Original Article

Sociooccupational and Physical Outcomes More Than 20 Years After the Diagnosis of Osteosarcoma in Children and Adolescents

Limb Salvage Versus Amputation

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BACKGROUND: To the best of the authors' knowledge, there has been relatively little research published to date regarding very long-term survivors of childhood and adolescent osteosarcoma. In the current study, the authors compared the very long-term survival outcomes of patients with osteosarcoma who were treated with either limb salvage procedures or amputation. **METHODS:** A total of 38 patients with osteosarcoma who survived ≥20 years from the time of diagnosis were divided into 2 groups according to whether they underwent amputation or limb salvage. Participants were asked to complete a questionnaire concerning their 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 were not found to differ significantly between the 2 groups of survivors, who described themselves as being similar to their siblings. Eight percent of survivors underwent secondary amputation because of complications with an endoprosthesis. The cumulative incidence of second primary neoplasms was 13%, and this finding was significantly higher in females and in survivors who underwent radiotherapy and had a genetic predisposition. The second primary malignancies were breast cancer (ductal invasive carcinoma, ductal in situ carcinoma, and leiomyosarcoma), mediastinal leiomyosarcoma, and squamocellular carcinoma of the oral cavity and the uterine cervix. Amputees required more assistive walking support than survivors who received limb salvage treatment ($P < .05$, chi-square test). **CONCLUSIONS:** Despite the many challenges that osteosarcoma survivors face, patients who survived ≥20 years after their initial diagnosis reported having overall adjusted well to their physical limitations and were productive individuals. ***Cancer* 2013;119:3727-36**. © *2013 American Cancer Society*.

KEYWORDS: osteosarcoma survival; amputation; limb salvage; reoperation; long-term survivors; marital status; education; employment; secondary amputation; second primary cancer.

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 and the functional impairments of treated limbs, as well as sociooccupational outcomes, are a growing health care concern.[2-6]

To the best of our knowledge, there is a paucity of information regarding the prevalence of complications and health issues, as well as the psychosocial and occupational outcomes, related to amputation and limb salvage among patients with osteosarcoma who survive ≥ 20 years after their diagnoses. Limb salvage has replaced amputation as the standard surgical procedure for patients with high-grade nonmetastatic osteosarcoma.[3,7] Nagarajan et al[8] reported a long-term follow-up study of > 700 survivors of osteosarcoma, but to the best of our knowledge that study did not go beyond 20 years.

The objective of the current study was to evaluate the very long-term outcomes of patients undergoing limb salvage procedures compared with those treated with amputations in survivors of osteosarcoma treated ≥ 20 years ago at 1 institution. We also sought to analyze the inherent complications and benefits of these 2 surgical procedures along with the frequency of therapy-related side effects and second primary cancers.

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MATERIALS AND METHODS

Study Population

All study participants were treated for childhood or adolescent osteosarcoma at The University of Texas MD Anderson Cancer Center (MDACC) in Houston. This study was initiated preliminarily in 2007 when a total of 112 survivors of osteosarcoma of the limb aged 16 years to 52 years who were aged < 20 years at the time of diagnosis were investigated.[9] Of these 112 survivors, 49 (44%) were considered 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 because they completed the treatments < 20 years before the questionnaire was administered. Finally, 38 participants (34%) were enrolled in the current study after meeting the following criteria: a diagnosis of extremity osteosarcoma, diagnosis and treatment at MDACC, aged < 20 years at the time of diagnosis, and survival of at least 20 years after diagnosis.

The participants were divided into 2 groups and selected with regard to sex, ethnicity, osteosarcoma stage of disease and treatments, site of the tumor, age at the time of diagnosis, and age at which the survivors participated in the study. Group 1 was composed of 19 long-term survivors who were treated with amputation (16 primary amputations and 3 secondary amputations). Secondary amputation was defined as an amputation performed after the primary effects of the cancer had subsided. Group 2 was composed of 19 long-term survivors who underwent limb salvage.

Data Collection and Questionnaire

The Institutional Review Board at MDACC 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 reported previously.[4]

Survivors were asked to complete a 29-page, 208-item questionnaire that explored their physical health and medical conditions, including details regarding the onset of the condition, treatments, and all procedures performed. The questionnaire also investigated the marital status, education, employment, annual income from work, and lifestyle of the survivors. In our analyses, the fertility percentage 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 (the electronic medical record system developed at MDACC), and from basic national and international databases.

Statistical Analysis

We calculated descriptive statistics for the overall group and the 2 treatment groups. The significance of differences between treatment group parameters was evaluated using the chi-square test or Fisher exact test. In case of skewed distribution, a nonparametric Whitney rank sum test was used. All statistics were compiled using SigmaStat and plotted using SigmaPlot software (SPSS Inc, Chicago, Ill). The selected level of significance was $P < .05$ (two-tailed).

RESULTS

Patient Characteristics

The mean age (± the standard error of the mean [SEM]) of the 38 participating survivors at the time of the study was 37.9 years (± 1.1 years) (range, 22 years-52 years), and the mean age at diagnosis (± the SEM) of survivors of osteosarcoma was 13.2 years (± 0.7 years) (range, 3 years-19 years). The mean interval from the date of diagnosis of osteosarcoma to the date of completion of the questionnaire (± the SEM) was 24.3 years (± 0.7 years) (range, 20 years-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 noted between those patients who underwent amputation and those treated with limb salvage with regard to sex, 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 and neoadjuvant and adjuvant chemotherapy comprising doxorubicin, methotrexate, and intraarterial cisplatin, with or without ifosfamide. The majority of participants (60%), received intraarterial cisplatin in an attempt at limb preservation.[10]

Nine participants (24%) were treated for lung metastases, which were detected within 6 years of diagnosis; they were treated with chemotherapy, surgery, and radiotherapy. Four participants (11%) developed a local recurrence, which generally was treated with chemotherapy for 1 additional year and surgery consisting of amputation in 3 cases and implantation of a mega-endoprosthesis in 1 case.

Three long-term survivors (8%), all of whom were female, were found to have a genetic predisposition toward osteosarcoma: 1 individual in group 1 who was diagnosed with both hereditary retinoblastoma and Li-Fraumeni syndrome; 1 individual in group 2 who reported having had a brother affected by osteosarcoma but with an unknown genetic cause, as previously reported[11]; and 1 survivor with Diamond-Blackfan anemia.

Social and Occupational Outcomes

The majority of survivors (82%) reported achieving an educational level beyond high school (Fig. 1), employment for wages, and economical independence, with 24% of survivors having an annual income > $75,000; no significant differences were noted between the 2 groups. Several survivors had become professional accountants (8%), teachers (8%), nurses (8%), physicians (5%), lawyers (3%), and successful business executives (13%), with a similar distribution noted between the 2 groups. Educational level and annual net individual income were found to be higher than the average of the US general population.[12]

Approximately 61% of survivors were married, 24% were never married, and 16% were divorced, with no statistically significant differences noted between men and women. No survivors declared that they were cohabiting or separated. Approximately 51% had children. Survivors in the amputation group reported having no more than 2 children, whereas those in the group treated with limb salvage had up to 4 children, although there were no significant differences in the total number of children noted between the groups. The fertility percentage was 81% (21 of 26 participants), and a diagnosis of infertility was established in 11% of survivors, all of whom were men: 3 were amputees and 1 received limb salvage surgery. Two of these patients had oligospermia and the other 2 had azoospermia.

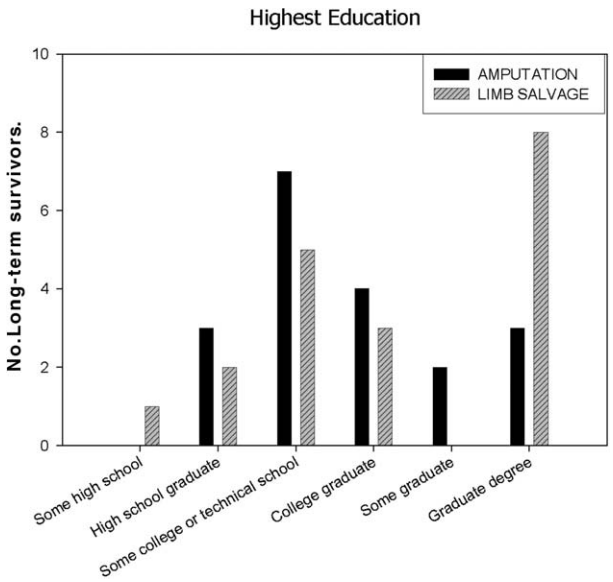

Figure 1. Educational attainment in long-term survivors of osteosarcoma is shown. Survivors who underwent amputation were found to be less likely than those treated with limb salvage to have a graduate degree (16% vs 42%), although the differences between the 2 groups did not reach statistical significance ($P > .05$, chi-square test).

Health insurance covered 84% of survivors and was identical between the groups.

The number of siblings of survivors ranged from 0 to 9, with an average of 2 siblings for each survivor; 5 survivors did not have siblings. There was no statistically significant difference in the number of siblings between the 2 treatment groups. Compared with siblings, the majority of the survivors had achieved the same (49%) or higher (42%) level of education. Approximately 5% of siblings did not have health insurance. The health insurance, marital, and employment statuses of the survivors did not differ significantly from that of their siblings.

Treatment Outcomes and Health Status

The most frequent surgeries that were performed were transfemoral amputation in the amputation group (58%) and implantation of a metal endoprosthesis in the survivors treated with limb salvage (47%) (Table 1). Four survivors (11%) reported no complications related to their amputation or limb salvage surgeries, with no significant differences noted between the groups. Postoperative complications are shown in Table 1 and Figure 2. Some complications were exclusive to those treated with amputation (eg, amputation neuroma, phantom sensation, and stump problems), whereas others were exclusive to patients treated with limb salvage (eg, 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 3 patients and in arthrodesis through the Ilizarov treatment in 1 patient. Of the 22 participants (58%) whose cancer was removed with a limb-sparing surgery, 3 (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 years, 12 years, and 13 years, respectively, after the first

TABLE 1. Surgery Types, Surgery-Related Complications, and Other Health Issues in Long-Term Survivors of Osteosarcoma Treated With Amputation (Group 1) Versus Limb Salvage (Group 2)

Characteristic		Group 1: Amputation (N = 19)	Group 2: Limb Salvage (N = 19)	*P*
Surgery type		Transfemoral: 11 (58%) Transtibial: 1 (5%) Rotationplasty: 1 (5%) Hip disarticulation: 3 (16%) Hemipelvectomy: 2 (11%) Shoulder disarticulation: 1 (5%)	Metal endoprosthesis: 9 (47%) Metal prosthesis and bone allograft: 7 (37%) Internal hemipelvectomy: 2 (11%) Arthrodesis by Ilizarov procedure: 1 (5%)	NA
Surgery-related complications	Delayed union or nonunion	—	3 (16%)	.230
	Fracture	1 (5%)	2 (11%)	1.000
	Inadequate wound healing	3 (16%)	1 (5%)	.604
	Infection	2 (11%)	4 (21%)	.660
	Limb-length discrepancy	NA	10 (53%)	NA
	Muscle atrophy	2 (11%)	2 (11%)	1.000
	Amputation neuroma	1 (5%)	NA	NA
	Nerve palsy	—	4 (21%)	.105
	Other stump problems	9 (47%)	NA	NA
	Pain	9 (47%)	13 (68%)	.324
	Phantom sensation	7 (37%)	NA	NA
	Poor joint motion	—	6 (32%)	.020
	Prosthetic problems, NOS	12 (63%)	4 (21%)	.021
	Protracted periods of no weight-bearing	7 (37%)	3 (16%)	.269
	Soft-tissue necrosis	1 (5%)	3 (16%)	.604
	Stump bony overgrowth	2 (11%)	NA	NA
	No complications	1 (5%)	3 (16%)	.605
Assistive devices	None	5 (26%)	15 (79%)	
	One crutch or cane	2 (11%)	1 (5%)	
	Two crutches	11 (58%)	2 (11%)	.009[a]
	Wheelchair	1 (5%)	1 (5%)	
Level of satisfaction with limb salvage/ amputation	Very satisfied	3 (16%)	9 (47%)	
	Satisfied	10 (53%)	10 (53%)	
	Neutral	3 (16%)	—	.06
	Not satisfied	2 (11%)	—	
	Very unsatisfied	1 (5%)	—	
Other health issues	Hearing loss	7 (37%)	7 (37%)	.737
	Heart disease	7 (37%): ventricular hypertrophy (1); CHF (3); low ejection fraction (2); arrhythmia (1).	4 (21%): low ejection fraction	.474
	Hypertension	5 (26%)	3 (16%)	.693
	Mental distress	5 (26%): anxiety (3); bipolar disorder (1); attention deficit disorder (1)	—	.046[a]
	Problems in the contralateral limb	3 (16%)	—	.230
	Hyperglycemia	2 (11%)	—	.486
	Peripheral neuropathy	2 (11%)	2 (11%)	1.000
	Infertility	3 (16%)	1 (5%)	.604
	High cholesterol and/or hyperlipidemia	3 (16%)	—	.230
	Renal damage	3 (16%)	—	.230
	HCV+	1 (5%)	2 (11%)	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%)	.230

TABLE 1. *Continued*

Characteristic		Group 1: Amputation (N = 19)	Group 2: Limb Salvage (N = 19)	*P*
Current medications	Cardiovascular drugs	8 (42%)	7 (37%)	1.000
	Analgesic and antiinflammatory drugs	7 (37%)	4 (21%)	.474
	Endocrine and metabolic drugs	5 (26%)	3 (16%)	.693
	Nervous system drugs	4 (21%)	3 (16%)	1.000
	Renal drugs and mineral supplements	1 (5%)	2 (11%)	1.000
	Antihistamine drugs	1 (5%)	2 (11%)	1.000
	Gastrointestinal drugs	1 (5%)	1 (5%)	1.000
	Antianemic bone marrow-stimulating drugs	1 (5%)	1 (5%)	1.000
	Antiviral drugs	—	1 (5%)	1.000
	No medications	3 (16%)	7 (37%)	.269
Fear of a second primary cancer	No fear	6 (32%)	7 (37%)	
	Moderate fear	3 (16%)	—	
	Severe fear	8 (42%)	7 (37%)	.219
	Extreme fear	2 (11%)	5 (27%)	

Abbreviations: CHF, congestive heart failure; HCV+, hepatitis C virus positivity; NA, not applicable; NOS, not otherwise specified.
[a] *P* value was statistically significant.

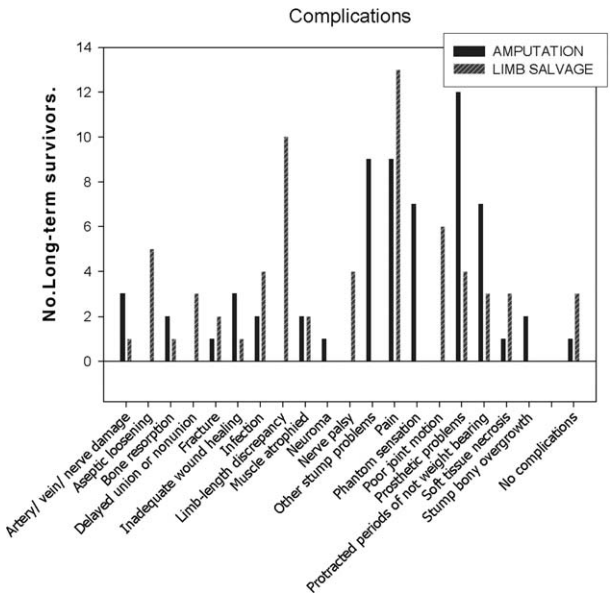

Figure 2. Postoperative complications related to treatment with amputation or limb salvage are shown in survivors of osteosarcoma. Some complications were not comparable because they were exclusive to either those patients treated with amputation (ie, amputation neuroma, phantom sensation, and stump problems) or those treated with limb salvage (ie, delayed union or nonunion, limb-length discrepancy, and poor joint motion).

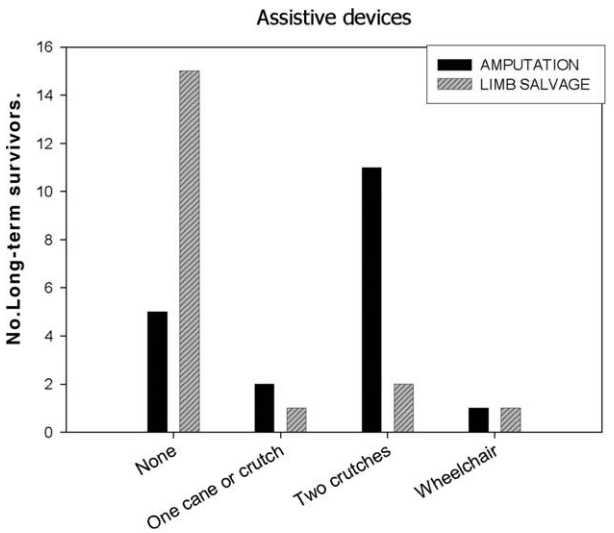

Figure 3. Survivors treated with amputation required statistically significantly more assistive supports to walk compared with survivors treated with limb salvage ($P < .05$; chi-square test).

limb salvage surgery. Of these secondary amputations, 2 were transfemoral and 1 was a rotationplasty.

Survivors who underwent amputation were more likely to require assistive supports to walk than those treated with limb salvage ($P < .05$) (Fig. 3). The assistive walking supports correlated with the location of the osteosarcoma in both groups; hemipelvectomy and femoral disarticulation were associated with the use of 2 crutches and/or a wheelchair in all but 1 case. Secondary amputation was accompanied by constant pain in 2 of the 3 cases (1 transfemoral and 1 rotationplasty), the constant use of 2 crutches in 1 case of a transfemoral amputation, the constant use of 1 cane in the patient treated with rotationplasty, and the occasional use of 2 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% of the participating survivors were in favor of limb salvage, 1 amputee stated that amputation was better than a possible limb salvage, and 1 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 survivors treated with limb salvage had a higher level of satisfaction than those treated with amputation, although the difference did not reach statistical significance ($P = .06$) (Table 1).

Other health issues were hepatitis C virus positivity because of repeated blood transfusions in 3 patients (8%) and underlying diseases such as epilepsy in 1 patient (3%) and Diamond-Blackfan anemia in another patient (3%). The most frequent health issues were hearing loss in 37% of patients and heart disease in 29% of survivors. No other significant differences with regard to health issues were found between the 2 groups (Fig. 4).

Five participants (13%), all of whom were women, developed a second primary cancer: bilateral invasive ductal carcinoma of the breast 24 years after the diagnosis of osteosarcoma in a patient who had received extensive chest radiotherapy; leiomyosarcoma of the breast and mediastinal leiomyosarcoma occurring 24 years and 28 years, respectively, after a diagnosis of osteosarcoma in a patient with Li-Fraumeni syndrome and previous bilateral retinoblastoma; ductal carcinoma in situ of the breast 19 years after the diagnosis of osteosarcoma; squamocellular carcinoma of the uterine cervix 15 years after the diagnosis of osteosarcoma of the pelvis; and squamocellular carcinoma of the oral cavity 17 years after the diagnosis of osteosarcoma in a patient with Diamond-Blackfan anemia. Approximately 39% of survivors reported having a severe fear of developing a second primary cancer, and there was no significant difference in this fear level noted between the 2 groups (Table 1) (Fig. 5).

Prescription medications taken by survivors were mainly cardiovascular (40%) or analgesic/antiinflammatory (29%). There were no significant differences noted with regard to prescription rates between the 2 groups (Table 1). No participants were receiving chemotherapy or radiotherapy for a second primary cancer at the time of questionnaire completion.

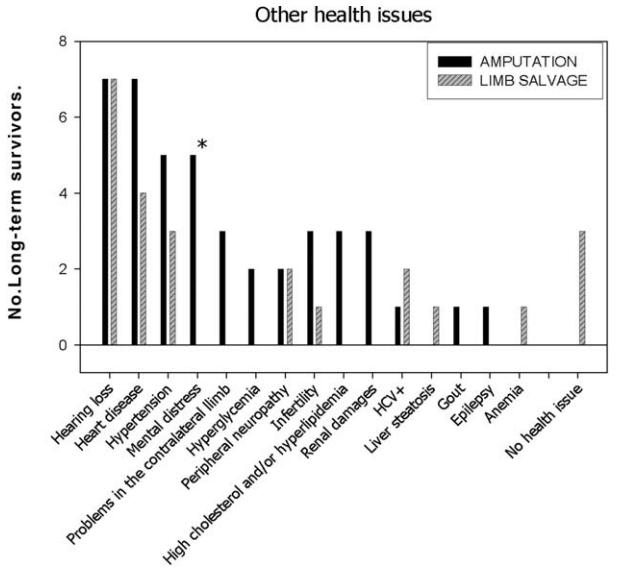

Figure 4. Other health issues among long-term survivors of osteosarcoma are shown, limited to the time of the survey. Patients treated with amputation experienced statistically more (*) mental distress compared with patients treated with limb salvage ($P < .05$; chi-square test). HCV+ indicates hepatitis C virus positivity.

DISCUSSION

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

Social and Professional Outcomes

Educational level and annual net individual income in the patients in the current study were found to be higher than

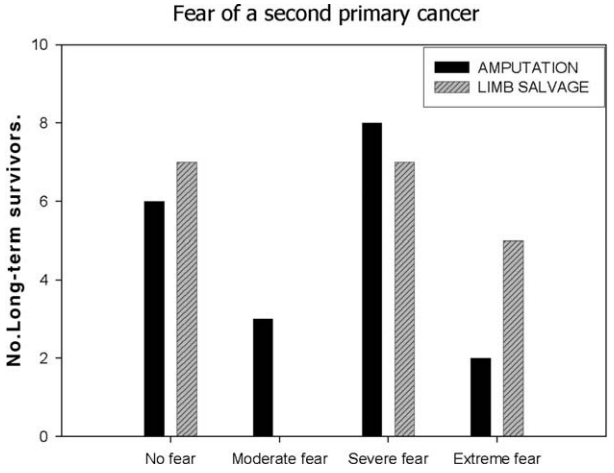

Figure 5. Patients' fear of developing a second primary cancer is shown. No statistically significant differences were found between those patients treated with amputation compared with those treated with limb salvage ($P > .05$; chi-square test).

the average of the US population[12] and were similar between the 2 treatment groups. In contrast, Yonemoto et al[13] reported a significantly higher percentage of college and university graduates among patients treated with limb salvage compared with those treated with amputation, although no differences in annual income were found. The percentage of married survivors (58%), which was found to be similar between the 2 treatment groups and between men and women, differed from the findings of Yonemoto et al,[14] who reported a higher percentage of married individuals among women (76%) compared with men (21%). The fertility percentage in the cases in the current study (80%) was higher than that reported by Yonemoto et al.[14]

Compared with 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 educational level, higher unemployment rate, and lower marital percentage in survivors compared with their siblings.

The outcomes of survivors of osteosarcoma < 20 years after the diagnosis as reported by other authors[8,13,14] are informative, but considering that osteosarcoma mainly strikes young people aged 10 years to 14 years,[1] the follow-up is still performed on young adult subjects. The follow-up of young pediatric and adolescent cancer survivors must be a lifelong process. This applies not only to patients cured of osteosarcoma or other pediatric cancers, 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 1970s and 1980s, when surviving osteosarcoma was the greatest challenge.

The favorable results of the current study would indicate that the care we have provided to patients with osteosarcoma has been successful overall. However, the current study has limitations related to the self-reported questionnaires and, when comparing educational 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% ultimately underwent amputation, whereas Nagarajan et al[8] reported a much higher ratio of amputation/limb salvage procedures (531 and 187, respectively) at 20 years after diagnosis. To our knowledge, MDACC has the highest percentage of long-term survivors with salvaged limbs (50%), which we attribute to our pioneering attempts to avoid amputation using intraarterial cisplatin.[10]

Patients undergoing amputation have a higher risk of developing metastases than those treated with limb salvage because greater tumor size is often the factor prompting amputation.[15] Lung metastases were detected in a greater percentage of patients who underwent amputation in the current study compared with those undergoing limb salvage (26% vs 21%), but the difference did not reach statistical significance.

The need for assistive walking devices was found to be significantly higher in patients treated with amputation than in those treated with limb salvage (Fig. 3). The current study 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.

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. The survivors in the current study who were treated with amputation and who underwent hemipelvectomy and femoral disarticulation needed significantly more assistive walking supports than the other amputee survivors.

Although rotationplasty has been reported to provide the best functional outcome in long-term survivors,[17] in the only case of rotationplasty in the current 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 patients treated with amputation and remain substantial and unpredictable problems. Other stump problems, such as bleeding, infections, and stump bony overgrowth, were detected in 74% of survivors treated with amputation (Table 1).

Limb Salvage

Currently, patients affected by osteosarcoma almost always undergo limb salvage procedures. Local recurrence occurred in 11% of the current study cases within the first 5 years after diagnosis and was addressed with amputation or surgical resection and megaloprosthesis implantation followed by high-dose chemotherapy.

Over time, long-term survivors of osteosarcoma 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 eventually may require replacement or joint arthrodesis to fuse the tibia and femur bones or even a secondary amputation, as in 8% of the cases reported herein.

Approximately 21% of our long-term survivors of osteosarcoma who were treated with limb salvage 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 1980s.[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 patients with osteosarcoma who are treated with chemotherapy because of immunosuppression, compared with patients who undergo prosthesis placement for other conditions, but patients have a much higher survival rate if infections occur within the first postoperative year (84% vs 62%).[21] Periprosthetic infections and osteomyelitis in long-term survivors of osteosarcoma 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 1980s.[19]

Secondary Amputation

After a period of good short-term results with 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 $\geq$ 20 years from diagnosis leads to worrisome outcomes, with patients then accepting a secondary amputation in the desperate hope of improving their situation, as in 8% of the cases in the current study. 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.

Approximately 3% of patients who had undergone limb salvage procedures in the current study thought that they might have fared 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 that were 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-tissue 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 long-term survivors of bone cancer.[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% (vs 8% in the current study), 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 survivors of osteosarcoma treated with amputation and limb salvage does not differ, except that those treated with amputation require more assistive supports to walk (Fig. 3). This is consistent with the report from Aksnes et al[7] indicating that limb-sparing surgery preserves a better functioning.

Survivors of osteosarcoma not only have to deal with problems related to limb function but also have an excess risk of therapy-related late effects, which were reported in 84% of the current study participants. The most frequent health issues reported were hearing loss (37%) and heart disease (29%). Regardless of surgery, survivors of osteosarcoma are likely to experience diminished bone mineral density because of polychemotherapy, a deficient nutritional status, reduced physical activity levels, a delayed onset of puberty, an 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 the patients in the current study at a mean of 24 years after diagnosis was 13%, and was found to be significantly higher in females and in survivors who underwent radiotherapy and had a genetic predisposition. The subsequent neoplasms were breast cancer (ductal invasive carcinoma, ductal in situ carcinoma, and leiomyosarcoma), mediastinal leiomyosarcoma, and squamocellular carcinoma of the oral cavity and of the uterine cervix. The

mean period between the 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 of 509 osteosarcoma survivors (3%), but the follow-up in the current study was significantly longer. According to a previous report,[1] our most recent findings confirm that the increased risk of a second primary malignancy is more frequent in survivors who are female, underwent radiotherapy, and have genetic predisposition. In fact, 3 of the 5 survivors diagnosed with a second primary cancer (60%) developed a cancer in body areas exposed to radiotherapy (breast cancer after radiotherapy for lung metastases in 2 patients and cancer of the uterine cervix in a patient with pelvic osteosarcoma). Genetic predisposition appears to play an important role in the development of second primary cancers because it was detected in 40% of long-term survivors affected by a second primary neoplasm (1 patient affected by hereditary retinoblastoma with Li-Fraumeni syndrome and 1 patient affected by Diamond-Blackfan anemia). A total of 39% of survivors stated that they have a severe fear of developing a second primary cancer (Table 1) (Fig. 5). To the best of our knowledge, no other authors to date have reported on the frequency and fear of second primary cancers in survivors up to 35 years after a diagnosis of osteosarcoma.

Conclusions

Follow-up for survivors of childhood and adolescent osteosarcoma is important and should be a lifelong process. Long-term survivors of osteosarcoma have many challenges to overcome, such as the negative effects of therapies, surgeries, possible disease recurrence and metastases, frequent limb function-related problems, risk of therapy-related side effects, secondary amputation, and even the risk of a second primary malignancy. Despite the many challenges, the survivors in the current study, all of whom were ≥ 20 years from the time of diagnosis, have adjusted well overall, having become productive individuals with higher educational attainment and annual income than the average of the rest of the US population. These positive aspects should be recognized and emphasized to patients and their parents when discussing very long-term outcomes.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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