An in-depth analysis on the effects of body composition in patients receiving neoadjuvant chemotherapy for urothelial cell carcinoma

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Cite as: MacDonald L, Rendon RA, Thana M, et al. An in-depth analysis on the effects of body composition in patients receiving neoadjuvant chemotherapy for urothelial cell carcinoma. *Can Urol Assoc J* 2024 February 15; Epub ahead of print. http://dx.doi.org/10.5489/cuaj.8542

Published online February 15, 2024

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ABSTRACT

Introduction: Neoadjuvant chemotherapy (NAC) is the standard of care for patients undergoing radical cystectomy (RC) for muscle-invasive bladder cancer (MIBC); however, NAC can be associated with significant side effects and morbidity in some patients. NAC may contribute to sarcopenia, obesity, and the combination of the two. Our study examined the effects of NAC on body composition and the association between body composition and adverse events.
Methods: We created a retrospective database of patients with non-metastatic MIBC receiving NAC prior to RC. The change in skeletal muscle index (SMI) and fat mass index (FMI) was calculated using computed tomography (CT) scans done within three months prior to NAC and after the first two cycles. The association between body composition (sarcopenia, obesity, and sarcopenic obesity) and preoperative adverse events was investigated using a multivariable logistic regression. Changes in body composition were calculated using a paired Student's t-test.
Results: A total of 70 patients were included in our study. There was a mean decrease in SMI of 2.2±3.2 cm^2/m^2. Adiposity and FMI were unchanged by NAC. Sarcopenic obesity was found to be associated with adverse events among patients receiving NAC in the multivariable analysis.

KEY MESSAGES

- Neoadjuvant chemotherapy is associated with significant morbidity.
- Neoadjuvant chemotherapy increases rates of sarcopenia.
- Sarcopenic obesity is associated with higher-grade adverse events.
- Body composition should be considered when deciding on neoadjuvant chemotherapy.

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There were a total of 637 preoperative complications with grades 1–2 and 33 complications with grades 3–5.
Conclusions: Based on our retrospective cohort study, NAC did not affect obesity and FMI, but there was a significant decrease in SMI. Sarcopenic obesity was associated with increased severity of NAC adverse events. As such, the presence of this factor may help predict tolerance of NAC.

INTRODUCTION

Among patients with muscle invasive bladder cancer (MIBC), the standard of care is neoadjuvant chemotherapy followed by radical cystectomy (RC) with bilateral pelvic lymph node dissection. A 2005 meta-analysis demonstrated that NAC was associated with an absolute improvement in overall survival (OS) of 5% at 5-years, compared to local treatment only.[1] Despite this improvement in OS, NAC is associated with toxicity that can lead to morbidity and potentially delayed definitive treatment in some patients.[2] Predicting which patients will not tolerate NAC is challenging.[3]

Sarcopenia is defined as the loss of skeletal muscle with associated decreased strength. It can contribute to patients' overall frailty[4] and is correlated with disability, lower quality of life, and even death.[5] Multiple studies have linked sarcopenia with inferior outcomes in cancer patients. Specific to urothelial carcinoma, cancer-specific survival (CSS) and OS following RC is negatively affected by sarcopenia.[6–9] It is currently not known if NAC tolerability is affected by sarcopenia.

Because sarcopenia, sarcopenic obesity, and frailty are correlated, we hypothesized that these patients would have increased rates of NAC adverse events (AEs) due to decreased physiologic reserve. In addition, we hypothesized that NAC would worsen skeletal muscle index (SMI) and therefore increase the rate of sarcopenia. The present study describes the results of body composition analysis using a retrospective cohort of patients with MIBC who underwent NAC prior to RC.

METHODS

After receiving approval from the local research ethics committee (NSHA REB 1024534), a retrospective database was created consisting of patients with MIBC who underwent RC by one of three uro-oncologists between 2013 and 2018. Patients with cN1 or greater were excluded from our analysis. Patient demographics, details of neoadjuvant chemotherapy, and post-operative course following RC were documented.

Computed tomography (CT) scans are not routinely performed after completion of NAC at our institution. For each patient staging CT scans, done prior to and during NAC administration (usually after two cycles), were obtained as DICOM files. Determination of body composition was completed by one member of the data analysis team using SliceOmatic version

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5.0 (Tomovision, Magog, Canada). This software uses attenuation data from DICOM files to give an estimate of skeletal muscle surface area.

Skeletal muscle surface area at the L3 level was calculated by measuring the tissue surface area within the following muscles with attenuation limits of -29 to 150 HU: rectus abdominus, internal oblique, external oblique, and lateral oblique, psoas, quadratus lumborum, and erector spinae muscles. SMI was calculated using:

$$\text{SMI}\left(\frac{\text{cm}^2}{\text{m}^2}\right) = \frac{\text{Surface area of muscle at L3}}{\text{height}^2}$$

Sarcopenia was defined as <55 cm^2/m^2 for men, and <39 cm^2/m^2 for women.[10]

Measurements of fat mass index were calculated by using the equation proposed by Mourtzakis et al which was developed to convert measurements of cross sectional adipose area at the L3 level to fat mass (FM).[11] This methodology has been used previously in studies of bladder cancer.[12] The fat mass index was calculated for each patient by dividing FM by height in meters squared:

$$\text{FMI}\left(\frac{\text{kg}}{\text{m}^2}\right) = \frac{\left(0.042\ \frac{\text{kg}}{\text{cm}^2}\right)(\text{Surface area of adipose tissue at L3}[\text{cm}^2]) + 11.2}{\text{height}^2}$$

Patients were then classified as obese or non-obese by using the National Health and Nutrition Examination Survey (NHANES) standards for obesity (FMI >13kg/m^2 for women, and FMI >9kg/m^2 for men).[13] SMI and FMI were calculated for each patient at two specific times: the staging CT scan prior to NAC, and a follow-up CT scan after two rounds of NAC used to measure response. Statistical significance in SMI and FMI changes were calculated between each CT scan using a paired student's t-test. Patients were classified as having sarcopenic obesity (SO) if they reached the cut-off values for both sarcopenia and obesity.

As part of routine follow up, after each round of NAC, patients met with specialized oncology nurses who meticulously documented the number, type, and grade of AEs using the Common Terminology Criteria for Adverse Events (CTCAE). AE data was extracted from these standardized assessments. Post-operative outcomes included in the database were length of hospital stay, number of transfusions received, and highest Clavien-Dindo complication.

After confirming that the data was normally distributed (D'Agostino and Pearson's test), changes in body composition were calculated using a paired student's t-test. Clinical characteristics were compared using descriptive statistics. A logistic regression was performed to predict factors that contribute to the presence of grade 3 or higher AEs. A stepwise regression strategy (significance of at least 0.10 on univariable analysis) was employed to determine the factors included in the multivariable logistic regression, which included patient characteristics, disease stage, and body composition.

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RESULTS

Seventy patients were included in our study. Cohort demographic data is shown in Table 1. The average patient age was 65, with 83 percent being male. The average BMI was 28 kg/m^2. Most patients (71%) had cT2 pathology prior to NAC. The average time between CT scans was 69 days. NAC consisted of gemcitabine/cisplatin for 68 patients (97%), with the remaining two patients receiving carboplatin/gemcitabine.

Table 2 summarizes the body composition changes of the cohort. Most patients were sarcopenic (54%) at baseline. Of the males, 32 (55%) were sarcopenic with an average SMI of 54.6 cm^2/m^2. Six female patients (50%) were sarcopenic with an average SMI of 41.2 cm^2/m^2. The mean reduction of SMI after two rounds of NAC was 2.2 cm^2/m^2 (median reduction of 3.4%), this was statistically significant ($p<0.001$). Figure 1 shows the distribution of SMI changes using a violin plot.

Thirty-six (51%) of patients were obese with an average FMI of 9.72 kg/m^2 (males: 9.74 kg/m^2, females: 9.61 kg/m^2) prior to initiating NAC. The mean increase in FMI between CT scans was 0.03 kg/m^2 and was not statistically significant ($p = 0.78$). Figure 1 shows the distribution of FMI changes. Fifteen (21%) of patients were classified as having SO prior to NAC, this increased to 17 (24%) following NAC.

Table 3 summarizes adverse events associated with NAC. In total, there were 670 documented toxicities. Outcomes of the logistic regression are found in Table 4. To control for comorbidities and performance status, ASA score was included in the logistic regression. The presence of high-grade AEs (greater than or equal to CTCAE grade 3) were significantly increased by the presence of SO.

Using linear regression, obesity was predictive of increased length of hospital stay, increased transfusions, and higher Clavien-Dindo complications. This result did not hold true when performing a multivariable analysis; body composition was not associated with any increased risk of worse post-operative outcomes.

DISCUSSION

Our study shows that SMI decreases after initiating NAC for MIBC, however, measures of obesity are unaffected. Higher grade adverse events were correlated with the presence of SO.

The rate of sarcopenia in BC patients ranges from 25 – 69%.[14] Sarcopenia is known to negatively affect overall survival, cancer-specific survival and all-cause mortality following RC.[6–9] Five-year OS decreases by up to 31% for sarcopenic patients.[8] Sarcopenia also predicts 90-day mortality and postoperative complications following RC.[15,16] Furthermore, NAC has been shown to cause a measurable decrease in SMI of 3 – 8.4%.[17,18] In our study, we hypothesized that NAC is associated with increased chances of a decrease in SMI, and that sarcopenic patients would have a higher number and grade of adverse events associated with NAC (prior to RC).

We found a median change in SMI of -3.4% in 70 patients which is consistent with published values for patients receiving cisplatin-based chemotherapy prior to RC. One retrospective review calculated the change in SMI in 30 patients before and after receiving NAC.

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They found a median SMI decrease of 3%, with 73.3% of the patients experiencing some decrease in SMI.[18] Another study found a median decrease of 8.4% in SMI attributed to NAC. The authors also concluded that SMI was not associated with downstaging after NAC and RC.[17] Another retrospective study examined the relationship between NAC and SMI using 26 patients. The authors found a median decrease of 6.4%.[19] Finally, psoas muscle volumes were measured in 60 patients undergoing NAC prior to RC. A decline of 4.9% in psoas muscle volume was found and was associated with NAC dose reductions, although there were no surgical outcomes affected by this decrease.[20]

The effects of sarcopenia on NAC toxicity have been studied in other cancers but not BC specifically. For example, cisplatin-based NAC was associated with higher rates of serious adverse events in patients with esophageal cancer.[21] Because body surface area (BSA) is used to calculate dosing of chemotherapy agents, sarcopenic patients have less lean body mass to metabolize chemotherapy, theoretically leading to a higher incidence of toxicity.[22] Our study found that the presence of sarcopenia, specifically sarcopenic-obesity, increased the chances of having higher grade adverse events (CTCAE grade 3 and higher). The combination of sarcopenia and obesity may have a synergistic effect on toxicity; when sarcopenia and obesity were used as separate variables in the logistic regression, neither were strong predictors of higher-grade AEs.

SO, specifically, has been shown to negatively affect overall survival, recurrence free survival, disease free survival, and cancer specific survival for many different cancers.[23] It is theorized that SO worsens these outcomes due to increased metabolic derangements, increased surgical complications, and decreased tolerance to chemotherapy.[24,25] Chemotherapy toxicity associated with SO has conflicting evidence. SO increased the risk of dose limiting toxicity for patients receiving neo-adjuvant chemotherapy for esophageal cancer.[26] Another study found that patients with SO had increased rates of hematologic toxicity when being treated with FOLFIRINOX chemotherapy.[27] However, SO was not found to be associated with toxicity for patients treated with palliative chemotherapy for esophageal cancer.[28]

Several limitations to the current study are worth mentioning. First, the observational design of this study lends it to potential selection bias, whereby more robust individuals were selected to receive NAC. Only patients who went on to receive a RC were included in our database. Second, we were unable to control the interval between CT scans, introducing inaccuracy in measuring the impact of NAC on sarcopenia. The CT scans are performed midway through the chemotherapy course; therefore, we are not capturing effects of chemotherapy on sarcopenia later in the treatment course. Third, we relied on adverse events as a measure of the impact of NAC, whereas sarcopenia may impact other factors such as quality of life that we could not capture with this study design. Fourth, our design is unable to determine if reverse causality is playing a role in our analysis, meaning that the adverse events may be the cause of changes in body composition. Finally, given the relatively small number of patients and events, our model may be over-specified to the data and must therefore be interpreted with caution.

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CONCLUSIONS

A significant proportion of patients with BC undergoing NAC have pre-existing sarcopenia and were found to have a further decline in skeletal muscle mass throughout chemotherapy. Sarcopenic obesity was associated with higher grade adverse events, even when compared to sarcopenia or obesity alone. As such, the presence of this factor may help predict tolerance of NAC.

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REFERENCES

1. Advanced bladder cancer (ABC) meta-analysis collaboration: Neoadjuvant chemotherapy in invasive bladder cancer: Update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. *Eur Urol* 2005;48:202-6. https://doi.org/10.1016/j.eururo.2005.04.006
2. Jan AS, Dolan DE, Lombardi K, et al. Tolerability of gemcitabine plus cisplatin for treatment of urothelial cancer in the elderly population. *Clin Genitourin Cancer* 2016;14:e257-63. https://doi.org/10.1016/j.clgc.2015.09.003
3. Lee L, Cheung WY, Atkinson E, et al. Impact of comorbidity on chemotherapy use and outcomes in solid tumors: A systematic review. J Clin Oncol 2011;29:106-17. https://doi.org/10.1200/JCO.2010.31.3049
4. Rizzoli R, Reginster J-Y, Arnal J-F, et al. Quality of life in sarcopenia and frailty. *Calcif Tissue Int* 2013;93:101-20. https://doi.org/10.1007/s00223-013-9758-y
5. Santilli V, Bernetti A, Mangone M, et al. Clinical definition of sarcopenia. *Clin Cases Miner Bone Metab* 2014;11:177-80. https://doi.org/10.11138/ccmbm/2014.11.3.177
6. Yamashita S, Iguchi T, Koike H, et al. Impact of preoperative sarcopenia and myosteatosis on prognosis after radical cystectomy in patients with bladder cancer. *Int J Urol* 2021;28:757-62. https://doi.org/10.1111/iju.14569
7. Mayr R, Gierth M, Zeman F, et al. Sarcopenia as a comorbidity-independent predictor of survival following radical cystectomy for bladder cancer. *J Cachexia Sarcopenia Muscle* 2018;9:505-13. https://doi.org/10.1002/jcsm.12279
8. Psutka SP, Carrasco A, Schmit GD, et al. Sarcopenia in patients with bladder cancer undergoing radical cystectomy: Impact on cancer-specific and all-cause mortality. *Cancer* 2014;120:2910-18. https://doi.org/10.1002/cncr.28798
9. Hirasawa Y, Nakashima J, Yunaiyama D, et al. Sarcopenia as a novel preoperative prognostic predictor for survival in patients with bladder cancer undergoing radical cystectomy. *Ann Surg Oncol* 2016;23:1048-54. https://doi.org/10.1245/s10434-016-5606-4
10. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: An international consensus. *Lancet Oncol* 2011;12:489-95. https://doi.org/10.1016/S1470-2045(10)70218-7
11. Mourtzakis M, Prado CMM, Lieffers JR, et al. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* 2008;33:997-1006. https://doi.org/10.1139/H08-075
12. Psutka SP, Boorjian SA, Moynagh MR, et al. Mortality after radical cystectomy: Impact of obesity versus adiposity after adjusting for skeletal muscle wasting. *J Urol* 2015;193:1507-13. https://doi.org/10.1016/j.juro.2014.11.088
13. Kelly TL, Wilson KE and Heymsfield SB. Dual energy X-ray absorptiometry body composition reference values from NHANES. *PLoS One* 2009;4:e7038. https://doi.org/10.1371/journal.pone.0007038
14. Hansen TTD, Omland LH, von Heymann A, et al. Development of sarcopenia in patients with bladder cancer: A systematic review. *Semin Oncol Nurs* 2021;37:151108. https://doi.org/10.1016/j.soncn.2020.151108

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15. Mayr R, Fritsche H-M, Zeman F, et al. Sarcopenia predicts 90-day mortality and postoperative complications after radical cystectomy for bladder cancer. *World J Urol* 2018;36:1201-7. https://doi.org/10.1007/s00345-018-2259-x
16. Gao J, Shi Y, Zhou D, et al. Sarcopenia as an independent predictor for venous thromboembolism events in bladder cancer patients undergoing radical cystectomy. *Support Care Cancer* 2022;30:1191-8. https://doi.org/10.1007/s00520-021-06423-2
17. Lyon TD, Frank I, Takahashi N, et al. Sarcopenia and response to neoadjuvant chemotherapy for muscle-invasive bladder cancer. *Clin Genitourin Cancer* 2019;17:216-22.e5. https://doi.org/10.1016/j.clgc.2019.03.007
18. Mari A, D'Andrea D, Kimura S, et al. Sarcopenia as a predictive factor for response to upfront cisplatin-based chemotherapy in patients with muscle-invasive urothelial bladder cancer. *Urol Int* 2018;101:197-200. https://doi.org/10.1159/000489013
19. Rimar KJ, Glaser AP, Kundu S, et al. Changes in lean muscle mass associated with neoadjuvant platinum-based chemotherapy in patients with muscle invasive bladder cancer. *Bladder Cancer* 2018;4:411-8. https://doi.org/10.3233/BLC-180188
20. Zargar H, Almassi N, Kovac E, et al. Change in psoas muscle volume as a predictor of outcomes in patients treated with chemotherapy and radical cystectomy for muscle-invasive bladder cancer. *Bladder Cancer* 2017;3:57-63. https://doi.org/10.3233/BLC-160080
21. Huang C-H, Lue K-H, Hsieh T-C, et al. Association between sarcopenia and clinical outcomes in patients with esophageal cancer under neoadjuvant therapy. *Anticancer Res* 2020;40:1175-81. https://doi.org/10.21873/anticanres.14060
22. Baracos VE and Arribas L. Sarcopenic obesity: Hidden muscle wasting and its impact for survival and complications of cancer therapy. *Ann Oncol* 2018;29:ii1-9. https://doi.org/10.1093/annonc/mdx810
23. Gao Q, Hu K, Gao J, et al. Prevalence and prognostic value of sarcopenic obesity in patients with cancer: a systematic review and meta-analysis. *Nutrition* 2022;101:111704. https://doi.org/10.1016/j.nut.2022.111704
24. Gortan Cappellari G, Brasacchio C, Laudisio D, et al. Sarcopenic obesity: What about in the cancer setting? *Nutrition* 2022;98:111624. https://doi.org/10.1016/j.nut.2022.111624
25. Carneiro IP, Mazurak VC and Prado CM. Clinical implications of sarcopenic obesity in cancer. *Curr Oncol Rep* 2016;18:62. https://doi.org/10.1007/s11912-016-0546-5
26. Anandavadivelan P, Brismar TB, Nilsson M, et al. Sarcopenic obesity: A probable risk factor for dose limiting toxicity during neo-adjuvant chemotherapy in oesophageal cancer patients. *Clin Nutr* 2016;35:724-30. https://doi.org/10.1016/j.clnu.2015.05.011
27. Kurita Y, Kobayashi N, Tokuhisa M, et al. Sarcopenia is a reliable prognostic factor in patients with advanced pancreatic cancer receiving FOLFIRINOX chemotherapy. *Pancreatology* 2019;19:127-35. https://doi.org/10.1016/j.pan.2018.11.001
28. Dijksterhuis WPM, Pruijt MJ, van der Woude SO, et al. Association between body composition, survival, and toxicity in advanced esophagogastric cancer patients receiving palliative chemotherapy. *J Cachexia Sarcopenia Muscle* 2019;10:199-206. https://doi.org/10.1002/jcsm.12371

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FIGURES AND TABLES

Figure 1. Violin plots showing distribution of the change in (a) skeletal muscle index (SMI); and (b) fat mass index (FMI). Solid lines denote the mean and extremes of the distribution.

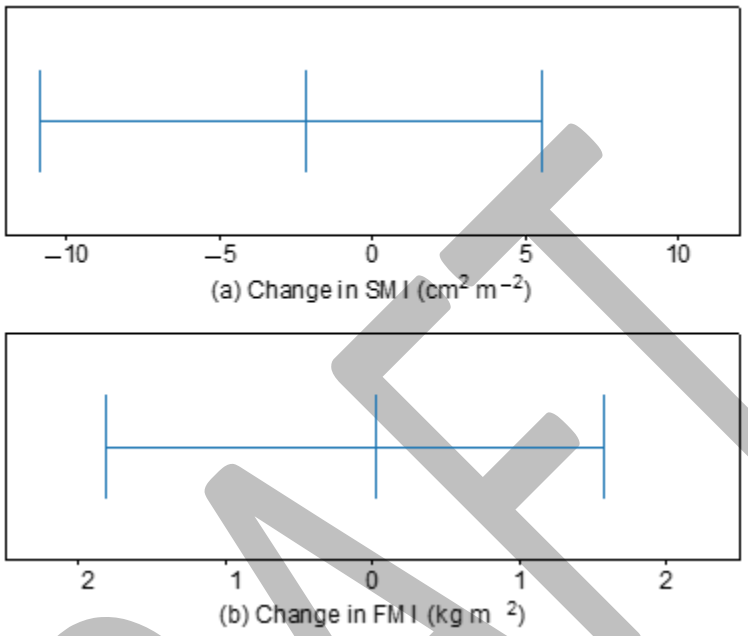

Table 1. Demographic information for patient population (N=73)				
Demographic	**n**	**(%)**	**Mean**	**SD**
Age			65	8
BMI			28	5
Gender				
Male	59	83		
Female	11	17		
Smoker	50	71		
ASA score			2.4	0.6
BCG	6	9		
Presence of CIS	16	23		
cT-stage				
cT1	9	13		
cT2	50	71		
cT3	6	9		
cT4	5	7		

ASA: American Society of Anesthesiologists; BCG: bacillus Calmette-Guérin; BMI: body mass index; CIS: carcinoma in situ; SD: standard deviation.

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Table 2. Change in sarcopenia and obesity before and after NAC				
	Baseline	**Post-NAC**	**Difference**	**p**
Sarcopenic, n (%)	38 (54%)	41 (58%)	3 (4%)	0.73*
Obese, n (%)	36 (51%)	36 (51%)	0 (0%)	1.00*
Sarcopenic and obese, n (%)	15 (21%)	17 (24%)	2 (3%)	0.84*
SMI, mean ± SD, cm^2/m^2				
Male	54.6±10.3	52.4±9.4	-2.2±3.2	<0.001†
Female	41.2±4.0	39.2±4.5	-2.0 2.7	0.003†
All patients	52.3 ± 10.8	50.1±10.1	-2.2±3.2	<0.001†
FMI, mean ± SD, kg/m^2				
Male	9.8±2.7	9.8±2.7	0.01±0.64	0.88†
Female	9.7±1.6	9.6±1.5	0.09±0.70	0.66†
All patients	9.8±2.6	9.8±2.5	0.03±0.65	0.73†

p-values calculated using Fisher's exact test* and paired Student's t-tests.† FMI: fat mass index; NAC: neoadjuvant chemotherapy; SD: standard deviation; SMI: skeletal muscle index.

Table 3. Number and severity of adverse events by body composition						
Group	**Number of adverse events by grade**					
	1	**2**	**3**	**4**	**5**	**Total**
All patients	517	120	33	0	0	670
Sarcopenic	307	67	16	0	0	390
Non-sarcopenic	210	53	14	0	0	277
Obese	240	63	21	0	0	324
Non-obese	277	57	12	0	0	346

Table 4. Logistic regression using the presence of any high-grade AE (CTCAE ≥grade 3)					
Variable	**Odds ratio**	**95% CI**			**p**
Constant	7.37				
Age	0.94	0.86	–	1.02	0.13
Male gender	0.39	0.08	–	1.95	0.25
Sarcopenic obesity	8.37	2.06	–	34.04	0.003*
>cT2	0.42	0.07	–	2.62	0.35
ASA score	1.94	0.70	–	5.40	0.20

*Statistically significant. AE: adverse event; ASA: American Society of Anesthesiologists; CI: confidence interval; CTCAE: common terminology criteria for adverse events.

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