Interventional Management of Hypervascular Osseous Metastasis: Role of Embolotherapy Before Orthopedic Tumor Resection and Bone Stabilization

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OBJECTIVE. The purpose of this study was to evaluate, in relation to intraoperative estimated blood loss (EBL), the effectiveness of preoperative transcatheter arterial embolization of hypervascular osseous metastatic lesions before orthopedic resection and stabilization.

MATERIALS AND METHODS. Between June 1987 and November 2007, 22 patients underwent transcatheter arterial embolization of tumors of the long bone, hip, or vertebrae before resection and stabilization. Osseous metastatic lesions from renal cell carcinoma, malignant melanoma, leiomyosarcoma, and prostate cancer were embolized. All patients were treated with a coaxial catheter technique with polyvinyl alcohol (PVA) particles alone or a combination of PVA particles and coils. After embolization, each tumor was angiographically graded according to devascularization (grades 1–3) based on tumor blush after contrast injection into the main tumor-feeding arteries.

RESULTS. In patients with complete devascularization (grade 1), mean EBL was calculated to be 1,119 mL, whereas in patients with partial embolization (grades 2 and 3) EBL was 1,788 mL and 2,500 mL. With respect to intraoperative EBL, no significant difference between devascularization grades was found ($p > 0.05$). Moderate correlation ($r = 0.51$, $p = 0.019$) was observed between intraoperative EBL and tumor size before embolization. Only low correlation ($r = 0.44$, $p = 0.046$) was found between intraoperative EBL and operating time. Major complications included transient palsy of the sciatic nerve and gluteal abscess in one patient.

CONCLUSION. The results of this study support the concept that there is no statistically significant difference among amounts of intraoperative EBL with varying degrees of embolization.

Keywords: bone tumor, embolization, orthopedic surgery

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Pain from skeletal metastasis can be multifactorial. Major causes of intractable pain include mechanical instability, impending fracture, and existing pathologic fracture [1–3]. Orthopedic surgery is generally accepted as the primary management of these entities [2, 3]. The purpose of surgical therapy is palliation and improvement of the quality of life remaining for the patient [2–4]. These aims are usually reached by relieving pain, preserving the function of the affected skeletal part, preventing complications, and shortening the hospital stay. The choice of surgical procedure usually depends on the localization, number, and size of the skeletal metastatic lesions and the degree of functional deficit.

The often hypervascular nature of metastatic lesions of the bone can cause technical difficulties with respect to the extent of surgery and primary stability for pain relief [2, 3, 5, 6]. Adequate surgical procedures are associated with substantial blood loss [2, 3, 7–9]. The resulting high transfusion requirements are frequently complicated by depletion of clotting factors and by complex acquired coagulopathies, which cause variation in intraoperative bleeding [3, 4]. Blood salvage techniques are contraindicated because of the risk of further dissemination of tumor cells [10]. Compared with the amount of information on the effects of preoperative embolization of hypervascular spinal tumors, few data exist concerning embolization of hypervascular metastatic lesions of the long bones and hip [1–4, 11, 12]. Moreover, awareness of this kind of treatment among oncologic surgeons seems low. The aim of our study was to assess in relation to intraoperative estimated blood loss (EBL) the effectiveness of transcatheter arterial embolization (TAE) of hypervascular metastatic lesions of the bone before orthopedic resection and stabilization.

Materials and Methods

A retrospective review of the archives of our interventional radiology department between June 1987 and November 2007 yielded the cases of 22 patients who had consecutively undergone diagnostic angiography and selective TAE of hypervascular metastatic lesions of the long bones, hip, or vertebrae for reduction of EBL during orthopedic resection and stabilization. The patient's demographic and baseline characteristics are presented in Table 1. The indications for orthopedic surgery were impending fracture in 13 patients, pathologic fracture in eight patients, and neurologic deficit due to spinal cord compression in one patient. The following hypervascular secondary bone tumors were identified: metastasis from renal cell carcinoma (n = 18), metastasis from malignant melanoma (n = 1), metastasis from leiomyosarcoma (n = 1), metastasis from hepatocellular carcinoma (n = 1), and metastasis from prostate carcinoma (n = 1). Eighteen patients had a solitary metastatic bone lesion, and four patients had multiple metastatic lesions. In patients with multiple metastatic lesions, only one selected lesion was treated.

Orthopedic surgery included curettage, polymethylmethacrylate (PMMA) insertion, and fixation with a dynamic compression plate in 13 patients; tumor resection and prosthetic replacement of the humeral or femoral head in four patients; curettage, PMMA insertion, and fixation with a blade plate in one patient; curettage, PMMA insertion, insertion of intramedullary rods, and fixation with a dynamic compression plate in one patient; curettage, PMMA insertion, and insertion of intramedullary rods in one patient; curettage and femoral neck osteotomy resulting in a Girdlestone procedure in one patient; and tumor resection, vertebrectomy, and replacement with a titanium basket and plate fixation in one patient. In all patients, orthopedic surgery was performed within 48 hours after embolotherapy. Over the years, two experienced teams of orthopedic surgeons were involved in the surgical procedures. Primary preoperative evaluation of the patients included conventional radiography in 20 cases and CT in two cases. All patients were examined and treated as part of routine care. Informed consent was obtained from all patients before treatment. Our institution does not require institutional review board approval for retrospective studies.

Angiographic and Embolization Technique

Local anesthesia was used for all 22 embolization procedures, which were performed through a contralateral (18 patients) or ipsilateral (four patients) transfemoral approach with a 4- to 5-French vascular sheath (Radifocus, Terumo). All embolizations were performed in our angiography suite. None of the patients received antibiotics.

TABLE 1: Patient Demographic and Baseline Characteristics (n = 22)

Characteristic	No.
Sex (n)	
Men	16 (73)
Women	6 (27)
Age (y)	
Mean ± SD	66.2 ± 10.9
Median	66.5
Range	47–85
Age group (n)	
< 65 y	13 (59)
≥ 65 y	9 (41)
Tumor location (n)	
Femur	14 (64)
Humerus	4 (18)
Acetabulum	1 (4.5)
Tibia	1 (4.5)
Ulna	1 (4.5)
L2 vertebral body	1 (4.5)
Origin of tumor feeders (n)	
Deep femoral artery	8
Lateral circumflex femoral artery	7
Medial circumflex femoral artery	3
Superior gluteal artery	3
Ulnar artery	3
Superficial femoral artery	2
Popliteal artery	2
Obturator artery	2
Brachial artery	2
Anterior circumflex humeral artery	2
Anterior tibial artery	1
Posterior tibial artery	1
Fibular artery	1
Radial artery	1
Medial circumflex humeral artery	1
Lumbar artery	1
No. of embolized vessels per patient	
Mean ± SD	2.0 ± 1.0
Median	2
Range	1–4
Duration of operation (min)	
Mean ± SD	163.0 ± 42.7
Median	150
Range	75–240
No. of patients needing transfusion	
Devascularization grade 1	4 (18)
Devascularization grade 2	6 (27)

Note—Values in parentheses are percentages.

In all patients a selective diagnostic arteriogram was obtained to ascertain the hypervascularity of all bone tumors and to identify the main feeding arteries and corresponding tumor blush. This selective angiography was performed with a Cobra-shaped catheter (4- to 5-French C-1, Cook) or a single-curve catheter (4- to 5-French). Diagnostic catheter maneuvers usually were performed with a steerable 0.035-inch guidewire (Radifocus, Terumo).

In all 22 patients, TAE was performed with a coaxial 2.7-French (Progreat, Terumo) or 3-French (Fast Tracker, Target Therapeutics) microcatheter placed in proximity to the tumor-feeding vessels (Figs. 1–3). Fourteen patients underwent TAE with polyvinyl alcohol (PVA) particles (150–300 μm and 350–500 μm, Contour, Boston Scientific) alone. The particles were reconstituted with 20 mL of contrast medium per vial to guarantee adequate visualization and were suspended by agitated mixing between two syringes before injection. Eight patients underwent embolization with a combination of PVA particles (150–300 and 350–500 μm) and microcoils. The coils were either fibered 0.018-inch platinum microcoils (VortX, Boston Scientific) with a nominal configured diameter of 2 × 3 mm, 2 × 4 mm, or 2 × 5 mm and a stretched length of 22–42 mm or fibered 0.018-inch platinum microcoils (Complex Helical, Boston Scientific) with a nominal configured diameter of 2 mm and a stretched length of 10 mm. Microcoils as an additional embolic agent were generally used in vascular branches originating from the main tumor-feeding artery but not principally supplying the tumor itself, preventing downstream embolization. Transcatheter coil embolization was performed with an ultrathin coil pusher wire (Coil Pusher, Boston Scientific) or, more frequently, by saline injection. In general, embolic agents were selected on the

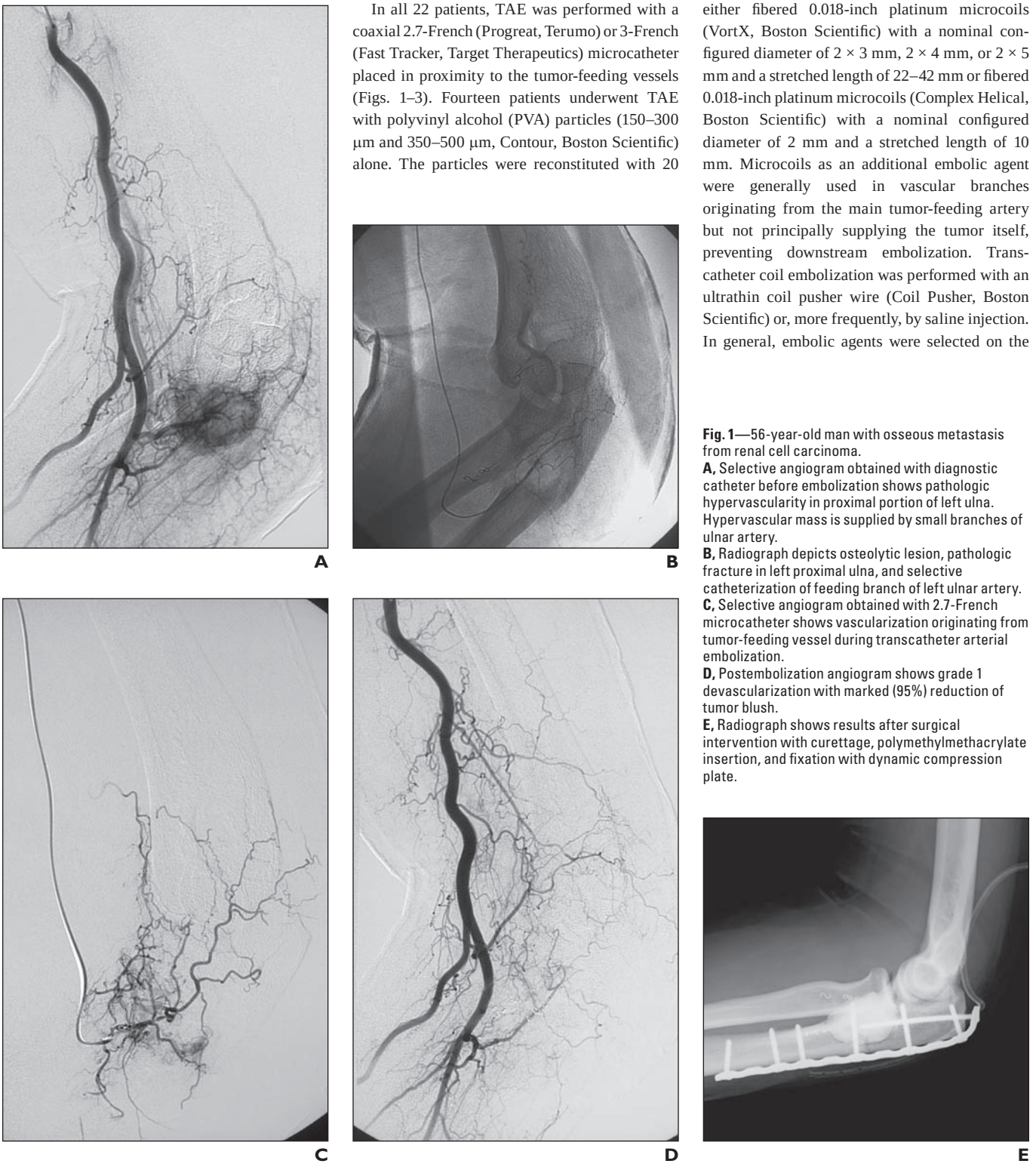

Fig. 1—56-year-old man with osseous metastasis from renal cell carcinoma.
A, Selective angiogram obtained with diagnostic catheter before embolization shows pathologic hypervascularity in proximal portion of left ulna. Hypervascular mass is supplied by small branches of ulnar artery.
B, Radiograph depicts osteolytic lesion, pathologic fracture in left proximal ulna, and selective catheterization of feeding branch of left ulnar artery.
C, Selective angiogram obtained with 2.7-French microcatheter shows vascularization originating from tumor-feeding vessel during transcatheter arterial embolization.
D, Postembolization angiogram shows grade 1 devascularization with marked (95%) reduction of tumor blush.
E, Radiograph shows results after surgical intervention with curettage, polymethylmethacrylate insertion, and fixation with dynamic compression plate.

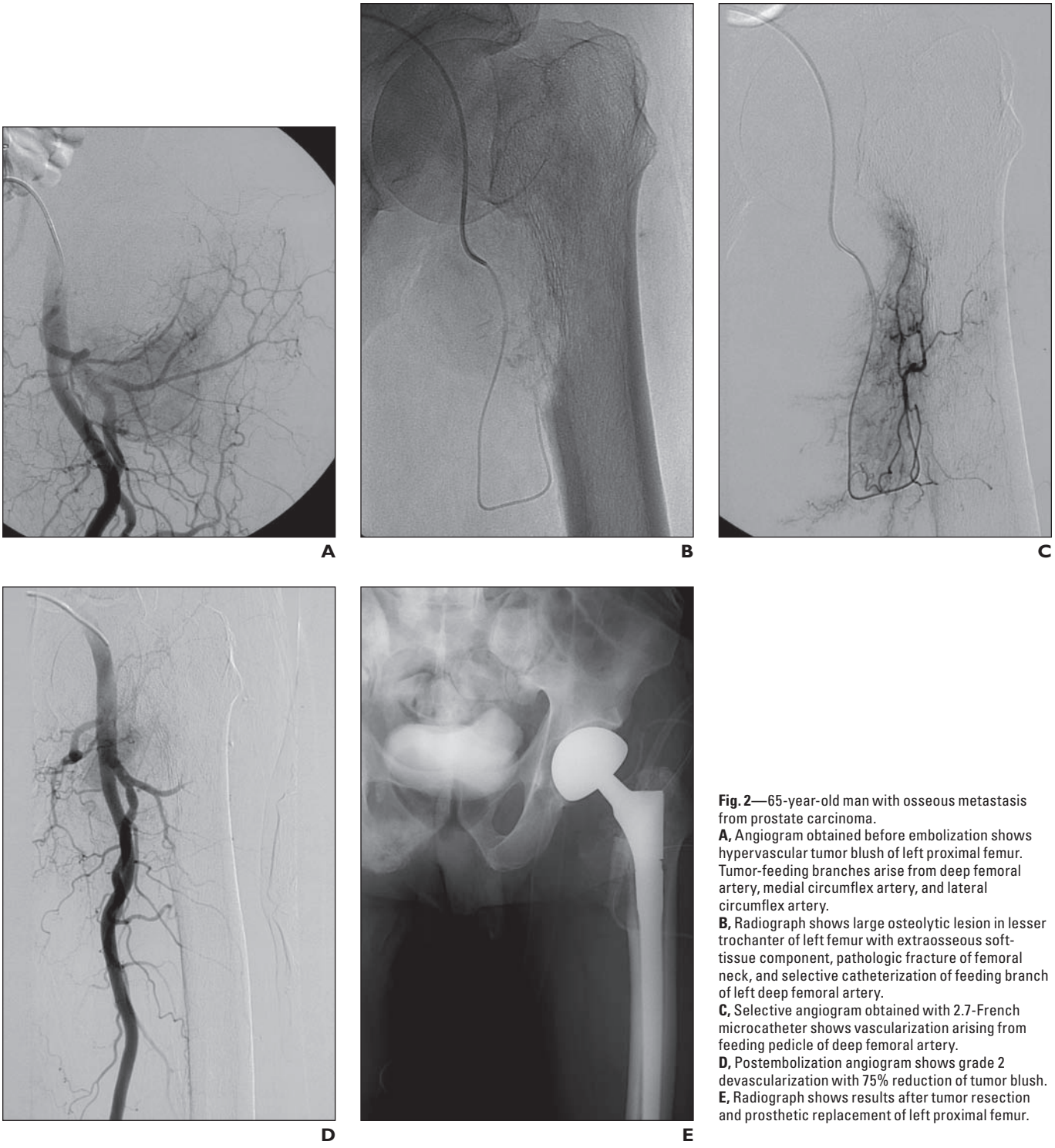

Fig. 2—65-year-old man with osseous metastasis from prostate carcinoma.
A, Angiogram obtained before embolization shows hypervascular tumor blush of left proximal femur. Tumor-feeding branches arise from deep femoral artery, medial circumflex artery, and lateral circumflex artery.
B, Radiograph shows large osteolytic lesion in lesser trochanter of left femur with extraosseous soft-tissue component, pathologic fracture of femoral neck, and selective catheterization of feeding branch of left deep femoral artery.
C, Selective angiogram obtained with 2.7-French microcatheter shows vascularization arising from feeding pedicle of deep femoral artery.
D, Postembolization angiogram shows grade 2 devascularization with 75% reduction of tumor blush.
E, Radiograph shows results after tumor resection and prosthetic replacement of left proximal femur.

basis of personal preference, catheter location, catheter size, and vessel size, as previously recommended [13]. All embolization procedures were performed by four interventional radiologists who had 6–20 years of experience with this kind of catheter therapy.

Data Evaluation and End Point Definition

Angiograms and angiographic records before and after embolization were reviewed by three radiologists together to gather information on the technical outcome and complication rate of TAE. Medical records and surgical notes were analyzed by an orthopedic surgeon to assign the medical outcome and complication rate of preoperative embolotherapy. The primary end points of our study were technical outcome, clinical outcome, side effects, and rates of minor and major complications.

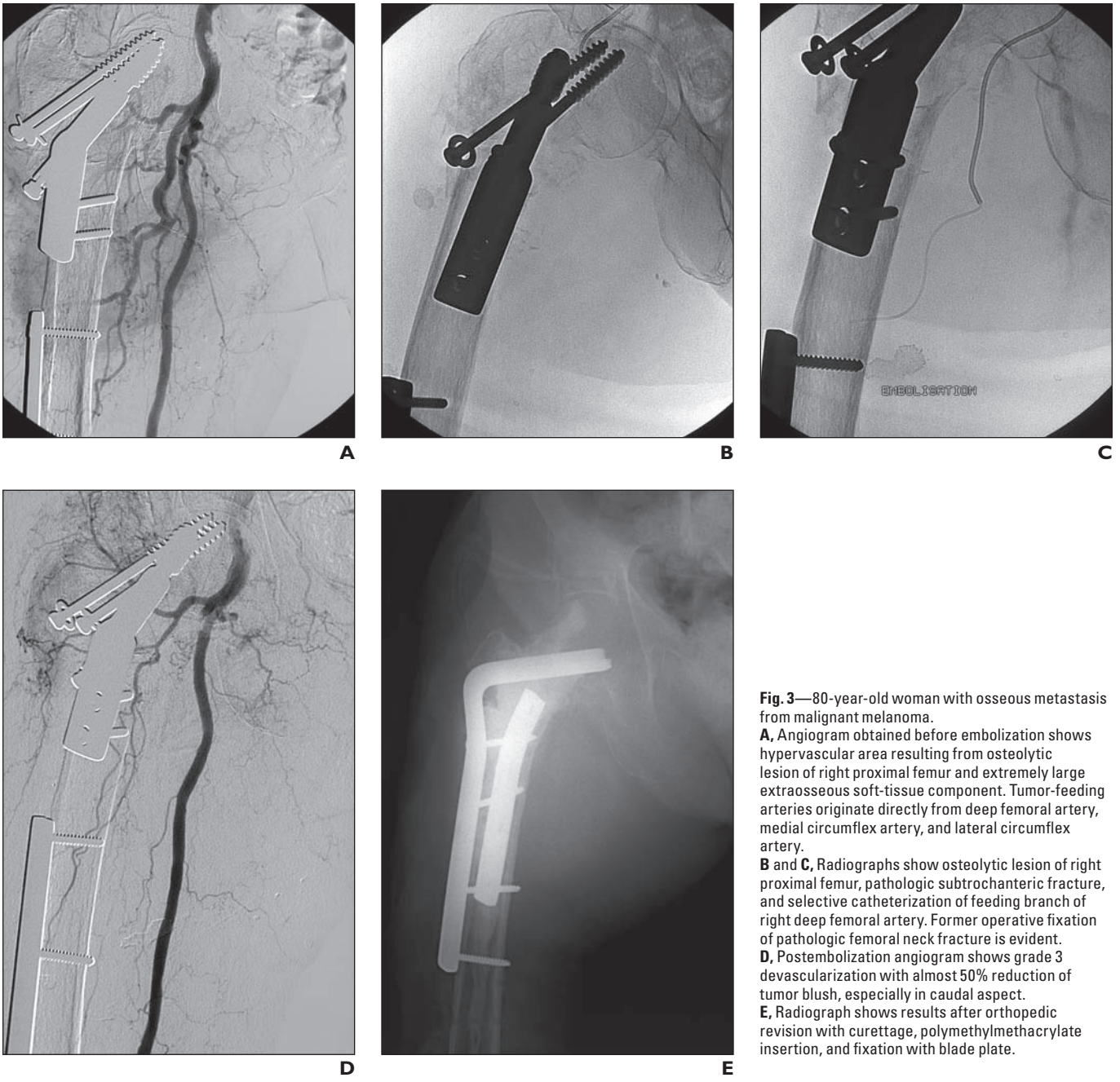

Fig. 3—80-year-old woman with osseous metastasis from malignant melanoma.
A, Angiogram obtained before embolization shows hypervascular area resulting from osteolytic lesion of right proximal femur and extremely large extraosseous soft-tissue component. Tumor-feeding arteries originate directly from deep femoral artery, medial circumflex artery, and lateral circumflex artery.
B and **C,** Radiographs show osteolytic lesion of right proximal femur, pathologic subtrochanteric fracture, and selective catheterization of feeding branch of right deep femoral artery. Former operative fixation of pathologic femoral neck fracture is evident.
D, Postembolization angiogram shows grade 3 devascularization with almost 50% reduction of tumor blush, especially in caudal aspect.
E, Radiograph shows results after orthopedic revision with curettage, polymethylmethacrylate insertion, and fixation with blade plate.

Technical outcome reflected immediate results and was typically evaluated with completion angiography. It was determined to be intentional reduction or cessation of antegrade blood flow to the vascular tumor bed. In this setting, each embolized osseous metastatic lesion (including the extraosseous soft-tissue component) was angiographically categorized on the basis of devascularization (embolization) grade, as in previous studies [2, 4]. Grade 1 was greater than 75% reduction of tumor blush; grade 2, 50–75% reduction of tumor blush; and grade 3, less than 50% reduction of tumor blush. Clinical outcome reflected the effect of embolotherapy on intraoperative EBL. This EBL had usually been documented in the patients' operative records and charts. Clinical side effects included symptoms such as fever, pain, and malaise and were attributed to development of a postembolization syndrome.

Complications of treatment were categorized on the basis of outcome according to the reporting standards of the Society of Interventional Radiology [14]. Minor complications included those necessitating no therapy and having no consequences (class A) and those necessitating nominal therapy and having no consequence except overnight admission for observation only (class B). Major complications included those necessitating minor therapy, that is, less than 48 hours of hospitalization (class C); those necessitating major therapy, that is, an unplanned increase in the level of care and hospitalization longer than 48 hours (class D); those resulting in permanent adverse sequelae (class E); and those resulting in death (class F).

Statistical Analysis

Descriptive data were presented as medians with ranges, if appropriate; categoric data were counts and percentages. Spearman's rank correlation test was used to describe the relation between tumor size and intraoperative EBL and between operating time and intraoperative EBL and to predict one variable from another. Intergroup differences were analyzed with the nonparametric two-sample Mann-Whitney *U* test and the nonparametric Kruskal-Wallis *H* test for more than two samples. Statistical significance was set at $p < 0.05$. Statistical analysis was performed with a specialized computer algorithm (MedCalc version 6, MedCalc Software).

Results

Technical and Clinical Results

The sex ratio in the study was eight men to three women ($p < 0.0004$, Mann-Whitney *U* test). Initial diagnostic angiograms confirmed the hypervascularity of bone tumors in all patients. Among 22 patients who underwent preoperative embolotherapy for hypervascular secondary bone tumors, completion angiography showed grade 1 devascularization in 13 patients (59%), grade 2 devascularization in eight patients (36%), and grade 3 devascularization in one patient (5%). The average maximal tumor diameter before embolotherapy was 8.3 ± 5.2 (SD) cm (range, 3–20 cm). The total number of embolized tumor-feeding vessels was 45. In general, a statistically significant difference was not found in the number of embolized vessels for lesions in which grade 1 (median, two vessels) versus grade 2 (median, two vessels) and grade 3 (median, three vessels) devascularization was achieved ($p = 0.38$, Kruskal-Wallis *H* test).

The median intraoperative EBL during orthopedic surgery was 600 mL (range, 200–4,000 mL). In patients with grade 1 devascularization, the median intraoperative EBL was 500 mL (range, 200–4,000 mL). In patients with a grade 2 devascularization, the median intraoperative EBL measured 1,475 mL (range, 350–3,800 mL). In the patient with grade 3 devascularization, the median intraoperative EBL was 2,500 mL. The median number of units of packed RBCs transfused to our patients was zero (range, 0–8). A moderate correlation ($r = 0.51$, $p = 0.019$, Spearman's rank correlation test) was found between intraoperative EBL and tumor size before embolization. There was no significant correlation between intraoperative EBL and operating time ($r = 0.44$, $p = 0.046$, Spearman's rank correlation test). Nor was there a significant difference in amounts of EBL for devascularization grade 1, 2, and 3 lesions ($p = 0.22$, Kruskal-Wallis *H* test); between the intraoperative EBL of men and that of women ($p = 0.08$, Mann-Whitney *U* test); in EBL for the group younger than 65 years and the group 65 years and older ($p > 0.1$, Mann-Whitney *U* test); or in amounts of EBL according to location of metastasis (proximal upper extremity vs distal upper extremity vs proximal lower extremity vs distal lower extremity vs spine vs pelvis) ($p = 0.49$, Kruskal-Wallis *H* test). Side effects associated with postembolization syndrome did not occur.

Complications

The overall rate of complications was 9% (two cases of complications in 22 patients). The rate of major complications was 4.5% (one case in 22 patients); that of minor complications also was 4.5%. A major complication categorized as class D occurred in a patient with renal cell carcinoma who underwent embolization of an osseous metastasis of the left femur. After complete occlusion of the left deep femoral artery and superior gluteal artery, palsy of the sciatic nerve and a gluteal abscess developed. The symptoms of palsy completely resolved over a period of 3 weeks. However, surgical removal of the gluteal abscess was necessary to prevent further infection and sepsis. Another patient, who had malignant melanoma, had a class A minor complication: temporary spasm of the right deep femoral artery during embolization of an osseous metastatic lesion of the right femur.

Discussion

Since the pioneering study of Feldman et al. [15], who initially described selective TAE as a useful adjunct in the management of selected bone tumors, there has been increasing interest in this kind of therapy [16–22]. It is a commonly held opinion [2, 4, 8] that preoperative TAE of hypervascular malignant bone tumors is a safe and effective procedure for reduction of intraoperative EBL and surgical morbidity, even if only partial devascularization has been achieved. Many reports [2–4, 11, 18], however, describe a wide spectrum of technical outcomes, clinical outcomes, and complication rates. Results of some of the trials emphasized that successful embolization can decrease intraoperative EBL to approximately 500 mL [2, 4]. Barton et al. [11] reported intraoperative EBL of 500–1,500 mL in patients who had undergone preoperative embolotherapy; patients who had not undergone TAE had an EBL of 2,000–18,500 mL. In a more recent study, Wirbel et al. [3] found an average intraoperative EBL of 1,650 mL for spinal lesions and 2,250 mL for peripheral pelvic lesions after the patients had undergone TAE.

In our series, we found a threefold to fourfold wider range of EBL than in the trials by Rowe et al. [1] and Sun and Lang [2]. This finding was most likely caused by a higher rate of grades 2 and 3 devascularization. On the one hand, the increased rate of partially embolized tumors in our study was the result of a careful embolization strategy. In cases in which tumor-feeding vessels originated directly from a first-order branch, the embolization approach was performed in a rather conservative manner to minimize the risk of ischemic symptoms (claudication, critical limb ischemia, sexual dysfunction, large area of tissue loss). On the other hand, there was an element of difficulty in cannulating all feeding vessels in the lesions that were incompletely embolized.

Like other investigators [2], we did not find a significantly high correlation between average maximal tumor size and intraoperative EBL. With respect to the relation between operating time and quantity of intraoperative EBL, directly comparable information is not available in the literature, to our knowledge. We also could not calculate a significantly strong correlation between these two variables.

Some investigators [2, 4] have found that intraoperative EBL depends on the residual area of tumor blush. They reported a significantly higher amount of intraoperative blood loss in patients with partial embolization than in those with complete tumor devascularization. In contrast, we did not find a significant difference between tumor lesions with and those without residual tumor blushes. The different procedures performed in our study could have affected the EBL because plating of a femur, as opposed to femoral nailing, required opening the area of tumor. Aside from the surgical procedure, inherent factors such as tumor location and tumor type might have had great effect on the variation in intraoperative EBL among cases.

We substantially agree with Manke et al. [23], who considered intraoperative EBL dependent on the surgeons' individual technical skills. In this context, we do not believe that our series was significantly influenced

by the fact that during the time period reviewed, two different teams of surgeons were involved in tumor resection and stabilization. All those board-certified surgical colleagues were experienced and highly sophisticated with regard to orthopedic techniques on hypervascular bone tumors.

In our study, it could be expected that grade 2 and grade 3 lesions would have greater intraoperative EBL, perhaps necessitating transfusion. Some patients with grade 1 lesions needed transfusions because they had tumor-associated sideropenic anemia or elevated intraoperative EBL. It remains unclear why embolization in two cases appeared to be clinically ineffective (intraoperative EBL, 3,000 and 4,000 mL) despite good angiographic results.

Complications and side effects due to preoperative TAE of hypervascular bone tumors are rare, but a few relevant disadvantages exist [2, 24]. A postembolization syndrome with symptoms such as fever, pain, and malaise is a major side effect. TAE can result in a large zone of tissue loss not expected before therapy. TAE of adjacent or distant nontargeted vessels, such as the inferior or superior gluteal artery, may be associated with risk of development of palsy of the sciatic nerve or of buttock necrosis. Placement of tissue at risk of ischemia is another complication of TAE that can occur, with its inherent symptoms such as infection and dramatically increased leukocytosis. Some of the embolization procedures in our study could have been performed with a 4-French diagnostic catheter alone. Nonetheless, we generally preferred the coaxial approach to minimize the incidence of dissection, vasospasm, and errant TAE.

Use of PVA particles has been widely considered [2, 13, 23] the workhorse of preoperative TAE of hypervascular osseous metastatic lesions, as was documented in our trial. The use of coaxial microcatheter systems and PVA particles may ensure rapid and permanent occlusion of tumor-feeding vessels with minimized risk of complications [2]. One should be aware, however, that the size of PVA particles has to be adjusted to the diameter of potential collateral vessels and shunts because these entities often are present in hypervascular malignant bone tumors [2, 23]. Otherwise, embolization of nontargeted vessels and ensuing complications can result. In this study, all of the patients were treated predominantly with medium to large particles to avoid arterial compromise of the skin and muscle supply. With special regard to particulate embolic agents, a study [25] has been conducted to compare the use of trisacryl gelatin microspheres with the use of PVA particles in preoperative embolotherapy of bone tumors. The investigators reported a significant difference between these particulate agents, a minor amount of intraoperative EBL occurring with the use of trisacryl gelatin microspheres. They also found that the use of trisacryl gelatin microspheres was associated with a delay in revascularization of osseous tumors.

The use of coils in the management of hypervascular bone tumors has been reported [2, 13, 23] to be ineffective because the rich vascularization of these lesions can open collateral channels within hours. The combined use of coils and PVA particles has been addressed, but a significant benefit has not been found as far as TAE of the main tumor feeders is concerned. However, some authors [2, 23] have pointed out that protective coil placement in arteries distal to the origin of tumor feeders or in vessels arising from the main tumor feeder but not essentially contributing to the tumor supply may be useful for avoiding unintentional downstream embolization.

There were two main limitations to our study. First, the sample size was small, preventing us from generalizing the results. Second, the study was retrospective and lacked randomization. A prospective randomized trial would be beneficial for defining the exact value of preoperative embolization compared with a surgical approach without embolotherapy. Such a trial, however, would be ethically difficult to design and perform. Owing to the small number of patients and low statistical power, we consider the results of our study preliminary. In our clinical practice, we perform this embolization procedure at the special request of orthopedic surgeons. However, patient selection is restricted to cases in which the tumor is likely to be violated, as in fractures, large soft-tissue masses, and curettage.

Our experience with minimally invasive preoperative microcatheter embolotherapy for hypervascular metastatic lesions of the bone shows that there is no statistically significant difference in amounts of intraoperative EBL with varying degrees of embolization. Because of the limitations of this study, this finding is contradictory to that of previous investigations. Additional studies that integrate broad multicenter experience into a treatment strategy with coaxial embolization are desirable for collection of reliable data on this innovative procedure compared with a surgical approach without embolotherapy.

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