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CLINICAL INVESTIGATION **Benign Disease**

A PROSPECTIVE EVALUATION OF THE TIMING OF POSTOPERATIVE RADIOTHERAPY FOR PREVENTING HETEROTOPIC OSSIFICATION FOLLOWING TRAUMATIC ACETABULAR FRACTURES

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Purpose: Preoperative and immediate postoperative irradiation of traumatic acetabular fractures (TAF), although known to reduce heterotopic ossification (HO), can cause significant organizational and logistic difficulties. We sought to determine an acceptable time interval between surgery and radiation without compromising control, as well as to update our large experience and to further validate our treatment philosophy.

Methods and Materials: Beginning in June 1995, we began a prospective study, irradiating 152 patients on postoperative days 1, 2, or 3. There were also 17 patients delayed further secondary to medical difficulties.

Results: All patients treated since June 1995 received 700 cGy/1 fx. Fifty-eight patients received radiation within 24 hours of surgery, 41 within 2 days, 53 within 3 days, 13 within 4 days, and 4 were delayed further. Delaying irradiation for up to 4 days postoperatively caused no statistical increase in HO ($p = 0.625$). Of 263 patients in our retrospective cohort, HO occurred in 5.3% of patients who received irradiation versus 60% of patients who did not.

Conclusion: In our prospective study, we noted no perceptible increase in HO with up to a 3-day interval between surgery and radiotherapy. This allows a more structured treatment schedule and allows the patient more time to heal and recover. Updated results from our overall series continue to demonstrate that adjuvant radiation decreases the incidence and severity of HO after TAF. © 2000 Elsevier Science Inc.

Heterotopic, Ossification, Radiation, Traumatic.

INTRODUCTION

Heterotopic ossification (HO) is defined as the formation of mature lamellar bone in nonosseous tissues. This was first described in 1883 by a German physician named Reidel (1). The most common cause is trauma but others include neurogenic causes and myositis ossificans (2, 3). Traumatic causes include fractures, dislocations, and open reduction and internal fixation (ORIF) either of traumatic fractures or for total hip arthroplasty (THA) (4–8). This report addresses HO after ORIF for traumatic acetabular fractures (TAF) and specifically addresses timing issues related to adjuvant radiotherapy for HO prophylaxis.

In patients who have THA, the reported incidence of HO ranges from 8–90% with a range of 35–57% in the largest series (6, 9–15). Compared to the wealth of data for THA, there is a relative paucity of data dealing with HO after repair of TAF, although this body of data is growing (16–23). However, for TAF, the accepted incidence of HO is also in the range of 50% (8). This incidence fluctuates somewhat based on known risk factors such as previous HO after hip surgery, prior trauma, prior operations, hypertrophic osteoarthritis, diffuse idiopathic skeletal hyperostosis (DISH), and ankylosing spondylitis (4, 5, 24).

The incidence of HO is known to be lowered by radiation therapy and it is thought that the radiation acts in some way to impede the proliferation of pluripotential mesenchymal cells that could differentiate into osteoblastic stem cells (25–27). This incidence is also known to be lowered by the use of nonsteroidal anti-inflammatory drugs (NSAIDs), most particularly indomethacin; however, compliance is questionable and approximately 37% of patients do not complete therapy secondary to side effects (9, 28).

With these thoughts in mind, we have routinely treated our patients after ORIF for TAF with prophylactic radiotherapy since 1987. An earlier report from our institution in 1995 demonstrated dramatic reductions in the incidence of HO with radiotherapy after surgical repair of TAF (29). After this report and from a review of the literature at that

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time, we have been treating all of our patients with 700 cGy in 1 fraction AP/PA. Also, there is a growing body of literature supporting the efficacy of adjuvant radiotherapy given within 72 hours of surgery although most institutions, including ours, strive to complete the irradiation within 24 hours of surgery (4, 6, 15, 25, 30–33). A 72-hour window would allow the patient to recover more from the surgery, thereby improving safety, especially for those who were ventilator-dependent or medically unstable. This would also allow the department of radiation oncology more flexibility with simulation and delivery of treatment, thus improving patient satisfaction with less delays. Because of this, we organized a prospective study to analyze potential differences in the incidence of HO with radiation on postoperative days 1 through 3.

METHODS AND MATERIALS

Between 1987 and 1998, 274 patients have had these fractures repaired through surgical approaches at high risk of HO. High-risk operations, as defined in our previous report, are considered to be a TAF repaired through either a posterior, triradiate, or extended iliofemoral approaches or some combination of these. Of these patients, 236 have had adjuvant radiotherapy and 225 of these had adequate follow-up.

Beginning in June 1995, we began a prospective study, irradiating 152 patients on postoperative days 1, 2, or 3. Although not randomized, the decision was made to take patients who had surgery on Friday and treat them on Monday (postoperative day 3). Patients with surgery on Monday through Thursday were treated within 24–48 hours. There were 17 additional patients who were delayed further secondary to medical instability, 13 of whom were irradiated on day 4. We had four additional patients who were not treated with RT at all as they refused treatment or were pregnant at the time. As mentioned previously, all patients were simulated and then received 700 cGy in one fraction through an AP/PA port prescribed to midline. During simulation, care was taken to cover potential heterotopic bridging areas including from the supra-acetabular region to the greater trochanter and from the infra-acetabular region to the lesser trochanter (Fig. 1). We did not intentionally treat the entire orthopedic hardware if this extended out of the area of interest. Collimator rotation was often used to minimize irradiation of normal tissues and cerrobend blocks were also used if needed. Photon energy was a heterogeneous mix of 4 MV, 15 MV, and 24 MV. Patients were followed with history, physical exam, and serial X-rays.

The addition of NSAIDs, most often indocin, was left to the discretion of the surgeon. We had 84 patients who received NSAIDs in addition to radiotherapy and another 85 patients who received radiation alone. We compared the incidence and severity of HO in these two groups. We used the standard Brooker classification scheme to grade the severity of HO formation (5) (see Fig. 2 and Table 1).

As there is not much data endorsing the utility of RT for the repair of TAF, we sought to further quantify the role of RT in this setting. The entire cohort of patients from 1987 to April 1999 was then combined and retrospectively analyzed to compare with patients who did not receive radiotherapy. There were 38 patients who did not receive radia-

Fig. 1. Typical simulation film.

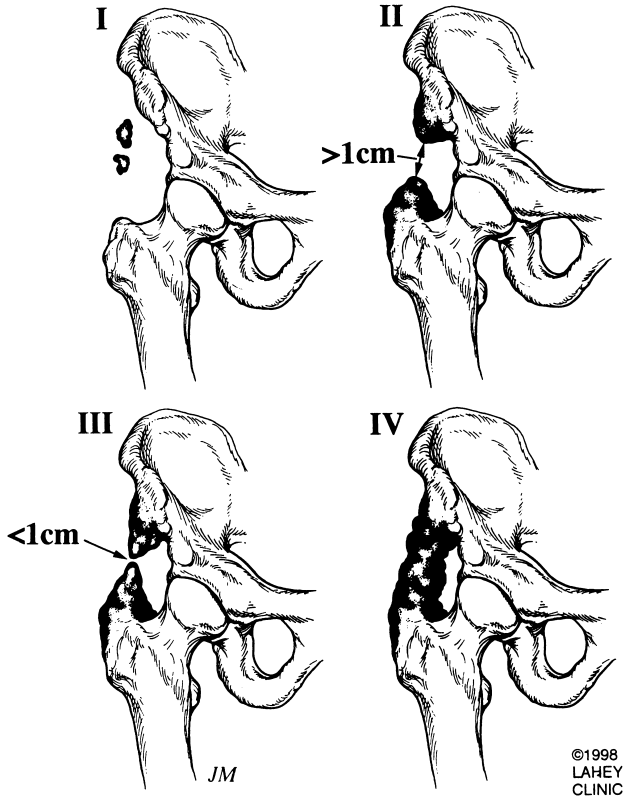

Fig. 2. Brooker classification scheme. Reprinted with permission of Lahey Clinic, Burlington, MA.

Table 1. Brooker classification

Class I	Islands on bone within the soft tissue around the hip
Class II	Bone spurs from the pelvis or proximal end of the femur, leaving at least 1 cm between the opposing bone surfaces
Class III	As in Class II but with less than 1 cm between opposing bone surfaces
Class IV	Apparent bony ankylosis

tion secondary to either medical instability or patient refusal and these served as our surgery alone control group by default. Univariate analysis was performed to quantify potential risk factors for HO. Lastly, we analyzed the incidence of potential complications between the groups that did and did not receive RT.

RESULTS

The patients treated since June 1995 had a median follow-up of 238 days. There was a fairly homogeneous distribution of patients regarding the surgery to radiation time: 58 patients received radiation within 24 hours of surgery, 41 within 2 days, 53 within 3 days, 13 within 4 days, and 4 were delayed greater than 4 days. There was no statistical difference in incidence of HO with delaying irradiation for up to 4 days postoperatively ($p = 0.625$ with Fisher's exact test, two-tailed), although admittedly the number of patients in the 4-day subgroup was relatively small. HO occurred in 4.7% of the patients who received irradiation within 4 days versus 25% of those patients receiving radiation after 4 days, with a mean Brooker grade of 1.6 versus 2 respectively ($p = 0.001$) (Table 2). Three of the four additional patients (75%) who did not receive RT developed HO. Interestingly, we also have fairly equal numbers of patients who did and did not receive NSAIDs in addition to radiation

Table 2. Patient characteristics with the timing of postoperative RT—prospective cohort

	Day 1	Day 2	Day 3	Day 4	>Day 4
HO					
Yes	1	2	3	1	1
No	57	39	50	12	3
Gender (N)					
Male	36	26	31	11	0
Female	20	15	21	2	4
Median age (yr)	33	32	31	32	25
Sx Approach					
Triradiate	3	3	1	3	0
Posterior	31	25	31	6	1
Combination	16	6	15	2	3
Other	8	5	4	1	0
NSAIDs					
Yes	31	19	25	8	1
No	27	22	28	5	3
Injury to RT interval (median days)	6	7	8	12	13

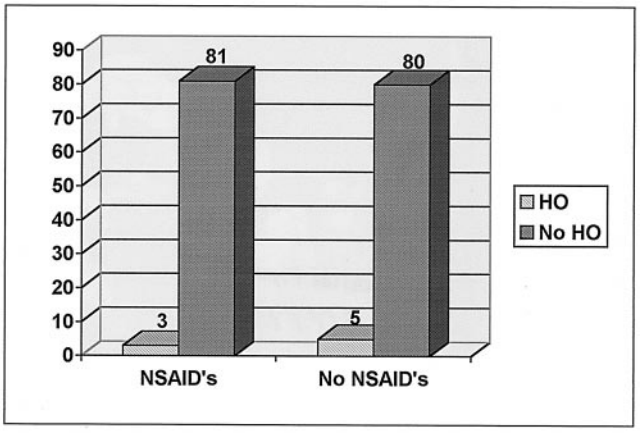

Fig. 3. Number of patients with and without HO versus addition of NSAIDs.

and there was no difference in HO formation ($p = 0.479$ with Fisher's exact two-tailed test) (Fig. 3 and Table 3).

We then reanalyzed the entire cohort to update our retrospective review. There were two other radiation dosing schedules used: 3 patients received 800 cGy/1 fx and 6 received 1000 cGy/5 fx. The overall incidence of HO after radiation was 5.3% and only 2 of 225 patients had a Brooker grade of III. Thirty-eight patients who did not receive radiation served as controls and had a 60% incidence of HO with 21% having grades III or IV. We analyzed potential variables associated with HO and found that only the surgery to radiation time interval ($p = 0.007$), type of surgery (triradiate vs. posterior vs. combination vs. other; $p < 0.001$), and dose of radiation ($p = 0.003$) were significant (Table 4). However, as only 9 of 225 patients received different RT fractionation schedules, we note that the population is askew, thus the validity of statistical analysis for dose may not be pertinent. Also, 3 of 6 receiving 1000 cGy/5 fx developed HO whereas none who received 800 cGy/1 fx did (Table 5). We also examined potential complications and found no increase in wound complications or delayed healing with radiation (Table 6).

Table 3. Patient characteristics with and without NSAIDs

	NSAIDs	No NSAIDs	*p*-Value
N	84	85	
Age (median, yr)	33	31	0.54
Gender			0.84
M	52	52	
F	30	32	
Type of Sx			0.14
Triradiate	3	7	
Posterior	51	43	
Combination	16	26	
Other	11	7	
Injury to RT interval (median, days)	7	8	0.008*

* Wilcoxon 2-sample test.

Table 4. Potential risk factors for development of HO

Risk factor analyzed	*p*-Value
Surgery to RT time interval	0.007
Type of surgery	<0.001
Dose of RT	0.003
Energy of RT	0.089
Blocks	0.849
Area of port	0.775
Field size	0.443
Depth	0.301
Injury to RT time interval	0.101
Age of patient	0.235

DISCUSSION

Heterotopic ossification is a well-recognized potential complication of total hip arthroplasty in high-risk patients, as previously mentioned. The first report of a benefit of RT in these patients was demonstrated by Coventry and Scanlon in 1981 and there have been continued efforts to determine the optimum dose and timing of therapy in an effort to maximize control of the process, patient comfort, and RT staff convenience (6, 11, 34, 35). Other institutions have also examined preoperative RT for THA patients at high risk for HO (12, 13, 15, 36–38). There is also a growing body of data that HO after repair of traumatic acetabular fractures is a frequent complication of surgery and that low-dose radiotherapy can significantly decrease the incidence of this occurrence (Table 7). Two reports from the University of Maryland, Slawson *et al.* in 1989 and Haas *et al.* in 1999, demonstrate remarkable decreases in the incidence of clinically symptomatic HO (Brooker grades III and IV) with RT from 50% to 10% ($p = 0.01$) (16, 19). They also report a decrease in the incidence of bony ankylosis (Brooker grade IV) with 3/20 control patients versus none in the irradiated group of 30 patients. Their second report of an additional 47 evaluable patients confirms the incidence of HO after RT at about 10%. Another institution reported on their experience of postoperative RT for TAF (17, 23). With 8 Gy in one fraction of irradiation, they noted 3 patients with grade III HO and no grade IV of 33 hips treated and no grade III or IV of 20 hips treated in each study respectively.

These figures coincide with four previous reports by Meyer *et al.* demonstrating HO in 19 of 34 patients without RT (56%) versus 5 of 36 patients with RT (13.9%) (29). In light of this data, we have been treating our TAF patients at high risk of developing HO with adjuvant RT. We have, however, noted increasing difficulties treating patients within a 24-hour window from surgery due to several factors. First, many patients are transferred to our facility and have severe polytrauma. They are often maintained on the ventilator for several days after their surgery and are in severe pain. Also, realistically, we have to work these patients into the simulator schedule and, when there might be a couple of work-ins per day, these patients as well as others suffer with long wait times and discomfort. We began a prospective evaluation of the timing of adjuvant RT for TAF in June 1995; we sought to prove that a longer time interval could be used without sacrificing efficacy and thus allow further patient healing and a more structured treatment format.

Table 5. Number of patients with and without HO per postoperative day for all patients

RT Dose	HO	Day 1	Day 2	Day 3	Day 4	>Day 4
7 Gy/1 fx	Yes	2	2	3	1	1
	No	75	50	63	16	3
8 Gy/1 fx	Yes	0	0	0	0	0
	No	1	1	1	0	0
10 Gy/5 fx	Yes	0	0	1	0	2
	No	0	2	1	0	0

Table 6. Potential complications after ORIF for TAF with and without XRT

Complication	Number of patients
None	235
Infection	5
Delayed wound healing	2
Other	11
Deep vein thrombosis	
Aseptic vascular necrosis	
Traumatic arthritis	

We have since followed 169 patients at high risk for HO after repair of TAF. All received similar radiotherapy. Many received NSAIDs in addition at the discretion of the orthopedic surgeon. We have noted no statistical increase in HO with a delay of RT for up to the third postoperative day (4.7% overall). Although the number of patients who were treated on day 4 was small, there was no statistical increase in HO either. The four patients who were delayed more than 4 days did seem to have a higher incidence of HO (75%). Our overall rate of HO formation after RT seems to be lower than some series and currently we cannot explain this. Only 8 of 169 patients developed HO and of these only two had clinically significant ossification (Brooker grade III). Moed and Letournel described a very low rate of HO formation with a combination of NSAIDs and low-dose RT similar to the treatment approach used with some of our patients (18). Interestingly, in our patient cohort, although not randomized or stratified, there did not seem to be a benefit to the addition of NSAIDs with RT as compared to RT alone.

As a second objective, we compiled our entire patient cohort treated with RT since 1987 and performed a retrospective review. The conclusions continue to validate RT as an extremely effective tool for reducing both the incidence and severity of HO after repair of TAF. As we also noted no increase in complications with the addition of RT, this is now regarded as a standard treatment for the high-risk patient at our institution.

Table 7. Summary of results using postoperative RT for TAF

Authors	No. hips	Dose (Gy/fxs)	Incidence of any HO	Incidence of Grade III/IV HO
Slawson *et al*. (19)	30	10/5	50%	10%
	20	No RT	90%	50%
Haas *et al*. (16)	47	10/5, 8/1, 6/1	51%	13%
Meyer *et al*. (29)	36	7/1, 8/1, 10/5	13.9%	—
	34	No RT	56%	—
Moore *et al*. (23)	20	8/1	—	0
Anglen *et al*. (17)	33	8/1	—	9% (all Grd 3)
Current series				
Prospective	169	7/1	4.7%	1.2%
	4	No RT	75%	25%
Retrospective	225	7/1, 8/1, 10/5	5.3%	0.1% (Grd 3)
	38	No RT	60%	21%

CONCLUSION

We report the largest known series of traumatic acetabular fractures treated with routine postoperative radiation to prevent heterotopic bone formation. In our prospective study, we noted no perceptible increase in heterotopic bone formation with up to a 3-day interval between surgery and radiotherapy, even in high-risk patients. This allows for a more structured treatment schedule as well as allowing the patient more time to heal and recover from surgery, thus making them more comfortable as well. Updated results from our overall series continue to demonstrate that postoperative radiation decreases the incidence and severity of HO after TAF.

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