

Embolization of Hypervascular Bone Metastases Reduces Intraoperative Blood Loss: A Case-control Study

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Abstract

Background Small case series suggest that preoperative transcatheter arterial embolization minimizes bleeding and facilitates surgery for hypervascular metastatic bone tumors. However, control groups would make our confidence in clinical recommendations stronger, but small patient numbers make prospective trials difficult to conduct on this topic.

Questions/purposes In this case-control study, we asked whether (1) patients who undergo embolization have less estimated blood loss and/or shorter operative time than

patients who do not have embolization; (2) larger tumor size, greater initial tumor vascularity, and longer interval from embolization to surgery are associated with greater estimated blood loss and packed red blood cell transfusion volume; and (3) embolization does not affect renal function in patients with normal preoperative renal function.

Methods We retrospectively reviewed records of patients with hypervascular bone metastases treated at our institution between 1998 and 2008. Twenty-seven patients with renal cell carcinoma and 12 with thyroid carcinoma who underwent embolization before 41 surgical procedures were matched to 41 patients who did not have embolization with respect to age, diagnosis, tumor size and potential vascularity, and procedure type; matching was performed without knowledge of outcomes. In univariate and multivariate analyses, age, tumor size, use of embolization, surgery type and risk, embolization-to-surgery interval, and degree of devascularization were evaluated for correlations with estimated blood loss, packed red blood cell transfusion volume, operative time, and postembolization renal function.

Results Overall, patients who had embolization had less mean estimated blood loss (0.90 versus 1.77 L; $p = 0.002$), packed red blood cell transfusion volume (2.15 versus 3.56 U; $p = 0.020$), and operative time (3.13 versus 3.91 hours; $p < 0.001$). Larger tumor size correlated with greater estimated blood loss ($r = 0.451$; $p = 0.003$), packed

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red blood cell transfusion volume ($r = 0.50$; $p = 0.002$), and operative time ($r = 0.595$; $p < 0.001$). Neither the interval for embolization to surgery nor the degree of devascularization correlated with estimated blood loss or transfusion volume. In open rodding with intralesional curettage, transcatheter arterial embolization was associated with reduced estimated blood loss, transfusion volume, and operative time. Packed red blood cell transfusion volume was not reduced by embolization in intramedullary nailing procedures with the patient numbers available. Among patients with normal preoperative renal function who had embolization, creatinine levels remained normal. Mild transient, reversible renal function change occurred in one patient with preoperatively abnormal renal function.

Conclusions This study suggests that preoperative embolization probably reduces estimated blood loss, particularly for large tumors and during open femoral procedures.

Level of Evidence Level III, therapeutic study. See the Instructions for Authors for a complete description of levels of evidence.

Introduction

Transcatheter arterial embolization is widely considered to be an effective preoperative procedure to minimize hemorrhage risk during surgery for bone metastases [1–3, 5, 7, 14, 16, 19, 20]. Without embolization, uncontrolled bleeding can increase patient morbidity, and a significant hemorrhage risk may render surgical intervention infeasible. At our institution, embolization often is done for patients with hypervascular pelvic tumors occurring with either extensive bony destruction or fracture associated with a soft tissue component or for patients with hypervascular soft tissue or bony multifocal disease of the extremity. We also believe that the presence of pathologic fracture further increases the bleeding risk. Patient factors that tend to make surgeons more likely to use preoperative embolization include recent myocardial infarction or a significant cardiac history, which consequently increases risk of mortality from perioperative anemia.

Current recommendations for preoperative transcatheter arterial embolization derive from Levels IV and V evidence, therefore further investigation including controlled studies are needed in patients at high risk for hemorrhage. Limitations of previous studies also highlight the need for further elucidation of the influence of tumor size, initial tumor vascularity, degree of devascularization, and embolization-to-surgery interval on the benefits of embolization [1, 7, 12, 13, 16].

We therefore performed a retrospective, case-control study to compare the estimated blood loss, packed red blood cell transfusion volume, operative time, and embolization-related

complication rate among patients with hypervascular metastatic pelvic and extremity tumors who were treated with and without preoperative embolization. Unlike previously published studies [1, 5, 13, 21], we matched patients who had embolization with patients who did not have embolization with respect to age, surgery type, and tumor size. We sought to determine whether (1) patients who have embolization have less estimated blood loss and/or shorter operative time than patients who do not have embolization; (2) larger tumor size, higher initial tumor vascularity, and longer embolization-to-surgery interval, are associated with greater estimated blood loss and packed red blood cell transfusion volume; and (3) embolization has an effect on renal function in patients with normal preoperative renal function.

Patients and Methods

Patients

After obtaining a waiver of patient informed consent requirements from our institutional review board, we searched our institutional database for patients who underwent surgical resection of hypervascular bone metastases to the pelvis or extremities between 1998 and 2008. Our determination of the hypervascular potential of metastatic bone lesions was based on the underlying histologic diagnosis and an extensive lytic radiographic appearance. Medical records were assessed for age, sex, oncologic diagnosis, tumor characteristics, and surgical data including embolization use, preoperative hemoglobin, combined intraoperative and postoperative transfusion volume, and postoperative complications and renal function. All preoperative imaging and records were reviewed by an interventional radiologist (MM) who did not perform the angiographic interventions on patients in this study. Records were reviewed for embolization-associated complications that occurred within 30 days postoperatively. At our institution, complications are documented prospectively by a dedicated nursing team who actively monitor for embolization-associated adverse events and postoperative complications. Symptoms of postembolization syndrome, including nausea, vomiting, pain, and low-grade fever, were not considered complications. For venous thromboembolism prophylaxis, combined low molecular weight heparin and mechanical compression boots were used in all patients, as previously reported [11].

We identified 118 patients with extensive lytic, potentially hypervascular bone metastases from all primary malignancies treated during the study period (Table 1). Fifty-three patients (33 males, 20 females) of the 118 with metastases to the pelvis or extremities from either renal cell carcinoma or thyroid cancer had embolization. We excluded patients with preoperative embolization in whom no

Table 1. Demographics, disease characteristics, and surgery data for 118 patients

Variable	With embolization	Without embolization
Number of patients (female:male)	53 (20:33)	65 (28:37)
Age (years)	30–86 (mean, 61.5; median, 63)	33–85 (mean, 62.6; median, 63)
Number of transcatheter arterial embolization sessions	55*	N/A
Anatomic sites	57 [†]	65 [†]
Femur	20	29
Humerus	16	19
Pelvis	18	13
Scapula	3	4
Tumor size (cm)	2.5–13.5 (mean, 5.8; median, 4.9)	2–13 (mean, 5.2; median, 5)
Tumor type		
Renal	37	36
Thyroid	12	17
Multiple myeloma	2	12
Hepatoma	1	
Paraganglioma	1	
Tumor vascularity on angiography [‡]		N/A
Hypervascular	46	
Mildly hypervascular	9	
Embolization-to-surgery interval		N/A
Same day	11	
1 day	39	
2 days	5	
Surgery type		
Pelvic surgery	6	4
Resection Type III	3	3
Saddle prosthesis	2	1
Resection Type I	1	0
Nailing humerus	12	13
Harrington reconstruction	12	8
Nailing femur	10	13
Long-stem hemiarthroplasty	8	14
Megaprosthesis	5	8
Humerus	4	6
Femur	1	2
Scapulectomy	3	4
Hip arthroplasty	1	1
Combined [§]	3	0

* Two patients underwent two separate preoperative transcatheter arterial embolization sessions; [†]four patients underwent embolization of two sites in the same session; [‡]53 patients underwent 55 embolization sessions; [§]intramedullary nailing of femur and humerus (n = 2); hemiarthroplasty and intramedullary nailing of the humerus (n = 1); N/A = not applicable.

suitable match could be found and patients who, according to institutional treatment philosophies, would never undergo surgical resection without embolization. Two patients had two separate embolization sessions before their respective surgical resections, yielding 55 embolization sessions. Surgical procedures included major pelvic or shoulder girdle resection; intramedullary nailing with or without local tumor curettage; major acetabular and hip reconstruction; long-stem hemiarthroplasty; and proximal long-bone resection and reconstruction. Patients at high risk of major hemorrhage (those with proximal nonspinal disease in whom potential hemorrhage would not be controlled by tourniquet alone) had been prospectively referred for preoperative embolization. Other factors considered in the hemorrhage risk assessment were oncologic diagnosis, evidence of soft tissue extension, regional hyperemia, or a pulsatile mass. Despite hemorrhagic risk factors, however, some patients with potentially hypervascular bone lesions did not undergo preoperative embolization because of renal impairment, interventional radiology or surgical scheduling constraints, or the need for emergent surgical treatment.

We matched the patients who had embolization with patients without embolization who had undergone surgery for metastatic hypervascular tumors from renal cell carcinoma or thyroid carcinoma. Patient matching was based primarily on potential hypervascularity (ie, the underlying histologic diagnosis and lytic radiographic pattern), tumor size (including soft tissue and bony components), and operation type; patients were matched secondarily with respect to oncologic diagnosis, presence of a fracture, and patient age. When no appropriate patient without embolization with renal cell carcinoma or thyroid cancer match could be found, we included patients with multiple myeloma in the comparison group (n = 6). Because not all potentially hypervascular bone lesions were embolized, we assumed that there was no systematic bias that would have caused the patients without embolization to bleed less, given the lytic similarity of the matched pairs and, wherever possible, identical histologic diagnoses. Sixty-five patients without embolization were matched to 53 patients with embolization in this initial phase.

Two independent Memorial Sloan Kettering Cancer Center-affiliated researchers (JG and TJCP) examined the data for matching purposes (one-to-one match), without knowledge of patient outcomes. Each occurrence of embolization with subsequent resection was treated as an independent “patient” for data purposes. Two patients were included twice in the embolization data set, having undergone two separate embolization sessions and surgical resections. Fourteen patients were eliminated from the embolization group: four because no suitable matches were found in the nonembolized group and 10 because either

Table 2. Tumor characteristics that precluded excision without preoperative transcatheter arterial embolization (N = 10)

Patient number	Location	Tumor characteristics
1	Humerus	Multifocal disease with segmental fracture
2	Distal humerus	Pathologic fracture with large soft tissue mass
3	Femur	Multifocal femoral disease with 17-cm soft tissue mass
4	Pelvis	Large hypervascular mass with extensive bony destruction and soft tissue component (6 × 5 cm)
5	Pelvis	Supraacetabular lesion with fracture and soft tissue component (2 × 2 cm)
6	Pelvis	Extensive mass with acetabular destruction and soft tissue component (6 × 5 cm)
7	Pelvis	Lesion with large soft tissue component (6.0 × 3.2 cm) and acetabular fracture
8	Pelvis	Disease with 18 × 9-cm soft tissue periacetabular mass and myocardial infarction the previous week
9	Pelvis/proximal femur	Acetabular lesion with fracture and dislocation of femoral head, soft tissue component (7.1 × 7.6 cm)
10	Proximal femur	Multifocal soft tissue and bony metastatic disease in proximal femur with extension to pelvis and ischium

patient or tumor factors precluded use of nonembolized procedures (Table 2), thereby eliminating any possibility of “true” control subjects without embolization. Thirty-nine patients who underwent 41 procedures with embolization were matched with 41 patients who had 41 procedures without embolization (Table 3). A majority of patients in both groups had renal cell carcinoma metastases. Patients with smaller contained lesions of impending fractures did not have embolization, so they are not included in our patient cohort. In general, insofar as is possible in a retrospective study, we sought to analyze only patients for whom there is currently no consensus regarding the use of preoperative embolization. We tried to limit this study to cases that are the most controversial. The least controversial are eliminated on each end of the spectrum. For example, the large pelvic tumors with extraosseous tumor extension are not included because they would distort the results and the results would not be useful to the clinician trying to decide if embolization were beneficial. Similarly, a simple closed nailing of a contained femoral or humeral lesion was not included since embolization probably would not be done in such cases and their inclusion would distort the results in the opposite direction. We have limited the analysis to patients where the use of embolization is debated.

Transcatheter Arterial Embolization Procedures

Embolizations were performed by our institutional interventional radiology service, with the patient under sedation, using intravenous midazolam and meperidine hydrochloride or fentanyl citrate. Sedation time correlated with embolization time (50–250 minutes; median, 105 minutes). Using a transfemoral approach, a diagnostic arteriogram was performed with a 4- or 5-French catheter (COBRA 2; AngioDynamics Inc, Queensbury, NY, USA). After evaluation of arterial anatomy and tumor vascularity, the main tumor-feeding arteries were chosen and embolization was done through a coaxial 2.7- to 3-French microcatheter (Progreat®, Terumo, Tokyo, Japan; or Renegade™, Boston Scientific Corp, Fremont, CA, USA). Polyvinyl alcohol (PVA) particles (50–500 μm) (Cook Medical, Bloomington, IN, USA) or Contour SE™ Microspheres or Contour™ PVA embolization particles (150 to 700 μm) (Boston Scientific Corp, Marlborough, MA, USA) were used in most cases (n = 48). Embosphere® microspheres (100 to 700 μm) (Biosphere Medical, Paris, France) were used in seven cases. When arteriovenous shunting was present, larger embolic particles were used first during the embolization to avoid systemic embolization. After blood flow ceased in abnormal veins, smaller embolic particles were used until embolization was complete. Embolization microcoils (Tornado®; Cook Medical) were used to isolate distal nontumor-feeding arteries in seven cases. Iohexol (Omnipaque™; GE Healthcare, Chalfont St Giles, UK) or iodixanol (Visipaque™; GE Healthcare, Shanghai, China) was administered as the contrast agent (mean volume, 140 mL; range, 60–300 mL). The choice of catheters and embolic agents was at the discretion of the interventional radiologist.

The primary endpoint of each embolization procedure was the highest degree of devascularization of the target tumor(s) that was safely achievable. The technical success of the embolization was defined as the ability to identify and selectively cannulate main arterial feeders of the target tumor(s). Based on the angiographic appearance of tumor blush before embolization, we classified tumor vascularity as hypervascular (the visible tumor blush was as intense as the contrast-filled normal adjacent artery), mildly hypervascular (visible tumor blush was less intense than the contrast-filled normal adjacent artery), or nonhypervascular (no visible tumor blush). To ensure that the angiographic evaluation of tumor blush before and after embolization was performed at the same time after contrast injection, the intensity of contrast in an adjacent artery was used as a reference, as its preembolization and postembolization intensity should be identical.

Of 27 patients with renal cell carcinoma, 24 had hypervascular metastases and three had mildly hypervascular metastases. Among 12 patients with thyroid cancer,

Table 3. Demographics and disease characteristics of patients matched by tumor site and surgery

Variable	With embolization	Without embolization
Number of patients	39	41
Age (years)	30–86 (mean, 61.2; median, 64)	33–85 (mean, 61.2; median, 63)
Number of embolization sessions	41*	N/A
Tumor size (cm)	2.5–13.3 (mean, 5.3; median, 4.7)	2–13 (mean, 5.3; median, 5)
Tumor type		
Renal	27	25
Thyroid	14	10
Multiple myeloma		6
Tumor vascularity on angiography		N/A
Hypervascular	35	
Mildly hypervascular	6	
Embolization-to-surgery interval		N/A
Same day	9	
1 day	28	
2 days	4	
Estimated blood loss (L)	0.90 L ± 1.23 L [†] (0–7 L; mean, 0.90; median, 0.50)	1.77 L ± 2.59 L (0.1–15.5 L; mean, 1.77; median, 1.00)
Packed red blood cell transfusion volume (U) [‡]	2.15 U ± 3.03 U (0–16 U; mean, 2.15; median, 2.00)	3.56 U ± 5.37 U (0–31 mean, 3.56; median, 2.00)
Operative time (hours)	3.13 ± 1.55 [§] (1.5–9; mean, 3.13; median, 3.00)	3.91 ± 2.47 (1.5–17; mean, 3.91; median, 3.50)
Anatomic sites	41	41 Matched for both groups
Femur	30	30
Humerus	4	4
Pelvis	4	4
Scapula	3	3
Surgery type		Matched for both groups
Pelvic surgery	4	4
Resection	3	3
Saddle prosthesis	1	1
Femur/acetabular reconstruction	30	30
Femoral nailing or limited excision–open nailing combination	16	16
Open femoral surgery (long-term hemiarthroplasty, THA, Harrington reconstruction, proximal femoral resection)	14	14
Proximal humeral resection	4	4
Scapulectomy	3	3

* Two patients underwent two separate preoperative embolization sessions; †*p* = 0.002 versus without embolization group; ‡transfusion within 48 hours of surgery; ||*p* = 0.02 versus group without embolization; §*p* = 0.009 versus group without embolization.

11 had hypervascular metastases and three had mildly hypervascular metastases. Two patients with thyroid cancer each had two separate lesions. A mean of 2.8 vessels per case were embolized (median, 3; range, 1–7) (Table 3). Technical success was achieved in all cases, with greater than 80% devascularization in 38 cases and 50% to 70% devascularization in three cases.

Data and Statistical Analyses

Descriptive statistics were performed on all dependent and independent variables in the groups with embolization and without embolization. Estimated blood loss, packed red blood cell transfusion volume, and operative time were set as dependent variables, and possible independent variables

were age, sex, anatomic location, lesion size in greatest diameter, oncologic diagnosis, initial tumor vascularity, degree of devascularization, embolization-to-surgery interval, operation type, and surgical margins. Preoperative hemoglobin was considered for inclusion as an independent variable, especially for predicting packed red blood cell transfusion volume. However, the preoperative hemoglobin of both groups did not differ with respect to statistical or clinical significance, nor did they correlate with any of the three dependent variables in an individual univariate correlation. Therefore, the preoperative hemoglobin was viewed as a population descriptor as opposed to an independent variable to be explored.

We performed univariate analysis using paired t-tests to compare estimated blood loss, packed red blood cell transfusion volume, and operative time between the groups. Further, paired t-tests were used to compare these dependent variables in each of the following anatomic subgroups: humerus; intramedullary nailing or limited excision–open nailing combination; open femoral surgery including long-stem hemiarthroplasty, THA, Harrington reconstruction (reinforcement of acetabular deficiency with pins, cement, and antiprotrusion ring prostheses) [8]; proximal femoral resection; and pelvic or scapular surgery.

Univariate analyses with Pearson and Spearman correlation coefficients were used to determine if age, sex, degree of devascularization, surgical margin status, embolization-to-surgery interval, lesion size, location, tumor vascularity, oncologic diagnosis, or operation type were correlated with estimated blood loss, operative time, and/or packed red blood cell transfusion volume. Examination of the initial descriptive statistics showed that degree of devascularization and oncologic diagnosis were of significant homogeneity (near complete devascularization and predominantly renal cell or thyroid carcinoma) that they acted more as descriptors of our population and were not logically useful to include in further analysis. Neither was correlated with the dependent variables on independently performed univariate analyses. In finality, three outcome measures (estimated blood loss, packed red blood cell transfusion volume, and operative time) were tested against six hypothesized predictors (embolization-to-surgery interval, initial tumor vascularity, surgical margins, age, surgery type, and tumor size). Using the Bonferroni correction for 18 correlations decreases the alpha value for statistical significance from 0.05 to 0.003 for each correlation coefficient. This adjustment generally is useful when comparing groups of variables; however, caution must be used in interpreting the results of smaller clinical studies such as ours. Our statistical findings remained the same, regardless of whether we applied the correction.

We performed multivariate regression analyses for each of the three dependent variables (estimated blood loss,

packed red blood cell transfusion volume, and operative time), with four independent variables (age, tumor size, vascularity, and high/low risk level of operation) to maintain adequate degrees of freedom respecting the confines imposed by our sample set of 41. Treating each regression as a separate entity, alpha was set at 0.05 for statistical significance. To minimize the number of dummy variables used and retain degrees of freedom, we stratified operation types ordinally by anatomic site and extent of surgical dissection involved: (1) humerus ($n = 4$); (2) intramedullary nailing or limited excision–open nailing combination ($n = 16$); (3) open femoral surgery (long-stem hemiarthroplasty, THA, Harrington reconstruction, proximal femoral resection) ($n = 14$); and (4) pelvic or scapular surgery ($n = 7$).

“Low-risk/minimal exposure” included humeral surgeries and intramedullary procedures with lesional curettage, and “high-risk/extensive surgical dissection” included open proximal femoral surgery and pelvis or scapular surgery. Tumor size was the only independent variable significantly correlated with estimated blood loss, packed red blood cell transfusion volume, and operative time on univariate analysis (see [Results](#)). We expected that initial tumor vascularity and operative risk level would be clinically significant and therefore included those as independent variables in the multivariate regression. Margin status and embolization-to-surgery interval were not correlated with estimated blood loss, operative time, or packed red blood cell transfusion volume, in part owing to homogeneity, on univariate analysis and were not included subsequently in the multivariate analysis. Although age and sex are commonly included as covariates in multilinear regression, we included only age, as sex was not expected to play a role in influencing the above-mentioned dependent variables.

Using the paired t-test, we compared preoperative and postoperative creatinine levels to evaluate embolization-related renal function changes. For postoperative values, the last creatinine level measured in the first postoperative week was used.

Statistical analyses were performed with SPSS software (Version 15.0; SPSS Inc, Chicago, IL, USA). Statistical significance was defined as a probability less than 0.05.

Results

Compared with patients who did not have embolization, patients who had embolization had less mean estimated blood loss, less packed red blood cell transfusion volume, and shorter operative time (Table 3). Univariate analysis of the group with embolization showed that larger tumor size was strongly correlated with greater estimated blood loss

Table 4. Univariate analysis of outcome measures by surgery type

Surgery type	Outcome measure	p value* (95% CI [†])
Open femoral (n = 14)	Estimated blood loss	0.009 (−1.827–0.315) [§]
	Packed red blood cells	0.018 (−3.601–0.399) [§]
	Operative time	0.007 (−2.169–0.413) [§]
Pelvic and scapular (n = 7)	Estimated blood loss	0.181 (−4.896, −1.153)
	Packed red blood cells	0.281 (−9.204, −3.204)
	Operative time	0.558 (−4.209, −2.509)
Femoral nailing (n = 16)	Estimated blood loss	0.029 (−0.943, −0.057) [§]
	Packed red blood cells	0.483 (−2.119, 0.993)
	Operative time	0.125 (−0.934, 0.126)
Humeral (n = 4)	Estimated blood loss	0.876 (−0.692, 0.617)
	Packed red blood cells	0.092 (−0.299, 2.299)
	Operative time	0.131 (−3.270, 0.697)

* Patients with embolization versus without embolization; [†]95% CI values represent the difference in the mean values of the two patient groups; [§]significant values.

($r = 0.451$; $p = 0.003$), packed red blood cell transfusion volume ($r = 0.50$; $p = 0.002$), and operative time ($r = 0.595$; $p < 0.001$).

Significant differences in estimated blood loss, packed red blood cell transfusion volume, and operative time were not found in every anatomic subgroup. In the open femoral surgery group, embolization reduced estimated blood loss ($p = 0.012$), packed red blood cell transfusion volume ($p = 0.008$), and operative time ($p = 0.024$). In the intramedullary nailing plus curettage group, less estimated blood loss ($p = 0.029$) was associated with embolization. There was low power in rejecting the possibility that embolization influenced transfusion volume and operative time. In the pelvic and scapular group, there was poor power to reject the possibility of a relationship between embolization and reduced estimated blood loss, packed red blood cell transfusion volume, and operative time, and in the humerus group, that there was a relationship between embolization and estimated blood loss and operative time (Table 4). Postoperatively, no patient had blood loss estimated at greater than 100 mL, and none had blood loss that contributed to the decision to transfuse.

Multivariate regression analyses showed that only larger tumor size was correlated with greater estimated blood loss ($p = 0.017$), packed red blood cell transfusion volume ($p = 0.010$), and operation time ($p < 0.001$) at the 5% level. Age was not correlated with increased estimated

Table 5. Multivariate analysis of factors influencing primary endpoints

Outcome measure	p value
Estimated blood loss	
Age	0.295
Tumor size	0.017*
Vascularity	0.869
Operation type (high/low risk)	0.089
Packed red blood cell transfusion volume	
Age	0.200
Tumor size	0.010*
Vascularity	0.813
Operation type (high/low risk)	0.240
Operative time	
Age	0.813
Tumor size	< 0.001*
Vascularity	0.491
Operation type (high/low risk)	0.062

* Significant values.

blood loss or packed red blood cell transfusion volume, nor was oncologic diagnosis (Table 5).

Patients with normal preexisting renal function did not develop impaired renal function after transcatheter arterial embolization. Excluding one patient with preexisting renal failure, the mean increase in creatinine levels was 0.06 mg/dL ($p = 0.123$). No complications were noted immediately after embolization; however, two patients eventually had surgical wound healing problems that required local, non-surgical wound care. No other complications occurred during the 30-day postoperative period.

Discussion

In this case-control study, we found that (1) patients who have embolization have less estimated blood loss and/or shorter operative time than patients who do not have embolization; (2) larger tumor size, higher initial tumor vascularity, longer embolization-to-surgery interval, and positive surgical margins are associated with greater estimated blood loss and packed red blood cell transfusion volume; and (3) embolization does not affect renal function in patients with normal preoperative renal function.

We acknowledge significant limitations in our study. Our case series is retrospective, and sample selection bias likely influenced our analysis. By excluding patients for whom it would be unreasonable to consider surgical intervention without embolization, we effectively only consider “borderline” patients in our analysis. In some patient subgroups, this resulted in a small sample, limiting

the statistical effect of the analysis. This was particularly true in the circumstances where we rarely would consider performing the procedure without prior embolization. The conclusions, including the lack of statistical significance, had low power and easily could have missed a clinically significant result that would have supported embolization in these patients.

There are numerous problems with our study. First, it is retrospective and our questions can be answered definitively only through a prospective randomized trial that is logistically impossible to perform. Second, there are insurmountable problems associated with matching cases. By matching the top five variables that correlate with blood loss in these cases, we hopefully minimized this systematic error. In retrospect, it is impossible to determine why patients in the comparison group did not have embolization. Any of the factors that dissuaded the surgeon from embolization could have influenced the results. However, one might suspect that patients who did not have embolization were thought to have a lower bleeding potential. Because the patients who had embolization had an expectedly lower blood loss, it suggests that the comparison group was actually a suitable control and that the control group was representative of the population at large. We also acknowledge that estimated blood loss is a semi-quantitative variable with multiple potential sources of bias that could lead to misleading results; despite its being performed prospectively, and routinely being derived and agreed on by consensus of the surgery and anesthesia team, the value of this variable may be inaccurate.

Owing to the wide array of reasons that could account for the surgeon not ordering embolization, we assumed that there was no systematic bias that would have caused the patients who did not have embolization to have bled less. If there had been major bias, the patients without embolization would have had less bleeding and transfusions; however, this did not occur. Thus, the actual study data undermine the potential concerns regarding selection bias.

The clinical value of embolization in patients undergoing intramedullary nailing may be less than that in patients undergoing open extremity surgery, but embolization still may be warranted, depending on the specific patient risk-benefit profile. Barton et al. [1] reported a mean estimated blood loss of 0.5 to 2.8 L with embolization versus 6.8 L without embolization, and Roscoe et al. [13] reported a mean estimated blood loss of 0.9 L versus 1.9 L. However, both studies report only historical groups and do not include either patient matching or statistical analysis. Wirbel et al. [21], who did include a statistical analysis, reported a difference in estimated blood loss between patients with and without embolization.

Only tumor size correlated with estimated blood loss, packed red blood cell transfusion volume, and operating

room time. Possible explanations for these results are that (1) larger tumors take longer to remove and bleed more; and (2) there is an increased propensity to transfuse patients during longer cases in which greater blood loss is likely. Packed red blood cell transfusion volume is determined by the surgical and anesthesiology teams. Little consensus exists in the literature regarding the effect of tumor size on estimated blood loss. Sun and Lang [16] reported a weak correlation ($r^2 = 0.02$) between tumor size and estimated blood loss, whereas Kickuth et al. [7] found a moderate correlation ($r = 0.51$). We found a strong correlation between tumor size and estimated blood loss on multivariate analysis. No agreement exists on the effect of degree of devascularization on estimated blood loss. Some authors suggest that tumor devascularization reduces estimated blood loss [2, 4, 6, 16]; however, some have found no correlation between tumor devascularization and estimated blood loss [7]. In our study, we found no correlation between degree of devascularization and estimated blood loss. This finding may be attributable to the homogeneity of the dataset (38 of 41 patients had full embolization). Even with successful embolization, substantial blood loss is still possible. Because embolization blocks arterial blood inflow but not venous outflow, bleeding from venous blood pooling can occur, particularly in sites that drain into Batson's plexus of valveless veins (pelvis, spine, proximal femur, and proximal humerus). Acknowledging these caveats, we continue to endorse the strategy of maximizing the degree of devascularization, as permitted by patient safety. Furthermore, we suggest that embolization should be performed when intralesional tumor excision (curettage) is planned [1]. The small number of patients with intralesional positive margins did not allow us to show statistical significance; however, clinical prudence dictates the use of strategies to reduce blood loss while dissecting a highly vascular tumor bed.

Although beneficial, embolization is not without risk. In our patient cohort, most patients had undergone nephrectomy. However, no complications or notable changes in creatinine levels occurred immediately after embolization in patients with preexisting normal renal function. In patients with preexisting renal impairment, a nephrologist should assess the risk of postprocedural dialysis. In all patients, we advocate careful technique, minimal contrast load, and adequate postprocedural hydration [9, 18]. Despite these precautions, catastrophic renal failure risk may remain, as the precise pathophysiology of contrast-induced nephropathy has yet to be identified [10, 15, 17]. This low-frequency, high-significance complication must be considered when opting to use embolization.

Our retrospective, case-control analysis showed that preoperative embolization is a safe procedure associated with minimal morbidity and no significant adverse effect

on patients with preoperative normal renal function. Our findings are consistent with those of others who have suggested that embolization is associated with reduced blood loss and transfusion volume and shorter operative time. Unlike previously published studies [1, 5, 13, 21], which lacked control groups, we compared outcomes in patients who underwent preoperative embolization with other patients who did not, matching subgroups for operation type and tumor size. Despite the retrospective nature of this study and the lack of a truly valid comparison group, we believe these results further confirm our institutional experience. We recommend embolization for patients with large hypervascular tumors of the pelvis, scapula, and femur, and for associated pathologic fracture.

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