Radiotherapy and Oncology 113 (2014) 10–17

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

Radiotherapy for the prophylaxis of heterotopic ossification: A systematic review and meta-analysis of published data

Marko Popovic [a], Arnav Agarwal [a], Liying Zhang [a], Cheryl Yip [a], Hans J. Kreder [b], Markku T. Nousiainen [b], Richard Jenkinson [b], May Tsao [a], Henry Lam [a], Milica Milakovic [a], Erin Wong [a], Edward Chow [a,*]

[a] Rapid Response Radiotherapy Program, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto; and [b] Division of Orthopaedics, Sunnybrook Health Science Centre, Toronto, Canada

ARTICLE INFO

Article history:
Received 22 May 2014
Received in revised form 8 August 2014
Accepted 12 August 2014
Available online 11 September 2014

Keywords:
Radiotherapy
Dose fractionation
Heterotopic ossification
Orthopedic surgery

ABSTRACT

Introduction: Following surgery, the formation of heterotopic ossification (HTO) can limit mobility and impair quality of life. Radiotherapy has been proven to provide efficacious prophylaxis against HTO, especially in high-risk settings.
Purpose: The current review aims to determine the factors influencing HTO formation in patients receiving prophylactic radiotherapy.
Methods: A systematic search of the literature was conducted on Ovid Medline, Embase and the Cochrane Central Register of Controlled Trials. Studies were included if they reported the percentage of sites developing heterotopic ossification after receiving a specified dose of prophylactic radiotherapy. Weighted linear regression analysis was conducted for continuous or categorical predictors.
Results: Extracted from 61 articles, a total of 5464 treatment sites were included, spanning 85 separate study arms. Most sites were from the hip (97.7%), from United States patients (55.2%), and had radiation prescribed postoperatively (61.6%) at a dose of 700 cGy (61.0%). After adjusting for radiation site, there was no statistically significant relationship between the percentage of sites developing HTO and radiation dose ($p = 0.1$) or whether radiation was administered preoperatively or postoperatively ($p = 0.1$). Sites with previous HTO formation were more likely to develop recurrent HTO than those without previous HTO formation ($p = 0.04$). There was a statistically significant negative relationship between the HTO development and the cohort mean year of treatment ($p = 0.007$).
Conclusion: Decreases in rates of HTO over time in this patient population may be a function of more efficacious surgical regimens and prophylactic radiotherapy.

Heterotopic ossification (HTO) is characterized by the formation of ectopic bone within muscles, connective tissue, or nerves [1]. Although HTO can be an indolent condition, more severe cases can be painful, inflamed, or impair a patient's mobility [2]. HTO formation has been shown to be induced by bone morphogenic protein 2 (BMP2) in several primary cancer sites [3]. Currently, it is postulated that BMP2 interacts with the Wnt/β-catenin signaling pathway in osteoblasts to lead to osteoplastic differentiation and bone formation [4]. Heterotopic ossification may be caused by surgical intervention or trauma. Common risk factors for heterotopic ossification include diffuse idiopathic skeletal hyperostosis, ankylosing spondylitis, osteoarthritis, and previous heterotopic ossification formation.

Literature examining HTO incidence following surgery has nearly exclusively focused on hip operations. For example, following total hip arthroplasty, total incidence of HTO approximates 60% without prophylaxis [5]. In the hip setting, a classification system by Brooker et al. [6] is commonly used to categorize the degree of HTO. In this classification mechanism, five classifications are used: grade 0 – no soft tissue calcification; grade 1 – separate small foci of ossification about the hip; grade 2 – ossification projecting from the proximal femur or pelvis with at least 1 cm between opposing bone surfaces; grade 4 – ossification completely bridging the proximal femur and pelvis. Nonetheless, reports of HTO have included other sites, such as the knee, elbow, and temporomandibular joint (TMJ).

In the surgical setting, prophylaxis for HTO is regularly indicated due to the considerable risk of functional impairment. The two most common preventative modalities are radiotherapy and indomethacin, a non-steroidal anti-inflammatory drug (NSAID). In a meta-analysis of 1295 patients receiving surgery to the hip

* Corresponding author. Address: Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, ON M4N3M5, Canada.
E-mail address: Edward.Chow@sunnybrook.ca (E. Chow).

http://dx.doi.org/10.1016/j.radonc.2014.08.025
0167-8140/

and randomized to either indomethacin or radiotherapy for prophylaxis against HTO, Vavken et al. demonstrated no statistically or clinically significant differences between arms (test for overall effectiveness: risk ratio (RR) = 1.2; 95% CI = 0.8–1.8; $p = 0.48$) [7]. Both treatment modalities carry the risk of particular side effects; for instance, indomethacin can cause peripheral edema and hypertension, whereas radiotherapy may induce carcinogenesis. Vavken et al. showed that no statistically significant difference in treatment-associated side effects between radiotherapy and indomethacin existed (RR = 0.79; 95% CI = 0.5–1.4; $p = 0.4$) [7].

For prevention of HTO, radiotherapy prevents bone repair and consequently prevents the abnormal formation of bone. Specifically, radiotherapy inhibits the differentiation of mesenchymal stem cells to osteogenic pathways [8]. Numerous radiotherapy prescription parameters, such as fractionation schedule, timing, and dose are currently commonplace in the literature. Although a multitude of prospective and retrospective cohorts, case series, and randomized controlled trials have described the radiotherapy prescription patterns in HTO, thus far there has been no formal synthesis of the vast quantity of data in a meta-analysis. Further, no evidence-based guidelines have been devised to aid the clinician in decision-making for HTO prophylaxis with radiotherapy.

The following systematic review and meta-analysis aims to explore pertinent issues to the prescribing radiation oncologist in the prophylaxis of HTO: (1) what dose of radiotherapy is optimal? (2) Should radiotherapy be prescribed postoperatively or preoperatively? (3) What does the evidence suggest about prophylactic radiotherapy for recurrent versus new HTO? and (4) Is there a difference in outcomes between radiotherapy prescribed to the hip, elbow, knee and other sites?

Methods

Literature search

A literature search on Ovid Medline and Ovid OldMedline (1946 to June Week 1 2013), Embase and Embase Classic (1947 to 2013 Week 24), and the Cochrane Central Register of Controlled Trials (May 2013) was performed. The search term "heterotopic ossification" was combined in various methods with the terms "radiotherapy", "radiation therapy", "radiation prophylaxis", and "cancer radiotherapy" to elicit relevant literature. Search results were limited to English language human trials.

Inclusion/exclusion criteria

Large (i.e. >5 site) case series, prospective and retrospective cohort studies and randomized controlled trials were included. For inclusion, relevant HTO outcomes needed to be stratified by dose of radiotherapy and radiation treatment site. Cohorts were only included if the average or median length of radiographic follow-up exceeded 8 weeks. This approach is in line with other authors, who have reported that 89% of HTO formation can be recognized on radiography at 3 weeks [2], and all ossification may be appreciated 8 weeks postoperatively [9].

Data collection

In data collection, each included cohort was stratified by radiation dose. Collected data included: type of study, year of treatment, treatment center location, author-reported categorical risk of developing HTO, number of sites undergoing prophylactic radiotherapy, type of site, type of orthopedic intervention, radiation dose, formation of HTO prior to irradiation in the current study protocol, time of radiotherapy (postoperative versus preoperative), percentage of sites developing HTO, Brooker grade 1 or 2 HTO, and Brooker grade 3 or 4 HTO before and adequately after radiotherapy.

Statistical analysis

Demographic information was summarized as a proportion for categorical variables, and as a weighted mean (with a corresponding standard deviation (SD), 95% confidence interval (CI)), median, and range for continuous variables. To compare primary outcomes in patients with different socio-demographic and clinical parameters from different study arms, weighted linear regression analysis was conducted for continuous or categorical predictors. Procedure General Linear Models (GLMs) were performed for the unbalanced data, with the total number of treatment sites from each study considered as a weighted variable.

The weighted mean was defined as $\bar{x}_w = \frac{\Sigma_i w_i x_i}{\Sigma_i w_i}$, while the weighted variance was defined as $S_w^2 = \frac{1}{d}\Sigma_i w_i (x_i - \bar{x}_w)^2$, where w_i is the weight for the ith study, x_i is the ith variable value, and the divisor d is $n-1$. The weighted variance is a measure of variability, and it is the sum of the weighted squared distance of data value from the mean divided by the variance divisor which is defined to be $n-1$.

Three primary outcomes were considered in the study: the percentage of sites developing any type of HTO, the percentage of sites developing Brooker grades 1 or 2 HTO, and the percentage of sites developing Brooker grades 3 or 4 HTO. Weighted Pearson correlations (r) between the mean year treated and the three primary outcomes were also calculated and presented on bubble charts. In the bubble charts, the size of the bubbles was related to the number of weighted sites, with large bubbles representing a larger number of sites. A weighted trend line was added based on the weighted linear regression model for each outcome.

A p-value of less than 0.05 was considered to be statistically significant. All analyses were conducted by Statistical Analysis of Software (SAS version 9.3 for Windows).

Results

From a literature search of 528 articles, 407 articles were excluded in title and abstract screening (Fig. 1). Of 121 articles included in full-text screening, 60 were deemed ineligible; thus, a total of 61 studies [9–69] spanning 85 separate study arms were included (Fig. 1). In total, 5464 treatment sites were included.

In terms of demographic characteristics, 3015 treatment sites (55.18%) came from patients treated in the United States, while 1762 sites were treated in Germany (32.25%) (Table 1). As determined by self-reported criteria, 1529 treatment sites (27.98%) were deemed to be at a high risk of developing future HTO. Radiation was prescribed mostly to the hip ($n = 5336$; 97.66%); other treatment sites included the elbow [21,26,38,40–41,56], temporomandibular joint [18,51], and knee [41,62]. A few studies reported on whether their patient sample had any past history of HTO; of these, 280 treatment sites (5.12%) were being treated for solely recurrent HTO, whereas 176 sites (3.22%) did not have a past history of HTO [11,17,23–24,36,56,62]. In terms of radiation parameters, radiation was prescribed mostly postoperatively ($n = 3364$; 61.57%) and over 60% at a dose of 700 cGy ($n = 3331$). Nonetheless, there existed a great variability in the dose prescription of radiotherapy (mean ± SD: 816.2 ± 2421.1 cGy; median total dose (range): 700 (500–2000); range of dose per fraction: 200–800). The median year of treatment was 1999, which ranged from 1974 to 2007.

Regarding the distributions of primary outcomes, the percentage of sites developing HTO after any type of radiotherapy was, on average, 24.8% (median: 18%; 95% CI of mean: 20.9–28.8%) (Table 2). Similarly, the mean percentage of sites developing

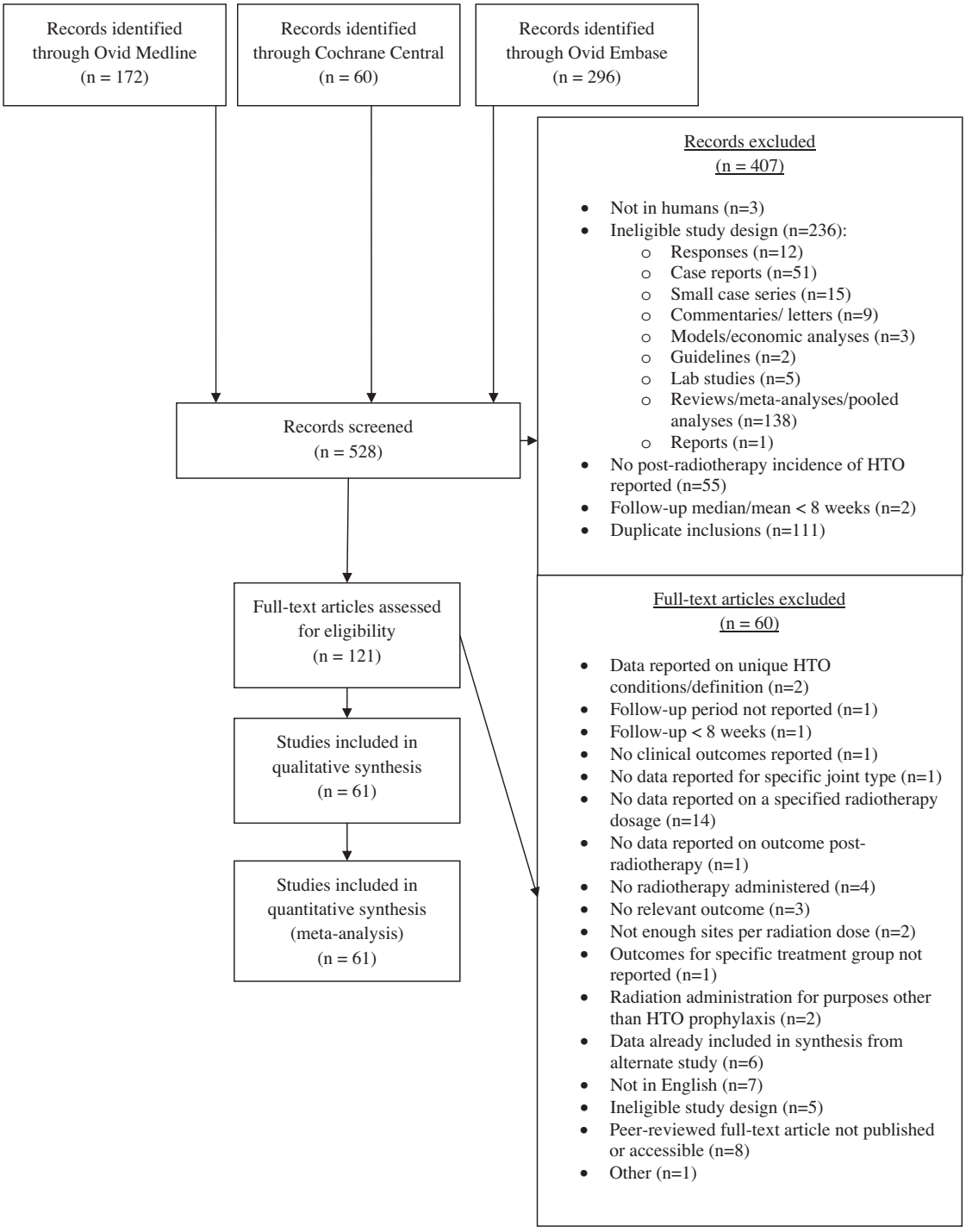

Fig. 1. Modified preferred reporting items for systematic reviews and meta-analyses flow of information diagram for included studies.

Brooker grade 1 or 2 HTO was 22.1% (median: 17%; 95% CI of mean: 18.1–26.2%), whereas the mean percentage of sites developing Brooker grade 3 or 4 HTO was 4.1% (median: 2%; 95% CI of mean: 2.9–5.3%).

The association between the percentage of sites developing HTO and the prescribed dose of radiation was investigated after adjusting for radiation site (i.e. hip, knee, TMJ, elbow) as a confounding factor. This particular analysis was completed on all included treatment sites, irrespective of prior history of HTO and preoperative versus postoperative status. Overall, it was found that there was no statistically significant relationship between the percentage of sites developing HTO and radiation dose (coefficient = 0.011; SE = 0.007; $p = 0.095$).

We next examined the impact of preoperative versus postoperative status on the percentage of sites developing HTO. It was found that, after adjusting for radiation site as a confounding factor, there was no statistically significant relationship between preoperative/postoperative status and the percentage of sites developing HTO (coefficient = 6.93; SE = 4.20; $p = 0.10$), as well as Brooker grade 3 or 4 HTO (coefficient = 2.07; SE = 1.25; $p = 0.10$). Conversely, sites which were prescribed radiotherapy postoperatively had a significantly higher percentage of sites developing

Brooker grade 1 or 2 HTO, relative to preoperatively prescribed sites (coefficient = 8.19; SE = 4.10; $p = 0.0499$). The confounding factor of radiation site was not significantly related to any outcome.

It was also possible that past medical history of patients may have influenced results, especially if history was significant for previous HTO. As such, an analysis was conducted to determine whether the incidence of HTO was different in sites undertaking prophylaxis for recurrence rather than HTO for the first time. Adjusted for radiation site, there was a statistically significant difference between new and recurrent cohorts in the percentage of sites developing HTO (coefficient = 32.14; SE = 15.31; $p = 0.041$) as well as the percentage of sites developing Brooker grade 1 or 2 HTO (coefficient = 37.21; SE = 14.80; $p = 0.016$). The analysis for Brooker grade 3 or 4 HTO was statistically insignificant (coefficient = 2.34; SE = 3.05; $p = 0.45$). Further, the confounding factor of radiation site was not significantly related to any outcome.

In ascertaining the development of HTO as a result of radiotherapy, it was also critical to document the efficacy of prescription patterns over the course of many years. Accordingly, a time trend analysis was performed, adjusting for site of radiation. A statistically significant trend was found in which the percentage of sites developing HTO (coefficient = 0.85; SE = 0.32; $p = 0.009$) and developing Brooker grade 1/2 HTO (coefficient = 1.08; SE = 0.35; $p = 0.003$) decreased significantly over time. However, there was no statistically significant trend found in analyzing the incidence of Brooker grade 3/4 HTO (coefficient = 0.15; SE = 0.12; $p = 0.22$). Once again, the confounding factor of radiation site did not influence any outcome. The data were then graphically presented in a bubble chart, with the x axis represented as the mean year treated and the y axis as each primary outcome. Upon computing the weighted Pearson correlation coefficient, it was discovered that a moderate, negative relationship existed between the percentage of sites developing HTO and mean year of treatment ($r = -0.32$; $p = 0.007$; Fig. 2a). When this analysis was subdivided into Brooker grade groups, a similarly moderate, downward sloping relationship was found for Brooker grades 1/2 ($r = -0.39$; $p = 0.002$; Fig. 2b), whereas no statistically significant relationship was discovered for Brooker grades 3/4 ($r = 0.16$; $p = 0.21$; Fig. 2c).

A time trend analysis was also completed for radiation dose (Fig. 3), which demonstrated a highly significant downward sloping relationship between the prescribed dose and the mean year of treatment ($r = -0.53$; $p < 0.0001$).

Table 1
Demographic information for the included sample.

Type of study	
Retrospective	2061 (37.72%)
Randomized controlled trial	1253 (22.93%)
Prospective	1012 (18.52%)
Unknown	695 (12.72%)
N/A	443 (8.11%)
Treatment center	
United States	3015 (55.18%)
Germany	1762 (32.25%)
Italy	279 (5.11%)
Greece	89 (1.63%)
Belgium	83 (1.52%)
France	54 (0.99%)
Canada	47 (0.86%)
Switzerland	47 (0.86%)
The Netherlands	43 (0.79%)
South Korea	19 (0.35%)
United Kingdom	14 (0.26%)
Australia	12 (0.22%)
Risk of developing heterotopic ossification	
High risk	1529 (27.98%)
At risk	291 (5.33%)
Mixed risk	194 (3.55%)
Standard risk	47 (0.86%)
Unknown	3403 (62.28%)
Site of radiation	
Hip	5336 (97.66%)
Elbow	87 (1.59%)
Temporomandibular joint	22 (0.40%)
Knee	19 (0.35%)
New heterotopic ossification or recurrence of old ossification	
Recurrence	280 (5.12%)
New	176 (3.22%)
Mixed	1830 (33.49%)
Unknown	3178 (58.16%)
Radiation prescribed preoperatively or postoperatively	
Postoperatively	3364 (61.57%)
Preoperatively	2072 (37.92%)
Mixed	28 (0.51%)
Radiation dose (cGy)	
500	165 (3.02%)
550	19 (0.35%)
600	321 (5.87%)
700	3331 (60.96%)
750	182 (3.33%)
800	286 (5.23%)
990	77 (1.41%)
1000	613 (11.22%)
1200	120 (2.20%)
1500	13 (0.24%)
1750	199 (3.64%)
2000	138 (2.53%)
Radiation dose (cGy)	
n	85
Mean ± SD	816.2 ± 2421.1
95% confidence interval (CI) of mean	751.0–881.3
Median (range)	700 (500–2000)
Mean year treated	
n	77
Mean ± SD	1996.2 ± 54.8
95% confidence interval (CI) of mean	1994.7–1997.7
Median (range)	1999 (1974–2007)

Note: All values indicate number of treatment sites treated by radiotherapy rather than number of patients.

Discussion

In the heterotopic ossification setting, radiation has been used consistently as a prophylaxis [7]. Over the years, evidence-based guidelines aiming to standardize radiotherapy regimens for these patients have not been devised, leading to a wide variability in the prescription patterns of radiation oncologists. This systematic

Table 2
Distribution of heterotopic ossification incidence following any prophylactic radiotherapy regimen.

Percentage of sites developing heterotopic ossification	
n	79
Mean ± SD	24.8 ± 146.1
95% confidence interval (CI) of mean	20.9–28.8
Median (range)	18(0–100)
Percentage of sites developing Brooker grade 1/2 heterotopic ossification	
n	70
Mean ± SD	22.1 ± 137.4
95% confidence interval (CI) of mean	18.1–26.2
Median (range)	17(0–92)
Percentage of sites developing Brooker grade 3/4 heterotopic ossification	
n	69
Mean ± SD	4.1 ± 41.7
95% confidence interval (CI) of mean	2.9–5.3
Median (range)	2(0–38)

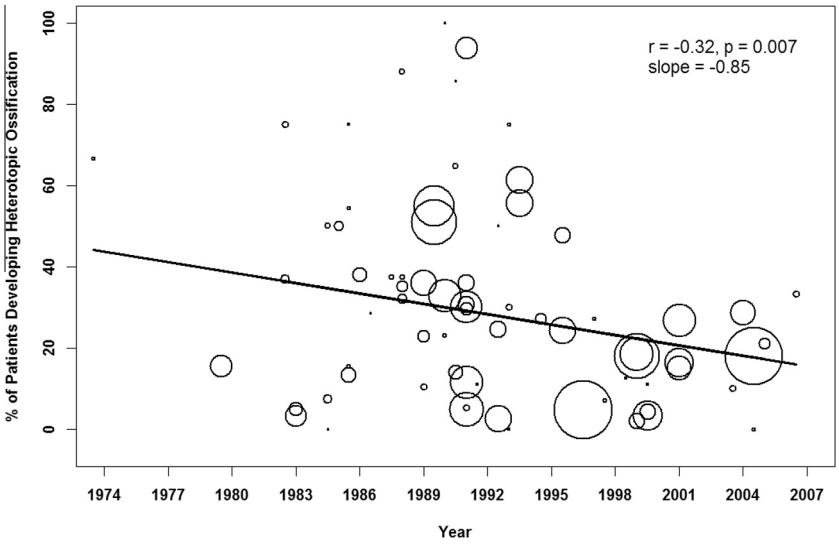

Fig. 2a. Bubble chart demonstrating the distribution of the percentage of sites developing heterotopic ossification within individual cohorts as a function of mean year treated.

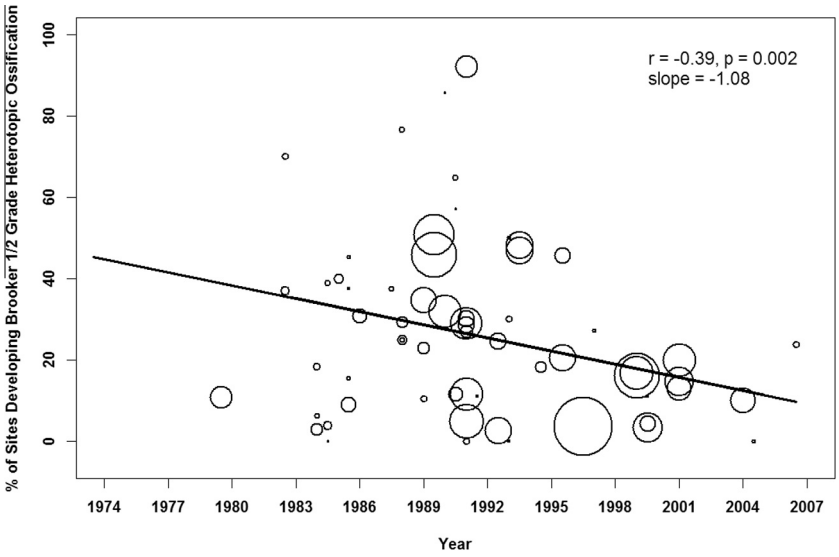

Fig. 2b. Brooker grades 1 or 2 heterotopic ossification.

review and meta-analysis has examined critical areas in this respect, especially in terms of appropriate dosing, preoperative versus postoperative prophylaxis, as well as differences in efficacy in various treatment sites and in patients with dissimilar medical histories.

Given the large number of treatment sites involved ($n = 5464$), it is the hope of the authors that these results will be generalizable and useful to the practicing radiation oncologist. Nonetheless, it is important to emphasize that the vast majority of included sites (97.7%) were exclusively in the hip region. Although there was no statistically significant difference in outcomes between various treatment sites, these results should be interpreted with caution, as only 87, 22, and 19 sites were the elbow [21,26,38,40–41,56], temporomandibular joint [18,51], and knee [41,62], respectively. As such, future research in diverse sites of HTO prophylaxis is encouraged.

In terms of dosing, 700 cGy has been by far the most common dose prescribed, especially in recent years (Fig. 3). This finding is in line with numerous included studies that have supported the efficacy of such a regimen [14–15,17,21,23–24,26]. When radiation dose was compared to the incidence of HTO, a positive relationship was found between the predictor and outcome (weighted coefficient: 0.01). However, this was statistically insignificant even with such high statistical power ($p = 0.1$). Given that higher doses of radiotherapy readily require more protracted fractionation schedules [70], our analysis confirms that low doses, such as 700 cGy, provide an efficacious prophylaxis while minimizing patient burden.

Although postoperative radiotherapy has traditionally been the gold standard for HTO prophylaxis, more recently the role of preoperative administration [31–32,34,36,49–50,53,59–60,65] has been explored. In our analysis, most sites were indeed prescribed radiotherapy postoperatively ($n = 3364$; 61.6%), with a smaller proportion being prescribed preoperative prophylaxis ($n = 2072$; 37.9%). For all three primary outcomes, p-values achieved or were close to achieving statistical significance. The only statistically significant finding that was discovered was in the proportion of sites developing Brooker grades 1/2 HTO: the proportion was

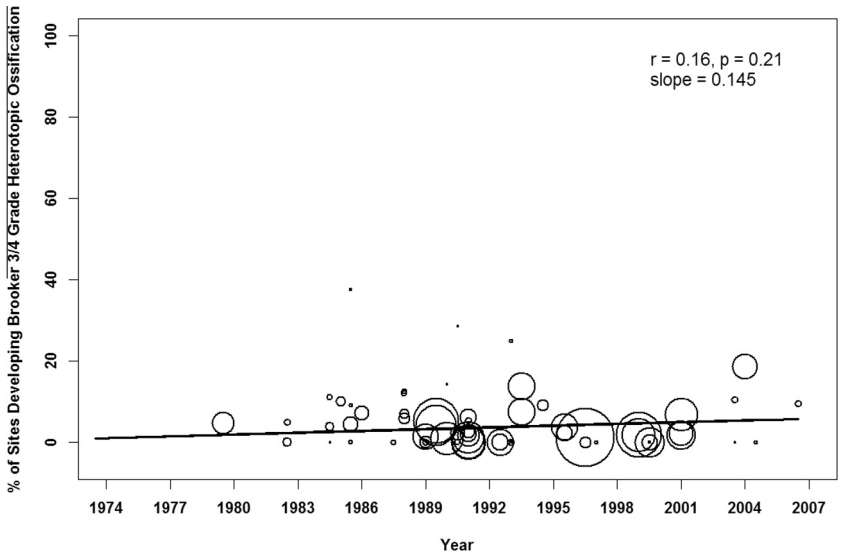

Fig. 2c. Brooker grades 3 or 4 heterotopic ossification.

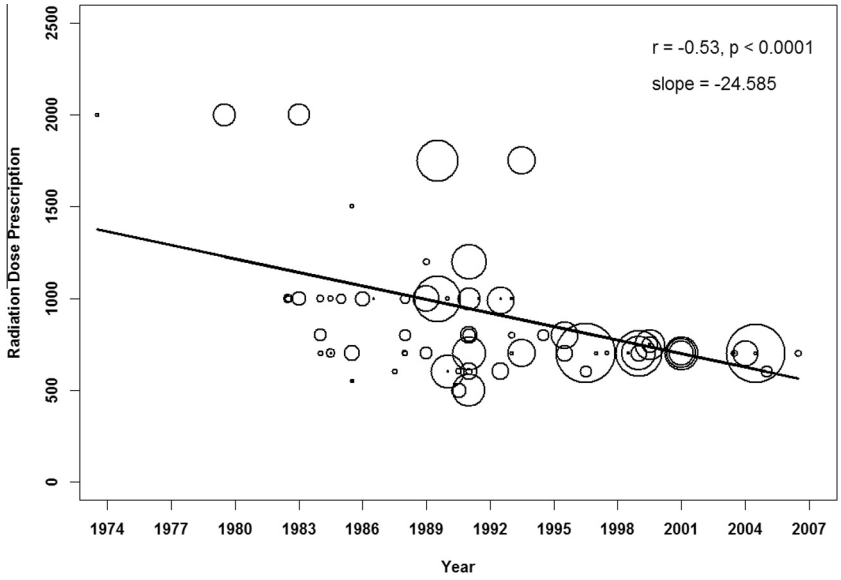

Fig. 3. Bubble chart visualizing the distribution of radiation dose prescription patterns across all sites in relation to the mean year of treatment.

considerably higher in sites that were treated postoperatively, relative to preoperative treatment ($p = 0.0499$). Although reaching statistical significance, it is unclear how clinically relevant these results may be, given the large sample sizes involved. Specifically, it is uncertain whether patient outcomes would be improved substantially by diminishing the flexibility of the radiotherapy center to prescribe prophylaxis either pre or postoperatively. Future research investigating this issue is warranted.

As Fig. 3 suggests, there has not been a dramatic shift in radiotherapy prescription patterns over the last twenty years. Nevertheless, the percentage of sites developing heterotopic ossification after prophylaxis with radiotherapy has consistently diminished over time ($r = -0.32$, $p = 0.007$). In the present day, it is common for the incidence of HTO to be anywhere between 0% and 30% of sites (Fig. 2a). This is in contrast to rates of 0–80% of sites observed in the 1980s (Fig. 2a). Of the sites which develop HTO today, most cases will be Brooker grade 1 or 2 HTO and thus less clinically significant (Fig. 2b). Ultimately, the sustained reduction in HTO incidence over time may be more a result of the large surgical advances in this setting, as there is no evidence to support a relationship between modified radiotherapy parameters and drastically improved clinical outcomes. Future studies should aim to examine the role of changing surgical technique in the improvement of outcomes over time in this setting.

There are limitations to the methodology employed in the present study. First, all data were analyzed at the level of the cohort as opposed to the patient; although all analyses were weighted by the number of treatment sites receiving radiotherapy per cohort, the relationships that may hold true at the cohort level may not necessarily be true at the patient level. Further, as a means of increasing statistical power, especially in treatment sites that are traditionally underreported in the literature, the results of different study designs were pooled. As well, the total dose was used in all analyses as opposed to the biologically effective dose because certain included trials did not disclose the dose fractionation schedules that were employed.

In closing, this meta-analysis has served to consolidate the vast research that has accumulated in the HTO setting over the last 40 years. Low dose radiotherapy is a safe and efficacious method of preventing HTO formation in sites such as the hip, elbow, knee, and temporomandibular joint.

Conflicts of interest

None to disclose.

Acknowledgements

We thank the generous support of the Bratty Family Fund, Michael and Karyn Goldstein Cancer Research Fund, Pulenzas Cancer Research Fund, Joseph and Silvana Melara Cancer Research Fund, and the Ofelia Cancer Research Fund.

References

[1] Shimono K, Tung WE, Macolino C, et al. Potent inhibition of heterotopic ossification by nuclear retinoic acid receptor γ agonists. Nat Med 2011;17:454–60.
[2] Jowsey J, Coventry MB, Robins PR. Heterotopic ossification: theoretical consideration, possible etiologic factors, and a clinical review of total hip arthroplasty patients exhibiting this phenomenon. In: The hip, proceedings of the fifth open scientific meeting of the hip society. St. Louis: CV Mosby; 1977. p. 210.
[3] Imai N, Iwai A, Hatsuko S, et al. Expression of bone morphogenetic proteins in colon carcinoma with heterotopic ossification. Pathol Int 2001;51:643–8.
[4] Zhang R, Oyajobi BO, Jarris SE, et al. Wnt/β-catenin signaling activates bone morphogenetic protein 2 expression in osteoblasts. Bone 2013;52:145–56.
[5] Errico TJ, Fetto JF, Waugh TR. Heterotopic ossification. Incidence and relation to trochanteric osteotomy in 100 total hip arthroplasties. Clin Orthop Relat Res 1984;190:138–41.
[6] Brooker AF, Bowerman JW, Robinson RA, Riley LH. Ectopic ossification following total hip replacement. Incidence and method of classification. J Bone Joint Surg Am 1973;58:233–6.
[7] 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.
[8] Ellerin BE, Helfet D, Parikh S, 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.
[9] Anthony P, Keys H, McCollister Evarts C, Rubin P, Lush C. Prevention of heterotopic bone formation with early postoperative irradiation in high risk patients undergoing total hip arthroplasty: comparison of 10.00 Gy vs 20.00 Gy schedules. Int J Radiat Oncol Biol Phys 1987;13:365–9.
[10] Anglen JO, Moore KD. Prevention of heterotopic bone formation after acetabular fracture fixation by single-dose radiation therapy: a preliminary report. J Orthop Trauma 1996;10:258–63.
[11] Ayers DC, McCollister Evarts C, Parkinson JR. The prevention of heterotopic ossification in high-risk patients by low-dose radiation therapy after total hip arthroplasty. J Bone Joint Surg Am 1986;68:1423–30.
[12] Bosse MJ, Reinert CM, Ellwanger F, Slawson R, McDevitt ER. Heterotopic ossification as a complication of acetabular fracture. Prophylaxis with low-dose irradiation. J Bone Joint Surg Am 1988;70:1231–7.
[13] Burd TA, Lowry KJ, Anglen JO. Indomethacin compared with localized irradiation for the prevention of heterotopic ossification following surgical treatment of acetabular fractures. J Bone Joint Surg Am 2001;83A:1783–8.
[14] Childs HA, Cole T, Falkenberg E, et al. A prospective evaluation of the timing of postoperative radiotherapy for preventing heterotopic ossification following traumatic acetabular fractures. Int J Radiat Oncol Biol Phys 2000;47:1347–52.
[15] Cornes PGS, Shahidi M, Glees JP. Heterotopic bone formation: irradiation of high risk patients. Br J Radiol 2002;75:448–52.
[16] Coventry MB, Scanlon PW. The use of radiation to discourage ectopic bone. A nine-year study in surgery about the hip. J Bone Joint Surg Am 1981;63A:201–8.
[17] DeFlitch CJ, Stryker JA. Postoperative hip irradiation in prevention of heterotopic ossification: causes of treatment failure. Radiology 1993;188:265–70.
[18] Durr ED, Turlington EG, Foote RL. Radiation treatment of heterotopic bone formation in the temporomandibular joint articulation. Int J Radiat Oncol Biol Phys 1993;27:863–9.
[19] Ebinger T, Roesch M, Kiefer H, et al. Influence of etiology in heterotopic bone formation of the hip. J Trauma 2000;48:1058–62.
[20] Fingeroth RJ, Ahmed AQ. Single dose 6 Gy prophylaxis for heterotopic ossification after total hip arthroplasty. Clin Orthop Relat Res 1995;317:131–40.
[21] Hamid N, Ashraf N, Bosse MJ, et al. Radiation therapy for heterotopic ossification prophylaxis acutely after elbow trauma. J Bone Joint Surg Am 2010;92:2032–8.
[22] Han CD, Choi CH, Suh CO. Prevention of heterotopic bone formation after total hip arthroplasty using 600 rad in single dose in high risk patient. Yonsei Med J 1997;38:96–100.
[23] Healy WL, Lo TCM, Covall DJ, et al. Single-dose radiation therapy for prevention of heterotopic ossification after total hip arthroplasty. J Arthroplasty 1990;5:369–75.
[24] Healy WL, Lo TCM, DeSimone AA, Rask B, Pfeifer BA. Single-dose irradiation for the prevention of heterotopic ossification after total hip arthroplasty. J Bone Joint Surg Am 1995;77A:590–5.
[25] Hedley AK, Mead LP, Hendren DH. The prevention of heterotopic bone formation following total hip arthroplasty using 600 rad in a single dose. J Arthroplasty 1989;4:319–25.
[26] Heyd R, Buhleier T, Zamboglou N. Radiation therapy for prevention of heterotopic ossification about the elbow. Strahlenther Onkol 2009;185:506–11.
[27] Jasty M, Schutzer S, Tepper J, Willett C, Stracher MA, Harris WH. Radiation-blocking shields to localize periarticular radiation precisely for prevention of heterotopic bone formation around uncemented total hip arthroplasties. Clin Orthop Relat Res 1990;257:138–45.
[28] Kennedy WF, Gruen TA, Chessin H, Gasparini G, Thompson W. Radiation therapy to prevent heterotopic ossification after cementless total hip arthroplasty. Clin Orthop Relat Res 1991;262:185–91.
[29] Kienapfel H, Koller M, Wust A, et al. Prevention of heterotopic bone formation after total hip arthroplasty: a prospective randomised study comparing postoperative radiation therapy with indomethacin medication. Arch Orthop Trauma Surg 1999;119:296–302.
[30] Knelles D, Barthel T, Karrer A, et al. Prevention of heterotopic ossification after total hip replacement. A prospective, randomised study using acetylsalicylic acid, indomethacin and fractional or single-dose irradiation. J Bone Joint Surg Br 1997;79:596–602.
[31] Koelbl O, Seufert J, Pohl F, et al. Preoperative irradiation for prevention of heterotopic ossification following prosthetic total hip replacement. Results of a prospective study in 462 hips. Strahlenther Onkol 2003;179:767–73.
[32] Kolbl O, Knelles D, Barthel T, Raunecker F, Flentje M, Eulert J. Preoperative irradiation versus the use of nonsteroidal anti-inflammatory drugs for prevention of heterotopic ossification following total hip replacement: the results of a randomized trial. Int J Radiat Oncol Biol Phys 1998;42:397–401.
[33] Kruser TJ, Kozak KR, Cannon DM, et al. Low rates of heterotopic ossification after resurfacing hip arthroplasty with use of prophylactic radiotherapy in select patients. J Arthroplasty 2012;27:1349–53.
[34] Le Duff MJ, Takamura KB, Amstutz HC. Incidence of heterotopic ossification and effects of various prophylactic methods after hip resurfacing. Bull NYU Hosp Jt Dis 2011;69:S36–41.
[35] Linclau L, Dokter G, Debois JM, Gutwirth P. Radiation therapy to prevent heterotopic ossification in cementless total hip arthroplasty. Acta Orthop Belg 1994;60:220–4.
[36] Lonardi F, Gioga G, Coeli M, et al. Preoperative, single-fraction irradiation for prophylaxis of heterotopic ossification after total hip arthroplasty. Int Orthop 2001;25:371–4.
[37] MacLennan I, Keys HM, McCollister Evarts C, Rubin P. Usefulness of postoperative hip irradiation in the prevention of heterotopic bone formation in a high risk group of patients. Int J Radiat Oncol Biol Phys 1984;10:49–53.
[38] 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.
[39] Mavrogenis AF, Guerra G, Staals EL, et al. A classification method for neurogenic heterotopic ossification of the hip. J Orthop Traumatol 2012;13:69–78.
[40] McAuliffe JA, Wolfson AH. Early excision of heterotopic ossification about the elbow followed by radiation therapy. J Bone Joint Surg Am 1997;79A:749–55.
[41] 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 Imag Radiat Oncol 2011;55:333–6.
[42] Moed BR, Letournel E. Low-dose irradiation and indomethacin prevent heterotopic ossification after acetabular fracture surgery. J Bone Joint Surg Br 1994;76B:895–900.
[43] Moore KD, Goss K, Anglen JO. Indomethacin versus radiation therapy for prophylaxis against heterotopic ossification in acetabular fractures: a randomised, prospective study. J Bone Joint Surg Br 1998;80:259–63.
[44] Mourad WF, Packianathan S, Shourbaji RA, et al. The impact of body mass index on heterotopic ossification. Int J Radiat Oncol Biol Phys 2012;82:e831–6.
[45] Padgett DE, Holley KG, Cummings M, et al. The efficacy of 500 centigray radiation in the prevention of heterotopic ossification after total hip arthroplasty: a prospective randomized, pilot study. J Arthroplasty 2003;18:677–86.
[46] Pakos EE, Pitouli EJ, Tsekeris PG, et al. Prevention of heterotopic ossification in high-risk patients with total hip arthroplasty: the experience of a combined therapeutic protocol. Int Orthop 2006;30:79–83.
[47] Pakos EE, Tsekeris PG, Paschos NK, et al. The role of radiation dose in a combined therapeutic protocol for the prevention of heterotopic ossification after total hip replacement. J BUON 2010;15:74–8.

[48] Pellegrini VD, Konski AA, Gastel JA, et al. Prevention of heterotopic ossification with irradiation after total hip arthroplasty. Radiation therapy with a single dose of eight hundred centigray administered to a limited field. J Bone Joint Surg Am 1992;74:186–200.
[49] Pellegrini VD, Gregoritch SJ. Preoperative irradiation for prevention of heterotopic ossification following total hip arthroplasty. J Bone Joint Surg Am 1996;78:870–81.
[50] Pohl F, Seufert J, Tauscher A, et al. The influence of heterotopic ossification on functional status of hip joint following total hip arthroplasty. Strahlenther Onkol 2005;181:529–33.
[51] Reid R, Cooke H. Postoperative ionizing radiation in the management of heterotopic bone formation in the temporomandibular joint. J Oral Maxillofac Surg 1999;57:900–5.
[52] Schai P, Brunner R, Morscher E, Schubert KH. Prevention of heterotopic ossification in hip arthroplasties by means of early single-dose radiotherapy (6 Gy). Arch Orthop Trauma Surg 1995;114:153–8.
[53] Seegenschmiedt MH, Keilholz L, Martus P, 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.
[54] Sell S, Willms R, Jany R, et al. The suppression of heterotopic ossifications: radiation versus NSAID therapy—a prospective study. J Arthroplasty 1998;13:854–9.
[55] Slawson RG, Poka A, Bathon H, Salazar OM, Bromback RJ, Burgess AR. The role of post-operative radiation in the prevention of heterotopic ossification in patients with post-traumatic acetabular fracture. Int J Radiat Oncol Biol Phys 1989;17:669–72.
[56] 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.
[57] Sudanese A, Tabarroni M, Busanelli L, et al. The use of cobalt therapy to prevent heterotopic ossification after total hip arthroplasty. Chir Organi Mov 1996;81:89–106.
[58] Sylvester JE, Blount LH, Selch MT. Technical considerations in the use of prophylactic radiation therapy to prevent heterotopic bone formation. Semin Arthroplasty 1992;3:167–71.
[59] Taussky D, Cserhati M, Pescia R. Preoperative radiotherapy without femoral shielding for prevention of heterotopic ossification in hydroxyapatite-coated hip prostheses. Arch Orthop Trauma Surg 2001;121:271–3.
[60] van Leeuwen WM, Deckers P, de Lange WJ. Preoperative irradiation for prophylaxis of ectopic ossification after hip arthroplasty. A randomized study in 62 hips. Acta Orthop Scand 1998;69:116–8.
[61] Warren SB, Brooker AF. Excision of heterotopic bone followed by irradiation after total hip arthroplasty. J Bone Joint Surg Am 1992;74:201–10.
[62] Daugherty LC, Bell JR, Fisher BJ, et al. Radiation prophylaxis as primary prevention of heterotopic ossification of the knee: classification of disease and indications for treatment. J Radiat Oncol 2013;2:87–94.
[63] Mourad WF, Packianathan S, Shourbaji RA, et al. A prolonged time interval between trauma and prophylactic radiation therapy significantly increases the risk of heterotopic ossification. Int J Radiat Oncol Biol Phys 2012;82:e339–44.
[64] Hashem R, Tanzer M, Rene N, Evans M, Souhami L. Postoperative radiation therapy after hip replacement in high-risk patients for development of heterotopic bone formation. Cancer Radiother 2011;15:261–4.
[65] De Smet K, Pattyn C, Verdonk R. Early resection of heterotopic ossification after total hip arthroplasty: a review of the literature. Hip Int 2002;12:383–7.
[66] Starr AJ, Watson JT, Reinert CM, Jones AL, Whitlock S, Griffin DR, et al. Complications following the "t extensile" approach: a modified extensile approach for acetabular fracture surgery—report of forty-three patients. J Orthop Trauma 2002;16:535–42.
[67] Ashton LA, Bruce W, Goldberg J, Walsh W. Prevention of heterotopic bone formation in high risk patients post-total hip arthroplasty. J Orthop Surg 2000;8:53–7.
[68] Busanelli L, Sudanese A, Toni A, Brizio TL, Giunti A. Removal of heterotopic ossification followed by cobalt therapy after total hip arthroplasty. Chir Organi Mov 1996;81:341–5.
[69] Maloney WJ, Jasty M, Willett C, Mulroy RD, Harris WH. Prophylaxis for heterotopic bone formation after total hip arthroplasty using low-dose radiation in high-risk patients. Clin Orthop Relat Res 1992;280:230–4.
[70] Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. Clin Oncol 2012;24:112–24.