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Avascular osteonecrosis after hyperthermia in children and adolescents with pelvic malignancies: A retrospective analysis of potential risk factors

S. BALZER¹, D. T. SCHNEIDER¹, M. B. BERNBECK¹, M. JÄGER²,
O. MILS¹, J. SCHAPER³, R. WILLERS⁴, R. KRAUSPE²,
U. GÖBEL¹, & R. WESSALOWSKI¹

¹*Clinic of Pediatric Oncology, Hematology and Immunology,* ²*Clinic of Orthopedics,* ³*Institute of Diagnostic Radiology, and* ⁴*Institute of Computer Science, Heinrich-Heine-University Düsseldorf, Germany*

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Abstract

Purpose: In children with locally advanced or recurrent malignant tumours, prognosis can be improved by regional deep hyperthermia (RHT) in combination with platin-based chemotherapy. However, because of the increasing number of patients that achieve long-time remission with this therapy, it is necessary to evaluate long-term sequelae of thermochemotherapy. During the years 1993–2004 one has observed avascular osteonecrosis (AON) of the femoral head after RHT in seven children with pelvic germ cell tumours or rhabdomyosarcomas.

Methods: Although AON may develop in patients with malignancies treated with chemo- or radiotherapy alone, RHT might nevertheless contribute to the occurrence of AON. In order to determine potential risk factors for AON after RHT, this study analysed the relationship of AON to the patient's age, medical history and treatment parameters such as thermal dose equivalent and power output.

Results and conclusions: In the present study AON was associated with young age as well as intensity of hyperthermia indicated by high power levels that exceed 20 W per kg body weight and/or application of eight or more heat sessions as well as additional radiotherapy. Based on this observation, it was assumed that an optimized three dimensional thermal field modelling may be helpful to avoid hazardous temperatures in the femoral heads during RHT treatment and to reduce AON of the femoral heads.

Keywords: *Hyperthermia, osteonecrosis, side effects, thermometry, children*

Introduction

The majority of clinical studies on the use of hyperthermia for the treatment of malignancies have been performed in superficially located malignancies, including melanoma or breast cancer [1–3]. In these studies, the combination of hyperthermia and irradiation resulted in improved local tumour control. In the last two decades, the development of annular-phased array systems has allowed for the inclusion of deeply-seated tumours in the pelvis and abdomen in clinical phase II/III hyperthermia protocols [4, 5]. It has been shown that local heat application also enhances the local anti-cancer effects of systemically applied chemotherapy regimens [6, 7]. There is experimental evidence that this therapeutic effect appears to be predominantly mediated through the sensitization of tumour cells to alkylating agents under hyperthermic conditions [8–10]. In refractory and unresectable germ cell tumours of children and adolescents, the addition of hyperthermia to a cisplatin-based chemotherapy protocol (Hyper-PEI) improved the event-free survival rate by up to 65% with a median follow-up of 36 months [7]. Because of the improved prognosis in this group of young patients, additional attention has to be focused on potential long-term sequelae of the combined (radio-) thermochemotherapy.

In the literature few hyperthermia related side effects have been reported. Most of the reported side effects are related to the systemic chemotherapy, e.g. myelosuppression with subsequent severe infections and nephrotoxic or ototoxic effects. Possible specific side effects of hyperthermia itself include local burn injuries, pain or complications that are related to the invasive thermometry such as infections caused by the catheters [11]. One case of tumour growth along the thermometry catheter track has also been reported [12]. Other than these acute side effects, peripheral neuropathy constitutes the only long-term sequela following hyperthermia described so far and is extremely rare [13].

In this patient population, avascular osteonecrosis (AON) of the femoral head was found after delivery of regional hyperthermia (RHT) in combination with platinum-based chemotherapy \pm radiotherapy. This complication has not been reported in the literature to date. Common reasons for AON in patients with malignancy include irradiation, application of corticosteroids [14–16] and, in a few cases, chemotherapy with platinum compounds [17]. Therefore, the patients were analysed for potential risk factors of the development of AON in order to evaluate whether specific measures might allow for reducing the risk of AON in future RHT treatments.

Patients

Seventy-two patients aged between 1–72 years (median 16.1 years) have been included in the present analysis. Patients suffered from locoregional pelvic malignancies that were refractory to prior standard cytostatic treatment. Twenty-four patients were male and 48 were female. The patients did not have any distant metastases. All patients received RHT in combination with systemic chemotherapy, including cisplatin, etoposide, ifosfamide, 5-fluorouracil and adriamycin. Twenty of the paediatric patients received subsequent pelvic irradiation (19.2–50.4 Gy). Patients were treated under analgo-sedation using midazolam, promethazine and pethidine. If enduring pain of the hip or any discomfort in walking were observed, MRI of the pelvis including the hip joints was performed in order to detect possible injuries. The follow-up for the whole patient cohort after start of RHT treatment was 3–137 months (median 15 months).

Methods

RHT was performed with three annular phased array applicators that had the same design and operational characteristics (Sigma-30, -40 and -60 applicator, BSD 2000, Medical Corporation, Salt Lake City, Utah, USA). The number of heat applications per patient ranged from 2–30 sessions (median 10 sessions). Maximum radiofrequency (RF) power varied between 130–1300 W. Frequencies ranged from 87–140 MHz. Temperature distribution was monitored using non-perturbing thermometers (Bowman probes) at fixed points, including bladder, vagina, rectum and skin. Temperatures in the tumour area were measured using catheters placed in close proximity to the tumour, either under computer-tomographic control or surgically during tumour resection or biopsy.

In order to evaluate potential risk factors for femoral AON, a retrospective descriptive analysis of the 72 patients was performed. Patients were assigned to different sub-groups according to age at the time of treatment, previous medical history, number of heat sessions, RF power level and the achieved thermal isoeffective dose ($CEM43T_{90}$):

- Patients were assigned to four different age groups: ≤ 5 years (22 patients), 6–10 years (eight patients), 11–15 years (six patients), >15 years (36 patients).
- The number of heat sessions was sub-divided into the following groups: <8 sessions (21 patients), 8–9 sessions (14 patients), 10–11 sessions (18 patients), 12–13 sessions (six patients), ≥ 14 sessions (13 patients).
- RF power level per body weight was classified into four distinct groups: $\leq 10 \text{ W kg}^{-1}$ (six patients), $10\text{--}20 \text{ W kg}^{-1}$ (44 patients), $20\text{--}30 \text{ W kg}^{-1}$ (18 patients), $\geq 30 \text{ W kg}^{-1}$ (four patients).

To estimate the thermal isoeffect dose, this study used the method of the Arrhenius relation according to Dewey [18]. The measured time–temperature results were converted to an equivalent number of minutes at a standard temperature of 43°C for 90% of the tumour volume ($CEM43T_{90} = \sum(\Delta t)R^{(43-T)}$, with $CEM43T_{90}$ equal to cumulative equivalent minutes at a T_{90} converted to 43°C , Δt equal to the time increments at which the data are acquired during treatment, T equal to the average temperature over the time interval Δt and R equal to 0.25 when $T < 43^\circ\text{C}$ and 0.5 when it is $\geq 43^\circ\text{C}$). Patients were sub-divided according to the achieved thermal dose equivalent into five different $CEM43T_{90}$ categories: ≤ 10 min (41 patients), 10–20 min (18 patients), 20–50 min (six patients), 50–100 min (two patients), >100 min (three patients), two patients with incomplete data. Results were tested for statistical significance by the two-sided Cochran-Armitage trend test in SAS (statistical analysis system). Only p -values <0.05 were considered statistically significant.

Results

Between 1993–2004, 72 patients were treated with RHT and chemotherapy \pm additional radiotherapy. Seven out of these 72 patients developed AON of the femoral head.

Diagnoses and age of the patient population as well as the administered chemotherapy and the occurrence of AON are summarized in Table I. These data show that AON occurred only in patients that suffered from germ cell tumours or rhabdomyosarcomas and were treated with PEI and/or additional EIA. As 22 additional patients with other diagnoses received the same chemotherapeutic agents (PEI, resp. EIA) without developing AON, other factors than the chemotherapy administered concomitant to hyperthermia might constitute important risk factors.

Table I. Diagnoses, age, cytostatic treatment and occurrence of AON in 72 patients treated with RHT.

Diagnosis	Number of patients	Min. age	Max. age	Age median	Chemotherapy during RHT	Number of patients with AON	Number of patients without AON
Granulosa cells' tumour	4	4;03	18;02	15;02	PEI	—	4
Germ cell tumour	25	1;01	23;03	2;11	PEI	5	20
Rhabdomyosarcoma	9	1;03	19;02	5;11	PEI, EIA	2	7
Ewing's sarcoma	5	3;01	15;07	7;10	PEI, EIA, Eto, Ifo, AD, Vcr	—	5
Osteosarcoma	1	8;09	8;09	8;09	PEI	—	1
Chondrosarcoma	2	17;06	23;01	20;04	PEI, EIA	—	2
Liposarcoma	1	34;11	34;11	34;11	none	—	1
Leiomyosarcoma	1	34;04	34;04	34;04	EIA	—	1
Cervical carcinoma	7	19;04	66;05	44;09	PEI	—	7
Rectal carcinoma	14	33;09	70;05	53;10	5FU, Cisplatin	—	14
Anal carcinoma	1	56;01	56;01	56;01	5FU, Cisplatin	—	1
Mesonephroid carcinoma	1	67;09	67;09	67;09	PEI	—	1
Aggressive fibromatosis	1	35;09	35;09	35;09	EIA	—	1

PEI: cisplatin/carboplatin + etoposide + ifosfamide; EIA: etoposide + ifosfamide + adriamycine; AD: actinomycine-D; Vcr: vincristine; 5-FU: fluorouracile.

Table II. Cytostatic treatment prior to RHT in patients with germ cell tumours ($n = 25$) or rhabdomyosarcoma ($n = 9$).

Chemotherapy cycles before RHT	Number of patients with AON	Number of patients without AON
<5	5	17
5–6	2	3
7–8	0	3
>8	0	4

Table III. AON related to dose equivalent $CEM43T_{90}$ in 70 patients. From technical reasons calculation was not possible in two patients.

$CEM43T_{90}$ (min)	Number of patients without AON	Number of patients with AON
>100	3	0
>50–100	2	0
>20–50	6	0
>10–20	17	1
≤ 10	35	6

Table IV. AON related to power level.

Power/body weight ($W\ kg^{-1}$)	Number of patients with AON	Number of patients without AON
<10	0	6
10–20	2	42
20–30	5	13
>30	0	4

To ascertain this result, this study analysed the patients with germ cell tumours or rhabdomyosarcomas for a potential impact of high cumulative doses of chemotherapy prior to RHT on the risk of AON (Table II). However, there is no obvious correlation. Nevertheless, as five out of the patients with AON suffered from germ cell tumours, the effect of prolonged administration of PEI chemotherapy cannot be excluded.

To evaluate the thermal effect in the treated area, the achieved intra-tumoural temperatures were compared in patients with and without AON. To this end, the thermal isoeffective dose was determined using the Arrhenius relation (Table III). Only 11 patients achieved a $CEM43T_{90}$ longer than 20 min and in none of them AON occurred. In contrast, six out of 41 patients with a shorter time of high isoeffective thermal dose developed AON (Table III).

The power needed to achieve temperatures in the presumed therapeutic range was highly variable when it was calculated per kg body weight (Table IV). The risk for AON increased with a higher power level ($p = 0.04$), which was necessary especially in young children. However notably, none of the four patients treated with $>30\ W\ kg^{-1}$ was affected. This might be a result of the small number of patients in this group.

As shown in Table I, patients with germ cell tumours and rhabdomyosarcomas had the lowest median age, however the age range was grossly overlapping to patients with

other diseases. Therefore, this study correlated the occurrence of AON with the defined age group at the start of thermochemotherapy (Table V). Onset of AON was clearly correlated with young age ($p=0.004$). In fact, no case of AON was detected in patients older than 15 years ($n=36$).

In addition, one also compared the number of heat sessions and additional radiotherapy in patients up to 15 years with and without AON (Figure 1). A number of more than eight heat

Table V. AON related to defined age groups.

Age (years)	Number of patients with AON	Number of patients without AON
<5	5	19
6–10	1	5
11–15	1	5
>15	0	36

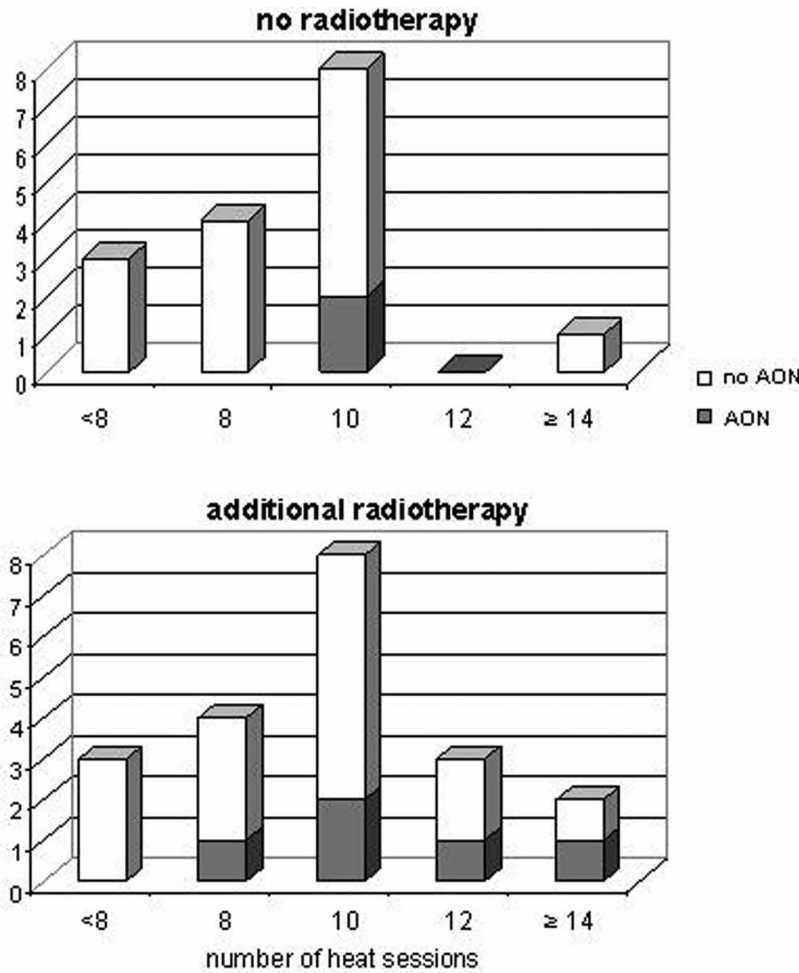


Figure 1. AON related to number of heat sessions. Only patients aged under 16 years are shown.

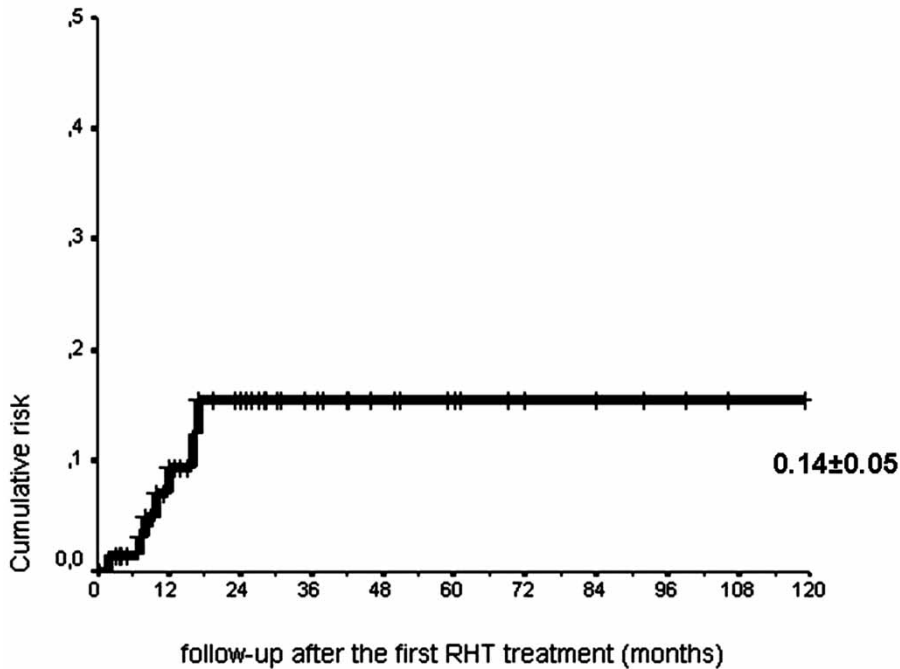


Figure 2. Cumulative risk of AON after RHT.

sessions was correlated with growing risk for AON ($p=0.03$). Only two of the 16 children treated with thermochemotherapy alone developed AON, whereas five of 20 patients with additional radiotherapy were affected. These five patients had received radiation dosages from 45–50.4 Gy. However, in the latter group there is a trend to more heat sessions. In the group of five patients treated 12 or more times, two patients developed AON.

Furthermore, the patients' charts were examined for documented pain after thermochemotherapy and the time point when AON was detected by MRI. In four out of the seven patients the initial clinical presentation of AON was characterized by acute pain that occurred within 48 h after the hyperthermia sessions but often disappeared within 1 week after the end of treatment and was therefore not considered a contraindication for the continuation of treatment. Acute hip pain was also reported in 12 of 72 patients who subsequently never developed any radiological signs of AON. Figure 2 shows a Kaplan-Meier estimation of the cumulative risk of AON after the start of RHT treatment. Only in a few patients, the onset of AON was observed during thermochemotherapy, while in most of the affected patients AON was diagnosed after the end of therapy. Therefore, AON of the femoral head can be considered a real long time sequela of thermochemotherapy. The cumulative risk in the patient population (all age groups) was estimated as 14% and 28% in children up to 15 years.

Discussion

The adoption of the quality guidelines of the European Society for Hyperthermic Oncology (ESHO) [19] for the application of loco-regional RF hyperthermia for superficially and

deeply located tumours during the last two decades has significantly improved the safety and feasibility of hyperthermia treatment delivery in the intended temperature range from 42–44°C. The subsequent temperature monitoring and the analysis of specific absorption rate (SAR) distribution [20] in phantom models of tumour and normal tissues that is included in the ESHO quality guidelines have made severe complications of hyperthermia rather rare. In addition, a protective effect against thermal injuries is provided by the naturally occurring increased blood flow in normal tissues during hyperthermia. However, a certain risk of accidental damage to normal tissues remains, especially during analgo-sedation. To a certain extent, this risk may be related to the difficulties in accurately estimating the temperature in the surrounding normal tissues, if only data sampled through the interstitial temperature probes used for thermal mappings are available.

In the present study, AON was identified in seven out of 72 patients that were treated with RHT in combination with chemotherapy \pm irradiation for tumours located in the pelvis or the abdomen. Remarkably, six of the seven cancer patients with AON were long-term survivors with a median survival time of 4 years after hyperthermia. Five of the seven patients who developed AON were children under 5 years and the two other patients were a 6-year old boy and a 12-year-old girl. The data are supported by the current literature, which includes no reports of AON in adult patients, although similar hyperthermia protocols have been utilized.

In paediatric oncology, the risk of AON correlates with the application of treatment protocols that include high-dose corticosteroids as anti-cancer agents [14, 16] or additional radiotherapy in order to improve local tumour control. In children with acute lymphoblastic leukaemia, the incidence of asymptomatic AON ranges from 1.1–9.3% [21–25] and there is a significant increase after higher doses of corticosteroids and in girls older than 10 years. The fact that AON has also been observed as an occasional complication in adults treated with platinum-based chemotherapy suggests that this therapy may constitute a risk factor for AON that is independent from the patient's age [17]. In correspondent studies of children and adolescents treated for germ cell tumours osteonecrosis has not been mentioned as a side-effect [26].

Osteonecroses after anti-cancer therapy usually occur in long bones including hip and knees. Isolated osteonecroses of the femoral head after chemotherapy in children are extremely rare. In the literature only three cases of AON have been reported in children after cytostatic therapy without the use of steroids [27, 28]. Idiopathic AON occurs in one of 1000–5000 children [29, 30] and is usually associated with a certain risk profile such as extreme obesity or extreme sports. In contrast to the self-limited idiopathic juvenile osteonecrosis (Legg-Calve-Perthes disease) which is characterized by spontaneous healing, these patients with AON of the femoral head showed progressive course and poor self-healing tendencies. Therefore, this disorder seems to be a specific complication of thermochemotherapy.

Osteonecrosis of the hip joint has also been observed as a possible complication of radiotherapy of pelvic tumours [31]. However, this complication is very rare and is not mentioned as a side effect in children with solid tumours such as soft tissue sarcoma who have been treated with chemoradiotherapy [32, 33]. In this patient cohort, an increased incidence of AON was observed in patients who underwent additional radiotherapy. Accordingly, irradiation may also be an additional risk factor for the development of AON in this patient population.

It has been previously shown that hyperthermia increases the cytotoxic effects of cisplatin exposure during the period of increased temperatures, with increases up to 10-fold *in vitro* and *in vivo* [8, 10]. As the patients in this study did not receive

corticosteroids, one can, therefore, postulate that cisplatin-based chemotherapy, which is potentiated by hyperthermia, is one of the main risk factors for the development of AON in children. In addition, the clear correlation of the risk of AON with both the higher dose intensity (preferentially necessary in young children) as well as the cumulative doses (as reflected by the number of RHT sessions) indicates that thermal injuries most probably constitute the driving force for the development of AON.

Therefore, preventive measures such as optimized temperature monitoring have to be considered. In this context, it has to be noted that, while invasive thermometry can be performed by catheters placed in the tumour area, the temperature distribution in surrounding tissues, especially in the femoral heads, cannot be assessed. As has been demonstrated, the risk of AON does not correlate with high temperatures reached in the tumour area itself but with increasing power levels. Consequently, it is assumed that non-invasive thermometry during RHT would be very useful to monitor temperature distribution in the treated area surrounding the tumour in order to avoid dangerous temperatures in normal tissues. One possibility could be non-invasive temperature monitoring with nuclear magnetic imaging [34]. Thus, an optimization of the energy application based on an optimized temperature monitoring during RHT rather than changes in the chemotherapeutic regimen might help to reduce the risk of AON. In small children it is more difficult to exactly adjust the field of hyperthermic treatment using the described sigma applicator with four pairs of antennae. In this context applicators that consist of more antennae like the 'sigma eye' applicator in combination with three dimensional temperature monitoring could be very helpful to adjust the therapeutic field more exactly and to avoid toxic temperatures in the femoral heads.

In a previous extensive comparative analysis of different factors of temperature distribution, e.g. T_{\max} , T_{90} , T_{50} , T_{20} , T_{\min} and CEM43 T_{90} in tumour and surrounding normal tissue, one did not observe significant differences between adults and children [3]. Hence, the development of AON cannot be deduced from the observed temperature parameters obtained through invasive thermometry. The observation that AON after hyperthermia has not been observed in adults substantiates the assumption that anatomical or physiological features in children may promote the development of AON after the application of platinum-based chemotherapy in combination with RHT.

In a pathophysiological perspective, AON in children and adolescents commonly results from an interruption of the capital femoris epiphysis blood supply. During thermochemotherapy of pelvic tumours the femoral heads could be affected by the applied radiofrequency due to their location in the vicinity of the treated tumour. Therefore, heat-induced alterations of blood perfusion and consecutive osseous injuries of the hip might constitute a mechanism of AON development in children after RHT. The alteration of the blood supply to the area of later AON appears in some patients early after the start of thermochemotherapy, however in most patients after the end of treatment suggesting the induction of an autonomous process. In contrast to children it has been demonstrated that in adults, after obliteration of the foveolar artery (*A. capitis femoris*), blood perfusion of the femoral head is physiologically maintained by vessels from the metaphysis. This anatomical difference might, therefore, be a potential explanation for the higher risk of AON in children, if it is assumed that the affection of the blood flow of the foveolar artery causes the AON of the femoral head.

There are some similarities to children with ALL and AON, where also a wide time range of AON manifestation after start of therapy has been observed [24]. AON in dia- and metaphysis of ALL patients show a self-healing capacity whereas epiphyseal manifestations do worse [35]. Although recent data in the literature demonstrate a good therapeutic

response of osteoedema to vasoactive agents such as prostacyclin analogs it remains unclear whether these treatment regimes are able to prevent a progression of an thermochemotherapy induced AON [36]. The clinical manifestation of AON in the seven patients as well as treatment options and the influence on quality of life are the subject of a separate paper in preparation.

In conclusion, a cumulative risk of AON was observed of 14% of the patients receiving thermochemotherapy. These patients are characterized by young age (<5 years), high power supply (>20 W kg⁻¹) and long duration of thermochemotherapy with more than eight RHT sessions. As a result of this experience, the number of thermochemotherapy sessions in the ongoing protocol was reduced to eight sessions in patients with germ cell tumours whereas in patients with rhabdomyosarcomas 16 sessions will be planned because of the lower AON risk and the higher risk of recurrence. Nevertheless, the risk of AON has to be accepted in some children with otherwise refractory tumours of the pelvis or abdomen, if a curative approach is intended. Notably, in this report six of seven children with AON of the femoral head are longtime survivors.

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