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Factors Influencing Immunotherapy Outcomes in Cancer: Sarcopenia and Systemic Inflammation

Erkan Topkan, MD[1], Nilüfer Kılıç Durankuş, MD[2], Şükran Şenyürek, MD[2], and Ugur Selek, MD[2]

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Dear Editor,

Congratulations to Ucgul and colleagues for their study examining the impact of sarcopenia on the response to immunotherapy in 100 cancer patients.[1] Sarcopenia was defined by the skeletal muscle index (SMI), calculated utilizing computerized tomography (CT) data at the L3 vertebral level. Sarcopenia was diagnosed in 41% of the study population, which was identified as a significant prognostic factor linked to poor progression-free survival (hazard ratio [HR], 2.33; $P < 0.001$). However, although sarcopenia was associated with significantly lower overall survival (OS) in univariate analysis, it lost significance in multivariate analysis (HR, 1.24; $P = 0.0432$). The study results offer important insights into how sarcopenia relates to the response to immunotherapy in cancer patients. However, 2 concerns must be addressed to comprehend the findings in a more balanced manner.

First, Ucgul and colleagues defined sarcopenia by evaluating the SMI at the L3 vertebra level, which measures muscle mass.[1] However, the European Working Group on Sarcopenia in Older People-2 (EWGSOP-2) report, published in 2019, considers sarcopenia probable when dynapenia (muscle strength loss) is present, and its diagnosis is confirmed when myopenia (muscle mass loss) is added to the clinical picture.[2] According to this definition, sarcopenia is classified as severe when kratopenia (muscle power deficit) is diagnosed.[2] Moreover, it is posited that dynapenia and kratopenia may be adequate for sarcopenia diagnosis, implying that myopenia may be less significant in this context.[2] Therefore, although erroneously used in many studies and meta-analyses,[3] measuring myopenia by assessing SMI alone via radiological measures in cancer patients does not meet the comprehensive criteria for diagnosing sarcopenia. Considering this fact, terminologically, using "myopenia" rather than "sarcopenia" is more rational to avoid overstating the actual sarcopenia rates in such studies where dynapenia is not assessed with or without kratopenia. Otherwise, the unfit use of "myopenia" as a synonym for "sarcopenia" may not only introduce biases into the reported findings but could also mislead future research on sarcopenia, as some pharmacological agents may enhance muscle mass without concomitantly improving muscle strength or contraction power.

And second, in contrast to the substantial body of existing cancer literature, Ucgul and colleagues were unable to establish a significant association between sarcopenia status and overall survival outcomes. For example, Shiroyama and colleagues reported that sarcopenia at baseline, as assessed through CT, serves as a significant predictor of adverse outcomes in patients with advanced non-small cell lung cancer (NSCLC) who underwent immunotherapy.[4] Similarly,

[1]Department of Radiation Oncology, Faculty of Medicine, Baskent University, Ankara, Turkey
[2]Department of Radiation Oncology, School of Medicine, Koç University, Istanbul, Turkey

Corresponding Author:
Erkan Topkan, Department of Radiation Oncology, Baskent University Medical Faculty, Adana 01120, Turkey.
Email: docdretopkan@gmail.com

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Tsukagoshi and colleagues reported that skeletal muscle loss independent prognostic factor of poor survival patients undergoing nivolumab therapy.[5] Considering the evidence mentioned above, together with the observation that the OS curves diverge shortly after treatment in the study by Ucgul and colleagues, it is likely that the research lacks adequate statistical power to identify a modest yet significant survival difference between sarcopenic and non-sarcopenic cancer patients.[1] Therefore, the results of future large-scale studies, which clearly define and assess sarcopenia according to established guidelines, are necessary to draw conclusive conclusions about the actual impact of sarcopenia status on the OS outcomes of cancer patients.

Author Contributions

E.T., N.K.D., S.S. and U.S. conceived the study, participated in the study's design, and performed clinical examination and statistical analysis. All authors contributed significantly and equally, and all authors approved the final form of the manuscript.

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ORCID iD

Erkan Topkan https://orcid.org/0000-0001-8120-7123

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