Functional outcome of infected endoprosthesis: A 20-year retrospective analysis

Vivek Ajit Singh, Sashi Darshan Balakrishnan, Amreeta Dhanoa, Rupini Devi Santharalinggam and Nor Faissal Yasin

Abstract

Purpose: Bone tumours are increasingly treated with limb-salvage surgeries. However, implant infection is a devastating complication, greatly affecting the functional outcome. Yet, data on functional outcome post-implant infection are scarce. This study aims to determine the functional outcome and implant survival of these patients.

Methods: Patients’ data on endoprosthetic replacement surgeries at our institution (January 1996–December 2016) was retrospectively reviewed. Information was available for 161 patients and was analysed using SPSS and SMART Partial Least Squares. Functional outcome was determined using the Musculoskeletal Tumor Society (MSTS) and Toronto Extremity Salvage Score (TESS) scoring system.

Results: Both mean rank MSTS (33.14 vs 87.02) and TESS (48.17 vs 85.13) scores were significantly lower in the infected group. These differences remained statistically significant after excluding amputation and rotationplasty cases within the infected group. Even after the resolution of infection, both MSTS and TESS remained significantly higher in the non-infected group. However, analysis of the infected group showed no significant differences in functional outcome between persistent and resolved infections (implant in situ). Age significantly impacted the functional outcome for both the non-infected and infected groups, while local recurrence and metastasis significantly impacted the non-infected cases. Local tumour recurrence was lower in infected endoprosthetic patients (8.3% vs 10.5%). 56% of infected implants were removed; the majority were treated with two-stage revision surgery.

Conclusion: Endoprosthesis infection worsens the overall functional outcome. Additional factors affecting functional outcome were age, presence of local recurrence and metastatic disease. Local tumour recurrence was lower amongst infected endoprosthesis cases, and >50% of infected implants were removed.

Keywords
infected, endoprosthesis, outcome, functional

Introduction

The effective management of malignant tumours of the limb remains one of the most significant challenges for orthopaedic surgeons. Amputation was once the standard surgical treatment for these tumours. However, management of bone malignancies has become more specific and advanced with limb-sparing surgeries performed in up to 90% of all
patients with bone and soft tissue sarcomas of the extremities. This is due to advancements in diagnostic imaging and effective chemotherapy. Limb-salvage surgeries are now performed worldwide, and the outcome has improved with modern medical implant technology. Implant materials such as Vitallium and a series of different metals such as stainless steel have now been replaced by titanium alloys. Some of these implants are coated with silver to reduce infection risk.

With an increase in the number of surgeries involving endoprostheses over the past decade, an inevitable rise in complications associated with these surgeries have been reported, such as aseptic loosening, infection, and mechanical failure. These complications occur at higher rates than other clean orthopaedic surgeries as soft tissue dissection is more complex, the implants are more extensive, and the biomechanical reconstruction following the surgery is complicated.

Endoprosthetic infections can be considered the most devastating complication in limb-salvage surgeries. These surgeries are associated with higher infection rates as the procedures are more complex, with more extensive surgical wounds and longer operative time. Such resections often leave behind large areas of tissue defects, which lead to seroma formation, a potential nidus for infection. Furthermore, these patients usually undergo chemotherapy and radiotherapy and are at the extremes of age as a result of which they are generally immunocompromised and are prone to infection.

To date, although many studies involving endoprosthetic infections have been reported worldwide, the focus has been on common sites involved, modalities of salvage surgeries, factors contributing to the development of these infections, and the types of microorganisms involved. However, data focussing on the functional outcome of patients who develop endoprosthetic infections are scarce.

Thus, this study explores the functional outcomes of patients who develop an infection after undergoing an endoprosthetic replacement for primary bone tumours. We also analysed the implant survival in these patients.

**Materials and methods**

We performed a retrospective cohort study involving patients with primary bone tumours treated with wide resection and endoprostheses over 20 years (1 January 1996 to 31 December 2016). We excluded cases that defaulted follow-up. This study was conducted at a tertiary referral centre for Orthopaedic Oncology and was approved by the Hospital Medical Ethics Committee (MEC ID No:2017911-5563). As this was a retrospective study, informed consent was not obtained from the patients. All patients were followed up for at least 24 months post-surgery.

Clinical information was collected by reviewing the medical records and the orthopaedic oncology database. The picture archiving and communication service (PACS) retrieved data related to radiological images and reports. Demographic and clinical data collected included age and gender, primary tumour site, local recurrence, metastasis of tumour, type of implant used and the implant outcome, including salvage surgery required for infected cases. The patients were divided into three age groups, that is, <20 years, 20–50 years and >50 years old. This is because types of tumours vary by age group. Children and adolescents under 20 years are mainly affected by primary bone tumours such as osteosarcoma and Ewing sarcoma. In adults aged between 20 and 50 years, chondrosarcoma makes up the majority of primary bone tumours, while metastatic disease predominates in adults above 50 years.

The functional outcome was determined by the Musculoskeletal Tumor Society (MSTS) and the Toronto Extremity Salvage Score (TESS) scoring system. These functional scores were taken from the patient’s latest follow-up. The MSTS scoring system focuses on an overall evaluation of the limb involved and patients’ physical health. The physician asked specific questions and examined the patient to determine factors contributing to this scoring, such as pain, functional activity, and emotional acceptance. For the upper limb, specific characteristics were analysed, such as positioning of the hand, manual dexterity and the ability to lift. For the lower limb, the ability to walk, gait and the use of orthosis or supports were evaluated. These factors were then scored based on the proportion of expected typical outcomes for the patient. The Toronto Extremity Salvage Score (TESS) determines the functional outcome from the patient’s perspective. This scoring system was developed by adapting the definition of disability, handicap and impairment described by the World Health Organization (WHO). These questions are site-specific, and a score is given based on their ability to perform day-to-day tasks.

We compared the MSTS and TESS scores for both the infected and non-infected endoprostheses groups. We aim to establish if factors such as age, gender, limb involved, local tumour recurrence and metastatic spread would affect their functional outcome, as reflected by the MSTS and TESS scoring. Implant survivability was also determined in cases that had their implant retained.

There were two analyses involved in this research. The Mann–Whitney U test was performed using the Statistical Package for the Social Sciences (SPSS) software version 23. The non-parametric test was used when data were not normally distributed. The Mann–Whitney U test was used to compare the significant distribution in two dependent groups (MSTS and TESS) and independent groups (infected and non-infected) to ensure equal distribution of both groups.

To further understand an independent variable’s effect on the dependent variable, the SMART Partial Least Squares (PLS) modelling was performed using the SMART PLS software version 2.0. PLS-SEM was used to determine the
factors contributing to or affecting functional outcome scoring in infected and non-infected groups. Factors analysed included age, gender, local recurrence, cancer spread and the limb involved. This data was then analysed using Variance Inflation Factors (VIF) to check on multicollinearity. A cut off value for VIF is expected to be lower than 5 to avoid affecting the loadings. Indicators that hit the critical values were omitted. The \( p \)-value < 0.05 (two-tailed) at 95% confidence intervals was considered the level of significance.

Results

During the 20-year study period, 168 patients underwent endoprosthesis replacement for primary bone tumours. However, seven cases were excluded either due to loss to follow up or untraceable medical records. Of the remaining 161 patients, 18 (11.2%) had infected endoprosthesis. Table 1 shows the demographic distribution of patients. The majority of patients were aged between 21-50 years in both the infected and non-infected groups. There was a slight male predominance in both groups. Infected endoprosthesis was more common in males (61.1%) and in patients aged 50 and above (15.4%). There are 5 patients who are ages 50 and above. Out of which 4 are primary tumours (1 case of fibrosarcoma, 2 cases of Chondrosarcoma and 1 case of osteosarcoma) and 1 bone metastasis (Carcinoma of Cervix). As shown in Table 2, the lower limb was the commonest site for endoprosthesis replacement in both groups, followed by the pelvis and upper limb. The local recurrence rate in the infected group of patients was 8.3% compared to 10.5% in the non-infected group. This is statically insignificant \( (p = 0.961) \). However, the rate of metastasis was almost similar in both groups.

The details of the 18 infected endoprosthesis cases are shown in Table 3. The average age of the patients with infected endoprosthesis was 31.1 years (range: 12–66). The average duration of infection post-implantation was 473 days (range: 9–1890 days). The majority (44%) were late infections (presenting after >12 months), 33% were early infections (presenting within the first 90 days), while 22% were delayed infections (presenting within 3–12 months). The commonest site of endoprosthesis infection was proximal tibia (8/18, 44%), followed by the distal femur (4/18, 22%) and pelvis (3/18, 17%). In contrast, the distal humerus, distal tibia and proximal humerus endoprosthesis contributed to one case each. There were 14 cases (78%) of the modular endoprosthesis and 4 cases (22%) of the expandable endoprosthesis. Forty-four per cent of patients had metastasis either at presentation or noted at follow-up. However, there was only one case of local recurrence.

Table 1. Characteristics of endoprosthetic patients based on age, gender, and presence of infection.

| Characteristics | Total | Infected | Not infected |
|-----------------|-------|----------|--------------|
| Age (years)     |       |          |              |
| <20             | 56    | 7 (12.5%)* | 38.9%        | 49 | 34.3% |
| 21–50           | 79    | 7 (8.9%)*  | 38.9%        | 72 | 50.3% |
| >50             | 26    | 4 (15.4%)* | 22.2%        | 22 | 15.4% |
| Gender          |       |          |              |
| Male            | 89    | 11       | 61.1%        | 78 | 54.5% |
| Female          | 72    | 7        | 38.9%        | 65 | 45.5% |
| Total           | 161   | 18       | 11.2%        | 143 | 88.8% |

*Shows the percentage of cases with infected endoprosthesis within the age group.

Table 2. Comparison between sites, local recurrence, and metastasis between infected and non-infected group.

| Characteristics | Infected |                     | Not infected |                     |
|-----------------|----------|----------------------|--------------|----------------------|
|                 | Frequency | Percentage, %         | Frequency    | Percentage, %         |
| Limb            |          |                      |              |                      |
| Lower limb      | 13       | 72.0                 | 105          | 73.0                 |
| Pelvis          | 3        | 16.7                 | 23           | 16.0                 |
| Upper limb      | 2        | 11.3                 | 15           | 11.0                 |
| Total           | 18       | 100                  | 143          | 100                  |
| Local recurrence* |    |                      |              |                      |
| Yes             | 1        | 8.3                  | 15           | 10.5                 |
| No              | 11       | 91.7                 | 128          | 89.5                 |
| Total           | 12       | 100                  | 143          | 100                  |
| Metastasis      |          |                      |              |                      |
| Yes             | 8        | 44.4                 | 58           | 40.6                 |
| No              | 10       | 55.6                 | 85           | 59.4                 |
| Total           | 18       | 100                  | 143          | 100                  |

Note: * excludes amputations and rotationplasty.
Table 3. Infected endoprosthetic patients ($n = 18$): Demographic, clinical data and implant outcome.

| No | Age | Sex | Timing of infection post-surgery (days) | Classification of timing of infection | Site of tumour | Type of endoprosthesis | Metastasis | Local recurrence | Implant outcome |
|----|-----|-----|----------------------------------------|--------------------------------------|----------------|------------------------|------------|-----------------|----------------|
| 1  | 18  | M   | 420                                    | Late                                 | Proximal tibia | Modular                | Yes        | No              | Rotationplasty  |
| 2  | 53  | F   | 20                                     | Early                                | Distal humerus | Modular                | Yes        | No              | Not removed    |
| 3  | 19  | M   | 570                                    | Late                                 | Proximal tibia | Modular                | No         | No              | Not removed    |
| 4  | 13  | M   | 1890                                   | Late                                 | Proximal tibia | Expandable             | No         | No              | 2-Stage revision|
| 5  | 65  | F   | 360                                    | Delayed                              | Distal femur   | Modular                | No         | No              | Amputation      |
| 6  | 21  | F   | 30                                     | Early                                | Distal tibia   | Modular                | Yes        | No              | Not removed    |
| 7  | 50  | M   | 240                                    | Delayed                              | Proximal tibia | Modular                | No         | No              | Not removed    |
| 8  | 31  | F   | 20                                     | Early                                | Proximal tibia | Modular                | No         | No              | Not removed    |
| 9  | 26  | M   | 1830                                   | Late                                 | Proximal tibia | Modular                | Yes        | No              | Amputation      |
| 10 | 41  | M   | 9                                      | Early                                | Pelvis         | Modular                | Yes        | No              | Hemipelvectomy  |
| 11 | 32  | M   | 14                                     | Early                                | Pelvis         | Modular                | Yes        | No              | Not removed    |
| 12 | 66  | M   | 90                                     | Delayed                              | Pelvis         | Modular                | Yes        | No              | Not removed    |
| 13 | 10  | M   | 720                                    | Late                                 | Distal femur   | Expandable             | No         | Yes             | Rotationplasty  |
| 14 | 55  | M   | 900                                    | Late                                 | Distal femur   | Modular                | No         | No              | Not removed    |
| 15 | 23  | M   | 20                                     | Early                                | Proximal tibia | Modular                | No         | No              | 2-Stage revision|
| 16 | 12  | F   | 480                                    | Late                                 | Proximal humerus | Modular                | No         | No              | 2-Stage revision|
| 17 | 12  | F   | 600                                    | Late                                 | Proximal tibia | Expandable             | Yes        | No              | Rotationplasty  |
| 18 | 13  | F   | 300                                    | Delayed                              | Distal femur   | Expandable             | No         | No              | 2-Stage revision|

*Early: less than 90 days, Delayed: 90–365 days, Late: more than 365 days.
The mean rank MSTS score was 87.02 in the non-infected compared to 33.14 in the infected group (Tables 4–8). Likewise, the mean TESS score was 85.13 and 48.17 in the non-infected and infected groups, respectively. These findings suggest a significant worsening of functional scoring in the presence of infection. There were 6 cases of amputations and rotationplasty within the infected group. After excluding these cases, the mean rank MSTS score for the infected versus non-infected group was 28.29 vs 82.17, and the TESS score was 42.58 vs 80.97; the difference remained statistically significant. Amongst the infected cases, if we compared cases of persistent infection and those whose infection had resolved with implant in-situ, there were no significant differences in the MSTS (4.83 vs 7.06, \( p = 0.352 \)) and TESS (4.67 vs 7.11, \( p = 0.307 \)). However, comparison between infected implants with resolved infection and the non-infected implants, showed statistically significant differences in the MSTS (32.94 vs 79.24, \( p = 0.002 \)) and TESS (41.56 vs 78.70, \( p = 0.014 \)) scores. Likewise, comparison between implants with persistent infection and non-infected implants, revealed significant differences between the MSTS (5.33 vs 74.94, \( p = 0.005 \)) and TESS (24.33 vs 74.53, \( p = 0.042 \)) scores.

The data was further analysed using the SEM-PLS technique to determine the factors contributing to the functional outcome scoring in the infected and non-infected groups (Table 9). These variables were omitted during the analysis: the primary tumour site and the type of implant used were omitted due to multicollinearity and critical loading value. Age and gender were analysed as independent variables. Metastasis and local recurrence of the tumour were combined and analysed as ‘other factors’ as these factors were dependent on each other. Age had a significant impact on the functional outcome for both the non-infected and infected groups. As for gender, the difference was statistically not significant for both groups. The analysis of the ‘other factors’ (combined local recurrence and metastasis) significantly impacted the functional scoring of the non-infected group. In contrast, the infected group showed no statistical difference.

Implant survivability analysis was done for cases of the infected endoprosthesis, and results are shown in Figure 1.
Out of the 18 patients with infected endoprosthesis, 10 (56%) had their implants removed. Of the 10 cases with removed implants, six were modular implants, and four were expandable implants. Out of the four cases involving expandable endoprosthesis, two (50%) underwent two-stage revision surgery. They had their implant changed to the modular type, while the remaining two cases underwent a rotationplasty. Of the six cases involving a modular endoprosthesis, two (33%) underwent two-stage revision surgery. One case underwent a rotationplasty, two cases underwent high transfemoral amputation and one patient underwent a hemipelvectomy (Figure 1).

The eight cases where implants were retained were the modular type. Six patients underwent repeated wound debridement. Out of these six cases, two cases involving the proximal tibia and one involving the distal tibia were cleared of infection. However, two cases involving pelvic tumours and one distal femur endoprosthesis had a persistent infection. The remaining two cases involving the distal humerus and the proximal tibia were not fit for two-stage surgery due to poor general condition.

**Discussion**

Deep surgical site infection is a devastating complication of endoprosthetic surgery. Out of 161 patients who underwent endoprosthetic replacement for primary bone tumours, 11.8% developed infected endoprosthesis. This rate concurs with other published studies, where the infection rates range from 10% to 17%. Infection rates of endoprosthesis replacements are generally higher than other orthopaedic implant-related surgeries as the surgical procedure is more complex, involving larger implants. The duration of surgery is also longer than routine orthopaedic surgeries, thus exposing large wounds to the external environment for extended periods. The bone tumour resection often leads to the formation of sizeable dead space, which eventually gets filled with seroma and haematoma, creating a focus for

---

**Table 9.** Factors contributing to functional outcome of infected endoprosthesis.

| Pathway                              | Pathway coefficients | p-value | Significant |
|--------------------------------------|----------------------|---------|-------------|
|                                      | Infected             | Not infected | Infected | Not infected | Infected | Not infected |
| Age-> functional outcome             | -0.3656              | 0.2050  | 0.0159**  | 0.0077 Signi           |
| Gender-> functional outcome          | 0.1290               | 0.0491  | 0.6037     | 0.6213 Not signi      |
| Other Factors-> functional outcome   | -0.0938              | -0.6492 | 0.4425     | 0.0022 Significant     |

Asterisks indicate significant results. **p < 0.01, * p < 0.05.

**Figure 1.** Outcome infected endoprosthesis cases.
infection. Furthermore, many of these patients undergo neoadjuvant chemotherapy, which impairs their immunity, making them further susceptible to infection.

This study’s main objective was to analyse the functional outcome of patients who developed infected endoprostheses compared to patients without such infection. To the best of our knowledge, no other study has explored the functional outcomes of patients with an infected endoprosthesis in detail. Similarly, data are scarce on the contribution of age, gender, tumour site, infection, local recurrence, and metastatic disease on the functional outcome scoring in patients with an endoprosthesis. Thus, we carried out a detailed analysis to determine the functional outcome with other possible contributing factors.

Our results showed that the MSTS and TESS scores were significantly higher in those without an infected endoprosthesis, supporting the hypothesis that patients have a more unsatisfactory functional outcome once deep surgical site infection develops. Concurring with our findings, a recent study in Malaysia showed worsening functional outcomes in a small group of patients with endoprostheses that developed deep surgical site infection. We also found that patients’ age significantly impacted the functional outcome in both the infected and non-infected groups. The favourable results in younger patients could be attributed to higher motivation, active lifestyle and better recovery compared to older patients.

Local tumour recurrence and metastatic spread contributed significantly to the functional outcome in the non-infected group but not the infected group. This disparity may be explained by patients with infected endoprostheses already having lower functional scores due to the infection. Thus, local recurrence or metastatic spread did not contribute significantly to the worsening of the score. Gender did not significantly impact the functional outcome in both the infected and non-infected endoprosthesis cases.

Our findings showed that tumour recurrence was lower in cases of an infected endoprosthesis compared to uninfected subjects, however it was statistically insignificant. This is probably due to the small number of patients with local recurrence in the infected endoprosthesis group. We postulate that infection might confer a protective effect on the local recurrence of the tumour. Similarly, previous studies have shown that postoperative infection in osteosarcoma patients was associated with prolonged survival and reduced local recurrence compared to non-infected patients.

Reports of tumours spontaneously regressing following infections had been described historically. In 1891, William B. Coley, often regarded as the ‘Father of Immunotherapy’, purposely injected live streptococcal organisms into a patient with an inoperable sarcoma, ultimately shrinking the tumour. Because of the threats of live streptococcal, Coley developed a heat-killed streptococci vaccine combined with Bacillus prodigiosus (known as Coley’s toxin), mainly in used inoperable sarcomas. Overall, Coley injected more than 1000 cancer patients and reported successful Coley’s toxin-inducing tumour regression cases. However, these findings remained controversial, and FDA had re-categorized Coley’s toxins in 1963 as an investigational drug lacking safety and efficacy data. These criticisms, along with the advent of broadly applicable chemotherapy and radiotherapy, caused Coley’s toxin to be phased out. Since Coley’s death, the potential role of the enhanced immune system associated with infection has been widely explored, indicating that immunotherapy could be a valuable adjuvant therapy for cancers including bone and soft tissue sarcomas.

The exact mechanism of how infection reduces the local recurrence rate is still unclear. Some authors believe that the infection has an antitumour effect by up-regulating the cellular immune system, which causes an increased release of tumour necrosis factor-α. Buddingh et al. (2012) stated that chemotherapy-resistant osteosarcomas could be lysed by natural killer cells (NK cells). Laboratory studies have shown that infection causes angiogenic suppressive effects on tumour cells. These factors enhance the innate immune response and have a protective effect, which reduces the tumour recurrence rate. However, despite the findings that infection protects against local tumour recurrence, more advanced studies are needed to support the validity of these postulations.

In case of an infected endoprosthesis, treatment options include surgical debridement with irrigation, a single-stage or two-stage revision. Most surgeons currently perform a two-staged revision, as the success rate is higher than a single-staged revision in controlling the infection. The success rate of a two-stage surgery with the usage of antibiotic-impregnated cement is 90%. The cases with persistent or repeated infections despite multiple surgical debridements or a two-staged surgery can be offered revisionplasty or amputation, depending on the tumour site. In our series, revisionplasty was performed in three patients and amputations in another three patients (2 above knee amputations and one hemipelvectomy). Other options, such as arthrodesis or resection arthroplasty are not commonly done in our centre as there huge bone gap after removal of these prosthesis and we do not use have the availability of fusion prosthesis.
titanium implants. In 158 patients, these implants were inserted in patients with compromised status to prevent infection, while in 64 patients, it was inserted to treat an implant infection. Only three patients from the preventive therapy group developed an infection, which resolved without implant removal. In the infected group, all 64 cases had resolution of the infection. Another modality that is currently available is the silver-coated endoprosthesis. Silver has excellent antimicrobial activity and low toxicity and has reduced the infection rate in primary and revision cases. Even in cases of an infected endoprosthesis, patients with silver-coated implants needed more minor interventions, for example, debridement or one-stage revision, to overcome the infection than those without silver coating. Eradication of an established biofilm entails disrupting the extracellular polymeric substances (EPSs) and killing bacteria cells. Phage therapy can achieve both, making it a promising new paradigm for the treatment of orthopaedic-device related infections. This treatment uses viruses with specific lysis ability injected into the infection site to kill the infecting organism. Preclinical and clinical studies using phage therapy have shown promising therapeutic effects and safety profiles, especially when combined with antibiotics, as both agents can work synergistically against biofilms.

This study has helped us improve our practise over the years to minimise the incidence of infection. We have now standardised our antibiotic regime. We now give intravenous antibiotics until the drains are removed and continue with oral for a total of 2 weeks. In additional to that, we intervene early in cases of wound dehiscence and those cases with persistent high drainage postoperatively by doing wound wash outs.

We acknowledge that our study has a few limitations. Since this was a retrospective study, the functional scores for patients before developing infection were not available. Thus, the comparison could not be made between the functional scores before and after infection. Moreover, this study had a relatively small number of infected cases, resulting in a low statistical power to detect true association.

Conclusion

We found that infection significantly affected the functional outcome of patients with an endoprosthesis. Age was a significant contributing factor for the functional scoring in both the infected and non-infected endoprosthesis cases. Local recurrence and metastatic cancer spread significantly impacted the scoring of the non-infected group compared to the infected group. Intriguingly, patients with infected endoprosthesis had a significantly lower recurrence rate of the tumour. In only 44% of the infected endoprosthesis cases, the primary implant was retained.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Vivek Ajit Singh https://orcid.org/0000-0001-8899-9266
Amreeta Dhanoa https://orcid.org/0000-0002-4541-4819
Nor Faissal Yasin https://orcid.org/0000-0001-6524-8451

References

1. Henshaw R and Malawer M. Review of endoprosthetic reconstruction in limb-sparing surgery. In: InMusculoskeletal cancer surgery: Dordrecht: Springer, 2004, pp. 383–403.
2. Ambrose J. Computerized transverse axial scanning (tomography): part 2. Clinical application. Br J Radiol 1973; 46(552): 1023–1047.
3. Mansfield P and Maudsley AA. Medical imaging by NMR. Br J Radiol 1977; 50(591): 188–194.
4. Moore AT and Bohlman HR. Metal hip joint. A case report. JBJS 1943; 25(3): 688–692.
5. Golish SR and Mihalko WM. Principles of biomechanics and biomaterials in orthopaedic surgery. JBJS 2011; 93(2): 207–212.
6. Ghani Y, Coatham MJ, Hing KA, et al. Development of a hydroxyapatite coating containing silver for the prevention of peri-prosthetic infection. J Orthop Res 2012; 30(3): 356–363.
7. Gosheger G, Gebert C, Ahrens H, et al. Endoprosthetic reconstruction in 250 patients with sarcoma. Clin Orth Relat Res 2006; 450: 164–171.
8. Mavrogenis AF, Pala E, Angelini A, et al. Proximal tibial resections and reconstructions: clinical outcome of 225 patients. J Surg Oncol 2013; 107(4): 335–342.
9. Orlic D, Smerdelj M, Kolumdzic R, et al. Lower limb salvage surgery: modular endoprostheses in bone tumour treatment. Int Orthop 2006; 30(6): 458–464.
10. Zeegen EN, Aponte-Tinao LA, Hornicek FJ, et al. Survivorship analysis of 141 modular metallic endoprostheses at early followup. Clin Orth Relat Res (1976-2007) 2004; 420: 239–250.
11. Choong PFM, Sim FH, Pritchard DJ, et al. Megaprostheses after resection of distal femoral tumours: a rotating hinge design in 30 patients followed for 2-7 years. Acta Orthop Scand 1996; 67(4): 345–351.
12. Gerrand CH, Currie D, Grigoris P, et al. Prosthetic reconstruction of the femur for primary bone sarcoma. Int Orthop 1999; 23(5): 286–290.
13. Shin D-S, Choong PFM, Chao EYH, et al. Large tumor endoprostheses and extracortical bone-bridging: 28 patients followed 10-20 years. Acta Orthop Scand 2000; 71(3): 305–311.
14. Jeys LM, Grimer RJ, Carter SR, et al. Periprosthetic infection in patients treated for an orthopaedic oncological condition. *JBJS* 2005; 87(4): 842–849.

15. Racano A, Pazionis T, Farrakhyar F, et al. High infection rate outcomes in long-bone tumor surgery with endoprosthetic reconstruction in adults: a systematic review. *Clin Orthop Relat Res* 2013; 471(6): 2017–2027.

16. Dhanoa A, Ajit Singh V and Elbahri H. Deep infections after endoprosthetic replacement operations in orthopedic oncology patients. *Surg Infect (Larchmt)* 2015; 16(3): 323–332.

17. Morii T, Yabe H, Morioka H, et al. Postoperative deep infection in tumor endoprosthesys reconstruction around the knee. *J Orthop Sci* 2010; 15(3): 331–339.

18. Enneking WF, Dunham W, Gehhardt MC, et al. A system for the functional evaluation of reconstructive procedures after surgical treatment of tumors of the musculoskeletal system. *Clin Orthop Relat Res* 1993; 286: 241–246.

19. Davis AM, Wright JG, Williams JI, et al. development of a measure of physical function for patients with bone and soft tissue sarcoma. *Qual Life Res* 1996; 5(5): 508–516.

20. Davis AM, Sennik S, Griffin AM, et al. Predictors of functional outcomes following limb salvage surgery for lower-extremity soft tissue sarcoma. *J Surg Oncol* 2000; 73(4): 206–211.

21. Tunn PU, Pomraenke D, Goerling U, et al. Functional outcome after endoprosthetic limb-salvage therapy of primary bone tumors—a comparative analysis using the MSTS score, the TESS and the RNL index. *Int Orthop* 2008; 32(5): 619–625.

22. Shehadeh A, Noveau J, Malawer M, et al. Late complications and survival of endoprosthetic reconstruction after resection of bone tumors. *Clin Orthop Relat Res* 2010; 468(11): 2885–2895.

23. Sharil A, Nawaz A, Nor Azman M, et al. Early functional outcome of resection and endoprosthesis replacement for primary tumor around the knee. *Malays Orthop J* 2013; 7(1): 30–35.

24. Chen Y, Xu S-F, Xu M, et al. Postoperative infection and survival in osteosarcoma patients: reconsideration of immunotherapy for osteosarcoma. *Mol Clin Oncol* 2015; 3(3): 495–500.

25. Jeys LM, Grimer RJ, Carter SR, et al. Post operative infection and increased survival in osteosarcoma patients: are they associated? *Ann Surg Oncol* 2007; 14(10): 2887–2895.

26. Lee JA, Kim MS, Kim DH, et al. Postoperative infection and survival in osteosarcoma patients. *Ann Surg Oncol* 2009; 16(1): 147–151.

27. Wiemann B and Starnes CO. Coley’s toxins, tumor necrosis factor and cancer research: a historical perspective. *Pharmaco Ther* 1994; 64(3): 529–564.

28. McCarthy EF. The toxins of William B. Coley and the treatment of bone and soft-tissue sarcomas. *Iowa Orthop J* 2006; 26: 154–158.

29. Buddingh EP, Ruslan SEN, Berghuis D, et al. Intact interferon signaling in peripheral blood leukocytes of high-grade osteosarcoma patients. *Cancer Immunol Immunother* 2012; 61(6): 941–947.

30. Thomas-Tikhonenko A and Hunter CA. Infection and cancer: the common vein. *Cytokine Growth Factor Rev* 2003; 14(1): 67–77.

31. Bengston S, Knutson K and Lidgren L. Treatment of infected knee arthroplasty. *Clin Orthop Relat Res* 1989; 245: 173–178.

32. Holzer G, Windhager R and Kotz R. One-stage revision surgery for infected megaprosthesis. *J Bone Joint Surg Br* 1997; 79-B(1): 31–35.

33. Malawer MM and Chou LB. Prosthetic survival and clinical results with use of large-segment replacements in the treatment of high-grade bone sarcomas. *J Bone Joint Surg Am* 1995; 77(8): 1154–1165.

34. Hanssen AD, Trousdale RT and Osmon DR. Patient outcome with reimplantation for infected total knee arthroplasty. *Clin Orthop Relat Res* 1995; 321: 55–67.

35. Rao K, Lahiri A and Peart FC. Role of staged endoprosthetic revision with flap cover for limb salvage in endoprosthetic failure. *Int Orthop* 2006; 30(6): 473–477.

36. Grimer RJ, Belthur M, Chandrasekar C, et al. Two-stage revision for infected endoprostheses used in tumor surgery. *Clin Orthop Relat Res (1976-2007)* 2002; 395: 193–203.

37. Shirai T, Shimizu T, Ohtani K, et al. Antibacterial iodine-supported titanium implants. *Acta Biomater* 2011; 7: 1928–1933.

38. Tsuchiya H, Shirai T, Nishida H, et al. Innovative antimicrobial coating of titanium implants with iodine. *J Orthopaedic Sci* 2012; 17(5): 595–604.

39. Schmidt-Braeckling T, Streitbuerger A, Gosheger G, et al. Silver-coated megaprosthesis: review of the literature. *Eur J Orthopaedic Surg Traumatol* 2017; 27(4): 483–489.

40. Onsea J, Wagemans J, Wagemans J, et al. Bacteriophage therapy as a treatment strategy for orthopaedic-device-related infections: where do we stand?. *Eur Cell Mater* 2020; 39: 193–210. DOI: 10.22203/eCM.v039a13.