



REVIEW ARTICLES

Radiotherapy for prevention of heterotopic ossification of the elbow: a systematic review of the literature

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Background: Heterotopic ossification is a pathological process characterized by abnormal formation of bone in nonskeletal tissue. Radiotherapy for heterotopic ossification of the elbow is questionable because of possible adverse effects.

Methods: A systematic review of the literature was conducted in MEDLINE, Scopus, ISI Web of Science, National Institute for Health and Clinical Excellence, National Guideline Clearinghouse, System for Information on Grey Literature in Europe, ClinicalTrials.gov, Cochrane Central Register of Clinical Trials, and Cochrane Database of Systematic Reviews up to April 2012. All published articles assessing interventions including radiotherapy for prevention of heterotopic ossification in the elbow of adult patients were considered. Information was recorded by the first two authors, and disagreements in interpretation were resolved by consensus.

Results: In total, 27 studies using radiotherapy for elbow heterotopic ossification were identified (1 randomized clinical trial, 1 case-control study, and 25 case reports and case series) in the literature. Most of them used a single dose of 7.0 Gy. The randomized clinical trial was stopped early because of severe adverse effects (pseudarthrosis) caused by radiation. The case-control study showed that radiotherapy did not effectively prevent recurrence of heterotopic ossification. The case reports and case series mentioned only sparse adverse events.

Conclusion: The use of radiation therapy for prevention of heterotopic ossification of the elbow is supported by weak evidence.

Level of evidence: Review Article.

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Keywords: Radiotherapy; heterotopic ossification; elbow; prevention; systematic review

Heterotopic ossification (HO) is the production of mature bone within soft tissue at sites where bone normally does not exist.⁵⁶ It results from an alteration in the normal regulation

of skeletogenesis, specifically from differentiation of primitive mesenchymal stem cells within soft tissue into bone-forming cells (osteoblasts-osteogenic cells), in response to a variety of biochemical or mechanical signals.^{9,32}

The most common cases of HO have been most frequently reported after trauma, arthroplasty, burns, spinal cord injury, and traumatic brain injury.³⁰ Traumatic HO typically follows fractures, dislocations, and operative procedures. Neurogenic

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HO is seen after central nervous system insult, including spinal trauma and head injuries. HO can also occur in the setting of genetic disorders like fibrodysplasia ossificans progressiva. Several risk factors have been proposed for the development of HO about the elbow. They include genetic predisposition, severity of trauma, concomitant neurologic injury, surgical approach, hematoma formation, and presence of metabolic bone diseases (e.g., hypertrophic osteoarthritis, ankylosing spondylitis, Paget disease, and idiopathic skeletal hyperostosis).⁵

The incidence of primary occurrence of HO about the elbow varies widely in different published reports. It ranges from 1% to 3% in burn patients¹⁵ and patients suffering isolated elbow dislocations⁶³ and reaches 15% to 20% in fracture-dislocations and in common forms of elbow injury (spinal cord injury, brain injury, and trauma).²⁰ In the case of radial head fracture, it has been reported to be as high as 56%.^{29,39} Up to 89% of patients with concomitant traumatic brain and elbow injuries have been reported to develop HO.^{20,21} For patients with HO established about the elbow, the incidence of recurrent HO after excision has not been well documented. The respective numbers pertinent to the hip are 63% to 90% without specific intervention.^{14,18}

Early HO is suggested primarily by clinical signs and symptoms, including severe pain, redness, swelling, warmth, and loss of joint motion. Diagnosis of HO is confirmed by radiographic examination (plain radiography, ultrasound, bone scan, and magnetic resonance imaging).^{12,37}

The management of patients with clinically significant HO (either primary or secondary) most of the times includes surgical excision. Surgical removal of HO is followed by prophylactic measures, given its tendency to recur. The two main prophylactic modalities for HO occurrence (as primary prevention in high-risk patients) or recurrence (as secondary prevention together with surgical excision) are radiation therapy (RT) and nonsteroidal anti-inflammatory drugs (NSAIDs).⁴

The rationale of RT use for prevention of HO is based on the hypothesis that the osteoprogenitor cells, presented in the early phase of HO development, are particularly radiosensitive. Their radiosensitivity may be partly due to their high mitotic rate because they are in the process of proliferating and differentiating into specialized forms, such as osteoblasts and chondrocytes.⁴ The mechanism of action of radiation is based on the suppression of the pluripotent mesenchymal cells' transformation into osteoprogenitor cells and osteoblasts.^{53,54} In addition, experimental data revealed that irradiation significantly reduces the expression of biologic factors, such as bone morphogenic protein-7, which plays a key role in the cellular process of differentiation of osteoblasts and therefore the consecutive formation of ectopic bone tissue.¹⁰

Until now, there is no "gold standard" of care regarding the indications, timing, and dosage of prophylactic RT for elbow HO differentiating it from hip HO. In the present study, a systematic review of the published literature on the

safety and efficacy of RT for the prevention of elbow HO was performed.

Methods

The design of our study and the report of results were based on the PRISMA statement.³⁴

Inclusion criteria

All published articles including RT for the prevention of HO of the elbow in adult patients were considered, regardless of the etiology of HO. Only human studies were included, regardless of the outcome assessed. No language restrictions were set. Studies not providing information about patients' outcome were excluded.

Information resources and search strategy

We searched MEDLINE (until April 2012), Scopus (until April 2012), and ISI Web of Science (until April 2012). The search strategy included the keywords *heterotopic ossification*, *myositis ossificans*, *ectopic ossification*, *radiotherapy*, *radiation*, *irradiation*, and *elbow*. In addition, we searched the Cochrane Central Register of Clinical Trials and the Cochrane Database of Systematic Reviews until April 2012. We also investigated the National Guideline Clearinghouse⁴² and the National Institute for Health and Clinical Excellence⁴³ for published clinical guidelines related to RT for elbow HO. Furthermore, ClinicalTrials.gov¹³ was explored for unpublished information about the use of RT for HO of the elbow. We also searched the System for Information on Grey Literature in Europe (OpenSIGLE)⁶¹ for unpublished evidence until April 2012. The reference lists of the included articles were also hand searched for additional studies.

Data extraction

We recorded information pertaining to study characteristics and demographics, such as authors, publication year and journal, study design, sample size, mean age, etiology of HO, surgical excision of HO before RT (yes or no), radiation dose (total dose and number of fractions) and timing, duration of follow-up, functional and radiologic outcome, number of failures of HO prevention, and number of adverse events. The failure of HO prevention was defined as the occurrence or recurrence of HO. We also recorded the use of adjuvant interventions, such as NSAIDs and physical therapy. Two investigators (A.P. and L.B.) assessed the eligible articles according to the predefined criteria. The data were included as available. Disagreements in interpretation were resolved by consensus between the investigators.

Data analysis

We used the classification of medical evidence published by Wright et al.⁶⁶ We divided the radiation time into two categories: RT after patients' exposure to etiologic factors, mentioned as primary prevention of HO (e.g., after trauma, burns); and RT after excision of established HO, mentioned as secondary prevention of HO. The measure of efficacy was the odds ratio for randomized

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