EDITORIAL

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A tale of two CT studies: the combined impact of multiple human body composition projects in cancer

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In this month's *JCSM*, we see the publication of two excellent studies assessing the relationship between CT body composition (BC) analysis, systemic inflammation (SI), and survival in patients with colorectal cancer. Both studies identify markers of worsened BC and SI as independent, and potentially additive, determinants of patient prognosis, over and above standard clinical prognostic measures of tumour staging. This editorial will describe additional lessons that may be gleaned by comparing the epidemiology, methodology, and interpretation of these two studies and other human BC projects in cancer. Moreover, it will highlight the emerging importance of host phenotyping in the delivery of modern oncological care.

The authors of our two considered papers this month should be congratulated for the aims, scope, and integrity of their studies. Although the emphases of the two papers are subtly different (in part reflecting the research histories of the respective groups), the findings are essentially, and reassuringly, similar. Dolan *et al*.[1] discuss their findings with regard to a large cohort of Scottish patients in the early stage of the cancer journey, undergoing elective primary surgery for colorectal cancer (n = 650). In comparison, van Dijk *et al*.[2] consider Dutch patients further along the cancer pathway, undergoing surgical resection of colorectal liver metastases (CLRM; n = 97). In both studies, worsened BC as assessed by staging CT and SI were each independent prognostic factors in determining overall patient survival during median follow-up periods of several years. Furthermore, it was shown that adverse BC phenotypes [including low skeletal muscle index (SMI; sarcopenia) or low skeletal muscle radiodensity (SMD)] could exist independently from SI (and vice versa). In the Dolan study, measures of BC were still weakly associated with overall survival even after stratification of patients in to different SI groups. Moreover, in the van Dijk study, a composite host phenotype consisting of adverse BC and SI was shown to have an additive and synergistic deleterious effect on survival (HR of death >4) and was also statistically independent of the Fong clinical prognostic score (a 5-point score that assesses nodal status of the primary tumour, the disease-free interval, the size and number of secondary hepatic tumours, and the preoperative serum CEA level).

Despite the apparent separation of survival impact, interestingly, the presence of SI still appears to be correlated with worsened BC. Thus, the relationship between BC and SI in cancer appears to be a complex one, for which direct causality is difficult to prove. To quote Dolan *et al*., 'Such cross sectional data cannot determine whether a low SMI or SMD results in the presence of SI or whether the presence of SI results in low SMI or SMD. From the present results, it is clear that a low SMI, SMD or both can occur in the absence of SI.

So why is causation, and the role of SI as a driver of nutritional depletion, so difficult to prove in human studies? When placed side by side, studies such as the two published in this month's edition offer us the opportunity to help answer this question by providing valuable insights into the methodology, epidemiology, and interpretation of multivariable BC data in human cachexia research. Initially, one can compare and contrast the potential idiosyncrasies of patient populations across different studies. In the two considered studies this month, disease status and geography appear to have had profound effects on the prevalence of the experimental variables in question (namely, SI and BC). With regard to the 'earlier' patients in the Dolan study, only approximately 25% of patients had SI [evidenced by modified Glasgow Prognostic Score (mGPS) 1 or 2], whereas the implied prevalence of SI in the 'later' van Dijk cohort was almost twice as high (CRP ≥ 5 mg/L = 48%). Some of the observed disparities may be due to alternative approaches to SI measurement: the mGPS requires a serum CRP level >10 mg/L, compared with the ≥5 mg/L cut-off used by

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van Dijk *et al*. However, the results also imply that SI is associated with disease progression and that patients with metastatic disease are more likely to have elevated CRP, an observation noted in previous studies.

With regard to BC, approximately 47–60% of patients in the Dolan study exhibited myosteatosis (by CT criteria), whereas, on the whole, patients were not frankly myosteatotic in the van Dijk study. Assuming that progressive myosteatosis is associated with cancer cachexia,[3] this observation seems counterintuitive considering the position of the respective patient populations on their disease trajectory. Although patients in the Dolan study were likely to be slightly older on average than the van Dijk study, and there was a higher preponderance of females, this propensity of myosteatosis likely reflects the background inequalities in BC between a deprived Scottish population (co-morbidity 88%; visceral adiposity 73%) compared with a leaner, possibly healthier, Dutch one (visceral adiposity 52%). The authors do not comment specifically on the survival impact of sarcopenic obesity in their populations, a body habitus that has been identified as a negative prognostic indicator in some surgical and cancer cohorts.[4] Further studies in this area will help to elucidate the onlay of the obesity paradox on patients with cancer and cachexia. CT BC data should always be analysed with respect to patient sex and BMI,[5] but such unanticipated differences in BC across international populations also highlight the importance of examining BC data in the context of the local geographical and ethnic norms, and they strongly support the aim of current multicentre strategies to generate international, disease-specific CT BC cutpoints (e.g. INSPECT study for oesophageal cancer).

In a similar way to the SI data, some of the observed disparities in BC status might also be the result of alternative methods of data analysis. Dolan *et al*. used a diverse range of published cutpoints to establish their CT definitions of sarcopenia and myosteatosis. In comparison, van Dijk *et al*. used *Z*-scores (to indicate how many standard deviations an element is from the mean) derived from CT values of a larger cohort of patients with metastatic colorectal cancer.[4] Although both studies used similar source data for their analytical techniques (see Martin *et al*.[5]), the actual CT cutpoints employed will have differed. These varying, and apparently valid, approaches to BC analysis reinforce the current calls for technical standardization in CT BC. At the present time, even the terminology surrounding CT BC can be confusing. For example, *sarcopenia*, a term used classically to mean a primary and dynamic age-related deterioration in muscle mass and function, is now often meant to mean a static, one-off measure of muscle cross-sectional area or volume on a single CT. Likewise, across the two studies considered this month, various terms have been used to represent low average Hounsfield units across muscles, including reduced *muscle attenuation* or *muscle radiodensity*, leading to poor *muscle quality* and *myosteatosis*, the latter two terms reflecting assumptions rather than true measures of muscle power, strength, or fat infiltration. In short, attempts at standardization of language, as well as technique, would also be beneficial.

In the past few years, there has been a tendency for surgical publications to simply concentrate on a single measure of CT BC (usually either SMI or SMD) or to utilize less well-validated methods of BCA, such as psoas cross-sectional area rather than L3 analysis. The authors of the studies reviewed this month should be applauded for taking the opportunity to perform rigorous analyses of all of the well-described facets of CT BC, including measurements of muscle, fat, volume, and attenuation. However, the authors do identify the lack of repeated CT measures as a potential shortcoming of their studies. Without repeated assessments, 'it is difficult to distinguish BC features that are constitutional from those that are secondary to the disease state'. Sequential assessments would allow the interpretation of dynamic wasting and the identification of different wasting phenotypes that describe the natural history of cachexia, the negative impact of treatment, and the relationship with survival.[6] They would also help account for variations in local geographical norms.

In summary, there is added value to be gained from such exercises in study comparison. However, to return to the beginning, the crucial and invaluable findings of the present studies are that they identify host phenotypes (including BC and SI) as major determinants of patient survival that are equivalent in effect to standard clinical assessments of tumour phenotype (e.g. disease stage). Van Dijk *et al*. have chosen to employ the term 'tumour biology' rather than 'tumour phenotype', and they state that the effect of tumour biology on prognosis in CRLM is 'well known'. However, I would argue that this is not entirely the case. The Fong score (as a measure of tumour biology) is not wholly representative of biological processes; rather, it is an indirect composite measure of disease burden and some aspects of metastatic behaviour. The field of tumour biology, including analyses of tumour genetics, immunology, cell heterogeneity/stromal cells, and metastatic potential, is largely unexplored in relation to human wasting, the pathogenesis of SI, or the determination of survival. In cachexia research, only recently are we beginning to investigate the roles of tumour-specific mediators, extracellular vesicles,[7] and the roles of host immune cells[8] (e.g. tumour-associated macrophages). Without cancer, there can be no cancer cachexia, and thus, the field of tumour biology is a key unmet need in cachexia research. Exploration of this area is even more pressing during the current era of immune checkpoint inhibitors, which have revolutionized treatments in some tumour types (e.g. PD-1 and PDL-1 inhibitors). At this stage, we are not even fully cognizant of the natural history of BC along varying treatment pathways, and prospective studies are an aspiration for the future.

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In conclusion, van Dijk *et al*. assert that 'the true value of our observations is that we have recognized independent host-derived features that can adversely affect survival in addition to tumor-derived features', whereas Dolan *et al*. support the '… incorporation of the SMI, SMD and mGPS as part of the clinical and nutritional assessment in patients with cancer'. Both sets of authors highlight the need for host-specific strategies for intervention. These studies underline the current lack of host phenotyping in modern oncological care. A fundamental paradigm shift is required to incorporate the relevance of host phenotype in clinical prognostication, treatment decisions, and the calculation of chemotherapy dosing. The final message is that we should stage the tumour and stage the host and then treat the tumour and treat the host.

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The author certifies that they comply with the ethical guidelines for authorship and publishing of the *Journal of Cachexia, Sarcopenia and Muscle*.[9]

Conflict of interest

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