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ORIGINAL ARTICLE

Early Skeletal Muscle Loss in Non-Small Cell Lung Cancer Patients Receiving Chemoradiation and Relationship to Survival

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Abstract

Purpose Sarcopenia is associated with reduced survival in cancer. Currently, data on sarcopenia at presentation and muscle loss throughout treatment are unknown in patients receiving chemoradiation therapy (CRT) for non-small cell lung cancer (NSCLC). This study evaluated skeletal muscle changes in NSCLC patients receiving CRT and relationship with survival.

Methods Secondary analysis of 41 patients with NSCLC treated with CRT assessed for skeletal muscle area and muscle density by computed tomography pre-treatment and 3 months post-treatment. Images at week 4 of treatment were available for 32 (78%) patients. Linear mixed models were applied to determine changes in skeletal muscle over time and related to overall survival using Kaplan-Meier plots.

Results Muscle area and muscle density decreased significantly by week 4 of CRT (− 6.6 cm^2, 95% CI − 9.7 to − 3.1, $p < 0.001$; − 1.3 HU, 95% CI − 1.9 to − 0.64, $p < 0.001$, respectively), with minimal change between week 4 of CRT and 3 months post-CRT follow-up (− 0.2 cm^2, 95% CI − 3.6–3.1, $p = 0.91$; − 0.27, 95% CI − 0.91–0.36, $p = 0.36$, respectively). Sarcopenia was present in 25 (61%) and sarcopenic obesity in 6 (14%) of patients prior to CRT, but not associated with poorer survival. Median survival was shorter in patients with low muscle density prior to treatment although not statistically significant (25 months $\pm$ 8.3 vs 53 months $\pm$ 13.0, log-rank $p = 0.17$).

Conclusion Significant loss of muscle area and muscle density occurs in NSCLC patients early during CRT. A high proportion of patients are sarcopenic prior to CRT; however, this was not significantly associated with poorer survival.

Keywords Non-small cell lung cancer · Body composition · Muscle loss · Sarcopenia · Nutrition

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Introduction

In the past decade, there has been an increasing focus on investigating sarcopenia, a condition characterised by loss of skeletal muscle mass, in patients with cancer. Studies across multiple tumour types report rates of sarcopenia on initial presentation of 25% in breast cancer, [1] 47% in non-small cell lung cancer (NSCLC) [2] and up to 57% in gastrointestinal cancers [3–5]. This is in the context of an increasing proportion of patients presenting as overweight or obese at commencement of cancer treatment where the presence of sarcopenia may not be immediately apparent, despite multiple studies revealing that sarcopenia is present across all BMI categories [1, 2]. Sarcopenia is associated with reduced survival and an increased likelihood of dose-limiting chemotherapy toxicities [1, 5–8]. While sarcopenic obesity, a condition where sarcopenia and obesity coexist, is associated with poorer functional status and is an independent predictor of survival [8, 9].

Studies investigating sarcopenia in NSCLC have focused on patients with advanced disease receiving chemotherapy [2, 8–10]. Radiotherapy, with or without concurrent chemotherapy, is frequently used for the treatment of stage III NSCLC or inoperable stage I or II NSCLC [11]. Previous reports have demonstrated a substantial proportion of NSCLC patients treated with radiotherapy experience involuntary weight loss of $\geq$ 5%, and this has long been associated with poorer outcomes [12–14]. Recently, it has been shown that patients with involuntary weight loss of > 5% in the first 3 weeks of chemoradiation therapy (CRT) for NSCLC have significantly poorer survival [15]. However, measuring weight loss alone may not capture underlying muscle loss and it is the extent of muscle loss that is associated with increased morbidity and reduced survival. Currently, there is limited data on sarcopenia on presentation or the trajectory of skeletal muscle loss over the course of CRT in patients with NSCLC.

The ready availability of computed tomography (CT) scans as part of the medical management of cancer has led to an increase in their use for the assessment of skeletal muscle and has become a robust technique to analyse body composition at the tissue level [16]. In patients with NSCLC, positron emission tomography (PET)/CT scans are acquired prior to treatment for diagnostic and staging purposes and for tumour response evaluation following treatment completion. Their use at other time points for body composition assessment is precluded by the high radiation dose generated. Our team identified a unique opportunity for analysis of skeletal muscle at a mid-treatment time point (when patients would not normally have a routine scan) as part of a secondary analysis of a study investigating interim tumour response in patients with NSCLC receiving CRT. Developing an understanding of the trajectory of skeletal muscle changes over the course of CRT will support the development of multi-modal nutrition and exercise programs to minimise muscle loss and the associated consequences in patients with NSCLC.

The objective of this study was to evaluate the trajectory of skeletal muscle changes in NSCLC patients receiving CRT and the relationship with survival.

Materials and methods

This was a secondary analysis of a prospective study of 60 patients with NSCLC which investigated the associations between interim tumour responses on ^{18}F-flurodeoxyglucose (^{18}F-FDG) PET/CT and ^{18}F-fluoro-thymidine (^{18}F-FLT) PET/CT and patient outcomes including progression-free survival and overall survival. Approval to conduct the study was granted by the Institutional Research and Ethics committees (ACTRN 12611001283965), all patients provided written, informed consent and the methodology for the original study has previously been described [17, 18].

Patients

Patients were recruited between 2008 and 2013 at the Peter MacCallum Cancer Centre. Eligibility criteria included a histologically or cytologically confirmed stage I–III NSCLC, an Eastern Cooperative Oncology Group performance status of 0 to 1, < 10% pre-treatment weight loss and suitability for curative intent CRT. Patients were excluded if they had received previous thoracic radiotherapy or had complete surgical tumour excision, and for the secondary analysis, if the scans did not extend inferiorly to include the third lumbar vertebrae, which is the landmark required for skeletal muscle analysis.

Treatment

All patients received concurrent CRT according to two standard protocols consisting of 60 Gy in 30 fractions over 6 weeks. Patients received one of two chemotherapy protocols delivered intravenously: (1) weekly cisplatin and paclitaxel (45 mg/m^2) or (2) cisplatin (50 mg/m^2) on days 1, 8, 29 and 36 and etoposide (50 mg/m^2) during weeks 1 and 5.

Image and body composition analysis

Routine PET/CT scans were taken for diagnostic or staging purposes (baseline) and treatment evaluation (follow-up) on one of two scanners (GE STE, GE Medical Systems Milwaukee, WI or Biograph, Siemens Medical Solutions, Erlangen, Germany). In addition to these routine scans, a study PET/CT was taken at week 4 of radiotherapy after 38 Gy $\pm$ 4 Gy. Median time between the baseline and week 4 scan was 43.4 days. Median time between the baseline and follow-up scan was 149.6 days. Weight (kg) and height (m) were obtained at each PET/CT scan. The CT component of scans was acquired in helical mode at 140 kV, using an automatically variable mA dependent on patient size (40–150 mA). Images were reconstructed with slices of thickness 3.75 mm. Data was transferred via the picture archiving and communication system (PACS, Siemens Healthcare, Malvern, PA, USA) to specialised medical imaging analysis software MIM (version 6.3.2, MIM Software Inc., Cleveland, OH, USA). Muscle attenuation measured in Hounsfield Units (HU) and skeletal muscle cross-sectional area (cm^2) were analysed from the mean of two axial images at the third lumbar vertebrae as the standard landmark by trained observers using the Alberta Protocol [19, 20]. Skeletal muscle area (cm^2) was identified and quantified within a HU range of − 19 to 150 and normalised for height (m^2) to determine the skeletal muscle index (SMI, cm^2/m^2) by a single observer. Muscle density was measured from muscle attenuation (HU). Sarcopenia was defined as SMI < 41cm^2 in women, < 43cm^2 in men with a body mass index (BMI) < 24.9 kg/m^2 and < 53 cm^2 in men with a BMI $\geq$ 25 kg/m^2 according to reference values [8]. Low muscle density was defined as < 41 HU in men and women with a BMI < 24.9 kg/m^2 and < 33 HU in men and women with a BMI ≥ 25 kg/m^2 [8]. Absolute and relative change (%) in weight, muscle density and muscle area at week 4 and follow-up were determined from baseline. Weight loss of > 5% [21] and muscle area loss of ≥ 6cm^2 were considered clinically important [22].

Survival

Survival time (months) was calculated from the day of the baseline PET/CT until death or the close out date of December 4, 2015. The observer who completed the skeletal muscle analysis was blind to the survival status of participants.

Data analysis

Data analysis was conducted using SPSS version 24 (IBM SPSS, Chicago, IL, USA). Descriptive statistics were used to summarise the demographic and medical characteristics of the sample. Linear mixed models were fitted to each body composition variable (weight, muscle area, muscle density) to determine the effect over time for all 41 patients and accounted for missing data at week 4 in nine patients. Models were estimated by maximum likelihood and using a compound symmetry covariance type among repeated measures. Overall survival was estimated using the Kaplan-Meier method and log-rank test to determine the effect of sarcopenia at the baseline scan, low muscle density at the baseline scan, involuntary weight loss of > 5% between the baseline scan and week 4 and follow-up scans and muscle loss of ≥ 6cm^2 between the baseline scan and week 4 and follow-up scans. Cox regression analysis was performed, using the covariates age, gender, disease stage, sarcopenia at baseline, low muscle density at baseline, > 5% weight loss and ≥ 6 cm^2 muscle loss between baseline and follow-up. Alpha was set at 0.05 (two-tailed) for all analysis.

Results

Forty-one patients of the original 60 patients were included, representing 68% of the original cohort. Reasons for exclusion included no follow-up scan performed (*n* = 10), treatment altered to palliative (*n* = 7), declined week 4 and follow-up scan (n = 1) and excessive artefact for calculation (*n* = 1). In 32 of these 41 (78%) patients, assessable images at L3 were also available at the week 4 scan. The mean age was 65 years, the majority had stage III disease and were predominantly male (Table 1). At baseline, over half of the patients were either overweight or obese (*N* = 25, 61%); whereas, only 3 (7%) were underweight. However, sarcopenia was present in 25 (61%) and low muscle density in 17 (41%). Of the eight (19%) patients who were obese, all were male and 6 (14% of the full cohort) had sarcopenic obesity. Nutritional characteristics at baseline are described in Table 2.

Table 1 Participant characteristics at baseline (*N* = 41)

Characteristic	Full cohort	Males *n* = 29	Females *n* = 12
Age (years)			
Mean	65.6	69.3	56.7
SD	10.6	8.7	9.7
Gender, *n* (%)			
Males	29 (71)	–	–
Females	12 (29)	–	–
Overall stage, *n* (%)			
1a	1 (2)	1 (2)	0 (0)
1b	0 (0)	0 (0)	0 (0)
2a	4 (10)	3 (8)	1 (2)
2b	1 (2)	1 (2)	0 (0)
3a	17 (42)	15 (37)	2 (5)
3b	18 (44)	9 (22)	9 (22)
4	0 (0)	0 (0)	0 (0)

Relative weight and muscle loss

In total, six (14.6%) patients experienced > 5% weight loss by week 4 of CRT and 11 (27%) by the follow-up scan. Muscle loss of ≥ 6cm^2 had occurred in 16 (39%) patients by the week 4 scan and 22 (54%) patients by the follow-up scan. At

Table 2 Nutritional characteristics at baseline (*N* = 41)

Characteristic	Full cohort
Height (m)	
Mean	1.71
SD	0.11
Weight (kg)	
Mean	79.6
SD	20.7
BMI (kg/m^2)	
Mean	27.1
SD	5.8
BMI category (kg/m^2), *n* (%)	
< 20	3 (7)
20.0 to 24.9	13 (32)
25 to 29.9	17 (41)
≥ 30	8 (20)
SMI < reference value[a], *n* (%)	25 (61)
Muscle density < reference value[a], *n* (%)	17 (41)
Sarcopenic obesity, *n* (%)	6 (14)

[a] Reference values from Martin et al. [8]

BMI, body mass index; *SMI*, skeletal mass index baseline, 25 (61%) patients were sarcopenic increasing to 35 (85%) by the follow-up scan. Seventeen (41%) patients had low muscle density at baseline, increasing to 22 (54%) patients by the follow-up scan. There was a significant positive correlation between change in weight (%) and change in muscle area (%) between baseline and week 4 (Spearman's rho = 0.49, $p = 0.004$) and between baseline and follow-up (Spearman's rho = 0.37, $p = 0.02$).

Trajectory of weight and skeletal muscle changes

The trajectory of weight, muscle area and muscle density changes are described in Tables 2 and 3. There was a significant decrease in weight between baseline and follow-up (− 2.1 kg, $p = 0.02$) but not between baseline and week 4 (− 1.3 kg, $p = 0.12$) or week 4 and follow-up (0.71 kg, $p = 0.39$). Loss of skeletal muscle area was both statistically significant and clinically important between baseline and follow-up (− 6.6 cm^2, $p < 0.001$) and baseline and week 4 (− 6.4 cm^2, $p < 0.001$) but not between week 4 and follow-up (− 0.2 cm^2, $p = 0.91$). A significant reduction in muscle density was observed between baseline and follow-up (− 1.5 HU, $p < 0.001$) and baseline and week 4 (− 1.3 HU, $p < 0.001$), but not between week 4 and follow-up (− 0.27 HU, $p = 0.91$). For each variable, weight, muscle area and muscle density, the largest losses occurred between the baseline and week 4 scans with minimal change occurring between week 4 and follow-up.

Survival

By the close out date, 23 (56%) patients had died. There was a trend toward shorter median survival in patients who had low muscle density at the baseline scan (25 months, 95% CI 8.9 to 41.1) compared to those with a normal muscle density (53 months, 95% CI 27.4 to 78.6); however, this did not reach statistical significance (log-rank $p = 0.13$; Fig. 1). Median survival did not differ between patients with sarcopenia at baseline compared to those who were not sarcopenic, who had > 5% weight loss between baseline and week 4 or baseline and follow-up. Likewise, median survival did not differ between patients who lost ≥6 cm^2 muscle area between baseline and week 4 or baseline and follow-up. This did not change with regression analysis (Table 4).

Discussion

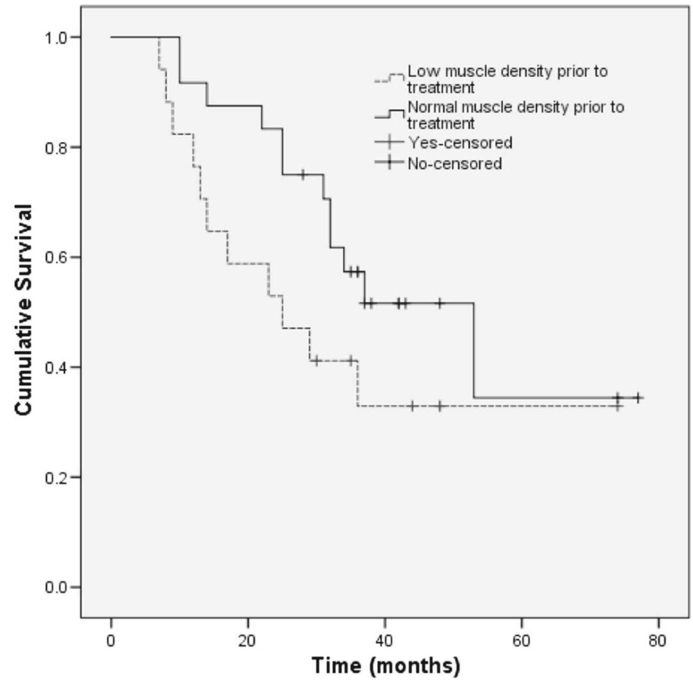
Sarcopenia on presentation and skeletal muscle loss throughout treatment have long been recognised as important indicators of nutritional status in patients with cancer [12, 23, 24]. Recently, there has been a growth in studies reporting on the negative impact of sarcopenia on survival, coinciding with an

Table 3 Change in body composition parameters in lung cancer patients treated with chemoradiation therapy ($N = 41$)

Variable	Time 1 (prior to RT)		Time 2 (week 4 of RT)		Time 3 (3 months post-RT)		Change between time 1 to time 2			Change between time 1 to time 3			Change between time 2 to time 3		
	Mean	SE	Mean	SD	Mean	SD	Mean difference[a]	95% CI	*P*	Mean difference[a]	95% CI	*P*	Mean difference[a]	95% CI	*P*
Body weight (kg)	79.6	3.1	78.0	3.1	77.5	3.1	− 1.6	− 3.5 to 0.25	0.09	− 2.1	− 3.7 to − 0.36	0.02	0.44	− 2.3 to 1.4	0.64
Muscle area (cm^2)	129.8	5.0	123.4	5.1	123.2	5.0	− 6.4	− 9.7 to − 3.1	< 0.001	− 6.6	− 9.6 to − 3.6	< 0.001	− 0.2	− 3.6 to 3.1	0.91
Muscle density (HU)	35.9	1.4	34.6	1.4	34.4	1.4	− 1.3	− 1.9 to − 0.64	< 0.001	− 1.5	− 2.1 to − 0.97	< 0.001	− 0.27	− 0.91 to 0.36	0.39

[a] Estimated marginal means were used for mean and standard error at each time point

RT, radiotherapy; *SE*, standard error; *SD*, standard deviation



Patients at risk

	0	20	40	60	80
Low muscle density	17	10	4	0	0
Normal muscle density	24	20	7	1	0

Fig. 1 Kaplan-Meier survival curve of patients with low muscle density prior to starting treatment compared to those with normal muscle density

increased emphasis and quantification of skeletal muscle as a parameter within international definitions and frameworks for the classification of malnutrition and cachexia [21, 25, 26]. The majority of the research has been completed in patients with advanced disease receiving chemotherapy [4, 8, 9]. To our knowledge, this is the first study to report on skeletal muscle changes from images at multiple time points in NSCLC patient receiving CRT.

Recognising malnutrition and cachexia and implementing appropriate nutritional management is an increasing challenge in the age of obesity. The traditional picture of the malnourished or cachectic patient with cancer presenting with a low BMI and muscle wasting is becoming less and less common. More than half of the patients in our study were overweight or obese on presentation, with only 7% categorised as underweight. Despite this, sarcopenia was present in almost two thirds (61%) of patients. Our observations are consistent with previous studies of advanced cancer patients treated with chemotherapy, with the prevalence of overweight and obesity ranging from 40 to 63% while the proportion of patients who present underweight may be as few as 3% [4, 8, 10, 27]. However, the prevalence of sarcopenic obesity in our study was higher than previous reports; 6 of 8 (75%) obese patients were classified as sarcopenic, in contrast to studies by Prado et al. (2008), of 15% prevalence and Blauwhoff-Buskermolen et al. (2016), of 20% prevalence [4, 9]. This may be due to the differences in the treatment modality in our study, concurrent CRT compared to chemotherapy alone in previous studies or related to the small sample size. Further, both previous studies included patients with gastrointestinal tumours with a substantial proportion experiencing large weight loss prior to treatment potentially reducing the number of obese patients in the cohort. Sarcopenia and sarcopenic obesity are both independently associated with poorer survival highlighting the increasing importance of identifying patients with sarcopenia and the need for intervention [8, 9].

An area of recent interest is the detrimental impact of early weight loss on survival. A study of 151 patients diagnosed with NSCLC by Sanders et al. [15] demonstrated that patients experiencing more than 5% weight loss in the first 3 weeks of CRT experienced significantly shorter survival ($p = 0.017$) [15] Such weight loss occurred in a time frame typically before the onset of acute treatment-related toxicities, such as oesophagitis, which may affect nutritional intake. We observed that a significant reduction in muscle area and muscle density occurred in a similarly early time period, by week 4 of CRT, with minimal reductions thereafter. Importantly, the magnitude of mean weight change was relatively small up to week 4 of CRT, 1.3 kg or 1.6% of baseline weight, in comparison to the magnitude of mean muscle area loss of 6.4 cm^2 or 5% of baseline muscle area over an average 6-week period. It has previously been reported that people with cancer experience substantially more rapid muscle loss than that which occurs during the normal ageing process [4]. A recent study

Table 4 Multivariate analysis for predictors of overall survival

Variable	HR	95% CI	*P*
Age	0.97	0.92 to 1.03	0.35
Gender			
Male	1		
Female	1.33	0.37 to 4.80	0.66
Disease stage			
1a	1		
2a	1.96	0.18 to 21.23	0.62
2b	0.54	0.06 to 4.04	
3a	0.00	0.00 to 0.00	
3b	1.92	0.71 to 5.20	
Sarcopenia at baseline			
Yes	1		
No	0.66	0.23 to 1.95	0.45
Low muscle density at baseline			
Yes	1		
No	1.60	0.58 to 4.41	0.36
> 5% weight loss from T1 to T3			
Yes	1		
No	1.62	0.58 to 4.46	0.36
$\geq$ 6cm^2 muscle loss from T1 to T3			
Yes	1		
No	0.75	0.26 to 2.17	0.59

by Blauwhoff-Buskermolen et al. [4], demonstrated the severe consequences of muscle loss during chemotherapy where muscle loss of 9% or greater over a period of 3 months was independently associated with poorer survival in colorectal cancer patients [4]. Like Blauwhoff-Buskermolen et al., our study found patients were losing clinically and statistically significant muscle area during active cancer treatment. Further, in our study, this occurred during curative intent treatment and early in the treatment course. In contrast to the findings of Buskermolen et al., we found no association with muscle loss during active cancer treatment and overall survival. The potential reasons for this difference may include the small sample size of our study, different treatment modality or that patients in our study were suitable for curative intent treatment.

Visually on the Kaplan-Meier plots, there appears to be poorer survival in patients with low muscle density prior to treatment. However, this did not reach statistical significance which may be related to the small sample size or the aforementioned differences in the patient group. Previous studies have consistently demonstrated an association between low muscle density and reduced survival across a range of tumour types, albeit in patients receiving chemotherapy alone [4, 7, 8]. We did not observe poorer survival in patients who were sarcopenic prior to treatment. Of the studies previously investigating the impact of sarcopenia on survival, the majority reported poorer survival in patients with sarcopenia [1, 5, 8, 9]. However, there are some studies which have also failed to find an association between sarcopenia and reduced survival [4, 7]. The variability in findings may be related to the diversity of disease stages, tumour and treatment types across these studies.

The phenomenon of muscle loss occurring early in the CRT treatment period observed in our study, as well as the association of early weight loss with survival in previous studies, suggests that the early treatment or pre-treatment period may be the most important time to deliver interventions to minimise muscle loss. In various cancer types, personalised nutrition counselling has been shown to improve physical function and nutritional status [28]. Likewise, exercise interventions across multiple cancer types have been shown to improve physical functioning and muscle strength and may have the ability to prevent muscle loss [29, 30]. Multi-modal cancer rehabilitation programs encompassing nutrition and exercise interventions report improvements in performance status, strength, shortness of breath, fatigue and nutritional status [31–33]. However, these programs are targeted toward patients with existing functional and nutritional decline. There is a need to investigate the efficacy of delivering nutrition and exercise interventions to prevent or minimise muscle loss in the early stages of CRT for NSCLC.

Strengths of this study lie in the homogenous patient population and the unique opportunity to investigate skeletal muscle from computed tomography at a mid-treatment time point. The original trial, from which this study was a secondary analysis, did not collect data on pre-treatment weight loss and therefore although eligible patients were required to have < 10% pre-treatment weight loss; we were unable to investigate any impact of weight loss prior to commencement of CRT which is a limitation of this work. A further limitation of the study is the small sample size and results require confirmation in a larger sample.

In conclusion, our study suggests that significant muscle loss and reduction in muscle density occur early in the course of CRT for NSCLC. Further, a high proportion of patients present with sarcopenia, sarcopenic obesity and low muscle density prior to commencement of CRT. However, low muscle density and sarcopenia prior to treatment, and muscle loss over the course of CRT, were not significantly associated with reduced survival. Future research is required to confirm these findings in a larger sample and to investigate the efficacy of combined nutrition and exercise interventions to prevent or minimise early muscle loss.

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Statement of authorship NK participated in the design of the study, performed the statistical analysis, interpretation of results and drafted the manuscript. JB participated in data collection, interpretation of results and writing the manuscript. SE participated in the design of the study, interpretation of results and writing the manuscript.

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Compliance with ethical standards

Approval to conduct the study was granted by the Institutional Research and Ethics committees (ACTRN 12611001283965), all patients provided written, informed consent.

Conflict of interest The authors declare that they have no conflict of interest.

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