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CLINICAL STUDY

Selective Embolization with *N*-butyl Cyanoacrylate for Metastatic Bone Disease

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ABSTRACT

Purpose: To evaluate the clinical and imaging effect of selective embolization using *N*-butyl cyanoacrylate (NBCA) as palliation for bone metastases.

Materials and Methods: The procedures and effect of 309 embolizations performed in 243 patients were retrospectively analyzed; 56 patients had repeat embolization at the same location at 1–3 months; 197 patients had embolization for progressive bone metastases after radiation therapy. The mean tumor diameter before embolization was 7.8 cm (range 5–30 cm). In all patients, embolizations were performed under local anesthesia through transfemoral catheterization using NBCA in 33% ethiodized oil (Lipiodol). The technical success of embolization was evaluated by angiography after completion of the procedure. The clinical and imaging effect was evaluated at follow-up examinations with a pain score scale and use of analgesics, hypoattenuating areas, tumor size, and ossification.

Results: In all 309 embolizations, postprocedural angiography showed complete occlusion of metastatic blood supply and greater than 80% devascularization of the lesions. Greater than 50% reduction of pain score and analgesic doses was achieved in 97% of procedures. The mean duration of pain relief was 8.1 months (range 1–12 months). The mean maximal tumor diameter after embolization was 5.5 cm (range 2–20 cm). Variable ossification appeared in 65 patients. Postembolization syndrome, ischemic pain at the site of embolization, paresthesias, skin breakdown, and subcutaneous necrosis were observed in 87 patients.

Conclusions: Selective embolization with NBCA is safe and effective palliative treatment for metastatic bone lesions of various primary cancers; pain relief is temporary.

ABBREVIATION

NBCA = N-butyl cyanoacrylate

Metastatic disease is the most common malignancy of bone. Prostate, breast, lung, kidney, and thyroid cancer account for 80% of skeletal metastases (1). The most common sites of bone metastases are the spine, pelvis, ribs, skull, and proximal femur. The most common manifestations are pain, pathologic fractures, and spinal cord compression (2). Pain from bone metastases can be caused by tumor biology, local chemical release of cytokines by tumor cells causing stimulation of intraosseous nerves, pressure or mass effect of the tumor tissue within the bone, and bone destruction causing mechanical instability and pathologic fractures (3).

Treatment options in patients with bone metastases are mostly aimed at palliation. The goals of treatment in these patients are pain control, prevention and treatment of fractures, prevention of tumor progression, maintenance of independence, and improvement of quality of remaining life (4,5). Traditional palliative treatments include surgery, if the metastatic lesion is accessible, and external-beam radiation therapy (6–9). The main indications for surgery are persistent pain refractory to medical therapy, tumors with poor radioisotope uptake, and spinal instability with or without neural compression (1,8–11). Bone pain without structural insufficiency is often effectively treated with narcotic analgesics, radiation therapy, hormonal therapy, cytotoxic therapy, and bisphosphonates (6,7).

All metastatic lesions are progressive, however, causing bone failure. Tumor cell adhesive molecules bind the tumor cells to marrow stromal cells and bone matrix allowing them to grow and produce angiogenic and bone-resorbing factors (1,9). In addition, most, if not all, metastatic

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Table 1. Details of 243 Patients in Study

Primary Cancer	No. Patients (Gender; Mean Age [y])	Median Follow-up (Range)	Preembolization Tumor Diameter (cm) (Mean 7.8 cm)	Postembolization Tumor Diameter (cm) (Mean 5.5 cm)
Renal	84 (56 M, 28 F; 74)	4.5 y (6 mo–5 y)	5–30	2–20
Lung	22 (16 M, 6 F; 67)	1.5 y (9 mo–2.5 y)	5–15	2–9
Breast	20 (F; 61)	7 y (2–8 y)	5–15	2–8
Gastrointestinal	20 (12 M, 8 F; 77)	3.5 y (9 mo–5 y)	5–10	2–7
Thyroid	19 (12 M, 7 F; 69)	4 y (2–6 y)	5–15	2–6
Uterus	8 (F; 67)	4 y (1–6 y)	5–10	2–7
Nerve tissue	7 (5 M, 2 F; 69)	4 y (2–6 y)	5–20	2–15
Bladder	6 (5 M, 1 F; 70)	2.5 y (9 mo–4 y)	5–10	2–7
Prostate	7 (M; 69)	4.5 y (1–6 y)	5–10	2–8
Musculoskeletal sarcoma	5 (3 M, 2 F; 54)	1 y (3 mo–2 y)	5–20	5–14
Melanoma	1 (M; 56)	1 y	6	5
Other	21 (14 M, 7 F; 69)	3.5 (6 mo–6 y)	5–10	5–8
Unknown origin	23 (17 M, 6 F; 71)	2.5 y (6 mo–5 y)	5–15	5–10

Table 2. Tumor Diameter and Number of Embolizations According to Site

Site	Preembolization Tumor Diameter (cm) (Mean 7.8 cm)	Embolizations (n = 309)	Postembolization Tumor Diameter (cm) (Mean 5.5 cm)
Pelvis	5–30	154	2–20
Spine	5–6	83	2
Lower limb	5–20	38	2–10
Upper limb	5–15	13	2–6
Thoracic cage	5–10	21	2–5

lesions are hypervascular. Some lesions such as renal and thyroid metastases are highly hypervascular (12,13). This hypervascularity may cause technical difficulties with respect to the extent of surgery and primary stability for pain relief (4,5,10). The resulting high transfusion requirements are frequently complicated by depletion of clotting factors and coagulopathy that cause further variable intraoperative bleeding, and blood salvage techniques are contraindicated because of the risk of further dissemination of tumor cells (5,11).

Embolization is a useful adjunctive procedure for the treatment of metastatic bone disease. Preoperative or serial embolization techniques employing Gelfoam, polyvinyl alcohol particles, alcohol emulsions, coils, tissue adhesives, ethanol, and microfibrillar collagen can be used as primary or adjuvant treatment to surgery or radiation therapy (14). Serial embolization provides devascularization, size reduction, calcification of margins, and pain relief (12,13,15). Serial embolization is typically performed in 4- to 6-week intervals until symptomatic improvement occurs or the tumor's vascularity disappears as judged by angiography, magnetic resonance imaging, or computed tomography (CT) scan. Preoperative embolization provides tumor devascularization; typically, surgery should be performed within 24–48 hours after embolization to prevent recanalization (12,13,15).

Embolization can also be used for palliative relief of skeletal pain and prevention of further tumor growth in patients who are not candidates for surgery (4,5,9,11,12,15–19). By hyperselective catheterization and embolization of the pathologic feeding arteries to the lesion with the most appropriate embolic agent, embolization can be expected to be successful in up to 90% of cases; multiple procedures are frequently necessary (4,20). In this study, we describe selective embolization using *N*-butyl cyanoacrylate (NBCA) for palliative or adjuvant treatment of bone metastases and discuss the clinical and imaging results.

MATERIALS AND METHODS

We retrospectively studied the medical files of 243 consecutive cancer patients with skeletal metastases treated by selective transfemoral embolization using NBCA during an 8-year period from December 2002 to April 2010. There were 148 men and 95 women with a mean age of 67 years (range 20–87 years). The primary cancer histology varied (**Table 1**). Overall, 309 embolizations were performed (**Table 2**); 187 patients had one embolization, and 56 patients had repeat embolization at the same location (46 patients had two embolizations, and 10 patients had three embolizations). The mean tumor diameter before emboli-

zation was 7.8 cm (range 5–30 cm). All patients had intense pain from skeletal metastases; one patient had a pathologic fracture.

The indication for embolization was palliation. In 12 patients, surgical treatment was performed after embolization; surgery was not feasible before embolization in any of these patients. Indications for repeat embolization included pain and imaging evidence of progressive disease. Embolization for progressive metastatic bone disease after radiation therapy was performed in 197 patients; in these patients, embolization with or without chemotherapy was done depending on the primary cancer and patients' age and general health status. In the remaining 46 patients, embolization was combined with radiation therapy or chemotherapy or both. The mean follow-up was 4 years (median 3.4 years, range 3 months to 8 years). All patients or their relatives gave written informed consent to undergo embolization and for their data to be included in this retrospective study. This study was approved by the institutional review board/ethics committee of our institution.

Diagnostic digital subtraction angiography (contrast media iomeprol 300 mg/mL [Iomeron; Bracco, Milan, Italy] and iohexol 350 mg/mL [Omnipaque; GE Healthcare, Milan, Italy]) was performed before embolization to identify the feeding vessels. In all patients, angiography and selective arterial embolization were performed under local anesthesia using the Seldinger technique through femoral artery transarterial catheterization. In patients with metastases in the pelvis or lower extremities, contralateral transfemoral access was used. The femoral artery was catheterized with a 4-F Introducer (Cordis Corporation, Miami, Florida) or a 5-F Introducer (Terumo Corporation, Tokyo, Japan). In patients with spinal and pelvic lesions, panoramic aortography was performed using 4-F pigtail catheters (Cordis Corporation), followed by selective and superselective arteriography using Cobra, Simmons, and Vertebral catheters (Terumo Corporation) or 2.7-F to 2.9-F preshaped MC-PP27131, 130-cm microcatheters (Coaxial Catheters System; Terumo Corporation). Shapeable and stiff types of guide wires were used, with a diameter of 0.035 inch (0.89 mm), a length of 150 cm and 180 cm, and a flexible tip length of 3 cm (Radifocus Guide Wire M; Terumo Corporation).

In patients with extremity lesions, aortography was not performed. In all patients, the embolic agent used was the NBCA (Glubran 2; GEM, Viareggio, Italy) in 33% Lipiodol (1 flacon [10 mL], Lipiodol Ultrafluido; Guerber, Villepinte, France) "sandwiched" with 5% glucosate solution to prevent polymerization with blood until administration of the embolic agent through the catheter. NBCA, 1 mL, was mixed with 33% Lipiodol, 2 mL. From the mixture, 1 mL was aspirated in an insulin (1 mL) syringe; depending on the pathologic vasculature, 0.1–0.2 mL of the aspirate mixture was injected "sandwiched" with 2 + 2 mL of 5% glucosate solution under fluoroscopic control. If occlusion was incomplete or more feeding vessels were observed, the procedure was repeated in the same method. If more than 1 mL of NBCA was necessary because of high vascularization of the lesions, a new mixture was prepared in a similar manner; overall, a mean of 0.5–2 mL of NBCA has been used for the embolization procedures in this series. All embolization procedures were performed by the same interventional radiologists (G.R., L.B., and E.R.).

Embolization was considered technically complete when there was stasis of intravascular contrast material and either complete elimination of hypervascular staining of the tumor or 80% or greater elimination of the tumor pathologic vasculature compared with the initial diagnostic angiogram (15). In six cases with metastatic spinal tumors, embolization was not performed because of the risk of paraplegia secondary to errant embolization of the angiographically shown artery of Adamkiewicz; these cases were excluded from this series.

The clinical and imaging effect of treatment was evaluated at routine follow-up examinations for the entire study period or until death. Evaluations occurred at 2-month intervals for the first 6 months, at 3-month intervals for the next 6 months, every 6 months thereafter for 3 years, then annually. The presence of local recurrence, metastasis, or death was recorded. Each follow-up evaluation included clinical and imaging with standard radiographs and CT scan; magnetic resonance imaging was performed every 6 months for the 1st year and then every 12 months; a CT scan of the chest was performed annually.

The clinical effect was determined by visual pain scale from 0 (no pain) to 10 (severe and constant pain) (21) and the use of analgesics. A clinical response was defined as 50% or greater reduction in pain score and 50% or greater reduction in analgesic doses; no response was defined as less than 50% decrease. Analgesics included acetaminophen, nonsteroidal antiinflammatory drugs, narcotics, and combinations depending on the severity of pain. The duration of clinical relief was measured until relapse, latest follow-up, or death. Specific survival data were not collected. Imaging tumor response was evaluated on CT scans obtained at 3 months, 6 months, and 12 months or at the latest follow-up, based on hypoattenuating areas within the tumor that resembled necrosis, tumor size, and ossification. Metastatic lesions that underwent a repeat embolization procedure were considered for the purpose of this study as a new procedure and were included in the overall number (309) of embolizations.

RESULTS

Technical Success

All 309 embolization procedures were technically successful; selective catheterization and embolization of the feeding vessels was achieved in all cases; two to four feeding vessels were occluded in each embolization procedure. The efficacy and safety of each procedure were ensured by the bolus administration in low doses (0.1–0.2 mL) of the sandwiched embolic agent under fluoroscopic control fol-

lowed by arteriography and new embolization if occlusion was incomplete or more feeding vessels were found. Postprocedural angiography showed complete interruption of metastatic blood supply and more than 80% devascularization of the tumor in all cases.

Clinical Response

A clinical response was achieved in 300 procedures (97%), and no response occurred in 9 procedures. The time to maximal response varied, but in all responding patients it occurred within 15 days postembolization. However, embolization had a temporary palliative effect; the mean duration of pain relief was 8.1 months (range 1–12 months). Almost complete pain relief (0–3 points on visual pain scale postembolization) occurred in all patients with severe pain before the procedure (7–10 points on visual pain scale preembolization), such as patients with extremity and shoulder girdle lesions that were most painful before the embolization; these patients had more than 50% reduction of analgesic daily doses. Moderate pain relief (4–6 points on visual pain scale postembolization) was observed in patients with spinal lesions (5–8 points on visual pain scale preembolization); these patients had 50% reduction of analgesic daily doses. No pain relief or reduction in analgesic doses was observed in nine patients with sacroiliac metastatic bone lesions; these patients had continuous postembolization pain with the same intensity as before embolization (5–8 points on visual pain scale preembolization and postembolization).

Imaging Response

Hypoattenuating areas attributed to bony tumor necrosis appeared in all patients. The mean amount of hypoattenuating areas on CT scans after embolization was 60% (range 40%–80%) of the overall tumor size. The mean maximal tumor diameter after embolization was 5.5 cm (range 2–20 cm). The best imaging results, by both CT attenuation and tumor shrinkage, were observed in highly hypervascular tumors, such as renal and thyroid bone metastases, and lesions of the shoulder girdle. Variable ossification appeared in 65 patients: 35 patients with renal (**Figs 1** and **2**), 15 patients with thyroid, 8 patients with breast, and 7 patients with lung cancer (**Fig 3**). Abundant ossification was seen in six patients; the remaining patients showed primarily a rim of peripheral bone formation. In patients with abundant calcification, progression of the metastatic lesion was not observed on follow-up imaging.

Recurrence

Recurrent disease was defined as recurrent pain or progression of the disease on routine follow-up imaging at the same skeletal location of previous embolization. Recurrent pain was never as intense as preembolization pain; the mean score of recurrent pain on visual pain scale was 2–3 points lower than the respective preembolization pain score. In 56 patients with recurrent pain and imaging evidence of progression of metastatic disease, repeat angiography showed increased pathologic vasculature at the same skeletal location; in all these patients, initial embolization was complete, as verified by angiography after completion of the initial procedure. These patients had repeat embolization in the same location; 46 patients had one repeat embolization, and 10 patients had a second repeat embolization within an interval of 1–3 months. The remaining 187 patients had combined radiation therapy or chemotherapy or both based on tumor histology and the discretion of the treating physicians or surgical treatment (12 of 187 patients).

Adverse Events

During the immediate postembolization period, 86 minor complications and 1 major complication occurred. Forty-nine patients (20.2%) exhibited clinical signs of postembolization syndrome as diagnosed by fever or chills, nausea and vomiting, and increased ischemic pain (8–10 points mean pain score on visual pain scale) at the site of embolization. Symptoms resolved completely within less than 1 week in all patients with symptomatic treatment including analgesic and antiemetic medications. Paresthesias were observed in 37 patients (15%) with sacroiliac metastatic lesions and were treated with methylprednisolone 1 g per day for 1 week; in 36 of these patients, paresthesias resolved completely within 1 week, whereas in 1 patient paresthesias persisted for 8 months after embolization. One major complication (0.4%), skin breakdown and subcutaneous necrosis, occurred in a patient with a metastatic paraganglioma of the pelvis after two embolizations.

DISCUSSION

Many studies have reported embolization as an effective treatment for selected primary tumors and bone metastases, associated with rapid reduction in pain and tumor volume lasting 1–9 months (12,15,17,18,20,22–30). However, most of these studies include case reports and small series. In addition, clinical improvement was not always concordant with tumor regression on imaging (15,18,24). In this study, we explored the role of selective embolization for bone metastases in a large series of patients. Embolization had an immediate palliative effect in 97% of the procedures. Imaging showed evidence of tumor necrosis in all cases and variable ossification in 65 patients. This palliative effect is transient, however; symptoms recurred after 8.1 months.

Owing to the heterogeneous group of patients and the retrospective design, we consider our study observational; this may be considered a limitation. However, we believe that the large sample size increased the power of this study. As in the present study, embolization can be repeated without side effects and combined with radiation therapy and chemotherapy (12,19,30). In our series, 197 patients had previous radiation therapy, and 46 patients had chemotherapy or radiation therapy or both; this did not make the

Figure 1. **(a)** Axial computed tomography (CT) scan of the lumbar spine of a 40-year-old man with metastatic renal cell carcinoma at the L4 vertebra. **(b)** Early (left) and late (right) phase digital subtraction aortography shows a hypervascular lesion at L4 level. The feeding vessels originate from bilateral L4 arteries and the left L3 artery. **(c)** Selective embolization through bilateral L4 arteries (left) and left L3 artery (right) was done. **(d)** Late phase digital subtraction aortography after embolization shows complete occlusion of feeding vessels to the hypervascular lesion. **(e)** At 6 months, axial CT scan at the same level shows tumor size reduction and ossification.

procedure more difficult. All embolizations were technically successful and were accompanied by acute improvement in symptoms. However, it can be questioned whether the additional treatments contributed to the success of embolizations or even that the success of embolization may be entirely attributed to these treatments. Oxygen deprivation after embolization is a stimulus for tumor neovascularization and relapse; radiation may prevent this effect (31). Our results have to be interpreted with caution because we did not perform the additional treatments in a randomized fashion and we did not compare with a control group of patients who had either treatment alone; in addition, we did not

Figure 2. (a) Anteroposterior radiograph of left hip joint of a 58-year-old woman with metastatic renal cell carcinoma of the pelvis. (b) Digital subtraction arteriography by selective catheterization of left common iliac artery (arrow). (c) Preembolization (left) digital subtraction arteriography after selective catheterization of left superior gluteal artery (arrow) shows a hypervascular lesion at the left hemipelvis. Postembolization (right) digital subtraction arteriography shows occlusion of feeding vessel originating from left superior gluteal artery (arrow). Repeat embolization was performed at 3 months because of recurrent left hip pain (not shown). (d) Anteroposterior (left) and lateral (right) radiographs of left hip joint at 12 months show extensive ossification of metastatic lesion.

perform a subgroup analysis because of the risk of statistical error as almost all our patients had preembolization radiation therapy.

Because all metastatic bone lesions are hypervascular (12,13), embolization may be indicated for all patients with these lesions. Indications for embolization of bone metastases include control of hemorrhage, facilitation of subsequent surgery, inhibition of tumor growth, and relief of pain secondary to decrease in tumor volume and pressure on the richly innervated periosteum and adjacent structures (12,13,17,18,24,29). In our clinical practice, we perform embolization at the request of orthopaedic surgeons. In the current large series, embolization was employed in all patients for palliation. After embolization, surgical treatment was performed in 12 patients; surgery was impossible in all of these patients until embolization was performed.

Despite our lack of data on blood loss and transfusions

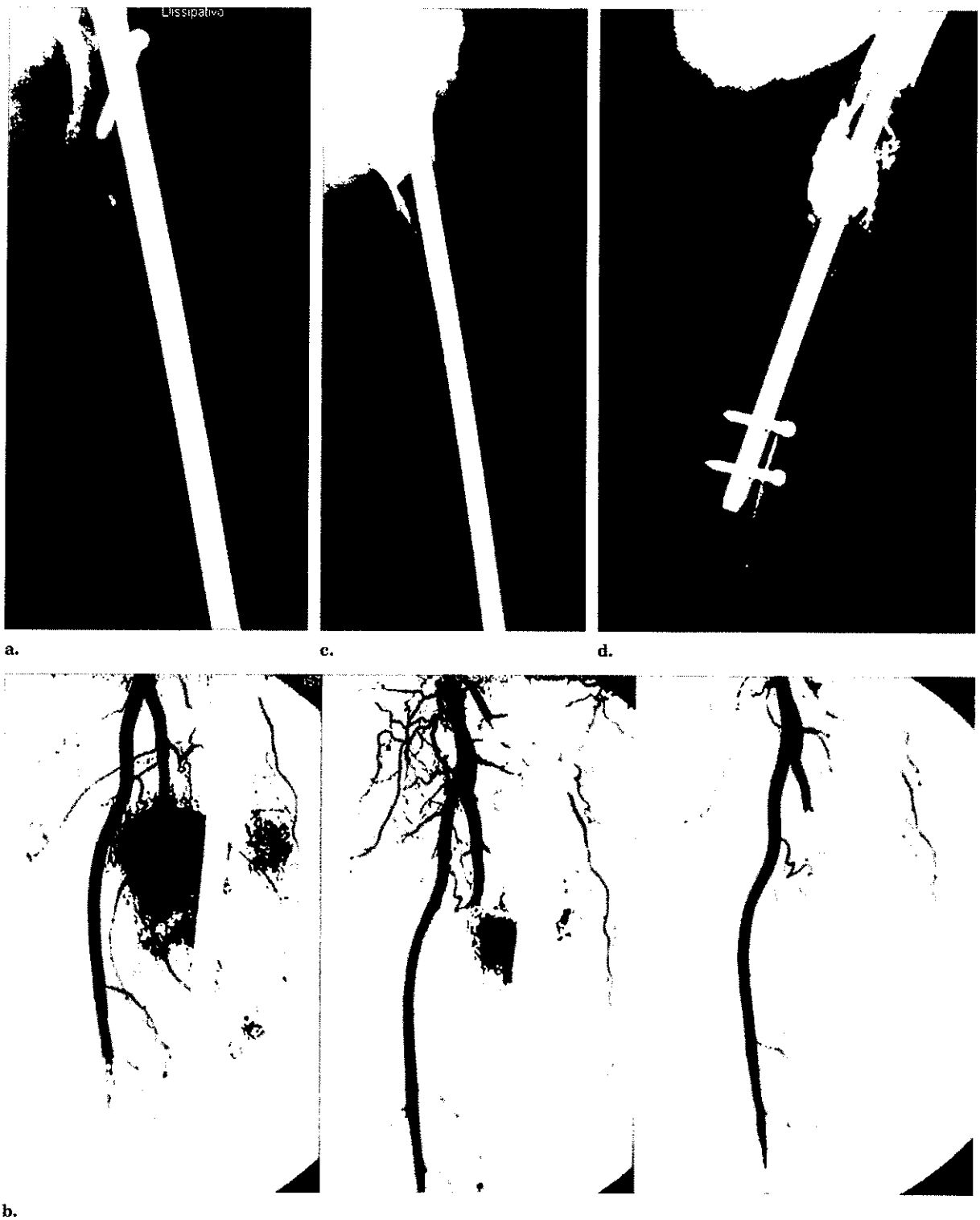

Figure 3. **(a)** Lateral radiograph of the left femur of a 62-year-old man with pathologic fracture from metastatic lung cancer treated with intramedullary nailing, cementation, and postoperative radiation therapy. **(b)** Because of progressive osteolysis and nonunion, embolization through the deep femoral artery was done. Lateral radiographs at 6 months **(c)** and at 12 months **(d)** after embolization show extensive ossification.

for subsequent surgery, we recommend preoperative embolization for highly vascular tumors to reduce intraoperative blood loss if curettage is planned. In the few cases in which wide resection is planned, such as renal or thyroid solitary bone metastases without extraskeletal metastases, there is no indication for preoperative embolization because it

would lead to marked hypervascularity in the area surrounding the tumor, which would result in heavy bleeding during surgery (15).

Previous studies have shown that clinical improvement was not always concordant with tumor regression on imaging (15,18). In the present series, as expected, the best clinical and imaging results were observed in highly hypervascular tumors such as renal and thyroid, followed by breast and lung bone metastases. Hypoattenuating areas resembling necrosis and tumor size reduction were observed in all patients; variable ossification was observed in 65 patients with renal, thyroid, breast, and lung cancer. We explain that observation by the high hypervascularity of these lesions. In six of these patients, ossification was abundant; in these patients, progression of the disease was not observed at imaging follow-up evaluation. However, even among patients who do not show postembolization ossification of the tumor, embolization can reduce the pathologic vascularity and blood loss during surgery (32). Increased hypoattenuating areas and reduction of tumor size were also observed in lesions of the shoulder girdle; this can be explained by the high vascularity of the area. Based on these results, we believe that the most important factor for embolization of metastatic lesions is the vascularity of the lesions rather than the histology or the tumor size.

Even if partial devascularization has been achieved, embolization has been associated with low complication rates (4,5,11,12,15,17,18). Postembolization syndrome with symptoms such as fever, pain, and malaise is a complication reported in 18%–86% of cases (4,15). Embolization of adjacent or distant nontargeted vessels can result in normal tissue loss and may be associated with nerve palsy, skin breakdown, and subcutaneous or muscle necrosis and infection (4,12,19,33). The risk of complications is higher in certain anatomic regions. In the spine, a connection between the artery of Adamkiewicz that originates between the T5 and L2 vertebra and the tumor-feeding vessels must be recognized on preembolization angiography. During pelvic embolizations through the iliac artery and its branches, ischemic neuropathies of the sciatic and femoral nerves may occur if neural vessels were occluded. To prevent these complications, the posterior branch of the internal iliac artery and the inferior gluteal artery must be spared at embolization (34).

Complications related to the embolic agents have also been reported (4,31,35). Gelfoam, polyvinyl alcohol particles, liquid (absolute alcohol), coils, tissue adhesives, ethanol, microfibrillar collagen, and autologous blood clot have been used as embolic agents (23,28). Major considerations for choosing an embolic agent are speed and reliability of delivery, duration of occlusive effect, and preservation of normal tissue (4,12,19,23,28,30). Liquid embolic agents have low viscosity that allows for easy injection through small catheters or catheters with many bends through tortuous blood vessels. NBCA, or "liquid glue," is a liquid embolic agent that spreads according to its polymerization time and the vascular flow. A distinct advantage of NBCA in Lipiodol is its dense radiopacity. Its exact site of occlusion can be observed and documented. It can be used in patients with clotting pathologies (23,28). Bolus administration of small doses (0.1–0.2 mL) of sandwiched NBCA under fluoroscopic control followed by arteriography ensures the efficacy and safety of the procedure. In our practice and the present study, NBCA was the preferred embolic agent because we consider it the most appropriate embolic agent for controlled and permanent occlusion of the target vessels and tumor devascularization. The low number of complications in this study (overall 87 in 309 procedures) suggests that strict adherence to the principles of transcatheter embolization and bolus administration of small doses (0.1–0.2 mL) of sandwiched NBCA under fluoroscopic control are important.

The present study was not designed to determine the effect of embolization on survival; in line with the literature, life expectancy is not influenced by embolization therapy, and embolization therapy does not appear to improve survival (5,29,36). For the most part, embolization targets only a portion of the tumor burden. In the future, specific systemic treatment modalities for cancer patients with bone metastases possibly may be more effective to improve survival; however, local therapies for tumor control such as embolization are valuable, although with a temporary palliative effect.

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