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Review

Personalizing Prophylactic Radiotherapy for Hip Heterotopic Ossification: An AMSTAR-2 Compliant Review of Meta-analyses

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Abstract. *Background/Aim: Heterotopic ossification (HO) is a common complication following total hip arthroplasty. Various prophylactic treatments have been proposed, including radiotherapy (RT). This review summarizes the evidence from meta-analyses on the efficacy of RT in preventing hip HO. Materials and Methods: A literature search was conducted on PubMed. The quality of the meta-analyses was assessed using the AMSTAR-2 tool. Results: Seven meta-analyses were included. One meta-analysis reported a significant reduction in HO occurrence after RT compared to the control group. Comparing RT and non-steroidal anti-inflammatory drugs, one and two meta-analyses showed significantly greater efficacy of RT in preventing severe HO and better outcomes in patients receiving drugs, respectively. Regarding RT settings, the postoperative and preoperative RT were each supported by one meta-analysis. Furthermore, two meta-analyses showed an advantage of multi-fractionated RT over single fraction RT. The overall confidence rate of the meta-analyses was moderate, low, and critically low in one, three, and three meta-analyses, respectively. Conclusion: RT is a confirmed prophylactic intervention for HO. However, the precise optimization of timing, dosage, and fractionation requires elucidation. Future research should focus on the development of predictive models through large-scale data collection and advanced analytics to refine individualized treatment strategies and assess RT comparative effectiveness with drugs.*

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Key Words: Heterotopic ossification, hip, prophylaxis, radiotherapy, intensity-modulated radiation therapy, review.

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Heterotopic ossification (HO) is the abnormal formation of lamellar bone in soft tissue (1). HO can be classified into three categories: traumatic, non-traumatic, and neurological (2). Male sex, hip ankylosis, and previous history of HO are among the main risk factors (3, 4). HO is a common complication following total hip arthroplasty, occurring in 15 to 90% of cases, and can lead to hip impairment if significant ossification occurs (5). The Brooker classification is widely used to grade HO based on anteroposterior X-ray

images, ranging from grade I (islands of bone around hip soft tissue) to grade IV (joint ankylosis), which is considered the most severe condition (6, 7).

While surgical resection is the most effective treatment for symptomatic HO (8), various prophylactic treatments have been recommended for hip HO. These include non-steroidal anti-inflammatory drugs (NSAIDs), Noggin (an inhibitor of bone morphogenetic proteins), pulsed electromagnetic fields, and free radical scavengers (9, 10). Additionally, radiotherapy (RT) has been utilized in this context (11).

Evidence on the efficacy of RT as a prophylactic treatment for HO comes from both non-randomized and randomized trials (12-18). However, several aspects of RT's efficacy in this setting remain unclear. These include: i) a comparison between the prophylactic effects of RT and NSAIDs; ii) potential benefits of combining RT with drug therapy; iii) determining the optimal timing of RT delivery (post-operative *versus* pre-operative); and iv) identifying the optimal RT dose, technique, and timing (interval between RT and surgery) (19).

To provide an overview of the primary evidence regarding RT efficacy in preventing hip HO, we conducted a review of available meta-analyses. The objective was to summarize the existing evidence and shed light on the effectiveness of RT as a prophylactic treatment for HO in the hip.

Materials and Methods

A multidisciplinary team consisting of radiation oncologists (EG, GM, FD, SC, AA, AGM), orthopedic surgeons (LG, CG, AS, MF, MDP), medical physicists (SC, LS) and a radiological engineer (MB) conducted the literature review.

Eligibility criteria. This review included only meta-analyses that examined the efficacy of RT in preventing HO. Papers written in languages other than English and conference abstracts were excluded.

Bibliographic search. A literature search was performed on PubMed using the search terms "heterotopic ossification" AND "hip" AND ("radiotherapy" OR "radiation"). We included all meta-analyses published in English after 1990 that focused on the role of RT as a prophylactic treatment for hip HO. Moreover, reviews concerning the use of RT in the prevention of HO relapses (HOR), *i.e.*, in the preventive treatment of the relapse in patients operated on for HO, were also included in the review. Further details of the research are provided in Figure 1. Duplicate papers were removed after the search. Subsequently, three authors (EG, MB and AA) independently assessed the titles and abstracts of the remaining articles, removing non-significant ones. The same authors then read the full text of the remaining articles and excluded those that did not meet the inclusion criteria.

Data extraction. Three authors (GM, SC, and FD) separately reviewed the remaining articles to extract the following data: authors, year of publication, study type (meta-analysis), number and type of studies included in the analysis, number of patients included in each review, setting of RT (prophylaxis for HO or HO recurrence, or both), comparisons made, and main findings. The senior author (AGM) was consulted during the bibliographic selection and data extraction process to address any issues.

Quality assessment. Two authors (EG and AGM) independently assessed the quality of the papers included in this review using A MeaSurement Tool to Assess systematic Reviews (AMSTAR-2 tool). Based on the guidelines provided by AMSTAR-2, an overall confidence rating was assigned as follows: "high" if there were 0-1 non-critical weaknesses, "moderate" if there were more than 1 non-critical weaknesses, "low" if there was 1 critical flaw±non-critical weaknesses, and "critically low" if there were more than 1 critical flaw±non-critical weaknesses.

Data analysis. Due to the heterogeneity of the included articles, a quantitative analysis (meta-analysis) was not performed. However, we reported the main findings of the reviews, focusing on their quality, to provide a comprehensive overview for guiding clinical work and future studies.

Results

Search results. The initial literature search yielded 291 papers. After removing duplicates, 89 papers were screened, and 8 full-text articles met the inclusion criteria. One review was excluded because the patients included were not treated with RT. Therefore, a total of seven articles were included in this review (12-18). All the meta-analyses included randomized trials, with four of them also including non-randomized trials (12-14, 18). Two articles focused on treated sites rather than specifically on patients (14, 15). The included meta-analyses were published between 2004 and 2021. Two articles were solely meta-analyses (12, 16), while the others were systematic reviews and meta-analyses (13-15, 17, 18). Three meta-analyses also considered the prophylactic setting for HO recurrence (14, 15, 17). Four meta-analyses focused on comparisons between RT and non-steroidal anti-inflammatory drugs (NSAIDs) (12, 13, 16, 18), as well as on preoperative *versus* postoperative RT and dose aspects (12, 14, 15, 17). The characteristics of the included reviews are described in Table I.

Main findings. The results of the included articles are summarized in Table I.

Radiotherapy versus control: A single meta-analysis, conducted in the context of HO prophylaxis, reported a comparison between RT and control patients, demonstrating a significant reduction in HO occurrence among those treated with RT [odds ratio (OR)=0.17, 95% confidence interval (CI)=0.076-0.37] (16).

Radiotherapy versus NSAIDs: Four meta-analyses have compared RT and NSAIDs for the prevention of HO (12, 13, 16, 18). Among these, one meta-analysis did not find significant differences between the two treatments (13), one

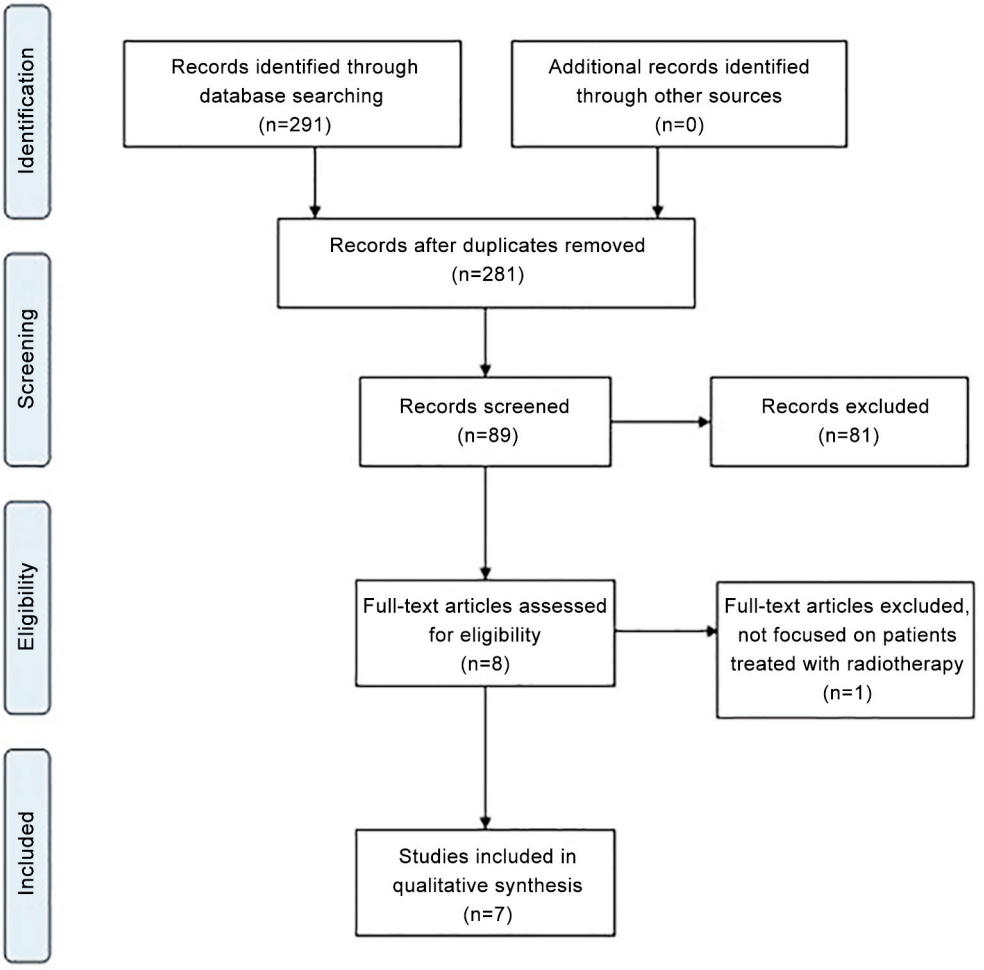

Figure 1. *PRISMA flow chart of the included studies.*

showed significantly greater efficacy of RT only in preventing grade III-IV HO (12), while two meta-analyses comparing the reduction rates of HO after NSAIDs or RT, as compared to controls, observed better outcomes in patients receiving NSAIDs (6, 18). In terms of toxicity, one meta-analysis found no differences between RT and NSAIDs (13), while another meta-analysis reported higher rates of gastrointestinal toxicity in patients treated with non-selective NSAIDs compared to those treated with RT or selective NSAIDs (16).

Preoperative versus postoperative radiotherapy: Four meta-analyses compared the efficacy of preoperative *versus* postoperative RT in preventing HO (12, 14, 15, 17). Among these, two meta-analyses found no significant differences (15, 17), one meta-analysis showed an advantage of postoperative RT (12), and one meta-analysis showed an advantage of preoperative RT, specifically for preventing grade I-II HO (14).

Single fraction radiotherapy versus multifraction radiotherapy: Regarding this topic, two meta-analyses are available (15, 17), both conducted in the setting of HO recurrence prevention. They showed an advantage of multifractional RT over single fraction RT, but only for the prevention of grade I-II recurrence. Additionally, in the subanalysis by Hu *et al*., which included studies on both primary and secondary prevention of HO, a higher rate of HO was observed in patients receiving single-fraction RT, although statistical significance was not reported (17).

Impact of radiotherapy dose. Four meta-analyses assessed the impact of radiotherapy (RT) dose on the prevention of HO. Two meta-analyses, focusing on studies specifically addressing HO prevention (12) and prevention of HO recurrence (17), respectively, demonstrated improved outcomes in patients receiving higher RT doses. In contrast,

Table I. *Characteristics of the included systematic reviews and meta-analyses.*

Authors, year (Ref)	Review type	No. and design of studies	No. of patients	Setting	Comparisons	Main findings
Pakos *et al.*, 2004 (12)	MA	8: 7 RCTs 1 Non-RCTs	1,143	HOP	RT *vs.* NSAIDs	• No difference between the two arms considering all HO grades (RR=0.75, 95%CI=0.37-1.71) • RT more effective than NSAIDs in preventing Grade III-IV HOs (RR=0.42; 95%CI=0.18-0.9, *p*=0.043).
					Preop RT *vs.* Postop RT	• RR after preop RT: 4.30 (1.91-9.70): after postop RT >8 Gy: 0.17 (0.08-0.36). (*p*=NR)
					RT dose	• Significant dose-response relationship in patients treated with postop RT (*p*=0.008).
Vavken *et al.*, 2009 (13)	SR & MA	9: 8 RCTs 1 Non-RCTs	1,295	HOP	RT *vs.* NSAIDs	• No statistically significant difference among RT and NSAIDs (*p*=0.474). • No difference in risk of complications between the two arms (*p*=0.431).
Popovic *et al.*, 2014 (14)	SR & MA	61: 14 RCTs 34 Non- RCTs 12 NR	5,464 sites	HOP/ HORP	Preop RT *vs.* postop RT	• No relationship between postop *vs.* preop RT and B III-IV HTO (*p*=0.1). • Postop treated sites developed B I-II HO more than those treated preoperatively (*p*=0.05).
					RT dose	• After adjusting for RT site, no relationship between HTO and prescribed RT dose (*p*=0.1).
Milakovic *et al.*, 2015 (15)	SR & MA	12 RCTs	1,253 sites	HOP/ HORP	Preop *vs.* postop RT	• Overall prevalence of HO: postop RT: 32.4%, preop RT: 42.2% (*p*=0.43). • B I-II HO were 35.8% and 29% in the preop and postop RT groups, respectively (*p*>0.05). • prevalence of HO: 5/1 Gy: postop RT: 39.3%, preop RT: 14% (*p*=NR); 7/1 Gy, postop RT: 15.5%, preop RT: 56.3% (*p*=NR); 8/1 Gy: postop RT: 28%, preop RT: 30.6% (*p*=NR).
					RT dose	• 7 Gy: 26.4% HO (B I-II HO: 23.5%). 8 Gy: 42.8% HO (B I-II: 37.7%).
				HORP	Preop *vs.* postop RT	• No difference in HO progression between preop *vs.* postop RT (*p*=0.43)
					BED >25 Gy *vs.* ≤25 Gy	• No difference in HO progression between high and low BED (*p*=0.28).
					SFRT *vs.* MFRT	• MFRT more effective than SFRT in reducing HO risk (*p*=0.04); B: I-II (*p*=0.0009), III-IV HO (*p*=0.32).
Cai *et al.*, 2019 (16)	MA	31 RCTs	7,769	HOP	Nonselective NSAIDs and selective NSAIDs *vs.* RT *vs.* controls	• Lower HO rate after nonselective NSAIDs, selective NSAIDs and RT *vs.* control (OR=0.34, 95%CI=0.22-0.51; OR=0.42, 95%CI=0.24-0.73; OR=0.17, 95%CI=0.076-0.37, respectively). • Lower HO rate after nonselective NSAIDs, selective NSAIDs *vs.* RT: (OR=0.50, 95%CI=0.25-1.0; OR=0.41, 95%CI=0.17-0.97, respectively). • Higher GI toxicity with nonselective NSAIDs *vs.* other treatments and control. • Same non-GI toxicity comparing different treatments and control • Lower incidence of postop toxicity after selective NSAIDs *vs.* nonselective NSAIDs, controls and RT.
Hu *et al.*, 2021 (17)	SR & MA	10 RCTs	1,203	HOP/ HORP	Preop RT *vs.* postop RT	• Preop RT: HO=25.2% (21.6 % B I/II and 3.7% B III/IV); postop RT: HO=18% (16% B I/II and 2% B III/IV) (*p*=NS).

Table I. *Continued*

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Authors, year (Ref)	Review type	No. and design of studies	No. of patients	Setting	Comparisons	Main findings
						• HO - 5/1 Gy: postop RT: 30.1%, preop RT: 14%; 7/1 Gy: postop RT: 17.5%, preop RT: 29.3%; 8/1 Gy: postop RT: 23.9%, preop RT: 24.5%. (p=NR)
					SFRT *vs.* MFRT	• SFRT: HO=25.6% (22.9% B I/II and 2.7% B III/IV); MFRT: HO=12.1% (10.3% B I/II and 1.8% B III/IV) (p=NR).
				HORP	Preop RT *vs.* postop RT	• No difference between preop and postop RT for overall progression of HO (p=0.43).
					Low BED *vs.* medium BED *vs.* high BED group	• Lower HO progression in medium *vs.* low BED (p=0.003). (B I/II HO. p<0.0001; B III/IV HO, p=0.73) • No difference in low *vs.* high BED group (p=0.21).
					SFRT *vs.* MFRT	• Higher overall HO progression between SFRT *vs.* MFRT (p=0.04), especially for B I/II HO (p=0.003) compared to B III/IV HO (p=0.55).
Shapira *et al.*, 2021 (18)	SR & MA	37: 27 RCTs 10 Non-RCTs	8,653	HOP	RT *vs.* NSAIDs	• Patients without HO: RT: 28.6%-97.4% (severe HO: 0.0%-11.9%); NSAIDs: 76.6%-88.9% (severe HO: 0.0%-1.8%). NSAIDs may be more effective than RT in high-risk patients.

B: Brooker; BED: biologically effective dose; GI: gastrointestinal; HO: heterotopic ossification; HOP: heterotopic ossification prophylaxis; HORP: heterotopic ossification recurrence prophylaxis; MA: meta-analysis; MFRT: multifractionated radiotherapy; NR: not reported; NS: not significant; NSAIDS: nonsteroidal anti-inflammatory drug; postop: postoperative; preop: preoperative; RCT: randomized controlled trial; RR: risk ratio; THA: total hip arthroplasty; RT: radiotherapy; SFRT: single fraction radiotherapy; SR: systematic review

two meta-analyses found no significant differences in outcomes based on the delivered RT dose (14, 15).

Quality assessment of the analyzed studies. Based on the quality assessment, one meta-analysis was classified as having a moderate overall confidence rating (13), three meta-analyses were classified as having a low overall confidence rating (16-18), while three meta-analyses were considered as having critically low confidence rating (12, 14, 15). The AMSTAR 2 domain with the highest number of critical weaknesses was "Impact of risk of bias on pooled results" (Table II).

Discussion

Our systematic review aimed to synthesize the body of meta-analyses examining RT for the prevention of HO in patients undergoing total hip arthroplasty. While the meta-analysis comparing RT to control showed a significant benefit of RT in preventing HO (16), the comparison between RT and NSAIDs revealed a lack of consensus, with more recent studies favoring NSAIDs (16, 18) despite their methodological differences in comparison.

The studies on the timing of RT presented discordant results, with no clear superiority of preoperative or postoperative RT (12, 14, 15, 17). This inconsistency was also observed in the investigation of RT doses, with conflicting evidence on the effectiveness of higher doses (12, 17) *versus* no dose-related differences (14, 15). These findings highlight the complexity of determining optimal RT strategies and suggest that current research may not fully account for patient-specific variables.

In fact, our comprehensive review underscores the absence of definitive evidence guiding the choice between RT and NSAIDs for the prophylaxis of HO post-hip arthroplasty. Given this uncertainty, clinicians are advised to base their treatment decisions on practical considerations and individual patient profiles. For instance, preoperative RT may be more convenient, avoiding the need to transport a patient post-surgery. Meanwhile, younger patients might favor NSAIDs due to the theoretical, albeit unproven, carcinogenic risks associated with RT (19). Conversely, RT is advisable for patients with gastrointestinal comorbidities or NSAID contraindications. This patient-centric approach is pragmatic and aligns with the current understanding of the relative benefits and risks of the treatments in question.

Moreover, the traditional scientific approach, relying on randomized trials and meta-analyses, has yet to resolve the debate over the optimal prophylactic treatment for HO in terms of efficacy between RT and NSAIDs, as well as the most beneficial RT parameters (doses and timing). Our findings suggest that this may be due to the multifactorial nature of HO development, which is influenced by a myriad of patient-specific variables. To advance our understanding, we advocate for a shift towards harnessing large-scale, multicenter databases. These repositories will facilitate the

Table II. *Summary of quality evaluation of the included reviews based on AMSTAR 2 domains.*

AMSTAR Questions	Pakos *et al*. 2004	Vavken *et al*. 2009	Popovic *et al*. 2014	Milakovic *et al*. 2015	Cai *et al*. 2019	Hu *et al*. 2021	Shapira *et al*. 2021
1-Review question (PICO)[a]	Y	Y	Y	Y	Y	Y	Y
2-A priori protocol	N	N	N	N	N	N	N
3-Study designs included/explained	Y	P	P	Y	P	Y	Y
4-Comprehensive literature search[a]	Y	Y	Y	Y	Y	Y	Y
5-Duplicate study selection[a]	N	Y	N	N	N	Y	Y
6-Duplicate data extraction[a]	Y	Y	N	N	Y	Y	Y
7-List and justification of excluded studies	P	P	P	P	N	P	P
8-Adequate description of included studies	P	P	P	Y	Y	P	P
9-Satisfactory technique for assessing RoB in non-randomized studies[a]	N	Y	N	N	P	Y	Y
10-Funding sources reported for included studies	N	N	N	N	N	N	N
11-Appropriate methods for quantitative synthesis	N	Y	N	Y	Y	P	N
12-Impact of RoB on pooled results[a]	N	Y	N	N	Y	N	N
13-Impact of RoB on interpretation of pooled results[a]	N	Y	N	N	P	Y	Y
14-Heterogeneity explained[a]	Y	Y	P	N	P	Y	Y
15-Publication (small study) bias assessed[a]	Y	Y	P	P	Y	Y	Y
16-Funding sources and conflict of review authors	N	Y	Y	Y	Y	N	Y
Overall confidence rating	Critically low	Moderate	Critically low	Critically low	Low	Low	Low

[a]Key domains for overall confidence ratings of adherence-outcomes reviews; N: no; NMA: no meta-analysis conducted; P: partial yes; PICO: population, indication, comparator, outcomes; RoB: risk of bias; Y: yes.

construction of predictive models that account for the broad spectrum of patient characteristics, surgical interventions, and treatment outcomes. Such models have the potential to revolutionize prophylactic strategies, offering personalized treatment plans that are tailored to the individual characteristics of each patient.

The strength of our review lies in its adherence to the AMSTAR-2 guidelines, ensuring rigorous methodological quality in our synthesis of the existing literature. Our work provides a much-needed consolidation of the current meta-analyses, offering a panoramic view of the research landscape concerning HO prophylaxis.

Nonetheless, our analysis is not without limitations. The heterogeneity in the meta-analyses, which includes studies of varying design, patient populations, and outcome measures, presents a challenge. The Brooker classification system, commonly employed across studies to assess HO incidence, has its own limitations that may not translate well across different clinical contexts (20). These factors may impede the direct comparability of results and limit the generalizability of our conclusions.

Furthermore, the quality assessment of the included studies revealed a spectrum of confidence levels, underscoring the need for a cautious interpretation of the cumulative evidence. This variability in quality emphasizes the need for standardized reporting and methodological rigor in future research.

In conclusion, our review highlights a critical junction in HO prophylaxis research, advocating for a novel, data-intensive approach to patient care. By bridging the gap between clinical pragmatism and scientific innovation, we can pave the way towards more personalized, effective treatment paradigms for HO prevention following hip arthroplasty.

Conclusion

Our review underscores the need for further research that transcends the current paradigm, advocating for a shift towards data-intensive methodologies to clarify the complexity of HO prevention following hip arthroplasty. By combining rigorous data collection with advanced analytical techniques, we can aspire to a future where predictive analytics inform tailored, patient-centric prophylactic strategies.

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Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

EG, AGM and MDP had the idea for the article; EG, LG, CG, MB, and SC performed the literature search and data collection and analysis; EG, CG, MB, and AGM drafted the manuscript; all Authors critically revised the work.

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