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Systematic review

Radiotherapy for the prophylaxis of heterotopic ossification: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Heterotopic ossification (HO) involves the formation of lamellar bone in nonosseous tissue. For HO, radiotherapy has been shown to be an effective prophylactic modality.
Objective: To compare HO outcomes following radiotherapy and to investigate the comparative efficacy of preoperative versus postoperative radiotherapy.
Methods: A systematic search was conducted on Ovid MEDLINE, EMBASE and Cochrane CENTRAL. Studies were included if they were randomized controlled trials (RCTs) that included patients who were prescribed prophylactic radiation for whom relevant HO progression outcomes were reported.
Results: From a literature search of 528 articles, 12 RCTs were included. There was a statistically significant reduction in HO prevalence with multiple as opposed to single fraction radiotherapy ($p = 0.04$), however there was no statistically significant difference when examining HO progression ($p = 0.34$). There was no statistically significant difference in HO progression when comparing a biologically effective radiation dose (BED) of >2500 cGy versus $\leqslant$2500 cGy ($p = 0.28$). As well, no statistically significant difference existed in HO progression between postoperative versus preoperative radiation ($p = 0.43$).
Conclusion: There was no difference between postoperative or preoperative radiotherapy in preventing HO progression. There seems to be no relationship between BED greater or less than 2500 cGy and the efficacy of HO prophylaxis. Multiple fractions seem to be more effective than single fraction radiotherapy in preventing HO progression.
 Radiotherapy and Oncology 116 (2015) 4–9

Heterotopic ossification (HO) is the formation of lamellar bone in non-osseous tissues such as muscles, nerves and connective tissue [1,2]. HO can develop in various sites, including the hip, knee, shoulder and elbow and is usually the result of traumatic acetabular fracture, total hip arthroplasty or central nervous injury [3,4]. The incidence of HO after open reduction of acetabular fractures ranges from 5% to 90% [5].

HO formation is presumed to result from differentiation of pluripotent mesenchymal cells into osteoblasts [6]. Bone morphogenic protein (BMP2) has been shown to induce this process [7]. Specifically, BMP2 interacts with the Wnt/β-catenin in osteoblasts, which leads to differentiation. Differentiation usually occurs 16 h after surgery and peaks at around 32 h postoperatively. It normally takes at least 4–6 weeks for mineralization to be detected by radiographs [6].

The risk factors for developing HO include male gender, osteoarthritis, and previous development of HO at a particular anatomic site [8]. In many cases, HO is asymptomatic and is only detected on imaging. In other cases, it is asymptomatic until it has reached higher degrees of ossification that may affect patients' function [9]. Pain and decreased range of motion are the most common symptoms of advanced HO [10]. To classify the degree of ossification, the Brooker classification system is most commonly employed [11]. The classification is based on AP radiographic views only and is divided into five grades: grade 0, which represents no soft tissue calcification; grade 1, which represents islands of bone within the soft tissue about the hip; grade 2, which represents bone spurs in the pelvis or proximal end of the femur with at least 1 cm between the opposing bone surfaces; grade 3, which represents bone spurs from the pelvis or proximal end of femur with less than 1 cm between opposing bone surfaces; and grade 4, which represents radiographic ankylosis [11].

Two common methods of prophylaxis of HO development are radiotherapy and non-steroidal anti-inflammatory drugs (NSAIDs). In a meta-analysis of randomized controlled trials (RCTs) by Vavken et al., HO outcomes were compared in NSAID vs. radiotherapy treatment arms. In total, 634 patients who received radiation and 661 patients who received NSAIDs were included in the study. There was no significant difference in the

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two prophylactic modalities seen (risk ratio (RR) = 1.2; 95% confidence interval (CI) = 0.8–1.8; $p = 0.48$) [12]. However, there is a significant difference between the cost effectiveness of radiotherapy versus NSAIDs [13]. In another meta-analysis by Vavken et al., results strongly supported the conclusion that NSAIDs are considerably more cost effective than radiotherapy [13]. However, compared to NSAIDs, radiation therapy may be associated with lower incidence of grade 3 and 4 HO. Therefore, radiotherapy may be a preferred option in very high risk patients or in patients with contraindications to NSAIDs.

Currently, it is hypothesized that radiation works as a method of prophylaxis by inactivating pluripotent mesenchymal cells before they start differentiating into osteoblasts [14]. Radiation can be either given preoperatively or postoperatively, although the latter remains a more common treatment choice [15,16]. A meta-analysis by Popovic et al. examined the published literature to examine optimal prescription parameters in 5464 patients receiving prophylactic radiotherapy. They found that there was no statistically significant relationship between the percentage of patients receiving HO and radiation dose, and no significant difference in the effectiveness between preoperative versus postoperative radiotherapy [15]. The purpose of our meta-analysis is to determine if these previous findings could be corroborated in a more controlled environment by only considering the results of randomized controlled trials (RCTs). Specifically, our meta-analysis asks whether there is a difference in the development of HO based on fractionation schedule (single vs. multiple), preoperative versus postoperative radiotherapy administration, and high versus low biologically effective radiation dose (BED).

Methods

A systematic literature search on Ovid MEDLINE and Ovid OLDMEDLINE (1946 to February week 4 2015), EMBASE and EMBASE Classic (1947–2015 week 8) and the Cochrane Central Register of Controlled Trials (January 2015) was conducted utilizing the keyword "heterotopic ossification" combined with either "radiotherapy", "radiation prophylaxis", "radiation therapy" or "cancer radiotherapy".

Studies that were included had to be RCTs that contained patients who had all been prescribed a known dose of radiotherapy. The prevalence of HO had to be reported and stratified by radiation site. Studies were only included if the average or median length of radiographic follow-up exceeded eight weeks. Only English trials were included.

Data collection

Collected data included the year of treatment, treatment center, site of radiation, number of treatment sites with radiographic follow-up, radiation dose, timing of radiation (postoperative or preoperative), past history of HO, percentage of sites with any HO prior to study inclusion, percentage of sites developing any HO over the study duration, as well as Brooker grade-specific data for HO prevalence prior to and during the study.

Statistical analysis

Review Manager (RevMan 5.2) by Cochrane IMS was used to conduct the meta-analysis. The Mantel–Haenszel method was applied and a random effects model was used to generate odds ratios (OR) and accompanying 95% confidence intervals (CI). A p-value of $p < 0.05$ was considered statistically significant. The intention-to-treat principle was utilized in all statistical analyses. For the pooled analysis, prevalence rates were used because not all studies included information about baseline HO rates.

Table 1
Baseline demographic data for included randomized controlled trials.

Study (Author, year)	Year of treatment	Treatment center	Site of radiation	Number of Treatment sites with radiographic follow-up	Radiation dose (cGy)/ fractionation	Postoperative versus preoperative radiation	Past patient history of HO	Percentage of sites with any HO previous to study inclusion	Percentage of sites with Brooker grade 1/2 HO previous to study inclusion	Percentage of sites with Brooker grade 3/4 HO previous to study inclusion
Burd (2001)	1992–1999	USA	Hip	78	800/1	Postoperative	Unknown	n/a	n/a	n/a
Hamid (2010)	2005–2008	USA	Elbow	21	700/1	Postoperative	Unknown	n/a	n/a	n/a
Kienapfel (1999)	1992–1993	Germany	Hip	49	600/1	Postoperative	Unknown	n/a	n/a	n/a
Knelles (1997)	1988–1994	Germany	Hip	101	1200/4	Postoperative	Unknown	n/a	n/a	n/a
Knelles 2nd study arm (1997)	1988–1994	Germany	Hip	95	700/1	Postoperative	Unknown	n/a	n/a	n/a
Knelles 3rd study arm (1997)	1988–1994	Germany	Hip	93	500/1	Postoperative	Unknown	n/a	n/a	n/a
Kölbl (1998)	1995–1996	Germany	Hip	46	700/1	Preoperative	Mixed	n/a	n/a	n/a
Moore (1998)	1993–1996	USA	Hip	33	800/1	Postoperative	Unknown	n/a	n/a	n/a
Padgett (2003)	n/a	USA	Hip	29	500/2	Postoperative	Mixed	6/29 = 20.7%	n/a	n/a
Padgett 2nd study arm (2003)	n/a	USA	Hip	30	1000/5	Postoperative	Mixed	7/30 = 23.3%	n/a	n/a
Pellegrini (1992)	1987–1989	USA	Hip	34	800/1	Postoperative	Mixed	12/34 = 35.3%	5/34 = 14.7%	7/34 = 20.6%
Pellegrini 2nd study arm (1992)	1987–1989	USA	Hip	28	1000/2	Postoperative	Mixed	15/28 = 53.6%	5/28 = 17.9%	10/28 = 35.7%
Pellegrini (1996)	1990–1992	USA	Hip	49	800/1	Preoperative	Mixed	15/49 = 30.6%	4/49 = 8.2%	11/49 = 22.4%
Pellegrini 2nd study arm (1996)	1990–1992	USA	Hip	37	800/1	Postoperative	Mixed	8/37 = 21.6%	5/37 = 13.5%	3/37 = 8.1%
Seegenschmiedt (1997)	1992–1995	Germany	Hip	80	700/1	Preoperative	Mixed	54/80 = 67.5%	25/80 = 31.3%	29/80 = 36.3%
Seegenschmiedt 2nd study arm (1997)	1992–1995	Germany	Hip	81	1750/5	Postoperative	Mixed	55/81 = 67.9%	33/81 = 40.7%	22/81 = 27.2%
Seegenschmiedt 3rd study arm (1997)	1987–1992	Germany	Hip	118	1750/5	Postoperative	Mixed	59/118 = 50%	29/118 = 24.6%	30/118 = 25.4%
Seegenschmiedt 4th (1997)	1987–1992	Germany	Hip	131	1000/2	Postoperative	Mixed	66/131 = 50.4%	35/131 = 26.7%	31/131 = 23.7%
Sell (1998)	1992–1993	Germany	Hip	77	990/3	Postoperative	Mixed	6/77 = 7.8%	5/77 = 6.5%	1/77 = 1.3%
Van Leeuwen (1998)	1989–1992	The Netherlands	Hip	43	500/1	Preoperative	Mixed	4/43 = 9.3%	n/a	n/a

However, incidence of progression is a more accurate measure of the efficacy of prophylaxis; since some studies being considered have this information, different endpoints were used.

Results

From a literature search of 577 articles, title and abstract screening revealed 456 exclusions. Of the 121 remaining articles, a total of 12 RCTs that spanned 20 study arms were selected for inclusion to the present study.

Of the included studies, six, five and one came from the United States [17–22], Germany [4,23–26] and the Netherlands [27], respectively (Table 1; Supplementary Material 1). The studies were published between 1992 and 2010 with the majority published before 2000 [4,19,21–25]. All treatment arms reported outcomes for hip radiotherapy [4,17,19–27] except for one trial that included patients receiving radiotherapy to the elbow [18]. According to self-reported criteria, 469 sites (37.4%) had a high risk of developing HO. In terms of radiotherapy administration, 1035 sites (82.6%) received postoperative treatment while 218 sites (17.4%) received treatment preoperatively. The treatment year ranged from 1987–2008 (mean: 1992.5), while mean latest radiographic follow-up ranged from 6 to 31 months with a mean of 21.9 months between the studies. Only Pellegrini et al. included median follow-up which was 31 months for the first study arm and 46 weeks for the second arm [22]. Combining the data, 658 sites received single fraction radiation doses while 595 received multiple fractions (Table 1).

A full summary of HO outcomes in individual study arms is presented in Table 2. Briefly, the overall percentage of sites developing any HO was 34.1% (Brooker grades 1 or 2 HO: 30.2%; Brooker grades 3 or 4 HO: 3.9%). BED calculations were performed for all applicable study arms; BED refers to the true biological dose that a tissue receives and it depends on the total dose, fraction per dose and specific tissue characteristics (Supplementary Material 2). Arms were grouped into >2500 cGy ('high BED') and $\leqslant$2500 cGy ('low BED') to allow for head-to-head comparisons of HO outcomes between arms, and all BED values were calculated using a generic late effects alpha/beta ratio of 3. 2500 cGy was chosen as the cutoff to separate the commonly used fractionation schemes of 700/1 (=2333 cGy BED) and 800/1 cGy (=2933 cGy BED) and to have similar sample sizes between the two groups. For BED values less than or equal to 2500 cGy, the mean percentage of sites developing HO was 26.4% (range: 2.6–69%). Further, most cases involved Brooker grades 1 or 2 HO (mean 23.5%, range: 2.6–62.1%), while fewer cases of Brooker grades 3 or 4 HO were found (mean: 2.86%, range: 0–6.9%). Data with BED values greater than 2500 cGy revealed higher rates of HO formation (mean: 42.8%, range: 28.6–55.3%). For Brooker grades 1 or 2 HO formation, 37.7% (range: 24.2–49.7%) of sites developed HO while only 5.1% of sites developed Brooker grades 3 or 4 HO (range: 4.3–5.7%).

Next, the effect of preoperative versus postoperative radiotherapy on prevalence of HO was examined (Table 3). The overall prevalence of HO with preoperative radiotherapy was 42.2% while postoperative radiotherapy yielded 32.4% of sites that had HO development. For Brooker grades 1 or 2 HO development in the preoperative group, the prevalence was 35.8% while 6.4% of sites developed Brooker grades 3 or 4. In contrast, 29% of sites developed Brooker grade 1 or 2 HO when treated postoperatively and only 3.4% of sites were Brooker grades 3 or 4. Doses for which there was a direct comparison between preoperative and postoperative radiotherapy RCT arms were 500/1, 700/1 and 800/1 cGy and all were single fractions. The percentage of sites developing HO with preoperative 500/1 cGy radiotherapy was 14% while it was 39.3% for postoperative radiotherapy of the same dose. However, 56.3% of sites developed HO after 700/1 cGy was prescribed preoperatively compared to 15.5% of sites that developed HO after receiving postoperative radiotherapy of the same dose. Finally, prescribing 800/1 cGy preoperatively resulted in 30.6% of sites developing HO whereas postoperative radiotherapy led to HO development in 28% of sites.

Five included RCTs contained multiple fraction study arms which allowed for head-to-head comparison of different radiotherapy schedules [4,20–22,24]. The study by Knelles et al. compared 1200/4 cGy with 700/1 cGy and 500/1 cGy all prescribed postoperatively [24]. The total number of sites receiving radiation was 289; of this total, 101 sites were randomized to 1200/4 cGy, 95 were randomized to 700/1 cGy and 93 were randomized to 500/1 cGy. There was a statistically significant difference in HO prevalence following 1200/4 and 500/1 cGy regimens ($p = 0.001$) as well as between 700/1 and 500/1 cGy arms ($p < 0.015$) with the 500/1 cGy arm being statistically inferior to other treatment arms. When comparing 1200/4 with 700/1 cGy, there was no statistically significant difference between arms ($p = 0.087$) [24]. Padgett et al. compared postoperative 500/2 cGy ($n = 29$) with 1000/5 cGy ($n = 30$). For the sites given 500/2 cGy, 20 out of 29 developed HO (69%), while 13 out of 30 sites (43.3%) developed HO after

Table 2
Development rates of heterotopic ossification in individual study arms.

Study (Author and year)	Dose (cGy)/ fractionation	Average time of radiographic follow-up (months)	Development rates of heterotopic ossification		
			Overall (any Brooker grade HO)	Brooker grades 1/2 HO	Brooker grades 3/4 HO
Burd (2001)	800/1	16	19/78 = 24.4%	16/78 = 20.5%	3/78 = 3.85%
Hamid (2010)	700/1	7.5	7/21 = 33.3%	5/21 = 23.8%	2/21 = 9.5%
Kienapfel (1999)	600/1	18	12/49 = 24.5%	12/49 = 24.5%	0/49 = 0%
Knelles (1997)	1200/4	12	5/101 = 5%	5/101 = 5%	0/101 = 0%
Knelles 2nd study arm (1997)	700/1	12	11/95 = 11.6%	11/95 = 11.6%	0/95 = 0%
Knelles 3rd study arm (1997)	500/1	12	28/93 = 30.1%	27/93 = 29%	1/93 = 1.1%
Kölbl (1998)	700/1	6	22/46 = 47.8%	21/46 = 45.6%	1/46 = 2.2%
Moore (1998)	800/1	12	9/33 = 27.3%	6/33 = 18.2%	3/33 = 9.1%
Padgett (2003)	500/2	13	20/29 = 69%	18/29 = 62.1%	2/29 = 6.9%
Padgett 2nd study arm (2003)	1000/5	12	13/30 = 43.3%	12/30 = 40%	1/30 = 3.3%
Pellegrini (1992)	800/1	11	12/34 = 35.3%	10/34 = 29.4%	2/34 = 5.9%
Pellegrini 2nd study arm (1992)	1000/2	13.5	9/28 = 32.1%	7/28 = 25%	2/28 = 7.1%
Pellegrini (1996)	800/1	Minimum of 6 months	15/49 = 30.6%	14/49 = 28.6%	1/49 = 2%
Pellegrini 2nd study arm (1996)	800/1	Minimum of 6 months	11/37 = 29.7%	10/37 = 27%	1/37 = 2.7%
Seegenschmiedt (1997)	700/1	Minimum of 6 months	49/80 = 61.3%	38/80 = 47.5%	11/80 = 13.8%
Seegenschmiedt 2nd study arm (1997)	1750/5	Minimum of 6 months	45/81 = 55.6%	39/81 = 48.1%	6/81 = 7.4%
Seegenschmiedt 3rd study arm (1997)	1750/5	Minimum of 6 months	65/118 = 55.1%	60/118 = 50.8%	5/118 = 4.2%
Seegenschmiedt 4th (1997)	1000/2	Minimum of 6 months	67/131 = 51.1%	60/131 = 45.8%	7/131 = 5.3%
Sell (1998)	990/3	Minimum of 6 months	2/77 = 2.6%	2/77 = 2.6%	0/77 = 0%
Van Leeuwen (1998)	500/1	31	6/43 = 14%	5/43 = 11.6%	1/43 = 2.3%

Table 3
Pooled development rates of heterotopic ossification based on radiotherapy dose and preoperative versus postoperative prescription.

Pooled study references	Radiotherapy dose (cGy)	BED	Overall (any Brooker grade)	Brooker grades 1/2	Brooker grades 3/4	Overall outcome after preoperative radiotherapy	Brooker grades 1/2 HO after preoperative radiotherapy	Brooker grades 3/4 HO after preoperative radiotherapy	Overall outcome after postoperative radiotherapy	Brooker grades 1/2 HO after postoperative radiotherapy	Brooker grades 3/4 HO after postoperative radiotherapy
24,27	500/1	12.33 Gy	34/136 = 25%	32/136 = 24%	2/136 = 1.47%	6/43 = 14%	5/43 = 11.6%	1/43 = 2.3%	28/93 = 30.1%	27/93 = 29%	1/93 = 1.1%
20	500/2	9.17 Gy	20/29 = 69%	18/29 = 62.1%	2/29 = 6.9%	n/a	n/a	n/a	20/29 = 69%	18/29 = 62.1%	2/29 = 6.9%
23	600/1	18 Gy	12/49 = 24.5%	12/49 = 24.5%	0/49 = 0%	n/a	n/a	n/a	12/49 = 24.5%	12/49 = 24.5%	0/49 = 0%
4,18,24–25	700/1	23.33 Gy	89/242 = 36.8%	75/242 = 31%	14/242 = 5.8%	71/126 = 56.3%	59/126 = 46.8%	12/126 = 9.5%	18/116 = 15.5%	16/116 = 13.6%	2/116 = 17%
17,19,21–22	800/1	29.33 Gy	66/231 = 28.6%	56/231 = 24.2%	10/231 = 4.3%	15/49 = 30.6%	14/49 = 28.8%	1/49 = 2%	51/182 = 28%	42/182 = 23.1%	9/182 = 4.9%
26	990/3	20.79 Gy	2/77 = 2.6%	2/77 = 2.6%	0/77 = 0%	n/a	n/a	n/a	2/77 = 2.6%	2/77 = 2.6%	0/77 = 0%
4,21	1000/2	26.67 Gy	76/159 = 47.8%	67/159 = 42.1%	9/159 = 5.7%	n/a	n/a	n/a	76/159 = 47.8%	67/159 = 42.1%	9/159 = 5.66%
20	1000/5	16.67 Gy	13/30 = 43.3%	12/30 = 40%	1/30 = 3.3%	n/a	n/a	n/a	13/30 = 43.3%	12/30 = 40%	1/30 = 3.3%
24	1200/4	24 Gy	5/101 = 5%	5/101 = 5%	0/101 = 0%	n/a	n/a	n/a	5/101 = 5%	5/101 = 5%	0/101 = 0%
4	1750/5	37.92 Gy	110/199 = 55.3%	99/199 = 49.7%	11/199 = 5.5%	n/a	n/a	n/a	110/199 = 55.3%	99/199 = 49.7%	11/199 = 5.5%
4,17–27	Overall		427/1253 = 34.1%	378/1253 = 30.2%	49/1253 = 3.9%	92/218 = 42.2%	78/218 = 35.8%	14/218 = 6.4%	335/1035 = 32.4%	300/1035 = 29.0%	35/1035=3.4%

receiving 1000/5 cGy ($p = 0.086$) [20]. An RCT by Pellegrini et al. examined HO outcomes for 800/1 cGy and 1000/2 cGy [21]. The total number of sites in the study was 62; 34 were randomized to 800/1 cGy and 28 were randomized to 1000/2 cGy. Although no statistical comparison was performed between treatment arms, the number of sites developing HO was 12 out of 34 (35.3%) for 800/1 cGy and 9 out of 28 exposed sites (32.1%) for the 1000/2 cGy group [21]. A follow-up study by Pellegrini et al. examined preoperative ($n = 49$) compared with postoperative ($n = 355$) radiotherapy both at a dose of 800/1 cGy. For those sites that received preoperative radiation, 15 out of 49 developed HO (30.6%) while 12 sites out of 34 (35.3%) developed HO after postoperative 800/1 cGy radiation ($p = 0.99$) [22].The final article that included multiple study arms was conducted by Seegenschmiedt et al. [4]. This article was a compilation of two studies, the first of which looked at HO outcomes following 1000/2 cGy versus 1750/5 cGy postoperative radiotherapy, while the second study examined 700/1 cGy prescribed preoperatively versus 1750/5 cGy prescribed postoperatively. A total of 410 sites were randomized into four groups. From study one, the number of sites developing HO after 1000/2 cGy was 67 out of 131 (51.1%) and for 1750/5 cGy, the number of sites was 65 out of 118 (55.1%). For study 2, 49 of 80 sites (61.3%) developed HO following preoperative administration of 700/1 cGy while 45 of 81 sites (55.6%) developed HO after receiving postoperative 1750/5 cGy radiotherapy [4].

Either development of new HO and progression of Brooker grade can both be used to assess the efficacy of prophylaxis. Progression of HO was reported in three trials and was used as an endpoint for this meta-analysis [4,21,24]. This endpoint accounts for some of the trials which included patients with HO at baseline. Overall, there was no statistically significant difference in HO progression between high and low BED treatment arms ($p = 0.28$, OR: 0.46) (Supplementary Material 3a). As well, no statistically significant difference existed between high or low BED arms in terms of Brooker grades 1 or 2 ($p = 0.61$, OR = 0.66) and Brooker grades 3 or 4 HO development ($p = 0.22$, OR = 0.35) (Supplementary Material 3b and 3c).

The second analysis for the progression of HO compared single versus multiple fractions. Overall, there was a statistically significant reduction in HO progression with multiple as opposed to single fraction radiotherapy ($p = 0.04$, OR = 0.34); similarly, progression of HO in Brooker grades 1 or 2 was statistically significant ($p = 0.0009$, OR = 0.29) (Supplementary Material 4a and 4b). However, progression of Brooker grades 3 or 4 HO was not significant between single versus multiple fraction arms ($p = 0.32$, OR = 0.39) (Supplementary Material 4c).

The last comparison in treatment efficacy concerned preoperative versus postoperative radiotherapy. No statistically significant differences existed between preoperative versus postoperative radiation for overall HO ($p = 0.43$, OR = 1.91), Brooker grades 1 or 2 HO ($p = 0.51$, OR = 1.52), and Brooker grade 3 or 4 ($p = 0.27$, OR = 2.88) (Supplementary Material 5a–5c).

Lastly, assessing side effects in the included studies was not possible because only one study reported side effects data [24]. Therefore, a meta-analysis was not performed.

Discussion

Radiation is a commonly used prophylactic method for the development of HO. Radiation is either prescribed postoperatively or preoperatively with the former more commonly employed in the literature [4,17,18–24,26]. The present meta-analysis examined the effects of radiation dose, fractionation scheme and timing on the prevalence of HO and the incidence of HO progression.

In our study, the most commonly prescribed dose was 700/1 cGy (n = 242 out of 1253) with radiation mostly prescribed postoperatively (82.6%). Overall, the prevalence of any Brooker grade HO was 34.1% and there were very few cases of Brooker grades 3 or 4 HO (weighted mean: 3.9%). For BED less than or equal to 2500 cGy, the number of sites that developed HO was 26.4%, while BED greater than 2500 cGy yielded a much higher result of 42.8%. However, in terms of progression of HO, our analysis showed no significant difference between high (>2500 cGy) vs. low BED ($\leqslant$2500 cGy) treatment arms. In the meta-analysis by Popovic et al., [15] the authors found a statistically non-significant relationship between radiation dose and the prevalence of HO, which is in agreement with the progression analysis.

Although the percentage of sites developing HO was higher with a higher BED, we found no difference between high (>2500 cGy) and low ($\leqslant$2500 cGy) BED treatment arms for all conducted progression analyses. Therefore, given that higher doses of radiotherapy can lead to further possible side effects, such as secondary malignancies and infertility [28], and given that the present results show an inconclusive relationship for the progression of HO, we believe that lower BED treatments should be used to prevent the progression of HO. This holds especially true for patients with poor performance status, for whom it is important to minimize any associated psychosocial burden associated with further visits to the radiotherapy center.

Radiotherapy may be more efficacious when administered in multiple fractions as opposed to single fractions. For the overall progression endpoint and for Brooker grades 1 or 2 HO, multiple fractions were statistically superior to single fractions. Given that we found no significant effect of BED on HO progression, the effect of fraction schedule seems to be an independent contribution. Even though this difference in efficacy may exist, single fraction radiotherapy could minimize visits to the radiotherapy center and could thus lower associated patient burden. As such, administration of single fraction radiotherapy may be more appropriate if the prognosis and performance status of the patient is poor.

In terms of preoperative versus postoperative radiotherapy, arms administering preoperative radiation had a higher resultant prevalence of HO (overall mean: 42.2% compared with 32.4% for postoperative radiation). For both Brooker grades 1 or 2 and grades 3 or 4 HO development, preoperative radiotherapy resulted in a higher proportion of HO development than postoperative radiation. However, when examining the data for progression of HO, there was no statistically significant difference between the administration of preoperative and postoperative radiotherapy for any of the included endpoints. This is in contrast to the findings published by Popovic et al., who found a statistically significantly higher proportion of Brooker grade 1 or 2 HO development in sites that were treated postoperatively (p = 0.0499) [15].

There are limitations to the current meta-analysis. Despite having a large sample size of radiation sites (n = 1253) and including only RCTs, the population of patients in published RCTs may not reflect the entire population of patients receiving radiotherapy for the prevention of HO. Also, due to the inclusion criteria of our study, only a subset of the RCT's could be included, limiting the generalizability of our results. Finally, due to the nature of the meta-analysis, interpretations based on our data should be made at the level of the cohort instead of the patient.

The importance of performing a meta-analysis in a controlled environment using appropriate endpoints is highlighted in this paper. Despite a pooled analysis showing a difference in HO incidence based on dose and radiotherapy timing, our meta-analysis shows that low-dose is as effective as high-dose radiotherapy for preventing HO progression. Likewise, based on our findings, there is no difference between the efficacy of pre-operative and post-operative radiotherapy. Finally, our meta-analysis does show that multiple fraction radiation is superior to single fractions. The results of this study can help optimize radiation prescription parameters and develop future guidelines for optimal use of resources. Ultimately, the present analysis has shown that low-dose radiotherapy is an effective method of prophylaxis for HO development, either when prescribed postoperatively or preoperatively.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.05.022.

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