Perioperative Infection Rate in Patients with Osteosarcomas Treated with Resection and Prosthetic Reconstruction

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Abstract

Background The incidence of perioperative infection after segmental tumor endoprosthetic replacement in previous reports varies from a high of 7.4% to a low of 2.6%. Appropriate antibiotic use for this group is unknown and controversial, whereas the relationship of antibiotic use and perioperative infection is unclear.

Questions/purposes We determined the incidence of perioperative infection in patients with osteosarcoma treated with segmental prosthetic replacement using a standard perioperative antibiotic regimen and the incidence of late infections and wound complications.

Patients and Methods We retrospectively reviewed the records of 53 patients with osteosarcoma undergoing segmental prosthetic replacements from 1993 to 2008. There were 30 males and 23 females ranging from 10 to 78 years

of age. All patients were given intraoperative antibiotics (intravenous cefazolin), continued for 3 days postoperatively and then given orally for 5 days. Patients who were allergic to penicillin or cefazolin were given vancomycin followed by clindamycin. A perioperative infection was defined as a deep infection within 2 months after prosthetic reconstruction. The minimum followup was 1 year (range, 1–15 years).

Results We identified one confirmed perioperative prosthetic infection (1/53; 1.9%) (*Enterobacter cloacae* and methicillin-resistant *Staphylococcus*) in a 78-year-old woman after proximal tibial replacement, gastrocnemius flap, and skin graft. Her infection was controlled with débridement, drainage, and intravenous antibiotics. Three patients had late infections, two of which were culture negative. Four patients had wound complications that required further surgery.

Conclusion The antibiotic regimen we used is longer than that recommended for patients having routine total joint arthroplasty. Its appropriateness will require comparison with alternate regimens, including those of shorter duration.

Level of Evidence Level IV, therapeutic study. See the Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution has approved or waived approval for the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles for research.

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Introduction

During the last 20 years, the clinical outcome for patients with osteosarcoma has improved owing to developments in neoadjuvant chemotherapy, imaging, and surgical techniques. Most patients have been treated with limb salvage surgery instead of amputation to retain function and improve their quality of life. The reconstruction methods include allografts, tumor endoprostheses, and allograft-prosthetic

composites. Tumor endoprostheses have been widely used because they offer immediate postoperative stability, rapid rehabilitation, and off-the-shelf availability [29, 30]. However, deep infection is one of the most important factors negatively affecting tumor endoprosthetic survival. A review of the literature [1–3, 5–10, 12, 14–17, 19, 21, 22, 25, 26, 28–30] showed higher infection rates of tumor endoprostheses, from 2.2% [28] to 19.5% [21] compared with 1.1% for conventional THA [4] and the latest reported 0.9% for conventional TKA [13]. Most prior studies of tumor prostheses include various kinds of tumors such as Ewing's sarcomas, osteosarcomas, soft tissue sarcomas, metastatic carcinomas, and giant cell tumors. These different diagnoses may affect the perioperative infection rate. One study of endoprosthetic reconstruction of 78 patients with osteosarcoma reported a 2.6% infection rate [5]. Several additional studies [9, 10, 14, 17, 26] have reported rates of perioperative infection from 2.6% to 7.4% for patients undergoing tumor endoprosthetic reconstruction, although they included various kinds of tumors and used various criteria for early (perioperative) infection.

For conventional arthroplasty, perioperative antibiotics are widely used to reduce infection, and the low infection rate of conventional arthroplasty presumably has been facilitated by the use of perioperative antibiotic prophylaxis [11]. The AAOS recommendations suggest that preferred prophylactic antibiotics (cefazolin and cefuroxime) should be administered within 1 hour before skin incision, and should be discontinued within 24 hours of the end of surgery [23]. However, whether antibiotics for patients having tumor endoprosthetic replacement should be used in the same way as recommended by the AAOS for patients undergoing conventional arthroplasty is unclear.

We therefore determined the incidence of perioperative infection in patients with osteosarcoma treated with endoprosthetic reconstruction and our long-standing perioperative antibiotics regimen and the incidence of late infections and wound complications.

Patients and Methods

We retrospectively reviewed all 53 patients with osteosarcoma treated with wide resection and endoprosthetic reconstruction from 1993 to 2008. Patients treated with wide resection without reconstruction or with allograft reconstruction or amputation were excluded from this study. Among the 53 patients, there were 42 with conventional-type osteosarcoma, six with parosteal osteosarcoma, three with radiation-induced osteosarcoma, one with Pagetoid osteosarcoma, and one with multicentric osteosarcoma. All diagnoses were proved histologically. The population of this study consisted of 30 males and

23 females ranging in age from 10 to 78 years (mean, 31.4 years; median, 22 years); the Musculoskeletal Tumor Society stages were IB (six), IIB (39), and IIIB (eight). Twenty-six of the 53 patients (49%) were alive at the last followup; among these, 24 were alive with no evidence of disease and two were alive with disease. The other 27 patients died of disease. Kaplan-Meier analysis showed that the overall survival of the whole study group was 57.8% at 5 years followup. The minimum followup was 1 year (median, 8 years; range, 1–15 years). No patients were lost to followup. No patients were recalled specifically for this study as all data were obtained from medical records and radiographs. We had prior Institutional Review Board approval.

The pathologic tumor types included 41 osteoblastic, four chondroblastic, six parosteal (including one dedifferentiated parosteal), one fibroblastic, and one giant cell rich-type. Fifty-two patients had primary osteosarcomas and one had recurrent parosteal osteosarcoma. The tumor sites included: 34 distal femur, 11 proximal tibia, four proximal femur, two humerus, one proximal radius, and one multicentric location, including the distal femur and sacrum. Forty-six patients had two to six cycles of preoperative chemotherapy after biopsy; 42 patients underwent one to six cycles of postoperative chemotherapy. Twenty-one of the 46 patients treated with preoperative chemotherapy (45.7%) had cytopenia, leukopenia, neutropenia, or anemia, even though growth factors were routinely used. Two patients had port infections, and one patient had *Staphylococcus aureus* septicemia.

Definitive surgery was performed within 4 weeks after completion of the preoperative chemotherapy. All definitive surgery was performed by surgeons wearing body exhaust suits in laminar airflow operating rooms during the 15-year period of the study. Fifty-two patients had intra-articular resections and one had an extra-articular resection. Hinged TKAs were performed in 45 patients with osteosarcoma around the knee, one patient with osteosarcoma in the proximal tibia underwent hinged TKA with allograft tendon reconstruction, four patients had proximal femur replacement with a bipolar prosthesis, one patient underwent shoulder hemiarthroplasty, and one patient had total elbow arthroplasty and contiguous shoulder hemiarthroplasty for osteosarcoma in the whole humerus. One patient underwent proximal radius replacement with a prosthesis and allograft. A gastrocnemius flap was used in three of 11 patients with osteosarcoma in the proximal tibia. Tobramycin-impregnated cement was used in only two patients. All prostheses were from Stryker-Howmedica Osteonics Inc (Rutherford, NJ, USA). Cemented prostheses were used in 48 patients and uncemented prostheses were used in four. An expandable distal femoral replacement prosthesis was used in one patient.

All patients were given perioperative antibiotics. During the 15 years from 1993 to 2008, we used the same antibiotic regimen for patients undergoing tumor prosthetic reconstruction. The regimen consisted of cephalosporins (1 g) given intraoperatively. These were continued intravenously for 3 days postoperatively and then given for an additional 5 days orally. Patients with a history of allergy to penicillin or cephalosporins were given vancomycin (1 g) intraoperatively, which was continued for 3 days postoperatively and then changed to clindamycin for 5 days orally. Drainage tubes were used routinely and remained in place for 3 days after surgery.

All patients were followed every 3 months for the first 2 years with radiographs and MRI of the tumor site and CT of the chest. This regimen was continued every 6 months until 5 years after surgery and once per year until 10 years after surgery. Physical examinations were performed at each visit.

A wide variety of definitions have been used to define periprosthetic infections for conventional and tumor arthroplasties [15, 20, 24, 27]. We defined periprosthetic infection as follows: an infection that occurs following definitive prosthetic surgery involving the joint and/or bone related to the site of the operation with any other tissues, and meeting at least one of the following criteria: (1) purulent drainage from a surgical drain extending into the joint; (2) purulent material in a joint; (3) positive growth of organisms in aseptically obtained swab/tissue from the joint/bone. These criteria were modified from a reported definition of a bone/joint infection in a study of infection of hip arthroplasties [24]. Time zero was defined as the date of the primary prosthetic surgery. A perioperative infection was defined as a deep infection within 2 months after prosthetic reconstruction. A late infection was defined as an infection that occurred later than 2 months after prosthetic surgery.

We used SPSS 10.0 (SPSS Inc, Chicago, IL, USA) for the Kaplan-Meier analysis.

Results

We identified one perioperative prosthetic infection (1/53; 1.9%). This occurred in a 78-year-old woman after proximal tibial replacement, gastrocnemius flap, and skin graft. *Enterobacter cloacae* and methicillin-resistant *Staphylococcus* grew on the culture from the initial débridement. This was treated with débridement, drainage, and intravenous antibiotics. This patient died 11 months after surgery with no additional infection.

Three patients experienced late infections. One 68-year-old male patient underwent pacemaker placement, but the pacemaker became infected and was changed. He had a late

infection as evidenced by purulent material in the joint 14 months after a hinged TKA for a right proximal tibia osteosarcoma and 2 months after the pacemaker was changed. The infection was treated with an arthroscopic washout and antibiotics. The culture was negative and the infection was controlled. A second patient had a late infection 4 weeks subsequent to a human bite to the leg and 52 months after hinged TKA for a left distal femur osteosarcoma. The patient's knee infection was treated with débridement and antibiotics; however, revision for subsequent loosening was performed 22 months later, at which time cultures were negative. A third patient had a late infection develop after open quadricepsplasty for stiffness of the prosthetic knee 9 months after hinged TKA with an expandable prosthesis for a right distal femur osteosarcoma. *Staphylococcus aureus* grew in the culture specimen of the knee aspirate. This was treated with open débridement, washout, and antibiotics, but the prosthesis loosened and was revised 19 months later with no further infectious sequelae.

Four patients experienced wound complications requiring repeat surgery during the perioperative period. These complications included wound dehiscence in three patients and hematoma and dehiscence in one patient. All underwent débridement and closure. All four patients had joint culture during reoperations with no bacterial growth and no subsequent evidence of infection. During the débridement and closure, the patients were given intraoperative antibiotics that were continued intravenously for 3 days and then oral antibiotics for 5 days.

Discussion

The incidence of perioperative infection after segmental tumor endoprosthetic replacement varies from 2.6% [17] to 7.4% [26] in previous reports, which is much higher than that for conventional arthroplasty [4, 13]. This may be attributable to many factors including immunosuppressive effects of preoperative chemotherapy, longer duration of surgical procedures, larger dead space after tumor resection, and lack of soft tissue coverage. Perioperative infection is an especially severe problem in patients with sarcoma as it contraindicates or retards postoperative chemotherapy and may have a negative impact on the prognosis in patients requiring such chemotherapy. Some studies have focused on perioperative infections [9, 10, 14, 17, 26] and perioperative antibiotic use [2, 3, 5, 15, 18, 21, 25, 26, 29, 30] after tumor endoprosthetic reconstruction. However, appropriate antibiotic use for patients having tumor prosthetic surgery is unknown and remains controversial [5, 7, 15, 18, 21, 25, 29]. We determined the incidence of perioperative infection in patients with osteosarcoma treated with segmental prosthetic replacement using a standard perioperative

Table 1. Literature review of perioperative infection (early infection)

Study (early)	Study period	Sample size	Tumor types	Site of prosthetic reconstruction	Incidence of perioperative (early) infection (%)	Criteria or reports of perioperative infection (followup)
Guo et al. [9]	1997–2005	104	OS, GCT, MFH, CS, Ewing's, other	DF, PT	6.7	Within 1 year
Sharma et al. [26]	1989–2004	135	Bone and soft tissue metastasis	DF, PF, PH, PT, DH	7.4	Within 3 months
Kinkel et al. [17]	1995–2005	77	OS, MFH, CS, GCT, other	Femur, tibia	2.6	Within 3 months
Jeon et al. [14]	1979–1994	40	OS, MFH, MGCT, CS, Ewing's, FS, LM	PT	5	Within 6 months
Current study	1993–2008	53	OS	DF, PT, PF, humerus PR, multicentric	1.9	Within 2 months

OS = osteosarcoma; GCT = giant cell tumor; MFH = malignant fibrous histiocytoma; CS = chondrosarcoma; Ewing's = Ewing's sarcoma; MGCT = malignant giant cell tumor; FS = fibrosarcoma; LM = leiomyosarcoma; DF = distal femur; PT = proximal tibia; PF = proximal femur; PH = proximal humerus; DH = distal humerus; PR = proximal radius.

antibiotic regimen and the incidence of late infections and wound complications.

This study has several limitations. First, we studied only one antibiotic regimen. A study of a single regimen cannot determine whether another regimen, including a shorter one, would produce similar rates. Second, we believe it is important to distinguish perioperative infections (infections occurring within 2 months after prosthetic reconstruction) from those occurring over long periods of time. We suspect those occurring much later are not the result of residual surgical infection which became active. All three of the patients with late infections had other sources to explain the infections. Third, our definition of infection would allow a diagnosis with only a positive culture, which could result from contamination. However, the only patient with a perioperative infection had a positive culture and the two organisms grown would unlikely be contaminants. Fourth, only one patient had a perioperative infection, which made it impossible to explore factors potentially contributing to this complication.

We identified one patient (1.9%) with a confirmed perioperative infection. Numerous studies [9, 10, 14, 17, 26] have reported perioperative (early) infection rates after tumor endoprostheses from 2.6% to 7.4%. However, the criteria of early infection varied from infections occurring within 3 months [10, 17], or within 6 months [14], to infections within 1 year after definitive surgery [9]. Without consideration of tumor types and surgical sites, the 1.9% (1/53) perioperative infection rate in our study is lower than the 7.4% early infection rate (within 3 months after surgery) reported in one study [26] with shorter duration of antibiotic use (2 days versus 8 days in our study). However, our perioperative infection rate for tumors at the knee of 2.2% (1/45) is similar to the 2.6%

(2/77) early infection rate reported in another study [17]. Collectively, the incidence of perioperative infection after tumor endoprosthetic replacement varied from a high of 7.4% [26], to a low of 1.9% for our patients with osteosarcoma treated with our current perioperative antibiotic regimen (Table 1). Other studies reported their perioperative antibiotic regimen and deep infection rate after tumor endoprosthetic reconstruction, but did not focus on perioperative (early) infection [5, 7, 15, 21, 25, 29] (Table 2). Perioperative antibiotic use varies among studies reporting tumor endoprosthetic reconstruction [2, 3, 5, 15, 18, 21, 25, 26, 29, 30]. Although the antibiotic regimen we used is longer than those reported in most studies focusing on tumor endoprostheses [5, 15, 21, 25, 26], it is difficult to draw any firm conclusions based on these studies, because of different inclusion criteria. Multicenter prospective randomized studies would likely be required to determine whether prolonged perioperative antibiotic use decreases perioperative infections in this population. Also, studies with larger sample sizes might identify risk factors for perioperative infections in patients with osteosarcoma with limb salvage and endoprosthetic reconstruction.

The incidence of perioperative infections after tumor resection and segmental prosthesis replacement have varied from 1.9% (our study) to 7.4% [26] in patients with osteosarcoma. Many factors may be related to deep infections in these populations and little data exist concerning appropriate antibiotic use for this group. The antibiotic regimen we used is longer than that reported in most studies focusing on tumor endoprosthetic replacement. However, further study would be required to determine whether longer prolonged antibiotic reduces the rate of perioperative infections in this population.

Table 2. Literature review of perioperative antibiotic use and deep infection rate for tumor endoprosthetic reconstruction

Study	Study period	Sample size	Tumor types	Site of prosthetic reconstruction	Perioperative antibiotic use	Incidence of deep infection
Jey's et al. [15]	N/A	1264	N/A	T, F, H, P	Preoperative IV dose of a cephalosporin	11%
Myers et al. [21]	1977–2002	194	OS, Ewing's, CS, GCT, metastasis, MFH, other	PT	At the time of surgery and up to 24 hours	19.5%
Sharma et al. [25]	1990–2004	77	OS, CS, LM, Ewing's, MFH, other	DF	Perioperative prophylaxis for 48 hours	7.8%
Sharma et al. [26]	1989–2004	135	Bone and soft tissue sarcoma, metastasis, GCT	DF, PF, PH, PT, DH	Perioperative prophylaxis for 48 hours	8.1%
Gosheger et al. [7]	1992–2003	250	OS, CS, Ewing's, MFH, LM, other	DF, PT, PF, PH, other	Postoperative IV cephalosporin for 3 to 7 days followed by oral use until wound healing	12%
Eckardt et al. [5]	1980–1988	78	Stage IIB OS	F, T, S, H	Preoperative IV and drains were removed for 3 to 4 days until surgical	2.6%
Wirganowicz et al. [29]	1980–1995	278	N/A	DF, PT, PF, PH, other	Preoperative IV and continued until drains were removed, then 5 days oral regimen	4%
Current study	1993–2008	53	OS	DF, PT, PF, H, PR, multicentric	Intraoperative followed by postoperative IV for 3 days, then oral use for 5 days	7.5%

OS = osteosarcoma; GCT = giant cell tumor; MFH = malignant fibrous histiocytoma; CS = chondrosarcoma; Ewing's = Ewing's sarcoma; FS = fibrosarcoma; LM = leiomyosarcoma; DF = distal femur; PT = proximal tibia; PF = proximal femur; PH = proximal humerus; DH = distal humerus; PR = proximal radius; T = tibia; F = femur; H = humerus; P = pelvis; S = scapula; IV = intravenous.

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