

Sarcoma European and Latin American Network (SELNET) Recommendations on Prioritization in Sarcoma Care During the COVID-19 Pandemic

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. COVID-19 • Sarcoma • Guidelines • Patient care • Multidisciplinary

ABSTRACT

Background. The COVID-19 outbreak has resulted in collision between patients infected with SARS-CoV-2 and those with cancer on different fronts. Patients with cancer have been impacted by deferral, modification, and even cessation of therapy. Adaptive measures to minimize hospital exposure, following the precautionary principle, have been proposed for cancer care during

COVID-19 era. We present here a consensus on prioritizing recommendations across the continuum of sarcoma patient care.

Material and Methods. A total of 125 recommendations were proposed in soft-tissue, bone, and visceral sarcoma care. Recommendations were assigned as higher or lower priority if they cannot or can be postponed at least 2–3 months, respectively. The

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consensus level for each recommendation was classified as “strongly recommended” (SR) if more than 90% of experts agreed, “recommended” (R) if 75%–90% of experts agreed and “no consensus” (NC) if fewer than 75% agreed. Sarcoma experts from 11 countries within the Sarcoma European-Latin American Network (SELNET) consortium participated, including countries in the Americas and Europe. The European Society for Medical Oncology-Magnitude of clinical benefit scale was applied to systemic-treatment recommendations to support prioritization.

Results. There were 80 SRs, 35 Rs, and 10 NCs among the 125 recommendations issued and completed by 31 multi-

disciplinary sarcoma experts. The consensus was higher among the 75 higher-priority recommendations (85%, 12%, and 3% for SR, R, and NC, respectively) than in the 50 lower-priority recommendations (32%, 52%, and 16% for SR, R, and NC, respectively).

Conclusion. The consensus on 115 of 125 recommendations indicates a high-level of convergence among experts. The SELNET consensus provides a tool for sarcoma multidisciplinary treatment committees during the COVID-19 outbreak. *The Oncologist* 2020;25:e1562–e1573

Implications for Practice: The Sarcoma European-Latin American Network (SELNET) consensus on sarcoma prioritization care during the COVID-19 era issued 125 pragmatical recommendations distributed as higher or lower priority to protect critical decisions on sarcoma care during the COVID-19 pandemic. A multidisciplinary team from 11 countries reached consensus on 115 recommendations. The consensus was lower among lower-priority recommendations, which shows reticence to postpone actions even in indolent tumors. The European Society for Medical Oncology-Magnitude of Clinical Benefit scale was applied as support for prioritizing systemic treatment. Consensus on 115 of 125 recommendations indicates a high level of convergence among experts. The SELNET consensus provides a practice tool for guidance in the decisions of sarcoma multidisciplinary treatment committees during the COVID-19 outbreak.

INTRODUCTION

Deferral, modification, and even cessation of therapy are hindrances affecting patients with cancer during the current COVID-19 outbreak. The balance between adapting measures to minimize hospital exposure, following the precautionary principle, and offering a more relaxed diagnostic or therapeutic management while preserving the patient's survival options is not easy.

More than 80 reports, often short reports and letters, have addressed the intersection of cancer and COVID-19 care. Although the risk of morbidity and mortality is almost always higher in patients with cancer than in patients infected with COVID-19 (i.e., risk of death for pancreatic cancer is greater than 90%, whereas for COVID-19-infected patients, it is usually lower than 5%) [1], the truth is that the precautionary principle has prevailed over cancer care continuation in many cases [2]. Elective surgeries were largely suspended, in some instances, because of shortage of ventilators, and thus the operating theaters became extemporaneous intensive care units. Some reports have focused on the real impact (direct and indirect) of the COVID-19 outbreak in patients with cancer. In some locales where the admissions for SARS-CoV-2 far exceeded the hospital capacity, it was to be expected that cancer care would be compromised in a variety of ways.

Patients with cancer constitute a large population with a spectrum of risk with respect to immunosuppression. Cancer immunoediting, which represents the interplay between tumor and immune system, ultimately leads to changes in immune cells, immune modulators, cytokines, and molecules expression toward the escape phase and the development of an immunosuppressive tumor microenvironment [3]. Both specific diagnoses and their treatment with chemotherapy, surgical resection, and newer treatments variably compromise immune

function and render some patients with cancer more susceptible to infections [4].

As with other infections, the innate and adaptive arms of the immune system play different key roles in the COVID-19 infection and evolution. SARS-CoV-2 causes an overwhelming persistent innate-induced inflammation that can lead to a cytokine storm, cytokine-associated lung injury, and diffuse organ involvement [5]. Alterations of the CD4⁺ and CD8⁺ T cells subsets have been observed, with loss of functional diversity in CD4⁺ T cells and increased expression of regulatory molecules in CD8⁺ T cells [6, 7]. Hence, it can be assumed that the systemic immunosuppressive state of patients with cancer might result in an increased risk of COVID-19 infection and poorer prognosis for this group of patients.

Epidemiological statistics of the cases in China suggested that patients with cancer were at greater risk than the general population, data which appear to be borne out more for hematologic malignancies than solid tumors, although there still appears to be greater risk even for patients with solid tumor for fatal outcomes from SARS-CoV-2 [8]. Noteworthy, it has been reported that COVID-19-related deaths were strongly associated with male sex, older age, and deprivation; severe asthma; uncontrolled diabetes; cancer; and several other previous, clinical conditions [9].

Importantly, a recent epidemiological report from the U.K. based on 800 patients with cancer with COVID-19 infection observed a mortality rate of 28%, with older age, male gender, and comorbidities, such as cardiovascular disease, significant prognostic factors related to higher mortality. Remarkably, chemotherapy or other systemic therapy administered within 4 weeks of testing positive for COVID-19 did not have significant effect on mortality from COVID-19 disease [10].

Taken together, rapidly evolving data indicate that oncologic patients, such as patients with sarcoma, constitute a high-risk group more likely to suffer higher mortality and morbidities than in the general population if infected by SARS-CoV-2.

Additionally, during the COVID-19 outbreak, the major risk for patients with cancer is the inability to receive necessary medical services. Decisions on whether or not to postpone cancer treatment and clinical trials need to be made on a patient-by-patient basis and according to the inherent tumor risk in each patient and the prevailing situation, because delays could lead to tumor progression and, ultimately, poorer outcomes [11]. An article on patients' perspectives reported that up to 30% of oncologic patients have had changes in their treatment or follow-up care during the COVID-19 pandemic [12]. Beyond the increased risks, including requiring mechanical ventilation and death, that should be prospectively analyzed in oncologic patients with COVID-19 infection, it is also relevant to take into account the impact of the precautionary principle that is implemented in our patients [13]. The latter implies that patients with cancer have suffered delays or cancellation of diagnostic tests, surgeries, radiation therapies, or systemic treatments.

The aim of this article is to build a consensus on prioritization aspects in sarcoma care during the current COVID-19 outbreak or future outbreaks, which could appropriately balance the precautionary principle while preserving the highest survival probabilities in sarcoma patients.

This consensus has been developed within the Sarcoma European-Latin American Network (SELNET). This is a consortium granted by the European Commission within the Horizon 2020 Call, within the program H2020-SC1-BHC-2018-2020 (better health and care, economic growth, and sustainable health systems). The aim of the SELNET consortium is to improve clinical outcome in sarcoma care, through a network of reference centers in sarcoma [14].

These guidelines are intended to add value over and above other clinical practice guidelines reported for oncologic patients in the context of COVID-19 outbreak. Thus, our guidance focuses specifically on patients with sarcoma and thoroughly provides precise details on prioritization of 125 clinical sarcoma situations, whereas the National Institute for Health and Care Excellence (NICE) offers a general recommendation for any oncologic patient [15], and the European Society for Medical Oncology (ESMO) offers a more general recommendation of prioritization for patients with sarcoma [16].

MATERIALS AND METHODS

The recommendations have been divided into two scenarios, higher and lower priority, to make them simple and replicable. Higher priority is defined as an undelayable procedure, because the inherent risk of the tumor, affecting survival or morbidity, would likely exceed the risk of COVID-19 infection if this procedure had not been performed. By contrast, lower priority is defined as a delayable procedure (at least 2–3 months), because the inherent risk of the tumor, affecting survival or morbidity, would be low enough

that the patient could minimize or avoid hospital frequentation and, consequently, reduce the risk of infection by COVID-19. A total of 125 recommendations have been proposed in soft tissue, bone, and visceral sarcomas to thoroughly cover details for diagnosis, surgery, radiation therapy, systemic treatments, follow-up, and clinical research.

These recommendations were proposed by the SELNET coordinator team and shared with the official partners of SELNET network. Associated partners were not involved in this consensus. Each point derived from multidisciplinary (MDT) expertise discussion from the SELNET coordination aimed to be pragmatic, detailed, and patient-oriented for each recommendation.

Official partners had the competence to give their own opinion if this was clear enough for them or to give the opinion of their MDT on certain recommendations.

In this consensus, MDT experts participated from AC Camargo Cancer Center (Sao Paulo, Brazil), Instituto Alexander Fleming (Buenos Aires, Argentina), Instituto Nacional de Enfermedades Neoplásicas (Lima, Peru), Instituto Nacional de Cancerología (Mexico DF, Mexico), Hospital Calderon Guardia (San José, Costa Rica), Centre Leon Berard (Lyon, France), Istituto Nazionale dei Tumori (Milan, Italy), IRCCS Istituto Ortopedico Rizzoli (Bologna, Italy), Abramson Cancer Center (Philadelphia, Pennsylvania), University Hospital Lund (Lund, Sweden), Mannheim University Medical Center (Mannheim, Germany), MD Anderson Cancer Center (Houston, Texas), Spanish group for Research on Sarcomas, and University Hospital Virgen del Rocío (Sevilla, Spain). Besides that, a European patient advocacy group (Sarcoma Patients EuroNet) was also involved in this consensus, as well as the external scientific and ethics committees of SELNET.

Among 31 participating experts in the consensus, there were 18 oncologists (15 for adults and 3 for pediatrics), 4 orthopedic surgeons, 4 surgical oncologists, 2 radiation oncologists, 1 pathologist, and 1 radiologist. As SELNET mainly focuses on adult-type sarcomas, no exclusive pediatric oncologist participated in the consensus. Fourteen Latin American sarcoma experts participated in the consensus: nine oncologists, four surgeons, and one radiation therapist. Correlations between Latin American and European Union (E.U.)-U.S. expert recommendations were evaluated using Pearson's χ^2 test for bivariate options (agreement or disagreement) and Mann-Whitney U test for multivariate options (strongly agree, agree, disagree, and strongly disagree).

For each recommendation, every participant chose from the following options: strongly agree, agree, disagree, and strongly disagree. The neutral option was not offered to avoid ambiguity.

Those recommendations with $\geq 90\%$ of consensus (at least strongly agree plus agree obtained in $\geq 90\%$ of participants) were considered as strongly recommended. Those with $\geq 75\%$ but $< 90\%$ were considered as recommended, and the remaining recommendations were considered as "no consensus was obtained." The cutoff of 75% has been the median threshold to define consensus in Delphi studies [17], whereas the demanding 90% cut-off was arbitrarily chosen to indicate the highest consensus range if at least this percentage was reached.

To mitigate the subjectiveness, the ESMO-Magnitude of Clinical Benefit Scale (MCBS) V1.1 was applied to recommendations involving systemic treatments to support this prioritization strategy (supplemental online Appendix 1) [18, 19]. Although MCBS has not been formally evaluated for sarcoma therapies, MCBS methodology was followed for the estimation of the benefit obtained with different sarcoma systemic treatments (supplemental online Appendix 2).

RESULTS

From a total of 31 fulfilled questionnaires analyzed, the recommendations were distributed as strongly recommended (SR) in 80, recommended (R) in 35, and no consensus (NC) in 10. The consensus was higher among the 75 higher-priority recommendations (85%, 12%, and 3% for SR, R, and NC, respectively) than in the 50 lower-priority recommendations (32%, 52%, and 16% for SR, R, and NC, respectively).

Table 1 describes the consensus level for each recommendation and indicates the MCBS in most contexts of systemic treatments. The statistical distribution for each recommendation is presented in supplemental online Appendix 1.

Of note, statistically significant differences between Latin American and E.U.-U.S. expert recommendations were only detected by Pearson's χ^2 and Mann-Whitney *U* test in 3 of 125 recommendations (Table 2). E.U.-U.S. experts proved to be more conservative for the advice of adjuvant chemotherapy in high grade chondrosarcoma, the advice of adjuvant radiotherapy in low-grade, deep soft-tissue sarcoma (STS) larger than 5 cm, and for the advice of adjuvant radiotherapy in superficial STS larger than 5 cm.

DISCUSSION

Because sarcoma multidisciplinary committees are so critical to patient outcomes [20–27], we emphasize the message that these meetings should continue, at least in tele-committee format, in the COVID-19 era. Tele-committees should be scheduled on a regular basis (e.g., weekly), and the following specialists should participate: pathologists, radiologists, surgeons, radiation oncologists, and medical oncologists.

In this article, a prioritization of diagnostic, care, and follow-up procedures across different sarcoma contexts has been reached by consensus among sarcoma experts from different disciplines and from 11 countries among Latin American, North America, and Europe. This consensus has been developed within the SELNET consortium as a guide to protect cancer care in the complex and heterogeneous field of sarcoma during the COVID-19 outbreak. This consensus is intended to offer precise advice on different clinical sarcoma scenarios that the oncology community could face, with the aim of prioritizing or postponing different clinical decisions in patients with sarcoma. The general oncology community should network with expert centers from sarcoma suspicion, and these guidelines can be used to determine which actions can and cannot be postponed

in the management of patients with sarcoma in the COVID-19 era.

Several oncology societies and health care providers issued recommendations, most often on their websites, regarding adaptive strategies for emergent standards of care in patients with cancer during the COVID-19 pandemic [28]. The Cancer Core Europe, which encompasses seven cancer centers and oncologic institutes in seven European countries, published a general consensus on the adaptive measures to minimize the number of hospital visits and to prevent anticancer treatment that could induce complications of COVID-19 infections. The methodology for these recommendations was not defined, however [29].

The NICE issued prioritization guidelines on the use of systemic and radiation treatments for cancer. This guide established six prioritization levels, from the first for curative treatments offering more than 50% chance of success and adjuvant or neoadjuvant treatment that adds at least 50% chance of cure compared with surgery or radiation therapy alone, to the last level, which is defined as a non-curative regimen with a 15%–50% chance of palliation or temporary tumor control and less than 1 year expected extension of life [30]. Similarly, a radiotherapy prioritization guide was issued with five levels. The general modifications are based on postponing or avoiding radiation therapy in cases of little added value or changing treatment plans to shorten the number of visits to a health care facility [15]. ESMO issued several guidelines, by tumor type, for prioritizing care into three or four categories. In the case of sarcoma, the low-priority profile is typified by a stable patient who can safely have delays in treatment for the duration of the COVID-19 pandemic. The intermediate profile is exemplified by a patient with a noncritical situation but one in which delay beyond 6 weeks could impair clinical outcomes [16]. The Society of Surgical Oncology has joined individual sarcoma expert opinions and has issued six recommendation points based on prioritizing actions considering several sarcoma contexts [31].

Certainly, this prioritization does not focus only on individual patient risk but also highlights the community risks and benefit: the reduction of people in transit and the isolation of patients in general decreases contagion risk in the community, leaving more resources to treat the impact of COVID-19 pandemic. However, there are consequences for other group of patients, such as patients with cancer. In The Netherlands, a remarkable drop in cancer diagnosis was noticed from pandemic initiation according to a nationwide cancer registry [32].

There are three principal approaches to conducting consensus methodology research: the consensus development panel, the nominal group process, and the Delphi technique [33]. The latter two require at least two sessions or rounds, being more complex. The consensus development panel is the most common approach used in health care research. This approach consists of organized meetings of experts in a given field and usually requires experts in different disciplines to make a multidisciplinary consensus. Usually, this approach is supported by the literature evidence, and there are some face-to-face discussions. In sarcoma oncology, ESMO guidelines follow this consensus development panel

Table 1. Prioritizing recommendations classified by higher and lower priority with consensus results for each recommendation (percentage agreeing with the recommendation)

Higher Priority	Multidisciplinary Sarcoma Telecommittees	Lower Priority
Soft-tissue, bone, or visceral sarcoma: Localized and advanced disease		
1. Every new suspicion of sarcoma (soft tissue, bone, or visceral) diagnosis. The only exceptions being the cases likely to be well-differentiated liposarcoma or low-risk gastric GIST [Strongly recommended, 97%]	4. Cases with diagnostic suspicion of bone lesions likely to be benign; desmoid tumors; lipomas; TGCT [Strongly recommended, 97%].	
2. Therapeutic plan for patients previously diagnosed with any sarcoma with metastatic life-threatening lesions; Ewing sarcoma; high-grade recurrent resectable tumors; high-risk localized sarcoma; osteosarcoma; rhabdomyosarcoma (embryonal, alveolar, and sclerosing) [Strongly recommended, 100%]	5. Indolent tumors for which the committee discussion can be delayed, at physician discretion. (i.e., those in follow-up with length intervals of 6 mo or longer) [Strongly recommended, 94%]	
3. Therapeutic plan for recurrent or progressing sarcomas [Strongly recommended, 97%]		
Diagnostic Process		
Soft-tissue sarcoma: Localized disease		
6. Deep lesions larger than 3 cm or any tumor larger than 5 cm in limbs or trunk wall with no lipoma aspect [Strongly recommended, 100%]	12. Lesions not fitting with the points 1 or 2 of the higher priority [Strongly recommended, 97%]	
7. Any lump that even not fitting with point 1 had experienced a recent fast growth [Strongly recommended, 97%]	13. Retroperitoneal mass with the appearance of well-differentiated liposarcoma [No consensus, only 74% agreed]	
8. Lesions with suspicion of local recurrence [Strongly recommended, 97%]	14. Lesions with appearance of desmoid tumors or oligosymptomatic lesions with appearance of TGCT [No consensus, 74%]	
9. Local neurofibroma or TGCT with suspicion of malignant transformation [Strongly recommended, 97%]		
Soft-tissue sarcoma: Advanced disease		
10. Any new tumoral lesion in somatic tissues with apparent metastatic spread [Strongly recommended, 100%]	15. Lung micronodules (<1 cm) [Recommended, 81%]	
11. Any new metastatic recurrence with unexpected behavior for the tumor context [Strongly recommended, 94%]	16. Appearance of metastatic spread in the context of indolent tumors (i.e. EMCh, or ASPS) [No consensus, only 74% agreed]	
Bone sarcoma: Localized disease		
17. Any new tumoral lesion with suspicion of malignancy [Strongly recommended, 100%]		
18. Bone tumors without suspicion of malignancy but with risk of fracture [Strongly recommended, 100%]		
19. Osteochondromas or GCTB with suspicion of malignant transformation [Strongly recommended, 97%]		
20. Any suspicion of local recurrence [Strongly recommended, 100%]		
Bone sarcoma: Advanced disease		
21. Any new bone tumor with metastatic spread [Strongly recommended, 97%]		
22. Any new metastatic recurrence with unexpected behavior for the tumor context [Strongly recommended, 97%]		
GIST or other visceral sarcomas: Localized disease		
26. Clinically evident intramural gastrointestinal lesion [Strongly recommended, 97%]		
27. Clinical and radiological suspicion of uterine leiomyosarcoma (subserosal mass, with recent symptoms) [Strongly recommended, 97%]		
GIST or other visceral sarcomas: Advanced disease		
28. Any appearance of new nodules suspected of metastatic spread (except for micronodules or indolent). Biopsy of metastatic nodules will not be necessary in the context of consistent natural history [Recommended, 84%]		
Surgery		
Soft-tissue sarcoma: Localized disease		
32. High-risk (≥40% risk for death, assessed by Sarculator) localized STS of limbs/trunk wall (after neoadjuvant treatment if indicated) [Strongly recommended, 100%]		
33. Intermediate-risk STS (20%–40% risk for death, assessed by Sarculator) [Strongly recommended, 97%]		
		40. Low-risk tumors (<20% risk for death) (well-differentiated liposarcoma; atypical liposarcoma; low-risk SFT) [Recommended, 81%]
		41. Local recurrence of low-risk tumor [Recommended, 87%]
		42. Intramural lesions <1–2 cm in the gastrointestinal tract [Strongly recommended, 90%]
		43. Uterine mass predominantly intramural, no recent history of symptoms or signs, more likely to be myofibromas [Recommended, 87%]
		44. Appearance of metastatic spread in the context of indolent GIST (<i>PDGFRA</i> mutant, <i>KIT/PDGFR</i> wild type) [Recommended, 81%]

(continued)

Table 1. (continued)

	Higher Priority	Lower Priority
34.	Any local recurrence of grade 2 or 3 STS of limbs/trunk wall [Strongly recommended, 100%]	42. Retroperitoneal sarcoma (well-differentiated liposarcoma, low-grade SFT, desmoid tumors) [Recommended, 84%]
35.	Local therapy for extraskeletal Ewing sarcoma, or rhabdomyosarcoma (embryonal, alveolar, and sclerosing) [Strongly recommended, 97%]	Soft-tissue sarcoma: Advanced disease
36.	Any surgical complication entailing risk for the patient [Recommended, 87%]	43. Indicate metastasectomy but due to indolent behavior of STS, this can be postponed (i.e. EMCh, ASPs) [Recommended, 87%]
37.	Retroperitoneal sarcoma (dedifferentiated liposarcoma, leiomyosarcoma, other high/intermediate grade sarcomas) [Strongly recommended, 100%]	44. Synchronous metastatic STS or metachronous metastatic STS with a short relapse interval, where systemic therapy could be tried first [Recommended, 87%]
	Soft-tissue sarcoma: Advanced disease	45. Pulmonary micronodules with uncertain malignant nature [Recommended, 84%]
38.	Metastasectomies in oligometastatic patients with an adequate time interval without progression [Strongly recommended, 94%]	
39.	Any life-threatening resectable metastatic spread in adequate MDT discussion [Strongly recommended, 97%]	
	Bone sarcoma: Localized disease	Bone sarcoma: Localized disease
46.	High-grade conventional osteosarcoma and skeletal Ewing sarcoma after neoadjuvant chemotherapy [Strongly recommended, 97%]	55. Low-grade osteosarcoma (parosteal and other variants) [Recommended, 84%]
47.	High-grade conventional chondrosarcoma [Strongly recommended, 100%]	56. Low-grade chondrosarcoma [Strongly recommended, 90.32%]
48.	Mesenchymal chondrosarcoma (upfront or after neoadjuvant chemotherapy, following MDT decision) [Strongly recommended, 100%]	57. Adamantinoma [Recommended, 87%]
49.	Other high-grade primary bone tumors [Strongly recommended, 97%]	58. GCTB without suspicion of malignant transformation (consider induction with denosumab) [Recommended, 87%]
50.	High-grade or intermediate grade in local recurrence [Strongly recommended, 97%]	59. Any other low-grade bone sarcoma [Recommended, 84%]
51.	Any surgical complication that would be solved by surgery [Strongly recommended, 100%]	Bone sarcoma: Advanced disease
	Bone sarcoma: Advanced disease	60. Indicated metastasectomy but due to indolent behavior, this can be postponed (i.e., adamantinoma, low-grade bone tumors) [Strongly recommended, 90%]
52.	Metastasectomies as part of multimodality treatment in osteosarcoma or Ewing sarcoma [Strongly recommended, 94%]	61. Metastatic GCTB (denosumab can be a therapeutic option) [Strongly recommended, 90%]
53.	Oligometastatic chondrosarcoma without evidence of local recurrence [Strongly recommended, 97%]	62. Pulmonary micronodules with uncertain malignant nature [Strongly recommended, 90%]
54.	Oligometastatic high-grade bone sarcoma without evidence of local recurrence [Strongly recommended, 97%]	
	GIST or other visceral sarcomas: Localized disease	GIST or other visceral sarcomas: Localized disease
63.	Clinically evident GIST (consider neoadjuvant imatinib for gastroesophageal junction or gastric antrum or duodenal or rectal GIST or any bulky GIST to facilitate surgery) [Strongly recommended, 100%]	69. Low-risk or very-low-risk GIST without clinical complications [Recommended, 87%]
64.	Symptomatic GIST not suitable for neoadjuvant imatinib (i.e., imatinib intolerant or genotype resistant to imatinib) [Strongly recommended, 97%]	70. In the context of indolent GISTs (i.e., <i>PDGFRA</i> mutants or <i>KIT/PDGFR</i> wild type) consider postponing surgery based on other relevant factors [Strongly recommended, 100%]
65.	Any other visceral grade 2 or grade 3 sarcomas or symptomatic low-grade [Strongly recommended, 100%]	71. Any low-grade visceral sarcoma without relevant symptoms or other complications [Recommended, 87%]
	GIST or other visceral sarcomas: Advanced disease	GIST and other visceral sarcomas: Advanced disease
66.	In the context of unique or oligometastatic responding patients for whom extending 3-mo imatinib could be difficult [Strongly recommended, 90%]	72. Nodule within mass as GIST progression that could be postponed or managed with radiofrequency [Strongly recommended, 97%]
67.	Multicentric GIST or with nodal involvement (i.e. <i>KIT/PDGFR</i> wild type GIST) [Strongly recommended, 94%]	73. Metastatic indolent GIST (even oligometastatic) (i.e. <i>PDGFRA</i>) that could be postponed [Strongly recommended, 97%]
68.	Metastatic lesion causing symptomatic or other serious effect not amenable with imatinib [Strongly recommended, 97%]	
	Medical Oncology	Medical Oncology
	Soft-tissue sarcoma: Localized disease	Soft-tissue sarcoma: Localized disease
74.	Neoadjuvant chemotherapy for extraskeletal Ewing sarcoma ^{ab} and pediatric-type rhabdomyosarcoma ^c (embryonal, alveolar, and sclerosing) [Strongly recommended, 97%]	82. Perioperative chemotherapy in localized STS of limbs/trunk wall larger than 5 cm, grade 3, and deep tumors but with risk of death less than 40% based on Sarculator would be postponed or not recommended [Strongly recommended, 90%]

(continued)

Table 1. (continued)

	Higher Priority	Lower Priority
75.	Perioperative chemotherapy in high-risk STS of limbs/trunk wall (>40% death-risk based on Sarculator) (3 cycles of epirubicin + ifosfamide) in selected patients ^d [Strongly recommended, 97%]	
76.	Potentially resectable localized STS [No consensus, only 74% agreed]	
	Soft-tissue sarcoma: Advanced disease^e	Soft-tissue sarcoma: Advanced disease
77.	Overtly disease progression [Strongly recommended, 94%]	83. Newly diagnosed metastatic disease with micronodules [Recommended, 84%]
78.	Newly diagnosed metastatic disease (other than doubtful micronodules) [Strongly recommended, 97%]	84. Indolent STS or slow progressive STS with barely or no symptomatic impact [Strongly recommended, 90%]
79.	Symptomatic patients in relation to their tumor volume [Strongly recommended, 94%]	85. Progressive disease beyond second with low probability of clinical benefit [Recommended, 84%]
80.	Patients with already initiated chemotherapy, or other systemic treatment with clinical or radiological benefit [Strongly recommended, 100%]	
81.	Potentially resectable advanced STS [Strongly recommended, 90%]	
	Bone sarcoma: Localized disease	Bone sarcoma: Localized disease
86.	Neoadjuvant chemotherapy in osteosarcoma ^{f,g} or Ewing skeletal sarcoma ^{a,b} [Strongly recommended, 94%]	92. Perioperative chemotherapy in high-grade bone sarcoma (i.e. Undifferentiated high-grade pleomorphic bone sarcoma) [No consensus, only 68% agreed]
87.	Neoadjuvant chemotherapy in mesenchymal chondrosarcoma potentially resectable. [Recommended, 87%]	93. Perioperative chemotherapy in high-grade chondrosarcoma [Recommended, 81%]
	Bone sarcoma: Advanced disease	Bone sarcoma: Advanced disease
88.	Upright chemotherapy in metastatic osteosarcoma or Ewing sarcoma ^b [Strongly recommended, 100%]	94. Systemic treatment beyond second line of metastatic disease in osteosarcoma or beyond third line in Ewing sarcoma [Recommended, 81%]
89.	Chemotherapy in recurrent advanced osteosarcoma not suitable for surgery ^h [Strongly recommended, 100%]	95. Any chemotherapy line in chondrosarcoma [Recommended, 87%]
90.	Chemotherapy in recurrent advanced Ewing sarcoma ⁱ [Strongly recommended, 100%]	96. Imatinib in advanced/recurrent asymptomatic chordoma [Strongly recommended, 94%]
91.	Metastatic undifferentiated high-grade bone sarcoma [Strongly recommended, 94%]	
	GIST and other visceral sarcomas: Localized disease^j	GIST and other visceral sarcomas: Localized disease
97.	Neoadjuvant imatinib in locally advanced GIST with sensitive genotype (to facilitate posterior surgery) [Strongly recommended, 94%]	101. Adjuvant imatinib with <40% of recurrence risk (heat maps) [Recommended, 81%]
98.	Neoadjuvant imatinib in gastro-esophageal junction, or gastric antrum or rectal GIST (to minimize morbidity) with sensitive genotype [Strongly recommended, 100%]	GIST and other visceral sarcomas: Advanced disease
99.	Adjuvant imatinib in patients with >40% of recurrence risk (heat maps) [Strongly recommended, 100%]	102. Metastatic indolent disease (i.e., PDGFRA mutant) [Recommended, 87%]
	GIST and other visceral sarcomas: Advanced disease^k	103. Radiological progression without clinical impact [No consensus, 68%]
100.	TKI for first, second, and third line in metastatic disease with imatinib, sunitinib, and regorafenib, respectively [Strongly recommended, 94%]	
		Radiation Oncology
	Soft-tissue sarcoma: Localized disease	Soft-tissue sarcoma: Localized disease
104.	Perioperative radiation therapy (preferably postoperative during COVID-19 outbreak) in grade 2–3, >5 cm, and deep STS of limbs/trunk wall [Strongly recommended, 97%]	111. Postoperative radiation therapy in low grade, >5 cm, and deep STS of limbs or trunk wall [No consensus, 71%]
105.	Perioperative radiation therapy (preferably postoperative during COVID-19 outbreak) in >5 cm and superficial STS of any grade in limbs/trunk wall [Recommended, 77%]	Soft-tissue sarcoma: Advanced disease
106.	Perioperative radiation therapy (preferably postoperative during COVID-19 outbreak) in <5 cm and deep STS of any grade in limbs/trunk wall [No consensus, only 61% agreed]	112. Radiation therapy for local control of asymptomatic primary tumor in the context of metastatic STS [Recommended, 84%]
107.	Radiation therapy in cases of head and neck sarcomas [Strongly recommended, 90%]	
108.	Radiation therapy in rhabdomyosarcomas (embryonal, alveolar, and sclerosing) and extraskeletal Ewing sarcoma [Strongly recommended, 100%]	
	Soft-tissue sarcoma: Advanced disease	
109.	Any symptomatic metastatic lesion that could be alleviated with radiation therapy, balancing risk/benefit [Strongly recommended, 97%]	

(continued)

Table 1. (continued)

Higher Priority	Lower Priority
110. Radiation therapy for symptomatic primary tumor in the context of metastasis [Strongly recommended, 100%]	
Bone sarcoma: Localized disease	
113. Radiation therapy is skeletal Ewing sarcoma according to CPG [Strongly recommended, 100%]	
114. Unresectable osteosarcoma after induction chemotherapy [Strongly recommended, 94%]	
115. Definitive radiation therapy for grade 3 chondrosarcoma [Recommended, 87%]	
Bone sarcoma: Advanced disease	
116. Any symptomatic metastatic lesion that could be alleviated with radiation therapy, balancing risk/benefit [Strongly recommended, 97%]	
GIST and other visceral sarcomas: Localized disease	
117. Radiation therapy for unresectable breast or uterine sarcoma [Strongly recommended, 97%]	GIST and other visceral sarcomas: Localized disease 119. Postoperative radiation therapy in breast sarcoma larger than 5 cm or high grade [No consensus, only 65% agreed]
GIST and other visceral sarcomas: Advanced disease	GIST and other visceral sarcomas: Advanced disease
118. Any symptomatic metastatic lesion that could be alleviated with radiation therapy, balancing risk/benefit [Strongly recommended, 100%]	120. Radiation therapy for unresectable breast or uterine sarcoma with metastatic spread [No consensus, only 74% agreed]
Follow-Up	
Soft-tissue, bone, or visceral sarcoma: Localized and advanced disease	
121. The follow-up recommendation for high-risk STS, conventional osteosarcoma, Ewing sarcoma, rhabdomyosarcoma (embryonal, alveolar, or sclerosing), high-risk GIST after completion of adjuvant imatinib is to schedule CT scans or chest x-ray (in some cases) every 3–4 mo for the first 3 years; every 6 mo in fourth or fifth years; every year after the fifth year [Strongly recommended, 97%]	122. The follow-up recommendation for low-intermediate risk of STS, low-grade osteosarcoma, high-risk GIST under adjuvant imatinib, intermediate-low-risk of localized GIST is to schedule CT scans or chest x-ray (in some cases): every 5–6 mo for the first 5 years; every year after the fifth year [Strongly recommended, 97%]
Consider, in the appropriate context, to prolong the interval 2–3 mo if the patient is beyond the first 3 years of follow-up.	The objective is to minimize patient contact with the hospital during the COVID-19 outbreak. As much as possible, teleconsultations should be used during follow-up.
Clinical Trials	
Soft-tissue, bone, or visceral sarcoma: Localized and advanced disease	
123. To new enrollment: therapies likely to improve clinical outcome (drugs with strong preclinical rationale, drugs showing promising results in previous clinical trials, drugs with robust predictive biomarker, therapy targeting additive signaling pathway in some tumors; therapy targeting relevant signaling in orphan diseases) [Strongly recommended, 97%]	125. To new enrollment: therapies for indolent entities (TGCT, GCTB, desmoid tumors) for which the enrollment can be postponed, phase I trials with substantial number of procedures, serious logistic difficulties due to the pandemic situation, CAR-T cells based trials (it could require intensive care support), immunomodulation therapies that could exacerbate the inflammatory response to SARS-CoV-2 [Strongly recommended, 90%]
124. To maintain the treatment under trial: patients with clinical or radiological benefit, patients still not assessed for efficacy without relevant toxicity [Strongly recommended, 100%]	Consider adapting procedures in agreement with the trial sponsor as relax the interval of clinical visits, to minimize as much as possible hospital frequentation.

^aThe benefit from alternating cycles of VDC (vincristine, doxorubicin, cyclophosphamide) and IE (ifosfamide and etoposide) over vincristine, doxorubicin, cyclophosphamide chemotherapy in Ewing sarcoma [39] shows level A of recommendation when applying the European Society for Medical Oncology (ESMO)-Magnitude of Clinical Benefit Scale (MCBS) V1.1: Form 1.

^bThe benefit from VDC/IE over vincristine, ifosfamide, doxorubicin, etoposide chemotherapy in Ewing sarcoma [40] shows level B of recommendation when applying the ESMO-MCBS V1.1: Form 1.

^cThe benefit from ifosfamide, vincristine, actinomycin D when compared with other regimens with more drugs (IVA + Carbo-etoposide-epirubicin and IVA [ifosfamide, vincristine, actinomycin D] + doxorubicin) in rhabdomyosarcoma [41, 42] shows level B of recommendation when applying the ESMO-MCBS V1.1: Form 1 (IVA is the recommended option as resulted in less toxicity with the same survival outcome).

^dThe benefit from three cycles of epirubicin and ifosfamide in the perioperative setting in high-risk patients with STS [43–45] shows level A of recommendation when applying the ESMO-MCBS V1.1: Form 1. (Advanced disease)

^eThe benefit from eribulin in liposarcoma [46] shows level 4 of recommendation when applying the ESMO-MCBS V1.1: Form 2A (benefit in overall survival [OS]). The benefit from eribulin in L-sarcoma (liposarcoma and leiomyosarcoma) [46] shows level 3 of recommendation when applying the ESMO-MCBS V1.1: Form 2A. The benefit from trabectedin in L-sarcoma (liposarcoma and leiomyosarcoma) [47] shows level 3 of recommendation when applying the ESMO-MCBS V1.1: Form 2B. The benefit from trabectedin in translocation-related sarcoma [48] shows level 4 of recommendation when applying the ESMO-MCBS V1.1: Form 2A (benefit in OS). The benefit from pazopanib in pretreated STS excluding liposarcoma [49] shows level 3 of recommendation when applying the ESMO-MCBS V1.1: Form 2B. The benefit from the combination of gemcitabine and dacarbazine in pretreated STS [50] shows level 4 of recommendation when applying the ESMO-MCBS V1.1: Form 2A (benefit in OS). The benefit from

the combination of gemcitabine and docetaxel in advanced STS [51] and in advanced leiomyosarcoma [52] shows level 1 of recommendation when applying the ESMO-MCBS V1.1: Form 2C. The benefit from high-dose ifosfamide in advanced STS [53] shows level 4 of recommendation when applying the ESMO-MCBS V1.1: Form 3. The benefit from doxorubicin in advanced STS [54] shows level 4 of recommendation when applying the ESMO-Magnitude of Clinical Benefit Scale (MCBS) V1.1: Form 3.

^aThe benefit from adjuvant chemotherapy in resected conventional osteosarcoma [55, 56] shows level A of recommendation when applying the ESMO-MCBS V1.1: Form 1.

^bThe benefit from the addition of Mifamurtide to adjuvant chemotherapy in resected conventional osteosarcoma [57] shows level A of recommendation when applying the ESMO-MCBS V1.1: Form 1.

^cThe benefit from cisplatin in advanced osteosarcoma [58] shows level 4 of recommendation when applying the ESMO-MCBS V1.1: Form C. The benefit from cisplatin + doxorubicin + ifosfamide in advanced osteosarcoma [59] shows level 4 of recommendation when applying the ESMO-MCBS V1.1: Form C. The benefit from ifosfamide-epitoposide in advanced osteosarcoma [60] shows level 3 of recommendation when applying the ESMO-MCBS V1.1: Form C. The benefit from sorafenib plus everolimus [62] and regorafenib [63] in advanced osteosarcoma shows level 2 of recommendation when applying the ESMO-MCBS V1.1: Form C. The benefit from gemcitabine and docetaxel in Ewing sarcoma [64, 65] shows level 2 of recommendation when applying the ESMO-MCBS V1.1: Form C.

^dThe benefit from gemcitabine and docetaxel in Ewing sarcoma [64, 65] shows level 2 of recommendation when applying the ESMO-MCBS V1.1: Form C. The benefit from Cyclophosphamide-topotecan cannot be properly assessed with the currently available evidence. The benefit from high-dose ifosfamide in Ewing sarcoma [66] shows level 3 of recommendation when applying the ESMO-MCBS V1.1: Form C.

^eThe benefit from 3 years of adjuvant imatinib in localized GIST [67] shows level A of recommendation when applying the ESMO-MCBS V1.1: Form 1.

^fThe benefit from imatinib in advanced GIST [68] shows level 4 of recommendation when applying the ESMO-MCBS V1.1: Form 3. The benefit from sunitinib in advanced GIST [69, 70] shows level 4 of recommendation when applying the ESMO-MCBS V1.1: Form 2A and Form 2A, respectively. The benefit from regorafenib in advanced GIST [71] shows level 3 of recommendation when applying the ESMO-MCBS V1.1: Form 2B. The benefit from ripretinib in advanced GIST [72] shows level 4 of recommendation when applying the ESMO-MCBS V1.1: Form 2B and Form 2A, respectively.

Abbreviations: ASPS, alveolar soft part sarcoma; CAR-T, chimeric antigen receptor T-Cell; CT, computed tomography; EMCh extraskelatal myxoid chondrosarcoma; GCTB, giant cell tumor of bone; GIST, gastrointestinal stromal tumor; MCBS, Magnitude of Clinical Benefit Scale; MDT, multidisciplinary; SFT, solitary fibrous tumor; STS, soft-tissue sarcoma; TGCT, tenosynovial giant cell tumor; TKI, tyrosine kinase inhibitor.

approach [25, 27, 34]. The consensus we present here has two main differences in comparison with the consensus development panel. Despite the proposed prioritizing recommendations based on the published evidence, there are no comparative studies analyzing, for instance, the delay of some treatments in patients with sarcoma. In addition, no formal face-to-face meeting was organized because of inherent confinement constraints. In contrast, the fact that all expert participants provided their own opinion on each recommendation ensures more independence and the quality of the conclusions, avoiding interferences that could arise in a face-to-face discussion.

In contrast, with the aim to minimize the subjectivity in the recommendation process, the ESMO-MCBS was fulfilled, at least for systemic therapies applied in sarcoma. We tried to adopt the grade 3 or higher and grades A or B scores, in the systemic treatment, as the cut-off for preserving the use of such treatments in the COVID-19 pandemic era. The ESMO-MCBS v1.1 is a validated scale measuring the magnitude of clinical benefit and adds value with just the statistical significance focus [18]. Although there is not yet an ESMO-MCBS for sarcoma, our exercise has followed the rules of the scale and is an additional support for this consensus.

The fact that 80 of 125 recommendations were “strongly recommended” and only 10 were “no consensus” indicates a high grade of accord among sarcoma experts in this consensus on prioritization. The fact that lower consensus was obtained in the low priority group might indicate the reticence of sarcoma experts in postponing treatment, even in indolent or low-risk cases.

This consensus has been mainly addressed keeping in mind Latin-American communities, and thus it has pursued simplicity and concision, taking into consideration that there are many health care providers in each country. Hence, assigning higher or lower priority to those undelayable or delayable treatments, respectively, facilitates the decision-making process in patients with sarcoma. Additionally, this SELNET consensus issues 125 recommendations, which indicates a high level of thoroughness, covering a substantial spectrum of sarcoma care.

Follow-up recommendations in the context of sarcoma remains largely unstudied [35] and usually are based on conventions; thus, in high-risk patients, for example, the imaging tests are performed every 3–4 months for the first 3 years, then every 6 months for the 4th and 5th years, and so on, once per year. This strategy is based on the higher risk of recurrence observed in the first 3 years after treatment for localized disease and the fact that the asymptomatic recurrence, detected by computed tomography scan for instance, could potentially have higher curative options. There are some reports addressing the relevance of smaller size as independent prognostic relevance, at the time of metastatic disease, for longer survival [36–38]. Nevertheless, the truth is that convincing evidence that determined strategy is related with better survival is lacking, and a lead-time bias can occur in highly interventionist follow-up.

Table 2. Mann-Whitney U and Pearson's χ^2 test for those recommendations with statistical differences between LATAM and E.U.-U.S. experts

Recommendations	Mann-Whitney test			Recommendations	Pearson's χ^2 test		
	LATAM, %	E.U.-U.S., %	p value		LATAM, %	E.U.-U.S., %	p value
Recommendation no. 93			.001	Recommendation no. 93			.009
Strongly agree	38	7		Strongly agree	38	7	
Agree	31	64		Agree	57	100	
Disagree	31	22		Disagree	43	0	
Strongly disagree	0	7		Strongly disagree	0	7	
Recommendation no. 105			.008	Recommendation no. 105			.01
Strongly agree	25	64		Strongly agree	25	64	
Agree	38	36		Agree	100	63	
Disagree	31	0		Disagree	0	37	
Strongly disagree	6	0		Strongly disagree	6	0	
Recommendation no. 111			.021	Recommendation no. 111			.002
Strongly agree	41	21		Strongly agree	41	21	
Agree	53	21		Agree	43	94	
Disagree	6	58		Disagree	57	6	
Strongly disagree	0	0		Strongly disagree	0	0	

Recommendation (R) no. 93 collects agreement as a low priority for adjuvant chemotherapy in high-grade localized chondrosarcoma. R no. 105 collects agreement as a high priority for perioperative radiation therapy in superficial soft-tissue sarcoma (STS) larger than 5 cm, and R no. 114 collects agreement as a lower priority for low-grade, deep STS and larger than 5 cm. Abbreviations: E.U., European Union; LATAM, Latin-American.

CONCLUSION

This SELNET consensus provides a tool for multidisciplinary sarcoma committees during the COVID-19 outbreak. The detail of different recommendations and the distinction between the two levels of prioritization enables a practical approach for Latin-American health care providers and sarcoma expert centers.

ACKNOWLEDGMENTS

The authors would like to thank the SELNET project. SELNET has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 825806.

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DISCLOSURES

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institutional); **Robert Maki**: Bayer, Deciphera Eisai, Morphotek Immune Design Janssen, Pharma Mar, Karyopharm, Eli Lilly & Co, Imclone Presage Springworks (C/A), Bayer, Karyopharm, Lilly, Pfizer Springworks, Regeneron, Presage (RF-institution); **Jorge Luis Martinez-Tlahuel**: Amgen, Eli Lilly & Co (C/A); **Emanuela Palmerini**: Deciphera, Eusa Pharma, Daichi Sankyo (C/A); **David**

S. Moura: PharmaMar, Eisai, Immix BioPharma, Novartis (RF-institution), PharmaMar, Eisai, Celgene, Bayer, Pfizer (Other). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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