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EDITORIAL

Precision guidelines for soft tissue and visceral sarcomas: the evidence, expert experience and ensuring optimal care for rare cancers, a 2021 update from ESMO—EURACAN—GENTURIS

INTRODUCTION

In this issue of *Annals of Oncology*, expert guidelines on the management of soft tissue and visceral sarcomas (STS) are updated from 2018 by members of European Society for Medical Oncology (ESMO), EURACAN and Genetic Tumour Risk Syndromes (GENTURIS).[1,2] Certainly, the sarcoma global community continues to be indebted to this dedicated and productive effort that provides clinical recommendations using an evidence-based approach when available to ensure standardized care for these rare tumors. Specifically, recommendations were generated by a consensus meeting including >70 multidisciplinary experts from European countries that are members of ESMO and EURACAN, with the addition of GENTURIS—European Reference Network for Genetic Tumour Risk Syndromes.

The overall goal of this endeavor is to provide a set of recommendations for standards of care based on evidence-based medicine for clinicians. Thus, there is a need to continually revise and renew guidelines for STS including uterine disease, as with these rare entities many patients continue to be managed in centers with low to medium volumes, of which clinicians may see a limited number of these highly heterogeneous tumors with a wide range of behaviors.[3,4] Specifically, there are >80 separate diagnostic STS entities,[5] and while surgery remains a mainstay of curative treatment, in the past 2-3 years advances have been made in diagnostic criteria, multidisciplinary care and prognostication. This editorial therefore serves to highlight the advances incorporated in the latest ESMO—EURACAN—GENTURIS guidelines and provide direction for issues that would improve care for sarcoma patients in the future.

WHAT'S NEW?

In the latest version of ESMO soft tissue guidelines, levels of evidence and consensus recommendations are integrated following each section, which provides a balanced interpretation for clinicians. A more robust definition of centers of expertise is presented as recent publications from many sarcoma networks have provided evidence that care in a higher volume center improves overall survival.[3,4] In the diagnostic section, newer diagnostic entities such as NTRK-driven sarcoma are presented, data supporting how critical subspecialized pathologists' assessments are, and the use of International Collaboration for Cancer Reporting guidelines for standardized reporting. Also, more explicit pathology reporting for post-treatment specimens is defined. Finally, clinical criteria are provided for when TP53 testing should be carried out in high-risk patients.[6]

There is an emphasis on site-directed multidisciplinary management, along with histotype-specific multidisciplinary treatment. For example, when to consider the use of radiation therapy (RT) based on more RT-responsive subtypes such as myxoid round cell liposarcoma, solitary fibrous tumor and myxofibrosarcoma. Strikingly, these recommendations are also based on the ever-evolving prognostic tool—the Sarculator, which is a patient-centric higher-order nomogram.[7,8] Furthermore, progress in defining which patients should be considered high risk for recurrence and what histotype-specific chemotherapy to consider in the neoadjuvant setting is articulated.

A comprehensive Table 1 provides state-of-the-art data on the use and response rates of newer agents in sarcoma. The section on advanced/metastatic systemic agents is extensive and a must read for those managing sarcoma patients in this context. Also notable is the modification of clinical algorithms in Figures 1 and 2, which is now restricted to extremity and truncal lesions. Although grade is the main discriminator in the localized setting for multidisciplinary care, in Supplementary Table S1 an effort is made to integrate how histologic type should be perceived with respect to grade and overall biology. This will no doubt require ongoing refinement as we better characterize histotype-specific outcomes in the years to come.

WHAT REMAINS TO BE DEFINED?

Although the sarcoma community continues to develop and execute clinical trials to provide evidence-based data, the majority to date have been in the advanced/metastatic systemic agents' space. Many key aspects of local-regional control are based on retrospective series which are emerging beyond single institutional series that were arguably more likely to be biased by local clinical practices. With the establishment of global collaborative efforts such as the Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG), critical clinical dilemmas are being evaluated and expert guidelines have been developed to address the management of primary and recurrent retroperitoneal sarcomas.[9,10] Certainly, the ESMO—EUROCAN—GENTURIS soft tissue sarcoma

guidelines are comprehensive, yet in the future clinicians would be well served to have additional guidance on the following issues:

1. State-of-the-art genetic testing beyond TP53, as other genetic disorders such as neurofibromatosis type 1, familial adenomatous polyposis and RB1 are not addressed in this directive, which hopefully will be clarified in an ESMO consensus document for this at-risk population, where it is estimated that up to 20% of sarcoma patients may have an underlying genetic disorder.[11]
2. Evidence-based data to support limiting the use of re-excision for close/involved margins in patients with more favorable biology such as dermatofibrosarcoma protuberans, and while this is provocative with some data to support,[12] a watch-and-wait policy has yet to be adopted in other global sarcoma centers in this context.
3. An opportunity to evaluate quality of life-based decision-making tools for patients along with an update to the ESMO patient guide generated in 2016.
4. We have not realized advances in management of uterine sarcomas, as they remain ungraded, primarily diagnosed post-operatively, perhaps limiting the potential benefit of neoadjuvant therapies. As we work together as experts in the sarcoma community, it is critical that principles of sarcoma care—expert pathologic review, multidisciplinary care and the development and opportunity to participate in clinical trials—are employed at all sites of disease and not siloed based on current clinical teams.[13] Special considerations are employed for uterine sarcoma patients such as the use of hormonal blockade in leiomyosarcoma and endometrial stromal sarcoma, which is highlighted by Gronchi et al.[2]

In summary, the ESMO—EURACAN—GENTURIS STS 2021 guidelines are a welcome update for the community, which allows clinicians to ensure standards of care are identified and met, creates benchmarks of progress with ongoing iterations and provides refinement of new directions and unmet needs to ultimately improve our sarcoma patients' outcomes.

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