Osseointegration Reduces Aseptic Loosening of Primary Distal Femoral Implants in Pediatric and Adolescent Osteosarcoma Patients: A Retrospective Clinical and Radiographic Study

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Abstract

Aim

The challenge of distal femoral replacement (DFR) longevity remains a priority for orthopaedic oncologists as the overall survival and activity level of young patients with osteosarcoma continues to improve. This study hypothesised that increased extracortical osseointegration at the bone-implant shoulder will improve stress transfer adjacent to the implant, as evidenced by reduced cortical bone loss, radiolucent line progression and implant failure in young patients (<20-years) following DFR surgery.

Methods

Twenty-nine patients of mean age 13.09±0.56y received a primary DFR. The clinical outcome of 11 CPS®, 10 GMRS®, 5 Stanmore® and 3 Repiphysis® implants were evaluated over a mean follow-up period of 4.25±0.55y. The osseous response to an implant shoulder composed of either a hydroxyapatite-coated grooved ingrowth collar (Stanmore®), a porous metal coating (GMRS®) or a polished metal surface (Repiphysis®) was quantified radiographically.

Results

All (100.0%) of the Stanmore® implants, 90.0% of GMRS®, 81.8% of CPS® and 33.3% of the Repiphysis® implants survived. Significantly increased extracortical bone and osseointegration was measured adjacent to the Stanmore® implants when compared with the GMRS® and Repiphysis® implants (p<0.0001 in both cases). Significantly decreased cortical loss was identified in the Stanmore® group (p=0.005, GMRS® and p<0.0001, Repiphysis®) and at 3-years, the progression of radiolucent lines was reduced when compared with the GMRS® and Repiphysis® implants (p=0.012 and 0.026 respectively).

Conclusions

Implants designed to augment osseointegration at the bone-implant shoulder may be critical in reducing short- to mid-term aseptic loosening in this vulnerable DFR patient group. Further longer-term studies are required to confirm these preliminary findings.

Introduction

Osteosarcoma is a primary malignancy of bone that most commonly impacts the distal femur, predominantly affecting those between the ages of 10 and 14 and those over the age of 65 years [1]. Neoadjuvant chemotherapy combined with tumor resection is accepted as the treatment of choice [2]. Replacement of the distal femur with a mega endoprosthesis after wide tumor resection offers the benefits of same-day weight bearing, faster rehabilitation, and early walking [3]. Long-term 10- and 15-year survival rates following total knee replacement surgery are reported to range between 90.9–95.4% [4]. In contrast, Haijie *et al.* [5] recently reported that the mean 5-, 10-, 15- and 20-year implant survival rate

of a distal femoral replacement (DFR) in adults was 78.3%, 70.1%, 61.6% and 38.3% respectively. The identifiable risk factors are younger age, an increased level of bone resection and increased time of follow-up, which places the pediatric population at particularly high risk [6]. Implant infection and aseptic loosening (ASL) of the intramedullary stem remain the recognized major causes of failure [7–9]. At the tissue level, ASL begins with localized cortical bone loss at the bone-shoulder implant junction [10]. With time, this cortical bone loss is accompanied by the progression of radiolucent lines between the cement-bone interface adjacent to the intramedullary stem, eventually leading to ASL and implant failure. Concerns for successful long-term fixation stimulated modifications in implant materials and design and to date several are in use, each with varying features targeted to reduce bone loss and ASL. Modern designs incorporate a bone ingrowth collar at the bone-implant shoulder with the goal of encouraging extracortical bone-implant osseointegration. This is reported to reduce disadvantageous high stresses within the stem fixation and protect the implant against ASL and surgical revision [11–14]. Typically, bone does not directly adhere to a polished metal surface and varying types of ingrowth surfaces including fibermetal, porous metal coatings and more recently a hydroxyapatite (HA) coating have been assessed clinically [10, 14–19]. Other prosthetic advancements include Biomet's Compress Compliant Pre-Stress (CPS®) technology (ZimmerBiomet Inc, Warsaw, IN, USA), designed to apply beneficial dynamic compressive loads to the bone cortex at the shoulder. This may eliminate ASL and is secured to bone without reliance on an intramedullary stem [20–24].

The aim of this study was to retrospectively review the clinical outcome of primary DFRs in young patients (< 20-years) in the short- and mid-term. All patients had received either a Stanmore® implant, a CPS® implant, the Stryker Global Modular Replacement System (GMRS®, Stryker, Mahwah NJ, USA) or a Repiphysis® implant (Repiphysis Limb Salvage System; Wright Medical Technology, Arlington, TN, USA). This study also aimed to evaluate the effect of an implant shoulder composed of a HA coated grooved ingrowth collar (Stanmore®), a plasma sprayed porous titanium coating (GMRS®) or a polished metal surface (Repiphysis®) on the level of osseointegration and incidence and progression of radiolucent lines adjacent to the intramedullary stem fixation. Our hypothesis was that increased extracortical osseointegration at the bone-implant shoulder will improve stress transfer adjacent to the stem, as evidenced by reduced cortical bone loss, radiolucent line progression and implant failure.

Methods

Between 2000 and 2020, 30 patients underwent primary DFR limb salvage surgery within the Nemours Children's Health system at hospitals based in Orlando, Pensacola and Jacksonville in Florida, and at the Nemours/Alfred I. duPont Hospital for Children in Wilmington, Delaware, United States. This study received ethical board approval from the Nemours Office of Human Subjects Protection (IRB# 1351573). Our study was retrospective and as such, written informed consent was not required. Data was retrieved from the EPIC electronic medical record system. Surgery was performed by one of six orthopaedic surgeons and all patients were treated following a biopsy-proven diagnosis of high-grade osteosarcoma. Patients who received a DFR for the reconstruction of a metastatic lesion or in a revision procedure were excluded. One patient was excluded as the DFR was a revision, leaving 29 patients (Figs. 1 and 2).

All patients received neoadjuvant and adjuvant multidrug combination chemotherapy in accordance with the Children's Oncology Group AOST 0331 study (**Table 1**). Patients received cisplatin, doxorubicin and methotrexate (MAP) and during DFR surgery, chemotherapeutic efficacy was determined according to changes in tumor size. Those patients with no or limited tumor regression at the time of surgery were categorized as non-responders and their chemotherapeutic treatment was modified accordingly. The implant design variables are presented in **Table 2** and implant removal and clinical complications were assessed in accordance with the Henderson Classification system of endoprosthetic failure [25] (**Table 3**).

Radiographic Analysis

Radiographic analysis was performed by examining both antero-posterior (AP) and medio-lateral (ML) radiographs taken of each patient throughout the length of the follow-up period. In total, 99 radiographs were analyzed with a mean of 6 (range, 1–18) radiographs per patient. The number of radiographs available varied according to length of follow up, frequency of follow up imaging, and availability of radiographs. Analysis included determination of, (1) extracortical bone growth over the bone-implant junction, (2) osseointegration at the bone-implant shoulder, (3) cortical bone loss at the shoulder of the prosthesis and, (4) radiolucent line (RL) progression adjacent to the cemented stem fixation (Figs. 3a *and b*). As the CPS® device does not feature a cemented stem, these implants were not included in the radiographic analysis. Radiographic images taken immediately post-operation were used to measure the most proximal point on the greater trochanter down to the most distal point of the patellar surface, and %bone resection was calculated.

Extracortical Bone Formation and Osseointegration

The implant shoulder was divided into four quadrants (antero-posterior and medio-lateral) and the presence of extracortical bone growth scored as 0 where no extracortical growth was observed, and 1 when bone growth was observed in any 1 of the 4 quadrants. Similarly, evidence of radiographic osseointegration was also scored, where the presence of a radiolucent line separating the bony pedicle from the implant surface in any 1 of the 4 quadrants deemed the collar non-osseointegrated (score of 0). When radiographic osseointegration was present, the collar was given a score of 1.

Cortical Bone Loss

Cortical bone loss was defined as the clear separation of bone (> 1mm) from the shoulder of the implant. If a gap of > 1mm was observed, a score of 1 was given, while no cortical bone loss at the interface was given a score of 0.

Radiolucent Line Score

The progression of a radiolucent line at the bone-cement interface adjacent to the stem was quantified from serial radiographs. Each AP and ML radiograph were divided into 12 equidistant zones (Fig. 3c) [10]. A score of zero indicated that no radiolucent lines were observed. A score of 1 was given when a radiolucent line was observed in 1 zone and a maximal score of 24 indicated a loose stem fixation

surrounded by radiolucent lines along the entire length, in both AP and ML planes. The progression of these lines was measured over the follow-up period.

Statistics

Implant survival was determined using a Kaplan-Meier analysis starting from the date of the original surgery with an end point of failure for any reason. Endoprosthetic failure was defined as the need for complete revision of the cemented component and conversion to a different prosthesis. Removal of the implant due to disease progression and amputation was not included as a cause of implant failure. Replacement of mechanically worn parts (*e.g.*, bushings for the hinge knee replacement) were counted as complications and not as implant failures. The parameters of implant type, sex, age, %bone resection, implant lengthening, and length of follow-up were correlated with implant complications and the need for revision surgery. Differences in the prevalence of complications were assessed using the chi-square test. A Mann Whitney U test was used to compare radiographic scores between groups. All analyses were performed using IBM SPSS software (v25.0, SPSS, Illinois, USA) where p values < 0.05 were considered significant.

Results

Patient Survival

A total of 7 patients died (75.9% survival) (**Table 4**) where 3 of the 7 deaths showed poor response to chemotherapy at the time of surgical tumor resection. Femoral tumor recurrence occurred in 3 patients (10.3%) and an amputation was performed in 2 patients at a mean follow up of 1.64 ± 0.95y (0.97 and 2.31y). The third patient was converted to a total femoral implant at 10-years follow up.

Implant Removal

Kaplan-Meier analysis showed an implant survivorship of 100.0% in the Stanmore® group, 90.0% in the GMRS®, 81.8% in the CPS®, and 33.3% in the Repiphysis® group over the follow up period (Fig. 4). When all implant types were combined, overall implant survival was 82.8%. A total of 5 implants (17.2%) were revised (Fig. 5 and **Table 5**). A trend of increased implant revision in male patients was observed (71.4%, $p = 0.058$). The use of the extendable Stanmore® prosthesis was favored in the younger age group ($p = 0.025$) whereas the GMRS® implant was most commonly used in older patients ($p = 0.043$). No significant differences in the total dose of MAP given per patient were found when compared between each of the implant groups (**Table 6**).

Complications, lengthening and %bone resection

Sixteen of 29 patients (55.2%) were re-admitted during the follow up period and clinical complications were identified in 83.3% of patients. A trend was seen where the incidence of complications increased as the length of follow up increased ($p = 0.057$). All 5 of the Stanmore® prostheses were lengthened in addition to 2 Repiphysis® and 1 CPS® implant. The mean number of lengthening sessions was 10.9 ±

3.1 (range, 4–28) and the mean lengthening amount was 56.2 ± 20.3mm (range, 17–175mm). Percentage bone resection varied between groups (**Table 7**).

Radiographic Findings

A significantly increased incidence of extracortical bone growth was measured adjacent to the Stanmore® implants (mean score, 0.83 ± 0.06) when compared with the GMRS® (0.44 ± 0.08, $p < 0.0001$) and Repiphysis® (0.31 ± 0.12, $p < 0.0001$) implants (Fig. 6). Thirty-one of the 41 radiographs analyzed in the Stanmore® group demonstrated osseointegration (75.6%), and 11 of the 39 radiographs (29.2%) showed evidence of osseointegration at the collar region in the GMRS® group, while none of the 19 radiographs had osseointegrated in the Repiphysis® group (Fig. 7). Significantly decreased cortical bone loss was measured in the Stanmore® group (mean, 0.10 ± 0.05) when compared with the GMRS® (0.36 ± 0.08, $p = 0.005$) and Repiphysis® implants (0.69 ± 0.12, $p < 0.0001$; Fig. 8). The progression of radiolucent line formation progressed most rapidly in the Repiphysis® group (Fig. 9). Significant correlations between implant failure and increased cortical loss ($p = 0.017$) and increased radiolucent line score and cortical loss ($p = 0.049$) were found. No other significant correlations were found.

Qualitative Analysis: CPS® Implant

Radiographic analysis of all patients with a CPS® implant showed stable bone-implant fixation with no evidence of aseptic failure. Bone hypertrophy at the implant shoulder was observed in all patients in the years following surgery, with hypertrophy also seen associated with the pins in some patients (Fig. 1*0*).

Discussion

Bone tumors in children are rare and prior to the use of effective chemotherapy, overall patient survival rates were reported to be 15–20% at 2-years following surgical resection and/or radiotherapy [26, 27]. This study demonstrated a patient survival rate of 75.9% over a mean follow up of 4.25 years. Although patient survival is highly dependent on the stage of osteosarcoma at diagnosis, our result is similar to other recent studies who report contemporary 5-year patient survival rates ranging between 60–78% in pediatric patients following limb-salvage and MAP treatment [28–31]. Thus, the challenges of DFR longevity remains a priority as overall survival and activity levels continues to improve however, surgery is challenging in growing children and problems can result in loss of joint function, high-level amputation, and systemic sequelae for the patient [32]. Aseptic loosening in young and physically active patients who place high demands on their prosthesis is a major concern [33]. A study by Unwin *et al.* [6] reported a 67.4% probability of a Stanmore® DFR survival at 10 years with a significantly higher risk of ASL (13.6%) in patients < 20-years of age. Further, this study also identified that patients < 20-years of age and with > 60% of bone resection, having the poorest prognosis. In this study, an encouraging overall implant survival rate of 82.8% was found and the incidence of ASL that required revision was 10.3%. No correlation between %bone resection and implant failure was seen although mean levels were less than 60%. To determine load distribution within the intramedullary fixation in adults, a clinical study by Taylor *et al.* [34] added strain gauges and telemetric instrumentation to a massive implant. At 100 weeks post-

surgery, 60% of the applied load was directed through the cemented stem fixation when compared with 25% in the more immediate post-op period. These findings suggested a progressive mechanical cause of ASL and led to the concept that osseointegration at the shoulder offered more beneficial load distributions. As such, the Stanmore® and CPS® implants were designed to maximize osseous growth at the shoulder, and in this study, none of these implants failed due to ASL. Hydroxyapatite is classified as a bioactive, osseoconductive and osseoinductive material and bone is able to chemically bond with it providing increased interfacial and mechanical coupling, to superior levels when compared with a polished titanium implant surface [35, 36]. Our results showed significantly increased extracortical bone growth and osseointegration to the HA collar in the Stanmore® group when compared with both the GMRS® and Repiphysis® implants. Significantly reduced cortical loss and the progression of radiolucent lines was also evident in Stanmore-given patients over the follow up period. These results are similar to other studies that investigated osseointegration and ASL [10, 13, 14]. This study demonstrated poor performance of the Repiphysis® design where 2 of the 3 implants inserted were revised. Results are similar to other studies that report high rates of ASL as well as mechanical failure in young patients [37–41]. Two recent studies also reported a 100% implant survival rate of the Stanmore® implant in pediatric patients and both demonstrated overall poor survival (79.2% at 2-years and 21% at 5-years) of the Phenix-Rephiphysis® implant at a mean follow-up of 6.2 years [42] and 32% survival at 6-years [43].

Infection of massive endoprostheses ranges between 8–40% [44, 45] with CPS® implant infection reported as 14% over a 20-year follow-up [46]. In this study, none of the DFR implants were revised due to infection and 3 patients were successfully treated for implant-associated infection. Two of these 3 patients had received a CPS® implant, however this group of patients also experienced significantly higher %bone resection levels and the increased tissue exposed during surgery may account for the infections observed. Two CPS® implants failed due to fracture of the titanium traction bar. In both patients the implants appeared radiographically well fixed. Traction bar fracture has been reported in the same location in other studies [47, 48] however, the reason for fracture remains unclear. Nevertheless, our results indicate that the CPS® implant continues to be a reliable option for distal femoral limb salvage surgery and the absence of ASL is encouraging. Finally, multidrug chemotherapy impairs bone growth and causes early radiological signs of loosening in DFRs [49]. No significant differences were found when the total dose and length of treatment was compared between implant groups.

Our study had several limitations. First, osteosarcoma is rare and as such, the study is limited by its small sample size as well as loss of follow-up as patients transitioned out of the hospital system and into adult care. Furthermore, the cohort of patients presented individual differences in their activity levels, which would impact prosthetic survival. Because this study was a retrospective study, both AP and ML radiographs were not always available for review and this reduced the number of patients followed-up beyond 6-years post-operatively.

In conclusion, chemotherapy and limb-salvage surgery yield good oncologic outcomes. Results from this study suggest that implant designs modified to augment osseointegration at the bone-implant shoulder may be critical in reducing the initiation and development of ASL in this vulnerable patient group. While

the limitations of this study do not allow us to conclude that extracortical bone growth and osseointegration is directly responsible for a lower incidence of ASL, our results do confirm the ability of the HA collar to increase radiographic bone-implant contact at the implant shoulder. Further studies that involve a larger cohort over a longer follow-up are needed to confirm these preliminary findings.

Declarations

Acknowledgments and Conflicts of Interests

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Tables

Tables 1-7 are available in the Supplementary Files section.

Figures

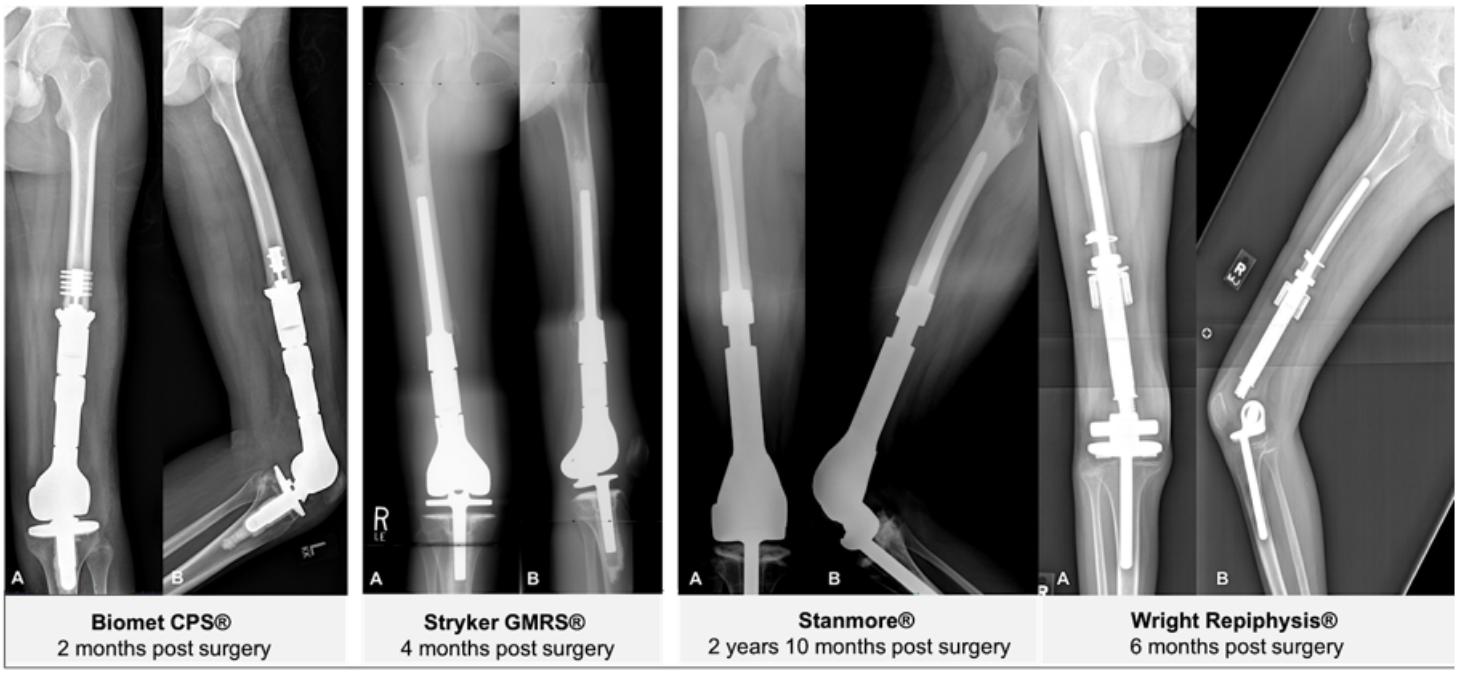

Figure 1

Antero-posterior [A] and medio-lateral [B] radiographs of each of the endoprosthetic designs investigated. Fifteen (51.7%) male and 14 (48.3%) female patients at a mean (and standard error of the mean) age of 13.09 ± 0.56 years (y) (range, 7.9 – 18.9y) were followed up for a mean of 4.25 ± 0.55 y (range, 0.04 – 10.5y). Thirteen implants were inserted into the left femur and 16 into the right. Of those implants fixed using an intramedullary stem, all were cemented in place.

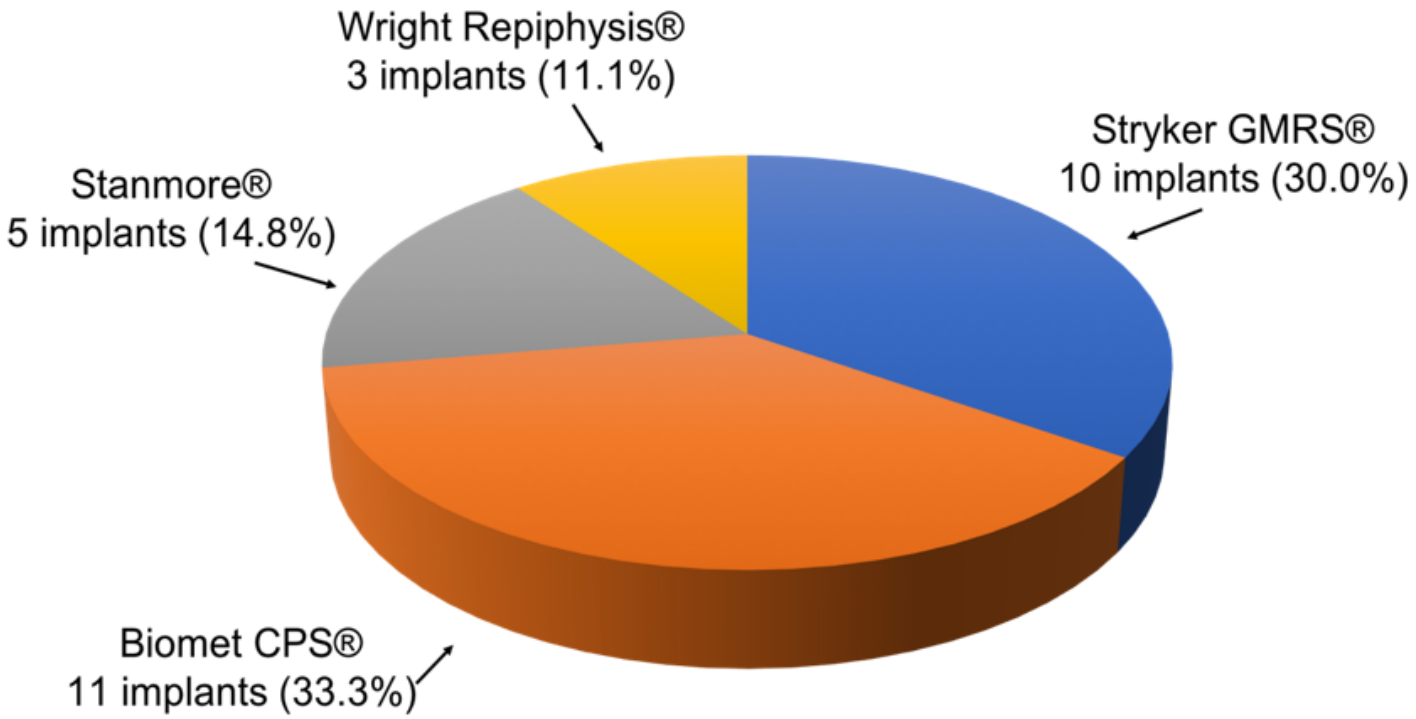

Figure 2

A pie chart showing the number and distribution of implant designs investigated. Of the endoprostheses inserted, 11 were CPS® implants (33.3%, mean FU 4.07 ± 0.88 y (range, 0.85 – 8.41y)), 10 were GMRS® (30%, mean follow up 3.61 ± 1.04y (range, 0.04 – 10y)), 5 were of the Stanmore® design (14.8%, 4.85 ± 1.19y (range, 1.14 – 7.32y)) and 3 were Repiphysis® implants (11.1%, 6.54 ± 2.20y (range, 2.92 – 10.5y))

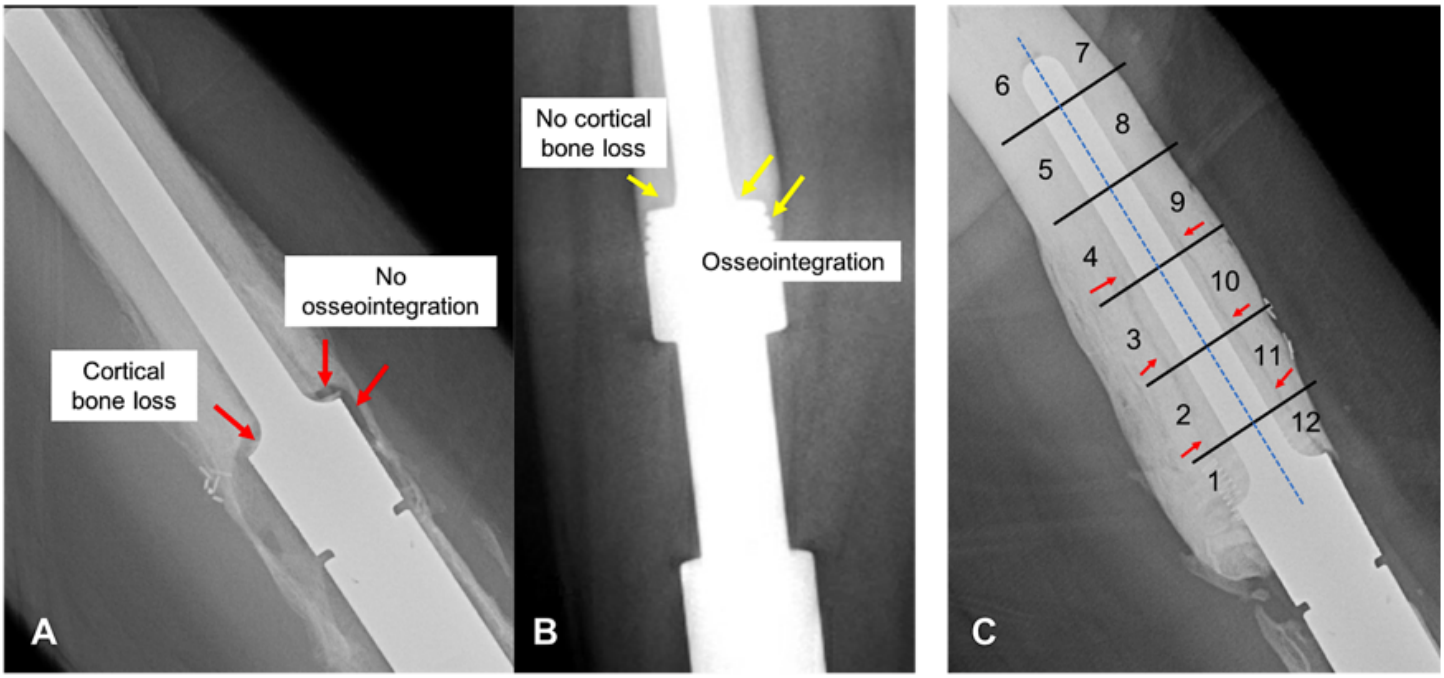

Figure 3

[A] An AP radiograph of a GMRS® implant showing cortical bone loss at the at the shoulder of the implant with a clear radiolucent line separating the implant surface from extracortical bone (a non-osseointegrated implant). [B] An AP radiograph of a Stanmore® implant showing bone in direct contact with the implant surface (an osseointegrated implant), with no cortical bone loss at the shoulder. [C] An AP radiograph showing the equidistant dividing lines that created six zones along the medial and 6 along the lateral aspects adjacent to the intramedullary stem. The arrows show a RL line. A maximal score of 12 indicated the presence of a radiolucent line in all 12 of these divided zones. A total score of 24 indicated additional radiolucent lines in the 12 zones measured in the corresponding ML radiograph.

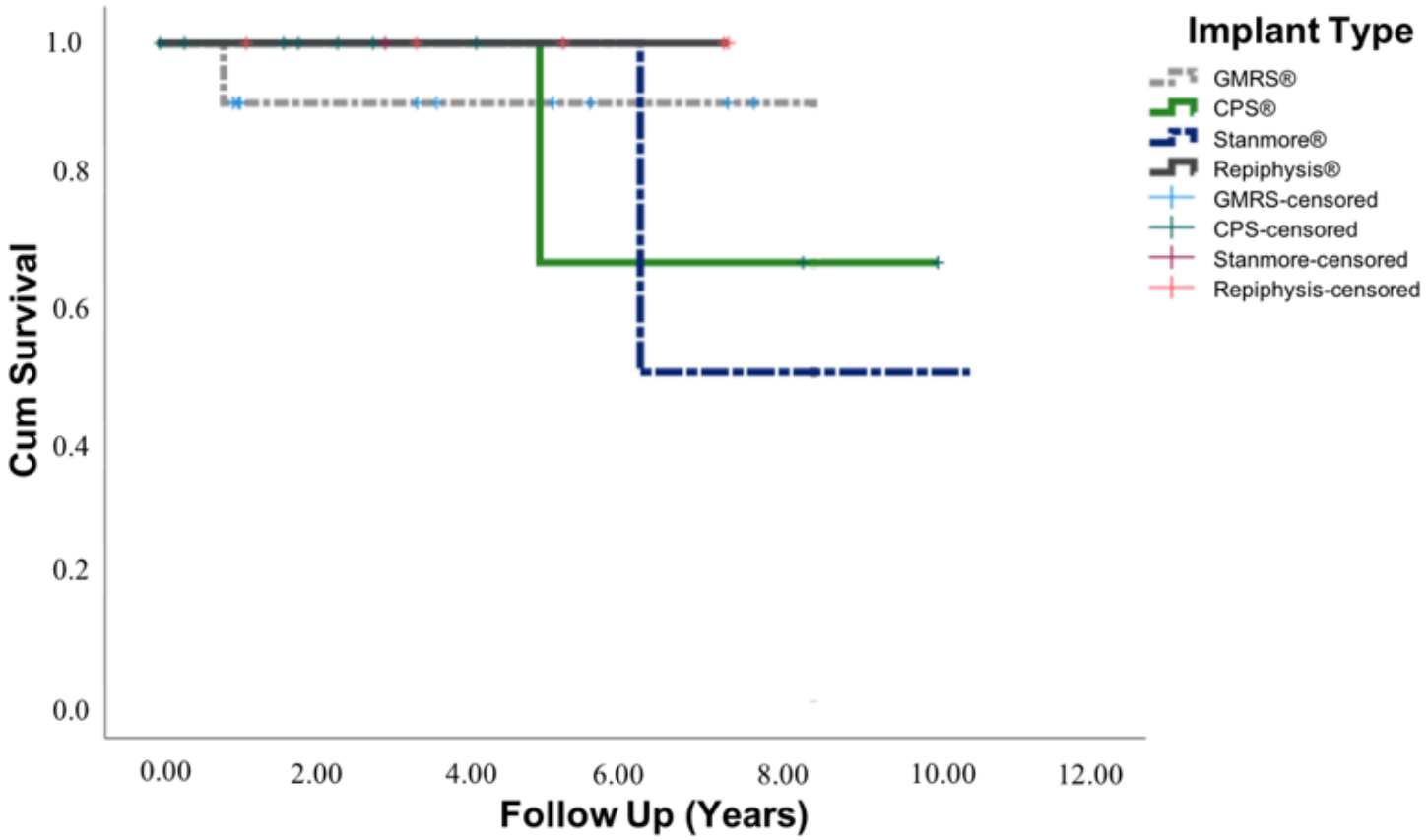

Figure 4

Kaplan-Meier survival analysis of the DFRs with respect to implant manufacturer and implant fixation failure for any reason. The percentages presented in the brackets are the survival rates of each implant design. A total of 5 implants (17.2%) were revised; 2 CPS®, 2 Repiphysis® and 1 GMRS®. Three of the 5 implants were revised due to ASL (10.3% of 29 patients), and 2 to implant fracture (6.9% of 29 patients)

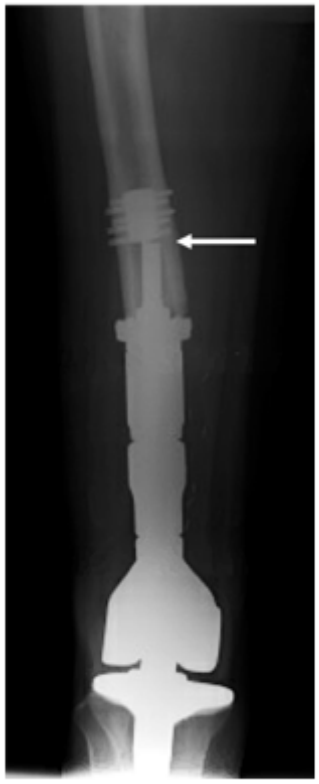

Figure 5

An AP radiograph showing fracture of a CPS® implant 2 year 8 months post-surgery. The second CPS® implant fractured in the same region.

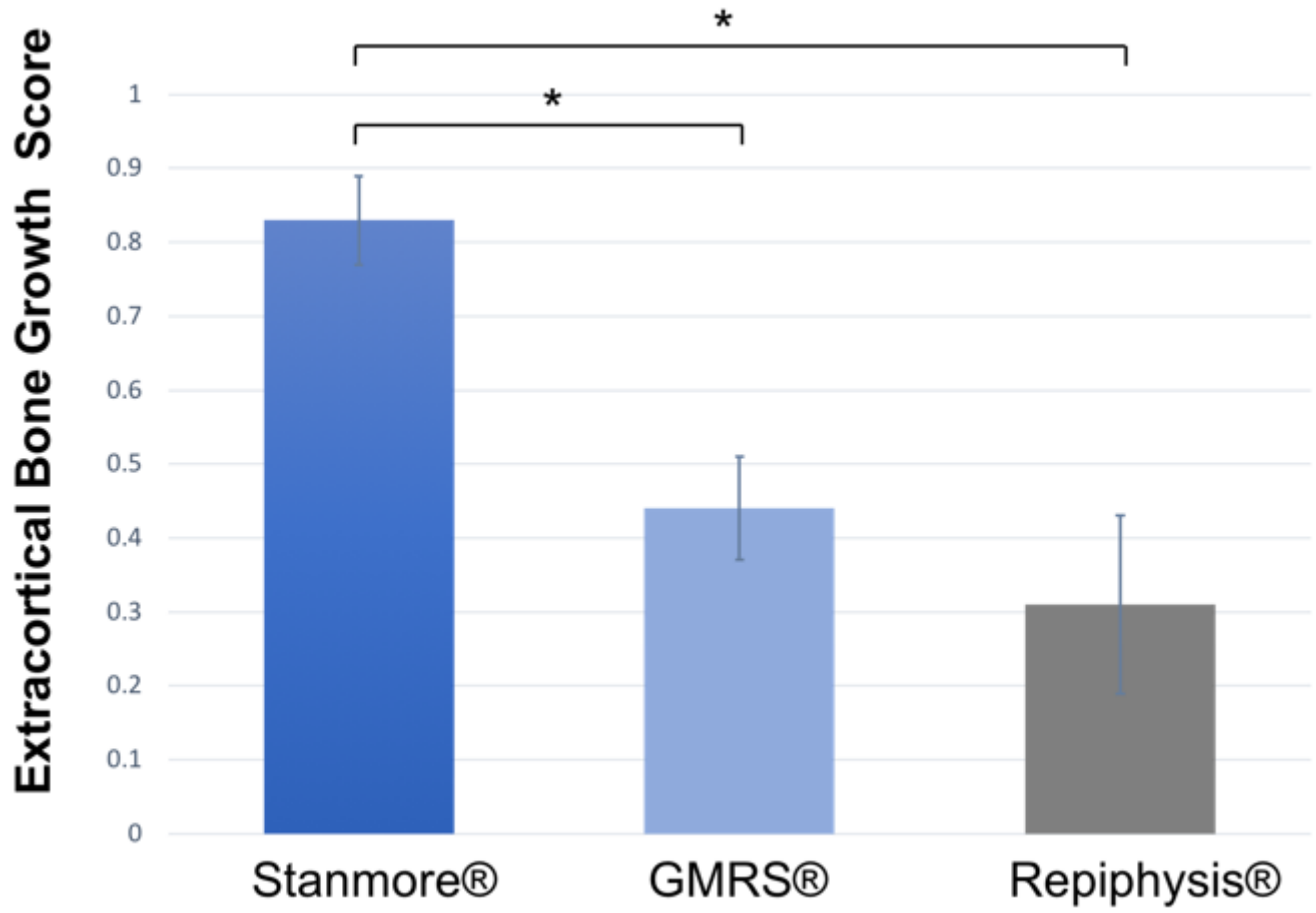

Figure 6

Extracortical bone growth score between groups. *$p < 0.0001$

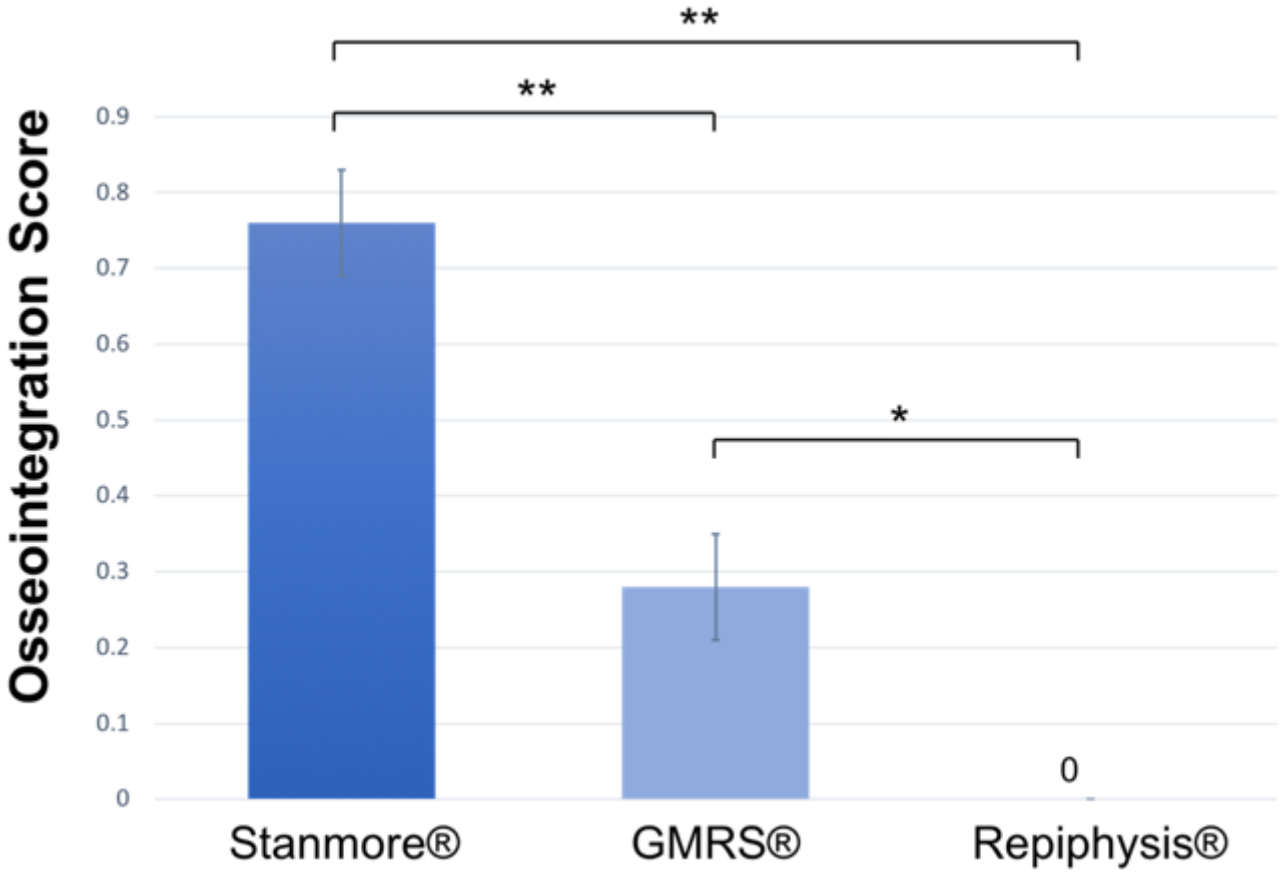

Figure 7

Osseointegration score between groups. The mean osseointegration score was significantly increased in the Stanmore® group (0.76 ± 0.07), when compared with the GMRS® (0.28 ± 0.07) and Repiphysis® implants. The non-osseointegrated Stanmore® implants were all in the first- or second-year following surgery and all went on to integrate in the subsequent years post-surgery. *$p = 0.019$, **$p < 0.0001$.

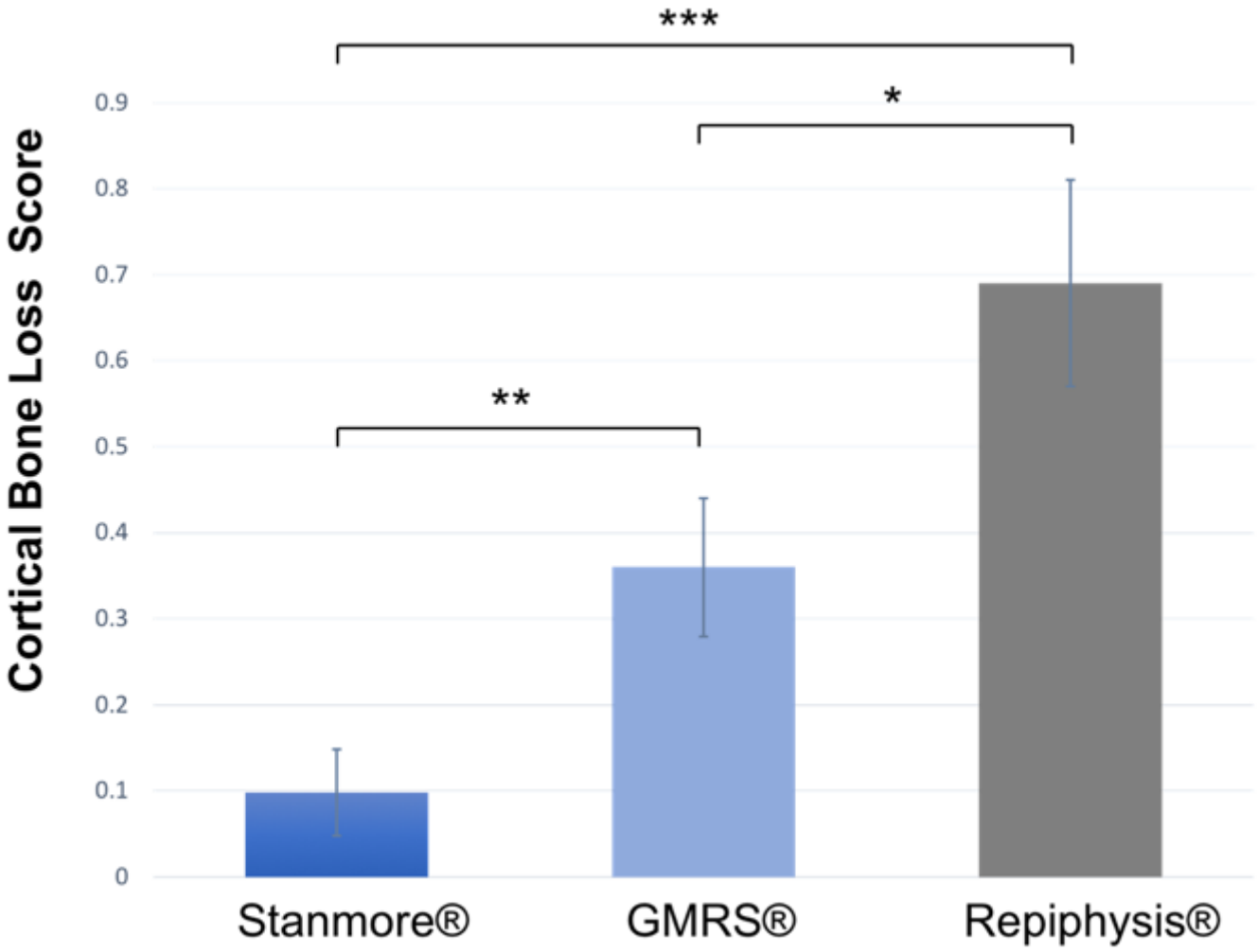

Figure 8

Cortical bone loss score between groups. 57.9% and 35.8% of the radiographs assessed in the Repiphysis® and GMRS® group respectively, demonstrated cortical bone loss at levels > 1 mm while 9.76% of radiographs showed signs of loss in the Stanmore® group of implants. The number of patients with both AP and ML radiographs at a follow up period > 5 years were limited, and as such, comparisons at 6-, 7- and 8-years post-surgery were not conducted. *p = 0.028, **p = 0.005, ***p < 0.0001

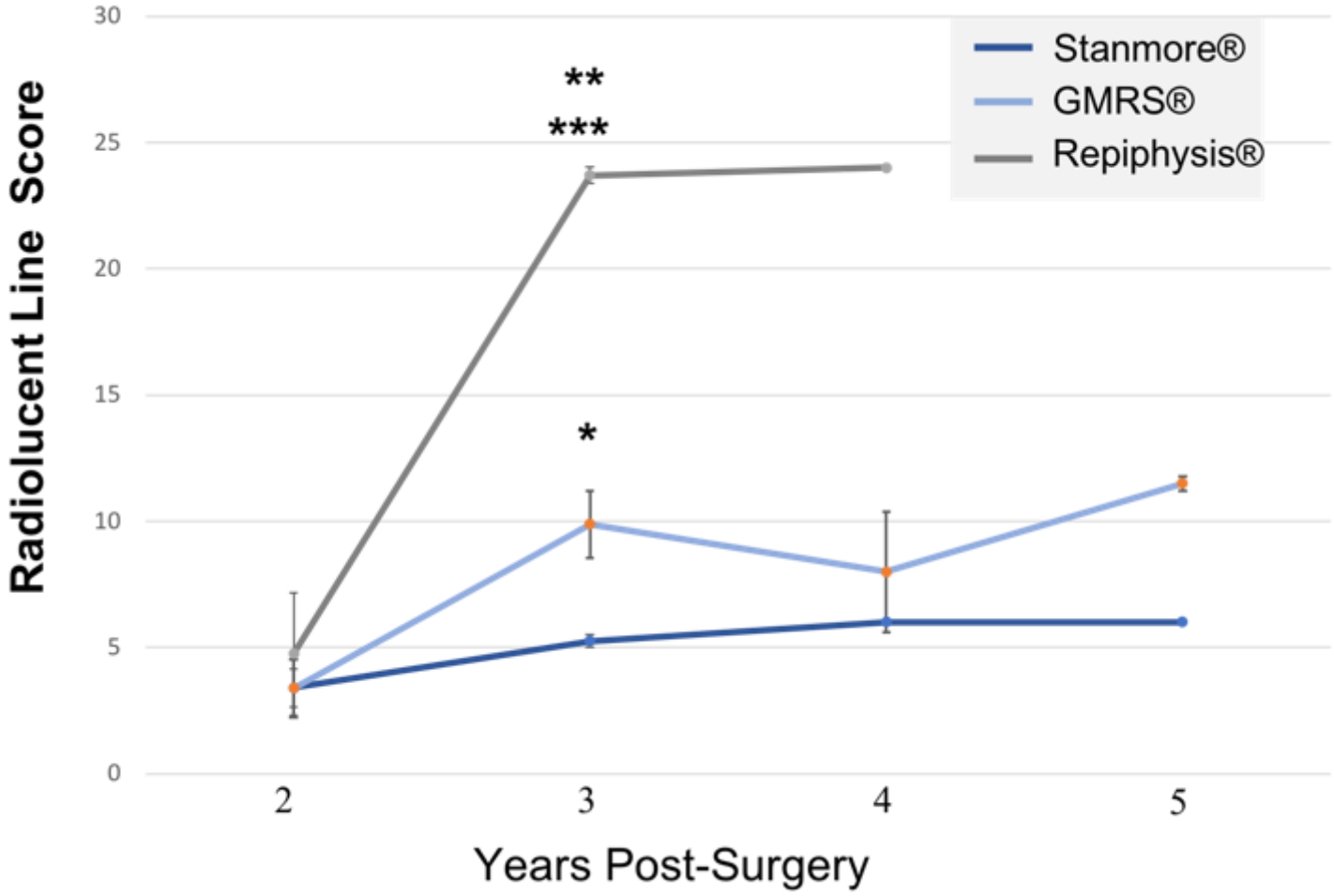

Figure 9

A graph showing the radiolucent line score in each of the groups over the first 5-year period post-surgery. At 2-years post-operatively, the mean RL score in the Repiphysis® group was 4.75 ± 2.42, higher than the 3.40 ± 0.75 scored in the Stanmore® group of implants and 2.86 ± 1.18 in the GMRS® group. However, no significant differences were found at this time-point. At 3-years post-operatively, the RL incidence had increased in the Repiphysis® group (23.7 ± 0.33) and was significantly higher than both the GMRS® group (9.88 ± 1.32) and Stanmore® group of implants (5.25 ± 0.25, $p = 0.012$ and 0.026 respectively). A significantly increased RL score was measured in GMRS® implants when compared with the Stanmore® group ($p = 0.008$). At 5-years follow up, the RL score had increased to 11.5 ± 0.29 in the GMRS® group, and 6.00 ± 0.01 in the Stanmore® group ($p = 0.053$). *$p = 0.008$, **$p = 0.026$, ***$p = 0.012$.

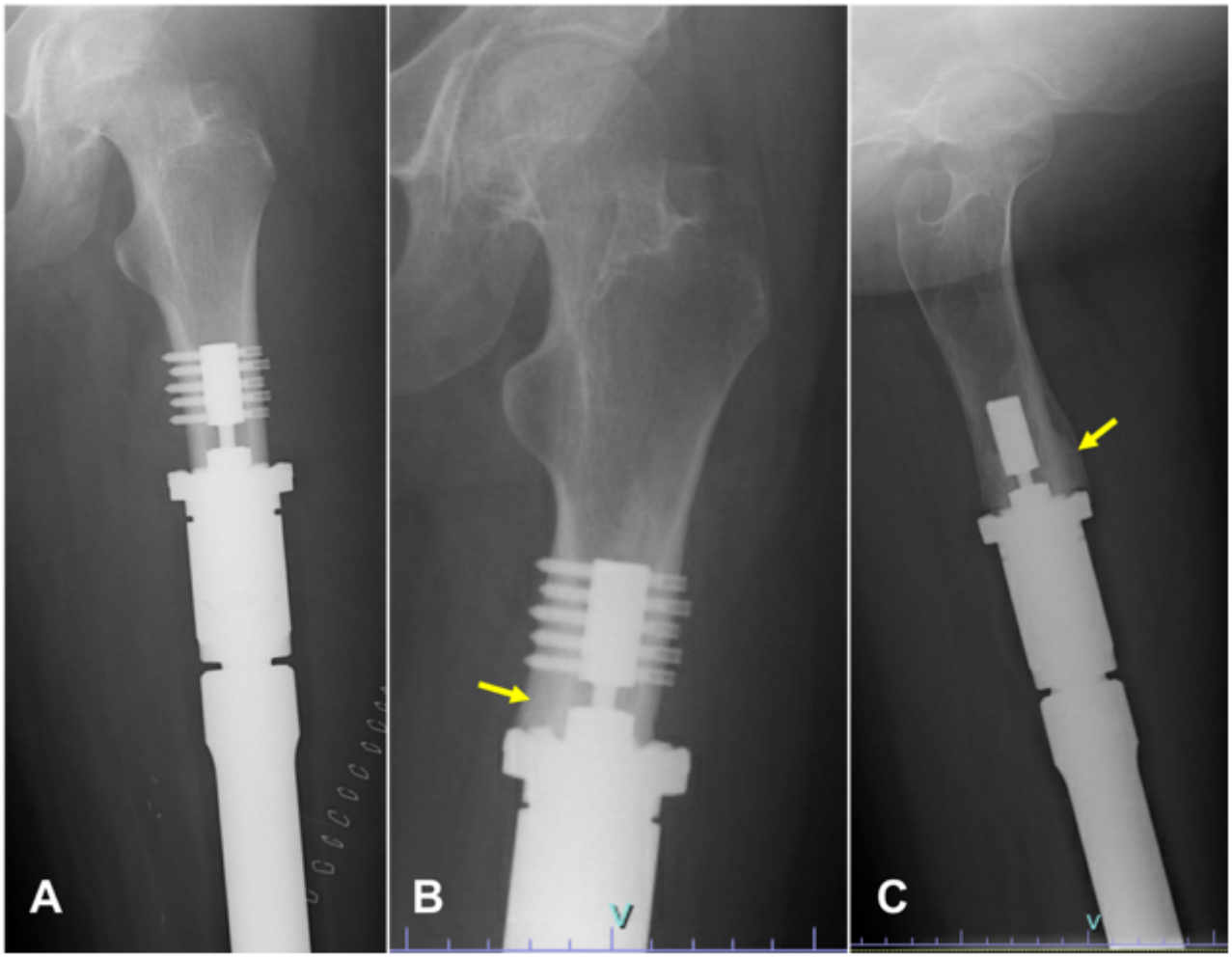

Figure 10

[A] A radiograph of a CPS® implant taken immediately post-surgery. [B] The same patient 2-years post-operation showing cortical hypertrophy at the implant shoulder (arrow) in the AP and [C] ML aspect. No cortical bone loss > 1 mm was evident and no extracortical bone growth was observed in any of the patients.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1to7.docx