Multidisciplinary management of soft tissue sarcomas: it's time to make a team!

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Musculoskeletal sarcomas are a heterogeneous group of malignant neoplasms derived from connective tissue. Sarcomas represent about 1% of cancer in adults. The annual incidence in adults in Europe is around 14,000 new cases of soft tissue sarcomas and 4,800 new cases of bone sarcomas [1]. Musculoskeletal sarcomas originate from elements of the mesodermal embryonic layer and are classified according to the adult tissue resembled in the case of soft-tissue sarcomas (STS) and according to the type of matrix (i.e. osteoid or chondroid) produced in bone sarcoma (BS). Musculoskeletal tumours arise anywhere in the body, although lower extremities are the most common site of appearance followed by upper extremities, trunk, retroperitoneum and head and neck area [1–5].

The most frequent presentation of STS is as an asymptomatic mass. However, sarcomas are locally invasive tumours with high propensity to recur locally. Higher-grade and larger sarcomas are more prone to metastasise in distant sites and more likely to be lethal.

The adequate management STS is a stimulating challenge for oncologists. The aim of treatment should be focused on four main aspects: improving survival, avoiding local recurrence, maximising organ function and minimising morbidity. Surgery, radiotherapy and –sometimes, though increasingly– chemotherapy, are the pillars on which rests the modern treatment of sarcomas. The optimal management of musculoskeletal tumours requires multidisciplinary integration of these different approaches in treatment planning right from the initial diagnoses. Nevertheless, the timing and order of local resection, preoperative or postoperative, and even chemotherapy require a multidisciplinary and well-coordinated team.

Surgical resection remains the mainstay of treatment for STS, and it is still considered the dominant curative

therapy. The surgeon's ability to perform a complete tumour resection with a rim of several centimetres of normal tissue to guarantee a free margin is the cornerstone for optimal treatment. Despite the technical advances of radiation therapy and even the promising results of new chemotherapy regimens, surgical removal of the entire tumour with a wide margin of free tissue is indicated in each and every STS. Appropriate surgical management with wide local excision achieving negative surgical margins should result in excellent local control for patients with small (<5 cm), low-grade, superficial tumours. Traditionally, high-grade STS of the extremities were treated with limb amputation in order to obtain a wide free margin, achieving a high rate of local control [6]. A randomised trial conducted by the National Cancer Institute between 1975 and 1981 comparing amputation versus limb-preserving surgery in extremity STS is considered the first evidence of the effectiveness of a conservative approach. Successive randomised trials comparing limb-sparing surgery against conservative resection alone confirmed these results, and limb-sparing surgery followed by radiation therapy attained the gold standard level of treatment, being as effective as the more aggressive surgical amputation and resulting in 5-year actuarial local control rates of 74–87% [7–9]. Nowadays, amputation is reserved for patients with huge tumours not amenable to an en bloc excision with negative margins, extensive involvement of the neurovascular bundle and nonfunctional limbs at diagnosis.

Conservative treatment of STS of the extremities, combining a wide resection of the tumour along with pre- or postoperative radiotherapy has achieved locoregional control and survival rates similar to those obtained after amputation. Conservative surgery is associated exclusively with local recurrence rates of around 30%. Local recurrence is a well-known risk factor for the development of distant metastases. Radiotherapy after limb-sparing surgery is associated with local control rates exceeding 90% in many series. Intuitively, it seems logical to consider that a treatment to increase local control and reduce the incidence of distant metastases should be associated with increased survival. The radiation associated with conservative surgery increases locoregional control in the affected limb compared with conservative surgery without radiation

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therapy but had not shown an increase in overall survival. Recently, Koshy et al. analysed the results of 6,960 patients with STS of the extremities treated with limb-sparing surgery between 1988 and 2005 and included in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) registry. Forty-seven percent of patients received radiotherapy, in most cases (86.5%) postoperatively. In all patients, radiotherapy was associated with increased overall and cause-specific survival, even when rates were adjusted according to patient characteristics or tumour. The benefit seen in survival was significant in the case of high histological-grade tumours [hazard ratio (HR) 0.67] and even more in tumours larger than 5 cm (HR) 0.63. For low-grade sarcomas, this benefit was not statistically significant, although the authors noted that the use of radiotherapy in these patients was significantly lower than in those with high-grade tumours. There were no differences between the way radiation therapy was given pre- or postoperatively. Despite the limitations of the analysis, such as the lack of information about the technical aspects of radiotherapy, surgery or patient condition, the authors conclude that this is the first study, based on a wide enough number of patients, to demonstrate a benefit of radiotherapy not only in local control but also in overall survival after limb-conserving surgery in STS of the extremities. According to these results, radiotherapy in combination with conservative surgery is indicated in all patients with high-grade sarcomas, especially T2 tumours, and low-grade tumours with adverse factors, such as large tumours or those that affect the existence of margins [10].

Regardless of this evidence, some questions remain unsolved with respect to radiotherapy in STS. Randomised studies showed that radiotherapy either pre- or postoperatively allowed more conservative resections without worsening local outcome rates. Pre- and postoperative timing for radiation therapy show potential advantages and potential disadvantages, which are discussed by defenders of each one without a clear superiority of one over the other. Furthermore, toxicity associated with radiotherapy in the context of conservative treatment that seeks to preserve both the member as its functionality is an aspect to keep in mind. On the one hand, postoperative external-beam radiotherapy (EBRT) doses below 62 Gy result in impaired local control rates. On the other hand, postoperative EBRT 64–66 Gy is associated with the development of late moderate to severe complications in terms of fibroses, limb oedema or joint stiffness in nearly 50% of patients. Attempts to improve the local control benefit obtained with radiotherapy while minimising toxicity have led to alternative targeting and delivery methods and the use of highly conformal therapies. The chance of delivering a high radiation dose to the areas of higher risk of tumour relapse has made brachytherapy and intraoperative electron radiotherapy (IOeRT) attractive alternatives in the conservative management of STS.

A particular issue is that of retroperitoneal sarcomas, which represent about 15% of all STS. Their particular

location makes their management, both surgical and radiotherapeutic, quite problematic. The possibility of obtaining a complete excision with wide tumour-free margins is considerably more complicated than in the case of sarcomas of the extremities. The subsequent irradiation of the surgical bed considering the existence –often in close proximity to it– of low-tolerance structures such as spinal cord, kidney, spleen, liver and intestines, makes it a difficult decision. However, despite the limitation imposed by radiation tolerance, postoperative radiotherapy was considered indicated in most of these patients. The development of techniques such as intraoperative brachytherapy or IOeRT allows administration of higher doses to the tumour bed without compromising the integrity of organs and should be considered in the treatment of retroperitoneal sarcomas [11].

Chemotherapy has been largely studied in primary STS because metastases develop in 25–50% of patients with intermediate- or high-grade sarcomas larger than 5 cm. However, it is still not considered by many as a standard practice for resected primary STS despite its role in metastatic tumours. Unfortunately, it has not shown a gain in survival in sarcomas in adults, unlike that observed in paediatric rhabdomyosarcoma, Ewing sarcoma or osteogenic sarcoma. The decision to use chemotherapy needs to be weighed against the magnitude of potential clinical advantages versus the frequently associated severe, acute and chronic toxicities. A classic meta-analysis of 14 clinical trials evaluating adjuvant chemotherapy in patients with resectable STS found chemotherapy to have an absolute benefit of 10% in recurrence-free survival at 10 years, with an HR of 0.75 for recurrence or death. However, when the analysis was limited to overall survival at 10 years, the difference between patients who received adjuvant chemotherapy and those who did not was not statistically significant [12].

What is the reason, then, despite the research activity developed in recent decades, that chemotherapy is still not accepted as a first-line treatment for STS? The answer is not unique. Several factors seem to contribute to this apparent lack of efficacy. First, sarcomas are a very heterogeneous group of tumours with different clinical and genetic profiles, so the results are difficult to interpret. Moreover, many studies include a small number of patients, not enough to reach consistent conclusions. Finally, many chemotherapy schedules analysed are considered, in the light of current knowledge, as suboptimal because of the combination of drugs as well as their dosages, which could justify the poor results. The development of new drugs such as Trabectedin (ET-743), which offers promising results but must be confirmed by well-designed phase III studies, opens the door to a reconsideration of chemotherapy in the treatment of sarcomas. Future research on drug design based on the knowledge of molecular mechanisms underlying biological processes associated with growth and distant spread of sarcomas should lead to more individualised and effective treatments [13].

In conclusion, a multimodal approach based upon an integrated team is now an unavoidable necessity in the

management of STS. A multidisciplinary team should comprise surgeons, radiation oncologists, medical oncologists, radiologists and pathologists to provide a comprehensive view of each case. Referring patients to qualified centres is desirable to achieve the maximum probability of control, and even cure, of STS. Both overall survival and the maintenance of functionality are significantly better when patients are treated in a tertiary centre of ex-

cellence with access to experienced teams working in a coordinated manner. The availability of guidelines and recommendations for the proper treatment of sarcomas is always desirable, but it is of much more interest to provide multidisciplinary teams, when feasible, that are amenable to addressing the treatment of these patients or that are prompt to remit them to the experienced centres of excellence [14].

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