Muscle Mass Matters in Patients with Renal Cell Carcinoma, but That Is Only the Beginning...

Sarah P. Psutka, MD, MS

Department of Urology, University of Washington, Seattle Cancer Care Alliance, Seattle, WA

There is a rapidly growing recognition of the need to improve how we risk stratify patients with malignancies. Whereas traditional metrics based on granular tumor-based characteristics can be used in a validated nomogram to estimate risks of recurrence and cancer-specific mortality, clinicians are increasingly acknowledging the complex interplay between patient-specific factors and tumors that influence overall and disease-specific survival.

Although subjective assessments of a patient's fitness for complex therapies, often colloquially described as the "eyeball test," are commonly employed, we have an imperative need at this point to advance the science of risk stratification incorporating objective, quantifiable, and reproducible metrics of frailty, vulnerability, or resilience across multiple relevant domains.¹ Improving risk stratification in this manner has implications for how we counsel patients regarding their prognosis and treatment election, and also for how we can determine who might benefit from adjuvant supportive therapies to improve their odds of a successful outcome.

During the past decade, detailed body composition analyses, specifically with respect to muscle mass, have garnered significant attention as a potential part of the solution to this problem. This approach is driven by the observations that (1) typical aging-related loss of muscle mass appears to be accelerated by both the presence of malignancies and their treatments, and that (2) severe deficiencies in muscle mass and related functional status,

termed sarcopenia,² are independent predictors of adverse short- and long-term outcomes for patients with cancer. Together with methodologic advancements that permit estimation of body composition from cross-sectional imaging studies routinely obtained in clinical practice, novel supervised machine-learning algorithms are bringing body composition analysis to the forefront of detailed, personalized, patient-focused risk stratification procedures.

In this month's *Annals of Surgical Oncology*, Lee et al.³ presents a single-institution retrospective cohort study of 632 patients who had localized, pT1–2 renal cell carcinoma (RCC) treated with radical nephrectomy. The authors quantified skeletal muscle index (SMI) at the mid third lumbar vertebra using validated methodology.⁴ They classified the patients as sarcopenic or not sarcopenic using previously defined and widely accepted sex-specific SMI thresholds ascertained using optimum stratification for the outcome of mortality from a cohort of 250 obese patients with solid tumors of the respiratory or gastrointestinal tract from Alberta, Canada.⁵ These SMI thresholds were subsequently reported in a widely cited consensus statement defining cancer cachexia.⁶

Lee and colleagues³ observed that the prevalence of sarcopenia was 42.4% in their study cohort. During a median follow-up period of 83 months, a multivariable analysis adjusted for age, nuclear grade, and tumor size showed that sarcopenia was independently associated with overall survival (hazard ratio [HR], 2.58, 95% confidence interval [CI], 1.02–6.54; $p = 0.045$) and cancer-specific survival (HR, 3.07; 95% CI, 1.38–6.83; $p = 0.006$) but not progression-free survival (PFS).

The authors are to be congratulated for their robust series that adds to the burgeoning literature supporting the predictive utility of detailed body composition analyses of patients with cancer. Notably, these assessments leverage routine baseline staging via imaging obtained as a standard

of care during tumor staging at diagnosis. As the authors state, findings show that deficiencies in muscle mass are independently associated with relevant short-term clinical outcomes (complications, functional deficits, systemic-therapy-associated adverse events) and long-term clinical outcomes (cancer-specific and all-cause mortality) across malignancies.⁷⁻⁹ These results are consistent with those from prior cohorts of patients with localized RCC (pT1–4 Nx/0)^{10,11} treated surgically and those from patients with metastatic RCC treated with cytoreductive nephrectomy.¹²

Other authors have observed an association between sarcopenia and postoperative surgical complications, but not overall survival.¹³ However, methodologic differences regarding the quantification of muscle mass¹⁴ as well as a limited sample size may have contributed to these discrepant findings. As the authors point out, their findings are notable for the fact that even among a patient population younger on the average than previously reported cohorts with localized and less advanced disease, baseline sarcopenia was both highly prevalent and independently associated with survival.³

As we develop a growing understanding of the predictive utility of low muscle mass at a single time point for patients with cancers, numerous unanswered questions remain that currently are active areas of research. First and foremost, we need a better understanding of the mechanisms underlying these macroscopic observations regarding body composition and their reflections of the interplay between the tumor itself, the cancer treatment, and the kinetics of muscle loss. We also need a better understanding of how dynamic changes in lean muscularity may influence a patient's ability to tolerate antineoplastic therapy, and ultimately, the patient's survival.¹⁵

Second, the relationships between observations of muscle loss and potentially additive risk factors such as malnutrition, low activity, and multimorbidity remain to be fully characterized, as well as key outcomes beyond survival such as physical function, independence, cognition, and quality of life.^{11,16,17}

Finally, numerous outstanding methodologic questions are salient for the continued pursuit of high-quality body composition research. One key knowledge gap is associated with the need to describe robust population-based body composition norms across racial and ethnic groups, ages, and disease states.¹⁸ This is highly relevant to the paper at hand given that the thresholds used in this study to characterize severe deficiencies in lean muscle mass were developed in a population of obese (body mass index [BMI] > 30 kg/m²) Caucasian patients with gastrointestinal and respiratory malignancies⁵ and therefore may be less generalizable to the study population of patients from Korea with a median BMI of 24.7 kg/m² (interquartile

range [IQR], 22.6–26.9 kg/m²). This difference in BMI may have implications for the definitions of sarcopenia in the study cohort.¹⁹

Other key methodologic questions remain that relate to image acquisition, quality control, and analysis such as defining the most appropriate interval during which a CT scan can be assumed to reflect body composition at a specific time point (e.g., the acceptable interval between a scan date and an index date). Ways to adjust these analyses need to be outlined for varying characteristics of the actual CT such as contrast utilization and timing, as well as ways to incorporate or use data from other axial levels or imaging methods to permit wider acquisition of these assessments and to permit more objective assessments of the quality of the data and their interpretation.^{18,20,21}

Finally, artificial intelligence-based machine-learning algorithms are actively being developed and validated to automate the processing images.²² These algorithms will increase the accessibility of the predictive data more widely and someday facilitate the adoption of these radiomic biomarkers into routine clinical practice. Papers such as this one lay the foundation for this work more broadly, defining the relevance of these body composition variables for our patients as independent predictors of outcome. In the coming years, we can expect significant advances in our understanding of how best to obtain these data, interpret them, augment them, and act on them to improve our patients' outcomes.

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