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ORIGINAL PAPER

Treatment of osteonecrosis of the femoral head in lymphoma patients by free vascularised fibular grafting

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Abstract The purpose of this study was to assess the outcomes of treatment of femoral head osteonecrosis using free vascularised fibular grafting in patients with Hodgkin's disease and non-Hodgkin's lymphoma. We retrospectively reviewed seven patients (14 hips) with lymphoma who underwent free vascularised fibular grafting for osteonecrosis of the femoral head, evaluating pre- and postoperative Harris hip scores, visual analog scale (VAS) pain scores, hip range of motion and radiographs. Patients were followed up for a minimum of 1.5 years (mean, 3.3 years). All these patients exhibited good recovery without severe life-threatening complications. The mean Harris hip score improved from 69 to 88, while average VAS pain score decreased from 54 to 18. At the latest follow-up, we found improvement or unchanged radiographs in all three hips with initial Steinberg stage II osteonecrosis and in nine of 11 hips with stage III or IV osteonecrosis. No hips failed treatment and underwent total hip arthroplasty. The clinical data demonstrated that free vascularised fibular grafting can slow or even halt progression of necrosis, and improve the function of the hip and quality of life in lymphoma patients.

Introduction

Osteonecrosis of femoral head (ONFH) is a severe complication of therapy for Hodgkin's disease and non-Hodgkin's lymphoma. The incidence of osteonecrosis in lymphoma patients has been reported to be about 1–11.3% [1–3]. Within many of these patients, surgical intervention is required for pain relief and better hip joint function. Surgical options include joint preserving procedures such as core decompression, osteotomy, vascularised or non-vascularised fibular grafting; and joint replacement procedures such as resurfacing and hemi- or total hip arthroplasty (THA) [4–6].

Free vascularised fibular grafting (FVFG) has been successfully used as a joint preserving procedure for treatment of ONFH, and many reports demonstrate satisfying mid- and long-term outcome on general patients [7–9]. However, reports of FVFG for treatment of ONFH in lymphoma patients are rare. Surgical benefit and safety remain to be systematically assessed.

Materials and methods

We retrospectively reviewed seven patients (14 hips) with lymphoma (two cases of Hodgkin's disease and five cases of non-Hodgkin's lymphoma) who underwent FVFG for femoral head osteonecrosis in our hospital between February 2005 and June 2008. The patients included four men and three women with a average age 34 at the time of surgery (range, 16–48 years). All of the patients were ethnic Chinese. The mean follow-up was 3.3 years (range, 1.5–4.2 years). No patients were lost to follow-up. Of these patients, primary lymph node biopsy and other examinations such as immunophenotyping, molecular genetic and cytogenetic analysis, chest/abdominal/pelvic computed tomography and lumbar puncture were selected to identify the diagnosis and staging of lymphoma. Chemotherapy including cortico-

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steroids combined in some cases with radiotherapy were administered for the treatment of lymphoma in each patient. The following data were recorded in those who developed ONFH: the demographic characteristics, the clinical features of lymphoma (histology and staging according to Ann-Arbor classification [10]), the chemotherapy regimen employed and the information regarding corticosteroid administration (total cumulative dose, mean daily dose, total cumulative time). An equivalent dose of prednisolone was calculated for any other preparation of corticosteroid used in the chemotherapy regimen. Osteonecrosis of the femoral head was identified by at least one of the following imaging techniques: anteroposterior hip radiography, magnetic resonance (MR) imaging and/or computed tomography. All seven patients were initially diagnosed with bilateral osteonecrosis.

Before surgery, the patients' preoperative condition was assessed by a series of examinations including complete blood cell count, erythrocyte sedimentation rate, C-reactive protein level, blood urea nitrogen, serum creatinine and electrolytes. Preoperative radiographs of the patients were also examined to determine the location and size of the necrosis including the presence or absence of collapse. For the evaluation of radiographic change, we used the Steinberg classification [11], in which hips with osteonecrosis were placed into one of six stages from I to VI. Stage I hips were radiographically normal but clinically symptomatic. Stage II hips manifested subchondral sclerosis and cysts radiographically. Stage III hips had collapse of subchondral bone, which produced a crescent sign. In stage IV, there was definite flattening of articular surface radiographically. Stage V and VI hips showed joint space narrowing with acetabular involvement secondary to articular collapse and deformation of the femoral head. Indications for the surgery included stage II, III, IV and occasionally stage V osteonecrosis and pain at the time of evaluation. According to the Steinberg classification, three hips were in stage II (22%), nine hips were in stage III (64%), two hips were in stage IV (14%) and no hips were in stage V. The operative technique performed in these patients has been previously described by the senior author [8]. Of those with bilateral osteonecrosis, only one patient underwent unilateral FVFG twice in 13 months, whereas the others underwent direct bilateral procedures. During the surgery a histological examination of subchondral bone was performed from a core biopsy to confirm the diagnosis of osteonecrosis.

Patients were followed-up every three months for the first year, every six months for the second year, and yearly thereafter. Before surgery and on each follow-up visit patients were evaluated clinically by use of the Harris hip score (HHS) [12], visual analog scale (VAS) pain score, [13] and by radiographs (anteroposterior pelvis and frog leg lateral view). Postoperative complications were noted and patients who required subsequent THA were recorded. A clinical success was defined as a HHS≥ 80 points. A clinical failure was defined as a HHS less than 70 points or conversion to THA.

Radiographic evaluation was performed by two individuals who were blind to the functional outcome. Final radiographs (anteroposterior pelvis and frog leg lateral view) were categorised in one of three classes:

Improved	Those cases in which the osteonecrosis had healed or was being replaced with new bone formation. For the stage II lesion, the crescent had disappeared or the density of cystic lesion had increased with trabecular formation of the tip of the vascularised fibula. For the stage III lesion, the collapsed lesion healed or became more rounded with trabecular formation of the tip of the vascularised fibula.
No change	Compared with the preoperative status.
Progressed	Those cases with progression based on stage or those with more than 3 mm of collapse.

Paired *t* tests were used for statistical analysis of the relationship between preoperative and the latest HHS and VAS pain scores. All analyses were performed using SAS software (version 8.2, SAS Institute, Cary, NC).

Approvals from ethics committees were obtained and the study was conducted in accordance with the Declaration of Helsinki. Prior to study participation each patient gave written informed consent.

Results

The results of surgery were evaluated by the change in HHS and VAS pain score to that at the last follow-up visit, the radiographic progression, and the need for subsequent conversion to THA. The safety of the procedure was determined by the incidence of postoperative major and minor complications [4, 14].

Fortunately, no patients were lost to follow-up or died during the period of follow-up. The demographic characteristics, the clinical features of lymphoma, and the information regarding corticosteroid adiministration of these patients are summarised in Tables 1 and 2. The mean postoperative hospital stay time was 7.8 days (range, 5–12 days). No patients exhibited serious acute complication during the early postoperative course. Mean perioperative blood loss was 450 ml (range, 250–700 ml), and no patients required blood transfusion. Clawing of the big toe developed in one case, the patient was treated

Table 1 Demographic data of patients with lymphoma with osteonecrosis of femoral head (n=7)

Demographic	Value
Female:male	3:4
Duration of lymphoma disease (months)	70.4 (range, 42–86)
Duration of ON disease (months)	34.6 (range, 20–54)
Duration of chemotherapy containing corticosteroid (days)	177 (range, 126–378)
Total cumulative prednisolone dose (g)	7.4 (range, 5.0–10.1)
Mean daily dose of prednisolone (mg)	46.6 (range, 26.6–76.7)
Age at the time of FVFG	34.4 (range, 16–48)

ON osteonecrosis, *FVFG* free vascularised fibular grafting

nonoperatively including physiotherapy and recovered gradually. Partial lateral femoral cutaneous nerve palsy occurred in one patient; her symptom resolved within six months. Pulmonary embolus, deep vein thrombosis, subtrochanteric fracture or superficial infection were not observed.

Harris hip scores and VAS pain scores

Clinical improvements of the average HHS and VAS pain score in different Steinberg stages of osteonecrosis at a mean follow-up of 3.3 years is shown in Table 3. The mean preoperative HHS was 83 points (range, 65–93 points) for cases with stage II disease, 68 points (range, 36–93 points) for cases with stage III disease and 61 points (range, 58–64 points) for cases with stage IV disease, respectively. According to the outcome of the most recent follow-up, the mean HHS hip scores improved for the three groups previously mentioned: to 92 points (range, 81–100 points) for cases with stage II disease, to 86 points (range, 72–97 points) for cases with stage III disease and to 78 points (range, 72–84 points) for cases with stage IV disease. The overall preoperative average HHS hip score of these cases improved from 69 (range, 36–93) to 88 (range, 72–100) at the latest follow-up ($p<$ 0.0001). Postoperatively, HHS over 80 points was observed in 12 of all 14 hips (86%).

VAS pain scores were also separately recorded to evaluate an improvement in or absence of pain before surgery and on each follow-up visit. Preoperative VAS pain scores of these patients decreased from 54 points (range, 40–70 points) to 18 points (range, 0–30 points) at latest follow-up visit ($p<0.0001$).

Radiographic assessment

Of 14 hips, radiographically three hips (21.4%) improved, nine hips (64.3%) were unchanged, and just two hips (14.3%) progressed. According to Steinberg staging, three hips of staging II (100%), eight hips of staging III (88.9%) and one hip of staging IV (50%) showed improvement or were unchanged (representative Fig. 1). Only one hip of stage III (11.1%) and one hip of stage IV (50%) appeared worse.

No hips were treated by THA during the follow-up period.

Discussion

The possibility of curing patients from Hodgkin's disease and non-Hodgkin's lymphoma have improved dramatically over recent decades. With higher survival rates for lymphoma patients, the long-term complications of treatment such as ONFH become recognised [1–3]. Prolonged high-dose corticosteroid administration in some chemotherapy regimens is considered to be the most important reason for osteonecrosis in lymphoma patients [1, 3]. The mechanism of steroid-induced osteonecrosis of the femoral head includes thrombus due to the hypercoagulable state, fat embolism, increase in intraosseous pressure, and degenerative changes in the hip capsule [15]. Additionally,

Table 2 Patients' clinical features of lymphoma disease (n=7)

Patients	n
Histology of lymphoma	
Hodgkin's disease	
Nodular sclerosis (CHL)	2
Non-Hodgkin's lymphoma	
Diffuse large B-cell lymphoma	2
Mantle cell lymphoma	1
Anaplastic large cell lymphoma	1
Plasma cell myeloma	1
Stage of lymphoma according to Ann-Arbor classification	
I	2
II	3
III	2
IV	0

CHL classical Hodgkin lymphoma

Table 3 Clinical improvements of the average HHS and VAS pain score in different Steinberg stages of osteonecrosis (average 3.3-years follow-up)

Steinberg stages	Number (hips)	HHS preoperative	HHS postoperative	VAS pain score preoperative	VAS pain score postoperative	Clinical success rate (%)
II	3	83	92	48	8	100
III	9	68	86	55	19	89
IV	2	61	78	60	25	50

HHS Harris hip score, *VAS* visual analog scale

subdiaphragmatic radiotherapy, especially pelvic radiotherapy, was reported as a causative factor associated with ONFH [16].

Management of osteonecrosis of the femoral head is difficult, especially in lymphoma patients. Both patients and physicians are concerned about progression of lymphoma disease and response to chemotherapy and radiotherapy regimens. They may pay little attention to the hip joint, although there are early sighs of osteonecrosis. In many patients, severe joint pain and irreversible collapse of the femoral head have already developed when the diagnosis of osteonecrosis is established. Furthermore, steroid-induced osteonecrosis of the femoral head after prolonged corticosteroid containing chemotherapy tends to demonstrate larger necrotic areas, and bilateral involvement is more common than unilateral involvement [17].

Treatment of osteonecrosis of the femoral head depends on stage and severity of clinical symptoms. Current treatment options include weight restriction and observation, core decompression, pelvic and femoral osteotomies, bone grafting (structural or non structural and vascularised or nonvascularised), and arthroplasty (resurfacing and hemi- or total hip replacements) [4–6]. Conservative nonoperative treatment in adults leads to uniformly poor results. Musso et al. [18] reported a 67% rate of progressive femoral head collapse and a 68% rate of conversion to THA in 50 hips with conservative treatment.

In comparison with other joint-preserving options, core decompression is less invasive and more commonly done. It has demonstrated some success in treatment of hips without preoperative collapse, but it has been less successful for hips that had already collapsed [19]. Osteotomies are effective for hips with preoperative collapse, but these procedures are technically demanding and the successful results are difficult to reproduce [20]. Curettage of the lesion followed by bone grafting is insufficient for revascularisation [21]. Vascularised iliac bone grafting has been partially successful for hips without preoperative collapse, but it is still thought to be insufficient for biomechanical support [22]. Prosthetic replacement is also unsuitable for younger patients because of their higher activity level and longer life span [23].

FVFG is an attractive alternative to all the aforementioned options, especially for younger patients without severe osteoarthritis of hip joint [14]. The advantage of FVFG lies in the combination of femoral head decompression, removal of necrotic lesion, introduction of osteoinductive cancellous bone, and vascularised cortical bone support of the subchondral surface [24]. There are multiple reports on the successful mid- and long-term outcomes of FVFG [7–9]. Zhang et al. [8] used FVFG to treat 56 hips in 48 patients, with mean follow-up of 16 months. The HHSs of all stages were improved, ranging from 11 to 13, and most femoral heads showed improvement (39 hips, 69.6%) or were at least unchanged (14 hips, 25.0%) on radiographs. Yoo et al. [7] reported on 110 patients (124 hips) who underwent FVFG, with a minimum follow-up of ten years. Of these, 37 of 59 hips which were initially stage II hips and 39 of 65 stage III hips were found improved or unchanged radiographically at the latest follow-up, with mean HHS improved from 72 to 88. These results showed that FVFG is an effective technique in the precollapse stage and serves as an alternative in the postcollapse stage of ONFH [9].

In our study, FVFG was performed in seven patients (14 hips) with ONFH with lymphoma diseases. There was a low rate of conversion to THA, significant increases in HHSs and decreases in VAS pain scores across stages, without severe life-threatening complications. Clinical results demonstrate that FVFG is safe, effective, and feasible in lymphoma patients for treatment of ONFH. However, the safety of the operation, especially the bilateral procedure, may also be attributed to proficient surgical technique, meticulous clinical monitoring, and deliberate perioperative supportive treatment. We are also aware of some limitations of our study. First, due to relatively low incidence with both lymphoma disease and ONFH, the study has only seven patients (14 hips) and significant statistical

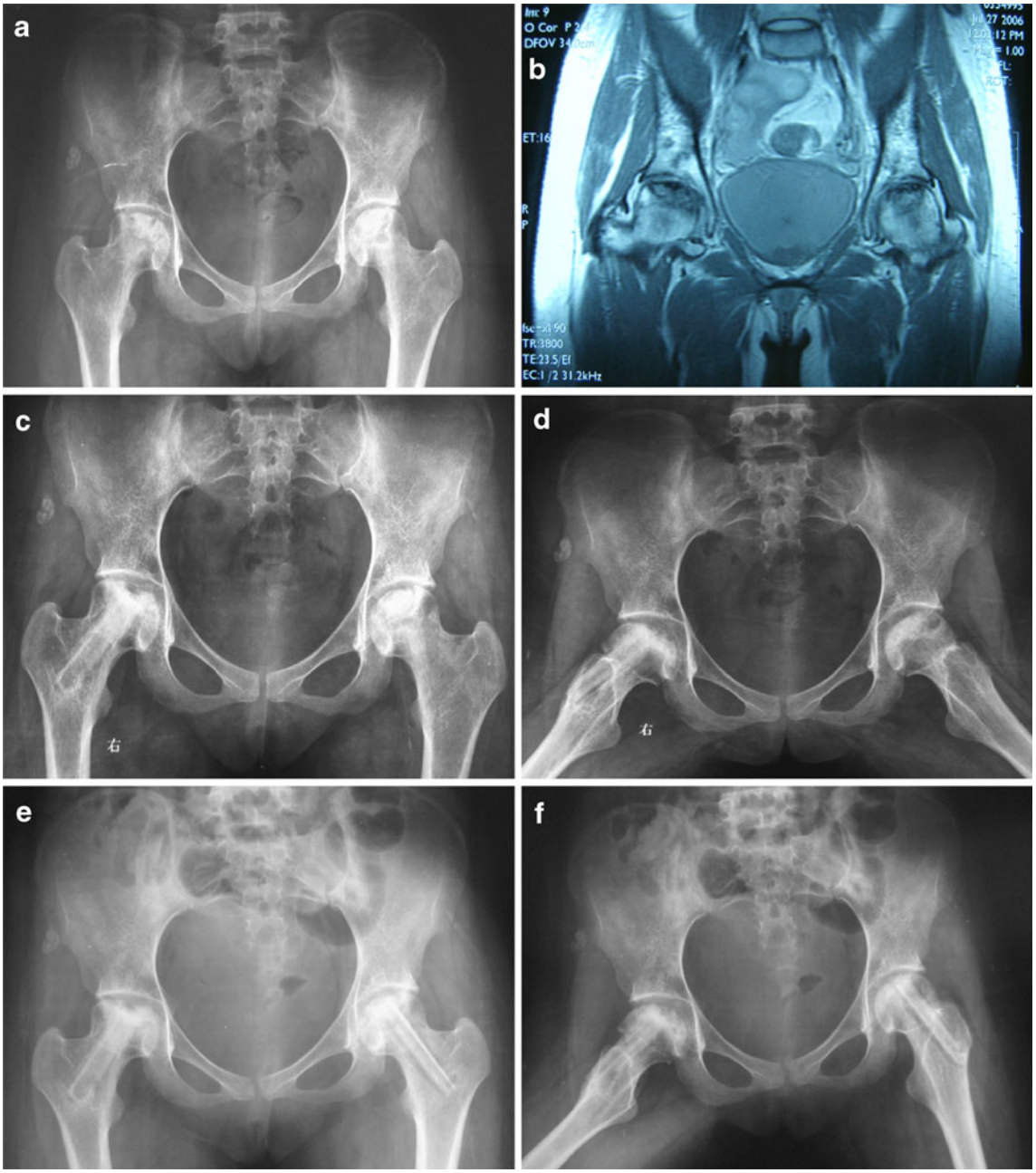

Fig. 1 **a** A 19-year-old woman with non-Hodgkin's lymphoma and bilateral osteonecrosis (the right side was classified as stage IV, and the left side as stage III initially). Recurrent hip joint pain mainly focussed on the right side. The preoperative HHSs were 58 on the right side and 84 on the left. **b** Preoperative MRI of this patient. **c**, **d** Postoperative radiograph (anteroposterior and frog-leg position) 13 months after unilateral free vascularised fibular graft on the right side. The procedure on the left side was also performed at that time because of the progression of osteonecrosis of left femoral head. **e**, **f** Postoperative radiograph (anteroposterior and frog-leg position) two years after the first surgery. The pain was substantially relieved and joint motion was improved, with the HHSs increased to 95 on the left side and 82 on the right at the latest follow-up

conclusions are more difficult to make. Second, we had no control group treated with alternative joint-preserving procedures. Furthermore, clinical research is needed to verify the long-term outcomes of FVFG in these patients.

Conclusion

FVFG in patients with lymphoma disease has shown favourable outcomes on radiographical changes, HHSs and VAS pain scores, because it can enhance revascularisa-

tion of bone tissue and arrest progression of necrosis. Thus, we conclude that this method is a viable option as a joint-preserving treatment in patients with lymphoma and ONFH.

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