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CRITICAL REVIEW

HETEROTOPIC OSSIFICATION: PATHOPHYSIOLOGY, CLINICAL FEATURES, AND THE ROLE OF RADIOTHERAPY FOR PROPHYLAXIS

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Heterotopic ossification (HO) is a benign condition of abnormal formation of bone in soft tissue. HO is frequently asymptomatic, though when it is more severe it typically manifests as decreased range of motion at a nearby joint. HO has been recognized to occur in three distinct contexts—trauma, neurologic injury, and genetic abnormalities. The etiology of HO is incompletely understood. A posited theory is that HO results from the presence of osteoprogenitor cells pathologically induced by an imbalance in local or systemic factors. Individuals at high risk for HO development frequently undergo prophylaxis to prevent HO formation. The two most commonly employed modalities for prophylaxis are nonsteroidal anti-inflammatory drugs and radiation therapy. This review discusses HO pathophysiology, clinical features, and the role of radiotherapy for prophylaxis. © 2006 Elsevier Inc.

Heterotopic ossification, Heterotopic bone, Radiation therapy, Prophylaxis.

INTRODUCTION

Heterotopic ossification (HO) is defined as the abnormal formation of mature, lamellar bone in soft tissues, often containing bone marrow. Heterotopic ossification was first identified in 1883 by Riedel, a German physician. It was later described as "paraosteoarthropathy" by French physicians Dejerne and Ceillier based on observations of patients with traumatic paraplegia in World War I (1). HO has been given multiple names including paraosteoarthropathy, myositis ossificans, periarticular new bone formation, periarticular ectopic ossification, neurogenic osteoma, neurogenic ossifying fibromyopathy, and heterotopic calcification (2). HO is the more accurate descriptor.

Soft-tissue calcifications can be divided into two categories—dystrophic and metastatic. Dystrophic calcification is calcium deposition that occurs in the setting of soft-tissue insult. HO is one etiology of dystrophic soft-tissue calcification, though it can be distinguished histologically from other forms of dystrophic calcification by the presence of a trabecular pattern characteristic of bone. Metastatic calcification is characterized by the development of diffuse pathologic calcification resulting from an elevated calcium-phosphate product as seen in renal failure and hyperparathyroidism.

There are three recognized etiologies of HO: traumatic, neurogenic, and genetic. Traumatic HO typically follows fractures, dislocations, operative procedures, and severe burns. Most commonly, HO is seen around the hip after fracture and open reduction-internal fixation (ORIF) procedures or total hip arthroplasties (THA) (Fig. 1). HO of the hip often involves the abductor compartment, though any compartment surrounding the hip can be involved (3). Burns from either thermal or electrical injury can precipitate HO, with the most frequently involved joint being the elbow (Fig. 2a), though any major joint can be affected (4). Other reported sites of joint HO after trauma include the knee (5) (Fig. 2b), shoulder (6), ankle (7), and temporomandibular joint (8). HO has also been reported in soft-tissue locations not surrounding joints in the setting of trauma, including the quadriceps muscles after contusion (9) and abdominal wounds after surgery (10).

Neurogenic HO is seen after central nervous system insult, including spinal trauma and head injuries. The most commonly involved joint is the hip followed by the shoulder and elbow (11). Other neurologic conditions have also been implicated in the development of HO, including encephalitis (12), meningitis (13), myelitis (14), tetanus (15), brain tumors (16), epidural abscess (17), and subarachnoid hemorrhage (18).

Finally, HO can occur in the setting of genetic disorders, including fibrodysplasia ossificans progressiva (FOP), progressive osseous heteroplasia (POH), and Albright's hereditary osteodystrophy (AHO). FOP is a rare, autosomal dominant genetic disorder associated with progressive, disabling HO. HO begins in childhood and can be spontaneous or trauma-induced. By early adulthood, progressive ossifica-

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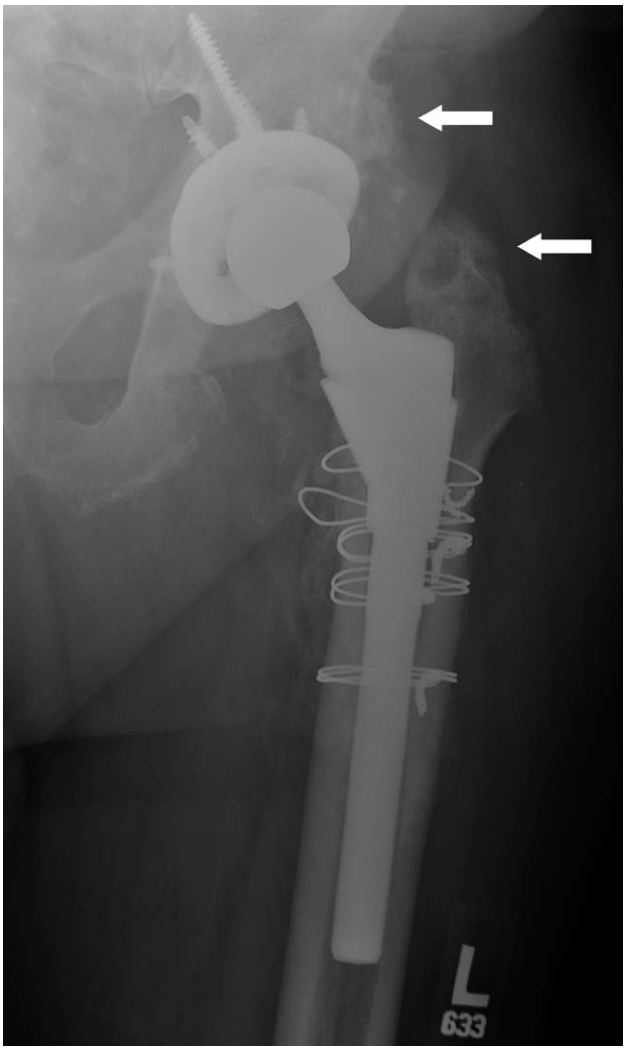

Fig. 1. Heterotopic ossification (arrows) following total hip arthroplasty.

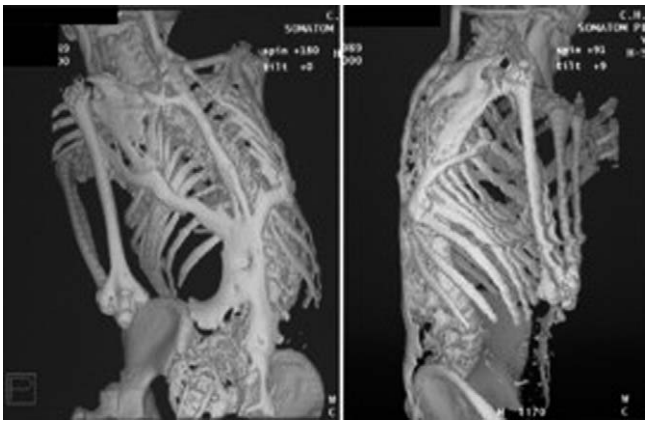

Fig. 3. Reconstructed computed tomography scan of a 12-year-old child with fibrodysplasia ossificans progressiva. Reprinted from Glaser DL, Economides AN, Wang L, *et al.* In vivo somatic cell gene transfer of an engineered Noggin mutein prevents BMP-4–induced heterotopic ossification. *J Bone Joint Surg* 2003;85-A: 2332. Reproduced with permission of the *Journal of Bone and Joint Surgery*.

tion leads to ankylosis of all major joints of the axial and appendicular skeleton, eventually eliminating joint motion (Fig. 3) (19). POH is a rare genetic condition causing extensive dermal HO in infancy that progresses to HO of the deeper tissues. AHO is a complex disorder involving developmental defects often coupled with resistance to parathyroid hormone. AHO can also involve dermal and subcutaneous HO. POH and AHO are believed to be related conditions stemming from mutations of the *GNAS1* gene, resulting in decreased expression or dysfunction of the alpha subunit of the stimulatory G protein of adenylyl cyclase (20).

Clinical presentation

Heterotopic ossification is typically asymptomatic and detected only as an incidental finding on a radiograph.

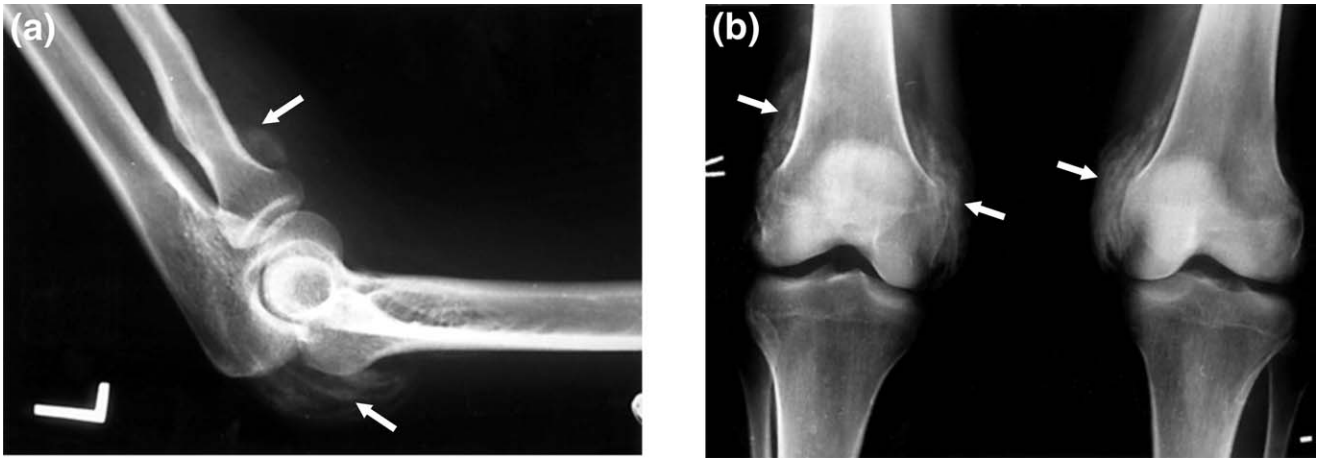

Fig. 2. (a) Heterotopic ossification (arrows) of the elbow. Reprinted from Lane JE, Dean RJ, Foulkes GD, *et al.* Idiopathic heterotopic ossification in the intensive care setting. *Postgrad Med J* 2002;78:494. Reproduced with permission of the British Medical Journal Publishing Group. (b) Heterotopic ossification (arrows) of the knee. Reprinted from Lane JE, Dean RJ, Foulkes GD, *et al.* Idiopathic heterotopic ossification in the intensive care setting. *Postgrad Med J* 2002;78:495. Reproduced with permission of the British Medical Journal Publishing Group.

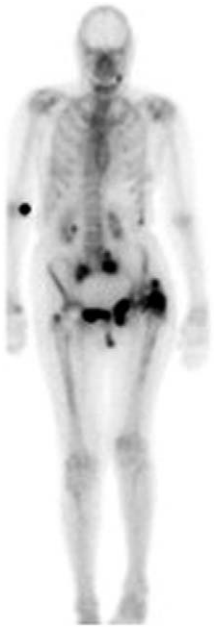

Fig. 4. Bone scan findings in heterotopic ossification of the left hip.

When symptomatic, it most commonly causes decreased range of motion at the involved joint, and in severe cases complete bony ankylosis may occur. HO can also cause local pain, and if located superficially, there may be symptoms such as localized warmth, mild edema, and erythema (21). Bone scan can detect evidence of HO (Fig. 4) 3 weeks after insult, whereas plain film reveals HO at approximately 4–6 weeks (21). Plain films are typically sufficient to detect HO formation, though computed tomography scans can provide more detailed information about HO extent and location. The most commonly used radiographic classification for HO is the Brooker classification (22). This classification schema is based on radiographic findings of HO at the hip after THA, and includes four classes (Fig. 5). Classes I and II are considered clinically insignificant given that symptoms rarely manifest with this extent of HO. Classes III and IV are considered to be clinically significant given that symptoms are typically present.

Pathophysiology

Heterotopic ossification is believed to result from the inappropriate differentiation of pluripotential mesenchymal cells into osteoblastic stem cells; however the definitive pathophysiologic causal factors remain uncertain (1). In 1965, Urist *et al.* (23) showed that demineralized bone matrix induces ectopic bone formation when implanted in the musculature of animals, and the authors hypothesized that the demineralized matrix contains "bone morphogenic proteins" responsible for stimulating the transformation of perivascular mesenchymal cells into osteoblasts. Chalmers *et al.* (24) performed further studies of demineralized bone matrix revealing that implanting demineralized bone matrix in muscle and fascia regularly permitted bone induction, whereas implantation into the liver, spleen, and kidney suppressed bone induction. Given these findings, the authors postulated that HO depends on three entities: *(1)* an osteogenic precursor cell, *(2)* inducing agents, and *(3)* a permissive environment. Chalmers *et al.* further proposed that HO formation depends on a fine balance of osteogenic and osteo-inhibitory influences acting both locally and systemically.

Local and systemic factors in HO

Potential local factors include bone morphogenic proteins (BMPs), first proposed by Urist *et al.* as the agent responsible for the induction of HO by demineralized bone matrix (22). BMPs are members of the transforming growth factor-β family and are implicated in endochondral osteogenesis and fracture healing (25). Furthermore, BMPs have been shown to govern three key steps in the osteogenic cascade: chemotaxis, mitosis, and differentiation (26). They can also readily be used to induce HO *in vivo* (27). Shafritz *et al.*, in a study of patients with fibrodysplasia ossificans progressiva, demonstrated an association between this genetic disorder and overexpression of BMP-4 (25). Furthermore, Hannallah *et al.* (27) demonstrated that a BMP antagonist, Noggin, is capable of inhibiting BMP-4–induced

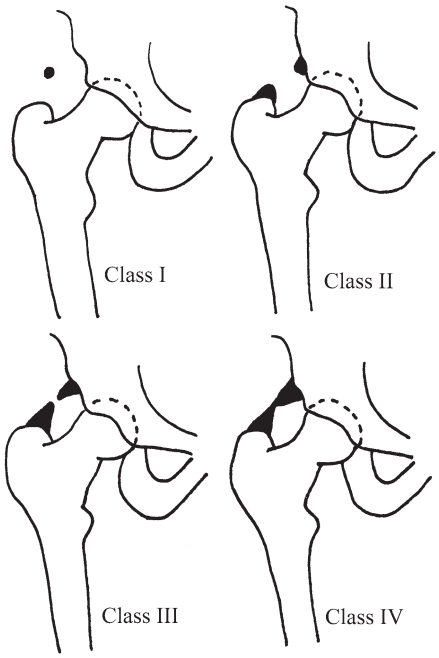

Fig. 5. The Brooker classification of heterotopic ossification around the hip joint (64). Class I—islands of bone within the soft tissues. Class II—bone spurs from the pelvis or proximal end of the femur, leaving at least 1 cm between opposing surfaces. Class III—bone spurs from the pelvis or proximal end of the femur, reducing the space between opposing bone surfaces to less than 1 cm. Class IV—bone ankylosis of the hip. From Schafer SJ, Schafer LO, Anglen JO, *et al.* Heterotopic ossification in rehabilitation patients who have had internal fixation of an acetabular fracture. *J Rehab Res Develop* 2000;37:390. Reprinted with the permission of the *Journal of Rehabilitation Research and Development* and the corresponding author.

HO in a dose-dependent manner. HO induced by demineralized bone matrix was also inhibited by Noggin, as was HO produced by Achilles tenotomy, an established traumatic model of HO.

The participation of systemic factors in the regulation of bone formation has been implied by the observation that many patients with head injury develop HO despite often having no traumatic injury to a joint. Furthermore, patients with head injuries have been found to have accelerated fracture healing (28). Specific systemic factors thus far have not been definitively identified, although one proposed factor is prostaglandin-E_2. Inhibitors of prostaglandins, specifically indomethacin, have been shown to significantly reduce the incidence of HO (29–31).

In summary, HO is an entity stemming from the dysfunction of the intricate, dynamic system of bone formation and remodeling. Studies thus far have implicated the role of bone osteoprogenitor cells existing either locally or systemically. These stem cells are acted on by inductive agents (e.g., BMP-4) and a permissive environment (e.g., muscle) to yield bone formation. Local trauma (e.g., THA) is thought to disrupt the normal balance of bone formation and inhibition, perhaps by inducing a cascade of inflammatory factors that ultimately promote the activity of inductive agents. Burns and neurologic injury may act in a similar

Table 1. Heterotopic ossification incidence according to etiology and Brooker grade

Etiology (reference)	Any grade	Grade III or IV
THA (32)	43%	9%
ORIF for acetabular fracture (32)	52%	19%
Spinal cord injury (33)	20–25%	4–9%
Head injury (33, 34)	10–20%	1–2%

Abbreviations: THA = total hip arthroplasty; ORIF = open reduction internal fixation.

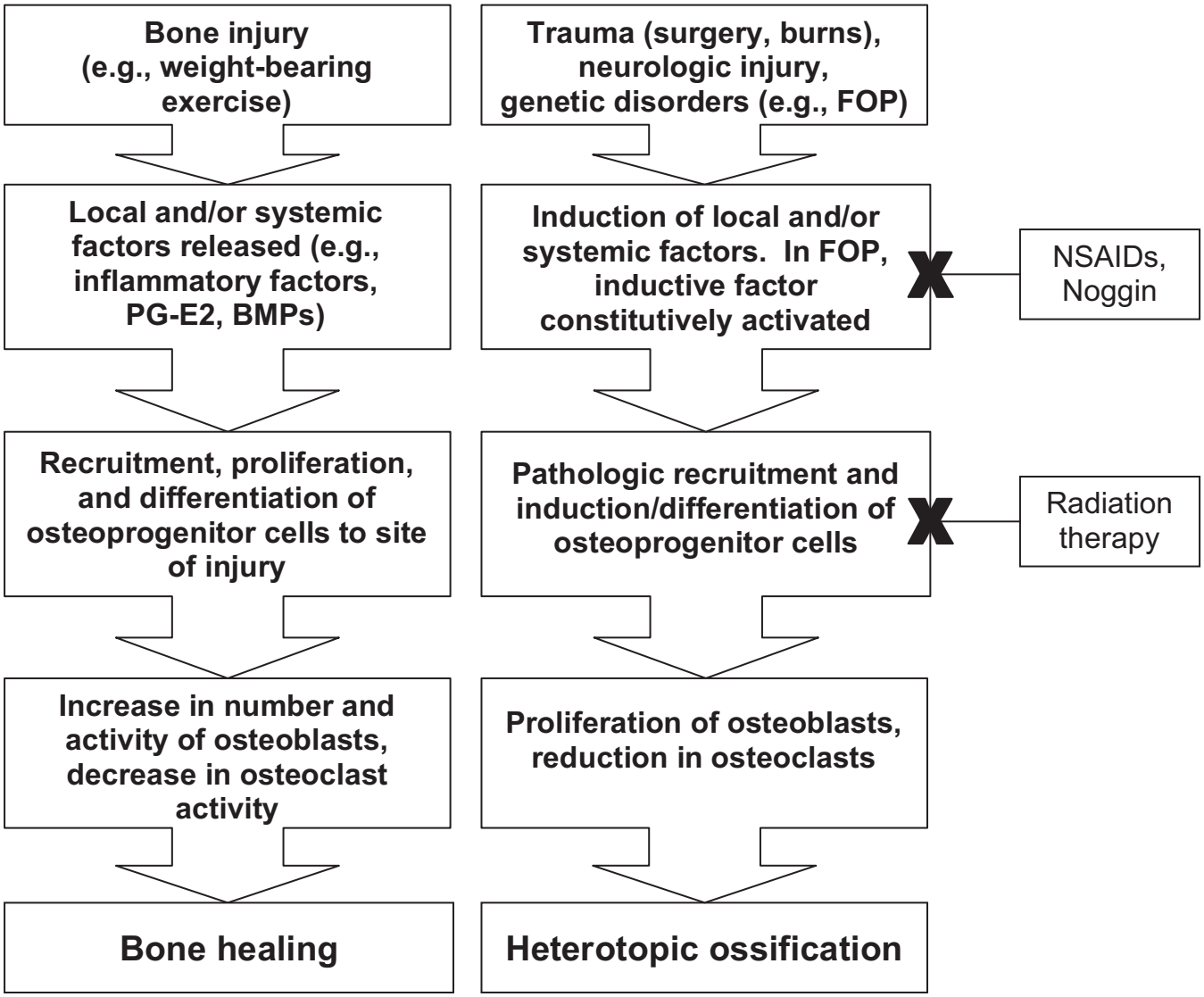

Fig. 6. (a) Basic schema of the normal bone injury response. (b) Proposed schema of heterotopic ossification. FOP = fibrodysplasia ossificans progressiva; NSAIDs = non-steroidal anti-inflammatory drugs.

Table 2. Risk factors for heterotopic ossification (HO) after hip surgery

Patient-related risk factors (2, 35, 36, 65)	Clinical risk factors (32, 66)	Surgical risk factors (35, 36)
History of HO	T-type fractures	Lateral and anterolateral approach in THA
Male gender	Fracture with dislocation	Trochanteric or femoral osteotomy
Hypertrophic osteoarthritis	Multiple injuries	Extended iliofemoral approach in ORIF
Ankylosing spondylitis		
Diffuse idiopathic skeletal hyperostosis		
Prior hip surgery		

Abbreviations: THA = total hip arthroplasty; ORIF = open reduction internal fixation.

manner by disrupting the balance of osteogenic and osteoinhibitory factors. Figure 6 demonstrates the current theory of HO pathogenesis.

Incidence and risk factors for HO

The incidence of HO varies according to etiology (32–34). Furthermore, even within etiologies, HO incidence varies substantially from study to study. This variability is thought to be due partly to differences in scoring the presence of HO, especially clinically silent Grade 1 and 2 lesions. Table 1 summarizes the incidence rates of HO according to etiology.

Risk factors for HO have been most extensively studied after surgical procedures of the hip. These can be divided into patient-related, clinical, and surgical risk factors (Table 2). A history of HO is thought to be the most important risk factor, with HO incidence ranging from 63% to 90% in patients undergoing THA with a history of HO after THA of the contralateral hip (35, 36). Furthermore, for those with a history of HO, the severity of the HO appears to be a risk factor for developing clinically significant HO. Eggli *et al.* (36), in a prospective analysis of 928 patients undergoing THA, reported that 50% of patients with a history of Grade 3 or 4 HO in the contralateral hip went on to develop Grade 3 or 4 HO. The use of cemented prostheses in THA has been hypothesized to increase the risk of HO. However, data thus far on patients with cemented acetabular prostheses have not demonstrated an increased risk of HO as compared with those who receive cementless prostheses (37).

In neurogenic HO, risk factors include the severity of the neurologic injury, presence of spastic as compared with flaccid paralysis, multiple injuries at the time of trauma, and any trauma to a joint at the time of neurologic insult or afterward (2, 3, 37, 38). Likewise, pressure ulcers near a proximal joint also increase the risk of HO (3).

Finally, risk factors in burn-related HO include the depth of the burn, with third-degree burns demonstrating an increased risk of HO as compared with second-degree burns (39).

The management of HO

For patients in whom clinically significant HO has already developed, management often includes surgical excision. Surgical removal of HO is followed by prophylactic measures given its tendency to recur. HO prophylaxis is also performed when there are other indications of high risk for HO development, such as when there is a history of HO or after acetabular fracture. The decision to provide prophylactic treatment must balance a patient's risk of heterotopic bone formation against the potential risks of preventive treatment. The two primary prophylactic modalities are radiation therapy (RT) and nonsteroidal anti-inflammatory drugs (NSAIDs), most commonly indomethacin. In the past, diphosphonates were also used for prophylaxis. These agents were largely abandoned after they were found to only prevent mineralization of the ectopic bone matrix (40). As a result, after the drug was discontinued, ossification would occur.

Rationale for the use of radiation therapy in HO prophylaxis

In 1958, Cooley and Goss (41) demonstrated that the administration of a single dose of 30 Gy to a fractured rat bone within the first week of healing would prevent bone repair. In contrast, the same dose given more than a week after fracture injury did not prevent bone repair. This finding established the understanding that radiation could prevent bone healing, but only within an early window of its development. In 1971, Craven and Urist (42) performed studies detailing the impact of radiation on HO after implantation of demineralized bone matrix in the rat hamstring. To determine the key interval during which time radiation would prevent HO, 18 Gy in 1 fraction was delivered at intervals of 2, 4, 6, 8, 10, and 12 days after implantation. The authors noted that the rats irradiated in the first week after implantation had markedly reduced bone yield, whereas those irradiated during the second week had bone formation similar to the controls that had not received radiation. The authors hypothesized that osteoprogenitor cells present in the early phase of HO development are particularly radiosensitive. Their radiosensitivity may in part be due to their high mitotic rate, because they are in the process of proliferating and differentiating into specialized forms, such as osteoblasts and chondrocytes. Radiation is thought no longer to be effective after the proportion of radioresistant, specialized cells in relation to stem cells is sufficiently high.

The impact of RT on developing bone in humans has long been recognized, in particular in children receiving radiation. In 1952, Neuhauser *et al.* (43) documented the impact of radiation on the growing vertebrae of children. The authors found that doses of greater than 20 Gy caused

inhibition of bony growth, in particular in very young children. Applying this observation, Coventry *et al.* (44) chose a dose of 20 Gy in 10 fractions in an attempt to determine if RT can be used to prevent HO after hip surgery. A total of 48 hips were treated, and all were considered to be at high risk for HO. Radiation was initiated postoperatively up to 69 days after surgery. Parallel-opposed fields were used with fields encompassing the ipsilateral hip and proximal femur. With minimum follow-up of 12 months, severe HO developed in 19% of the hips treated. They also noted that patients treated "relatively early" experienced lower rates of HO, though specific rates were not provided. The authors concluded that RT may be an effective means of preventing HO.

The evolution of radiotherapy for HO prophylaxis

Coventry *et al.* established that RT could successfully be used in the prevention of HO. The next step was to pursue reduced doses for prophylaxis, especially in light of the concern regarding radiation-induced malignancies. Sylvester *et al.* (45) reported on a retrospective comparison of patients receiving 20 Gy in 10 fractions as compared with 10 Gy in 5 fractions. A total of 27 hips were irradiated after THA. Two hips receiving 20 Gy and one hip receiving 10 Gy developed clinically significant HO. Additionally, all three of the hips developing clinically significant HO had radiation delivered >4 days after surgery. The authors concluded that, though the sample size was small, the two radiation regimens appear to be similarly effective. They also noted that RT should be delivered postoperatively within 4 days of surgery.

The impetus for a decrease in dose from 20 Gy to 10 Gy according to Sylvester *et al.*, was the need to decrease hospital stays. Further supporting this trend to decrease dose and fractions is that the decrease in dose theoretically may diminish radiation-induced cancer risk, and the decrease in fractionation reduces cost and inconvenience to patients. Hence, the next step in the evolution of RT for HO prevention was the exploration of single-fraction treatment. Lo *et al.* (46), in a retrospective series, reviewed the use of single-fraction RT in patients considered to be at high risk for HO after THA. A total of 24 hips in 23 patients were treated with a single dose of 7 Gy. Only 1 patient was treated beyond 72 h and anteroposterior/posteroanterior fields were used. None of the patients developed Brooker Grade 3 or 4 HO. The authors concluded that single-dose RT with 7 Gy is effective in preventing HO. Pellegrini *et al.* (47) further explored the efficacy of single-fraction therapy for HO prophylaxis after THA in a prospective, randomized trial of single fraction vs. fractionated therapy. A total of 62 hips in 55 patients undergoing hip surgery and considered to be at high risk for HO were randomized to 10 Gy in five fractions vs. 8 Gy in one fraction postoperatively. RT was initiated within 4 days of surgery in all but 1 patient. HO (of any grade) developed in 21% of the hips receiving 10 Gy and in 21% of those receiving 8 Gy. The authors concluded that single-fraction therapy is similar in efficacy to fractionated therapy.

Having established the effectiveness of single-dose RT of 7–8 Gy, an attempt was made to consider lower doses of single fraction treatment. Healy *et al.* (48) examined single-dose irradiation with 7 Gy in comparison to 5.5 Gy. This was a retrospective analysis of 107 hips deemed to be at high risk for the development of HO after THA. All except 1 patient were treated within 3 days of the procedure and anteroposterior/posteroanterior fields were used. HO developed in 10% of those receiving 7 Gy and in 63% of those receiving 5.5 Gy ($p = 0.03$). Clinically significant HO (Grade 3 or 4) was noted in 2 patients receiving 7 Gy and 4 patients receiving 5 Gy. The authors concluded that 5.5 Gy is not a sufficient dose for HO prophylaxis. Reduced-dose RT was more recently tested by Padgett *et al.* (40) in a prospective, randomized trial. Fifty-nine patients considered to be at high risk for HO after THA were randomized to receive either 5 Gy in two fractions or 10 Gy in five fractions. All patients were treated within 4 days of surgery. There was a trend toward increased HO of any grade in the 5-Gy group (69% vs. 43%, $p = 0.09$). Most HO was clinically insignificant, however. Clinically significant HO was noted in 2 of 19 patients receiving 5 Gy vs. 1 of 30 patients receiving 10 Gy (no p value indicated). The authors concluded that there was no significant difference in HO development between those receiving 5 Gy in two fractions vs. 10 Gy in five fractions, but added that a true difference may not have been detected because of a small sample size. Though 5 Gy may be inferior to 10 Gy for HO prophylaxis, the difference may be marginal when comparing the incidence of clinically significant HO. Studies with larger numbers are needed to determine whether reduced radiation doses are indeed sufficient for HO prophylaxis.

The limited interval after a surgical procedure during which radiation has the potential to inhibit HO can create significant obstacles to treatment. First, patients in the immediate postoperative period are often difficult to transport and maneuver because of significant postoperative pain. Furthermore, mobilization of the hip immediately after surgery should be minimized. These obstacles coupled with the theory that multipotential mesenchymal cells responsible for HO reside in the local soft tissues and are radiosensitive led to an investigation into the efficacy of preoperative RT in HO prophylaxis. Kantorowitz *et al.* (49) first studied the value of preoperative RT in rats. The rats were randomized into three groups according to timing of radiation in relation to the implantation of demineralized bone matrix into the thigh. Timing of radiation in relation to surgery was: 2 days preoperatively, 1 h preoperatively, or 2 days postoperatively. There was no difference in HO formation between the 1-h preoperative group and the 2-day postoperative group (5.3% vs. 7.1%, respectively). However, rats receiving the 2-day preoperative RT had significantly more bone formation (12.6%). The authors concluded that HO may be preventable via preoperative RT and that the proliferation and differentiation of multipotent stem cells may be inhibited by RT given before the stimulus.

With evidence to support the effectiveness of preopera-

tive RT in HO prevention, Seegenschmiedt *et al.* (50) performed a prospective, randomized trial of preoperative vs. postoperative radiotherapy. One hundred and sixty-one patients considered to be at high risk for HO development were randomized to receive RT either preoperatively (<4 h before surgery) or postoperatively (<72 h after surgery). Patients receiving preoperative treatment received 7 Gy in one fraction. Patients receiving postoperative treatment received 17.5 Gy in five fractions. Within the preoperative therapy group ($n = 80$), there were 19 treatment failures, and in the postoperative therapy group ($n = 81$), there were 4 treatment failures. The difference between the groups was statistically significant ($p < 0.05$). However, the authors did note that this difference was not apparent when comparing patients who preoperatively had a low "preload of ectopic bone"—Brooker grades 0–2. Though it is unclear if this should impact efficacy of HO prevention, there is a notable difference in the biologic equivalent dose between the preoperative and postoperative RT regimens (based on an α/β of 10, biologic equivalent dose = 11.9 and 23.6, respectively). A randomized, controlled trial of preoperative vs. postoperative therapy was performed by Gregoritch *et al.*, in this case using the same RT dose and fractionation (51). A total of 122 patients (124 hips) receiving THA and at high risk of HO were randomized to receive 7–8 Gy in one fraction either preoperatively (<4 h before surgery) or postoperatively (<72 hours postoperatively). The authors reported no significant difference between the treatment groups with an HO overall incidence of 26% in the preoperative RT group vs. 28% in the postoperative RT group. Clinically significant HO was noted in 2% of the preoperative group vs. 5% in the postoperative group. The authors concluded that the preoperative and postoperative regimens are similar in efficacy. However, the sample size was insufficient to determine true equivalence.

Shielding of the prosthesis in radiation therapy for HO prevention

The majority of prostheses used in THA are cementless prostheses with porous elements permitting bony ingrowth. Concern has arisen that RT may inhibit bony ingrowth into the prosthesis and cause prosthesis failure at either the bony interface of the prosthetic acetabulum or at the proximal femoral region where the shaft of the prosthesis abuts the native femur. Konski *et al.* (52) studied the impact of RT on bony growth into a porous coated rod in rabbits to investigate the validity of this concern. The rabbits underwent a procedure placing porous coated rods into the bilateral tibias. Each animal had one tibia irradiated 1 day postoperatively to a total of 10 Gy in five fractions. The animals were then sacrificed at weekly intervals beginning at 2 weeks and up to 6 weeks after surgery, and the amount of force necessary to pull the rod out of the medullary cavity of the treated and untreated tibias was compared. The authors noted that at 2 weeks, there was a statistically significant difference between the amount of force necessary to remove the rod, with less force required for the treated tibia as compared with the untreated tibia. After 3 weeks, there was no difference in force required to remove the rod. The authors concluded that there is decreased bony ingrowth in radiated bone, but that this only results in transient instability of the implanted prosthesis. Given these findings, the authors advocated shielding of the prosthesis. Despite these findings, however, clinical data thus far have not substantiated an increased risk of prosthesis failure in the setting of RT. For example, in the aforementioned study of preoperative vs. postoperative RT by Seegenschmiedt *et al.* ($n = 188$ patients with uncemented implants), there was no evidence of prosthesis failure despite the fact that the prostheses were not shielded (50).

Shielding of the prosthesis has raised concern for potential reduced efficacy of prophylactic RT for HO. One study by Jasty *et al.* (53) evaluated the impact of shielding of the acetabular and femoral prosthetic components in a small population of patients undergoing THA. This was a retrospective review of 16 patients (18 hips) who were considered to be at high risk for HO development. Patients received prophylactic RT to a total of 15 Gy in five fractions initiated within 48 h of surgery. The femoral and acetabular components of the prosthesis were shielded with Cerrobend blocks. Only 2 of 18 hips developed HO and both were Brooker Grade 1 lesions. Although the number of patients was small, the authors concluded that RT with precision shielding of the prosthetic components remains an effective means of preventing heterotopic bone formation.

Indomethacin in the prevention of HO

Indomethacin is commonly used for prophylaxis, given its ease of administration and low cost. It is typically given over a period of 5–6 weeks at 25 mg three times per day. However, prophylaxis with indomethacin is not without drawbacks. First, many patients find it difficult to comply with the prescribed treatment course. Second, prolonged use of NSAIDs is associated with gastrointestinal side effects, such as gastritis and ulcer formation. Gastrointestinal bleeding is of particular concern because these patients require deep vein thrombosis prophylaxis with warfarin or low-molecular-weight heparin. Finally, indomethacin has been found to increase the rate of bone nonunion after fracture (54). In patients treated with RT, however, the risk of nonunion can be minimized by appropriate shielding.

The effectiveness of indomethacin in HO prevention was compared with that of radiation in a prospective, randomized trial by Burd *et al.* (55). A total of 166 patients who had fractures of the acetabulum and underwent ORIF were randomized to receive either indomethacin or RT postoperatively. Patients received either 800 cGy in one fraction within 3 days postoperatively vs. 6 weeks of indomethacin given three times per day and initiated within 24 h of surgery. Grades 3 and 4 HO occurred in 14% of the patients randomized to the indomethacin group as compared with 7% of the RT group ($p = 0.22$; 95% confidence interval [CI], −1.1 to +15.7%). The authors concluded that there is no difference in the rates of HO according to prevention

modality. In the same patient population, Burd *et al.* noted a significant increase in long bone nonunion in patients receiving indomethacin as compared with RT (26% vs. 7%, $p = 0.004$) (54). More recently, Pakos and Ioannidis (56) performed a meta-analysis of seven randomized studies (1,143 patients) comparing RT with NSAIDs for HO prophylaxis in patients undergoing ORIF for acetabular fracture or THA. They demonstrated RT to be more effective than NSAIDs in preventing clinically significant (Brooker Grade 3 or 4) HO (risk ratio = 0.42; 95% CI, 0.18–0.97). However, the absolute risk difference was only 1.2%.

Radiation side effects

The most concerning potential side effect of RT is carcinogenesis, although there have been no documented cases of radiation-induced tumors after RT for HO prevention. This may reflect the relatively low dose used for treatment. In a review of their 50-year experience of radiation-induced sarcomas, Kim *et al.* reported no cases of bone or soft-tissue sarcomas in patients exposed to doses lower than 30 Gy (57). In addition to the low doses used, another factor that may contribute to the lack of observed cases of second malignancies in patients receiving RT for HO prophylaxis is

Table 3. Summary of studies evaluating radiation therapy (RT) for prevention of hetrotopic ossification (HO) at the hip

Authors/year (reference)	Topic	Study design	*n* (hips)	Findings (Brooker grading)	Conclusions
Coventry *et al.* 1981 (44)	RT for HO	Retrospective study of postop RT	48	19% severe HO	RT appears effective for HO prevention.
Sylvester *et al.* 1988 (45)	Reduced dose RT for HO	Retrospective study of postop 20 Gy (10 fx) and 10 Gy (5 fx)	27	Grade 3–4 HO: 20 Gy = 2 pt 10 Gy = 1 pt (All 3 treated >4 days postop)	Reduced dose RT (10 Gy in 5 fx) appears effective for HO prevention. RT should be delivered <4 days postop.
Lo *et al.* 1988 (46)	Single fraction RT for HO	Retrospective study of postop 7 Gy (1 fx)	24	No Grade 3–4 HO	Single fraction of 7 Gy appears effective for HO prevention.
Pelligrini *et al.* 1992 (47)	Single fraction RT for HO	PRT of postop 8 Gy (1 fx) vs. postop 10 Gy (5 fx)	62	Grade 1–4 HO: Single fraction = 21% Fractionated = 21%	Single fraction appears similar in efficacy to fractionated RT.
Healy *et al.* 1995 (48)	Reduced dose RT for HO	Retrospective study of postop 7 Gy (1 fx) and postop 5.5 Gy (1 fx)	107	Grade 1–4 HO: 7 Gy = 10% 5.5 Gy = 63% ($p = 0.03$)	5.5 Gy (1 fx) is insufficient for HO prevention.
Padgett *et al.* 2003 (40)	Reduced dose RT for HO	PRT of postop 5 Gy (2 fx) vs. 10 Gy (5 fx)	59	Grade 1–4 HO: 5 Gy = 69% 10 Gy = 43% ($p = 0.09$)	5 Gy (2 fx) may be inferior to 10 Gy (5 fx) for HO prevention.
Seegenschmiedt *et al.* 1997 (50)	Preop vs. postop RT for HO	PRT of preop 7 Gy (1 fx) vs. postop 17.5 (5 fx)	161	Grade 1–4 HO: Preop = 24% Postop = 5% ($p < 0.05$)	Preop inferior to postop for HO prevention (no difference in patients with preop HO Grade 0–2).
Gregoritch *et al.* 1994 (50)	Preop vs. postop RT for HO	PRT of 7–8 Gy (1 fx) preop vs. postop	124	Grade 1–4 HO: Preop = 26% Postop = 28% (p = NS)	Preop may be similar to postop in HO prevention.
Burd *et al.* 2003 (55)	RT vs. NSAIDs for HO	PRT of RT (8 Gy in 1 fx vs. indomethacin × 6 wk	166	Grade 3–4 HO: RT = 7% Indomethacin = 14% ($p = 0.22$)	NSAIDs not statistically inferior to RT for HO prevention, sample insufficient to determine true equivalence.
Pakos and Iannidis 2004 (56)	RT vs. NSAIDs for HO	Meta-analysis 7 PRTs of RT vs. NSAIDs	1143	Grade 3–4 HO: OR = 0.42 (95% CI = 0.18–0.97) favoring RT	RT more effective than NSAIDs for HO prevention. 1.2% absolute risk difference.
Jasty *et al.* 1990 (53)	Shielding of THA in RT for HO	Retrospective study of 15 Gy (5 fx) shielding the acetabulum and femur	18	Grade 1–4 HO: 11% (2 grade 1)	Shielding does not reduce efficacy of RT for HO prevention.

Abbreviations: postop = postoperative; pts = patient(s); preop = preoperative; fx = fraction(s); PRT = prospective, randomized trial; vs. = versus; NSAIDs = nonsteroidal anti-inflammatory drugs; OR = odds ratio; THA = total hip arthroplasty; CI = confidence interval.

that these patients tend to be older. In the meta-analysis of Pakos and Ioannidies, for example, the average age of 1143 patients receiving HO prophylaxis was 61 (56). With the latency for radiation-induced tumors typically 10 years or longer, it is possible that the lack of documented second malignancies is partially attributable to the relatively small number of patients exposed to radiation who live long enough to experience a second tumor. It therefore remains possible that as more patients are followed for a longer interval after exposure to radiation for HO prophylaxis, second tumors may be observed. This concern seems particularly worthy of consideration when young patients at risk for HO development are referred for RT prophylaxis.

Trochanteric nonunion is also a potential side effect of RT. Trochanteric osteotomy is occasionally necessary to facilitate removal of a hip prosthesis at the time of revision. Studies not using shielding of the osteotomy site have found trochanteric nonunion rates of approximately 12–30% after RT (44, 46, 47). For comparison, rates of nonunion after trochanteric osteotomy range from approximately 2–15% (47). The use of shielding to lower the risk of nonunion does not thus far appear to diminish the efficacy of radiation as prophylaxis for HO, though there are few data to answer this question (53). Of note, the osteotomy technique in these studies—the Charnley trochanteric osteotomy—has largely been abandoned given the high rate of nonunion in unirradiated patients. An extended trochanteric osteotomy—in which the excision of the greater trochanter extends into the diaphysis of the femur—is now typically performed to access and remove the prosthesis as this permits a greater surface area for bony union to occur. The authors are unaware of any studies examining the effect of RT on rates of union after this procedure.

Last, radiation dose to the testis is also of concern given the potential for reduction in sperm counts and the theoretical risk of radiation-produced hereditary effects. Doses as low as 20 to 70 cGy have been noted to result in reversible oligospermia and doses of 120 cGy or higher are considered to confer a risk of permanent azoospermia (58). Furthermore, according to the Committee on the Biologic Effects of Ionizing Radiation and the United Nations Scientific Committee on the Effects of Atomic Radiation, the doubling dose for hereditary genetic effects is 100 cGy. These data are subject to controversy, however, given that they are largely based on animal data. In an abstract by Patel *et al.* (59), 800 cGy in one fraction for HO prophylaxis was found to result in a mean testicular dose of 25.1 cGy (range, 13–50 cGy). A testicular shield was found to reduce this dose by approximately 54%, yielding an average dose of 11.3 cGy (range, 3–26 cGy). Given these findings, the authors advocate the use of a testicular shield in men. They also recommend informing patients in whom shielding is not used of a potential reduction in sperm count and possible genetic abnormalities within the sperm for 6–12 months after RT.

CONCLUSIONS

Radiation therapy has emerged as an effective modality for preventing HO for patients at high risk after surgeries of the hip. It provides an alternative to indomethacin that assures compliance and eliminates the risk of NSAID-related gastrointestinal toxicity and bleeding in the setting of postsurgery deep vein thrombosis prophylaxis. In trauma patients with multiple fractures, RT for prophylaxis also reduces the risk of bone nonunion associated with NSAIDs. It is, however, considerably more expensive than NSAID therapy. The risk of radiation-induced malignancies, although thus far not evident after HO prophylaxis with RT, warrants consideration, in particular in younger patients.

The data discussed have focused solely on the prevention of HO at the hip joint, though the same treatment approaches have been used effectively in treating other sites, such as the knee and elbow (60, 61). Data are limited, however, regarding these less common sites of HO. Studies in dosing, dose fractionation, and timing of RT to prevent HO at the hip have transformed treatment methods since its inception in the 1970s (Table 3). Note should be made of the limitations of many of these studies, in particular small sample sizes and suboptimal research designs. Nevertheless, the available data support the current standards including single-fraction treatment given <4 h preoperatively or <72 h postoperatively. Treatment portals (Fig. 7) typically include the region medial to the center of the hip between the lesser trochanter and the ischial ramus, the area lateral to the center of the hip between the greater trochanter and the ilium, and the region surrounding the prosthetic femoral

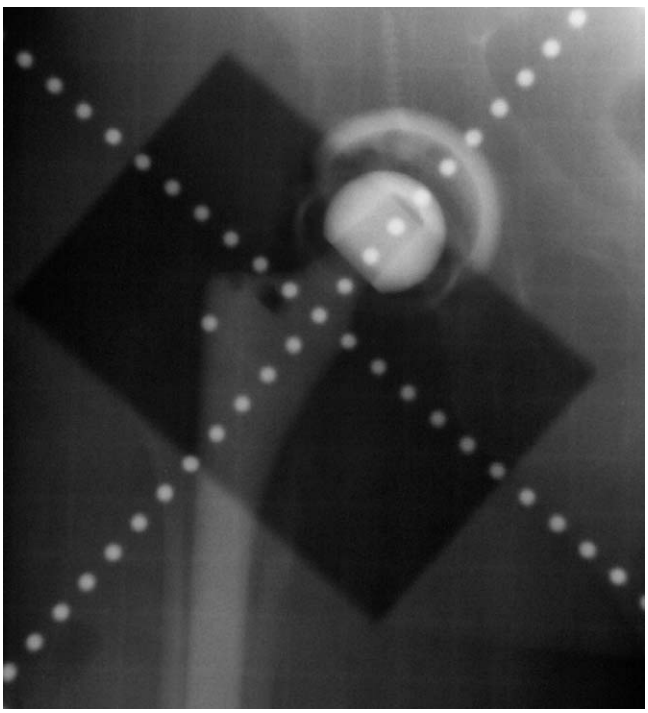

Fig. 7. Simulation film for heterotopic ossification radiotherapy prophylaxis.

neck. Furthermore, the acetabulum is often shielded when noncemented prostheses are used, though there are no clinical data demonstrating an increased risk of failure of acetabular union in the setting of RT for HO prevention. In the past, shielding of the osteotomy site (in the infrequent scenario when osteotomy is necessary to revise a THA) was often performed to reduce the risk of nonunion. However, given that this technique has largely been abandoned in favor of the extended trochanteric osteotomy, the necessity of this practice is unclear. Last, when treating men, shielding of the testes should also be strongly considered. Generally, doses of approximately 700 to 800 cGy given in one fraction or a biologically equivalent dose (given the overall dose and fractionation scheme) are administered for prophylaxis. The data suggest that reduced doses may yield inferior results, though the difference in clinically significant HO appears to be small. Further studies are needed to optimize dose reduction in light of preserving efficacy of HO prevention. Nevertheless, reduced doses might be a reasonable consideration for prophylaxis in young patients for whom the carcinogenic risk is of concern.

Finally, the investigation of heterotopic ossification and its prevention has furthered an understanding of the intricate balance of bone regulation. Considerable gaps in knowledge remain; though recent findings, such as the identification of BMP-4 as a key player in osteogenesis and its association with fibrodysplasia ossificans progressiva, hold promise for our future understanding of bone regulation. This knowledge will ultimately optimize treatment of bony disorders ranging from benign entities such as HO to debilitating, life-threatening conditions such as fibrodysplasia ossificans progressiva.

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