Int. J. Radiation Oncology Biol. Phys., Vol. 51, No. 3, pp. 756–765, 2001

0360-3016/01/$–see front matter

ELSEVIER

PII S0360-3016(01)01640-6

CLINICAL INVESTIGATION **Benign Disease**

RADIATION PROPHYLAXIS FOR HETEROTOPIC OSSIFICATION ABOUT THE HIP JOINT—A MULTICENTER STUDY

Michael Heinrich Seegenschmiedt, M.D.,* Hans-Bruno Makoski, M.D.,† Oliver Micke, M.D.,‡ and the German Cooperative Group on Radiotherapy for Benign Diseases

*Department of Radiation Oncology, Therapy and Nuclear Medicine, Alfried-Krupp-Hospital, Essen, Essen, Germany; †Department of Radiation Oncology and Nuclear Medicine, Community Hospital Duisburg, Duisburg, Germany; ‡Department of Radiation Oncology, Westfalian Wilhelms-University Münster, Münster, Germany

Purpose: Prophylactic radiotherapy (RT) can prevent ectopic bone formation about the hip after total hip arthroplasty. The German Cooperative Group on Radiotherapy for Benign Diseases conducted a patterns of care study about this indication addressing the involved institutions, RT dose concepts, clinical handling, and treatment outcome of prophylactic RT about the hip joint.

Methods and Materials: In 1999, a patterns of care study was conducted in all German institutions to analyze the accrual pattern, number of patients, and different indications for the use and performance of prophylactic RT about the hip. The applied RT concepts of prophylactic RT were evaluated with regard to the RT technique, timing of RT (pre- or postoperative), RT dose prescription (median, range of single and total doses), and treatment outcome. All institutions were asked about the radiologic and functional failure rates at least 1 year after the completion of RT using the established radiologic (Brooker) and functional (Harris) scores with objective and subjective evaluation components.

Results: One hundred fourteen institutions reported their clinical experience with prophylactic RT for the prevention of heterotopic ossification about the hip joint: 70 community hospitals, 23 university hospitals, and 21 private RT practices. In 1999, 5677 patients (5989 hips) had received prophylactic RT. The median number per institution was 36 patients (range 8–240). The interdisciplinary referral included orthopedic surgery (89 institutions; 3763 patients), trauma surgery (82 institutions; 1611 patients), or other disciplines (8 institutions; 298 patients). Preoperative RT was applied in 53 institutions 0.5–24 h before surgery, and postoperative RT was applied in 54 institutions 1–120 h after surgery. Most patients received 1 × 7 Gy either pre- or postoperatively. The total dose range was 5–10 Gy (preoperative RT) or 5–16 Gy (postoperative RT); the median total RT dose of both RT concepts was 7 Gy. Cobalt-60 ($n = 15$), linear accelerators ($n = 95$), and a few lower energy units ($n = 4$) were used. Bony structures or prostheses were shielded with standard blocks in 31 and with individual blocks in 27 institutions. Long-term clinical evaluation was available in 30 institutions from 4377 hips. Of those, 475 (11%) developed radiologic failures according to Brooker's criteria. Functional hip evaluation was available in 5 institutions from 685 hips. Of those, 34 (5%) had functional failures according to the criteria of Harris. No difference in outcome was found between pre- and postoperative RT, but was with regard to the patient's referral and the timing of RT. The patients who were treated >8 h before surgery or >72 h after surgery experienced a higher radiologic failure rate; radiologic failures were an important precondition for functional failures ($p < 0.05$).

Conclusion: This patterns of care study comprises the largest number of cases reported for prophylactic hip RT to date. The results reveal that both preoperative (within 24 h) and postoperative RT (within 72 h) are effective in preventing heterotopic ossification after hip surgery. Both RT concepts achieved a similar low radiologic and functional failure rate. Single-dose RT concepts, especially, can be recommended as an excellent treatment alternative for patients with contraindications to long-term steroid or nonsteroidal anti-inflammatory agents, and this approach has become standard in most German RT institutions. © 2001 Elsevier Science Inc.

Radiotherapy of nonmalignant diseases, Benign diseases, Patterns of care study, Quality assurance, Radiation protection, Heterotopic ossification, Ectopic bone formation, Hip surgery, Total hip arthroplasty.

Reprint requests to: Michael Heinrich Seegenschmiedt, M.D., Department of Radiation Oncology, Therapy and Nuclear Medicine, Alfried-Krupp-Hospital, Alfried-Krupp-Strasse 21, Essen 45133 Germany. Tel: + 49 201 434 2559; Fax: + 49 201 434 2371; E-mail: seegenschmiedt.heinrich@krupp-krankenhaus.de

Presented at the 42nd Annual ASTRO Meeting, Boston, MA, October 22–26, 2000.

Received Jan 17, 2001, and in revised form Apr 26, 2001. Accepted for publication May 1, 2001.

INTRODUCTION

Heterotopic ossification (HO) is a major complication after total hip arthroplasty (THA), hip trauma, acetabular fracture, or central nervous injury. Depending on the individual risk factors, the incidence of HO varies between 2% and 90% (1–3). Some conditions place patients at high risk of HO: ipsilateral or contralateral HO (4, 5), acetabular fracture (6–9), ankylosing spondylitis (10), diffuse idiopathic skeletal hyperostosis (11), hypertrophic osteoarthritis with large periacetabular osteophytes, posttraumatic arthritis, and previous or repeated hip surgery. Unfortunately, HO is detectable on radiographs as late as 4–12 weeks after injury, when no efficient therapy is available. Almost 30% of all patients presenting with HO about the hip will develop symptoms, including pain, restricted motion, or ankylosis of the hip joint, that may require secondary surgical procedures. For Germany, with about 80 million inhabitants, it is estimated that every year at least 10,000 of 100,000 patients with THA will require appropriate HO prophylaxis. Radiotherapy (RT) is known to effectively prevent HO about the hip after THA, and this relatively new treatment concept is now a well-accepted indication for RT of benign disorders (12).

From 1994 to 1996, the German Cooperative Group (GCG) on Radiotherapy for Benign Diseases (BD) has conducted a general patterns of care study (PCS) in Germany to obtain a nationwide survey on the treatment standards of RT for benign diseases (13). This PCS comprised almost 90% of all German RT facilities and provided detailed information about RT equipment, specific RT indications, accrual and number of patients annually, and individual RT concepts. The survey revealed that >20,000 patients were reported to receive RT for benign conditions every year, including about 3680 patients for HO prophylaxis. Stimulated by this positive experience, the GCG started a disease-specific PCS that included the use of prophylactic RT for the prevention of HO. The data and final analysis of this PCS are presented and discussed.

METHODS AND MATERIALS

After a PCS in Germany in 1994–1996 (13), in 1999, the GCG conducted a disease-specific PCS about the use of prophylactic RT to prevent HO in all German RT institutions. Of 200 institutions, 22 (11%) did not answer; 114 (64%) of the 178 responding institutions reported clinical experience with prophylactic RT: 23 (72%) of 32 university hospitals, 70 (52%) of 135 community hospitals, and 21 (64%) of 33 private RT practices in Germany. In 42 (66%) of 64 RT institutions without clinical experience with prophylactic RT, trauma or orthopedic surgery was not a part of the hospital or was not closely

Table 1. Questionnaire from the German Cooperative Group on Radiotherapy for Benign Diseases: prophylactic radiotherapy for prevention of heterotopic ossification

1. General data of radiotherapy institution
   Type of institution: ☐ Freestanding RT practice ☐ Community hospital
   ☐ University hospital ☐ Other type: ______
   Address (stamp): ______
   ______
   Responsible person: ______

2. Prophylactic RT performance ☐ Yes ☐ No; if yes, since when: ______
   Referral type ☐ Orthopedic surgery ☐ Trauma surgery ☐ Other: ______
   No. of cases Cases ______ Cases ______ Cases ______ (per year)
   RT concept ☐ Postoperative ______ hours **after** surgery
   Dose concept Single dose: ______ Total dose: ______
   ☐ Preoperative ______ hours **before** surgery
   Dose concept Single dose: ______ Total dose: ______
   RT Technique ☐ Linear accelerator ______ MV; ☐ Cobalt-60 ☐ Other
   Field sizes ☐ Single field AP ______ ☐ Opposing fields AP-PA: ______
   Shielding ☐ No shielding ☐ Standard blocks ☐ Individual blocks
3. Clinical outcome analysis ☐ Yes ☐ No; if yes, since when: ______
   No. cases analyzed: ______ From ______ / 19______ until ______ / 19______
   Radiologic failure: ______ (%) [Brooker score] Functional failure: ______ (%) [Harris score]
   Prognostic factors (for failure): ______
   ______

4. Scientific publications ☐ Yes ☐ No; if yes, when/where: ______
   Sources or copies of papers: ______
   ______

Table 2. Classification of heterotopic ossification about the hip (on AP radiographs)

Grade 0	No bone islands visible
Grade 1	Islands of bone visible within soft tissue about the hip
Grade 2	Bone spurs from pelvis or proximal end of femur, leaving ≥1 cm between opposing surfaces
Grade 3	Like Grade II, except that space between opposing surfaces is <1 cm
Grade 4	Apparent bony ankylosis

Modification by MacLennon *et al.* (17) of the Brooker classification (10).

located to the RT facility, and in the other 22 institutions (34%), prophylactic RT was stated to be not an established strategy for HO prophylaxis.

A mailed questionnaire (Table 1) and additional telephone interviews were used to analyze the general data of all RT institutions (type of institution, clinical investigator, start of clinical experience), patient accrual (referring institutions, RT indications, number of patients), standard performance of RT (timing, concept, and technique). The timing of the prophylactic RT was grouped as either preoperative or postoperative, or both. The applied RT concepts were evaluated with regard to the single and total RT dose and fractionation. The specific RT technique was analyzed in terms of the RT equipment and technique and the typical field size and field arrangement, including the possible use of standard or individualized shielding.

All RT institutions were asked whether they had evaluated the outcome of their patients in the past. We asked specifically for the institutional rate of radiologic failures at least 1 year after the completion of prophylactic RT using the Brooker classification (14) (Table 2), and for the functional failure rate using the Harris score (15) (Table 3), which includes both objective and subjective criteria for functional analysis. Regarding the evaluation of the treatment outcome of prophylactic RT, only those clinical data were taken into account that had been presented during the past decade either in a published report or as a scientific abstract from an oral presentation or a poster that had been presented at a national and/or an international scientific conference. For some RT institutions, additional telephone interviews were necessary to clarify their means of data assessment and to obtain specific information about those patients who had experienced either radiologic or functional treatment failure. Generally, some variations in the use of the outcome measures may have occurred in the different institutions, as no individual case review was performed by an independent board of radiation oncology or orthopedic experts.

Table 3. Harris score for evaluation of hip function

	Points
A. Pain (44 points)	
None	44
Slight	40
Mild	30
Moderate	20
Marked	10
Disabled	10
B. Function (47 points)	
Limp (11 points)	
None	11
Slight	8
Moderate	5
Severe	0
Support (11 points)	
None	11
Cane for long walks	7
Cane most of time	5
Not able to walk (specify reason)	0
1 crutch	3
2 canes	2
2 crutches	1
Walking (11 points)	
Unlimited	11
6 blocks	8
2–3 blocks	5
Indoors only	2
Bed and chair	0
Activities (14 points)	
Walking stairs (4 points)	
Normally without using a railing	4
Normally using a railing	2
In any manner	1
Unable to do stairs	0
Shoes and socks (4 points)	
With ease	4
With difficulty	2
Unable	0
Sitting chair (5 points)	
Comfortably in ordinary chair 1 h	5
On a high chair for 30 min	3
Unable to sit comfortably in any chair	0
Transportation (1 point)	
Able to enter public transportation	1
Unable to enter public transportation	0
C. Absence of deformity (4 points)	
30° fixed flexion contracture	1
10° fixed adduction	1
10° fixed internal rotation in extension	1
Limb-length discrepancy <3.2 cm	1
D. Range of motion (5 points)	
Flexion/extension/rotation/abduction/adduction	5
Total hip score:	
Sum of A + B + C + D = 100 (maximum)	

Modified from Harris (15), with permission.

Statistically, all categorical variables were described with their absolute and relative values, and all continuous variables were defined with their mean and median values, standard deviation, and range (minimum and maximum). Comparisons of frequencies were tested using Fisher's exact test and chi-square analysis. Paired comparisons of the mean were analyzed with the Student *t* test, and the differences between the means of continuous variables were analyzed with the two-sample *t* test (16). All raw data were stored and the calculations were performed by using Excel (Microsoft, Redman, WA) and Statistical Package for Social Sciences (SPSS, Chicago, IL).

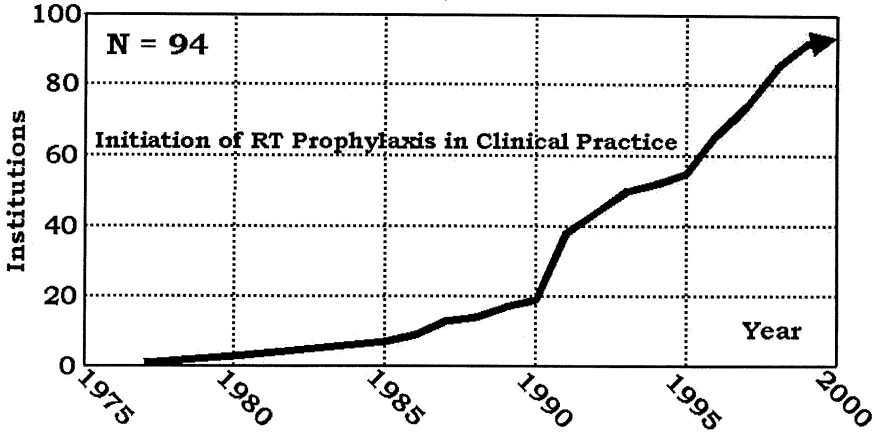

Fig. 1. Development of RT prophylaxis about the hip joint in Germany. Year of RT prophylaxis initiation stated by 94 German RT institutions

RESULTS

Of the 178 responding RT institutions, 114 (64%) reported having had clinical experience with prophylactic RT. Of those, 94 institutions stated the exact year their clinical experience had started: 4 institutions (3 university and 1 community hospital) before 1980, 20 institutions (11 university hospitals, 8 community hospitals, and 1 private RT practice) were active in 1990. During the past decade, especially after 1995, the number of institutions implementing RT prophylaxis dramatically increased (Fig. 1). In 1999, a total of 5677 patients or 5989 hips had received prophylactic RT. Of those, 1480 patients (26.1%) were treated in

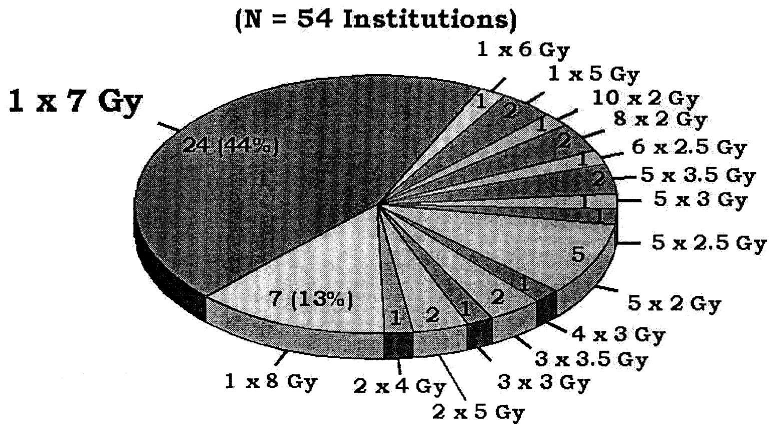

Fig. 2. Postoperative RT dose and fraction concepts. Postoperative RT schedules were used in 54 (47.4%) of the 114 RT institutions.

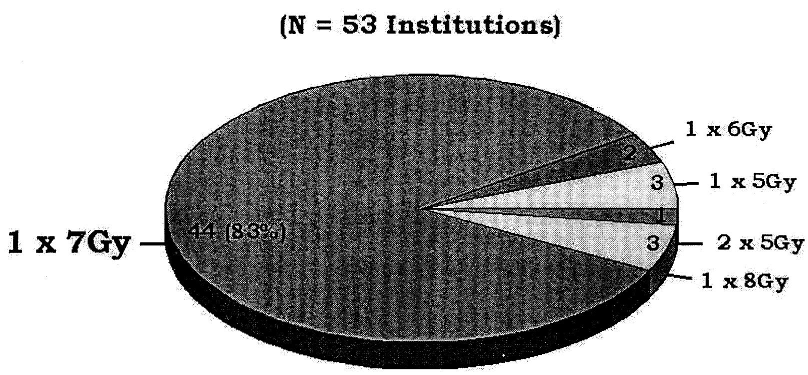

Fig. 3. Preoperative RT dose and fraction concepts. Preoperative RT schedules were used in 53 (46.5%) of the 114 RT institutions.

Table 4. Radiologic outcome and institutional type and referral pattern ($n = 30$)

Radiologic analysis*	Institutions	Radiated hips	Failure (Brooker)
All RT institutions	30 (100)	4.377 (100)	475 (10.9)
University hospital	9 (30)	1.939 (44.3)	209 (10.8)
Community hospital	19 (63)	2.342 (53.5)	258 (11.0)
Private RT practice	2 (7)	96 (2.2)	8 (8.8)
Referral from†‡			
Orthopedic surgery	26 (87)	3.262 (74.5)	290 (9.0)
Trauma surgery	18 (60)	1.091 (25.2)	179 (16.4)
Other disciplines	2 (7)	24 (0.5)	6 (25.0)

Numbers in parentheses are percentages.
*Radiologic evaluation according to Brooker classification (14).
† Twelve institutions had referrals from orthopedic and trauma surgery, 2 institutions from all disciplines.
‡ Only referral was found to be significant ($p < 0.01$).
Abbreviations: RT = radiotherapy.

university hospitals, 3579 patients (63.0%) in community hospitals, and 618 patients (10.9%) in private RT practices (mean 50 ± 18, median 36, range 2–592 patients per institution and year).

Most radiotherapists worked closely together with the orthopedic ($n = 89$; 78%) and trauma ($n = 82$; 72%) surgeons; referral from other disciplines such as neurology or rehabilitation medicine ($n = 8$; 7%) was quite rare. The interdisciplinary referral accrued a total of 3933 patients (69.3%) from orthopedic and 1446 patients (25.5%) from trauma surgery, but only 298 patients (5.2%) from other medical disciplines. Most patients who were referred by orthopedic surgeons had undergone a planned THA or another elective surgical procedure. Those patients referred by trauma surgeons had a high risk of HO, as they usually underwent surgery or THA because of hip, acetabular, or other pelvic trauma. Patients referred by neurologists and rehabilitation medicine specialists also may have had a higher risk of HO development because RT prophylaxis was mostly performed after surgical removal of extensive HO that had developed after central nervous system trauma, spinal cord injury, or other polytraumatic accidents that involved the pelvic bones and hip joints (6–9, 17, 18).

The RT concepts varied considerably among all RT institutions. Preoperative RT was used in 53 (46.5%) and postoperative RT in 54 (47.4%) institutions; 6 institutions used both; 1 institution did not specify the RT concept. Postoperative RT was started as early as 1977. It was usually applied 1–120 h after hip surgery (mean 50 ± 22; median 24). Preoperative RT was introduced in most RT institutions after 1995 and was usually delivered 0.5–24 h (mean 10 ± 8, median 4) before hip surgery.

Most patients were treated with a single fraction of 1 × 7 Gy either pre- or postoperatively. The total RT dose range was 5–16 Gy in postoperative RT and 5–10 Gy in preoperative RT. The median total RT dose for both was 7 Gy. Regarding postoperative RT, 34 (63%) of 54 institutions used a single RT fraction (1 × 5 up to 1 × 8 Gy) (Fig. 2). In contrast, a higher proportion of RT institutions (52 [98%] of 53) used a single fraction (1 × 5 up to 1 × 8 Gy) for preoperative RT (Fig. 3). The different frequencies of the single or fractionated RT concepts are shown in Figs. 2 and 3.

The RT technique varied among all RT institutions. Most institutions used linear accelerators with photon energies of more than 6 MeV ($n = 95$; 83%); lower photon energies of 1 MeV were only used by 15 institutions (13%) using cobalt-60 machines. Even lower energies from telecaesium or orthovolt units were applied in 4 institutions (4%; 2 community hospitals and 2 private RT practices). After receiving these data, the GCG-BD board recommended that these institutions not apply additional RT prophylaxis until the RT equipment had been replaced.

A total of 54 institutions (47%) specified details of their standard field setup. The RT portals varied considerably with regard to the length (mean 13 ± 3 cm, median 14, range 10–18) and width (mean 11 ± 3 cm, median 13, range 10–16) of the applied fields. All RT institutions reported positioning patients supine. The institutions that

Table 5. Radiologic outcome according to preoperative or postoperative RT ($n = 30$)

Radiologic analysis*	Institutions	Radiated hips	Brooker failure	p (univariate)
All RT institutions	30 (100)	4.377 (100)	475 (10.9)	NS
Preoperative RT†	19 (63)	1.480 (33.8)	172 (11.6)	
Postoperative RT†	15 (50)	2.897 (66.2)	303 (10.5)	
Preoperative RT ≤8 h‡	17 (89)	1.116 (75.4)	97 (8.7)	<0.005
Preoperative RT >8 h‡	8 (42)	364 (24.6)	75 (20.6)	
Postoperative RT ≤72 h§	15 (100)	2.065 (71.3)	124 (6.0)	<0.001
Postoperative RT >72 h§	9 (60)	832 (28.7)	179 (21.5)	

Abbreviations: RT = radiotherapy; NS = not significant.
Numbers in parentheses are percentages.
*Radiologic evaluation according to Brooker classification (14).
†Two institutions with preoperative and postoperative RT concepts; relative values for 30 institutions with $n = 4377$ hips.
‡Six institutions with short-term (<8 h) and long-term (≥8 h) preoperative RT; relative values for 19 institutions with $n = 1480$ hips.
§Nine institutions with short-term (<96 h) and long-term (≥96 h) postoperative RT; relative values for 15 institutions with $n = 2897$ hips.

Table 6. Functional outcome according to radiologic failure ($n = 5$)

Functional analysis*	Institutions	Radiated hips	Failure (Harris)	p (univariate)
All radiotherapy Institutions	5 (100)	685 (100)	34/685 (5.0)	
Without radiologic failure	5 (100)	609 (11.1)	19/609 (3.1)	<0.05
With radiologic failure	5 (100)	76 (11.1)	15/76 (19.7)	
Radiologic failure Brooker Grade 1 and 2†	5 (100)	48 (7.0)	4/48 (4.2)	<0.01
Radiologic failure Brooker Grade 3 and 4†	3 (60)	28 (4.1)	11/28 (39.3)	

Numbers in parentheses are percentages.
* Functional evaluation according to the Harris score (15).
† Radiologic evaluation according to Brooker classification (14); relative values for 5 institutions with $n = 685$ hips and $n = 15$ functional failures.

used cobalt-60 equipment angled the head of the machine and treated patients in bed. In most institutions, the treatment setup consisted of two opposing AP–PA portals ($n = 47$; 87%). Very few institutions used an oblique or unilateral AP technique ($n = 7$; 13%), and some institutions used a collimator rotation (0–10°) to adapt for the femoral bone angle. The shielding of bony structures or some components of the implanted prosthesis was performed with standard blocks in 31 (27%) or individual blocks in 27 (24%) institutions, 52 (46%) used no shielding at all, and 4 (3%) provided no data. All RT institutions that reported using only a single AP portal were approached by the GCG-BD board to suggest improving the RT quality by implementing an AP–PA field arrangement.

Fifty-one institutions (45%) had received consistent information on the follow-up of their patients who had undergone prophylactic RT. Follow-up visits to orthopedic or trauma surgeons within 1 year after hip surgery with performance of clinical examination and radiologic evaluation and resulting in a written report to the radiation therapist were regarded as sufficient. Thirty RT institutions (26%) were able to provide details about the prospective clinical evaluation of their patients, with a total of 4377 hips treated between 1985 and 1999. They were treated at 9 university hospitals ($n = 1939$ hips; 44.3%), 19 community hospitals ($n = 2342$; 53.5%) and 2 RT practices ($n = 96$; 2.2%). The patients were referred by orthopedic surgeons in 3262 (74.6%), trauma surgeons in 1091 (24.9%), and other medical disciplines in 24 (0.5%) cases. The radiologic evaluation according to the Brooker classification (14) (Table 2) was performed in all 30 institutions; 475 cases (10.9%) were reported to have had radiologic failures (i.e., any radiologic increase of HO about the hip during a 1-year follow-up after prophylactic RT). No statistical difference was found between different institution types. A difference was found between those cases referred by orthopedic or trauma surgeons and other disciplines (Table 4). In addition, no difference was observed between patients treated with pre- or postoperative RT; however, when the timing of RT was considered, a higher failure rate was observed for delayed RT prophylaxis (>8 h before surgery or >72 h after surgery) (Table 5).

Only 5 RT institutions (4%) qualified with sufficient data for the evaluation of the operated hip function according to the Harris score (15). The analysis was performed in 3 community and 2 university hospitals (total 685 patients treated between 1985 and 1999). The analysis revealed a functional failure rate in 34 cases (5.0%) according to the Harris score (15–21). No difference in functional outcome was seen between the different institution types, referring medical disciplines, or pre- or postoperative RT. However, in patients who developed a radiologic failure (especially with a high Brooker Grade 3–4), a higher functional failure rate was experienced (Table 6).

DISCUSSION

Our PCS comprised a very large number of institutions and patients surveyed for the indication, technical and clinical performance, and treatment outcome of prophylactic RT to prevent HO. The results of our study reveal a rapid evolution and very high acceptance of this benign disorder as an RT indication in Germany. We demonstrated that comparably good results are achieved at all RT facility types and with pre- and postoperative RT concepts. A similarly high acceptance has been reported from an American review of RT for benign diseases (19) and a recent European study (20), reflecting the worldwide acceptance of prophylactic RT to prevent HO, in addition to a few other benign disease entities. In the U.S. and European surveys, the RT indication was approved by >50% of all RT institutions (19, 20).

Our PCS reflects the evolution of RT during the past 2 decades when it was shown to prevent HO after hip surgery. The first clinical observations came from the Mayo Clinic, where fractionated RT (10 × 2 Gy) was effectively applied early after hip surgery (21). Later, other RT concepts were tested. The first postoperative RT concept (10 × 2 Gy; total dose 20) was eventually reduced to 5 × 2 Gy (total dose 10), 4 × 2 Gy (total 8) and 2 × 2.5 Gy (total 5) (6, 9, 22–25). Radiologic failure after prophylactic RT occurred in 3–50%, depending on the RT dose, timing, and risk factors (Table 7). In the 1990s, postoperative concepts were changed to a single RT fraction of 5.5–8 Gy, which proved as effective as fractionated RT (5, 24, 26–28). Some clinical studies showed higher failure rates with single RT doses of <6 Gy (29–32) (Table 8).

In the 1990s, 2 experimental *in vivo* studies suggested

Table 7. Fractionated postoperative RT for prevention of HO

Study	Year	Hips (*n*)	RT dose schedule (cGy)	Failure rate (Brooker) (%)
Coventry and Scanlon (21)	1981	48	10 × 200 (2000)	50 (R >4 days postoperatively)
Parkinson *et al.* (40)	1982	64	10 × 200 (2000)	8
MacLennan *et al.* (17)	1984	67	10 × 200 (2000)	16
Anthony *et al.* (22)	1987	62	10 × 200 (2000)	3
Brunner *et al.* (43)	1987	16	10 × 200 (2000)	19
Seegenschmiedt *et al.* (49)	1993	68	5 × 350 (1750)	4
Seegenschmiedt *et al.* (37)	1994	21	5 × 350 (1750)	5
Seegenschmiedt *et al.* (38)	1997	111	5 × 350 (1750)	6
Seegenschmiedt *et al.* (38)	1997	81	5 × 350 (1750)	5
Knelles *et al.* (32)	1997	101	4 × 300 (1200)	5
Evarts *et al.* (41)	1987	47	5 × 200 (1000)	28
Anthony *et al.* (22)	1987	41	5 × 200 (1000)	5
Kennedy *et al.* (50)	1991	42	5 × 200 (1000)	38
Blount *et al.* (26)	1990	27	5 × 200 (1000)	7
Konski *et al.* (27)	1990	20	5 × 200 (1000)	10
Pellegrini *et al.* (5)	1992	28	5 × 200 (1000)	21
Seegenschmiedt *et al.* (49)	1993	73	5 × 200 (1000)	12
Seegenschmiedt *et al.* (38)	1997	131	5 × 200 (1000)	11
Blount *et al.* (26)	1990	38	4 × 200 (800)	3
Conterato *et al.* (24)	1989	30	2 × 250 (500)	20

Numbers in parentheses are total RT dose.
Abbreviations: RT = radiotherapy; HO = heterotopic ossification.

that preoperative RT may be as effective as a similar RT dose given postoperatively (33, 34). A few clinical studies confirmed this rather attractive RT concept (35–39) (Table 9). However, prophylactic RT >16 h before hip surgery resulted in a higher radiologic failure rate. Nevertheless, the incidence of a high HO Brooker grade, often associated with a functional hip deficit, was low (36). Moreover, it was also found that patients with high ipsilateral HO Brooker Grade 3–4 before hip surgery had a higher failure rate with preoperative RT to the hip than with postoperative RT (38). Thus, preoperative RT is not recommended for patients undergoing surgery to remove large amounts of HO. Other compromising factors for preoperative RT, which is otherwise a very attractive and practical treatment concept, may be detected in future trials.

Typical reasons for treatment failure have been reported. Radiologic failures represent an increase of HO from the immediately postoperative to the follow-up radiographs (≥6 months after hip surgery) (40, 41). Functional failures are a decrease of the Harris score comparing the pre- and postoperative hip function. In contrast to functional failures, radiologic failures have been often analyzed in the literature, and few studies have revealed an association between radiologic and functional failures (37, 38, 42). Some series found a high radiologic failure rate of 20–60% (24, 26, 43, 44), which was associated with incomplete HO resection (45), insufficient RT coverage of soft tissue ("geographic miss") (44), delayed (21–23, 25–27, 46–49) or protracted (48, 49) RT application, and the presence of numerous, high-risk factors for HO development (44).

Table 8. Single-dose postoperative RT for prevention of HO

Study	Year	Hips (*n*)	RT dose schedule (cGy)	Failure rate (Brooker) (%)
Konski *et al.* (27)	1990	17	1 × 800 (800)	6
Pellegrini *et al.* (5)	1992	34	1 × 800 (800)	21
Pellegrini and Gregoritch (39)	1996	37	1 × 800 (800)	27
Blount *et al.* (26)	1990	18	1 × 700 (700)	6
Healy *et al.* (47)	1990	34	1 × 700 (700)	8
Healy *et al.* (30)	1995	88	1 × 700 (700)	10
Knelles *et al.* (32)	1997	95	1 × 700 (700)	12
Lo *et al.* (28)	1988	24	1 × 700 (700)	16
DeFlitch and Stryker (44)	1993	33	1 × 700 (700)	21
Gregoritch *et al.* (35)	1994	43	1 × 700 (700)	30
Hedley *et al.* (31)	1989	16	1 × 600 (600)	27
Fingeroth and Ahmed (29)	1995	50	1 × 600 (600)	36
Healy *et al.* (30)	1995	19	1 × 550 (550)	63
Knelles *et al.* (32)	1997	93	1 × 500 (500)	30

Abbreviations as in Table 7.
Numbers in parentheses are total RT dose.

Table 9. Single-dose preoperative RT for prevention of HO

Study	Year	Hips (*n*)	RT dose schedule (cGy)	Failure rate (Brooker grade) %
Gregoritch *et al.* (35)	1994	55	1 × 700 (700)	Grade I–IV: 26%
(RT <4 h preop)			1 × 800 (800)	Grade III–IV: 2%
Seegenschmiedt *et al.* (37, 38)	1994	23	1 × 700 (700)	Overall I–IV: 19%; but patients with ipsilateral
(RT <4 h preop)	1997	80	1 × 700 (700)	preoperative HO Grade I–II: 6%;
				preoperative HO Grade III: 33%;
				preoperative HO Grade IV: 45%
Kantorowitz and Muff (42)	1998	9	1 × 700 (700)	Grade I–IV: 11%
(RT <4 h preop)			1 × 800 (800)	Grade III–IV: 0%
Kölbl *et al.* (36)	1998	46	1 × 700 (700)	Control group: 65%
(RT >16 h preop)				Grade I–II: 48%
				Grade III–IV: 2%

Abbreviations as in Table 7.
Numbers in parentheses are total RT dose.

Many of the above mentioned prognostic factors for treatment failure could not be analyzed in our PCS, because no expert review panel was available for a case-by-case evaluation. However, as the Brooker classification has been well known for years, we relied on the appropriate classification within each of the involved RT institutions. However, regarding the functional hip analysis, we found only 5 RT institutions that used the Harris score for long-term follow-up evaluations of their patients. Despite these limitations, a few of the prognostic factors for radiologic failure (50) have been confirmed by our PCS: delayed onset of preoperative RT (>8 h before surgery) and postoperative RT (>72 h after surgery). Such a delay in RT may be caused by unexpected intra- or postoperative complications (e.g., thrombosis, infection, bleeding) or any interdisciplinary or organizational deficiencies, such as planning the hip surgery before a weekend or holiday, too short a lead time to warrant appropriate informed consent by the patient, or difficulty fitting the patient into the daily RT schedule of a busy RT institution.

The referral pattern may be another important factor to be analyzed in future clinical studies. Patients with traumatic conditions such as pelvic or hip fractures have a much higher risk of developing radiologic failures (6–9, 17, 18, 50) than patients who undergo a planned or an elective surgical procedure about the hip. Patients from rehabilitative medicine were also found to have a worse outcome after prophylactic RT. This factor was not well addressed by studies in the past, but may be revealed by PCSs in other countries.

Only a few RT institutions were involved in this prospective analysis ($n = 30$; 26%), which may limit the conclusions, but this study can serve as basis for future comparative PCSs in Germany and other countries using the same questionnaire and methods (Table 1). Obviously, large differences in the applied RT technique have been found in our study. The impact of an inadequate RT technique on treatment outcome was found only in the case of poor coverage of the target volume (i.e., too small a field size or false shielding of the target tissue) (44). Additional use of insufficient RT equipment was obviated in 4 institutions, but our study was not able to reveal all the structural insufficiencies or inadequate clinical RT procedures. At the least, it could help RT institutions adopt better documentation and RT quality, possibly having an impact on the treatment outcome of future patients.

The GCG-BD has recently adopted written guidelines for the conduct of RT of benign disorders, including prophylactic RT to prevent HO. These guidelines address the following aspects: (*1*) general RT indications; (*2*) radiobiologic basis for RT; (*3*) RT protection; (*4*) quality assurance procedures; (*5*) indication setup; (*6*) conduct of informed consent; (*7*) RT documentation; (*8*) follow-up; and (*9*) defined RT concepts for benign disorders (51).

The increasing acceptance of RT for benign diseases will change the training requirements of RT staff, patient load, and organization of RT facilities. The capacities and financial resources of RT facilities need to be increased. For example, about one-third of all patients undergoing THA will develop HO; thus, almost 50,000 patients in the United States will require prophylactic measures such as RT. Patient accrual is far more than for any single tumor entity, underlining the potential role of RT when including only this disease entity in the actual therapeutic spectrum of all RT institutions.

Prophylactic RT for HO will be broadly accepted if a favorable risk/benefit ratio is established. Prophylactic measures are required for 30% of high-risk patients (32, 38). Two methods are effective: nonsteroidal anti-inflammatory drugs (NSAIDs) (1, 32, 36, 52, 53) and irradiation. Bisphosphonates are ineffective (3). Both methods offer significantly better function compared with no therapy (32, 36). Regarding patient compliance and acute toxicity, prophylactic RT has advantages over NSAID, although NSAIDs are more available and easy to use. When accounting for primary costs, RT is more expensive, but when accounting for secondary costs possibly induced by gastrointestinal bleeding or other complications (54), RT has advantages over NSAID. Late radiogenic effects and the long-term outcome of prophylactic RT require continuous follow-up and multicenter assessment for several years.

CONCLUSIONS

This German PCS comprised the largest number of cases reported to date on the performance of prophylactic RT to prevent HO about the hip. The results demonstrate that RT has become standard care in most RT institutions. Both preoperative RT within 8 h and postoperative RT within 72 h are equally effective in preventing HO about the hip. The radiologic failure rates of both RT concepts are comparably low, independent of the involved RT institution and RT technique. In particular, single-dose RT is an excellent treatment alternative for patients with contraindications to long-term use of NSAIDs. The potential patient load should be taken into account in the time and personnel planning in all RT institutions, which are currently focused only on tumor therapy. The technical and clinical quality assurance should be routinely assessed on an international level, and written guidelines for RT of benign diseases should be established.

REFERENCES

1. Ritter MA, Vaughan RB. Ectopic ossification after total hip arthroplasty: Predisposing factors, frequency and effect on results. *J Bone Joint Surg* 1977;59A:345–351.
2. Rosendahl S, Christoffersen JK, Nörgaard M. Paraarticular ossification following hip replacement. *Acta Orthop Scand* 1977;48:400–404.
3. Thomas BJ, Amstutz HC. Results of administration of diphosphonate for prevention of heterotopic ossification after total hip arthroplasty. *J Bone Joint Surg* 1985;67A:400–403.
4. Pedersen NW, Kristensen SS, Schmidt SA, *et al.* Factors associated with heterotopic bone formation following total hip replacement. *Arch Orthop Trauma Surg* 1989;108:92–95.
5. Pellegrini VD Jr, Konski AA, Gastel JA, *et al.* Prevention of heterotopic ossification with irradiation after total hip arthroplasty. *J Bone Joint Surg* 1992;74A:186–200.
6. Bosse MJ, Poka A, Reinert CM, *et al.* Heterotopic ossification as a complication of acetabular fracture: Prophylaxis with low-dose irradiation. *J Bone Joint Surg* 1988;70A:1231–1237.
7. Ghalambor N, Matta JM, Bernstein L. Heterotopic ossification following operative treatment of acetabular fracture: An analysis of risk factors. *Clin Orthop* 1994;305:96–105.
8. Johnston EE, Kay RM, Dorey FJ. Heterotopic ossification prophylaxis following operative treatment of acetabular fracture. *Clin Orthop* 1994;305:88–95.
9. Slawson RG, Poka A, Bathon H, *et al.* Post-operative radiation for prevention of heterotopic ossification in traumatic acetabular fracture. *Int J Radiat Oncol Biol Phys* 1988;17:669–672.
10. Bisla RS, Ranawat CS, Inglis AE. Total hip replacement in patients with ankylosing spondylitis with involvement of the hip. *J Bone Joint Surg* 1976;58A:233–236.
11. Blasingame JP, Resnick D, Coutts RD. Extensive spinal osteophytosis as a risk factor for heterotopic bone after total hip arthroplasty. *Clin Orthop* 1981;161:191–197.
12. Lo TCM. Radiotherapy for heterotopic ossification. *Semin Radiat Oncol* 1999;9:163–170.
13. Seegenschmiedt MH, Katalinic A, Makoski H-B, *et al.* Radiation therapy for benign diseases: A patterns of care study in Germany. *Int J Radiat Oncol Biol Phys* 2000;47:195–202.
14. Brooker AF, Bowerman JW, Robinson RA, *et al.* Ectopic ossification following total hip replacement. *J Bone Joint Surg* 1973;55A:1629–1632.
15. Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fractures: Treatment by mold arthroplasty. *J Bone Joint Surg* 1969;51A:737–755.
16. Armitage P, Berry G. Statistical methods in medical research. 2nd ed. Oxford: Blackwell; 1987.
17. 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.
18. Moed BR, Letournel E. Low-dose irradiation and indomethacin prevent heterotopic ossification after acetabular fracture surgery. *J Bone Joint Surg* 1994;76A:895–900.
19. Order S, Donaldson SS. Radiation therapy of benign diseases. 2nd ed. New York: Springer; 1998.
20. Leer JWH, van Houtte P, Daelaar J. Indications and treatment schedules for irradiation of benign diseases: A survey. *Radiother Oncol* 1998;48:249–257.
21. Coventry MB, Scanlon PW. The use of radiation to discourage ectopic bone: A nine-year study in surgery about the hip. *J Bone Joint Surg* 1981;63A:201–208.
22. Anthony P, Keys H, McCollister-Evarts C, *et al.* Prevention of heterotopic bone formation with early postoperative irradiation in high risk patients undergoing total hip arthroplasty: Comparison of 10 Gy versus 20 Gy schedules. *Int J Radiat Oncol Biol Phys* 1987;13:365–369.
23. Ayers DC, Evarts CM, Parkinson JR. The prevention of heterotopic ossification in high-risk patients by low-dose radiation therapy after total hip arthroplasty. *J Bone Joint Surg* 1986;68A:1423–1430.
24. Conterato DJ, Verner J, Hartsell WF, *et al.* Prevention of heterotopic bone formation: Comparison of 5 Gy versus 10 Gy. *Int J Radiat Oncol Biol Phys* 1989;17(Suppl. 1):232.
25. Sylvester JE, Greenberg P, Selch MT, *et al.* The use of postoperative irradiation for the prevention of heterotopic bone formation after total hip replacement. *Int J Radiat Oncol Biol Phys* 1988;14:471–476.
26. Blount LH, Thomas BJ, Tran L, *et al.* Postoperative irradiation for the prophylaxis of heterotopic bone: Analysis of different dose schedules and shielding considerations. *Int J Radiat Oncol Biol Phys* 1990;19:557–581.
27. Konski A, Pellegrini V, Poulter C, *et al.* Randomized trial comparing single dose versus fractionated irradiation for prevention of heterotopic bone. *Int J Radiat Oncol Biol Phys* 1990;18:1139–1142.
28. Lo TCM, Healy WL, Covall DJ, *et al.* Heterotopic bone formation after hip surgery: Prevention with single-dose postoperative hip irradiation. *Radiology* 1988;168:851–854.
29. Fingeroth RJ, Ahmed AQ. Single dose 6 Gy prophylaxis for heterotopic ossification after total hip arthroplasty. *Clin Orthop* 1995;317:131–149.
30. Healy WL, Lo TC, DeSimone AA, *et al.* Single-dose irradiation for the prevention of heterotopic ossification after total hip arthroplasty: A comparison of dose of five hundred and fifty and seven hundred centigray. *J Bone Joint Surg* 1995; 77A:590–595.
31. 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;4:319–325.
32. Knelles D, Barthel T, Karrer A, *et al.* Prevention of heterotopic ossification after total hip replacement: A prospective, randomised study using acetylsalicylic acid, indomethacin and fractional or single-dose irradiation. *J Bone Joint Surg* 1997; 79B:596–602.
33. Arnold M, Stas P, Kummermehr J, *et al.* Radiation-induced impairment of bone healing in the rat femur: Effects of dose,

sequence and interval between surgery and irradiation. *Radiother Oncol* 1998;48:259–265.
34. 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;19:1431–1438.
35. Gregoritch SJ, Chadha M, Pellegrini VD, *et al.* Randomized trial comparing pre- versus postoperative irradiation for prevention of heterotopic ossification following prosthetic total hip replacement: Preliminary results. *Int J Radiat Oncol Biol Phys* 1994;30:55–62.
36. Kölbl O, Knelles D, Barthel T, *et al.* Preoperative irradiation versus 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.
37. Seegenschmiedt MH, Martus P, Goldmann AR, *et al.* Preversus 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.
38. 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;39:161–171.
39. Pellegrini VD Jr, Gregoritch SJ. Preoperative irradiation for prevention of heterotopic ossification following total hip arthroplasty. *J Bone Joint Surg* 1996;78A:870–881.
40. Parkinson JR, Evarts CM, Hubbard LF. Radiation therapy in the prevention of heterotopic ossification after total hip arthroplasty. In The Hip: Proceedings of the 10th Open Scientific Meeting of The Hip Society. St. Louis: CV Mosby; 1982, p. 211–227.
41. Evarts CM, Ayers DC, Puzas JE. Prevention of heterotopic bone formation in high-risk patients by postoperative irradiation. In The Hip: Proceedings of the 14th Open Scientific Meeting of The Hip Society. St. Louis: CV Mosby; 1987, p. 70–83.
42. Kantorowitz DA, Muff NS. Preoperative versus postoperative radiation prophylaxis of heterotopic ossification: A rural community hospital's experience. *Int J Radiat Oncol Biol Phys* 1998;40:171–176.
43. Brunner R, Morscher E, Hünig R. Paraarticular ossification in total hip replacement: An indication for irradiation therapy. *Arch Orthop Trauma Surg* 1987;106:102–107.
44. DeFlitch CJ, Stryker JA. Postoperative hip irradiation in prevention of heterotopic ossification: Causes of treatment failure. *Radiology* 1993;188:265–270.
45. Chalmers J, Gray DH, Rush J. Observations on the induction of bone in the soft tissue. *J Bone Joint Surg* 1975;57B:36–45.
46. Ayers DC, Pellegrini VD, Evarts CM. Prevention of heterotopic ossification in high-risk patients by radiation therapy. *Clin Orthop* 1991;263:87–93.
47. Healy WL, Lo TCM, Covall D, *et al.* Single-dose radiotherapy for prevention of heterotopic ossification after total hip arthroplasty. *J Arthroplasty* 1990;5:369–375.
48. Seegenschmiedt MH, Goldmann AR, Wölfel R, *et al.* Prevention of heterotopic ossification after total hip replacement: Randomized high vs. low dose radiotherapy. *Radiother Oncol* 1993;26:271–274.
49. Seegenschmiedt MH, Goldmann AR, Martus P, *et al.* Prophylactic radiation therapy for prevention of heterotopic ossification after hip arthroplasty: Results in 141 high-risk hips. *Radiology* 1993;188:257–264.
50. Kennedy WF, Gruen TA, Chessin H, *et al.* Radiotherapy to prevent heterotopic ossification after cementless total hip arthroplasty. *Clin Orthop* 1991;262:185–191.
51. Micke O, Seegenschmiedt MH, Makoski HB, *et al.* Consensus guidelines for radiation therapy of benign diseases—A multicenter approach (abstract). *Int J Radiat Oncol Biol Phys* 2000;48(Suppl. 3):240.
52. Elmstedt E, Lindholm TS, Nilsson OS, *et al.* Effect of ibuprofen on heterotopic ossification after hip replacement. *Acta Orthop Scand* 1985;56:25–27.
53. Ritter MA, Sieber JM. Prophylactic indomethacin for the prevention of heterotopic bone formation following total hip arthroplasty. *Clin Orthop* 1985;196:217–225.
54. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999;340:1888–1899.