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Impact of Amputation Level and Oncologic Prognosis on Activities of Daily Living in Patients with Lower Limb Amputation for Musculoskeletal Malignancies

Hiromori Sagae,[1] Masato Sugawara,[1] Daiichiro Takahara,[1] Michiaki Takagi[1] and Yuya Takakubo[1]

[1]Department of Orthopaedic Surgery, Yamagata University Faculty of Medicine, Yamagata, Japan

Activities of daily living (ADLs) with phantom limb pain (PLP) and prosthesis use in patients who underwent lower limb amputation for musculoskeletal malignancies has been reported just by a few researchers. This study aimed to investigate the influence of PLP and prosthesis use on ADLs after lower limb amputation for musculoskeletal malignancies. We conducted a retrospective study on 19 patients (10 males and 9 females) who underwent lower limb amputation for musculoskeletal malignancies between 2003 and 2011 and were followed up until 2021. The mean age was 60.4 (range, 10-85) years. We investigated PLP, prosthesis use, and ADLs after lower limb amputation; we used the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) to assess ADLs. PLP was present in 16 patients (84%), and 4 of 5 survivors (80%) were medication-free at the final follow-up. Prostheses were prescribed in 16 patients (84%), and 11 patients (69%) continued to use the prosthesis after discharge. In a multiple linear regression analysis of ADLs at discharge for the 15 patients with confirmed survival or death, excluding the four patients whose outcome was unknown at the last follow-up, lower-level amputation and good oncologic prognosis were positive independent factors, while age was the only negative independent factor. PLP and prosthesis use did not influence ADLs.

Keywords: activities of daily living; lower limb amputation; musculoskeletal malignancy; phantom limb pain; prosthesis; rehabilitation
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Introduction

Amputation surgery is an essential treatment for musculoskeletal malignancies, although limb-sparing surgery has gained attention recently (Stevenson et al. 2018; Wilke et al. 2019; Kirilova et al. 2021; Reijers et al. 2022). Phantom limb pain (PLP) and gait impairment are common problems after lower limb amputation, affecting the quality of life and activities of daily living (ADLs) of amputees (Dijkstra et al. 2002; Collins et al. 2018; Döring et al. 2021). However, most research on PLP, prostheses, and ADLs has focused on amputations due to vascular disease and trauma, which are more prevalent than musculoskeletal malignancies. Musculoskeletal malignancies account for 1%-9% of lower limb amputations (Dijkstra et al. 2002; Ziegler-Graham et al. 2008). There are few reports on PLP, prosthesis, or ADLs in patients who underwent lower limb amputation due to musculoskeletal malignancies (Kauzlarić et al. 2007; Probstner et al. 2010; Jiang et al. 2021). Therefore, the influence of PLP and prosthesis use on ADLs after lower limb amputation due to musculoskeletal malignancies remains unclear. This study aims to investigate the incidence of PLP, prosthesis use, and ADL status to determine the influence of PLP and prosthesis use on ADLs after lower limb amputation due to musculoskeletal malignancies. Identifying ADLs after lower limb amputation and factors affecting ADLs can aid in the selection of surgical strategies for musculoskeletal malignancies.

Materials and Methods

Ethical approval

This study has been approved by the Ethics Review

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Correspondence: Hiromori Sagae, Department of Orthopaedic Surgery, Yamagata University Faculty of Medicine, 2-2-2 Iida-Nishi, Yamagata, Yamagata 990-9585, Japan.
e-mail: smoking.wolf.18@gmail.com

Committee of Yamagata University Faculty of Medicine (ethical code # 2020-81). The patients and/or their families were informed that data from the study would be submitted for publication, and gave their consent.

Patients

The study included 19 patients (10 males and 9 females) who underwent lower limb amputation for musculoskeletal malignancy treatment at our institution between August 2003 and November 2011 and were followed up until November 2021. The mean age was 60.4 (range, 10-85) years, and the mean period that patient information was available was 71.7 (range, 2-179) months. The outcomes on the last day that patient information was available after discharge were alive, dead, and unknown in five, ten, and four patients, respectively. Therefore, for oncologic outcomes in this study, 5 cases with confirmed survival at last follow-up were defined as good oncologic prognosis, and 10 cases with confirmed death were defined as poor oncologic prognosis. The incidence and suffering duration of PLP, preventive measures, and medications for PLP were retrospectively investigated from medical records. For the prostheses, prescriptions, and usage status after discharge were investigated.

Amputation level

The amputation levels of the lower limbs were classified as hemipelvectomy, hip disarticulation, transfemoral amputation, and transtibial amputation.

ADL measurements

We assessed ADLs before and after hospitalization using the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (Oken et al. 1982; Buccheri et al. 1996). The ECOG-PS is a long-established measure of the general condition of oncological patients: 0 means fully active, 1 means restricted in physically strenuous activity, 2 means unable to carry out any work activities, 3 means capable of only limited selfcare, and 4 means completely disabled. ECOG-PS has been reported to be associated with Barthel Index (BI), a common ADL measure (Wade and Collin 1988; Chan et al. 2019; Kanda et al. 2020), so in this study, we defined ECOG-PS 0-2 as ADL independence and ECOG-PS 3 and 4 as ADL assistance.

Statistical analysis

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan, version 1.55), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 4.1.2). More precisely, it is a modified version of R commander (version 2.7-1) designed to add statistical functions frequently used in biostatistics (Kanda 2013). Mann-Whitney's U test was used for continuous variables. Fisher's test was used for categorical variables. Statistical significance was set at $p < 0.05$. For correlations, Spearman's correlation coefficient was used. Logistic regression analysis on ADL independence at discharge and multiple regression analysis on ADLs at discharge were performed on 15 patients alive or dead at the last follow-up.

Results

Patient characteristics, diagnosis, amputation level, adjuvant chemotherapy, follow-up period, outcome, oncologic prognosis, PLP, prosthesis prescription, and prosthesis use are listed in Table 1. PLP was present in 16 patients (84%), and their mean onset time was 3.6 (range, 0-16) days. The mean age was 47.3 years (0-75) for patients without PLP and 62.9 years (17-85) for those with PLP. The age between the two groups showed no significant difference. ($p = 0.34$). In terms of amputation levels, patients with PLP tended to be older for higher amputation levels ($r = -0.49$, $p = 0.05$). As preventive measures against PLP, continuous epidural anesthesia, continuous nerve block at the resected nerve, and their combined methods were used in 14, 12, and 11 patients, respectively. Among them, only two patients with combined methods did not develop PLP at all.

All patients with PLP were treated with medication, either single or multiple drugs. Anti-inflammatory drugs (NSAIDs) and antidepressants ($n = 12$) were prescribed more than other drugs (Fig. 1). The mean time to start medication for PLP was 4.6 (range, 1-16) days postoperatively. The medication was discontinued at an average of 3.3 (range, 2-5) months postoperatively. Four of five survivors (80%) were medication-free at the final follow-up.

Prostheses were prescribed for 16 patients (84%) at an average of 65.2 (range, 14-330) days postoperatively (Table 1). The mean age of patients with prosthesis use was 53.5 years (10-75), and those of patients without prosthesis use was 68.2 years (18-83), showing that patients with prosthesis use were significantly younger than patients without prosthesis use ($p = 0.04$). Regarding PLP, 9 patients with prosthesis use and 5 patients without prosthesis use had PLP, and there was no significant difference between them ($p = 1.00$). The amputation levels of patients with and without prosthesis use showed no significant difference. ($p = 0.52$).

All patients were ADL-independent at admission. On the other hand, 11 patients (58%) were ADL-independent (ECOG-PS scores 0-2) at discharge (Table 2). All five survivors were ADL-independent, while only 3 of the 10 deceased patients were ADL-independent ($p = 0.03$). In the 15 patients with confirmed survival or death, excluding the four patients whose outcome was unknown at the last follow-up, the mean age of patients with ADL independence at discharge was significantly younger than that of patients with ADL assistance (41.1 years vs. 79.4 years; $p < 0.01$). Furthermore, the proportion of prosthesis use in patients with ADL independence was significantly higher than in patients with ADL assistance (75% vs. 14%; $p = 0.04$). PLP

Table 1. Patient characteristics.

Case	Age	Sex	Histological diagnosis	Amputation level	Adjuvant chemotherapy	Follow-up period (month)	Outcome	Oncologic prognosis	PLP	Prosthesis prescription	Prosthesis use
1	71	Male	Liposarcoma	Hemipelvectomy	no	13.4	death	poor	yes	yes	yes
2	78	Female	Leiomyosarcoma	Hemipelvectomy	no	17.3	death	poor	yes	yes	no
3	83	Male	Undifferentiated pleomorphic sarcoma	Hemipelvectomy	no	5.6	death	poor	yes	yes	no
4	48	Male	Epithelioid sarcoma	Hip disarticulation	yes	155.1	survive	good	yes	no	no
5	57	Male	Dermatofibrosarcoma protuberans	Hip disarticulation	yes	87.7	death	poor	no	no	no
6	77	Female	Myxofibrosarcoma	Hip disarticulation	no	51.0	death	poor	yes	no	no
7	85	Female	Liposarcoma	Hip disarticulation	no	64.7	death	poor	yes	yes	yes
8	10	Male	Osteosarcoma	Transfemoral amputation	yes	171.4	survive	good	no	yes	yes
9	17	Male	Osteosarcoma	Transfemoral amputation	yes	178.6	survive	good	yes	yes	yes
10	18	Female	Malignant peripheral nerve sheath tumor	Transfemoral amputation	no	48.7	death	poor	yes	yes	no
11	56	Female	Osteosarcoma	Transfemoral amputation	yes	55.2	unknown	-	yes	yes	yes
12	70	Female	Leiomyosarcoma	Transfemoral amputation	no	90.6	unknown	-	yes	yes	yes
13	71	Female	Undifferentiated pleomorphic sarcoma	Transfemoral amputation	no	60.4	unknown	-	yes	yes	yes
14	79	Female	Extraskeletal Ewing sarcoma	Transfemoral amputation	no	2.1	death	poor	yes	yes	no
15	83	Female	Undifferentiated pleomorphic sarcoma	Transfemoral amputation	no	14.3	death	poor	yes	yes	no
16	40	Male	Osteosarcoma	Transtibial amputation	yes	168.1	survive	good	yes	yes	yes
17	64	Male	Squamous cell carcinoma	Transtibial amputation	no	117.5	survive	good	yes	yes	yes
18	66	Male	Bone metastasis (renal cell carcinoma)	Transtibial amputation	no	52.5	unknown	-	yes	yes	yes
19	75	Male	Leiomyosarcoma	Transtibial amputation	no	7.4	death	poor	no	yes	yes
Total				Hemipelvectomy: 3 (16%) Hip disarticulation: 4 (21%) Transfemoral amputation: 8 (42%) Transtibial amputation: 4 (21%)	yes: 6 (32%) no: 13 (68%)		survive: 5 (26%) death: 10 (53%) unknown: 4 (21%)	good: 5 (33%) poor: 10 (67%)	yes: 16 (84%) no: 3 (16%)	yes: 16 (84%) no: 3 (16%)	yes: 11 (58%) no: 8 (42%)

PLP, phamtom limb pain.

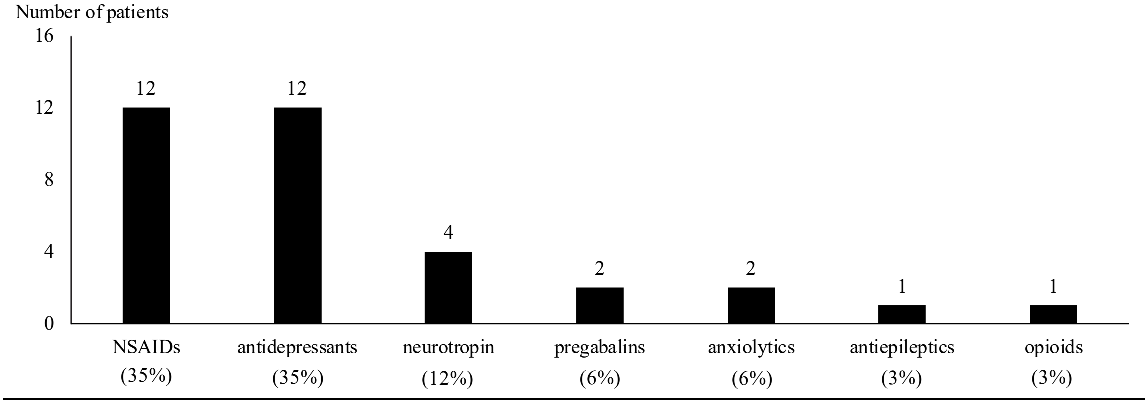

Fig. 1. Medications prescribed for the treatment of PLP.
All patients with PLP were treated with any medication, either single or multiple drugs. NSAIDs and antidepressants (n = 12, 35%, respectively) were prescribed more than other medications (neurotropin, pregabalins, anxiolytics, antiepileptics and opioids). NSAIDs, non-steroidal anti-inflammatory drugs.

Table 2. ECOG-PS and ADL independence at admission and discharge.

	Admission		Discharge	
Case	ECOG-PS	ADL indepedence	ECOG-PS	ADL indepedence
1	0	yes	3	no
2	0	yes	3	no
3	0	yes	3	no
4	0	yes	1	yes
5	0	yes	2	yes
6	0	yes	3	no
7	0	yes	3	no
8	0	yes	0	yes
9	0	yes	0	yes
10	0	yes	1	yes
11	0	yes	2	yes
12	0	yes	2	yes
13	0	yes	3	no
14	0	yes	3	no
15	2	yes	3	no
16	0	yes	0	yes
17	0	yes	0	yes
18	0	yes	1	yes
19	0	yes	2	yes
Total		yes: 19 (100%) No: 0 (0%)		yes: 11 (58%) no: 8 (42%)

ECOG-PS, the Eastern Cooperative Oncology Group Performance Status; ADL, activities of daily living.
ADL indepence (ECOG-PS=0 to 2).

showed no significant difference between patients with ADL independence and those with ADL assistance (63% vs. 100%; p = 0.20). Amputation levels also showed no significant difference between patients with ADL independence and those with ADL assistance (0/2/3/3 vs. 3/2/2/0, from proximal to distal; p = 0.16). To determine independent factors contributing to ADL independence at discharge, we performed a logistic regression analysis using amputation level, age, oncologic prognosis, PLP, and prosthesis use but were unable to determine the independent factors. Multiple regression analysis was performed for the factors for which regression equations were obtained by single regression analysis for ADLs at discharge (Table 3). Lower-level amputation and good oncologic prognosis were

Table 3. Multiple linear regression coefficients associated with ADLs at discharge among survivors and deceased patients.

	Single liner regression			Multiple liner regression			
				Unstandardized Coefficients		Standardized Coefficients	
	Coefficients	95% CI	p-value	B	95% CI	Beta	p-value
Amputation level	–0.79	–1.37, –0.21	0.01	–0.30	–0.54, –0.07	–0.24	0.02
Age	0.04	0.03, 0.06	< 0.01	0.02	0.01, 0.03	0.40	< 0.01
Good oncologic prognosis	–2.40	–3.14, –1.65	< 0.01	–1.35	–2.20, –0.49	–0.50	0.01
PLP	0.58	–1.29, 2.46	0.51				
Prosthesis use	–1.77	–2.87, –0.66	< 0.01	–0.04	–0.71, 0.63	–0.02	0.90

95% CI, 95% confidence interval; PLP, phantom limb pain.
Amputation level (hemipelvectomy/hip disarticulation/transfemoral amputation/transtibial amputation).

positive independent factors, while age was the only negative independent factor. PLP and prosthesis use did not influence ADLs.

Discussion

This study investigated PLP, prosthesis use, and ADLs in patients who underwent lower limb amputation for musculoskeletal malignancies. We assessed for the first time ADLs using ECOG-PS and reported independent factors on ADLs after lower limb amputation due to musculoskeletal malignancies. In the 15 patients with confirmed survival or death, excluding the 4 patients whose outcome was unknown at the last follow-up, lower-level amputation and good oncologic prognosis were positive independent factors for ADLs at discharge, while age was the only negative independent factor. PLP and prosthesis use did not influence ADLs.

Previous reports have also shown that amputation level was the independent factor of ADLs and ambulation function in patients with lower limb amputation (Frlan-Vrgoc et al. 2011; Kahle et al. 2016; Fajardo-Martos et al. 2018; Hagi et al. 2022). This finding aligns with our study results. Kahle et al. (2016) reviewed 13 articles on amputation level in lower limb amputees reported between 2007 and 2015, showing the association between amputation level and gait function and ADLs. Fajardo-Martos et al. (2018) and Hagi et al. (2022) also showed an association between amputation level and gait function in a retrospective study of 169 and 55 lower-limb amputees, respectively, citing as the reason that lower-level amputation consumes less energy in gait than higher-level amputation. Furthermore, Hagi (2022) reported on oncological survival and gait function in 55 patients, with a mean age of 60 years, amputated due to soft tissue sarcoma, and showed an association between tumor size and overall survival, but no association between tumor size and independent gait. In our study, we assessed ADLs at discharge using the ECOG-PS in 19 patients aged 60.4 years after lower limb amputation for musculoskeletal malignancies. The ECOG-PS was associated with the BI, a standard ADL measure (Kanda et al. 2020), so that we could understand the overall ADLs of patients with lower limb amputation. Our results showed that lower-level amputation and good oncologic prognosis were positive independent factors for ADLs at discharge. We considered the reason for the association between amputation level and ADLs to be the same as in the previous literature. The present study suggested for the first time that good ADLs can be expected after lower limb amputation when long-term survival is possible as the oncologic prognosis. We need to investigate further the factors that predict both good oncological prognosis and good ADLs after lower limb amputation in multi-centers large study. This study, in contrast to the previous study, showed no impact of PLP on ADLs (Furtado et al. 2015; Döring et al. 2021). Döring et al. (2021) reported that PLP restricts ADLs in patients who underwent lower limb amputation for musculoskeletal malignancies. The prevalence of PLP and ADL restrictions due to PLP was investigated using a 10-point self-rating questionnaire in 21 amputees with a median age of 60 years. The results showed that patients experienced a median intensity of 7 points for PLP and a median ADL restriction of 2 points due to PLP on a 10-point scale, where 0 indicates no pain and no ADL restrictions. Patients with lower limb amputation due to musculoskeletal malignancies had ADL restrictions due to PLP, although the exact details of the ADL restrictions were unclear. Additionally, Furtado et al. reported that pain impairs ADLs in patients with lower limb amputation for musculoskeletal malignancies (Furtado et al. 2015). They assessed ADLs using the Toronto Extremity Salvage Score (TESS) in 100 amputees aged 53.6 years. TESS is a disease-specific rating scale for musculoskeletal malignancies (Davis et al. 1996). Results showed that pain was a negative independent factor for TESS. Patients with lower limb amputation due to musculoskeletal malignancies had impaired ADLs due to pain, although the specific type of pain was not investigated. In our study, PLP had no influence on ADLs at discharge. The reason for this in contrast to previous studies, may be because all survivors had improved PLP and became medication-free at the final follow-up. In previous reports, PLP occurred in 60-80% of patients with limb amputations (Nikolajsen and Jensen 2001), and in 34% of 46 patients, 47% of 75 patients, or 60% of 94 patients with lower limb amputations due to musculoskeletal malignancies

(Kauzlarić et al. 2007; Probstner et al. 2010; Jiang et al. 2021). 53% of PLP patients were markedly improved or completely pain-free (Nikolajsen and Jensen 2001), and 42% of PLP patients improved with medication (Wartan et al. 1997). In this study, the incidence of PLP was 84% and the improvement of PLP was 80%, which compared to previous reports showed a similar incidence of PLP and a better improvement of PLP. However, the reason for the better improvement in PLP was not clarified in this study. Mechanisms of PLP are classified as cerebral, spinal, and peripheral (Hsu and Cohen 2013). Medication for PLP has been reported to be effective with N-methyl-D aspartate receptor antagonists, tricyclic antidepressants, anticonvulsants, opioids, calcitonin, and local anesthesia with sodium channel blockers (Fang et al. 2013; Hsu and Cohen 2013). In this study, the proportion of prescriptions for NSAIDs and antidepressants was high in the treatment of PLP. This may have contributed to the control of peripheral and cerebral mechanisms of PLP, leading to the improvement in PLP.

In this study, the prosthesis use had no influence on ADLs at discharge. Kauzlarić et al. (2007) reported that 46 patients aged 51 years who underwent lower limb amputation for musculoskeletal tumors were able to walk independently at the time of discharge, regardless of the amputation level, with an average of 5.5 h of prosthesis use per day following admission to a rehabilitation facility. However, ADLs after discharge were not investigated. In this study, 69% of patients continued to use prostheses after discharge, less than reported by Kauzlarić (2007). Further investigation is needed to determine the reasons that prosthesis use had no influence on ADLs.

Our study had several limitations. First, the number of patients in this study was small for multiple regression analysis. Since bone and soft tissue tumors are rare diseases, multicenter studies with larger sample sizes are needed to confirm the results of the present study. Second, for the ADL assessment, we used neither the BI and functional independence measures as a standard ADL measure nor TESS as a patient-reported outcome (Keith et al. 1987; Davis et al. 1996). It was difficult to reassess ADLs from medical records using these rating scales retrospectively. Although we could not specifically examine restricted ADLs, we were able to estimate ADLs based on previous studies associating ECOG-PS with BI (Chan et al. 2019; Kanda et al. 2020). Third, the details of prosthetic rehabilitation programs, type of prosthesis, and duration of prosthetic wearing were not investigated in our study, and further investigation is needed to correlate these factors with prosthesis use following discharge.

Conclusion

We investigated PLP, prosthesis use, and ADLs in 19 patients who underwent lower limb amputation due to musculoskeletal malignancies. PLP was present in 84% of the patients; however, the pain control was good with initial medication therapy. The prosthesis was prescribed to 84% of the patients, and 69% of the patients continued to use the prosthesis following discharge. Lower-level amputation and good oncologic prognosis were positive independent factors for ADLs at discharge among survivors and deceased patients, while age was the only negative independent factor. PLP and prosthesis use showed no impact on ADLs. Patients and clinicians should consider these factors when planning surgical strategies for lower limb amputation surgery. Rehabilitation therapy tailored to the amputation level is essential for improving ADLs after amputation. Multicenter studies with larger sample sizes are also warranted to validate the findings of this study.

Conflict of Interest

The authors declare no conflict of interest.

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