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Complications - Other

Heterotopic Ossification Prophylaxis After Total Hip Arthroplasty: Randomized Trial of 400 vs 700 cGy

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ABSTRACT

Background: Heterotopic ossification (HO) is a known complication following total hip arthroplasty. Radiation is an effective prophylaxis, but an optimal protocol has yet to be determined. We performed a randomized, double-blinded clinical trial in high-risk patients to determine the efficacy of 400 vs 700 cGy doses of radiation.

Methods: One hundred forty-seven patients undergoing total hip arthroplasty and at high risk for HO at an urban medical center were randomized to receive either a single 400 or 700 cGy dose of radiation postoperatively. High risk was defined as a diagnosis of diffuse idiopathic skeletal hyperostosis, hypertrophic osteoarthritis, ankylosing spondylitis, or history of previous HO. Radiation was administered on the first or second postoperative day. A single blinded reviewer graded radiographs taken immediately postoperatively and at a minimum of 6 months postoperatively using the Brooker classification. Progression was defined as an increase in Brooker classification. Operative data including surgical approach, implant fixation, revision surgery, and postoperative range of motion data were also collected.

Results: A significantly greater portion of patients who received the 400 cGy dose demonstrated progression of HO than patients who received the 700 cGy dose. There were no wound complications. No preoperative factors were associated with a higher rate of progression. Patients who progressed had less flexion on physical examination than patients who did not progress, but this was not clinically significant.

Conclusion: Seven hundred centigray was superior to 400 cGy in preventing HO formation following total hip arthroplasty in high-risk patients and may be the more effective treatment in this population. Further studies comparing 700 cGy to dosages between 400 and 700 cGy may help to clarify if a more optimal dose can be identified.

Heterotopic ossification (HO) following total hip arthroplasty has a reported incidence of 2%-90% and can result in impingement [1,2]. Patient risk factors for HO include male gender, ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis, hypertrophic osteoarthritis, as well as a history of post-traumatic arthritis with prominent osteophyte formation [2,3]. Operative risk factors have been identified as cementless implants and bilateral operations, while the lateral surgical approach remains controversial [2-5]. It is believed that surgical insult stimulates mesenchymal cells present in the soft tissue to transform into osteoblasts, peaking around 32-48 hours postoperatively [6,7]. Prophylaxis options include radiation therapy and anti-inflammatory medication. Indomethacin has been used with good results but is contraindicated for patients with gastrointestinal or renal pathology [8]. Additionally, indomethacin interferes with warfarin therapy and may inhibit bone ingrowth into porous-coated systems [9].

Radiation therapy is the only prophylaxis agent that can be administered locally rather than systematically to exclude the porous ingrowth surface and incision from the targeted treatment area. It is thought to work by preventing mesenchymal differentiation into osteoblastic cells [7]. Radiation is best given in a single dose to prevent decreasing its efficacy [10]. The ideal dose would be

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Table 1
Comparative Studies.

Authors	Number of Patients	Dose of Radiation	Radiation Protocol	Follow-Up	Outcome	Complications
Coventry and Scanlon 1981 [15]	48 patients in 42 hips	2000 rads	Ten fractions over a 12-d period	Minimum 1 y	No massive HO, defined as >3 cm in diameter, attached to the femur or pelvis, or produced severe restriction of motion	Prolonged hospital stay, nonunion of trochanteric osteotomy
Ayers et al 1986 [16]	48 hips in 42 patients	1000 rads	200 rads/d for 5-7 d via anterior and posterior portals	Average 29 mo	As effective as prior study using 2000 rads	Nonunion of trochanteric osteotomy
Hedley et al 1989 [12]	17 hips in 16 patients	600 cGy	Single dose	Minimum 6 mo	All hips Brooker 0 or 1	None reported
Pellegrini et al 1992 [17]	62 hips in 55 patients	800 cGy vs 1000 cGy	800 cGy dose given in a single dose; 1000 cGy given in 5 doses of 200 cGy	Minimum 6 mo	21% HO occurrence in both groups	Trochanteric bursitis
Fingeroth et al 1995 [18]	50 hips in 45 patients	600 cGy	Single dose	Minimum 6 mo	36% HO development compared with 88% historical control	None found
Healy et al 1995 [13]	107 hips in 94 patients	550 cGy vs 700 cGy	Both given as a single dose	Minimum 6 mo for 700 cGy group and minimum 9 mo for 550 cGy group	HO development in 63% of hips in 550 cGy group and 10% in 700 cGy ($P < .01$)	No acute or late complications noted
Padgett et al 2003 [14]	62 hips in 59 patients	500 cGy vs 1000 cGy	500 cGy given in 2 doses; 1000 cGy given in 5 doses	Minimum 6 mo	No significant difference in incidence of postoperative HO	No complications directly related to radiation treatment

high enough to prevent HO formation while being low enough to prevent future malignancy and failure of ingrowth [7,11].

While several studies have attempted to look at radiation prophylaxis for HO and progression, the ideal dose of radiation to prevent HO after total hip arthroplasty is yet unknown [10]. The current protocol at the lead authors' institution is a single dose of 700 cGy administered within 24 hours of surgery centered to the femoral neck. Prior studies show conflicting data about the minimum effective dose. Hedley et al [12] identified that a single dose of 600 cGy can be effective for HO prophylaxis. However, Healy et al found an increased rate of HO progression in a 550 cGy group compared to a 700 cGy group, while Padgett et al found no difference between a 500 cGy group and a 1000 cGy group [13,14]. A summary of these studies can be found in Table 1.

Our study aims to clarify the minimum effective dose of radiation. Padgett et al's study found that 500 cGy could be equivalent to 700 cGy; thus we wanted to study whether a dose lower than 500 could also match these results. We performed a randomized double-blinded clinical trial in patients who were at high risk for HO development after total hip arthroplasty to determine the difference in HO formation and progression between those receiving 400 vs 700 cGy prophylaxis. Our hypothesis was that there would be no difference between the 2 doses with regard to HO progression.

Materials and Methods

Patients undergoing total hip arthroplasty between July 1994 and September 1997 at an urban medical center were selected for review after institutional review board approval. High-risk patients were identified and included in the study if they met 1 or more of the following criteria: a diagnosis of diffuse idiopathic skeletal hyperostosis, hypertrophic osteoarthritis, ankylosing spondylitis, or a history of previous HO (Fig. 1). Written informed consent was obtained from all patients. Patients were assigned a preoperative risk class originally outlined by Ayers et al [16]. Class I consisted of patients diagnosed with hypertrophic osteoarthritis, ankylosing spondylitis, or diffuse idiopathic skeletal hyperostosis (Fig. 1). Class II included patients with previous contralateral HO and class III included those with ipsilateral HO. Class IV patients had prior ipsilateral HO that resulted in ankylosis. Overall demographic data were collected on all patients including age, gender, surgical side, and previous HO development.

Surgeries were performed by 1 of the 6 fellowship-trained arthroplasty surgeons at an urban medical center using a posterior or direct lateral approach (A. R., C. S., J. G., Mitchell B. Sheinkop, Josh J. Jacobs, Steven Giltilis). All acetabular components were cementless and both cemented and noncemented femoral components were used. Surgery was performed in a laminar flow suite with the use of body exhaust suits. All patients were given a first generation cephalosporin 1 hour preoperatively and for 48 hour postoperatively. Coumadin or low-molecular-weight heparin was used for deep venous thrombosis prophylaxis. Patients discontinued nonsteroidal anti-inflammatory medication 1 week preoperatively and did not restart them until 6 weeks postoperatively. Clinical Trials Number: 93090921.

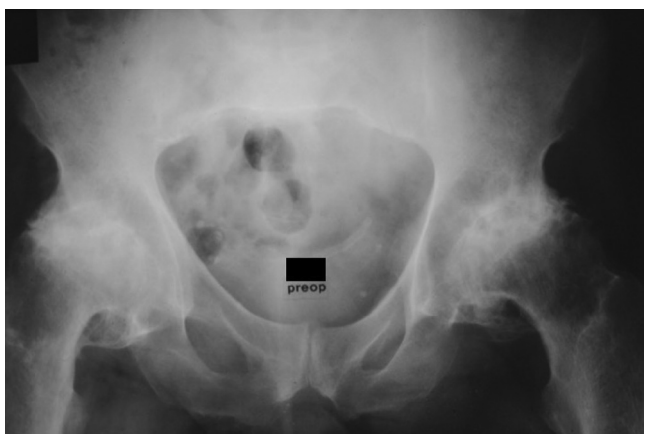

Fig. 1. Anterior-posterior pelvic radiograph demonstrating severe hypertrophic osteoarthritis in bilateral hip joints with marked joint degeneration.

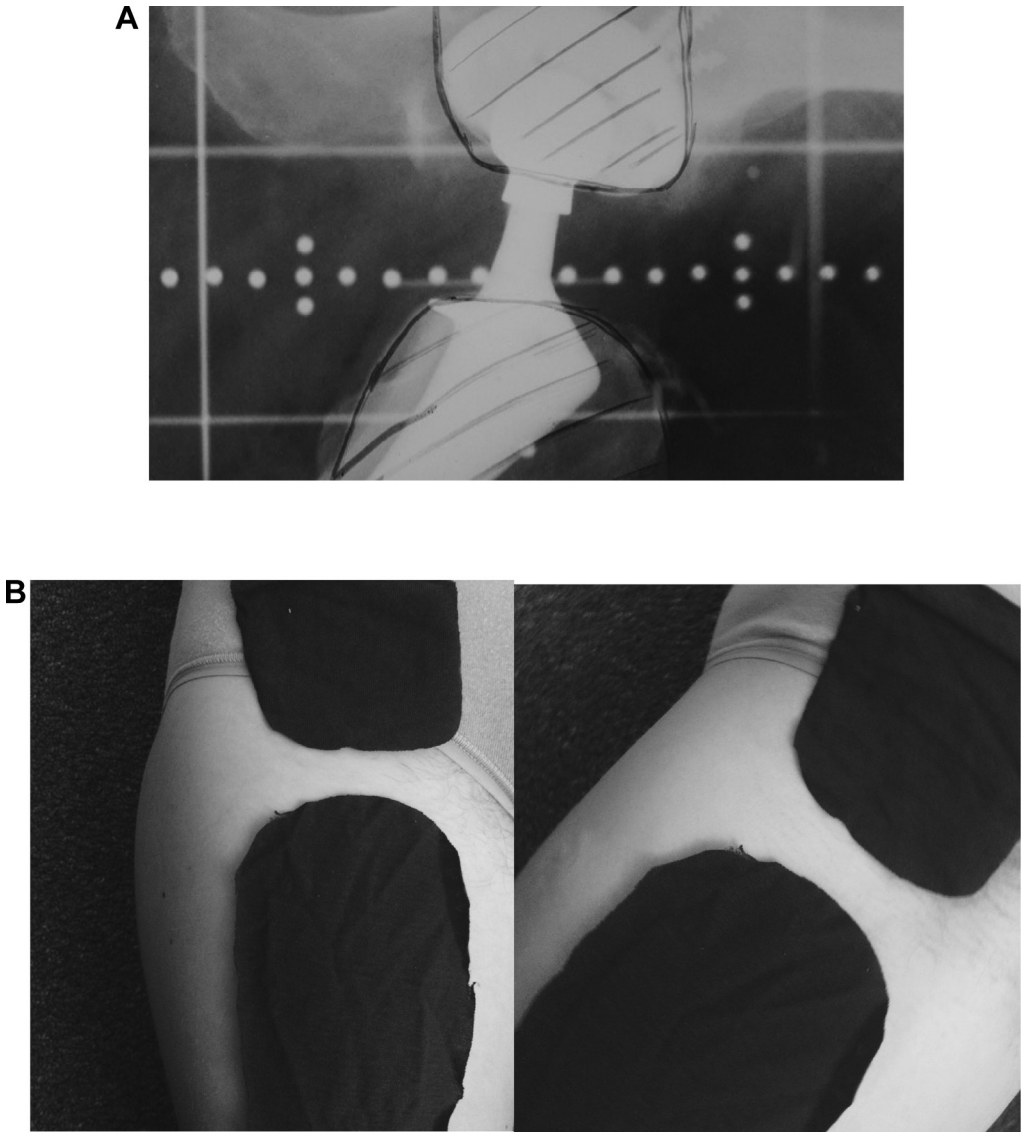

Fig. 2. (A) Cross table lateral radiograph of the right hip status post-right total hip arthroplasty. The shaded regions over the acetabular and femoral component represent the shielding device used for protection during administration of prophylactic, postoperative radiation. (B) A clinical photograph of a patient's right hip with custom shielding is shown.

One hundred forty-seven subjects participated in the study. Patients were randomized into 2 groups. Seventy-one subjects were randomized to receive a single dose of 400 cGy and 76 subjects were randomized to receive a single dose of 700 cGy given on the first or second postoperative day. There were no potentially confounding factors between the groups at baseline. Because 500 cGy was the previous lowest studied dose that seemed effective, we chose 400 as the lower dose to study [14]. Seven hundred centigray was found to be effective by Healy et al [13] and we chose this as our higher dose. A narrow field of 14 × 6 cm was used to treat only the soft tissue between the femur and pelvis; components were further protected using custom shielding based on the postoperative X-ray (Fig. 2). The dose was calculated to the isocenter of the field. Patients were followed up for a minimum of 6 months and a single blinded reviewer (C. S.) graded the radiographs (Fig. 3). The presence of HO was graded using the Brooker classification [19]: class 0 has no identifiable HO; class I has islands of ectopic bone in the soft tissues around the hip joint; class II demonstrates ectopic bone extending from the pelvis to the femur separated by at least 1-cm gap; class III had ectopic bone extending from the pelvis to the femur separated by <1-cm gap; class IV patients had bridging bone between the pelvis and femur. This classification has been found to be a valid grading system with high interobserver reliability [20]. Range of motion was tested postoperatively for flexion, extension, abduction, adduction, internal, and external rotation. Patients were asked if they experienced any uncontrolled pain at each visit.

Progression was defined as any change in Brooker score from the immediate postoperative X-ray to the minimum 6-month postoperative X-ray. For example, if a patient's immediate postoperative Brooker score was “1” and 6 months later it was “2,” this was scored as progression. However, if a patient's immediate postoperative Brooker score was 1 and 6 months later it was 1, this was scored as no progression.

The subset of patients who demonstrated progression were analyzed to see if radiation dosage was associated with the degree of change in Brooker classification. To calculate the degree of change, the immediate postoperative Brooker score was subtracted from the 6-month Brooker score. Change ranged from 1 to 3. For example, a patient whose immediate postoperative Brooker score was 1 and whose 6-month Brooker score was “3” had a degree of change of 2.

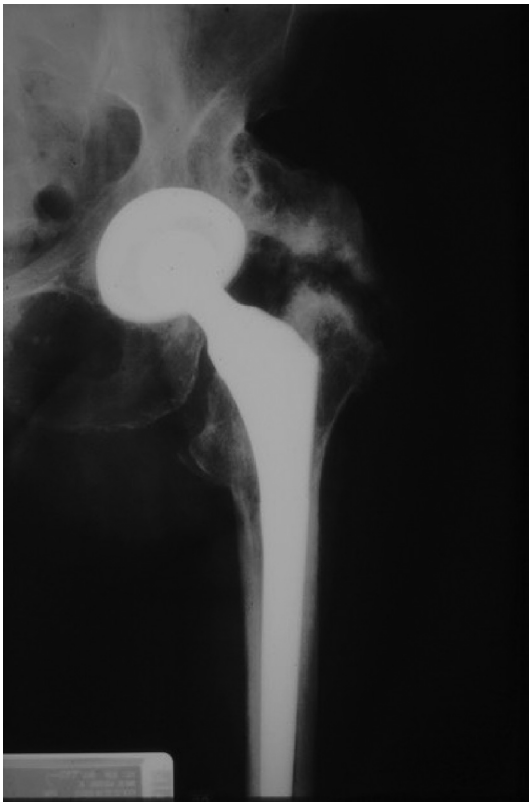

Fig. 3. Anterior-posterior left hip radiograph demonstrating changes consistent with postoperative Brooker class III heterotopic ossification.

Preoperative and intraoperative variables were analyzed for association with HO progression. Additionally, immediate postoperative radiograph Brooker score was analyzed to assess association with risk of progression. Categorical comparisons were analyzed with the chi-square test of independence and continuous variables were analyzed with the independent *t*-test. Correlation of Brooker classification based on radiation dosage, as well as immediate postoperative Brooker score with risk of progression, was performed with Fisher's exact test. Non-normally distributed continuous variables were compared using the Wilcoxon rank-sum test. All analyses were done using SAS 9.4 (SAS Institute, Inc., Cary, NC). Statistical significance was set at $P < .05$.

Results

Patient demographics and documented HO progression are demonstrated in Table 2. Of our total cohort, 33.3% of the patients demonstrated progression. There was no significant association among HO progression and patient gender ($P = .3548$), age ($P = .7332$), or surgical side ($P = .6536$) as demonstrated in Table 3. HO progression on radiographs was seen in 42.3% of the 400 cGy group, compared to 25.0% in the 700 cGy group ($P = .035$) (Table 4, Figs. 4 and 5).

Table 2
Overall Patient Demographics.

Variable	Percent
Progression	
No progression	66.7%
Progression	33.3%
Sex	
Female	29.4%
Male	70.6%
Side	
Left	43.9%
Right	56.1%
Mean age (y)	61.6

Table 3
Demographics by Presence of Progression.

Variable	No Progression (%)	Progression (%)	*P* Value
Sex			.3548
Female	71.4	28.6	
Male	63.4	36.6	
Side			.6536
Left	64.8	35.2	
Right	60.9	39.1	
Mean age (y)	61.3	62.2	.7332

Preoperative diagnosis of HO, preoperative diagnosis, revision procedure, and risk classification were not associated with HO progression (Table 5). There was no significant association between posterior or lateral approach and HO progression. The use of cementless implants was not associated with increased risk of HO progression when compared to cemented constructs.

In patients who demonstrated progression, radiation dose was not associated with degree of change in Brooker grade ($P = .6136$) (Table 6). Degree of change was calculated by subtracting the immediate postoperative Brooker score from the 6-month Brooker score. An immediate postoperative Brooker score of 0 or 1 was associated with increased risk of progression (Table 7). While there was a trend toward absolute range of motion restriction in patients with HO progression, a significant association was only found in hip flexion ($92.2^\circ \pm 15.0^\circ$ in patients who progressed vs $96.8^\circ \pm 8.9^\circ$ in patients who did not progress, $P = .0492$). No patients experienced wound complications.

Discussion

HO is a recognized postoperative complication after total hip arthroplasty, particularly in patients considered as high-risk patients. The ideal dose of radiation should be effective in preventing this complication and easy to administer while being low enough to avoid complications such as wound breakdown, trochanteric nonunion, and potential malignancies [10,21]. Our results suggest that a single dose of 700 cGy is more effective than a single dose of 400 cGy in preventing HO formation in high-risk patients. This suggests that our current protocol of administering a single 700 cGy is effective and should not be lowered to 400 cGy. Previous studies support the efficacy of both higher and lower dosages. Healy et al [13] studied high-risk patients (including those with previous HO around either the ipsilateral or contralateral hip, hypertrophic osteoarthritis, ankylosing spondylitis, post-traumatic osteoarthritis, and Paget disease) and found a significantly higher rate of HO progression in a group treated prophylactically with 550 cGy than in the group treated with 700 cGy (63% vs 10%). Padgett et al [14] studied high-risk patients using the same inclusion criteria as in our study, but did not find a difference comparing 500 cGy with 1000 cGy with no statistically significant difference in HO between the 2 doses.

Table 4
Radiation Dose Compared to Heterotopic Ossification Progression.

Dose (cGy)	No Progression	Progression
400	41 (57.8%)	30 (42.3%)
700	57 (75.0%)	19 (25.0%)

Chi-square test of independence: $P = .0266$.

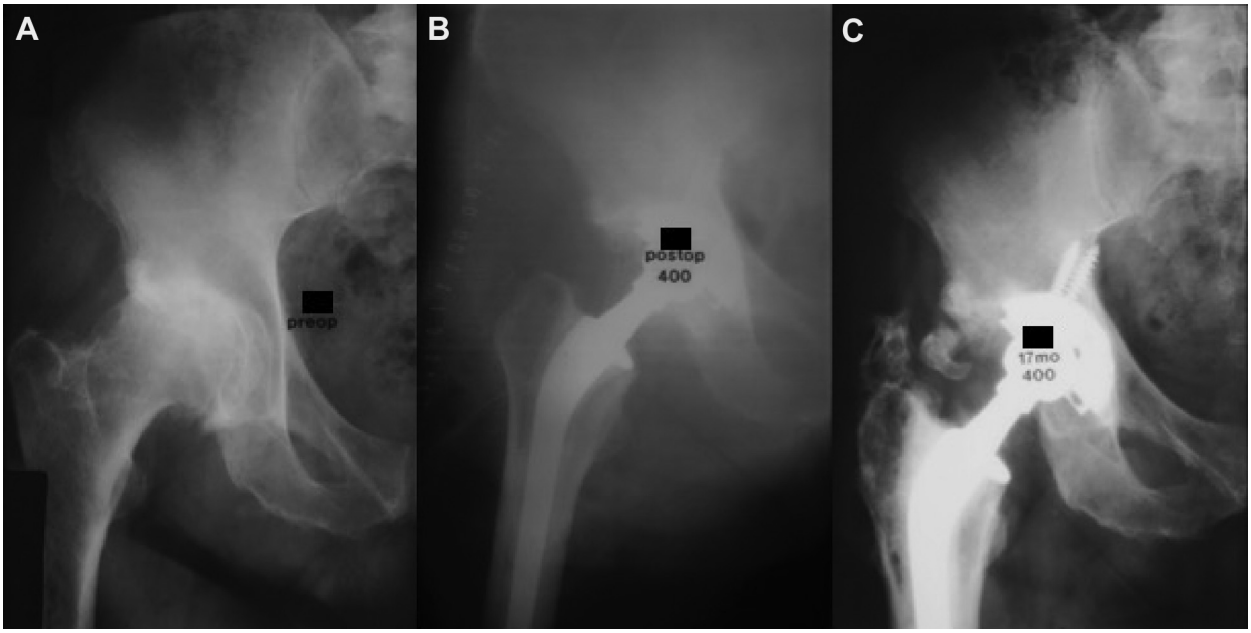

Fig. 4. Anterior-posterior radiographs of a right hip after total hip arthroplasty demonstrating progression of HO in a patient in the 400 cGy group. (A) Preoperative radiograph demonstrating osteoarthritis, (B) immediate postoperative radiograph demonstrating Brooker class 0, and (C) 6-month postoperative radiograph demonstrating Brooker class III.

Different dosing protocols make interpretation of the existing literature difficult to interpret. One must not only compare the cumulative total dose, but, as demonstrated by Padgett et al, the dosing protocol must also be assessed separately. The authors divided the 500 cGy treatment into 2 doses and the 1000 cGy treatment into 5 doses, which make these results difficult to compare directly. It has been previously documented that a single dose of radiation is more effective than when it is divided [10]. Studies looking at a single dose of radiation show mixed results. Hedley et al [12] found that a single dose of 600 cGy within 3 days after surgery was correlated with no development of Brooker class II or III in his sample of 17 high-risk patients. Despite these findings, the small sample size is likely underpowered to show a true association at this dose. Fingeroth and Ahmed found a 36% rate of HO development after treating 100 high-risk patients with 600 cGy [12,18]. When directly compared with our results, we found that 42.3% of patients in the 400 cGy group demonstrated HO progression on radiographs compared to 25.0% in the 700 cGy group. This comparison illustrates that there is a progressive decrease in HO formation as the dosing of radiation increases, from 42.3% at 400 cGy, 36% at 600 cGy, and 25% at 700 cGy. Combining our study data with this study supports the use of higher dose to decrease the rate

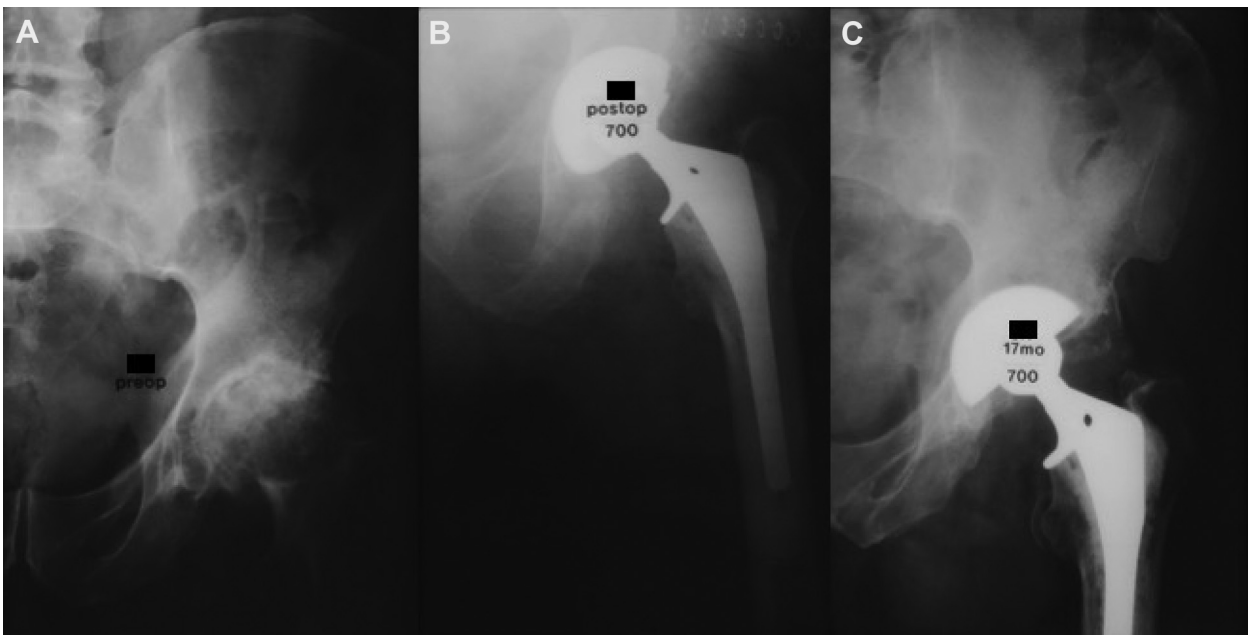

Fig. 5. Anterior-posterior radiographs of the left hip after total hip arthroplasty demonstrating progression of HO in a patient in the 700 cGy group from Brooker 0 immediately postoperatively to Brooker II 6 months postoperatively. (A) Preoperative radiograph demonstrating osteoarthritis, (B) immediate postoperative radiograph demonstrating Brooker class 0, and (C) 6-month postoperative radiograph demonstrating Brooker class II.

Table 5
Preoperative and Operative Variables.

Variables	No Progression	Progression	*P* Value
Risk class ($N = 141$)			.3149
1	69 (69.0%)	31 (31.0%)	
2	15 (57.7%)	11 (42.3%)	
3	12 (80.0%)	3 (20.0%)	
Approach ($N = 142$)			.7693
Posterior	63 (67.7%)	30 (32.3%)	
Lateral	32 (65.3%)	17 (34.7%)	
Diagnosis			.8268
Osteoarthritis/degenerative joint disease	78 (67.2%)	38 (32.8%)	
Post-traumatic	3 (100%)	0	
Ankylosing spondylitis	6 (54.6%)	5 (45.5%)	
Avascular necrosis	7 (70.0%)	3 (30.0%)	
Hip dysplasia	1 (50.0%)	1 (50.0%)	
Rheumatoid arthritis	1 (50.0%)	1 (50.0%)	
Revision	2 (66.7%)	1 (33.3%)	
Cemented femur			.7337
Yes	84 (66.1%)	43 (33.9%)	
No	14 (70.0%)	6 (30.0%)	
Revision			.4817
No	93 (67.4%)	45 (32.6%)	
Yes	5 (55.6%)	4 (44.4%)	
Previous HO			.6009
No	96 (67.1%)	47 (32.9%)	
Yes	2 (50.0%)	2 (50.0%)	

of HO formation. One point of note involves the use of shielding during administration of radiation. Balboni et al [22] found that shielding patients who received a 750 cGy dose was associated with increased failure of prophylaxis and that unshielded patients did not have increased failure of the prosthesis. The aforementioned studies used a narrow beam of radiation similar to our study but did not use custom shielding as we did.

The second question of importance in our study was whether the dose of radiation might attenuate the proliferative response in patients who did develop HO. In the subset of patients who did show progression from their immediate postoperative X-ray to their 6-month postoperative X-ray, we found no relationship between dose of radiation and degree of change. It is possible that a single radiation dose may be enough to decrease HO formation rate, but in patients in whom it cannot be prevented, radiation may not be enough to attenuate the response. There is no current evidence in the literature addressing this issue.

Demographic variables such as sex, age, risk class, and diagnosis were not correlated with increased risk of HO in our cohort. Prior studies have found that men have a higher risk of HO [1-3] (believed to be secondary to higher muscle mass). Diagnoses such as hypertrophic arthritis, diffuse idiopathic skeletal hyperostosis, post-traumatic arthritis, and ankylosing spondylitis have all been identified as risk factors for HO development [7,10] with the pathophysiology of these diseases thought to contribute to heterotopic bone formation after surgical insult. In our high-risk patient population, we did not detect a differential association between the formation and progression of HO based on specific preoperative diagnosis. A Brooker class of 0 and I on immediate postoperative radiograph was associated with risk of progression

Table 6
Degree of Change in Brooker Classification based on Radiation Dose.

Dose (cGy)	Degree of Change in Brooker Classification		
	I	II	III
400	12 (40.0%)	15 (50.0%)	3 (10.0%)
700	7 (36.8%)	8 (42.1%)	4 (21.1%)

Fisher's exact test: $P = .6136$.

Table 7
Association of Immediate Postoperative Brooker Score with HO Progression.

Variable	Response	No Progression	Progression	*P* Value
Immediate postoperative Brooker class	0	62.39%	37.61%	.028
	I	64.29%	35.71%	
	II	100%	0%	
	III	100%	0%	

(Table 7) and no patients with immediate postoperative grades III or IV demonstrated progression. This is likely because patients at a higher Brooker class have already had previous HO and any further progression is likely less noticeable at the higher Brooker grades or may have burnt out already metabolically.

Maloney et al [23] reported on 65 patients with cementless components compared to 70 patients with cemented components and noted an association between the use of cementless components and HO formation. Of those patients who did develop HO, 6% of patients with cementless femoral components underwent reoperation for excision of ectopic bone vs no patients with cemented femoral components. It is thought that increased debris in the soft tissues from cementless stem insertion leads to more mesenchymal stem cells in the soft tissue. All acetabular cups in our study were cementless and the majority of the femoral stems were cemented (86.4%). Cementless femoral stems in our study did not have a statistically significant higher rate of HO progression.

We did not find a higher rate of HO with a posterior or lateral approach. There are several studies that have found significant differences in HO formation depending on approach. Horwitz et al [4] found an increased rate of HO formation in patients who underwent the modified Hardinge approach when compared to a transtrochanteric lateral approach (45% vs 20%). Eggli and Woo [24] also found an increased risk of HO with a lateral or anterolateral vs a posterior approach. However, in a more recent single surgeon series of 355 primary total hip arthroplasties, Newman et al [25] found a decreased rate of clinically significant HO in normal risk patients with direct anterior approach when compared with posterior approach (3.0% vs 7.5%). Of the aforementioned studies, the reported patient populations were not stratified as high or low risk, and did not receive routine perioperative HO prophylaxis, and therefore were not directly comparable to our patient population. Our patients were documented high-risk patients. All received HO prophylaxis and based on our findings in this population, the use of cementless implants and choice of surgical approach were not associated with an increased risk of HO formation. All patients in our cohort also received radiation prophylaxis, which may further confound the results. Finally, with the patients available to study, a true association may not be detected.

The mere presence of HO formation is generally only as significant as its impact on the patient's function. As HO progresses in severity, there is a joint range of motion which may decrease and deleteriously affect functional outcome with several prior studies demonstrating decreased range of motion in patients with Brooker

Table 8
Postoperative Hip Range of Motion by HO Progression.

Variable	No Progression	Progression	*P* Value
Extension	60: 1.13 ± 4.1, 0	34: 2.1 ± 4.6, 0	.1586
Flexion	61: 96.8 ± 8.9, 95.0	34: 92.2 ± 15.0, 90.0	**.0492**
Abduction	30: 38.8 ± 7.7, 40.0	15: 33.0 ± 11.3, 30.0	.0832
Adduction	20: 26.5 ± 4.6, 27.5	7: 20.0 ± 8.2, 20.0	.0544
Internal rotation	3: 33.3 ± 20.2, 30.0	3: 23.3 ± 5.8, 20.0	.8222
External rotation	6: 35.0 ± 11.8, 35.0	3: 25.0 ± 8.7, 30.0	.3580

Data presented as *n*: mean ± standard deviation, median.
Bold values signifies Wilcoxon rank sum test.

class III and IV HO [26,27]. Zhang et al [28] evaluated the range of motion in 167 hips in 100 patients with ankylosing spondylitis and found that postoperative HO was associated with decreased range of motion (odds ratio 0.237, $P < .001$). Prior studies have not found an increase in Trendelenburg limp or decrease in hip muscle strength with increased HO [26]. In our patient population, patients with progressive HO demonstrated a decrease in flexion relative to patients who did not progress, but the difference was not clinically significant (92.2° ± 15.0° compared to 96.8° ± 8.9°, Table 8).

The strengths of our study include its randomized, double-blinded design and its relatively large sample size comprising known high-risk patients. We used a standardized, single dose radiation protocol as opposed to a multiple dose regimen. These patients were followed up and assessed for HO progression, which has not been well reported previously. There are several limitations to this study. Functional data were not collected postoperatively and our analysis was only inclusive of range of motion. The data were also collected 2 decades prior to this manuscript and while different approaches were used, advances in surgical technique may affect the rate of HO formation. The Brooker classification system is also highly subjective. We tried to limit the subjectivity by using a single blinded reviewer, but an amount of subjectivity is still inevitable with this method. The study was conducted in several phases and while previous results have been presented at conferences, the full series has not previously been published. All patients in our group were selectively shielded so that radiation only reached the soft tissue around the joint. Future studies could compare radiation dosages in patients with and without shielding. Studies quoted previously typically were not custom shielded but did use a narrow beam of radiation to limit the treatment area.

Conclusion

Seven hundred centigray postoperative radiation given as a single dose in the immediate postoperative period demonstrates superior prevention of HO formation relative to 400 cGy. There were no wound complications, and the use of cementless implants, regardless of approach, does not appear to increase the risk of HO formation. In those patients who did demonstrate HO progression, the radiation dose does not appear to correlate with the degree of change in Brooker classification. Further studies comparing 700 cGy to dosages between 400 and 700 cGy may help to clarify if a more optimal dose can be identified.

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