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SYMPOSIUM: CURRENT ISSUES IN ORTHOPAEDIC TRAUMA: TRIBUTE TO CLIFFORD H. TUREN

Does Postoperative Radiation Decrease Heterotopic Ossification After the Kocher-Langenbeck Approach for Acetabular Fracture?

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Abstract

Background Controversy regarding heterotopic ossification (HO) prophylaxis exists after Kocher-Langenbeck for treatment of acetabular fracture. Prophylaxis options include antiinflammatory oral medications, single-dose radiation therapy, and débridement of gluteus minimus muscle. Prior literature has suggested single-dose radiation therapy as the best prophylaxis to prevent HO fo‘rmation. However, recent reports have emerged of radiation-induced sarcoma after radiotherapy for HO prophylaxis, which has led many surgeons to reconsider the risks and benefits of single-dose radiation therapy. We set out to determine if radiotherapy, in addition to standard débridement of gluteus minimus muscle, affected postoperative HO formation after a Kocher-Langenbeck approach for acetabular fracture.

Questions/purposes (1) After the Kocher-Langenbeck approach and gluteus minimus débridement, is single-dose radiotherapy associated with a decreased risk of HO? (2) Does addition of single-dose radiotherapy prolong length of stay after a Kocher-Langenbeck approach and gluteus minimus débridement as compared with patients without radiotherapy?

Methods After institutional review board approval, all adult patients treated for acetabular fracture by a single surgeon with a Kocher-Langenbeck approach between August 2011 and October 2014 were identified (n = 60). Débridement of gluteus minimus muscle caudal to the superior gluteal bundle was standard in all patients. Radiotherapy was given with a single dose of 700 cGy within 72 hours of surgery from August 2011 until April 2013. Patients treated subsequently did not receive radiotherapy. Patients treated with indomethacin (n = 1) and with fewer than 10 weeks followup were excluded (n = 12) because several studies suggest that most HO that develops is visible by that point in time. Our study group totaled 46 patients with 24 in the radiotherapy and débridement group and 22 in the débridement group. Charts were reviewed to determine length of stay. Attending orthopaedic trauma surgeons who were blinded to the patient’s treatment group graded all followup radiographs according to the Brooker system, and Classes III and IV HO were considered clinically important Fisher’s exact test was used to analyze clinically significant differences HO between the two groups. Length of stay was compared using a t-test.

Results Single-dose radiotherapy is associated with a decreased risk of clinically important (Brooker III–IV) HO

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after a Kocher-Langenbeck approach and gluteus minimus débridement (radiotherapy: one of 24 [4%], no radiotherapy: seven of 22 [32%], relative risk: 0.131 [95% confidence interval {CI}, 0.018–0.981], p = 0.020). Addition of single-dose radiotherapy did not result in increased length of stay (radiotherapy: 12 ± 7.0 days; no radiotherapy: 11 ± 7.2 days; mean difference: 1.0 [95% CI, −3.2 to 5.2] days, p = 0.635).

Conclusions Single-dose radiation in combination with gluteus minimus débridement decreases the risk of clinically important HO compared with gluteus minimus débridement alone after a Kocher-Langenbeck approach for acetabular fracture. No differences in length of stay were seen. Surgeons who chose not to use radiotherapy as a result of concern for future sarcoma may see higher rates of clinically significant HO after a Kocher-Langenbeck approach for acetabular fracture fixation.

Level of Evidence Level III, therapeutic study.

Introduction

Heterotopic ossification (HO) is a common complication that can cause poor postoperative results and functional impairment in an otherwise well-performed acetabular fracture surgery [1, 4, 20]. The risk of HO, depending on surgical approach and patient/injury characteristics, has been reported to be as high as 40% [22]. Heterotopic bone formation is most commonly seen after extended iliofemoral or Kocher-Langenbeck approaches for acetabular reduction and fixation [1, 4, 11, 21]. Other reported risk factors for HO include craniocerebral trauma, fractures associated with posterior hip dislocation, operative delay, ventilation requirement > 72 hours, and race [1, 4, 10, 20, 24, 26]. The most commonly used prophylactic modalities are indomethacin, single-dose radiotherapy, and gluteus minimus débridement. No prophylactic measure has been proven to be superior to another in the prevention of HO [25]. There is substantial evidence to support the inflammatory etiology of HO; therefore, nonsteroidal antiinflammatory drugs such as indomethacin have been commonly prescribed as prophylaxis [12, 14, 15, 22]. Initial reports found indomethacin to be effective in preventing clinically important HO, which has been defined as Brooker Classes III and IV HO [4], although more recent prospective studies have found increased risk of posterior wall nonunion and no change in rates of clinically important HO [22]. Radiotherapy prevents abnormal formation of bone by inhibiting the differentiation of mesenchymal stem cells to osteogenic pathways [8, 19]. Although radiotherapy has been shown to be effective in numerous studies, the potential risk of malignant transformation and wound complications must be considered [1, 4, 9, 17]. Increased time of hospitalization and delay to the operating room to arrange for radiation should also be taken into account.

HO after a Kocher-Langenbeck approach to the acetabulum often mimics the course of the gluteus minimus muscle [20] and we routinely débride all gluteus minimus muscle caudal to the superior gluteal neurovascular bundle for this reason. The senior author (JLG) initially used radiotherapy within 72 hours of the completion of surgery, but ceased its use when multiple case reports of radiation-induced sarcoma after acetabular surgery were published [9, 17]. No study of which we are aware has compared the risk of HO as associated with and without radiotherapy prophylaxis in patients having undergone a Kocher-Langenbeck approach with gluteus minimus débridement.

We therefore asked: (1) After a Kocher-Langenbeck approach and gluteus minimus débridement, is single-dose radiotherapy associated with a decreased risk of HO? (2) Does addition of single-dose radiotherapy prolong length of stay after a Kocher-Langenbeck approach and gluteus minimus débridement as compared with patients without radiotherapy?

Patients and Methods

We performed a single-center retrospective study comparing the incidence of HO between gluteus minimus débridement with and without radiotherapy prophylaxis in patients treated from August 2011 to October 2014 in a Level I trauma center. All patients treated with open reduction and internal fixation using a Kocher-Langenbeck approach for acetabular fracture were eligible for the study. A Kocher-Langenbeck approach was routinely chosen for acetabular fractures associated with an unstable posterior dislocation of the hip or those isolated to the posterior column and/or wall. Most transverse fractures are also reduced and stabilized using this approach. The Kocher-Langenbeck approach was used in isolation in 63% (47 of 75) of patients treated with open reduction and internal fixation for acetabular fractures during this time period. Various windows of an ilioinguinal approach were combined with a Kocher-Langenbeck approach in 17% (13 of 75) of patients. During the study period there was a change in postoperative protocol regarding HO prophylaxis. Initially all patients were treated with radiotherapy and gluteus minimus débridement; then as a result of reports emerging of radiation-induced sarcoma [9, 17], radiotherapy was stopped in favor of gluteus minimus débridement only. The proportions of patients with of HO were compared between the two groups using a blinded radiographic review by fellowship-trained orthopaedic trauma surgeons.

During the study period of August 2011 to October 2014, 60 patients fit the inclusion criteria of acetabular

fracture treated with open reduction and internal fixation though a Kocher-Langenbeck approach. Patients with fewer than 10 weeks followup (n = 12) were excluded, because several studies [10, 19, 20] suggest that most HO that develops is visible by that point in time. Three of 27 patients in the radiotherapy and débridement group were excluded for insufficient followup and nine of 31 patients in the débridement-only group were excluded. Patients treated with indomethacin (n = 1) and those younger than 16 years of age (n = 1) were excluded, leaving 46 patients eligible for analysis. During the study period, two different prophylactic measures were administered for the prevention of HO. During the first 21 months (August 2011 to April 2013) of the study period, all patients were treated with radiotherapy; 24 patients thus treated were our radiotherapy group. During the last 18 months of the study period (April 2013 to October 2014), all patients were treated with gluteus minimus débridement only. These 22 patients made up the gluteus minimus débridement group.

There were no differences among age, sex, time to surgery, Injury Severity Score (ISS), history of posterior hip displocation, time of ventilator requirement, Abbreviated Injury Score (AIS) head, or AIS chest between the groups (Table 1).

The Kocher-Langenbeck approach was performed in either the prone or lateral position per the discretion of the senior author (JLG). Débridement of gluteus minimus muscle caudal to the superior gluteal bundle was standard in all patients. The muscle bellies of the superior and inferior gemelli muscles are also débrided from the obturator internus tendon to the level of the lesser sciatic notch [10, 20]. Open reduction and internal fixation then proceeded in a standard fashion as indicated per fracture type. Radiation was administered as a single dose of 700 cGy within 72 hours of surgery from August 2011 until April 2013. The remaining patients were treated without radiotherapy with only gluteus minimus débridement for HO prophylaxis.

All patients were mobilized with physical therapy postoperatively with toe-touch weightbearing to the affected lower extremity. Chemical anticoagulation with 30 mg enoxaparin (Sanofi-Aventis, Bridgewater, NJ, USA) twice daily and lower extremity sequential compression devices were started within 24 hours of surgery as prophylaxis for venous thromboembolic disease. Patients were discharged from the hospital after physical therapy clearance and completion of radiotherapy, if used.

In the débridement and radiotherapy group (n = 24), followup averaged 37 weeks (range, 11–149 weeks). All fractures in both groups were displaced. Fracture patterns included nine transverse with posterior wall (38%), eight posterior wall (33%), six associated both columns (25%), and one posterior column posterior wall (4%).

Table 1. Patient demographics and injury characteristics between the groups

Variable	XRT (n = 24)	GMD (n = 22)	p value
Age in years (mean ± SD)	33 ± 13.0	38 ± 13.6	0.209
Sex (male:female)	19:5	14:8	0.330
Associated anterior approach	7 (29%)	4 (18%)	0.310
Days from injury to operating room (mean ± SD)	3 ± 2.1	3 ± 3.1	1.000
Days in ICU (mean ± SD)	1.6 ± 3.6	1.3 ± 2.2	0.740
Days on ventilator (mean ± SD)	0.7 ± 2.5	0.4 ± 1.2	0.612
ISS (mean ± SD)	12 ± 7.9	13 ± 8.4	0.679
AIS			
Head (mean ± SD)	0.5 ± 1.2	0.4 ± 1.1	0.770
Chest (mean ± SD)	1 ± 1.2	1.4 ± 1.5	0.322
Posterior dislocation on arrival	15 (63%)	15 (68%)	0.763
Fracture pattern (Judet and Letournel)			
Posterior wall	8 (33%)	8 (36%)	1.000
Transverse-posterior wall	9 (38%)	8 (36%)	1.000
Associated* both columns	6 (25%)	2 (9%)	0.247
T-type	–	3 (14%)	0.101
Anterior column with posterior hemitransverse	–	1 (5%)	0.478
Posterior column with posterior wall	1 (4%)	–	1.000

* Associated approach: ilioinguinal or digastric trochanteric osteotomy; XRT = single-dose radiation therapy; GMD = gluteus minimus débridement; ICU = intensive care unit; ISS = Injury Severity Score; AIS = Abbreviated Injury Score.

In the débridement group (n = 22), followup averaged 27 weeks (range, 10–51 weeks). Fracture patterns included eight posterior wall (36%), eight transverse with posterior wall (36%), three T-type (14%), two associated both column (9%), and one anterior column posterior hemitransverse (5%).

Followup radiographs were routinely scheduled at 2, 6 to 8, and 10 to 12 weeks postoperatively. Weightbearing as tolerated was permitted between postoperative Weeks 8 and 12 based on fracture pattern, degree of osteochondral impaction, and other injuries at the senior surgeon's discretion.

The primary outcome was the presence of clinically important HO as seen on radiographs defined as Brooker Classes III and IV by prior studies of HO after open reduction and internal fixation of acetabular fracture [4]. All followup radiographs were independently graded by two fellowship-trained orthopaedic trauma surgeons (JWM, TSA) who were blinded to the treatment each patient received using the Moed modification of the Brooker classification, which uses two additional radiographic views–the iliac and obturator obliques–to measure

the extent of the HO [5, 16]. Any disagreements were resolved by consensus. Brooker classification at the time of final radiographs was used for statistical analysis. Charts were reviewed to determine demographic data. Fracture type according the Letournel and Judet, associated approach (ilioinguinal or digastric trochanteric osteotomy), ISS and AIS (head and chest), time from injury to operative fixation, and time of ventilator requirement were evaluated for each patient to determine if there was a difference between the two groups.

Statistical Analysis

Means and SDs were calculated for continuous variables and comparisons were made across the two treatment groups. An unpaired t-test on was used to compare continuous variables between the two groups. Fisher's exact test was used to compare categorical variables between the groups. All comparisons were made with GraphPad Software Inc (La Jolla, CA, USA). A p value < 0.05 was considered statistically significant.

Results

Single-dose radiotherapy is associated with decreased risk of clinically important (Brooker III–IV) HO after a Kocher-Langenbeck approach and gluteus minimus débridement (radiotherapy: one of 24 [4%], no radiotherapy: seven of 22 [32%], relative risk: 0.131 [95% confidence interval {CI}, 0.018–0.981], p = 0.020; Table 2). However, the proportions of patients having any presence of HO were not different between the two groups (radiotherapy: 15 of 24 [63%], no radiotherapy 16 of 22 [72%], relative risk 0.859 [95% CI, 0.575–1.285], p = 0.539). In the group without radiation, the senior author recommended surgical resection for decreased ROM of the hip and/or development of sensory changes in the distribution of the sciatic nerve in four patients. Two patients elected for surgical resection, and two were counseled to have surgical resection but have so far declined surgery. In the group treated with radiotherapy, only one patient was recommended for surgical resection. This was performed by a surgeon specializing in total joint arthroplasty at the time of conversion to THA for avascular necrosis that developed 4 months postoperatively. All five of these patients had Brooker Class IV HO. No other patients in either group had decreased hip ROM or functional limitations that precluded return to usual activity. Reviewers agreed on Brooker class in 40 of 46 (87%) of patients at final followup. Six patients (13%) required joint review to obtain consensus. No changes in Brooker classification of HO were made by either reviewer from 6 weeks to final followup, only maturation of existing HO.

Addition of single-dose radiotherapy did not result in increased length of stay (radiotherapy: 12 ± 7 days; no radiotherapy: 11 ± 7.2 days; mean difference: 1.0 [95% CI, −3.2 to 5.2] days, p = 0.635).

Discussion

HO can cause substantial functional impairment even after well-performed acetabular fracture surgery [1, 4, 20]. Although some studies support prophylaxis in high-risk patients [4, 6, 10, 21], there is currently no consensus as to which prophylactic measure is the most efficacious. Previous studies have demonstrated the value of gluteus minimus débridement in reducing the risk of HO and compared its effectiveness with that of indomethacin [10, 20, 22]. To our knowledge, this is the first study comparing the effectiveness of gluteus minimus débridement with and without radiotherapy. Therefore, we aimed to assess the effectiveness of radiotherapy in decreasing severe HO risk in patients with a Kocher-Langenbeck approach and gluteus minimus débridement.

The study has a number of limitations. First, patient compliance with followup appointments was low, especially once advancement to full weightbearing was permitted. We therefore chose 10-week followup as a

Table 2. Heterotopic ossification and length of hospital stay between groups*

Outcome	XRT + GMD (n = 24)	GMD (n = 22)	Relative risk (95% CI)	p value
Presence of HO	15 (60%)	16 (72%)	0.859 (0.575–1.285)	0.539
Mild (Brooker I–II)	14 (58%)	9 (41%)	1.426 (0.778–2.612	0.376
Clinically important (Brooker III–IV)	1 (4%)	7 (32%)	0.131 (0.018–0.981)	0.020
Recommended or performed HO resection	1 (4%)	4 (18%)	0.229 (0.028–1.897)	0.178
			Mean difference (95% CI)	
Length of stay (days ± SD)	12 ± 7.0	11 ± 7.2	1.0 (−3.2, 5.2)	0.635

* Two additional patients are pending HO resection; XRT = single-dose radiation therapy; GMD = gluteus minimus débridement; CI = confidence interval; HO = heterotopic ossification.

minimum for inclusion. One recent study has shown that HO does not progress beyond 6 weeks [20], and another meta-analysis has shown that 89% of HO is present by 3 weeks and 100% by 8 weeks [19]. In a review of 508 patients treated by a single surgeon, only two of 508 (0.4%) patients had progression in Brooker HO class from 6 weeks postoperative radiographs to final followup [10]. Therefore, we believe 10 weeks is sufficient to answer our primary study question. Furthermore, our findings agree with others [10, 20] in that there was no increase in volume of HO observed after 6 weeks, only maturation. We defined clinically important HO and Brooker Classes III and IV, according to criteria used by Bosse et al. [4]. However, only five of eight patients meeting these criteria were recommended to have surgical resection of HO as a result of functional limitations, questioning the clinical relevance of the radiographic finding in asymptomatic patients. The lack of patient-derived functional outcomes and precise postoperative measurements of hip ROM limit our ability to quantify the clinical consequences of Brooker Classes III and IV HO after acetabular surgery. A single surgeon early in his career performed all the procedures, and the results may not generalize to other surgeons with different levels of experience. As a surgeon progresses through the learning curve, it is intuitive that the amount of surgical trauma should decrease, possibly decreasing the formation of HO [7, 25]. This would seem to favor gluteus minimus débridement without radiotherapy group in this series, which had surgery further into the surgeon's learning curve. Despite this theoretical advantage, more HO was observed in the patients treated with gluteus minimus débridement without radiotherapy. Another limitation is the inability to assess sarcoma transformation risk, which would require followup to death for each of these patients. In addition, although aspirin was not prescribed to any patients postoperatively, they may have taken this over the counter, and aspirin has been shown to decrease HO after hip resurfacing arthroplasty [18].

Our study, along with numerous others, highlights the benefit of radiotherapy in the prevention of HO. Slawson et al. [23] compared 30 patients treated with radiotherapy versus 20 patients without prophylaxis and found that the incidence of severe HO decreased from 50% to 10% with the use of radiotherapy. In a similar study, when looking at extensile approaches only, Bosse et al. [4] found a decrease in the risk of severe HO with the use of radiotherapy. In these two and another study comparing preoperative with postoperative radiotherapy, Brooker Classes III and IV were considered severe [2, 4, 23]. When comparing radiotherapy with indomethacin, the findings are been less clear. In a randomized study comparing the two, both indomethacin and radiotherapy were found to be effective in preventing HO, but neither was superior to the other [6]. In a recent systematic review of five prospective studies including 384 patients, radiotherapy was found to have a lower risk of HO compared with indomethacin, although the quality of the studies reviewed made a proper meta-analysis inappropriate [3]. In our study, when considering the near equal incidence of HO, it appears that rather than preventing the formation of HO entirely, radiotherapy in addition to gluteus minimus débridement prevented the progression of HO from mild (Brooker I–II) to clinically important (Brooker III–IV) when compared with gluteus minimus débridement alone.

One argument against the use of radiotherapy is the potential for malignant transformation. There have been two case reports of radiation-induced sarcoma after radiation prophylaxis for HO in the literature. In one case a patient developed high-grade sarcoma 14 years after acetabular open reduction and internal fixation and radiotherapy, during which time he also received a second dose of 700 cGy before THA on the same side [17]. In the second case, a polytrauma patient was treated with radiotherapy after open reduction and internal fixation of the acetabulum for a hip fracture dislocation and was diagnosed with high-grade sarcoma of the affected region 11 years postinjury [9]. Although these reports are concerning, it is difficult to know whether the cancer is truly secondary to the radiation treatment [27]. Reports of more than 50 cases of local malignancy after THA [27] and 12 reports of sarcoma at sites of orthopaedic implants [13] have been published without a history of radiotherapy. Clearly, a discussion of risks and benefits that must be had between the patient and surgeon regarding radiotherapy as HO prophylaxis.

The need for postoperative radiotherapy could theoretically delay postoperative mobilization and/or discharge. In addition, radiotherapy is usually not available in most centers on weekend days or holidays, which may lead to a delay to surgery if radiotherapy is planned. Therefore, there is a theoretical potential for increased length of hospitalization compared with patients in whom no radiotherapy is prescribed. Despite these theoretical concerns, we found no increase in length of stay when radiotherapy was included in the treatment and no data for length of stay have been reported from prior studies of this subject.

Our study is the first of which we are aware to demonstrate a decreased risk of clinically important HO with the use of single-dose radiation therapy in addition to gluteus minimus débridement when compared with gluteus minimus débridement alone in the Kocher-Langenbeck approach. It has been proposed that by removing what is thought to be the main HO generator, gluteus minimus, no additional prophylaxis would be necessary, but our study shows that radiotherapy continues to have a benefit in this setting. Radiotherapy is associated with a legitimate concern of malignant transformation and this must be

discussed with the patient. Surgeons who choose not to use radiotherapy for concern of sarcoma may experience increased risks of severe HO after a Kocher-Langenbeck approach for acetabular fixation.

References

1. Anglen JO, Moore KD. Prevention of heterotopic bone formation after acetabular fracture fixation by single-dose radiation therapy: a preliminary report. *J Orthop Trauma.* 1996;10:258–263.
2. Archdeacon MT, d'Heurle A, Nemeth N, Budde B. Is preoperative radiation therapy as effective as postoperative radiation therapy for heterotopic ossification prevention in acetabular fractures? *Clin Orthop Relat Res.* 2014;472:3389–3394.
3. Blokhuis TJ, Frolke JP. Is radiation superior to indomethacin to prevent heterotopic ossification in acetabular fractures?: a systematic review. *Clin Orthop Relat Res.* 2009;467:526–530.
4. Bosse MJ, Poka A, Reinert CM, Ellwanger F, Slawson R, McDevitt ER. Heterotopic ossification as a complication of acetabular fracture. Prophylaxis with low-dose irradiation. *J Bone Joint Surg Am.* 1988;70:1231–1237.
5. Brooker AF, Bowerman JW, Robinson RA, Riley LH Jr. Ectopic ossification following total hip replacement. Incidence and a method of classification. *J Bone Joint Surg Am.* 1973;55:1629–1632.
6. Burd TA, Lowry KJ, Anglen JO. Indomethacin compared with localized irradiation for the prevention of heterotopic ossification following surgical treatment of acetabular fractures. *J Bone Joint Surg Am.* 2001;83:1783–1788.
7. Ekelund A, Brosjo O, Nilsson OS. Experimental induction of heterotopic bone. *Clin Orthop Relat Res.* 1991;263:102–112.
8. Ellerin BE, Helfet D, Parikh S, Hotchkiss RN, Levin N, Nisce L, Nori D, Moni J. Current therapy in the management of heterotopic ossification of the elbow: a review with case studies. *Am J Phys Med Rehabil.* 1999;78:259–271.
9. Farris MK, Chowdhry VK, Lemke S, Kilpatrick M, Lacombe M. Osteosarcoma following single fraction radiation prophylaxis for heterotopic ossification. *Radiat Oncol.* 2012;7:140.
10. Firoozabadi R, O'Mara TJ, Swenson A, Agel J, Beck JD, Routt M. Risk factors for the development of heterotopic ossification after acetabular fracture fixation. *Clin Orthop Relat Res.* 2014;472:3383–3388.
11. Ghalambor N, Matta JM, Bernstein L. Heterotopic ossification following operative treatment of acetabular fracture. An analysis of risk factors. *Clin Orthop Relat Res.* 1994;305:96–105.
12. Ho S, Stern P, Bruno L. Pharmacological inhibition of prostaglandin E-2 in bone and its effect on pathological new bone formation in a rat brain model. *Trans Orthop Res Soc.* 1988;13:536.
13. Keel SB, Jaffe KA, Petur Nielsen G, Rosenberg AE. Orthopaedic implant-related sarcoma: a study of twelve cases. *Mod Pathol.* 2001;14:969–977.
14. McLaren AC. Prophylaxis with indomethacin for heterotopic bone. After open reduction of fractures of the acetabulum. *J Bone Joint Surg Am.* 1990;72:245–247.
15. Moed BR, Maxey JW. The effect of indomethacin on heterotopic ossification following acetabular fracture surgery. *J Orthop Trauma.* 1993;7:33–38.
16. Moed BR, Smith ST. Three-view radiographic assessment of heterotopic ossification after acetabular fracture surgery. *J Orthop Trauma.* 1996;10:93–98.
17. Mourad WF, Packianathan S, Shourbaji RA, Russell G, Khan MA, Vijayakumar S. Radiation-induced sarcoma following radiation prophylaxis of heterotopic ossification. *Pract Radiat Oncol.* 2012;2:151–154.
18. Nunley RM, Zhu J, Clohisy JC, Barrack RL. Aspirin decreases heterotopic ossification after hip resurfacing. *Clin Orthop Relat Res.* 2011;469:1614–1620.
19. Popovic M, Agarwal A, Zhang L, Yip C, Kreder HJ, Nousiainen MT, Jenkinson R, Tsao M, Lam H, Milakovic M, Wong E, Chow E. Radiotherapy for the prophylaxis of heterotopic ossification: a systematic review and meta-analysis of published data. *Radiother Oncol.* 2014;113:10–17.
20. Rath EM, Russell GV Jr, Washington WJ, Routt ML Jr. Gluteus minimus necrotic muscle débridement diminishes heterotopic ossification after acetabular fracture fixation. *Injury.* 2002;33:751–756.
21. Routt ML Jr, Swiontkowski MF. Operative treatment of complex acetabular fractures. Combined anterior and posterior exposures during the same procedure. *J Bone Joint Surg Am.* 1990;72:897–904.
22. Sagi HC, Jordan CJ, Barei DP, Serrano-Riera R, Steverson B. Indomethacin prophylaxis for heterotopic ossification after acetabular fracture surgery increases the risk for nonunion of the posterior wall. *J Orthop Trauma.* 2014;28:377–383.
23. Slawson RG, Poka A, Bathon H, Salazar OM, Bromback RJ, Burgess AR. The role of post-operative radiation in the prevention of heterotopic ossification in patients with post-traumatic acetabular fracture. *Int J Radiat Oncol Biol Phys.* 1989;17:669–672.
24. Slone HS, Walton ZJ, Daly CA, Chapin RW, Barfield WR, Leddy LR, Hartsock LA. The impact of race on the development of severe heterotopic ossification following acetabular fracture surgery. *Injury.* 2015;46:1069–1073.
25. Tile M, Helfet D, Kellam J, Vrahas M. *Fractures of the Pelvis and Acetabulum.* New York, NY, USA: Thieme; 2015.
26. Webb LX, Bosse MJ, Mayo KA, Lange RH, Miller ME, Swiontkowski MF. Results in patients with craniocerebral trauma and an operatively managed acetabular fracture. *J Orthop Trauma.* 1990;4:376–382.
27. Welsh JS. Not all second cancers are secondary. In regard to Mourad et al: 'Radiation-induced sarcoma following radiation prophylaxis of heterotopic ossification.' *Pract Radiat Oncol.* 2013;3:e35–36.