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Outcomes of Sarcopenia Treatment for Malignant Bone and Soft Tissue Tumors in Elderly Patients

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Abstract. *Background/Aim: We determined the impact of sarcopenia on the treatment outcomes of malignant bone and soft tissue tumors in elderly patients. Patients and Methods: We retrospectively reviewed 76 patients (age ≥65 years) who were treated for malignant bone and soft tissue tumors. Sarcopenia was assessed by measuring the cross-sectional area of the psoas muscles at the L3 vertebra from preoperative computed tomography images and categorized using the total psoas area/m^2 (TPA/m^2) ≤5.0 cm^2/m^2. The patients' clinical data were then evaluated. Results: The operation time, length of hospital stay, and median overall survival were not different between the sarcopenia (n=41) and no-sarcopenia (n=35) groups. The local recurrence rate (p=0.01) and incidence of postoperative complications (p=0.02) significantly differed between both groups. The TPA/m^2 of both groups significantly decreased at the final follow-up. Conclusion: Sarcopenia negatively influenced wound healing and local recurrence, and was significantly exacerbated postoperatively in all elderly patients.*

In 2021, the total Japanese population was 125 million, which included 36 and 18 million individuals in the ≥65 and ≥75 years' age groups. The population of aging patients is increasing (1), and accordingly, the incidence of sarcopenia among patients has increased. Japan has a higher proportion of the elderly population in its so-called "super aging society," and the proportion of the population ≥65 years was estimated to be 28.9% in 2021 (1).

Sarcopenia (Greek *sarx* for flesh and *penia* for loss), a term proposed by Rosenberg is defined as an age-associated loss of muscle mass and function (2); this term actually describes important changes in the body composition and related functions. In recent years, sarcopenia was found to be related to poor surgical outcomes and mortality and longer hospital stay in patients who undergo resection of colorectal cancer (3).

To our knowledge, few studies have evaluated the relationship between sarcopenia and malignant bone and soft tissue tumors (4). This study aimed to investigate the impact of sarcopenia on the treatment outcomes of malignant bone and soft tissue tumors in elderly patients.

Patients and Methods

Clinical impact of treatment on the sarcopenia and no-sarcopenia groups. This retrospective, single-centre, comparative study included patients (age ≥65 years) with malignant bone and soft tissue tumors who were treated between January 2008 and December 2020 at the Osaka City University Hospital (Table I). The inclusion criteria were age ≥65 years and a diagnosis of malignant bone and soft tissue tumor, evaluated using computed tomography (CT) imaging that included the structures at the level of the L3 vertebra. The exclusion criteria were as follows: a diagnosis of benign tumor; the presence of bone metastases; nonavailability of pre-treatment CT imaging; incomplete medical records; and age ≤64 years. We assessed sarcopenia by manually measuring the cross-sectional area of the psoas muscles [total psoas muscle area (TPA)] on a single slice from CT scanning images obtained at the L3 level where the vertebral spinae were clearly visible. The TPA was then normalized for height (cm^2/m^2). We defined "no sarcopenia" and sarcopenia as a TPA/m^2 >5.0 and ≤5.0 cm^2/m^2 (Figure 1A and B), respectively, based on a previous report (5). The follow-up period was defined as the interval from the initial visit to the final visit.
The following clinical data were obtained from the medical records: age, body mass index (BMI), Eastern Cooperative Oncology Group performance status (PS), tumor size, primary tumor site, tumor grade [based on the French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading system (6) for soft tissue sarcomas

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Key Words: Sarcopenia, malignant bone, soft tissue tumor, local recurrence, wide resection, postoperative complications.

Table I. *Comparison of clinical information of sarcopenia vs. no sarcopenia.*

Characteristics	Sarcopenia N=41 (54%)	No sarcopenia N=35 (46%)	*p*-Value
Median age (years)±SD	75±7	74±6	0.49
BMI (kg/m^2)	22 (16-30)	23 (16-31)	0.1
PS	1 (0-2)	1 (0-2)	0.5
Median tumor size (cm)	7.5 (1.5-25)	6.5 (2-20)	0.4
Primary tumor site			
Trunk	10	12	
Upper extremity	10	3	
Lower extremity	21	20	
Tumor grade (FNCLCC grading system)			0.7
High grade	37	33	
Low grade	4	2	
Alb (g/dl)	4±0.6	4.1±0.5	0.13
Hb (g/dl)	12.9±1.9	13.8±2.3	0.005
CRP (mg/dl)	0.11±3.05	0.14±4.91	0.9
mGPS			0.5
High	30	28	
Low	11	7	
PNI	47.49±8.06	47.70±12.17	0.2
PLR	172.91±110.10	151.85±123.58	0.1
NLR	3.10±1.76	2.58±1.65	0.09
Operation time (min)	225±134	183±133	0.1
Volume of bleeding (ml)	90±844	50±235	0.2
Drainage interval (days)	7±3	6±4	0.2
Surgery			0.31
R0	28	29	
R1	6	4	
R2	2	0	
Postoperative complications (CTCAE v5.0)			0.02
Wound infection	6	0	
Wound necrosis	3	2	
Lymphorrhea	2	0	
Median length of hospital stay (days)	34±20	33±32	0.07
Hospital cost (US dollars)	19,523±15,146	16,825±11,327	0.12
Chemotherapy			0.2
Yes	10	5	
No	31	29	
Median follow-up (months)	26.2 (3.6-145.9)	44.5 (4.3-105.8)	0.03
Local recurrence			0.03
Yes	11	3	
No	28	30	
Outcomes			
CDF	12	18	
NED	7	8	
AWD	14	4	
DOD	6	5	
DOOD	2	0	

BMI: Body mass index; PS: performance status; FNCLCC: French Federation of Cancer Centers Sarcoma Group; Alb: albumin; Hb: hemoglobin; CRP: C-reactive protein; mGPS: modified Glasgow Prognostic Score; PNI: prognostic nutritional index; PLR: platelet/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; CTCAE: Common Terminology Criteria for Adverse Events; CDF: clinical disease free; NED: no evidence of disease; AWD: alive with disease; DOD: died of disease; DOOD: died of other disease.

(FNCLCC grade 2/3 and grade 1 tumors are considered "high grade" and "low grade", respectively) and the grading system described by Broders (7) for bone tumors (grade ¾ and grade 1/2 tumours are considered "high grade" and "low grade", respectively)]; laboratory values of albumin, hemoglobin, C-reactive protein (CRP), the neutrophil/lymphocyte ratio (NLR) (8), the platelet/lymphocyte ratio (PLR) (8), and the Modified Glasgow Prognostic Score (mGPS) (9); and whether chemotherapy was

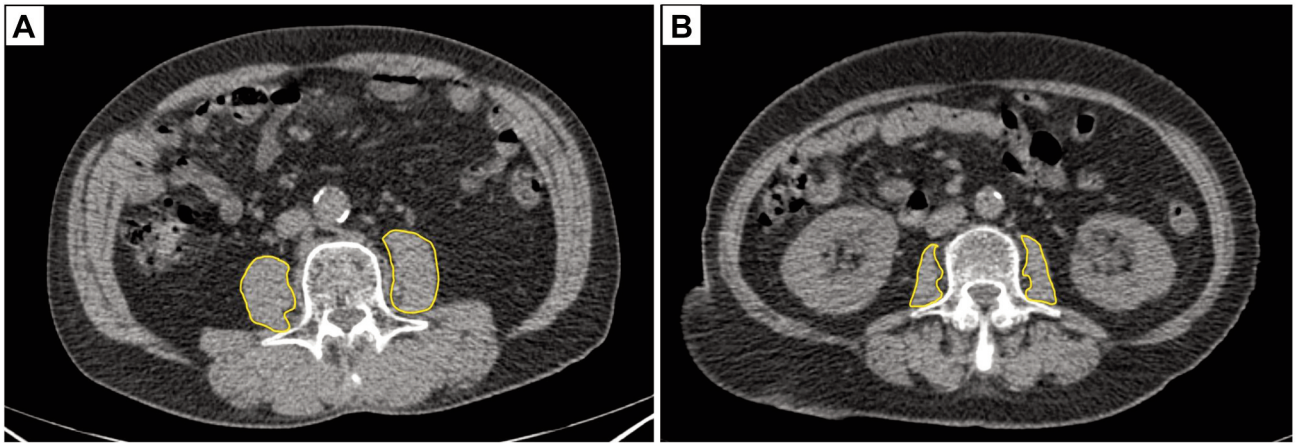

Figure 1. *Cross-sectional images from pre-treatment computed tomography (CT) scanning were used to measure the areas of the left and right psoas muscles of the third vertebra. (A) "No sarcopenia" was defined as a total psoas area/m^2 >5.0 cm^2/m^2. (B) "Sarcopenia" was defined as a total psoas area/m^2 ≤5.0 cm^2/m^2.*

Table II. *Intergroup comparison of the clinical information of patients followed up for more than 1 year.*

Characteristics	Sarcopenia N=20	No sarcopenia N=16	*p*-Value
Primary tumor site			0.21
Trunk	3	4	
Upper extremity	7	2	
Lower extremity	10	10	
Surgery			0.27
R0	15	15	
R1	3	1	
R2	2	0	
Chemotherapy			0.6
Yes	5	3	
No	19	13	
Median follow-up (months)	36.7 (17.3-145.9)	55.1 (18.6-100.1)	0.3

CTCAE: Common Terminology Criteria for Adverse Events; TPA: total psoas area.

administered. We extracted data on the clinical perioperative information, including the operation time, blood loss, drainage interval, length of hospital stay, and hospital cost. Information about local recurrence, overall survival (OS), and outcomes were obtained from the patients' medical records. The preoperative status of the patients was evaluated using the following methods: the mGPS was calculated based on preoperative data (CRP >0.5 mg/l and albumin <3.5 g/dl: 2 points; CRP >0.5 mg/l or albumin <3.5 g/dl: 1 point; and CRP ≤0.5 mg/l and albumin ≥3.5 g/dl: 0 point); the score ranged from 0 to 2 points, where a higher score (mGPS 1 and 2 points) was associated with high risk of postoperative mortality (9). We evaluated NLR (neutrophils/lymphocytes in mm^3/mm^3), and PLR (platelets/lymphocytes in μl/mm^3). Postoperative complications were recorded and defined as grade ≥3 based on the Common Terminology Criteria for Adverse Events (CTCAE v5.0; National Cancer Institute). We compared these factors between the sarcopenia and no sarcopenia groups.

Follow up of the postoperative transition in skeletal muscle loss. We retrospectively investigated the transition of TPA/m^2 of the patients from the initial visit to the final follow-up. Patients who were aged 65 and older and had undergone surgery for malignant bone and soft tissue tumors and were followed up postoperatively for more than 1 year, and evaluated based on CT scanning at the final follow-up. Thirty-six patients (49%) satisfied the abovementioned criteria and were assigned to one of the study groups (sarcopenia group, n=20 and no-sarcopenia group, n=16) based on their TPA/m^2 (Table II).

This comparative retrospective study was approved by the Institutional Review Board (IRB) of our university and informed consent from the study participants was obtained.

Statistical analysis. The Fisher's exact probability test was performed for analysing categorical variables (chemotherapy, postoperative complications, and local recurrence). The Mann–Whitney *U*-test was

used to compare various clinical factors. Values of $p<0.05$ were considered statistically significant. The 1-, 2-, and 5-year survival and median OS rates were evaluated using the non-parametric Kaplan–Meier method. The log-rank test was used to assess the statistically significant differences in the survival curves. Statistical analysis was performed using the Excel Statistics software for Windows (Version 2020; SSRI Co., Ltd., Tokyo, Japan).

Results

Clinical characteristics of the two study groups. A total of 76 patients met the eligibility criteria and were assigned to one of the two study groups (sarcopenia group, n=41 and no-sarcopenia group, n=35). In the entire study cohort, the mean±standard deviation (SD) for the age was 75±7 years. The median (range) follow-up duration in this study was 19.9 months (range=3.6-145.9 months).

Table I shows a comparison of the clinical and surgical characteristics of the sarcopenia and no-sarcopenia groups. Of the 76 patients treated for malignant bone and soft tissue tumours, 41 (54%) had sarcopenia, whereas 35 (46%) did not have sarcopenia. The median follow-up duration was 26.2 months (range=3.6-145.9 months) and 44.5 months (range=4.3-105.8 months) in the sarcopenia and no-sarcopenia groups, respectively. Histological subtyping of tumors in the overall study cohort showed the following distribution of tumor types: undifferentiated pleomorphic sarcoma (n=17; 22%), myxofibrosarcoma (n=11; 14%), dedifferentiated liposarcoma (n=8; 11%), myxoid liposarcoma (n=6; 8%), chordoma (n=2; 3%), osteosarcoma (n=2; 3%), and the others (chondrosarcoma, leiomyosarcoma, solitary fibrous tumor). The median (range) tumor size was 7.5 cm (range=1.5-25 cm) and 6.5 cm (range=2-20 cm) in the sarcopenia and no-sarcopenia groups, respectively. The majority of primary tumor sites was in the lower extremity (n=41; 54%). Tumour staging was based on the American Joint Committee Cancer (AJCC) 8th edition (10). The clinical stage of patients with soft tissue sarcoma was Stage IA (n=1; 1%), Stage IB (n=1; 1%), Stage II (n=20; 27%), Stage IIIA (n=18; 24%), Stage IIB (n=19; 25%), and Stage IV (n=6; 8%). The clinical stage of patients with bone sarcoma was Stage IA (n=2; 3%), Stage IB (n=1; 1%), Stage IIA (n=1; 1%), Stage IIB (n=1; 1%), Stage III (n=3; 5%), and Stage IV (n=2; 3%).

In the sarcopenia and no-sarcopenia groups, 21 (51%) and 20 (57%) patients, respectively, had primary tumor sites in the lower extremity. In addition, there were 37 and 33 patients with high-grade tumors in the sarcopenia and no-sarcopenia groups, respectively.

There was no significant difference in age, BMI, PS, albumin, mGPS, PLR, operation time, total blood loss, drainage interval, and median length of hospital stay between the sarcopenia and no-sarcopenia groups.

In total, 69 patients received surgical treatment, of whom 83% had R0 resections (negative resection margins without tumours in the linked resection margin), 14% had R1 resections (microscopic residual tumour at the resection margin), and 3% had R2 resections (macroscopic residual tumour at the resection margin).

The average length of hospital stay was 34 and 33 days in the sarcopenia and no-sarcopenia groups, respectively. The mean hospital cost was USD19,523 and 16,285 in the sarcopenia and no-sarcopenia groups, respectively, and there was no significant between-group difference ($p=0.12$). However, there was a trend toward higher NLR in the sarcopenia group ($p=0.09$). Patients in the sarcopenia group had more frequent postoperative complications (n=10; 24%), such as wound infection, wound necrosis, and lymphorrhoea, than those of patients in the no-sarcopenia group; thus, sarcopenia was significantly associated with postoperative complications ($p=0.02$).

At the last follow-up, the status was as follows: clinical disease-free (CDF), 30 (39%); no evidence of disease (NED), 15 (20%); alive with disease (AWD), 18 (24%); died of disease (DOD), 11 (14%); and died of other disease (DOOD), 2 (3%).

Survival rate and local recurrence. The survival rates at 1, 2, and 5 years in the sarcopenia and no-sarcopenia groups were 95%, 85%, and 67%; and 91%, 91%, and 91%, respectively. The median OS for this study population was 32.5 months (sarcopenia group: 26.3 months; no-sarcopenia group: 44.5 months), with no statistically significant difference between the study groups ($p=0.17$; Figure 2A).

In the sarcopenia and no-sarcopenia groups, 11 (27%) and 3 (9%) patients had local recurrences, respectively. Based on the local recurrence rate, six and two patients with malignant soft tissue tumours and malignant bone tumours, respectively, were excluded due to advanced stage cancer (Stage IV). The recurrence-free survival rates at 1, 2, and 5 years in the sarcopenia and no-sarcopenia groups were 76%, 68%, and 68%; and 93%, 93%, and 89%, respectively. The incidence of local recurrence was significantly higher in the sarcopenia group than in the no-sarcopenia group ($p=0.01$; Figure 2B).

Follow-up of postoperative transition of skeletal muscle loss in patients. Figure 3 shows the transition of skeletal muscle loss from the initial visit to the final follow-up, with significant differences in the TPA/m^2 between the two time points in the entire study group (4.6±1.6 cm^2/m^2 to 3.1±1.2 cm^2/m^2, respectively, $p<0.001$; Figure 3A). In patients who were initially diagnosed with sarcopenia (Figure 3B), the TPA/m^2 significantly reduced from the initial to the final visit (3.9±0.8 cm^2/m^2 to 2.7±1.1 cm^2/m^2, respectively, $p=0.002$). Even in patients who were initially assigned to the no-sarcopenia group (Figure 3C), TPA/m^2 significantly reduced from the initial to the final visit (6.0±1.2 cm^2/m^2 to 3.4±1.3 cm^2/m^2, respectively, $p<0.001$), especially in

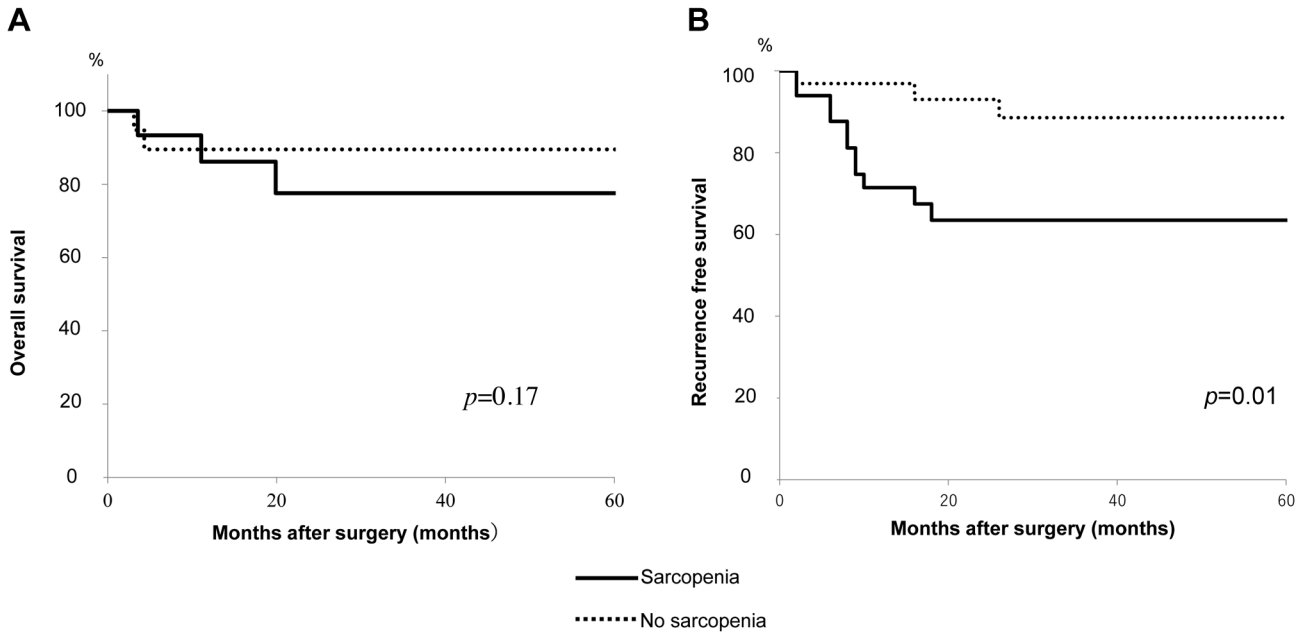

Figure 2. *Overall survival and recurrence-free survival rates at 1, 2, and 5 years. (A) Overall survival of the patients in the sarcopenia and no sarcopenia groups. The survival rates at 1, 2, and 5 years in the sarcopenia and no-sarcopenia groups were 95%, 85%, and 67% and 91%, 91%, and 91%, respectively. The median overall survival was 26.3 and 44.5 months in the sarcopenia and no-sarcopenia groups, respectively. (B) The recurrence-free survival rates at 1, 2, and 5 years in the sarcopenia and no-sarcopenia groups were 76%, 68%, and 68% and 93%, 93%, and 89%, respectively. The median recurrence-free survival was 15 and 38 months in the sarcopenia and no-sarcopenia groups, respectively.*

patients with tumors in the lower extremity (6.0±1.5 cm^2/m^2 to 3.2±1.5 cm^2/m^2, respectively, $p<0.001$) (Figure 3D).

Discussion

Irwin Rosenberg used "sarcopenia" to refer to age-related loss of skeletal muscle mass (2). For the diagnosis of sarcopenia, a single cross-sectional area at the level of the third or fourth lumbar vertebra on an axial CT is used as the gold standard imaging site. This is because CT is considered to be a very precise imaging tool that can distinguish fat from other soft tissues of the body, and a single abdominal cross-sectional image has been strongly related to the total skeletal muscle in a study (3). Calculation of the area of skeletal muscle mass using CT has been undertaken using various methods (3, 4, 6). Peng et al. investigated 259 patients who underwent liver resection for colorectal liver metastases (CRLM) by measuring TPA from CT images, and defined sarcopenia as a TPA of ≤5.0 cm^2/m^2, adjusted for height, as the most relevant cut-off value (6). In this study, we applied this definition of sarcopenia as a TPA of <5.0 cm^2/m^2, adjusted for height (cm^2/m^2). In this study, 51 out of 76 patients were assigned to the sarcopenia group.

Several treatment-related problems can occur in sarcopenic patients. Sarcopenia has a significantly negative effect on chemotherapy for patients with various cancers (11) and anticancer drugs induced frequent dose-limiting toxicities (DLT), such as diarrhoea and acute vascular toxicity, in patients with cancers (11). Furthermore, sarcopenia was associated with a poor survival rate and enhanced postoperative complications in patients with various types of cancer (3, 11).

The preoperative status of patients was evaluated using the mGPS, NLR, PLR. The NLR is a ratio of the absolute number of neutrophils, which have a well-known protumorigenic role, and the absolute number of lymphocytes, which instead have an antitumorigenic role (8). High NLR was associated with worse outcomes in patients with cervical cancer (12) and gastric cancers with regard to OS and cancer specific survival (13). With regard to the indicators of the preoperative status of patients, such as mGPS, NLR, and PLR, we hypothesized that sarcopenia influences the immune system against malignant bone and soft tissue tumors. The results showed no significant differences between the sarcopenia and no-sarcopenia groups with regard to NLR, but there was a trend toward a higher NLR value in the sarcopenia group compared to the no-sarcopenia group ($p=0.09$). The NLR is a marker of the systemic inflammatory response and could trigger postoperative infectious complications in patients who have undergone a gastrectomy. This is attributable to the innate function of neutrophils and lymphocytes. The higher the increase in neutrophilic infiltration near the site of bacterial

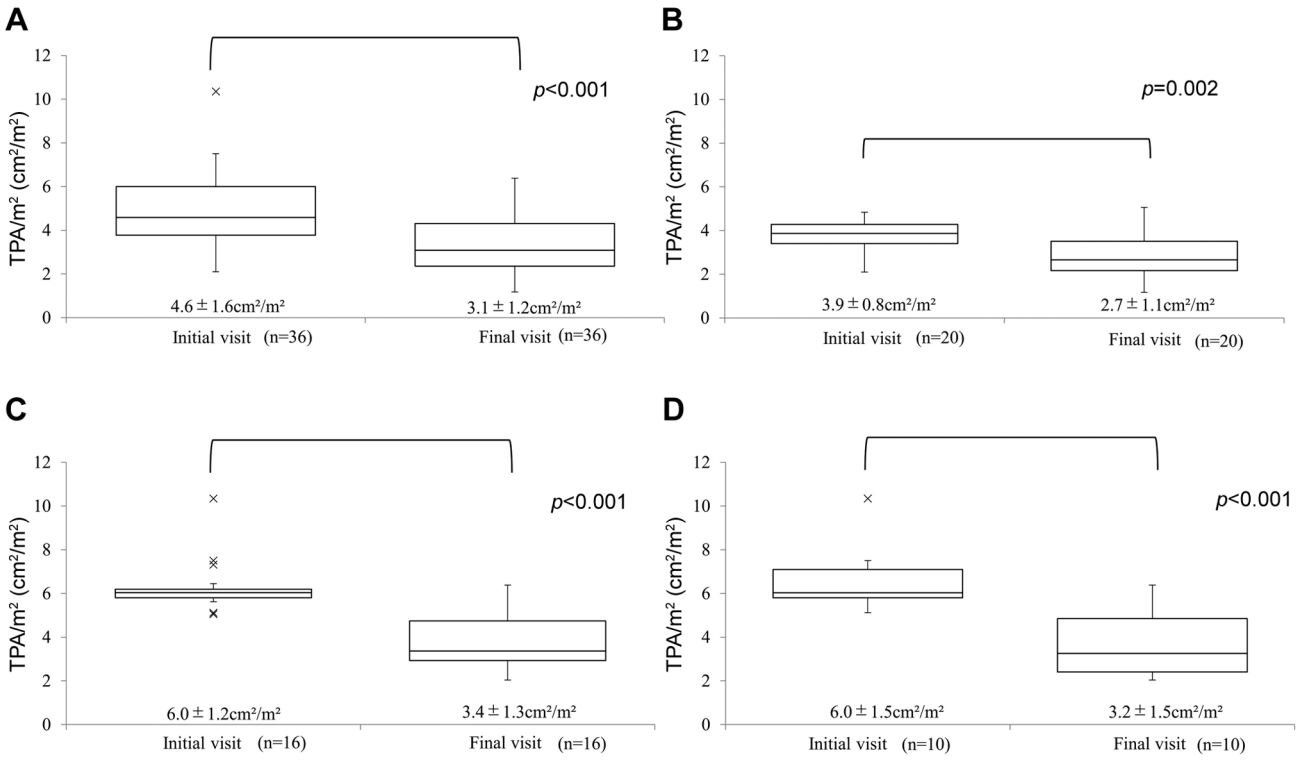

Figure 3. *Comparison of the total psoas area/m^2 (TPA/m^2) at the initial visit to that at the final visit. (A) TPA/m^2 in the whole study cohort at the initial and final visits (4.6±1.6 and 3.1±1.2 cm^2/m^2, respectively, p<0.001). (B) TPA/m^2 in the sarcopenia group at the initial and final visits (3.9±0.8 and 2.7±1.1 cm^2/m^2, respectively, p=0.002). C) TPA/m^2 in the no-sarcopenia group at the initial and final visits (6.0±1.2 and 3.4±1.3 cm^2/m^2, respectively, p<0.001). (D) TPA/m^2 in the no-sarcopenia group for the lower extremity at the initial and final visits (6.0±1.5 and 3.2±1.5 cm^2/m^2, respectively, p<0.001).*

contamination, the greater is the suppression of the antibacterial responses of natural killer cells and activated T cells (13).

With regard to malignant bone and soft tissue tumours, obtaining an adequate wide margin is essential for local control with surgical treatment (14). However, the sarcopenia group had a higher local recurrence rate than the no-sarcopenia group in this study, despite adequate wide resection and the absence of a statistically significant difference in surgical margins between the sarcopenia and no-sarcopenia groups (p=0.31; Table II). The trend toward a higher NLR value in the sarcopenia group (p=0.09) and the resultant functions of neutrophils and lymphocytes may have influenced local control. Neutrophils are the key mediators of tumour angiogenesis and can secrete clinical factors which stimulates increased production of vascular endothelial growth factor (VEGF) from tumor cells and resultant effects on the nearby vasculature to promote tumor angiogenesis (15). Inflammatory cells, such as neutrophils, mast cells, natural killer cells, and dendritic cells, not only contribute to tumor cell proliferation and cancer angiogenesis but also seem to alter the adaptive immune response.

The most interesting finding of this study was the extent of change in the TPA/m^2 from the initial visit to the final follow-up. Regardless of the presence of sarcopenia, all patients experienced a significant postoperative decrease in skeletal muscle mass. The TPA/m^2 of the patients with lower extremity tumors in the no-sarcopenia group had significantly decreased at the final follow-up (p<0.001). The lower extremity is a common anatomical site of malignant bone and soft tissue tumors. To ensure effective treatment of tumors, wide resection with an adequate margin is essential (14), although the massive sacrifice of healthy tissue translates to a loss of skeletal muscle mass that leads to reduced activities of daily living.

This study has several limitations. First, the follow-up period was short; therefore, the OS and disease-free survival could have been underestimated. Second, the number of patients was small. Third, other parameters of sarcopenia, such as walking speed, grip strength, and levels of exhaustion, were not investigated in this study. Fourth, this study was a retrospective comparative study that was conducted in a single institution.

Conclusion

We investigated the impact of sarcopenia on surgical outcomes of malignant bone and soft tissue tumors based on a single-centre Japanese institutional experience with elderly patients. The incidence of postoperative complications and local recurrence was higher in the sarcopenia group compared to that in the no-sarcopenia group. A preoperative high NLR might possibly be a risk predictor for postoperative complications. This study demonstrated that the amount of skeletal muscle mass greatly decreased in patients aged 65 and older who underwent surgery.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Yoshitaka Ban designed this study, analysed the data, prepared the figures, and wrote the original draft manuscript. All Authors reviewed the manuscript.

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