High economic burden of immunotherapy underlines the need of predictive biomarkers for the individual therapy algorithm in metastatic bladder cancer

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Editorial

Sarcopenia is a reliable predictor of outcomes following radical cystectomy for bladder cancer

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Radical cystectomy (RC) with pelvic lymph node dissection, preceded by cisplatin-based neoadjuvant chemotherapy in appropriate patients, remains the gold-standard in the treatment of muscle invasive bladder cancer (MIBC) (1,2). RC is a complex operation performed in an elderly (and sometimes unhealthy) patient population, with significant complication rates (as high as 60%) and perioperative mortality rates (9%) reported at 90-days (3,4).

Unfortunately, RC utilization in the MIBC population is low. In 2010 Gore *et al.* published on 3,262 patients with MIBC from the SEER-Medicare database and noted that RC utilization was only 21% in this population (5). Factors contributing to these observations included proximity to specialized medical care, patient comorbidities, and patient age. A subsequent similar analysis of this same dataset dating between 2002 to 2011 showing no progression in RC utilization (19%) with similar sociodemographic barriers (6). The underlying themes behind underutilization of RC can be broadly summarized as difficulties in either accessing or tolerating care. While issues with access to care reflect U.S. Healthcare System deficiencies that are not often modifiable in the short-term, an individual patient's ability to tolerate surgery may be improved. Thus, there exists a growing interest in identifying modifiable risk factors for post-RC morbidity, mortality, and prolonged recovery. In that regard, sarcopenia, as a potential sign of nutritional insufficiency, frailty, and poor exercise tolerance, is an interesting measure of potentially modifiable patient factors.

The article by Mayr *et al.* published in *World Journal of Urology*, evaluates pre-RC sarcopenia as a predictor of 90-day mortality and morbidity (7). The authors report on 327 patients with MIBC, all of whom had CT imaging of the abdomen within 30 days of surgery. Cross-sectional skeletal muscle surface area at L3 was used to calculate the lumbar skeletal muscle index with comparative evaluation using established gender and body mass index based cutoffs. In this population, 90-day mortality was more likely among sarcopenic patients, even after controlling for American Society of Anesthesiologists (ASA) score, age, and oncologic stage (OR 2.59; 95% CI: 1.13–5.95; P=0.025). Furthermore, sarcopenia was an independent predictor of complications greater than Clavien-Dindo 3b (OR 2.00; 95% CI :1.23–3.26; P=0.005) but only trended toward predicting all major complications (Clavien-Dindo ≥3a).

The current article adds to the existing body of literature on the subject of sarcopenia as a predictor of outcome following RC. Several groups have previously shown that sarcopenia is related to decreased overall survival and cancer-specific survival after RC (8,9). Others have suggested a relationship between pre-operative sarcopenia and length of hospital stay following RC (10). Smith *et al.* reported an association between sarcopenia and 30-day complication rates, particularly in female patients (11). They were unable to show a statistically significant relationship between sarcopenia and 30-day complications in the overall cohort using total psoas area as a continuous variable, but cutoff points determined via the Youden Index method identified significantly more complications

in patients meeting the criteria for sarcopenia. Wan *et al.* demonstrated that skeletal muscle index was significantly associated with major complications (Clavien-Dindo ≥3) on multivariate analysis (12). And in 466 patients undergoing RC, Ahmadi *et al.* showed that total psoas area was an independent predictor of complications at 30- and 90-days in a multivariate model (13).

Preoperative indicators of post-operative outcomes are most useful if they can be modified during the period between the pre-operative assessment and the surgery in question. A Japanese group studying elderly gastrectomy patients demonstrated that sarcopenic patients that participated in a preoperative nutrition and exercise program could increase their grip strength and in a few cases (4/22 patients) became non-sarcopenic (14). Effective initiation of a rehabilitation program for sarcopenic patients prior to RC (so-called pre-habilitation) can be challenging in patients undergoing oncologic surgery due to the time constraints imposed by progressing malignancy. The population of RC patients receiving neoadjuvant chemotherapy may therefore represent a particularly attractive target for pre-habilitation due to the delay in time to surgery necessitated by chemotherapy.

Based on the current paper and the existing literature, we may conclude that pre-operative sarcopenia (which can easily be measured in all patients from axial imaging) is an objective predictor of a patient's ability to tolerate and recover from RC. Furthermore, sarcopenia is an indicator of potentially modifiable issues with nutrition and exercise tolerance. Ideally, sarcopenia measured pre-cystectomy, will identify patients at risk for prolonged or complicated recovery after RC, and trigger the institution of appropriate pre-habilitative measures which may correct the underlying issues. Ongoing clinical trials which further explore this concept will contribute to our understanding of the potential impact of pre-habilitation, and our ability to intervene on at-risk patients prior to cystectomy with the ultimate goal of reduced treatment related morbidity.

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Footnote

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

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