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Review

Prophylactic Radiotherapy of Hip Heterotopic Ossification: A Narrative Mini Review

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Abstract. *Evidence on prophylactic radiotherapy (RT) in hip heterotopic ossification (HO) is sparse and conflicting. The aim of this literature review was to collect and summarize the available data on RT efficacy in preventing hip HO. The results of this review show that RT is effective in the prevention of hip HO, albeit with large variability across series. Effective prophylactic RT requires optimal treatment fields and time intervals with surgery. On the contrary, there is no clear evidence on the optimal timing (post-operative versus pre-operative RT). Comparisons between prophylactic RT and use of non-steroidal anti-inflammatory drugs showed conflicting results, although most were in favor of RT. In conclusion, RT is an established prophylactic treatment for hip HO. However, optimal dose, technique and timing remain unclear, as does the usefulness of combining RT with drugs.*

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Heterotopic ossification (HO) is defined as the formation of new bone in soft tissue outside the skeletal system (1). HO can be differentiated into three main groups: traumatic HO (mainly following fractures), non-traumatic HO (usually occurring after burns), and neurological HO (2).

Several prophylactic treatments for HO have been proposed, such as non-steroidal anti-inflammatory drugs (NSAIDs), Noggin (an extracellular peptide that binds and antagonizes bone morphogenetic proteins), pulsed electromagnetic fields, and free radical scavengers (3-11).

HO is a particularly frequent complication after total hip arthroplasty, with reported rates ranging from 15% to 90%. In patients with a significant amount of ossification, hip mobility can be impaired (12). Main risk factors for HO after total hip arthroplasty are male gender, hip ankylosis, and previous history of HO (13, 14). The only effective treatment of symptomatic, established HO is surgical resection (15).

From the early 1980s (16), radiotherapy (RT) has been extensively studied and used in this setting. Most evidence on RT efficacy in preventing hip HO comes from non-randomized studies (17-45), although some randomized trials (46-61) and systematic-reviews and meta-analyses (62-68) have been performed.

However, evidence on prophylactic RT is sparse and conflicting, no international guidelines are available, and several questions remain unanswered. Therefore, the aim of this literature review was to collect and summarize the main available evidence on RT efficacy in preventing hip HO.

Table I. *Number of patients and main findings of nonrandomized studies.*

Ref	Authors, year	Patients, n	Main findings
17	Sylvester *et al*., 1992	82	Only 6/92 assessable hips treated with postop RT developed HO. Five of these were explained by initiating treatment 5 days after surgery or by a block malposition. Of 78 hips irradiated before postoperative day 6 with adequate shielding, only 1 (1.3%) exhibited HO growth. RT is effective in HO prevention if delivered within 4 days after surgery and when technical aspects are taken into consideration.
18	Moed *et al*., 1994	53	The combination of postoperative RT and indomethacin was very effective in HO prevention: only 10 fractures presented class I HO. RT with 12 Gy in 3 daily doses and 7 Gy in a single fraction led to similarly improved results.
19	Fingeroth *et al*., 1995	87	Of the irradiated hips, 6% exhibited grade II or III HO and 0% grade IV, while in the control group: 34% grade II-III and 6% grade IV HOs were recorded. A progression of HO was estimated in 30% of the patients who underwent RT and in 84% of the control group, with a significant difference considering age and weight ($p<0.001$). A single 6-Gy postoperative RT dose within the first 3 days after surgery led to effective HO prophylaxis.
20	Healy *et al*., 1995	94	HOs developed in 12/19 hips treated with 5.5 Gy and in 9/88 hips treated with 7 Gy. A dose of 5.5 Gy seemed not as effective as 7 Gy dose in prophylaxis of HO after surgery ($p<0.01$). A single 7-Gy postoperative RT dose is recommended as effective HO prophylaxis.
21	Linclau *et al*., 1995	138	In patients who underwent RT (75 hips), the mean postoperative HHS was improved (95) while in patients not treated with RT (79 hips) the mean HHS was worse (92). HHS was increased by 11 points in irradiated hips with poor preoperative range of motion. HHS was higher in all patients but not significantly between the two groups (Mann-Whitney test: –0.8373). Regarding results with HHS <80, these were in two irradiated patients and in 11 unirradiated patients, with a significant risk of reduced HHS in patients not irradiated ($p<0.025$).
22	Sudanese *et al*., 1996	96	Overall, 1% of irradiated patients presented Brooker III-IV HOs, while 9% of non-treated patients had the same HO grades. Male elderly patients with primary arthrosis represent the group with higher HO risk.
23	Busanelli *et al*., 1999	130	After prosthetic re-implantation, incidence of HOs was 41% in patients treated with RT *vs*. 61% in the control group ($p=0.0328$); high-grade HOs occurred in 2% and 9%, respectively.
24	Haas *et al*., 1999	66	At radiographic follow-up (6 months after RT) of 47/66 patients, 6 developed grade III HO (4 had received 10 Gy/5 fractions and 2 received 8 Gy/1 fraction) while no patient showed grade IV HO (*p*-value not reported). Within 24 hours of surgery, 7-8 Gy should be delivered in order to prevent HO.
25	Ebinger *et al*., 2000	64	After surgery plus postoperative RT, no different in recurrence rates was observed between different HO etiologies after 1-year (ossification area: patients with multiple injuries 1.9 cm^2, with isolated brain injury, 2.0 cm^2, after local hip trauma, 2.1 cm^2) and 5-year follow-up period (patients with multiple injuries, 2.1 cm^2, with isolated brain injury, 2.2 cm^2, after local hip trauma, 2.3 cm^2). Patients after local hip trauma had progressively improved Merle d'Aubigne and Postel score*: preoperative, 7.5; 1-year follow-up, 13; follow-up 5 years, 13.4 points).
26	D'Lima *et al*., 2001	77	Patients treated with 10 Gy/5 fractions and 8 Gy/1 fraction postoperative RT who developed grade III-IV HO were 1/22 and 1/28, respectively, nobody between patients treated with indomethacin. Grade I-II HOs were observed in 3/25 of patients in the indomethacin group, in 3/28 of 8 Gy and no one in 10 Gy group. Between the two groups, the distribution of risk factor was significantly different ($p<0.05$). Indomethacin had the same efficacy as RT in lower risk patients, with reduced costs.
27	Lonardi *et al*., 2001	143	Six patients developed grade I-II HOs 12 months after RT (7.5 Gy preoperatively, within 16 h before surgery).
28	Seegenschmiedt *et al*., 2001	5,677	After prophylactic RT of 4,377 hips, 475 (11%) were suspicious for HO on radiographic exams. Functional impairment was recorded in 34/685 (5%) hips. Outcomes were similar in patients treated with pre- and postoperative RT. However, patients treated >8 h before surgery or >72 h after surgery had a worse radiological failure rate ($p<0.05$).
29	Koelbl *et al*., 2003	416	RT delivered the day before surgery is effective in higher grade HO prevention. The incidence of HO was as follows: any grade 18.1% (n=84), grade I 12.3% (n=57), grade II 3.9% (n=18), grade III 1.5% (n=7), and grade IV 0.4% (n=2).
30	Pohl *et al*., 2005	315	Of patients treated with prophylactic RT before surgery, 281 (81.5%) did not present HO, 58 had grade I-II HO, and six (1.7%) grade III-IV HO. RT must be used in hip HO prophylaxis. Higher grade HO affects physical functions.

Table I. *Continued*

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Ref	Authors, year	Patients, n	Main findings
31	Roth *et al*., 2005	90	Patients with total hip replacement were treated with RT: doses of 5×3 Gy were delivered in 14 patients between the first and the fifth postoperative day, 1×7 Gy in 13 patients within 24 h after surgery, 1×7 Gy in 63 patients within 24 h before the surgery. No significant HOs were recorded during the follow-up. Time from RT to surgery should be ≤24 h. RT should be delivered before surgery in order to reduce logistic problems.
32	Chao *et al*., 2006	124	Patients after THA or excision of HO underwent RT to prevent HO. Of patients in follow-up, 12.3% with ipsilateral HO had significant HO, while of those with contralateral HO, 10.5% had significant HO after THA. Patients treated with 6 Gy in 3 fractions experienced severe ipsilateral HO after surgery in 60% of cases, while only 13.8% of patients who received 7 Gy in 1 fraction had severe HO, similarly to other regimens.
33	Pakos *et al*., 2006	54	After THA and postoperative combined treatment (RT plus indomethacin), the 1-year overall HO rate was 20.4%, with only one patient showing high-grade HO.
34	Balboni *et al*., 2007	137	Of 137 included patients, only 84 were eligible. Eight out of 40 patients treated with unshielded fields had HO *vs*. 21/44 patients treated with shielded fields (p=0.009) and 5% of the patients of the first group developed grade III and IV HO, while 18% of patients of the second had severe HO (p=0.08). Therefore, a higher risk of RT failure was observed in patients treated with shielded fields.
35	Ince *et al*., 2007	286	RT plus short-course indomethacin in HO prophylaxis did not negatively affect the stability of cementless cups in patients operated for primary THA.
36	Cipriano *et al*., 2009	60	Standard RT doses did not reduce neurogenic HO recurrence rates. More HOs were recorded in the treatment group (15.0%) compared to the control group (5.1%) (p<0.05); 7 Gy RT in a single fraction seems not effective in preventing the recurrence of neurogenic HO in high-risk patients.
37	Pakos *et al*., 2009	99	After 6-months of follow-up, the incidence of HO in patients treated with indomethacin alone was higher (34.5%, 95% CI=22.2-48.6%) compared to patients receiving postoperative RT plus indomethacin (27.3%, 95% CI=15.0-42.8%) (p=0.5).
38	Pakos *et al*., 2010	71	After combined RT plus indomethacin, the overall radiographical incidence of HO after 1-year follow-up was 7.0% (95% CI=2.3-15.7) and no high-grade HOs was observed. Fractionated RT (total of 10 Gy) was effective as a single 7-Gy fraction.
39	Le Duff *et al*., 2011	838	Combined indomethacin plus RT is an effective prophylactic treatment: HO rates were reduced between patients treated with indomethacin and patients receiving indomethacin plus preoperative (7 Gy) RT (p=0.048).
40	Weng *et al*., 2015	91	In subjects with ankylosing spondylitis there was no difference in HO incidence between patients without postoperative prophylactic RT and patients treated with postoperative single fraction RT (5 Gy) (p=0.210).
41	d'Heurle *et al*., 2016	241	RT was effective in preventing HOs (OR=0.29, 95% CI=0.10-0.85).
42	Mourad *et al*., 2017	64	Based on dose-volume histograms, mean and maximum dose to the testicles were 1 Gy and 3.1 Gy, respectively. Using a split-beam technique, there was a decrease in both: 44% and 47%, respectively, and reached 26% and 14%, respectively, using 10-18 MV beams. Testicular shielding should be used in male patients receiving low-dose RT as HO prophylaxis.
43	Müseler *et al*., 2017	444	In patients with HO following spinal cord injury, no side-effects occurred in patients after single-fraction RT. Only one patient experienced ankylosis after repeated RT and was operated on subsequently.
44	Honore *et al*., 2020	95	Preoperative RT delivered in 89.5% of cases was not effective when combined with surgery in patients with significant HO: ORs for recurrence were similar for different groups (total population, OR=0.63, 95% CI=0.06-3. 27; p=0.72); spinal cord injury subgroup, OR=0.45; head injury subgroup, OR=1.04). RT appeared to be associated with a higher risk of sepsis after surgery (p<0.05).
45	Pakos *et al*., 2020	97	In patients treated with surgery and prophylactic RT, no cases of RT-induced tumors were observed during the 10-year follow-up period.

HHS: Harris Hip Score, an outcome measure after hip surgery; HO: heterotopic ossification; RT: radiotherapy; THA: total hip arthroplasty. *Based on pure pain, mobility of the leg and ability to walk, grading each from 1 to 6 points.

Review Method

A literature search was conducted on PubMed on 30 May 2021. The search strategy was as follows: "heterotopic ossification"[All Fields] AND "hip"[All Fields] AND ("radiotherapy"[All Fields] OR "radiation"[All Fields]). In this review, we included clinical studies and meta-analyses published in English after 1990 reporting on patients treated

Table II. *Number of patients and main findings of randomized trials.*

Ref	Authors, year	Patients, n	Treatment arms	Main findings
46	Konski *et al*., 1990	47	5×10 Gy *vs*. 1×8 Gy	In preventing HO, RT delivered with single-fraction 8 Gy is as effective as 10 Gy in 5 fractions (*p*-value not reported). Analyzing the differences in radiographic scores soon after surgery and radiographs performed 2 months later, the resulting score was increased in 4 patients (1 treated in the 8-Gy arm and 3 in the 10-Gy arm). However, no patient showed grade III-IV HO.
47	Seegenschmiedt *et al*., 1993	60	LD-RT: Arm A=5×2 Gy *vs*. HD-RT: Arm B1=10×2 Gy or Arm B2=5×3.5 Gy	Four patients developed treatment failure. Delayed post-operative RT on day 4 after surgery was significantly correlated with treatment failure ($p<0.001$). No difference was recorded between LD-RT and HD-RT.
48	Seegenschmiedt *et al*., 1993	137	LD-RT: 5×2 Gy *vs*. HD-RT: 10×2 Gy or 5×3.5 Gy	RT was effective as prophylactic treatment of HO in 129/137 hips (91.5%). HD-RT dose combined with NSAID was correlated with a successful result ($p=0.009$) compared to LD-RT.
49	Gregoritch *et al*., 1994	122	Preoperative RT (<4 h before surgery) *vs*. 'standard' postoperative RT (<48 h after surgery) schedules	Prophylactic RT delivered ≤4 h before surgery was equally effective compared to postoperative RT in preventing clinically significant hip HO. HO rates were 26% after preoperative RT and 28% after postoperative RT ($p>0.99$). Grade III-IV HOs were recorded in 2% and 5% of patients treated with preoperative and postoperative RT, respectively.
50	Pellegrini *et al*., 1996	85	Group I: 1×8 Gy preoperatively *vs*. Group II: 1×8 Gy postoperatively	HOs were observed in 12/49 hips treated with preoperative RT and 3/37 hips treated with postoperative RT ($p=0.05$). Preoperative RT is effective as prophylactic treatment of postsurgical HO while avoiding discomfort and complications related to the postoperative RT.
51	Knelles *et al*., 1997	723	Acetylsalicylic acid *vs*. 14-day indomethacin *vs*. 7-day indomethacin *vs*. irradiation 4×3 Gy *vs*. 1×7 Gy *vs*. 1×5 Gy (in all cases postoperatively) *vs*. control group	HO was found in 18.4% of the hips and no cases of ankylosis occurred. In 4×3 Gy and 1×7 Gy RT groups, HO presented as grade 0-I, whereas in patients treated with acetylsalicylic acid or 1×5 Gy RT, higher grade HOs were observed. All treatments showed a significant improvement compared with the control group ($p=0.001$).
52	Kölbl *et al*., 1997	301	Postoperative irradiation 1×5 Gy *vs*. 1×7 Gy *vs*. NSAIDs	The results suggested that after hip replacement, prophylactic RT with 7 Gy single-fraction is more effective than RT with 5 Gy in single-fraction or NSAID-based treatment. HO rates were 11.1% 30.1% and 16.0% respectively. The difference in HO overall was statistically significant between NSAID and with 5 Gy-RT ($p<0.015$) and between 7-Gy RT and 5-Gy RT ($p<0.0001$) groups, however no significant difference was observed between NSAID and 7 Gy-RT groups ($p>0.3$).
53	Seegenschmiedt *et al*., 1997	410	From 1987 to 1992: Postoperative 'low dose' 5×2 Gy or 'medium dose' 5×3.5 Gy RT. From 1992 to 1995: 1×7 Gy preoperatively (≤4 h) or 5×3.5 Gy postoperatively (≤96 h)	15 Progressions were found in the postoperative low-dose group and 7 in the medium-dose group ($p>0.05$). Comparing 1×7 Gy preoperatively and 5×3.5 Gy postoperatively, 11 and 4 cases of HO were recorded, respectively ($p<0.05$). Except for a small subset of patients with ipsilateral grade III-IV Brooker, pre- and post-operative RT are equally effective in preventing hip HO after surgery.
54	Kölbl *et al*., 1998	100	1×7 Gy Preoperatively *vs*. NSAID	HOs were recorded in 47.8% and in 11.1% in the 7 Gy preoperative group and in the NSAID group, respectively ($p<0.01$). However, no difference between the two arms with regard to grade III-IV HO was registered ($p>0.05$).
55	Sell *et al*., 1998	153	Group I: 3×3.3 Gy *vs*. Group II: 3×50 mg of diclofenac daily for 3 weeks	Two patients treated with postoperative RT presented grade I HO and 16 patients treated with NSAID had grade I-II HO ($p<0.001$). Both postoperative RT and NSAID were effective prophylactic treatments. The best results were achieved after RT (3×3.3 Gy).
56	van Leeuwen *et al*., 1998	57	1×5 Gy Preoperatively *vs*. control group	During a mean follow-up of 2.5 years, HO rates in the control group were higher (16/19) compared to patients treated with 5 Gy single-fraction RT (6/43) ($p=0.001$).
57	Kienapfel *et al*., 1999	154	1×6 Gy *vs*. indomethacin, post-operatively *vs*. control group	Grade III-IV HO occurred only in patients without postoperative RT or indomethacin, resulting in a statistically significant effect (chi square, $p<0.001$). Both RT and indomethacin are effective in preventing HO.

Table II. *Continued*

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Ref	Authors, year	Patients, n	Treatment arms	Main findings
58	Burd *et al*., 2001	166	8 Gy Within 72 h after surgery *vs*. indomethacin within 24 h after surgery *vs*. no prophylaxis	Grade III-IV HO occurred in 8 in the indomethacin group and 3 in the RT group (p=0.22). Furthermore, all 16 patients who did not undergo prophylactic therapy had HO (6 grade III-IV). RT and indomethacin are effective methods of prophylaxis against HO after surgery.
59	Padgett *et al*., 2003	59	Group A: 2×250 cGy *vs*. Group B: 5×200 cGy	The difference in terms of HO distribution in the two groups was not statistically significant (p=0.086). The success rates after 5 Gy (2×250 cGy) and 10 Gy (5×200 cGy) postoperative RT were 93% and 97%, respectively. RT delivered with 5 Gy dose is effective in HO prophylaxis.
60	Pakos *et al*., 2009	96	Postoperative RT of 1×7 Gy and indomethacin *vs*. indomethacin alone	HO was found in 4 patients treated with 7 Gy single-fraction postoperative RT, in 13 in the indomethacin group (p<0.05) and 13 in a historical group (p<0.05). One patient with grade III HO was recorded both in the combined treatment group and in the historical group. RT plus indomethacin was more effective in HO prophylaxis compared to indomethacin alone.
61	Z Liu *et al*., 2017	147	Postoperative RT: 1×4 Gy *vs*. 1×7 Gy	HOs were detected on radiographs in 42% and 25% of patients treated with 4 Gy and 7 Gy, respectively (p=0.035). RT delivered as 7-Gy single-fraction was more effective than 4-Gy single fraction in HO prophylaxis.

HO: Heterotopic ossification; LD-/HD-RT: low-dose/high-dose radiotherapy; NSAID: non-steroidal anti-inflammatory drug.

with RT to prevent hip HO development, including results in terms of efficacy or toxicity, with data on RT dose and fractionation, with prospective or retrospective design, and enrolling more than 50 patients. Studies were excluded in the case of their being a letter, commentary, editorial, case report, conference proceedings, reports on study protocols, preclinical studies, studies on animal models, imaging or planning studies, surveys, guidelines, or recommendations, or due to inclusion of prophylactic RT for sites other than the hip, or duplication of data.

A summary of the main findings of selected non-randomized studies, randomized trials, and meta-analyses are summarized in Table I, Table II, and Table III, respectively. Figure 1 shows computed tomographic scans of an extensive HO of the right hip of a 55-year-old male patient with paralysis of the lower extremity.

Discussion

All studies on the efficacy of RT in the prevention of hip HO reported a significant advantage over surgery alone (19, 22, 23, 41, 56, 57). However, the incidence of HO after prophylactic RT was highly variable, with overall rates ranging between 6% and 28% (17, 19, 27, 29, 30, 46, 49), and grade III-IV HO rates ranging from 0% to 5% (19, 24, 27, 29, 30, 46, 49, 57). Nevertheless, no grade III-IV hip HO cases were recorded in most series of patients treated with RT (19, 24, 27, 46, 57).

In terms of dose, many studies analyzed the impact of RT regimens on HO rates (18, 20, 26, 32, 38, 46, 48, 51, 52, 59, 61, 65-67). In some studies, single 7- to 8-Gy fractions were found to be equivalent to regimens of 3×4 Gy (18) and 5×2 Gy (26, 38, 46). Furthermore, other studies have shown the superiority of 1×7 Gy over regimens of 1×4 Gy (61), 1×5 Gy (51, 52), 1×5.5 Gy (20), and 3×2 Gy (32). Moreover, some analyses reported the equivalence of 5×2 Gy *versus* 1×7 Gy (38), 1×8 Gy (46), 10×2 Gy (48), 5×3.5 Gy (48), and 2×2.5 Gy (59). In addition, one study showed the greater efficacy of 4×3 Gy compared to 1×5 Gy (51). Finally, two meta-analyses did not record a significant impact of RT dose on postoperative HO incidence (64, 65), while another showed an advantage of multi-fractionated RT over single-fraction RT (67).

In terms of the timing between surgery and prophylactic RT, some studies reported superior results in patients with an interval of less than 6 days (17), and 3 days (19, 28). Furthermore, another study confirmed that delays in postoperative RT can reduce its efficacy in terms of HO prophylaxis (47). Finally, a study showed that the effectiveness of preoperative RT is greater in the case of an RT-surgery interval ≤8 hours (28).

Comparing pre- *versus* post-operative prophylactic RT, three studies did not show significant differences between the efficacy of the two strategies (28, 49, 50). This equivalence was confirmed by three meta-analyses (64, 65, 67).

Comparisons with other HO prophylaxis methods was conducted exclusively between RT and NSAIDs (37, 39, 51, 52, 54, 55, 58, 60, 63, 65, 66, 68). Three studies reported the superiority of RT over indomethacin (37, 39, 60) or acetylsalicylic acid (51). Two other studies confirmed the

Table III. *Number of patients, comparison, and main findings of meta-analyses*

Ref	Authors, year	Patients, n	Comparison	Main findings
62	Pakos *et al*., 2004	1,143	RT *vs*. NSAIDs	RT was more effective than NSAIDs in preventing grade III-IV HOs (RR=0.42, 95% CI=0.18-0.97) or any HO (RR=0.75; 95% CI=0.37-1.71). The overall absolute risk difference for grade III-IV was minimal (−1.18%, 95% CI=−2.45-0.09%). Preoperative RT was significantly less effective than NSAIDs and the postoperative RT resulted superior to NSAIDs especially with higher doses. A significant dose–response relationship was found in patients treated with postoperative RT (p=0.008).
63	Vavken *et al*., 2009	1,295	RT *vs*. NSAIDs	The pooled RR for efficacy of RT and NSAIDs in preventing HO was 0.96 (95% CI=0.88-1.06) and was not dependent on the surgical technique. No statistically significant difference was found between RT and NSAIDs.
64	Popovic *et al*., 2014	5,464 sites	RT doses; treatment sites; postoperative *vs*. preoperative RT	Most studies reported results after postoperative RT (61.6%) delivered as 7 Gy single-fraction. No significant relationship was observed between the number of sites where HO formed and RT dose (p=0.1) nor if RT was delivered before or after surgery (p=0.1).
65	Milakovic *et al*., 2015	1,253 sites	Multiple fractions *vs*. single-fraction RT; preoperative *vs*. postoperative RT; BED>25 Gy *vs*. ≤25 Gy	Multi-fractionated RT was more effective compared to single-dose RT in reducing HO risk (p=0.04). No difference between groups treated with single or multiple fractions was found in terms of HO progression (p=0.34) nor between BED>25 or ≤25 Gy (p=0.28), nor between preoperative and postoperative RT (p=0.43).
66	Cai *et al*., 2019	7,769	Nonselective *vs*. selective NSAIDs *vs*. RT *vs*. controls	Prophylaxis of HO appeared to be more effective with RT. In fact, HO rates after surgery were lower compared to nonselective NSAIDs and selective NSAIDs (OR=0.50, 95% CI=0.25-1.0; OR=0.41, 95% CI=0.17-0.97).
67	Hu *et al*., 2021	1,203	Low *vs*. medium *vs*. high BED; multiple fractions *vs*. single-fraction RT; preoperative *vs*. postoperative RT	A significantly improved prevention of HO progression was found for the medium BED group compared with the low one (p=0.003), while no difference was observed between low and high BED groups groups (p=0.21). A multi-fractionated RT significantly reduced HO progression compared to single fraction RT (p=0.04). No differences were recorded comparing preoperative and postoperative RT (p=0.43).
68	Shapira *et al*., 2021	8,653	RT *vs*. NSAIDs *vs*. no prophylaxis; non-selective NSAIDs *vs*. COX-II selective NSAIDs	In studies on prophylactic RT, 28.6-97.4% of patients showed no HO, with 0.0-11.9% severe HO. In studies on prophylactic NSAIDs-based treatment, 76.6%-88.9% of patients had no HO, while 0.0%-1.8% developed severe HO. Prophylactic treatment of HO with NSAIDs may be more effective than RT in high-risk patients after total arthroplasty of the hip.

BED: Biologically effective dose; CI: confidence interval; COX-II: cyclo-oxygenase 2; HO: heterotopic ossification; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; RR: risk ratio; RT: radiotherapy.

superiority of prophylactic RT over NSAIDs in general (52, 55). In contrast, one study showed the superiority of NSAIDs over RT in terms of preventing all HOs but equivalence between the two treatments in terms of grade III-IV HO (54). Finally, two meta-analyses showed the superiority of RT over NSAIDs (62, 66), two meta-analyses showed the two treatments to be equivalent (58, 63), and one meta-analysis showed the superiority of NSAIDs (68).

Only two studies provided information on different outcomes of prophylactic RT in different HO subgroups. Ebinger *et al*. compared the outcome after surgery and prophylactic RT in patients with hip HO that developed after brain injury, local hip trauma, or the combination of both (25). The authors recorded similar recurrence rates among groups, but better clinical outcome in patients with hip trauma. Cipriano *et al*. reported a lack of protective effect by prophylactic RT (1×7 Gy) in patients with resected neurogenic HO (36).

In terms of surgical outcome and side-effects, one study showed that prophylactic RT combined with indomethacin did not have an impact on the stability of cementless cups (35). Moreover, another article reported prophylactic RT to be associated with delayed wound-healing rates similar to those after surgery alone (36). Furthermore, one study showed the same rate of implant loosening after prophylactic RT or indomethacin (45). In contrast, another analysis

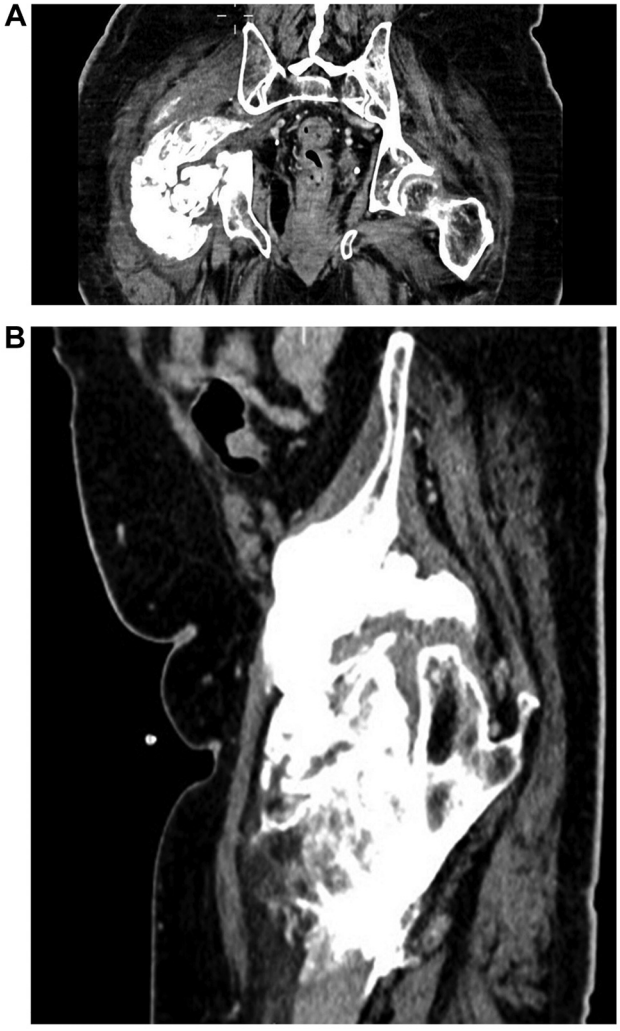

Figure 1. *Extensive heterotopic ossification of the right hip in a 55-year-old male patient with paralysis of the lower extremity. Computerized tomography: A: coronal reconstruction; B: sagittal reconstruction.*

showed a higher incidence of postoperative sepsis in patients undergoing prophylactic RT (44). Finally, one study showed the absence of radiation-induced toxicity in patients undergoing prophylactic RT (36) and another reported the absence of RT-induced tumors at the treated site after 10 years of follow-up (45).

In terms of RT technique, one study showed that incorrect positioning of shielding blocks is associated with a higher incidence of HO (17). Another study showed that shielding was associated with higher rates of HO (34). Finally, a planning study on patients treated with prophylactic RT reported lower mean and maximum doses to testicles in patients whose therapy was planned with a split-beam technique (42).

In summary, the results of this literature review show that RT is effective in the prevention of hip HO, albeit with wide ranges of efficacy across series. Low RT doses (4-5.5 Gy) seem to be less effective compared to intermediate doses (7-8 Gy), while higher doses do not provide further advantages. However, we can note that German guidelines recommend a 5×3.5 Gy regimen in patients with a high risk of developing HO (2). For effective prophylactic RT, it is important to respect the correct intervals between preoperative RT and surgery or between surgery and postoperative RT, and a careful definition of treatment fields is needed. On the contrary, clear evidence of the superiority of post-operative *versus* pre-operative RT is lacking. However, some authors suggested the use of pre-operative RT in order to reduce logistical problems (31) and discomfort and possible complications of post-operative RT (50).

Comparisons between prophylactic RT and administration of NSAIDs have shown conflicting results, although most evidence is in favor of RT. Furthermore, there is very little evidence on the efficacy of RT in the prevention of HO recurrence in patients undergoing HO removal and on the efficacy of RT in the different HO subgroups based on etiology. Moreover, RT is not correlated with clinically detectable side-effects, peri- or post-operative complications, or radiation-induced tumor rates.

This analysis has several limitations. Most of the evidence comes from retrospective studies. This type of study design is obviously associated with the risk of selection bias. Indeed, some authors explicitly admitted that patients at higher risk of HO were preferentially referred to RT over observation or drug treatment alone (26, 36). It is clear that this bias may have limited the detection of benefits in patients undergoing RT. In addition, many studies evaluated the incidence of HO based on the Brooker classification (69), a widely used quantitative and qualitative assessment tool. However, this classification presents some ambiguities that may limit its generalizability between different centers and specialists (70). Furthermore, no study included patient-reported outcome measures among the main objectives of the analysis. Therefore, there is a lack of data on the real impact of RT on quality of life. Finally, in most cases, the evaluation of prophylactic RT efficacy was performed considering all HO grades. However, only higher-grade HOs are known to affect physical functions (30).

In conclusion, after 40 years of experience, RT is an established prophylactic treatment for hip HO. However, optimal doses, techniques, and timing remain undefined, as does the usefulness of combining RT with drug treatments, at least for some categories of patients.

Therefore, further studies are needed, in particular to i) evaluate the efficacy of RT in secondary HO prevention in combination with the resection of already developed HOs; ii) evaluate the effectiveness of RT in different HO

subgroups based on etiology; iii) define optimal RT timing, technique, combinations with drugs, and dose to achieve the best therapeutic results, according to the risk categories.

Conflicts of Interest

None declared.

Authors' Contributions

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

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