Reconstructive Review
Volume 4, Number 3, September 2014

ORIGINAL ARTICLE

Peri-Prosthetic Infection in the Orthopedic Tumor Patient

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Abstract

Background: Infection complicates traditional joint reconstruction prostheses in up to 7% of cases, with even higher rates in oncologic cases.

Questions / Purposes: The authors ask if prosthetic infection in bone tumor patients is associated with any epidemiologic, treatment, or outcome variables that could influence management of these difficult conditions.

Patients and Methods: Authors retrospectively reviewed 329 consecutive bone tumor (malignant and benign) patients treated with hip or knee tumor resection and subsequent joint reconstruction, comparing infected and non-infected cases. Patients were followed for a mean of 34 months.

Results: Of lower extremity tumor reconstructions, 13.1% developed periprosthetic infection, with the knee significantly more involved than the hip (20.5% vs 6.1%). The most common organism cultured was Staphylococcus aureus (33%). The diagnosis of sarcoma was associated with a higher infection rate, and infections were associated with a two-fold increase in number of total surgeries. Adjuvant radiation alone and chemotherapy alone (but not in combination) was associated with statistically increased infection rates. Debridement with fixed implant retention achieved a 70% infection remission rate, as opposed to 62% with two-staged treatment, and 100% with amputation. The implants tended to survive longer than the patients.

Conclusions: Infection complicates lower extremity prosthetic joint reconstructions in tumor patients more frequently than in non-tumor arthroplasty cases, with eradication rates lower than that of non-tumor patients. Periprosthetic infection correlates with radiation and chemotherapy administration, as well as an overall increase in revision surgery. Single stage debridement procedures result in infection remission rates comparable to two-stage reconstructions.

Level of Evidence *Level III, Retrospective comparative study.*

Introduction

Periprosthetic joint infection remains a very common cause of failure of hip and knee arthroplasty [12]. The prevalence of infection in total knee arthroplasty ranges from 0.9% [13], to 2.01% [19], to 4.0% [1], while recent studies document the prevalence of infection in total hip arthroplasty at 1.1 – 2.2% [25, 26]. Another study notes a 1 – 7% infection prevalence in all primary joint arthroplasty cases [12]. The incidence and prevalence of joint arthroplasty infection is increasing, with a two-fold increase in hip and knee prosthetic infections documented from 1990–2004 [17,18,19].

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The clinical impact of periprosthetic joint infection remains severe, with infection noted to be the leading cause of morbidity following joint replacement [22], the #1 cause of joint arthoplasty failure [12], and associated with a statistically increased rate of revision surgery [1]. Periprosthetic infection has been shown to carry a 2.7 – 18% mortality rate [22]. The economic impact of periprosthetic joint infection remains a significant problem, with these cases totaling three to four times the cost of uncomplicated primary arthroplasty [3,4,18]. One study estimates a cost of $50,000 per periprosthetic infection [12], while another notes that septic revisions cost $60,000 more than aseptic revision [1].

Peri-endoprosthetic infection for tumor reconstruction has been documented to occur in 5.7 – 15% of cases [8,10,11,23,24,27]. One series of 650 endoprosthesis cases, notes a 9.6% infection rate [7]. Another series documents the infection prevalence to increase to 43% in revision endoprosthesis cases [5], and another notes peri-endoprosthetic infection results in amputation in 23.5% of cases [27]. A thorough review of previous endoprosthesis infection case series was performed in 2010 [2]. The study found staphylococcus was most common organism among multiple case series. Factors associated with infection were myeloma, radiation therapy, poor soft tissue condition, revision surgery, and extra-articular joint resection. These studies yielded mixed recommendations on treatments and outcomes [2].

The current study aims to investigate the incidence, prevalence, risk factors, treatments, and associated outcomes of infection of lower extremity arthroplasty cases performed for the treatment of musculoskeletal tumors in order to help improve their prevention and treatment. The authors post the question: is periprosthetic infection in our bone tumor patients associated with any disease, treatment, or outcome variables that could influence management of these difficult conditions?

Patients and Methods

All musculoskeletal tumor patients treated with lower extremity tumor resection and artificial joint reconstruction over a ten year period at a single institution were retrospectively reviewed, specifically evaluating those who developed deep periprosthetic infection, as determined by the clinical diagnosis of the evaluating surgeon. Non-tumor patients and those with infection prior to reconstruction were excluded.

Table 1 describes relevant patient demographics. Four basic lower extremity reconstructions were performed after surgical treatment of benign and malignant tumors: standard femoral stem arthroplasty, proximal femoral endoprosthetic reconstruction, distal femoral reconstruction, and proximal tibial reconstruction. Infection cases were then analyzed according to multiple variables, including patient epidemiology, pathology, adjuvant therapy, surgical history, type of prosthesis, previous implant surgeries, presentation time, causative organism, original treatment modality, and subsequent infection treatment. Patients were followed according to standard oncologic protocols for a mean of 34 months (range 4 to 251 months).

Table 1. Patient Demographics

Type of Prosthesis	n	Gender (M/F)	Age (Min - Max)	Follow up (months)
Hip Endoprosthesis	147	69/78	61 (14 - 86)	13 (0.5 to 217)
Hip Standard Prosthesis	16	5/11	59 (23 - 86)	21 (0.75 to 152)
Hinged Distal Femur Endoprosthesis	125	61/64	30 (12 - 90)	87 (1.8 to 251)
Hinged Proximal Tibia Endoprosthesis	41	23/18	31 (11 - 82)	70 (4.4 to 195)
Total	329	158/171	50 (11 - 90)	34 (0.4 to 251)

Variables were then compared within the infection cohort, using the student t-test to compare means and relative risk ratio. Kaplan-Meier survival analysis was performed to evaluate both implant and patient survival. Statistical confidence was set to a 95% interval, and data analysis was performed using Graphpad® statistical software. No power analysis was performed.

Results

The overall prevalence of infection in this tumor prosthetic patient cohort was 13.1%. Proximal femoral endoprostheses demonstrated a 5.4% rate of infection, as opposed to the 12.5% rate of standard hip prostheses, 19.2% in distal femoral endoprostheses, and 22% in proximal tibial endoprostheses (Table 2). Hip prosthesis reconstructions demonstrated a 6.1% infection rate as opposed to the 20.5% rate observed in knee endoprosthetic cases, a difference that was noted to be statistically significant ($p < 0.001$). When looking at infection rates with regard to specific diagnosis, sarcomas demonstrated the highest infection rate (21.7%), which was statistically increased when compared to non-sarcoma cases ($p = 0.001$ [Table 3]). Metastatic disease demonstrated the lowest overall infection rate at 7.4%, which was statistically lower than non-metastatic disease cases ($p = 0.006$ [Table 3]). Table

4 describes the cultured pathogens associated with the infections, with Staphylococcus aureus demonstrated in 33% of culture positive specimens, and Staphylococcus epidermidis in 17%. 50% of Staphylococcus Aureus specimens were methicillin resistant.

Table 2. Overall Infection Rate by Location

Type of Prosthesis	n	Time (mo)	Infection (n)	Infection %
Hip Endoprosthesis	147	12	8	5.4
Hip Standard Prosthesis	16	18	2	12.5
Hinged Distal Femur Endoprosthesis	125	70	24	19.2
Hinged Proximal Tibia Endoprosthesis	41	53	9	22.0
Total	329	28	43	13.1

Table 3. Overall Infection Rate by Disease

Disease	n	Infection Rate (%)	P-value
Sarcoma	106	21.7	0.001
Metastatic Disease	163	7.4	0.006
Benign Bone Tumor	60	15.3	0.64

Table 4. Microbiology

Pathogens	Patients (n)
Staphylococcus Aureus	10 (5 MRSA)
Coag Neg Staphylococcus	5
Diptheroids	3
Streptococcus	3
Enterobacter	3
Enterococcus	2
Escherichia Coli	2
Candida Albicans	1
Cryptococcus	1
No Growth (gross purulence)	9

The mean total number of surgeries performed (prior to infection) was doubled in the infection group when compared to that of the non-infected group (p= 0.005 [Table 5]). The knee endoprosthetic cases demonstrated a consistently stable incidence with time, while hip infections developed earlier, and their incidence decreased with time (Figure 1 & 2). With regard to adjuvant therapy, radiation therapy alone was noted to carry a significantly higher risk of infection (RR = 3.85, p = 0.03), as did chemotherapy alone (RR = 1.51, p =0.05). Interestingly, chemotherapy in combination with radiation was associated with a decreased rate of infection (RR = 0.66, p = 0.05 [Table 6]). With regard to the results of the final treatment modality, irrigation and debridement procedures alone (without any component exchange) were associated with 42% success at achieving remission of infection, while single stage irrigation and debridement procedures with the addition of modular component exchange and varying degrees of suppressive antibiotics was associated with a 70% success rate. Formal two-staged implant removal, antibiotic spacer placement with subsequent reimplantation was associated with a 62% success rate, while 100% of infection cases treated with amputation resulted in remission of infection.

Table 5. Number of Associated Surgeries (prior to infection diagnosis)

	Infection		No-Infection	
# of Surgeries	n	%	n	%
1	20	45	224	78
2	15	34	50	17
3	3	7	9	3
4	2	5	1	0
5	2	5	0	0
Mean (p=0.005)	2		1	

Table 6. Infection and Adjuvant Therapy

Adjuvant	Patients	Infection Rate	Relative Risk	p-value
Chemotherapy alone	97	0.20	1.51	0.05
Radiation alone	6	0.50	3.85	0.03
Chemotherapy & Radiation	139	0.09	0.66	0.05
No Adjuvant Therapy	87	0.13	1.00	0.81

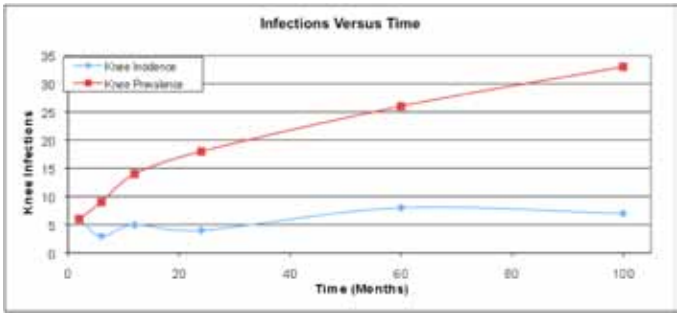

Figure 1. Incidence and prevalence of knee infections with regard to time

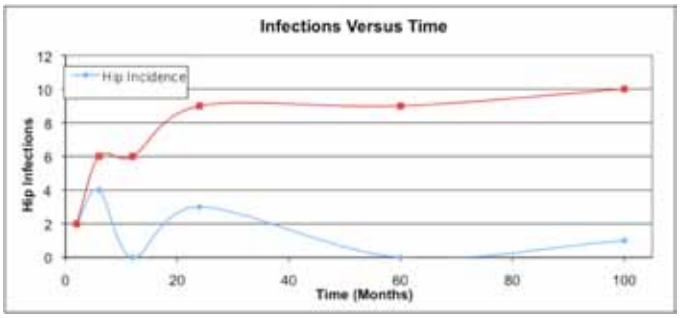

Figure 2. Incidence and prevalence of hip infections with regard to time

Figure 3 describes the overall implant survival in the entire base population, with over 70% of these implants surviving beyond a projected 20 years. Hip implants lasted longer than knee implants, when the subgroups were divided (Figure 4). Overall patient survival in the cohort hovered at roughly 40% for the long term (Figure 5), with

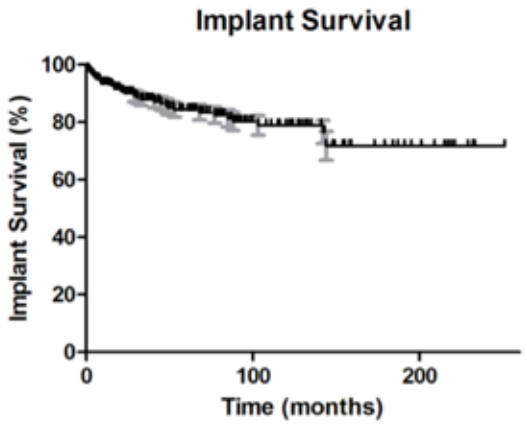

Figure 3. Kaplan-Meier curve decribing overall implant survival

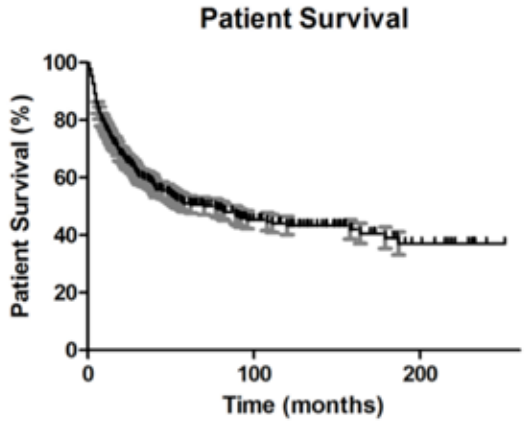

Figure 4. Kaplan-Meier curve describing implant survival with regard to location & type of implant (oncologic [endoprosthesis] vs non-oncologic [standard] implant)

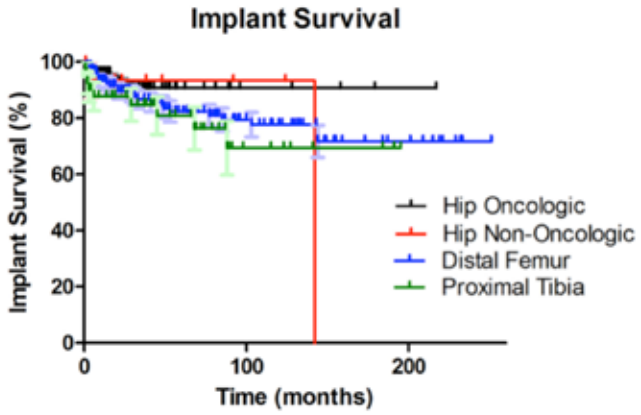

Figure 5. Kaplan-Meier curve describing overall patient survival

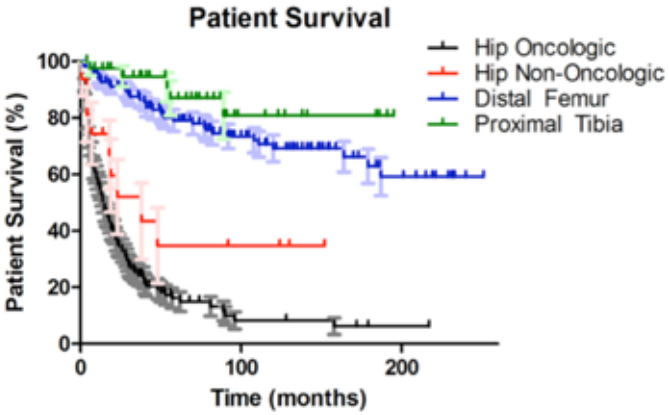

Figure 6. Kaplan-Meier curve describing patient survival with regard to location & type of implant (oncologic [endoprosthesis] vs non-oncologic [standard] implant)

knee patients surviving much longer than the hip counterparts (Figure 6). In all cases, implant survival was greater than patient survival.

Discussion

Periprosthetic infection represents a leading cause of failure, morbidity, and mortality in non-oncologic primary joint arthroplasty. Tumor prostheses are associated with increased infection rates when compared to traditional joint arthroplasty. The current study asks if periprosthetic infection in our bone tumor patients is associated with any epidemiologic, treatment, or outcome variables that could influence the prevention, diagnosis, and treatment of these conditions.

A major weakness of the study includes the lack of control and standardization of patients with multiple confounding variables with regard to their disease and treatment. For example, hip prosthesis were more often used in those with malignant diagnoses, especially metastatic disease. The decreased life expectancy seen in metastatic disease will influence the prevalence of infection. Despite this lack of control, and relatively small numbers, statistical differences were indeed discovered with analysis of the subgroups in the cohort. The diagnosis of deep periprosthetic infection was based on the clinical judgment of the treating surgeon, and the diagnosis of initial or recurrent infection can often be unclear. The fact that all treating surgeons in the study were well versed in the clinical diagnosis and management of periprosthetic infection may mitigate this weakness.

Disease variables that were associated with infection in this tumor prosthesis series include the location and type of implant, with the knee significantly more at risk than the hip (20.5% vs 6.1% [p = 0.0001]). This correlates with a former study finding 23% of proximal tibial endoprosthetic reconstructions became infected [14]. The malignant diagnosis of sarcoma was associated with a statistically higher infection rate (p = 0.001), while those with metastatic disease demonstrated a statistically lower infection rate (p = 0.006). This finding contrasts previous literature citing increased infection rates with myeloma, as opposed to other tumors [14]. Most hip infections occurred in the first

year, while knee infections with same incidence at 5 years out. Previous publications show that most infections occurred early, but could be seen as late as 210 months after implantation [2]. Staphylococcus species remain the most common pathogen (50% of culture positive cases), a finding which also corresponds to the previous literature review [2].

In this study, radiation alone was associated with significantly higher infection risk (50%, RR = 3.85, p = 0.03), and less so chemotherapy (20%, RR = 1.51, p = 0.05). Several previous publications demonstrate increased infection rates with adjuvant radiation therapy [9,14,15,20]. A previous review of endoprosthesis infection case series failed to find any studies showing a correlation between chemotherapy and implant infection [2]. In the current study, chemotherapy and radiation in combination demonstrated a statistically decreased overall infection rate, likely due to the fact that their combined use often indicated underlying metastatic disease, with treatments administered at lower doses in those with shorter life expectancies. Infections were associated with significantly increased number of associated prior to development of infection (p = 0.005). Previous studies have also indicated infection correlates with revision surgery rates [9,14,20]. In these cases, the increased number of surgeries could be a cause or an effect of the periprosthetic infection. Irrigation & debridement with modular component exchange was noted to have similar success rates when compared to formal, extensive 2-staged procedures (70% vs 62%) in the current study. This contrasts with several studies in previous literature, which often found two stage procedures to have higher resolution rates, with single stage procedure success rates ranging from 6% to 73% [6,7,9,14,16,21].

With regard to survival, the current study's long term (> 10 year projected) implant survival was noted to be well over 70%, which correlates with recent literature regarding modular oncologic endoprostheses [28]. In our study, standard primary hip implants lasted longer than "oncologic" endoprostheses, which also correlates with previous studies. This study's highest survival was documented in proximal tibia and knee cases. This difference occurred presumably because primary tumors (benign and malignant) more commonly occurred in the knee, as opposed to the increased proportion of metastatic disease occurring in the proximal femur.

In conclusion, periprosthetic joint infection in the tumor patient occurs at a higher Incidence and prevalence when compared to traditional primary joint arthroplasty. Stpahylococcus Aureus remains the most common cultured organism in these cases. Knee endoprosthetic infections can occur late, and the development of infection is associated with radiation therapy, chemotherapy, and revision surgery. Irrigation and debridement with modular component exchange may result in infection remission rates comparable to two-staged procedures.

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