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## The Journal of Foot & Ankle Surgery

journal homepage: www.jfas.org



## Radiation Therapy for Recurrent Heterotopic Ossification Prophylaxis After Partial Metatarsal Amputation



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#### ARTICLE INFO

Level of Clinical Evidence: 4

Keywords:
Charcot neuroarthropathy
complication
neuropathy
prophylactic radiation
ray resection
re-ulceration
transmetatarsal amputation
weightbearing surface

#### ABSTRACT

The formation of heterotopic ossification is a relatively common, yet rarely discussed, cause of re-ulceration after previous partial metatarsal amputation. Excessive bone growth at the amputation site has the potential to create an unwanted prominence on the weightbearing surface of the foot, intuitively increasing plantar pressure and placing the neuropathic patient at greater risk of re-ulceration and limb loss. The aim of the present study was to assess the efficacy of single-dose radiation therapy in preventing recurrent heterotopic ossification. The inclusion criteria consisted of a history of clinically relevant heterotopic ossification formation after partial metatarsal amputation with subsequent partial metatarsal amputation for heterotopic ossification resection, followed by prophylactic single-dose radiation therapy. Eleven consecutive patients meeting the inclusion criteria were identified for the present study. Before the intervention, 10 (91%) patients demonstrated formation of mid- to high-grade heterotopic ossification, and 9 (82%) patients exhibited an associated neuropathic ulceration. On follow-up at least 6 weeks after intervention, 2 (18%) patients exhibited low-grade heterotopic ossification reformation that was not clinically relevant and 9 (82%) did not show signs of heterotopic recurrence. Single-dose radiation therapy can help prevent the formation of heterotopic ossification in high-risk patients, acting as an effective adjunct to surgery in minimizing the risk of re-ulceration and reamputation in the neuropathic patient.

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Neuropathic ulcerations forming on the weightbearing portion of the foot often form secondary to underlying structural prominences that increase plantar pressures and lead to tissue breakdown. Neuropathic ulcerations are commonly recognized to develop secondary to intrinsic and extrinsic muscle contracture, prominences related to foot type, structural abnormality secondary to previous amputation, and collapse from Charcot neuroarthropathy. However, the development of plantar prominences as a result of heterotopic ossification (HO) formation at previous amputation resection sites has rarely been discussed despite being a relatively common occurrence. HO is a phenomenon that has been well described after trauma or surgical intervention throughout the body. It is defined as the abnormal formation of mature, lamellar bone in the connective soft tissue (1). It most commonly manifests in large joints and proximal

**Financial Disclosure:** None reported. **Conflict of Interest:** None reported.

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portions of long bones in the upper and lower extremities (1). Much of the existing data has focused on HO complications associated with total hip arthroplasty, because it has been reported as the most common complication, at a mean incidence of 53% (2). Although HO has previously been described in various other regions, it is not often discussed in relation to the foot and ankle. HO has been described in the setting of total ankle arthroplasty (3,4) but not routinely after partial foot amputation. We appreciate HO formation to be a relatively common finding after partial metatarsal resection in diabetic wound and infection surgery. This bone growth can, in turn, create a prominence, especially when forming on the plantar aspect of the foot, that will place the patient at risk of recurrent neuropathic ulceration, osteomyelitis, and soft tissue infection in this region. Resection of the involved bone is often necessary to eradicate infection and the underlying structural deformity. However, these patients are at high risk of HO recurrence, because a history of HO formation is considered to be the greatest risk factor for recurrence (5,6). Given that the diabetic patient population with peripheral neuropathy is already considered to be at high risk of infection and additional proximal amputation, strategies to minimize complications from HO formation in wound surgery should be attempted when possible.

**Table 1**Staging for metatarsal resection heterotopic ossification

Grade	Description
Criteria	
0	No heterotopic ossification
I	Isolated bone island adjacent to resection site
II	Adherent bone spur formation <1 cm
III	Adherent bone spur formation >1 cm
Subdivision	
a	No adjacent ulceration
b	Adjacent ulceration

<sup>\*</sup> Staging criteria established to quantify the severity of HO formation and associated clinical relevance; preoperative and 6-week postoperative radiographic findings were staged and compared.

Single-dose radiation therapy has traditionally been used in a prophylactic manner against HO formation in regions other than the foot and ankle, first described in this capacity by Coventry and Scanlon (7) in 1981. It has frequently been used in conjunction with total hip arthroplasty or fracture (8-18) and to a lesser extent in the knee and upper extremity (19-22). Although the pathophysiology of HO is poorly understood, it likely involves inappropriate differentiation of the osteoprogenitor stem cells at the site of insult into osteoblastic cells that begin osteoid formation (23–25). Radiation therapy targets the mesenchymal stem cells before differentiation, and they remain highly radiosensitive for the first 4 days after exacerbation (26,27). Additional investigations have supported that single-fraction administration (28) of relatively low-dose radiation (29) provides a safe and effective method of prophylactically treating HO. Several investigators have since confirmed the effectiveness of radiation therapy in preventing HO formation (30,31). However, this approach has neither been routinely discussed regarding treatment in the foot and ankle nor, more specifically, in the setting of local partial foot amputation. The aim of the present retrospective study was to assess the efficacy of single-dose radiation therapy on the prevention of HO in patients with a history of previous HO who were undergoing subsequent surgical resection of the involved metatarsal.

#### Patients and Methods

After obtaining institutional review board approval, a review was performed of consecutive patients with previous partial metatarsal amputation and associated HO formation, who subsequently underwent resection of HO combined with prophylactic radiation therapy. Subjects were identified by the radiation therapy department with

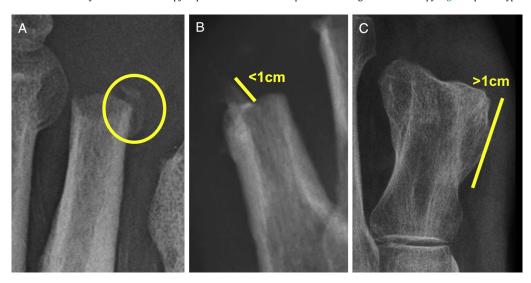
which the investigators are affiliated including records from January 2006 to May 2013 identified by CPT (Current Procedural Terminology, American Medical Association, Chicago, IL) code. Cases were included when coded with a CPT code for radiation treatment delivery (77401-77416) and one of the following CPT codes: incision bone cortex, foot (28005); transmetatarsal amputation, foot (28805); or amputation, metatarsal, with toe, single (28810). Cases with CPT code 28005 were individually reviewed by co-investigator (J.C.T.) via electronic medical record, and only those with amputation through a single or multiple metatarsals were included. The exclusion criteria consisted of concomitant nonsteroidal anti-inflammatory drug use, amputations allowed to heal secondarily, and additional systemic risk factors for HO formation (ankylosing spondylitis, idiopathic skeletal hyperostosis, Paget's disease, osteonecrosis). A staging system was developed to quantify the extent of HO formation preoperatively and at least 6 weeks postoperatively and to determine the associated clinical relevance regarding the presence of a corresponding ulceration (Table 1). Previous classification systems (32,33) created for HO staging around the hip joint were considered in establishing the present staging system. HO developing in the soft tissues adjacent to the amputation site was deemed early stage with the premise that formation typically begins in the soft tissue and advances toward the adjacent bone (Fig. 1)(34). Staging was performed independently by 2 separate boardcertified foot and ankle surgeons and a third-year foot and ankle surgical resident, and the interrater reliability was calculated. We hypothesized that this patient population, deemed at high risk of recurrent HO formation, would have a low recurrence rate with a lower grade of postoperative and postradiation HO staging compared with preoperatively.

#### Radiation Therapy Protocol

Radiation therapy has typically been used in our department for patients deemed to be at high risk of HO formation associated with partial metatarsal amputation. Because a history of HO formation is considered to be the greatest risk factor in determining the likelihood of HO formation (5,6), these patients have routinely received preventative radiation therapy. In accordance with the recommendations of the radiation therapy department and the treatment recommendations for HO prophylaxis of the hip (28), the patients have received a single-fraction radiation dose of 700 cGy directed at the forefoot. This was performed within 24 hours preoperatively to 72 hours postoperatively. Treatment consisted of placing the foot on a tissue-equivalent surface while radiation is administered, which can be performed either in the inpatient or outpatient setting (Fig. 2).

#### Surgical Technique to Minimize HO Formation

The surgical technique can also influence the development of HO, although each patient in the present study underwent the same surgical approach for the initial and subsequent procedures. When performing partial metatarsal resection, care should be taken to avoid excessive periosteal stripping. Sharp bone resection with a saw can also help minimize unnecessary localized trauma at the bone resection site. Furthermore, a staged surgical approach with or without antibiotic bead application can be used in situations in which excessive bleeding and hematoma formation could predispose the patient to HO formation. If staged bone resection is being performed, radiation therapy should be administered in conjunction with the main procedure requiring the most bone resection. Postoperative management was not altered from our typical protocol in the patient receiving radiation therapy. Fig. 3 depicts a typical patient who developed



**Fig. 1.** Radiographic examples of successive heterotopic ossification (HO) stages. (A) HO is believed to originate in the soft tissues adjacent to bone (31), which is characterized as grade I HO. (B) Grade II HO exhibits bone formation less than 1 cm in length. (C) Grade III HO is much more expansive, measuring greater than 1 cm in length. The distinction of "a" or "b" after the grade indicates HO without or with an associated ulcer, respectively.

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