Radiation Therapy for Heterotopic Ossification Prophylaxis After High-Risk Elbow Surgery

Jonathan B. Strauss, MD, MBA, Robert W. Wysocki, MD, Amar Shah, MD, Sea S. Chen, MD, PhD, Anand P. Shah, MD, Ross A. Abrams, MD, and Mark S. Cohen, MD

Abstract

Heterotopic ossification (HO) is a common complication of elbow trauma or surgery. HO can impair joint function; when it does, surgical removal is required. Radiotherapy (RT) prevents HO formation in the hip. However, few data exist on the efficacy of RT in preventing HO formation in the elbow.

We retrospectively analyzed the outcomes of elbow surgery followed by prophylactic single-fraction RT and use of nonsteroidal anti-inflammatory drugs (NSAIDs). All patients had ectopic bone resected at surgery or significant risk factors for development of ectopic bone.

Of the 52 patients who underwent RT after high-risk elbow surgery, 44 had postoperative radiographs of the treated elbow available for evaluation. At a median follow-up of 136 days, 21 patients (48%) had radiographic evidence of HO. In all cases, however, the HO was small and not functionally significant. No complications were attributed to RT use.

This retrospective review represents the largest published series of patients who have undergone postoperative RT to prevent HO formation in the elbow. Our findings support the idea that RT, in combination with NSAID use, is safe and efficacious in preventing development of clinically significant HO in the elbow.

Dr. Strauss is Assistant Professor, Department of Radiation Oncology, Northwestern Memorial Hospital, Chicago, Illinois.
Dr. Wysocki is Assistant Professor, Department of Orthopedic Surgery, and Dr. Amar Shah is Fellow, Department of Radiology, Rush University Medical Center, Chicago, Illinois.
Dr. Chen is Staff Radiation Oncologist, South Sacramento Medical Center, Kaiser Permanente, Sacramento, California.
Dr. Anand P. Shah is Chief Resident, and Dr. Abrams is Professor and Chairman, Department of Radiation Oncology, Rush University Medical Center.
Dr. Cohen is Professor and Director, Section of Hand and Elbow Surgery, Department of Orthopaedic Surgery, Rush University Medical Center.

Address correspondence to: Jonathan B. Strauss, MD, Department of Radiation Oncology, Northwestern Memorial Hospital, 201 E Huron St, Galter Pavilion, LC-178, Chicago, IL 60611 (tel, 312-926-3521; fax, 312-926-6524; e-mail, jonathan1804@gmail.com).

Am J Orthop. 2011;40(8):400-405.

Heterotopic ossification (HO) is a type of ectopic ossification that consists of mature lamellar bone formation in nonosseous soft tissues.[1] HO is a sequela of musculoskeletal trauma, joint surgery, central nervous system injury, and severe burns. Risk factors for HO development are categorized into 3 types: patient, clinical, and surgical.[2] Patient risk factors include prior HO formation, hypertrophic osteoarthritis, ankylosing spondylitis, Paget disease, idiopathic skeletal hyperostosis, and male sex. In addition, rare genetic disorders, such as fibrodysplasia ossificans progressiva, cause disseminated progressive ossification of soft tissues.[3] Clinical risk factors include elbow trauma (fracture and/or dislocation), brain or spinal cord injury, and severe burns. The likelihood of HO development increases with severity of trauma and degree of thermal burn.[4,5] Surgical risk factors are thought to include repeat surgeries and certain surgical approaches, and possibly bone dust in the operative bed and hematoma formation.[1] A delay in surgery after elbow trauma also has been implicated.[6]

Extent and location of HO formation vary widely, from small and functionally insignificant bony islands to large bony growths that bridge the joint space. The latter can cause pain and significantly impair joint mobility. HO formation first manifests as a local inflammatory reaction that can cause erythema and warmth. It is associated with a transient rise in serum alkaline phosphatase. Soft-tissue calcification becomes radiographically evident approximately 1 month after the inciting event.[7]

The pathogenesis of HO has not been entirely elucidated, but likely involves the differentiation of mesenchymal pluripotential stem cells into osteoblasts. Current theories postulate that a cascade of cellular activity is initiated by an inciting event such as trauma. If the cellular environment in the traumatized area is conducive to HO formation, then mesenchymal stem cells are induced to differentiate into chondroblasts and osteoblasts that deposit an osteoid matrix.[8] The osteoid matrix is subsequently mineralized and matures to become identical to orthotopic bone.[9] The putative factors that induce the mesenchymal cells to proliferate and differentiate into osteoblasts have been termed bone morphogenic proteins.[10]

Once formed, heterotopic bone must be surgically resected to restore function to a compromised joint (no

effective medical management exists). Given this situation, strategies to prevent HO development have been developed. Historically, diphosphonates were used for HO prophylaxis. They inhibit calcification of the osteoid matrix but do not block its formation. As a result, the matrix becomes mineralized rapidly on cessation of medication use in a phenomenon known as the rebound effect.[11] For this reason, use of diphosphonates has fallen out of favor.[12] Use of external-beam radiotherapy (RT) for HO prophylaxis was first described by Coventry and Scanlon[13] in 1981. RT is thought to inactivate mesenchymal pluripotent stem cells, preventing differentiation to osteoblastic cells.[14] Nonsteroidal anti-inflammatory drugs (NSAIDs), such as indomethacin, are often used with RT, or in lieu of it. The putative mechanism of action of NSAIDs involves a reduction in prostaglandin production and inactivation of mesenchymal stem cells.[15] Prospective randomized trials have validated the efficacy of both RT and NSAID use in preventing HO formation in the hip.[16-19] Although both strategies are superior to no intervention, RT is more efficacious than NSAID use alone.[20,21] In addition, prolonged NSAID use can induce dyspepsia and bleeding events, requiring discontinuation of therapy.[22] As a result, patient adherence can be difficult to ensure.

For reasons that are unclear, the elbow is especially susceptible to formation of heterotopic bone. Rates of HO formation range from up to 30% in elbow fracture-dislocations to 75% to 90% in cases of simultaneous elbow trauma and head injury.[23] Rates of symptomatic HO in patients with burn injuries are estimated at 1% to 3%, with risk related to extent and degree of the burn.[24] Depending on its specific location, HO in the elbow can cause pain, ulnar nerve compression, or impairment in elbow and forearm motion. Given the relative scarcity of cases, there are few published reports that detail the efficacy of RT for HO prophylaxis specifically in the elbow. The present study represents the largest reported cohort of high-risk elbows irradiated for prophylaxis against HO.

Methods

We retrospectively analyzed the outcomes of elbow surgery with postoperative RT at Rush University Medical Center to prevent HO in the elbow.

All patients underwent RT within the first day after surgery. They were treated with a single fraction of 5 Gy to 7 Gy to the elbow using opposed anteroposterior and posteroanterior fields with 6-megavolt (MV) photons prescribed to midplane. Field dimensions were individualized to include the periarticular tissues and the operative bed. In addition, all patients were given a prescription for indomethacin 75 mg to be taken orally 2 times per day for 10 days. All patients were to participate in formal physical therapy as well as a home program to maximize elbow and forearm mobility and function.

After surgery, patients were followed clinically and radiographically at frequent intervals. Data were collected with respect to recovery of motion and development of any radiographically evident or functionally limiting HO. Preoperative and postoperative radiographs were reviewed, and HO was rated using every available grading system, including those described by Garland and O'Hollaren,[23] Hastings and Graham,[25] Jupiter and Ring,[26] and Ilahi and colleagues.[27] All radiographs were evaluated by an independent radiologist, Dr. Amar Shah, solely for the purposes of this study.

Results

Between August 31, 2000 and April 1, 2008, 52 patients underwent elbow surgery followed by RT. Of these patients, 44 had postoperative radiographs of the treated elbow available for evaluation. All 44 were treated by the Director of Hand and Elbow Surgery at the medical center (M.S.C.). Of these patients, 32 had motion-limiting HO treated surgically; 15 of the 32 had partial or complete loss of elbow flexion/extension, and the other 17 had partial or complete loss of forearm supination/pronation. Of the remaining 12 patients, 1 had radiographically evident but non–motion-limiting HO, and 11 underwent RT in the absence of clinically significant HO, as they were thought to be at high risk for development of HO after surgery. These patients either had a delay in care or required revision surgery after severe trauma. The majority of patients experienced traumatic fracture as the initial insult to the elbow; other patients in the series initially presented with traumatic dislocation only, distal biceps tendon rupture, large osteophytes, or hemophilic arthropathy.

At median follow-up of 136 days (range, 41-2120 days), 21 (48%) of the 44 patients had radiographic evidence of HO. In all cases, the HO was small and not functionally significant or motion-limiting. This analysis was repeated, excluding all patients with radiographic follow-up shorter than 90 days. Of the 30 patients who met this criterion, 15 (50%) had radiographic evidence of HO. In addition, we compared the patients who had HO before RT and the patients at high risk for HO formation treated for prophylaxis. Of the 33 patients with prior HO, 16 (48%) had radiographic evidence of HO; of the 11 patients without prior HO, 5 (45%) had radiographic evidence of HO. None of the patients in the overall cohort required repeat surgery. No complications were thought to be directly attributable to RT. The preoperative and postoperative radiographs for each patient using all available classification systems for elbow HO are described completely in Table I. In addition, summaries of HO frequency and distribution using each of the 4 available systems are presented in Table II.

Discussion

The present study examined the outcomes of 44 patients who were treated with RT and NSAIDs after high-risk elbow surgery and for whom radiographic follow-up was available. Although 21 patients developed radiographical-

Table I. Preoperative and Postoperative Heterotopic Ossification (HO) Classifications

Case	Dose, Gy	Follow-Up, mo	Preoperative HO				Postoperative HO			
			Garland[23]	Hastings[25]	Jupiter[26]	Ilahi[27]	Garland[23]	Hastings[25]	Jupiter[26]	Ilahi[27]
1	7	7	None	None	None	None	Moderate	I	None	II
2	6	7	None	None	None	None	None	None	None	None
3	6	28	None	None	None	None	Mild	I	None	None
4	7	5	None	IIB	IIIA	None	Moderate	I	None	I
5	5	11	None	None	None	None	None	None	None	None
6	5	9	Severe	IIA	None	III	Severe	I	None	I
7	5	2	Severe	IIIA	None	IV	Mild	I	None	None
8	7	24	Severe	IIA	None	III	None	None	None	None
9	7	17	None	None	None	None	None	None	None	None
10	7	8	None	None	None	None	Mild	I	None	None
11	5	5	Severe	IIA	None	III	None	None	None	None
12	7	24	Severe	IIA	None	III	Mild	I	None	None
13	6	2	None	IIB	IIIA	None	Mild	I	None	None
14	6	6	Severe	IIA	None	II	Moderate	I	None	I
15	5	14	None	None	None	None	Mild	I	None	None
16	6	71	Severe	IIA	None	III	Moderate	I	None	I
17	7	2	None	None	None	None	None	None	None	None
18	5	3	Severe	IIA	None	III	None	None	None	None
19	7	34	None	None	None	None	None	None	None	None
20	6	4	None	IIB	IIIA	None	None	None	None	None
21	7	4	None	IIB	IIIA	None	None	None	None	None
22	6	37	Moderate	I	None	I	Moderate	I	None	I
23	6	2	None	IIIB	None	None	None	None	None	None
24	7	2	Severe	IIB	IIIA	None	None	None	None	None
25	7	2	Severe	IIIB	IIIA	None	None	None	None	None
26	7	1	Severe	IIA	None	III	Moderate	I	None	I
27	7	1	None	IIB	IIIA	None	None	None	None	None
28	7	9	Severe	IIIB	IIIC	III	Severe	I	None	I
29	7	3	Severe	IIB	IIIA	None	None	None	None	None
30	7	6	None	None	None	None	Mild	I	None	None
31	7	3	Severe	IIB	IIIA	None	None	None	None	None
32	7	3	Severe	IIIB	IIIC	III	Mild	I	None	None
33	7	3	Severe	IIB	IIIA	None	None	None	None	None
34	7	3	Severe	IIIB	IIIC	III	None	None	None	None
35	7	25	Severe	IIB	IIIA	None	Severe	I	None	I
36	7	2	Severe	IIA	None	III	Mild	I	None	None
37	7	5	Severe	IIA	None	III	Mild	I	None	None
38	7	11	None	None	None	None	None	None	None	None
39	7	3	Moderate	IIA	None	III	Mild	I	None	None
40	7	6	Moderate	IIA	None	III	None	None	None	None
41	7	1	Severe	IIB	IIIA	None	Moderate	I	None	II
42	7	3	Severe	IIA	None	III	None	None	None	None
43	7	4	Severe	IIIB	IIIA	None	None	None	None	None
44	7	2	Severe	IIA	None	III	None	None	None	None

ly apparent HO, no patient developed clinically significant HO. No patient had any side effects attributable to RT. Our findings strongly support the efficacy and safety of RT, in combination with NSAID use, as HO prophylaxis after high-risk elbow surgery.

We reported HO as present if it was visible on any screening radiograph. In the hip, the classification by Brooker and colleagues[28] is the accepted standard. Several systems for grading elbow HO have been described, but no single system is in common use. As all these systems have important limitations, and none is commonly used, we used every available and relevant rating system in this study. According to the system by Garland and O'Hollaren[23], 27 patients in our cohort had moderate to severe HO before surgery, and 10 developed moderate to severe HO after surgery (Table II-A). Hastings and Graham[25] described a classification system based on functional range of motion. According to this system, class II or III HO was present in 32 patients before surgery and none after surgery (Table II-B). In the system described by Vince and Miller,[29] which is based on anatomic location, HO in the distal third of the forearm is classified as type I, HO in the middle third as type II, and HO in the proximal third as type III. Jupiter and Ring[26] modified the system created by Vince and Miller to make it more relevant to elbow HO. According to this system, type III HO was present in 16 patients before surgery and none after surgery (Table II-C). Ilahi and colleagues[27] described an anatomic system of classification using a lateral radiograph that classifies HO into 4 grades based on the angle subtended by the heterotopic bone. Grade III or IV HO was present in 17 patients before surgery and none after surgery (Table II-D).

These results are in accord with earlier findings. Wolfson and colleagues[30] reported on 19 patients treated with 10 Gy in 5 fractions after elbow surgery; only 1 patient developed HO. Similarly, Park and colleagues[31] treated 18 patients after excision of HO about the elbow; only 2 of these patients had radiographic recurrence of HO. In the literature, we identified 8 studies on

Table II. Classification Scores, According to Differing Grading Systems, Before and After Surgery

Grading System for Elbow HO	Extent of HO							
A: Garland & O'Hollaren[23,a]	**None**	**Mild**	**Moderate**	**Severe**				
Preoperative HO	17	0	3	24				
Postoperative HO	23	11	7	3				
B: Hastings & Graham[25,b]	**None**	**I**	**IIA**	**IIB**	**IIC**	**IIIA**	**IIIB**	**IIIC**
Preoperative HO	11	1	15	11	0	0	6	0
Postoperative HO	23	11	0	0	0	0	0	0
C: Jupiter & Ring[26,c]	**None**	**IIIA**	**IIIB**	**IIIC**				
Preoperative HO	28	13	0	3				
Postoperative HO	44	0	0	0				
D: Ilahi et al[27,d]	**None**	**I**	**II**	**III**	**IV**			
Preoperative HO	25	1	1	16	1			
Postoperative HO	34	8	2	0	0			

Abbreviation: HO, heterotopic ossification.
[a]Small amounts of periarticular calcification (mild); HO in anterior or posterior soft tissue (moderate); HO in all tissue planes (severe).
[b]Ectopic bone formation without functional limitation (I); subtotal functional limitation of flexion/extension (IIA), pronation/supination (IIB), or both (IIC); bony ankylosis completely restricts movement of flexion/extension (IIIA), pronation/supination (IIIB), or both (IIIC).
[c]Synostosis at or distal to bicipital tuberosity (IIIA); synostosis of radial head and proximal radioulnar joint (IIIB); synostosis contiguous with heterotopic bone extending into distal aspect of humerus (IIIC).
[d]HO subtends angle of <30° (I); HO subtends angle of 30°-60° (II); HO subtends angle of >60° (III); bony ankylosis (IV).

Table III. Studies Using Radiotherapy for HO Prophylaxis After High-Risk Elbow Surgery

Study	No. of Joints	External-Beam Radiotherapy Dose	NSAIDs Used	Follow-up, mo (range)	Radiographs Obtained	Result
Heyd 2001[36]	9	6-10 Gy	No	7.7 (6-13)	Yes	No HO
McAuliffe 1997[37]	8	10 Gy, 5 fractions	Unclear	46 (25-72)	Yes	No HO
Wolfson 1993[30]	19	10 Gy, 5 fractions	Unclear	21	Yes	1 HO (on radiograph)
Stein 2003[38]	11	7 Gy, 1 fraction	Unclear	12 (9-24)	Yes	3 HO (1 symptomatic)
Poggi 1999[39]	3	7-8 Gy	Unclear	10.5 (4-17)	Yes	No HO
Ellerin 1999[40]	4	6-7 Gy	Unclear	(7-23)	Yes	2 HO (neither symptomatic)
Rubenstein 1992[41]	1	10 Gy / 5 fractions	Unclear	5	Yes	No HO
Park 2004[31]	18	7 Gy	Unclear	22.5 (12-43)	Unclear	2 HO (1 painful, 1 ROM)

Abbreviations: HO, heterotopic ossification; NSAID, nonsteroidal anti-inflammatory drug; ROM, range of motion.

the efficacy of RT for HO prophylaxis in the elbow. The 73 elbows in these studies were irradiated using a variety of dose schemes; 8 of these elbows had radiographic recurrence of HO, and, of these, 3 were symptomatic. Results of studies on RT for HO prophylaxis after high-risk elbow surgery are summarized in Table III.

The outcomes of patients who undergo RT appear superior to those of patients who undergo high-risk elbow surgery without HO prophylaxis. Hunt and colleagues[32] reported on patients who developed HO after severe burns. Of 43 patients treated with excision of HO about the elbow, 6 (14%) had HO recurrence substantial enough to significantly restrict their activities of daily living or cause complete ankylosis. Ilahi and colleagues[27] reported on 41 patients who underwent elbow surgery after trauma. Twenty (49%) of these patients developed HO (2 of the 20 had bony ankylosis of the elbow joint). The authors believed that delay of surgery contributed to this high rate. The results of published studies in which prophylaxis was omitted after high-risk elbow surgery are summarized in Table IV.

Comparisons of our results with those of published case series are fraught with biases. Risk for HO formation about the elbow is related to a variety of factors that differ between patient populations. For example, patients with severe burns or persistent neurologic injury may be at higher risk for HO recurrence than others. Because the risk for HO recurrence in a given patient cannot be quantified, we cannot know with certainty whether a group of patients has had a higher (or lower) than expected rate of HO formation. Similarly, the likelihood of discovering HO depends on the detection method; studies that incorporate regular screening radiographs identify HO cases that are not clinically significant and would be missed on physical examination. In addition, NSAIDs were used, either systematically or sporadically, in some studies, but not others. For these reasons, we cannot be certain that postoperative RT reduces risk for HO about the elbow, despite the appearance of an advantage in published case series.

Table IV. Results of HO Occurrence When Prophylaxis After High-Risk Elbow Surgery Omitted

Study	No. of Joints	NSAIDs Used	Follow-up (range)	Radiographs Obtained	Result
Wolfson 1993[30]	6	Unclear	21 mo	Unclear	1 HO (on radiograph)
de Palma 2002[42]	14	Indomethacin 25 mg, 3/d, 6 wk	23 (12-34) mo	Yes	No HO
Hunt 2006[32]	43	No	Unknown	No	6 HO (ankylosis or marginal function)
Garland 1982[23]	18	No	21 (6-70) mo	Yes	16 HO (most multiple sites)
Tsionos 2005[43]	35	Indomethacin 75 mg, every day, 3 wk	21 (2-93) mo	Yes	4 HO (all symptomatic)
Moritomo 2001[44]	9	No (5 patients received diphosphonates)	52 (14-89) mo	Yes	5 HO (none symptomatic)
Mortazavi 2006[45]	1	Unclear	5 y	Unclear	No HO
Park 2004[31]	9	Unclear	22.5 (12-43) mo	Unclear	1 HO
Garland 1985[46]	23	Unclear	28 (12-122) mo	Yes	11 HO (4 ankylosis)
Holguin 1996[47]	6	Unclear	6 mo–22 y	No	1 HO (ankylosis)
Ilahi 2001[27]	41	Unclear	13 (6-48) wk	Unclear	20 HO (2 ankylosis)
Denormandie 1999[48]	25	Unclear	17 (6-48) mo	Unclear	1 HO, 3 periarticular calcifications
Ring 2004[49]	20	Unclear	Unclear	Unclear	6 elbows required re-release
Jupiter 1998[26]	8	No	34 (24-60) mo	Yes	1 recurrent synostosis

Abbreviations: HO, heterotopic ossification; NSAID, nonsteroidal anti-inflammatory drug.

Several authors have called for a randomized trial to evaluate the efficacy of RT in this setting. However, the rarity of high-risk elbow surgery makes such a trial difficult to complete. At this time, recommendations concerning HO prophylaxis for the elbow must be based on the results of nonrandomized studies of the elbow and extrapolated from randomized trials of prophylaxis for HO in the hip. RT has shown clear efficacy in reducing HO formation after high-risk hip surgery.[20,21] HO in the elbow is histologically identical to HO in the hip and has the same pathophysiology and risk factors. It stands to reason that both sites respond to the same prophylactic treatment. This idea is supported by several published reports, including the present study, documenting low rates of symptomatic HO formation in patients who undergo postoperative RT.

The ideal dose regimen of prophylactic RT for the elbow is unknown. Multiple prospective randomized trials of RT for the hip have supported the finding that a single large fraction is equal in efficacy to more protracted fractionated regimens.[33] More recently, evidence has suggested that fractions of 7 Gy or higher are more efficacious than lower fraction sizes.[16,20,34] No clear dose–response relationship can be gleaned from the literature describing RT for the elbow, and both single-fraction and multifraction regimens appear effective. Extrapolating from randomized trials involving the hip, and given logistical considerations, we now use a single postoperative 7 Gy fraction of radiation for HO prophylaxis in all sites.

Some authors raise the specter of second-malignancy induction as a rationale for avoiding irradiation for HO prevention. Although second cancers are theoretically possible, the risk is very low when treating small radiation fields to a low dose. As evidence for this, there are no case reports in the literature describing a second cancer attributable to HO prophylaxis.[2] Furthermore, the risk for developing a sarcoma from low-dose irradiation appears to be extremely low.[35]

Conclusion

Randomized trials have established the role of RT for HO prophylaxis in the hip. Only a handful of case reports are available for supporting use of RT after high-risk elbow surgery. To our knowledge, the present study represents the largest published series of patients who have undergone postoperative RT for prophylaxis against HO in the elbow. Our findings support the idea that RT, in combination with NSAID use, is both effective and well tolerated in this setting.

Authors' Disclosure Statement

The authors report no actual or potential conflict of interest in relation to this article.

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