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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.

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 patients[15] and patients suffering isolated elbow dislocations[63] 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 Clearinghouse[42] and the National Institute for Health and Clinical Excellence[43] for published clinical guidelines related to RT for elbow HO. Furthermore, ClinicalTrials.gov[13] 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 clinical trials, case-control studies, and cohort studies; in case series and case report studies, the measure of efficacy was the number of patients without any evidence of new HO during the last follow-up.

Statistical analysis

We used the χ^2 test to compare the difference in the efficacy of RT administered as a measure of primary and secondary prevention and the difference in the efficacy of RT and the combination of RT with NSAIDs. For the secondary prevention of HO, we also compared the efficacy of preoperative and postoperative RT using Fisher's exact test. The statistical significance threshold was .05. *P* values are two-tailed. Statistical analysis was performed with SPSS 10.0 (Chicago, IL, USA).

Results

Literature search

The literature search retrieved 97 studies, and a hand search provided one more study. After duplicates were removed, 61 studies were examined according to eligibility criteria. Finally, our comprehensive literature search retrieved 27 published reports that met the inclusion criteria (Fig. 1); 1 represented a randomized clinical trial (level of evidence II), 1 was a case-control study (level of evidence III), and the remaining 25 were case reports or case series (level of evidence IV). In 3 studies,[47,49,65] the full text paper could not be obtained, and the data were retrieved by the study of Strauss et al.[60] There were no clinical guidelines available. The paucity of the retrieved evidence did not allow a high-quality quantitative synthesis. Details of available case reports and case series are presented in Tables I and II. Search of ClinicalTrials.gov and SIGLE did not provide any other completed or incomplete study on the same topic.

Randomized evidence (level II)

Hamid et al,[24] in an open-label study, randomized 48 patients to either RT (n = 22) or no intervention. Three patients were lost to follow-up, and the analysis included 24 patients from the RT group and 21 patients from the control group. Patients included in this study suffered from an intra-articular distal humeral fracture or a fracture-dislocation of the elbow with proximal radial or ulnar fractures. The RT group received 7.0 Gy postoperatively. The study was terminated before completion because of an unacceptably high number of adverse events reported in the treatment group. In total, 9 elbows presented nonunion, of which 8 (38%) were in the treatment group and 1 (4%) in the control group. The RT group had a significantly higher nonunion rate ($P = .007$). There were no statistically significant differences between the 2 groups for nonunion risk factors, such as age, sex, tobacco use, fracture classification, open or closed injury, or time to surgery. Moreover, the authors stated that the conclusions drawn from this study could be considerably affected by the small sample size.

Case-control study (level of evidence III)

Cypriano et al[11] conducted a small observational study on 17 elbows/patients with neurogenic HO undergoing HO surgical excision. In the control group of 12 patients with elbow HO, no RT was given, whereas RT of 7.0 Gy was given postoperatively in the treatment group of 5 patients with risk factors for HO recurrence. Detailed baseline characteristics and study results are not provided separately for the patients with HO of the elbow. The average range of motion for flexion-extension in the treatment group was 4° preoperatively, 132° intraoperatively, and 92° postoperatively. The average range of motion for flexion-extension in the control group was 66°, 150°, and 140° preoperatively, intraoperatively, and postoperatively, respectively. Patients in the treatment group lost an average of 40° of range of motion at the elbow, whereas patients in the control group lost an average range of motion of 10°. The rate of HO recurrence (15%) was considerably high in the high-risk treatment group compared with the control group (5%) despite the RT provided. Therefore, the authors claimed that the dose of 7.0 Gy should not be recommended for the use of RT as a postoperative preventive intervention for the recurrence of neurogenic HO. Finally, given the recurrence rate of 5% in the relatively low risk patients with neurogenic HO who did not receive RT prophylaxis, the authors raise the issue of whether these patients would have benefited from RT. Nevertheless, the conclusions drawn from this study could be considerably affected by the small sample size and the potential of confounding by indication bias since no high-risk patients were included in the ''control'' group.

Case series and case reports (level of evidence IV)

Our search identified 25 case series and case reports on RT for HO of the elbow published from 1992 to 2011 (Tables I and II). These studies included 258 patients (261 elbows), with the largest series[60] including 44 patients. The etiology of HO was local trauma (elbow fracture, elbow dislocation, or combination) in most of the studies (236 patients). Neurogenic cause of HO (spinal cord injury or traumatic brain injury) was reported for 6 elbows/patients; 1 patient developed HO of unknown etiology. In 11 patients, HO developed after biceps tendon repair or after transplantation (iatrogenic); in 9 patients (12 elbows), the etiology of HO was burn injury or equivalent (toxic epidermal necrolysis) to it. In 57 cases, RT was used prophylactically in patients at risk for development of HO; in 204 elbows (in 201 patients), RT was used as an ''adjuvant'' to surgical resection of HO. Also, in 8 studies (76 patients), NSAIDs were coadministered; and in 14 studies (95 patients), formal physiotherapy was used during inpatient rehabilitation, aiming for a more

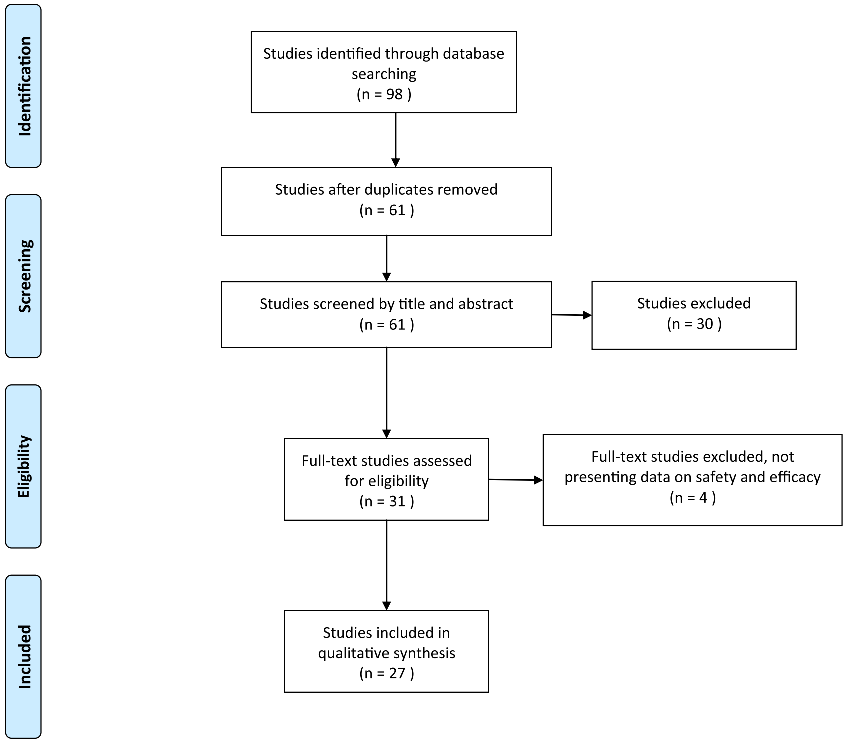

Figure 1 PRISMA flow diagram of literature search.

efficient improvement of the elbow's functionality. The described patients were followed up from 1 month to 5 years.

Most cases were reported to have a favorable outcome (212 of the 258 patients). Treatment failure expressed as occurrence or recurrence of HO during follow-up was reported for 42 patients in total. Among the 57 cases at risk in which RT was used for the prevention of HO occurrence, 12 (21%) patients developed HO, whereas HO recurred in another 30 (15%) patients among the 201 patients who received RT as adjuvant to HO surgical excision. In total, 4 patients from the secondary HO prevention group were reported to have experienced adverse events (1 patient needed manipulation because of ankylosis, 1 patient suffered ruptured triceps in rehabilitation, and 2 patients exhibited transient ulnar nerve paresthesia) of treatment, but no complication directly related to irradiation was reported.

Quantitative synthesis of case series and case reports

Regarding the use of RT for primary and secondary prevention, the 2 groups did not present statistically significant difference in the efficacy (on the basis of the number of treatment failures) of RT ($P = .258$). Furthermore, the difference in the efficacy of RT administered preoperatively and postoperatively was not statistically significant ($P = .496$). RT was more effective as a preventive measure for recurrence of HO than the combination of RT with NSAIDs ($P = .0009$). The data used for statistical analysis are presented in Table III.

Discussion

The available case series and case studies claimed that RT was an effective and safe intervention for prevention of HO after surgery without any complications. Our study did not recognize any statistically significant difference in the efficacy of RT for primary and secondary prevention and indicated that preoperative RT is comparably efficient to postoperative RT for prevention of elbow HO. The nearly complete absence of complications caused by RT, especially in cases treated prophylactically after osteosynthesis for elbow fractures, could possibly be attributed to the selective reporting of cases inherent in the case reports' literature and to the short-term follow-up. However, the only randomized controlled trial published so far, despite its small sample size, strongly supported that there are doubts about the safety of radiation.

The efficacy of preoperative and postoperative RT for prevention of HO has been studied in animal models and in human patients. A study conducted in rats indicated that preoperative RT had an efficacy comparable to postoperative RT.[31] A study of 20 patients mentioned that preoperative RT and postoperative RT are equally efficient for the prevention of recurrence of HO of the elbow.[25] Also, 2 randomized clinical trials concluded that preoperative RT is comparably effective to postoperative RT for the prevention of recurrence of HO of the hip after hip surgery.[23,55]

Table I Available case reports and case series of radiotherapy for primary prevention of elbow heterotopic ossification (in high-risk patients or with early signs of heterotopic ossification)

First author	Year	Total N of patients	Total N of elbows	Age of patients (mean/ median) in years	Etiology of HO	Follow-up (mean/ median)	Time of radiation‡	Total radiation dose (Gy)	Fractions	NSAIDs	PT	Result excellent/ good (N of patients)	Failure of HO prevention (N of patients)
Andreopoulos[2]	1998	13	13	43	Traumatic	Not stated	Postoperative	9.0	3	Not stated	Not stated	10	3
* Ellerin[19]	1999	1	1	69	Traumatic	21 months	Postoperative	6.0	1	None	Yes	1	0
* Heyd[25]	2009	5	5	47.4	Traumatic	43.3 months	Preoperative	7.0	1	None	Not stated	5	0
Holmenschlager[27]	2002	13	13	50.3	Traumatic	19 months	Postoperative	7.0	1	Indomethacin	Not stated	13	0
* Lo[35]	1996	1	1	63	Traumatic	2 months	Postoperative	6.0	1	Not stated	Yes	0	1
†Rubenstein[49]	1992	1	1	Unclear	Traumatic	5 months	Postoperative	10.0	5	Not stated	Not stated	1	0
Sautter-Bihl[50]	2001	1	1	Not stated	Neurogenic	Not stated	Unclear	10.0	4	Not stated	Yes	Unclear	Unclear
Stein[58]	2003	11	11	51	Traumatic	12 months	Postoperative	7.0	1	None	Not stated	8	3
* Strauss[60]	2011	11	11	Not stated	Traumatic	136 days	Postoperative	5.0-7.0	1	Indomethacin	Yes	6	5

HO, heterotopic ossification; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *PT,* physiotherapy.

* Study also includes other cases with radiation therapy used for secondary prevention of elbow heterotopic ossification.

† Data recorded through Strauss.[60]

‡ The terms *preoperative* and *postoperative* refer to surgery on the elbow not related to excision of established heterotopic ossification.

Vavken et al[64] examined the efficacy and safety of RT for prevention of HO of the hip. This systematic review, which provided a number of level I studies, indicated that there is not a statistically or clinically significant difference in the effect of NSAIDs or RT for the prevention of HO. The risk ratio was similar for the comparison between the 2 interventions of HO prevention. However, the cost of RT was higher compared with treatment with indomethacin.[59] Therefore, RT was not recommended as the primary mode for prevention of hip HO. Regarding the safety of RT and indomethacin, in trauma patients with multiple fractures, RT for prophylaxis reduces the risk of bone nonunion associated with indomethacin.[8] However, the elbow joint is a different anatomical site with more complex kinematics, less soft tissue coverage, less HO incidence, and younger population HO prevalence compared with the hip joint. Therefore, even if irradiation was not recommended as a primary intervention for prevention of hip HO, our systematic review attempts to assess the efficacy and safety of RT for elbow HO.

A recently published systematic review of HO treatment within the traumatic brain and spinal cord–injured population presented only level IV evidence on RT as a measure for HO prevention.[3] In another systematic review of the therapeutic interventions for HO after spinal cord injury, there was only level IV evidence available that RT was effective in limiting primary and secondary progression of HO.[62] Furthermore, NSAIDs were also found to be effective for prevention, whereas bisphosphonates limited the progression of HO after spinal cord injury.[62] In a comparison of indomethacin versus RT for the prevention of HO after acetabular fractures, the systematic appraisal of available evidence indicated that the incidence of HO was lower in patients treated with RT rather than with indomethacin.[7] In our systematic review, the use of RT only for elbow HO prevention was found to be more effective than the combination of RT with NSAIDs.

In the studies included, the most frequently used type of RT was a single dose of irradiation with 7.0 Gy, and this has not been related to complications except in cases after osteosynthesis, in which concerns of fracture union prevention by RT were raised. Adverse effects of RT depend on the radiosensitivity of the body tissues treated, the volume of normal tissue irradiated, the total dose, and the rate of dose accumulation.[16] The side effects are most evident in rapidly proliferating tissues, such as skin, mucosa, and bone marrow.[16] In the case of the elbow, the most vulnerable and the most affected tissue is the skin. In skin, the radiation could cause wound healing problems, which may lead to delayed or nonhealing ulceration, superimposed infection, carcinogenesis, and acosmesis.[16] Furthermore, the potential long-term risk of a radiation-induced malignant neoplasm should not be neglected, especially in young patients.[45,51]

Table II Available case reports and case series of radiotherapy for secondary prophylaxis of elbow heterotopic ossification (after surgical excision of heterotopic ossification)

First author	Year	N of patients	N of elbows	Age of patients (mean/median) in years	Etiology of HO	Follow-up (mean/median)	Time of radiation	Total radiation dose (Gy)	Fractions	NSAIDs	PT	Result excellent/good (N of patients)	Patients with recurrence of HO
Agrawal[1]	2005	1	1	38	Iatrogenic (DBTR)	3 months	Preoperative	7.0	1	Indomethacin	Yes	1	0
Bimmel[6]	2006	1	1	52	Traumatic	3 years	Preoperative	7.0	1	Not stated	Yes	1	0
Ebinger[17]	2002	14	14	38.5	Traumatic	5 years	Postoperative	7.0	1	Diclofenac	Yes	14	0
*Ellerin[19]	1999	3	3	46.7	Traumatic	15.1 months	Postoperative	7.0	1	Yes (1) No (2)	Yes	1	2
Gibson[22]	1997	1	2	49	Thermal (TEN)	Not stated	Postoperative	Not stated	Not stated	Not stated	Yes	1	0
*Heyd[25]	2009	15	15	47.4	Traumatic	43.3 months	Preoperative (8) Postoperative (7)	7.0	1	None	Not stated	13	2
Heyd[26]	2001	9	9	48.2	Neurogenic (1) Traumatic (7) Unknown (1)	7.7 months	Preoperative (4) Postoperative (5)	6.0 (3) 7.0 (1) 5.0 (5)	1 (4) 2 (5)	None	Not stated	9	0
Hughes[28]	2010	1	1	57	Traumatic	18 months	Preoperative	7.0	1	None	Yes	0	1
*Lo[35]	1996	1	1	71	Traumatic	8 months	Postoperative	7.0	1	Not stated	Yes	1	0
Maender[36]	2010	8	10	42	Thermal	5 years	Perioperative	7.0	1	None	None	7	1
McAuliffe[38]	1997	8	8	42	Neurogenic (5) Traumatic (3)	46 months	Postoperative	5.0	5	Yes (2)	None	8	0
Mishra[40]	2011	19	19	47	Traumatic	16 months	Postoperative	7.0	1	None	Not stated	17	2
Munin[41]	1995	2	2	40	Iatrogenic (transplantation)	Lost to follow-up	Postoperative	7.0 (1) 1.25 (1)	1	None	Yes (1) No (1)	Lost to follow-up	Lost to follow-up
Park[46]	2004	18	18	32.7	Traumatic	22.5 months	Postoperative	7.0	1	None	Yes	16	2
†Poggi[47]	1999	3	3	Unclear	Traumatic	10.5 months	Postoperative	7.0-8.0	1	None	None	3	0
Robinson[48]	2010	36	36	42	Traumatic	8.7 months	Postoperative	6.0 (2) 7.0 (34)	1	Not stated	None	33	3
Schaeffer[52]	1995	1	1	40	Traumatic	1 month	No surgery‡	7.0	1	Yes	Not stated	1	0
Sotereanos[57]	2004	8	8	38	Iatrogenic (DBTR)	27 months	Postoperative	7.0	2	None	Yes	8	0
*Strauss[60]	2011	33	33	Not stated	Traumatic	136 days	Postoperative	5.0-7.0	1	Indomethacin	Yes	17	16
†Wolfson[65]	1993	19	19	Not stated	Traumatic	21 months	Postoperative	10.0	5	Unclear	Not stated	18	1

DBTR, distal biceps tendon repair; *HO*, heterotopic ossification; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *PT*, physiotherapy; *TEN*, toxic epidermal necrolysis.

* Study also includes other cases with radiation therapy used for primary prevention of elbow heterotopic ossification.

† Data recorded through Strauss.[60]

‡ Radiation therapy administered to reduce the symptoms derived from established HO.

Table III Comparisons of radiation therapy efficacy

	HO +	HO −	*P* value
Primary prevention (prevention of occurrence)	12	44	.258*
Secondary prevention (prevention of recurrence)	30	169	
Preoperative RT	1	6	.496†
Postoperative RT	26	142	
RT only	13	93	.009‡
RT plus NSAIDs	21	55	

Comparisons of radiation therapy (RT) efficacy are expressed as number of patients receiving RT with or without evidence of heterotopic ossification (HO) in last follow-up with (1) type of HO prevention (primary versus secondary), (2) timing (preoperative versus preoperative) of RT administration for cases of secondary prevention, and (3) contemporary administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or not. The second comparison included only patients of secondary HO prevention.

* Studies excluded: Munin,[41] Sauter-Bihl.[50]

† Studies excluded: Maender,[36] Schaeffer,[52] Heyd,[25] Munin.[41]

‡ Studies excluded: Bimmel,[6] Gibson,[22] Lo,[35] Robinson,[48] Wolfson.[65]

Phantom measurements of the gonadal dose for single-field irradiation of the elbow have revealed that the treatment is not associated with gonadal damage.[33] The ovarian dose was 0.15% and the testicular dose 0.09% of the prescribed tumor dose. The estimated lifetime risk for induction of leukemia or solid malignant neoplasms is approximately 1% and therefore suggested to be comparable to the risk associated with diagnostic radiologic procedures.[44]

Limitations of study

Although the difference in HO occurrence and recurrence observed between the two respective groups of case series patients (Tables I and II) receiving RT is not statistically significant, we would be reluctant to assess the clinical importance of this observation because we compared two diverse groups of patients scattered both chronologically and geographically. Also, the quantitative analysis was based on small sample size derived from studies of low methodological quality. Given our current knowledge that the only randomized controlled trial in the field was truncated because of safety reasons, it is interesting that adverse events were scarcely reported in the assessed case series and case reports.

Conclusions

Our study incorporating all the published evidence reveals a knowledge gap regarding the use of RT for the prevention of HO of the elbow. Most of the currently available studies are of low methodological quality, and the only available randomized clinical trial was terminated early for reasons of safety. The paucity of the retrieved evidence did not allow a quantitative synthesis. In addition, the mean follow-up time in the studies was short, and as a consequence, they could not determine the risk of cancer in patients with RT. Our study indicates that in the medical literature, there are no high-quality, consistent research findings on the safety and efficacy of RT for HO of the elbow. Thus, RT should not be used as a first-line intervention for prevention of elbow HO.

Future research should place emphasis on the design and implementation of randomized controlled clinical trials, investigating the impact of different doses of irradiation regimens, the time of irradiation, and the number of irradiation fragments on presentation of complications and on occurrence or recurrence of HO.

Disclaimer

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References

1. Agrawal V, Stinson MJ. Case report: heterotopic ossification after repair of distal biceps tendon rupture utilizing a single-incision Endobutton technique. J Shoulder Elbow Surg 2005;14:107-9. http://dx.doi.org/10.1016/j.jse.2004.03.014
2. Andreopoulos D, Müller C, Schleicher UM, Paar O, Ammon J. Fraktionierte post-OP Radiotherapie (RT) zur Prophylaxe von heterotopen Ossifikationen (HO) nach Trümmerfrakturen (TF) [abstract]. Strahlenther Onkol 1998;174:129.
3. Aubut JL, Mehta S, Cullen N, Teasell RW. A comparison of heterotopic ossification treatment within the traumatic brain and spinal cord injured population: an evidence based systematic review. NeuroRehabilitation 2011;28:151-60. http://dx.doi.org/10.3233/NRE-2011-0643
4. Balboni TA, Gobezie R, Mamon HJ. Heterotopic ossification: pathophysiology, clinical features, and the role of radiotherapy for prophylaxis. Int J Radiat Oncol Biol Phys 2006;65:1289-99. http://dx.doi.org/10.1016/j.ijrobp.2006.03.053
5. Bauer AS, Lawson BK, Bliss RL, Dyer GSM. Risk factors for post-traumatic heterotopic ossification of the elbow: case-control study. J Hand Surg Am 2012;37:1422-9.e1-6. http://dx.doi.org/10.1016/j.jhsa.2012.03.013
6. Bimmel R, van Riet RP, Sys J. Heterotopic ossification causing proximal radioulnar synostosis after insertion of a radial head prosthesis. J Hand Surg Br 2006;31:383-4. http://dx.doi.org/10.1016/j.jhsb.2006.04.012
7. Blokhuis TJ, Frölke JPM. Is radiation superior to indomethacin to prevent heterotopic ossification in acetabular fractures?: a systematic

review. Clin Orthop Relat Res 2009;467:526-30. http://dx.doi.org/10.1007/s11999-008-0532-9
8. Burd TA, Hughes MS, Anglen JO. Heterotopic ossification prophylaxis with indomethacin increases the risk of long-bone nonunion. J Bone Joint Surg Br 2003;85:700-5. http://dx.doi.org/10.1302/0301-620X.85B5.13970
9. Cassar-Pullicino VN, McClelland M, Badwan DA, McCall IW, Pringle RG, el Masry W. Sonographic diagnosis of heterotopic bone formation in spinal injury patients. Paraplegia 1993;31:40-50. http://dx.doi.org/10.1038/sc.1993.7
10. Chen JB, Yu Y, Yang JL, Morgan DAF, Walsh WR. BMP-7 and CBFA1 in allograft bone in vivo bone formation and the influence of gamma-irradiation. J Biomed Mater Res A 2007;80:435-43. http://dx.doi.org/10.1002/jbm.a.30913
11. Cipriano C, Pill SG, Rosenstock J, Keenan MA. Radiation therapy for preventing recurrence of neurogenic heterotopic ossification. Orthopedics 2009:32. http://dx.doi.org/10.3928/01477447-20090728-33
12. Cipriano CA, Pill SG, Keenan MA. Heterotopic ossification following traumatic brain injury and spinal cord injury. J Am Acad Orthop Surg 2009;17:689-97.
13. Clinical Trials (2012). Available at: http://clinicaltrials.gov.
14. DeLee J, Ferrari A, Charnley J. Ectopic bone formation following low friction arthroplasty of the hip. Clin Orthop Relat Res 1976;121:53-9.
15. Dias DA. Heterotopic para-articular ossification of the elbow with soft tissue contracture in burns. Burns Incl Therm Inj 1982;9:128-34. http://dx.doi.org/10.1016/0305-4179(82)90061-4
16. Dormand E-L, Banwell PE, Goodacre TEE. Radiotherapy and wound healing. Int Wound J 2005;2:112-27. http://dx.doi.org/10.1111/j.1742-4801.2005.00079.x
17. Ebinger T, Schulte M, Mentzel M, Kinzl L. Frühzeitige Exzision periartikulärer Ossifikationen des Ellbogengelenkes. Aktuelle Traumatol 2002;32:153-6. http://dx.doi.org/10.1055/s-2002-33437
18. Eggli S, Woo A. Risk factors for heterotopic ossification in total hip arthroplasty. Arch Orthop Trauma Surg 2001;121:531-5. http://dx.doi.org/10.1007/s004020100287
19. Ellerin BE, Helfet D, Parikh S, Hotchkiss RN, Levin N, Nisce L, et al. Current therapy in the management of heterotopic ossification of the elbow: a review with case studies. Am J Phys Med Rehabil 1999;78:259-71. http://dx.doi.org/10.1097/00002060-199905000-00016
20. Garland DE. A clinical perspective on common forms of acquired heterotopic ossification. Clin Orthop Relat Res 1991:13-29.
21. Garland DE, O'Hollaren RM. Fractures and dislocations about the elbow in the head-injured adult. Clin Orthop Relat Res 1982;168:38-41.
22. Gibson CJ, Poduri KR. Heterotopic ossification as a complication of toxic epidermal necrolysis. Arch Phys Med Rehabil 1997;78:774-6. http://dx.doi.org/10.1016/S0003-9993(97)90088-5
23. Gregoritch SJ, Chadha M, Pelligrini VD, Rubin P, Kantorowitz DA. Randomized trial comparing preoperative versus postoperative irradiation for prevention of heterotopic ossification following prosthetic total hip replacement: preliminary results. Int J Radiat Oncol Biol Phys 1994;30:55-62. http://dx.doi.org/10.1016/0360-3016(94)90519-3
24. Hamid N, Ashraf N, Bosse MJ, Connor PM, Kellam JF, Sims SH, et al. Radiation therapy for heterotopic ossification prophylaxis acutely after elbow trauma: a prospective randomized study. J Bone Joint Surg Am 2010;92:2032-8. http://dx.doi.org/10.2106/JBJS.I.01435
25. Heyd R, Buhleier T, Zamboglou N. Radiation therapy for prevention of heterotopic ossification about the elbow. Strahlenther Onkol 2009;185:506-11. http://dx.doi.org/10.1007/s00066-009-1968-x
26. Heyd R, Strassmann G, Schopohl B, Zamboglou N. Radiation therapy for the prevention of heterotopic ossification at the elbow. J Bone Joint Surg Br 2001;83:332-4. http://dx.doi.org/10.1302/0301-620X.83B3.11428
27. Holmenschlager F, Halm JP, Winckler S. [Fresh fractures of the radial head: results with the Judet prosthesis]. Rev Chir Orthop Reparatrice Appar Mot 2002;88:387-97.
28. Hughes SC, Hildebrand KA. Heterotopic ossification—a complication of elbow arthroscopy: a case report. J Shoulder Elbow Surg 2010;19:e1-5. http://dx.doi.org/10.1016/j.jse.2009.04.015
29. Ilahi OA, Strausser DW, Gabel GT. Post-traumatic heterotopic ossification about the elbow. Orthopedics 1998;21:265-8.
30. Isaacson BM, Brown AA, Brunker LB, Higgins TF, Bloebaum RD. Clarifying the structure and bone mineral content of heterotopic ossification. J Surg Res 2011;167:e163-70. http://dx.doi.org/10.1016/j.jss.2010.12.047
31. Kantorowitz DA, Miller GJ, Ferrara JA, Ibbott GS, Fisher R, Ahrens CR. Preoperative versus postoperative irradiation in the prophylaxis of heterotopic bone formation in rats. Int J Radiat Oncol Biol Phys 1990;19:1431-8. http://dx.doi.org/10.1016/0360-3016(90)90355-N
32. Kaplan FS, Glaser DL, Hebela N, Shore EM. Heterotopic ossification. J Am Acad Orthop Surg 2004;12:116-25.
33. Kokona G, Mazonakis M, Varveris H, Liraraki E, Damilakis J. Treatment of benign diseases with megavoltage X-ray beams: is there a risk for gonadal damage? Clin Oncol (R Coll Radiol) 2006;18:658-62, http://dx.doi.org/10.1016/j.clon.2006.07.013
34. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100. http://dx.doi.org/10.1371/journal.pmed.1000100
35. Lo TC, Pfeifer BA, Smiley PM, Gumley GJ. Case report: radiation prevention of heterotopic ossification after bone and joint surgery in sites other than hips. Br J Radiol 1996;69:673-7. http://dx.doi.org/10.1259/0007-1285-69-823-673
36. Maender C, Sahajpal D, Wright TW. Treatment of heterotopic ossification of the elbow following burn injury: recommendations for surgical excision and perioperative prophylaxis using radiation therapy. J Shoulder Elbow Surg 2010;19:1269-75. http://dx.doi.org/10.1016/j.jse.2010.05.029
37. Mavrogenis AF, Soucacos PN, Papagelopoulos PJ. Heterotopic ossification revisited. Orthopedics 2011;34:177. http://dx.doi.org/10.3928/01477447-20110124-08
38. McAuliffe JA, Wolfson AH. Early excision of heterotopic ossification about the elbow followed by radiation therapy. J Bone Joint Surg Am 1997;79:749-55.
39. Mikíc ZD, Vukadinovíc SM. Late results in fractures of the radial head treated by excision. Clin Orthop Relat Res 1983;181:220-8.
40. Mishra MV, Austin L, Parvizi J, Ramsey M, Showalter TN. Safety and efficacy of radiation therapy as secondary prophylaxis for heterotopic ossification of non-hip joints. J Med Imaging Radiat Oncol 2011;55:333-6. http://dx.doi.org/10.1111/j.1754-9485.2011.02275.x
41. Munin MC, Balu G, Sotereanos DG. Elbow complications after organ transplantation. Case reports. Am J Phys Med Rehabil 1995;74:67-72. http://dx.doi.org/10.1097/00002060-199501000-00012
42. National Guideline Clearinghouse (2012). Available at: http://www.guideline.gov/index.aspx.
43. National Institute for Health and Clinical Excellence (2012). Available: http://www.nice.org.uk/.
44. Oertel S, Schneider U, Keel M, Lütolf UM, Bosshard G. Prophylaxis of heterotopic ossification in patients sedated after polytrauma: medical and ethical considerations. Strahlenther Onkol 2008;184:212-7. http://dx.doi.org/10.1007/s00066-008-1757-y
45. Pakos EE, Stafilas KS, Politis AN, Tsekeris PG, Mitsionis G, Xenakis TA. Heterotopic ossification after total hip arthroplasty (THA) in congenital hip disease: comparison of two different prophylactic protocols. Clin Transl Oncol 2009;11:103-8. http://dx.doi.org/10.1007/s12094-009-0322-1
46. Park MJ, Kim HG, Lee JY. Surgical treatment of post-traumatic stiffness of the elbow. J Bone Joint Surg Br 2004;86:1158-62. http://dx.doi.org/10.1302/0301-620X.86B8.14962
47. Poggi MM, Thomas BE, Johnstone PA. Excision and radiotherapy for heterotopic ossification of the elbow. Orthopedics 1999;22:1059-61.

48. Robinson CG, Polster JM, Reddy CA, Lyons JA, Evans PJ, Lawton JN, et al. Postoperative single-fraction radiation for prevention of heterotopic ossification of the elbow. Int J Radiat Oncol Biol Phys 2010;77:1493-9. http://dx.doi.org/10.1016/j.ijrobp.2009.06.072
49. Rubenstein JH, Salenius SA, Blitzer PH, Katin MJ, Dosoretz DE. Prevention of heterotopic bone formation with low dose radiation therapy. J Fla Med Assoc 1992;79:828-32.
50. Sautter-Bihl ML, Hültenschmidt B, Liebermeister E, Nanassy A. Fractionated and single-dose radiotherapy for heterotopic bone formation in patients with spinal cord injury. A phase-I/II study. Strahlenther Onkol 2001;177:200-5. http://dx.doi.org/10.1007/PL00002399
51. Sautter-Bihl ML, Liebermeister E, Nanassy A. Radiotherapy as a local treatment option for heterotopic ossifications in patients with spinal cord injury. Spinal Cord 2000;38:33-6. http://dx.doi.org/10.1038/sj.sc.3100847
52. Schaeffer MA, Sosner J. Heterotopic ossification: treatment of established bone with radiation therapy. Arch Phys Med Rehabil 1995;76:284-6. http://dx.doi.org/10.1016/S0003-9993(95)80617-2
53. Seegenschmiedt MH, Katalinic A, Makoski H, Haase W, Gademann G, Hassenstein E. Radiation therapy for benign diseases: patterns of care study in Germany. Int J Radiat Oncol Biol Phys 2000;47:195-202. http://dx.doi.org/10.1016/S0360-3016(99)00537-4
54. Seegenschmiedt MH, Keilholz L, Martus P, Goldmann A, Wölfel R, Henning F, et al. Prevention of heterotopic ossification about the hip: final results of two randomized trials in 410 patients using either preoperative or postoperative radiation therapy. Int J Radiat Oncol Biol Phys 1997;39:161-71. http://dx.doi.org/10.1016/S0360-3016(97)00285-X
55. Seegenschmiedt MH, Martus P, Goldmann AR, Wölfel R, Keilholz L, Sauer R. Preoperative versus postoperative radiotherapy for prevention of heterotopic ossification (HO): first results of a randomized trial in high-risk patients. Int J Radiat Oncol Biol Phys 1994;30:63-73. http://dx.doi.org/10.1016/0360-3016(94)90520-7
56. Shehab D, Elgazzar AH, Collier BD. Heterotopic ossification. J Nucl Med 2002;43:346-53.
57. Sotereanos DG, Sarris I, Chou KH. Radioulnar synostosis after the two-incision biceps repair: a standardized treatment protocol. J Shoulder Elbow Surg 2004;13:448-53. http://dx.doi.org/10.1016/S1058274604000758
58. Stein DA, Patel R, Egol KA, Kaplan FT, Tejwani NC, Koval KJ. Prevention of heterotopic ossification at the elbow following trauma using radiation therapy. Bull Hosp Jt Dis 2003;61:151-4.
59. Strauss JB, Chen SS, Shah AP, Coon AB, Dickler A. Cost of radiotherapy versus NSAID administration for prevention of heterotopic ossification after total hip arthroplasty. Int J Radiat Oncol Biol Phys 2008;71:1460-4. http://dx.doi.org/10.1016/j.ijrobp.2007.12.006
60. Strauss JB, Wysocki RW, Shah A, Chen SS, Shah AP, Abrams RA, et al. Radiation therapy for heterotopic ossification prophylaxis after high-risk elbow surgery. Am J Orthop (Belle Mead NJ) 2011;40:400-5.
61. System for Information on Grey Literature in Europe (SIGLE) (2012). Available at: http://www.opengrey.eu/.
62. Teasell RW, Mehta S, Aubut JL, Ashe MC, Sequeira K, Macaluso S, et al. A systematic review of the therapeutic interventions for heterotopic ossification after spinal cord injury. Spinal Cord 2010;48:512-21. http://dx.doi.org/10.1038/sc.2009.175
63. Thompson HC, Garcia A. Myositis ossificans: aftermath of elbow injuries. Clin Orthop Relat Res 1967;50:129-34.
64. Vavken P, Castellani L, Sculco TP. Prophylaxis of heterotopic ossification of the hip: systematic review and meta-analysis. Clin Orthop Relat Res 2009;467:3283-9. http://dx.doi.org/10.1007/s11999-009-0924-5
65. Wolfson AH, McAuliffe JA, Oulette EA. Role of postoperative radiation therapy of the elbow as prophylaxis against heterotopic reossification. Radiology 1993;189. 267-67.
66. Wright JG, Swiontkowski MF, Heckman JD. Introducing levels of evidence to the journal. J Bone Joint Surg Am 2003;85:1-3.