Older age at surgery and postoperative leg length discrepancy are risk factors for unfavourable patient-reported outcome measures of knee tumour endoprostheses following resection for musculoskeletal tumour of the lower limb

Cite this article:
Bone Jt Open 2023;4(12):
906–913.

DOI: 10.1302/2633-1462.
412.BJO-2023-0125.R1

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Aims

To evaluate mid-to long-term patient-reported outcome measures (PROMs) of endoprosthetic reconstruction after resection of malignant tumours arising around the knee, and to investigate the risk factors for unfavourable PROMs.

Methods

The medical records of 75 patients who underwent surgery between 2000 and 2020 were retrospectively reviewed, and 44 patients who were alive and available for follow-up (at a mean of 9.7 years postoperatively) were included in the study. Leg length discrepancy was measured on whole-leg radiographs, and functional assessment was performed with PROMs (Toronto Extremity Salvage Score (TESS) and Comprehensive Outcome Measure for Musculoskeletal Oncology Lower Extremity (COMMON-LE)) with two different aspects. The thresholds for unfavourable PROMs were determined using anchor questions regarding satisfaction, and the risk factors for unfavourable PROMs were investigated.

Results

The thresholds for favourable TESS and COMMON were 64.8 and 70.4 points, respectively. Multivariate analysis showed that age at surgery ($p = 0.004$) and postoperative leg length discrepancy ($p = 0.043$) were significant risk factors for unfavourable TESS results, while age at surgery ($p < 0.001$) was a significant risk factor for unfavourable COMMON-LE results. Following receiver operating characteristic analysis, the threshold for both TESS and COMMON-LE was 29 years of age at surgery. Additionally, a leg length discrepancy of 8.2 mm was the threshold for unfavourable TESS.

Conclusion

Patients aged > 29 years at the time of surgery require appropriate preoperative counselling and adequate postoperative physical and socioemotional support. Reconstruction equivalent to the length of the resected bone can reduce the risk of functional disabilities in daily living.

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Take home message

- Age at surgery and postoperative leg length discrepancy were associated with patient-reported outcomes after endoprosthetic knee arthroplasty.

Introduction

Improvement in multimodal treatment for musculoskeletal malignancies has enabled higher patient survival and limb-salvaging procedures.[1,2] Endoprosthetic reconstruction following the resection of malignant tumours arising in the limbs has been an established and widely used procedure for limb-salvaging.[3-6] A particularly common site for malignancies of the lower limbs is the knee; the oncological outcomes of patients with knee endoprosthetic reconstruction have improved. Therefore, evaluation of long-term postoperative functional outcomes around the knee is becoming increasingly important.

Recently, patient-reported outcome measures (PROMs) have been used to evaluate postoperative physical function, activity, and satisfaction after various musculoskeletal surgeries.[7-9] The Toronto Extremity Salvage Score (TESS) is the most commonly used PROM in lower limb salvage surgery,[10] and has been validated in languages worldwide.[11-13] The TESS evaluates physical function using a questionnaire on difficulties in activities of daily living. Health-related quality of life (HRQoL), including body image, mental status, and social activities, has also been the focus in recent years.[14,15] The Comprehensive Outcome Measure for Musculoskeletal Oncology Lower Extremity (COMMON-LE), a disease-specific PROM developed in Japan, comprehensively evaluates HRQOL in terms of pain, activities of daily living (ADLs), socioemotional conditions, and general health domain.[16] These PROMs have been used to compare cohorts with different treatment strategies[4,17] and observe changes over time.[18] However, the distribution, characteristics, success thresholds, and determinants of favourable PROMs remain unclear.

Despite good oncological achievements, the surgical procedure for endoprosthetic knee arthroplasty is invasive and requires resection of massive volumes of bone and soft-tissue around the tumour. This surgery often results in complications, such as infection, aseptic loosening, and prosthetic fractures, leading to revision surgery.[3,19-22] Furthermore, younger patients frequently have leg length discrepancies even with the use of expandable prostheses such as the Kotz Modular Femur Tibia Reconstruction system (Stryker, UK). Massive volumes of bone and soft-tissue resection and postoperative leg length differences may make ADLs more difficult and adversely affect PROMs.[17,23] However, few studies have assessed factors affecting PROMs in knee tumour endoprostheses.

In this study, we evaluated mid- to long-term postoperative PROMs after endoprosthetic knee arthroplasty and investigated the following clinical question: what are the risk factors for unfavourable PROMs after endoprosthetic knee arthroplasty? We studied two types of PROMs (TESS and COMMON-LE) with different evaluation aspects.

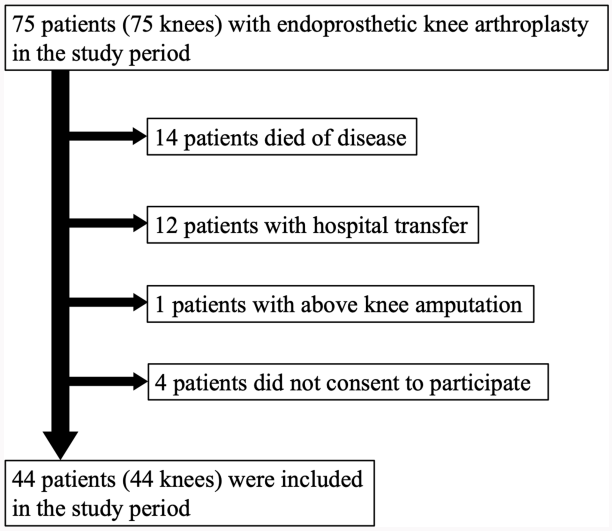

Fig. 1
The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) diagram for inclusion process.

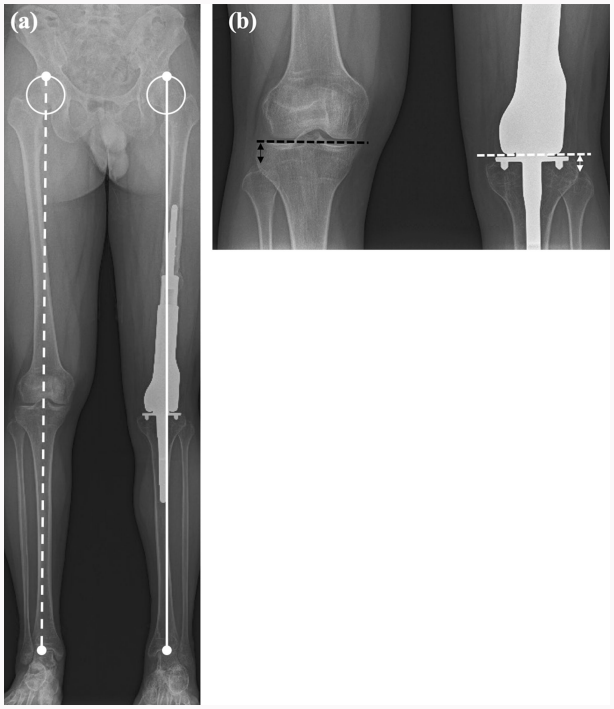

Fig. 2
a) Leg length was measured as the distance between the top of the femoral head and the centre of the ankle joint. The leg length discrepancy with the opposite lower leg was calculated. b) Measurement of joint line height. On the operative side, the distance from the fibular head to a line connecting the most distal points of the medial and lateral femoral condyle (white dashed line) was measured. On the opposite side, the distance from the fibular head to the mid-line through the joint space (black dashed line) was measured.

Methods

Patient selection and data acquisition

This study included 75 consecutive patients (75 knees) who underwent endoprosthetic reconstruction after resection of malignant tumours arising around the knee joint between January 2000 and December 2020. The exclusion criteria were as follows: 14 patients due to death, 12 due to hospital transfer, one due to secondary amputation for postoperative tumour recurrence, and four due to disagreement with the PROMs. After eligibility assessment, 44 patients were included

Table I. Patient demographic and radiological data (n = 44).

Parameters	Value
Mean age, yrs (SD)	29.9 (19.5)
Sex, n	
Male	26
Female	18
Mean height, cm (SD)	162.2 (10.1)
Mean body weight, kg (SD)	57.9 (12.8)
Mean BMI, kg/m^2 (SD)	21.8 (4.0)
Diagnosis, n	
Osteosarcoma	28
Giant cell tumour	6
Chondrosarcoma	5
Leiomyosarcoma	2
Ewing's sarcoma	1
Synovial sarcoma	1
Diffuse large B-cell lymphoma	1
Metastasis at surgery, n	
Yes	4
No	40
Localization, n	
Distal femur	28
Proximal tibia	16
Bone	41
Soft-tissue	3
Mean resected bone length, cm (SD)	14.4 (3.1)
Adjuvant treatment	
Chemotherapy, n	
Yes	30
No	14
Radiation, n	
Yes	0
No	44
Mean follow-up, yrs	9.7 (6.2)
Recurrence, n	1
Complications, n	
Surgical site infection	7
Implant-related complication	6
Additional surgeries, n	
Yes	15
No	29
Mean leg length discrepancy, mm (SD)	10.1 (21.3)
Mean difference of JLH, mm (SD)	4.4 (4.0)
Satisfaction, n	
1	1
2	3
3	5
4	22
5	13
Mean TESS (SD)	74.8 (21.7)
Mean COMMON-LE score (SD)	72.2 (20.9)

COMMON-LE, Comprehensive Outcome Measure for Musculoskeletal Oncology: Lower Extremity; JLH, joint line height; SD, standard deviation; TESS, Toronto Extremity Salvage Score.

in this study (Figure 1). For all enrolled patients, the following information was retrospectively obtained from the medical records: age at surgery, height, weight, BMI, tumour diagnosis, site of tumour origin (distal femur or proximal tibia), distant metastasis at surgery, bone resection length, follow-up duration, recurrence, postoperative complications, additional surgery, postoperative chemotherapy, and postoperative radiation therapy. All patients were Japanese, and informed consent was obtained before participation in the study. This retrospective study was approved by the local institutional review board for clinical research (No. 2020-184) and was conducted in accordance with the Declaration of Helsinki.[24] Demographic and radiological parameters and PROMs of the patients are shown in Table I.

Radiological and clinical evaluation

Postoperative whole-leg anteroposterior (AP) radiographs were obtained for all patients at the latest follow-up. Radiological images were imported into digital image processing software (OP-A; FUJIFILM Medical, Japan), and leg length was measured. Leg length was measured as the distance between the top of the femoral head and the centre of the ankle joint,[25] and the leg length discrepancy with the opposite lower leg was calculated (Figure 2a). The joint line height (JLH) was measured according to previous reports,[26,27] (Figure 2b) and the difference between the operative side and the opposite side was also calculated.

Questionnaires were administered at the latest follow-up to assess the TESS and COMMON-LE PROMs. The TESS, which is a rating system for physical function developed to evaluate physical and functional disability in daily living, consists of 30 questionnaires with a total score ranging from 0 to 100, with higher scores indicating better outcomes.[10,12] COMMON-LE is also a rating system for HRQOL in patients with musculoskeletal tumours and consists of a series of 27 questionnaires (three questions on pain, 15 questions on ADL, and nine questions in the socioemotional condition and general health domain) with a total score ranging from 0 to 100, with higher scores indicating better outcomes.[16] In addition, an anchor question for patient-acceptable symptomatic state (PASS) analysis was asked: "Do you have difficulty

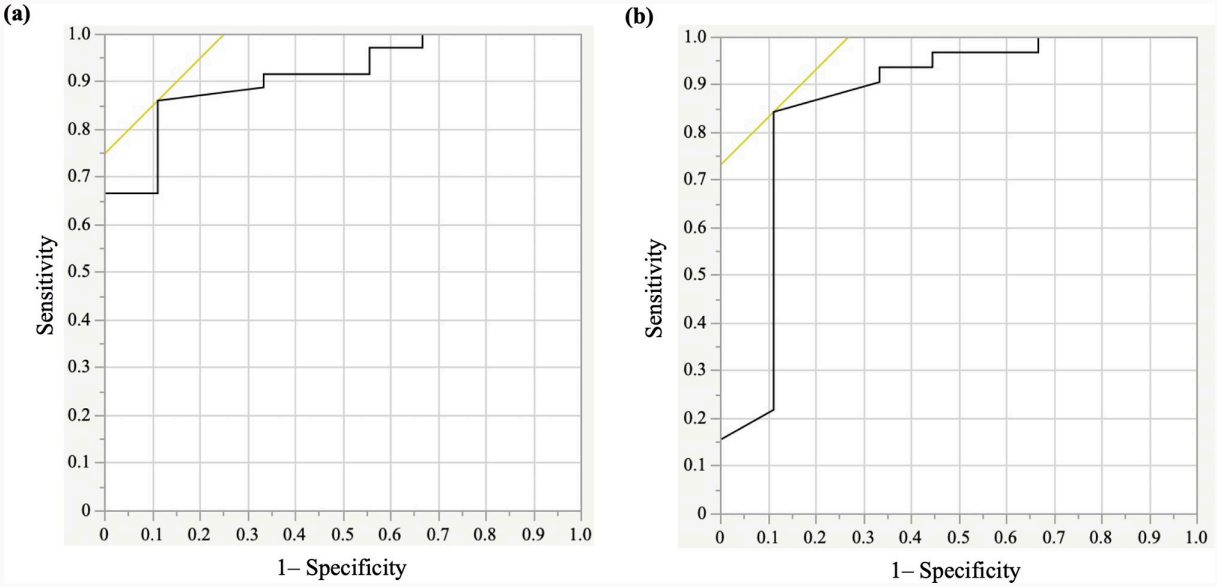

Fig. 3
Receiver operating characteristic curve for favourable Toronto Extremity Salvage Score (TESS) and Comprehensive Outcome Measure for Musculoskeletal Oncology: Lower Extremity (COMMON-LE). a) The threshold for TESS was 64.8 (sensitivity 86%, specificity 89%, area under the curve 0.91). b) The threshold for COMMON-LE was 70.4 (sensitivity 84%, specificity 89%, area under the curve 0.87).

with your ability to perform these activities for all the activities you perform in your daily life?" They were asked to rate their satisfaction on a five-point scale (1: Unacceptable, 2: Poor, 3: Fair, 4: Good, 5: Excellent – the higher the score, the higher the level of satisfaction). The PASS is defined as a value within the range in which the patient perceives the condition of the lower limb as good.[8,28] One way to determine the PASS is to analyze the answers to anchor questions using a receiver operating characteristic (ROC) curve.[8,28] Anchor questions are recommended to be intuitive and correlated with target PROMs.[8,29] In this study, after examining the correlation between the anchor question score and the total scores of the TESS and COMMON-LE, a score of 4 or 5 was defined as 'good'. The TESS and COMMON-LE threshold values for good anchor question results were calculated using ROC curve analysis.

Statistical analysis

Correlations between the anchor question and each PROMs were evaluated using Spearman's correlation coefficients. ROC analysis was performed to determine the PASS thresholds for TESS and COMMON-LE. Using the determined thresholds, TESS and COMMON-LE classified patients as above (favourable) or below (unfavourable) the threshold. Parameters were compared between groups achieving PASS (favourable) and those not achieving PASS (unfavourable) to screen for risk factors for unfavourable PROMs (TESS and COMMON-LE, respectively). Fisher's exact test and the chi-squared test were used as appropriate for categorical parameters, and the Mann-Whitney U test and independent-samples *t*-test were used as appropriate to compare continuous parameters. Statistical significance was set at $p < 0.05$. Variables with p-values < 0.05 were included in a multivariable model to identify the independent influence of each factor. ROC curves were plotted to calculate the sensitivity, specificity, and cutoff values of the independent factors of unfavourable PROMs.

Table II. Distributions and thresholds of patient-reported outcome measures after surgery.

PROM	Mean score (SD)	Threshold value	Favourable outcomes, n (%)
TESS	74.8 (21.7)	≥ 64.8	31 (69)
COMMON-LE	72.2 (20.9)	≥ 70.4	31 (69)

COMMON-LE, Comprehensive Outcome Measure for Musculoskeletal Oncology - Lower Extremity; PROM, patient-reported outcome measure; SD, standard deviation; TESS, Toronto Extremity Salvage Score.

Continuous variables are presented as mean and standard deviation (SD). Statistical analyses were performed using the JMP statistical analysis software (version 15.0; SAS Institute, USA).

Results

The correlation between the anchor question and the TESS was good ($r = 0.80$; $p < 0.001$, Spearman's correlation coefficients), and the correlation between the anchor question and the COMMON-LE was also good ($r = 0.82$; $p < 0.001$, Spearman's correlation coefficients). ROC analysis showed that the PASS thresholds for TESS and COMMON were 64.8 and 70.4 points, respectively (Table II, Figure 3). The demographic and radiological parameters were compared between the two groups of patients who achieved PASS (Table III). The group with unfavourable TESS was older ($p < 0.001$, Mann-Whitney U test), shorter ($p = 0.013$, Mann-Whitney U test), and had a large leg length discrepancy ($p = 0.001$, Mann-Whitney U test). The group with unfavourable COMMON-LE scores was older ($p = 0.003$, Mann-Whitney U test). Tumour location, additional surgery due to complications, chemotherapy, and follow-up duration had no significant effect on PROMs (Supplementary

Table III. Patient demographic and radiological data.

Parameter	Favourable	Unfavourable	p-value
TESS	≥ 64.8 (n = 31)	< 64.8 (n = 13)	
Mean age, yrs (SD)	21.2 (9.5)	50.8 (21.8)	< 0.001*
Sex, n			0.098†
Male	21	5	
Female	10	8	
Mean height, cm (SD)	164.8 (7.2)	156.0 (13.2)	0.013*
Mean body weight, kg (SD)	60.3 (11.3)	52.0 (14.5)	0.173‡
Mean BMI, kg/m^2 (SD)	22.1 (3.6)	21.0 (4.8)	0.529*
Metastasis, n			1.000†
Yes	3	1	
No	28	2	
Localization, n			
DF	19	9	0.739†
PT	12	4	
Bone	28	13	0.544†
Soft-tissue	3	0	
Mean resected bone length, cm (SD)	14.6 (3.0)	13.9 (3.5)	0.271*
Chemotherapy, n			1.000†
Yes	21	9	
No	10	4	
Mean follow-up, yrs (SD)	10.5 (6.6)	7.7 (5.2)	0.185*
Recurrence, n			0.296†
Yes	0	1	
No	31	12	
Additional surgeries, n			0.162†
Yes	13	2	
No	18	11	
Mean leg length discrepancy, mm (SD)	5.6 (5.4)	20.7 (37.1)	0.001*
Mean difference of JLH, mm (SD)	4.1 (3.6)	5.1 (4.8)	0.411‡
Mean TESS (SD)	86.2 (9.6)	47.6 (17.8)	< 0.001*
COMMON-LE	≥ 70.4 (n = 31)	< 70.4 (n = 13)	
Mean age, yrs (SD)	22.7 (13.1)	47.1 (22.0)	0.003*
Sex, n			0.098†
Male	21	5	
Female	10	8	
Mean height, cm (SD)	163.5 (10.9)	159.2 (7.4)	0.057*
Mean body weight, kg (SD)	58.5 (13.4)	56.4 (11.7)	0.787‡
Mean BMI, kg/m^2 (SD)	21.7 (3.9)	22.2 (4.2)	0.546*
Metastasis, n			0.071†
Yes	1	3	
No	30	10	
Localization, n			
Distal femur	19	9	0.738†
Proximal tibia	12	4	
Bone	29	12	1.000†
Soft-tissue	2	1	
Mean resected bone length, cm (SD)	14.5 (3.3)	14.2 (3.0)	0.816*
Chemotherapy, n			1.000†
Yes	21	9	
No	10	4	
Mean follow-up, yrs (SD)	10.9 (6.6)	6.8 (4.2)	0.059*
Recurrence, n			1.000†
Yes	1	0	
No	30	13	
Additional surgeries, n			0.162†
Yes	13	2	
No	18	11	
Mean leg length discrepancy, mm (SD)	10.5 (25.3)	9.0 (4.8)	0.068*
Mean difference of JLH, mm (SD)	3.8 (3.3)	5.6 (5.5)	0.231‡
Mean COMMON-LE score (SD)	83.7 (7.8)	47.5 (18.6)	< 0.001*

*Mann-Whitney U test.
†Fisher's exact test.
‡Independent-samples *t*-test.
COMMON-LE, Comprehensive Outcome Measure for Musculoskeletal Oncology - Lower Extremity; JLH, joint line height; SD, standard deviation; TESS, Toronto Extremity Salvage Score.

Tables i to iv). Multivariate analysis showed that older age at surgery and larger postoperative leg length discrepancy ($p = 0.004$ and 0.043, variables with $p < 0.05$ in comparison in the univariate model were included in the multivariate analysis) were risk factors for unfavourable TESS results, whereas older age at surgery ($p < 0.001$, variables with $p < 0.05$ in comparison in the univariate model were included in the multivariate analysis) was a risk factor for unfavourable COMMON-LE results (Table IV). Following ROC analysis, the threshold for both TESS and COMMON-LE was 29 years. The area under the curve (AUC) was 0.83 for TESS and 0.79 for COMMON-LE. A leg length discrepancy of more than 8.2 mm was the threshold for unfavourable TESS (AUC = 0.82) (Figure 4).

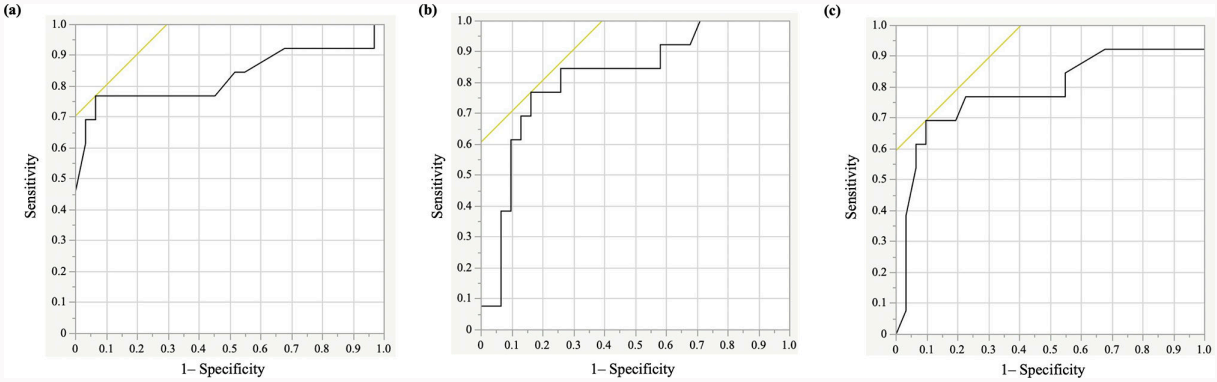

Fig. 4

Receiver operating characteristic (ROC) curve for setting thresholds for a) age at surgery and b) leg length discrepancy for unfavourable Toronto Extremity Salvage Score; c) ROC curve for setting thresholds for age at surgery for unfavourable Comprehensive Outcome Measure for Musculoskeletal Oncology: Lower Extremity. a) The threshold for age at surgery was 29 (sensitivity 77%, specificity 94%, area under the curve 0.83). b) The threshold for postoperative leg length discrepancy was 8.2 mm (sensitivity 77%, specificity 84%, area under the curve 0.82). c) The threshold for age at surgery was 29 (sensitivity 69%, specificity 90%, area under the curve 0.79).

Table IV. Multivariate analysis of factors associated with unfavourable Toronto Extremity Salvage Score and Comprehensive Outcome Measure for Musculoskeletal Oncology - Lower Extremity.

Parameters	Odds ratio (95% CI)	p-value
TESS		
Age, yrs	1.12 (1.04 to 1.21)	0.004
Height, cm	0.96 (0.81 to 1.15)	0.674
Leg length discrepancy, mm	1.22 (1.01 to 1.47)	0.043
COMMON-LE		
Age, yrs	1.07 (1.02 to 1.12)	< 0.001

CI, confidence interval; COMMON-LE, Comprehensive Outcome Measure for Musculoskeletal Oncology - Lower Extremity; TESS, Toronto Extremity Salvage Score.

Discussion

We evaluated mid- to long-term postoperative outcomes in 44 patients who underwent endoprosthetic knee arthroplasty using PROMs. An important finding of this study was that the postoperative PROMs of endoprosthetic knee arthroplasty were analyzed from two different perspectives, identifying factors that reduce the outcomes. Age at surgery and leg length discrepancy were associated with unfavourable PROMs.

Age at the time of surgery has been reported to be a factor leading to unfavourable PROMs.[4,30,31] Postoperative TESS decreases with advancing age due to less motivation for rehabilitation and higher use of analgesics and walking aids in daily life.[4] We established a threshold for age at surgery as a risk factor for unfavourable PROMs in the cohort (median 21, interquartile range 16 to 40). Interestingly, the results were similar for PROMs, TESS, and COMMON-LE, with age at surgery > 29 years resulting in unfavourable outcomes. From a physical perspective, young patients adapt to their changing physical circumstances and learn to live with their disabilities.[4] From a mental health perspective, the life stage of 18- to 29-year-olds is called "emerging adulthood", and after marriage, childbirth, and finding a stable job, they are said to transition to "adult" at age 30.[32,33] This mental health transition may explain the results of the current study, which showed similar thresholds in COMMON-LE, reflecting HRQoL. Appropriate preoperative coe anchor question aunselling should be provided to patients aged over 29 years, and adequate physical and socioemotional support may be important after surgery.

We identified postoperative leg length discrepancy as a risk factor for decreased TESS with a threshold of 8.2 mm. In postoperative total hip arthroplasty patients, leg length discrepancies of less than 10 mm have been acceptable,[23] while those greater than 10 mm cause limping and uneven weight distribution, decreasing patient satisfaction.[34–36] Although there are no reports on the relationship between leg length discrepancy and postoperative PROMs after endoprosthetic knee arthroplasty, patients with endoprosthetic knee arthroplasty following wide tumour resection might have unfavourable PROMs because the processes are similar. In the current study, postoperative leg length discrepancy significantly decreased TESS, whereas the resected bone length had no significant influence on TESS, suggesting that reconstructing a length equivalent to the resected length may reduce the risk of unfavourable functional outcomes. Leg length discrepancy was a risk factor for unfavourable TESS, but not for COMMON-LE, because of the differences in the characteristics of each PROMs. The TESS investigates the specific limitations of physical activities, whereas the COMMON-LE includes many categories that reflect mental status, health status, and overall HRQoL. The large leg length discrepancy made ADLs difficult, but did not affect HRQoL. These differences in outcomes may be explained by the different aspects assessed in each PROM.

Short stature at surgery was significant in univariate analysis but not a significant factor for unfavourable TESS in multivariate analysis. Younger age and short stature at the time of surgery may increase leg length differences with growth,[37] resulting in worse PROMs; however, in the present cohort, two patients (age at surgery: 11 and 13 years) underwent additional surgery to extend the prosthesis for improvement of leg length discrepancy due to postoperative

growth, and their PROMs achieved favourable outcomes (TESS: 86, 87, and COMMON-LE: 91, 85). These cases have been treated with extendable prostheses (the Kotz Growing type) in light of the potential need for leg lengthening, so that additional surgery could be performed with less invasive procedures. In cases with common rotating-hinge knee prostheses, additional surgery is highly invasive, requiring stem replacement and polyethylene bearing replacement, especially in cases of excessive leg length. For mild leg length discrepancies, shoe lifts should be recommended if the patient is symptomatic.

This study has several limitations. First, we used a retrospective study design to analyze clinical data. Second, we investigated only a small number of patients from a single institution. Third, the study did not evaluate preoperative PROMs. The relatively long follow-up period of ten years for the patients studied is a strength of this study; however, the common use of PROMs has been established relatively recently (the Japanese version of the TESS was developed in 2015 and COMMON-LE in 2019). Patients with long-term follow-up had undergone surgery before these PROMs were developed. TESS and COMMON-LE have been used to evaluate postoperative disability following limb salvage surgery,[38,39] indicating that preoperative function of most patients with tumour around the knee might be almost normal. New findings could be added if the minimal clinically important difference (MCID) is calculated by comparing preoperative and postoperative PROMs. Fourth, the follow-up duration in this study had a large level of variance, and the follow-up duration for some patients was relatively short. van Egmond-van Dam et al[18] reported that two years of postoperative follow-up is necessary to observe complications and minor life disabilities, but improvement in functional outcomes is relatively stable after that. In the present study, a follow-up period > two years was defined as the inclusion criterion. There were no significant differences in follow-up duration between the favourable and unfavourable PROM groups. In addition, there was no significant difference in PROMs between cases with a follow-up period of less than ten years and more than ten years (Supplementary Table iv). Finally, this study population was limited to Japanese subjects. Patients with an average BMI of 21.8 are standard for Asian populations,[40] but not the same for other races, therefore the results may not generalize to different races.

In summary, mid- to long-term postoperative PROMs for endoprosthetic knee arthroplasty after tumour resection were assessed. Age at surgery > 29 years and postoperative leg length discrepancy greater than 8.2 mm were associated with unfavourable PROMs. Appropriate counselling should be provided to preoperative patients, as well as adequate physical and postoperative socioemotional support. Depending on the extent of soft-tissue and bone resection for the treatment of tumours, reconstruction equivalent to the length of the resected bone may reduce the risk of functional disability in daily living.

Supplementary material

Tables showing comparison of the patient characteristics by localization, additional surgeries, chemotherapy, and follow-up period.

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Funding statement

The authors disclose receipt of the following financial or material support for the research, authorship, and/or publication of this article: this work was partially supported by the Grants-in-Aid for Young Scientists (grant number JP22K09359) from the Japan Society for the Promotion of Science.

ICMJE COI statement

Each author certifies that he has no commercial associations that might pose a conflict of interest in connection with the submitted article.

Data sharing

The data that support the findings for this study are available to other researchers from the corresponding author upon reasonable request.

Acknowledgements

The authors would like to thank Editage (www.editage.jp) for the English language review.

Ethical review statement

This study approval was obtained from the Institutional Review Board of our institution (No. 2020-184). The study was conducted in accordance with the Declaration of Helsinki.

Open access funding

The open access fee for this article was funded by the Japan College of Rheumatology Grant for Promoting Basic Rheumatology.