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LETTER TO THE EDITOR

Reply to comment on "Sarcopenia is a prognostic factor for overall survival in elderly patients with head and neck cancer"

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Dear Editor,

We would like to thank you for the opportunity to respond to the issues raised in the letter to the editor of Safer and Eyigör and to clarify aspects of our methodology in relation to their concerns. We would also like to thank these authors for their interest in our paper and for taking the time to comment.

In our recent paper in *European Archives of Oto-Rhino-Laryngology*, we presented the prognostic value of sarcopenia, as defined by EWGSOP1, for overall survival (OS) in elderly patients with head and neck squamous cell carcinoma [1]. Safer and Eyigör expressed some concerns regarding the measurement of skeletal muscle mass (SMM) and the definition of low hand grip strength (HGS).

First, these authors state that due to variation of attenuation between individual CT scanners this would easily lead to differences in SMM measurements. The scanners used in our study were the Philips (16, 64 and 256 detector rows) and Siemens (40 detector rows) scanner. We agree that the use of different CT scanners could have led to small variations of attenuation. However, the segmentation of SMM in CT imaging is dominantly based on manual contouring the muscles in a radiodensity range of −29 and +150 Hounsfield units. Therefore, it is unlikely that variation of attenuation between different CT scanners led to differences in the manual contouring in SMM measurements. Two recently published papers also provide evidence that differences in SMM measurements are small and insignificant for CT imaging with and without contrast [2, 3]. Low tube current (e.g. low-dose CT) does result in a significantly different skeletal muscle area, but low-dose CT images were not used in our study [4]. For muscle segmentation on magnetic resonance imaging (MRI), the same approach is used, with the exception that muscle-specific radiodensity range is not used as a tool for segmentation. Muscle segmentation on MRI is fully based on visual evaluation of muscle and manual contouring. In a recent study, we studied the agreement between SMM measurements as cross-sectional area (CSA) using CT and MRI [5]. This study showed an excellent intraclass correlation coefficient (ICC) for the CSA measurements of SM. This highlights the fact that with CT imaging, radiodensity is merely used as a supportive tool to speed up the contouring rather than a segmentation method. In addition, our research group has recently studied the inter-observer agreement for SMM measurements as CSA and found an excellent ICC for all CSA measurements (0.763–0.969, all

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$p < 0.001$) [6]. In conclusion, visual segmentation of SMM is a robust method to measure SMM. Clinically significant differences in SMM measurements due to small variations of attenuation are not likely.

Second, these authors suggest that the used cutoff values for low HGS in our study cohort do not correspond with the proposed cutoff values in the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) consensus and, therefore, could lead to a misclassification of patients [7]. However, as mentioned in our paper, we defined sarcopenia according to the former EWGSOP1 consensus with its corresponding definition of low HGS, which was the current version at the time of our research [8]. When applying the EWGSOP2 criteria on our study population, we found that 13 patients (15.3%) would shift from the subpopulation of patients with low HGS to the subpopulation of patients without low HGS. When applying the EWGSOP2 sarcopenia criteria, no significant prognostic value of sarcopenia for OS was seen in the study population. This phenome has been described earlier. Reiss et al. conducted a study in 144 geriatric patients and found a substantial mismatch in sarcopenia case finding according to EWGSOP1 and EWGSOP2 [9]. The overall prevalence and the number of men diagnosed with sarcopenia were significantly lower in EWGSOP2, whereas the absolute number of women identified as sarcopenic remained constant. Our study population consisted of 38 men (44.7%). Reiss et al. conclude that the EWGSOP1 algorithm yields high sensitivity and low specificity, whereas the EWGSOP2 algorithm yields lower sensitivity and higher specificity. Therefore, they state that the EWGSOP2 is not a suitable case-finding instrument in high prevalence settings like nursing homes or hospitals. A study of Locquet et al. was consistent with these results [10]. Further validation studies for the EWGSOP2 criteria are needed, whereas for EWGSOP1 the causative linkage with many clinical outcomes is already known [11].

Moreover, in the EWGSOP2 consensus paper, specific cutoff points are advised based on the available reference studies and populations. The authors state “The current EWGSOP recommendations focus on European populations and use of normative references (healthy young adults) whenever possible, with cutoff points usually set at −2 standard deviations compared to the mean reference value.” For HGS, the authors refer to the study of Dodds et al. in which cross-sectional centile values for grip strength across the life course were produced using 60,803 observations from 49,964 participants (26,687 female) of 12 general population studies in Great Britain [12]. They defined a T-score for grip strength as an individual’s value expressed as a multiple of the number of standard deviations below the peak mean value encountered in young adult life. They found that a T score of −2 equalize to HGS of 19 kg in females and 32 kg in males and a T score of −2.5 to HGS of 16 kg in females and 27 kg in males. From data of this study, it seems that the EWGSOP2 group took the −2.5 standard deviation scores instead of those from −2 standard deviations to produce more discriminative cutoff points with higher specificity but lower sensitivity. When −2 standard deviations compared to the mean reference values are used, as mentioned in the EWGSOP2 definitions, cutoff values of EWGSOP1 are almost similar: for females 19 and 20 and for men 32 and 30, respectively. It should be noted that the EWGSOP2 group concluded that some cutoff points are arbitrary and suggested more research on cutoff points. Specific cutoff points for elderly patients with cancer (or cancer patients in general) are not yet available.

Third, these authors mention that validation of measurements of SMM as cross-sectional muscle area (CSA) on pretreatment CT or MRI imaging at the level of the third cervical vertebrae (C3) should be validated against gold standards, i.e. whole-body magnetic resonance imaging scans (WB-MRI). The most commonly used method for the measurement of SM in cancer patients is based on MRI and CT imaging: skeletal muscle area is measured on a single transversal slice at the level of the third lumbar vertebra (L3) [13]. This method has been validated using WB-MRI; it has been shown that SM area on a single transversal slice at the level of L3 is strongly correlated with total SM volume as measured using WB-MRI [14–16]. Swartz et al. found a strong correlation between SM area at C3 and L3 ($r = 0.785$) [17]. Using a multivariate prediction equation, correlation between measured SM area at L3 and estimated SM area at L3 from C3 was even stronger ($r = 0.895$). We recognized also that measurements of SM area at the level of C3 are not directly validated against WB-MRI. Therefore, a study in 142 healthy Caucasians whom underwent WB-MRI was conducted (*manuscript in preparation*). A single MRI slice at the level of C3 strongly correlated with total SM volume ($r = 0.892$). It can be concluded that skeletal muscle area at the level of C3 can be used as an alternative to that of L3 to assess total SM volume in patients who have only received imaging of the head and neck area.

With the above-mentioned explanations, we hope that the concerns of Safer and Eyigör are solved and expect that these techniques can be used in future studies and clinical practice in head and neck cancer.

Author contributions EA: project development, data collection, data analysis, manuscript writing. CL: data analysis. EC: manuscript editing. PD: manuscript editing. DS: project development, data analysis, manuscript writing/editing

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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