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Socio-Occupational and Physical Outcomes More than 20 Years after Diagnosis for Osteosarcoma in Children and Adolescents: Limb Salvage versus Amputation

Giulia Ottaviani, MD, PhD[1,2], **Rhonda S. Robert, PhD**[1], **Winston W. Huh, MD**[1], **Shana Palla, MS**[3], and **Norman Jaffe, DSc, MD**[1]

[1]Children's Cancer Hospital, The University of Texas M. D. Anderson Cancer Center, Houston 77030, USA

[2]Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy

[3]Department of Biostatistics, The University of Texas M. D. Anderson Cancer Center, Houston 77030, USA

Abstract

BACKGROUND—To date, there has been relatively little research on very-long-term survivors of childhood and adolescent osteosarcoma. We sought to compare the very-long-term outcomes of osteosarcoma patients treated with either limb salvage procedures or amputation.

MATERIALS AND METHODS—Thirty-eight long-term osteosarcoma patients surviving 20 or more years from diagnosis were divided into two groups according to whether they underwent amputation or limb salvage. Participants were asked to complete a questionnaire about education, employment, annual income, marital status, health insurance, lifestyle, siblings, and all current and past health issues.

RESULTS—Education, employment, marital status, and health insurance did not differ significantly between the two groups of survivors, and they described themselves as similar to their siblings. Eight percent of survivors underwent secondary amputation due to complications with an endoprosthesis. The cumulative incidence of second primary neoplasms was 13%, and this was significantly higher in females and in survivors who underwent radiotherapy and had genetic predisposition. The second primary malignancies were breast cancer (ductal invasive carcinoma, ductal in situ carcinoma, leiomyosarcoma), mediastinal leiomyosarcoma, squamocellular carcinoma of the oral cavity and of the uterine cervix. Amputees required more assistive walking support than survivors who received limb salvage treatments (χ^2 test, $p < 0.05$).

CONCLUSIONS—Despite the many challenges that osteosarcoma survivors face, patients who survived over 20 years after their initial diagnosis reported having overall adjusted well to their physical limitations and were productive individuals.

Keywords

Osteosarcoma survival; amputation; limb salvage; reoperation; long-term survivors; marital status; education; employment; secondary amputation; second primary cancer

Corresponding author: Giulia Ottaviani, MD, PhD, Department of Clinical Sciences and Community Health, University of Milan, Via della Commenda, 9, 20122 Milan, Italy; Phone: +1-520-222-9707; giulia.ottaviani@unimi.it.

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INTRODUCTION

Osteosarcoma is the most common malignant primary bone tumor and has a 5-year overall survival rate of 68%.[1] With the number of survivors constantly increasing, sequelae attributed to the disease and its treatments, the functional impairments of treated limbs, as well as the socio-occupational outcomes are a growing healthcare concern.[2–6]

There is a paucity of information on the prevalence of complications and health issues, as well as the psychosocial and occupational outcomes, related to amputation and limb salvage among osteosarcoma patients surviving more than 20 years after their diagnoses. Limb salvage has replaced amputation as the standard surgical procedure for high-grade nonmetastatic osteosarcoma.[3,7] Nagarajan et al[8] reported a long-term follow-up study of over 700 osteosarcoma survivors, but that study did not go beyond 20 years.

The purpose of this study was to evaluate the very-long-term outcomes of limb salvage procedures compared to amputations in osteosarcoma survivors treated 20 or more years ago at one institution. We also sought to analyze the inherent complications and benefits of these two surgical procedures along with the frequency of therapy-related side effects and second primary cancers.

PATIENTS AND METHODS

Study Population

All study participants were treated for childhood or adolescent osteosarcoma at The University of Texas M. D. Anderson Cancer Center in Houston. This study was preliminarily started in 2007 when a total of 112 osteosarcoma of the limb survivors, aged 16–52 years, younger of 20 years at diagnosis, were investigated, as previously reported.[9] Of these 112 survivors, 49 survivors (44%) were lost to follow-up after efforts failed to locate them and/or to obtain a questionnaire reply; 25 survivors (22%) were subsequently excluded from this study as they completed the treatments less than 20 years before the questionnaire was administered. Finally, 38 participants (34%) were enrolled in this study as they met the following criteria: a diagnosis of extremity osteosarcoma, diagnosis and treatment at our institution, age younger than 20 years at diagnosis, and survival for at least 20 years after diagnosis.

The participants were divided into two groups and selected similar with regard to gender, ethnicity, osteosarcoma stage and treatments, site of the tumor, age at diagnosis, and age at which the survivors participated in the study:

- **I.** Amputee long term survivors: 19 participants (16 primary amputations and 3 secondary amputations). Secondary amputation was defined as an amputation performed after the primary effects of the cancer have subsided.
- **II.** Limb salvaged long term survivors: 19 participants.

Data Collection and Questionnaire

The institutional review board at The University of Texas M. D. Anderson Cancer Center, Houston, reviewed and approved the research protocol and questionnaires and documents sent to survivor participants. The study participants were asked to provide written informed consent for participation in the study and for the release of medical-record information. A description of the initial study design and characteristics of the questionnaire was previously reported.[4]

Survivors were asked to complete a 29-page, 208-item questionnaire that explored their physical health and medical conditions, including details on the onset of the condition, treatments, and all procedures they underwent. The questionnaire also investigated the marital status, education, employment, annual income from work, and lifestyle. In our analyses, the fertility proportion was defined as the number of participants who bore or fathered a child divided by the number of survivors who attempted to conceive. Participants were asked about their siblings' health, employment, and insurance status. Data were also retrieved from ClinicStation (Electronic Medical Record System) of The University of Texas M. D. Anderson Cancer Center, Houston, and from basic national and international databases.

Statistical Analysis

We calculated descriptive statistics for the overall group and the two treatment groups. The significance of differences between treatment group parameters was evaluated by the χ^2 test or Fisher's test. In case of skewed distribution, a nonparametric Whitney rank sum test was used. All statistics were compiled using SigmaStat and plotted using SigmaPlot (SPSS Inc, Chicago, IL). The selected level of significance was $p<0.05$ (two-tailed).

RESULTS

Patient Characteristics

The mean age ± standard error of the mean (SEM) of the 38 participating survivors at the time of the study was 37.9 ± 1.1 (range, 22 to 52) years, and the mean age at diagnosis ± SEM of osteosarcoma was 13.2 ± 0.7 (range, 3 to 19). The mean interval from the date of diagnosis of osteosarcoma to the date of completion of the questionnaire ± SEM was 24.3 ± 0.7 (range, 20 to 39) years. The majority of participants were women (63%). The most frequent sites of osteosarcoma were the distal femur (50%) and the proximal tibia (16%). There were no significant differences between the amputation and limb salvage groups with regard to gender, ethnicity, osteosarcoma stage and treatments, primary tumor site, age at diagnosis, and age at which they participated in the study.

The study survivors were treated with surgery, neoadjuvant and adjuvant chemotherapy comprising Adryamicin, Methotrexate, intra-arterial Cisplatin, with or without Ifosfamide. The majority of participants (60%), received intra-arterial Cisplatin in attempting limb preservation.[10]

Nine participants (24%) were treated for lung metastases, detected within six years of diagnosis; they were treated with chemotherapy, surgery, and radiation. Four participants (10%) had a local recurrence; this was treated with chemotherapy generally for one additional year and surgery comprising amputation in three cases and implantation of megaendoprosthesis in one case.

Three long term survivors (8%), all females, had a genetic predisposition to osteosarcoma: one, in group-I, was diagnosed with both hereditary retinoblastoma and Li-Fraumeni syndrome; one, in group-II, has had a brother affected by osteosarcoma but with genetic cause unknown, as previously reported;[11] and one, in group-II, was affected by Diamond–Blackfan anemia.

Social and Occupational Outcomes

The majority of survivors (82%) reported an educational level beyond high school (Figure 1), employment for wages and economical independence with 24% of survivors having an annual income above $75,000, without significant differences between the two groups.

Several survivors had become professional accountants (8%), teachers (8%), nurses (8%), physicians (5%), lawyers (3%) and successful business executives (13%), with similar distribution in the two groups. Education level and annual net individual income were higher than the average of the U.S. general population.[12]

Sixty-one percent of survivors were married, 24% were never married, and 16% were divorced, with no statistically significant differences between men and women. No survivors declared that they were cohabiting or separated. Fifty-five percent had children. The amputation group had no more than two children, whereas those in the limb salvage group had up to four children, although there were no significant differences in the total number of children between the groups. The fertility proportion was 81% (21/26), and a diagnosis of infertility was established in 11% of survivors, all men: three were amputees and one received limb salvage surgery. Two of these patients had oligospermia, and the other two had azoospermia. Health insurance covered 84% of survivors and was identical between the groups.

The number of survivors' siblings ranged from 0 to 9, with an average of two siblings for each survivor; five did not have siblings. There was no statistically significant difference in the number of siblings between the two treatment groups. Compared to siblings, most of the survivors had achievìed the same (49%) or higher (42%) level of education. Five percent of siblings did not have health insurance. The health insurance, marital, and employment statuses of survivors did not differ significantly from that of their siblings.

Treatment Outcomes and Health Status

The most frequent operations that were performed were: transfemoral amputation (58%) in the amputation group and implantation of a metal endoprosthesis (48%) in the limb salvage group (Table 1). Four (11%) survivors reported no complications related to their amputation or limb salvage surgeries, with no significant differences between the groups. Postoperative complications are shown in Table 1 and Figure 2. Some complications were exclusive to amputees (e.g., amputation neuroma, phantom sensation, and stump problems); others were exclusive to limb salvage patients (e.g., delayed union or nonunion, limb-length discrepancy, and poor joint motion).

Severe infection or degradation of the endoprosthesis over time resulted in secondary amputation in three patients and in arthrodesis through the Ilizarov treatment in one patient. Of the 22 (58%) participants whose cancer was removed with a limb-sparing surgery, three (14%) subsequently underwent secondary amputation because of long-term complications involving the endoprosthesis (infection refractory to intravenous antibiotics and multiple revision surgery, implant breakage, poor joint movement, pain, or a protracted period of non-weight bearing) 7, 12, and 13 years after the first limb salvage surgery. Of these secondary amputations, two were transfemoral and one was a rotationplasty.

Amputee survivors were more likely to require assistive supports to walk than limb salvage survivors (Figure 3) ($p<0.05$). The assistive walking supports correlated with the osteosarcoma location in both groups; hemipelvectomy and femoral disarticulation were associated with the use of two crutches and/or a wheelchair in all cases but one. Secondary amputation was accompanied by constant pain in two of the three cases (one transfemoral and one rotationplasty), constant use of two crutches in one case of transfemoral amputation and of one cane in the rotationplasty case and occasional use of two crutches in the other case of transfemoral amputation.

In their answers to the question "Do you think that an amputation/limb salvage from the start of the bone cancer would have been a better choice?", 95% survivors were in favor of limb

salvage; one amputee stated that amputation was better than a possible limb salvage; and one limb salvage survivor stated that amputation would have been a better initial choice.

When answering the question "What is your level of satisfaction with your limb salvage/amputation?", the limb salvage survivors had a higher level of satisfaction than the amputees, although the difference did not reach statistical significance ($p = 0.06$) (Table 1).

Other health issues were hepatitis C virus positivity due to repeated blood transfusions in 3 patients (8%) and underlying diseases such as epilepsy in one patient (3%) and Diamond–Blackfan anemia in another one (3%). The most frequent health issues were hearing loss in 37% and heart disease in 29% of survivors. No other significant differences on health issues were found between the two groups (Figure 4).

Five (13%) participants, all women, had a second primary cancer: bilateral invasive ductal carcinoma of the breast 24 years after osteosarcoma diagnosis in a patient who had received extensive chest radiotherapy; leyomyosarcoma of the breast and mediastinal leiomyosarcoma occurring 24 and 28 years, respectively, after osteosarcoma diagnosis in a patient with Li-Fraumeni syndrome and previous bilateral retinoblastoma; ductal carcinoma in situ of the breast 19 years after osteosarcoma diagnosis; squamocellular carcinoma of the uterine cervix 15 years after diagnosis of osteosarcoma of the pelvis; and squamocellular carcinoma of the oral cavity 17 years after osteosarcoma diagnosis in a patient with Diamond–Blackfan anemia. Thirty-nine percent of survivors reported that they have severe fear of a second primary cancer, and there was no significant difference in this fear level between the two groups (Table 1) (Figure 5).

Prescription medications taken by survivors were mainly cardiovascular (40%) or analgesic/anti-inflammatory (29%). There were no significant differences in prescription rates between groups (Table 1). No participants were under chemotherapy or radiation therapy for a second primary cancer at the time of questionnaire completion.

DISCUSSION

Our long-term follow-up study - 20 to 35 years after diagnosis - focused on mature adults. Overall, patients who survived over 20 years after their initial diagnosis reported having adjusted well to their physical limitations and were productive individuals.

Social and Professional Outcomes

Education level and annual net individual income in our patients were higher than the average of the U.S. population[12] and similar in the two treatment groups. In contrast, Yonemoto et al[13] reported a significantly higher percentage of college and university graduates in limb-salvage patients than amputees, although no differences in annual income were found. The proportion of married survivors (58%), which was similar in the two treatment groups and in men and women, differed from the findings of Yonemoto et al,[14] who reported a higher marriage proportion in women (76%) than men (21%). The fertility proportion in our cases (80%) is higher than that reported by Yonemoto et al.[14]

Compared to their siblings, the survivors had achieved the same (49%) or higher (42%) levels of education without differences in health insurance, employment, and marital status. These results differ from those of Nagarajan et al,[8] who reported a lower education level, higher unemployment rate, and lower marital percentage in survivors than siblings.

The outcomes less than twenty years after the diagnosis reported by other authors[8,13,14] are informative, but, considering that osteosarcoma mainly strikes young people 10–14 year-

old,[1] the follow-up is still carried out on young adult subjects. Follow-up of young pediatric and adolescent patients cured of cancer must be a life long process. This applies not only to patients cured of osteosarcoma or other pediatric cancer, but also to “normal” individuals. “*Tempora mutantur et nos mutamur in illis*”/“Times change and we change with them”. The participants have all benefited from having been treated at a single institution, by pediatric oncologists with uniform protocols, in the 1970’s and 1980’s, when surviving osteosarcoma was the greatest challenge.

Our favorable results would indicate that the care we have provided to osteosarcoma patients has been successful overall. However, this study has limitations related to the self-reported questionnaires, and, when comparing education level and income from the responding group, there could have been inherent selection bias, with less intelligent patients being less likely to respond.

Amputation

Among our 38 patients, 50% were ultimately amputees, whereas Nagarajan et al[8] reported a much higher ratio of amputation/limb salvage procedures (531/187) at 20 years after diagnosis. To our knowledge, our institution has the highest proportion of long-term survivors with salvaged limbs (50%), which we attribute to our pioneering attempts to avoid amputation using intra-arterial Cisplatin.[10]

Amputee patients have a higher risk of developing metastases than limb salvage patients because greater tumor size is often the factor prompting amputation.[15] Lung metastases were detected in a greater percentage of our amputees than our limb salvage patients (26% and 21%, respectively), but the difference did not reach statistical significance.

The need for assistive walking devices was significantly higher in amputees than in limb salvage survivors (Figure 3). Our results support previous data that severe disability always accompanies amputation above the ankle,[16] even though today’s artificial limbs are much more sophisticated than those used in the past.

In order to achieve the wider surgical margins, the level of amputation was selected at the most distal site from the osteosarcoma, nevertheless, the shorter the stump is, the lower the success rate in prosthetic fitting and function. Our amputee survivors who underwent hemipelvectomy and femoral disarticulation needed significantly more assistive walking supports than the other amputee survivors.

Although rotationplasty has been reported to give the best functional outcome in long-term survivors,[17] in the only case of rotationplasty in this study, the function was poor, and walking was difficult even when using a crutch. That patient also reported constant pain.

Amputation leaves patients with a lifelong requirement for a prosthetic leg, pain, and phantom limb sensations; these were reported by most of our amputees and remain substantial and unpredictable problems. Other stump problems, such as bleeding, infections, and stump bony overgrowth, were detected in 74% of our amputee survivors (Table 1).

Limb Salvage

Today, patients affected by osteosarcoma almost always undergo limb salvage procedures. Local recurrence occurred in 11% of our cases within the first five years after diagnosis and was addressed with amputation or resection and megaendoprosthesis implantation followed by high-dose chemotherapy.

Over time, long-term osteosarcoma survivors usually undergo repeated endoprosthesis revision or replacement surgeries, which are accompanied by an inexorable deterioration of the extensor apparatus and quadriceps muscle. Endoprostheses have limited range of motion and lifespans and may eventually require replacement or joint arthrodesis to fuse the tibia and femur bones or even a secondary amputation, as in 8% of our cases.

Twenty-one percent of our long-term limb salvage survivors presented with an infected and deteriorated endoprosthesis and underwent repeated surgeries with little benefit. Replacing an infected or severely deteriorated arthroplastic joint is technically demanding, especially if it has a long cemented stem, as in endoprostheses used in the early 1980's.[18,19]

In fact, infection represents a major complication of prosthetic joint implantation and subsequent revisions, despite advances in surgical technique, endoprosthesis design, and antibiotic therapy. Jeys et al[20] reported that periprosthetic infections occur more frequently in osteosarcoma patients treated with chemotherapy, because of immunosuppression, than in patients who undergo prosthesis placement for other conditions, but patients have a much higher survival rate if infections occur in the first postoperative year (84% vs. 62%).[21] Periprosthetic infections and osteomyelitis in long-term osteosarcoma survivors can be devastating complications of limb salvage procedures, resulting in complete loss of joint function, secondary amputation, and systemic complications. Periprosthetic severe metallosis can also complicate the outcome of long-term survivors; this was particularly common because of metal-to-metal impingement in custom-made prostheses of the Guepar type used in the 1980's.[19]

Secondary Amputation

After a period of good short term results of a resected knee joint reconstruction using a substitutive total knee prosthesis, the long term outcome of the prosthetic device is that it will likely fail over the years. This likelihood of failure after over 20 years or more from diagnosis, leads to worrisome outcomes, with patients then accepting a secondary amputation in the desperate hope to improve the situation, as in 8% of our cases. Is a secondary amputation better than a multiple revised and still not functional, infected salvaged limb? The question is wide open. The decision to keep a salvaged limb that has required multiple revisions and will likely require more revisions, or to undergo a secondary amputation remains a difficult choice.

Three percent of patients who had undergone limb salvage procedures in our study thought that they might have been better had they received an initial amputation. The survivors who underwent a secondary amputation, regardless of other parameters, were reported to have body image scores significantly lower than the other survivors.[4]

In addition to antibiotic-resistant infection, other causes of a failed total knee replacement that might necessitate a knee fusion include aseptic loosening, deficient extensor mechanism, poor soft tissues instability, pain, and severe metallosis.[3,19] Knee arthrodesis after failed total knee arthroplasty can be addressed using the Ilizarov method, which is gaining interest for its application in bone cancer long-term survivors.[3,19,22] There is evidence of high fusion rates using this method to replace extensive bone loss and to address limb length discrepancy.[18,22,23]

Aksnes et al[7] reported a secondary amputation rate of 7% (versus our 8%), but did not focus on survivors over 20 years after diagnosis. Other reports[24,25] stressed the survivors' function and quality of life, but did not describe the need for a secondary amputation.

Health-Related Quality of Life

The health related quality of life in amputee and limb salvaged survivors does not differ, except that the amputees require more assistive supports to walk (Figure 3). This is consistent with the report from Aksnes et al[7] that limb sparing surgery preserves a better functioning.

Osteosarcoma survivors not only have to deal with limb function-related problems, but also have an excess risk of therapy-related late effects, which were reported in 84% of our osteosarcoma survivors. The most frequent health issues reported were hearing loss (37%) and heart disease (29%). Regardless of surgery, osteosarcoma survivors are likely to experience diminished bone mineral density due to polychemotherapy, a deficient nutritional status, reduced physical activity levels, delayed onset of puberty, increased risk of pathologic fractures, and osteoporosis later in life,[5] as well as severe limitations of the affected limb resulting in physical inactivity that increases the risk of cardiovascular disease as survivors age.[6]

The cumulative incidence of second primary neoplasms in our patients at a mean of 24 years after diagnosis was 13%, significantly higher in females and in survivors who underwent radiotherapy and had genetic predisposition. The subsequent neoplasms were breast cancer (ductal invasive carcinoma, ductal in situ carcinoma, leiomyosarcoma), mediastinal leiomyosarcoma, squamocellular carcinoma of the oral cavity and of the uterine cervix. The mean period between diagnosis of osteosarcoma and of the second primary malignant tumor was 21.2 years. Aung et al[26] reported secondary malignant neoplasms in only 14 (3%) of 509 osteosarcoma survivors, but our follow-up was significantly longer. According to a previous report,[1] our most recent findings confirm that the increased risk for a second primary malignancy is more frequent in survivors who are females, underwent radiotherapy and have genetic predisposition. In fact, three of the five (60%) survivors diagnosed with a second primary cancer developed a cancer in body areas exposed to radiations (breast cancer following radiotherapy for lung metastases in two patients; uterine cervix cancer in a patient with pelvic osteosarcoma). Genetic predisposition plays an important role in development of second primary cancer as it was detected in 40% of long survivors affected by second primary neoplasm (one patient affected by hereditary retinoblastoma with Li-Fraumeni syndrome and one patient affected by Diamond–Blackfan anemia). A total of 39% of survivors stated that they to have severe fear of second primary cancer (Table 1) (Figure 5). To the best of our knowledge, no other authors report the frequency of second primary cancer up to 35 years after osteosarcoma diagnosis nor have other researchers studied the long survivors fear of developing this most dangerous late effect of osteosarcoma therapies, triggered by genetic predisposition.

Conclusions

Follow-up for survivors of childhood and adolescent osteosarcoma is important and should be a life-long process. Long-term osteosarcoma survivors have many challenges to overcome, such as “the negative effects of” therapies, surgeries, possible recurrence and metastases, frequent limb function-related problems, risk of therapy-related side effects, secondary amputation, and even the risk for a second primary malignancy. Despite the many challenges, our study’s survivors -at over 20 years after diagnosis - have adjusted well overall, having become productive individuals with higher educational attainment and annual income than the average of the rest of the U.S. population. These positive aspects should be recognized and emphasized to patients and their parents when discussing very-long-term outcome.

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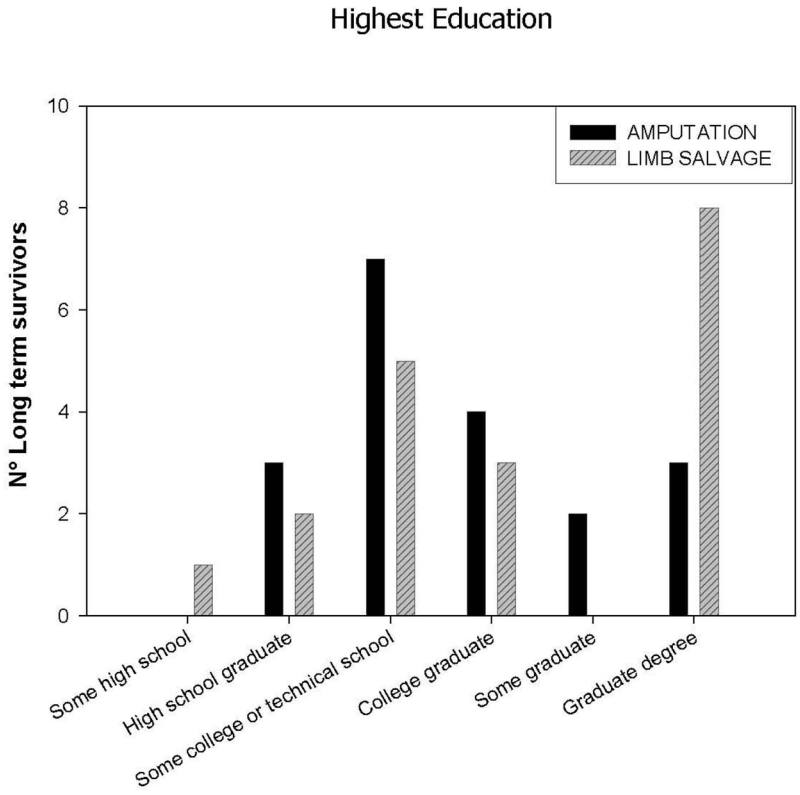

Figure 1.

Education attainment in long term survivors: amputee survivors were less likely than limb salvaged survivors to have a graduate degree (16% vs. 42%), although the differences between the two groups did not reach statistical significance (χ^2 test, $p > 0.05$).

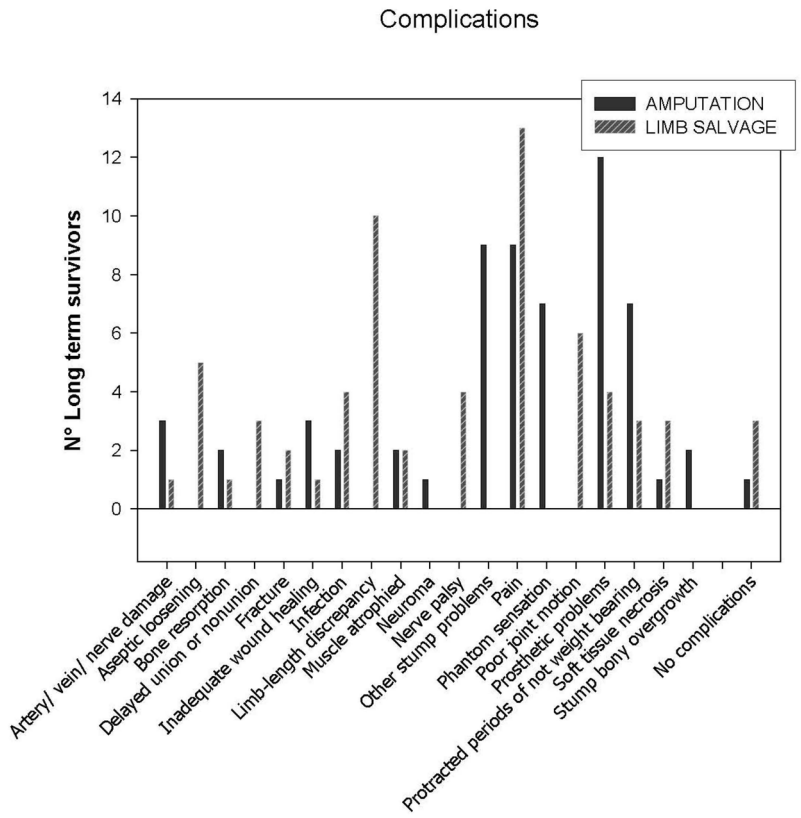

Figure 2.

Complications related to the amputation or limb salvaged surgeries. Some complications are not comparable as they are exclusive to one group-I, i.e., amputation neuroma, phantom sensation and stump problems; or exclusive to group-II, i.e., delayed union or nonunion, limb-length discrepancy, poor joint motion.

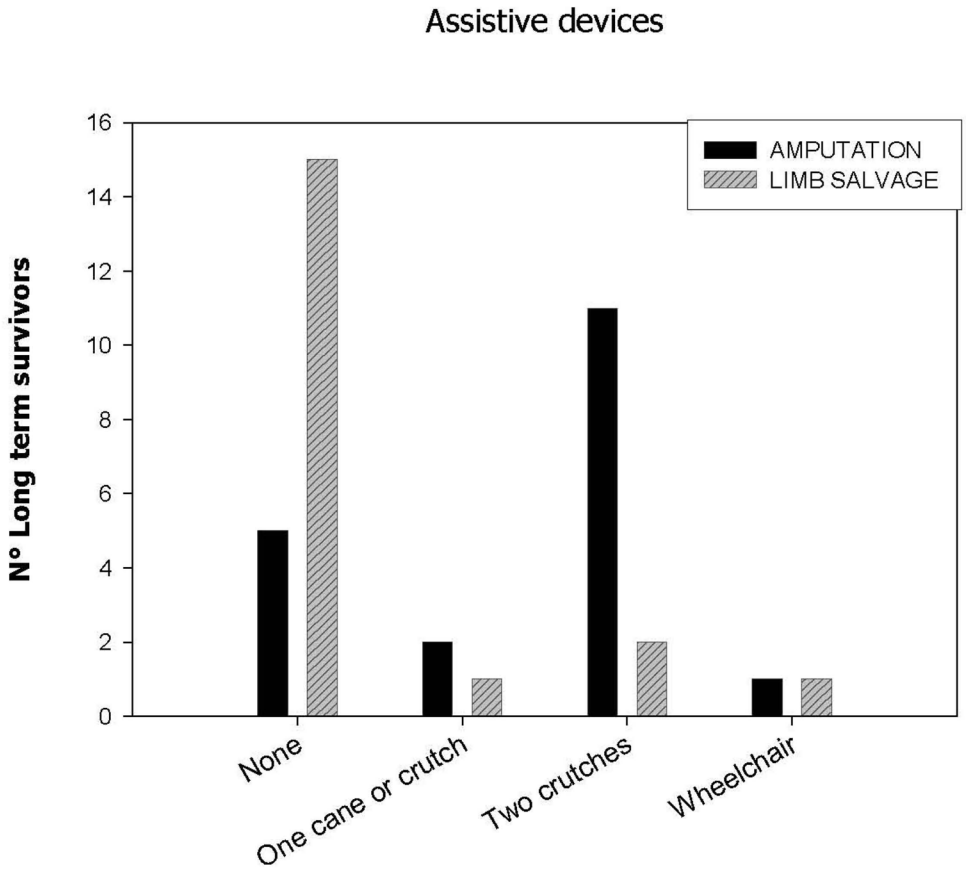

Figure 3.
The amputee survivors required statistically significant more assistive supports to walk compared to limb salvaged survivors (χ^2 test, $p < 0.05$).

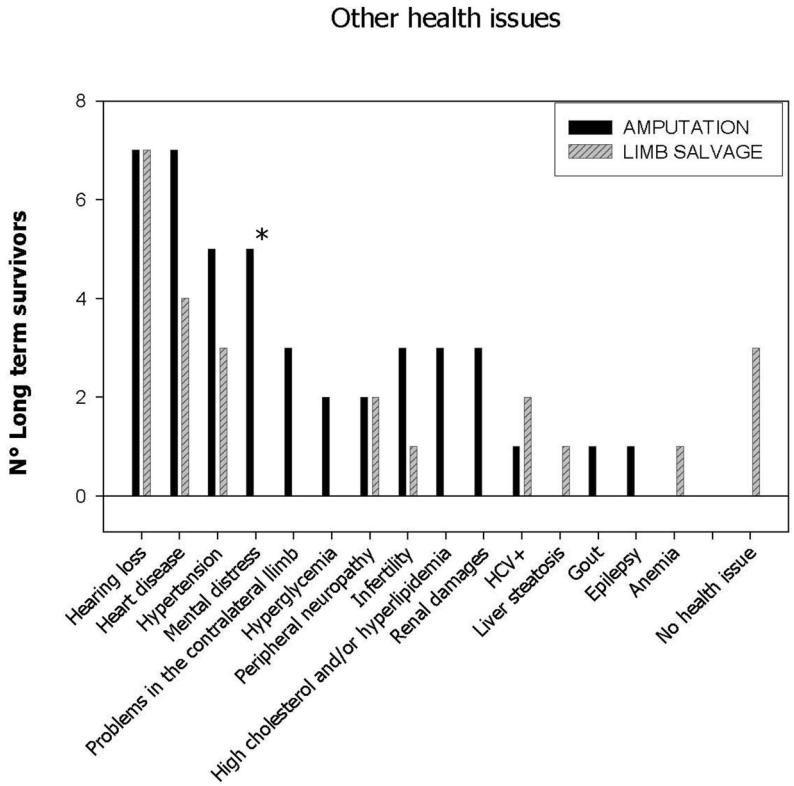

Figure 4.

Other health issues of long term osteosarcoma survivors, limited to the time of survey. Group-I suffered statistically more (*) of mental distress compared to group-II (χ^2 test, $p < 0.05$).

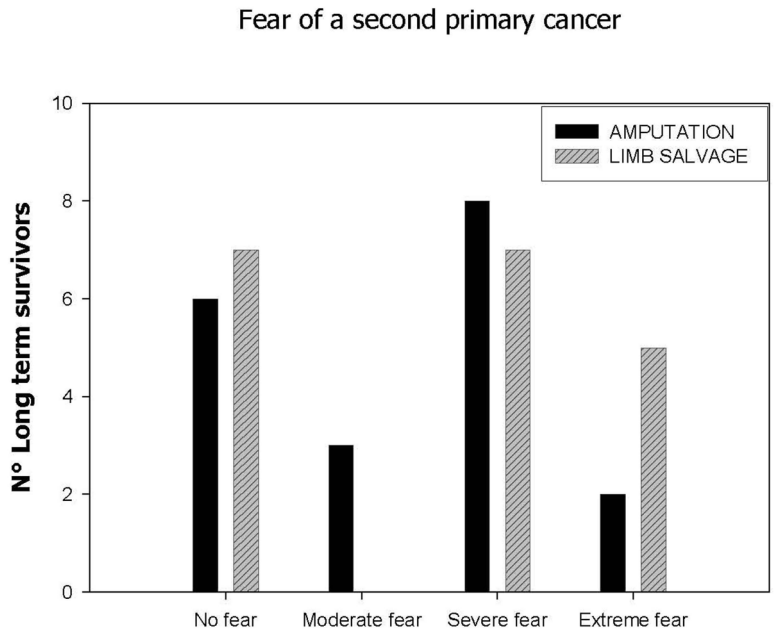

Figure 5.
Fear of a second cancer: no statistically significant differences were found between the two groups (χ^2 test, $p > 0.05$).

Table 1

Surgery types, surgery-related complications, and other health issues in group-I, amputee versus group-II limb salvaged long-term osteosarcoma survivors.

Characteristic	I-Amputation (N=19)	II-Limb Salvage (N=19)	*P*
Surgery type	transfemoral: 11 (58%) transtibial: 1 (5%) Rotationplasty: 1 (5%) Hip disarticulation:3 (16%) Hemipelvectomy: 2 (10.5%) Shoulder disarticulation: 1 (5%)	Metal endoprosthesis: 9 (47%) Metal prosthesis and bone allograft: 7 (37%) Internal hemipelvectomy: 2 (10.5%) Arthrodesis by Ilizarov procedure: 1 (5%)	N/A
Surgery-related complications			
Delayed union or nonunion	-	3 (16%)	0.230
Fracture	1 (5%)	2 (10.5%)	1.000
Inadequate wound healing	3 (16%)	1 (5%)	0.604
Infection	2 (10.5%)	4 (21.5%)	0.660
Limb length discrepancy	N/A	10 (53%)	N/A
Muscle atrophy	2 (10.5%)	2 (10.5%)	1.000
Amputation neuroma	1 (5%)	N/A	N/A
Nerve palsy	-	4 (21.5%)	0.105
Other stump problems	9 (47%)	N/A	N/A
Pain	9 (47%)	13 (68%)	0.324
Phantom sensation	7 (37%)	N/A	N/A
Poor joint motion	-	6 (32%)	0.020
Prosthetic problems, NOS	12 (63%)	4 (21.5%)	0.021
Protracted periods of no weight-bearing	7 (37%)	3 (16%)	0.269
Soft tissue necrosis	1 (5%)	3 (16%)	0.604
Stump bony overgrowth	2 (10.5%)	N/A	N/A
No complications	1 (5%)	3 (16%)	0.605
Assistive devices			
None	5 (26%)	15 (79%)	
One crutch or cane	2 (11%)	1 (5%)	
Two crutches	11 (58%)	2 (11%)	0.009 *
Wheelchair	1 (5%)	1 (5%)	
Level of satisfaction with limb salvage/ amputation			
Very satisfied	3 (16%)	9 (477%)	
Satisfied	10 (53%)	10 (53%)	
Neutral	3 (16%)	-	0.06
Not satisfied	2 (11%)	-	
Very unsatisfied	1 (5%)	-	
Other health issues			
Hearing loss	7 (37%)	7 (37%)	0.737
Heart disease	7 (37%): ventricular hypertrophy 1; CHF 3; low ejection fraction 2; arrhythmia 1.	4 (21.5%): low ejection fraction.	0.474
Hypertension	5 (26%)	3 (16%)	0.693

Characteristic	I-Amputation (N=19)	II-Limb Salvage (N=19)	*P*
Mental distress	5 (26%): anxiety 3; bipolar disorder: 1; attention deficit disorder: 1	-	0.046 *
Problems in the contralateral limb	3 (16%)	-	0.230
Hyperglycemia	2 (10.5%)	-	0.486
Peripheral neuropathy	2 (10.5%)	2 (10.5%)	1.000
Infertility	3 (16%)	1 (5%)	0.604
High cholesterol and/or hyperlipidemia	3 (16%)	-	0.230
Renal damage	3 (16%)	-	0.230
HCV+	1 (5%)	2 (10.5%)	1.000
Liver steatosis	-	1 (5%)	1.000
Gout	1 (5%)	-	1.000
Epilepsy	1 (5%)	-	1.000
Anemia	-	1 (5%): Diamond–Blackfan anemia	1.000
No health issue	-	3 (16%)	0.230
Current medications			
Cardiovascular drugs	8 (42%)	7 (37%)	1.000
Analgesic and anti- inflammatory drugs	7 (37%)	4 (21.5%)	0.474
Endocrine and metabolic drugs	5 (26%)	3 (16%)	0.693
Nervous system drugs	4 (21.5%)	3 (16%)	1.000
Renal drugs and mineral supplements	1 (5%)	2 (10.5%)	1.000
Antihistamine drugs	1 (5%)	2 (10.5%)	1.000
Gastrointestinal drugs	1 (5%)	1 (5%)	1.000
Anti-anemic bone marrow-stimulating drugs	1 (5%)	1 (5%)	1.000
Anti-viral drugs	-	1 (5%)	1.000
No medications	3 (16%)	7 (37%)	0.269
Fear of a second primary cancer			
No fear	6 (32%)	7 (37%)	
Moderate fear	3 (16%)	-	
Severe fear	8 (42%)	7 (37%)	0.219
Extreme fear	2 (11%)	5 (27%)	

Abbreviations: N/A, not applicable; NOS, not otherwise specified; CHF, congestive heart failure; HCV, hepatitis C virus.

* Statistically significant.