

Is There a Reliable Method to Predict the Limb Length Discrepancy after Chemotherapy and Limb Salvage Surgery in Children with Osteosarcoma?

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Abstract

Background: For a child with osteosarcoma, prediction of the limb length discrepancy at maturity is important when planning for limb salvage surgery. The purpose of this study was to provide a reliable prediction method.

Methods: A retrospective review of Chinese children receiving chemotherapy for osteosarcoma before skeletal maturity was conducted. Standing full-length radiographs of the lower extremity were used for length measurements. Length-for-age curves were constructed using the LMS method. The lower limb multiplier for a specific age and gender was calculated using the formula $M = L_m/L$, where M was the gender- and age-specific multiplier, L_m was the bone length at maturity, and L was the age-specific bone length. Prematurity and postmaturity radiographs were used to assess the accuracy of the prediction methods.

Results: A total of 513 radiographs of 131 boys and 314 radiographs of 86 girls were used to calculate the coefficients of the multiplier. The multipliers of 8-, 9-, 10-, 11-, 12-, 13-, 14-, 15-, 16-, 17-, and 18-year-old boys after chemotherapy for osteosarcoma were 1.394, 1.306, 1.231, 1.170, 1.119, 1.071, 1.032, 1.010, 1.004, 1.001, and 1.000, respectively; while for girls at the same ages, the multipliers were 1.311, 1.221, 1.146, 1.092, 1.049, 1.021, 1.006, 1.001, 1.000, 1.000, and 1.000, respectively. Prematurity and postmaturity femoral and tibial lengths of 21 patients were used to assess the prediction accuracy. The mean prediction error was 0 cm, 0.8 cm, and 1.6 cm for the multiplier method using our coefficients, Paley's coefficients, and Anderson's method, respectively.

Conclusions: Our coefficients for the multiplier method are reliable in predicting lower limb length growth of Chinese children with osteosarcoma.

Key words: Chemotherapy; Chinese Children; Lower Limb Length; Multiplier Method; Osteosarcoma

INTRODUCTION

Osteosarcoma is a common malignant bone tumor in children that involves the metaphysis of the distal femur and proximal tibia. Local control of osteosarcoma requires chemotherapy and surgery with a wide resection margin. After surgery, the normal growth of the uninvolved, contralateral extremity can result in limb length discrepancy (LLD). A discrepancy of <1 cm is acceptable because it is not noticeable and has no risk of complications. If the discrepancy is >2 cm, complications such as limping, scoliosis, osteoarthritis of the knee and hip, low back pain, and lower extremity stress fractures can develop.^[1-5] If the expected LLD at skeletal maturity is <3 cm, a discrepancy can be prevented by lengthening the limb 1–2 cm during reconstruction; otherwise, alternative reconstructions, for example, expandable prostheses, should be used.^[6]

Prediction of the discrepancy before surgery is important for planning the reconstruction. However, there is no accepted, reliable method to predict discrepancies for children who undergo limb salvage surgery and chemotherapy.

For healthy children, Anderson's growth remaining method,^[7] Moseley's straight line graph,^[8] and Paley's multiplier

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method^[9] have been the standards for predicting limb length and LLD. Among these, the multiplier method is simple and reliable.^[10,11] The length of limb or bone at maturity (L_m) can be predicted by using the formula $L_m = L \times M$, where L is the current length and M is the current age multiplier. The degree of discrepancy after epiphyseal plate injury equals the growth remaining on the physis (G_{physis}), which is predicted using the formula $G_{\text{physis}} = (L_m - L) \times \kappa$, where κ is a constant (0.71 for the distal femur and 0.57 for the proximal tibia). Thus, the accuracy of the coefficients (M , the current age) is the key to using the multiplier method.

Recently, Gilg *et al.*^[12] reported a decreased adult height in patients after chemotherapy and therefore Paley's multiplier method overestimated the height of patients with bone tumors (range: -17 to 8 cm, mean 2.3 cm, median absolute error 5 cm).

The purpose of this study was to adjust the coefficients of the multiplier method to more accurately predict the length of the limb at maturity based on the lower limb length of Chinese children with osteosarcoma.

METHODS

Patients

This retrospective study was approved by the Medical Ethics Committee of Beijing Jishuitan Hospital.

To calculate the coefficients of the multiplier, patients were selected according to these inclusion criteria: Osteosarcoma diagnosis, treated with adjuvant and neoadjuvant chemotherapy (high-dose methotrexate, doxorubicin, ifosfamide, and cisplatin) before skeletal maturity, and available standing full-length radiographs of the lower limb before 18-year-old.

To assess the accuracy of prediction methods, patients were selected according to these inclusion criteria: Osteosarcoma diagnosis, treated with adjuvant and neoadjuvant chemotherapy before skeletal maturity, and available pre-maturity and post-maturity standing full-length radiographs of the lower limb. Patients whose lower limb length data were included to calculate the coefficients of multiplier were excluded.

Lower limb length measurement

Standing full-length radiographs of the lower extremity were taken using Sonialvision Safire II equipment and slot-scanning technology (Shimadzu Corporation, Kyoto, Japan). Longitudinal length of the healthy (without a tumor, tumor-like lesion, deformity, or trauma) femur, tibia, and lower limb were measured from the proximal end of the femoral head to the intercondylar notch, the tibial crest to the center of the tibial plafond, and the proximal end of the femoral head to the center of the tibial plafond, respectively.

Statistical analysis

Statistical analyses were performed using the R Project for Statistical Computing (version 3.2.0; R Foundation for Statistical Computing, Vienna, Austria).

For constructing the length-for-age curves, the LMS method (package "gamlss") was used. Then, the lower limb multiplier value for a specific age and gender was calculated using the formula $M = L_m/L$, where M is the gender- and age-specific multiplier and L is the age-specific bone length. The maximal value under the curve was taken as the bone length at maturity (L_m).

The degrees of accuracy of the different prediction methods were compared. The lengths of the femur and tibia at maturity were predicted as Anderson *et al.*^[7] or Paley *et al.*^[9] reported. Predicted length minus actual length was defined as the prediction error. Statistical analyses included *t*-tests for paired variances and regression analysis. A value of $P < 0.05$ was considered statistically significant.

RESULTS

From January 2008 to September 2014, 217 patients met the inclusion criteria and 827 radiographs (513 radiographs of 131 boys and 314 radiographs of 86 girls) were used to construct the length-for-age curves and to calculate the coefficients of the multiplier method.

The median length of the femur, tibia, and lower limbs for specific ages and gender and the length-for-age curves are shown in Table 1 and Figure 1, respectively. The overall lower-limb multipliers for boys and girls are shown in Table 2 and Figure 2. Because the multipliers for the tibia and femur are nearly identical, we took the mean multipliers for both bones to obtain one, similar to what Paley *et al.*^[9] did.

Prematurity and postmaturity radiographs of 21 patients (15 boys and 6 girls) were used to assess the accuracy of the prediction methods. The mean error of our predictions was lower than that of the error from Paley's and Anderson's predictions, and the difference was statistically significant [Table 3]. When compared with actual measurements, our coefficients had a correlation of 0.98, whereas Paley's and Anderson's predictions had a correlation of 0.96 and 0.76, respectively [Figure 3].

DISCUSSION

For healthy children, there are three main methods to predict limb length and LLD; they are Anderson's growth remaining method, Moseley's straight line graph, and Paley's multiplier method. Anderson's method was designed only for Caucasian children and is less accurate than other methods, consistent with our results.^[7,10] Moseley's method uses limb lengths measured at two or three ages (interval ≥ 1 year) as parameters for prediction; therefore, it is not practical for a child who will soon undergo an operation.^[8] The multiplier method just uses current age and limb length measurements as parameters for prediction and has been proven to be more reliable than other methods.^[10,11] Therefore, the multiplier method is the best choice to

Table 1: Median Length and Interquartile Range of Femur, Tibia and Lower Limb of Chinese Boys and Girls with Osteosarcoma (cm)

Age (years)	Length of Lower Limb		Length of Femur		Length of Tibia	
	Boys (n = 131)	Girls (n = 86)	Boys (n = 131)	Girls (n = 86)	Boys (n = 131)	Girls (n = 86)
8	57.7 (1.8)	56.6 (2.5)	30.3 (1.4)	30.2 (0.5)	26.5 (1.3)	25.5 (1.7)
9	62.2 (2.7)	59.9 (3.3)	32.2 (1.7)	32.1 (1.7)	28.5 (1.7)	27.7 (1.9)
10	66.1 (4.4)	64.9 (4.7)	34.2 (2.1)	34.1 (2.5)	30.3 (2.3)	29.5 (2.3)
11	68.8 (4.7)	68.9 (5.1)	36.0 (2.4)	35.9 (2.7)	31.7 (2.8)	30.9 (2.7)
12	71.7 (4.8)	71.0 (5.5)	37.7 (3.1)	37.5 (3.2)	33.1 (2.8)	32.1 (3.4)
13	75.3 (5.5)	72.2 (5.4)	39.6 (3.1)	38.5 (3.6)	34.6 (3.2)	32.9 (3.8)
14	78.0 (6.4)	73.3 (6.3)	41.2 (3.1)	39.1 (3.4)	35.7 (3.2)	33.4 (3.7)
15	79.6 (6.8)	73.7 (5.7)	42.1 (2.6)	39.3 (2.9)	36.4 (3.2)	33.6 (3.7)
16	80.0 (5.9)	73.7 (5.2)	42.3 (2.4)	39.3 (2.9)	36.7 (2.3)	33.6 (3.3)
17	80.1 (5.0)	73.7 (4.9)	42.3 (2.3)	39.3 (2.5)	36.8 (2.8)	33.6 (3.1)
18	80.1 (4.1)	73.7 (4.8)	42.3 (2.1)	39.3 (2.4)	36.9 (1.9)	33.6 (2.8)

Data are shown as median (interquartile range).

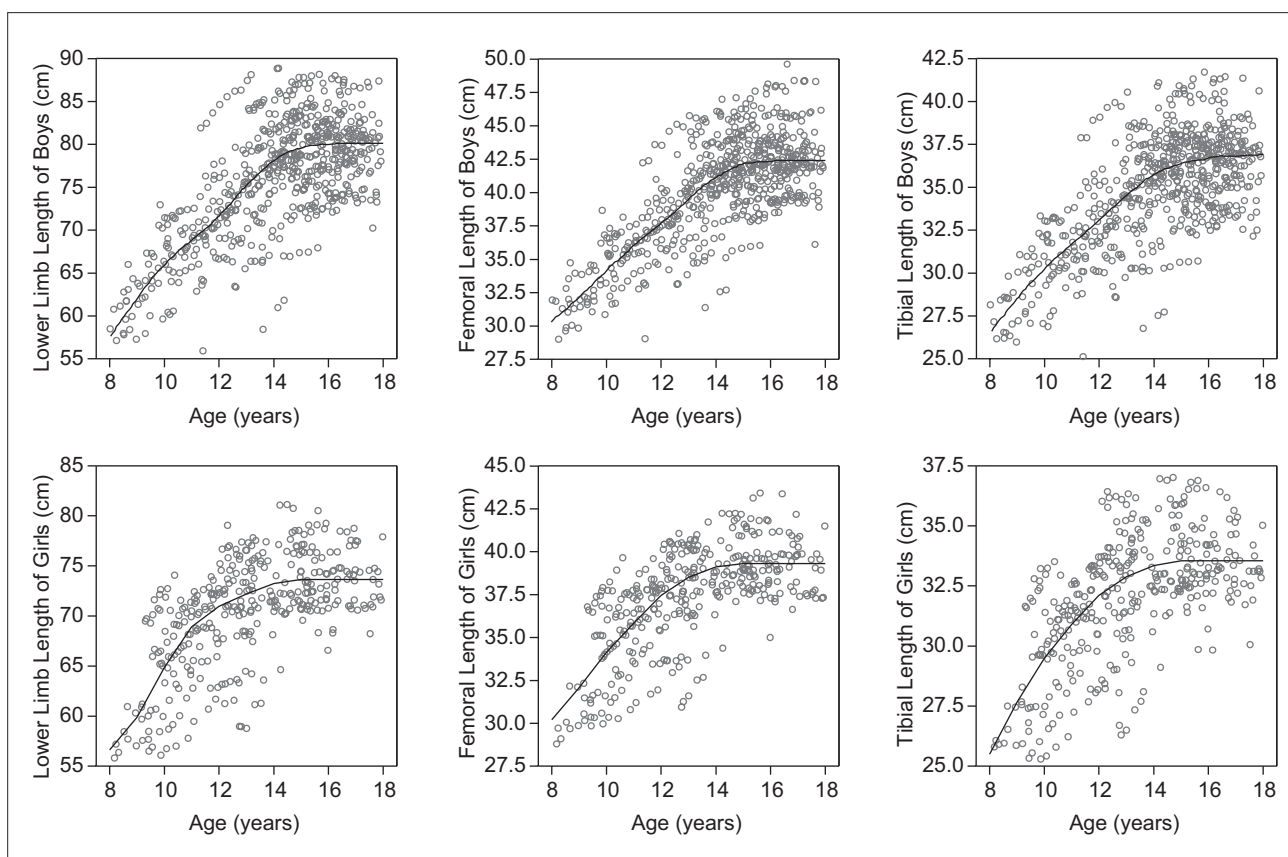


Figure 1: Lower limb, femoral, and tibial length-for-age curves of Chinese children with osteosarcoma, boys (n = 131), girls (n = 86).

predict limb length and LLD for Chinese children with osteosarcoma.

However, our results showed the mean femoral and tibial length of Chinese children with osteosarcoma was overestimated by the multiplier method by 0.8 cm (range: -1.2 to 3.4 cm). In 38.1% of cases, the error was more than 1 cm and in 11.9% more than 2 cm. Gilg *et al.*^[12] reported similar findings of overestimation by the multiplier method using Paley's coefficients (range: -17 to 8 cm, mean: 2.3 cm, median absolute error: 5 cm) after chemotherapy. Because an

LLD of more than 1 cm can lead to many complications,^[13] we need to be careful in predicting limb length and LLD using Paley's coefficients for young sarcoma patients.

All of the predicted femoral and tibial length errors using our coefficients were <1.6 cm, which means the predicted LLD errors were also very small. Because few complications occur if LLD is <1 cm,^[13] we believe our coefficients are able to accurately predict limb length and LLD of Chinese children undergoing limb-salvage surgery for osteosarcoma.

Table 2: Lower limb multipliers for Chinese children with osteosarcoma

Age (years)	Multiplier					
	Boys (n = 131)			Girls (n = 86)		
	Femur	Tibia	Mean	Femur	Tibia	Mean
8.0	1.397	1.390	1.394	1.310	1.311	1.311
8.5	1.358	1.339	1.349	1.267	1.262	1.265
9.0	1.320	1.292	1.306	1.226	1.216	1.221
9.5	1.279	1.252	1.266	1.189	1.175	1.182
10.0	1.242	1.220	1.231	1.153	1.139	1.146
10.5	1.208	1.189	1.199	1.123	1.111	1.117
11.0	1.177	1.162	1.170	1.097	1.086	1.092
11.5	1.151	1.139	1.145	1.073	1.063	1.068
12.0	1.124	1.114	1.119	1.052	1.045	1.049
12.5	1.100	1.089	1.095	1.035	1.030	1.033
13.0	1.074	1.067	1.071	1.021	1.021	1.021
13.5	1.049	1.049	1.049	1.011	1.013	1.012
14.0	1.031	1.032	1.032	1.005	1.006	1.006
14.5	1.017	1.021	1.019	1.002	1.002	1.002
15.0	1.006	1.013	1.010	1.001	1.001	1.001
15.5	1.003	1.009	1.006	1.000	1.000	1.000
16.0	1.002	1.005	1.004	1.000	1.000	1.000
16.5	1.001	1.002	1.002	1.000	1.000	1.000
17.0	1.000	1.002	1.001	1.000	1.000	1.000
17.5	1.000	1.000	1.000	1.000	1.000	1.000
18.0	1.000	1.000	1.000	1.000	1.000	1.000

Table 3: Comparison of errors between different methods of predicting lengths of the femur and tibia at maturity (n = 21)

Items	Multiplier method		Anderson method
	Our coefficients	Paley's coefficients	
M ± SD (cm)	0 ± 0.6	0.8 ± 0.9*	1.6 ± 2.4†
Range (cm)	-1.3 to 1.6	-1.2 to 3.4	-4.2 to 5.0
Absolute error >1 cm (%)	16.7	38.1	73.8
Absolute error >2 cm (%)	0	11.9	57.1
Absolute error >3 cm (%)	0	2.4	40.5

Compared with mean error of our predictions by paired *t*-test: **t* = 7.072, *P* < 0.001; †*t* = 4.872, *P* < 0.001. M: Mean error; SD: Standard deviation.

Paley's calculation was based on data from Caucasian children. After reviewing two studies of Chinese children and a study of black children, Paley *et al.*^[9] reported that the multipliers of different ethnic groups were similar. This implies the modified coefficients in our study could be applicable for all children with osteosarcoma receiving chemotherapy, regardless of ethnicity. However, further study with a larger sample size of diverse ethnicity is needed.

There are some limitations to our study. First, we could not calculate the mean length and standard deviation (SD) for a specific age and gender as Anderson *et al.*^[7] did because the radiographs of our patients were not all

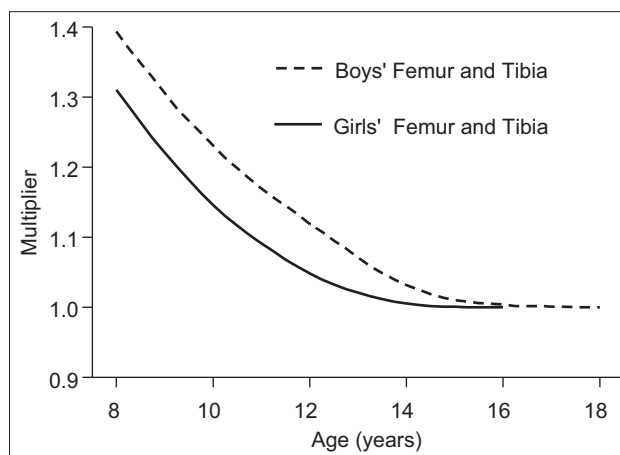


Figure 2: Femoral and tibial multipliers for Chinese children with osteosarcoma.

performed at the same age. Instead, we used the median length stratified by the LMS method to calculate the coefficients rather than the average of the multiplier for each percentile group as Paley *et al.*^[9] did. However, the multipliers for the mean group and average of each percentile group of 8- to 18-year-old children were approximately the same;^[7] the median and mean length of the femur, tibia, and lower limb for a specific age and gender follow the same normal distribution. Therefore, no essential differences between our statistical method and that of Paley's study exist.

Another limitation could be the LMS method used in this study to construct the growth curve because children with osteosarcoma have a decline in growth velocity during chemotherapy and a catchup phase after cessation of antineoplastic treatment.^[12] However, the influence of antineoplastic agents on the growing bone is very complex, and there is a lack of reported statistical methods to analyze this type of data. Considering the prediction error of our coefficients is acceptable, this limitation might be negligible in our study. We might be able to clarify this problem when more data are collected in the future.

Finally, using the constant κ (0.71 for the distal femur, 0.57 for the proximal tibia) to predict LLD is acceptable for a child who has undergone epiphysiodesis,^[7,11] but whether these values are equally applicable in predicting LLD of a child who has undergone limb salvage surgery is questionable. The collapse of the implant and growth of remaining bone might vary according to the reconstruction method. Therefore, the accuracy of the multiplier method in predicting LLD might need further research for these children. We will focus on this problem in the future.

In summary, the adjusted coefficients of the multiplier method are reliable in predicting the lower limb length of Chinese children with osteosarcoma.

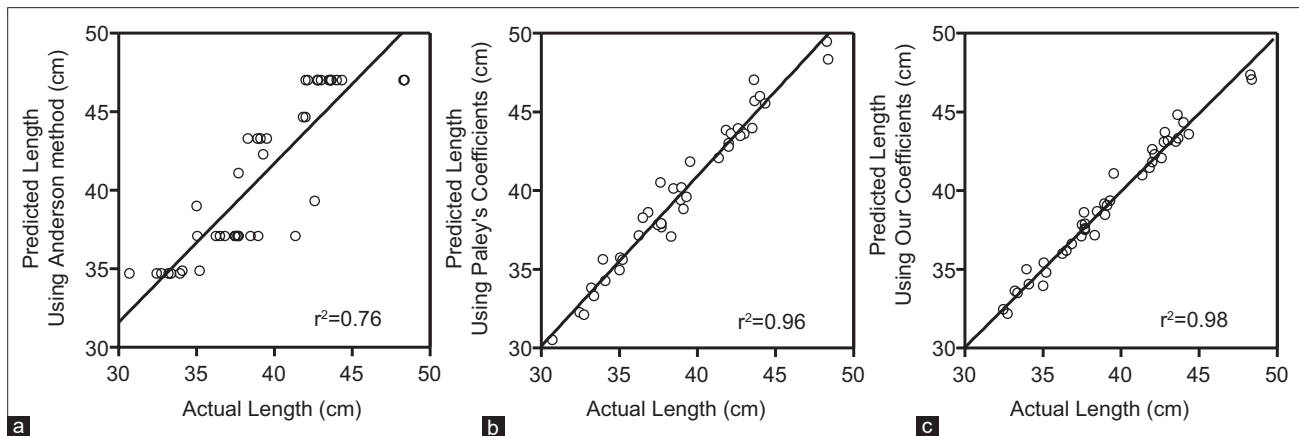


Figure 3: Correlation between actual measurements and predicted the length of the femur and tibia using Anderson's method (a), the multiplier method with Paley's coefficients (b), and the multiplier method with our coefficients (c), $n=21$.

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Conflicts of interest

There are no conflicts of interest.

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