ORIGINAL PAPER/PŮVODNÍ PRÁCE

Avascular Necrosis of the Femoral Head after Hodgkin Lymphoma Treatment: Analysis of Risk Factors and Mid-Term Outcomes after Total Hip Replacement

Avaskulární nekróza hlavice femuru po léčbě Hodgkinova lymfomu: analýza rizikových faktorů a střednědobé výsledky po implantaci totální endoprotézy kyčelního kloubu

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Dedicated to the 70th anniversary of the birth of Prof. Martin Krbec, MD, CSc.

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ABSTRACT

Purpose of the study
Treatment of classical Hodgkin lymphoma (cHL) can be eventually complicated by avascular necrosis of the femoral head (AVN FH). Stages 1 and 2 of AVN FH can be treated conservatively, but stages 3 and 4 are indicated for surgery. In adults, total hip replacement (THR) is the preferred method. The goal of our study was to analyze the risk factors for AVN FH and functional results after THR.

Material and methods
This is a single-center retrospective observational longitudinal study. Patients with AVN FH after previous cHL treatment were included. Basic epidemiological data, time to AVN FH and THR, and complications of hemato-oncological treatment and THRs were recorded. Risk ratios, derived from 2×2 tables and from univariate Cox regression and Kaplan-Meier graphs, were analyzed. Categorical data were evaluated using the Fisher exact test and quantitative data using the Mann-Whitney-Wilcoxon test. Outcomes were measured using the modified Harris Hip Score (MHHS).

Results
The mean incidence of AVN HF was 1.7 per year (95% CI 1.1–2.2). Patients with THRs tended to be older ($p = 0.0424$), the highest risk was ≥ 50 years. Mixed cellularity (MC) cHL had a higher risk of THR (log-rank test $p = 0.0249$) compared to nodular sclerosis (NS) cHL. Clinical stage IIB with massive mediastinal tumor was associated with the lowest risk of THR, $p = 0.0348$. The mean modified Harris Hip Score (MHHS) was higher in NS compared to MC subtype (85.1 (82.7–87.6) vs. only 75.4 (66.6–84.2), $p = 0.0311$).

Periarticular calcification grade 1 was diagnosed in 84.6% of patients (95% CI 54.6–98.1). Revision surgery with cup and stem replantation was performed in one patient. No infections or cases of deep venous thrombosis were recorded.

Conclusions
THR is a causal treatment of symptomatic AVN FH following cHL treatment. Age ≥ 50 years, MC subtype cHL, and AVN FH stages 3 and 4 were associated with a higher risk of THR. The mean MHHS was fully comparable with THRs for other indications. Higher calcification rates had no impact on the clinical outcome.

Key words: avascular necrosis of the femoral head, Hodgkin lymphoma, total hip arthroplasty, modified Harris Hip Score.

INTRODUCTION

Classical Hodgkin lymphoma (cHL) is a B-cell malignant neoplasm with a bimodal age distribution, mostly occurs in young adults in the third and fourth decades (1, 4, 5, 10, 13, 14). At the time of diagnosis, it affects lymph nodes and visceral organs. The pathologic hallmark of cHL is the presence of large malignant multinucleated Reed-Sternberg cells, which are present within a characteristic reactive cellular background. Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a unique pathologic entity that is distinct from cHL and represents only 5% of all HL patients.

Patients are allocated to three different risk groups (early favorable, early unfavorable, and advanced) according to the clinical stage and the presence or absence of adverse clinical features. Treatment of cHL is based on a combination of chemotherapy and radiotherapy (RT). Patients in early stages (favorable and unfavorable) are usually treated with brief chemotherapy and RT. Patients in advanced stages receive aggressive chemotherapy including corticotherapy, and additional RT in selected cases. More than 80% of patients are currently cured using these strategies. Younger patient in the first relapse have a 50% chance to be cured with salvage treatment and autologous stem cell transplantation. Treatment of additional relapses are less successful. Patients over 60 years of age have a significantly worse clinical course.

Morbidity and mortality of cured patients are affected by the late treatment toxicity. The most significant are secondary malignancies and cardiotoxicity; although, there is a spectrum of other disorders such as pulmonary toxicity, soft tissue damage, neuropathy, fertility disorders, immune disorders, secondary diabetes, and post-radiation hypothyroidism. Osteonecrosis, especially avascular necrosis of the femoral head (AVN FH), can be a serious consequence of treatment (2, 6–9, 11, 12). New treatment modalities, such as brentuximab vedotin and/or immune checkpoint inhibitors have already become a part of the first line of treatment to reduce the early and long-term toxicities (10).

Positron emission tomography combined with CT (PET/CT) is a standard imaging method for initial staging, interim and final evaluation of treatment. Similarly, the use of PET combined with magnetic resonance imaging (PET/MRI) is preferred in children and very young patients in order to reduce the radiation exposure.

In the diagnosis of AVN FH, MRI is of decisive importance, the classification of the stages of AVN FH created on the basis of MRI is a therapeutic guide that we used in our study (17).

The exact incidence of AVN FH in cHL patients after treatment is unknown. If the extent of AVN FH is limited, it is possible to manage it conservatively. Treatment of AVN FH grade 3 and 4 involves a total hip replacement (THR) (17, 19). **The aim of our study was** to analyze the risk factors for the AVN HF development, necessity for THR implantation, determination of the AVN HF THR incidence and **evaluation of the functional results of THR** in comparison with THR indicated for osteoarthritis due to other causes.

MATERIAL AND METHODS

This is a retrospective longitudinal study from hemato-oncology and trauma center in one institution.

We analyzed patients with newly diagnosed cHL since December 1997 to August 2017 (19.7 years); THRs were implanted between January 2000 and June 2022 (22.4 years). The mean time from the end of primary hemato-oncological therapy to the first THR was 53.8 months (95% CI 30.9–76.7), the mean time from the end of therapy to the second THR in patients with bilateral THRs was 47.0 months (95% CI 12.1–81.9), the mean interval between the first and second THR was 18.0 months (95% CI 0.2–35.8). Bilateral THRs were necessary in four patients out of 19 patients. THR was indicated for grades 3 and 4 according to the ARCO classification (i.e., an evaluation of a combination of X-ray and MRI findings) (17, 19). The mean follow-up time after THR was 10.3 years (95% CI 7.2–13.5). Sixteen patients had an MRI finding of AVN FH without head destruction (i.e., 1st or 2nd degree according to the ARCO classification).

The monitored group of AVN FH consisted of 35 patients (31 men and 4 women). There were 19 patients (17 men and 2 women) in the AVN FH with THR group and 16 patients (14 men and 2 women) in the AVN FH without THR group. The study monitored basic epidemiological data, as well as the type of therapy, including the cumulative dose of corticosteroids and the cumulative dose of radiotherapy, the clinical stage of the disease, and the type and number of chemotherapy cycles. Complications recorded from hemato-oncological therapy included the incidence of polyneuropathies, secondary diabetes after chemotherapy and corticotherapy, cardiovascular complications, pulmonary complications, post-treatment chronic renal failure, post-radiation hypothyroidism, and the

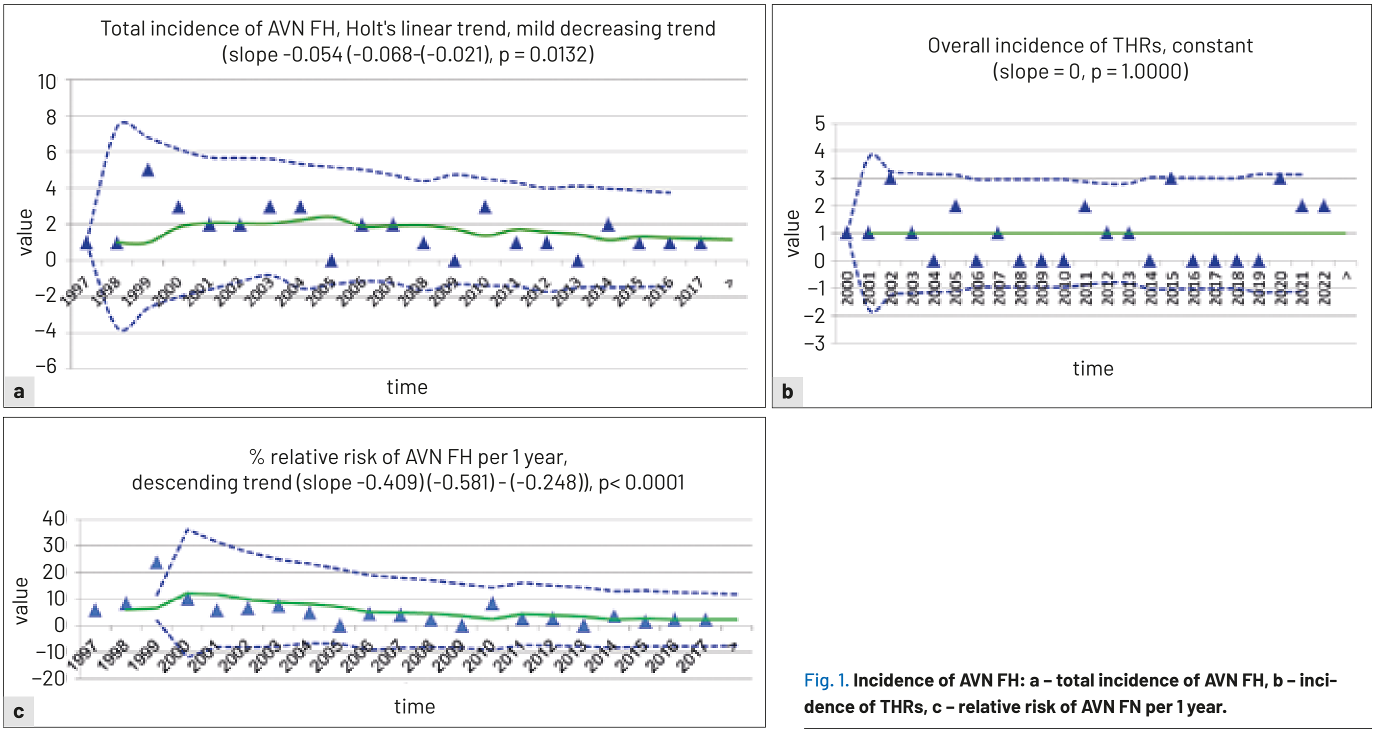

Fig. 1. **Incidence of AVN FH: a – total incidence of AVN FH, b – incidence of THRs, c – relative risk of AVN FN per 1 year.**

occurrence of secondary malignancies. In relapsed cases, the type of salvage therapy was analyzed.

Patients were treated with a combination of chemotherapy and radiotherapy according to the German Hodgkin's Study Group (GHSG) schemes (18). BEACOPP chemotherapy (bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin-vincristine, procarbazine, and prednisone) was used in escalated and reduced doses per protocol recommendations.

After THR implantation, the incidence of early postoperative complications (e.g., wound hematoma, infectious complications), the incidence of thromboembolic complications and the time to revision surgery (regardless of the type of revision) were analyzed. Using follow-up X-rays after THR implantation, the extent of bone-implant separation was evaluated according to individual zones on anteroposterior images of the hip joint and the occurrence of para-articular calcifications (according to Brooker's classification) was also monitored. Functional THR results were determined using the modified Harris Hip Score (MHHS) (16). The score has a maximum of 91 points when used without correction, the uncorrected value was used for paired comparisons with the tested factors. In other to compare the categorical results with other studies where classic HHS was analyzed, we used a corrected value, which is obtained by multiplying the score by 100/91 (0.91).

Potential risk factors were evaluated both in 2×2 tables and by Kaplan-Meier graph with a log-rank test. For multiple data groups, we used the Yates correction and the Bonferroni correction for post hoc comparisons in subgroups with fewer data points. The results were verified using a univariate Cox regression. Logistic regression analysis was used to determine the probability of THR implantation relative to patient age; the 95% CIs used for the regression curves were determined using the Wilson modification. The 95% CI intervals for binomial data were determined using the Clopper-Pearson exact method. Fisher's exact test was used for evaluation of categorical data and the Shapiro-Wilk test for assessment of the normality of quantitative data. This was followed by the Student's t-test for data with a Gaussian distribution, and the Mann-Whitney-Wilcoxon exact test was used for non-Gaussian distributions. We considered test results with a $p < 0.05$ to be statistically significant.

RESULTS

The incidence of AVN FH in patients after cHL treatment was 1.7/year (95% CI 1.1–2.2 per year), which corresponds to an annual incidence of 2.77 (95% CI 2.44–3.11) per 100,000 inhabitants in the monitored period.

Holt's linear trend showed a slight decrease in incidence in the given period (slope = –0.054 (95% CI (–0.068) – (–0.021), p = **0.0132**). The incidence of THR after cHL treatment was constant at 1/year (slope 0, p = 1.0000). The percentage of relative risk of developing AVN FH decreased over the analyzed period (slope –0.409 (95% CI –0.581) – (–0.248), **p < 0.0001**, Fig. 1).

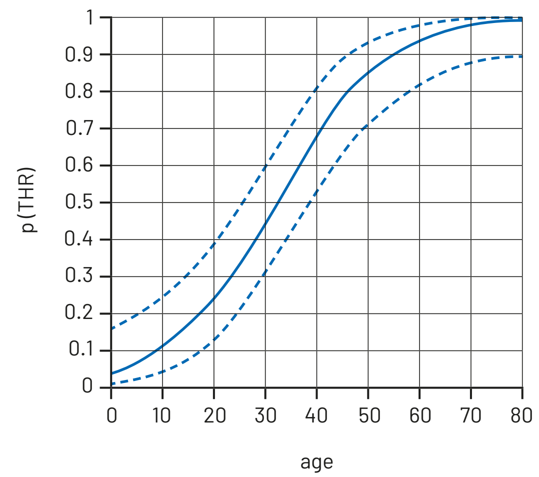

Fig. 2. **Logistic regression curve of dependence p(THR) on age (p = 0.0493).**

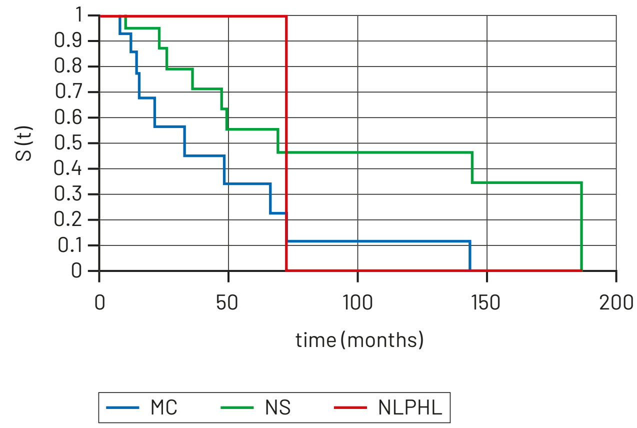

Fig. 3. **Time to AVN FH – comparison of histological types (multiple log-rank test, p = 0.0424).**

Men significantly predominated in both groups (for THR p = 0.0006, for patients without THR p = 0.0027, one sample proportion test). However, there was no difference in the ratio of men and women in both groups (p = 1.0000).

The mean age of the 19 patients in the AVN FH in the THR group was significantly higher **(p = 0.0424.)** when compared to 16 patients with AVN FH in the group without THR (39.5 years (95% CI 34.9–44.0 vs. 33.3 years (95% CI 30.0–36.5), respectively). When analyzing age by category, the highest risk was for those ≥ 50. We used the univariate Cox regression analysis to verify the significance of the lower risk for patients < 50 vs. ≥ 50 years (0.174 (95% CI 0.036–0.846), **p = 0.0302**). Due to the lack of data for a valid quantitative analysis in the Cox regression analysis, we used logistic regression to determine the probability of an implantation relative to age. The age for a 50% probability of a THR was 32.2 years (95% CI 25.9–38.5), **p = 0.0493** (Fig. 2).

The group of patients with THR included following histopathological subtypes: mixed cellularity subtype (MC) 10, nodular sclerosing (NS) 9. The group without THR implantation included: MC 4, NS 11, and NLPHL 1 (p = 0.1662). Histopathological subtype and initial clinical stage appeared as additional important factors related to THR implantation: histological type **p = 0.0142**, the risk ratio 3.222 (1.264–8.213), clinical stage **p = 0.0123**, the risk ratio 10.435 (1.665–65.400). Pairwise post hoc comparisons revealed, that histological subtype MC had

Table 1. Relative risk of THR according to treatment type

TYPE OF TREATMENT	RELATIVE RISK %	95% CI LOWER	95% CI UPPER
4xbBEA	66.7	9.4	99.2
eBEA + bBEA	50.0	15.7	84.3
eBEA	50.0	27.2	72.8
8xbBEA+RT	100.0	2.5	100.0
8xeBEA+RT	50.0	1.3	98.7
8x escalated BEACOPP (eBEA)+RT	100.0	2.5	100.0

TYPE OF TREATMENT 1	TYPE OF TREATMENT 2	RISK RATIO	95% CI LOWER	95% CI UPPER	P
eBEA	8xbBEA+RT	0.500	0.323	0.775	0.0019
eBEA	8x escalated BEACOPP (eBEA)+RT	0.500	0.323	0.775	0.0019
eBEA + bBEA	8xbBEA+RT	0.500	0.250	1.000	0.0499
eBEA + bBEA	8x escalated BEACOPP (eBEA)+RT	0.500	0.250	1.000	0.0499

Table 2. **Other complications of cHL treatment**

	PRESENT	ABSENT	% RISK	95% CI		FISHER 2×2	RISK RATIO	95% CI		P
Polyneuropathy	9	26	25.7	12.5	43.3	0.0498	0.241	0.058	0.999	0.0499
Hypothyreosis	3	32	8.6	1.8	23.1	0.5820	0.421	0.042	4.227	0.4623
Secondary diabetes	3	32	8.6	1.8	23.1	0.1874	4.211	0.547	32.429	0.1675
Cardiovascular	6	29	17.1	6.6	33.6	0.5820	0.421	0.042	4.227	0.4623
Lungs (COPD)	2	33	5.7	0.7	19.2	0.4891	NS	NS	NS	NS
Secondary malignancy	4	31	11.4	3.2	26.7	1.0000	0.8421	0.13	5.32	0.8550
Renal dysfunction	1	34	2.9	0.1	14.9	1.0000	NS	NS	NS	NS
Complication (per patient)	19.0	16	54.3	36.6	71.2	0.5001	0.758	0.413	1.391	0.3709
More than one complication	6.0	29	17.1	6.6	33.6	0.6550	0.692	0.178	2.687	0.5951

a significantly higher risk of THR compared to NS (**p = 0.0249**) (Fig. 3).

Comparisons involving the initial cHL stage diagnose the significantly lower risk of THR implantation in stage IIB with MMT, where there was no THR in 4 patients (Fisher test 2x2, **p = 0.0348**).

The overall comparison of chemotherapy schemes related to THR implantation revealed the lower risk of THR in groups with eBEA inclusion, there were 4 significant pairwise comparisons (Table 1).

Corticotherapy and radiotherapy increased the risk of THR, but due to the relatively small numbers of cases we were unable to demonstrate the significance. The highest risk ratio for THR implantation was seen in the combination of radiotherapy and corticotherapy 3.368 (0.417–27.179), p = 0.2543. Quantitative analyses for the cumulative dose of prednisone and for the cumulative dose of radiotherapy were not significant (p = 0.0952 and p = 0.2619, respectively).

MHHS measuring functional outcomes were excellent (9), good (5), fair (0), and poor (2). The impact of individual risk factors on the average MHHS was analyzed: significantly higher scores were found in type NS, unilateral THRs, and combined corticotherapy and radiotherapy. The average score for NS was 85.1 points (82.7–87.6) and for MC 75.4 points (66.6–84.2), **p = 0.0311**. The average MHHS was 83.2 points (79.1–87.2) for unilateral THRs and 71.0 (57.3–84.7) for bilateral THRs, **p = 0.0143**. MHHS in corticotherapy + radiotherapy group was 91.0 points (one patient) and in the group without corticotherapy and without radiotherapy 81.4 points (76.7–86.2), **p = 0.0005**. Neither age nor gender of patients had a significant impact on MHHS outcomes. Radiotherapy alone or corticotherapy alone did not affect significantly the mean results of MHHS, nor did the initial stage of cHL at diagnosis.

Polyneuropathy was the most frequent complications of initial hemato-oncological treatment (9 patients; 25.7% (95% CI 12.5–43.3%)), especially in NS subtype. Polyneuropathy was significantly less common in patients after THR implantation (risk ratio 0.24 (0.06–1.00); **p = 0.0499**) (Table 2). Other complications included: hypothyroidism (3 cases, 8.6%), steroid diabetes (3 patients, 8.6%), post-radiation pneumonitis (2 patients, 5.7%), cardiovascular complications (6 cases, 17.1%), renal insufficiency (1 patient, 2.9%). Secondary malignancies were diagnosed in 3 cases (8.6%): renal cell carcinoma (1 patient), colorectal cancer (1 patient) and peripheral T-cell lymphoma (1patient). One patient suffered from the relapse of cHL.

The overall incidence of complications was 19 cases (54.3%), with more than one complication detected in 6 cases (17.1%). In a sub-analysis of these complications, there were significantly more women with secondary hypothyroidism (risk ratio 15.5 (1.78–134.79); **p = 0.0130**). Cardiovascular complications only occurred in the MC histopathological type (**p = 0.0022**). There was a significantly lower risk of secondary diabetes in patients that did not undergo radiotherapy (**p = 0.0336**).

Complete radiodiagnostic documentation was available in 13 patients. Calcifications grade 1 (according to Brooker) were detected in 11 patients (84.6%, 95% CI 54.6–98.1). Radiolucency in the acetabular component was diagnosed in one patient (7.7%); radiolucency in the femoral component, radiolucency was more common – four patients (30.8%) (Table 3). Migration of implants requiring revision surgery and

Table 3. **Radiologic results**

RADIOLOGIC RESULTS	PRESENT	ABSENT	% RISK	95% CI	
Calcifications (grade 1)	11	2	84.6	54.6	98.1
Acetabular loosening	1	12	7.7	0.2	36.0
Femoral radiolucency	4	9	30.8	9.1	61.4
Data availability	13	10	56.5	34.5	76.8

replacement of both acetabular and femoral components was performed in one patient. The interval from primary implantation to revision surgery for implant migration was 15.8 years (the primary surgery used a cementless cup and the revision uncemented femoral stem). After the revision surgery, the patient was free of signs of implant detachment. Small number of revision surgeries did not allow to assess the risk factors contributing to revision surgeries and significant factors for development of periarticular calcifications identified. THR implantation was not accompanied by any infectious complication or septic loosening of THR in our cohort, and no deep vein thrombosis occurred in patients after THR (0.0% (0.0–17.6%)). There were three deaths (8.6% (1.8–23.1%)) in the cohort during the monitored period, none of them were causally related to THR implantation. In our cohort, we did not record any primary or secondary osteonecrosis in the acetabular area. One patient had a femoral bone infarction (avascular necrosis); however, it occurred outside of the femoral head area.

DISCUSSION

The etiology of the development of AVN FH is multifactorial in cHL, and the exact pathogenesis has not yet been identified (2). Toxic agents (e.g., ethanol and high-dose corticotherapy) are likely involved in AVN FH. The hypothesis suggests that mesenchymal cells transform into adipocytes instead of osteoblasts and osteocytes. This is followed by gradual hypertrophy of adipocyte vacuoles and an increase in intra-compartmental pressure within the femoral head and neck. The pressure increases leads to the venous flow restriction, then capillary flow restriction that causes persistent arterial flow restriction to the femoral head and neck. The above-mentioned process leads to the development of intra-osseous compartment syndrome and osteonecrosis (3). In addition to an increase of intra-compartmental pressure, microthrombosis can occur in the arteries of the femoral neck and head, and the risk of microthrombosis is increased under thrombophilic conditions. The extent and reversibility of osteonecrotic changes are related to sufficient fibrinolytic and angiogenic activity. In case of insufficient fibrinolysis and angiogenesis irreversible changes lead to subchondral necrosis of the head, followed by subchondral fracture, collapse of the head and development of secondary coxarthrosis (3, 7, 8).

The initial stage is characterized by an increased signal in the T1-weighted image in the area of the femoral proximal metaphysis on MRI. This is caused by an increased volume of fatty bone marrow, intraosseous hypertension, flow restriction in the venous sinusoids, and microthrombi in the affected capillary beds (3, 13). Annual MRI follow-up for at least 5 years after hemato-oncological therapy is recommended to detect early, clinically asymptomatic stages.

Advanced necrosis is characterized by a peripheral sequestration and subchondral fractures (visible on X-rays as a crescent sign (3). Once bone sequestration occurs, necrotic changes are irreversible. Subsequently, necrotic bone induces an immune response, which is caused, to some degree, by collagen I matrix proteins (i.e., osteocalcin and proteoglycans) and byproducts of dead bone marrow cells. Immune response causes encapsulation of the necrotic bone by a fibrous membrane (histologically defined as a reactive zone). Sequestration and encapsulation correlate with MRI band of low-signal intensity (3, 13).

MRI with its high sensitivity and specificity is a good tool for diagnostics of AVN FH in early stages. MRI should be always preferred in patients after cHL treatment as it is a radiation-free imaging method to detect the AVN FH (5, 13, 15).

There are several systems for classifying the stage and extent of AVN FH, but the most commonly used is the ARCO classification system, which is a combination of MRI findings and X-ray or CT images in stage 2 (17, 19).

According to ARCO classification, the collapse of the head is not evident on X-rays; on MRIs, the extent of the necrotic band should not extend (in the normal position of the hip joint) over the center of the head in stage 1 or over the lateral edge of the acetabulum in coronal bone remodeling in stage 2. Stage 3 is usually evident on X-rays as a subchondral fracture (crescent sign), and stage 4 is characterized by the collapse of the femoral head. MRI presents the collapse in the coronal plane above 30% of the height of the head, or depression of the articular surface above 4 mm (17). The new 2021 ARCO classification reduces the number of stages to 3, with 1 and 2 remaining the same; however, in stage 3, the extent of necrosis on MRI is such that it extends over the lateral margin of the acetabulum in the coronal plane (19). We used the classical ARCO classification in our analysis. THR was indicated in stages 3 and 4. Stages 1 and 2 were treated conservatively with long-term use of crutches. Experimental Zoledronic acid therapy (9), hyperbaric oxygen therapy, extracorporeal shock wave therapy, and electrostimulation methods were not used.

Newman et al. looked at the results of THR in hemato-oncological patients and found a higher proportion of both postoperative complications and other complications, and the patients had longer hospital stays than THRs from other indications (11). However, they included all hemato-oncology patients with a minority of cHL (4%), therefore only an indirect comparison with our study is possible (11).

Renedo et al. observed a group of 315 patients with cHL, of whom 18 (5.71%) had AVN FH (11). The average time to AVN FH development was 40 months and it is slightly shorter than in our study. THR occurred in 8 patients (three in stage 3 and five in stage 4), which is consistent with our study. The authors showed an increased risk associated with corticotherapy (12). Our patients received high-dose corticotherapy and had a higher relative risk of developing grade 3 and 4 AVN FH, but

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due to the smaller number of patients receiving corticotherapy, the risk ratio did not reach the statistical significance. The risk associated with corticotherapy was increased by concomitant radiotherapy (risk ratio 3.368 (0.417–27.179), p = 0.2543).

Salem et al. investigated the incidence of AVN FH in pediatric hemato-oncology patients. They found highly significant differences for cumulative doses of prednisone compared to patients without osteonecrosis (5,967 mg (4,425–9,599) vs. 3,943 mg (0–18,585); p = 0.005) (15).

Several mechanisms are involved in the development of AVN FH during corticotherapy: insufficient vascular supply and alteration of microcirculation, impact of inflammatory processes (change in the ratio of M1 and M2 macrophages), altered lipid metabolism and an imbalance between osteogenesis and lipogenesis in the bone marrow (7,8). Although the most of processes are mediated through nuclear receptors (GRs) that activate nuclear factor kappa B (NFκB), other interactions between nuclear comodulators and transcription factors can also play a role. High doses of corticosteroids may induce venoconstriction, endothelial dysfunction and increased intraosseous pressure and microthrombosis in the femoral head region. These changes are assumed to suppress the vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1α (HIF1α) gene expression in osteocytes and osteoblasts. Local hyperlipidemia induced by corticosteroids may contribute to fat microembolism, fat transformation of the bone marrow and increased intraosseous pressure. Activation of peroxisome proliferator-activated receptor gamma (PPARγ) and *adipose-specific gene 422* (*aP2*) is probably involved in the transformation of mesenchymal cells into adipocytes. Some studies reported, that corticosteroid-induced osteonecrosis was stopped by the administration of statins, which contributed to the inhibition of PPARγ and HIF1α (7). Only few studies have demonstrated the clear beneficial effects of statins on the development of AVN FH during corticotherapy (7).

Our study demonstrated a significantly higher risk of AVN FH associated with MC subtype. This histological subtype was also associated with worse functional MHHS outcomes. Significantly higher risk of cardiovascular complications was linked to hemato-oncological treatment. NS subtype tended to be more associated with polyneuropathy. We did not find any previously reported data that addressed the proportion of AVN FH to be associated with a specific subtype of cHL. Makita et al. reported an increased risk of cardiovascular complications of treatment in advanced stages of cHL (10).

Medium-term MHHS clinical outcomes in our study were comparable to studies that investigated this issue in patients with primary coxarthrosis (the most common indication for THR) (12, 15). We added the corrected average values (obtained by multiplying the uncorrected values by a coefficient of 100/91) in order to compare with classical HHS (16). The corrected MHHS was 88.9 points for the whole set (95% CI 83.8–93.9). These data are consistent with the recent meta-analysis of HHS in AVN FH vs. osteoarthritis without AVN FH performed by Salman et al. They found no differences in the mean HHS (standardized mean difference HHS −0.05 points (95% CI −0.36 – 0.25)) in their quantitative meta-analysis (15).

Radiological results revealed a higher proportion of periarticular calcifications grade 1, that had no significant impact on MHHS results. Based on our data, we could not define a clear cause of the higher risk of calcifications in cHL patients.

Our study has some limitations: retrospective data analysis, the absence of a control group of cHL patients without osteonecrosis, and a relatively small number of patients with complete image documentation. Advantages of our study: (1) long-term follow-up (average follow-up is 10.3 years), (2) the evaluation of THR complications and complications of primary hemato-oncological therapy, (3) the evaluation of functional outcomes, and (4) the determination of the incidence of AVN FH in cHL.

CONCLUSIONS

The overall incidence of AVN FH was 1.7/year. Following risk factors for the development of grade 3 and 4 AVN FH with THR implantation were defined: age ≥ 50 years, MC subtype, therapy BEACOPP + RT. Lower risk is for initial stage IIB with MMT.

Mean functional outcomes according to MHHS were significantly lower in MC subtype and in bilateral THR implants. Although the incidence of periarticular calcifications was higher than in THR for other indications, the calcifications did not affect functional outcomes. The proportion of revision surgeries was comparable to THR for other indications. Based on the results of the study we conclude that THR in patients with stage 3 and 4 AVN FH after cHL treatment is a recommended method with good medium-term functional outcomes.

Polyneuropathy was the most common complication of primary hemato-oncological therapy, especially in NS subtype. Cardiovascular complications were more commonly associated with MC subtype.

Treatment of AVN FH requires a multidisciplinary cooperation. PET-adapted approach enabled reduction of treatment intensity. New treatment strategies combine brentuximab vedotin or checkpoint inhibitors with AVD chemotherapy in the first line treatment. These new treatment strategies maintain high treatment efficacy and reduce early and possibly late complications of therapy. The reduction of AVN FH risk with new treatment combinations need to be verified in a long-term follow-up. ■

Abbreviations
ARCO classification – Association Research Circulation Osseous classification
AVD – combination chemotherapy Adriamycin® (doxorubicin), vinblastine, dacarbazine
AVN FH – avascular necrosis of the femoral head
BEACOPP – combination chemotherapy bleomycin, etoposide, Adriamycin® (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone
cHL – classic Hodgkin lymphoma
HIF1α – hypoxia-inducible factor 1α
MC – mixed cellularity subtype
MMT – massive mediastinal tumor
NLPHL – nodular lymphocyte predominant Hodgkin lymphoma, slow-growing CD20 positive form of Hodgkin lymphoma
NS – nodular sclerosis, nodular sclerosing cHL
PPARg – peroxisome proliferator-activated receptor γ
RT – radiotherapy

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