

ORIGINAL ARTICLE

# In-hospital outcomes following single-dose radiation therapy in the treatment of heterotopic ossification of the hip following spinal cord injury—an analysis of 444 cases

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**Study design:** Retrospective chart review.

**Objectives:** The objective of the study was to analyse the efficacy of single-dose radiation therapy in the treatment of heterotopic ossification (HO) following spinal cord injury (SCI).

**Setting:** Department of Spinal Cord Injury and Department of General and Trauma Surgery, BG-University Hospital Bergmannsheil Bochum, Ruhr-University Bochum, Germany.

**Methods:** Patients who were treated for HO around the hips following SCI at our institution between January 2003 and December 2013 were included in this retrospective cohort study. A total of 444 HO cases around the hip were treated with single-dose radiation therapy after a mean time interval of 4.9 days (0–97 days; s.d. = 8.1) after HO diagnosis. Primary outcome measures were the number of HO relapses and the occurrence of adverse side effects related to the radiation therapy.

**Results:** After a mean time interval of 63.2 days (8–295 days; s.d. = 39.6) subsequent to SCI HO occurred in 207 male (84.8%) and 37 female (15.2%) patients with a mean age of 46.4 years (18–81 years, s.d. = 18.2). In 200 patients both hips were affected, whereas the remaining 44 HO occurred unilateral. None of the patients suffered primary side effects due to the radiation therapy. However, in 13 out of 244 patients (5.3%), HO relapse occurred. After repeated single-dose radiotherapy, one patient suffered joint ankylosis and therefore required surgical resection.

**Conclusion:** Our results present that single-dose radiation therapy is a safe option in the treatment for spinal cord-injured patients suffering from HOs of the hips.

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## INTRODUCTION

Heterotopic ossification (HO) of the hips is considered to be a relatively common condition in spinal cord-injured patients.<sup>1,2</sup> Regardless the high incidence, the details of etiopathogenesis remain unknown. Complete lesions of the spinal cord (AIS A), concomitant thoracic trauma, spasticity and tracheostomy, acquired pneumonia and urinary tract infections have been reported as risk factors for HO.<sup>1,2</sup> Early diagnosis and targeted treatment of HO is crucial to avoid ankylosis and surgical intervention.<sup>3–6</sup> Despite the high incidence of HO, there is a lack of diagnostic and therapeutic regimen in order to achieve early treatment. Routine ultrasound examination may be considered a safe and reliable approach with high intervention and should be restricted to cases of ankylosis and/or severe limitations of range of motion.<sup>7,8</sup> The main objective in the treatment of HO due to spinal cord injury (SCI) should be in the early detection of HO. Patients in an early stage of HO should initially receive non-surgical treatment as a first choice. In this context, a regimen of radiation therapy has been established in the recent years.<sup>9–12</sup> In 1995, Sautter-Bihl *et al.*<sup>11</sup> reported on their preliminary results of 20 patients with HO after radiation therapy of 10 Gy in single fractions of 2 to

2.5 Gy and 8 MV. After a mean follow-up time of 12 weeks, no complications occurred and no patient showed any further progression. A follow-up study in 2001 by Sautter-Bihl *et al.*<sup>10</sup> presenting the results of a phase-I/II study of fractionated and single-dose radiation therapy in 52 patients and a mean follow-up period of 11 months concluded that single-dose radiotherapy may also be an effective local treatment for spinal cord-injured patients suffering from HO. More recently, Citak *et al.*<sup>13</sup> concluded that the electrode voltage with single-dose radiation therapy may influence the HO recurrence rate. Limitations of all studies mentioned above are the small number of recruited patients. Therefore, studies with larger cohorts are required to provide reliable evidence. Therefore, we present our in-hospital outcomes of 244 patients with a total of 444 HO cases around the hips following SCI treated with single-dose radiation therapy.

## MATERIALS AND METHODS

This retrospective study was initiated after obtaining approval from our institutional review board. Patients who received treatment for SCI, and who furthermore suffered from HO, were identified by querying the electronic database of our hospital from January 2003 through December 2013.

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**Table 1 Detailed information of patients who developed HO recurrence after initial treatment with single-dose radiation therapy**

Total no	Gender	Age	Type of neurological deficit	AIS classification	Time interval of developing HO (days)	Time interval HO diagnosis and treatment (days)	Time interval of treatment and HO recurrence (days)
1	Female	21	Tetraplegic	A	47	0	33
2	Male	32	Tetraplegic	B	19	4	31
3	Male	52	Paraplegic	A	32	2	66
4	Male	35	Paraplegic	A	155	2	69
5	Male	46	Paraplegic	A	28	0	49
6	Male	63	Paraplegic	A	20	13	69
7	Male	56	Paraplegic	A	8	2	90
8	Male	50	Tetraplegic	A	22	4	22
9	Male	58	Tetraplegic	A	44	10	32
10	Male	71	Tetraplegic	A	63	0	50
11	Male	21	Paraplegic	A	69	4	21
12	Male	47	Paraplegic	A	40	6	59
13	Male	43	Paraplegic	A	40	1	29

Abbreviations: AIS, American Spinal Injury Association Impairment Scale; HO, heterotopic ossification.

Patients with HO but without a single-dose radiation therapy were excluded from the study. HO localization other than hip joints was also an exclusion criteria. Consistently, patients with single-dose radiation of 7 Gy were enrolled in the final analysis. Two-hundred eighty one out of 1390 patients (20.2%) experienced HO and were subsequently treated with single-dose radiotherapy. Twenty-six patients suffered from HO on other than hip joints and eleven patients were treated with a different radiation dose than 7 Gy. Hence, a total of 244 patients met the inclusion criteria and were therefore recruited for final analysis. Bilateral HO was found in 200 patients, whereas unilateral HO occurred in 44 patients with a total number of 444 HO cases on the hip.

At our hospital, we perform biweekly routine ultrasound screening examinations in all patients after admission. The routine ultrasound examinations are conducted by experienced radiologists in the B-mode technique. Suspicious cases of HO were confirmed by computerized tomography or magnetic resonance imaging. Single-dose radiation therapy with 7 Gy was administered in all cases in a cooperation with the Department of Radiation Clinic.

### Data collection and outcome measures

On the basis of the patient medical records, the following information was obtained: age, gender, neurological level and the type of complete or incomplete lesion according to the American Spinal Injury Association (ASIA) Impairment Scale (AIS),<sup>14</sup> time interval of SCI and HO onset (in days), time interval of HO diagnosis and treatment with single-dose radiation therapy (in days), follow-up examination before discharge (in days) and length of hospitalization. Primary outcome measures were the number of HO relapses and the occurrence of adverse side effects related to the radiation therapy. The mandatory requirement of repeated radiation therapy was defined as HO recurrence. Descriptive statistics are presented in the form of a number of occurrences and percentage, or mean, s.d. and range. Statistical significance for these analyses was set to a *P*-value <0.05. All data were processed using software (Graph Pad Prism version 5.0d, La Jolla, CA, USA).

### RESULTS

After a mean time interval of 63.2 days (range from 8 to 295 days; s.d. = 39.6) subsequent to SCI HO occurred in 126 paraplegic (51.6%) and 118 tetraplegic (48.4%) patients. The cohort included 207 male (84.8%) and 37 female (15.2%) patients with a mean age of 46.4 years (range from 18 to 81 years, s.d. = 18.2). A total of 220 patients (90.2%) were classified as AIS A with complete neurological deficit. The remaining patients were categorized as follows: AIS B in 8 patients (3.3%), AIS C in 12 patients (4.9%) and AIS D in 4 patients (1.6%). In 200 patients both hips were affected, whereas the remaining 44 HO occurred unilateral. A total of 444 HO cases around the hip were treated with single-dose radiation therapy after a mean time interval of

4.9 days (range from 0 to 97 days; s.d. = 8.1) after HO diagnosis. In the majority of the patients (202 patients; 82.8%), the electrode voltage during radiotherapy was 15 MV. In the remaining 42 patients (17.2%), 6 MV were administered. At final follow-up examination before discharge during hospital stay with a mean of 89.4 days (range from 14 to 505 days; s.d. = 76.0) after single-dose radiation therapy, none of the patients suffered from primary side effects due to the radiation therapy. However, in 13 out of 244 patients (5.3%) HO relapse occurred. Looking at HO cases, 26 out of 444 cases (5.9%) experienced HO recurrence with the need of repeated single-dose radiation therapy. In all patients with HO relapse, the HO initially affected both hips. The mean time interval between radiation therapy and HO recurrence was 47.7 days (range from 21 to 90 days; s.d. = 21.7) (Table 1). All patients with HO relapse received repeated single-dose radiation therapy with 7 Gy and 15 MV. After repeated single-dose radiotherapy, one patient suffered from joint ankylosis and therefore required surgical resection.

### DISCUSSION

To the authors' best knowledge, this is the largest cohort analysis of in-hospital outcomes of single-dose radiation therapy in the treatment of HO. Our study results lead to the conclusion that single-dose radiation therapy is a safe and reliable method with a low rate of HO relapse. The study by Sautter-Bihl *et al.*<sup>10</sup> with a follow-up time interval of 11 months reported that the HO relapse rate was 8.5% in a cohort of 52 patients. The results of Citak *et al.*<sup>13</sup> with a follow up of ~ 3 years in a group of 55 patients reveal a HO recurrence rate of 7.2% and are therefore similar to the results reported by Sautter-Bihl *et al.*<sup>9,10</sup> One reason for the lower HO recurrence rate might be the shorter follow-up time period. Another reason may be related to the early HO diagnosis and treatment due to the standardized hospital protocol. However, we did not screen the patients after discharge, which is the main limitation of the study. However, there is no data reporting on the time interval of HO recurrence after initial radiation therapy. In our large cohort, HO relapse occurred after a mean of 47.7 days subsequent to single-dose radiation therapy, whereas the latest HO recurrence occurred 90 days after radiotherapy.

Focussing on the possible side effects of radiation therapy, our study did not reveal any primary side effects similarly reported by previous studies.<sup>9-12</sup> In our clinic, younger patients have also been treated with single-dose radiation therapy in order to avoid HO progression and

ankylosis of the hip joints, resulting in an additional handicap for those patients. In such cases, bed-to-chair transfers may be also impaired as well as activities of the daily living. All these factors may affect the quality of life of patients with HO and may jeopardize their long-term outcome. Therefore, we suggest that single-dose radiation therapy should be administered regardless the age, as spontaneous remission of HO has not been reported in the literature yet. Concerning secondary side effects, neither our follow-up period nor that of the other authors is sufficient, as the latency of tumor induction after radiation therapy is up to 27 years.<sup>15,16</sup> Nevertheless, at this point, none of the reported spinal cord-injured patients treated for HO with single-dose or fractionated radiation therapy experienced adverse secondary side effects due to the radiation.<sup>9–12</sup>

According to the results of other studies, we also conclude that single-dose radiation therapy is a safe method in the treatment of HO with a low recurrence rate. One of the strengths of our study is the large number of patients leading to a representative cohort. Further strength of the study is the standardized hospital protocol including routine ultrasound examinations of all patients after SCI. Limitations of the study are those related to the retrospective study design. However, the main limitation is the short follow-up time interval and the lack of detailed information about clinical signs of HO and the missing value of range of motion in all patients. Another major weakness is the fact that only patients with clinical symptoms for HO such as swelling or limited range of motion after radiation therapy were screened for HO relapse. Patients without screening could possibly suffer from HO relapse without obvious symptoms and therefore were grouped into the non-HO group.

Nevertheless, our study results show that single-dose radiation therapy is a safe option in the treatment for spinal cord-injured patients suffering from HOs of the hips, although the risk of secondary side effects related to the radiation remains unknown.

#### DATA ARCHIVING

There were no data to deposit.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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