PATIENT FACING SYSTEMS

Effect of Game Based Balance Exercises on Rehabilitation After Knee Surgery: A Controlled Observational Study

Mattia Morri [1] · Daniela Vigna [1] · Debora Raffa [1] · Davide Maria Donati [2] · Maria Grazia Benedetti [3]

Abstract

Does a rehabilitation protocol based on balance exercises using Serious Game improve walk performance in patients undergoing knee resection and reconstruction for bone primary tumor?. 30 patients undergoing modular prosthetic replacement, following a primary bone tumor, were consecutively enrolled. During each hospitalization a physiotherapy treatment was activated, included 25 min training phase aimed postural and proprioceptive control. In order to better evaluate the walking speed at one-year post surgery in the study group, data were compared with a group of 22 patients treated in a previous period, called the control group, collected retrospectively. The control group differed only for the type of physiotherapy treatment offered. No statistically significant differences emerged from the two groups, regarding baseline characteristics. Walking speed in the study group was improved compared to the control group with a median difference of 0.22 m/s ($p = 0.022$). A difference was also measured in the speed of centre mass, with a median reduction of 4.5 mm/s ($p = 0.005$) in the study group, showing an improvement in postural control in stand-up position. Exercises aimed at recovering balance and Serious Game should be proposed in order to improve motor performance and postural control in the medium and long term.

Keywords Rehabilitation · Postural balance · Walking speed · Bone neoplasms · Serious game

Introduction

Knee resection and prosthesis reconstruction in patients with a primary tumor of the musculoskeletal system is increasingly used as salvage surgery [1] Mid and long-term results show more than satisfactory functional outcomes [2, 3] as documented by the Musculoskeletal Tumor Society (MSTS) score [4] and the Toronto Extremity Salvage Score (TESS) [5]. Several authors [6, 7] have highlighted that together with the functional evaluation of the patient, it is also important to

consider more specific motor performance tests such as Time Up and Go (TUG) and walking speed (10 m WT). A study by Okita et al. [8] analyzed walking speed in this group of patients and suggested that an improvement in this parameter was an important factor to improve the patients' quality of life. Benedetti et al. [9], performed gait analysis in patients undergone distal femur resection and reported a correlation between the width of muscle resection and the final outcome. Bernthal et al. [10] found that patients undergoing knee reconstruction can resume efficient walking, while gait evaluation can be considered a good parameter to analyze and compare surgical techniques and rehabilitation protocols. The type of rehabilitation treatment can have an important role in improving deambulation. The rarity of musculoskeletal tumors makes it difficult to design suitable study protocols. Therefore, up to date rehabilitation is little described in literature. Some authors [11, 12] have designed some programs of treatment trying to establish appropriate timing and treatment guidelines; however, based on our knowledge, there are no studies analyzing the most effective rehabilitation treatments to achieve improvement in walking performance. Carty et al. [13] found that recovery of knee extensor muscle strength, together with the increment of flexion range, are two important elements to focus on during rehabilitation. De Visser et al.

This article is part of the Topical Collection on *Patient Facing Systems*

✉ Mattia Morri
mattia.morri@ior.it

1   Servizio di Assistenza Infermieristica, Tecnica e della Riabilitazione, IRCCS - Istituto Ortopedico Rizzoli, Via Pupilli 1, 40136 Bologna, Italy

2   Clinica Ortopedica e Traumatologica III a Prevalente Indirizzo Oncologico, IRCCS - Istituto Ortopedico Rizzoli, Bologna, Italy

3   Struttura Complessa di Medicina Fisica e Riabilitativa, IRCCS - Istituto Ortopedico Rizzoli, Bologna, Italy

[14] had highlighted a balance reduction in these patients compared to healthy subjects, underlining a posture automatism deficit. Serious Games in rehabilitation are becoming an important tool for treatment. In patients suffering from neurological diseases, such as Parkinson's disease and brain injuries, as well as for orthopedic patients, the use of Serious Game and balance exercises has spread with the aim of achieving an improvement in motor performance. [15–17]. The possibility of improving motor performance in patients with bone cancer and undergoing reconstruction through this approach, based on our knowledge, has not yet been investigated.

Therefore, the aim of the present study was to investigate the effect of a rehabilitation protocol based on balance exercises using Serious Game in improving walk performance in patients undergoing knee resection and reconstruction.

Materials and methods

Study design: Controlled observational study

Participants

Between September 2014 and January 2016 all patients undergoing knee resection and modular prosthetic replacement, following a primary tumor of the musculoskeletal apparatus, and treated at the Chemotherapy department of our Institute, were consecutively enrolled after the surgery. The only exclusion criterion was the patient refusal to take part in the study. At one-year post surgery follow-up, patients presenting complications that would hamper the patient's evaluation, including local tumor relapse, implant infection and problems with antiblastic drug administration, were withdrawn from the study. All patients gave their consent and the study protocol was approved by the local Ethics Committee. For their surgical treatment, adjuvant chemotherapy and post surgery rehabilitation, patients were followed at the same hospital and by the same team of healthcare professionals. Adjuvant chemotherapy was administered during hospital stay by continuous infusion for 2–6 days, repeated every 3 weeks, for a total of 6 months. During each hospitalization after the surgery a physiotherapy treatment was activated, consisting in two 45 min daily sessions of therapy until patient discharge. The physiotherapy treatment started from the first post-operative day and treatment was aimed at the recovery of patients in order to minimize the disabling effects of surgery and resume the best possible recovery of residual abilities. In order to better evaluate the outcome at one-year post surgery in the study group, data were compared with a group of patients treated in a previous period, between January 2013 and January 2014, called the control group, applying the same inclusion and exclusion criteria and collecting retrospectively the same data. The control group differed only for the type of physiotherapy treatment offered, while chemotherapy, surgery protocols, healthcare professional team and physiotherapists were the same. In order to describe the study sample and compare it with the control group, the research physiotherapist collected the following information through interviews and medical charts: age, sex, diagnosis, height of the patient, level of resection, length of resection, ratio between length of resection and length of resected bone, duration of post-surgery chemotherapy and follow-up timing.

Physiotherapy in the study group

Each rehabilitation session included a 20 min phase of exercises to recover articular range of motion, muscle strength and autonomy, followed by a 25 min training phase aimed balance. For this second part, exercises following the Liao et al. [18] protocol were employed: stand up exercises with variations of the support ground, bipodalic and monopodalic support, increasingly unstable load surfaces, Freeman balancing boards, control exercises combined with other motor tasks such as throwing a ball, and training with or without visual feedback. When patients were able to use 50% partial loading, the rehabilitation training was also performed using a Wii Fit Balance Board. Patients would receive an immediate visual feedback on their ability of load distribution and control on lower limbs and, consequently, they tried to modify and adjust it in order to reach the requested objective, with exercises requiring to move the load laterally and in antero-posterior direction, and with multi-directional balance exercises as described by Fung et al. [19].

Physiotherapy in the control group

The scheme of treatment for the control group shared some objectives with the study group and sessions lasted the same (45 min). Each physiotherapy session included exercises in bed aimed at the recovery of knee ROM and quadriceps muscle strength, and exercises in standing position aimed at recovering autonomy. The treatment did not include any specific training for postural control.

Primary outcome

Walking speed one-year post surgery. This test is easy to administer and has been demonstrated to be a valid, sensitive and reliable measure [20]. This test required the patients to start walking at their own speed judging their possibilities and confidence. No encouragements were given during the test. The test was carried out twice and the best performance was recorded.

Secondary outcomes

Further measures were recorded during the follow-up visit carried out one-year after surgery:

- Knee articular mobility (ROM) [21], measured with a manual articular goniometer.
- Maximal quadriceps strength, measured by the Medical Research Council [22] scale, and quadriceps muscle trophism, measured comparing healthy vs. operated thigh circumference 10 cm above the patella.
- Disability score according to MSTS [4]. This is a subjective non-parametric system evaluating several aspects of recovery: pain, general abilities, emotional aspects, use of aid devices, ability of deambulation and the way the patient can walk. For each category a score ranging from 0 (highest disability) to 5 (highest autonomy) is attributed, with a total minimum score of 0 and a maximum score of 30.
- Level of autonomy recovered and perceived by the patient in daily life according to the TESS [5]. This is a self-administered questionnaire composed of 30 items concerning the patient's motor ability in daily activities. Every item is attributed a score between 1, lower score, to 5, higher score. The total score is calculated a percentage of the higher possible score.
- Patient's balance measured by stabilometric analysis using the LorAN Engineering Srl- EPS-R1 system board, recording the mean oscillation speed of the centre mass. A lower speed of oscillation indicates a greater postural control. The test was carried out based on the De Visser et al. [14] method.
- Walk performance measured by Time Up and Go (TUG) [23] and six minutes Walking Test (6mWT) [24].

Sample size

The rarity of this pathology limits the sample size, therefore we collected data from all patients hospitalized in the study period. In 18 months, 30 patients were enrolled. The control group was a sample for 22 patients.

Statistical analysis

Statistical analysis was performed by using IBM SPSS Statistics v. 21. All continuous data were expressed in terms of median and interquartile; categorical variables were expressed as proportions or percentages. Because of the reduced sample size, which did not allow for a precise data distribution, the non-parametric Mann-Whitney test was used to compare characteristics of the two analyzed groups, and the exact Fisher test for dichotomy variables. Results were considered significant for $P < 0.05$.

Results

Thirty patients in total were enrolled in the study period, and 22 completed the one-year post-surgery follow-up. The control group included 22 patients, and data of 15 of them could be included in the statistical analysis. Figure 1 shows enrollment and follow-up work-flow for both groups. A total of 37 patients were analyzed. Median age of the pooled sample, study group and control group, was 21 years, 27% of patients were women, 83.8% had localized osteosarcoma, in 73% of cases at distal femoral level. Surgical treatment consisted of modular prosthetic replacement in 34 cases (91.9%), composite prosthesis with bone graft in 2 cases, one in the study group and one in the control group, and extensible prosthesis in 1 case in the control group. The rehabilitative pathway for these specific surgical approaches of composite and extensible prosthesis has been superimposable with the rehabilitative pathway of patients undergoing modular prosthesis surgery. Resection median length was 15 cm. The specific characteristics of the two samples are described in Table 1. No statistically significant differences emerged from the two groups, regarding baseline characteristics. Table 2 shows the outcomes at follow-up registered in the two groups. Walking speed in the study group was improved compared to the control group with a median difference of 0.22 m/s ($p = 0.022$), passing from a median of 1.26 m / sec (IQR = 0.6) in the comparison group to a value of 1.48 m / sec (IQR = 0.5) in the study group. A difference was also measured in the speed of centre mass, passing from a median value of 9.3 mm / sec (IQR = 5.2) in the comparison group to a value of 4.8 mm / sec (IQR = 2.5) in the study group ($p = 0.005$), showing an improvement in postural control in stand-up position. TUG data were improved in the study group, passing from a median value of 8.5 s (IQR = 4.3) in the study group to a value of 7.1 s (IQR = 1.8) in the study group with a reduction in median execution time of 1.4 s ($p = 0.074$). The other outcomes evidenced some differences, although not statistically significant.

Discussion

In patients who underwent knee resection and reconstruction for musculoskeletal system tumors, a specific rehabilitation treatment aimed at motor control of the knee and balance had a significant effect in improving postural control and motor performance recovery during walking. Data from patients in the study group showed a walking speed median value of 1.48 m/s one-year post-surgery, which is a better result compared to the control group (1.26 m/s) and it is in line with values calculated by Bohannon RW [25] in a

Fig. 1 Enrollment and follow-up process
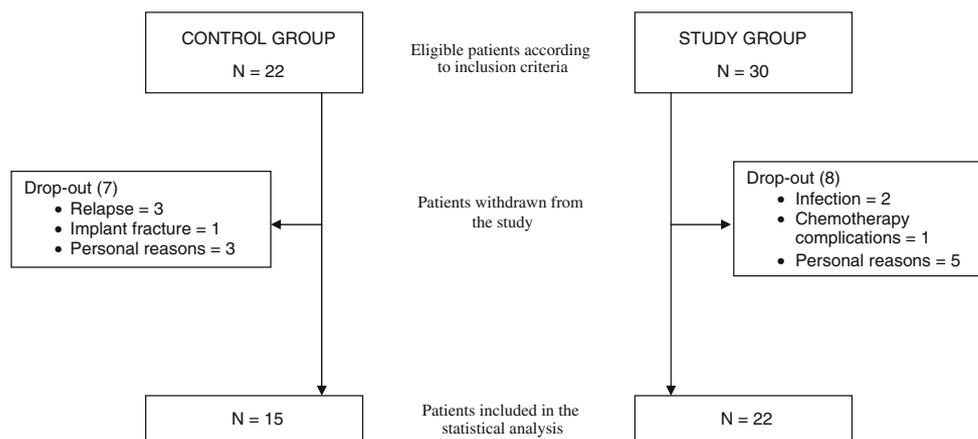
healthy population of the same age range, where mean speed was 1.27 m/s - 1.45 m/s for men aged between 20 and 30 years. It should also be taken into account that in the study group there was a higher percentage of patients with knee reconstruction due to proximal tibial tumor localization compared to the comparison group (31.8% in the study group vs 20% in the group control). For these patients, the type of intervention involves a recovery of ambulation in a longer time and a more difficult rehabilitative path, but despite these aspects the outcomes at one year were better in the study group. De Visser et al. [26] believe that, after a mega-prosthetic reconstruction surgery, the central nervous system should adapt to the new flux of information arriving from the operated limb, and only at the end of such process the patient will be able to recover the optimal level of performance during walking. Resection surgery causes a big loss both in term of bone and muscle stricture, and in terms of sensor-motor shock, leading to consequences in neuromotor control of knee and balance. In the hypothesis

of the present study, the choice of balance exercises and postural control had the scope of training the neuromotor controlling system of the patient in order to recover automatisms that are hampered by surgery. The result of the TUG test, despite being substantially different between the two groups, was not statistically significant ($p = 0.074$). The results recorded one year after surgery for this type of patient are in line with the studies available in the literature. Bekkering et al. [27] reported a mean TUG of 7.2 s, Carty et al. [13] a mean knee ROM of 125 ° and Ginsberg et al. [28] an average TESS score of 86.4. It should be noted that these studies did not focus on the description of the rehabilitation path carried out by the patients and that the outcomes reported were measured with a time interval of more than one year. In this study it is possible to observe an achievement of good functional outcomes already at one year from the surgical intervention, at the same time, they are evidenced by the need of being able to observe more samples in order to obtain more consistent statistical results. De

Table 1 Sample characteristics

	Control group (N = 15)	Study group (N = 22)	P value
Age, median (IQR)	21 (15)	21 (30)	0.710
Sex, women n (%)	5 (33.3)	5 (22.7)	0.708
Height, median (in cm)	170 (13)	176 (18)	0.252
Diagnosis, n (%)			
Osteosarcoma	13 (86.7)	18 (81.8)	1.000
Other tumours (condrosarcoma, Ewing sarcoma)	2 (13.3)	4 (18.2)	
Resection level, n (%)			
Distal femur	12 (80)	15 (68.2)	0.481
Proximal tibia	3 (20)	7 (31.8)	
Resection length (cm), median (IQR)	15 (6.5)	15 (8.6)	0.401
% of resection, median (IQR)	34.8 (9.7)	33.3 (20.9)*	1.000
Follow-up time since surgery (months), median (IQR)	12 (2)	13 (1)	0.860
Post-surgery chemotherapy (months), median (IQR)	8 (4)	6 (4)	0.303

% of resection (comparison) *1 missing

Table 2 Outcome measure - median (IQR)

	Control group (N = 15)	Study group (N = 22)	P value
Knee range of motion	100 (30)	110 (41)	0.575
Knee estension strength (0–5 scale)	4 (1)	4 (2)	0.648
Difference in thigh circometry (in cm)	2.5 (3)*	2.5 (1.3)	0.604
MSTS (in %)	83.3 (23.3)	78.3 (17.5)	0.630
TESS (in %)	89 (17)	85.0 (13)	0.189
Walking speed, 10 mWT (in m/s)	1.26 (0.6)	1.48 (0.5)	0.022
TUG (in sec)	8.5 (4.3)*	7.1 (1.8)	0.074
6mWT (in m)	425(224)*	450.5 (48)	0.465
CM speed (mm/s)	9.3 (5.2)*	4.8 (2.5)*	0.005

*Diff. Circometry 2 missing in control group; TUG 1 missing in control group; 6mWT 1 missing in control group; CM speed 1 missing in control group and 3 missing in study group

Visser et al. [17] registered the appearance of balance deficit for patients undergoing salvage surgery at the lower limb. Balance is a function determined by the integration of visual, vestibular and proprioceptive inputs, which allow the construction of a proper motor response by the subject. The analysis of data of the present study highlights a marked improvement in the study group, with a statistically significant reduction in speed of centre mass. The Balance Board is an instrument used for balance and postural control training, as already shown in other fields of application [29–31] such as post-stroke rehabilitation and prevention of the risk of fall. In the present study, it was chosen exactly with this aim. Fung et al. [19] had demonstrated the feasibility of Balance Board exercises for patients undergoing total knee prosthesis for arthrosis pathology. Data of the present study demonstrated that this choice could be considered useful also for patients undergoing wider knee resection and reconstruction and should be taken into consideration as therapeutic instrument to achieve a functional improvement of the patient. The remaining outcomes considered in this study did not show significant differences. At the end of the first-year post-surgery, patients did not show differences in recovery of autonomy, ROM and muscle strength. Carty et al. [13], highlighted the need for these patients to concentrate post-surgery recovery on residual abilities and, in particular, on recovery of knee ROM and muscle strength of the quadriceps. The proposed therapeutics choice in the study group did not seem to determine worst results compared to the control group. Walking endurance in the study group showed a better outcome compared to the control group, but it was not statistically significant. It can be hypothesized that walking endurance could be influenced by the duration of treatment rather than the choice of exercises, and the time allowed for recovery, from the end of chemotherapy to the one-year follow-up, seems too short to see performance differences between the two groups, despite the different walking speed registered.

This study presents some limitation linked to the dimensions of the studied sample and the study design. For both aspects, the rarity of bone tumor is a decisive aspect. The AIRTUM group for the Italian population of children and adolescents shows an incidence of bone tumors equal to 5.4 cases per million (IC95% 4.2–6.8) for boys and 3.1 (IC95% 2.2–4.3) for girls [32]. Regarding the sample size, this study was in line with the number of samples collected in other studies that had walking speed as the main outcome [8–10]. For what concerns the type of study design, according to our knowledge, in literature there are no randomized clinical trials of rehabilitation for these patients because of a reasonable period of time. In addition, the possibility to study patients followed within the same care facility and by the same medical and physiotherapy team, has allowed to limit the bias introduced by the need to build the two groups without randomization. In the present study, a comparison was only possible with the outcomes achieved by the patients one year after the intervention since the historical data used for the comparison were the available data. This aspect should be taken into account when planning new studies in this area. .

Conclusions

Walking speed is an ability that can be trained with exercise and that require many abilities by the patient, including muscle strength, balance, coordination, endurance and load control in the operated limb. Walking performance is an aspect that the physiotherapist should consider carefully for these patients since an unsuitable walking speed can imply a greater energy waste. Therefore, exercises aimed at recovering balance using Serious Game should be proposed to patients undergoing modular prosthetic surgery in order to improve motor performance and postural control in the medium and long term.

References

1. Hardes, J., Henrichs, M. P., Gosheger, G. et al., Endoprosthetic replacement after extra-articular resection of bone and soft-tissue tumours around the knee. *Bone Joint J.* 95-B(10):1425–1431, 2013.

2. Yalniz, E., Ciftdemir, M., and Memişoğlu, S., Functional results of patients treated with modular prosthetic replacement for bone tumors of the extremities. *Acta Orthop. Traumatol. Turc.* 42(4):238–245, 2008.

3. Qadir, I., Umer, M., and Baloch, N., Functional outcome of limb salvage surgery with mega-endoprosthetic reconstruction for bone tumors. *Arch. Orthop. Trauma Surg.* 132(9):1227–1232, 2012.

4. Enneking, W. F., Dunham, W., Gebhardt, M. C. et al., A system for the functional evaluation of reconstructive procedures after surgical treatment of tumors of the musculoskeletal system. Clin. Orthop. 286:241–246, 1993.

5. Davis, A. M., Wright, J. G., Williams, J. I. et al., Development of a measure of physical function for patients with bone and soft tissue sarcoma. *Qual. Life Res.* 5:508–516, 1996.

6. Beebe, K., Song, K. J., Ross, E. et al., Functional outcomes after limb-salvage surgery and endoprosthetic reconstruction with an expandable prosthesis: a report of 4 cases. *Arch. Phys. Med. Rehabil.* 90(6):1039–1047, 2009.

7. Bekkering, W. P., Vliet Vlieland, T. P., Koopman, H. M. et al., A prospective study on quality of life and functional outcome in children and adolescents after malignant bone tumor surgery. *Pediat. Blood Cancer* 58(6):978–985, 2012.

8. Okita, Y., Tatematsu, N., Nagai, K. et al., The effect of walking speed on gait kinematics and kinetics after endoprosthetic knee replacement following bone tumor resection. *Gait Post.* 40(4):622–627, 2014.

9. Benedetti, M. G., Catani, F., Donati, D. et al., Muscle performance about the knee joint in patients who had distal femoral replacement after resection of a bone tumor. An objective study with use of gait analysis. *J. Bone Joint Surg. Am.* 82-A(11):1619–1625, 2000.

10. Bernthal, N. M., Greenberg, M., Heberer, K. et al., What are the functional outcomes of endoprosthestic reconstructions after tumor resection? *Clin. Orthop. Relat. Res.* 473(3):812–819, 2015.

11. Lopresti, M., Rancati, J., Farina, E. et al., Rehabilitation pathway after knee arthroplasty with mega prosthesis in osteosarcoma. *Recenti Prog. Med.* 106(8):385–392, 2015.

12. Shehadeh, A., El Dahleh, M. et al., Standardization of rehabilitation after limb salvage surgery for sarcomas improves patients' outcome. *Hematol. Oncol. Stem Cell Ther.* 6(3–4):105–111, 2013.

13. Carty, C. P., Dickinson, I. C., Watts, M. C. et al., Impairment and disability following limb salvage procedures for bone sarcoma. *Knee* 16(5):405–408, 2009.

14. de Visser, E., Deckers, J. A., Veth, R. P. et al., Deterioration of balance control after limb-saving surgery. *Am. J. Phys. Med. Rehabil.* 80(5):358–365, 2001.

15. Meijer, H. A., Graafland, M., Goslings, J. C., and Schijven, M. P., Systematic review on the effects of serious games and wearable technology used in rehabilitation of patients with traumatic bone and soft tissue injuries. *Arch. Phys. Med. Rehabil.* 99(9):1890–1899, 2018.

16. Lopes, S., Magalhães, P., Pereira, A. et al., Games used with serious purposes: A systematic review of interventions in patients with cerebral palsy. *Front Psychol.* 9:1712, 2018.

17. Garcia-Agundez, A., Folkerts, A. K., Konrad, R., Caserman, P., Tregel, T., Goosses, M., Göbel, S., and Kalbe, E., Recent advances in rehabilitation for Parkinson's disease with Exergames: A systematic review. *J. Neuroeng. Rehabil.* 16(1):17, 2019.

18. Liao, C. D., Liou, T. H., Huang, Y. Y., and Huang, Y. C., Effects of balance training on functional outcome after total knee replacement in patients with knee osteoarthritis: a randomized controlled trial. *Clin. Rehabil.* 27(8):697–709, 2013.

19. Fung, V., Ho, A., Shaffer, J. et al., Use of Nintendo Wii Fit™ in the rehabilitation of outpatients following total knee replacement: a preliminary randomised controlled trial. *Physiotherapy* 98(3):183–188, 2012.

20. Graham, J. E., Ostir, G. V., Fisher, S. R., and Ottenbacher, K. J., Assessing walking speed in clinical research: A systematic review. J. Eval. Clin. Pract. 14(4):552–562, 2008.

21. Brosseau, L., Balmer, S., Tousignant, M. et al., Intra- and intertester reliability and criterion validity of the parallelogram and universal goniometers for measuring maximum active knee flexion and extension of patients with knee restrictions. *Arch. Phys. Med. Rehabil.* 82(3):396–402, 2001.

22. Medical Research Council, Aids to the investigation of peripheral nerve injuries. 2nd edition. London: Her Majesty's Stationary Office, 1943.

23. Butland, R. J. A., Pang, J., Woodcock, A. A., and Geddes, D. M., Two, six and twelve minute walking tests in respiratory disease. *BMJ* 284:1604–1608, 1982.

24. Podsiadlo, D., and Richardson, S., The timed "up and go": A test of basic functional mobility for frail elderly persons. *J. Am. Geriatr. Soc.* 39(2):142–148, 1991.

25. Bohannon, R. W., and Williams Andrews, A., Normal walking speed: A descriptive meta-analysis. *Physiotherapy* 97(3):182–189, 2011.

26. de Visser, E., Veth, R. P., Schreuder, H. W. et al., Reorganization of gait after limb-saving surgery of the lower limb. *Am. J. Phys. Med. Rehabil.* 82(11):825–831, 2003.

27. Bekkering, W. P., Vliet Vlieland, T. P., Koopman, H. M. et al., Functional ability and physical activity in children and young adults after limb-salvage or ablative surgery for lower extremity bone tumors. *J. Surg. Oncol.* 1(3):103, 2011.

28. Ginsberg, J. P., Rai, S. N., & Carlson, C. A., et al., A comparative analysis of functional outcomes in adolescents and young adults with lower-extremity bone sarcoma. *Pediatr. Blood Cancer.*, 49(7), 2007.

29. Manlapaz, D. G., Sole, G., Jayakaran, P., and Chapple, C. M., A narrative synthesis of Nintendo Wii fit gaming protocol in addressing balance among healthy older adults: What system works? *Games Health J.*, 2017. https://doi.org/10.1089/g4h.2016.0082.

30. Bonnechère, B., Jansen, B., Omelina, L., and Van Sint Jan, S., The use of commercial video games in rehabilitation: A systematic review. *Int. J. Rehabil. Res.* 39(4):277–290, 2016.

31. Iruthayarajah, J., McIntyre, A., Cotoi, A., Macaluso, S., and Teasell, R., The use of virtual reality for balance among individuals with chronic stroke: A systematic review and meta-analysis. *Top Stroke Rehabil.* 24(1):68–79, 2017.

32. AIRTUM Working Group and AIEOP Working Group, Cancer in children and adolescents. *Epidemiol. Prev.* 37(1 Suppl 1):1–296, 2013.