INTRODUCTION

Renal cell carcinoma (RCC) is among the most common and fatal cancers in the United States, with an estimated 81,800 new diagnoses and 14,890 deaths in 2023 [1]. Obesity is recognized as a primary risk factor for RCC development; however, overweight patients have, interestingly, demonstrated more favorable survival outcomes following treatment [2-4]. This phenomenon, known as “the obesity paradox,” suggests that obesity may be protective in cancer patients, prolonging overall survival (OS) and improving systemic treatment response; however, this benefit may be cancer-specific [5-8].

Traditionally, obesity is measured by body mass index (BMI, kg/m²) as a quantitative representation of a patient’s adiposity, with elevated BMI considered indicative of poor health [9]. However, BMI is recognized as a poor indicator of total percent body fat, fails to differentiate between lean muscle and body fat mass, and does not account for tissue-specific metabolic activity [9-11]. As a result, an emphasis has been placed on body composition, in which lean and fat body masses from various compartments have strong prognostic utility. Low muscle mass (i.e., sarcopenia) and low visceral adiposity are often associated with poorer survival outcomes in localized and advanced RCC. These patients tend to experience higher rates of recurrence, progression, treatment failure, and death from kidney cancer. Given the influence of body composition in RCC outcomes, further characterization of the role of prehabilitation programs is warranted to evaluate the feasibility and efficacy of interventions targeting these modifiable factors.

Key Words: Renal cell carcinoma, Body composition, Body mass index, Sarcopenia, Adiposity, Survival
nostic utility in patients with RCC. We first describe the common definitions and methods in body composition analysis. Then, we characterize the influence of BMI, muscle, and fat in predicting perioperative and survival outcomes in localized and metastatic RCC (mRCC). Furthermore, we describe the role of body composition in systemic treatment efficacy and tolerance in locally advanced RCC and mRCC. Finally, we discuss how exercise and nutritional prehabilitation programs may impact body composition and associated outcomes.

**DEFINITIONS AND EVALUATION OF BODY COMPOSITION MEASUREMENTS**

1. **Body Composition in RCC: Definitions**

   Muscle quantity is the most frequently considered body composition metric in patients with RCC. Sarcopenia, defined as a clinically significant deficiency of skeletal muscle mass and function, is closely associated with aging and poor health status [13]. Around 10% of patients in their 50s are believed to have sarcopenia, with the prevalence rising to 35%–50% in patients with RCC [14]. Sarcopenia results from several factors, including physical inactivity, malnutrition, comorbidities, hormonal alterations, neuromuscular changes, and inflammation [13]. Malignancy-associated muscle loss may be linked to similar factors, but is additionally associated with acutely increased systemic inflammation [13]. Muscle mass is typically measured as the skeletal muscle index (SMI, cm²/m²), with various thresholds reported in the literature to determine high versus low mass, often stratified by sex and BMI [13]. There is no universally agreed-upon threshold for SMI, which can lead to differing sarcopenia prevalence rates reported by various studies [13]. The global prevalence varies widely depending on the patient population and classification [15].

   Skeletal muscle quality has recently been recognized as a critical contributor to patient body composition. Skeletal muscle density (SMD) represents infiltration by fat tissue, with each 1 Hounsfield unit decrease in density representing an increase in adiposity of 1 g per 100-mL increase in adiposity, and correlates with muscle functionality [16,17]. SMD has been linked to inflammatory processes, while mass may relate more closely to nutrition and catabolic status [17]. SMD serves as a useful prognostic tool in multiple cancers, particularly when comparing patients with similar muscle mass but differing degrees of myosteatosis [18].

   Various methods of fat measurement are also implemented that offer more insight than BMI alone, with visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) being most often considered. Additionally, intramuscular adipose tissue (IMAT) is related to the aforementioned SMD. Visceral fat is believed to pose greater negative health implications, with SAT playing a lesser role, given the metabolic activity of VAT and the associated secretion of proinflammatory adipokines and cytokines [10,19,20]. These measurements are predominantly classified using median values from study cohorts to define high versus low fat content.

2. **Body Composition in RCC: Techniques**

   For patients with RCC, the predominant method of measuring body condition is using cross-sectional abdominal imaging, with both computed tomography and magnetic resonance imaging, routinely obtained in diagnosis, staging, and follow-up [13]. Given its representation of total body composition, the level of the third lumbar vertebra (L3) is primarily considered. With the use of specialized software, such as Slice-O-Matic (TomoVision, Quebec, Canada), semimanual mapping of body compartments can be conducted to generate quantitative data. An example of a completed L3 body composition analysis is presented in Fig. 1.

   Although beyond the scope of this review, other methods to expedite and ease body composition analysis (e.g., artificial intelligence, linear segmentation, psoas muscle measurements) have been frequently explored. However, technique standardization, threshold determination, and quality control remain crucial to minimize subjectivity for future research and clinical incorporation. For a full review on body composition imaging techniques and muscle analysis outcomes in patients with RCC, please refer to the review article by Schmeusser et al. [13]. Furthermore, a video article detailing the methods for body composition analysis using Slice-O-Matic software was published by Steele et al. [21].
BODY COMPOSITION MEASUREMENTS IN RELATION TO RCC OUTCOMES

1. Influence of BMI

BMI has been recognized as a principal risk factor for the development of kidney cancer, with obesity (BMI ≥30 kg/m²) increasing risk 2- to 3-fold compared with normal-weight individuals (BMI <25 kg/m²) [2]. BMI became a popular preoperative measurement given its association with prolonged operative time, risk of postsurgical complications, and higher mortality rates, although inconsistent results have been reported [22-24]. Table 1 provides a summary of the findings regarding BMI.

1) Perioperative outcomes

According to a series of studies examining perioperative outcomes following minimally invasive nephrectomy, BMI may have an association with estimated blood loss (EBL); however, it has not shown any major associations with complication rates or changes in the glomerular filtration rate, suggesting that surgery can be performed safely in obese patients [25-27]. Among patients undergoing retroperitoneal laparoscopic radical nephrectomy (RN) for T1–2 RCC, no association was observed between elevated BMI (≥25.0 kg/m²) and operative duration, EBL, or postoperative complications [28]. In a separate cohort, obesity increased the risk of wound infections and extended length of stay (LOS) following nephrectomy for non-mRCC, whereas the remaining body composition measures were nonpredictive [29].

2) Localized RCC outcomes

The role of BMI in RCC often supports the concept of the obesity paradox, as described above. Separate studies from the United States and France demonstrated an association between elevated BMI and longer OS following nephrectomy for localized RCC, compared to patients with lower BMI [29,30]. In a prospective randomized trial of high-risk RCC patients receiving adjuvant girentuximab, a monoclonal antibody to carbonic anhydrase IX that triggers antibody-dependent cell-mediated cytotoxicity, obesity was associated with improved recurrence-free survival (RFS) and OS rates [31]. Furthermore, when compared to normal-weight individuals, patients with a BMI of 30.0–30.49 kg/m² (hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.31–0.81) and ≥35.0 kg/m² (HR, 0.24; 95% CI, 0.09–0.60) had lower mortality risks [31].

3) Metastatic and locally advanced RCC outcomes

Kim et al. [27] reviewed the favorable impact of BMI on progression-free survival (PFS), cancer-specific survival (CSS), and OS in mRCC. However, in a series of mRCC patients receiving vascular endothelial growth factor (VEGF) inhibitors, obesity did not influence the prognosis, but patients with elevated BMI in combination with sarcopenia experienced lower rates of sorafenib and sunitinib dose-limiting toxicity (DLT) [32-34]. The role of BMI in immunotherapy patients has recently been described. De Giorgi et al. [35] examined the interplay between BMI and systemic
Table 1. Notable studies investigating the impact of body mass index on perioperative, survival, and treatment-related outcomes in localized, locally advanced, and metastatic renal cell carcinoma

<table>
<thead>
<tr>
<th>Study</th>
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<td>Perioperative outcomes</td>
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<tr>
<td>Hagiwara et al. 2012[25]</td>
<td>T1a &lt; 10 cm RCC after laparoscopic RN (121)</td>
<td>BMI, VAT, SAT, TAT</td>
<td>Operative time</td>
<td>BMI ≥25.0 kg/m²</td>
<td>Operative time: higher BMI exhibited a positive correlation (r = 0.348, p &lt; 0.001)</td>
</tr>
<tr>
<td>Akihata et al. 2013[28]</td>
<td>T1-2 RCC after laparoscopic RP RN (98)</td>
<td>BMI, anterior perirenal fat distance</td>
<td>Operative time</td>
<td>BMI ≥25.0 kg/m²</td>
<td>No BMI association in multivariable analysis</td>
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<tr>
<td>Darbas et al. 2020[29]</td>
<td>Localized RCC in overweight patients (96)</td>
<td>BMI, SMI, VAT, SAT, IMAT</td>
<td>Postoperative infections</td>
<td>BMI ≥30.0 kg/m²</td>
<td>No association between BMI, operative time, complications, or EBL was seen</td>
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<td>Survival outcomes in localized RCC</td>
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<td>Darbas et al. 2020[29]</td>
<td>Localized RCC in overweight patients (96)</td>
<td>BMI, SMI, VAT, SAT, IMAT</td>
<td>5-year DFS &amp; OS</td>
<td>BMI ≥30.0 kg/m²</td>
<td>No association between BMI, DFS, or OS was seen</td>
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<tr>
<td>Mano et al. 2014[30]</td>
<td>AJCC stage I–III ccRCC (220)</td>
<td>BMI, VAT, SAT</td>
<td>OS</td>
<td>WHO BMI categorization</td>
<td>OS: BMI association on univariable analysis only (p = 0.028)</td>
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<tr>
<td>Donin et al. 2016[31]</td>
<td>High-risk RCC receiving adjuvant girentixumab (84)</td>
<td>BMI</td>
<td>DFS, OS</td>
<td>BMI ≥30.0–34.9 kg/m²</td>
<td>No association between BC parameters were nonsignificant</td>
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<td>Survival outcomes in metastatic and locally advanced RCC</td>
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<tr>
<td>Steffens et al. 2011[32]</td>
<td>mRCC receiving anti-VEGF therapy (116)</td>
<td>BMI, VAT, SAT</td>
<td>PFS, OS</td>
<td>BMI ≥25.0 kg/m²</td>
<td>PFS: low VAT (HR, 3.26; p = 0.006); low VAT (HR, 2.86; p = 0.010)</td>
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<tr>
<td>Antoun et al. 2010[33]</td>
<td>mRCC receiving sorafenib (55)</td>
<td>BMI, SMI</td>
<td>DLT</td>
<td>BMI ≥25.0 kg/m²</td>
<td>DLT: 41% prevalence in sarcopenia + low BMI &lt; 25.0</td>
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<tr>
<td>Huillard et al. 2013[34]</td>
<td>mRCC receiving sunitinib (61)</td>
<td>BMI, SMI</td>
<td>DLT</td>
<td>BMI ≥25.0 kg/m²</td>
<td>DLT: Sarcopenia + low BMI (OR, 4.1; p = 0.01)</td>
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<tr>
<td>De Giorgi et al. 2019[35]</td>
<td>mRCC receiving nivolumab (313)</td>
<td>BMI, SII, NLR, PLR</td>
<td>OS</td>
<td>BMI ≥25.0 kg/m²</td>
<td>OS: low BMI (HR, 1.98; p = 0.01); BMI ≥25.0 + SII &gt; 1.375 (HR, 3.37; p &lt; 0.0001)</td>
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<td>Lalani et al. 2021[36]</td>
<td>aRCC receiving ICI therapy (735)</td>
<td>BMI</td>
<td>1 yr OS, ORR, TTF</td>
<td>BMI ≥25.0 kg/m²</td>
<td>OS: high BMI (79% vs. 66%; HR, 0.75; p = 0.03)</td>
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<tr>
<td>Martini et al. 2020[37]</td>
<td>mRCC receiving ICI therapy (100)</td>
<td>BMI, MLD, distant metastases</td>
<td>OS, PFS</td>
<td>Risk score with BMI &lt; 240 kg/m², MLD ≥ 0.93, number of distant metastases (0, 1, 2)</td>
<td>ORR: high BMI (30% vs. 21%; OR, 1.51, nonsignificant)</td>
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<tr>
<td>Boi et al. 2020[38]</td>
<td>aRCC receiving PD-1-based therapy (73)</td>
<td>BMI</td>
<td>2.5 yr OS, PFS</td>
<td>BMI ≥30.0 kg/m²</td>
<td>OS: low BMI (HR, 0.48; p = 0.037); PFS: low BMI (HR, 0.54; p = 0.032)</td>
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RCC, renal cell carcinoma; RN, radical nephrectomy; BMI, body mass index; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; TAT, total adipose tissue; RP, retroperitoneal; EBL, estimated blood loss, mL; SMI, skeletal muscle index; IMAT, intermuscular adipose tissue; PN, partial nephrectomy; LOS, length of stay; DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; BC, body composition; AJCC, American Joint Cancer Committee; cc, clear cell; WHO, World Health Organization; mRCC, metastatic RCC; VEGF, vascular endothelial growth factor; DLT, dose-limiting toxicity; SII, systemic immune inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ICI, immune checkpoint inhibitor; MLD, monocyte-to-lymphocyte ratio; PFS, progression-free survival; ORR, objective-response rate; TTF, time-to-treatment failure; aRCC, advanced RCC; PD-1, programmed cell death protein 1.
inflammation in relation to survival in patients with mRCC treated with nivolumab. Normal weight, compared with BMI >25.0 kg/m$^2$, independently predicted worse OS (HR, 1.59), and when high inflammatory markers were included, mortality risk was tripled (HR, 3.37) [35]. According to Lalani et al. [36], in 735 advanced RCC patients receiving immune checkpoint inhibitors (ICIs), elevated BMI improved 1-year OS (79% vs. 66%; HR, 0.75; p=0.03), the objective-response rate (30% vs. 21%), and time-to-treatment failure (7.4 months vs. 4.9 months). Martini et al. [37] developed a novel risk score for mRCC patients on ICIs, finding that a BMI ≥24 kg/m$^2$ was a protective factor in OS and PFS. However, in a multicenter study of 76 mRCC patients receiving nivolumab or pembrolizumab, obesity reduced the treatment response rate (73% vs. 44%), PFS, and OS [38].

Histopathology may explain these conflicting findings. Among patients with obesity, tumors showed greater angiogenesis and inflammation of peritumoral adipose tissue, which may permit lymphocytic infiltration [39]. This could clarify the survival advantage and improved immunotherapy response. However, obese mRCC mouse models revealed increased intratumoral interleukin-1β levels, which can inhibit the action of ICIs and limit their efficacy [38].

2. Influence of Muscle Measurements

Sarcopenia is highly prevalent among RCC patients and is associated with poor survival across a variety of malignancies, including RCC [40]. Table 2 provides a summary of the relevant findings.

1) Perioperative outcomes

Although sarcopenia has been associated with postoperative complications and 30-day mortality in patients undergoing oncological surgery, little has been reported regarding sarcopenia in patients with RCC [41]. In 2 series of patients undergoing nephrectomy with inferior vena cava tumor thrombectomy, no significant differences in surgical complications or LOS were found according to whether patients had sarcopenia [42,43]. However, in 137 American Joint Cancer Committee stage III–IV RCC patients undergoing RN, Peyton et al. [44] found that the psoas muscle index (PMI) was associated with the risk of high-grade Clavien complications, although PMI as a marker of total skeletal muscle mass is relatively unreliable [45]. Given the complexity and high complication rates of these procedures, it will be of interest in the future to examine perioperative outcomes of sarcopenic patients following nephrectomy for localized disease.

2) Localized RCC outcomes

In a group of 387 non-mRCC patients following RN, Psutka et al. [46] found that sarcopenia predicted worse 5-year CSS (79% vs. 85%, p=0.05) and OS (65% vs. 74%, p=0.005). Furthermore, Lee et al. [47] found sarcopenia to be a risk factor for all-cause mortality (HR, 2.58; 95% CI, 1.02–6.54) and cancer-specific mortality (HR, 3.07; 95% CI, 1.38–6.83) in over 600 pT1–2 RCC patients. In contrast, Darbas et al. [29] found no association between body composition measurements, including BMI, SMI, and VAT index and 5-year RFS, though this study was limited by the sample size and included only overweight patients. Nonetheless, multiple studies of various patient populations have repeatedly shown a connection between low skeletal muscle mass and shorter CSS and OS in localized RCC patients, which supports this association [47-50]. Patients who have sarcopenia present with larger, higher-grade, and higher-stage tumors with an increased risk of lymphovascular invasion, which may explain the poorer oncological outcomes [51]. In RCC, clinicopathologically aggressive tumors produce inflammatory cytokines and promote proinflammatory states, diminishing skeletal muscle mass and strength [52,53]. Therefore, sarcopenia is a significant prognostic factor in non-mRCC and may suggest clinically aggressive malignancy.

3) Metastatic and locally advanced RCC outcomes

Sarcopenia has further demonstrated its prognostic utility for mRCC. In 92 patients with mRCC, Fukushima et al. [54] found a high prevalence (68%) of sarcopenia, and the 3-year OS rates were 31% and 73% in patients with and without sarcopenia, respectively. Low SMI increased the risk of death nearly 3-fold. Sarcopenia at the time of CN has been shown to be highly prevalent and negatively associated with OS (HR, 2.13; p=0.016; 15.0 months vs. 29.4 months; p=0.04) [55,56]. Sarcopenia has also been examined in relation to survival and tolerance in patients receiving medical therapy. In those
Table 2. Notable studies investigating the impact of skeletal muscle measurements on perioperative, survival, and treatment-related outcomes in localized, locally advanced, and metastatic renal cell carcinoma

<table>
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| Watanabe et al. 2021 [42]     | Advanced RCC after nephrectomy and IVC thrombectomy (83) | SMI                           | Operative time                         | Sex-specific SMI thresholds                                                  | Operative time: sarcopenia (366 min vs. 372 min; p=0.974)  
EBL: sarcopenia (1,750 mL vs. 1,740 mL; p=0.903)  
Complications: sarcopenia (any grade, 35.2% vs. 27.6%; p=0.482)  
LOS: sarcopenia (11 days vs. 10 days; p=0.148) |                                                                                                                                                                                                           |
| Schmeusser et al. 2023 [43]   | Non-mRCC after nephrectomy and IVC thrombectomy (115) | SMI                           | 90-day high-grade complications        | Sex-specific SMI thresholds                                                  | No association with preoperative sarcopenia (HR, 2.04; 95% CI, 0.66–6.42)                                                                                                                                 |
| Peyton et al. 2016 [44]       | AJCC stage III–IV RCC after RN (128) | PMI                           | EBL, LOS, Clavien grade ≥III complication | Sex-specific cohort quartiles (sarcopenia = bottom quartile)                | EBL: sarcopenia (613 mL vs. 809 mL; p=0.49)  
LOS: sarcopenia (6.0 days vs. 4.7 days; p=0.15)  
Clavien grade ≥III complication: sarcopenia (18% vs. 5%; OR, 4.2; p=0.03)                                                                                                                                 |
| **Survival outcomes in localized RCC** |                                  |                               |                                        |                                                                               |                                                                                                                                                                                                          |
| Psutka et al. 2016 [46]       | Non-mRCC after RN (387)           | SMI                           | 5-yr CSS, OS                          | Sex-specific SMI thresholds                                                  | CSS: sarcopenia (79% vs. 85%; HR, 1.70; p=0.047)  
OS: sarcopenia (65% vs. 74%; HR, 1.48; p=0.039) |                                                                                                                                                                                                           |
| Noguchi et al. 2020 [48]      | Localized ccRCC in males (116)    | PMI                           | 5-yr RFS                              | Cohort median threshold for PMI                                             | RFS: Low PMI (HR, 2.31; p=0.022)                                                                                                                                                                      |
| Mao et al. 2021 [49]          | Localized RCC after PN or RN (443) | SMI, PMI                       | 5-yr CSS, OS                          | Sex-specific SMI, PMI thresholds                                            | OS: sarcopenia (SMI-HR, 2.9; p<0.001) & (PMI-HR, 2.8; p<0.001)  
CSS: sarcopenia (SMI-HR, 2.6; p=0.009) & (PMI-HR, 2.2; p=0.031) |                                                                                                                                                                                                           |
| Lee et al. 2022 [47]          | pT1-2 RCC after RN (632)          | SMI                           | 10-yr CSS, OS                         | Sex-specific SMI thresholds                                                  | OS: sarcopenia (HR, 2.58; p=0.045)  
CSS: sarcopenia (HR, 3.07; p=0.006) |                                                                                                                                                                                                           |
| Midenberg et al. 2023 [50]    | Localized RCC after PN or RN (473) | SMI, Albumin                   | 10-yr RFS, CSS, OS                    | Sex-specific SMI threshold Albumin <3.5 g/dL                                 | OS: Sarcopenia + hypoalbuminemia (HR, 2.62; p<0.001)  
RFS: Sarcopenia + hypoalbuminemia (HR, 2.42; p=0.003)  
CSS: Sarcopenia + hypoalbuminemia (HR, 2.98; p=0.007)  
No association between sarcopenia alone and OS, RFS, or CSS |                                                                                                                                                                                                           |
| Darbas et al. 2020 [29]       | Localized RCC in overweight patients (96) | BMI, SMI, VAT, SAT, IMAT       | 5-yr DFS & OS                         | Obesity-BMI ≥30.0 kg/m²                                                  | DFS: no associations between BC parameters  
OS: no associations between BC parameters |                                                                                                                                                                                                           |
| Makino et al. 2023 [51]       | Non-mRCC after PN or RN (239)     | PMI                           | 10-yr OS, CSS, MFS                    | Optimal cutoff analysis for PMI                                            | OS: Sarcopenia (HR, 2.58; p=0.030)  
MFS: Sarcopenia (HR, 1.18; p=0.628)  
CSS: No significant association with sarcopenia (p=0.207) |                                                                                                                                                                                                           |

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<tr>
<td>Fukushima et al. 2016</td>
<td>mRCC at initial diagnosis (92)</td>
<td>SMI</td>
<td>3-yr OS</td>
<td>Sex-specific SMI thresholds</td>
<td>OS: Sarcopenia (31% vs. 73%; HR, 2.58; p=0.015)</td>
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<tr>
<td>Sharma et al. 2015</td>
<td>mRCC after CN (93)</td>
<td>SMI</td>
<td>OS</td>
<td>Sex-specific SMI thresholds</td>
<td>OS: Sarcopenia (7 mo vs. 23 mo; HR, 2.13; p=0.016)</td>
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<tr>
<td>Khan et al. 2022</td>
<td>mRCC after CN (158)</td>
<td>SMI, VAT, SAT, IMAT</td>
<td>OS</td>
<td>Sex-specific SMI thresholds</td>
<td>OS: Sarcopenia negatively associated (15.0 mo vs. 29.4 mo; p=0.04)</td>
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<td>Cohort median thresholds for other BC measures</td>
<td>No significant associations with adiposity parameters</td>
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<tr>
<td>Lee et al. 2021</td>
<td>mRCC receiving sunitinib (78)</td>
<td>SMI</td>
<td>PFS, OS</td>
<td>Sex-specific SMI thresholds</td>
<td>Mean dose reduction: Sarcopenia (20.3% vs. 8.3%; p=0.004)</td>
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<td>PFS: Sarcopenia (HR, 2.62; p=0.001)</td>
<td>OS: Sarcopenia (HR, 1.79; p=0.038)</td>
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<td>Antoun et al. 2010</td>
<td>mRCC receiving sorafenib (55)</td>
<td>BMI, SMI</td>
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<td>DLT: 41% prevalence in sarcopenia + low BMI</td>
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<td>mRCC receiving sunitinib (61)</td>
<td>BMI, SMI</td>
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<td>BMI ≥25.0 kg/m²</td>
<td>DLT: Sarcopenia + low BMI (OR, 4.1; p=0.01)</td>
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<tr>
<td>Aslan et al. 2022</td>
<td>mRCC receiving ICI therapy (62)</td>
<td>SMI, Albumin, NLR</td>
<td>OS, PFS</td>
<td>Cohort median threshold for cachexia index [(SMI x albumin)/NLR]</td>
<td>OS: Sarcopenia (HR, 1.65; p=0.009); High BMI (HR, 0.66; p=0.036)</td>
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<td>OS: Sarcopenia &amp; high BMI after IMDC score adjustment</td>
<td>No association with adiposity parameters and OS</td>
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<tr>
<td>Ged et al. 2022</td>
<td>mRC receiving ICI therapy (705)</td>
<td>BMI, SMI, VAT, SAT</td>
<td>2-yr OS, PFS</td>
<td>BMI ≥25.0 kg/m²</td>
<td>No association with sarcopenia alone or BMI, high BMI after IMDC score adjustment</td>
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<td>No association with sarcopenia + BMI + high BMI after IMDC score adjustment</td>
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<td>Cohort median thresholds for other BC parameters</td>
<td>No association with sarcopenia and BMI in patients with toxicity</td>
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<tr>
<td>Fukushima et al. 2017</td>
<td>mRCC after CN (37)</td>
<td>SMI</td>
<td>3-yr OS</td>
<td>Continuous &amp; % change categorization for SMI</td>
<td>3-yr OS rates: 19% (&gt;5% SMI gain), 76% (stable SMI), 100% (&gt;5% SMI gain)</td>
</tr>
<tr>
<td>Gu et al.2017</td>
<td>mRCC receiving targeted therapy (101)</td>
<td>SMI</td>
<td>PFS, OS</td>
<td>% change in SMI</td>
<td>OS: positive SMI change (HR, 0.92; p=0.001)</td>
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<td></td>
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<td></td>
<td>PFS: &gt;5% SMI loss (HR, 1.744; p=0.024)</td>
<td>OS: &gt;5% SMI loss (HR, 2.387; p=0.006)</td>
</tr>
<tr>
<td>Ozaki et al. 2023</td>
<td>mRCC receiving targeted therapy (57)</td>
<td>PMI</td>
<td>PFS, OS</td>
<td>% change in PMI</td>
<td>PFS: &gt;10% PMI loss (HR, 3.25; p=0.043)</td>
</tr>
<tr>
<td></td>
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<td>OS: &gt;10% PMI loss (HR, 4.95; p=0.011)</td>
<td>OS: &gt;10% PMI loss (HR, 4.95; p=0.011)</td>
</tr>
<tr>
<td>Kazemi-Bajestani et al. 2019</td>
<td>mRCC receiving sunitinib or sunitinib (47)</td>
<td>SMI, PMI</td>
<td>Cardiotoxicity (LVEF fall &gt;10% to absolute &lt;55%)</td>
<td>% change in SM</td>
<td>High TAT associated with toxicity (87.5 vs. 41.0; p=0.02)</td>
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<td></td>
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<td></td>
<td></td>
<td>Sex-specific TAT median threshold</td>
<td>% SMI change greater in patients with toxicity (&gt;7% vs. 0%; p=0.04)</td>
</tr>
</tbody>
</table>

RCC, renal cell carcinoma; IVC, inferior vena cava; SMI, skeletal muscle index; EBL, estimated blood loss; HR, hazard ratio; CI, confidence interval; LOS, length of stay; mRCC, metastatic RCC; AJCC, American Joint Cancer Committee; RN, radical nephrectomy; PMI, psoas muscle index; CSS, cancer-specific survival; OS, overall survival; cccRCC, clear cell RCC; PN, partial nephrectomy; RFS, recurrence-free survival; BMI, body mass index; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; IMAT, intermuscular adipose tissue; DFS, disease-free survival; BC, body composition; MFS, metastasis-free survival; CN, cytoreductive nephrectomy; DLT, dose-limiting toxicity; ICI, immune checkpoint inhibitor; NLR, neutrophil-to-lymphocyte ratio; IMDC, International Metastatic RCC Database Consortium; LVEF, left ventricular ejection fraction; TAT, total adipose tissue.
receiving sunitinib, sarcopenia was associated with a mean dose reduction, and predicted poorer PFS and OS [57]. Low SMI, in conjunction with BMI, increased DLT rates for those receiving sunitinib or sorafenib, which may explain the worse survival outcomes seen in these patients, although it should be noted that SMI alone was not predictive of toxicity [33,34]. Inconsistent evidence has been reported regarding sarcopenia and immunotherapy. Aslan et al. [58] found that sarcopenia alone did not predict outcomes in mRCC patients receiving ICI treatment; however, when markers of inflammation (e.g., albumin and the neutrophil-to-lymphocyte ratio) were included, this new index was significantly predictive of PFS (HR, 2.6) and OS (HR, 4.5). In a separate study, SMI was associated with OS in clear cell RCC (ccRCC) patients receiving ICIs, although this was no longer significant when adjusting for the IMDC score [59]. However, Ged et al. [59] found that tumors from patients with sarcopenia displayed increased angiogenic, inflammatory, and myeloid signals, which warrants further investigation into the interplay between sarcopenia and the efficacy and tolerability of immunotherapy.

Changes in muscle mass over the course of treatment have been a significant focus in the study of metastatic disease. Fukushima et al. [60] further characterized postoperative changes in muscle mass following cytoreductive nephrectomy and found that there was significant variation in 3-year OS between tiers: 19% for >5% SMI loss, 76% for stable SMI, and 100% for >5% gain (p<0.001). In a series of mRCC patients receiving targeted therapy, ≥5% muscle loss demonstrated strong predictive ability for poorer PFS (HR, 1.744; p=0.024) and OS (HR, 2.367; p=0.008) [61]. This was further echoed by Ozaki et al. [62], who found that a loss of muscle mass during treatment with targeted therapy predicted OS, as opposed to a low initial SMI; this change was further associated with a low score on the prognostic nutritional index, indicating that declining nutritional status may account for this change and impact tolerability and overall efficacy. A greater percent loss of SMI has also shown an association with increased cardiotoxicity in patients receiving antiangiogenic therapy [63]. The impact of changes in muscle mass during immunotherapy in mRCC remains relatively underexamined.

4) Other methods of examining muscle

Further methods of examining sarcopenia by including measures of inflammation and muscle quality have proven insightful. Interleukin-6 (IL-6) is an inflammatory tumor cytokine correlated with mortality in RCC and overall muscle mass loss; the combination of IL-6 with low SMI demonstrated the strongest predictive ability for OS (26.1 months vs. not reached, p<0.001) and risk of mortality (HR, 5.95) in a group of stage I-IV ccRCC patients [52,64,65]. When including the modified Glasgow Prognostic Score (mGPS), a metric of inflammation, Higgins et al. found that high-risk patients (with sarcopenia and high mGPS) demonstrated a higher area under the curve in comparison with SSIGN and IMDC scores in predicting 5-year RFS and CSS [66]. Sarcopenia combined with inflammation has shown a strong association with the likelihood of cancer recurrence and death in RCC, along with treatment response. Myosteatosis, as evaluated by SMD, is prognostic for worse OS in multiple malignancies, including RCC [18]. Across cohorts, high SMD has proven to be a protective factor in both localized and advanced-stage RCC, and can help predict improved response to targeted therapies in mRCC [16,67]. The role of myosteatosis in immunotherapy is unclear in RCC, although results have been mixed for other malignancies [7,68].

3. Influence of Fat Measurements

Although BMI is readily measurable, its association with outcomes in kidney cancer is inconsistent. Originally intended to detect fat, BMI fails to account for age, comorbid metabolic conditions, and muscle mass, therefore limiting its interpretation and applicability [10]. Fat measurements are more accurate representations of body composition and demonstrate stronger correlations with cancer development and prognosis [10,12,69]. Table 3 provides a summary of the findings discussed in this section.

1) Perioperative outcomes

Studies that included visceral adiposity along with elevated BMI showed associations with increased operative time and EBL alongside postsurgical complications, LOS, and expenses [25,70]. In 2 studies conducted in Japan and China,
<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort (n)</th>
<th>Study measurement(s)</th>
<th>Outcome(s) of interest</th>
<th>Cutoffs used</th>
<th>Results</th>
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<tbody>
<tr>
<td><strong>Perioperative outcomes</strong></td>
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<tr>
<td>Hagiwara et al. 2012 [25]</td>
<td>T1-3a &lt;10 cm RCC after laparoscopic RN (121)</td>
<td>BMI, VAT, SAT, TAT</td>
<td>Operative time</td>
<td>BMI ≥25.0 kg/m², VAT area ≥100 cm²</td>
<td>Higher BMI (r=0.316, p=0.001) &amp; VAT (r=0.348; p&lt;0.001) showed a correlation with obesity; VAT alone associated with operative time (OR, 3.70; p=0.009)</td>
</tr>
<tr>
<td>Zhai et al. 2018 [70]</td>
<td>AJCC stage I–III ccRCC after RN (76)</td>
<td>BMI, VAT</td>
<td>Operative time</td>
<td>BMI &lt;28.0 kg/m² (Chinese obesity threshold)</td>
<td>Operative time: High VAT (172 vs. 141 min; p=0.012); High BMI (197 min vs. 153 min; p=0.013)</td>
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<td></td>
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<td></td>
<td>EBL, LOS, Complications</td>
<td>VAT area &gt;100 cm²</td>
<td>EBL: High VAT (132 mL vs. 84 mL; p=0.018); High BMI (215 mL vs. 93 mL; p=0.013)</td>
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<tr>
<td></td>
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<td>Total expenses</td>
<td></td>
<td>Complications: High VAT alone (26.9% vs. 4.2%; p=0.045) &amp; High BMI alone (26.9% vs. 4.2%; p=0.045)</td>
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<td></td>
<td>LOS: High VAT alone (8.7 days vs. 7.5 days; p=0.013)</td>
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<td></td>
<td></td>
<td>Total expenses: High VAT ($7.6k vs. $2.7k; p=0.040); High BMI ($8.4k vs. $6.9k; p=0.029)</td>
</tr>
<tr>
<td>Yuge et al. 2015 [71]</td>
<td>Laparoscopic RN (167)</td>
<td>VAT</td>
<td>Operative time</td>
<td>VAT ≥100 cm²</td>
<td>High VAT with nonexpert surgeon (&lt;50 cases/year) associated with prolonged time (HR, 5.15; p=0.004)</td>
</tr>
<tr>
<td>Darbas et al. 2020 [29]</td>
<td>Localized RCC after PN or RN in overweight (96)</td>
<td>BMI, SMI, VAT, SAT, IMAT</td>
<td>Postoperative infections</td>
<td>cohort-specific SMI thresholds for adiposity</td>
<td>No significant associations of BC parameters with perioperative outcomes measured, except BMI ≥30.0 with increased risk of infections and LOS</td>
</tr>
<tr>
<td>Demirel &amp; Dilek 2023 [72]</td>
<td>Localized RCC after PN or RN (210)</td>
<td>SMI, VAT, SAT, IMAT</td>
<td>High-grade complications</td>
<td>Continuous</td>
<td>No associations between BC parameters in patients with versus without HG complications</td>
</tr>
<tr>
<td>Akahata et al. 2013 [28]</td>
<td>T1-2 RCC after laparoscopic RP RN (96)</td>
<td>BMI, anterior perirenal fat distance</td>
<td>Operative time</td>
<td>BMI ≥25.0 kg/m²</td>
<td>Operative time: anterior perirenal fat (r=0.252; p=0.016)</td>
</tr>
<tr>
<td>Gorin et al. 2013 [73]</td>
<td>Localized RCC after MI-PN (257)</td>
<td>BMI, VAT, SAT</td>
<td>Operative time</td>
<td>Continuous fat distances</td>
<td>Continuous fat distances</td>
</tr>
<tr>
<td>Raman et al. 2016 [74]</td>
<td>Localized RCC after RPN (240)</td>
<td>BMI, VAT, SAT, IMAT</td>
<td>Operative time</td>
<td>Continuous BC measurements</td>
<td>All-grade complications: VAT only (OR, 1.05; p=0.005)</td>
</tr>
<tr>
<td>Ioffe et al. 2013 [75]</td>
<td>Localized RCC after MI-PN (118)</td>
<td>VAT, perinephric fat, perinephric to subcutaneous fat ratio</td>
<td>Operative time</td>
<td>Continuous BC measurements</td>
<td>No significant associations with operative time or LOS</td>
</tr>
<tr>
<td>Davidiuk et al. 2014 [76]</td>
<td>Localized RCC after RPN (100)</td>
<td>MAP score</td>
<td>Adherent perinephric fat</td>
<td>Continuous</td>
<td>Presence of adherent fat: MAP score 0 (6%), 1 (16%), 2 (31%), 3-4 (73%), 5 (100%)</td>
</tr>
<tr>
<td><strong>Survival outcomes in localized RCC</strong></td>
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<tr>
<td>Naya et al. 2010 [77]</td>
<td>Localized RCC after PN or RN (117)</td>
<td>VAT</td>
<td>Pathologic features, CSS</td>
<td>Cohort median threshold for VAT</td>
<td>Low VAT associated with advanced disease (AJCC II–IV, p=0.022), microvascular invasion (p=0.026), decreased CSS (p=0.026)</td>
</tr>
<tr>
<td>Maurits et al. 2022 [67]</td>
<td>AJCC Stage I–III RCC (719)</td>
<td>SMI, SMD, VAT, SAT</td>
<td>OS, RFS</td>
<td>Sex-specific median thresholds for BC parameters</td>
<td>OS: low VAT (Men: HR, 1.38; 95% CI, 1.05–1.83) &amp; (Women: HR, 1.67; 95% CI, 1.01–2.78) &amp; RFS: low VAT-Men only (HR, 1.46; 95% CI, 1.03–2.05)</td>
</tr>
<tr>
<td>Park et al. 2014 [78]</td>
<td>Localized RCC after PN or RN (706)</td>
<td>VAT%, VAT, SAT, TAT</td>
<td>RFS</td>
<td>Cohort VAT% Quartiles</td>
<td>RFS: VAT% (lowest quartile: HR, 3.2; p=0.038) &amp; (highest quartile: HR, 4.8; p=0.010)</td>
</tr>
</tbody>
</table>
### Table 3. Notable studies investigating the impact of adipose measurements on perioperative, survival, and treatment-related outcomes in localized, locally advanced, and metastatic renal cell carcinoma (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort (n)</th>
<th>Study measurement(s)</th>
<th>Outcome(s) of interest</th>
<th>Cutoffs used</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaneko et al. 2015 [79]</td>
<td>Localized RCC after PN or RN (285)</td>
<td>VAT</td>
<td>5-yr RFS</td>
<td>VAT area ≥120 cm²</td>
<td>RFS rates: all histologies, low VAT (76.9% vs. 91.3%; p=0.037) Low VAT only predictor of RFS in ccRCC (HR, 1.374; p=0.042)</td>
</tr>
<tr>
<td>Preza-Fernandes et al. 2022 [80]</td>
<td>Localized RCC after PN or RN (137)</td>
<td>SMI, VAT, SAT, perinephric fat</td>
<td>PFS, OS</td>
<td>Cohort tertiles for BC parameters</td>
<td>PFS: high perinephric fat area (HR, 0.3; p=0.019) OS: high perinephric fat area (HR, 0.3; p=0.009)</td>
</tr>
<tr>
<td>Maurits et al. 2022 [82]</td>
<td>AJCC Stage I–IV RCC (1039)</td>
<td>BMI, SMI, VAT, SAT, TAT, VAT%</td>
<td>Pathologic features, TNM stage</td>
<td>10-unit BC parameter increases</td>
<td>Stage IV in males: VAT (OR, 0.93; p&lt;0.001), TAT (OR, 0.95; p&lt;0.001), VAT% (OR, 0.97; p&lt;0.001) Stage IV in females: VAT only (OR, 0.95; p&lt;0.05) No significant associations of body composition with tumor grade</td>
</tr>
<tr>
<td>Tan et al. 2022 [83]</td>
<td>Localized vs. mRCC (188)</td>
<td>BMI, SMI, SAT, VAT</td>
<td>BC differences according to RCC stage</td>
<td>Continuous comparison</td>
<td>VAT: localized vs. mRCC (1986.7 vs. 1523.2 cm³; p=0.020) No associations with other BC parameters and higher-stage RCC</td>
</tr>
<tr>
<td>Thiel et al. 2016 [81]</td>
<td>Localized RCC (456)</td>
<td>MAP score</td>
<td>PFS</td>
<td>Dichotomized MAP score: low (1–3) vs. high (4–5)</td>
<td>PFS: High MAP (HR, 2.20; p=0.032)</td>
</tr>
<tr>
<td>Steffens et al. 2011 [32]</td>
<td>mRCC receiving anti-VEGF therapy (116)</td>
<td>BMI, VAT, SAT</td>
<td>PFS, OS</td>
<td>Cohort median thresholds for BC parameters</td>
<td>PFS: Low VAT (HR, 3.26; p=0.006); Low SAT (HR, 2.66; p=0.010) OS: Low VAT (HR, 2.97; p=0.006); Low SAT (HR, 3.41; p=0.001)</td>
</tr>
<tr>
<td>Ladoire et al. 2022 [84]</td>
<td>mRCC receiving anti-VEGF therapy (113)</td>
<td>BMI, VAT, SAT</td>
<td>PFS, OS</td>
<td>Cohort median thresholds for BC parameters</td>
<td>PFS: High VAT (HR, 3.07; p=0.011); SAT nonsignificant OS: High VAT (HR, 6.26; p=0.001); SAT nonsignificant</td>
</tr>
<tr>
<td>Gu et al. 2015 [85]</td>
<td>aRCC receiving targeted therapy (124)</td>
<td>VAT, SAT</td>
<td>OS</td>
<td>Continuous &amp; sex-specific optimal cutoff analysis</td>
<td>OS: association with higher VAT (HR, 0.981; p=0.002) &amp; higher SAT (HR, 0.987; p=0.048) OS: low VAT only (HR, 2.087; p=0.007)</td>
</tr>
<tr>
<td>Ning et al. 2022 [86]</td>
<td>mRCC receiving anti-VEGF therapy (358)</td>
<td>BMI, VAT, SAT, perinephric fat</td>
<td>PFS, OS</td>
<td>BMI -24.0 kg/m²</td>
<td>PFS: High perinephric fat (HR, 0.78; 95% CI, 0.61–0.98) OS: High perinephric fat (HR, 0.57; 95% CI, 0.35–0.83) No other significant parameter association on multivariable analysis</td>
</tr>
<tr>
<td>Park et al. 2020 [88]</td>
<td>mRCC receiving sunitinib (311)</td>
<td>BMI, SAT</td>
<td>DLT, PFS, CSS</td>
<td>Continuous &amp; Cohort median thresholds for BC parameters</td>
<td>DLT: increasing VAT (OR, 1.013; p=0.029) PFS: Low VAT (13.0 vs. 26.0 months; p=0.006) CSS: No significant associations with body composition</td>
</tr>
<tr>
<td>Kazemi-Bajestani et al. 2018 [83]</td>
<td>mRCC receiving sunitinib or sorafenib (47)</td>
<td>SMI, TAT</td>
<td>Cardiotoxicity (LVEF fall &gt;10% or absolute &lt;55%)</td>
<td>% change in SMI; sex-specific median threshold for TAT</td>
<td>High TAT associated with toxicity (87.5% vs. 41.0%; p&lt;0.02) % SMI change greater in patients with toxicity (-7% vs. 0%; p=0.04)</td>
</tr>
<tr>
<td>Martini et al. 2021 [89]</td>
<td>mRCC receiving ICI therapy (79)</td>
<td>SMI, SAT, IMAT, VAT, TAT</td>
<td>PFS, OS, ORR</td>
<td>Cohort optimal cutoff analysis</td>
<td>Risk score including IMAT, SAT ORR: poor risk (HR, 0.23; p=0.044); low TAT (OR, 0.25; p=0.008)</td>
</tr>
<tr>
<td>Wang et al. 2023 [90]</td>
<td>mRCC receiving ICI therapy (224)</td>
<td>BMI, SMI, VAT, SAT%</td>
<td>PFS, OS</td>
<td>Continuous BC parameters</td>
<td>PFS: SAT% (HR, 0.02; 95% CI, 0.00–0.04) OS: SAT% (HR, 0.08; 95% CI, 0.01–0.72)</td>
</tr>
<tr>
<td>Schmeusser et al. 2023 [87]</td>
<td>T3–4 locally aRCC (141)</td>
<td>MAP Score</td>
<td>PFS, OS</td>
<td>Dichotomized MAP score: low (1–3) vs. high (4–5)</td>
<td>No significant associations between MAP and PFS or OS</td>
</tr>
</tbody>
</table>

RCC, renal cell carcinoma; RN, radical nephrectomy; BMI, body mass index; VAT, visceral adipose tissue; OR, odds ratio; HR, hazard ratio; CI, confidence interval; SAT, subcutaneous adipose tissue; TAT, total adipose tissue; AJCC, American Joint Cancer Committee; ccRCC, clear cell RCC; EBL, estimated blood loss; LOS, length of stay; PN, partial nephrectomy; IMAT, intermuscular adipose tissue; WHO, World Health Organization; SMI, skeletal muscle index; BC, body composition; HG, high-grade; RP, retroperitoneal; MI, minimally invasive; RPN, robotic PN; MAP, Mayo Adhesive Probability; CSS, cancer-specific survival; SMD, skeletal muscle density; RFS, recurrence-free survival; OS, overall survival; PFS, progression-free survival; mRCC, metastatic RCC; VEGF, vascular endothelial growth factor; DLT, dose-limiting toxicity; LVEF, left ventricular ejection fraction; ORR, objective-response rate; ICI, immune checkpoint inhibitor; aRCC, advanced RCC.
elevated VAT was associated with prolonged operative time, increased EBL, longer LOS, and a higher rate of complications in patients undergoing laparoscopic RN for T stage I–III RCC [25,70]. However, in a separate Japanese cohort using the same VAT area cutoff (≥100 cm²), elevated VAT was only associated with prolonged operative time (HR, 5.15; p=0.004) among nonexpert surgeons (<50 laparoscopic RN procedures per year) [71]. Furthermore, Darbas et al. [29] analyzed 96 overweight patients following nephrectomy, and found no association between body composition measures, including VAT and SAT indices (cm²/m²), and the risk of infection or LOS, though this study was limited by its sample size and the inclusion of only overweight patients. In another study examining 210 patients undergoing nephrectomy, no significant difference in fat tissue distribution was found between those with and without high-grade postoperative complications [72].

Given the somewhat inconsistent influence of VAT on complications of nephrectomy, alternative visceral adipose surrogates have been considered. Akaibata et al. [28] found that anterior perirenal fat distance was predictive of higher operative time and EBL during retroperitoneal laparoscopic RN. Among patients undergoing minimally invasive partial nephrectomy (PN), excess intra-abdominal fat, as measured by distance from the posterior renal capsule to abdominal wall, increased the probability of all-grade (OR, 1.05; p=0.005) and grade 3–4 (OR, 1.05; p=0.04) Clavien complications; however, the operative time and LOS were not impacted [73]. These findings were supported by Raman et al. [74], who showed that perinephric fat thickness, including the SAT proportion, posed an increased risk for all complications without affecting EBL, ischemic time, or LOS. Ioffe et al. [75] used perinephric, visceral, and subcutaneous fat thicknesses at pre-specified levels on cross-sectional imaging to categorize 118 patients into low, medium, and high tertiles; however, in this cohort of minimally invasive PN with a single surgeon, none of the measurements were associated with EBL, ischemic time, or postoperative complications. There is moderate support for perinephric fat measurement as a predictor of the risk for postoperative complications, but its association with other perioperative outcomes is uncertain.

Furthermore, the Mayo Adhesive Probability (MAP) score utilizes both quantitative and qualitative perinephric fat measurements to determine the degree of PN complexity [76]. Scores are determined via the degree of perinephric fat stranding, in addition to distances between the posterior renal capsule to the posterior abdominal wall and from the lateral renal capsule in alignment with the renal vein to the abdominal wall. A higher score was strongly predictive of the presence of adherent perinephric fat, and therefore surgical difficulty [76].

2) Localized RCC outcomes

Although elevated visceral adiposity may promote tumorigenesis, it has often been described as a protective factor during localized malignancy treatment [69]. In a cohort of 117 patients undergoing nephrectomy for T1–3 RCC, VAT was significantly lower in patients with microvascular invasion and more advanced disease pathologically, and patients with elevated VAT, based on median cutoff, reported improved CSS [77]. Lee et al. [47] examined over 2000 localized and advanced RCC patients who underwent nephrectomy at a single South Korean institution and found that lower VAT predicted worse CSS (HR, 2.19; p=0.004) and OS (HR, 2.22; p=0.003). This finding was echoed by Maurits et al. in 719 T1–3 non-mRCC patients, finding an association between low VAT and worse OS for both men (HR, 1.38) and women (HR, 1.67) [67]. The percent VAT according to total adipose tissue (TAT) was analyzed by Park et al. [78] in 706 Japanese patients; interestingly, the highest (HR, 3.198, p=0.036) and lowest (HR, 4.760, p=0.010) VAT quartiles were associated with RFS. Furthermore, Kaneko et al. [79] found after curative surgery for localized RCC, patients with VAT <120 cm² exhibited shorter RFS (HR, 1.974; p=0.042), although this was only significant for clear cell histology. Perinephric fat has also been examined given its association with VAT and potential for direct tumor interaction. Preza-Fernandes et al. [80] found that a greater area was associated with improved PFS and OS. MAP was also applied to examine survival outcomes in patients treated surgically for localized RCC. In 456 pT1–T2 patients, Thiel et al. [81] found that high MAP scores (4–5) were associated with decreased PFS (HR, 2.20; p=0.032). Overall, a consistent association has been observed in patients with low visceral adiposity and aggressive, higher-stage kidney tumors with
worse oncological outcomes [82,83].

3) Metastatic and locally advanced RCC outcomes

A study by Steffens et al. [32] at a single German institution among 77 mRCC patients treated with antiangiogenic therapies found that higher VAT was associated with significantly longer PFS (11.5 months vs. 8.4 months, p=0.005) and OS (32.3 months vs. 16.9 months, p=0.04). In contrast, Ladoire et al. [84] reported on 64 French patients receiving antiangiogenic therapy, finding that high VAT was associated with shorter PFS (HR, 3.22) and OS (HR, 6.26). The positive impact of visceral adiposity on survival could be explained by a high nutritional status with resistance to malignancy-associated fat loss or a potential signaling effect from adipose tissue; in contrast, the angiogenic factors produced by adipocytes may promote tumor spread and limit the response to targeted therapy [32,84]. Furthermore, in a series of 124 mRCC patients receiving targeted therapy, higher levels of the continuous VAT (HR, 0.981; p=0.002) and SAT (0.987; p=0.048) indices remained positively associated with OS [85]. In addition, above-median perirenal fat thickness has shown predictive ability for improved OS and PFS in those receiving anti-VEGF therapy [86]. However, Schmeusser et al. [87] also examined the ability of MAP, which include markers of perirenal fat thickness, to predict OS and PFS in localized T3–4 RCC, and found no significant associations. Patients with high perirenal fat thickness had increased angiogenic gene expression, suggesting that this feature may instead aid in drug delivery to the tumor for improved response [86].

The role of adiposity in drug tolerance has also been examined. Across 8 sites in South Korea, a higher VAT index was associated with early-onset sunitinib-induced DLT; however, these patients experienced longer PFS [88]. VAT is a risk factor for fatty liver disease, and Park et al. [88] proposed that this could lower the metabolism of sunitinib, increase concentration, and promote DLT. Further evidence supports this finding, where patients with an above-median TAT index, adjusted by sex, demonstrated increased rates of sorafenib and sunitinib-associated cardiotoxicity [63].

Measurements of fat may play a role in immunotherapy. Martini et al. [89] developed a risk score for mRCC patients receiving ICIs based on body composition metrics, including SAT and IMAT indices; the poor-risk category demonstrated shorter OS (HR, 6.37; p<0.001), PFS (HR, 4.19; p<0.001), and lower clinical benefit (OR, 0.23; p=0.044) than the favorable risk group [89]. Overall, a below-median TAT index was associated with shorter OS, PFS, and lower clinical benefit than patients with a high TAT index. In contrast, Wang et al. [90] analyzed fat composition measurements in relation to survival outcomes in 251 Chinese mRCC patients receiving immunotherapy; only percent SAT was predictive of improved PFS and OS. Fat composition appears to predict immunotherapy responses in mRCC; however, further research is warranted to identify the principal contributing factors and biologic explanations.

FUTURE APPLICATIONS

Body composition has significant implications for perioperative and survival outcomes in patients with RCC. A principal question is whether body composition is practically modifiable to help direct clinical management. Prehabilitation programs aim to improve a patient’s functional status prior to surgery via medical optimization, physical exercise, nutritional supplementation, and psychological support [91]. Evidence suggests that interventions encourage positive muscle and fat changes [92,93]. A recent study of surgical patients randomized to a preoperative program involving activity, pulmonary function, nutrition, and mindfulness [94] reported significant reductions in postoperative mortality and need for discharge to a nursing facility [94]. However, in a review of prehabilitation exercises before prostate, bladder, and kidney cancer surgery, although presurgical fitness measures improved, no impact was observed on complications, mortality, LOS, or readmission rates [95].

The influence of prehabilitation programs on survival outcomes remains unexplored in RCC. In general, physical inactivity is associated with increased likelihood of death from kidney cancer [96]. Indeed, regular exercise may help prevent cancer development and improve treatment outcomes in patients with cancer diagnoses [97,98]. There may also be a prognostic role for diet in cancer-related outcomes, although existing studies vary widely and are dominated by select cancers [99,100]. Traditionally healthy diets may decrease RCC incidence, but further research is
needed to characterize the impact of nutrition throughout the disease course [101].

The early evidence for prehabilitation before and during other cancer treatments is encouraging. Halliday et al. [92] found, in a study of patients undergoing multimodal therapy for esophageal cancer, that exercise was feasible, mitigated SMI loss, and reduced VAT, leading to a lower risk of complications. In a separate study of 40 esophageal cancer patients receiving neoadjuvant chemotherapy, the exercise prehabilitation group experienced greater tumor regression and downstaging, possibly due to a decreased inflammatory response [102]. The physiological effects of exercise may reduce inflammation and limit muscle loss while promoting a decline in VAT. Visceral adiposity may represent nutritional status or the degree of disease aggressiveness; therefore, unintentional loss could indicate worsening oncologic outcomes, whereas intentional loss may correlate with improving health status and inflammation. Similar methodology is needed to evaluate the potential benefits and biological implications of prehabilitation programs for patients with RCC.

CONCLUSIONS

Accurate body composition measurements beyond BMI for patients with kidney cancer have become increasingly feasible and clinically accessible. Strong evidence supports low muscle mass as a predictor of shortened survival outcomes in both localized and advanced RCC; the prognostic utility becomes even stronger when combined with markers of inflammation and malnutrition. Fat quantity and quality measurements hold significant roles in prognosticating perioperative outcomes as well. Decreased visceral adiposity has been shown to negatively impact survival in patients with localized and advanced RCC; however, this may be reflective of nutritional status and the degree of tumor aggressiveness. Strategies aimed at maximizing these metrics hold significant promise in improving outcomes for RCC patients.

NOTES

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