Preoperative Irradiation for Prevention of Heterotopic Ossification Following Prosthetic Total Hip Replacement

Results of a Prospective Study in 462 Hips

Oliver Koelbl[1], Julia Seufert[1], Fabian Pohl[1], Annette Tauscher[2], Harald Lehmann[3], Hans-Werner Springorum[2], Michael Flentje[1]

Background: The effectiveness of pre- or postoperative radiotherapy for prevention of heterotopic ossification (HO) following total hip replacement (THR) has already been demonstrated in the past. Thereby, in most studies using preoperative radiotherapy patients were irradiated < 6 h before surgery. The purpose of this prospective study was to analyze the effectiveness of preoperative irradiation on the evening before surgery and to identify risk factors for HO in a homogeneous collective of patients.
Patients and Methods: From July 1997 to July 2001, 416 patients (462 hips; 235 males, 227 females) received preoperative radiotherapy of the hip on the evening before surgery with a 7-Gy single fraction. The patients' median age was 67.1 years. The most frequent indication for radiotherapy was hypertrophic osteoarthritis (383 hips, 82.9%). Treatment results were assessed by comparison of pre- and postoperative hip X-rays (immediately and 6 months after surgery). The analysis of radiographs was performed according to the Brooker score.
Results: The overall incidence of HO was 18.1% (n = 84), Brooker score 1 12.3% (n = 57), score 2 3.9% (n = 18), score 3 1.5% (n = 7), and score 4 0.4% (n = 2). Sex, body height, hypertrophic osteoarthritis of higher degree, size of the femoral component of the prosthesis, previous ipsi- or contralateral HO, and short course of nonsteroidal anti-inflammatory drug (diclofenac) therapy significantly influenced the HO rate in univariate analysis. In multivariate analysis, an interdependence of prosthesis size, sex and patient's height was found. From these three variables, only prosthesis size was statistically significant in multivariate analysis. The cumulative dose of diclofenac (≤ 300 mg or > 300 mg) within the first 7 postoperative days and previous ipsi- or contralateral HO influenced the incidence of HO in multivariate analysis.
Conclusion: Preoperative radiotherapy on the evening before surgery is an effective treatment modality to reduce overall (Brooker 1–4) and clinically relevant, severe HOs (Brooker 3–4), and includes several advantages compared to postoperative irradiation. Previous ipsi- and contralateral HOs were identified as high risk factors for HO in this study. In patients with these risk factors, the incidence of HO increased.

Key Words: Total hip arthroplasty · Heterotopic ossification · Preoperative radiotherapy · Nonsteroidal anti-inflammatory drugs

Strahlenther Onkol 2003;179:767–73
DOI 10.1007/s00066-003-1088-y

Präoperative Bestrahlung zur Vermeidung heterotoper Ossifikationen nach totalendoprothetischem Hüftgelenkersatz. Ergebnisse einer prospektiven Studie an 462 Hüften

Hintergrund: Die Wirksamkeit einer prä- oder postoperativen Radiatio zur Vermeidung heterotoper Ossifikationen (HO) nach totalendoprothetischem Hüftgelenkersatz (TEP) wurde in der Vergangenheit bereits gezeigt. Dabei wurde in den meisten Studien einer präoperativen Radiatio die Bestrahlung im Zeitraum von 6 h vor der Operation durchgeführt. Ziel dieser Arbeit war es, die Wirksamkeit einer präoperativen Bestrahlung am Abend vor dem Operationstag in einem homogenen Patientenkollektiv zu überprüfen.
Patienten und Methodik: Von 07/1997 bis 07/2001 wurde bei 416 Patienten (462 Hüften; 235 Männer, 227 Frauen) eine präoperative Einzeitbestrahlung der Hüfte mit einer Dosis von 7 Gy durchgeführt. Das mediane Alter der Patienten betrug 67,1 Jahre. Die häufigste Indikation für die prophylaktische Bestrahlung war eine hypertrophe Osteoarthritis (383 Hüften, 82,9%). Das Therapieergebnis wurde anhand von Röntgenbildern unmittelbar postoperativ und 6 Monate nach Operation gemäß dem Brooker-Score beurteilt.

[1] Clinic and Policlinic for Radiotherapy, University of Würzburg, Germany,
[2] Orthopedic Clinic, Caritas Hospital, Bad Mergentheim, Germany,
[3] Insitute of Radiology, Caritas Hospital, Bad Mergentheim, Germany.

Received: August 22, 2002; accepted: February 21, 2003

Ergebnisse: Die HO-Inzidenz betrug 18,1% (n = 84), Brooker-Grad 1 12,3% (n = 57), Grad 2 3,9% (n = 18), Grad 3 1,5% (n = 7) and Grad 4 0,4% (n = 2). Geschlecht, Körpergröße, Ausmaß der Osteoarthritis, Größe des Prothesenschafts, vorherige ipsi- oder kontralaterale HO und die zusätzliche Gabe von nichtsteroidalen Antiphlogistika (Diclofenac) hatten in der univariaten Analyse signifikanten Einfluss auf die HO-Rate. Es fand sich eine Korrelation von Geschlecht, Körpergröße und Schaftgröße, so dass in der multivariaten Analyse nur noch die Schaftgröße eine Signifikanz aufwies. Die kumulative Diclofenacdosis (≤ 300 mg bzw. > 300 mg) und vorherige ipsi- oder kontralaterale HO behielten auch in der multivariaten Analyse ihren signifikanten Einfluss auf die HO-Rate.
Schlussfolgerung: Eine präoperative Bestrahlung am Vorabend der Operation stellt eine effektive Behandlung zur Vermeidung von HO nach TEP dar und hat gegenüber einer postoperativen Bestrahlung Vorteile. Insbesondere vorherige ipsi- und kontralaterale HO stellen Hochrisikofaktoren für die Entstehung von HO auch nach Bestrahlung dar.

Schlüsselwörter: Totalendoprothese des Hüftgelenks · Heterotope Ossifikationen · Präoperative Bestrahlung · Nichtsteroidale Antiphlogistika

Introduction

Heterotopic ossification (HO) is a well-known complication after total hip replacement (THR). The reported prevalence varies between 8% and 90% [29, 39]. About 30% of these patients develop functional impairment [32, 40, 43]. Endogenous factors associated with the development of HO after THA include previous HO [7], sex and age [2, 23], idiopathic skeletal hyperostosis [4], ankylosing spondylitis [47], and hypertrophic osteoarthritis [1]. Various exogenous predisposing factors such as the operative approach [48] are in discussion. Because severe ossification reduces hip prosthesis function, prophylactic treatment was implemented in the last 3 decades. In 1975, Dahl [6] showed the effectiveness of nonsteroidal anti-inflammatory drugs (NSAIDs) for prevention of HO and in 1981, Coventry & Scanlon [5] demonstrated that the incidence of HO was reduced by postoperative irradiation. In the meantime, different drugs and different radiation doses and fractionations, respectively, were analyzed regarding the reduction of HO. Postoperative irradiation includes the disadvantage of necessary patient transport from the orthopedic clinic to the department of radiotherapy on the 1st or 2nd postoperative day, which means pain caused by the transport and risk of luxation of the prosthesis. A very important finding was that preoperative irradiation within 4 h before surgery was effective in preventing HO [12, 43]. The procedure of early (< 4 h before surgery) preoperative irradiation, however, can result in logistic problems, if there is a greater distance between the department of radiotherapy and the orthopedic clinic. To avoid these organizational problems, two prospective studies evaluated the effectiveness of irradiation on the evening before surgery [27, 31]. The reported incidences of HO varied considerably, ranging between 4% and 48%. There are several reasons for this: the great number of possible risk factors as described above, which were not included into analysis of most studies, an additional therapy with NSAIDs, which was often not well documented and therefore depreciated the evaluation of the effectiveness of radiotherapy, the small number of studied hips diminishing the statistical validity, and the different time of irradiation, i.e., immediately before surgery or on the evening before the day of surgery.

The purpose of this study was, therefore, to analyze a large, homogeneous collective of 462 operated hips and to evaluate the effectiveness of preoperative radiotherapy for prevention of ectopic ossification, to evaluate the effect of an additional therapy with NSAIDs, and to define risk factors for the development of HO.

Patients and Methods

From July 1997 to July 2001, 416 patients (462 hips) received preoperative radiotherapy of the hip on the evening before surgery with a 7-Gy single fraction. Prior to radiotherapy, all patients underwent simulation. Depending on body size, an individual portal of 12–14 × 12–14 cm was chosen to encompass all periarticular soft tissue. To protect intrapelvic and genital structures, a shielding was used in the medial part of the portal. Treatment was via anterior-posterior opposed fields with dose prescribed to the central axis midplane depth. Radiotherapy was delivered with cobalt-60. Source-to-axis distance was 80 cm [27].

The following information was obtained for each patient:

- preoperative factors: age and sex; height and weight (obesity); diagnosis of diseased hip; previous surgery on the ipsi- or contralateral side; previous HO on the ipsi- and contralateral side, time between radiotherapy and surgery (Table 1);
- operative factors: type and size of prosthesis, operative approach to the hip, fixation of prosthesis, blood loss, duration of surgery (Table 2);
- postoperative factors: development of HO, antibiotic therapy, NSAID therapy, other analgesic therapy, hematoma, swelling in the operative area (Table 3).

The patients' median age was 67.1 years (range 44.0–88.5 years). Hip surgery was done in 235 (50.9%) male and 227 (49.1%) female patients. Median height was 168.0 cm (range 142–187 cm), median weight 76.0 kg (38–130 kg). Moderate obesity was defined as "> (size–100)" and severe obesity as "> (size–100) + 20%". 119 patients (26.0%) showed moderate, 36 patients (7.9%) severe obesity. The indications for radiotherapy were hypertrophic osteoarthritis (383 hips, 82.9%), replacement of the prosthesis (n = 51, 11.0%), other previous

Table 1. Patient characteristics: preoperative factors. HO: heterotopic ossification.

Tabelle 1. Patientencharakteristik: präoperative Faktoren. HO: heterotope Ossifikationen.

	n	%
Number of patients	416	
Number of hips	462	100
Median age (years)	67.1	Range 44.0–88.5
Sex		
Male	235	50.9
Female	227	49.1
Median height (cm)	168.0	Range 142–187
Right side	243	52.6
Left side	219	47.4
Median weight (kg)	76.0	Range 38–130
Moderate obesity	119	26.0
Severe obesity	36	7.0
Hypertrophic osteoarthritis	383	82.9
Grade 1	6	1.3
Grade 2	78	16.9
Grade 3	124	26.8
Grade 4	175	37.9
Prosthesis replacement	51	11.0
Previous surgery on ipsilateral side	39	8.4
Previous surgery on contralateral side	99	21.4
Previous ipsilateral HO	15	3.2
Previous contralateral HO	28	6.1
Removal of HO	8	1.7
Median interval radiation – surgery (h)	15.5	Range 13.0–21.1

Table 2. Patient characteristics: operative factors.

Tabelle 2. Patientencharakteristik: operative Faktoren.

	n	%
Median duration of surgery (min)	60	Range 20–280
≤ 60 min	225	48.7
> 60 min	237	51.2
ESKA prosthesis		
Femoral component size 1–4	251	54.4
Femoral component size 5–7	169	36.6
Acetabular component size 1–3	169	26.6
Acetabular component size 4–7	265	57.4
Intraoperative standardized antibiotic	253	54.8
Median blood loss (ml)	500	Range 100–2,500

surgery on ipsilateral hip (n = 39, 8.5%), previous ipsilateral (n = 15, 3.2%) or contralateral HO (n = 28, 6.1%), or removal of previous HO (n = 8, 1.7%). The hypertrophic osteoarthritis was graded according to Kellgren & Lawrence [21] (Table 4). 39 patients (8.4%) had previous surgery on the ipsilateral side, 99 patients (21.4%) on the contralateral side.

38.5% (15/39) of patients had developed HO after previous hip surgery on the ipsilateral side, 28.3% (28/99) on the contralateral side. Median interval between radiotherapy and surgery was 15.5 h (13–21.1 h, Table 1).

For THR, an anterolateral approach to the hip was used. All operations were done by the same three experienced orthopedists. Generally, ESKA prostheses (ESKA IMPLANT, Lübeck) of different sizes (size 1–7) were implanted. The femoral component of the prosthesis was uncemented. All patients were supplied with three Redon drainages. The median duration of surgery was 60 min (20–280 min). Median blood loss amounted to 500 ml (100–2,500 ml). A standardized intraoperative antibiotic therapy (1.5 g cefotaxime) was used in 253 patients (54.8%), 156 patients (33.8%) were administered other antibiotic drugs (Table 2).

The analgesic each patient received was documented for the first 7 postoperative days in this study. The decision on kind and duration of analgesic therapy was not standardized but made individually by the ward physician. 76.4% (353/462) received NSAID (diclofenac) as postoperative analgesic, 23.6% (109/531) at least for 3 days within the 1st postoperative week. In 21.8% (101/462), the cumulative dose of diclofenac was > 300 mg within the first 7 postoperative days. The influence of the cumulative NSAID dose on HO rate was analyzed

Table 3. Patient characteristics: postoperative factors. NSAID: nonsteroidal anti-inflammatory drug.

Tabelle 3. Patientencharakteristik: postoperative Faktoren. NSAID: nichtsteroidales Antiphlogistikum.

	n	%
Postoperative swelling	262	56.7
Postoperative hematoma	140	30.3
Analgesics within the 1st postoperative week		
NSAID (cumulative dose of diclofenac)	353	76.4
– ≤ 300 mg	252	54.5
– > 300 mg and ≤ 600 mg	36	7.8
– > 600 mg	65	14.1
Tramadole-HCl	325	70.3
Metamizole-sodium	197	42.6
Postoperative antibiotic therapy	89	19.3
Pain 3 months after surgery	70	15.1

Table 4. Modified grading system of hypertrophic osteoarthritis according to Kellgren & Lawrence [21].

Tabelle 4. Klassifikation der hypertrophen Osteoarthritis nach Kellgren & Lawrence [21].

1	Definite osteophytes
2	Beginning joint space narrowing
3	Presence of two of the following: joint space narrowing, osteophytosis, subchondral sclerosis, cyst formation
4	Presence of three of the following: joint space narrowing, osteophytosis, subchondral sclerosis, cyst formation

Table 5. Modified Brooker grading system of heterotopic ossification [3].

Tabelle 5. Klassifikation heterotoper Ossifikationen modifiziert nach Brooker et al. [3].

0	No soft tissue ossification
1	Separate small foci of ossification about the hip
2	Ossification projecting from the proximal femur or pelvis with at least 1 cm between opposing bone surfaces
3	Ossification projecting from the proximal femur or pelvis with < 1 cm between opposing bone surfaces
4	Ossification completely bridging the proximal femur and pelvis

in 50-mg increments. 197 patients (42.6%) received metamizole-sodium, 325 (70.3%) tramadole-HCl as postoperative analgesic. 89 patients (19.3%) were treated with antibiotics postoperatively. Swelling or hematoma formation was found in 55.5% (295/531) and 29.7% (158/531), respectively.

Treatment results were assessed by comparison of pre- and postoperative hip X-rays (immediately and 6 months after surgery). The analysis of radiographs was performed by a panel of four experts (two radiotherapist, one orthopedist, one radiologist) according to the Brooker score (Table 5) [3].

70 patients (15.1%) reported moving pain 3 months after surgery (Table 3).

The χ^2-test of independence (significance level: p-value < 0.05) was used to evaluate dependency in categorical and grouped numerical data. For correlation of parameters, the Spearman rang test was used. Multivariate analysis was done using MANOVA (Statistica version 5.5). A stepwise logistic regression was performed.

Results

The overall incidence of HO at last follow-up was 18.1% (n = 84), Brooker score 1 12.3% (n = 57), score 2 3.9% (n = 18), score 3 1.5% (n = 7), and score 4 0.4% (n = 2).

Preoperative Factors

Of the preoperative parameters shown in Table 1, sex, body height, hypertrophic osteoarthritis of higher degree, and previous ipsi- or contralateral HO significantly influenced the HO rate (Table 6).

The incidence of HO was 21.7% for male and 14.5% for female patients. Patients with a body height < 170 cm developed significantly less HO than patients ≥ 170 cm (78.3% vs. 85.5%; p = 0.02). Hips diagnosed with hypertrophic osteoarthritis of higher degree (Kellgren 3 and 4) showed a positive correlation to HO of higher degree (Brooker 3 and 4; p = 0.03). Previous ipsi- or contralateral HO was a significant indicator of the presence and severity of HO in the hips studied. Those who had suffered ipsi- or contralateral HO previously were more likely to do so with the second operation (ipsilateral: 33.3% vs. 8.3%; p = 0.02; contralateral: 21.5% vs. 9.9%; p < 0.01).

The following factors were found not to correlate significantly with HO: age, weight, obesity, prosthesis replacement, and interval between radiotherapy and surgery.

Operative Factors

The size of the femoral component of the prosthesis correlated significantly with the incidence of HO. With prosthesis size 1–4, the incidence was 15.1%, with size 5–7, the incidence increased to 23.7% (p = 0.03). The size of the acetabular component had no influence on HO. Duration of surgery, blood loss,

Table 6. Heterotopic ossification (HO) according to Brooker classification [3] depending on risk factors. Significance in italics.

Tabelle 6. Heterotope Ossifikationen (HO) nach Brooker et al. [3] in Abhängigkeit von Risikofaktoren. Signifikanz kursiv.

		Grade 0		Grade 1–4		Grade 1		Grade 2		Grade 3		Grade 4		p-value univariate	p-value multivariate
		n	%	n	%	n	%	n	%	n	%	n	%		
All (n = 462)		378	81.9	84	18.1	57	12.3	18	3.9	7	1.5	2	0.4		
Sex	Male	*184*	*78.3*	*51*	*21.7*	34	14.5	8	3.4	7	3.0	2	0.8	p = 0.03	
	Female	*194*	*85.5*	*33*	*14.5*	23	10.1	10	4.4	0	0	0	0		
Height (cm)	< 170	*223*	*85.4*	*38*	*14.6*	25	9.6	11	4.2	2	0.8	0	0	p = 0.02	
	≥ 170	*151*	*76.7*	*46*	*23.3*	32	16.2	7	3.6	5	2.5	2	1.0		
Femoral component of prosthesis	Size 1–4	*213*	*84.9*	*38*	*15.1*	26	10.4	9	3.5	3	1.2	0	0	p = 0.03	p = 0.04
	Size 5–7	*129*	*76.3*	*40*	*23.7*	26	15.3	8	4.7	4	2.4	2	1.2		
Hypertrophic osteoarthritis	Kellgren 1/2	68	80.9	16	19.1	13	15.5	3	3.6	0	0	0	0	p = 0.03	
	Kellgren 3/4	243	81.3	56	18.7	37	12.4	14	4.7	4	1.3	1	0.3		
Previous ipsilateral HO	No	*22*	*91.7*	*2*	*8.3*	2	8.3	0	0	0	0	0	0	p = 0.02	p < 0.01
	Yes	*10*	*66.7*	*5*	*33.3*	1	6.7	2	13.3	2	13.3	0	0		
Previous contralateral HO	No	*64*	*90.1*	*7*	*9.9*	4	5.6	2	2.8	1	1.4	0	0	p < 0.01	p < 0.01
	Yes	*22*	*78.5*	*6*	*21.5*	4	14.3	1	3.6	1	3.6	0	0		
Diclofenac (mg)	0 mg	*86*	*78.9*	*23*	*21.1*	14	12.8	5	4.6	3	2.8	1	0.9	p < 0.01	p < 0.01
	≤ 300	*196*	*77.8*	*56*	*22.2*	39	15.5	12	4.7	4	1.6	1	0.4		
	> 300 / ≤ 600	*33*	*91.7*	*3*	*8.3*	2	5.5	1	2.8	0	0	0	0		
	> 600	*63*	*96.9*	*2*	*3.1*	0	0	0	0	0	0	0	0		

standardized or other intraoperative antibiotics did not correlate with HO.

Postoperative Factors

The cumulative dose of diclofenac within the first 7 postoperative days influenced the incidence of HO. Analyzing the influence of NSAID therapy in 50-mg increments, a threshold could be identified. No treatment with diclofenac and treatment with a cumulative dose ≤ 300 mg resulted in comparable HO rates (20.2%, 21.6%). Therapy with a cumulative dose > 300 mg reduced the incidence to 6.6% ($p < 0.01$). By increasing the dose up to > 600 mg, a trend toward further HO reduction was found, but was not statistically significant.

Postoperative swelling or hematoma, additional or exclusive analgesic with tramadole-HCl or metamizole-sodium, postoperative antibiotic therapy, or pain 3 months after surgery did not correlate with HO.

Multivariate Analysis

Some of the variables that were statistically significant in the univariate analysis showed interdependence during multivariate analysis. These included sex, body height, and size of femoral component of prosthesis. There was a correlation between prosthesis size and body height ($r = 0.38$; $p < 0.01$), prosthesis size and sex ($r = 0.33$; $p < 0.01$), and sex and body height ($r = 0.59$; $p < 0.01$), respectively. In the stepwise multivariate analysis, only the size of prosthesis kept its statistically significant influence on HO ($p = 0.04$; Table 6).

In the multivariate analysis, previous ipsi- or contralateral HO and therapy with > 300 mg diclofenac within the 1st postoperative week were independent variables influencing the incidence of HO (Table 6).

Discussion

With > 100,000 operations per year, THR is the surgical hip intervention most frequently performed in Germany [14]. HO is a common complication following hip arthroplasty [12, 32]. Although the incidence of HO ranges between 8% and 90% depending on risk factors [29, 39], a minority of patients with HO (10–30%) develop functional impairment [32, 40, 46]. The large number of hip operations, however, leads to a significant number of patients with clinically relevant symptoms [31].

The etiology of HO is still unknown. It is presumed that a protein called bone morphogenetic protein released by a local prostaglandin-inducing inflammation is responsible for the process [13, 25, 37, 40]. In the past, two different treatment modalities were analyzed regarding their effectiveness to reduce ossification after hip surgery: the use of NSAIDs [11, 18, 26, 34] and radiotherapy [12, 15, 22, 26, 27, 41, 43, 45].

The inhibition of HO development by NSAIDs is probably due to a nonspecific suppression of the inflammatory response by inhibiting the prostaglandin synthesis mechanism [22]. The use of NSAIDs for prevention of HO was introduced by Dahl [6] in 1975. Since then, many prospective and retrospective studies have been conducted using different NSAIDs and treatment durations.

Coventry & Scanlon [5] were the first to use postoperative irradiation for prevention of HO. It is generally assumed that radiation therapy may prevent pluripotential mesenchymal stem cells to proliferate and differentiate into osteogenic cells [22, 25]. In the past, radiotherapy regimens differed in dosage and fractionation showing the same effectiveness for single- and multifractionated irradiation [24, 28, 30, 42]. Kantorowitz et al. [19] indicated the effectiveness of preoperative radiotherapy for prevention of HO in a experimental model. In the meantime, several studies analyzed the effectiveness of preoperative radiotherapy in preventing HO. In the literature, the incidence of HO after preoperative radiotherapy ranges between 4% and 48% (Table 7). In a multicenter pattern-of-care study, Seegenschmiedt et al. [44] reported an HO incidence of 20.6% after radiotherapy > 8 h and of 8.7% after radiotherapy ≤ 8 h before surgery. The overall incidence of HO in our study was 18.1%, the incidence of severe HO (Brooker 3–4) 1.9%. These results are comparable to those reported by studies evaluating postoperative irradiation [26, 40], especially regarding the incidence of clinically relevant, severe HO. Gregoritch et al. [12] found a 28% and 4.6% incidence of overall (Brooker 1–4) and severe (Brooker 3–4) HO after postoperative single-fraction radiotherapy. Lo et al. [30] reported a 16% incidence of HO (Brooker 1–4) after postoperative radiotherapy. Showing a comparable effectiveness, preoperative radiotherapy offers

Table 7. Studies evaluating preoperative radiotherapy. HO: heterotopic ossification.

Tabelle 7. Studien zur präoperativen Radiatio. HO: heterotope Ossifikationen.

Year	Study	Intervall radiation – surgery	Dose (Gy)	Hips (n)	HO (%)
1994	Gregoritch et al. [12]	< 4 h	1 × 7–8	55	26
1996	Pellegrini & Gregoritch [38]	6 h	1 × 8	49	24
1997	Seegenschmiedt et al. [43]	≤ 4 h	1 × 7	59	19
		> 4 h		21	
1997	Heyd et al. [16]	≤ 4 h	1 × 6	20	5
1998	Van Leeuwen et al. [50]	1 d	1 × 5	43	14
1998	Kölbl et al. [27]	16–20 h	1 × 7	45	48
1998	Kantorowitz & Muff [20]	< 4 h	1 × 7–8	9	11
2001	Lonardi et al. [31]	< 16 h	1 × 7.5	118	4
2001	Seegenschmiedt et al. [44]	≤ 8 h	1 × 5 –7	1,116	8.7
		> 8 h		364	20.6
2002	Presented data	13–21 h	1 × 7	462	18

additional advantages: no postoperative pain caused by transport, no risk of luxation of hip prosthesis, and lower costs because patients are transported by taxi and not by ambulance.

The reported incidence of HO may vary due to different preoperative, operative and postoperative procedures and, particularly, to patient selection. Many factors suggested to be predisposing in the literature are based on an analysis of patients not receiving prophylactic treatment [9, 36], a systematic analysis of HO risk factors in patients treated prophylactically is missing so far.

Several studies showed a correlation between the incidence of HO and age [23], weight [17] and sex [9]. In our study, male patients had an incidence of HO that was 6.9% higher than in females. Additionally, patients' height was of importance. Patients ≥ 170 cm developed more HO (rate 7.9%) than those < 170 cm. Both results were statistically significant in univariate analysis. Age, weight, or obesity were no relevant variables in this study.

The influence of different operative procedures is controversially discussed in the literature. While some authors report a correlation between HO and operative approach or kind of fixation (cemented or uncemented) [14, 35], others describe the converse [8]. Because of the homogeneity of surgical procedure in our study with all patients receiving anterolateral approach and uncemented fixation, this was not a point at issue in our analysis. However, we found the size of the femoral component of the prosthesis to influence the incidence of HO. In patients with prosthesis size 1–4, the HO rate was higher (6.8%) than in patients with size 5–7. Mechanical trauma to the bone and soft tissue has been reported to influence HO [17]. Maloney et al. [33] suggested that increased extension of femoral canal reaming produces more bone debris. Prostheses of greater sizes require more extension of the femoral canal resulting in higher HO rate. In the multivariate analysis, we found an interdependence of sex, patient's height, and prosthesis size. Only prosthesis size showed statistical significance in multivariate analysis, whereas sex and patient's height lost their significance. This important result has not been described in the literature so far.

The development of HO after previous ipsi- or contralateral hip surgery is an important indicator of the presence and severity of future HO. Nollen & van Douveren [36] reported a concordance rate of 82% in the production of HO between a patient's two hips. Seegenschmiedt et al. [43] assumed that preoperative radiotherapy is less effective in patients in the high-risk situation. We found a three times higher incidence of HO after previous ipsi- or contralateral HO being statistically significant in uni- and multivariate analysis.

Another hip diagnosis has been identified as an important factor in determining the production of HO. Hypertrophic coxarthrosis [10] was found to increase the incidence of HO. In our study, only patients with coxarthrosis of higher degree (Kellgren 3–4) developed severe HO (Brooker grade 3–4).

Although the effectiveness of NSAIDs for prevention of HO is well known, as described above, the additional pain-adapted NSAID is often not documented in radiotherapy trials. There are studies without any NSAID therapy being performed, in some NSAID therapy is only rarely applied during the initial postoperative period, and in others no statements concerning NSAID therapy are made [20, 26–28, 46]. In our study, the therapy with NSAID and other analgesics within the first 7 postoperative days was exactly documented. We found a 21.1% and 22.2% incidence of HO in patients receiving no or ≤ 300 mg diclofenac within the 1st postoperative week, whereas patients receiving > 300 mg diclofenac showed an HO incidence < 10%. An increase of the diclofenac dose up to 600 mg or more did not result in a further significant decrease in HO rate. The effectiveness of extensive diclofenac therapy alone was demonstrated by Jockheck et al. [18] (3 × 50 mg/day for 3 weeks). They reported an HO incidence of 20% and a 15% rate of patients who had to stop therapy because of gastrointestinal side effects. Short-course therapy with NSAID alone (3 days) was not effective in preventing HO [49]. In our study, the combination of both radiotherapy and short-course diclofenac therapy resulted in an overall HO rate of 6.6%. Since we used no randomized study design testing the effectiveness of radiotherapy with and without NSAIDs, the conclusions based on our results have to be drawn carefully. But for all that the additional NSAID therapy with > 300 mg diclofenac was statistically significant in uni- and multivariate analysis.

Conclusion

Preoperative radiotherapy with an overnight interval between irradiation and surgery is an effective treatment modality to reduce HO after THR. Neither the overall HO rate nor the incidence of clinically relevant, severe HO were increased as compared to historical data reported by studies analyzing postoperative radiotherapy, and preoperative radiotherapy includes several advantages compared to postoperative irradiation. However, in regard to the high risk factors for HO defined in this study (previous ipsi- and contralateral ossification), the incidence of HO increased significantly. The effectiveness of radiotherapy was increased by an additional short-course NSAID therapy with diclofenac in the 1st postoperative week. To analyze the optimal dose and duration of an additional NSAID therapy, further prospective randomized studies should be conducted.

References

1. Ahrengart L, Lindgren U. Heterotopic bone after hip arthroplasty. Defining the patient at risk. Clin Orthop 1993;293:153–9.
2. Arcq M. Ectopic ossification: a complication after total hip replacement. Arch Orthop Unfallchir 1973;77:108–31.
3. Brooker AF, Bowerman JW, Robinson RA, et al. Ectopic ossification following total hip replacement. Incidence and method of classification. J Bone Joint Surg Am 1973;55:1629–32.
4. Bundrick TJ, Cook DE, Resnik CS. Heterotopic bone formation in patients with DISH following total hip replacement. Radiology 1985;155:595–7.
5. Coventry MB, Scanlon PW. The use of radiation to discourage ectopic bone. J Bone Joint Surg Am 1981;63:201–8.
6. Dahl HK. Klinske observasjoner In: Blindern MSD, ed. Symposium on arthrose. Drammen/Norway, 1975:37–46.

7. DeLee J, Ferrari A, Charnley J. Ectopic bone formation following low friction arthroplasty of the hip. Clin Orthop 1976;121:53–9.
8. Duck HJ, Mylod A Jr. Heterotopic bone in hip arthroplasties. Cemented versus noncemented. Clin Orthop 1992;282:145–53.
9. Eggli S, Woo A. Risk factors for heterotopic ossification in total hip arthroplasty. Arch Orthop Trauma Surg 2001;121:531–5.
10. Goel A, Sharp DJ. Heterotopic bone formation after hip replacement. The influence of the type of osteoarthritis. J Bone Joint Surg Am 1991;73:255–7.
11. Goutallier D, Colmar M, Penot P. Periprosthetic ossifications of the hip. Role of the duration of postoperative indomethacin therapy in the preventation of ossifications and role of scremed acetabulum in the occurrence of ossification. Rev Chir Orthop Reparatrice Appar Mot 1993;79:22–8.
12. Gregoritch SJ, Chadha M, Pelligrini VD, et al. Randomized trial comparing preoperative versus postoperative irradiation for prevention of heterotopic ossification following prothetic total hip replacement. Preliminary results. Int J Radiat Oncol Biol Phys 1994;30:55–62.
13. Ham AW, Cormack DH. Ectopic osteogenesis. In: Ham AW, Cormack DH, eds. Histology, 8th edn. Phyladelphia: Lippincott, 1979:393–4.
14. Hartwig CH, Sell S, Kusswetter W. Periarticular ossification following cement-free and cement-fixed total endoprosthesis implantation in the hip joint. Z Orthop Ihre Grenzgeb 1989;127:296–301.
15. Hedley AK, Mead LP, Hendren DH. The prevention of heterotopic bone formation following total hip arthroplasty using 600 rad in a single dose. J Arthroplasty 1989;4:319–25.
16. Heyd R, Schopohl B, Kirchner J, et al. Preoperative radiotherapy for prevention of heterotopic ossifications after hip endoprosthesis. Akt Radiol 1997;7:270–3.
17. Hierton C, Blomgren G, Lindgren U. Factors associated with heterotopic bone formation in cemened otal hip prostheses. Acta Orthop Scand 1983; 53:698–702.
18. Jockheck M, Willms R, Volkmann R, et al. Prevention of periarticular heterotopic ossification after endoprosthetic hip joint replacement by means of diclofenac. Arch Orthop Trauma Surg 1998;117:337–40.
19. Kantorowitz DA, Miller GJ, Ferrara JA, et al. Preoperative versus postoperative irradiation in the prophylaxis of heterotopic bone formation in rats. Int J Radiat Oncol Biol Phys 1990;19:1431–8.
20. Kantorowitz DA, Muff NS. Preoperative versus postoperative irradiation in the prophylaxis of heterotopic ossification: a rural community hospital's experience. Int J Radiat Oncol Biol Phys 1998;40:171–6.
21. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
22. Kienapfel H, Koller M, Wüst A, et al. Prevention of heterotopic bone formation after total hip arthroplasty. A prospective randomised study comparing postoperative radiation therapy with indomethacin medication. Arch Orthop Trauma Surg 1999;119:296–302.
23. Kjaersgaard AP, Hougard K, Linde F, et al. Heterotopic bone formation after total hip arthroplasty in patients with primary or secondary coxarthrosis. Orthopedics 1990;13:1211–7.
24. Kölbl O, Flentje M, Eulert J, et al. Prospective study on the prevention of heterotopic ossification after total hip replacement. Non-steroidal anti-inflammatory agents versus radiation therapy. Strahlenther Onkol 1997;173: 677–82.
25. Koelbl O, Knaus P, Pohl F, et al. Radiation-induced reduction of BMP-induced proteoglycan synthesis in an embryonal mesenchymal tissue equivalent using the chicken "limb bud" test. Strahlenther Onkol 2001;177: 432–6.
26. Kölbl O, Knelles D, Barthel T, et al. Randomized trial comparing early postoperative irradiation versus the use of non-steroidal-antiinflammatory drugs for prevention of heterotopic ossification following prosthetic total hip replacement. Int J Radiat Oncol Biol Phys 1997;39:961–6.
27. Kölbl O, Knelles D, Barthel T, et al. Preoperative irradiation versus the use of nonsteroidal anti-inflammatory drugs for prevention of heterotopic ossification following total hip replacement. The results of a randomized trial. Int J Radiat Oncol Biol Phys 1998;42:397–401.
28. Konski A, Pellegrini V, Poulter C, et al. Randomized trial comparing single dose versus fractionated irradiation for prevention of heterotopic bone: aa preliminary report. Int J Radiat Oncol Biol Phys 1990;18:1139–42.
29. Lazansky MG. Complications revisited – the debit side of total hip replacement. Clin Orthop 1973;95:96–103.
30. Lo TCM, Healy WL, Covall DJ, et al. Heterotopic bone formation after hip surgery: prevention with single-dose postoperative hip irradiation. Radiology 1988;168:851–4.
31. Lonardi F, Giogna G, Coeli M, et al. Preoperative, single-fraction irradiation for prophylaxis of heterotopic ossification after total hip arthroplasty. Int Orthop 2001;25:371–4.
32. MacLennan I, Keys HM, Evarts CM, et al. Usefulness of postoperative hip irradiation in the prevention of heterotopic bone formation in a high risk group of patients. Int J Radiat Oncol Biol Phys 1984;10:49–53.
33. Maloney WJ, Krushell RJ, Jasty M, et al. Incidence of heterotopic ossification after total hip replacement: effect of the type of fixation of the femoral component. J Bone Joint Surg Am 1991;73:191–3.
34. McMahon JS, Waddell JP, Morton J. Effect of short-course indomethacin on heterotopic bone formation after uncemented total hip arthroplasty. J Arthroplasty 1991;6:259–64.
35. Morrey BF, Adams RA, Cabanela ME. Comparison of heterotopic bone after anterolateral, transtrochanteric, and posterior approaches for total hip arthroplasty. Clin Orthop 1984;188:160–7.
36. Nollen JG, van Douveren FQ. Ectopic ossification in hip arthroplasty. A retrospective study of predisposing factors in 637 cases. Acta Orthop Scand 1993;64:185–7.
37. Owen M. Lineage of osteogenic cells and their relationship to the stromal system In: Peck WA, ed. Bone and mineral research, vol 3. New York: Elsevier Science, 1985:1–25.
38. Pellegrini VD, Gregoritch SJ. Preoperative irradiation for prevention of heterotopic ossification following total hip arthroplasty. J Bone Joint Surg Am 1996;78:870–81.
39. Rosendahl S, Christoffersen JK, Norgaard M. Paraarticular ossifications following hip replacement. Acta Orthop Scand 1977;48:400–4.
40. Rudicel S. Paraartikuläre ektopische oder heterotope Ossifikationen nach Hüfttotalprothese. Orthopäde 1985;14:54–7.
41. Sauer R, Seegenschmiedt MH, Goldmann A, et al. Prevention of periarticular ossification following endoprosthetic hip replacement using postoperative irradiation. Strahlenther Onkol 1992;168:89–99.
42. Sautter-Bihl ML, Hultenschmidt B, Liebermeister E, et al. Fractionated and single-dose radiotherapy for heterotopic bone formation in patients with spinal cord injury. A phase-I/II study. Strahlenther Onkol 2001;177:200–5.
43. Seegenschmiedt MH, Keilholz L, Martus P, et al. Prevention of heterotopic ossification about the hip: final results of two randomized trials in 410 patients using either preoperative or postoperative radiation therapy. Int J Radiat Oncol Biol Phys 1997;39:161–71.
44. Seegenschmiedt MH, Makoski HB, Micke O. Radiation prophylaxis for heterotopic ossification about the hip joint – a multicenter study. Int J Radiat Oncol Biol Phys 2001;51:756–65.
45. Seegenschmiedt MH, Martus P, Goldmann AR, et al. [Pre- and postoperative radiotherapy to prevent heterotopic ossification of the hip joint.] Strahlenther Onkol 1994;170:281–91.
46. Seegenschmiedt MH, Martus P, Goldmann AR, et al. Preoperative versus postoperative radiotherapy for prevention of heterotopic ossification HO. First results of a randomized trial in high-risk patients. Int J Radiat Oncol Biol Phys 1994;30:63–73.
47. Sundaram NA, Murphy JC. Heterotopic bone formation following total hip arthroplasty in ankylosing spondylitis. Clin Orthop 1986;207:223–6.
48. Testa NN, Mazur KU. Heterotopic ossification after direct lateral approach and transtrochanteric approach to the hip. Orthop Rev 1988;17:965–71.
49. Van der Heide HJ, Koorevaar RT, Schreurs BW, et al. Indomethacin for 3 days is not effective as prophylaxis for heterotopic ossification after primary total hip arthroplasty. J Arthroplasty 1999;14:796–9.
50. Van Leeuwen WM, Deckers P, De Lange WJ. Preoperative irradiation for prophylaxis of ectopic ossification after hip arthroplasty. A randomised study in 62 hips. Acta Orthop Scand 1998;69:116–8.

Address for Correspondence
Dr. Oliver Kölbl
Clinic and Policlinic for Radiotherapy
University of Würzburg
Josef-Schneider-Straße 11
97080 Würzburg
Germany
Phone (+49/931) 201-28400, Fax -28396
E-mail: Koelbl_O@klinik.uni-wuerzburg.de