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medical and ethical considerations**

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Prophylaxis of Heterotopic Ossification in Patients Sedated after Polytrauma

Medical and Ethical Considerations

Susanne Oertel¹, Uwe Schneider², Marius Keel³, Urs Martin Lütolf¹, Georg Bosshard⁴

Background and Purpose: Heterotopic ossification (HO) often follows acetabular fractures after multitrauma. Irradiation is a mean for prophylaxis. We established a standard procedure in our hospital for patients under sedation, when obtaining informed consent for HO prophylaxis is impossible.

Patients and Methods: We reviewed current scientific evidence, calculated the risks of radiation and presented the ethical and legal framework. The subject was scrutinised by an interdisciplinary panel.

Results: Irradiation is the most effective means for prophylaxis and has few adverse effects in adult patients with fractures of the acetabulum. The lifetime risk of radiation-induced cancer or infertility are insignificant.

Conclusions: Informed consent for irradiation should be obtained before operation whenever possible. When this cannot be done prophylaxis can be postponed for a maximum of 3 days in order to obtain consent. If the patient is not able to communicate within this period, prophylactic irradiation should be given after consulting the relatives. The patient must be informed as soon as possible.

Key Words: Heterotopic ossification · Prophylactic irradiation · Non-steroidal anti-inflammatory drugs (NSAIDs) · Acetabular fracture

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Prophylaxe heterotoper Ossifikationen bei sedierten Patienten nach Polytrauma. Medizinische und ethische Überlegungen

Hintergrund und Ziel: Heterotope Ossifikationen (HO) entstehen häufig nach Acetabulumfrakturen. Übliche Methode der HO-Prophylaxe ist die Bestrahlung. Ziel unserer Arbeit war die Erarbeitung einer standardisierten Vorgehensweise bei sedierten Patienten.

Patienten und Methodik: Der medizinische Kenntnisstand, rechtliche und ethische Aspekte wurden zusammengetragen und Berechnungen für strahleninduzierte Risiken durchgeführt. Auf dieser Basis wurde die Thematik von einer interdisziplinären Expertengruppe diskutiert.

Ergebnisse: Die Bestrahlung bei Patienten mit Acetabulumfraktur ist effektiv und risikoarm. Das Lebenszeitrisiko zur Entwicklung eines strahleninduzierten Malignoms ist gering. Es besteht kein Infertilitätsrisiko.

Schlussfolgerungen: Ist die Zustimmung des Patienten zur prophylaktischen Bestrahlung präoperativ nicht einholbar und der Patient auch postoperativ nicht aufklärbar, werden Aufklärung und Bestrahlung bis drei Tage nach der Operation aufgeschoben. Ist der Patient weiterhin nicht aufklärbar, wird nach Rücksprache mit den Angehörigen die prophylaktische Bestrahlung durchgeführt. Die Aufklärung des Patienten wird baldmöglichst nachgeholt.

Schlüsselwörter: Heterotope Ossifikation · Prophylaktische Bestrahlung · Nicht steroidale Antiphlogistika (NSAI) · Acetabulumfraktur

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Introduction

In recent years, radiotherapy of certain non-malignant diseases has experienced a remarkable comeback [9, 10, 24, 27, 33]. In heterotopic ossification (HO), which typically follows fractures, dislocations or operative procedures, irradiation is an effective prophylactic. HO often affects the hip and may result in severe functional impairment in up to 50% of patients with major acetabular fractures [22, 23]. It is believed to result from inappropriate differentiation of pluripotential mesenchymal progenitor cells, which are either spread during trauma or stimulated by immunological and inflammatory factors to form callus in situ [2]. Differentiation of mesenchymal cells occurs 16 hours after trauma and peaks at 36 hours [33]. Prophylaxis is based on either local irradiation or non-steroidal anti-inflammatory drugs.

In polytrauma patients, haemodynamic stabilisation and pain management are paramount – skeletal fixation has to be carefully timed. Acetabular fractures are mainly caused by high-energy trauma, frequently with further injuries requiring temporary sedation in an intensive care unit [15]. The best time for open reduction of acetabular fractures is 48 hours post-injury [17]. To guarantee optimal functional rehabilitation, decisions are often needed before the patient can communicate. Informed consent, the basis of modern elective medicine, is often not an option and medical staff has to decide according to the patient's presumed wishes.

Purpose and Method

Following a case where a patient with multiple injuries was extubated briefly in order to give his informed consent to radiotherapy, we realized that there was general uncertainty about the appropriate procedure for HO prophylaxis (Figure 1). In order to improve this unsatisfactory situation, we drew up a standard procedure for our hospital. Current scientific evidence about HO prophylaxis was collected. We calculated the specific risks and worked out a general framework for HO prophylaxis. The whole question was then considered by a panel of clinically-experienced radiooncologists and traumatologists, radiophysicists and clinical ethicists.

Clinical and radiophysical evidence

Incidence of HO

HO is a major complication affecting the hip after arthroplasty (THA), traumatic acetabular fracture or central nervous injury, with a peak incidence 6–12 weeks after the trauma. Minor HO consists of small ossification islands and is generally asymptomatic. Grades III and IV (Brooker's scale), however, are characterised by severely impaired leg movements and complete ankylosis, respectively [7, 13].

Clinically relevant Grade III/IV HO after central nervous injury, caused only by inflammatory/immunological factors, is rare: the incidence is about 2–5%. In contrast, the figure is 10% after THA, 20% after acetabular fractures, and up to

50% in patients with severe trauma, pre-existing HO or additional CNS injury [11].

Effectiveness and risks of HO prophylaxis alternative

Besides radiotherapy prevention of HO is based on non-steroidal anti-inflammatory drugs (NSAIDs), the effectiveness of which has been studied extensively in patients with THA [23].

A few retrospective analyses on NSAIDs also showed a significant decrease of HO after indomethacin in patients undergoing surgery for acetabular fractures [12, 19, 21]. However, Matta et al. terminated a prospective study on similar patients before statistical significance could be reached, because HO occurred in 27/50 patients on indomethacin and in 25/44 without therapy [18]. They concluded that indomethacin was not sufficiently effective. A problem in interpreting results is that the duration, dosage and type of medication vary considerably amongst published studies on NSAID prophylaxis [16].

Most important adverse effects of NSAIDs are *gastrointestinal complications*, including haemorrhage and perforated gastric ulcer. Pakos reviewed seven randomised studies comparing NSAIDs with radiotherapy in HO prophylaxis [23] and found gastrointestinal toxicity with discontinuation of NSAIDs in 4.6% of patients. However, in one of only two prospective studies on patients with acetabular fractures (rather than elective THA), complications causing discontinuation of medication were observed in 20% patients, including two life-threatening gastrointestinal complications. Similarly, Karunakar et al. had to terminate a prospective investigation on acetabular fracture early, because of serious gastrointestinal complications in two patients and poor compliance in the indomethacin group [14].

NSAID have also been reported to increase the *risk of long bone non-union* [4] with a rate of 26% vs. 7% in irradiated patients or those without prophylaxis [6]. After radiotherapy no increased risk of prosthesis instability or fracture healing disturbances has been observed [29].



Figure 1. 34-year old polytrauma patient with acetabular fracture.

Abbildung 1. 34-jähriger Polytraumapatient mit Acetabulumfraktur.

In contrast to NSAIDs, the effectiveness, timing and dose of *radiotherapy* as HO prophylaxis has been demonstrated in patients with acetabular fractures – the evidence is just as good as in patients treated for THA [1, 5, 8, 20, 25, 31, 34]. A single dose of 7–8 Gy (J/kg) is usually given. Higher doses have not proved superior and lower doses seem less effective [23]. Prophylactic irradiation can be given between 8 hours before and 72 hours after surgery, without diminishing its effectiveness [5, 28, 29].

In direct comparisons, six retrospective randomised studies showed NSAIDs to be slightly less effective than radiotherapy in patients receiving prophylactic therapy with THA [23]. Burd compared postoperative 8 Gy single-dose radiotherapy with a 6-week course of indomethacin (25 mg tds) in a prospective randomised study including patients with acetabular fractures. He reported 11% severe HO in the indomethacin group and 4% in the radiotherapy group, against 38% in untreated patients [3]. However, his data lack statistical significance because of the small number of patients.

Adverse effects of radiotherapy – specific risk calculations

Inducing malignancy is the most important fear of radiotherapy. Radiation-induced leukaemia may occur within 2–30 years, with a peak after 5 years, while the risk of solid tumors increases steadily after exposure [25, 34].

To assess these risks after HO prophylaxis, we calculated the dose distribution of typical hip irradiation in CT-slices

of the Zubal Phantom. The phantom was manually segmented as a computerised 3-D volume array, modelling all major internal structures [35]. The 3-D cube was reconstructed in a 512×512 matrix with a resolution of 1 mm (x, y plane)/10 mm (a z-axis). Each voxel was given an index number indicating the organ or internal structure to which it belonged. We used the Eclipse External Beam Planning system (Varian Oncology Systems, Palo Alto, CA), version 6.5, for treatment planning with corrected dose distributions for head-, phantom- and collimator-scatter also including the extremities. All treatment plans were calculated with 6 MV photons and consisted of two opposed 14×17 cm fields, shaped by MLC to protect pelvic structures. We used isocentric anterior-posterior (ap/pa) opposed fields to ensure dose homogeneity. The prescribed dose was 8.0 Gy. The organ equivalent dose (OED) distribution was obtained using a linear-exponential and a plateau dose-response relationship for radiation-induced cancer [26, 35]. To obtain the cumulative risk for solid cancer or for leukaemia as a function of age, for a patient irradiated at the age of 30, the OED averaged over the whole body and specifically in bone marrow was integrated with respective survival function and mortality rates of the general population.

Our calculations resulted in average OEDs of 0.28 Gy for the linear-exponential model and 0.26 Gy for the plateau dose-response model. The corresponding figures in bone marrow were 0.56 Gy and 0.52 Gy. Assuming irradiation for HO

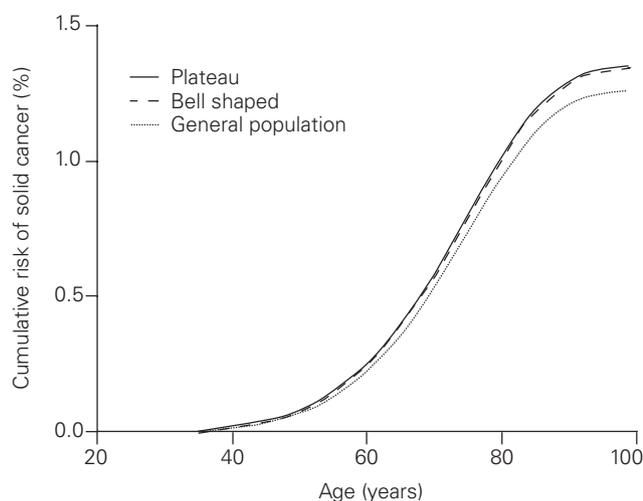


Figure 2. Cumulative risk of a patient irradiated at the age of 30 developing a solid cancer, estimated with a linear-exponential model (broken line) and a plateau model (solid line). For comparison, the dotted line shows the risk of spontaneously developing cancer in the general population.

Abbildung 2. Kumulatives Risiko für einen 30-jährigen Patienten, als Folge der Bestrahlung ein solides Karzinom zu entwickeln, geschätzt mittels eines linear-exponentialen Modells (gestrichelte Linie) sowie eines Plateaumodells (durchgezogene Linie). Zum Vergleich ist das Risiko der Allgemeinbevölkerung, spontan ein Karzinom zu entwickeln, als gepunktete Linie aufgeführt.

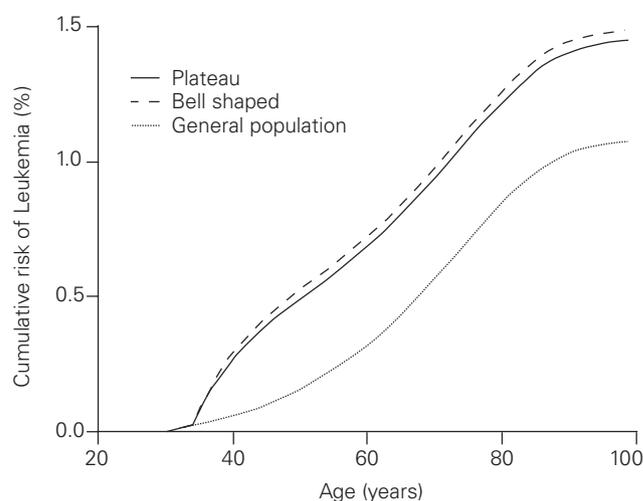


Figure 3. Cumulative risk of a patient irradiated at the age of 30 developing leukaemia, estimated with a linear-exponential model (broken line) and a plateau model (solid line). For comparison, the dotted line shows the risk of spontaneously developing leukaemia in the general population.

Abbildung 3. Kumulatives Risiko für einen 30-jährigen Patienten, als Folge der Bestrahlung eine Leukämie zu entwickeln, geschätzt mittels eines linear-exponentialen Modells (gestrichelte Linie) sowie eines Plateaumodells (durchgezogene Linie). Zum Vergleich ist das Risiko der Allgemeinbevölkerung, spontan eine Leukämie zu entwickeln, als gepunktete Linie aufgeführt.

prophylaxis at age of 30, the corresponding cumulative risks were plotted against age. Figure 2 shows the cumulative risk of all solid cancers for linear-exponential and plateau models. Figure 3 gives the plot for leukaemia.

It can be seen that the additional risk of developing a radiation-induced solid cancer increases with age, from 0.3% at 50 to around 1% at 65. This increase must be viewed in relation to the risk of developing cancer spontaneously – 9.5% at age 65 in the general population, compared with 10.5% for irradiated patients.

The risk of developing leukaemia peaks a few years after irradiation and decreases thereafter. The cumulative risk of irradiated patients is therefore increased for a short time after treatment but is more or less constant for the rest of their lives. The cumulative risk at 65 is 0.80% for irradiated patients, compared to about 0.43% in the general population.

In summary, lifetime risk of radiation-induced malignancies after radiotherapy to prevent HO is approximately 1%, assuming conservative factors. The corresponding OED is equivalent to an effective dose of 50 mSv from low dose diagnostic applications. A typical abdominal CT results in an effective dose of approximately 10 mSv, so the potential harm from hip irradiation with a dose of 8 Gy is five times that of one abdominal CT scan.

We assessed oligospermia after HO prophylaxis using the Yale phantom to evaluate the average dose in the testes: this was 0.21 Gy. Younger men are usually given additional lead shielding for the testes, reducing the dose received to approximately 0.1 Gy [12]. In otherwise healthy men, the spermogram is impaired only after a testicular dose of at least 0.2–0.7 Gy and recovers within 9 weeks. Permanent effects on fertility are not seen with less than 1.2 Gy [32].

In women, radiation may cause indeterminate damage to the ipsilateral ovary but, with a scattering dose of approximately 0.2 Gy and adequate pelvic shielding, reduced fertility is of no concern.

In contrast to all other radiation-induced adverse effects, no threshold dose exists for the occurrence of radiation-induced malignancies and genetic effects. Men should therefore be told not to father children in the nine weeks following radiotherapy, to prevent fertilisation by genetically damaged sperm. As geneti-

cally damaged eggs usually do not ovulate, contraception for a specified period is unnecessary for women.

Legal and ethical considerations

Art. 13 of the 2005 Patient Law of the Canton of Zurich [36], requires that “medical staff have to meet their responsibility by informing patients in due time, properly and comprehensively about the pros and cons of the recommended therapy and of any possible alternatives.” However, it is easy to obtain informed consent in elective orthopaedic surgery, but tends to be more difficult in traumatology.

Trauma patients usually need emergency surgery and are often on intensive care/ventilation afterwards. The question then arises how Art. 21 of the Zurich Patient Law should be applied: “If a patient is incapacitated and does not have a legal guardian, the attending doctors have to decide in the patient’s

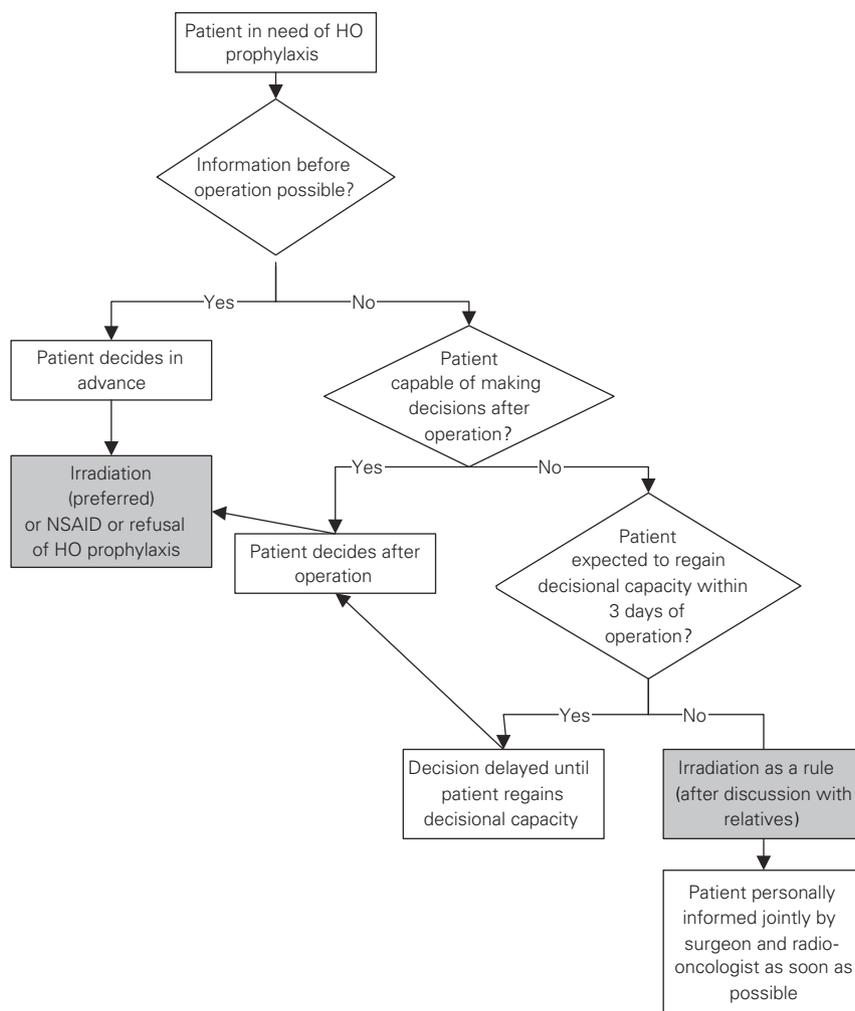


Figure 4. Flow chart of the proposed procedure. Decision-making process in heterotopic ossification (HO) prophylaxis.

Abbildung 4. Flussdiagramm des vorgeschlagenen Prozederes. Entscheidungsprozesse bei der Prophylaxe heterotoper Ossifikationen (HO).

best interest and according to his/her presumed will. If possible, relatives will be heard. Consent can be assumed in emergency situations." Art. 14 also has to be considered: "If the information cannot be given prior to the decision, this has to be rectified as soon as possible."

The situation is particularly delicate for radiotherapy; radiooncologists find that, despite medical evidence, many patients still have strong reservations about radiotherapy or associate it with cancer therapy. Therefore, although the evidence clearly shows irradiation is superior to NSAIDs to prevent HO after acetabular fractures, the ethical and legal needs to obtain informed consent for the proposed prophylaxis remain.

Discussion

All the points mentioned above were discussed during the multidisciplinary panel from the radiooncological, physical, ethical, legal and orthopaedic points of view.

For the above mentioned reasons the panel concluded that radiotherapy is the recommended mean for HO prophylaxis.

The panel agreed that it is essential for patients and their families to be informed comprehensively and considerately, as soon as possible. However, members gave little support to the option of letting the patient wake from coma in order to obtain informed consent: firstly, because the effects of sedatives may place in question the validity of the consent obtained and, secondly, because the arousal itself is risky. Instead, the panel developed following differentiated procedure (Figure 4).

In elective situations, the option should be discussed with the patient preoperatively. When this cannot be done, radiotherapy should be discussed with the patient immediately after operation. If this is still not possible the decision may be postponed up to three days post-surgery. If the patient is not expected to regain decisional capacity within this period, radiation can be given without the patient's explicit consent, but is discussed with relatives whenever possible. Once patients are conscious, they have to be informed by the orthopaedic surgeon and the radiooncologist together about any radiotherapy given.

We considered only adult patients. In children radiation may damage the epiphyseal cartilage leading to retarded growth. The tolerance dose of epiphyses are age-dependent. While 4 Gy may impair growth under the age of 6 years, 8 Gy are probably fairly safe for 16-year-old girls and 18-year-old boys. If children between these ages are given less than 10 Gy, permanent damage affecting growth is unlikely but possible. This possibility has to be weighed carefully against the risk of HO, given that the growth remaining in the femur is 30% in a 7-year-old and 15% in a 10-year-old, but only 1% in a 14-year-old [30].

Careful counselling of the parents is necessary. Whenever the risk-benefit ratio cannot be assessed, we recommend not giving radiotherapy to children.

Conclusions

Informed consent for irradiation as the preferred means of HO prophylaxis should be obtained before operation. If this cannot be done prophylaxis can be postponed up to three days to obtain consent. If patients are not to be extubated within this period, prophylactic irradiation should be given after consultation with relatives. Patients must be informed about this as soon as possible.

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