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Quality of life, functional ability and physical activity in children and adolescents after lower extremity bone tumour surgery

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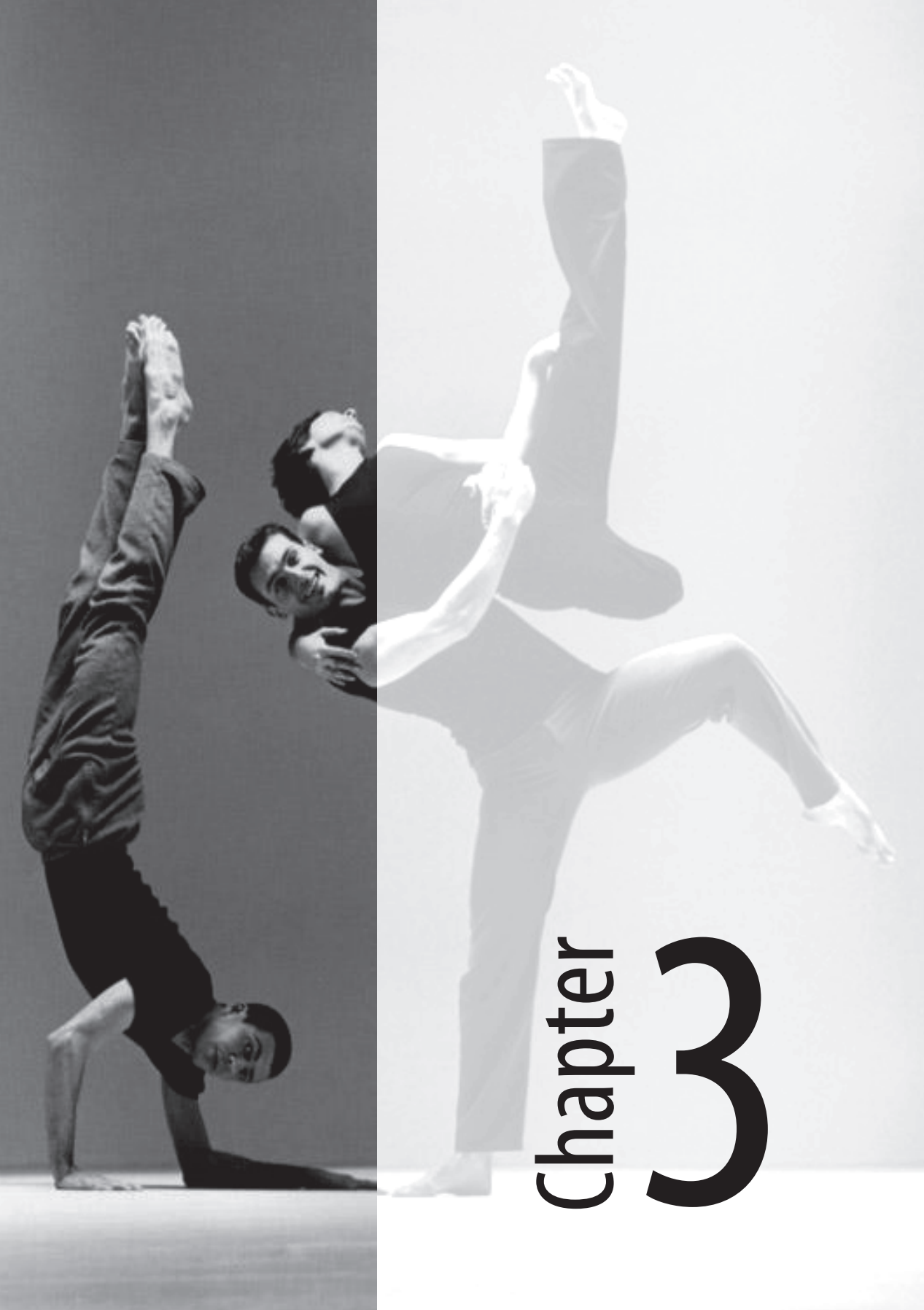
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Chapter 3

A PROSPECTIVE STUDY ON QUALITY OF LIFE AND FUNCTIONAL OUTCOME IN CHILDREN AND ADOLESCENTS AFTER MALIGNANT BONE TUMOR SURGERY

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ABSTRACT

Background: Few longitudinal data are available concerning quality of life and functioning of young patients undergoing surgical procedures for malignant bone tumors around the knee joint. Aim of the present study was to evaluate patients' quality of life (QoL), functional ability, and physical activity during a 2-year postoperative period.

Methods: This prospective study included patients who underwent surgery for a malignant bone tumor around the knee joint between 2004 and 2008. Assessments were done at 3, 6, 9, 12, 18 and 24 months after surgery. QoL was measured with the TNO-AZL Children's or Adult's Quality of Life Questionnaires (TACQOL and TAAQOL), the Short Form-36 (SF-36) and Bone tumor (Bt)-DUX; functional ability with the Toronto Extremity Salvage Scale (TESS), the 6-minutes walk test (6MWT) and four functional performance tests; and physical activity with the Baecke questionnaire and the ActiLog[®] activity monitor. Statistical analysis included linear mixed model analysis.

Results: Forty-four patients (27 males, 17 females, mean age 14.9 (SD 4.8) years) were included, 27 (61%) underwent limb-salvage and 17 (39%) ablative surgery. Twenty patients were lost during the 2 years follow-up as a consequence of oncological complications. Over the first year, survivors showed significant improvement of QoL, functional ability and physical activity, except for the mental dimension of the SF-36 and the activity monitor results. Over the second year, these improvements were less pronounced.

Conclusions: In the first two years after bone tumor surgery, survivors improved significantly with respect to QoL, functional ability, and physical activity levels.

INTRODUCTION

Malignant bone tumors account for approximately 6% of all cancers in children younger than 20 years of age [1]. Advances in malignant bone tumor treatment have led to improved survival rates and the need to study patients' health status in greater detail. Most publications on this topic were focused on the health status of adults or adult survivors of childhood sarcoma, determined at one single time point [2,3]. So far, three studies presented longitudinal assessments of quality of life (QoL) in children or adolescents after surgery for a malignant bone tumor [4-6]. Significant improvements of QoL were reported from surgery up to 24 months thereafter [5], until completion of chemotherapy [6] or in comparison with healthy peers [4]. Limitations of these studies were the inclusion of patients after bone cancer surgery of the arm as well as the leg [4-6], the focus on the chemotherapy [6] or the confined number of evaluations [4].

Longitudinal assessments of QoL, functional ability and physical activity levels specifically for patients after surgery for a malignant bone tumor of the leg were not reported in any study so far. The aim of this study was therefore to prospectively assess QoL, functional ability and physical activity levels in children and adolescents during the first two years after a surgical intervention for a malignant tumor around the knee joint..

MATERIALS AND METHODS

Study design and patient recruitment

The study had a prospective, multi-centre design. All consecutive patients who underwent a surgical intervention due to a malignant bone tumor around the knee joint in one of three university medical centers in the Netherlands (Leiden University Medical Center, Academic Medical Center University of Amsterdam and Erasmus MC University Medical Centre - Sophia Children's Hospital Rotterdam) between January 2004 and January 2008 were invited by their oncologist or orthopedic surgeon to participate in the study. Patients were eligible if they were aged between 8 and 25 years at the time of surgery, the malignant bone tumor (osteosarcoma or Ewing sarcoma) was located around the knee and the surgical intervention consisted of limb-sparing or ablative surgery. Patients were excluded if medical conditions other than the bone tumor surgery limited their physical activities. The Medical Ethics Committee of all three centers approved the study and all patients and their parents (children under the age of 18 years) gave informed consent.

Assessment methods

Assessments were scheduled at 3, 6, 9, 12, 18 and 24 months after surgery. The questionnaires and an activity monitor were sent by mail. The functional performance tests were done by the principal investigator (WPB). The patients' baseline socio-demographic and clinical characteristics (age, sex, morphology, chemotherapy regimen and the type of surgical intervention) as well as orthopedic or oncological complications occurring during the two years follow-up (lung metastases and the type of thoracic surgery, local recurrence and the resulting surgery, endoprosthetic or allograft failure, stump infection) were derived from

the medical record. If patients were, due to their physical or emotional health status, not able to complete assessments it was registered whether this was temporarily or definite. If it was not definite, patients were again invited for the next assessment.

Health Related Quality of Life

The TNO (Netherlands Organization for Applied Scientific Research) and AZL (Leiden University Medical Center) Children's Quality of Life Questionnaire (**TACQOL**) is a generic instrument to measure QoL in children aged 8-16 years old [7,8]. It measures health status problems, weighted by the impact of the problems on well-being and consists of seven domain scales. The TNO-AZL Questionnaire for Adult's Quality of Life (**TAAQOL**) is a similar instrument as the TACQOL, developed for adolescents and adults of 16 years and older [9] and consists of twelve domain scales.

As described in the literature [10-12] we used principal component analysis to aggregate TACQOL and TAAQOL scale scores into the Mental Component Scale (TACQOL and TAAQOL-MCS) and the Physical Component Scale (TACQOL and TAAQOL-PCS), standardized with norm values to a score with a mean of 50 and a standard deviation of 10, with scores above and below 50 indicating above and below average functioning, respectively.

The **Short Form (SF)-36** is a self-administered measure evaluating 8 health domains. Each scale score ranges from 0 (worst health state) to 100 (best health state). These eight health concept scales can be converted into a Physical Component Summary Scale (SF-36-PCS) and a Mental Component Summary scale (SF-36-MCS), both standardized to a score with a mean of 50 and a standard deviation of 10, with scores above and below 50 indicating above and below average functioning, respectively [13,14].

The **Bone tumor (Bt)-DUX** is a disease specific questionnaire for QoL assessment in patients after malignant bone cancer surgery of the leg [15] comprising 20 items within four domains. The scoring of the items is done by abstract faces with varying expressions, ranging from very happy (score 1) to sad (score 5). The raw item scores are converted into total and domain scores, ranging from 0-100, with the highest scores indicating better QoL. The BT-DUX proved to be a practically applicable, internally consistent and valid instrument [15].

Functional ability

The **Toronto Extremity Salvage Score (TESS)** is a self-report measure of physical disability in patients after limb-salvage surgery for a bone tumor of the leg. It assesses the level of difficulty experienced in dressing, grooming, mobility, work, sports, and leisure [16]. It consists of 30 items, with each item rated on a scale from 1 to 5, with 5 representing "not at all difficult" and 0 representing "impossible to do". The total score is calculated as a percentage of the maximum score.

Performance tests

To assess patient's objective functional ability, three lower extremity specific tasks were selected: The timed up and down stairs (TUDS) time [17,18], the time it takes for a patient

to walk up and down 10 stairs (seconds). A combination of 3 various walking activities (VWA) [19] consisting of 10 meter normal, slalom and obstacle walking (seconds). The 6-minutes walk test (6MWT) [20-21]; patients were informed to walk and not run during 6 minutes, with the objective to cover the largest distance as possible (meters). In addition, the patient's heart rate before and after the test were recorded. With the available data, the physiological cost index (PCI) was computed, defined as; the average speed of walking / average heart rate [22-23].

Physical Activity

The **Baecke questionnaire** is a measure of physical activity [24]. Responses to 13 questions, ranging from never to always is resulting in four indices reflecting physical activity during sport, leisure time and work. Each index score ranges from 0 to 5 with higher scores indicating greater activity. The total activity score is the summation of the three index scores, ranging from 0 (inactive) to 15 (very active). The reliability and validity have been described in different populations and considered to be **uitable** for research purposes [25].

ActiLog® The amount of physical activity was measured by an activity monitor (ActiLog V3.0; Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands). This activity monitor is the size of a matchbox and consists of a piezoelectric sensor that is sensitive in 3 directions [26,27]. In this study, the activity monitor was worn around the ankle for 24 hours on 7 consecutive days. Specialized software was used to calculate a General Physical Activity score (GPA) and the average number of high (peak) activity periods throughout the day.

Statistical analysis

All analyses were performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

Data are presented as means with standard deviation. Rates of surgical and oncological complications among different surgery groups were compared with the Chi-square test. To analyze QoL, functional ability and physical activity over time a linear mixed model [28] was used, with subject as random variable, time points as fixed variables and the outcome measures as dependent variables. This model allows accounting for dependency of repeated outcome measures on the same subject and missing data. Based on estimated marginal means pairwise comparisons were performed to evaluate the changes with the 95% confidence interval (CI) within the first year (between 3 and 12 months) and with the second year (between 12 and 24 months). For all analyses, the level of significance level was set at $p < 0.05$.

RESULTS

Patients

Between 2004 and 2008 49 patients who underwent surgery for a malignant bone tumor located around the knee fulfilled the inclusion criteria and were invited to participate. Before the evaluation started 5 patients withdrew, 2 due to social emotional problems and 3

for other reasons. At 3 months after surgery, nine patients were willing to participate in the study but their health status did not yet allow taking part in the assessments. These patients were assessed for the first time at the 6 months time point. At each of the various follow-up points 4 to 6 assessments of patients who were still participating in the study were missing, mainly because they were undergoing surgical interventions. Twenty patients withdrew from the study between 6 and 24 months. In 18 of these 20 patients palliative treatment was started, 11 of whom died. In addition, one patient withdrew because of emotional problems and one moved abroad. All 24 patients who participated until the end of the two-year follow-up were able to complete the final evaluation (Figure 1).

The socio-demographic and disease characteristics of the 44 included patients are presented in Table I. Twenty-seven were male and 17 female, with a mean age at surgery of

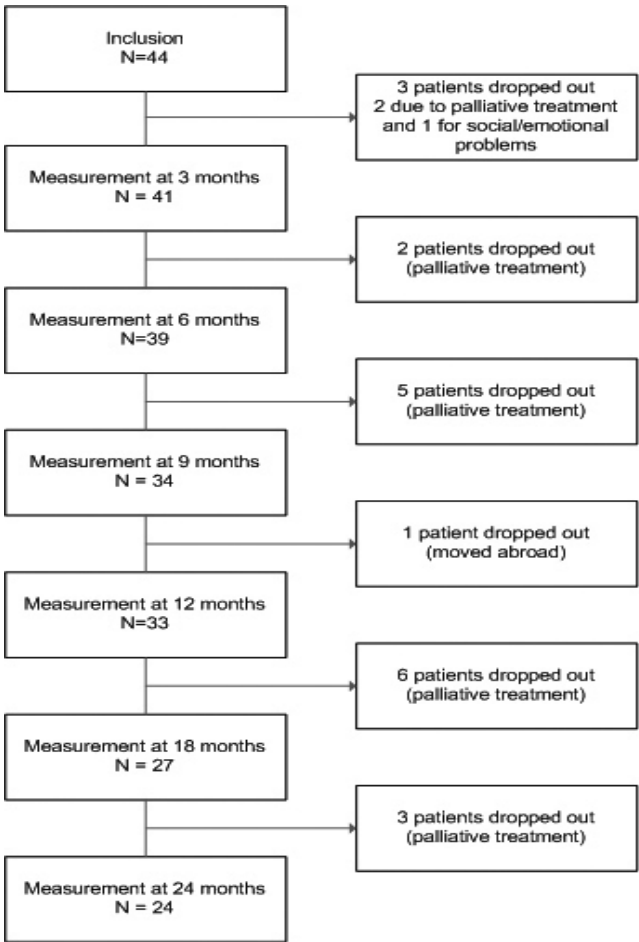


Figure 1. Flow chart; showing the number of patients in the study and those who dropped out at different stages of the study.

Table I. Socio Demographic and Disease Characteristics of all 44 Patients in Study, Patients who Completed the Full Study (N=24) and those who Completed the Study without Complications (N=14)

	All patients N=44	Limb-Salvage N=27	Ablative surgery N=17	Study completers N=24
Gender, No (%)				
Female	17 (39%)	9 (33%)	8 (47%)	10 (42%)
Male	27 (61%)	18 (67%)	9 (53%)	14 (58%)
Age at surgery, years (SD)	14.9 (4.8)	15.1 (5.1)	14.5 (4.4)	15.5 (4.1)
Type of surgery, No (%)				
Allograft	8 (18%)	Femur 6 Tibia 2		6 (25%)
Prosthesis	19 (43%)	Femur 14 Tibia 5		11 (46%)
Amputation	10 (20%)		Femur 7 Tibia 3	6 (25%)
Rotationplasty	7 (16%)			1 (5%)
Morphology, No (%)				
Osteosarcoma	41 (93%)	25 (93%)	16 (94%)	21 (79%)
Ewing sarcoma	3 (7%)	2 (7%)	1 (6%)	3 (21%)
Localization, No (%)				
Distal Femur	32 (73%)	20 (74%)	12 (70%)	13 (54%)
Proximal Tibia	12 (27%)	7 (26%)	5 (30%)	11 (46%)
Side, No (%)				
Left	23 (52%)	15 (56%)	8 (47%)	13 (54%)
Right	21 (48%)	12 (44%)	9 (53%)	11 (46%)
Progression of disease*				
Lung metastases	24 (55%)	11 (39%)	13 (81%)	
Local recurrence	10 (23%)	7 (26%)	3 (18%)	
Palliative treatment*	18 (41%)	9 (32%)	9 (56%)	
Died of disease during study	11 (25%)	5 (19%)	6 (35%)	
Surgery related complications*		8 (30%)	2 (12%)	
Endoprosthetic failure		5 (26%)		
Allograft failure		3 (38%)		
Stump infection			2 (12%)	

* Orthopedic or oncological complications occurring from the moment of surgery till the end of the study or drop out

14.9 years (SD 4.8). Limb-sparing surgery was performed in 27 patients (massive allograft in 8 and cementless endoprosthesis reconstructions in 19 patients). Ablative surgery was performed in 17 patients (amputation in 10 and rotationplasty [29] in 7 patients). Forty-one patients underwent surgery due to an osteosarcoma and 3 patients due to a Ewing sarcoma. The chemotherapy regimen varied. Thirty-two patients received chemotherapy according to the EURAMOS-protocol (www.euramos.org), 9 patients were included into the EORTC/EOI-80931 protocol [30] and 3 patients with a Ewing sarcoma were treated according to the Euro-Ewing-99 protocol [31].

Fourteen of the 44 patients (34%; 3 amputation, 7 endoprosthesis and 3 allograft patients) had no oncological or orthopedic complications during follow-up. Orthopedic complications included one stump infection and one late stump correction after ablative surgery. After limb-salvage surgery endoprosthetic problems ($n=5$), allograft problems ($n=3$) and one late amputation were seen. The frequencies of orthopedic complications did not differ significantly between limb-salvage and ablative surgery (Chi-Square; $p=0.17$).

With respect to oncological complications lung metastases occurred most frequently and were evident in 24 patients. Thoracic surgery consisted of one or more resections of isolated metastases and in 11 patients a wedge excision was undertaken. In addition, metastases in the central nervous system ($n=1$), vertebral column ($n=1$) and soft tissue ($n=1$) were seen. Oncological complications occurred significantly more often in the ablative surgery group than in the limb-salvage group (Chi-square; $p<0.05$).

Quality of Life

Table II and figure 2 show that between the 3 and 12 months patients improved significantly regarding the social, physical and cosmetics dimension scores and the total scores of the Bt-DUX questionnaire ($p<0.05$), the motor, body and PCS scores of the TACQOL questionnaire (8-15 years old patients, $p<0.01$), the gross motor functioning, daily activities and PCS scores of the TAAQOL and the physical functioning, social functioning, role physical and PCS scores of the SF-36 questionnaire (16-25 years old patients, $p<0.01$). Changes between 12 and 24 months were not significant, except for the physical functioning and PCS scales of the SF-36 questionnaire (16-25 years old; $p<0.05$).

Functional ability

Table III and Figure 3 show that patients improved significantly between 3 and 12 months according to the TESS questionnaire, functional performance tests and the 6MWT ($p<0.01$). In addition, the functional performance tests and the 6MWT improved significantly between 12 and 24 months ($p<0.05$).

Physical activity

Table III and figure 3 show that according to the Baecke questionnaire physical activity levels increased significantly between 3 and 12 months for all four indexes ($p<0.01$). Moreover, further statistically significant improvements were seen for the work, leisure time and total activity indices between 12 and 24 months ($p<0.05$). None of the changes in physical activity as measured with the activity monitor reached statistical significance.

Table II. Estimated Marginal Mean Scores (Standard Error of the Estimated Mean) and Change Scores (95% Confidence Interval) of Health Related Quality of Life Measures in Children and Adolescents who Underwent Surgery for a Malignant Tumor Around the Knee.

	Time points (in months)					Time points			
	3	6	9	12	Change score 1 (CI)	18	24	Change score 2 (CI)	
	N=34	N=30	N=27	N=26		N=23	N=24		
Bt-DUX Range 1-100	Emotional	68 (3.4)	71 (3.1)	76 (3.2)	73 (3.3)	6 (-2;13) ns	80 (3.5)	80 (3.4)	6 (-2;14) ns
	Social	70 (2.9)	76 (3.0)	79 (3.1)	79 (3.2)	8 (1;15) *	85 (3.3)	83 (3.3)	4 (-3;12) ns
	Cosmetically	64 (2.9)	67 (3.0)	72 (3.1)	72 (3.2)	9 (2;16) *	78 (3.2)	78 (3.3)	6 (-2;13) ns
	Physical	39 (3.6)	38 (3.8)	46 (4.0)	50 (4.0)	11 (2;19) *	57 (4.2)	57 (4.2)	7 (-2;17) ns
	Total	60 (2.5)	63 (2.7)	68 (2.8)	69 (2.8)	10 (2;14) **	75 (2.9)	74 (2.9)	5 (-5;12) ns
	N=16	N=17	N=12	N=16		N=11	N=9		
TACQOL 8-15 years	Body	57 (2.1)	66 (2.0)	68 (2.4)	69 (2.1)	12 (6;17)**	72 (2.5)	71 (2.7)	2 (-4;9) ns
	Motor	40 (3.6)	53 (3.5)	54 (4.0)	62 (3.6)	22 (15;30) **	66 (4.1)	64 (4.4)	2 (-7;11) ns
	PCS-TACQOL	7 (3.6)	25 (3.6)	32 (4.1)	40 (3.7)	33 (25;42) **	45 (4.2)	46 (4.6)	6 (-4;15) ns
	MCS-TACQOL	56 (2.6)	58 (2.6)	55 (2.9)	59 (2.7)	4 (-1;9) ns	59 (3.0)	58 (3.2)	-1 (-4;8) ns
		N=15	N=15	N=13	N=13		N=14	N=15	
TAAQOL 16-25 years	Gross motor function	40 (6.0)	55 (6.0)	59 (6.0)	75 (6.3)	35 (21;48) **	81 (6.2)	79 (5.9)	5 (-9;17) ns
	Daily activities	50 (6.7)	57 (6.8)	71 (6.8)	74 (7.1)	24 (8;39) **	80 (6.9)	84 (6.6)	10 (-5;26) ns
	PCS-TAAQOL	18 (4.0)	23 (4.3)	27 (4.1)	35 (4.4)	17 (7;26) **	41 (4.1)	45 (4.1)	10 (0;20) ns
	MCS-TAAQOL	40 (2.6)	48 (2.7)	49 (2.6)	48 (2.8)	8 (2;14) **	50 (2.6)	51 (2.6)	3 (-4;9) ns
		N=13	N=13	N=14	N=13		N=14	N=14	
SF-36 15-25 years	Physical functioning	35 (4.8)	43 (4.8)	56 (4.6)	66 (4.8)	31 (19;42) **	81 (4.7)	82 (4.6)	17 (4;28) **
	Social functioning	56 (5.5)	64 (5.5)	84 (5.3)	85 (5.5)	29 (16;42) **	92 (5.3)	89 (5.3)	4 (-8;18) ns
	Role physical	21 (8.5)	30 (8.5)	47 (8.3)	68 (8.5)	47 (26;68) **	79 (8.3)	87 (8.3)	19 (-2;40) ns
	PCS	8 (3.1)	17 (3.1)	25 (3.0)	34 (3.1)	26 (18;34) **	41 (3.1)	44 (3.0)	10 (1;17) *
	MCS	60 (2.8)	58 (2.8)	63 (2.8)	58 (2.8)	-2 (-8;4) ns	57 (2.8)	56 (2.8)	-2 (-8;4) ns

PCS: Physical component summary score; MCS: Mental component summary score; **Change score 1**: Mean difference between measures at 3 and 12 months after surgery; **Change score 2**: Mean difference between measure at 12 and 24 months after surgery; CI: 95% Confidence interval; **Linear Mixed Model Analysis** *: significant at the 0.05 level, ** significant at the 0.01 level.

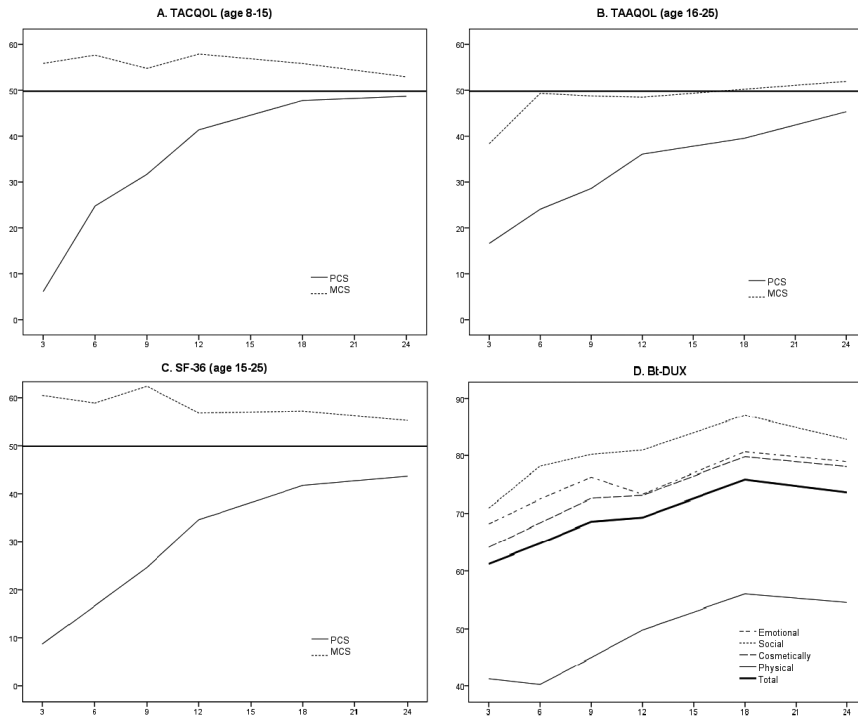


Figure 2. Health Related Quality of Life in patients over measurement occasions: Mean PCS and MCS scores of SF-36, TAAQOL (16-25 years of age) and TACQOL (8-15 years) over time compared with the norm (50) and the disease specific Bt-DUX scores.

DISCUSSION

The present prospective study on QoL, functional ability and physical activity levels of children and adolescents after malignant bone tumor surgery around the knee joint showed that survivors improve over two years, with the exception of the mental QoL domains. These improvements were most evident in the first year after surgery

Our findings concerning QoL are in line with earlier longitudinal studies among patients after bone cancer surgery that demonstrated improved physical QoL scores over time [4-6], in particular within the first year [5,6]. Our study differs from these studies as it only concerned children and adolescents, malignant bone tumors around the knee and included 6 time points. In addition to the currently available literature mainly reporting on QoL, we demonstrated significant improvements of functional ability and physical activity as measured with a questionnaire over the first year. Concerning physical activity, no significant improvements were seen with an activity monitor. These findings are in line with previous studies where results of the self-report measures correlated only slightly to moderately with the results of the objective measure, indicating that the perception of physical activity differs from the actual performance [27,32,33].

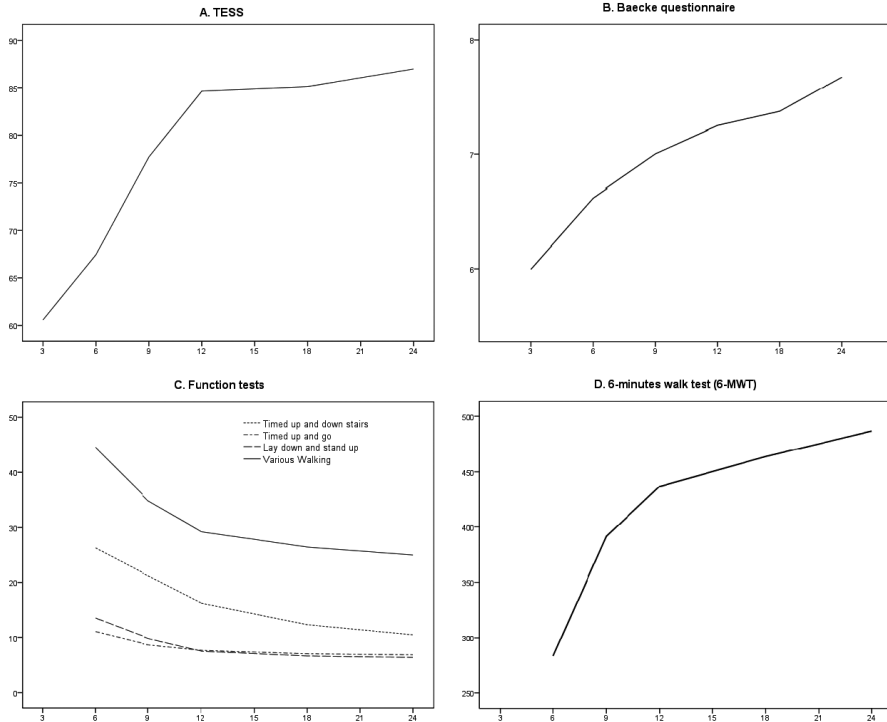


Figure 3. Functional ability and physical activity scores in patients over measurement occasions: Mean TESS, 6-MLT, TUDS, VW and Baecke scores.

In contrast to improvements in physical functioning, the mental summary scores of the three generic questionnaires and the Bt-DUX pointed into the direction of a status quo in the first year and a slight deterioration in the second year. However, overall the mental status of patients was relatively favorable in comparison with healthy peers. This observation could probably be explained by feelings of happiness to have survived the disease and passed the treatment, and the fast regain of functional independency, resulting in the under-reporting of problems. This phenomenon, which has been previously described among children and adult populations, is called “response shift” [34,35]. The trend towards a slight deterioration in mental status in the second year could probably reflect the transition from patient to “healthy” persons in the longer term. After completion of the chemotherapy and rehabilitation, the patients may experience a number of barriers when returning to school, study or work. This other side of the response shift phenomenon could lead to less positive emotional feelings and lower QoL scores. These findings could indicate that in particular in this stage of the rehabilitation process, adequate support is needed.

With respect to the interpretation of functioning and QoL in the early postoperative period, various factors are important. First, in both the limb-salvage and amputation groups, patients have to adapt to the new limb. After limb-salvage surgery full weight-bearing will in general be limited for weeks after endoprosthetic reconstructions and for several months

Table III. Mean Scores (SD) and Change Scores (95% Confidence Interval) of Functional Ability and Physical Activity Measures at Six Time Points During Two Year Follow-up.

	Time points (in months)					Time points				Change score 2 (CI)
	3	6	9	12	Change score 1 (CI)		18	24		
	N=32	N=33	N=27	N=29			N=23	N=24		
TESS	60 (2.3)	68 (2.3)	79 (2.4)	85 (2.4)	25 (20;30) **		85 (2.6)	88 (2.6)	3 (-2;8) ns	
		N=34	N=26	N=27			N=23	N=24		
Function										
Timed Up / Down Stairs		30 (1.8)	21 (2.1)	17 (2.0)	-13 (-8;-17) **		12 (2.2)	11 (2.2)	-6 (-.6;-11) *	
Various Walking Activities		45 (1.5)	35 (1.6)	30 (1.6)	-15 (-12;-18) **		27 (1.7)	25 (1.7)	-5 (-1;-8) *	
Distance (meter)		283 (17)	391 (19)	430 (18)	147 (108;186) **		465 (20)	486 (20)	55 (12;23) *	
Physical Cost Index		.85 (.09)	.53 (.10)	.43 (.10)	-.4 (-.13;- .66) **		.46 (.10)	.39 (.11)	-.04 (-.31; .22) ns	
	N=21	N=27	N=24	N=27			N=23	N=24		
Work index	1.9 (.12)	2.5 (.11)	2.4 (.12)	2.3 (.12)	.4 (.1; .7) **		2.3 (.12)	2.6 (.13)	.3 (0; .6) *	
Sport index	1.9 (.12)	2.0 (.11)	2.2 (.12)	2.3 (.12)	.4 (.1; .6) **		2.2 (.12)	2.4 (.12)	.1 (-.1; .4) ns	
Leisure time index	2.1 (.15)	2.3 (.14)	2.5 (.14)	2.6 (.14)	.5 (.1; .8) **		2.8 (.14)	2.9 (.15)	.3 (0; .6) *	
Total activity index	6.0 (.27)	6.8 (.25)	7.1 (.26)	7.2 (.25)	1.2 (.6;1.8) **		7.5 (.26)	7.9 (.27)	.7 (.1;1.3) *	
		N=22	N=22	N=18			N=15	N=13		
ActiLog										
GPA score		81 (6.8)	87 (6.8)	92 (7.3)	11 (-4;27) ns		98 (7.8)	93 (8.2)	1 (-17;18) ns	
Average peaks		121 (4.9)	125 (5.0)	127 (5.4)	6 (-7;17) ns		126 (5.7)	127 (6.1)	0 (-13;14) ns	

Change score 1: Mean difference between measures at 3 (or 6) and 12 months after surgery; **Change score 2:** Mean difference between measure at 12 and 24 months after surgery; **CI:** 95% Confidence interval; **Linear Mixed Model Analysis ***: significant at the 0.05 level, ** significant at the 0.01.

after allograft reconstructions. After amputation the (external) prosthesis will usually be optimally fitted after approximately two months. In the Netherlands rehabilitation after rotationplasty usually starts after approximately four weeks with a temporary pelvis bearing prosthesis. The definite prosthesis will be fitted after at least four months. The variations in early postoperative rehabilitation related to differences in surgical techniques may have had a considerable impact on the observed function and QoL in the present study. Second, the localization of the tumor may have played a role. When limb-salvage surgery is performed in proximal tibia tumors, an extensor mechanism reconstruction almost always needs to be performed. The necessary protective actions and the recovery period are markedly different from limb-salvage surgery for distal femur tumors. Thirdly, all patients received postoperative chemotherapy, which is likely to have had a significant impact on their QoL and functional ability. As a result of the variation in duration as well as intensity of the different chemotherapy regimens employed, the consequences of the chemotherapy may have varied considerably among patients. In the later stages after surgery, complications and disease-related sequelae like metastases and the resulting surgery may also have had an important impact on function and QoL. However, the impact of all of these factors could not be analyzed in this study, due to the relatively small sample size. As a consequence, the nature of this study is mainly descriptive.

Analysis of longitudinal data in bone cancer patients is in general complicated by the fact that during the follow-up patients can be in different disease states, such as remission, relapse, complications or death. If both the response and the amount of missing data depend on the disease state, ignoring the disease state will yield biased means [36,37]. QoL and functional scores will in general be worse after relapses or complications, or patients are also less likely to participate or will not be able to complete assessments. In addition, if the data of patients who die or withdraw from the study because of deteriorating health status are excluded from the analyses, the limited number of patients remaining in the study could limit the statistical power and probably enhance a positive selection of the study population. In this study, linear mixed model analyses were performed to examine the course of QoL, functional ability and physical activity. The major advantage of linear mixed model analysis is that all available data are incorporated into the analysis, including data from survivors who missed one or more measurement occasions and patients who had a definite deterioration of their health status and were excluded from further analysis from that point. Despite these efforts, the risk of selection bias with overestimation of the patients' health status is substantial.

Another limitation, related to longitudinal research in children in general, is that different age groups need different age-specific questionnaires. For this reasons, we used two versions of a QoL questionnaire, the TACQOL and the TAAQOL and divided the patients into two age groups for some analyses, thereby limiting the statistical power. We have tried to solve this problem partly by composing Physical and Mental Component Summary scores. Although this procedure has been executed analogue to the SF-36 [10] and applied previously in research among pediatric cancer survivors [11,12], this method has not been validated for the TACQOL and TAAQOL, indicating that additional research for the composition, validity and reliability of these summary scales is needed. Despite these limitations, the overall patterns of improvement of QoL over the two years were similar in the two age groups.

The substantial number of patients who died or were lost to follow-up due to a worsening of their health status in this study illustrates that in a future study on the outcomes in this patient group, a much larger cohort of patients is needed. Moreover, a more elaborate description of all the medical and surgical characteristics and complications over time and a much longer observational period should be employed.

Despite these limitations, this study is the first to prospectively examine a comprehensive set of aspects of health status (QoL, functional ability and physical activity levels) in children and adolescents after malignant bone tumor surgery around the knee at several time points during a two year follow-up period. A number of strengths of the current study can be applied to future research, including the prospective, longitudinal design; the inclusion of patients from various age groups; and a comprehensive set of validated measures of QoL, functional ability and physical activity.

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