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Original Article

Sarcopenia with decreased total psoas muscle area in children with high-risk neuroblastoma

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ABSTRACT

Background: We calculated psoas muscle area (PMA) z-scores in high-risk neuroblastoma patients undergoing treatment to examine the clinical significance of sarcopenia in this cohort.
Methods: We analyzed retrospective data from patients aged 0–18 who were diagnosed with abdominal neuroblastoma between 2005 and 2019 at Samsung Medical Center. Patients categorized as high-risk undergone induction chemotherapy, neuroblastoma excision, and tandem high-dose chemotherapy with autologous stem cell transplantation (HDCT/auto-SCT) were selected. L3-4 lumbar levels on axial CT images were identified and we measured the areas of the left and right psoas muscles to determine tPMA. Total PMA z-scores were calculated using an open online tool.
Results: There were 45 boys and 25 girls with a mean age of 3.86 years. CT images taken at initial diagnosis and after tandem HDCT/auto-SCT were selected to calculate tPMA z-scores. Mean elapsed time between the two measurements was 12.91 ± 1.73 months. Mean tPMA z-score significantly decreased from −0.21 ± 1.29 to −0.66 ± 0.97 ($p = 0.022$). Length of hospital stay was significantly longer in the group of patients whose tPMA z-scores decreased by more than .45 (177.62 ± 28.82 days vs. 165.75 ± 21.34 days, $p = 0.049$). Presence of sarcopenia at initial diagnosis was a significant risk factor for bacterial infection during neuroblastoma treatment.
Conclusion: tPMA z-scores in high-risk neuroblastoma patients decreased significantly following a treatment regimen that included induction chemotherapy, tumor resection surgery, and HDCT/auto-SCT. A greater decrease in tPMA z-score was associated with longer hospital stay during treatment.

1. Introduction

Sarcopenia is a progressive and generalized loss of skeletal muscle mass, strength, and function, associated with an increased risk of adverse outcomes including physical disability and mortality.[1] Chronic diseases such as malignancies are associated with systemic inflammation, malnutrition, and physical inactivity, which lead to unintended muscle loss.[2,3] Studies of sarcopenia in adult patients with malignancies have identified sarcopenia to be associated with postoperative morbidities and poor survival outcomes.[4–6] Neuroblastoma is the most common solid extracranial tumor in childhood and high-risk neuroblastoma patients undergo an extensive treatment regimen consisting of induction chemotherapy, surgery, and high-dose chemotherapy with autologous stem cell transplantation (HDCT/auto-SCT).[7–9] Previous studies addressing sarcopenia in pediatric malignancies have been reported, however few have incorporated sarcopenia with clinical outcome measures in the setting of neuroblastoma treatment.[10–13]

Abbreviations: HDCT/auto-SCT, high-dose chemotherapy with autologous stem cell transplantation; PMA, psoas muscle area; PACS, Picture Archiving and Communication System; DEXA, dual-energy x-ray absorptiometry.

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An easily accessible and reproducible method of assessing sarcopenia is through psoas muscle area (PMA) measurements from CT or MRI images, and several reports have advocated this method for the assessment of pediatric sarcopenia.[10–15]

In this study, we calculated PMA z-scores in high-risk neuroblastoma patients undergoing treatment to examine the clinical significance of sarcopenia in this cohort. We hypothesized that the presence of decreased muscle mass or progressive loss of muscle mass during treatment was associated with adverse outcomes.

2. Methods

2.1. Patients

We collected and analyzed retrospective data from patients aged 0–18 who were newly diagnosed with neuroblastoma of the abdomen between 2005 and 2019 at Samsung Medical Center. Patients categorized as high-risk who completed nine cycles of induction chemotherapy and underwent surgical resection of neuroblastoma, followed by tandem HDCT/auto-SCT were selected for the study (Fig. 1). All patients included in the analysis received treatment according to either NB-2004, NB-2009, or NB-2014 protocol, as previously described.[8,9]

2.2. Psoas muscle area measurements

CT images were retrieved and analyzed from our institute's Picture Archiving and Communication System (PACS). L3-4 lumbar levels on axial CT images were identified by cross-referencing on sagittal reconstruction images. We measured the areas of the left and right psoas muscles in mm^2 and determined the sum of the two measurements as tPMA. If the contour of the lesion-side psoas muscle was distorted by external compression from the tumor, we measured the contralateral psoas muscle and multiplied it by two to calculate tPMA. All measurements were performed by MJB. Total psoas muscle area z-scores were calculated using an open online tool (https://ahrc-apps.shinyapps.io/sarcopenia/).[2] Patients were classified as having sarcopenia when z-scores were smaller than −2 at the time of CT imaging.

2.3. Statistical analysis

We performed standard statistical analyses to determine differences between groups. For continuous variables, we used the Mann–Whitney test or paired t-test. For categorical variables, we used the Chi-square test. We analyzed relapse-free survival and overall survival using Kaplan–Meier and compared survival between groups using log-rank test. Data analyses and generation of figures were performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 9.0 (GraphPad Software, Boston, MA, USA). The results were described as statistically significant with a 95% CI at $p < 0.05$ (two-tailed).

3. Results

After excluding cases with missing data, 70 children were included in the analysis. The demographic characteristics of patients are outlined in Table 1. There were 45 boys and 25 girls with a mean age of 3.86 years. 60 cases were INSS stage 4 and 10 were INSS stage 3. *MYCN* amplification was present in 32 cases. Mean size of the tumor at initial diagnosis was 9.21 cm, which decreased to 5.98 cm at the time of surgical resection.

CT images taken at two time points, one at initial diagnosis and the other after tandem HDCT/auto-SCT, were selected to measure tPMA and calculate tPMA z-scores. The mean elapsed time between the two measurements was 12.91 ± 1.73 months. Measured tPMA was 706.3 ± 334.9 mm^2 at initial diagnosis and 725.2 ± 260.7 mm^2 after treatment completion ($p = 0.71$, Table 2). Mean tPMA z-score significantly decreased from −0.21 ± 1.29 to −0.66 ± 0.97 during neuroblastoma treatment ($p = 0.022$, Fig. 2). Body weight percentile decreased significantly ($p = 0.026$), while BMI was not different between the two time points ($p = 0.179$).

Table 3 outlines the clinical outcomes of patients categorized into groups according to tPMA z-score decrement during neuroblastoma treatment. The length of hospital stay was significantly longer in the group of patients whose tPMA z-scores decreased by more than .45 from initial diagnosis to completion of treatment (177.62 ± 28.82 days vs. 165.75 ± 21.34 days, $p = 0.049$). All other outcomes including ED visits, number of admissions, bacterial infections, complications following surgery, reoperations, neuroblastoma relapses, and deaths were not significantly different

Table 1
Patient and tumor characteristics.

	N = 70
Gender, n (%)	
Boys	45 (64.3)
Girls	25 (35.7)
Age, years (mean ± SD)	3.86 ± 2.45
INSS stage, n (%)	
3	10 (14.3)
4	60 (85.7)
Histology, n (%)	
Neuroblastoma	60 (85.7)
Ganglioneuroblastoma	10 (14.3)
MYCN amplification, n (%)	32 (45.7)
Primary tumor site, n (%)	
Left adrenal gland	35 (50)
Right adrenal gland	30 (42.8)
Retroperitoneal	3 (4.3)
Others	2 (2.9)
Initial tumor size, cm (mean ± SD)	9.21 ± 3.70
Tumor size at resection, cm (mean ± SD)	5.98 ± 3.32
Sarcopenia, n (%)	
At initial diagnosis	5 (7.2)
After treatment completion	7 (10)

Abbreviations: SD, standard deviation; INSS, international neuroblastoma staging system.

Fig. 1. Treatment flow of high-risk neuroblastoma patients. Abdominal CT and tPMA measurements were done at the time of diagnosis and after completion of tandem HDCT/auto-SCT. Surgical excision of neuroblastoma was typically performed after six cycles of induction chemotherapy. However, surgery was delayed if the mass was considered unresectable at that time. PMA, psoas muscle area; HDCT/auto-SCT, high-dose chemotherapy and autologous stem cell transplantation; RT, radiotherapy; CRA, 13-cis-retinoic acid.

Table 2
tPMA and anthropometric data of patients undergone neuroblastoma treatment.

	Initial diagnosis (N = 70)	After treatment (N = 70)	P-value
tPMA, mm^2 (mean ± SD)	706.3 ± 334.9	725.2 ± 260.7	0.71
tPMA z-score (mean ± SD)	−0.21 ± 1.29	−0.66 ± 0.97	**0.022**
Sarcopenia (tPMA z-score < −2)	5 (7.2%)	7 (10%)	0.974
Weight percentile (mean ± SD)	45.04 ± 29.15	34.12 ± 28.34	**0.026**
BMI, kg/m^2 (mean ± SD)	15.72 ± 2.05	15.28 ± 1.73	0.179

Abbreviations: tPMA, total psoas muscle area; SD, standard deviation; BMI, body mass index.

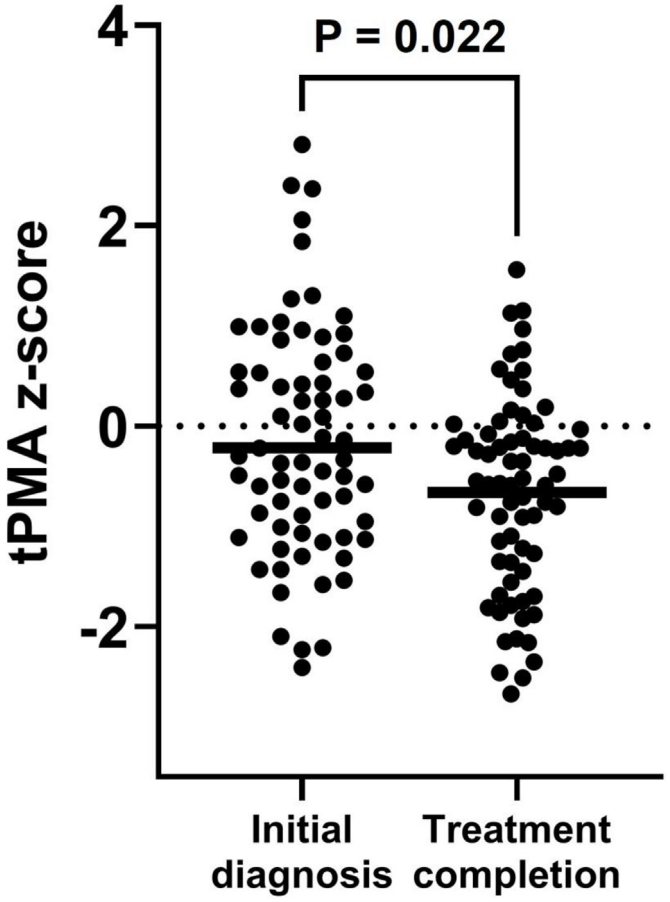

Fig. 2. Total PMA z-scores of patients at initial diagnosis and after tandem high-dose chemotherapy with autologous stem cell transplantation. Mean tPMA z-score significantly decreased from −0.21 ± 1.29 at initial diagnosis to −0.66 ± 0.97 after treatment (p = 0.022).

Table 4
Multivariate logistic regression analysis of risk factors for bacterial infection during neuroblastoma treatment.

	P-value	OR	95% confidence interval		
Age at diagnosis	0.192	0.774	0.527	~	1.137
Boys (vs. girls)	0.155	3.065	0.654	~	14.349
INSS stage 4 (vs. stage 3)	0.339	0.453	0.090	~	2.295
Larger initial tumor size	0.784	0.976	0.818	~	1.164
Sarcopenia at initial diagnosis	0.012	24.762	2.040	~	300.600
Decreased tPMA during treatment*	0.281	2.264	0.512	~	10.016

*tPMA z-score decrement ≥0.45 (vs. < 0.45).
Abbreviations: OR, odds ratio; INSS, international neuroblastoma staging system; tPMA, total psoas muscle area.

between the two groups. Multivariate logistic regression analysis showed that the presence of sarcopenia at initial diagnosis was a significant risk factor for bacterial infection during neuroblastoma treatment (p = 0.012, OR 24.762, 95% CI 2.040–300.600, Table 4).

Relapse-free survival was not different between patients at a cut-off of 0.45 z-score decrement during treatment (p = 0.823, Fig. 3A). Kaplan–Meier survival curves showed a trend of decreased overall survival in patients with ≥0.45 tPMA z-score decrement, although the difference was not statistically significant (p = 0.240, Fig. 3B).

4. Discussions

In this study, we measured tPMA at L3-4 levels on CT to determine tPMA z-scores in high-risk neuroblastoma patients undergoing a treatment regimen that included induction chemotherapy, tumor resection surgery, and HDCT/auto-SCT. Our analyses revealed a significant decrease in tPMA z-score from the time of initial diagnosis to after treatment completion. We also found that a larger decrease in tPMA z-score was associated with a longer hospital stay during the treatment course.

Sarcopenia is a relatively novel concept in the pediatric literature which has recently been attracting more attention from researchers and clinicians. While much of the clinical and academic interests in sarcopenia has been focused on the adult population, particularly the elderly, children are not exempt from experiencing these changes and the negative clinical outcomes associated with sarcopenia. Sarcopenia was associated with longer hospital stay and risk of fungal infection in children undergoing induction therapy for acute lymphoblastic leukemia.[10,16] The presence of sarcopenia increased the risk of surgical complications and readmission in children undergoing colon resection.[17] Sarcopenia was associated with longer perioperative stay in the intensive care unit, ventilator dependence, poor growth, and readmission in pediatric liver transplant recipients.[18]

Table 3
Outcomes of patient according to tPMA z-score decrement.

	Total (N = 70)	tPMA z-score decrement ≥0.45 (N = 42)	tPMA z-score decrement <0.45 (N = 28)	P-value
ED visits, n (mean ± SD)	6.93 ± 3.75	7.21 ± 3.66	6.50 ± 3.90	0.439
Hospital admissions, n (mean ± SD)	20.96 ± 4.46	21.43 ± 4.62	20.25 ± 4.05	0.282
Length of hospital stay, days (mean ± SD)	172.87 ± 26.53	177.62 ± 28.82	165.75 ± 21.34	**0.049**
Bacterial infection, n (%)	15 (21.4)	10 (23.8)	5 (17.8)	0.767
Surgical complication, *n* (%)	2 (2.9)	1 (2.4)	1 (3.6)	0.999
Reoperation, *n* (%)	11 (15.7)	7 (16.7)	4 (14.3)	0.999
Relapse, *n* (%)	18 (25.7)	14 (33.3)	4 (14.3)	0.097
Death, *n* (%)	14 (20)	11 (26.2)	3 (10.7)	0.138

Abbreviations: tPMA, total psoas muscle area; ED, emergency department; SD, standard deviation.

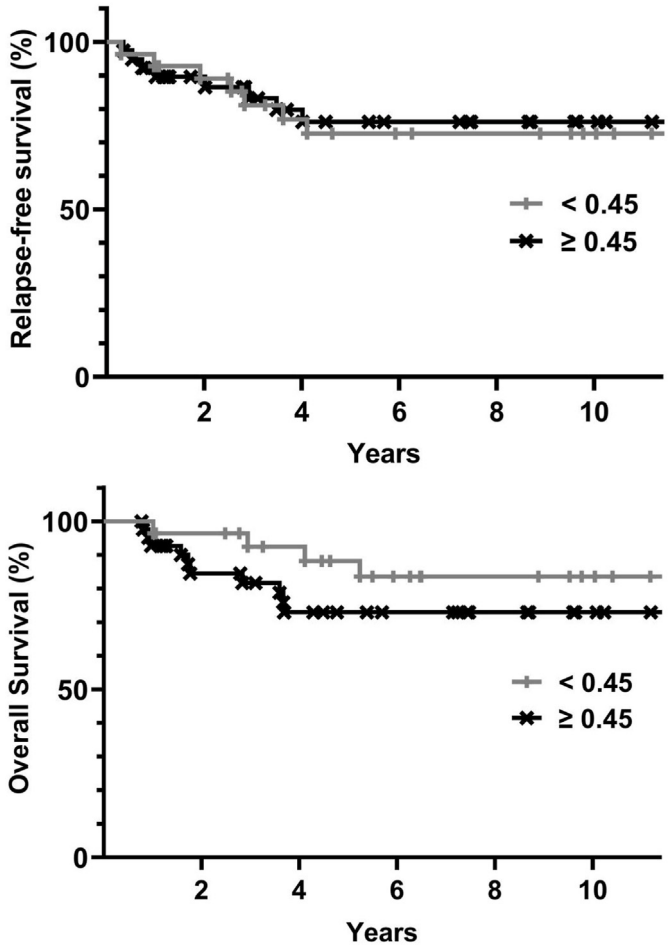

Fig. 3. Relapse-free survival (A) and overall survival (B) of patients according to tPMA z-score decrements during neuroblastoma treatment. Survival curves were not significantly different between groups for relapse-free survival ($p = 0.823$) and overall survival ($p = 0.240$).

Several factors contribute to sarcopenia in patients with malignant diseases. Protein synthesis is decreased with decreased physical activity and protein degradation is increased by TNF-α and NF-κB.[19–21] Tumor metabolism and increased stress hormone release also leads to negative protein balance.[20–22] Chemotherapy is another crucial factor in the development of sarcopenia in cancer patients. Common side effects of chemotherapy such as vomiting, mucositis, and diarrhea can limit oral and enteral intake, which significantly contributes to malnutrition and sarcopenia. Moreover, chemotherapeutic agents may directly affect sarcopenia. Cisplatin, doxorubicin, and etoposide activate NF-κB leading to increased protein degradation.[23,24] We observed a significant decrease in tPMA z-scores in our patients during the course of neuroblastoma treatment. A decrease greater than 0.45 was associated with longer length of hospital stay and survival analysis showed a trend towards decreased overall survival in these patients, although the difference was not significant. Future studies should focus on identifying factors that contribute to the progression of sarcopenia and examine the potential effects of focused nutritional support in improving muscle mass loss and clinical outcome in neuroblastoma patients.

One major obstacle in studying sarcopenia in children is the lack of a consensus in its definition and diagnosis. Previously published studies have incorporated various methods of assessing and defining pediatric sarcopenia. Modalities including dual-energy x-ray absorptiometry (DEXA), bioelectrical impedance analysis, and imaging techniques such as CT and MRI have been used to measure muscle mass.[10,17,18] We used PMA measurements taken from cross-sectional abdominal CT images in this study because it is an easily accessible and reproducible method of assessing the presence of sarcopenia.[25,26] PMA measurements from CT images have been applied in studies of pediatric sarcopenia among patient cohorts including leukemia, end-stage liver disease, chronic kidney disease, and intestinal failure.[10,11,27,28] With the online accessibility of age- and gender-specific reference values of tPMA in children (https://ahrc-apps.shinyapps.io/sarcopenia/), it has become an effective tool for the assessment of pediatric sarcopenia. Two studies were recently published that utilized this tool to assess sarcopenia with tPMA z-scores and included analyses of clinical outcomes in pediatric malignant diseases. In their analysis of tPMA z-scores in neuroblastoma patients, Ritz et al found that 63% were sarcopenic and that sarcopenia was a risk factor for decreased 5-year survival.[13] They applied a similar methodology to a cohort of hepatoblastoma patients and found that 52% of patients were sarcopenic, while sarcopenia was a risk factor for relapse in high-risk hepatoblastoma.[11] There is a substantial discrepancy in the proportion of children with sarcopenia between this study compared to that reported by Ritz et al. Prevalence of sarcopenia was noticeably lower in our patients with 7.2% at initial diagnosis and 10% after treatment completion. It is challenging to accurately determine the cause of the significant discrepancy between the two studies. However, a possible explanation would be the differences in the ethnic composition of the study participants, as this study entirely consisted of individuals of East Asian descent.

The limitation of this study is in its design as a retrospective analysis in a single center. Although the number of patients analyzed is small, it is important to take into account the low prevalence of childhood malignancies, such as neuroblastoma, compared to those in adults. The strength of this study is in the heterogeneous composition of our patient cohort, which we narrowed down to high-risk neuroblastoma patients who completed the entire course of the treatment regimen. With this study population, we were able to assess tPMA at two time-points, thereby examining the progression of sarcopenia and its associated clinical outcomes.

In conclusion, tPMA z-scores derived from tPMA measurements at L3-4 levels on abdominal CT in high-risk neuroblastoma patients decreased significantly following a treatment regimen that included induction chemotherapy, tumor resection surgery, and HDCT/auto-SCT. A greater decrease in tPMA z-score was associated with longer hospital stay during the course of treatment. Further randomized prospective studies with a larger number of patients are warranted to confirm the findings of our study.

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Declaration of competing interest

The authors report no conflict of interest.

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