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Outcomes of Pre-Operative vs. Post-Operative Radiation for Heterotopic Ossification Prevention in Children with Neuromuscular Hip Dysplasia Undergoing Proximal Femoral Resection

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Abstract

Background—Few studies exist to inform the extrapolated practice of irradiating children for heterotopic ossification (HO) prevention. We report the incidence of HO formation following prophylactic pre-operative compared to post-operative radiation therapy (RT) in children with neuromuscular hip dysplasia following proximal femoral resection (PFR).

Methods—A retrospective, two-institution chart review was performed. Eligibility was limited to patients with at least one year of follow up. Evaluation included radiographic HO grading by a combined severity scale, assessment of synchronous symptoms of pain or decreased range of motion, and stratification by pre- vs. post-operative reception of RT. A control cohort included 4 non-irradiated hips after PFR.

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Author Contribution:
Study conception and design: All authors
Data acquisition: Hess, Stein-Wexler, Davids
Data analysis: Hess, Qi
Data interpretation: All authors
Manuscript preparation: All authors

Level of Evidence: Therapeutic retrospective comparative study (Level III).

Results—Twenty-five hips in 20 children met eligibility criteria. Eleven hips were irradiated pre-operatively and 14 post-operatively. Radiographic evidence of post-RT development of HO (rHO) was found in all 25 hips and earlier in patients irradiated preoperatively (median time to rHO was 4.0 vs 15.7 months, p=0.03, CI 0.24–21.5). There was no statistically-significant difference in the development of symptomatic HO (p=0.62) between the pre-operative (45.5%) and post-operative (35.7%) groups, nor in HO grade (p=0.34). Seven (28%) of the 25 hips (5 pre-operative and 2 post-operative) had documentation of rHO-free intervals after surgery, with an average duration of 5.6 months, while the remaining presented with rHO at first follow-up visit. All eligible control hips (100%) developed rHO and sHO.

Conclusions—Peri-operative RT did not prevent the formation of rHO in any child with neuromuscular hip dysplasia after PFR. Extrapolation of evidence of the efficacy of RT for HO prevention in ambulatory adults after traumatic hip injury to a population of children with central nervous system injury and NHD may be premature. Additional studies are needed to clarify optimal prevention of HO in this population.

Introduction

Central nervous system (CNS) injury is a risk factor for the formation of heterotopic ossification (HO).(1, 2) Compared to the more well-known risk factor of traumatic hip injury, however, the mechanism by which CNS injury induces HO formation is less well understood.(1) Most studies evaluating peri-operative interventions for the prevention of HO have been conducted in adult populations without prior CNS injury following traumatic hip injury and repair.(3) The findings of these studies have informed a single study on the use of radiation therapy (RT) as an intervention for HO prevention in adult patients with paraplegia, albeit with short follow up of only 12 weeks.(4)By extrapolation, our clinical practice has historically included use of peri-operative radiation in children with CNS injury undergoing proximal femoral resection interposition arthroplasty (PFR), a common palliative intervention in children for alleviation of hip pain and joint immobility. Post-PFR HO formation can lead to functional decline and require repeat surgical intervention.(2) Few studies exist to inform the extrapolative practice of irradiating these children for HO prevention. We report the incidence and severity of HO in quadriplegic children with neuromuscular hip dysplasia (NHD) following preventative pre- vs. post-operative single-fraction, low-dose RT.

Materials and Methods

With Institutional Review Board approval, a retrospective review of electronic and available paper and radiographic medical records was performed of children ages 19 and under with with NHD (mostly from cerebral palsy [CP])and resulting spastic or dystonic plegiatreated with palliative PFR and peri-operative RT between 1998 and 2012. The primary endpoint was the post-operative development of radiographic evidence of heterotopic ossification (rHO), stratified by the reception of pre- versus post-operative RT. Secondary endpoints were the development of symptomatic heterotopic ossification (sHO) and grade of rHO. We defined grade using the scale described by Toom, et al.(5) (Figure 1), which combines numerous prior scales into one, including the well-known classification by Brooker, et al(6).

Assignment of HO grade was determined by a board-certified pediatric diagnostic radiologist [RSW]. Presence of rHO was either confirmed by image review (grade assigned) or by radiographic report if images were unavailable (no grade assigned).Symptomatic HO (sHO) was defined as new pain, progressive pain, or increased limited range of motion during clinical follow up, in hips previously documented as having developed rHO.

Cross-sectional evaluation of current functional status and patient- or guardian-reported symptom severity (pain and range of motion) was performed using paper surveys sent via U.S. mail to all eligible participants' last known place of residence. Because so few completed surveys were received (n=2), findings are not reported herein.

Per institutional protocol and previously-reported data,(1, 7) the ideal timeframe for delivery of pre- and post-operative RT in children for HO prophylaxis was considered to be no more than 4 hours before and no later than 24 hours after surgery, respectively. Exclusion criteria included age over 19 at the time of RT delivery, less than 1 year of either clinical or radiographic follow up (unless HO developed earlier), prior un- or partially-resected HO (prior completely-resected HO was allowed), and surgery other than PFR (ie, resection of pre-formed HO without subsequent PFR, or other osteotomy).

Descriptive statistics were obtained for categorical (frequency and percent) and continuous (mean, standard deviation) variables, stratified by pre-operative versus post-operative radiation. Boxplots were generated to compare the distribution of the continuous variables between pre-operative and post-operative radiation. Simple and multiple logistic regression models were used to obtain odds ratios (OR) and corresponding 95% confidence intervals (CIs) to study the relationship between pre- versus post-operative RT and the formation of symptomatic HO. Since five of the 25 patients had bilateral HO, mixed effects logistic regression models were also used to account for the correlation between the measurements on the same patients when needed. Simple and multiple linear regression models as well as linear mixed effects models were used to assess pre- versus post-operative RT on HO grade at first discovery. Kaplan-Meier curves were generated to demonstrate time to development of rHO and sHO. Fisher's exact test was used to study the association of HO grade (B2 vs. C2/C3), respectively. A control group of children with undergoing PFR without adjuvant RT consisted of 7 non-irradiated hips in 5 children, of whom 4 and 3 hips (in 2 children) met eligibility criteria and had sufficient follow up for evaluation of rHO and sHO, respectively.

Results

Fifty-two hips in 40 children were treated with RT for HO prevention between 1999 and 2012 following PFR. After exclusions for ineligibility, 25 hips in 20 children were analyzed (Figure 2). Median radiographic and clinical follow-up were 34.6 months (range 4.40 to 143, IQR 11.3 to 80.2) and 36.0 months (range 2.40 to 94.8, IQR 26.4 to 61.2), respectively. The single-fraction radiation dose was 7 Gy in all hips except one (8 Gy). Eleven hips were irradiated pre-operatively between 2004 and 2012, while 14 were irradiated post-operatively between 1999 and 2009. Demographics are reported in Table 1. The average age was respectively 13.8 and 13.4 years for the pre-operatively and the post-operatively groups with no significant difference in laterality (p=0.62). Actual time from pre-operative RT to PFR

incision was available in 10/11 hips and was ≤4 hours in 4 hips of 11 hips (median 4.7 hours, range 1.6–25.7), while time from PFR incision to post-operative RT was available in 6/14 hips and was ≤ 72 and ≤24 hours in 6/6 hips and1/6 hips, respectively (median 26.5 hours, range 22.9–28.3).

The total number of radiographic images reviewed was 226; three were computed tomography, one was magnetic resonance, and 222 were anterior-posterior, oblique, or lateral x-ray studies, most commonly of the spine, pelvis, or abdomen. Images were unavailable for review for 48 studies due to unsuccessful de-archival of records. Two patients with prior HO met inclusion criteria: the first had previously undergone PFR without adjuvant RT and later developed HO and was treated with HO resection and post-op RT; the other developed HO after prior hip surgery (non-PFR) and then underwent HO resection, PFR, and post-op RT.

Radiographic evidence of post-RT rHO was found in all 25 hips (Figure 3 and 4). Children in the group receiving pre-operative irradiation developed rHO earlier than those receiving it post-operatively, with mean 4.8 vs 15.7 months (Table 1) (beta = 10.87, 95% CI 0.24–21.5, p=0.03). This association declined to borderline significance when controlling for age and for correlation of bilateral HO, using linear regression (beta= 9.85, 95% CI −0.63–20.33, p=0.06). When using the linear mixed effects model, results were not significant (p=0.10 and 0.15 respectively for unadjusted and adjusted analysis) Symptomatic HO occurred in 45.5% and 35.7% children in the pre-operative and post-operative groups respectively (Figure 5). The difference was not statistically significant (OR 0.67, 95% CI 0.13–3.35, p = 0.62), and remained insignificant after adjusting for laterality and age (OR 0.61, 95% CI 0.11–3.37, p = 0.57). There was no difference in rHO grade (p=0.19) (Table 1). Seven (28%) of the 25 hips (5 pre-operative and 2 post-operative) had documentation of rHO-free intervals after surgery, with an average duration of 5.6 months, while the remainder presented with rHO at first follow-up visit. All four (100%) eligible hips in the control group developed rHO and 3/3 hips (100%) with sufficient clinical follow-up records developed sHO recorded at a median time of 7.2 months (range 7.2–39.6 months) following surgery. There was no statistically-significant difference observed in freedom from rHO (HR 1.1, p=0.88) or sHO (HR 2.6, p=0.29) between those treated with or without RT, although the control arm sample size was small (n≤4). There was also no significant difference observed (p=0.55) in HO grade in the RT versus no-RT groups.

Discussion

The principle findings of this study are (1) that single-fraction RT failed to prevent radiographic development of HO in any quadriplegic child after PFR, regardless of the sequence of therapy, and (2) that the observation thatchildren given pre-operative RT developed rHO earlier than those irradiated post-operatively, which approached statistical significance. Secondary findings are (1) that the sequence of peri-operative RT had no effect on the grade of rHO or later development of sHO and (2) that the observed improvement in freedom from rHO, sHO, and rHO grade with RT compared to a non-irradiated control cohort, did not reach statistical significance. Confidence in the negative findings of the

control cohort is limited by small sample size and insufficient power to detect a potential true difference.

When juxtaposed with the historical success of radiotherapeutic HO prevention in ambulatory adults, the pervasive failure of RT to prevent rHO in any child with NHD suggests a need to re-evaluate the biologic etiology of HO formation in children with central nervous system injury and the appropriateness of extrapolating outcomes between the two populations. A brief discussion of the biology of HO formation and a review of literature contextualizes our findings.

Biology of Heterotopic Ossification

There are generally three incompletely understood etiologies of HO: traumatic, neurogenic, and genetic, with the first being the most common and well studied.(1) Three prerequisites for HO formation mimic normal bone healing in soft tissue: (1) an osteogenic precursor, (2) inducing agents, and (3) a permissive environment.(1) Osteogenic precursor cells are introduced into the surrounding tissue by trauma, surgery, neurologic injury, or genetic predisposition. Inducing agents consist of local factors (such as bone morphogenic proteins that modulate chemotaxis, mitosis, and differentiation) and systemic factors (such as prostaglandin E-2 that has been identified in patients with CNS injury who develop HO without a traumatic joint insult). Thereafter, a permissive environment facilitates osteoplastic proliferation.(1) Non-steroidal anti-inflammatory drugs (NSAIDS) inhibit the production of induction factors and radiation therapy inhibits the proliferation of osteopregenitor cells. The extent to which synchronous local and systemic factors (such as in children with CP who undergo PFR) contribute synergistically or additively to the development of HO in children with NHD is unknown.

Heterotopic Ossification in Children with Cerebral Palsy

Various hip salvage surgeries options exist for children with neuromuscular hip dysplasia that varying by clinical outcomes and HO risk profile. Of these, PFR, valgus osteotomy (VO), varus derotational osteotomy (VDRO), and total hip arthroplasty (THA) relieved pain better and fewer complications than arthrodesis. In a recent meta-analysis of 25 studies and over 480 procedures performed in cerebral palsy children, of 313 PFRs performed, 75 (24%) developed complications including 10 cases of HO (3.2%), the timeline of follow-up, radiographic evaluation, grading of HO were not specified. Incidence of HO following TO, THA, or arthrodesis was also not specified.(8)

Individual reports of hip surgery sequelae in children with CP treated without RT are retrospective and report highly-discrepant rates of HO formation with some reporting extremely low rates of HO. In 1998, Song, et al.(9) reported that 1 in 39 cerebral palsy children developed clinically significant HO after VO, but this was not a primary endpoint of the study and no systematic evaluation for HO was performed. In 2006, Schmale, et al.(10) reported that only a single case out of 52 hips developed HO after VDRO while Knaus, et al. (11) reported only one incidence of HO requiring re-resection out of a cohort of 20 patients in 2009 following PFR. However, higher rates of HO formation in children with CP have also been reported. In 1992, Herndon, et al. reported 6 cases (18%) of HO as a non-primary

outcome among 33 children with cerebral palsy, ages 4 to 21, who underwent femoral osteotomy.(12) No validated scale was utilized to grade HO and no details of the number or expertise of radiograph reviewers were provided. In 1993, Payne et al. retrospectively reported a 27% rate of HO [4 of 15 patients (4 of 8 quadriplegic and zero of 7 diplegic CP)] after selective posterior rhizotomy and osteotomy, compared to zero of 118 hips treated with osteotomy alone, suggesting a neurogenic contribution to its formation.(13) Much higher rates of HO formation were reported in 2007, by Abu-Rajab, et al, who retrospectively reported an 80% rate of HO formation in a cohort of 15 patients, ages 11–26, with a mean follow-up of 3.4 years following PFR. (14) In this study, tadiograph review was based on a scale defined by McCarthy, et al(15), mainly classifying HO by anatomic position in relation to the femoral stump and acetabulum and not by size or radiographic length.

The largest identified study by Inan, et al. evaluated the development of HO as a primary endpoint and retrospectively reported a 16% rate of HO in a large sample size of 219 patients following femoral osteotomies with or without pelvic osteotomies, identifying the following five risk factors for HO formation: quadriplegia, ambulatory status, infection, capsular release, and prior hip operations.(16) Due to the vast discrepancy of reported incidence rates of HO formation and the limits of retrospective analysis, the true incidence of HO in children with CP undergoing PFR is not known.

Heterotopic Ossification Prevention in Adults

Prevention of HO in ambulatory adults with local risk-factors has been rigorously studied. Both peri-operative single-dose radiation therapy and post-operative indomethacin have been found to prevent the formation and severity of HO.(1, 7, 17, 18) Numerous prospective randomized trials and meta-analyses of RT before or after hip surgery have reported HO formation rates ranging between 5% and 28%.(1, 3, 7, 17, 18) These studies have concluded that there is no difference between fractionated versus one-time RT or between pre-operative versus post-operative RT, as long as at least 7 Gy is delivered no more than 4 hours before or no later than 24 to 72 hours after surgery. Six weeks of indomethacin has also been shown to be efficacious, and a recent meta-analysis reported no difference in HO formation rates using it compared to RT. A single German study of paraplegic adults reports 100% rate of controlling known or prevented HO at a short median follow-up of 12 weeks.(4)

To our knowledge, there are only two retrospective studies informing whether these results apply to children with systemic risk factors for HO. Widmann, et al. retrospectively evaluated institutional outcomes of 13 children from New York and showed “significantly lower grade of HO at final follow-up,” among the five who received RT.(19) Dartnell, et al. recently reported a retrospective British study of 41 children with cerebral palsy undergoing PFR and found equal rates of HO among the approximately 50% who received indomethacin compared to those who did not.(20) Given the void of additional evidence, existing clinical rationale for irradiating these children remains limited to extrapolation of the previously-mentioned results from studies of mainly ambulatory adults.

Our finding of 100% rate of development of HO post-operatively is substantially higher than previously-reported rates. We hypothesize that numerous details of our methodology help to explain this. First, our use of the combined grading scale by Toom, et al.(5) may have

increased sensitivity for identifying lower-grade HO than prior studies that did not systemically grade HO or that used a scale that did not account for size or length, published by McCarthy, et al.(15) Second, our eligibility criteria excluded patients with less than a year of clinical or radiographic follow up, which may have excluded falsely-negative radiographs in hips with short follow-up. Third, our use of the expertise of a board-certified pediatric radiologist and our relatively thorough imaging (226 images reviewed for 25 hips) may also have yielded fewer false negatives. Four, our study intentionally distinguished between symptomatic and purely radiographic HO, found in 46% and 100% of patients, respectively. Other reports have reported post-operative HO only when identified symptomatically after clinical evaluation with radiographic confirmation, without screening for subclinical HO on radiographs alone, which methodology is subject to both length and selection bias.(9–12)

To inform this high rate of rHO in our cohort, we also evaluated a control cohort of children who underwent PFR without adjuvant RT. Using identical eligibility criteria, we observed that 4 out of 4 (100%) and 3 out of 3 (100%) of the controls also developed rHO and sHO, respectively, compared to 100% and 35–45% of the study cohort. Freedom from rHO was not found to be statistically different in irradiated versus non-irradiated children (p=0.88 rHO, p=0.29 sHO).

We also observed that HO developed more quickly in the pre-operative group, which contradicts those previously-mentioned studies concluding equivalence with pre- versus post-operative sequencing of RT in ambulatory adults.(3, 18) Temporal confounders may influence the accuracy of this finding, as most patients treated pre-operatively were treated more recently and therefore had more readily available records. Five hips which were pre-operatively irradiated had documentation of rHO-free intervals after surgery, compared to only 2 in the post-operative group. This suggests that the difference between the pre- and post-operative RT groups may reflect the improved availability and frequency of follow-up records in recently-treated (mostly pre-op) patients. These findings require prospective confirmation.

Limitations

Our study has numerous additional limitations, including small sample size with a possible type II error, retrospective design, lead-time bias induced by variable frequencies of follow-up compliance, and competing causes of pain and contractures in non-verbal CP patients. Symptoms were not systematically graded by any validated metric and were limited to retrospective review of the medical record. This significantly limits the external validity of our reported rate of symptomatic HO. These biases would be much better controlled with prospective analysis. Power analysis was not feasible given the lack of previously-reported incidence of HO in children with NHD.

Paradigm Re-evaluation

Children with cerebral palsy or other CNS injury, resulting in NHD, who undergo palliative PFR have both systemic and local risk factors for HO. We hypothesize that a single 7 Gy fraction of RT either inadequately ablates local HO progenitor cells or that unaddressed

systemic factors overwhelm local preventative measures, leading to HO formation despite RT, although HO formation may be delayed or HO grade improved with RT. This may be due to prolonged periods of inflammation, since a single surgical stimulus introduced into an environment of chronic immobility may potentially induce a cascading effect wherein a more prolonged and durable inflammatory and pro-osteoblastic reactionary period is catalyzed. Pre-existing factors that circulate systemically in patients with central nervous system insult may also prolong the duration of a local inflammatory response, or may influence the formation of HO by an entirely separate and neurogenic pathway.

Regardless of the exact mechanism, our study suggests that extrapolating doses, sequencing, and timelines for peri-operative RT for HO prevention in quadri- or paraplegic children may not yield the benefits reported in ambulatory adults. Given the risks of irradiating developing adolescent and pediatric tissue (including risk of growth delay of growth plates), further prospective studies are needed to justify treatment in this patient population and determine whether RT can prevent or improve the severity of or freedom from sHO. Alternative surgical strategies to mitigate risk of HO formation, such as pelvic support osteotomy, may also prove beneficial in these children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A	Ossification absent or small	A0	No ossification
		A1	Isolated ossifications <1cm in length
B	Ossification leaving >1 cm distance between pelvis and femur	B1	Isolated ossifications ≥1cm in length
		B2	*Marginal ossifications (leave at least 1 cm distance between pelvis and femur)
C	Ossification leaving <1 cm distance between pelvis and femur or ankylosis	C1	Isolated ossifications ≥1cm in length
		C2	*Marginal ossifications
		C3	Ankylosis

Figure 1.
Grade Classification by Toom, et al. combines numerous prior scales into one, including the well-known classification by Brooker, et al.(6)

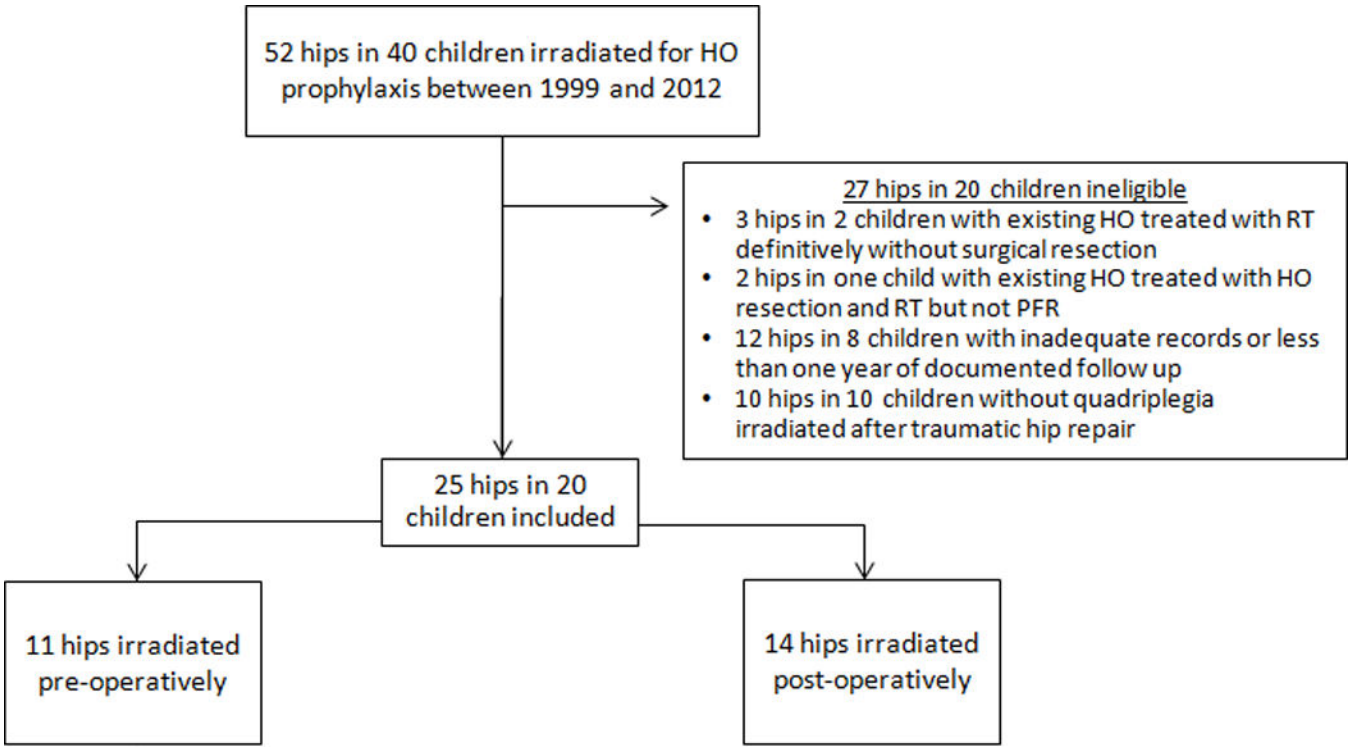

Figure 2.
Enrollment Flow Diagram

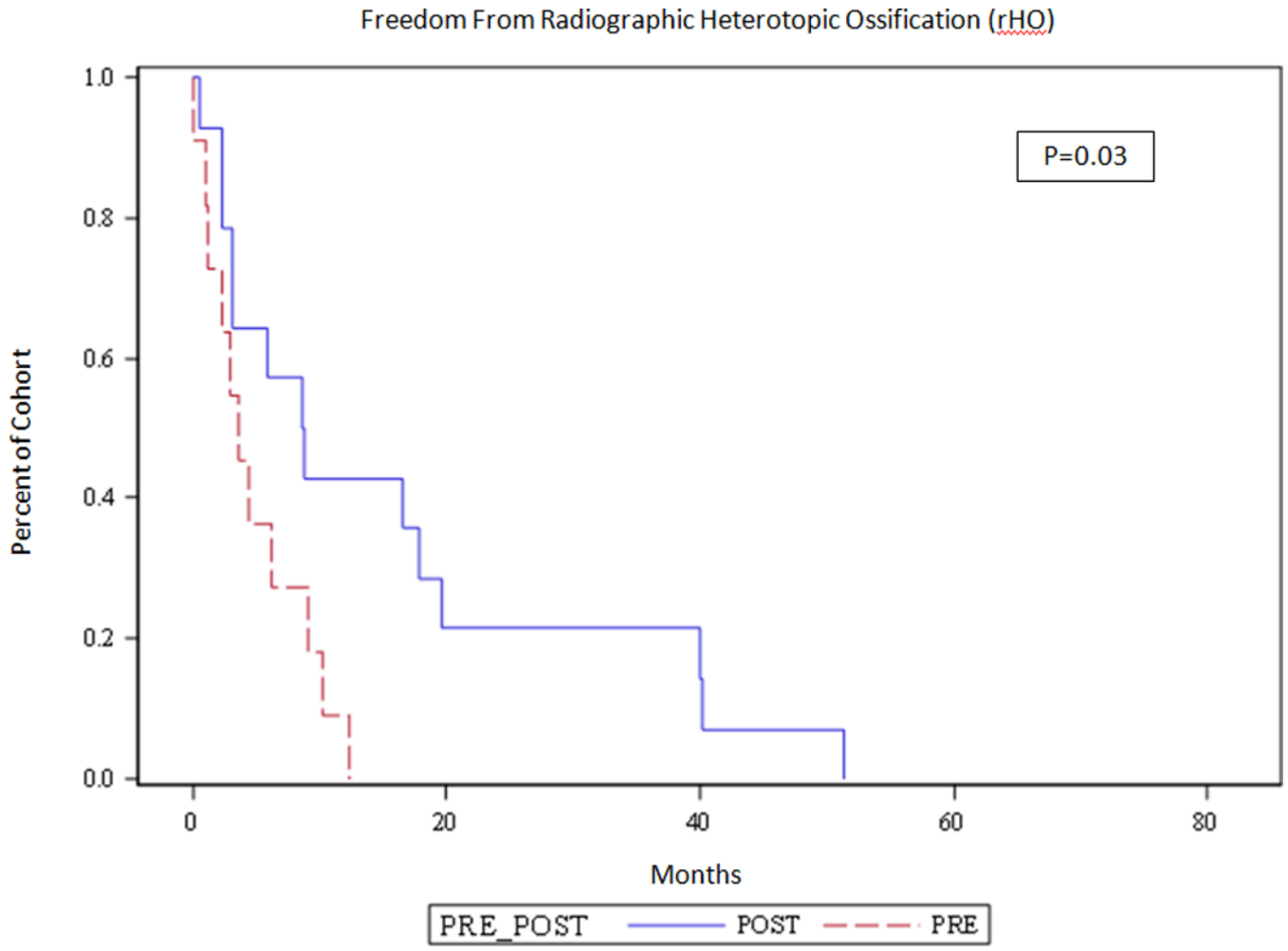

Figure 3.
Freedom from Radiographic Evidence of Heterotopic Ossification (rHO).

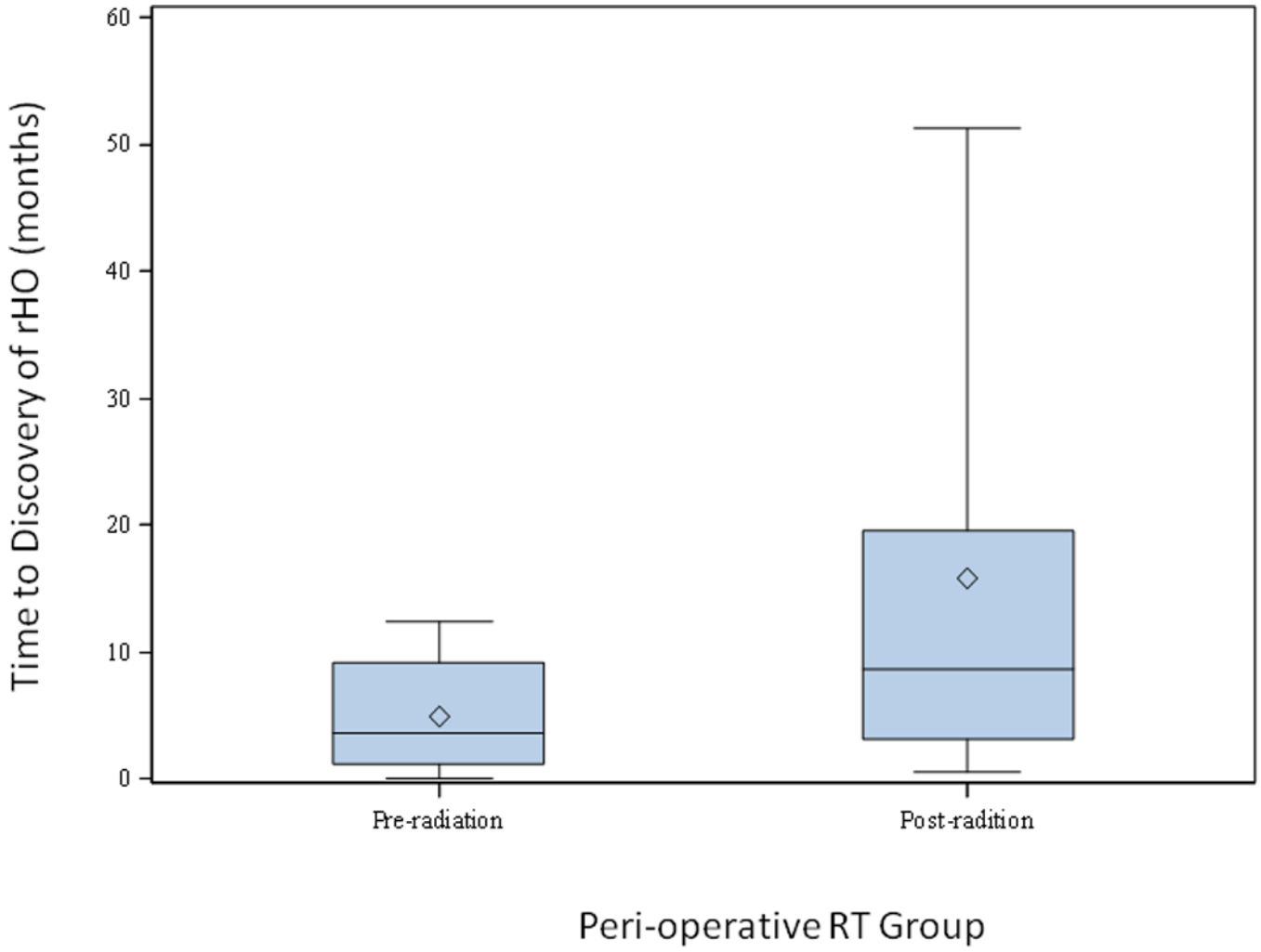

Figure 4.
Box Plot for Time to Discovery of rHO, by peri-operative Grouping

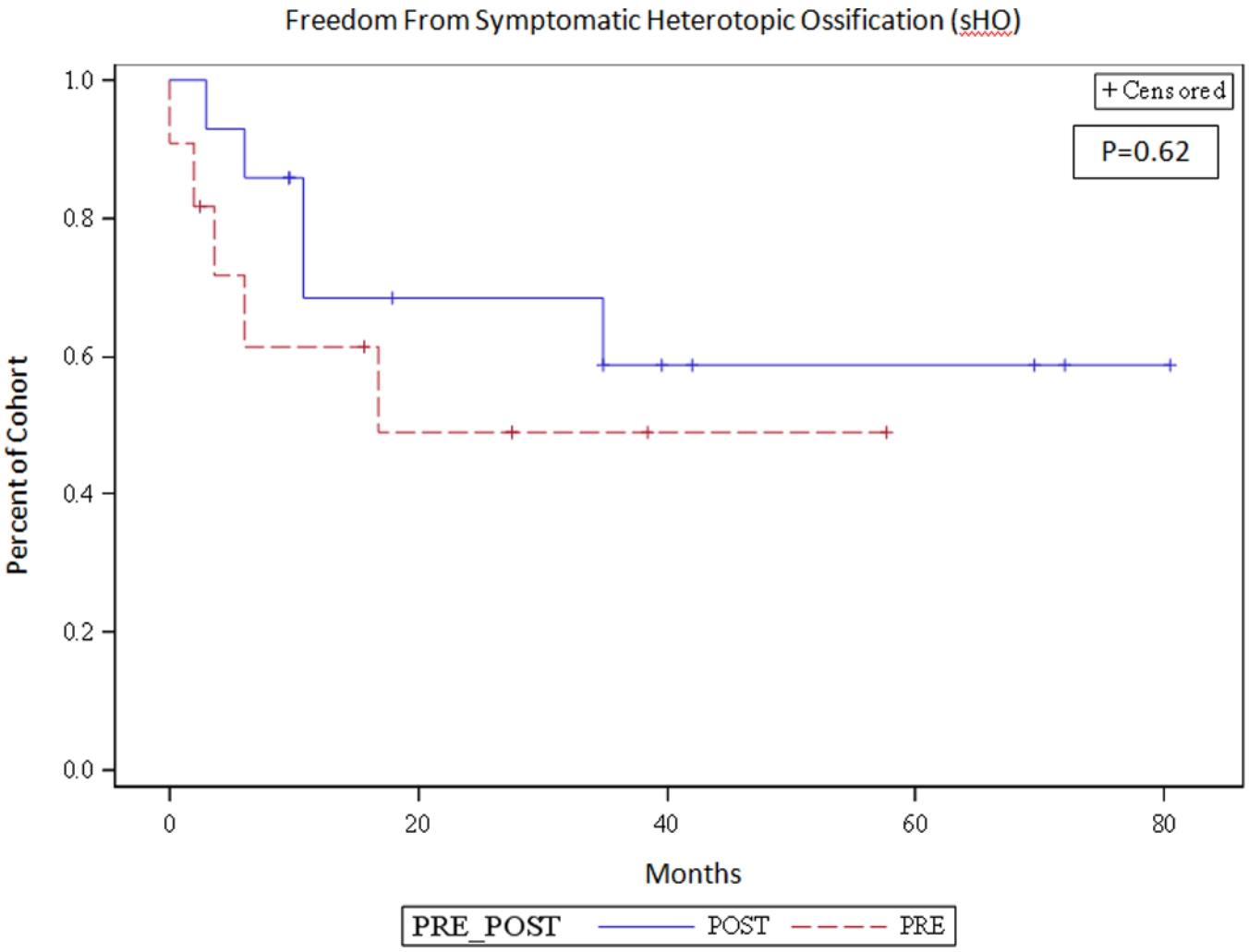

Figure 5.
Freedom from Symptomatic Heterotopic Ossification (sHO).

Table 1

Patient Demographics and Select Outcomes

	Pre-op n = 11		Post-op n = 14		P
Age (mean, SD)	13.8	2.4	13.4	4.6	0.77*
Laterality (n, %)					
left	5	45.5	5	35.7	0.62‡
right	6	54.6	9	64.3	
rHO Grade (n, %)¶					
B2	4	40	2	14.3	0.19#
C (C2, C3)	6	60	12	85.7	
Freedom from rHO (mean months, SD)	4.8	4.1	15.7	16.6	0.03†
sHO (n, %)					
ABSENT	6	54.5	9	64.3	0.62§
PRESENT	5	45.5	5	35.7	

Abbreviations: SD= standard deviation, rHO= radiographic evidence of heterotopic ossification, sHO= symptomatic heterotopic ossification

*Two sample t-test.

‡Logistic regression.

#Fisher's exact test.

†Unadjusted linear regression. Result with mixed effect model was p=0.10.

§Mixed effects logistic regression.

¶Grade score as highest grade of all images reviewed and not of initial grade at first diagnosis, if longitudinal follow-up was available. Pre-op total does not sum to 11 because the grade of one patient was unknown due to lack of available imaging.

-RHO= defined by documentation of HO in the radiographic report alone but grading of rHO was unassigned if images were unavailable
-sHO= defined as new pain, progressive pain, or increased limited range of motion during clinical follow up, in hips previously documented as having developed rHO