Hyperthermia Associated Osteonecrosis in Young Patients with Pelvic Malignancies

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Abstract: Introduction: Progressive and non-juvenile avascular osteonecrosis (AVN) is a rare condition in children. During the last decade, some data indicate that regional deep hyperthermia therapy (RHT) combined with either chemo- and / or radiotherapy in malignancies is associated with AVN in young patients. In this study, we present our data on AVN following RHT in children with intra-pelvic malignancies.

Material and Methods: Localization, extent of AVN, and associated joint effusions were evaluated *via* MRI and X-ray findings in 37 patients treated with RHT and chemotherapy ± additional radiotherapy for intra-pelvic malignancies in our study. AVN was classified in accordance to the Association Research Circulation Osseus (ARCO). In addition, the recurrence of sarcoma after RHT, the number of total joint replacements, and level of activity including sport activities were recorded in all patients. The mean follow-up was 6.2 years (SD: 4.1, range: 1-12 years).

Results: Eight out of 37 pediatric patients treated with RHT and chemotherapy ± additional radiotherapy showed AVN of the femoral head within our follow-up period. Five out of the eight children developed bone marrow edema within 6 months after RHT procedure and three additional patients within the first year. All patients except one showed a rapid progression of AVN from ARCO stage 0 to the post-collapse-stages III and IV in our study. Seven out of eight AVN patients survived without evidence of further malignancy. Although advanced stages of AVN were observed in our patient group, they were able to still maintain a high quality of life. No patients in our group have undergone total hip replacement thus far.

Conclusion: Based on our findings, we hypothesize a high risk of AVN in young children who receive RHT for pelvic sarcoma. However, further clinical investigation needs to be done to prove our hypothesis.

INTRODUCTION

Hyperthermia is a therapeutic procedure ultilized to improve the outcome of patients with solid malignant tumors refractory to standard therapy regimens. The rationale to use hyperthermia in cancer treatment is based on the findings that tumor cells can be sensitized when exposed to alkylating agents under hyperthermic conditions *in vitro* [1-4]. Hyperthermia also increases the effects of radiotherapy by inhibition of DNA-repair enzymes [4]. *In vitro* studies have shown that temperatures between 42 and 44 °C can induce apoptosis in tumor cells [5, 6].

The majority of clinical studies on the use of hyperthermia for the treatment of malignancies have been performed in superficial malignancies such as melanoma or breast cancer [7, 8]. In these studies, the combination of hyperthermia and irradiation resulted in improved local tumor control. Local hyperthermia can be achieved by superficial antennas emitting electromagnetic waves reaching therapeutic depths up to 3 cm [9]. In the last two decades, the development of annular-phased array systems resulted in the possibility of delivering therapeutic electromagnetic waves into the deep regions of the body [9]. Thus, allowing RHT to reach deeply-seated tumors in the pelvis and abdomen of adult and pediatric patients. These studies are currently in clinical trial phase II/III [10,11]. With a combination of RHT and cisplatin-based chemotherapy, the event free survival rate was improved by up to 65% with a median follow-up of 36 months in pediatric patients with refractory and unresectable germ cell tumors [11,12]. 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-) thermo-chemotherapy regiment. Most side effects of this combined thermo- and chemotherapy including myelo-suppression with subsequent infections, nephrotoxicity and/or ototoxicity are associated with the applied cytostatic chemo agents. So far, the only specific long term sequela following hyperthermia that has been reported in the literature is peripheral neuropathy, which is extremely rare [13, 14].

As reported previously [15], we found AVN of the femoral head in seven out of 36 children who had been treated with RHT with chemotherapy and +/- radiotherapy as a salvage therapy for refractory or relapsed pelvic malignancies. Since the incidence of AVN is low in children treated by radiotherapy [16] or chemotherapy for malignant diseases [17, 18] and most cases are related to the application of steroids [19-21], we postulate a correlation of AVN of the hip secondary to RHT treatment in intra-pelvic malignancies. In contrast to the self-limited idiopathic juvenile osteonecrosis (Legg-Calve-Perthes disease) which occurs commonly in the age range between 4 to 8 years [22-25], all of our patients had progressive AVN of the femoral head and most were younger than six years of age. As reported previously [15], we found an increased incidence of AVN in children with pelvic malignancies treated with regional hyperthermia and chemotherapy. It is evident that in these patients, AVN showed progressive course and poor self healing tendencies. Onset of AVN of the femoral head was correlated to young age, additional radiotherapy, high power supply during the RHT treatment, and treatment frequency of more than eight RHT sessions. Here, we performed a retrospective analysis of radiological imaging (X-rays and MRI), surgical interventions and clinical records to elucidate the outcome and long-term follow-up in these patients.

PATIENTS AND METHODS

We report the clinical and radiological findings of eight children (three male and five female patients) with RHT-associated

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AVN. Six of these eight patients were six years or younger when starting RHT and one patient was 16 years old. Six patients were treated with RHT because of a relapsed or non-resectable malignant germ cell tumor and two patients had non-resectable rhabdomyosarcoma treated with RHT. All eight patients received 8 to 16 sessions (median 10) of RHT in combination with PEI chemotherapy protocol (cisplatinum, etoposide and ifosfamide). Six of the eight patients received additional radiotherapy during their treatment. The RHT protocol corresponded to our previously published data [15]. Table **1** summarizes the relevant technical data.

Fig. (**1**) shows the ring applicators consisting of 8 antennas that were used to heat up the tumors by application of radiofrequency. During the hyperthermic treatment, temperature distribution was monitored by non-pertubing thermometers (Bowman probes) at fixed points (bladder, vagina, rectum, skin and tumor).

To judge the clinical and radiological outcome of the affected children, the following parameters served for evaluation:

- MRI and X-ray findings: localization, extent, and stage of the AVN according to the Association Research Circulation Osseus (ARCO), and associated joint effusions,
- recurrence of sarcoma after hyperthermia,
- number of total joint replacements within follow-up,
- ability to perform sport activities.

Mean values (X), standard deviations (SD) served as descriptive statistical parameters.

RESULTS

During a follow-up period of 6.2 years (SD: 4.1, range: 1 to 12.5 years), we found AVN of the femoral head in eight out of 37 pediatric patients treated with RHT and chemotherapy ± radiotherapy for intra-pelvic malignancies. In all eight patients, the femoral head was affected by AVN. One patient showed bilateral femoral head AVN involvement. In eight out of nine femoral heads, the extent of AVN was more than 50% of the femoral head diameter. Three patients presented with joint effusions confirmed by MRI scans.

Table 1. The Table Presents Technical Details of RHT Treatment

Number of heat applications per patient	8–16 sessions (median 10 sessions)
Maximum radiofrequency (RF) power	130–1300 W
Frequencies	87–140 MHz

The temperature distribution was monitored by non-pertubing thermometers (Bowman probes) at fixed points (bladder, vagina, rectum, skin and tumor).

Five of eight patients developed bone marrow edema within six months after RHT procedures and the three remaining patients within the first year. All patients except one female showed a rapid progression of AVN from ARCO stage 0 to the post-collapse-stages III and IV during the follow-up (Fig. **2**).

Although we found a fast progression of AVN, four out of eight patients were still able to do sport activities at the last follow-up appointment (handball, karate, 2 x school sport activities). It was evident that the RHT-associated AVN affected not only the subchondral area typically seen in adults with AVN, but also the metaphysis. In one male patient, the AVN of the metaphysis induced an early slipped capital epiphysis at 6 years of age which was treated by a femoral osteotomy (Fig. **3**). One 5-year old male patient with pelvic embryonal rhabdomyosarcoma died because of tumor pro-

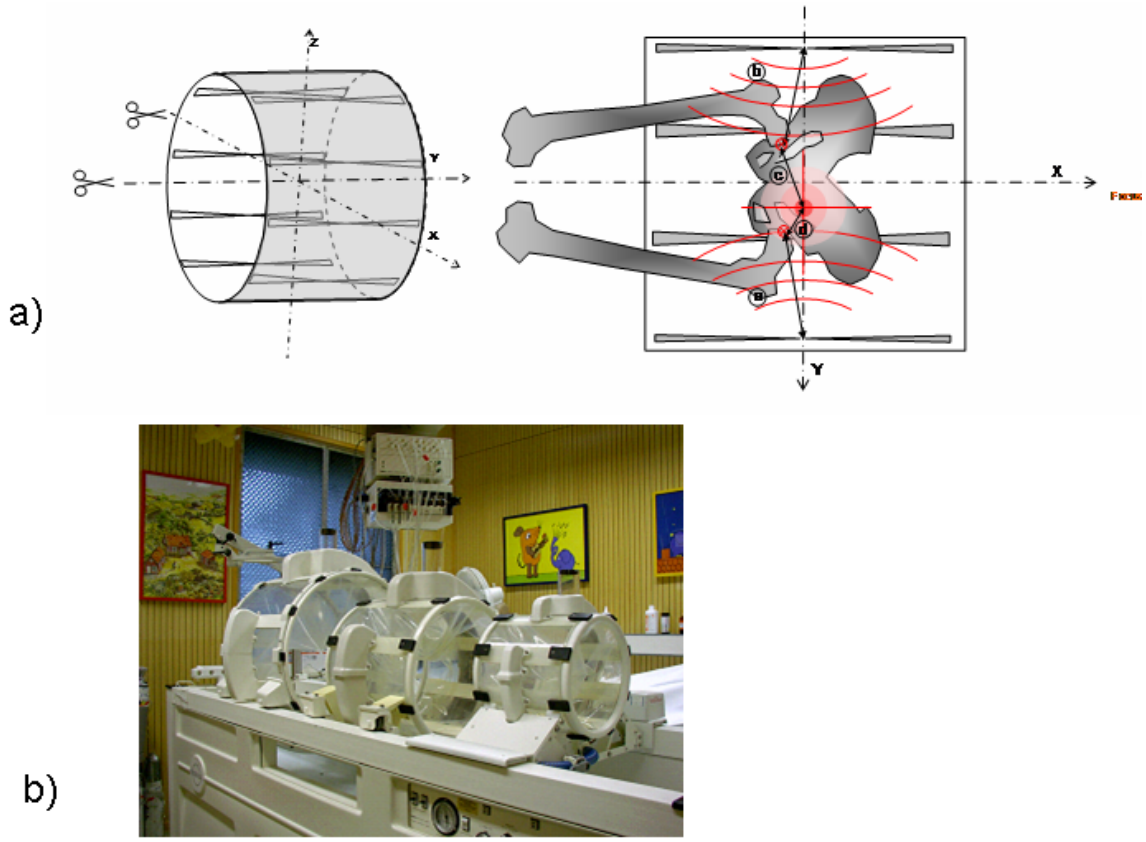

Fig. (1a-b). Clinical setting of a regional deep hyperthermia (RTH) including annular phased array applicators. **a**) During hyperthermic treatment of intrapelvine tumors the femoral heads are hit directly by the radiofrequency applied *via* the eight antennas. **b**) Annular phased array applicators of three different sizes (Sigma-30, -40 and -60 applicator, BSD 2000, Medical, Corporation, Salt Lake City, Utah, USA) for RHT treatment of infants, children and adults.

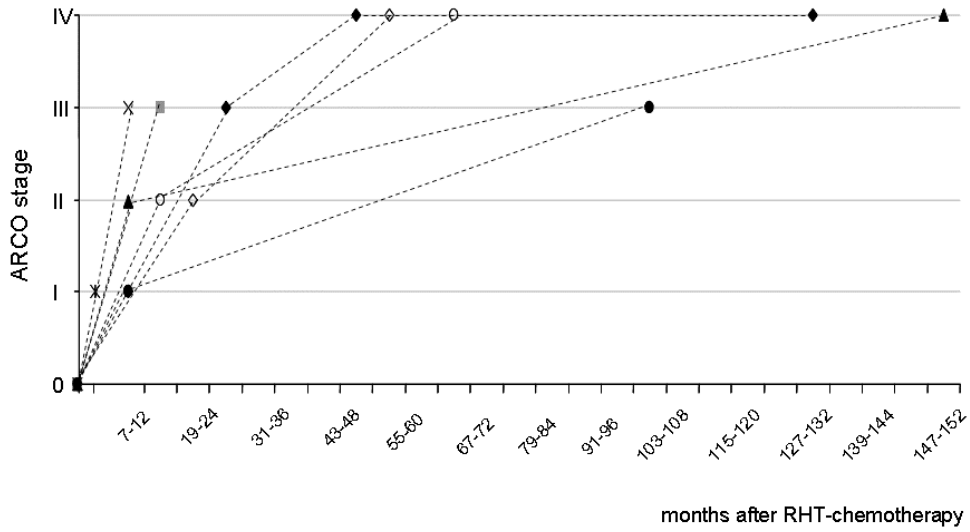

Fig. (2). Development of avascular osteonecrosis after RHT in 8 children with solid tumors in dependency of the AVN stage according to the ARCO classification [42].

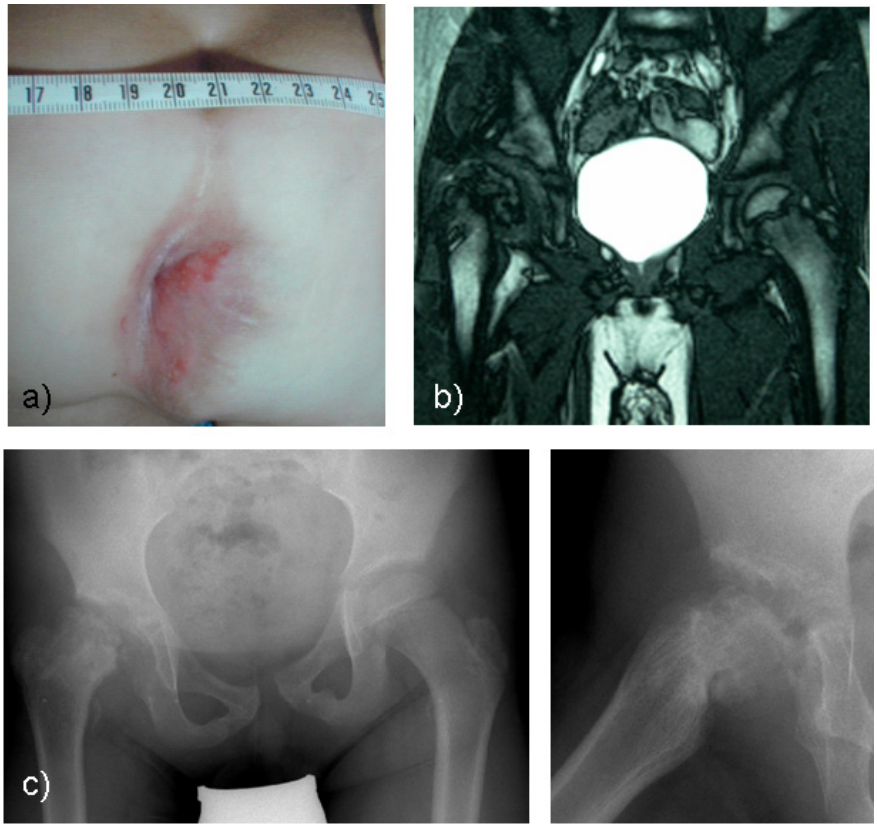

Fig. (3a-c). Presacral sarcoma with an exulceration of the skin (**a**). The MRI scan (**b**) and the X-rays (**c**) of both hip joints and the pelvis shows an osteonecrotic femoral head of the right side. Four years later the patient is free of pain and showed no disabilities except a leg length discrepancy of -1.5 cm at the affected side.

gression eight months after treatment. None of our patients underwent total hip replacement (THR) up to date. Correcting osteotomies were performed in two of the seven patients. In addition, one patient underwent epiphysiodesis of the greater trochanter. It has to be stressed, that 7 of these 8 high risk patients are still alive today with no evidence of further malignant disease.

DISCUSSION

Regional deep hyperthermia (RHT) in combination with cisplatin-based chemotherapy significantly improves the outcome of children with relapsed or irresectable malignant germ cell tumors [11]. A possible side effect of this therapy may be AVN of the femoral head, as the hip joint is directly in line with the radiofre-

quency waves during the RHT treatment. We found AVN in eight out of 37 children treated with RHT and chemotherapy ± radiotherapy for pelvic malignancies in our study. In contrast to the previous study published by our group, none of the 36 adult patients treated with RHT and chemotherapy +/- radiotherapy developed AVN [15]. Furthermore, after a literature review, we found no reports of AVN secondary to RHT in adults. Also no AVN have been reported after RHT of the extremities.

In contrast to the aseptic juvenile AVN of the femoral head (Legg-Calvé-Perthes disease), which is characterized by different stages and self limiting behavior that leads to secondary revascularization, the typical AVN seen in adults shows progressive destruction of the femoral head and frequently results in total joint replacement [26-28]. In our study, we found RHT-associated AVN of the femoral head that showed typical signs of AVN in terms of progression and absence of Perthes stages seen in the adult patients. However, the degree of bone remodelling and reorganization in terms of higher flexibility in growth and revascularization demonstrated on the radiological and clinical findings was not typical of the AVN manifestation seen in adult patients. In addition, functionally, most of our patients were able to return to sports activities at the final follow-up.

It was shown in literature that age have a strong effect on the risk of chemotherapy-associated AVN in addition to the dose effect of applied chemo agents or steroids [29]. This is especially seen after the age of ten years where the rate of AVN is increased significantly [21, 30]. These results are supported by Burger *et al*. in a multi-center study of 1,951 patients below 18 years of age. They showed that the risk of AVN in patients below the age of 10 years was 0.2%, AVN was seen in 8.9% of patients between the age of 10 to 15 years and 16.7% in patients who are older than 15 years [19]. Another study done by Raab *et al*. [29] found no AVN in patients under the age of 10 after poly-chemotherapy out of a total of 121 patients. They reported onset of AVN at an average of 12 months after the induction of chemotherapy during the maintenance dose phase. All the above results supported our findings of an increased risk of progressive AVN in young children status post RHT and chemotherapy +/- radiotherapy. Therefore, we hypothesize a pathogenic factor which may be responsible for the higher vulnerability of the growing femoral head to RHT therapy.

Furthermore, compared with adults with advanced AVN stages, our pediatric AVN patients after RHT presented with only mild or moderate symptoms. Considering the radiological findings and the severity of osteonecrosis in association with joint destruction, only one of the eight patients was recommended for a total hip replacement. Except for this one particular patient, all of the patients in our study group were able to walk without crutches for at least 30 min at one setting. Half of the patients were able to participate in normal school sports activities or even sport clubs despite the severe radiological findings. However, a limitation in our study is the small number of patients (n=8).

The classic presentation of AVN in adults is seen in the subchondral bone that is due to a lack of microcirculation in the small vessels. However, our young patients showed an involvement of AVN in the growth plate and the metaphysial region. In one 6 year old male patient, we found a slipped capital femoral epiphysis corresponding to the biomechanical instability of the growth plate caused by the RHT treatment (Fig. **3**).

The damaging effects of hyperthermia in solid tumors treatment are supported by data from several investigators [31-33]. Bogovic *et al*. [31] found a subtotal to total devitalization of tumor parenchyma of 39% (chemotherapy combined with hyperthermia) and 36% (radiotherapy combined with hyperthermia) with significant signs of disturbances in the microcirculation tree predominantly in the central areas of the tumor compared to the control group. Currently, there are almost no data available in the literature studying the etiology and significance of RHT with chemotherapy +/- radiotherapy mediated AVN in children.

Based on our data, RHT in combination with chemotherapy significantly improves the survival in patients with recurrent malignant germ cell tumors but may contribute to the onset of rapid, progressive, and irreversible AVN. However, it is unclear from our study the contribution of local radiotherapy in the development of AVN in our patient group.

Therefore, we recommend an early MRI-screening and at distinct intervals during the RHT-based chemo- and/or radiotherapy in these young patients with recurrent solid tumors to detect early stages of AVN which may be treated with medications such as iloprost [34-37]. Another joint preserving and potential therapy in the near future may be the local application of autologous bone marrow cells [38-40] and / or growths factors to pediatric patients who develop AVN secondary to RHT treatment for recurrent pelvic tumors [41]. However, further clinical prospective studies are needed to show the contributing effects of RHT versus chemotherapy versus radiotherapy in the development of AVN in this pediatric patient population status post sarcoma treatment.

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