

# Revisiting the prognostic relevance of muscle mass among non-metastatic colorectal cancer

Omar Abdel-Rahman<sup>1,2</sup>, Winson Y. Cheung<sup>2</sup>

<sup>1</sup>Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt; <sup>2</sup>Department of Oncology, University of Calgary, Tom Baker Cancer Centre, Calgary, Alberta, Canada

*Correspondence to:* Winson Y. Cheung, MD, MPH, FRCPC. Department of Oncology, University of Calgary, Tom Baker Cancer Centre, 1331 29 ST NW, Calgary AB, T2N 4N2, Canada. Email: winson.cheung@ahs.ca.

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*Comment on:* Brown JC, Caan BJ, Meyerhardt JA, *et al.* The Deterioration of Muscle Mass and Radiodensity is Prognostic of Poor Survival in Stage I–III Colorectal Cancer: A Population-Based Cohort Study. *J Cachexia Sarcopenia Muscle* 2018. [Epub ahead of print].

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Colorectal cancer represents a global health problem, particularly as the general population continues to age. Currently, it ranks as the third most common cause of cancer mortality worldwide (1). To assist with clinical management, colorectal cancer is frequently categorized according to the American Joint Committee on Cancer (AJCC) staging system that considers tumor extent, nodal involvement, and presence of metastasis (2). Staging helps to stratify patients into different risk levels of cancer recurrence and survival. In doing so, it informs the appropriate use of systemic therapy and represents one major example of a tailored and risk-adjusted approach to guide the treatment of early stage colorectal cancer patients.

In addition to staging, numerous additional factors have been described to play an important role in the prognostication of non-metastatic colorectal cancer (3). These include patient-related variables (4), such as age, comorbidity burden, and performance status, as well as other disease-related parameters (5), including tumor location and serum biomarkers of tumor biology (e.g., KRAS, BRAF mutations). Importantly, some of these factors are not always available, measurable, or objective. For this reason, there is ongoing interest in exploring additional factors that may improve and refine prognostication. Our own research group has previously conducted population-based studies to examine the association of body composition as measured by body mass

index (BMI), body surface area (BSA), and weight changes with outcomes in early stage colorectal cancer (6,7). In these prior studies, consistent prognostic relationships between baseline BMI/BSA and weight changes with survival were not observed. However, there are conflicting findings in this important area of study, with emerging data to suggest that body composition as measured by other metrics could be more clinically useful for determining prognosis. These alternative metrics include muscle mass and skeletal muscle density (8,9).

In the recent article published by Brown and colleagues in the *Journal of Cachexia, Sarcopenia, and Muscle* (10,11), the authors characterized the relationship between muscle wasting and mortality in a large population-based study of patients with non-metastatic colorectal cancer. Using data from the Kaiser Permanente North California Health System, a population-based sample of 1,924 patients with surgically resected stage I to III colorectal cancer were analyzed. Muscle mass and radiodensity were quantified using computed tomography images obtained at baseline and approximately one year after cancer diagnosis. Cox proportional-hazards models were constructed to estimate hazard ratios for all-cause mortality. Specifically, the investigators found that the risk of death was significantly higher among colorectal cancer patients who experienced the largest decrease in muscle mass (HR 2.15, 95% CI, 1.59–2.92,  $P < 0.001$ ) or largest decline in muscle

radiodensity (HR 1.61, 95% CI, 1.20–2.15, P=0.002) from baseline, independent of changes in body mass or other body composition parameters.

The authors are to be commended for their important work, which adds significantly to the growing body of evidence that indicates an increasingly robust correlation between muscle wasting and worse cancer prognosis. In a similar observational study of 3,262 colorectal cancer patients conducted by some of the same investigators and recently published in *Cancer* (10,11), an association was also observed between those with low skeletal muscle density and an elevated risk of cancer-specific mortality, independent of muscle mass and obesity. The authors concluded that body composition measures should be incorporated into routine clinical assessments of colorectal cancer patients and considered in the treatment decision making process. It is important to note that the observed patterns of muscle density and malignancy outcomes do not appear to be confined to colorectal cancer cases only as these findings are also largely consistent with those seen in other solid tumors, including breast and prostate cancer (12,13). This strongly suggests that there may be a common mechanism to explain the relationship. Although the precise underpinnings are as yet unclear, early data imply that anti-tumor proteins produced by the liver as well as pro-inflammatory cytokines released by the body in response to cancer can trigger downstream effects, such as cachexia, sarcopenia, and muscle wasting (14,15).

At the current time, muscle mass and skeletal muscle density are not typically collected as part of comprehensive assessments of cancer patients seen and managed in routine clinical practice. There could be many reasons for this, but a major challenge is the lack of a standardized clinical and/or radiographic definition of muscle wasting that can be used broadly in oncology and operationalized consistently across different jurisdictions. It is also possible that the personnel and resources needed to measure muscle mass and skeletal muscle density regularly are substantial and intensive, which could be prohibitive for some institutions to adopt, especially if these measurements are meant to be ascertained serially at each clinical visit or before each treatment. The logistics and feasibility of implementing these measurements in busy oncology clinics represent key areas that must be addressed.

The authors also propose that therapeutic interventions aimed at slowing muscle wasting should be endorsed since these may improve the outcomes of affected patients. While this area certainly warrants further prospective evaluation,

we would contend that recommending the use of such interventions is presently premature and not fully supported by the available data. Rather, aggressive treatment directed at the underlying colorectal cancer remains the priority. In conclusion, Brown *et al.*'s recent article adds to the increasingly strong evidence base that underscores the notion that muscle wasting is a relevant marker of poorer prognosis in early stage colorectal cancer. One advantage of muscle mass and skeletal muscle density is that these metrics are relatively quantifiable and likely more objective than conventional measures, such as performance status or frailty. Therefore, if possible, integrating the measurement of these body composition parameters should be considered for all future early stage colorectal cancer patients since they can be potentially meaningful in informing therapeutic and prognostic discussions.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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