ones [52]. The intraoperative frozen section biopsy may be useful for the evaluation of surgical margins. In the case of positive pathological results, either further excision or adjuvant RT is needed [53]. A re-excision is useful to fully determine the extent of horizontal, lateral and vertical tumor growth as well as the defect size of the tumor [51]. The intraoperative frozen analysis may effectively reveal surgical margins, thus leading to decreased rates of incomplete resections [54]. In the absence of this technique, both the extent of the tumor and the depth of invasion may be assessed by magnetic resonance (MR) imaging [53]. Furthermore, several studies reported better local control evaluation with the use of 3D histology, to assess both lateral and deep surgical margins [55]. The use of high-quality paraffin sections with 3D histology might deeply reveal subclinical extensions leading to reduced local recurrence rates and accordingly to better local control of the tumor [56].

Treatment options

The management of cutaneous soft tissue sarcomas requires a multidisciplinary approach. Surgery is the main therapeutic approach, which in combination with radiation therapy, chemotherapy, and molecular targeted therapies ensures the most favorable outcomes [57]. Multiple studies have widely described the significant association between clear surgical margins and lower recurrence rates, and accordingly better prognostic outcomes [58]. However, it should be mentioned that the anatomic region where the tumor is located (e.g., the head and neck region), is associated with better or worse outcomes, despite the fact that surgical resection margins are similar [57].

A wide local excision (WLE) or Mohs micrographic surgery (MMS) may be applied to remove the lesion, although it is not well-defined which modality is superior to the other [58]. Obviously, factors, such as tumor characteristics and the existence of expertized clinicians, should always be taken into consideration before the final choice [59]. However, although WLE was traditionally used as the main treatment, MMS seems to be a more effective modality. Specifically, the reduction of surgical margins may offer a tissue-sparing advantage, which implies improved outcomes, both cosmetically and functionally [7]. MMS especially benefits more superficial lesions, where there is an increased cosmetic interest. Furthermore, its effective contribution to the reduction of recurrences is attributed to the fact that both deep and circumferential margins can be well assessed and evaluated by this approach, which is highlighted by multiple reviews and studies [62, 63]. Nonetheless, in case of inadequate surgical margins, repeated excisions, or in palliative occasions, RT, chemotherapy, and targeted therapies may be incorporated in the whole therapeutic procedure aiming to improve the prognosis of these patients [64].

Radiotherapy is described as more efficacious in larger and more aggressive tumors as well as in case of close margins, perineural invasion, or when there appears increased morbidity after a possible re-excision [65]. Several studies have described the beneficial role of RT in DFSP either preoperatively or as an adjuvant treatment in case of unclear surgical margins with good local control [66]. Doses of 50–70 Gy have been employed, with more recent studies showing that 50 Gy may be adequate [67]. Despite the fact that there are no forceful data about the role of RT in LMS, it should be considered in case of unclear margins and high-grade tumors with size larger than 5 cm [68].

The gold standard of treatment for undifferentiated sarcomas is the complete surgical resection, which may be accompanied by RT in case of unclear resection margins [15]. Additionally, given the management of patients with CA, apart from the clear benefit of adjuvant RT in large unresectable tumors, some studies also investigate the potentially favorable role of adjuvant chemotherapy in combination with targeted drug therapies to the improvement of poor survival of these patients [69]. Furthermore, regarding the rare modality of Myxofibrosarcoma that presents a high rate of local recurrence and poor prognosis, there are conflicting data about the role of RT because of the radio-resistant nature of these tumors [70]. On the contrary, RT may possess a valuable role in the case of unresectable or recurrent tumors in patients with PDS, which is well illustrated by several studies [71].

The role of chemotherapy in patients with both DFSP and LMS in the adjuvant setting is debatable. Nonetheless, chemotherapy might be beneficial for locally advanced high-risk tumors. In the case of metastasis, systemic therapy is given with palliative intent [72]. Both ESMO and NCCN guidelines describe the most efficacious therapeutic options for cutaneous sarcomas. Specifically, in advanced, unresectable, recurrent, or metastatic disease of DFSP, some studies highlight the role of targeted drug therapies such as imatinib [73-75]. In cases of metastasized LMS, conventional cytotoxic chemotherapy regimens used in soft tissue sarcomas are usually applied. For angiosarcomas, systemic treatment with taxane-based chemotherapy is currently used. However, promising results regarding the efficacy of immunotherapy agents to CA were recently published including anti-VEGF monoclonal antibody and tyrosine kinase inhibitors [76]. Finally, KS, when treated with chemotherapy systematically,

liposomal doxorubicin, or paclitaxel, has shown positive results [77, 78].

Unfortunately, problems may arise from past management, due to short follow-up periods, retrospective and single-center experience data. To pool and enhance experience concerning sarcomas, more trials and data sharing are needed (phase 1b to phase 2 at least required). Cooperation will have a positive impact on time of accrual and diminished lead time biases. Informatics may also be useful in overcoming the problems of the past. Additionally, timing data sharing and cooperation will be useful in defining the role of different methods, such as molecular diagnostic and modern treatment procedures.

Conclusion

Cutaneous sarcomas are a heterogeneous group of rare mesenchymal neoplasms. The most common entities are DFSP, LMS, CA and KS. The histology report is important for the correct diagnosis of these tumors, while the exclusion of melanoma is crucial. Surgery remains the mainstay of therapy for patients with cutaneous sarcomas. Systemic treatment with RT, cytotoxic chemotherapy, targeted therapies and immunotherapy are offered to metastasized patients.

Multiple clinical trials are currently underway to evaluate novel therapies for sarcomas [79]. Despite an overall favorable prognosis, new therapeutic options, diagnostic and prognostic tools need to be developed to enhance the care for patients with cutaneous soft tissue sarcomas.

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Declarations

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