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出版情報：Kyushu University, 2022, 博士（医学），課程博士
バージョン：

Effects of changes in skeletal muscle mass on the prognosis of pediatric malignant solid tumors

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Acknowredgement: This study was funded by a Research Grand from Gold Ribbon Network.

Abstract

Purpose This study aims to clarify the relationship between changes in skeletal muscle mass during treatment and prognosis of pediatric malignant solid tumors.

Methods Patients with pediatric malignant solid tumors who were treated at Kyushu University Hospital from 2007 to 2017 were divided into two groups: the progression-free survival (PFS) group and the relapse/death (R/D) group; the psoas major muscle volume (PMV) was then compared. We also measured the PMV and psoas muscle area (PMA) of pediatric patients with no complications who underwent surgery for acute appendicitis (control) and compared the values with those of patients with malignant tumors.

Results No significant differences were observed in the PMV and PMA between patients with appendicitis and those with malignant tumors. Significant differences were found in the rate of change in PMV between the PFS (1.424) and R/D groups (1.071) ($P = 0.0024$). When the cutoff value of the rate of change in the PMV was 1.20, patients whose rate of change in PMV was ≥1.20 had longer PFS ($P = 0.0231$) and overall survival ($P = 0.0229$) than those whose rate of change was <1.20.

Conclusion Pediatric patients with malignant solid tumors and increased skeletal muscle mass during treatment have a good prognosis.

Keywords psoas muscle area, psoas muscle volume, sarcopenia, pediatric malignant solid tumor

INTRODUCTION

Sarcopenia, a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength [1], has attracted substantial attention. It has been reported that sarcopenia affects the prognosis of malignant tumors and the incidence of postoperative complications [2, 3]. In pediatric patients, some studies have reported on sarcopenia in cases of leukemia, chronic liver disease, kidney disease, intestinal failure, and liver transplantation [4–7]. However, few reports on sarcopenia in pediatric patients with malignant solid tumors have been published [8, 9]. We previously reported that the change rate of skeletal muscle mass during treatment affects the prognosis of high-risk neuroblastoma [10]. In that study, we evaluated skeletal muscle mass measuring Psoas muscle area (PMA) using computed tomography (CT). However, we consider this evaluation method using PMA has somewhat inaccuracy. It is difficult to accurately evaluate skeletal muscle mass in children because of the size or growth of children. Moreover, the methods by which skeletal muscle mass is evaluated are different depending on the reports [6, 10–12]. Analysis using CT or magnetic resonance imaging (MRI), bioelectrical impedance analysis (BIA), and dual-energy X-ray absorptiometry (DXA) have often been adopted to evaluate skeletal muscle mass. In previous reports using CT measurements, whole-body skeletal muscle mass was evaluated according to

the psoas muscle area (PMA) [4, 9, 10]. In this study, we use the psoas muscle volume (PMV), which is a more accurate measure of skeletal muscle mass and this point is a definite difference to our previous study using PMA. Using an automatic analysis tool, we evaluated the PMV using CT scan data. We also considered a more accurate measurement method for skeletal muscle mass.

In this study, we clarify the relationship between changes in skeletal muscle mass using not PMA but PMV during treatment and prognosis of pediatric malignant solid tumors.

METHODS

Patients

This study included pediatric patients with malignant solid tumors who were treated in our department from 2007 to 2017. Of these patients, we excluded those with complications that may have affected the psoas muscle mass (chromosomal abnormalities, cerebral palsy), unanalyzable CT images, no multidisciplinary treatment, and no remission and those who were transferred to another hospital. CT images were routinely obtained before treatment initiation and after completion of the standard treatment protocol.

The patients who survived without tumor recurrence or progression after the

remission were defined as the progression-free survival group (PFS group) (n = 21), whereas those who experienced recurrence after the remission were defined as the relapse/death group (R/D group) (n = 7). The demographic and diagnostic data, treatment details, serum albumin level, neutrophil–lymphocyte ratio (NLR), and body mass index (BMI) (weight [kg] / [height {m} × height {m}] × 100) during therapy were collected.

Furthermore, to compare the accuracy of PMA and PMV in measuring skeletal muscle mass, we targeted patients with acute appendicitis to serve as the standard control population. This study population comprised 310 patients who underwent appendectomy for acute appendicitis at our hospital from 2007 to 2017. We excluded infants and patients aged 16 years and older and also excluded cases with complications, such as scoliosis, hypoxic encephalopathy, developmental retardation, and malignant tumors. Of the remaining patients, we statistically analyzed 185 patients who had received a preoperative CT in the proper range. Patient characteristics, such as age and gender, were obtained from medical records.

Ethics approval was obtained from the Ethics Committee of the Institute of Health Science at Kyushu University (approval #2020-208). This retrospective study was performed according to the Ethical Guidelines for Clinical Research, published by the

Ministry of Health, Labour and Welfare, Japan on July 30, 2003 (revised in 2008). The study complied with the 1964 Declaration of Helsinki (revised in 2008). In this research, the Institutional review board have exempted informed consent.

Measurement of PMA and PMV

We measured PMA at the lower end of the vertebral body by automatic outlining of CT images using the elliptical region of interest with a picture archiving and communication system (SYNAPSE VINCENT Ver.5.1; Fujifilm Medical, Tokyo, Japan) (Fig.1a). Furthermore, PMA was measured respectively at a position shifted up and down by 3 mm from the lower end of the vertebral body. PMV was also measured using SYNAPSE VINCENT. This system automatically traces the psoas major muscles on both sides, slice by slice, and constructs them in 3D to calculate the volume (Fig.1b). If PMA or PMV could not be measured automatically, we performed some manual corrections. The rate of change in the PMA during treatment was calculated according to the following formula: (left and right PMA after treatment/left and right PMA before treatment). The rate of change in the PMV was calculated in the same way.

Statistical analyses

Statistical analyses were conducted using JMP® Pro 14 (SAS Institute, Cary, NC), which was also used to produce graphic representations of the data. For categorical variables, Fisher's exact test was used to identify the statistical difference, and for continuous variables, the Mann–Whitney *U*-test or paired *t*-test was used. *P* values of <0.05 indicated statistical significance.

RESULTS

Error in PMA measurement in patients with appendicitis

First, we classified the patients with appendicitis into three groups: 1–5 years old, 6–10 years old, and 11–15 years old. Table 1 shows the gender and age of each group. Online resource 1 lists the trends of PMV and PMA by age. We divided each of the three groups by gender, and the difference between the PMA measured at the lower end of the L3 vertebral body and the PMA measured when moving up and down by 3 mm from there was compared by a paired t-test. In all three groups, a statistically significant error in PMA measurement on CT occurred when one slice (3 mm) deviated from the lower end level of L3 (Fig.2).

Changes in skeletal muscle mass and prognosis of malignant solid tumors

During the above period, 124 patients with malignant solid tumors were treated in our department. Of these patients, we excluded 96 patients according to the inclusion criteria (Fig.2). As shown in Table 2, gender, age, duration of therapy, NLR at diagnosis, and the tumor type did not differ markedly between the PFS and R/D groups. Next, we compared the rates of change in the PMA and PMV during treatment, the BMI, and the serum albumin level. Significant differences were observed between the rates of change in the PMV in the PFS (1.424) and R/D (1.071) groups ($P = 0.0024$).

On the contrary, both the pretreatment and posttreatment PMV values of the R/D group were not statistically different than the PMV values of patients with appendicitis in each age group (data not shown). Moreover, we compared the pretreatment and posttreatment PMA and the PMA of the appendicitis group using an online tool for PMA calculation (https://ahrc-apps.shinyapps.io/sarcopenia/). The mean Z scores of the pretreatment and posttreatment PMA were -3.32 and -2.25, respectively. Even in patients with appendicitis, the mean Z score of the PMA was -1.54, and thus, we believed that this online tool for PMA calculation showed regional bias.

The rates of change in the PMA, BMI, and serum albumin level were not statistically different (Table 3). The scatter plot in Fig.3 shows the difference in the rate of change in the PMV between the two groups.

The cutoff value of the rate of change in the PMV was set to 1.20 (Fig.4). The patients were divided into two groups: those whose rate of change was ≥1.20 and those whose rate of change was <1.20. As shown in Table 4, the gender, duration of therapy, tumor type, and serum albumin level did not differ markedly between the two groups. The age at diagnosis was younger in the group whose rate of change was ≥1.20, and the rate of change in BMI during treatment was larger in the group with a rate of change ≥1.20. The patients whose rate of change in the PMV was ≥1.20 had a longer PFS (P = 0.0231) and overall survival (OS) (P = 0.0229) than those whose rate of change was <1.20 (Fig.5). A multivariate analysis was not conducted because of the small case number.

DISCUSSION

Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes, such as physical disability, poor quality of life, and death [1]. The European Working Group on Sarcopenia in Older People recommends using the presence of both low muscle mass and low muscle function (strength or performance) to diagnose sarcopenia [1]. However, no gold standard tool currently exists that can assess motor function impairment in children

assessed for sarcopenia [13]. Thus far, to evaluate skeletal muscle mass in children, analysis using CT and MRI images, BIA, and DXA has been adopted [6, 9–11]. Since CT is often performed to evaluate therapeutic effects in pediatric patients with malignant solid tumors, we elected to use CT to measure skeletal muscle mass in this study. In previous reports using CT measurements, whole-body skeletal muscle mass was evaluated using the PMA [4, 9, 10]. Muscle area is commonly retrieved at L3, as it correlates with whole-body composition [14]. However, in children, the measurement site may shift even if one slice on the CT image deviates, which results in an error in the measurement result. When we measured the PMA using CT images of patients with acute appendicitis, an error occurred in the PMA when the measurement position deviated by 3 mm. The importance of the difference in PMA when the measurement position deviates by one slice is controversial, and we need to be more careful when assessing psoas muscle mass, especially in children. Furthermore, both PMA and PMV are measured by one person, and we could not examine about the error between measurers in this study, which is a subject for future study. In this study, we evaluated skeletal muscle mass in pediatric patients with malignant solid tumors using PMV instead of PMA. This point is a definite difference to our previous study using PMA. Mitsui et al. reported a poor prognosis of patients with testicular cancer whose PMV

had decreased during chemotherapy. They calculated the PMV using CT similar to our procedure [15].

In our study, even in patients with appendicitis, the PMA tended to be lower compared with that of the standard control (PMA: https://ahrc-apps.shinyapps.io/sarcopenia/). The online tool was developed in a North American cohort, and thus, there may be some biases, and we should pay attention to these potential biases when the results are interpreted with such an online tool.

Compared with the PMV of patients with appendicitis, the pretreatment PMV of patients with malignant tumors did not show any statistical difference. These data suggest that the behavior of the malignant tumors did not affect the skeletal muscle mass reduction when the tumor first developed.

To investigate the relationship between changes in skeletal muscle mass and the prognosis of pediatric malignant solid tumors, we divided the target patients into the PFS and R/D groups. Significant differences were observed in the rates of change in the PMV between the PFS (1.424) and R/D (1.071) groups ($P = 0.0024$). As opposed to the rate of change in the PMV, the rates of change in the PMA and the serum albumin level were not correlated with outcomes. We performed an receiver operating characteristic (ROC) curve analysis and set the cutoff value of the rate of change in the PMV to 1.20,

which means that in many cases skeletal muscle mass increased during treatment. This is thought to be due to the increase of the PMV with growth, as online resource 1 shows. The patients whose rate of change in the PMV was ≥1.20 had a longer PFS ($P = 0.0231$) and OS ($P = 0.0229$) than those whose rate of change was <1.20. Children with increased skeletal muscle mass after treatment had a better prognosis. In this study, we excluded the patients who showed recurrence of the tumor without first remission. When the posttreatment CT was taken, there were no active tumors in the patients. From this result, it can be thought that the decrease of skeletal muscle mass worsen the prognosis of pediatric malignant tumor. However, for solid tumors, we could not evaluate invisible residual tumors. In addition, the prognosis was classified according to the recurrence after treatment, but the crossing of treatment intensity has not been examined. This is because the number of cases was small, and we have to increase the number of cases and revalidate in the future.

The mechanism specific to childhood sarcopenia is not well understood, but it could be related to reduced nutrition intake, physical inactivity, hypermetabolism [16], and immunosuppression [17]. In adults, upregulation of myostatin, reduction in mammalian target of rapamycin signaling, and activation of the ubiquitin–proteasome pathway are proposed to contribute to sarcopenia [18]. Nevertheless, whether these

pathways may be directly applicable to pediatric populations is not known [19]. In pediatric patients, the coexistence of sarcopenia and malnutrition translates to growth failure and a potential neurodevelopmental delay in gross and fine motor development and cognition [19]. Whether incorporation of exercise therapy and nutritional management into conventional multidisciplinary treatment is required to improve the prognosis of pediatric malignant solid tumors that develop after treatment is an additional consideration.

CONCLUSION

In pediatric patients with malignant solid tumors, the OS and PFS were longer in cases with increased skeletal muscle mass before and after treatment. For the reason mentioned above, it is expected that nutritional management and exercise therapy to increase skeletal muscle mass in combination with conventional multidisciplinary treatment will improve the prognosis of pediatric patients with malignant solid tumors.

Additionally, changes in skeletal muscle mass have often been evaluated using PMA. However, for children with difficulty in unifying measurement sites, PMV can be evaluated more accurately than PMA.

DECLARATIONS

Conflicts of interest A.O, N.K, J.T, R.S, S.O, K.N, T.M, T.T, and T.T have no competing interests to declare that are relevant to the content of this article.

Funding This study was funded by a Research Grand from Gold Ribbon Network (2020).

Ethics approval This study was conducted according to the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Kyushu University (No. 2020-208).

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Figure Captions

Fig.1 Psoas muscle extracted from CT images by the image analysis software to measure skeletal muscle mass (a) The green area shows the cross section of the psoas muscle at the lower end level of L3. (b) Psoas muscle constructed three-dimensionally

Fig.2 Comparison of PMA measured at the lower end level of L3 and PMA measured at the level 3 mm (a) above the lower end of L3 and (b) below the lower end of L3. The horizontal line in the figure shows the average difference in PMA, whereas the dotted line shows the 95% confidence interval

Fig.3 Study flow diagram of the enrollment process. Data from 28 patients were finally analyzed

Fig.4 The rate of change in the psoas muscle volume (PMV). The scatter plot shows the rate of change in the PMV of the progression-free survival (PFS) group and the relapse/death (R/D) group. The rates of change in the PMA in the PFS (1.424) and R/D (1.071) groups ($P = 0.0024$) were significantly different

Fig.5 A receiver operating characteristic (ROC) curve analysis was conducted to determine the cutoff value of the rate of change in the PMV. The optimal cutoff value of the rate of change in the PMV was determined as the point on the ROC curve at which (sensitivity-[1-specificity]) was maximized (Youden index)

Fig.6 Kaplan–Meier estimates of the progression-free survival (PFS) (a) and overall survival (OS) (b) of the patients in this study. Patients in whom the rate of change in the PMA was ≥1.20 exhibited a longer PFS (a) ($P = 0.0231$) and OS (b) ($P = 0.0229$) than those in whom the rate of change in the PMA was <1.20. The red and blue lines represent the Kaplan–Meier curves of the rate of change of ≥1.20 and <1.20 in the PMV, respectively (color version of the figure is available online)

Online Resource 1. The scatter plots show the trends of PMV (a) and PMA (b) by age in patients with appendicitis

Table 1 Characteristics of the patients with acute appendicitis divided into the 1–5, 6–10, and 11–15 year age groups

Table 2 Characteristics of the patients with pediatric malignant solid tumors according to prognosis

Table 3 Rates of change in the PMA, PMV, BMI, and serum albumin level according to patient prognosis

Table 4 Characteristics of the patients with pediatric malignant solid tumors according to the rate of change in the PMV

Table1

	1–5 y (n = 20)		**6–10 y (n = 126)**		**11–15 y (n = 39)**	
	Male	Female	Male	Female	Male	Female
Sex	7	13	74	52	20	19
Age, years (mean [range])	4.4 (3–5)	4.1 (1–5)	8.6 (6–10)	8.1 (6–10)	12.2 (11–14)	12.3 (11–15)

Table2

	PFS (*n*=21)	R/D (*n*=7)	*P*-value
Sex, *n* (%)			0.823
Male	8 (38.1%)	3 (42.9%)	
Female	13 (61.9%)	4 (57.1%)	
Age at diagnosis (mean[range])(days)	1135.5 [232–3337]	1956 [657–3568]	0.115
Duration of therapy (mean[range])(days)	307.9 [163–655]	306.0 [192–463]	0.971
NLR at the diagnosis (mean[range])	2.064 [0.363–7.939]	3.288 [1.112–11.449]	0.439
Tumor type, *n* (%)			0.695
Neuroblastoma	9 (42.9%)	3 (42.9%)	
Hepatoblastoma	4 (19.1%)	0 (0.0%)	
Wilms tumor	4 (19.1%)	2 (28.6%)	
Rhabdomyosarcoma	3 (14.3%)	1 (14.3%)	
Others	1 (4.8%)	1 (14.3%)	

Table3

	PFS (n=21)	R/D (n=7)	*P*-value
Rate of change in the PMA (mean[range])	1.355 [0.735–1.898]	1.106 [0.772–1.617]	0.0775
in the PMV (mean[range])	1.424 [0.899–2.772]	1.071 [0.930–1.240]	0.0024*
in the BMI (mean[range])	0.964 [0.821–1.070]	0.933 [0.769–1.140]	0.513
in the serum albumin(mean[range])	1.089 [0.745–1.833]	1.102 [0.833–1.333]	0.887

Table4

	Rate of change in the PMV<1.20 (n=13)	Rate of change in the PMV≥1.20 (n=15)	*P*-value
Sex, n (%)			0.246
Male	7 (54%)	4 (27%)	
Female	6 (46%)	11 (73%)	
Age at diagnosis (mean[range])(days)	1988.0 (510–3568)	779.6 (232–3337)	0.002*
Duration of therapy (mean[range])(days)	307.8 (169–596)	307.1 (163–655)	0.836
Tumor type, n (%)			0.423
Neuroblastoma	6 (46%)	6 (40%)	
Hepatoblastoma	1 (8%)	3 (20%)	
Wilms tumor	3 (23%)	3 (20%)	
Rhabdomyosarcoma	1 (8%)	3 (20%)	
Other	2 (15%)	0 (0%)	
Rate of change in the BMI (mean[range])	0.925 [0.769–1.140]	0.982 [0.821–1.070]	0.018*
in the serum albumin (mean[range])	1.149 [0.833–1.833]	1.044 [0.745–1.607]	0.279

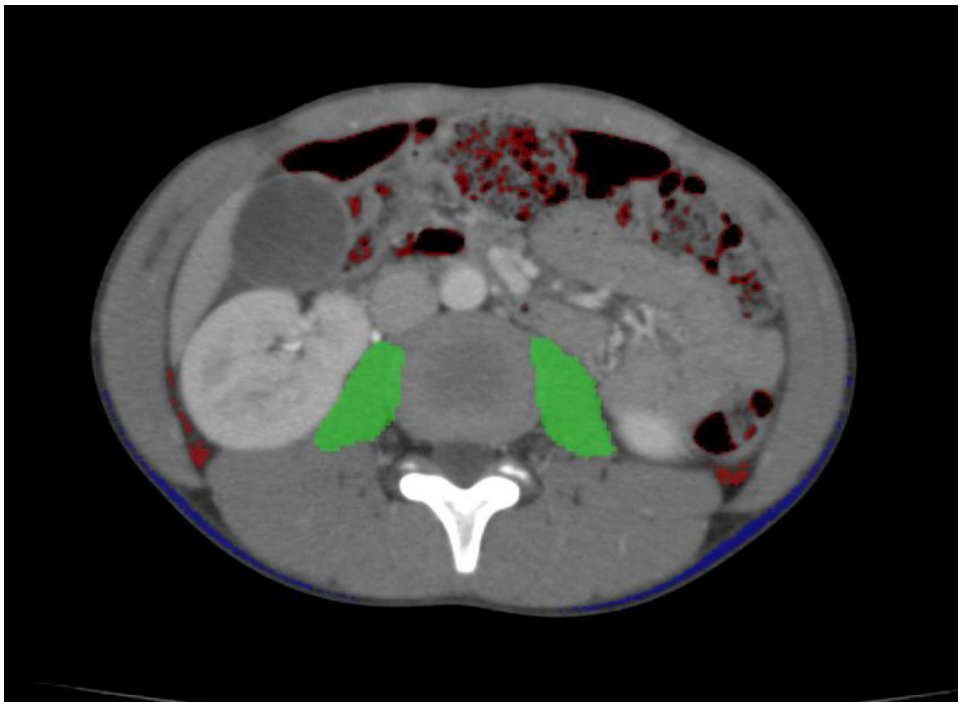


Fig. 1a

Fig.1b

(a) <Lower end of vertebral body of L3 vs 3 mm above>

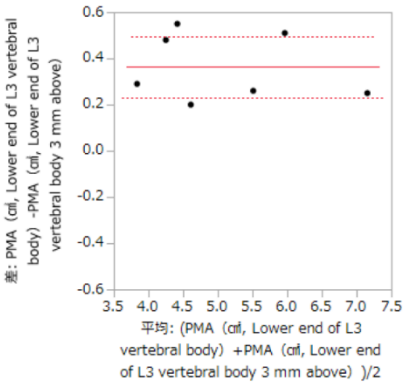
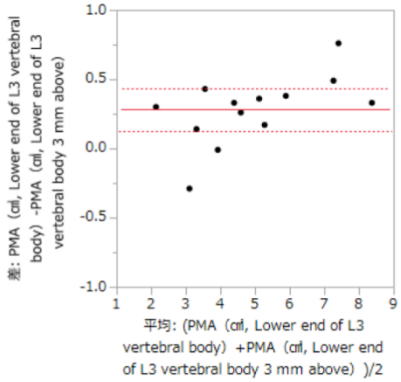
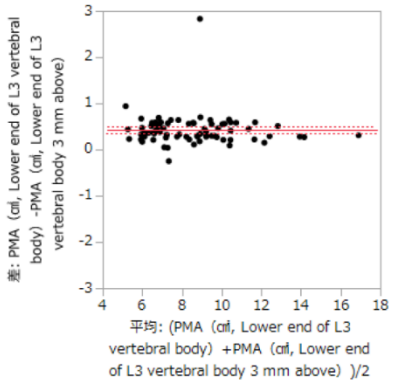
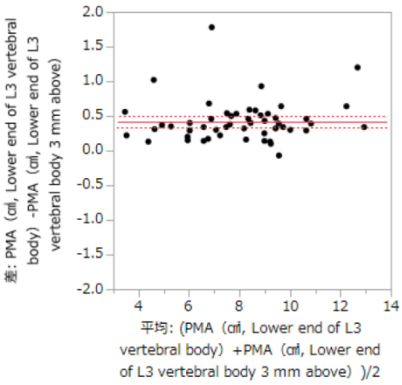
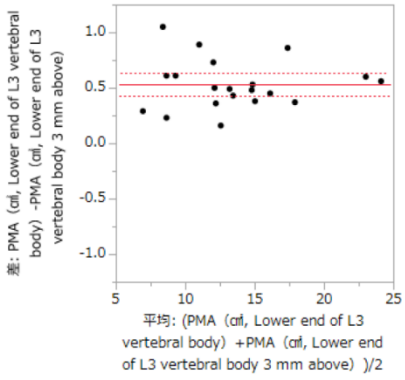
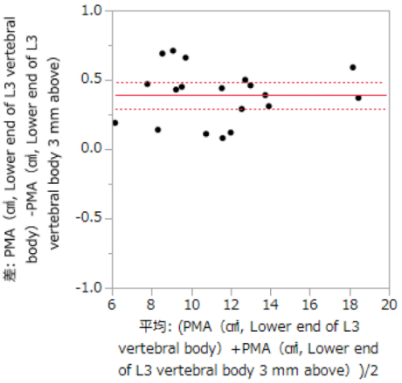
	Male	Female
1–5 y		
	P (Prob > |t|)=0.0006	*P* (Prob > |t|) <0.0001
6–10 y		
	P (Prob > |t|) <0.0001	*P* (Prob > |t|) <0.0001
11–15 y		
	P (Prob > |t|) <0.0001	*P* (Prob > |t|) <0.0001

Fig. 2a

(b) <Lower end of vertebral body of L3 vs 3 mm below>

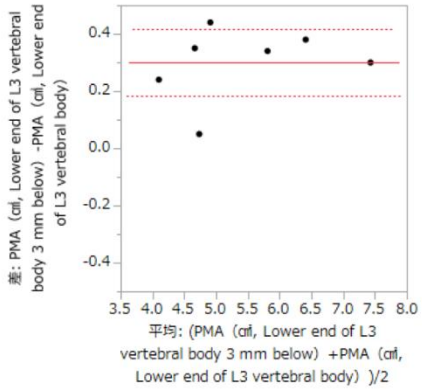
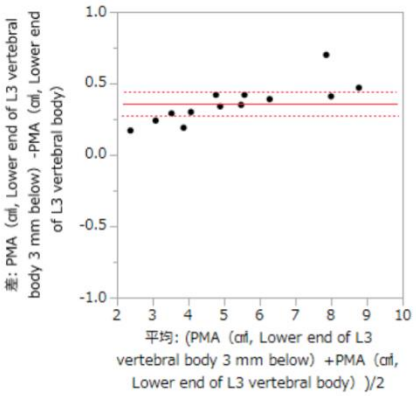
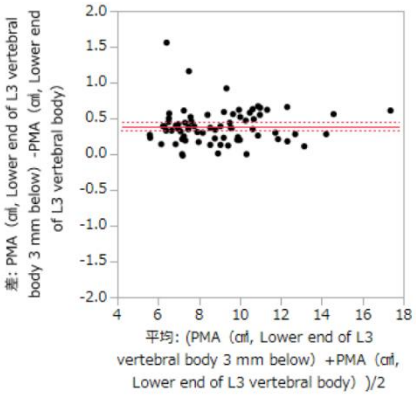
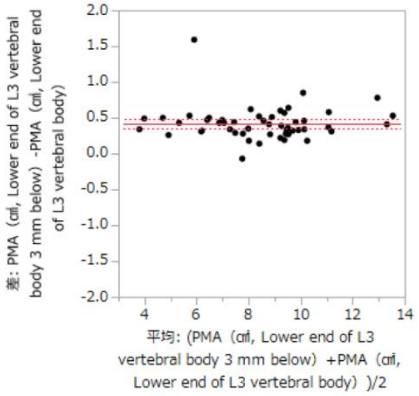
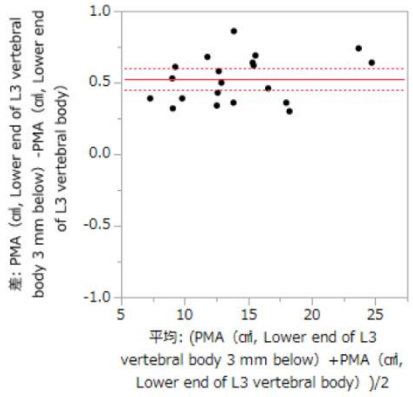
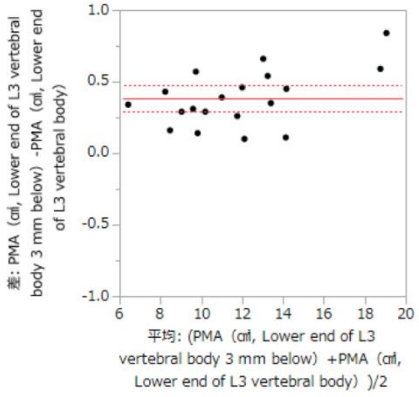
	Male	Female
1–5 y		
	P (Prob > |t|)=0.0008	*P* (Prob > |t|) <0.0001
6–10 y		
	P (Prob > |t|) <0.0001	*P* (Prob > |t|) <0.0001
11–15 y		
	P (Prob > |t|) <0.0001	*P* (Prob > |t|) <0.0001

Fig .2b

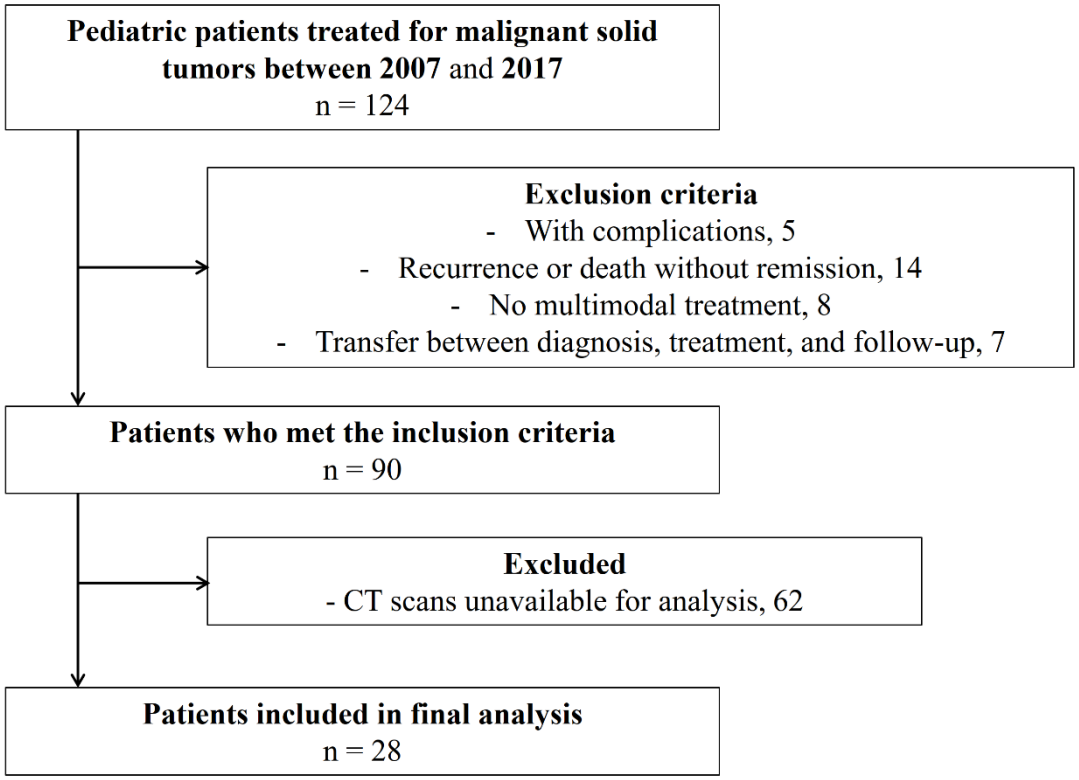

Pediatric patients treated for malignant solid tumors between 2007 and 2017
n = 124
Exclusion criteria
- With complications, 5
- Recurrence or death without remission, 14
- No multimodal treatment, 8
- Transfer between diagnosis, treatment, and follow-up, 7
Patients who met the inclusion criteria
n = 90
Excluded
- CT scans unavailable for analysis, 62
Patients included in final analysis
n = 28

Fig. 3

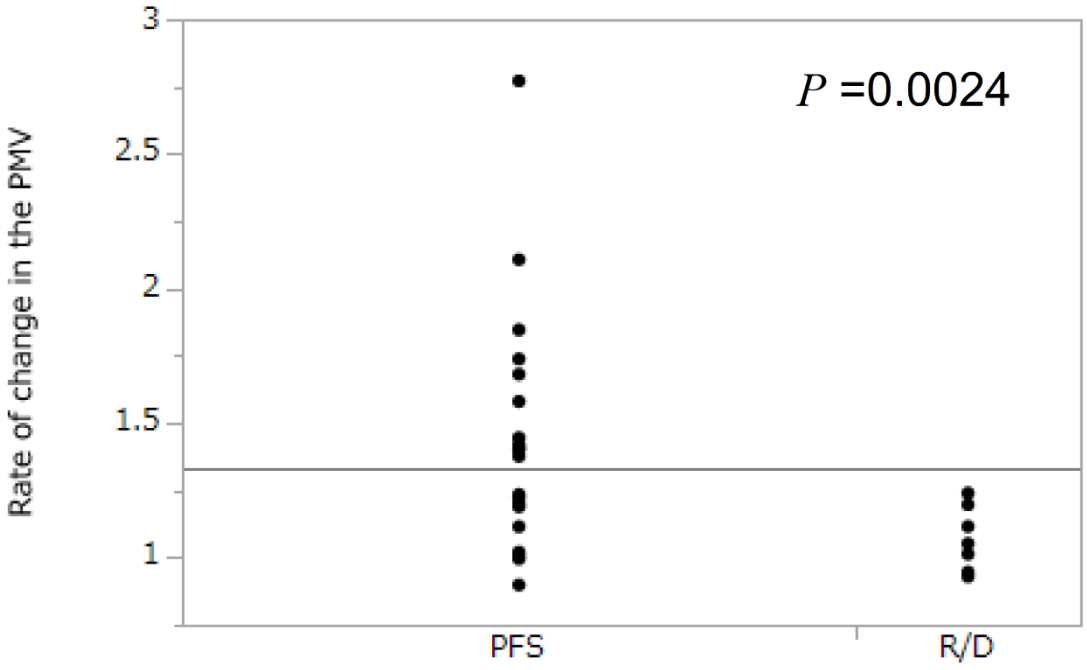

Rate of change in the PMV
3
2.5
2
1.5
1
P =0.0024
PFS
R/D

Fig. 4

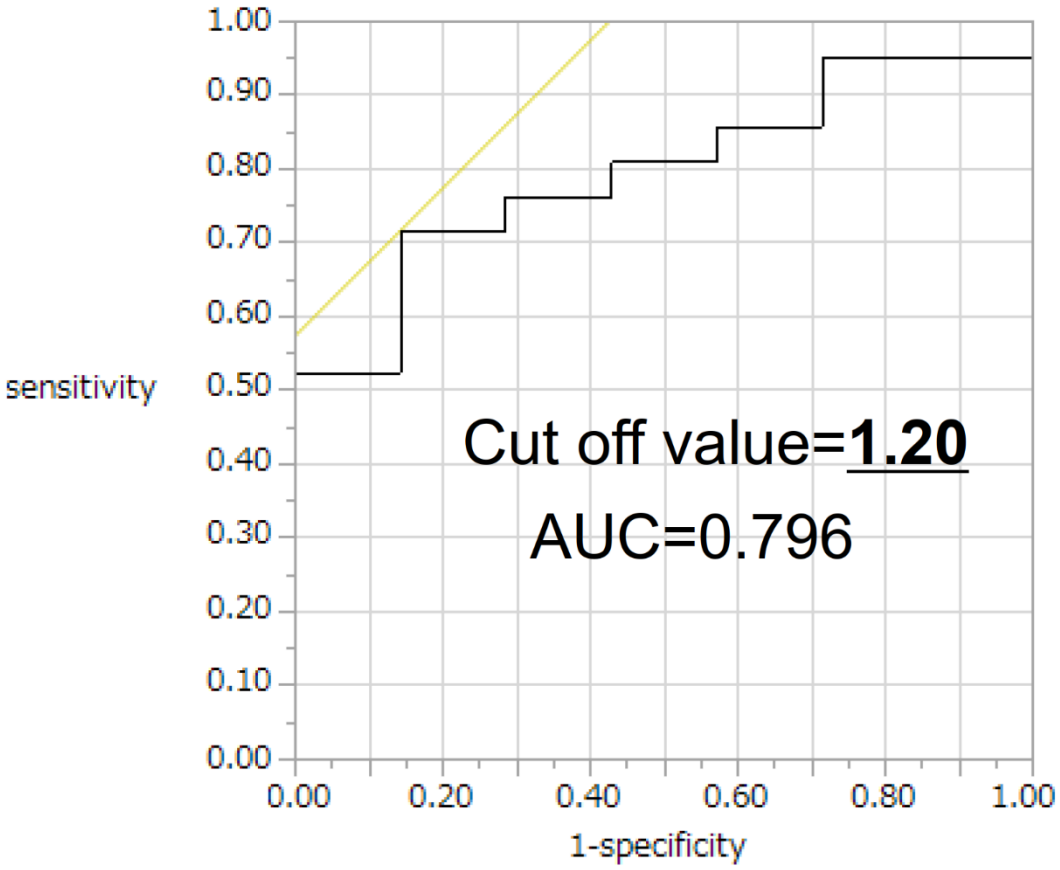

sensitivity
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.00
0.20
0.40
0.60
0.80
1.00
1-specificity
Cut off value=1.20
AUC=0.796

Fig. 5

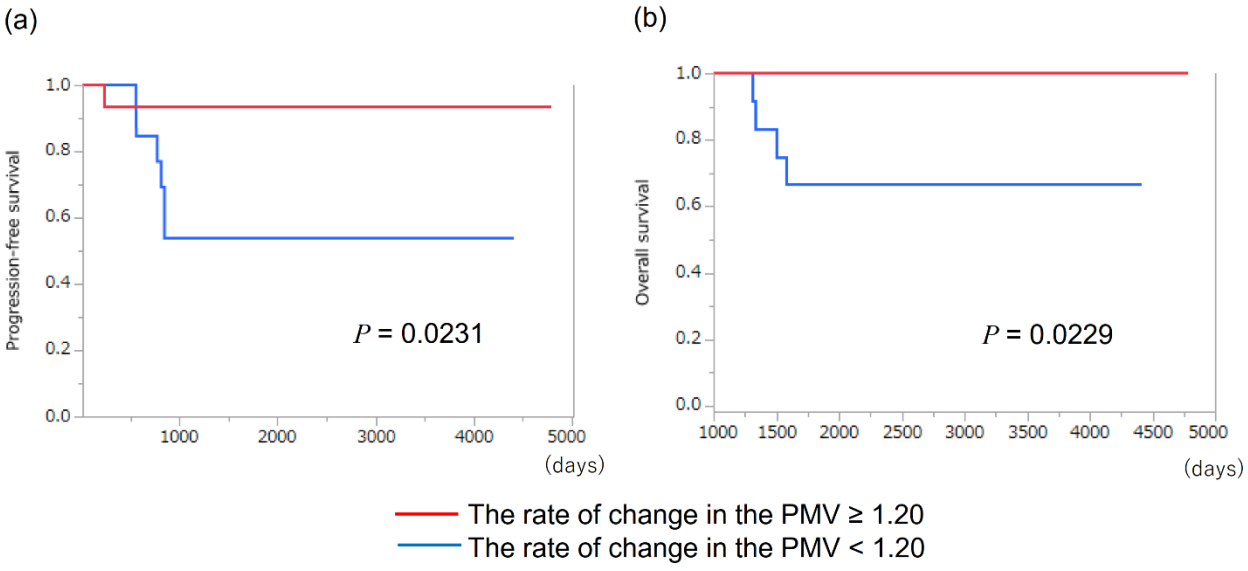
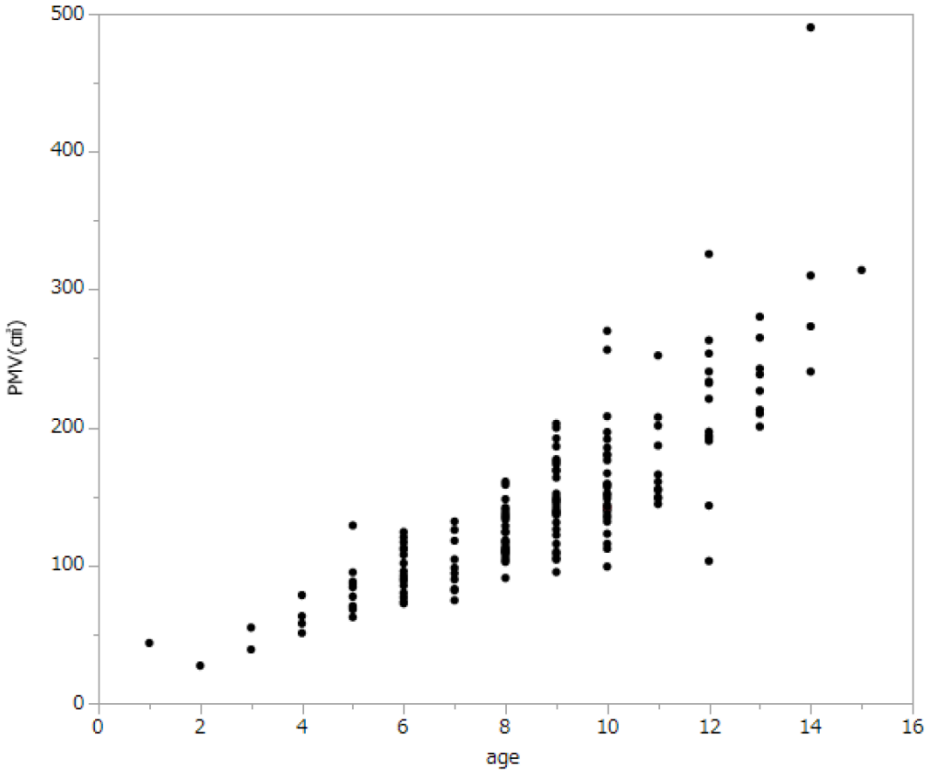
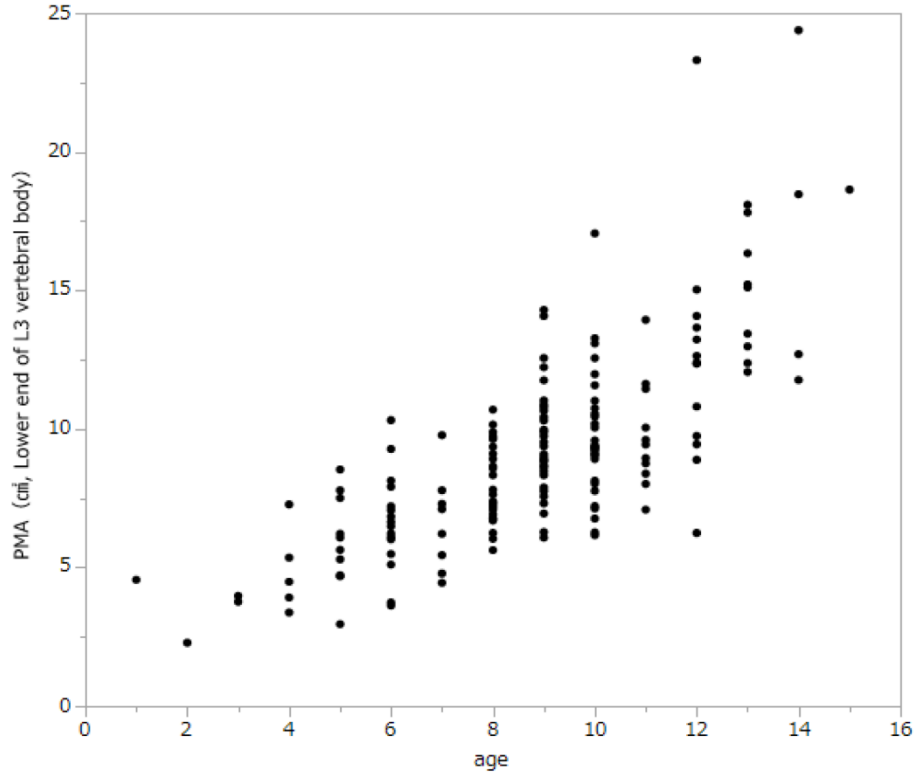

(a)
Progression-free survival
1.0
0.8
0.6
0.4
0.2
0.0
1000
2000
3000
4000
5000
(days)
P = 0.0231
(b)
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
1000
1500
2000
2500
3000
3500
4000
4500
5000
(days)
P = 0.0229
The rate of change in the PMV ≥ 1.20
The rate of change in the PMV < 1.20

Fig. 6



Online resource 1



Online resource 2