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Pilot study on the in-vitro effect of radiation therapy on bending stiffness of intramedullary photodynamic implants

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Abstract
Photodynamic implants are an increasingly popular minimally invasive option for the surgical treatment of metastatic bone disease. Following surgery, adjuvant radiation therapy (RT) is frequently administered to achieve better disease control and improve patient quality of life, but the role of RT in implant failures associated with photodynamic implants remains unclear. The aim of this study is to determine if the therapeutic RT range of 10–50 Gy affects the biomechanical properties of photodynamic implants. For the experimental group, 15 photodynamic implants were divided evenly into 5 groups that were exposed to different doses of RT (10, 20, 30, 40 and 50 Gy). The control group consisted of 14 non-irradiated photodynamic implants. Four-point bending tests were conducted on all implants to determine bending stiffness. One-way ANOVA was conducted. Bending stiffness (N/mm) mean ± standard deviation for the non-irradiated control group was 38.0 ± 1.2. Bending stiffness (N/mm) mean ± standard deviation for the irradiated experimental groups was 39.2 ± 1.0. No significant difference was found between any groups. RT doses at a range of 10–50 Gy do not affect the bending stiffness of photodynamic implants. The yield and ultimate failure loads were 263.4 ± 5.2 (N) and 305.9 ± 5.5 (N) in the non-irradiated group vs. 266.8 ± 6.4 (N) and 306.8 ± 6.4 (N) in the irradiated group, respectively. The lack of statistical significance in the difference in stiffness, yield, and ultimate load properties among the groups means that it is less likely that RT at the evaluated doses contributes to intrinsic implant failure. Further studies need to be conducted to conclude the potential effect of RT on other mechanical properties of photodynamic implants.

Keywords Oncology, Radiation therapy, Photodynamic implants, Biomechanics

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Introduction

Bone is one of the most common sites of metastatic disease, occurring in an estimated 30–75% of patients with advanced cancer [1, 2]. Skeletal-related events (SRE) such as pathologic fractures occur in 9–29% of patients with bone metastases, resulting in substantial morbidity and mortality [1]. Consequently, bone metastases reduce quality of life (QOL) and negatively impact patients physically, functionally, and psychosocially [2, 3]. While the treatment of skeletal metastases is rarely curative, multidisciplinary palliative measures can be taken to improve patient QOL with supportive treatments such as chemotherapy, radiation therapy (RT), and surgery.

For long bone osteolytic metastases, where impending or pathologic fracture is present and the patient has a poor overall prognosis, the combined use of intramedullary nails and postoperative RT is often considered as a palliative option [4–6]. Post-operative RT doses range from 8 to 50 Gy [7–9]. Traditionally, metallic implants have been used in orthopedic oncology for the stabilization of affected bones. However, metallic implants have several disadvantages such as introducing imaging artifacts that impact CT planning for RT, modulating radiation dosage at the implant interface, and obscuring potential local tumor recurrence and/or progression [5]. Recent biomaterial innovations such as the Photodynamic Bone Stabilization System (PBSS; IlluminOss Medical, Inc.) attempt to circumvent the major drawbacks of metallic implants in the treatment of metastatic bone disease [10, 11].

PBSS is an intramedullary photodynamic implant composed of two major components: (1) a polyethylene terephthalate (PET) balloon component, also known as Dacron, which is a thermoplastic polymer resin material with excellent mechanical strength and good biocompatibility [12–14], and (2) a liquid monomer component that is polymerized through a blue light curing process and has biomechanical properties similar to dental cement [15]. Because the balloon and liquid monomer can be introduced into the lesion before undergoing the polymerization process, each patient will have a custom intramedullary nail that internally augments osteolytic bones that have suffered structural compromise due to tumor infiltration. The unique flexibility of the PBSS is especially valuable in matching the contour of curved bones affected by metastatic bone disease. Further, due to the radiolucent nature of the components of the PBSS, there are limited imaging artifacts, which enables improved visualization of bone healing, potential tumor recurrence and/or progression, and accurate postoperative RT planning [16].

As postoperative RT plays a pivotal role in improving patient QOL and local tumor control, it is important to understand the potential effects of RT on the mechanical properties of photodynamic implants such as the PBSS to mitigate the risks of implant failure. The goal of this study is to determine if the therapeutic RT range of 10–50 Gy affects the biomechanical properties of photodynamic implants. In this pilot study, four-point bending tests on irradiated and non-irradiated photodynamic implants were conducted to determine if RT at a range of 10–50 Gy affects the bending stiffness, yield, and ultimate failure loads of irradiated versus non-irradiated photodynamic implants. It was hypothesized that the mechanical properties of the PBSS would not be affected by RT regardless of dose.

Materials and methods

Sample preparation

Twenty-nine 9×180 mm photodynamic implants were prepared by three trained IlluminOss technicians (B.R., G.D., and T.O.). Samples were prepared using the IlluminOss technique guide. Each PET balloon was attached to a flow tube and filled with 13 mL of liquid monomer. The liquid monomer-filled balloon was then cured under blue light in a light-curing oven (DYMAX UV Light Curing System) for 400 s to polymerize the monomer. The flow tube was then detached from the completed photodynamic implants.

All 29 photodynamic implants were sent to a collaborator in Germany, who randomly selected 15 of the 29 to be split into the experimental radiation groups. The 15 photodynamic implants were equally split into 5 groups and exposed to different dosages of photon RT: (1) 10 Gy, (2) 20 Gy, (3) 30 Gy, (4) 40 Gy, and (5) 50 Gy. Thus, there were five experimental groups each with 3 photodynamic implants that were exposed to varying degrees of radiation and one control group composed of 14 non-irradiated implants. To limit bias, only the collaborator had access to a record of the irradiated and non-irradiated samples. As such, when the implants were returned, the researchers who conducted the mechanical testing were blinded to which samples were irradiated versus non-irradiated.

Radiation procedure

The photodynamic implants that were randomly assorted into the irradiated groups were individually placed on two polymer-radiolucent support bridges above the therapeutic table. Support bridges were tested prior to experimentation to confirm radiolucency and ensure there was no photon RT beam distortion. The contact area of the PBSS and support bridges was <5 mm. The photon RT beam was directed at each implant from multiple directions to ensure the entirety of the implant was irradiated evenly. Each dose of photon RT was administered in a single fraction.

Static four-point bend testing

Four-point bending test fixtures were attached to the Instron device Instron Electropuls E3000 Test Frame (Cal. No. GA-0014)] to conduct the bending tests (Fig. 1A). Each photodynamic implant was centered across the support pins of the four-point bending fixture base, such that the test sample had uniform overhang on both ends of the support pins (Fig. 1B). The implant was pre-loaded with 2 N. A continual loading rate of 5 mm/min was applied until failure or until a maximum displacement of 20–30 mm was reached (Fig. 1C) based on the ASTM F1264-03 protocol. Loading and displacement data from the Instron was collected. Bending stiffness (N/mm) was calculated. These steps were repeated for each sample.

Statistical analysis

Descriptive statistics were reported as mean and standard deviations. Shapiro-Wilk tests were used to confirm the normality distribution of data. One-way analysis of variance (ANOVA) was used to evaluate differences between the experimental irradiated groups and non-irradiated control group. Post hoc power analysis was conducted to assess the study's sensitivity to detect effects given the fixed sample sizes. P-values <0.05 were considered statistically significant.

Results

The load-displacement graphs for the non-irradiated and irradiated groups in the 4-point bending test are shown in Fig. 2. Load-displacement curves showed similar trends for all specimens in both groups. Bending stiffness (N/mm) mean ± standard deviation for the non-irradiated control group was 38.0 ± 1.2 (Fig. 3). Bending stiffness (N/mm) mean ± standard deviation for the irradiated experimental groups was 39.31 ± 0.27, 39.48 ± 1.10, 38.38 ± 0.53, 38.95 ± 0.99, and 38.94 ± 1.14, for 10 Gy, 20 Gy, 30 Gy, 40 Gy, and 50 Gy, respectively. There was no statistically significant difference in the bending stiffness amongst the irradiated groups ($p=0.761$), between the different irradiated groups and control group ($p=0.738$), and between the general combined irradiated group (defined as the collective group of 15 photodynamic implants that received any dose of radiation) and control group ($p=0.322$). The yield and ultimate failure loads were 263.4 ± 5.2 (N) and 305.9 ± 5.5 (N) in the non-irradiated group vs. 266.8 ± 6.4 (N) and 306.8 ± 6.4 (N) in the irradiated group, respectively (Fig. 4). There were no statistically significant differences ($p>0.05$) among the groups in both yield and ultimate load properties.

Discussion

To date, there have been no dedicated studies that have examined the potential effects of RT on the mechanical properties of photodynamic implants such as the PBSS.

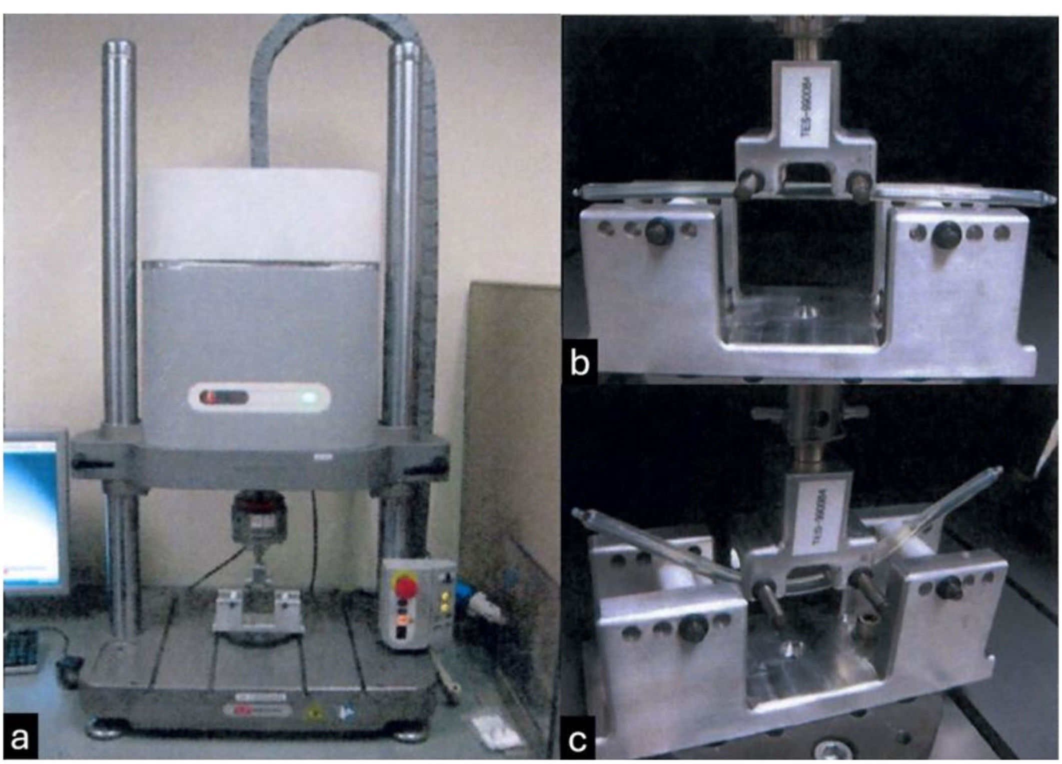

Fig. 1 Four-point bending biomechanical testing set-up

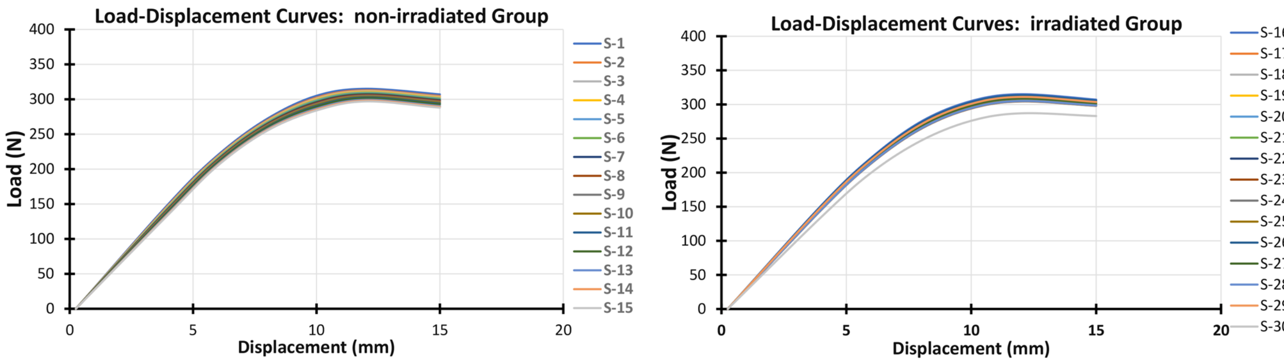

Fig. 2 Load-displacement curves for non-irradiated and irradiated photodynamic implants

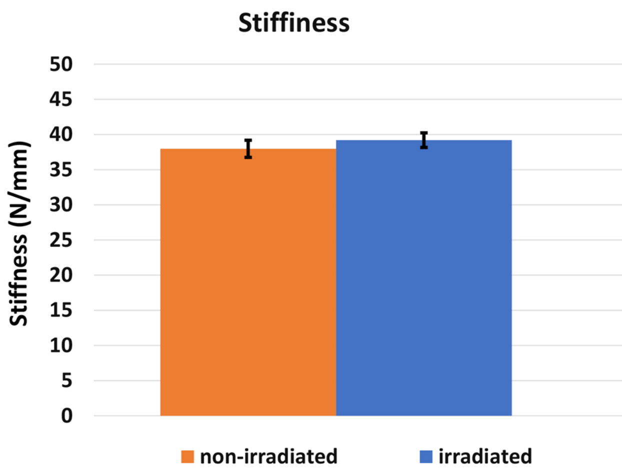

Fig. 3 Bending stiffness of non-irradiated and irradiated photodynamic implants

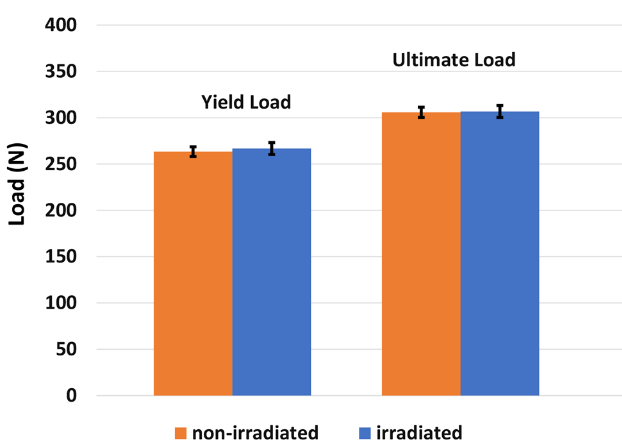

Fig. 4 Yield and ultimate loads of non-irradiated and irradiated photodynamic implants

Further, there is a paucity of research investigating the overall impact of RT on the biomechanical properties of any class of intramedullary nail. Preclinical orthopaedic studies on the effects of RT have been primarily focused on bioresorbable implants [17], in vitro assessments of titanium implants [18], and porous-coated femoral implants [19]. In this study, the mechanical properties (bending stiffness, yield and ultimate loads) of irradiated versus non-irradiated photodynamic implants were evaluated through four-point bending tests. The results aligned with the initial hypothesis as there was no significant difference found in the bending stiffness, yield, and ultimate load values between the experimental and control groups across radiation doses spanning 10–50 Gy.

This study showed several limitations. First, this study had a fixed sample size due to budgetary limitations; thus, a post hoc power analysis was conducted to evaluate the sensitivity of the study to detect significant differences between the control and experimental groups. The effect size was quantified using Cohen's f, which measures the proportion of variance in the outcome attributable to group differences, relative to within-group variance [20]. With a Cohen's f of 0.823, the post hoc analysis indicated that the study achieved a power of 87.9%, assuming a significance level of $\alpha = 0.05$. Based on this analysis, the study would be sensitive enough to detect a significant bending stiffness difference as small as 4.7% between groups. There is no literature that defines clinically meaningful difference in the bending stiffness of intramedullary implants. Although, prior literature by Reddy et al. [21] observed that for load bearing bones such as the femur and tibia a 38% change in bending stiffness led to a significant reduction in maximum load and energy absorption capacity. Using this 38% change as a reference for a clinically meaningful difference in bending stiffness, our study would have been sufficiently powered to detect such a difference if it existed. Thus, despite this study's fixed sample size, the high power suggests confidence in the finding that RT does not affect the bending stiffness, yield, or ultimate failure loads of PBSS. Second, this study was limited by the fact that only one size and configuration of the PBSS was tested. Only the 9 × 180 mm implant in a straight configuration was evaluated under in-vitro conditions, which would not mimic endogenous states. After implantation, the PBSS may assume varied shapes and configurations to fill irregular osteolytic lesion spaces, which could have structural weak points that RT may affect differently. Third, while four-point bending tests enable uniform loading across the sample between the support pin fixtures, loading forces will vary depending on the site where the PBSS is used. This mechanical testing method may not be fully representative of the forces that will be applied to the PBSS after implantation. Fourth, as this was a preliminary pilot study, only static mechanical properties of the implants were assessed. Further follow-up studies with different mechanical testing methods must be conducted to determine the potential impact of RT on dynamic mechanical properties of these implants. Fifth, only one type of RT, delivered in only one fraction, was used in this study, so conclusions about the potential impact of RT modality and fractionation on the mechanical properties of the PBSS would require further studies.

The liquid polymer of the PBSS has been compared to aluminum-free glass-polyalkenoate cement, which is a class of glass-ionomer cement used in dentistry [22, 23]. While the effects of RT on the mechanical properties of the PBSS have not been directly assessed, evaluations of the individual components and/or proxies of them (i.e. PET balloon and liquid monomer) have been investigated. Radiation exposure to PET has shown degradation of the polymer with changes to its microstructure [24, 25], but no studies were found to have evaluated mechanical property changes in relation to RT. As for the liquid monomer, several studies have investigated the survival of dental implants following RT to treat head and neck cancers [26–29]. Interestingly, the majority of these studies do not evaluate the intrinsic biomechanical properties of the dental implant itself but rather examine the survivability of the implant through the context of RT affecting the surrounding native bone. The preliminary study results show that RT within the range of typical postoperative palliative doses does not affect the mechanical properties of the PBSS. Further, as there appears to be a void of research directly assessing the effect of RT on the mechanical properties of the PBSS, this presents an opportunity for further research to be conducted.

Rather than an intrinsic PBSS implant failure, postoperative complications could be the result of the surrounding native bone having poor baseline quality. This potential confound is further exacerbated by postoperative RT, which is associated with decreased bone healing and remodeling [13]. Radiation is known to affect bone morphology and microstructure, decreasing the quality and density of bone [30]. Wright et al. [14] utilized murine models to explore the effects of RT on bone and found evidence of trabecular bone changes in as little as one week after a low dose radiation exposure of 2 Gy. Lima et al. [12] found that at an even lower dose of 1 Gy, mesenchymal stromal cell damage was seen three days post-radiation, and microarchitectural changes were seen in the bone 21 days post-radiation. Thus, while it is reassuring that the bending stiffness of the PBSS remained unaffected across the tested RT doses, this does not preclude the PBSS from implant failure. Postoperative radiation protocols often call for RT to be delivered along the entire length of the implant to reduce local tumor recurrence [13], which subsequently increases the fragility of the bone surrounding the implant. Damage sustained from RT to the surrounding native bone around the PBSS offers a possible explanation for implant failures.

Pathologic fractures are devastating complications in metastatic bone disease that drastically impact patient QOL. The primary goals of treatment for skeletal metastases focus on the reduction of pain, restoration of function, prevention of SRE, and local disease control [31]. Surgical intervention with non-traditional intramedullary nails like the PBSS – which are radiolucent and offer better imaging follow-up compared to their metallic counterparts – in conjunction with postoperative RT, is a viable palliative option for patients with metastatic bone disease. Available clinical studies investigating the use of the PBSS demonstrate good clinical outcomes at mid-term follow-up [32, 33]. However, given the destructive nature of metastatic bone disease, implant failures are generally expected, with a reported failure range between 15.8%[7] and 27.5%[11]. Evaluating potential causes of implant failure is crucial in metastatic bone disease, as reoperations cause a higher risk of implant replacement, infection, and delay in medical oncologic treatment. This study investigated the potential role of RT as a possible cause of implant failure for the PBSS, which found that radiation doses of 10–50 Gy did not result in any intrinsic reduction in the static mechanical property of bending stiffness.

In conclusion, the PBSS offers a viable, minimally invasive intramedullary option for stabilizing impending or pathologic fractures in long bones. Importantly, this pilot study has relieved initial concerns about RT-induced alterations to the bending structure of the PBSS implants; however, further studies are required to understand the effects of RT more holistically on the biomechanical properties of PBSS such as torsional, compressive, and tension testing.

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Author contributions
S.A.L. conception of research idea, management of project. M.H.G. analysis of data, original manuscript writing. A.K. analysis of data, manuscript revision, preparation of figures. J.J.C. original manuscript writing, manuscript revision. A.M.P. manuscript revision, management of project. E.O. original manuscript writing, statistical analysis. T.G. experimental design, data collection. All authors reviewed and approved the final manuscript.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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