Heterotopic ossification is defined as bone formation in nonosseous tissues. Heterotopic ossification usually occurs in trauma such as fractures and surgical procedures. Heterotopic ossification of the hip, for example, is the most common complication of total hip arthroplasty (THA). It can occur in as many as 53% of THA patients, and it causes postoperative disability from pain and limited range of motion (ROM) 7% of the time. Heterotopic ossification also is seen in neurologic disorders such as spinal cord and brain injury.

Etiology

The exact cause of heterotopic ossification remains unknown. It is presumed that pluripotential mesenchymal cells differentiate into osteoblasts, which in turn causes heterotopic ossification. Research has yet to determine the source of these mesenchymal cells and the stimulus that causes them to differentiate. The mesenchymal cells may originate from the bone itself, the bone marrow, or muscle. An inducing substance, such as bone morphogenetic protein, is most likely responsible for the differentiation. Differentiation occurs within 16 hours after surgery and peaks at 32 hours.

Reaming of the bone may allow bone marrow, which is capable of forming bone, to spread into well-vascularized muscle tissue. This, combined with growth factors from traumatized tissues, may lead to bone development and heterotopic ossification.

Histologically, in the acute phase of heterotopic ossification, there is infiltration of round cells along with edema and degeneration of the muscle. After a few weeks, the inflammation is replaced with cartilage and bone. At that time, the bone undergoes intensive turnover. A high content of growth factors is indicative of metabolically active tissue. This process cannot be distinguished histologically from callus seen in fractures.

Risk Factors

Risk factors for heterotopic bone formation include a history of heterotopic ossification in the ipsilateral or contralateral hip, hypertrophic osteoarthritis, ankylosing spondylitis, and diffuse idiopathic skeletal hyperostosis. Table 1 lists the risk factors for heterotopic ossification. Men are at a higher risk than women.

Clinical Aspects

Heterotopic ossification occurs as early as 2 weeks following surgery or injury. Typically, the ectopic bone matures 6 to
9 months following the trauma.10,11 Patients with heterotopic ossification typically present with limited ROM and pain. In addition, there may be swelling and tenderness, which can mimic a low-grade infection. Heterotopic ossification starts to appear on plain radiographs 4 to 6 weeks after the trauma, which is when mineralization occurs.

Heterotopic ossification of the hip is graded according to Brooker’s Grading scale.10

- Grade 1. Islands of bone within the soft tissues about the hip.
- Grade 2. Bone spurs in the pelvis or the proximal end of the femur with at least 1 cm between the opposing bone surfaces.
- Grade 3. Bone spurs from the pelvis or proximal end of the femur with <1 cm between opposing bone structures.
- Grade 4. Radiographic ankylosis.

Typically, only patients with significant heterotopic ossification, namely Grade 3 and 4, present with symptoms.

Treatment

Surgery

The only effective treatment of symptomatic established heterotopic bone is surgical resection. Surgery is delayed for 6 months after the initial trauma to allow the bone to mature and a distinct fibrous capsule to develop, which facilitates resection and minimizes trauma to the surrounding tissue.12 This also allows the acute inflammatory phase of heterotopic ossification to resolve, which minimizes trauma to the tissues and decreases local recurrence of heterotopic ossification. During the resection, care is taken to avoid injuring the surrounding soft tissues. Hemostasis is essential to prevent hematoma formation, which may increase the risk of recurrence. Greater trochanteric osteotomy is associated with higher rates of heterotopic ossification and is avoided if possible. Occasionally, an anterior and posterior approach is necessary for adequate resection. Figure 1 shows heterotopic ossification pre- and postoperatively.
Because the only treatment for established heterotopic ossification is further surgery, it is prudent to prevent the formation of heterotopic bone in high-risk patients. Prevention begins in the operating room where care is taken to avoid soft-tissue trauma. Complete wound lavage and removal of all bone debris and reamings also are thought to decrease the risk of heterotopic bone formation. Additional therapy such as radiation and nonsteroidal anti-inflammatory drugs (NSAIDS), as described below, further decreases the risk.

Radiation

Doses. Radiating pluripotential mesenchymal cells, which are most likely responsible for heterotopic ossification, may effectively prevent this condition. Coventry and Scanlon reported the prevention of heterotopic ossification with a fractionated course of radiation. The authors first offered the preventive radiation therapy while at the Mayo Clinic in 1970, one year after the Mayo Clinic began performing THA and noticed that a number of patients developed ectopic bone. At the time, the pathogenesis of heterotopic ossification was unknown, but it was known that radiation inhibited the growth of vertebrae in children at doses >20 Gy. Therefore, 20 Gy in 10 fractions was used in patients at high risk for heterotopic ossification to discourage the growth of ectopic bone. Despite the fact that the patients were at high risk of heterotopic ossification, none developed massive formation of ectopic bone.

Because radiation potentially can cause secondary malignancy at higher doses, researchers began testing lower doses. These studies showed that 10 Gy in 5 fractions was as effective at preventing heterotopic ossification as the higher doses. In one study, 3.2% of the patients treated with 20 Gy in 10 fractions and 4.9% of the patients treated with 10 Gy in 5 fractions developed minimal heterotopic ossification. The historical controls with no radiation developed heterotopic ossification 68.5% of the time.
Lo et al\textsuperscript{19} used a total dose of 7 Gy in one fraction successfully. In that study, 23 patients were treated and only 1 (4\%) patient developed Grade 2 heterotopic ossification. Lo et al\textsuperscript{19} study was followed by a randomized controlled trial at the University of Rochester that compared a single 8 Gy dose with a 10 Gy dose in five 2 Gy fractions; 62 hips in 55 patients were studied. Two (5.9\%) of the 34 hips in the single-fraction group developed Brooker Grade 3 heterotopic ossification versus 2 (7.1\%) of the 28 hips in the 5-fraction group. None developed Grade 4 ossification. No statistically significant difference was noted between the two doses.\textsuperscript{20} Thus, single fraction radiation was found to be as effective as fractionated therapy.

Healy et al\textsuperscript{21} compared a 5.5 Gy dose in one fraction with a 7 Gy dose in one fraction and found that 63\% of the hips radiated with 5.5 Gy developed heterotopic ossification; 2 (10\%) of the patients were symptomatic. Only 10\% of the patients in the 7 Gy group developed heterotopic ossification and none were symptomatic. Therefore, 5.5 Gy was concluded to be ineffective in preventing symptomatic heterotopic ossification compared to 7 Gy in a single fraction.

Hedly et al\textsuperscript{22} used 6 Gy in a single dose to prevent heterotopic ossification in 17 hips. All 17 hips developed Brooker Grade 0 or 1 heterotopic ossification. The lowest effective dose appears to be 6 Gy. Table 2 summarizes the results of mentioned studies.

Based on the concept of biologically effective doses, a single fraction of 7 Gy is not equivalent to 7 Gy divided into multiple fractions. Dividing a dose allows for cell repopulation between fractions. Thus, a higher total dose is necessary to control the pluripotent mesenchymal cells and prevent heterotopic ossification. For example, 10 Gy in 5 fractions would be required to achieve the same control rates as 7 Gy in 1 fraction.

Timing of Radiation. Timing is critical when using radiation to prevent heterotopic bone formation. Radiation should be delivered within 72 hours after surgery.\textsuperscript{19} After 72 hours, the mesenchymal cells become differentiated and bone matrix starts being synthesized. After 72 hours, the rate of heterotopic bone formation increases.\textsuperscript{23} In a study on treatment failures, 75\% of patients treated >72 hours from surgery developed heterotopic ossification compared to 55\% when treated within the first 3 days.
Preoperative radiation also has been studied. This initially would seem counterintuitive, as only rapidly dividing cells such as mesenchymal cells would be sensitive to radiation following surgery. Both Seegenschmiedt et al24,25 and Kantorowitz et al26, 27 studied whether preoperative radiation can effectively prevent heterotopic ossification. Kantorowitz et al26,27 showed dose-related suppression in bone formation in rats by radiation given prior to a stimulus-inducing proliferation. This was extended clinically when patients were given 7 Gy of radiation within 4 hours prior to hip surgery and compared to patients receiving 7 Gy <72 hours postoperatively. No statistically significant difference was noted between the two arms in Brooker grades and improvements in Harris functional scores.

Seegenschmiedt et al24,25 performed a similar trial comparing preoperative and postoperative radiation. Patients were randomized to receive 7 Gy of radiation within 4 hours prior to hip surgery or 17.5 Gy in 5 fractions <96 hours postoperatively. In the postoperative radiation arm, 5% of patients developed heterotopic ossification versus 19% in the preoperative radiation arm (P<.05). According to a subgroup analysis, no difference was noted between the preoperative and postoperative radiation groups in the progression of heterotopic ossification in the patients without Grade 3 or 4 heterotopic ossification prior to surgery. However, in the patients who had radiation prior to the removal of their ipsilateral Grade 3 or 4 heterotopic ossification, progression of heterotopic ossification occurred in 39%. This was statistically significant (P<.001) when compared to the postoperative arm, which progressed 9% of the time. As such, preoperative radiation was determined to be not as effective when compared to postoperative radiation in high-risk patients.

Figure 2: Shielding for porous devices.

Technique. Because ingrowth components are being used for THA, concern exists that radiating the components would prevent bone ingrowth. Konski et al28 placed porous-coated implants in rabbit tibia and radiated them at 10
Gy in 5 fractions. Two weeks postoperatively, the animals were sacrificed and the implants were removed. The force necessary to remove the implant in the radiated tibia was significantly less than that needed to remove the untreated tibia after 2 weeks (P<.01). The difference was not statistically significant at >3 weeks, however. Histologically, the untreated hip showed bone formation while the treated hip did not. The authors suggested shielding the prosthetic device from radiation.

Despite Konski et al's study, Seegenschmiedt et al did not report increased rates of loosening or instability after radiating porous-coated prostheses without shielding. However, it is customary to shield porous prosthetic devices from radiation (Figure 2).

Radiation may prevent bony ingrowth for porous components and also hinders fracture healing of trochanteric osteotomies. As such, trochanteric osteotomies also need to be shielded during radiation. In one study, 5 migrations and 7 fibrous unions occurred in 36 patients whose osteotomies were not shielded, for a total nonosseous union rate of 33%. With shielding, 2 fibrous unions and no migrations occurred in 28 patients for a total nonosseous union rate of 7%.

Repeat Prophylactic Radiation Treatment.
In some patients, failed hip prostheses must be replaced. Retreatment of the hip with a history of radiation for heterotopic ossification is indicated. Lo and Healy performed a case study of 4 patients who were re-irradiated after repeat hip surgery. Re-treatment was effective in preventing heterotopic ossification without any known side effects in this small group of patients.

Side effects.
No reports exist of acute or subacute side effects associated with postoperative radiation following THA. This includes surgical complications and impaired wound healing. As previously mentioned, increased nonunion rates may occur following trochanteric osteotomy without shielding. But with shielding, the risk of nonunion may be reduced. In addition, radiation has been associated with malignancies. However, this risk is minimal given the dose of radiation and no neoplasm as a result of radiation to the hip for heterotopic ossification has been reported.

Nonsteroidal Anti-inflammatory Drugs

In addition to radiation, NSAIDs, particularly indomethacin, have been successfully used to prevent heterotopic ossification. Nonsteroidal anti-inflammatory drugs may work by suppressing the migration and proliferation of inducible mesenchymal cells.
prospectively studied the use of NSAID therapy in the prevention of heterotopic ossification and compared it to radiation therapy. Moore et al33 randomized 39 patients to indomethacin (25 mg three times a day for 6 weeks) and 33 patients to radiation (8 Gy in a single fraction). Three (9%) patients in the radiation group failed, which was defined as Brooker grade 3 or 4 heterotopic ossification, versus 7 (18%) patients in the indomethacin group. The authors reported that indomethacin was as effective as radiation.

Similarly, Kienapfel et al32 prospectively studied a single fraction of 6 Gy postoperatively versus indomethacin (50 mg twice a day) starting on postoperative day 1 for 42 days versus no therapy. Both treatment groups showed significantly decreased heterotopic bone formation, and neither group developed Brooker Grade 3 or 4 ossification (P<.001 for both groups).

Sell et al31 compared diclofenac 50 mg three times a day for 3 weeks versus postoperative radiation (9.9 Gy in 3 fractions) and obtained similar results. None of the hips in either treatment arms developed Brooker Grade 3 or 4 heterotopic ossification.

Unfortunately, NSAID therapy has side effects, most notably gastrointestinal ulceration, decreased platelet aggregation, and renal toxicity. In Sell et al’s31 study, 11 (14%) of 77 patients in the diclofenac group developed gastrointestinal side effects that led to the discontinuation of therapy. Also, some patients are not compliant with their NSAID regimen because the drugs need to be taken at specific times for many weeks. Reducing the dose and length of treatment may decrease the side effects and increase compliance.

Sell et al34 performed another study comparing cholestyramine-bound diclofenac at 150 mg per day versus 75 mg per day for 14 days total. No difference in heterotopic ossification rates between the two arms was noted. The incidence of adverse gastrointestinal events was 23% in the low-dose arm compared with 38% in the high-dose arm (P=.02). As such, the low-dose of diclofenac was recommended in the pharmacologic prevention of heterotopic ossification.

Another study of 201 patients compared 100 mg of indomethacin daily over 14 days versus 7 days and found no difference in the rate of heterotopic ossification.35 No patients in this study developed Brooker Grade 3 or 4 heterotopic ossification.

Other NSAIDs have been studied with the aim of reducing adverse
gastrointestinal events. One large study was performed in New Zealand using low-dose aspirin.36 This was a subgroup of their Pulmonary Embolism Prevention Trial. In this study, 2649 patients were randomized to receive low-dose aspirin 162 mg per day for 35 days, or placebo. The dose was selected primarily for its effect on thrombotic outcomes, not for prevention of heterotopic ossification. Radiographs of each patient were obtained 6 months later. Patients were allowed to use NSAIDs outside of the study aspirin, but no difference was noted between the two arms in the percentage of patients using non-trial aspirin or other NSAIDs. No difference was detectable in the relative risk of heterotopic ossification formation between the low-dose aspirin group and the placebo group.

A higher dose of aspirin also has been studied prospectively. Knelles et al37 randomized 723 patients into 6 arms. Three arms used 3 different radiation schemes: 5 Gy in one fraction, 7 Gy in one fraction, and 12 Gy in 3 fractions. Two other arms used 7 days of indomethacin (50 mg twice a day) and 14 days of indomethacin (50 mg twice a day). The sixth arm used 14 days of aspirin at a dose of 750 mg, three times a day. The patients were compared to a historic control group whose patients received no prophylaxis. In this study, aspirin was less effective than radiation or indomethacin in the prevention of heterotopic ossification. The aspirin group developed Brooker Grade 3 heterotopic ossification 5.3% of the time versus 0% to 1.7% for the other treatment groups. No patients in any of the treatment groups developed Brooker Grade 4 heterotopic ossification. In comparison, 19% developed Brooker Grade 3 heterotopic ossification and 5% developed Brooker Grade 4 heterotopic ossification in the control group. Also, the aspirin group developed the most side effects with 6.1% of the patients discontinuing therapy because of intolerance. Most of these were due to gastrointestinal intolerance.

The gastrointestinal side effects associated with NSAID use are due to the inhibition of the enzyme cyclooxygenase. Selective inhibition of cyclooxygenase-2 (COX-2) was thought to minimize the gastrointestinal side effects. This led to several studies investigating whether COX-2 inhibitors can more effectively prevent heterotopic ossification than a non-selective NSAID. One study initially randomized 272 patients into 3 groups following THA.38 One group received 7.5 mg of meloxicam, a COX-2 inhibitor, another group received 15 mg of meloxicam, and the third group received indomethacin 50 mg twice a day. The drugs were given over 14 days. The group with 7.5 mg of meloxicam developed heterotopic ossification one-third of the time, so this arm was stopped early. There was less heterotopic ossification in the indomethacin group (10%) than in the 15 mg meloxicam group (25%); the difference was statistically significant (P=.03). Only 1% in the 15 mg of meloxicam group and 2% in the indomethacin group developed Brooker Grade 3 heterotopic ossification. None of the patients developed Brooker Grade 4 heterotopic ossification. Two percent of the patients receiving meloxicam developed gastrointestinal side effects compared with 4% in the indomethacin arm.

Another study compared indomethacin 50 mg twice daily to meloxicam 7.5 mg daily over 12 days.39 No statistically significant difference was observed between the 2 arms in terms of heterotopic ossification formation. Although the patients who received meloxicam developed fewer gastrointestinal side effects,
the authors recommended indomethacin, given that it is less expensive.

Celecoxib also has been studied and compared to indomethacin in a randomized, prospective setting. In this study, indomethacin was given 50 mg twice daily for 20 days and celecoxib was given 200 mg twice daily for 20 days. There was no difference in the rate of heterotopic ossification between the two groups. Neither group developed Brooker Grade 3 or 4 heterotopic ossification. However, therapy was discontinued more frequently in the indomethacin group due to intolerance, predominately from gastrointestinal side effects. In the indomethacin group, 8.4% of the patients stopped therapy after a mean of 9.5 days. In the celecoxib group, 2.0% stopped therapy after a mean of 14 days. The difference in the rate of discontinuation of therapy was significant (P<.05). Celecoxib appears to be equally efficacious and better tolerated than indomethacin.

Another concern with NSAID therapy is its effect on bone ingrowth in cementless stems. One study involving implantation of porous-coated components in rabbits showed a dose response with indomethacin, ibuprofen, and high-dose aspirin and bone ingrowth into the pores. A similar study with indomethacin showed that bone ingrowth significantly increased from 2 to 8 weeks postoperatively in the control group, but not in the indomethacin group. However, the effect of NSAIDs on bone ingrowth has not been shown clinically. In a study where 80 patients were obtained prospectively, given indomethacin prophylaxis, and compared to 82 patients without indomethacin prophylaxis obtained retrospectively, no difference was noted in the development of radiolucenty or radiologic changes around the cementless stem after 6 years. In fact, the patients receiving indomethacin had more patients achieving a Harris hip score >90.

Similar to their effect on bony ingrowth, NSAIDs have been associated with weaker callus formation and may pose a problem in healing of other long bones that may have been fractured at the same time. This was studied prospectively at the University of Missouri where 282 patients underwent open reduction and internal fixation of their acetabular fracture. They were at risk of heterotopic ossification due to use of a posterior or extensile surgical approach and were randomized to treatment with indomethacin or radiation. The indomethacin group received 25 mg three times a day for 6 weeks. The radiation group received a single dose of 8 Gy radiation within 72 hours of surgery. Of these 282 patients, 112 patients had a concomitant fracture of a long bone. It was noted that 7% of the patients in the radiation arm had nonunion of their long-bone fracture whereas 29% of the patients in the indomethacin arm had nonunion (P=.004). In patients with concomitant fractures of the long bones, radiation may be a better choice in the prevention of heterotopic ossification.

Given the effectiveness of NSAID therapy in preventing heterotopic ossification, a recent meta-analysis was performed using eight studies that compared radiation to NSAID therapy. The NSAIDs used by the studies included indomethacin, diclofenac, and aspirin. The meta-analysis showed a...
decreased risk of clinically significant heterotopic ossification, defined as Brooker Grade 3 or 4, with radiation (P=.043), but the absolute difference was small (1.18%). In addition, a significant dose-response relationship was noted (P=.008). 6 Gy was equivalent to NSAID therapy but higher doses of radiation were more effective. Duration of NSAID therapy did not impact on the effectiveness of NSAID therapy. The type of NSAID made a difference. Of the three drugs studied, aspirin was found to be less effective than radiation.

Logistical difficulties exist when using NSAID therapy. Occasionally, a patient is on NSAID therapy, is out 72 hours after surgery, and develops gastrointestinal complications or requires anticoagulation with heparin or warfarin. This prevents further NSAID therapy. Since it is 72 hours after surgery, radiation is no longer as effective. This would put the patient at high risk for developing heterotopic ossification with the discontinuation of therapy. For this reason, our institution favors radiation upfront over NSAID therapy in the prevention of heterotopic ossification.

Diphosphonates have been studied to prevent heterotopic ossification, but after the drug is withdrawn, the osteoid becomes mineralized. 46 Thus, diphosphonates are ineffective in the prevention of heterotopic ossification.

Sites Other Than The Hip

Heterotopic bone can occur at sites other than the hip, including the elbow, knee, shoulder, and temporomandibular joint. Lo et al 47 reported 5 case studies of radiation to the elbow, spine, and knee, and the results suggested that radiation can prevent heterotopic ossification at these sites as well.

Heterotopic ossification occurs 9% of the time after total knee arthroplasty (TKA), with rare cases becoming symptomatic. 48 In one study of 615 patients who underwent TKA, 4 (0.7%) developed symptoms. Hypertrophic arthrosis was found to be risk factor for heterotopic ossification after TKA in this series. A variety of systems have been proposed to grade heterotopic ossification of the knee, including one by the authors of the aforementioned series. These authors also recommended considering prophylaxis in patients with marked hypertrophic arthrosis or periosteal damage to the anterior distal femur. 48

Prophylaxis of the knee was studied retrospectively in 5 patients (6 knees) with symptomatic heterotopic ossification after TKA. 49 All patients received 7 Gy in one fraction following excision of their heterotopic ossification. Of the 6 knees, 2 (33%) had minimal evidence of heterotopic ossification, showing that radiation may reduce the recurrence of heterotopic ossification after TKA.
Clinically significant heterotopic ossification develops in 10%-20% of patients in common settings of elbow injury (eg, trauma, brain injury, and spinal cord injury). The elbow is the most common site of heterotopic ossification in burn patients, of whom 1%-3% may be affected. Heterotopic ossification of the elbow is classified according to the Hastings and Graham system. Class I patients have evidence of heterotopic ossification without functional limitation. Class II patients have heterotopic ossification with some limitation of ROM. Class III patients have ankylosis. Radiation in preventing heterotopic ossification of the elbow following excision of heterotopic ossification was reviewed in a single institution. This study of 27 patients (29 elbows) showed that ROM was maintained in bone-forming patients who received radiation postoperatively at 6-7 Gy in a single fraction following heterotopic ossification removal. Another study involved 11 patients with trauma to the elbow that was repaired with open reduction and internal fixation. These patients were treated with a single dose of 7 Gy to prevent heterotopic ossification. While 27% had heterotopic ossification on radiograph, 91% had no functional limitations. Case studies also support the efficacy of radiation in preventing heterotopic ossification about the elbow.

In the shoulder, patients with heterotopic ossification were retrospectively compared to patients without heterotopic ossification. No statistically significant identifiable characteristics were associated with the development of heterotopic ossification of the shoulder. Also, no statistically significant difference was noted in the ROM or pain in patients with heterotopic ossification when compared to the patients without heterotopic ossification. However, ankylosis can develop, although it is rare, and prophylaxis may be warranted. Reports on prophylaxis to the shoulder have been limited. Figure 3 shows an example of heterotopic ossification of the shoulder.
Figure 3: Plain radiograph (A), CT scan (B), and CT-reconstructed image (C) showing heterotopic ossification of the shoulder.

Ankylosis of the temporomandibular joint from heterotopic ossification can be disabling. The Turlington-Durr classification is used to grade heterotopic ossification of the temporomandibular joint, and is similar to the Brooker Grading system. This uses a scale from 0 to 3. Grade 0 is no bone island visible. Grade 1 is island of bone visible within soft tissues around the joint. Grade 2 is periarticular bone formation. Grade 3 is apparent bony ankylosis. Following gap arthroplasty, heterotopic ossification recurs 53% of the time. In a study by Durr et al, 10 patients (15 temporomandibular with ankylosis) who required reconstruction received radiation: 10 to 11.25 Gy in 4 to 5 fractions. Ten (67%) of the 15 temporomandibulars had no heterotopic ossification reformation and in 13 (87%), the Turlington-Durr score improved. None of the joints developed ankylosis. Eight of the 10 patients remained asymptomatic and 3 patients developed parotitis.

Another study involving 14 patients with temporomandibular ankylosis showed that 13 (93%) had radiographic evidence of decreased heterotopic ossification formation after postsurgical radiation to 20 Gy in 10 fractions or 10 Gy in 5 fractions; no patient redeveloped ankylosis. Transient xerostomia was the only complication. The authors of this study concluded that radiation is safe and effective in the prevention of the recurring temporomandibular ankylosis from heterotopic ossification.

Conclusion

Heterotopic ossification occurs in as many as 53% of patients who undergo THA and can result in morbidity in 7%. As such, in high-risk patients, prophylaxis with NSAIDs or radiation is recommended. The effectiveness of NSAIDs in very high-risk patients, such as those with a history of Brooker Grade 3 or 4 heterotopic ossification, needs to be compared to radiation, which has been shown to be effective in these patients. Once heterotopic ossification develops, surgical removal is the only effective treatment, followed by radiation or NSAIDs to prevent recurrence. Other areas of the body such as the knee, elbow, shoulder, spine, and mandible may develop significant heterotopic ossification requiring removal. In those cases, radiation has been shown to be effective in preventing recurrence. More studies are needed assessing the effectiveness of NSAIDs in preventing heterotopic ossification in these sites.

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Authors

Drs Chao and Suh are from the Department of Radiation Oncology and Dr Joyce is from the Department of Orthopedics, The Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, Ohio 44195.

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Correspondence should be addressed to:
John H. Suh, MD, Dept of Radiation Oncology, 9500 Euclid Ave, Desk T-28, Cleveland, OH 44195.

For details click here