Published in final edited form as:

Pediatr Blood Cancer. 2017 March ; 64(3): . doi:10.1002/pbc.26162.

Prospective study of neuropathic pain after definitive surgery for extremity osteosarcoma in a pediatric population

Doralina L. Anghelescu¹, Brenda D. Steen², Huiyun Wu³, Jianrong Wu³, Najat C. Daw⁴, Bhaskar N. Rao⁵, Michael D. Neel⁶, and Fariba Navid⁷

¹Pain Management Service, Division of Anesthesiology, Department of Pediatric Medicine, St Jude Children's Research Hospital, Memphis, Tennessee

²Department of Anesthesiology, St Jude Children's Research Hospital, Memphis, Tennessee

³Department of Biostatistics, St Jude Children's Research Hospital, Memphis, Tennessee

⁴Division of Pediatrics, MD Anderson Cancer Center, Houston, Texas

⁵Department of Surgery, St Jude Children's Research Hospital, Memphis, Tennessee

⁶St. Jude Children's Research Hospital, Memphis, Tennessee

⁷Department of Oncology, St Jude Children's Research Hospital, Memphis, Tennessee

Abstract

Background—Neuropathic pain (NP) after definitive surgery for extremity osteosarcoma (OS) has not been previously characterized. This study prospectively investigates the incidence, duration, and treatment of NP in limb sparing surgery and amputation groups.

Procedure—In patients treated for OS on a chemotherapy and definitive surgery (limb sparing vs. amputation) protocol (OS08), we prospectively collected the following data: (i) demographical data (age, sex, race); (ii) NP time of onset and duration; and (iii) dose (starting, maximum) and duration of gabapentin, amitriptyline, and methadone treatment.

Results—Thirty-seven patients underwent 38 definitive surgeries: limb sparing (26, 68.4%) or amputations (12, 31.6%). Localization included lower extremity (30, 81%), upper extremity (6, 16%), or pelvis (1, 3%). Thirty patients (81%) developed NP and 26 of them required NP-specific medications (87.7%). The mean [standard deviation (SD)] duration of NP was 6.5 weeks (7.2) (median 4.4, range 0.3–29.9). All 26 patients (27 surgeries) treated with NP medications received gabapentin, either as single therapy (65.4%) (17 patients, 18 surgeries), dual therapy with gabapentin and amitriptyline (five patients), or triple therapy with gabapentin, amitriptyline, and methadone (four patients). The mean starting (maximum) doses of gabapentin, amitriptyline, and methadone (mg/kg/day) were 20.2 (43.8), 0.5 (0.7), and 0.3 (0.3), respectively. The incidence and duration of NP, duration of treatment, and NP-specific dose regimens were similar in the limb sparing and the amputation groups.

Correspondence Doralina L. Anghelescu, Division of Anesthesiology, MS 130, St Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105. doralina.anghelescu@stjude.org.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Conclusions—NP after definitive surgery for OS is frequently encountered, can persist for a significant time, and NP outcomes are similar in limb sparing and amputation groups.

Keywords

amputation; limb sparing; neuropathic pain; osteosarcoma

1 INTRODUCTION

Osteosarcoma (OS) is the most common bone malignancy in children and adolescents.¹ The primary tumor site in approximately 80% of patients is the extremity, most commonly the distal femur followed by the proximal tibia. The standard treatment for patients with OS is comprised of intensive chemotherapy and complete surgical resection of the primary tumor.² Most patients with extremity tumors are candidates for limb sparing surgery, which usually entails an en bloc removal of the tumor and involved bone and reconstruction with an endoprosthesis or allograft. In cases where a limb sparing procedure is not feasible, an amputation is recommended.

It is generally accepted that pain is frequently neuropathic in patients with cancer (19–39%),^{3–7} either as cancer-related neuropathic pain (NP), cancer therapy–induced NP, or cancer-associated NP. Neuropathic pediatric cancer pain has been characterized^{8–11} in four retrospective studies, one of them specifically investigating mixed nociceptive and NP after limb sparing surgery for bone cancer⁹; nevertheless, no prospective studies of neuropathic pediatric cancer pain have been published so far. In this study, we prospectively investigate NP after definitive surgery for extremity OS in a pediatric population to determine its incidence and describe the details of therapy for NP: monotherapy versus multiple lines of NP therapy, duration of treatment, and dose regimens; and to compare the NP outcomes in patients having limb sparing surgery versus amputation.

2 PATIENTS AND METHODS

As part of a multi-institutional, institutional review board approved therapeutic trial, patients with OS undergoing surgical removal of the primary tumor with either amputation or limb sparing procedure involving endoprosthetic or allograft reconstruction, following 10 weeks of preoperative chemotherapy, were prospectively followed for development, duration, and treatment of NP related to surgery. The data collected included patient characteristics (age at diagnostic, sex, race, weight), location of extremity OS (lower or upper extremity, pelvis), disease stage (localized vs. metastatic), and type of surgery (limb sparing or amputation). A standardized data collection form was used to record the presence or absence and intensity of NP, and the type, duration, and dose regimens of NP medication at the following time points: preoperatively, each postoperative day for the first week, weekly for the first month, and then monthly until resolution of NP symptoms and weaning off the NP medication regimen. The same data collection tool was applied at all collaborating institutions. NP was diagnosed based on the characteristics of pain as tingling, burning, shooting, “needles and pins”-like pain, localized in the surgical extremity, and distal to the surgical site. For the purposes of this study, the medications specific to the treatment of NP were gabapentin,

amitriptyline, and methadone. These medications are part of the guidelines and NP treatment algorithm at our institution. The pain medication regimens were at the discretion of the treating physicians. For each patient, the starting dose, maximum dose, and dose at completion of therapy for each medication was calculated (mg/kg/day). Data pertaining to therapy with opioids were also collected: type of opioid, dose, duration of therapy. Opioid dose data were calculated based on documented administered doses (not on availability of as needed doses).

Thirty-seven of the 43 patients enrolled on the therapeutic trial met the criteria for evaluation of NP following definitive surgery. Six patients were excluded for various reasons: one patient was deemed ineligible for the trial 5 days after enrollment due to deep vein thrombosis, two patients were removed from study prior to undergoing surgery, one patient was removed from study immediately after surgery to receive radiation therapy for a positive margin and modified chemotherapy, one patient had a nonextremity OS, and one patient had a fibula resection without reconstruction (Fig. 1).

2.1 Statistical analysis

Descriptive statistics were computed for patient characteristics for the overall group, the limb sparing group, and the amputation group. The incidence of NP was calculated as the rate of patients with occurrence of NP among the entire group, the limb sparing group and the amputation group separately. The difference of NP incidence between the limb sparing and amputation groups was tested using chi-square test. The duration of NP and the duration of treatment with NP medications were calculated for the overall group and the two groups of patients. The distribution of the NP duration was examined using histogram and the difference of durations between the two groups was tested for each of the two durations using Wilcoxon rank-sum test. In order to explore the relationship between NP duration and NP medication duration, patients with NP duration and patients with NP medication duration were plotted into two different time frames. Doses were derived and computed for the three NP medications (gabapentin, amitriptyline, and methadone), and the dose difference between the two patient groups was examined for gabapentin using Wilcoxon rank-sum test. All the tests were two-sided and the significant level was set at 0.05. All the computations were implemented using SAS software version 9.3 (SAS Institute Inc., Cary, NC).

3 RESULTS

3.1 Patient characteristics and incidence and duration of NP

Thirty-seven patients underwent 38 definitive surgeries: limb sparing (26, 68.4%) or amputations (12, 31.6%). Localization included lower extremity (30, 81%), upper extremity (6, 16%), or pelvis (1, 3%). The patient characteristics are described in Table 1. Thirty patients (81%) experienced NP postoperatively. The NP diagnosis was established on the first day postoperatively for 14 patients (15 surgeries) and during the first week postoperatively for all patients with NP. The incidence of NP in the limb sparing and the amputation groups were 81 and 83%, respectively (Table 2). The mean (SD) duration of NP in the entire study group was 6.5 weeks (7.2) (median 4.4, range 0.3–29.9) (Table 2 and Fig. 2). A shorter mean (SD) duration of NP was experienced in the amputation group than in the

limb sparing group, 4.9 (4.0) versus 7.2 (8.4), but the difference was not statistically significant ($P = 0.893$).

3.2 NP-specific medications—type, duration, and dose

Four of 30 patients diagnosed with NP were treated with opioids only (i.e., no NP-specific medications were prescribed); the other 26 patients received both opioids and NP-specific medication therapy. One patient experienced two surgeries evaluable for the study, for a total of 27 surgeries/observations with NP and NP-specific medication information available for analysis.

Medications specific for NP were administered for a mean (SD) duration of 9.5 (8.1) weeks (median, 7, range 1.7–30). The patient who had two surgeries had the NP diagnosis established on the first day postoperatively each time and had medications specific for NP started on postoperative day 4 after the first surgery and continued through the second surgery and postoperatively. When analyzed separately for the limb sparing group and the amputation group, the duration and dose regimens of NP medications administered were similar between groups (Table 2). No correlations were found between demographic characteristics (age <13 vs. ≥13 years; sex: male vs. female; race: white vs. other) and incidence of NP, duration of NP, or NP medication duration or dose. All 26 patients (27 surgeries) treated with NP medications received gabapentin. Gabapentin was initiated pre-operatively, with prophylactic intent, for the majority of patients (20 of 37). The other patients treated with gabapentin had this regimen started during the first week postoperatively. The majority (65.4%) received gabapentin as a single NP therapy (17 patients, 18 surgeries). Five patients received dual therapy with gabapentin and amitriptyline and four patients received triple therapy with gabapentin, amitriptyline, and methadone. The mean starting and maximum doses of gabapentin, amitriptyline, and methadone (mg/kg/day) for the entire group were 20 and 43.5, 0.5 and 0.6, and 0.2 and 0.2, respectively, and were similar between the limb sparing and the amputation groups (Table 2).

3.3 Opioid treatment—incidence, duration, and dose

Opioid treatment data were available for 30 patients diagnosed with NP (31 surgeries) (18% missing data). Twenty-six patients (27 surgeries) (71%) were treated with both opioids and NP-specific medications and four patients were treated with opioids only (11%). The mean (SD) duration of treatment with opioids in 30 patients (31 surgeries) was 8.4 (7.3) (median 6, range 0.1–28). The opioid dose, expressed as mean (SD) i.v. morphine equivalent dose (mg/kg/day), at the initiation of opioids treatment and at the maximum dose was 0.9 (2.6) and 14.7 (2.8), respectively.

4 DISCUSSION

This is the first prospective investigation of NP in pediatric oncology, describing specifically NP after definitive surgery for extremity OS. Our main findings are as follows: (i) high incidence of NP after definitive surgery for extremity OS; (ii) long duration of NP after definitive surgery for extremity OS; (iii) necessity of prolonged and often complex NP-specific medication therapies, including dual or triple therapy regimens; (iv) similar pain

outcomes for limb sparing and amputation (duration of NP, duration of NP medications administration, and dose regimens for gabapentin, amitriptyline, and methadone).

In adults, a systematic literature review of 281 studies found the prevalence of postsurgical NP to be between 6% after total hip or knee arthroplasty and 66 and 68% after thoracic and breast surgery, respectively¹²; NP after amputation or limb reconstructive surgery was not reported in this review. Review articles report persistent post-surgical pain after cancer surgery to be encountered in an estimate of 5% of surgical cases and to be underreported and underdiagnosed¹³; cancer-related NP in general is viewed as being common in adults.¹⁴

Two recent review articles of NP in children¹⁵ and specifically NP in children with cancer¹⁶ have emphasized the characteristics of NP as a component of chronic pain states, which is complex, can be of prolonged duration, and poorly responsive to currently available treatments. Few original investigations of NP in pediatric cancer are available, including NP under specific circumstances in pediatric oncology: pain after limb sparing,⁹ NP related to vincristine chemotherapy for acute lymphoblastic leukemia,¹⁰ and methadone therapy for NP in pediatric cancer patients.⁸

Our finding of high incidence of NP after definitive surgery of 81.6% is among the highest rates reported for NP after surgery. The concept of surgically induced NP has recently been introduced as a significant clinical problem, estimated to occur in 10–50% of individuals after common operations,¹⁷ especially related to transection, contusion, stretching, or inflammation of the nerves, and predictive factors for surgically induced NP have been evaluated.^{18,19} While data regarding pain post limb sparing are limited, phantom limb pain (PLP), the sensation of pain experienced in a limb that is no longer there, is a very common result of limb amputation²⁰ and has been better characterized. Sixty to 90% of amputees experience PLP at some point in their lifetime.²¹ The incidence of PLP is thought to be lower in children, and PLP has not been reported in patients younger than 4 years.²⁰ In a study of children and young adults (ages 6–27 years, of which 64% were younger than 18 years) with cancer-related surgical amputations, 64% suffered pre-amputation pain, 76% experienced PLP within the first year after amputation, and 10% experienced PLP at 1 year postamputation.²² Furthermore, in a subsequent study from the same group of 21 adolescents and young adults (ages 8–24 years) who underwent an amputation during the prior 6 years at our institution (2009–2015), 18 (85.7%) experienced PLP; of them, 38.9% still experienced PLP at 1 year postamputation. We attribute the high incidence of NP found in our study to the prospective design, which provides higher sensitivity in establishing the diagnosis as compared with retrospective studies. The active involvement of a specialized pediatric pain service may have also contributed to the high accuracy of diagnosis of NP. Furthermore, the diagnosis of NP was established early in our patient population, with 26 of 30 patients with NP being diagnosed during the first week postoperatively. This finding may be a reflection of the fact that in our practice we actively investigate for the presence of NP, with the intent of early diagnosis and specific treatment for NP. Of interest, the early diagnosis of NP directs attention to the possibility of acute NP related to acute nerve damage, which is implicated in development of chronic postsurgical pain.¹³ The duration of NP in our study group, of mean (SD) 6.5 weeks (7.2) (median 4.4, range 0.3–29.9), is

significant and for some patients it qualifies for the “true” definition of chronic pain as exceeding 3 months.

It is meaningful to note that our institutional approach to preventing NP after limb sparing or amputation is to initiate therapy with gabapentin 3–5 days preoperatively, a practice that is reflected by this study. A recent review article emphasizes that there is a critical time frame before and immediately after nerve injury during which interventions collectively described as “preventative analgesia” may reduce the incidence and severity of chronic NP.²³ Among such interventions, the perioperative use of gabapentinoids is in general suggested to be beneficial in reducing the incidence of persistent pain and reducing the pain scores.²³ The mean starting dose of 20 mg/kg/day reported in this prospective study is somewhat higher than the mean starting dose of 15.5 mg/kg/day, which we previously reported in our retrospective single-institution study (n = 498) of patients with NP related to chemotherapy for acute lymphoblastic leukemia.¹⁰ Consistent with the literature recommendations, we escalate the gabapentin dose regimen to 50 mg/kg/day before adding another line of therapy. In the context of neuropathic cancer pain, there is strong evidence from randomized controlled trials that the addition of gabapentin improves analgesia provided by opioid monotherapy^{24,25}; furthermore, treatment-related side effects are significantly less frequent with dual opioid and gabapentin therapy.²⁵ Similarly, the addition of both gabapentin and a tricyclic antidepressant to an opioid regimen was found to effectively manage neuropathic cancer pain by decreasing the total pain score and the paroxysmal pain episodes.²⁶ Comparative efficacy of amitriptyline and gabapentinoids was demonstrated in a randomized placebo-controlled study in neuropathic cancer pain.²⁷ In our institutional practice, methadone is added as a third line therapy for NP, starting with a low dose (0.1–0.2 mg/kg or 5–10 mg for adolescent patients every 8–12 h), to supplement the regimen of gabapentin and tricyclic antidepressant. In a retrospective review of 37 patients treated with methadone at our institution, the starting dose was 0.06–3.8 mg/kg/day (median 0.32 mg/kg/day).²⁸

The finding of similar pain outcomes for limb sparing and amputation (duration of NP, duration of NP medications administration, and dose regimens for gabapentin, amitriptyline, and methadone) may be the most striking contribution of our study. While the high incidence and persistence in time as well as the poor responsiveness to multiple therapies encountered with postamputation NP (PLP) are well established in the literature, there has been no prior evidence to indicate that the pain outcomes are profoundly similar between limb sparing and amputation. This finding leads to recommendations for clinicians to approach pain after limb sparing with the same preemptive and aggressive approach reserved for postamputation PLP, such as preoperative use of gabapentinoids and regional and neuraxial preemptive analgesia.

On the specific protocol for treatment of OS at our institution, cisplatin is administered during the weeks following definitive surgery for OS. This can be a contributing factor to NP after surgery, creating the context of a mixed source NP syndrome—both postsurgical and related to chemotherapy.

It has been suggested that many types of persistent postsurgical pain are associated with younger age,¹³ with an approximate 5% reduction in probability of developing chronic pain

with every year of increasing age.²⁹ These facts may explain the high incidence observed in our study, given the young median age in our study population.

Based on the findings of this study, we recommend that limb sparing patients, just like amputation patients, should be approached with increased vigilance regarding the high likelihood of postoperative NP. Recommended preemptive measures should include initiation of gabapentin therapy before surgery takes place. Medication regimens escalation should be expected in one third of patients, which may require addition of tricyclic antidepressant and possible methadone to the gabapentin regimen.

Acknowledgments

The authors thank the investigators from the collaborative institutions, Jennifer Reikes Willert, MD, and Hyunah Ahn, MD (Department of Pediatric Hematology/Oncology/Blood and Marrow Transplant, Rady Children's Hospital, San Diego, CA), and David M. Loeb, MD (Department of Pediatrics, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD), for data collection for five and two subjects, respectively, and Gisele Hankins, BSN, and Lane G. Faughnan, BSN, for data collection at St Jude, and Angela J. McArthur, PhD, ELS, for support with scientific editing. This study was in part supported by the American Lebanese Syrian Associated Charities (ALSAC).

ABBREVIATIONS

i.v	intravenous
NP	neuropathic pain
OS	osteosarcoma
OS08	Osteosarcoma 2008
PLP	phantom limb pain
SD	standard deviation

References

1. Ries, LAG., Smith, MA., Gurney, JG., et al. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995. National Cancer Institute, SEER Program; Bethesda, MD: 1999. p. 99-110. NIH Pub. No. 99-4649
2. Marina N, Gebhardt M, Teot L, Gorlick R. Biology and therapeutic advances for pediatric osteosarcoma. *Oncologist*. 2004; 9(4):422–441. [PubMed: 15266096]
3. Piano V, Verhagen S, Schalkwijk A, et al. Diagnosing neuropathic pain in patients with cancer: Comparative analysis of recommendations in national guidelines from European countries. *Pain Practice*. 2013; 13(6):433–439. [PubMed: 23279302]
4. Caraceni A, Portenoy R. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. *Pain*. 1999; 82:263–274. [PubMed: 10488677]
5. Bennett M, Rayment C, Hjermstad M, Aass N, Caraceni A, Kaasa S. Prevalence and aetiology of neuropathic pain in cancer patients: A systematic review. *Pain*. 2012; 153:359–365. [PubMed: 22115921]
6. van den Beuken-van Everdingen M, de Rijke J, Kessels A, Schouten H, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: A systematic review of the past 40 years. *Ann Oncol*. 2007; 18(9):1437–1449. [PubMed: 17355955]

7. Naleschinski D, Baron R, Miaskowski C. Identification and treatment of neuropathic pain in patients with cancer. *Pain Clin Updates*. 2012; 20(2):1–4.
8. Anghelescu D, Faughnan L, Hankins G, Ward D, Oakes L. Methadone use in children and young adults at a cancer center: A retrospective study. *J Opioid Manag*. 2011; 7(5):353–361. [PubMed: 22165034]
9. Anghelescu D, Oakes L, Hankins G. Treatment of pain in children after limb-sparing surgery: An institution's 26-year experience. *Pain Manag Nurs*. 2011; 12(2):82–94. [PubMed: 21620310]
10. Anghelescu DL, Faughnan LG, Jeha S, et al. Neuropathic pain during treatment for childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2011; 57(7):1147–1153. [PubMed: 21319291]
11. Simon T, Niemann C, Hero B, et al. Short- and long-term outcome of patients with symptoms of spinal cord compression by neuroblastoma. *Dev Med Child Neurol*. 2012; 54(4):347–352. [PubMed: 22329756]
12. Haroutiunian S, Nikolaisen L, Finnerup N, Jensen T. The neuropathic component in persistent postsurgical pain: A systematic literature review. *Pain*. 2013; 154(1):95–102. [PubMed: 23273105]
13. Cregg R, Anwar S, Farquhar-Smith P. Persistent postsurgical pain. *Curr Opin Support Palliat Care*. 2013; 7(2):144–152. [PubMed: 23591162]
14. Fallon M. Neuropathic pain in cancer. *Br J Anaesth*. 2013; 111(1):105–111. [PubMed: 23794652]
15. Howard R, Wiener S, Walker S. Neuropathic pain in children. *Arch Dis Child*. 2014; 99(1):84–89. [PubMed: 24114955]
16. Friedrichsdorf S, Nugent A. Management of neuropathic pain in children with cancer. *Curr Opin Support Palliat Care*. 2013; 7(2):131–138. [PubMed: 23635878]
17. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: Risk factors and prevention. *Lancet*. 2006; 367(9522):1618–1625. [PubMed: 16698416]
18. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: Risk factors and protective factors. *Expert Rev Neurother*. 2009; 9(5):723–744. [PubMed: 19402781]
19. Raja S, Jensen T. Predicting postoperative pain based on preoperative pain perception: Are we doing better than the weatherman? *Anesthesiology*. 2010; 112(6):1311–1312.
20. Pirowska A, Wloch T, Nowobilski R, Plaszcwski M, Hocini A, Menager D. Phantom phenomena and body scheme after limb amputation: A literature review. *Neurol Neurochir Pol*. 2014; 48(1): 52–59. [PubMed: 24636771]
21. Foell J, Bekrater-Bodmann R, Diers M, Flor H. Mirror therapy for phantom limb pain: Brain changes and the role of body representation. *Eur J Pain*. 2014; 18(5):729–739. [PubMed: 24327313]
22. Burgoyne L, Billups C, Jiron J, et al. Phantom limb pain in young cancer-related amputees: Recent experience at St Jude Children's Research Hospital. *Clin J Pain*. 2012; 28(3):222–225. [PubMed: 21785344]
23. Carroll I, Hah J, Mackey S, et al. Perioperative interventions to reduce chronic postsurgical pain. *J Reconst Microsurg*. 2012; 29(4):213–222.
24. Caraceni A, Zecca E, Bonezzi C, et al. Gabapentin for neuropathic cancer pain: A randomized controlled trial from the Gabapentin Cancer Pain Study Group. *J Clin Oncol*. 2004; 22(14):2909–2917. [PubMed: 15254060]
25. Keskinbora K, Pekel AF, Aydinli I. Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain: a randomized open trial. *J Pain Symptom Manage*. 2007; 34(2):183–189. [PubMed: 17604592]
26. Arai YC, Matsubara T, Shimo K, et al. Low-dose gabapentin as useful adjuvant to opioids for neuropathic cancer pain when combined with low-dose imipramine. *J Anesth*. 2010; 24(3):407–410. [PubMed: 20217150]
27. Mishra S, Bhatnagar S, Goyal GN, Rana SP, Upadhyay SP. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: A prospective randomized double-blind placebo-controlled study. *Am J Hosp Palliat Care*. 2012; 29(3):177–182. [PubMed: 21745832]
28. Anghelescu DL, Faughnan LG, Hankins GM, Ward DA, Oakes LL. Methadone use in children and young adults at a cancer center: A retrospective study. *J Opioid Manag*. 2011; 7(5):353–361. [PubMed: 22165034]

29. Macrae W. Chronic post-surgical pain: 10 years on. Br J Anaesth. 2008; 101(1):77–86. [PubMed: 18434337]

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FIGURE 1.
Flowchart: patients after definitive surgery for extremity OS

FIGURE 2.
Duration of NP in patients receiving NP medications (N = 26 patients, 27 surgeries)

TABLE 1

Characteristics of patients treated with definitive surgery for extremity OS: limb sparing versus amputation

Characteristic No. of patients (%)	Amputation group N = 12 (31.6)	Limb sparing group N = 26 (68.4)	Entire study group N = 38
Age			
Median (min, max)	10.5	13.7	13.3 (6.8, 20.2)
<13 years	8	12	18 (49)
13 years	4 *	16 *	19 (51)
Sex			
Male	6 *	14 *	19 * (51)
Female	6	12	18 (49)
Race			
White	9 *	14 *	22 * (59)
Other	3	12	15 (41)
Stage			
Localized disease	8	18	26 (70)
Metastatic disease	4 *	8 *	11 (30)
Primary site			
Lower extremity	6 *	25 *	30 (81)
Upper extremity	5	1	6 (16)
Pelvis	1	0	1 (3)

* One patient had two surgeries (limb sparing and amputation)

TABLE 2

Incidence and duration of NP and NP medication requirements in patients treated with definitive surgery for extremity OS: amputation versus limb sparing [N = 38 surgeries (37 patients)]

	Amputation group (N = 12)	Limb sparing group (N = 26)	Entire study group (N = 38)	P value
NP incidence	N = 10/12 (83%)	N = 21/26 (81%)	N = 31/38 (81.6%)	
Duration of NP (weeks)	N = 10	N = 21	N = 31	
Median (range)	3.5 (0.9–12.9)	4.9 (0.3–29.9)	4.4 (0.3–29.9)	
Mean (SD)	4.9 (4.0)	7.2 (8.4)	6.5 (7.2)	0.893
Duration of NP medication (weeks)	N = 10	N = 17	N = 27	
Median (range)	6.5 (3–30)	7 (1.7–29.9)	7 (1.7–30.0)	
Mean (SD)	9.0 (8.0)	9.8 (8.4)	9.5 (8.1)	0.990
Gabapentin starting dose (mg/kg/day)	N = 10	N = 17	N = 27	0.990
Mean (SD)	23.6 (20.1)	18.2 (9.7)	20.2 (14.3)	
Median (range)	12.8 (7.1–58.0)	14 (6.4–38.0)	13.6 (6.4–58.0)	
Gabapentin max dose (mg/kg/day)	N = 10	N = 17	N = 27	
Mean	48.0 (23.0)	41.3 (14.4)	43.8 (17.9)	
Median (range)	53.0 (11.0–81.0)	42.0 (11.0–63.0)	42.0 (11.0–81.0)	0.327
Amitriptyline start/max dose (mg/kg/day)	N = 5	N = 4	N = 9	
Mean	0.5/0.7	0.5/0.5	(0.5/0.7)	
Methadone start/max dose (mg/kg/day)	N = 4	NA	N = 4	
Mean	0.3/0.3		(0.3/0.3)	

NA, not applicable.