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Complications of Bone and Soft Tissue Sarcoma Patients Following Limb Salvage and Amputation Procedures

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COMPLICATIONS OF BONE AND SOFT TISSUE SARCOMA PATIENTS FOLLOWING LIMB SALVAGE AND AMPUTATION PROCEDURES

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ABSTRACT

Background: Extremity bone and soft tissue sarcoma are a rare type of cancer with treatment modalities to include chemotherapy and radiation and surgical procedures. Surgery can be limb salvage or limb amputation. Patients of extremity bone and soft tissue sarcomas may experience physical and psychosocial effects due to sarcoma treatments impacting physical performance, quality of life, and social support. Therefore, this study sought to evaluate the complications of extremity bone and soft tissue sarcoma in patients following limb salvage and amputation surgeries.

Methods: Patients were selected from the University of Minnesota Fairview Hospital database and had a primary tumor located in the lower extremity. A medical chart review was conducted and complications encountered by bone and extremity soft tissue sarcoma patients were reviewed and recorded.

Results: Local recurrence was greatest in limb salvage reconstruction, n=10 (20%) compared to amputation reconstruction n=1 (2%). Infection was greatest in the limb salvage group, n=8 (16%) versus amputation group, n=2 (4%). Physical limitations were reported in 95% of the limb salvage patients and 100% of the amputation patients. Pain was reported in all the 50 patients. Nineteen patients (38%) in limb salvage group and twenty-five patients (50%) in amputation group had revision surgeries. Cardiomyopathy induced by anthracycline treatment was reported in three patients. One patient had sensorineural hearing loss due to high dose methotrexate exposure.

Conclusions: Extremity bone and soft tissue sarcoma patients can suffer long term effects from their surgical and chemotherapy or radiation treatment. Local recurrence,

infection, pain, physical limitations are some of the complications arising from such treatments which can impact their quality of life. Limb salvage group had a greater local recurrence and infection rate than the amputation group. Therefore, amputation was not associated with greater post-surgical complications than limb salvage.

Keywords: Extremity bone and soft tissue sarcoma, complications, limb salvage surgery, and amputation.

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Chapter 1: Introduction

Introduction

Bone and soft tissue sarcomas are very rare and account for less than 2% of all adult cancers in the world (Paredes, Pereira, Moreira, Simões & Canavarro, 2011). The treatment of choice is limb salvage surgery, or limb amputation with chemotherapy, or radiation (Paredes et al., 2011). Patients can have either chemotherapy or radiation and this is dependent on the standard of care of the sarcoma. When compared to other cancers, little information is known regarding the complications of standard treatment of sarcoma. Patients and survivors generally experience lifelong effects from treatment and may not be able to return to their baseline function (Paredes et al., 2011). This chapter will cover the background information about sarcomas, problem statement, purpose of the study, research question, significance of the problem, limitations of the study and definition of terms.

Background Information

Studies have examined the complications faced by extremity bone and soft tissue sarcoma patients following treatment. Wide resection of the tumor is important to achieve negative margins and limb salvage reconstruction may present with reconstructive complications (Papanastasiou et al., 2016). Complications of limb salvage reconstruction include infection, mechanical failure, and local recurrence (Papanastasiou et al., 2016). Infection following a limb salvage procedure can lead to serious complications that can result in amputation. The common pathogens causing infection are staphylococcus and streptococcus species (Lee, OH, Lee, Yoo, & Kim, 2002). However, some rare pathogens

have been identified. Leishmania infection of a distal femoral megaprosthesis in a patient treated with limb salvage of distal femoral osteosarcoma resulted in sepsis and ultimately death (Papanastasiou et al., 2016).

Reconstruction procedures in children is more complicated by the loss of physis (Ruggieri, Mavrogenis, Pala, Romantini, Manfrini, & Mercuri, 2013). Most tumors occur in the metaphyseal region and limb salvage reconstruction can result in leg length discrepancies. Expandable endoprosthesis have been developed to address the issue of leg length discrepancies (Cipriano, Gruzinova, Frank, Gitelis, & Virkus, 2015). Expandable endoprosthesis is used mostly for tumors of the distal femur, proximal tibia, and proximal humerus. The disadvantage of this type of reconstruction is that many pediatric patients will require revision in the first 5 years due to complications.

Amputation is usually recommended when no negative margins can be obtained after tumor resection or when the tumor has invaded vascular structures and a limb salvage procedure would not result in a functional limb (Levin, Arkader, & Morris 2017). Amputation occurs in about 10% of cases. Complications of amputation include physical limitations due to increased oxygen demand during activities such as walking (Levin et al., 2017). Amputation often leads to phantom pain, bleeding, infection, bone overgrowth at the amputation site (Levin et al., 2017)

Problem Statement

While research has been conducted on the complications following sarcoma treatments for bone and soft tissue, there has been limited research in Minnesota. Bone and extremity soft tissue sarcoma treatment usually includes chemotherapy or radiation, and surgery (Paredes et al., 2011). Surgery can be limb salvaging or amputation. Bone

and extremity soft tissue sarcoma patients who undergo surgery may need to rebuild the bone and joint and more than one surgery may be needed in order to optimize function of limb. Joint pain and discomfort may be constantly lifelong for patients with bone or extremity soft tissue sarcoma such that ongoing physical therapy is needed. Participation in strenuous or athletic activity may also be limited following surgical procedure. Studying the complications of sarcoma patients and survivors who have undergone chemotherapy/radiation and limb salvaging or amputation surgery is important in order to determine how the diagnoses and treatments have altered their lives.

Purpose

Although various research studies have demonstrated that treatment of extremity soft tissue and bone sarcoma do result in complications, much research is based on bone sarcoma. This research aims to detail the different types of complications that both extremity bone and soft tissue sarcoma patients face. The purpose of this study is to evaluate the complications of sarcoma treatments through medical chart review.

Research Questions

1. For extremity sarcoma patients treated with tumor excision, is amputation associated with greater post-surgical complications compared to a limb salvage procedure?
2. Is there a difference in post-surgical complications for patients who had an amputation versus limb salvage procedure?

Significance of the problem

Patients with bone and extremity soft tissue sarcoma may experience lifelong effects such as physical, emotional, and psychological harm from their treatments. Although the extent of the complications resulting from the limb salvage and amputation

procedures have been documented in literature, we need to understand the complications patients and survivors face in Minnesota. We cannot underestimate the impact of cancer treatment on the patients and their families. Therefore, ongoing support to optimize the patient`s function is needed. To avoid stagnation or decline in function, health care providers have a responsibility of educating, encouraging, and ordering relevant treatments. In addition, the importance of social, emotional and psychological support cannot be underestimated, this makes a difference in mental stability.

Limitations of the Study

The most significant limitation is obtaining a large enough sample size to review their medical records due to the rarity of sarcoma diagnoses. This may have an impact on the success of doing a comprehensive review on the complications faced by sarcoma patients.

Definition of Terms

The following definition of terms are core in understanding the purpose of study:

Sarcoma "is a type of cancer that develops from certain tissues like bone or muscle. Bone and soft tissue sarcomas are the main types. Soft tissue sarcoma arises from fat, muscle, nerves, fibrous tissue, blood vessels or deep skin tissues"

Bone sarcoma "is a type of cancer that starts in the bone" (American Cancer Society, 2015)

Extremity soft tissue sarcoma is "a soft tissue sarcoma of the extremities" (American Cancer Society, 2015)

Cancer survivor is "someone who has been free of any sign of the disease for 5 years" (American Cancer Society, 2015)

Limb salvage is a surgical technique in which there is limb sparing resection after tumor removal (Paredes et al., 2011)

Limb amputation is a surgical technique in which there is total limb removal (Paredes et al., 2011)

Chapter 2: Review of Literature

Sarcoma

Sarcomas are a tumor of the connective tissue and comprise a diverse group of mesenchymal neoplasms (Skubitz & D'Adamo, 2007). Sarcomas can be classified into two categories: soft tissue and bone. Patients may present with an asymptomatic mass or pain if the tumor distorts normal structure (Skubitz & D'Adamo, 2007). Biopsy is performed to obtain tissue for diagnoses of sarcomas. Care is taken when performing a biopsy in order not to interfere with subsequent surgery to remove the whole tumor (Skubitz & D'Adamo, 2007).

Bone Sarcoma

Bone sarcomas originate from the bone cells or bone cell precursors (Mavrogenis & Ruggieri, 2015). Bone sarcomas have a potential for metastases, especially to the lungs. The majority of bone sarcomas are diagnosed in children and young adults, although older adults and elderly may also develop bone sarcomas (Mavrogenis & Ruggieri, 2015). The most common type of bone sarcoma is Osteosarcoma (Ferrari, Balladelli, Palmerini, & Vanel, 2013), and the second most common type of bone sarcoma is Ewing Sarcoma Family Tumors (EFT). Ewing Sarcoma Family Tumors is usually diagnosed in children, adolescents, and young adults (Ferrari et al., 2013). Chondrosarcoma is the third most common bone sarcoma diagnosed mostly in the 3rd to the 6th decade of life (Mavrogenis & Ruggieri, 2015).

Bone sarcomas usually develop in the extremities, especially the long bones (Skubitz & D'Adamo, 2007). Patients with bone sarcoma usually present with pain, swelling, or functional impairment. A bone sarcoma tumor can also be identified

following radiography in incidences of fracture or trauma (Ferrari et al., 2013). Magnetic resonance imaging (MRI) is the primary imaging method for evaluation of bone tumors (Ferrari et al., 2013).

Once imaging has been completed, an orthopedic surgeon performs a biopsy and the subsequent pathologic findings makes the diagnoses (Ferrari et al., 2013). Biopsy can be closed (core needle biopsy-image guided) or open (surgery biopsy). Core needle biopsy-image guided involves using a large introducer gauge needle, advancing it to the proximal margin of tumor and then a smaller core biopsy needle (cutting needle) to obtain tissue sample for pathology testing (Kachroo et al., 2012). Open surgical biopsy involves making an incision where the tumor is located and taking out tissue sample (Kachroo et al., 2012). Open surgical biopsy is often indicated because a large sample size tissue can be obtained for further studies such as cytogenetics. Risks associated with open surgical procedure are infection, bleeding, scarring or inflammation.

Treatment of bone sarcomas involves chemotherapy and/or radiation. Patients then undergo limb sparing or amputation procedures (Ferrari et al., 2013). The patient is preferentially treated with chemotherapy prior to surgical treatment in order to treat potential metastases and to reduce tumor size allowing for easier resection (Mavrogenis & Ruggieri, 2015).

Osteosarcoma Excision

The primary osteogenic malignant tumor is rare and represents less than 4% of cancers in children under the age of 14 (Gurney, Scott, Severson, Fang, Robison & Ross, 1996). The traditional standard treatment following chemotherapy is wide excision of the bone with 2-3 cm margins in order to prevent local recurrences (Chen, Wu, Chen, Chung,

Liu, & Chen, 2012). Wide excision should achieve histologically negative margins (National Comprehensive Cancer Network, 2016). However, the limb resection sacrifices healthy bone and may have an impact on joint function (Chen et al., 2012). Important surrounding tissues such as ligaments, menisci, and articular cartilages may be resected if they are invaded by the tumor or to prevent local recurrences. In a small number of patients, hemicortical resection with biological reconstruction using frozen autograft and fresh-frozen allograft is a potentially successful treatment for patients with high-grade osteosarcoma (Chen et al., 2012). Autograft is the patient`s own bone and allograft is bone from donor. Patients had better limb functionality and minimal complications with hemicortical resection. Hemicortical resection is possible only in patients with a small tumor volume, appropriate tumor margin and good response to chemotherapy (Chen et al., 2012). The type of tumor excision has an impact on the functionality of the reconstructed limb and careful consideration of the surgical treatment by both patient and surgeon is required.

Chemotherapy and Radiation

Chemotherapy remains the treatment of choice in bone sarcoma (Arndt & Crist, 1999). Chemotherapy has improved the prognosis of children with osteosarcoma since the 1960s and the five-year survival rate in non-metastatic sarcoma is approximately 60-70% (Skubitz & D'Adamo, 2007). In the past, prior to neoadjuvant chemotherapy, survival rate was 20% due to distant metastases (Skubitz & D'Adamo, 2007). In addition, adjuvant chemotherapy has proven to be effective in reducing metastases and local recurrences especially in osteosarcoma (Skubitz & D'Adamo, 2007). The first randomized controlled trial showing the benefit of adjuvant chemotherapy in

osteosarcoma was conducted by Link, et al. (1986). Two years following adjuvant chemotherapy, 66% of patients who had received adjuvant chemotherapy had no recurrences compared to 17% from the group that did not receive adjuvant treatment. Based on this study, adjuvant chemotherapy has been the standard of care in treating osteosarcoma in addition to surgical treatments. Survival rates have been increased compared to surgical treatments alone due to relapse prevention.

According to the National Comprehensive Cancer Network guidelines (2016), the chemotherapy drug recommended for osteosarcoma includes one of three first line regiments: 1. cisplatin, doxorubicin, and high-dose methotrexate, 2. cisplatin, doxorubicin with or without ifosfamide and ifosfamide, cisplatin, and epirubicin. The clinical significance for multi-agent chemotherapy regimen for bone sarcoma has been discussed by Subbiah, Anderson, Lazar, Burdett, Raymond and Ludwig, (2009). The alkylating agents (cisplatin and doxorubicin) contribute to severe late side effects such as leukemia or anthracycline-induced cardiomyopathy (Arndt & Crist, 1999). Vincristine, doxorubicin, cyclophosphamide, and actinomycin D combination treatments are indicated for Ewing sarcoma. Chondrosarcoma, which are malignant cartilaginous tumors are considered chemotherapy and radiation resistant and surgery is the treatment of choice (Harwood, Alexander, Mayerson, & Scharschmidt, 2015). Neoadjuvant radiation therapy may be indicated for patients with chondrosarcoma of the skull base and axial skeleton in which the tumor is located in a place difficult for resection (Gelderblom, Hogendoorn, Dijkstra, Van Rijswijk, Krol, Taminiau, & Bovee, 2008).

Extremity Soft Tissue Sarcoma

Soft tissue sarcomas are rare malignant tumors originating from "fat, muscle, nerves, fibrous tissue, blood vessels or deep skin tissues" (American Cancer Society, 2015). The most common site for soft-tissue sarcomas in the extremities are in the lower limbs (Beckingsale & Shaw, 2015). While bone sarcomas are common in childhood, soft tissue sarcomas are common in adulthood, especially in persons 50 years old and older. The first line therapy for large, high-grade, soft tissue sarcoma is surgery followed by radiation therapy (Skubitz & D`Amano, 2007). Small, low-grade tumors can be treated with surgery alone. Chemotherapy may be used to shrink the soft tissue tumors before and after surgery to prevent recurrences, and the chemotherapy agents which are used are doxorubicin and ifosamide (Skubitz & D`Amano, 2007).

Reconstruction and Complications

Patients with bone and extremity soft tissue sarcomas may need to undergo limb sparing or amputation surgery (Wang et al., 2015). Amputation is indicated if a functionally viable extremity and negative margins cannot be obtained (Mavrogenis & Ruggieri, 2015). Reconstruction of the limb after malignant tumor removal, in particular around the knee, is difficult because wide excision is performed so that histologically negative margins are obtained minimizing local recurrence (Wang et al., 2015). In addition, reasonable functional expectations of the limb have to be achieved. Methods for reconstruction include tumor prosthesis, biological reconstruction with osteochondral autograft and allograft, frozen autograft-prosthesis or bone prosthesis composite (Wang et al., 2015; Chen et al., 2012; Yoshida, Osaka, Kojima, Taniguchi, Osaka, & Tokuhashi, 2012). Bone prosthesis composite (BPC) with rotating hinge knee prosthesis for

reconstruction following resection of the knee showed excellent durability for the first five years with minimal complications (Wang et al., 2015). In biological reconstruction, bone allografts are used and obtained from a bone bank. For an osteochondral autografts, a surgeon harvests a bone graft from the patient section of bone that does not have the tumor and transplants it into the area where the excised tumor was present.

Tumor prosthesis remains the primary treatment because it allows for stable limb function (Yoshida et al., 2012). However, complications may arise including infection, or the prosthesis stem breaking or loosening necessitating revision (Yoshida et al., 2012). Tumor prosthesis is an artificial implant that is used to replace the excised bone during tumor resection. Following tumor prosthesis, seven (17.5%) out of forty patients reported stem breakages or loosening necessitating revision surgery (Yoshida et al., 2012). Infection rates were reported to be 6% in 104 osteosarcoma patients who had undergone neoadjuvant chemotherapy and reconstruction surgery with tumor prosthesis (Bi, Wang, Han, Jia, & Xu, 2013). Infection is related to bacteria growing in biofilms on the implant especially the *Staphylococci* specie. Suggestions to minimize stem breakage or loosening following tumor prosthesis have been to limit resection of the affected bone to not greater than 30% and using a prosthesis with a thicker stem of at least 12 mm (Yoshida et al., 2012).

Frozen autograft-prosthesis composite reconstruction is preferable for malignant bone tumors of the proximal humerus, tibia, and pelvis which allows for optimal soft-tissue reattachment to the prosthesis (Subhadrabandhu,et al., 2015). One of the procedures for frozen autograft-prosthesis involves free freezing the tumor bearing bone in liquid nitrogen for 20 minutes, thawing for 15 minutes at room temperature and then in

distilled water for ten minutes (Subhadrabandhu,et al., 2015). The advantages of frozen autograft include biological reconstruction without the need for a bone bank and no immunological reactions or possibility of disease transmission from donor bone. However, there are disadvantages, mainly fracture and infection. Frozen autograft-prosthesis composite reconstruction performed in 22 patients and followed up for an average of 14.7 years resulted in one fracture, two infections, three soft tissue recurrences, and one posterior interosseous nerve palsy (Subhadrabandhu et al., 2015). The average Musculoskeletal Tumor Society score (MSTS) was high, 89.3% which suggested frozen autograft-prosthesis composite reconstruction may be highly recommended in certain malignant bone tumors. Musculoskeletal Tumor Society score is a measure of physical function for patients of bone sarcomas.

There are complications that arise with limb salvage reconstruction (Shehadeh, Noveau, Malawer, & Henshaw, 2010). Generally, patients are having longer survival rates and usually outlive the functional life of the endoprosthesis implants. Complications that arise later include breakage or fracture of implant, instability due to wear, and infection. Patients usually require revision surgeries thereafter and that also increases the risk of infection of the implant and incision wound. Shehadeh et al. (2010) found that rates of complications increased with each successive revision surgery. They also attributed implant failure to mechanical complications such as implant loosening. In addition, infection led to amputation in some patients.

Amputation is usually above-knee amputation or hip disarticulation due to most tumors occurring on the proximal femur or tibia (Li, Wang, Ji, Chen, Liu, & Zhu, 2010). Above knee amputation often leads to less favorable psychosocial outcomes.

Rotationplasty is available as a means to effectively convert an above-knee amputation to a below-knee amputation for certain tumors. During rotationplasty, the distal femur and proximal tibia are resected and distal tibia and foot are rotated 180^{o}. Tibiofemoral osteosynthesis occurs, and distal tibia augments to femur. The reversed ankle operates as the knee and prosthesis fits on foot. Patient functions as a below knee amputee (Li et al., 2010).

Quality of Life

A bone sarcoma and extremity soft tissue sarcoma diagnoses can have devastating outcomes which affect the quality of life. Reconstruction surgery following limb resection can affect the functionality of the limb (Sachsenmaier et al., 2015). Some patients may not qualify for limb salvage surgery leading to limb amputation. Mason et al. (2013) found that cancer survivors who had limb preservation surgery had statistically significant superior quality of life than survivors who had amputation surgery in several domains such as: Material well-being, occupational relations, job satisfaction, and sports activity. Sachsenmaier et al. (2015) were able to study the impact of psychological therapy, family, social and educational background, occupation, and physical status on the quality of life after sarcoma diagnoses. The researchers found the presence of family and social support, psychological therapy and better physical status contributed to better quality of life and survivors who could still work at their jobs after treatment showed better emotional status.

Osteosarcoma survivor's psychosocial and functional outcomes were compared after limb-salvage surgery and amputation. The greatest predictor on the quality of life was the functionality of lower limb, not surgery type (Robert, Ottaviani, Huh, Palla, &

Jaffe, 2010). Limb amputation affected body image and quality of life when performed after failed limb salvage surgery (Robert et al., 2010). Thijssens, Hoekstra-Weebers, Van Ginkel, and Hoekstra, (2006) studied the quality of life as it related to post-traumatic stress symptoms (PTSS) in patients with extremity soft tissue sarcoma. The patient self-reported on their physical functioning, social functioning, role impairment due to physical problems, mental health, vitality, pain, general health perception and health change (Thijssens et al., 2006). Patients who were more satisfied with their treatment goals reported less PTSS and had a better QOL (Thijssens et al., 2006). In addition, patients with an amputated limb had a worse quality of life score in physical and social functioning and role limitations (Thijssens et al., 2006).

Summary

Bone and soft tissue sarcomas are very rare. The survival rates have increased since the incorporation of neoadjuvant chemotherapy in the treatment protocol. Limb sparing and amputation surgeries have an impact on the functionality of the limb and may affect physical status and unexpected complications. This research is focused on studying the complications following limb salvage and amputation procedures by conducting a medical chart review.

Chapter 3: Methodology

Introduction

The purpose of the research was to evaluate the complications of extremity bone and soft tissue sarcoma patients who have undergone surgical resection of their tumor. There are two research questions for the study:

1. For extremity sarcoma patients treated with tumor excision, is amputation associated with greater post-surgical complications compared to a limb salvage procedure?
2. Is there a difference in post-surgical complications for patients who had an amputation versus limb salvage procedure?

Study Design

This study's design is that of a quantitative chart review. A retrospective review of 50 medical records was done for patients who underwent limb salvage reconstruction and amputation between 1995 and 2014. The musculoskeletal tumor computerized database at the University of Minnesota of patients who had limb salvage and amputation reconstruction was reviewed. Complications were classified as infection, revision surgeries, recurrences, mechanical failure of implant, physical limitations.

Study Participants

The entry criteria for the study participants was:1) diagnosis of bone or soft tissue sarcoma, 2) current age > 18 years, 3) male or female, 4) surgical resection of sarcoma of the extremity, 5) chart review > 2 years after index surgery.

Data Collection

Data collection included demographic and treatment related data of the study participants. Demographic data was: 1) age of patient at time of diagnosis, 2) date of

birth, 3) diagnosis, 4) date of diagnosis, 5) tumor site: **bone:** pelvis, proximal femur, distal femur, proximal tibia, distal tibia, fibula, distal fibula, proximal humerus, distal humerus, forearm, hand, other; **soft tissue:** buttock, thigh, leg, hindfoot (calcaneus, talus), midfoot/forefoot (cuboid, navicular, cuneiforms, metatarsals, phalanges), arm, forearm, hand/wrist.

Treatment information included: 1) surgical procedure: reconstruction [soft tissue, prosthesis or structural bone graft, and plastic surgical (e.g, muscle flap or skin graft)], amputation (partial foot, below knee, above knee, hip disarticulation, hemipelvectomy, above elbow, below elbow, shoulder girdle), 2) surgery date, 3) chemotherapy: cytotoxic (total duration relative to surgery date), 4) radiation: total dose (Gy), 5) additional surgery and date.

Relevant Variables

Independent variables were study population: extremity bone sarcoma and extremity soft tissue sarcoma patients. Dependent variables complications, amputation vs limb salvage.

Storage of Data

The patient completed demographic data form was kept on the Fairview password protected encrypted computer drive at the University of Minnesota Orthopaedic Department for a period of five years. The medical chart review was conducted on the Fairview computer.

Limitations of study

Bone and extremity soft tissue sarcoma are a rare type of malignancy and the results of the study was confounded by small sample size.

Statistical Analysis

Statistical analysis was carried out using IBM® SPSS® for windows**.** Unpaired t-test was done to determine the mean difference between the complications scores for amputation group versus limb salvage group. An unpaired t-test was done to determine the mean difference in the complication scores between the amputation versus amputation after limb salvage procedure.

Chapter 4: Results

Demographic Data

The data collection included sex, age at diagnosis, current age, type of sarcoma, site of the primary tumor, surgical treatment, chemotherapy/radiation, and revision surgeries.

All the patients included in the medical chart review were 2 years post sarcoma diagnosis and treatment. There were 50 medical chart reviews.

The following table shows the range, median and average age at diagnosis and current age

Table 1.0: Current age and age at diagnosis

	Age at diagnosis (years)	Current age (years)
Median	23.6	45
Mean	29.7	45.8
Range	7-62	22-71

Type of Sarcoma

Osteosarcoma and Ewing sarcoma were diagnosed in childhood. The tumors occurred mostly in the tibia and femur. The malignant tumors that occurred in the distal tibia and femur were associated with above the knee amputation if amputation was indicated. The most common bone sarcoma in adults was malignant fibrous histiocytoma and chondrosarcoma. For extremity soft tissue sarcoma, synovial, neurofibrosarcoma, peripheral nerve sheath sarcoma, clear cell sarcoma were diagnosed in adults.

Table 2.0: Type of sarcoma diagnosis and common sites of primary tumor (n=50)

Bone or soft tissue sarcoma of extremity	Site of primary tumor	# patients
Osteosarcoma	Tibia, femur	16 (32%)
Ewing sarcoma	Tibia, femur, foot bone	9 (18%)
Chondrosarcoma	Femur, thigh	7 (14%)
Peripheral nerve sheath sarcoma	Antecubital region, posterior thigh, leg	4 (8%)
Pleomorphic sarcoma	Tibia and patella	1 (2%)
Desmoplastic small round cell tumor	Radius	1(2%)
Epithelioid sarcoma	Femur	1(2%)
Neurofibrosarcoma	Calf, ankle	2 (4%)
Clear cell sarcoma	Foot bone	1 (2%)
Synovial sarcoma	Ankle, foot bone, midfoot	3 (6%)
Malignant fibrous histiocytoma	Femur, elbow, leg and calf	3 (6%)
Angiosarcoma	Leg and knee	1(2%)
Leimyosarcoma	pelvis	1(2%)

Most of the patients were diagnosed with a malignant tumor located in the lower limbs, n=45. There were patients whose tumor was in the upper limb, n=4 and pelvis, n=1. Forty-seven of the patients had localized disease and three had metastases at the time of diagnosis. Nineteen patients had limb salvage reconstruction, twenty-five patients

had amputation and six patients had amputation after failed limb salvage. Amputation after failed limb salvage reconstruction was due to infection of the endoprosthesis, bone allograft and local recurrence.

Treatment Protocols

Forty-three patients had neoadjuvant chemotherapy/radiation prior to surgical treatment, followed by adjuvant treatments after surgical reconstruction. Seven patients with chondrosarcoma were treated by limb sparing resection or limb amputation only. These patients did not receive chemotherapy or radiation. Osteosarcoma was diagnosed in sixteen patients and they were treated with cisplatin and doxorubicin, or MAP (high dose methotrexate, cisplatin and doxorubicin), or doxorubicin, cisplatin, ifosfamide and high dose methotrexate, or ifosfamide, cisplatin and epirubicin prior and post to surgical treatments.

The nine Ewing sarcoma patients had neoadjuvant and adjuvant VAC/IE (vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide), or VAI (vincristine, doxorubicin, and ifosfamide), or VIDE (vincristine, doxorubicin, ifosfamide, and etoposide) as the primary chemotherapy treatment.

Local Recurrences

Local recurrences occurred in 12% (6 patients: n=5 limb salvage and n=1 amputation) leading to revisions. Five patients (10%) had prior exposure to radiation therapy for their sarcoma and then limb salvage reconstruction, n=2 had malignant peripheral sheath sarcoma and n=2 had neurofibrosarcoma. These patients were in remission for over 20 years. One patient (2%) had radiation induced pleomorphic sarcoma. The patient had received radiation treatment 30 years prior. Amputation was

performed in all the patients following recurrence. The decision to amputate was solely based on soft tissue complications such as encasement of nerves or neurovascular bundle by tumor. The recurrences occurred around the same site as the primary tumor. One patient (2%) had a primary below knee amputation but when the tumor recurred, an above knee amputation was performed. More patients in the limb salvage group ($p < 0.05$) had local recurrence of tumor than the amputation group. The risk factors for recurrences were radiation and limb salvage.

Table 3.0. Comparison of local recurrence

Group	Local recurrence	
	Yes	No
Limb salvage	5 (10%)	14 (28%)
Amputation	1(2%)	24 (48%)

Complications

Complications occurred in all 50 patients and included infection, revision surgeries, physical limitations, cardiomyopathy, pain, and reproductive health issues.

Infection

Infection was reported in 10 patients (20%). The average time to infection was immediately following reconstruction surgeries. There were two patients (4%) in the amputation group who had non-healing wound which lead to infection. The infection was at the amputation stump and led to chronic osteomyelitis. One of the patient`s wound was infected with *Staphylococcus Epidermis* species. The patient was on a long course of antibiotics (Augmentin) for 85 days. The non-healing wound was caused by skin edges

overlapping and for some reason this caused a small area of pinpoint drainage which was exacerbated by the use of prosthesis. The infection led to a surgical revision. Six patients (12%) had infection of the megaprosthesis following limb salvage reconstruction. One patient (2%), a 47-year-old had infection of megaprosthesis that ultimately led to above the knee amputation. The decision to amputate was because the infection could not be controlled. The incidence of infection was also reported in two patients (4%) who had limb salvage reconstruction using bone allograft. These patients also had non-union of bone allograft to bone. The infection of bone allograft led to bacteremia, sepsis and use of antibiotics for at least 3 months.

Physical Limitations

Physical limitations were reported in 18 patients in the limb salvage group and 31 patients in the amputation group. The physical limitations ranged from minor such as inability to fully extent and flex limb to major limitations such as walking up a steep hill. The patients reported that they could not return to their baseline function before the sarcoma diagnosis. Limb salvage patients were cautioned against participation in high impact activities such as skiing or sprinting. Gait problems were experienced in the amputation groups. Therefore, the pattern of physical limitations differed between the two groups. For example, one patient had to relearn driving using her amputated limb fitted with a prosthetic leg. A limb salvage patient had difficulties walking uphill or downhill, performing household tasks such as mowing the lawn.

Pain

Pain was reported in all the patients in the limb salvage and amputation group (n=50). Eight patients (16%) were on narcotics for management of the severe chronic

pain. In the limb salvage group, pain was experienced especially at the knee or hip. Phantom pain was experienced in 100% of the amputation patients. In severe cases, patients used higher doses of Neurontin per day to reduce the pain sensation. One patient required 900 mg Neurontin daily to help with the pain. Patients in the amputation group also experienced pain or discomfort at the amputation stump.

Revisions

Revision surgeries occurred in all limb salvage reconstruction (n=19). The revision surgeries ranged from two to five per patient. The number of surgeries a patient had depended on the initial surgery, implant used and number of years post sarcoma diagnosis. The reasons for revisions included implant loosening, infection, and fracture in biological implants.

An example was a patient who had a total of 5 surgeries for osteosarcoma of the proximal tibia. The patient was diagnosed 17 years ago at 15 years of age. Initial surgery was limb salvage with wide excision and osteoarticular allograft reconstruction. Second surgery was open reduction and internal fixation of the biological implant following prosthetic fracture. The third surgery was knee arthroplasty for ongoing degenerative changes, and then revision of knee arthroplasty. The most recent surgery was knee manipulation under anesthesia.

Revision surgeries with amputation, n=25 were due to infection, removal of nodule on amputation stump, wound revision, wound closure, stump ulceration, or correction of stump deformity. The revision surgeries ranged from one to three. An example is one patient who had a nodule at the site of the amputation stump, this tumor

was excised. The patient had recurrence of the nodule two years later which required surgical excision.

Complications in Pediatrics Sarcoma Patients

Twenty-four patients had osteosarcoma or Ewing sarcoma in childhood. Limb salvage reconstruction was done using endoprosthesis and biological allografts. Biological allograft was done in seven patients (14%), eight patients (16%) had endoprosthesis for limb salvage and nine patients (18%) had amputation. Complications in pediatric patients included: Need for lengthening of prosthetic legs in the amputation group, leg length discrepancies in limb salvage group, ovarian dysfunction secondary to chemotherapy, and risk for early menopause in females. An example is an Ewing sarcoma patient who had below knee amputation when she was 13. When the patient reached adulthood, her prosthetic leg had to be lengthened.

Chemotherapy/Radiation Induced Complications

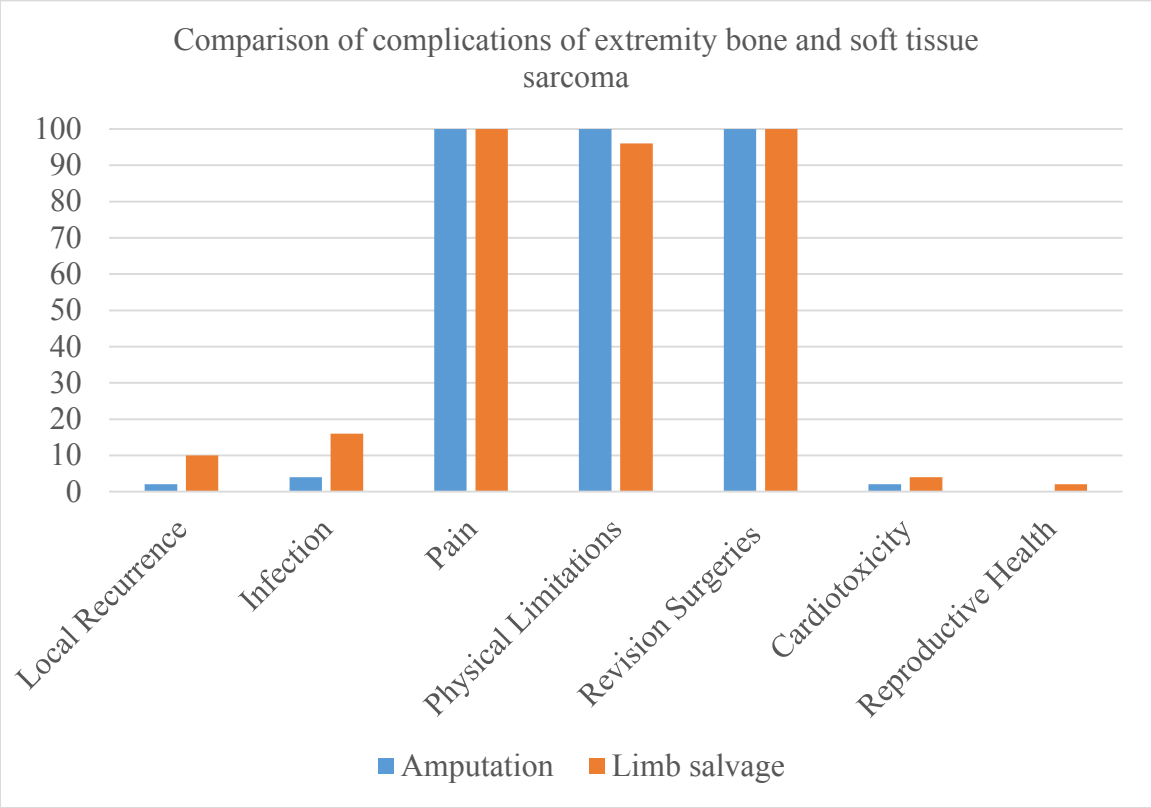
Patients who were treated with doxorubicin, which is an anthracycline, were at risk for cardiotoxicity. The number of patients with cardiomyopathy induced by anthracycline treatment were n=3 (6%). The patients had subclinical left ventricular dysfunction, reduced ejection fractions, and were followed closely by cardiology. Sensorineural hearing loss was reported in one patient due to methotrexate exposure.

Pattern and Onset of Complications

Complications following treatments for extremity bone and soft tissue sarcoma were evident soon after the treatments and would persist for years following the treatments. Overall, the difference in complications of extremity bone and soft tissue sarcoma was in the incidences of local recurrence. Limb salvage group had a greater

recurrence rate compared to amputation. Infection was greatest in limb salvage reconstruction compared to amputation.

Figure 1.0. Comparison of complications of extremity bone and soft tissue sarcoma



Chapter 5: Discussion

Extremity bone and soft tissue sarcoma are a rare type of cancer whose treatment modalities include chemotherapy and or radiation followed by limb salvage or amputation reconstruction. Complications arise with both limb salvage and amputation. Although early and late complications have been reported, there has been limited research on the comparison complications of amputation and limb salvage procedures for extremity bone and soft tissue sarcoma. A detailed analysis of these complications is still needed. This research attempted to determine if 1) amputation reconstruction was associated with greater complications than limb salvage and 2) if there was a difference in post-surgical complications following limb salvage versus amputation.

Local Recurrence

Limb salvage reconstruction is favored compared to amputation because this type of reconstruction may provide a functional and durable limb unlike in amputation reconstruction (Levin et al., 2017). Limb salvage is preferred especially in young patients who are expected to remain active. From the study limb salvage was associated with a higher local recurrence than amputation. The results of this study showed that these patients had received radiation therapy for their cancer many years before the recurrence. This is important to note that even after 5 years of complete remission, the tumors can recur due to the exposure to radiation therapy. Also, local recurrences in our patients may have been attributed to inadequate resection margin. When local recurrence occurred, the surgical decision was to amputate.

Infection and Fracture in Limb Salvage Reconstruction

Endoprostheses implants are the most preferred reconstruction implants today (Levin et al., 2017). One of the drawbacks of limb salvage is the eventual need for revision reconstruction. Patients in our study all had revision reconstruction. Revisions occurred because of prosthetic fracture, prosthetic loosening, infection, pain, or physical limitations. Patients who had limb salvage using bone allograft all experienced complications due to infection, non-union of bone allograft to bone leading to fracture. Loosening and infection of implant are the most common complications with limb salvage reconstruction (Biau, Faure, & Katsahian, 2006). When an infection occurs in a endoprosthesis, the implant has to be revised and often leads to amputation if the infection cannot be controlled. Rates of infection of megaprosthesis have been reported to be 2.2% (Torbert, Fox, & Hosalkar, 2005). This study infection rates for limb salvage were 16% and much higher than reported in literature. As stated earlier in the literature review, the most common specie responsible for infection are Staphylococci and Streptococci (Lee et al., 2002). In addition, when patients are receiving chemotherapy treatments, they are susceptible to opportunistic infections (Papanastasiou et al., 2017).

Pattern and Onset of Complications

Pain was reported in all patients regardless of the type of reconstruction. Pain was inevitable due to stiffness of the implant, limited range of motion with limb salvage reconstruction or pain at the amputation site due to stump ulceration, benign nodules, or non-healing amputation wound. Complications arising from amputation after limb salvage were similar to those when amputation was done as the initial treatment. The patients had issues with phantom pain and physical limitations.

Cardiotoxicity is associated with the use of anthracyclines, like doxorubicin, daunorubicin and epirubicin (Van Dalen, Raphaël, Caron, & Kremer, 2014). These chemotherapy drugs are used in bone sarcoma treatment protocols. This study showed that patients who had cardiomyopathy induced by anthracyclines were diagnosed and treated for osteosarcoma when they were children. Anthracycline-induced cardiotoxicity is widely reported in children (Van Dalen et al., 2014). Cardiotoxicity can lead to long term morbidity and reduction in quality of life. The damage to the heart may occur as heart failure or asymptomatic dysfunction of the heart that is found on imaging such as echocardiogram.

Limitations

There were limitations to the chart review study. First the number of patients were small (n=50). This was expected because of the rareness of extremity bone and soft tissue sarcoma. Second, this study did not determine if the complications improved as the number of years post diagnosis increased. However, there were patients who continued to have more problems many years post diagnosis. To better understand the complications, conducting surveys using standardized instruments would be ideal especially when trying to gather information about physical limitations. These standardized instruments would include Quality of Life-Cancer Survivor Score (QLS-CS), Toronto Extremity Salvage Score (TESS), Musculoskeletal Tumor Society (MSTS). Third, this study was a retrospective study of patients treated over a long period of time with some patient records not current.

Summary

Limb salvage reconstruction was associated with greater local recurrence than the amputation group. However, the patients had received radiation therapy > 20 years ago for their primary tumor which may have increased recurrence rates. Infection was reported more with limb salvage reconstruction than amputation. Therefore, amputation was not associated with greater complications than limb salvage. Overall, the post-surgical complications in the amputation group and limb salvage were similar. This study was important in order to better understand the complications sarcoma patients face following treatments and to better find ways to offer support. Clinicians can use this information to better tailor treatments to the cancer patients.

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APPENDIX A

University of Minnesota IRB

University of Minnesota IRB

Subject:

1605E87424 - PI Cheng - IRB - Exempt Study Notification

Date:

Wed, 5 Oct 2016 09:20:25 -0500 (CDT)

From:

irb@umn.edu

To:

agelx001@umn.edu

TO : cheng002@umn.edu, clohi001@umn.edu, agelx001@umn.edu, cogilvie@umn.edu,

The IRB: Human Subjects Committee determined that the referenced study is exempt from review under federal guidelines 45 CFR Part 46.101(b) category #2 SURVEYS/INTERVIEWS; STANDARDIZED EDUCATIONAL TESTS; OBSERVATION OF PUBLIC BEHAVIOR.

Study Number: 1605E87424

Principal Investigator: Edward Cheng

Title(s):

Outcome of extremity bone and soft tissue sarcoma patients following limb salvage and amputation procedures

This e-mail confirmation is your official University of Minnesota HRPP notification of exemption from full committee review. You will not receive a hard copy or letter.

This secure electronic notification between password protected authentications has been deemed by the University of Minnesota to constitute a legal signature.

The study number above is assigned to your research. That number and the title of your study must be used in all communication with the IRB office.

Research that involves observation can be approved under this category without obtaining consent.

SURVEY OR INTERVIEW RESEARCH APPROVED AS EXEMPT UNDER THIS CATEGORY IS LIMITED TO ADULT SUBJECTS.

This exemption is valid for five years from the date of this correspondence and will be filed inactive at that time. You will receive a notification prior to inactivation. If this research will extend beyond five years, you must submit a new application to the IRB before the study's expiration date. Please inform the IRB when you intend to close this study.

Upon receipt of this email, you may begin your research. If you have questions, please call the IRB office at (612) 626-5654.

You may go to the View Completed section of eResearch Central at http://eresearch.umn.edu/ to view further details on your study.

The IRB wishes you success with this research.

We value your feedback. We have created a short survey that will only take a couple of minutes to complete. The questions are basic, but your responses will provide us with insight regarding what we do well and areas that may need improvement. Thanks in advance for completing the survey. http://tinyurl.com/exempt-survey

APPENDIX B

Demographic Data Form

Demographic data

Patient Study ID#_____

Patient Name_____
First/Middle/Last

Date of Birth_____
Month/Day/Year

Age of Patient at time of diagnosis_____

(years)

Diagnosis: _____

Date of Diagnosis: _____
Month/ Day/Year

Tumor Site: **Bone**: 1) pelvis, 2) proximal femur, 3) distal femur, 4) proximal tibia, 5) distal

tibia, 6) proximal fibula, 7) distal fibula, 8) proximal humerus, 9) distal humerus,

10) forearm bone (radius or ulna) 11) hand bone, 12) ankle or foot bone

13) other_____

Soft Tissue: 1) buttock, 2) thigh, 3) leg (below knee), 4) hindfoot, 5)

midfoot/forefoot , 6) arm, 7) forearm (below elbow), 8) hand/wrist,

9) other_____

Treatment: Surgical procedure:

1) **Bone Reconstruction**: prosthesis, structural allograft bone graft

2) **Soft Tissue Reconstruction**: muscle flap, skin graft

3) **Amputation:** 1) partial foot, 2) below knee, 3) above knee, 4) at knee, 5) hip disarticulation,

6) hemipelvectomy, 7) below elbow, 8) above elbow, 9) shoulder girdle

Surgery (tumor excision and/or reconstruction) date: _____

Month/ Day/Year

Chemotherapy: Cytotoxic drugs_____

Total duration of chemotherapy (months) _____

Radiation: Total Dose (Gy) _____

Total duration of radiation (month): _____

Additional Surgery: _____

Date of additional surgery: _____