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CLINICAL INVESTIGATION **Benign Disease**

SHIELDING OF THE HIP PROSTHESIS DURING RADIATION THERAPY FOR HETEROTOPIC OSSIFICATION IS ASSOCIATED WITH INCREASED FAILURE OF PROPHYLAXIS

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Purpose: Radiation therapy (RT) is frequently administered to prevent heterotopic ossification (HO) after total hip arthroplasty (THA). The purpose of this study was to determine if there is an increased risk of HO after RT prophylaxis with shielding of the THA components.

Methods and Materials: This is a retrospective analysis of THA patients undergoing RT prophylaxis of HO at Brigham and Women's Hospital between June 1994 and February 2004. Univariate and multivariate logistic regressions were used to assess the relationships of all variables to failure of RT prophylaxis.

Results: A total of 137 patients were identified and 84 were eligible for analysis (61%). The median RT dose was 750 cGy in one fraction, and the median follow-up was 24 months. Eight of 40 unshielded patients (20%) developed any progression of HO compared with 21 of 44 shielded patients (48%) ($p = 0.009$). Brooker Grade III-IV HO developed in 5% of unshielded and 18% of shielded patients ($p = 0.08$). Multivariate analysis revealed shielding ($p = 0.02$) and THA for prosthesis infection ($p = 0.03$) to be significant predictors of RT failure, with a trend toward an increasing risk of HO progression with age ($p = 0.07$). There was no significant difference in the prosthesis failure rates between shielded and unshielded patients.

Conclusions: A significantly increased risk of failure of RT prophylaxis for HO was noted in those receiving shielding of the hip prosthesis. Shielding did not appear to reduce the risk of prosthesis failure. **© 2007 Elsevier Inc.**

Heterotopic ossification, Radiation therapy, Treatment planning, Total hip arthroplasty.

INTRODUCTION

Heterotopic ossification (HO) is a benign condition characterized by the abnormal formation of mature lamellar bone in soft tissues classically surrounding a major appendicular joint. The most commonly involved joint is the hip (1, 2), although others may be affected, including the elbow (3), knee (4), shoulder (5), and temporomandibular joint (6). HO typically occurs after local trauma, including surgery (2) and burns (7), but it may also occur in the setting of such systemic insults as neurologic injury (8) or genetic disorders (*e.g.*, fibrodysplasia ossificans progressiva) (9). An HO is frequently asymptomatic, but when sufficiently extensive can cause pain and restriction of joint motion. Modalities to prevent the formation of HO in those with a high risk for its development, include nonsteroidal anti-inflammatory drugs (NSAIDs) (10) and radiation therapy (11).

Radiation therapy (RT) is recognized as a modality for HO prevention that offers the flexibility of being administered either preoperatively or postoperatively (12–14) and efficacy at least comparable to that of NSAIDs (15, 16). RT prophylaxis offers the additional benefits over NSAIDs of: *(1)* reducing additional bleeding risks among postsurgical patients receiving pharmacologic anticoagulation; *(2)* limiting the risk of bone-nonunion seen with systemic antiprostaglandin therapies (17); and *(3)* eliminating the need for patient compliance with a 6-week NSAID regimen. However, given that prophylaxis is typically given surrounding replacement of a joint with a prosthesis—most commonly total hip arthroplasty (THA)—concern has arisen regarding the possible increased risk of prosthesis failure because of bone nonunion. Konski *et al.* performed a study in rabbits demonstrating transient instability of femoral rods irradiated 1 day after insertion as compared with controls (18). Because of this concern, shielding of the hip prosthesis is often performed (19). Shielding typically involves the region where the prosthetic acetabular cup inserts into the native pelvis. The proximal femur may also be shielded. Shielding

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may also be performed preoperatively because radiation exposure immediately before the insertion of the hip prosthesis may similarly reduce bony ingrowth of the native bone into the prosthesis. Preoperative shielding also typically involves coverage of regions of the hip anticipated to require bony union with the prosthesis. However, to our knowledge, prosthesis instability after radiotherapeutic prophylaxis has not been demonstrated in humans. In fact Seegenschmiedt *et al.*, in a study of preoperative vs. postoperative RT, noted no evidence of prosthesis failure in 188 patients with uncemented implants that were not shielded (14). Given that radiotherapeutic shielding of the THA components involves bony regions where HO commonly arises, it is also possible that shielding may compromise the efficacy of RT prophylaxis. The only available data addressing this issue were reported by Jasty *et al.* (19). Though no increased risk of HO development was noted, these data are limited by a small sample size (16 patients) and by the lack of a comparison group of unshielded patients.

Hence, the current study aimed to determine whether there is an increased risk of HO development after shielding of the THA components. Additionally, the incidence of prosthesis failure with and without shielding was analyzed.

METHODS AND MATERIALS

Description of study cohort and endpoints

This is a retrospective review of patients undergoing RT prophylaxis at the Brigham and Women's Hospital between June 1994 and February 2004. Patient inclusion criteria included RT prophylaxis (given preoperatively or postoperatively) for THA or for surgical excision of HO after prior THA. Shielding of the prosthetic hip components was performed at the discretion of the radiation oncologist. All patients were required to have an RT simulation film available to assess shielding. Guidelines for determining shielding were established before data collection and are detailed in Fig. 1. If either or both the acetabular or femoral regions were shielded, shielding was considered to be present. Shielding of the prosthetic acetabulum (or native acetabulum in the case of preoperative treatment) was scored as present if more than one-third of the acetabulum was blocked. Shielding of the femoral components was scored as present if the region between the greater trochanter and lesser trochanter or any portion of the femoral neck was outside the radiation field. Eligible patients were additionally required to have plain hip films sufficient to document HO involvement within 1 week postoperatively to assess baseline HO and at least 4 months postoperatively to assess HO development. HO was scored according to the Brooker grading system (Grades I-IV) (20). Grade I is characterized by islands of bone in the soft tissue surrounding the hip. Grade II is growth of bone from the pelvis and femur separated by at least 1 cm. Grade III is growth of bone from the pelvis and femur separated by less than 1 cm, and Grade IV is complete bony ankylosis of the hip. The study endpoints included: *(1)* development of any grade of HO; *(2)* development of clinically significant HO (Brooker Grade III or IV); and *(3)* evidence of prosthesis failure, including dislocations, prosthesis migration, and prosthesis loosening. Prosthesis failure was based on a review of the orthopedic follow-up notes, films, and any operative procedures subsequent to the time of RT prophylaxis.

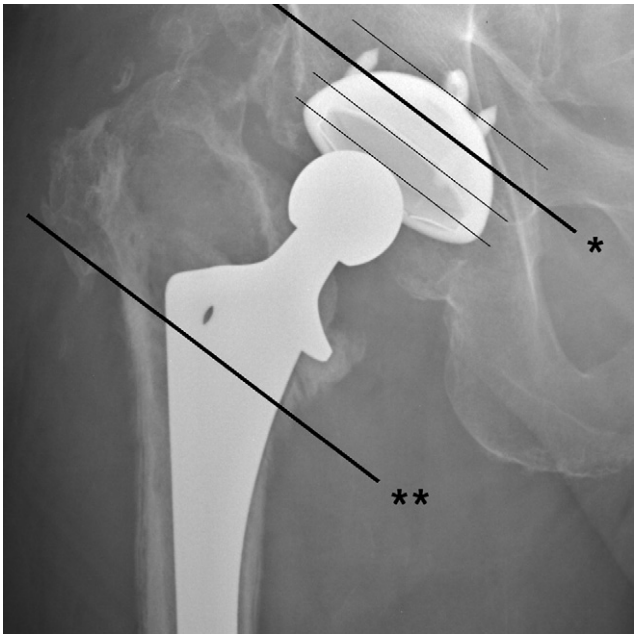


Fig. 1. Guidelines for determining simulation film shielding status. If either the acetabulum or femur was shielded, the film was scored as shielded. Acetabular shielding was determined by dividing the distance between the widest point of the acetabular cup and the top of the dome of the prosthetic acetabulum into three parts. If more than one-third of the acetabulum was shielded (asterisk), it was considered shielded. Femoral shielding was determined by drawing a line between the base of the greater and lesser trochanters. If the treatment field did not completely encompass the femoral region proximal to this line (asterisks), the femur was scored as shielded.

Additional patient information obtained from medical chart review included: age, sex, history of HO, timing of RT prophylaxis (hours preoperatively and postoperatively), RT dose, field size, and whether or not the THA was a revision after a prior THA complicated by chronic periprosthetic joint infection.

Statistical methods

Descriptive statistics were used to describe the study cohort. Any HO development, the development of clinically significant HO, and prosthesis failure were assessed as dichotomous outcomes. Analysis of variance, the Kruskal-Wallis test, or the Fisher's exact t test were used to assess differences in clinical factors, treatment-related factors, and prosthesis complications among patients according to HO development (no HO, Brooker Grade I-II HO, and Brooker Grade III-IV HO). Logistic regression was used to analyze the association of shielding with HO development. First, univariate analysis was performed to assess the unadjusted relationship of shielding to HO outcomes. Additionally, the univariate relationships of age, sex, HO history, preoperative vs. postoperative RT, RT dose, field size, and revision THA after chronic periprosthetic joint infection to HO development were assessed. Multivariate analysis included all univariate predictors with p values < 0.20. The Fisher's exact t test was used to analyze the incidence of any evidence of prosthesis failure vs. the shielding status. A two-sided p value < 0.05 was considered significant for all analyses. Analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

Table 1. Sample characteristics among shielded and unshielded patients ($n = 84$)

Characteristic	Shielded ($n = 44$)	Unshielded ($n = 40$)	p
Male; *n* (%)	33 (75)	29 (73)	0.81*
Age, years; mean (SD)	63 (13)	61.3 (12)	0.47†
History of HO; *n* (%)	37 (84)	32 (80)	0.78*
Follow-up, months; mean (SD)	31 (25)	30 (23)	0.90†
Surgery			
THA; *n* (%)	44 (100)	37 (93)	
Excision of HO after prior THA; *n* (%)	0 (0)	3 (8)	0.10*
Revision THA for infection; *n* (%)	7 (16)	3 (8)	0.32*
RT timing			
Preop RT, *n* (%)	10 (23)	17 (43)	0.06*
Hours preop; mean (SD)	5.2 (1.5)	4.4 (2.6)	0.12†
Postop RT, *n* (%)	34 (77)	23 (58)	0.06*
Hours postop; mean (SD)	45 (20)	40 (16)	0.34†
Dose‡, cGy; median (range)	750 (700–800)	750 (500–800)	0.65§
Field size, cm^2; mean (SD)	124 (30)	134 (27)	0.13†

Abbreviations: SD = standard deviation; HO = heterotopic ossification; THA = total hip arthroplasty.
* Fisher's exact *t* test used for comparison.
† *t* test used for comparison.
‡ All patients received total dose in one fraction.
§ Wilcoxon rank sum test used for comparison.

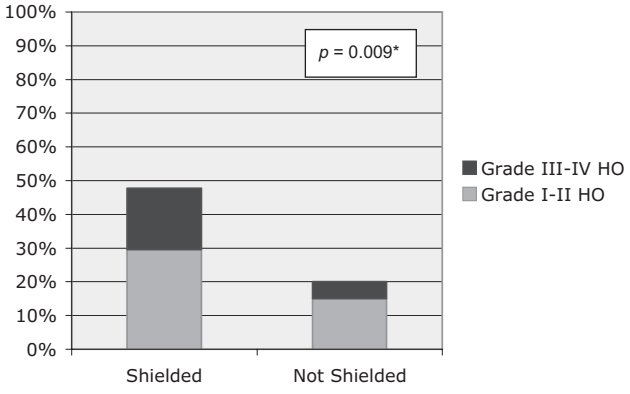
RESULTS

Sample characteristics

A total of 137 patients were identified and 84 had sufficient follow-up data to be eligible for analysis (61%). Seventy-two percent were male and the median age was 62 years. The median follow-up was 24 months, and the median RT dose was 750 cGy in one fraction (range, 500–800 cGy). Twenty-seven patients were treated preoperatively and 57 were treated postoperatively. Forty-four of the patients had RT performed with shielding. The shielding involved the acetabulum in all cases. The proximal femur was additionally shielded in ten cases. The acetabulum was uncemented in all cases. The femoral component was cemented in 15 patients. Sample characteristics were not significantly different between shielded and unshielded patients (Table 1), though there was a suggestion that more shielded patients received postoperative RT.

Shielding and the development of heterotopic ossification

Eight of 40 unshielded patients (20%) developed any progression of HO compared with 21 of 44 shielded patients (48%) (OR = 3.65, 95% CI = 1.38–9.68; $p = 0.009$) (Fig. 2). Brooker Grade III-IV HO developed in 5% of unshielded and 18% of shielded patients (OR = 4.22, 95% CI = 0.84–21.2; $p = 0.08$). Another significant univariate predictor of HO progression despite RT prophylaxis was THA after chronic periprosthetic infection (OR = 5.52, 95% CI = 1.31–23.31; $p = 0.02$). Of 10 patients with THA for joint infection, 70% developed any HO and 50% developed Brooker Grade III or IV HO. There was a trend toward a higher risk of RT failure with continuously increasing age (OR = 1.04, 95% CI = 1.00–1.08; $p = 0.06$). Gender, prior history of HO, dose, field size, and postoperative vs. preoperative timing of RT were not significant predictors. Additionally, in a univariate analysis limited to patients receiving preoperative treatment, time interval between RT and surgery did not predict HO development. A similar analysis limited to patients receiving postoperative treatment also demonstrated that hours to RT was not associated with HO development. Multivariate logistic regression revealed shielding (OR = 3.37, 95% CI = 1.21–9.43; $p = 0.02$) and infection (OR = 5.21, 95% CI = 1.15–23.65; $p = 0.03$) to continue to be significant predictors of RT failure. The trend toward an increasing risk of HO progression with age persisted (OR = 1.04, 95% CI = 1.00–1.09; $p = 0.07$). Univariate and multivariate regression of the relationship of shielding status and other variables to HO progression are shown in Table 2. Analyses of clinical and treatment-related



Abbreviations: HO = heterotopic ossification
*Univariate logistic regression predicting development of heterotopic ossification.

Fig. 2. Development of heterotopic ossification among patients undergoing radiotherapy prophylaxis with ($n = 44$) and without ($n = 40$) shielding of the prosthetic components ($p = 0.009$).

Table 2. Univariate and multivariate predictors of development of heterotopic ossification after radiotherapeutic prophylaxis

Univariate analyses			Multivariate analyses*		
Predictor	OR (95% CI)	*p*	Predictor	OR (95% CI)	*p*
Shielding	3.65 (1.38–9.68)	0.009	Shielding	3.37 (1.21–9.43)	0.02
Male	0.69 (0.25–1.88)	0.46	Age	1.04 (1.00–1.09)	0.07
Age	1.04 (1.00–1.08)	0.06	Infection	5.21 (1.21–9.43)	0.03
HO history	1.07 (0.33–3.48)	0.91			
Infection†	5.52 (1.31–23.31)	0.02			
RT dose	1.00 (0.99–1.01)	0.71			
Postop RT	0.67 (0.26–1.74)	0.41			
Field size	1.00 (0.93–1.01)	0.85			

Abbreviations: OR = odds ratio; CI = confidence interval; HO = heterotopic ossification; RT = radiation therapy; Postop = postoperative.

* Multivariate analysis performed with all variables with univariate p values < 0.20 entered simultaneously into the model.

† Revision total hip arthroplasty required by presence of a chronic periprosthetic hip infection.

parameters according to HO outcomes (no HO, Grade I-II HO, and Grade III-IV HO) are detailed in Table 3. There were significant differences across classes of HO development in the number of patients undergoing THA for chronic periprosthetic joint infection, and in the frequency of patients receiving shielding.

Total hip arthroplasty prosthesis failure

Among those patients undergoing THA ($n = 81$), 5 patients (6%) developed any evidence of prosthesis failure. Two patients had a single episode of dislocation, and 1 of these patients had an associated trochanteric fracture requiring revision THA. There was no evidence of prosthesis loosening noted at the time of surgery. The other patient's single episode of dislocation was managed with closed reduction after no radiographic evidence of prosthesis loosening was found. Three patients developed recurrent hip dislocations. Only 1 of these patients had evidence of loosening of the prosthetic hip components at the time of surgery. There were no documented postoperative infections.

Of the 5 patients with any evidence of prosthesis failure, 4 had RT performed with shielding and 1 had no shielding ($p = 0.37$). Because the 1 patient with prosthesis loosening had femoral loosening after receiving no femoral shielding (acetabular shielding only), the analysis was also performed looking at failures only according to femoral shielding status. Two of the 10 patients (20%) who had femoral shielding developed any evidence of prosthesis failure,

Table 3. Clinical factors, treatment-related factors, and prosthesis complications among patients according to the development of heterotopic ossification after radiotherapeutic prophylaxis

Characteristic	No HO ($n = 55$)	Brooker Grade I-II HO ($n = 19$)	Brooker Grade III-IV HO ($n = 10$)	p*
Male; *n* (%)	42 (76)	12 (63)	8 (80)	0.50
Age, years; mean (SD)	60 (12)	65 (12)	69 (14)	0.10
History of HO; *n* (%)	45 (82)	14 (74)	10 (100)	0.26
Surgery				
THA; *n* (%)	53 (96)	18 (95)	10 (100)	1.0
Excision of HO after prior THA; *n* (%)	2 (4)	1 (5)	0 (0)	
Revision THA for infection; *n* (%)	3 (5)	2 (11)	5 (50)	0.002
RT timing				
Preop RT, *n* (%)	16 (29)	9 (47)	2 (20)	0.25
Hours preop; mean (SD)	4.0 (1.5)	5.6 (3.3)	5.0 (1.4)	0.56
Postop RT, *n* (%)	39 (71)	10 (53)	8 (80)	0.25
Hours postop; mean (SD)	41 (17)	55 (26)	35 (12)	0.10
Dose‡, cGy; median (range)	750 (500–800)	700 (700–800)	750 (700–750)	0.77
Field size, cm^2; mean (SD)	129 (31)	124 (25)	124 (30)	0.55
Shielding; *n* (%)	23 (42)	13 (68)	8 (80)	0.02
Prosthesis complications; *n* (%)	5 (9)	0 (0)	0 (0)	0.48

Abbreviations: SD = standard deviation; HO = heterotopic ossification; THA = total hip arthroplasty.

* Analysis of variance or Kruskal-Wallis test used to compare continuous variables and Fisher's exact t test used to compare categoric variables.

whereas 3 of the 71 patients whose femurs were not shielded (4%) developed any evidence of prosthesis failure ($p = 0.11$).

DISCUSSION

Radiation therapy, in the setting of joint procedures such as THA, is an effective modality for HO prophylaxis. In an effort to minimize possible prosthesis failure from the impact of RT on bony ingrowth into the hip prosthesis, shielding of the prosthetic components is often performed. This study aimed to determine if shielding is associated with decreased efficacy of RT prophylaxis for HO while simultaneously assessing if there is an increased risk of prosthesis failure among those patients whose RT is administered without shielding.

Shielding and development of heterotopic ossification

Shielding was associated with an increased risk of HO development in this study population, and the impact of shielding persisted after adjusting for other predictors of HO development. Additionally, there was a trend toward more shielded patients experiencing clinically significant (Brooker Grade III or IV) HO as compared with unshielded patients (18% vs. 5%). These findings are consistent with the current theory of HO pathogenesis. Heterotopic ossification is believed to result from the inappropriate differentiation of pluripotential mesenchymal cells into osteoblastic stem cells (21, 22). Radiation therapy has been hypothesized to prevent HO development because of: *(1)* the presence of these osteoprogenitor cells in the local soft tissues and *(2)* the radiosensitivity of these cells from their high mitotic rate as they are proliferating and differentiating into specialized forms (23). Shielding may reduce the effectiveness of RT prophylaxis by reducing the region surrounding the hip receiving sufficient dose to curb osteoprogenitor cell proliferation and differentiation. Furthermore, the finding that field size was not associated with HO development suggests that the relationship of shielding to HO development is not simply the result of the volume of tissue treated; rather, it suggests that insufficient coverage at the acetabulum and femur confers a higher risk of HO development. Finally, the discrepancy between the results of this analysis and the findings of Jasty *et al.* (19), in which 11% of hips developed minor HO after shielding of the THA prosthesis, warrants consideration. First, the small sample size (16 patients, 18 hips) and the lack of a control group in the Jasty *et al.* article may at least in part explain this discrepancy. Other notable differences between these analyses include that patients in the current analysis were primarily treated with 7–8 Gy in one fraction; whereas those in the Jasty *et al.* article were treated with 15 Gy in five fractions. A meta-analysis of 32 studies of HO outcomes according to dose fractionation schedules does not suggest a difference in outcomes between these two schedules, however (24). Furthermore, all of the patients in the Jasty *et al.* study were treated postoperatively as compared with 68% in this analysis. However, timing of RT did not predict outcomes in this analysis. Though one study has suggested inferior results with preoperative RT prophylaxis (14), a multicenter study of 4,377 hips receiving RT prophylaxis for HO development did not note a difference in outcomes according to preoperative vs. postoperative RT delivery (25).

Other factors associated with failure of RT prophylaxis

Radiotherapeutic prophylaxis in the setting of revision THA for chronic periprosthetic infection was also found to be associated with a high risk of HO, with 70% of patients experiencing any HO development and 50% developing clinically significant HO. Infection may predispose these individuals to develop HO given the association of inflammatory cytokines with heterotopic bone formation (26). This association is further corroborated by the efficacy of NSAIDs in preventing HO (27, 28). Furthermore, chronic periprosthetic infection about THA prosthesis is usually managed with resection arthroplasty followed by implantation of antibiotic spacers for 12 weeks before reimplantation (29). That this management process requires multiple surgical procedures at the hip may further contribute to HO development given the repeated episodes of local trauma and associated inflammation. This analysis additionally suggests that older age may be associated with an increased risk of failure after RT prophylaxis, whereas history of HO and male gender were not predictive of HO development after RT. The time interval between RT and surgery (preoperatively and postoperatively) and RT dose also did not predict for HO outcomes, though this is likely from the narrow range of times and doses used in this cohort.

Prosthesis failure after radiotherapeutic prophylaxis for heterotopic ossification

Prosthesis shielding was not associated with a reduced risk of prosthesis failure. Furthermore, the incidence of prosthesis failure was low, with only 1 patient having documented prosthesis loosening. The incidence of dislocations in this cohort was consistent with prior documented dislocation rates after THA without RT for HO prophylaxis (30, 31). The finding that there is no increased risk of prosthesis failure without shielding is consistent with the prior study reported by Seegenschmiedt *et al.* (14). In 188 uncemented THA patients treated with RT for HO prophylaxis without shielding, there were no prosthesis failures. The lack of prosthesis failures, in particular in the region of the prosthetic acetabulum, may in part be due to the common practice of securing the acetabulum with screws (32). Additionally, in the study by Konski *et al.* (18), the impact of RT on bony ingrowth into a porous coated rod implanted into the rabbit tibia was transient. Decreased rod stability in radiated rabbits as compared with controls was only significant at 2 weeks after surgery; by 3 weeks postsurgery, there was no longer a significant difference between groups. Hence, the duration of the effect of RT on bone proliferation may be sufficiently long to prevent HO development yet

transient enough to not have a clinically significant impact on prosthesis stability.

Clinical implications, limitations, and future directions

The clinical implications of the finding that patients undergoing RT prophylaxis with shielding of the prosthetic hip have an increased risk of HO development and that unshielded patients do not have an increased risk of prosthesis failure suggests that RT prophylaxis should be performed without shielding of the prosthetic components. Though there was only a trend toward an increased rate of clinically significant HO among shielded patients, the lack of significance may be due to the small number of patients in this analysis. It is, therefore, possible that performing RT without shielding will diminish the rate of clinically significant HO development after RT prophylaxis.

Limitations of the study findings include the retrospective nature of the analysis that precludes controlling for all potential factors that may impact the development of HO after RT prophylaxis. Furthermore, among shielded patients, all received shielding of the acetabular component and no patients received shielding of the femoral component alone. Hence, it is unclear if shielding of the femoral component is similarly associated with an increased risk of HO development.

Further research would be needed to determine if there is a causal association between shielding and an increased risk of HO development after RT, in particular in a prospective, randomized fashion to control for confounding variables. Simultaneously, the impact of shielding on prosthesis failure should be analyzed. With this information, RT can be used more effectively as a modality to prevent HO development after THA. In the absence of such a randomized study, our data and other available studies suggest radiation for HO prophylaxis after THA may be performed without shielding of the prosthetic components to minimize the likelihood of HO without affecting the risk of prosthesis failure.

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