Muscle mass change using linear measurement analysis after nephrectomy for pT3 and pT4 renal cell carcinoma is associated with mortality

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Abstract

Background Preoperative skeletal muscle deficiency is an established risk factor for poor survival outcomes in patients with renal cell carcinoma (RCC). However, given the dynamic nature of skeletal muscle associated with malignancy, there is a need to evaluate the prognostic benefit of muscle area change from the preoperative to postoperative period. We hypothesize that an improvement in muscle area following nephrectomy, measured by linear segmentation of L3 psoas and paraspinal musculature, is associated with improvement in overall survival (OS) and cancer specific survival (CSS) for patients with pT3 and pT4 RCC.

Methods We retrospectively analysed 270 pT3 and pT4 RCC patients who underwent nephrectomy from March 2004 to February 2020 with available preoperative and postoperative axial CT or MRI studies segmented at the L3 vertebrae. The majority were N0 (79%) and M0 (68%). Psoas and paraspinal muscles were measured bilaterally using a validated digital ruler tool. Total muscle area (TMA) was calculated by aggregating the area of all four muscles and total muscle area index (TMI) by dividing the TMA by height squared (m²). The prognostic value of postoperative muscle improvement, defined as any increase in muscle area index, was analysed using Kaplan–Meier and Cox proportional stepwise hazard models.

Results Median time between preoperative scans and surgery was approximately 22 days and between surgery and postoperative scans 172 days. One hundred twenty-one patients (44.8%) had an increase in total muscle area index post-nephrectomy (IQR = 33.4; \(P \leq 0.0001\)). On Kaplan–Meier analysis, postoperative improvement in TMI was associated with decreased odds of mortality (\(P = 0.0024\)) with a median follow-up of 38.6 months. In a multivariable Cox regression analysis, improvement of TMI was associated with increased OS (HR = 0.52, 95% CI 0.35–0.78, \(P < 0.001\)) and increased CSS (HR = 0.55, 95% CI 0.32–0.94, \(P = 0.030\)). A 5% or more improvement in TMI was also associated with increased OS (HR = 0.53, 95% CI 0.34–0.84, \(P = 0.006\)) and increased CSS (HR = 0.46, 95% CI 0.24–0.86, \(P = 0.015\)).

Conclusions Any improvement in TMI between preoperative and initial postoperative imaging after nephrectomy was associated with increased OS and CSS in patients with pT3 and pT4 RCC. Perioperative linear segmentation is an efficient tool that may improve current prognostication methods and can be performed on any imaging software platform.

Keywords Muscle area recovery; Renal cell carcinoma; Linear measurement analysis; RCC prognostication

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Introduction

Renal cell carcinoma (RCC), currently the ninth most frequently diagnosed malignancy in the USA, has more than doubled in incidence in the developed world over the past half-century. While radical or partial nephrectomy is the gold standard for managing localized RCC, recurrence rates post-nephrectomy are high with 30% of RCC patients eventually developing metastases and succumbing to their disease. Given the insidious and aggressive nature of this disease, there is a growing interest in identifying prognostic factors to tailor treatment, improve patient counselling, and direct clinical decision making.

Importantly, its ability to accurately assess skeletal muscle deficiency correlates well with conventional methods. However, this gold standard metric requires specialized training, expensive software, and is time consuming, all of which may potentially disturb the clinical workflow. By contrast, measuring the linear area of the lumbar psoas and paraspinal musculature offers a reliable substitute, as it can be quickly performed and only requires a digital ruler tool found in virtually all radiologic software programs. Importantly, its ability to accurately assess skeletal muscle deficiency correlates well with conventional methods.

It has been widely established that preoperative skeletal muscle deficiency is associated with adverse outcomes in patients with various malignancies, including RCC, bladder cancer, and urothelial carcinoma. However, these studies fail to consider the dynamic nature of skeletal muscle change during cancer and its associated treatments, and how continuous degeneration or potential recovery may influence a patient’s clinical trajectory. Studies that have evaluated postoperative muscle restoration have demonstrated its prognostic capability, but by contrast, have been among patients undergoing extirpative surgery for malignancies other than those of renal origin, such as pancreatic, periampullary, non-small cell lung, gastric, and oesophageal cancer. By contrast, to our knowledge, only one study thus far has investigated the prognostic effects of skeletal muscle recovery in surgical RCC patients. In this study, a positive preoperative to postoperative change in skeletal muscle index was associated an increase in overall survival in metastatic RCC patients undergoing cytoreductive nephrectomy. Nonetheless, these findings have not yet been validated among non-metastatic RCC patients nor among a larger sample size. Furthermore, while body composition analysis using gold standard metrics has shown potential value in the prognostication of urologic cancer patients, the use of linear segmentation for this purpose is poorly elucidated.

This study aims to build on the current body of literature to evaluate whether a dynamic preoperative to postoperative recovery in muscle area is associated with increased survival outcomes among patients with pT3 and pT4 RCC. Linear segmentation, which as aforementioned confers several benefits compared to more traditional cross-sectional methods of muscle measurement, will be used to quantify muscle area. We hypothesize that a dynamic preoperative to postoperative recovery in psoas and paraspinal muscle area is associated with an improvement in overall survival for pT3 and pT4 RCC patients undergoing nephrectomy.

Methods

Patient demographics

We retrospectively analysed a cohort of 270 patients with either pT3 or pT4 RCC who underwent partial or radical nephrectomy between March 2004 and February 2020. Inclusion criteria for the study were (i) histologically confirmed diagnosis of pT3 or pT4 RCC of any histology, (ii) a preoperative computerized tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis within 90 days prior to surgery, and (iii) a post-operative image within one year following surgery. We used postoperative images within one year given that this was a clinically practical duration of time during which postoperative images were most likely to be obtained. Given that our cohort is comprised of only patients with either locally advanced or metastatic disease, the purpose of the postoperative imaging was as an active surveillance measure and for early detection of metastatic disease.

Covariates of interest included preoperative patient-specific data including age, gender, race, body mass index (BMI; kg/m²), Eastern Cooperative Oncology Group (ECOG) score, and Charlson Comorbidity Index (CCI). Postoperative tumour data included TNM staging, Fuhrman grade, Stage, Size, Grade, and Necrosis (SSIGN) score, and tumour size, as determined by the longest tumour diameter recorded in the pathology report. The 8th edition of American Joint Committee on Cancer (AJCC) staging system for renal tumour classification was used for pathologic staging. This study received Institutional Review Board approval.

Linear segmentation

Preoperative and postoperative axial CT or MRI studies were segmented at the mid-level of the third lumbar vertebrae, as
done in previous studies. The skeletal muscle surface area at this lumbar level has been found to be the strongest correlate of total skeletal muscle mass. Linear segmentation was performed using the detailed protocol described by Avrutin et al. and was completed by two trained observers (E.M. and M.H.) following training and requiring <1% interobserver variability. Each observer was blinded to patient history and outcomes. Horos™ Imaging Software was used to measure the length and width of the individual psoas and paraspinal muscles at their longest and widest points, respectively. This was performed by orienting the vertical and horizontal digital ruler tool at an intersecting angle of approximately 90° or by using the rectangular tool function, which measures the same dimensions and ensures the 90° angle is met (Figure 1). In this study, the rectangular tool was used. To account for potential inaccuracies in linear segmentation measurements in patients not perfectly oriented during their imaging study, psoas and paraspinal measurements were obtained at their longest and widest points in their vertical and horizontal orientation (Figure 2).

Individual psoas and paraspinal muscle areas were calculated in cm² by multiplying muscle length and width. Total muscle area (TMA) was calculated by aggregating the area of all four muscle groups. The total muscle index (TMI) was calculated by dividing the TMA by height in m². Changes in muscle area relative to surgery was determined by subtracting the preoperative muscle area from the postoperative muscle area, with a positive number indicating muscle recovery.

**Statistical analysis**

The primary exposure was the improvement in muscle area after surgery, defined as a (i) binary variable (any muscle recovery vs. no muscle recovery) and as (ii) three-level categorical variables based on postoperative percentage change in total muscle area index. The three categorical groups included those with a 5% or more decrease in muscle area, a 5% or more increase in muscle area, and a change in muscle area ranging from −5% to +5%, all between preoperative and postoperative time points. The choice of 5% as a cut-off was two-fold; to be able to provide patients with an approximate clinical threshold of risk in addition to having enough patients in our cohort to compare between groups. Our primary outcome was overall survival (OS), and our secondary outcome measure was cancer-specific survival (CSS). OS was defined as the time from surgery to death from any cause. Cancer-specific survival (CSS) was defined as the duration from the date of surgery until death due to RCC.
Differences in patient and clinical characteristics were tested with a generalized chi-square test or Fisher’s exact test for categorical variables and a Wilcoxon rank-sum test for continuous variables. The effect of preoperative to postoperative changes in muscle index on OS and CSS were analysed using the Kaplan–Meier (KM) method. Univariable models were fitted to observe the effect of age at time of surgery, sex, race, BMI, TNM staging, ECOG status, tumour length, Fuhrman grade, and necrosis. These covariates were selected a priori based on widespread acceptance as prognostic factors. After interaction assessment, we fit multivariable Cox proportional stepwise regression models for both OS and CSS. All statistical tests were two-sided with type I error set at 0.05. All analyses were performed using SAS version 9.4 (Cary, NC, USA).

Results

The study cohort included 270 patients with pT3 and pT4 RCC with a median follow-up of 38.6 months after surgery. Most patients were male (n = 191, 70.7%) with a mean age of 61.2 years (±11.5) at the time of surgery, and a mean BMI of 29.4 (±7.2). Most patients had M0 (n = 184, 68.1%) and Fuhrman grade 3–4 (n = 325, 88.3%) disease. There was a median of 25 days between preoperative scans and surgery (Q1–Q3: 11–36) and a median of 172 days between surgery and postoperative imaging (Q1–Q3: 116–225) (Table 1).

Table 1 Sample characteristics of overall analytical cohort (n = 270)

| Covariate                        | N (%) |
|----------------------------------|-------|
| Age at surgery (years)*          | 61.2 ± 11.5 |
| Female                           | 79 (29.3) |
| Race                             |       |
| White                            | 202 (74.8) |
| Black                            | 53 (19.6) |
| Other                            | 11 (4.1) |
| Unknown                          | 4 (1.5) |
| Preoperative ECOG status 1 or more| 61 (22.6) |
| Obesity (BMI 30 kg/M or more)    | 104 (38.5) |
| BMI*                             | 28.4 (16.9–75) |
| Clear cell RCC histology         | 212 (78.5) |
| Necrosis on histology            | 185 (68.5) |
| Fuhrman grade 3–4 disease        | 235 (88.3) |
| Clinical M1 at surgery           | 86 (31.9) |
| Maximum 1D length of tumour (pathologic)* | 9.4 (0.9–27) |
| Preoperative scan to surgery (days)* | 22 (0–90) |
| Surgery to post-op scan (days)*  | 162.5 (28–357) |
| Improvement in total muscle area index after surgery | |
| No                               | 149 (55.2) |
| Yes                              | 121 (44.8) |
| Percent change in total muscle area index after surgery | |
| Gain more than 5%                | 88 (32.6) |
| Within –5 to +5%                 | 72 (26.7) |
| Loss of more than 5%             | 110 (40.7) |

*Mean ± Std.
*Median (min-max).

Of the 270 patients, 121 patients (44.8%) had a significant improvement in total muscle area index (TMI) post-nephrectomy [Median (Q1–Q3): −0.6 (−17–12); P ≤ .001], while 149 patients (55.2%) experienced a loss of muscle area post-nephrectomy. Of the total cohort, 110 patients (40.7%) experienced a loss of more than 5% in muscle area, whereas 88 (32.8%) patients experienced a 5% increase in muscle area. The remaining 72 patients (26.7%) experienced a change ranging from −5% to +5%. The mean change in TMI was −0.6 (±4.6). On Kaplan–Meier analysis, postoperative improvement in TMI was associated with increased OS (P = 0.0024; Figure 3A) and well as increased CSS (P = 0.0118; Figure 3B). A 5% or more increase in TMI was associated with increased OS (P = 0.0005; Figure 3C) and well as increased CSS (P = 0.0028; Figure 3D).

On univariable analysis, an improvement in TMI was significantly associated with increased OS and CSS, while pathologic M1 and N1 stage, ECOG status ≥1, clear cell RCC histology, and a SSIGN score of 3–5 were significantly associated with decreased OS and CSS (Supporting Information, Table S1). Table 2 provides the results of multivariable stepwise COX proportional regression analysis. An increase in TMI after nephrectomy was associated with increased OS (HR = 0.52, 95% CI 0.35–0.78, P = 0.001), while ECOG Status ≥1 (HR = 2.05, 95% CI 1.35–3.10, P < 0.001), and pathologic M1 stage (HR = 2.46, 95% CI 1.70–3.57, P < 0.001) were associated with decreased OS. These findings were replicated when total muscle index change was evaluated as a categorical percent change: a 5% or more increase in TMI independently predicted increased OS (HR = 0.53, 95% CI 0.34–0.84, P = 0.006) and increased CSS (HR = 0.55, 95% CI 0.32–0.94, P = 0.030). Simultaneously, ECOG status ≥1 (HR = 2.16, 95% CI 1.26–3.70, P = 0.005), pathologic N1 (HR = 1.82, 95% CI 1.06–3.15, P = 0.031) and M1 stage (HR = 3.13, 95% CI 1.86–5.29, P < 0.001) were associated with decreased CSS. Additionally, a 5% or more reduction in TMI was associated with decreased CSS (HR = 2.16, 95% CI 1.26–3.70, P = 0.005).

Discussion

The findings from this study demonstrate that an improvement of total muscle area index was associated with an approximate two-fold increased odds of survival (HR = 0.52, 95% CI 0.35–0.78, P = 0.001). Similarly, a 5% or more increase in total muscle area index also independently predicted improved OS (HR = 0.53, 95% CI 0.34–0.84, P = 0.006) in patients with pT3 and pT4 ccRCC. Importantly, these relationships persisted while adjusting for established predictive factors, such as age, sex, BMI, ECOG status, N and M-stage, necrosis, and grade. This finding is particularly relevant given that the majority of related research has concentrated on the prognos-
tic utility of pre-existing skeletal muscle deficiency, placing less emphasis on the evaluation of preoperative to postoperative muscle kinetics.15 Our study demonstrated strength of effect for both OS and CSS outcomes using linear analysis, which has been previously validated as highly correlated with total cross-sectional area using traditional standard methods.14,17 To our knowledge, only one study has evaluated the effects of preoperative to postoperative skeletal muscle kinetics on survival outcomes in patients with RCC. Fukushima et al.’s retrospective study of 37 metastatic RCC patients undergoing cytoreductive nephrectomy found postoperative improvements in skeletal muscle area to be

### Table 2 Multivariable model summary of Cox hazard model overall survival

| Covariate                                      | Overall survival time (months) | Cancer specific survival (months) |
|------------------------------------------------|-------------------------------|---------------------------------|
|                                                | Hazard ratio (95% CI)         | HR P-value                      |
|                                                |                               | Hazard ratio (95% CI)           | HR P-value |
| Improvement in total muscle area index after surgery |                               | 0.001                           | 0.030     |
| Yes                                            | 0.52 (0.35–0.78)              |                                 |           |
| No                                             | Ref                           |                                 |           |
| Percent change in total muscle area index after surgery |                               | 0.006                           | 0.015     |
| Gain more than 5%                              | 0.53 (0.34–0.84)              |                                 |           |
| Within –5 to +5%                               | 0.43 (0.27–0.68)              | <0.001                          | 0.002     |
| Loss of more than 5%                           | Ref                           |                                 |           |

Multivariable COX proportional stepwise final models evaluating any improvement in total muscle area as a binary variable were simultaneously adjusted for ECOG status and clinical M-stage for overall survival and cancer specific survival models. Multivariable Cox proportional stepwise final models evaluating percentage change in total muscle area as a categorical variable were simultaneously adjusted for age at time of surgery >60 years of age, ECOG status and clinical N-stage and M-stage for overall survival and cancer specific survival models.

Figure 3 Kaplan–Meier survival curve demonstrating the protective effect of preoperative and postoperative muscle recovery on RCC patients undergoing nephrectomy. (A) Improvement in total muscle area index and overall survival. (B) Improvement in total muscle area index and cancer specific survival. (C) Percent change in muscle area index and overall survival. (D) Percent change in muscle area index and cancer specific survival.

(A) Improvement in Total Muscle Area Index

(B) Improvement in Total Muscle Area Index

(C) Change in muscle area index after surgery

(D) Percent change in muscle area index and overall survival. (D) Percent change in muscle area index and cancer specific survival.
significantly predictive of overall survival (HR 0.92; \( P < 0.001 \)).\textsuperscript{12} Our findings build on Fukushima 	extit{et al.}'s important study by similarly demonstrating the protective effect of postoperative skeletal muscle area improvement. Notably, however, our study provides validation with a larger sample size, among metastatic and nonmetastatic RCC patients, and by using linear measurement analysis rather than traditional cross-sectional methods of muscle measurement.

The finding that postoperative muscle recovery can have significant impact on survival translates to the importance of not only preoperative, but also postoperative multimodal methods to target sarcopenia prevention and muscle mass improvement. There is a need for more robust studies regarding the efficacy of these multimodal methods, some of which have been shown to be beneficial among various malignancies,\textsuperscript{10,18} including physical exercise, vitamin D or omega-3 fatty acid dietary supplementation.\textsuperscript{15,19–22} Future studies should be directed at how these interventions may influence indicators of morbidity and mortality among patients treated for ccRCC.

In addition to highlighting the importance of postoperative interventions to preserve muscle quality and mass, our findings also have important clinical implications given that the linear measurement of total psoas and paraspinal area is a quick and efficient way to assess body composition. In contrast to the traditional methods of manually measuring skeletal muscle area, linear measurements can be quickly performed and only require a digital ruler tool found in virtually all radiologic software programs. Furthermore, the ability of linear measurements to accurately assess skeletal muscle deficiency correlates well with conventional methods.\textsuperscript{14,15} This type of muscle compositional assessment composition could be incredibly useful in the clinical setting because its integration into daily clinical practice may not impede workflow.

Limitations of our study include its retrospective nature as well as the heterogeneity in timing of postoperative imaging. However, we hypothesize that the potential effect of this bias is mitigated given that the most recent preoperative image was taken for each patient and that no image was taken more than one year postoperatively.

## Conclusions

An improvement of muscle area index, as indicated by a positive change in muscle area from pre-nephrectomy to post-nephrectomy, is an independent predictor of OS and CSS in pT3 and pT4 RCC. While it has already been widely acknowledged that preoperative muscle decomposition can predict long term outcomes in local RCC patients,\textsuperscript{15} our findings from this study indicate that the improvement in muscle recovery in the postoperative period can have profound effects on patient outcomes for those with locally advanced disease. Perioperative linear segmentation can efficiently measure muscle area without disturbing the clinical workflow in comparison with time consuming gold standard metrics and in doing so, improve current prognostication methods.

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## Conflict of interests

The authors declare there are no competing interests.

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## Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Univariable associations of overall survival and cancer specific survival in analytical cohort.

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