

## Surgical Site Infections in Treatment of Musculoskeletal Tumors: Experience from a Single Oncologic Orthopedic Institution

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### Abstract

**Objective:** Limb-sparing surgery is the mainstay treatment for musculoskeletal tumors thanks to advances in surgical techniques, imaging modalities and multimodal therapies. As patients survive longer, plastic reconstructive procedures and revision surgery are increasingly required after tumor excision. Infection rate is reported to be up to 20% after prosthetic replacement and 30-44% after pelvic resection. The purpose of this study was to investigate the incidence of surgical site infections (SSIs), identifying the causative microorganisms related to specific surgical procedures and significant risk factors for SSIs.

**Methods:** We retrospectively reviewed 723 interventions performed between 2009 and 2015 for oncological conditions. Non neoplastic lesions, aseptic wound complications, non-skeletally mature patients were excluded. Standardised antibiotic prophylaxis was used for different surgical procedures and maintained until removal of surgical drains.

**Results:** Without considering tumor types and surgical sites, the overall infection rate was 8.7% (63/724). Infection occurred in prosthetic reconstruction with an incidence rate of 7.8%, whereas almost half of patients having undergone pelvic surgery got infected and about 20% of patients with spinal surgery and amputations were infected. Pelvic location, malignancy and radiotherapy were related to a major risk of SSI. The causative pathogens were detected in all examined cases. The most frequent pathogens detected by culture included *Staphylococcus aureus* (27 cases, 47.4%) and *S. epidermidis* (10 cases, 17.5%). Among the *S. aureus* cases, 10/27 cases (37%) were methicillin-resistant *S. aureus* (MRSA). Sixty-three out of 130 microbial isolations (47.7%) were nosocomial ALERT organisms.

**Conclusion:** Oncologic orthopedic surgery is burdened by frequent and challenging SSIs because of extensive soft tissues dissection, long operative times and poor skin conditions. Patients are immunosuppressed and often have concomitant comorbidities predisposing to SSIs. Monitoring of local bacterial aetiology of SSIs could help orthopedic oncologic specialized centres in achieving the optimisation of antibiotic prophylactic regimens.

**Keywords:** Surgical site infections; Bone and soft tissues tumors; Epidemiology; Risk factors; Orthopedic oncologic surgery; Microbial isolations; Tumor prostheses

### Introduction

Limb-sparing surgery is the mainstay for treatment of musculoskeletal tumors, due to advances in surgical techniques, imaging examinations and multimodal therapies [1-4]. Reconstruction requires prosthetic implants, allograft, nails, plates or other metallic devices, vascular procedures and plastic surgery [4]. Moreover, as patients survive longer, revision surgery is increasingly required for implant failure, loosening or biomaterial overuse. Consequently, improvements in limb-salvage and prognosis have made surgical site infection (SSI) one of the most serious and discussed complications of musculoskeletal tumor surgery [2,3]. The hazard of infection can have devastating complications for all the main surgical procedures used in musculoskeletal oncology: bone resection and prosthetic

reconstruction, spinal surgery, osteosynthesis with plates, nailing, acrylic cement after curettage, allograft reconstructions; also other procedures without reconstruction such as soft tissue excisions and amputations or disarticulations. Surgical site infections are a main concern in oncologic orthopaedics and have become as challenging as recurrence, as reflected by a great number of literature reviews, monothematic meetings, multicentre prospective studies [5-8]. Literature over the last decade shows an urgent need to focus on epidemiology, early diagnosis, antimicrobial coverage for metal implants, identification of risk factors and, most of all, on the urgent need to define guidelines for antibiotic prophylaxis [7-9].

The aim of the study was to investigate the frequency and aetiology of SSIs in a single specialized Oncologic Orthopedic Center, determining whether infection is associated with particular risk factors and to compare the preliminar findings to the current literature.

## Incidence and risk factors for SSIs: Background from literature

Infection rate in tumor megaprotheses is reported to be 8-35% for primary implants, 30%-43% after revision surgery and up to 22% for lower-extremity endoprosthetic reconstruction, with an average rate of 8.6-9.5% [8-12]. Infection rate in pelvic resection is 14% but increases up to 40% when it is followed by reconstruction [13,14]. The infection rate associated with excision for soft tissues sarcomas is 6-15% [3,15]. Patients affected by sarcomas have several potential risk factors for SSIs owing to tumour malignancy, depth and invasion, immunosuppression and iponutrition from neoadjuvant chemotherapy, radiotherapy, large incisions, wound complications, additional surgical procedures, along with other comorbidities such as anaemia, corticosteroids or diabetes (Table 1) [15-18].

Malignancy	Prosthetic implants
Prior site irradiation	Trunk, pelvic and hip localization
Preoperative anemia	Prolonged hospitalization
Immunosuppression	Hematoma
Chemotherapy	Anticoagulation
Repeated accesses in hospital	Soft tissues necrosis
Inadequate antibiotic prophylaxis	Wound failure
Prolonged operative time	Drains

**Table 1:** Independent risk factors associated with SSIs in musculoskeletal cancer patients [5,15-18].

From a retrospective analysis reported by Morii et al. [3] on 84 patients affected by soft tissues sarcomas, no association was actually detected between SSIs and age, chemotherapy, tumor grading or size or plastic surgery. Saddegh and Bauer [15] reviewed 103 patients with soft tissue sarcoma managed without adjuvant therapy from 1987 to 1990, finding a significant association between wound complications in deep tumors and age, tumor size and long operating time. Larger intraoperative blood loss and a trunk location were identified as statistically significant risk factors for deep infections from both aforementioned studies. Gradl et al. [17] recently reported a review of 1521 surgical procedures for bone and soft tissues tumors, finding eight independent risk factors: body mass index, age, preceding surgery, infection at another site, preexisting implants, tumor malignancy, hip location, duration of surgery. Although many different antibiotic regimens are used for prophylaxis to prevent SSIs, current practice among orthopedic oncologic surgeons seem to be in favour of long term duration therapy, from 2 to several postoperative days or at least until removal wound drains, and wide coverage against both Gram positive and negative bacteria [7-9].

## Materials and Methods

All surgical activities performed at the Oncologic Orthopedic Unit of "Regina Elena" National Cancer Institute between January 2009 and December 2015 for primary malignant or benign, bony and soft tissue lesions and metastases were retrospectively reviewed. All non-previously surgically treated lesions, revisions for prosthetic aseptic loosening and re-excision for local recurrences were included. Non neoplastic lesions, aseptic wound complications, and non-skeletally

mature patients were excluded. Data from each medical record were collected, including histology, age, location of surgery, surgical intervention, adjuvant treatments and other perioperative conditions as potential predictor of infection [14-17]. All surgeries were performed by the same team of surgeons. The same patterns of preoperative intravenous antibiotics were used for specific modalities of surgery (Table 2) and continued until wound drain removal (for 5 days in case of pelvic surgery, 2-3 days for all other procedures). Surgical site infections were identified in accordance with the Guidelines for Disease Control and Prevention Centers [19] as infection occurring at the site of surgery within 30 days from the operative date or up to 1 year if implant was inserted and the infection appears in relation to the surgery.

First generation cephalosporin 1 g × 3 + aminoglycoside (tobramycin 100 mg × 2)	Hemipelvectomy Hip disarticulation Sacrum, pelvic resection Spinal surgery
Glycopeptide (teicoplanin 10-12 mg/kg) + aminoglycoside (amikacin BBK8 500 mg only for 24 h)	Extremity long-bones resection Prosthetic reconstruction Allografts
First generation cephalosporin 1 g × 3	Biopsy Soft tissues excision Fibula, scapula, clavícula resection Osteosynthesis (nails, plates, screws)

**Table 2:** Different regimens of antibiotic prophylaxis adopted based on specific surgical procedures

All SSI diagnoses were detected from the register of Nosocomial Infection Control Group of our Institute and were compared with the medical records from clinical examination, radiographic studies and laboratory results including erythrocyte sedimentation rate, C-reactive protein, white blood cell count in joint fluid analysis. Once discharged, patients were followed up at 1 month, 3 months, 6 months and at 1 year postoperatively, prolonged on the basis of the most appropriate timing of follow up for the neoplasm or until patient death. The causative microorganisms were isolated from positive wound swabs or joint bacterial culture. No patients were recalled specifically for this study; all data were obtained from the medical records. Descriptive statistics were calculated. Calculations of the relative risk were performed to assess independent risk factors for SSIs.

## Results

A total of 724 cases were evaluated for the inclusion of this study. Patient characteristics are reported in Table 3. Without considering tumor types and location, 63 of these 724 cases were detected to have a SSI, the overall infection rate being 8.7%. Among recorded comorbidities and adjuvants treatments currently related to SSI, prior or adjuvant radiotherapy, malignant histotype and hip and pelvic location showed a higher relative risk (Figure 1). Infection rate for each surgical procedure is reported in Table 4. The causative pathogens were detected in all cases examined. Most infections were monomicrobial (34/63), and 29 were polymicrobial. A total of 130 microbial isolations were found in the 63 infected patients (mean 2.06 for each patient, range 1-8).

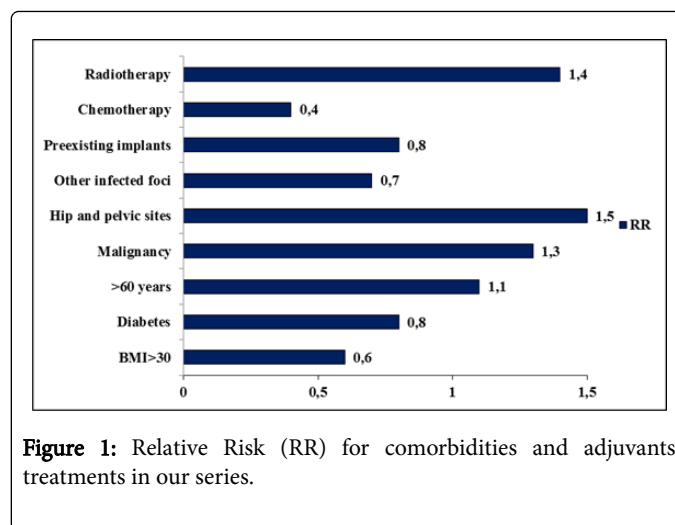
Characteristics	Tumor origin and Location	n° patients
Surgical procedures		724
Patients age (mean)		14-85 yr (52.5 yr)
Tumor origin:	Primary Bone	368
	Soft-tissues	229
	Metastasis	126
Location:	Spine	26
	Pelvis	41
	Extremities	656
Risk factors for SSI [14-17]: BMI>30 Diabetes >60 years Malignancy Hip and pelvic sites Other infected foci Preexisting implants		280/724
Chemotherapy		365/724
Radiotherapy		156/724

**Table 3:** Main case series' characteristics

The most frequent pathogens detected by culture included *Staphylococcus aureus* (27 cases, 47.4%) and *S. epidermidis* (10 cases, 17.5%). Among the *S. aureus* cases, 10/27 cases (37%) were methicillin-resistant *S. aureus* (MRSA). Sixty-three of 130 microbial isolations (47.7%) were nosocomial ALERT organisms as MRSA, Enterobacteriaceae-producing extended-spectrum  $\beta$ -lactamases (ESBL), vancomycin-resistant *Enterococci* (VRE), *Acinetobacter baumannii*. Table 5 shows the microbial isolations for different oncologic surgical procedures.

Surgical procedure	n° patients	n° SSIs	SSIs rate
Extremity bone resection + prosthetic reconstruction	128	10	7.8%
Pelvic resection ± prosthetic reconstruction	36	17	47.2%
Soft-tissues tumors excision	218	13	6%
Extremity and pelvic + bone allograft reconstruction	105	10	9.5%
Spinal surgery	43	8	18.6%
Amputations	54	10	18.5%
Nailing	56	0	0%
Embolization, radiofrequency ablation	74	1	1.4%

**Table 4:** SSIs rates specifically distinguished for different surgical procedures.



**Figure 1:** Relative Risk (RR) for comorbidities and adjuvants treatments in our series.

## Discussion

The vulnerability of patients with bone and soft tissue tumors to SSIs goes beyond wound closure. Concern related to SSIs, already well-known in conventional arthroplasty or osteosynthesis for degenerative or traumatic conditions, has largely increased in musculoskeletal tumors surgery due to a multitude of scarcely modifiable risk factors related to: 1) the complexity of surgical procedures with long operative times, wide resections with sacrifice of bone and soft tissues; 2) poor conditions of patients who are usually debilitated from the cancer itself and chemotherapy. Patients are immunosuppressed and often have comorbidities predisposed to poor local skin conditions and wound failure [3,4,15]. Infection is a major complication of oncologic surgery: it represents the most common failure of tumor endoprostheses, leading to amputation in 20% of cases. It undermines limb function and patients' health conditions, it can delay or even prevent adjuvant treatment, thus seriously affecting the prognosis and life expectancy of cancer patients.

Similar to the data present in literature, we found that infection occurred in prosthetic reconstruction with a 7.8% incidence, in 50% of patients undergoing pelvic surgery and about 20% of patients after spinal surgery and amputations. Observational investigation on risk factors showed that pelvic site, malignant tumor and radiotherapy had a direct correlation to the development of infection. Treatment for the SSI cases observed is not discussed here because the purpose of the study was only limited to an epidemiological investigation on etiology. Microbial isolations were investigated for each modality of surgical intervention. To our knowledge, this is the first study that focuses on the correlation between a surgical technique and the causative microorganisms in surgical treatment of sarcomas.

*Staphylococcus epidermidis* and *S. aureus* account for most infections of permanently implanted material, thus prophylaxis is mainly against *staphylococci* [1-3,6,12]. However, having knowledge of local epidemiological data is fundamental in order to carry out the most effective antibiotic prophylaxis [7-9]. Thus, the choice on the most appropriate antibiotic should be done not only on the basis of literary reports about etiology of periprosthetic infections, but also on considering the features of local ecosystem in terms of antibiotic resistance and decisional politics from single medical institutes depending on individual plan of epidemiological surveillance.

Surgical procedures	MSSA MRSA	<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>	<i>Enterococcus group D</i>	<i>Enterobacter cloacae</i>	<i>Proteus mirabilis</i>	<i>Psuedomonas aeruginosa</i>	<i>Acinetobacter baumannii</i>
Extremity bone resection + prosthetic reconstruction	4 23.5%	4 23.5%	3 17.6%	0 0%	1 5.9%	2 10.5%	3 17.6%	2 11.8%
Soft-tissues excision	5 31.3%	4 25%	0 0%	2 12.5%	2 12.5%	0 0%	1 6.3%	2 12.5%
Amputations	6 27.3%	3 13.6%	2 9.7%	5 22.7%	2 9.1%	3 12%	3 13.6%	1 4.5%
Spinal sugery	4 57.1%	2 28.6%	1 14.3%	0 0%	0 0%	1 12.5%	0 0%	0 0%
Pelvic resection ± prosthetic reconstruction	7 18.4%	6 15.8%	7 18.4%	8 21.1%	2 5.3%	3 7.3%	5 13.2%	3 7.9%
Extremity and pelvic resection + bone allograft reconstruction	5 37.5%	3 21.4%	7 18.4%	1 7.1%	1 7.1%	0 0%	4 28.6%	0 0%

**Table 5:** Absolute value and incidence rate of microbial isolations in different surgical procedures.

*S. epidermidis* is traditionally reported to be dominant over *S. aureus* in periprosthetic infection [2,6,12]. In last ten years, the incidence of SSIs from *S. aureus* has increased from what was reported previously [1,8,18]. It may be partially explained by postoperative use of antibiotics and drains >24 hours, extension of surgical fields with soft tissue damage [18]. Large defect of quadriceps muscle and knee extraarticular resection, diabetes mellitus, lack of a gastrocnemius flap in the tibia and prolonged operation time are especially related to MRSA infection [5,18]. Different to what is reported in literature our results show that a high rate of infection from Gram negative and difficult-to-treat bacteria was found in joint prosthetic replacement after bone tumor resection of the extremities.

Already 20 years ago, Saddegh and Bauer [15] assessed the trunk and lower extremity as potential risk factors for the development of wound complications. Although anatomic location may be an independent risk factor for infection, distinction among surgical procedures is not a simple topographic distribution [17]. In our opinion, the affected site can be useful in stratifying specific surgical-related factors that could be a predictive indicator for the infection risk. In pelvic surgery, the high complication rate is attributed to the wide dead space after soft tissue excision, the proximity of rectal and urinary tract and long operative time. Wide periacetabular defects or massive reconstruction with prostheses or allograft implanted through a large wound are other contributing factors [10,16]. In surgery for soft tissue tumours, infection is related to large excision, sacrifice of even healthy tissues in order to guarantee wide margins, haematomas or sieromas and radiotherapy. Infections after osteosynthesis are less frequent but the incidence increases with open reduction, curettage and scarce tissue coverage as in tibial location. Low extremity amputations and hip disarticulations can be at risk of infections similarly to pelvic surgery especially in case of previously irradiated sites, lack of adequate bone stump coverage, complicated wounds with necrosis, eschars and consequently prolonged hospitalisation for medications and/or surgical wound revisions [3,4,16].

Gram negative nosocomial widespread is changing the scenario of orthopedic infections and patients affected from musculoskeletal cancer are at particularly high risk from colonization from

multiresistant organisms, in all pre, intra- and postoperative periods [18]. Prosthetic surgery for bone tumors is usually done in highly-specialized centers where multiresistant germs are selected. The issue of SSIs troubles the oncologic field because it involves “frail” cancer patients and an equally “poor” surgery due to its complexity, extensive dissection, long and repeated operative times. Moreover, the inappropriate use of antibiotics along with migratory streams and nosocomial contaminations has selected, especially in the last decade, multiresistant germs.

## Conclusion

Despite limitations and rarity of musculoskeletal tumors, further investigations are required. Our experience highlights the importance of an interdisciplinary team, involving orthopaedics, microbiologists, infectivologists, anaesthesiologists, and oncologists. Antibiotic prophylactic guidelines are still lacking in terms of molecules, dosage and duration [7-8]. Identification and stratification of patients at risk for multidrug-resistant colonization are fundamental, guidelines are expected, and antibiotic therapy should be appropriate for each single, specific case. Monitoring of local bacterial aetiology of SSIs could help orthopedic oncologic specialized centres in achieving the optimisation of antibiotic prophylactic regimens.

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