International Orthopaedics (SICOT) (2001) 25:371–374
DOI 10.1007/s002640100281

ORIGINAL PAPER

**Federico Lonardi · Gloria Gioga · Manuela Coeli
Pierantonio Ruffo · Graziella Agus · Antonio Pizzoli
Franco Campostrini**

Preoperative, single-fraction irradiation for prophylaxis of heterotopic ossification after total hip arthroplasty

Accepted: 10 May 2001 / Published online: 13 July 2001

Abstract We gave a single fraction of 750 cGy preoperatively (within 16 h of surgery) to 143 patients prior to total hip arthroplasty. The patients were evaluated for heterotopic ossification at 1, 3 and 6 months. The preoperative radiation did not affect the surgical procedure. After a median follow-up of 12 (6–24) months we encountered six patients with heterotopic ossifications of Brooker grade I–II. Potential late risks from ionising radiation should be considered when treating younger patients.

Résumé Cent quarante trois patients ont reçus avant le remplacement prothétique de la hanche (en moyenne 16 heures avant l'intervention) une radiothérapie par une dose unique de 750 cGy. Les patients ont été évalués pour recherche des ossification hétérotopiques à 1, 3 et 6 mois. L'irradiation préopératoire n'a pas affecté la procédure chirurgicale. Avec une médiane de suivi de 12 (6–24) mois six patients ont présentés des ossifications hétérotopiques de niveau Brooker I–II. Les risques tardifs potentiels des radiations ionisantes doivent être pris en compte lorsque on traite des patients jeunes.

Introduction

The mean incidence of heterotopic ossification (HO) after total hip arthroplasty (THA) is 13–15%, but may be 60% or more in patients with associated risk factors [25]. The use of postoperative radiotherapy (RT) and nonsteroidal anti-inflammatory drugs (NSAIDs) in preventing ossification has been extensively reported [6, 13, 14, 15, 21, 27, 29]. However, post-surgical irradiation is uncomfortable as patients have to be moved to a different department for treatment, and there is an associated risk of dislocation with the required changes of position. Preoperative irradiation prevents such complications. Randomised studies have shown that preoperative treatment is effective in preventing HO when administered 4–6 h before surgery [18, 20]. However, there are considerable administrative difficulties associated with giving this treatment so soon before surgery. Although the effects of early irradiation (24 h or more before surgery) are uncertain [11, 19], promising results have been reported from a preliminary evaluation of treatment at an intermediate preoperative interval (less than 24 h) [16].

In this study we evaluated the clinical effectiveness of radiotherapy administered 16 h before surgery.

F. Lonardi (✉) · G. Gioga · G. Agus · F. Campostrini
Unità Operativa di Radioterapia, ASL 21, Ospedale Civile,
Via Gianella 1, 37045 Legnago (VR), Italy
e-mail: flonar@hotmail.com or rtlegnago@hotmail.com
Tel.: +39-0442-632275, Fax: +39-0442-632364

M. Coeli
Servizio di Fisica Sanitaria, ASL 21, Ospedale Civile,
Via Gianella 1, 37045 Legnago (VR), Italy

P. Ruffo · A. Pizzoli
Unità Operativa di Ortopedia, ASL 21, Ospedale Civile,
Via Gianella 1, 37045 Legnago (VR), Italy

Patients and methods

Between January 1999 and June 2000, we enrolled 143 patients who were undergoing primary THA, a revision procedure or removal of heterotopic bone, into the study. The indications for THA were osteoarthritis, or other degenerative diseases, fractures of the hip and osteonecrosis. Revision procedures were performed in 23 patients, seven of whom had severe ectopic ossification (Brooker grade III–IV), which was removed at operation. Two further patients, with severe pain and limitation of movement, underwent the removal of ectopic bone from around a hip prosthesis. Three patients had staged bilateral radiation and hip surgery within 6 to 9 months. Forty-seven patients were considered to have a "standard" risk of developing HO, whereas 71 had one or more conditions associated with an increased risk of the development of HO (hypertrophic osteoarthritis, previous acetabular or femoral fractures). Twenty-five patients who had undergone previous hip surgery (with or without the development of HO) were also classified as high risk. The characteristics of the patient population are summarised in Table 1. A minority of patients (23%) had been taking regular NSAID-based anti-inflammatory medication, with different drugs, schedules and doses prior to surgery. They were asked to stop treatment at least 7 days before surgery and only replace it with non-NSAID analgesics as required. Radiation was given as a single dose of 750 centiGray (cGy) in the late afternoon (5.00 p.m. to 6.00 p.m.) on the day before surgery (scheduled to

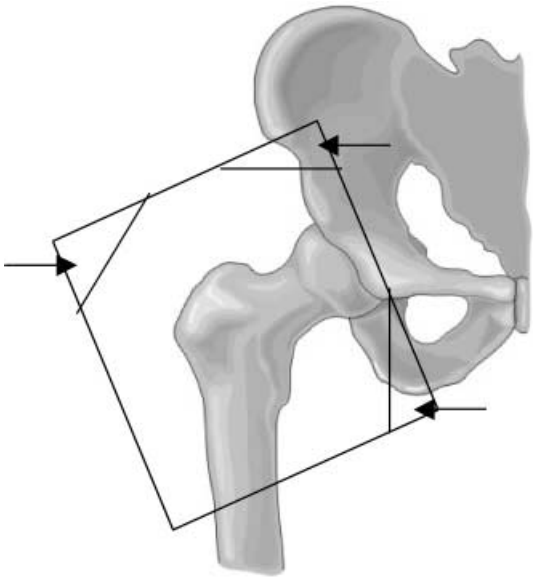

Fig. 1 Radiation field largely encompassing soft tissues around the external border of the proximal femur. Collimator rotation to exclude as many inner pelvic structures as possible from radiation fields. Volumes in excess may eventually be shielded (*arrows*)

Table 1 Characteristics of patients

No. of patients	143
Male/female	55/88
Median age (range; years)	
Male	65 (43–80)
Female	72 (43–85)
Surgical indication	
Coxarthrosis	112
Avascular necrosis	2
Fracture	4
Prosthesis replacement	16
HO surgical removal	2
Prosthesis replacement and HO removal	7

start at 8.00 a.m. to 9.00 a.m.), so as not to exceed 16 h. All patients underwent standard simulation. Although the size of the treatment field depended on the size of the patients, portals of 11–12 cm × 12–13 cm fitted almost all cases. Fields were chosen to include the soft tissue around the hip and a margin of at least 3 cm around the border of the proximal femur (Fig. 1). The medial margin was usually not more than 1.5 cm from the femoral head in order to spare the pelvic organs. Portals were occasionally shielded, or the collimator rotated, for adequate protection in younger patients. Treatment was delivered by means of a linear accelerator, 10-MV photon beams, through anterior-posterior opposed fields with the dose prescribed to the central axis at mid-plane depth. Signed informed consent was obtained from all patients before treatment. Non-NSAID analgesics were administered on demand for the management of postoperative pain. Evaluation of results included standard hip X-rays, performed at 1, 3 and 6 months after treatment and compared with preoperative X-rays. The scoring of the ossifications was based on the Brooker grading scale [1]. The mean follow-up was 12 (6–24) months.

Results

Four of the 118 patients who underwent primary THA developed Brooker grade I–II asymptomatic ossification within 3 months of surgery (Table 2). Two further patients, in the group of 25 high risk patients who underwent a revision procedure or removal of ectopic bone, also developed grade II ossification. All ossification was within the irradiated area. There were no cases of significant ossification above grade II. Preoperative RT did not adversely affect the outcome of surgery, and there was no discomfort associated with the treatment. Healthcare personnel reported that they found this treatment protocol to be “less demanding and time consuming; compared with the postoperative treatment protocol”. There were no early or late side or toxic effects of treatment, in particular no increased haemorrhage during surgery and no failure of bony ingrowth into cementless prostheses.

Table 2 Incidence of HO after preoperative radiotherapy and hip surgery, according to the Brooker scale (143 patients)

	Patients	Brooker grading			
		I	II	III	IV
Arthroplasty					
Standard risk group	47	1	1	–	–
Increased risk group	71	–	2	–	–
Prosthesis replacement	16	–	1	–	–
HO removal	2	–	–	–	–
Prosthesis replacement and HO removal	7	–	1	–	–

Table 3 Studies evaluating preoperative RT given within less than 24 h of surgery

Year	Study	RT dose (Gy)	Timing (h)[a]	Patients	HO (%)[b]
1994	Gregoritch et al. [7]	7–8	<4	55	26
1998	Kölbl et al. [16]	7	16–20	45	48
1997	Seegenschmiedt et al. [20]	7	≤4	80	19
1996	Pellegrini and Gregoritch [18]	8	6	49	24
1997	Heid et al. [10]	6	≤4	20	5

[a] Hours before surgery
[b] Overall incidence of HO, all Brooker grades considered

Discussion

Adjuvant treatments to hip surgery have been used in the last decades in order to reduce the incidence of HO, and to extend the life of implants. New bone formation after THA, although relatively common, is usually painless and of limited clinical significance. Only a minority (5–10%) of patients with HO around a prosthesis have significant symptoms. The large number of operations on the hip, however, make the number of patients with symptoms related to HO significant. Repeated surgery, long operating time, previous acetabular or femoral fractures, hypertrophic osteoarthritis, ankylosing spondylitis and diffuse idiopathic hyperostosis are factors which increase the risk of the development of severe ossification (Brooker grade III–IV) after THA [17, 23, 26]. Although the mechanism of ectopic bone formation is not understood, it is assumed that inflammation from local trauma may cause mesenchymal cells and/or fibroblasts to proliferate and differentiate into osteoblastic cells, producing ectopic osteoid tissue. Calcification may be seen on X-ray as early as 3 weeks after surgery, progress to bone occurs within 3 or 4 months and this bone becomes mature at 12 months [2]. Anti-inflammatory drugs and low-dose radiation therapy can reduce the incidence of significant HO.

The anti-inflammatory mechanisms of radiotherapy remain hypothetical and under investigation [24]. Inhibition of the proliferating connective tissue cells seems to play a role in the prevention of HO. The efficacy of local RT is consistent with the hypothesis that these cells do not derive from distant blood-borne precursors, but differentiate from local soft tissue cell lines within the irradiated area [18]. However, the lack of understanding of the exact mechanisms involved and the awareness of the potential risks associated with irradiation probably mean that this therapeutic option has not been used often enough [12]. The role of postoperative irradiation in preventing ossification was first reported 20 years ago [4] and has been confirmed by subsequent studies. Although RT regimes differed greatly with regard to dose, fractionation and timing, the recommended dose has been gradually reduced. The lowest effective prophylactic dose to be recommended was 700 cGy [9]. Based on these experiences two critical points have been identified; firstly, single-fraction treatments are as effective as longer fractionated schedules and less time consuming and demanding for patients. Secondly, the interval between surgery and RT should not exceed 4 days in order to achieve effective inhibition of differentiating mesenchymal cells. A recent report from Childs et al. [3] showed no increase in the incidence of HO with an interval of 3 days between surgery and RT. Preoperative radiotherapy was used in an experimental model by Kantorowitz et al. [11] and shown to be effective in preventing ectopic ossification. Preoperative trials [7, 10, 16, 18, 20, 25] were initiated with the aim of testing the clinical efficacy whilst eliminating the drawbacks associated with postoperative administration. Two randomised studies [20] supported the efficacy of RT given 4 h preoperatively and showed that this approach was as effective as a postoperative regime. The preliminary evaluation of the effectiveness of an “earlier” irradiation protocol, with a 16-h interval, was reported by Kölbl et al. [16].

The advantages of preoperative treatment are that it is more comfortable for the patient and spares the prosthetic material from irradiation, thus, for instance, avoiding interference with bony ingrowth into porous surfaces. Shorter time intervals between irradiation and surgery pose organisational problems. A 4–6 h interval may be impracticable in the daily routine of a general hospital. Longer intervals, not exceeding 24 h, do not seem to affect the outcome and offer better compliance. The failure of preoperative RT to prevent the development of HO varies from 5% to 48% (Table 3), depending on the Brooker grading, risk factors, and, to a certain extent, radiation doses. A study by Kölbl et al. [16] is apparently discouraging as they reported an incidence of 48%; however, if only clinically significant HO is considered, the incidence becomes almost insignificant: HO grade III 2.2%, HO grade IV 0%. The authors emphasise that the higher incidence of mild or symptomatic Brooker grade I–II (36.9% and 8.7%, respectively) in the preoperative arm of the study is balanced by the advantages of the procedure, with lower costs and risks, more comfort to the patients and less demand on healthcare personnel.

We achieved control of HO in 96% of the whole group and 92% in the high risk group, with no ossification exceeding Brooker grade II. Since no ossification occurred outside the irradiated field, it is concluded that the irradiated areas correctly encompassed the surgical field which was at risk. Our results compare favourably with those from other preoperative studies (Table 3). Seventy-one at risk patients, 23 undergoing revision procedures and two procedures to remove ectopic bone were free of clinically significant symptomatic HO (Table 2).

There remains the possibility of late development of malignancy within the irradiated tissue, though this is not a major concern in a population of patients whose mean age is more than 70 years. According to Thomas [22] there is no report of malignant change in the literature at dose levels below 3000 cGy, and the dose we used was much lower. The possibility of the development of haematological malignancy should also be considered. Two large reviews [5, 28], published in 1995, considered 34,791 patients irradiated for painful benign conditions of the locomotor system in the period between 1935 and 1964, and both reported an increased risk of the development of leukaemia. However, this irradiation usually involved skeletal areas other than the hip with a larger volume of bone marrow in the radiation fields, and there was less precision in the calculation of the dose administered as compared with current practice. The risk of developing a malignancy in an irradiated patient decreases with increasing age and exposure [8]. Caution, however, should be exercised when irradiating patients younger than 60 years of age; and as much in-

formation as possible concerning the development of malignancy should be given as part of informed consent for treatment.

In conclusion, preoperative RT, 16 h before surgery, is effective in the prophylaxis of HO after major hip surgery and should replace the more complicated postoperative regimes. In our centre this approach has become the standard procedure in patients undergoing major hip surgery who are at risk of the development of HO.

References

1. Brooker AF, Bowerman JW, Robinson RA, et al (1973) Ectopic ossification following total hip replacement. Incidence and method of classification. J Bone Joint Surg [Am] 55:1629–1632
2. Canale ST, Campbell WC (1998) Heterotopic ossification. In: Campbell's operative orthopaedics, 9th edn. Mosby, St. Louis, pp 391–393
3. Childs HA, Cole T, Falkenberg E, et al (2000) A prospective evaluation of the timing of postoperative radiotherapy for preventing heterotopic ossification following traumatic acetabular fractures. Int J Radiat Oncol Biol Phys 47:1347–1352
4. Coventry MB, Scanlon PW (1981) The use of radiation to discourage ectopic bone. J Bone Joint Surg [Am] 63:201–208
5. Damber L, Larsson LG, Johansson L, Norin T (1995) A cohort study with regard to the risk of haematological malignancies in patients treated with X-rays for benign lesions of the locomotor system. I. Epidemiological analyses. Acta Oncol 34: 713–719
6. Fingeroth RJ, Ahmed AQ (1995) Single dose 6 Gy prophylaxis for heterotopic ossification after total hip arthroplasty. Clin Orthop 317:131–140
7. Gregoritch SJ, Chadha M, Pellegrini VD, et al (1994) Randomised trial comparing preoperative versus postoperative irradiation for prevention of heterotopic ossification following prosthetic total hip replacement: preliminary results. Int J Radiat Oncol Biol Phys 30:55–62
8. Hall PF (1991) Cancer risks after medical radiation. Med Oncol 8:141–145
9. Healy WL, Lo TC, De Simone AA, et al (1995) Single-dose irradiation for the prevention of heterotopic ossification after total hip arthroplasty. A comparison of doses of five hundred and fifty and seven hundred centigray. J Bone Joint Surg [Am] 77:590–595
10. Heid R, Schopohl B, Kirchner J, et al (1997) Preoperative radiotherapy for prevention of heterotopic ossifications after hip endoprosthesis. Aktuelle Radiol 7:270–273
11. Kantorowitz DA, Miller GJ, Ferrara JA, et al (1990) Preoperative versus postoperative irradiation in the prophylaxis of heterotopic bone formation in rats. Int J Radiat Oncol Biol Phys 19:1431–1438
12. Keilholz L, Seegenshmiedt MH, Sauer R (1998) Radiotherapy for painful degenerative joint disorders. Indications, technique and clinical results. Strahlenther Onkol 174:243–250
13. Kienapfel H, Koller M, Wust A, et al (1999) Prevention of heterotopic bone formation after total hip arthroplasty: a prospective randomised study comparing postoperative radiation therapy with indomethacin medication. Arch Orthop Trauma Surg 119:296–302
14. Knelles D, Barthel T, Karrer A, et al (1997) 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 [Br] 79:596–602
15. Kölbl O, Knelles D, Barthel T (1997) Randomised trial comparing early postoperative irradiation vs. the use of nonsteroidal anti-inflammatory drugs for prevention of heterotopic ossification following prosthetic total hip replacement. Int J Radiat Oncol Biol Phys 39:961–966
16. Kölbl O, Knelles D, Barthel T, et al (1998) Preoperative irradiation versus the use of nonsteroidal anti-inflammatory drugs for prevention of heterotopic ossification following total hip replacement: the results of a randomised trial. Int J Radiat Oncol Biol Phys 42:397–401
17. Nilsson OS, Persson PE (1999) Heterotopic bone formation after joint replacement. Curr Opin Rheumatol 11:127–131
18. Pellegrini VD, Gregoritch SJ (1996) Preoperative irradiation for prevention of heterotopic ossification following total hip arthroplasty. J Bone Joint Surg [Am] 78:870–881
19. Schneider DJ, Moulton MJ, Singapuri K, et al (1998) The Frank Stinchfield Award. Inhibition of heterotopic ossification with radiation therapy in an animal model. Clin Orthop 355: 35–46
20. Seegenschmiedt MH, Keilholz L, Martus P, et al (1997) 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 39:161–171
21. Sell S, Willms R, Jany R, et al (1998) The suppression of heterotopic ossification: radiation versus NSAID-therapy – a prospective study. J Arthroplasty 13:854–859
22. Thomas BJ (1992) Heterotopic bone formation after total hip arthroplasty. Orthop Clin North Am 23:347–358
23. Toom A, Haviko T, Rips L (2001) Heterotopic ossification after total hip arthroplasty. Int Orthop 24:323–326
24. Trott KR, Kamprad F (1999) Radiobiological mechanisms of anti-inflammatory radiotherapy. Radiother Oncol 51:197–203
25. Van Leeuwen WM, Deckers P, De Lange WJ (1998) Preoperative irradiation for prophylaxis of ectopic ossification after hip arthroplasty. A randomised study in 62 hips. Acta Orthop Scand 69:116–118
26. Vastel L, Kerboull L, Anract P, et al (1998) Heterotopic ossification after total hip arthroplasty: risk factors and prevention. Rev Rhum Engl Ed 65:238–244
27. Vastel L, Kerboull L, Dejean O, et al (1999) Prevention of heterotopic ossification in hip arthroplasty. The influence of the duration of treatment. Int Orthop 23:107–110
28. Weiss HA, Darby SC, Fearn T, Doll R (1995) Leukemia mortality after X-ray treatment for ankylosing spondylitis. Radiat Res 142:1–11
29. Wurnig C, Auersperg V, Boehler N, et al (1997) Short term prophylaxis against heterotopic bone after cementless hip replacement. Clin Orthop 334:175–183