Predicting adverse outcomes in oncological nephrectomy: let's take a look at the patient around the tumor

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The management of renal cell carcinoma (RCC) underwent a revolution in the last decades. From an exclusively surgical alternative—open radical nephrectomy, we have seen the rise of ablation and surveillance, which ultimately made their way into the guidelines (1). On the surgical front, there was a shift towards nephron-sparing and minimally invasive procedures, even for larger and more challenging cases (2). At the same time, we are operating on older and more frail patients, often presenting with locally advanced and metastatic disease. Finally, there was a 50% increase in the overall incidence of RCC between 1996 and 2016 in the United States (3).

Therefore, clinical decision-making for patients with RCC has grown in complexity. To refine conventional risk assessment comprising clinical tumor, node, metastasis (TNM) staging, performance status, and patient comorbidities, tumor scores like the RENAL or Padua were developed to estimate the difficulty and risks involved in tumor resection, while improving uniformity of studies on partial nephrectomy (4,5). Still, there remains a gap of unexplained variation in the occurrence of adverse outcomes, which are often missed by conventional evaluation, with potential implications for the management of RCC (6).

The study presented by Maurits *et al.* (7) on this issue of *Translational Andrology and Urology* addresses the equally important, and less investigated, determinant of nephrectomy outcomes: patient features. More specifically, they investigated whether body composition variables—skeletal muscle density (SMD), body mass index (BMI), and adipose tissue distribution—impact on postoperative morbidity of RCC patients.

Nutritional status is a key determinant of perioperative complications, as both obesity (8) and malnutrition (9) may negatively impact on surgical outcomes of cancer patients. The challenge, however, is to evaluate them in a standard, simple, and readily available way that predicts adverse outcomes, making it useful in clinical practice. Even though the picture is evident in the extremes of cachexia and morbid obesity (BMI >40 kg/m²), most RCC patients present within intermediate nutritional categories, whose evaluation is further complicated by the fact that obesity can hide sarcopenia (10).

The authors evaluated SMD and adipose tissue by the BMI and its distribution in the subcutaneous (SAT) and visceral compartments (VAT) in patients undergoing radical or partial nephrectomy for RCC. They sought to verify whether these CT-derived variables had any

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impact on surgical outcomes, namely major postoperative complications (Clavien-Dindo 3 or higher) and prolonged length of hospital stay (LOHS), defined as ≥7 days.

This large, retrospective multicenter series found obesity significantly associated with major postoperative complications. On the other hand, CT-based body composition variables concerning skeletal muscle (SMD and skeletal muscle index) and adipose tissue (VAT, SAT) showed no significant association with major complications after radical or partial nephrectomy.

The impact of obesity on nephrectomy for RCC has been extensively studied, especially with the advent of laparoscopy. Initially regarded as a contraindication to this technique, subsequent series reported no significant increase in warm ischemia time, blood loss, positive margins, complications, and length of stay (LOS) for obese patients undergoing partial or radical nephrectomy (11-15). Indeed, overweight and class I obesity have been associated with *better* surgical and oncologic outcomes, resulting in the so-called 'obesity paradox' (10). Such paradox consists in that surgical complications (13) and cancer specific survival (16) do not differ from the general population despite obesity being a recognized risk factor for RCC and obese patients presenting with more comorbidities (14).

The reason for Maurits et al.'s (7) observation of increased major postoperative complications among obese patients may be found in their high rate of radical nephrectomy (78%), especially considering that 42% were performed for pT1 tumors, and in about a third the access was open. Although compatible with clinical practice at the study period [2008–2012], these features differ from the series that have reported oncological nephrectomy to be safe in obese patients based on nephron sparing and minimally invasive surgery (11-15).

BMI's inconsistency to accurately determine prognosis in oncological nephrectomy population has fueled research on alternative surrogates, such as the distribution of adipose tissue. The literature yields conflicting observations on this topic: while some studies report increased adverse outcomes (12,17), others (11,18) found no association with high visceral or perinephric fat on CT.

The lack of significant association between SAT, and especially visceral adipose tissue with complications in this (7) and previous studies (11,18) leaves the value of this marker to be determined. Accordingly, skeletal muscle and adipose tissue indexes failed to improve the accuracy of a model based on established predictors of major complications [age, stage, and American Society of

Anesthesiologists (ASA) score] as reported by Maurits et al. (7). In their series, 78% of patients undergoing radical nephrectomy harbored a pT1 tumor, suggesting that the utility of CT-based body composition analysis in the general RCC population RCC is limited by its heterogeneity and the low number of major complications in the study population.

On the other hand, the same authors (7) showed a high SMD at the level of L3 vertebrae on CT scan to be associated with a 38% reduction in the risk of prolonged hospital stay. Interestingly, the adipose tissue parameters (VAT, SAT, and BMI) did not significantly affect LOHS in the study population.

Skeletal muscle and its deficiency (sarcopenia) are promising prognostic markers, which have been associated with adverse surgical and clinical outcomes in other malignancies (19,20). They have emerged not only as indicators of nutritional status, but low skeletal muscle radiodensity has also been linked with increased postoperative systemic inflammation (21) and dose-limiting toxicity in systemic therapy for metastatic disease (6). The few studies investigating sarcopenia's role in RCC report increased rates of major complications in nephrectomy for locally advanced disease (22), and worse overall survival in cytoreductive nephrectomy (23). The present study (7) adds to the existing evidence by showing increased LOS in patients with low SMD. Interestingly, low SMD was associated with major complications in subgroups of patients undergoing radical (but not partial), and laparoscopic/robot-assisted (but not open) nephrectomy (7).

Finally, body composition assessment is plagued with disagreement on measurement criteria and reference values in the general and oncologic populations (6). CT-based SMD has been measured either as total psoas muscle area (22) or SMD index, which comprises all muscle at the level of L3 vertebrae (16,23). Whereas the former is simple and can be measured by non-radiologists, the latter is more accurate but requires specific software and a specialized reader. No consensus has been reached so far; to illustrate one of the many issues to be overcome before such tools be adopted into clinical practice.

Still, the present study (7) connects with previous research on locally advanced (22), and cytoreductive nephrectomy (23) to suggest a possible role for CT-based body composition analysis in subgroups with such an elevated risk that it becomes clinically significant. Patients with vena cava thrombus, metastatic disease, and those >80 years old are at particular risk of adverse outcomes, for

whom we often hesitate to propose surgery. Future studies on CT-based body composition variables should focus on these patients for whom nephrectomy yields a narrow risk-benefit ratio, preferably relying on prospectively collected imaging and multicenter collaboration to overcome their low frequency.

Footnote

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