Prevention of heterotopic ossification about the hip: Final results of two randomized trials in 410 patients using either preoperative or postoperative radiotherapy

ARTICLE *in* INTERNATIONAL JOURNAL OF RADIATION ONCOLOGYBIOLOGYPHYSICS · AUGUST 1997

Impact Factor: 4.26 · DOI: 10.1016/S0360-3016(97)00285-X · Source: PubMed

7 AUTHORS, INCLUDING:

Michael-Heinrich Seegenschmiedt
Strahlenzentrum Hamburg
353 PUBLICATIONS **2,490** CITATIONS

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 39, No. 1, pp. 161–171, 1997

0360-3016/97 $17.00 + .00

PII S0360-3016(97)00285-X

● *Clinical Investigation*

PREVENTION OF HETEROTOPIC OSSIFICATION ABOUT THE HIP: FINAL RESULTS OF TWO RANDOMIZED TRIALS IN 410 PATIENTS USING EITHER PREOPERATIVE OR POSTOPERATIVE RADIATION THERAPY

M. HEINRICH SEEGENSCHMIEDT, M. D.,*,‖ LUDWIG KEILHOLZ, M.D.,* PETER MARTUS, Ph.D.,† AXEL GOLDMANN, M.D.,‡ RAINER WÖLFEL, M.D.,§ FRIEDRICH HENNING, M.D.§ AND ROLF SAUER, M.D.*

Departments of *Radiation Oncology, †Medical Statistics and Documentation, ‡Orthopedics, and §Surgery, University Erlangen-Nürnberg, 91054 Erlangen, Germany; and ‖Department of Radiation Oncology, Therapeutic Radiology and Nuclear Medicine, Alfried Krupp von Bohlen und Halbach Hospital, 45117 Essen-Rüttenscheid, Germany

Purpose: Experimental and clinical data support effectiveness of perioperative radiotherapy to prevent heterotopic ossification after hip surgery or trauma. Since 1987, two prospectively randomized trials were performed in patients with high-risk factors to develop heterotopic ossification: the first (HOP 1) to assess the prophylactic efficacy of postoperative low vs. medium dose radiotherapy, and the second (HOP 2) to assess the prophylactic efficacy of pre vs. postoperative radiotherapy.

Methods and Material: 410 patients with high risk to develop heterotopic ossifications about the hip following hip surgery were recruited. Between June 1987 and June 1992, 249 patients were randomized in HOP 1 to postoperative "low dose" (5 × 2 Gy; total: 10 Gy) or "medium dose" (5 × 3.5 Gy; total: 17.5 Gy) radiotherapy. Between July 1992 and December 1995, 161 patients were randomized in HOP 2 to either 1 × 7 Gy preoperatively (≤4 h before surgery) or 5 × 3.5 Gy (total: 17.5 Gy) postoperatively (≤96 h after surgery). With exception of age and type of implant (cemented vs. uncemented prosthesis) all confounding patient variables (gender, prior surgery) and predisposing risk factors were similarly distributed between both trials and treatment arms. Portals encompassed the periacetabular and intertrochanteric soft tissues. Radiographs were obtained prior and immediately after surgery and at least 6 months after surgery to assess the extent of ectopic bone formation about the hip. Modified Brooker grading was used to score the extent of heterotopic ossification. Harris scoring was applied to evaluate the functional hip status. If the scores decreased from immediate post or preoperative status, respectively, to the last follow-up, radiological or functional failures were assumed.

Results: Effective prophylaxis was achieved in 227 (91%) hips of HOP 1 and in 142 (88%) of HOP 2. In HOP 1, 15 (11%) radiological failures were observed in the low-dose group compared to 7 (6%) in the medium dose group ($p > 0.05$). In HOP 2, 4 (5%) radiological failures were observed in the postoperative and 11 (19%) in the preoperative group ($p < 0.05$). Subgroup analysis of the preoperative group revealed that the highest failure rate occurred in patients with prophylactic radiotherapy prior to removal of ipsilateral Brooker Grade III and IV ossification (39%) ($p < 0.001$), while all other patients in the preoperative group had a failure rate that was comparable to postoperative treatment groups. In multivariate logistic regression analysis the number of high-risk factors for development of heterotopic ossification ($p = 0.03$) and the time to RT initiation ($p = 0.05$) were independent prognostic factors in the HOP 1 study. For the HOP 2 study, the multivariate logistic regression analysis revealed the number of high-risk factors for development of heterotopic ossification ($p = 0.003$), the preoperative HO grade ($p = 0.001$) and the RT dose concept ($p = 0.05$) as independent prognostic factors. Other factors including type of implant (cemented vs. uncemented) did not affect the prophylactic efficacy of radiotherapy. There were no increased intra- and postoperative complications seen in the preoperative group, and no long-term complications were observed in both HOP studies. For functional failures (decrease of Harris score) no statistically prognostic factors were found. There were less functional failures in HOP 1 (18 = 7%) than in HOP 2 (23 = 14%, but this difference was not statistically significant. Only patients with high Brooker Grade III and IV at last FU achieved a lower Harris score than those with low Brooker Grade 0, I and II ($p < 0.05$).

Presentation at the 38th Annual Scientific Meeting of ASTRO, Los Angeles, CA, October 27–30, 1996.

Reprint requests to: Priv. Doz. Dr. med. M. Heinrich Seegenschmiedt, Klinik für Radioonkologie, Strahlentherapie & Nuklearmedizin, Alfried Krupp von Bohlen und Halbach Krankenhaus, Alfried Krupp Straße 21, D-45117 Essen, Germany.

Accepted for publication 7 April 1997.

Conclusion: With the exception of a small subgroup of patients with ipsilateral high Brooker Grade III and IV, pre- and postoperative radiotherapy are equally effective to prevent heterotopic ossification about the hip after hip surgery and total hip arthroplasty. Fractionated medium dose radiotherapy resulted in the lowest failure rate. © 1997 Elsevier Science Inc.

Radiotherapy for benign diseases, Hip abnormalities, Heterotopic ossification, Ectopic bone formation, Total hip arthroplasty, Post- and preoperative hip irradiation.

INTRODUCTION

The formation of mature lamellar bone in nonosseous tissues is termed heterotopic ossification (HO). Although HO has radiographic and histologic similarities with myositis ossificans and periarticular calcification, these disorders are distinct from each other (23). HO can occur in various body sites and is a major complication after total hip arthroplasty, traumatic acetabular fracture, or central nervous injury. Ectopic bone may form small islands of bone or bridging ossifications in the soft tissues about the hip joint. Depending on individual risk factors, the incidence of HO varies between 2% (52) and 90% (45). Various preexisting conditions that place patients at high risk of HO have been identified including ipsi- or contralateral HO (40, 41), acetabular fracture (9, 19, 27), ankylosing spondylitis (6), diffuse idiopathic skeletal hyperostosis (7), hypertrophic osteoarthritis with massive periacetabular osteophyte formation, posttraumatic arthritis, and previous extensive or repeated hip surgery. Men with hypertrophic osteoarthritis are also at a higher risk than women (43). Unfortunately, HO is only detectable on radiographs as late as 4–12 weeks after the injury when no efficient therapy is available. Almost 30% of patients presenting with HO of the periarticular region of the hip will develop severe clinical symptoms including pain, restricted motion, and hip function, and sometimes even complete ankylosis of the hip joint. For Germany, with about 80 million inhabitants, it is estimated that about 10,000 of 100,000 patients with total hip arthroplasty require effective HO prophylaxis.

Several preventive strategies have not shown to decrease the incidence of HO in high-risk patients including meticulous surgical techniques, suction drainage to avoid hematoma formation, and careful irrigation of the operative bed to remove bone chips. In contrast, corticosteroids and nonsteroid antiinflammatory drugs have proven efficacy to avoid development of HO (1, 18, 35, 44, 50).

Postoperative radiotherapy (RT) has been found to effectively prevent HO about the hip. In 1981, the Mayo Clinic series was the first to demonstrate that 10 fractions of 2 Gy applied early after surgery prevented reformation of HO (14). Further studies showed that 10 Gy given in five fractions is as effective as 20 Gy (2, 4, 9, 32, 33, 49, 51). Recent studies suggest that single or divided doses as low as 5 Gy (13), 7 Gy (8, 36), or 8 Gy (8, 34, 41) successfully prevent ectopic bone formation. Nowadays, we can conclude that single-fraction RT (8, 16, 24, 25, 34, 36, 38, 41) is as effective as multifraction RT (2, 4, 8, 11, 13, 14, 26, 30, 34, 37, 41, 42, 46, 47, 49, 51, 55).

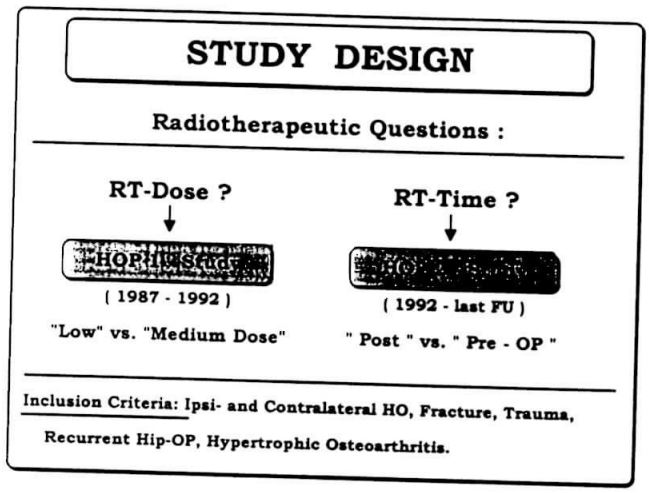


Fig. 1. Study design and inclusion criteria of HOP 1 and HOP 2 studies.

Moreover, in 1990 a carefully conducted *in vivo* study provided clear evidence that preoperative RT may be comparably effective in preventing HO as similar doses in the immediate postoperative period (29), but so far only a few studies have successfully tested this attractive preoperative treatment concept (21, 48).

Our clinics have been involved in clinical research of HO prophylaxis since 1987. At that time, a first randomized trial (HOP 1) was initiated to compare fractionated postoperative low-dose RT (10 Gy) vs. medium-dose RT (17.5 Gy) (46, 47). In 1992, a second randomized trial (HOP 2) was started to compare preoperative RT (7 Gy) vs. a historical control of fractionated postoperative RT (17.5 Gy) (48). Because of the investigational nature of both studies, only those patients were enrolled in the study who were at high risk to develop HO after hip surgery. Herein we summarize outcome of both studies.

METHODS AND MATERIALS

Study concepts

Between June 1987 and June 1992, 249 patients were enrolled in the HOP 1 study (HOP 1), which compared postoperative fractionated low dose (10 Gy, n = 131) and medium dose RT (17.5 Gy, n = 118). Between July 1992 and December 1995, the HOP 2 study (HOP 2) compared preoperative single-fraction (1 × 7 Gy) and postoperative fractionated RT (17.5 Gy). Postoperative RT was prescribed to start ≤96 h after and preoperative RT ≤4 hs before hip surgery. Both treatment schemes are shown on Fig. 1.

Table 1. Patient and HO risk parameters prior to RT according to study groups

Variables	Study groups			
	Study 1 (1987–1992) $n = 249$		Study 2 (1992–1995) $n = 161$	
	Group 1A: 10 Gy ($n = 131$)	Group 1B: 17.5 Gy ($n = 118$)	Group 2A: 17.5 Gy ($n = 81$)	Group 2B: 7 Gy ($n = 80$)
Gender				
Male/female	67/64	64/54	48/33	45/35
Age (years)				
Mean ± SD	61 ± 14	62 ± 12	67 ± 12	63 ± 11
Range	39–81	37–84	34–85	32–87
HO Risk Factors (+)				
Ipsi-/contralat. HO	69/51	61/44	49/40	50/32
Hypertrophic OA	65	64	27	35
Repeated surgery	50	45	50	45
Hip fractures	8	11	4	4
M. Bechterew	—	2	1	1
HO Risk Profile				
1 Risk factor	52	40	19	19
2 Risk factors	54	48	40	30
>2 Risk factors	25	30	22	31
Type of Surgery				
First THA	90	82	46	45
Subsequent THA	22	23	25	24
Removal of HO	19	12	10	11
Type of Prosthesis				
Full cemented	22	25	26	27
Partially cemented	35	32	26	29
Uncemented	74	61	29	24
Preoperative HO (Brooker score)				
0	65	59	26	26
1	23	15	16	11
2	12	14	17	14
3	21	22	14	18
4	10	8	8	11
Preoperative Function (Harris score)				
Mean ± SD	49 ± 15	46 ± 14	47 ± 17	48 ± 15
Range	14–95	12–92	10–93	11–91

SD = standard deviation; HO = heterotopic ossification; THA = total hip arthroplasty; (+) more than one event per patient possible; (*) = one patient had a replacement of the acetabular component of the implant only.

Eligibility criteria

Eligible patients had to have a high-risk profile to develop HO after hip surgery including the following: (a) preoperative radiological evidence of HO about ipsi- or contralateral hips; (b) hypertrophic ostearthritis with massive periacetabular osteophyte formation; (c) diffuse idiopathic skeletal hyperostosis (M. Forrestier); (d) ankylosing spondylitis (M. Bechterew); (e) previous acetabular or femoral fractures; (f) repeated hip surgery. Because most patients exhibited several HO risk factors, the potential risk to develop HO without prophylaxis was at least 50–90% (4, 5). Due to this high-risk level, it was ethically justified to evaluate the efficacy in both trials without a control group.

Patients and treatment sites

Most patient variables (sex, prior surgery) were equally distributed between both studies and respective treatment arms (Table 1). The unbalanced number of patients in HOP 1 derives from the initial RT concept to use 10 × 2 Gy instead of 5 × 3.5 Gy, which was not useful due to the long in-patient status. Thus, the first 10 patients who had received 10 × 2 Gy were not evaluated. Another imbalance between both studies was related to the type of implanted prosthesis: in the HOP 1 study 135 (54%) patients had an uncemented prosthesis type compared to 53 (33%) in the HOP 2 study ($p < 0.05$). However, this difference is well explained by the different age profile in both studies (Table 1).

The basic risk profile for development of HO was high: in HOP 1, 157 (63%) patients had at least two HO risk factors compared to 123 (76%) patients in HOP 2. Ipsilateral HO was present in 130 (52%) patients (HOP 1) and 99 (61%) patients (HOP 2), respectively. Contralateral HO was present in 95 (38%) patients (HOP 1) and 62 (39%) patients (HOP 2), respectively. In contrast, pe-

vious or actual hip fractures and ankylosing spondylitis were rare conditions. The HO risk profile was equal for all treatment groups. Similarly, the type of hip surgery (i.e., first or subsequent hip arthroplasty, removal of HO), the preoperative HO grade and the functional hip status were well balanced (Table 1).

All patients underwent a preoperative, postoperative, and a last FU examination at least 6 months after hip surgery, including evaluation of standardized anterior–posterior and lateral radiographs. The amount of HO was classified according to MacLennan s modification (37) of the Brooker classification (10) (Table 2) and other scores (20, 31, 40). Clinical assessment of hip function and hip mobility was performed according to the hip score of Harris (22) (Table 3) and other scores (28, 39). Informed consent was obtained prior to RT planning either postoperatively (HOP 1) or preoperatively (HOP 2).

RT prescription and technique

Patients were stratified for the two paricipating departments (orthopedics, surgery) and randomly assigned to the treatment arms. The HOP 1 study prescribed postoperative (low-dose) RT (five fractions of 2 Gy; total dose: 10 Gy) (or medium-dose) RT (five fractions of 3.5 Gy; total dose: 17.5 Gy). Postoperative RT was scheduled to start ≤96 h after hip surgery. The HOP 2 study compared postoperative fractionated RT (5 × 3.5 Gy; total dose: 17.5 Gy) as historical (control group and preoperative single-fraction) RT (1 × 7 Gy). Preoperative RT was initiated ≤4 h before hip surgery (Fig. 1).

Our RT technique has been described previously (46–48). RT was delivered with 6–10 MV linac photons[1] to anterior–posterior/posterior–anterior isocentrically arranged portals. The RT dose was calculated at midplane depth with a source-to-axis distance of 100 cm. Depending on the body size, an individual portal was chosen to encompass all periarticular soft tissues of the hip. Five half-value layer blocks (3% transmission) were placed individually to protect the intrapelvic and genital structures. There was no effort undertaken to shield the sites of implants in the femoral shaft and/or pelvic bone.

In HOP 1, 26 of 131 (20%, arm A) and 25 of 118 (21%, arm B) patients had a delayed RT start according to the RT prescription, while the respective rates in HOP 2 were 4 of 81 (5%, arm A) and 21 of 80 (26%, arm B) patients. Patients who were treated delayed postoperatively had schedule deviations due to medical (medical complications), organizational (delays through weekends or surgical time table), or technical reasons (machine failure/maintainance), while patients who were treated delayed preoperatively had deviations due to organizational reasons (changes of the surgical time table). The most important RT variables are compiled in Table 4. The use of nonsteroid antiinflammatory drugs (NSAID) and acetylsalicyl acid (ASA) was avoided during the postoperative period. These drugs were only rarely applied for a few days (≤7 days), if an increased painful swelling and hematoma formation was observed. Only one patient, who experienced an infection of the hip implant about 3 weeks

Table 2. Brooker classification of heterotopic ossification about the hip

Grade 0	No bone islands visible.
Grade I	Islands of bone visible within soft tissues about the hip.
Grade II	Bone spurs from pelvis or proximal end of femur, leaving at least 1 cm between opposing surfaces.
Grade III	Like Grade II, except that the space between opposing surfaces is less than 1 cm.
Grade IV	Apparent bony ankylosis.

Table 3. Harris score for evaluation of functional hip status [modified from Harris (1969) (22)]

1. Pain			(44 points possible)
None	(= 44 points)	moderate	(= 20 points)
Slight	(= 40 points)	marked	(= 10 points)
Mild	(= 30 points)	disabled	(= 10 points)
2. Function			(47 points possible)
a) Limp			*(11 points possible)*
None	(= 11 points)	moderate	(= 5 points)
Slight	(= 8 points)	severe	(= 0 points)
b) Support			*(11 points possible)*
None	(= 11 points)	one crutch	(= 3 points)
Cane for long walks	(= 7 points)	two canes	(= 2 points)
Cane most of the time	(= 5 points)	two crutches	(= 1 point)
Not able to walk (specify reason)			= 0 point)
c) Walking distance			*(11 points possible)*
Unlimited	(= 11 points)	2–3 blocks	(= 5 points)
Six blocks	(= 8 points)	indoors only	(= 2 points)
		bed & chair	(= 0 point)
d) Daily activities			*(14 points possible)*
Walking stairs (4 points)			
normally without using a railing			(= 4 points)
normally using a railing			(= 2 points)
in any manner			(= 1 point)
unable to do stairs			(= 0 point)
Shoes and socks (4 points)			
with ease			(= 4 points)
with difficulty			(= 2 points)
unable			(= 0 point)
Sitting chair (5 points)			
comfortably in ordinary chair 1 h			(= 5 points)
on a high chair for half an hour			(= 3 points)
unable to sit comfortably in any chair			(= 0 point)
Transportation (1 point)			
able to enter public transportation			(= 1 point)
unable to enter public transportation			(= 0 point)
3. Absence of deformity			(4 points possible)
Less than 30° fixed flexion contracture			(= 1 points)
Less than 10° fixed adduction			(= 1 points)
Less than 10° fixed internal rotation in extension			(= 1 points)
Limb-length discrepancy less than 3.2 cm			(= 1 point)
4. Range of motion			(5 points possible)

[1] Mevatron 20/67, Siemens Corporation, Erlangen, Germany.

Table 5. Change in heterotopic ossification (Brooker grade) after prophylactic RT

Variables	Study groups			
	HOP-Study 1 (n = 249)		HOP Study 2 (n = 161)	
	Group 1A: (n = 131)	Group 1B: (n = 118)	Group 2A: (n = 81)	Group 2B: (n = 81)
Postoperative HO (absolute Brooker)				
0	66	55	38	37
1	48	45	25	30
2	13	15	13	5
3	3	3	5	6
4	1	—	0	2
Last follow-up HO (absolute Brooker)				
0	64	53	36	31
1	42	42	25	27
2	18	18	14	11
3	6	5	6	7
4	1	0	0	4
Overall HO change (relative Brooker)				
0/−1	116	111	77	65
+1	12	5	3	10
+2	3	1	1	5
+3	—	1	0	0
(see Tables 3A/3B)				
Treatment failure	15/131 (11%)	7/111 (6%)	4/81 (5%)	15/80 (19%)
Follow-up period				
Mean ± SD)	477 ± 145	486 ± 161	457 ± 121	437 ± 117
Postoperatively	193–945	181–979	171–694	168–640

HO = heterotopic ossification.

score (functional failure). No failures with Brooker grade IV were observed. In HOP 2, 6 of 18 (33%) patients failed with Brooker Grade III or IV, and 2 of those had a decreasing Harris score (functional failure). Five of six patients who failed with a Brooker Grade III/IV were in the preoperative group (arm B) ($p < 0.05$).

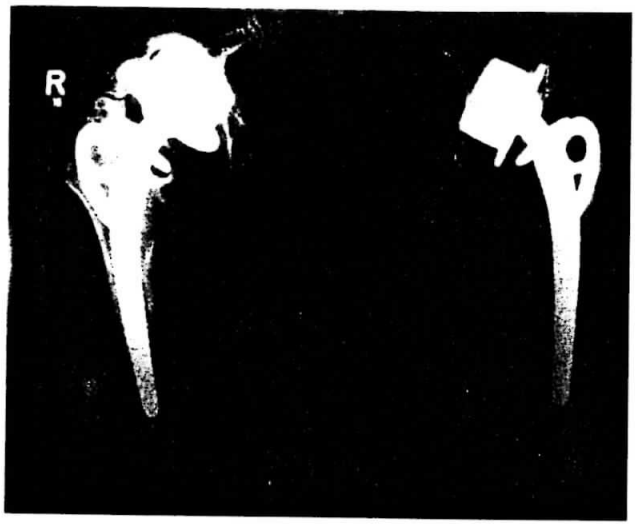
The overall Harris score improved in 231 (93%) patients of HOP 1 and in 138 (86%) of HOP 2. The functional failure rates in HOP 1 (arm A: 10 of 131 = 8%; arm B: 8 of 118 = 7%) and HOP 2 (arm A: 10 of 81 = 12%; arm B: 13 of 80 = 16%) were almost equal ($p > 0.05$). The overall Harris score in HOP 1 increased by 36 ± 16 points (arm A: 35 ± 17; arm B: 37 ± 19) from 47 ± 16 points preoperatively (arm A: 49 ± 15; arm B: 46 ± 14) to 83 ± 20 points (arm A: 84 ± 19; arm B: 83 ± 18) at last FU. Comparable values were observed in HOP 2: the overall Harris score increased by 37 ± 17 points (arm A: 36 ± 16; arm B: 38 ± 15) from 47 ± 15 points (arm A: 47 ± 17; arm B: 48 ± 15) preoperatively to 85 ± 18 points (arm A: 83 ± 19; arm B: 86 ± 17) at last FU. Thus, there were no significant differences in the functional status at all FU situations between the HOP 1 and HOP 2 studies and between the respective treatment arms.

Typical clinical examples of a successful HO prophylaxis is demonstrated for postoperative radiotherapy in Fig. 2A and B and for preoperative radiotherapy in Fig. 3A and B.

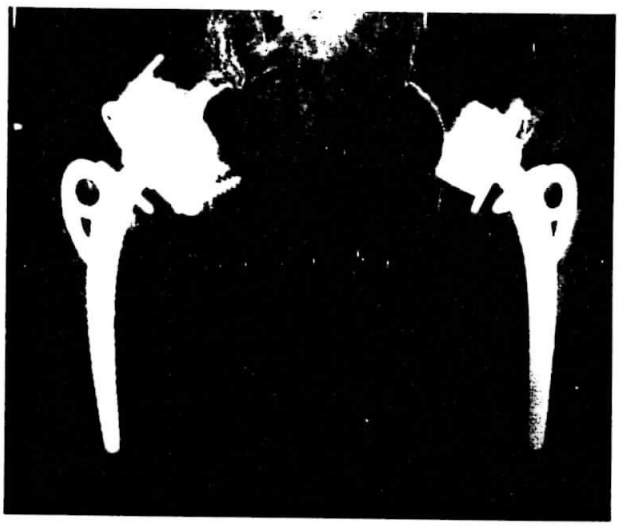
Failure analysis and prognostic factors

For univariate analysis of radiological failures only patients were considered who had at least a failure of Brooker Grade II, i.e., 16 of 22 patients in the HOP 1 study and 13 of 19 patients in the HOP 2 study. When using this discrimination two prognostic factors were identified in HOP 1: (a) initiation of RT >4 days postoperatively (8 of 51 = 16%) resulted in a significantly higher failure rate than initiation of RT ≤4 days (8 of 198 = 4%) ($p < 0.05$); and (b) patients with ≥2 high HO risk factors (i.e., ipsi- or contralateral HO or acetabular fracture) had a significantly higher failure rate (8 of 62 = 13%) than those with one high HO risk factor (7 of 110 = 6%) or none (1 of 77 = 1%) ($p < 0.05$). In contrast, other factors like gender, age, RT dose, RT duration, type of hip implant (cemented vs. uncemented), and several perioperative variables had no prognostic impact on treatment outcome. In multivariate logistic regression analysis only "the number of high HO risk factors" ($p = 0.03$) and "the time to RT initiation" ($p = 0.05$) were independent prognostic factors.

For HOP 2, other prognostic factors were identified in univariate analysis: (a) postoperative RT resulted in a lower radiological failure rate (arm A: 4 of 81 = 5%) than preoperative RT (arm B: 15 of 80 = 19%) ($p < 0.05$); (b) patients with a high preoperative ipsilateral Brooker Grade III or IV (13 of 51 = 25%) had a higher failure



(a)



(b)

Fig. 2. Postoperative prophylactic RT: Case study in a 62-year-old male. (a) Clinical situation prior to prophylactic RT. Eight months after total hip arthroplasty (THA) a severe HO (Brooker Grade IV) has developed. The patient had not received prophylactic RT despite contralateral HO (Brooker Grade II). Severe pain and restricted hip mobility have lead to a second surgery for deossification. The patient was randomized to fractionated 5 × 3.5 Gy postoperative RT to prevent the development of HO. (b) Clinical situation at last FU. A control radiograph 11 months later revealed no HO on the reoperated right hip; thus, the prophylactic treatment had been successful, and the patient had regained nearly full functional activity (Harris score value of 92 points).

(a)

(b)

Fig. 3. Preoperative prophylactic RT: Case study in a 58-year-old female. (a) Clinical situation prior to prophylactic RT. Twelve months after total hip arthroplasty (THA) a severe HO (Brooker Grade IV) has developed. The patient had not received prophylactic RT. Severe pain and restricted hip mobility have lead to a second surgery for deossification. The patient was randomized to a single fraction of 7 Gy preoperative RT to prevent the development of HO. (b) Clinical situation at last FU. A control radiograph 7 months later revealed no HO on the reoperated right hip; thus, the prophylactic treatment had been successful. Despite the effective prophylaxis, some pain symptoms remained and the patient did not regain full functional activity (Harris score value of 72 points).

rate than those with low preoperative ipsilateral Brooker Grade 0 to II (6 of 110 = 5%) ($p < 0.05$); the difference was also statistically significant for preoperative patients with preoperative ipsilateral Brooker Grade III (6 of 18 = 33%) or Grade IV (5 of 11 = 45%) (Table 6); (c) patients with increased postoperative hematoma had a higher failure rate (7 of 31 = 23%) than those without (12 of 130 = 9%) ($p < 0.05$); and (d) patients with

Table 6. HOP 2 treatment failures according to ipsilateral preoperative hip status

Ipsilateral preoperative hip status/Brooker	Postoperative RT (arm A; n = 81)	Preoperative RT (arm B; n = 80)	Total group (n = 161)
Grade 0	0/26 (0%)	2/26 (8%)	2/52 (4%)
Grade 1	1/16 (6%)	0/11 (0%)	1/27 (4%)
Grade 2	1/17 (6%)	2/14 (14%)	3/31 (10%)
Grade 3 (*)	1/14 (7%)	6/18 (33%)	7/32 (22%)
Grade 4 (*)	1/8 (13%)	5/11 (45%)	6/19 (32%)
Total	4/81 (5%)	15/80 (19%)	19/161 (12%)

Agenda: RT = Radiotherapy; (*) difference between arm A and arm B failures statistically significant ($p < 0.05$).

postoperative infection about the implant also had a higher failure rate (2 of 5 = 40%) than those without (17 of 156 = 11%) ($p < 0.05$). In multivariate logistic regression analysis "number of high HO risk factors" ($p = 0.003$), "preoperative HO grade" ($p = 0.001$), and "RT dose concept" ($p = 0.05$) were independent prognostic factors.

For development of functional failures (decrease of Harris score) no statistical prognostic factors were found which predicted in long-term FU. Neither pre- and immediate postoperative Brooker score, nor preoperative functional status, type of implant (cemented vs. noncemented), and RT initiation (delayed vs. correct) were significantly correlated with functional differences. Although there were less patients with functional failures in HOP 1 (18 = 7%; arm A: 10 = 8%; arm B: 8 = 7%) than in HOP 2 (23 = 14%; arm A: 10 = 12%; arm B: 13 = 16), this difference was not statistically significant. Patients with high Brooker Grade III and IV at last FU had a lower Harris score than those with low Brooker Grade 0 to II at last FU ($p < 0.05$). This result reflects the well known negative correlation between the Brooker grade and the Harris score. In addition, as expected, a low preoperative Harris score resulted in a significantly larger functional improvement than a high preoperative Harris score.

Treatment toxicity

For HOP 2 careful analysis was performed to identify possible toxicity differences during the perioperative period in all groups: intra- and postoperative complications were not increased in patients who were irradiated preoperatively compared to those irradiated postoperatively. Means and ranges of different variables were similiarly distributed in both groups including duration of surgery, intraoperative blood loss, number of supplied blood units, postoperative drainage volume from the operated hip, and the decrease of hemoglobin and increase of leucocytes. All observed complications were minimal and within the range of historically expected incidences found in operative series alone. An increased rate of postoperative hematoma in 31 patients (arm A: 15 = 19%; arm B: 16 = 20%) or swelling in 51 patients (arm A: 24 = 30%; arm B: 27 = 34%) was sometimes associated with increasing pain, and required the removal of the hematoma in eight patients (arm A: 5 = 6%; arm B: 3= 4%). An infection of the implant occured in five patients, but only in one patient the prosthesis had to be removed after 3 weeks and replaced within 3 weeks by another implant without further complications. Thus, it is concluded that preoperative RT as an equal low acute risk profile compared to postoperative RT. There were also no differences regarding the postoperative mobilization process following hip surgery between the two studies and treatment arms, respectively. The interval of partial strain (≤50% body weight) at the operated hip was not considerably longer in preoperative patients (9 days 19) compared to postoperative patients (8 days 16). The interval to use full strain at the operated hip (100% body weight) was equal in both groups (arm A: 33 ± 37 days; arm B: 34 ± 42 days) ($p > 0.05$). No increased long-term complications were observed in both groups. Nonunion formation did not occur in the only four cases that had undergone trochanteric osteotomy as part of their total hip arthroplasty. In long-term FU no acetabular or femoral component of the implant revealed subsidence, radiolucent lines, or change in position; moreover, early loosening of noncemented or porous-coated prostheses was not seen, despite the fact that no individual shielding of the implant site was performed.

DISCUSSION

Biological aspects

There is still insufficient knowledge about the triggering mechanisms and different actions involved in the formation of ectopic bone and the individual risk factors that place patients at risk to develop HO. The highest risk to develop HO is in patients with evident HO formation about the ipsi- or contralateral hip. The radiobiologic target for ionizing radiation appears to be radiosensitive pluripotent mesenchymal cells, which are stimulated to proliferate and differentiate after a specific trauma (15, 54). The osteogenitor mesenchymal cells, which transform into bone-producing osteoblasts, could be recruited from distant body sites outsite of the surgical field and are possibly brought to the traumatized tissue through the blood stream and during the process of hematoma formation. However, these cells may also be resident in the local tissues within the operative field and, thus, may be directly stimulated by specific traumatic events to produce ectopic bone (53, 54). In an *in vivo* study the differentiation of mesenchymal cells has been observed to occur as early as 16 h after a traumatic event, and this reaction peaked at around 36 h (53).

Induction of cell differentiation has been observed from measurements of quantities of bone formed in response to implants of bone matrix or purified bone morphogenetic protein (BMP) in extraskeletal and intraskeletal sites. The

osteoprogenitor cell proliferation process is known for a long time. It has been measured in reactions of periosteum and endosteum to injury, diet, vitamines, and hormones. Bone-derived growth factors (BDGF) can stimulate osteoprogenitor cells to proliferate in serum-free tissue culture media. These mechanisms of action of both BMP and BDGF are primarily local, but secondary systemic imunologic reactions could have permissive and/or depressive effects. Recent progress in this research field suggests that BMP and BDGF are coefficient; while PMP initiates the covert stage of bone formation, BDGF stimulates the overt stage of bone development (54). *In vivo* data of Kantorowitz *et al.* (29) demonstrate the prophylactic efficacy of ionizing radiation and a dose–response relationship. The data have important clinical implications and suggest to deliver at least 7–8 Gy to potential sites at risk. It was the first study to show the prophylactic potential of preoperative RT. Preoperative RT within 1 h prior to surgery revealed an equal prophylactic efficacy compared to RT delivered 2 days postoperatively, but the 2-day preoperative RT regimen was inadequate to prevent HO. This data provides a strong rationale for preoperative prophylactic RT immediately before surgery.

Postoperative RT can affect all osteoprogenitor mesenchymal cells in the treated volume, including those that are resident and those that are brought to the operated site perioperatively. In contrast, the efficacy of preoperative RT, which is delivered to the surgical field prior to the insult stimulating ingress of blood-borne cellular elements, relies on the effect of resident osteoprogenitor cells, which may participate in the process of HO formation. Interestingly in our study preoperative RT was less effective for cases with a "high preload of ectopic bone," i.e., in patients with preoperative ipsilateral HO Booker Grade III to IV. If the "preload of ectopic bone" was only minor or not existing, i.e., HO Brooker Grade 0 to II, the results of prophylactic RT were equal in the pre- and the postoperative RT group.

Review of clinical experience

Literature data should be cautiously interpreted due to several confounding factors, i.e., lack of high-risk factors to develop HO, small patient numbers and low accrual, and uncontrolled study design. Few groups have conducted prospectively randomized trials to study different RT regimens including our previous comparative studies (21, 34, 41, 46, 47). Our data suggests, that preoperative RT is equivalent to postoperative RT as long as no severe ipsilateral HO is present. The radiological failure rate of the postoperative RT arms in HOP 1 and HOP 2 are within the range of most published series, i.e., below 10% (2, 4, 14, 24–26, 30, 34, 36–38, 41, 42, 46–48, 51, 55). Some series reported a high failure rate (8, 11, 13, 16), which was associated with incomplete resection of HO (12), insufficient coverage of soft tissues about the hip ("geographical miss") (16); delayed inititiation of RT (2, 4, 5, 8, 14, 24, 34, 46, 47, 51), protracted RT application (46, 47), and presence of numerous high-risk factors (16).

Some known prognostic factors have been confirmed in our two studies: postoperative prophylactic RT should be initiated within the first 3 days after surgery. The number of high-risk factors is another important prognostic parameter. Patients with ipsi- and contralateral HO have a higher risk to fail prophylactic RT than those with medium risk factors, such as hypertrophic osteoarthritis with periacetabular osteophyte formation. From our study it can be concluded that most patients irradiated preoperatively yield a good prophylaxis. Only patients with ipsilateral HO Grade III and IV may not be successfully treated. These patients could benefit from multifractionated postoperative prophylactic RT or from single-fraction RT supplemented by NSAID application. Thus, it is important to cooperate with all referring orthopedic surgeons. Future protocols should stratify patients according to individual risks.

Positive results obtained with single-fraction RT are important, as the reduced RT setup time renders prophylactic RT as a more economic, less hazardous, and easier to handle method. It also provides a far better compliance than the long-term prescription of NSAID medication. From a practical point, it would be even more convenient if patients would receive prophylactic RT a day before surgery. This would require that the radiobiological target responds to the prophylactic RT within a "prophylactic window" of at least 16 h prior to hip surgery.

The functional aspects of prophylactic RT for prevention of HO are rarely addressed. "Functional failures" involve an impairment of the preoperative Harris score, which is mostly related to the lack of success of surgery and sometimes to the inefficacy of prophylactic RT. In the final analysis of the two randomized studies the mean functional gain (i.e., change of Harris score) improved similarly in all groups, and the number of "functional failures" were well balanced in both studies and respective treatment arms. However, severe "radiological failures," i.e., Brooker Grades III and IV, may induce a functional impairment. Otherwise both endpoints do not correlate with each other.

Treatment Sequelae

Acute toxicity of prophylactic RT is minor and confined to the immediate postoperative period. The rate of increased hematoma and swelling is not increased compared to incidences reported in series involving surgery alone. Only in a few patients reoperation was necessary, mostly for removal of large painful hematomas and in one case to explant an infected prosthesis.

Possible long-term effects may include delayed ingrowth of uncemented implants possibly resulting in a reduced short- and long-term stability of the prosthesis (14, 29, 56). Other concerns include the induction of transient oligospermia or infertility and initiation of secondary malignancies. The shielding of acetabular and femoral components of the implant has been recommended when using porous coated

or biologic fixation prostheses as well as shielding of intrapelvic and genital structures (8, 26, 34, 36, 55). While we have conducted the latter procedure, we have not shielded osseous implant sites for fear of shielding areas in soft tissues underneath of such blocks from which ectopic bone formation may derive. During our past 10-year clinical experience no concerns regarding a higher instability or loosening rate of irradiated vs. unirradiated hips have been brought up by our orthopedic surgeons.

Our two randomized trials overcome common disadvantages of historical studies such as uncontrolled study design, low patient number and long accrual period, variable HO risk profile among patients receiving prophylactic RT, and short FU. Our methodical center has provided a stringent control and analysis of all clinical and statistical data including multivariate assessment of prognostic factors. Due to the high radiological failure rate for ipsilateral Brooker Grade III to IV treated with preoperative RT, the HOP 2 study was terminated prematurely. It is now replaced by two other prospective protocols.

CONCLUSIONS

The presented data indicate the high prophylactic potential of both preoperative and postoperative RT for patients at high risk to develop HO. Only patients with a high ipsilateral preload of ectopic bone formation (Brooker Grade III and IV) should not receive preoperative RT. Preoperative RT should be applied within 4 h prior to surgery or postoperatively within 96 h after hip surgery. The application of RT induces none or only minor additional toxicity, but reduces the risk for the development of HO from nearly 80–90% to as low as 10%. The major advantage of the preoperative treatment concept is the improved patient comfort, the ease of treatment management, and the avoidance of possible postoperative complications associated with transportation and positioning of the patient during the immediate postoperative period. Both studies provide interesting insights into the biological mechanisms involved in radiation injury to osteoprogenitor cell lines.

REFERENCES

1. Ahrengart, L.; Lindgren, U.; Reinholt, F. P. Comparative study of the effect of radiation, indomethacin, prednisolone and ethane-1-hydroxy-1,1-diphosphonate (EHDP) in the prevention of ectopic bone formation. Clin. Orthop. 229:265–273; 1988.
2. Anthony, P.; Keys, H.; McCollister-Evarts, C.; Rubin, P.; Lush, C. Prevention of heterotopic bone formation with early postoperative irradiation in high risk patients undergoing total hip arthroplasty: Comparison of 10 Gy vs. 20 Gy schedules. Int. J. Radiat. Oncol. Biol. Phys. 13:365–369; 1987.
3. Armitage, P.; Berry, G. Statistical methods in medical research, 2nd ed. Oxford: Blackwell Publishers; 1987.
4. Ayers, D. C.; Evarts, C. M.; Parkinson, J. R. The prevention of heterotopic ossification in high-risk patients by low-dose radiation therapy after total hip arthroplasty. J. Bone Joint Surg. 68A:1423–1430; 1986.
5. Ayers, D. C.; Pellegrini, V. D.; Evarts, C. M. Prevention of heterotopic ossification in high-risk patients by radiation therapy. Clin. Orthop. 263:87–93; 1991.
6. Bisla, R. S.; Ranawat, C. S.; Inglis, A. E. Total hip replacement in patients with ankylosing spondylitis with involvement of the hip. J. Bone Joint Surg. 58:233–236; 1976.
7. Blasingame, J. P.; Resnick, D.; Coutts, R. D. Extensive spinal osteophytosis as a risk factor for heterotopic bone after total hip arthroplasty. Clin. Orthop. 161:191–197; 1981.
8. Blount, L. H.; Thomas, B. J.; Tran, L.; Selch, M. T.; Sylvester, J. E.; Parker, R. G. Postoperative irradiation for the prophylaxis of heterotopic bone: Analysis of different dose schedules and shielding considerations. Int. J. Radiat. Oncol. Biol. Phys. 19:557–581; 1990.
9. Bosse, M. J.; Poka, A.; Reinert, C. M.; Ellwanger, F.; Slawson, R.; McDewitt, E. R. Heterotopic ossification as a complication of acetabular fracture: Prophylaxis with low-dose irradiation. J. Bone Joint Surg. 70A:1231–1237; 1988.
10. Brooker, A. F.; Bowerman, J. W.; Robinson, R.A.; Riley, L. H. Ectopic ossification following total hip replacement. J. Bone Joint Surg. 55A:1629–1632; 1973.
11. Brunner, R.; Morscher, E.; Hünig, R. Paraarticular ossification in total hip replacement: An indication for irradiation therapy. Arch. Orthop. Trauma. Surg. 106:102–107; 1987.
12. Chalmers, J.; Gray, D. H.; Rush, J. Observations on the induction of bone in the soft tissue. J. Bone Joint Surg. 57B:36–45; 1975.
13. Conterato, D. J.; Verner, J.; Hartsell, W. F.; Murthy, A. K.; Galante, J. O.; Hendrickson, F. R. Prevention of heterotopic bone formation. Comparison of 5 Gy vs. 10 Gy. Int. J. Radiat. Oncol. Biol. Phys. 17(Suppl. 1):232; 1989.
14. Coventry, M. B.; Scanlon, P. W. The use of radiation to discourage ectopic bone. A nine-year study in surgery about the hip. J. Bone Joint Surg. 63A:201–208; 1981.
15. Craven, P. L.; Urist, M. R. Osteogenesis by radioisotope labeled cell populations in implants of bone matrix under the influence of ionizing radiation. Clin. Orthop. 76:231–243; 1971.
16. DeFlitch, C. J.; Stryker, J. A. Postoperative hip irradiation in prevention of heterotopic ossification: Causes of treatment failure. Radiology 188:265–270; 1993
17. DeLee, J.; Ferrari, A.; Charnley, J. Ectopic bone formation following low friction arthroplasty of the hip. Clin. Orthop. 121:53–58; 1976.
18. Elmstedt, E.; Lindholm, T. S.; Nilsson, O. S.; Törnkvist, H. Effect of ibuprofen on heterotopic ossification after hip replacement. Acta Orthop. Scand. 56:25–27; 1985.
19. Ghalambor, N.; Matta, J. M.; Bernstein, L. Heterotopic ossification following operative treatment of acetabular fracture: An analysis of risk factors. Clin. Orthop. 305:96–105; 1994.
20. Goel, A.; Sharp, D. J. Heterotopic bone formation after hip replacement. J. Bone Joint Surg. 73B:255–257; 1991.
21. Gregoritch, S.; Chadha, M.; Pellegrini, V. D.; Rubin, P.; Kantorowitz, D. A. Randomized trial comparing preoperative vs. postoperative irradiation for prevention of heterotopic ossification following prosthetic total hip replacement: Preliminary results. Int. J. Radiat. Oncol. Biol. Phys. 30:55–62; 1994.
22. Harris, W. H. Traumatic arthritis of the hip after dislocation and acetabular fractures: Treatment by mold arthroplasty. J. Bone Joint Surg. 51A:737–755; 1969.
23. Hastings, H., II; Graham, T. J. The classification and treatment of heterotopic ossification about the elbow and forearm. Hand Clin. 10:417–437; 1994.

24. Healy, W. L.; Lo, T. C. M.; Covall, D. J.; Pfeifer, B. A.; Wasilewski, S. A. Single-dose radiation therapy for prevention of heterotopic ossification after total hip arthroplasty. J. Arthroplasty 5:369–375; 1990.
25. Hedley, K. A.; Mead, L. P.; Hendren, D. H. The prevention of heterotopic bone formation following total hip arthroplasty using 600 rad in a single dose. J. Arthroplasty 4:319–325; 1989.
26. Jasty, M.; Schutzer, S.; Tepper, J.; Willett, C.; Stracher, M. A.; Harris, W. H. Radiation-blocking shields to localize periarticular radiation precisely for prevention of heterotopic bone formation around uncemented total hip arthroplasties. Clin. Orthop. 257:138–145; 1990.
27. Johnston, E. E.; Kay, R. M.; Dorey, F. J. Heterotopic ossification prophylaxis following operative treatment of acetabular fracture. Clin. Orthop. 305:88–95; 1994.
28. Johnston, R. C.; Fitzgerald, R. H.; Harris, W. H.; Poss, R.; Müller, M. E.; Sledge, C. B. Clinical and radiographic evaluation of total hip replacement. J. Bone Joint Surg. 72A:161–168; 1990.
29. Kantorowitz, D. A.; Miller, G. J.; Ferrara, J. A.; Ibbott, G. S.; Fisher, R.; Ahrens, C. R. Preoperative vs. postoperative irradiation in the prophylaxis of heterotopic bone formation in rats. Int. J. Radiat. Oncol. Biol. Phys. 19:1431–1438; 1990.
30. Karstens, J. H.; Gehl, H. B.; Savvidis, E.; Casser, H. R.; Löer, F. Strahlentherapie—Eine wirksame Prophylaxe periartikulärer Verknöcherungen nach Implantation von Hüfttotalendoprothesen. Med. Welt 41:1101–1103; 1990.
31. Kellgren, J. H.; Lawrence, J. S. Radiological assessment of osteo-arthrosis. Ann. Rheum. Dis. 16:494–501; 1957.
32. Kennedy, W. F.; Gruen, T. A.; Chessin, H.; Gasparini, G.; Thompson, W. Radiation therapy to prevent heterotopic ossification after cementless total hip arthroplasty. Clin. Orthop. 262:185–191; 1991.
33. Kersh, C. R.; Eisert, D. R.; Cook, D. E. Heterotopic bone formation: Control of progression by radiotherapy (Abstract). Int. J. Radiat. Oncol. Biol. Phys. 12(Suppl 1):171; 1986.
34. Konski, A.; Pellegrini, V.; Poulter, C.; DeVanny, J.; Rosier, R.; Evarts, C. M.; Henzler, M.; Rubin, P. Randomized trial comparing single dose vs. fractionated irradiation for prevention of heterotopic bone. Int. J. Radiat. Oncol. Biol. Phys. 18:1139–1142; 1990.
35. Kristensen, S. S.; Pedersen, P.; Pedersen, N. W.; Schmidt, S. A.; Kjærsgaard-Andersen, P. Combined treatment with indomethacin and low-dose heparin after total hip replacement. A double-blind, placebo-controlled clinical trial. J. Bone Joint Surg. 72B:447–449; 1990.
36. Lo, T. C. M.; Healy, W. L.; Covall, D. J.; Dotter, W. E.; Pfeiffer, B. A.; Torgerson, W. R.; Wasilewski, S. A. Heterotopic bone formation after hip surgery: Prevention with single-dose postoperative hip irradiation. Radiology 168:851–854; 1988.
37. MacLennan, I.; Keys, H. M.; Evarts, C. M.; Rubin, P. Usefullness of postoperative hip irradiation in the prevention of bone formation in a high risk group of patients. Int. J. Radiat. Oncol. Biol. Phys. 10:49–53; 1984.
38. Maloney, W. J.; Jasty, M.; Willet, C.; Wilroy, R. D.; Harris, W. H. Prophylaxis for heterotopic bone formations after total hip arthroplasty using low-dose radiation in high-risk patients. Clin. Orthop. 282:230–234; 1992.
39. Merle D'Aubigné, R.; Postel, M. Functional results of hip arthroplasty with acrylic prostheses. J. Bone Joint Surg. 36A:451–475; 1954.
40. Pedersen, N. W.; Kristensen, S. S.; Schmidt, S. A.; Pedersen, P.; Kjærsgaard-Andersen, P. Factors associated with heterotopic bone formation following total hip replacement. Arch. Orthop. Trauma Surg. 108:92–95; 1989.
41. Pellegrini, V. D.; Konski, A. A.; Gastel, J. A.; Rubin, P.; Evarts, C. M. Prevention of heterotopic ossification with irradiation after total hip arthroplasty. J. Bone Joint Surg. 74A:186–200; 1992.
42. Reining, J.; Schäfer, T.; Pfab, R.; Hess, F. Postoperative Strahlenbehandlung nach Hüfttotalendoprothese zur Prophylaxe periartikulärer Verknöcherungen—Ein therapeutisches Konzept. Med. Welt 39:1542–1544; 1988.
43. Ritter, M. A.; Vaughan, R. B. Ectopic ossification after total hip arthroplasty: Predisposing factors, frequency and effect on results. J. Bone Joint Surg. 59A:345–351; 1977.
44. Ritter, M. A.; Sieber, J. M. Prophylactic indomethacin for the prevention of heterotopic bone formation following total hip arthroplasty. Clin. Orthop. 196:217–225; 1985.
45. Rosendahl, S.; Christoffersen, J. K.; Nörgaard, M. Paraarticular ossification following hip replacement. Acta Orthop. Scand. 48:400–404; 1977.
46. Seegenschmiedt, M. H.; Goldmann, A. R.; Wölfel, R.; Hohmann, D.; Beck, H.; Sauer, R. Prevention of heterotopic ossification (HO) after total hip replacement: Randomized high vs. low dose radiotherapy. Radiother. Oncol. 26:271–274; 1993.
47. Seegenschmiedt, M. H.; Goldmann, A. R.; Martus, P.; Wölfel, R.; Hohmann, D.; Sauer, R. Prophylactic radiation therapy for prevention of heterotopic ossification after hip arthroplasty: Results in 141 high-risk hips. Radiology 188:257–264; 1993.
48. Seegenschmiedt, M. H.; Martus, P.; Goldmann, A. R.; Wölfel, R.; Keilholz, L.; Sauer, R. Preoperative vs. postoperative radiotherapy for prevention of heterotopic ossification (HO): First results of a randomized trial in high-risk patients. Int. J. Radiat. Oncol. Biol. Phys. 30:63–73; 1994.
49. Slawson, R. G.; Poka, A.; Bathon, H.; Salazar, O. M. Postoperative radiation for prevention of heterotopic ossification in traumatic acetabular fracture. Int. J. Radiat. Oncol. Biol. Phys. 17:669–672; 1988.
50. Sodemann, B.; Persson, P.-E.; Nilsson, O. S. Prevention of heterotopic ossification by nonsteroid anti-inflammatory drugs after total hip arthroplasty. Clin. Orthop. 237:158–237; 1988.
51. Sylvester, J. E.; Greenberg, P.; Selch, M. T.; Thomas, B. J.; Amstutz, H. The use of postoperative irradiation for the prevention of heterotopic bone formation after total hip replacement. Int. J. Radiat. Oncol. Biol. Phys 14:471–476; 1988.
52. Thomas, B. J.; Amstutz, H. C. Results of administration of diphosphonate for prevention of heterotopic ossification after total hip arthroplasty. J. Bone Joint Surg. 67A:400–403; 1985.
53. Tonna, E. A.; Cronkite, E. P. Autoradiographic studies of cell proliferation in the periostium of intact and fractured femora of mice utilizing DNA-labeling with H-3 thymidine. Proc. Soc. Exp. Biol. Med. 107:719–721; 1961.
54. Urist, M. R.; DeLange, R. J.; Finerman, G. A. M. Bone cell differentiation and growth factors. Science 220:680–686; 1983.
55. van der Werf, G. J. I. M.; van Hasselt, N. G. M.; Tonino, A. J. Radiotherapy in the prevention of recurrence of paraarticular ossification in total hip prosthesis. Arch. Orthop. Trauma Surg. 104:85–88; 1985.
56. Wise, M. W.; Robertson, I. D.; Lachiewicz, P. F.; Thrall, D. E.; Metcalf, M. The effect of radiation therapy on the fixation strength of an experimental porous-coated implant in dogs. Clin. Orthop. 261:276–280; 1990.