

# The Value of Serial Arteriography in Osteosarcoma: Delivery of Chemotherapy, Determination of Therapy Duration, and Prediction of Necrosis

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**PURPOSE:** To investigate the value of serial arteriography to assess tumor response, predict necrosis, and individualize the duration of a combined intravenous (IV) and intraarterial (IA) neoadjuvant chemotherapy protocol in patients with biopsy-proven high-grade osteosarcoma or malignant fibrohistiocytoma of bone.

**MATERIALS AND METHODS:** Between July 1987 and March 2003, 109 patients completed a chemotherapy protocol of neoadjuvant IV doxorubicin and IA cisplatin. Patients were eligible regardless of age, disease stage, or disease site. A minimum of three IA cycles followed by definitive surgery was required for inclusion in the final analysis. IA dose and duration were increased for tumors larger than 10 cm. Initial arteriograms were scored as indicating mild, moderate, or marked tumor neovascularity (TNV). Subsequent arteriograms were prospectively compared with the baseline image for percent change in TNV. Treatment continued until a maximum of five cycles were administered or one of three criteria were met: (i) at least 90% decrease in TNV, (ii) plateau of effect, or (iii) no response.

**RESULTS:** Of 408 IA procedures, 42 patients underwent three cycles, 53 underwent four, and 14 required five cycles of neoadjuvant therapy. There was a 2.5% minor complication rate. Eighty-six percent of patients exhibited at least 90% decrease in TNV and 82% exhibited good histologic response ( $\geq 90\%$  tumor necrosis). Serial arteriography predicted a good histologic response with an accuracy of 90% and a sensitivity of 97%.

**CONCLUSIONS:** Serial arteriography was highly sensitive and accurately predicted good responses. This individually modified, dose-intensified neoadjuvant protocol yielded an excellent histologic response rate with minimal complications. Future endeavors should involve a multiinstitutional study of this unique approach.

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**Abbreviations:** IA = intraarterial, IV = intravenous, MFH = malignant fibrohistiocytoma, PET = positron emission tomography, TBR = tumor/background ratio, TNV = tumor neovascularity

INTRAAARTERIAL (IA) chemotherapy has been used for decades to treat different malignancies with a variable

but overall positive response. The areas of greatest historic interest for IA therapy include primary and second-

ary hepatic malignancies, advanced bladder and cervical cancers, and head and neck neoplasms. More recently, this therapeutic approach has been applied to treat high-grade soft-tissue sarcomas and bone cancers such as osteosarcoma and malignant fibrohistiocytoma (MFH) (1-8).

This article will focus on the use of serial arteriography during neoadjuvant chemotherapy to treat patients with high-grade osteosarcoma or MFH of bone. Four objectives are outlined: (i) to assess tumor response and

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predict necrosis; (ii) to determine if the duration of neoadjuvant chemotherapy can be individualized and response-based; (iii) to determine if good histologic response rates ( $\geq 90\%$  necrosis) can be increased by intensifying the administration of neoadjuvant agents; and (iv) to determine the sensitivity, specificity, and accuracy of arteriography in predicting a good histologic response.

## MATERIALS AND METHODS

### Study Design

This was a prospective, institutional review board-approved, single-arm study of newly diagnosed high-grade osteosarcoma and MFH of bone. All arteriography procedures and IA infusions were performed at a single institution (Presbyterian/St. Luke's Medical Center, Denver, CO).

To be eligible, patients were required to have biopsy-proven newly diagnosed high-grade osteosarcoma or MFH of bone. In the majority of cases, adequate biopsy tissue was obtained via core needle technique. If this sample proved to be nondiagnostic, an open incisional biopsy was performed. Residual primary tumor after biopsy with tumor neovascularity (TNV) demonstrable by arteriography was required for study entry. Acceptable variants of osteosarcoma included chondroblastic, fibroblastic, telangiectatic, and periosteal variants. Parosteal and other low-grade osteosarcomas were excluded. Inclusion was not limited by patient age, site of primary tumor, or disease stage. Normal cardiac and renal function were required before study entry. No previous chemotherapy or radiation therapy was allowed.

To be evaluable, patients had to receive a minimum of three cycles of neoadjuvant intravenous (IV) doxorubicin and IA cisplatin and have the percent decrease in TNV quantified on the final preoperative arteriogram. In addition, evaluable patients had to undergo definitive resection of the primary tumor after neoadjuvant chemotherapy and have documentation of the percentage of tumor necrosis in the pathologic analysis of the resected tumor. Off-protocol therapy between the final IA treatment and definitive surgery was not allowed.

### Patient Group

Between July 1987 and January 2003, 147 consecutive patients were diagnosed with high-grade osteosarcoma or MFH of bone. Fifteen patients were ineligible as a result of previous tumor excision ( $n = 9$ ), lack of identifiable TNV ( $n = 4$ ), and a preexisting cardiac condition ( $n = 2$ ). Eleven patients declined to participate. Twelve patients were not evaluable for the following reasons: no pathologic specimen available because of unresectable sacral tumor ( $n = 3$ ), failure to complete three cycles because of chemotherapy-related toxicity ( $n = 3$ ), protocol noncompliance ( $n = 2$ ), definitive surgery performed elsewhere and unavailable pathologic specimen ( $n = 2$ ), unrelated early death ( $n = 1$ ), and refusal of surgery ( $n = 1$ ). Of the 121 patients who entered the study, 109 (75 male patients and 34 female patients) were fully evaluable.

There were three patients with stage IIA disease, 90 with stage IIB disease, and 16 with stage III disease according to the Enneking surgical staging system (9). In this staging system, stage I tumors are of low pathologic grade and therefore ineligible for this study. Stage IIA (intracompartmental) and stage IIB (extracompartmental) tumors are of high grade without metastasis, and stage III tumors have metastasis present at diagnosis. The average age of the 109 evaluable patients was 24 years (range, 5–77 years). Ninety-nine patients had osteosarcoma and 10 were diagnosed with MFH of bone. Patient demographics are detailed in **Table 1**. Fourteen patients presented with pathologic fracture at diagnosis and one patient incurred a fracture during neoadjuvant therapy.

### Neoadjuvant Therapy Methods

After biopsy, patients were scheduled as soon as possible for their first cycle of chemotherapy. Patients had a central venous access device placed before commencement of therapy. Neoadjuvant therapy consisted of repetitive cycles of IV doxorubicin administered at a dose of 90 mg/m<sup>2</sup> as a continuous infusion over 48–72 hours beginning on day 0 of each cycle. The majority of infusions were delivered in the outpatient setting, allowing pa-

**Table 1**  
Patient Demographics (N = 109)

Characteristic	No. of Patients
Sex	
Male	75
Female	34
Age Group (y)	
0–19	67
20–29	15
30–39	11
40–49	6
50–77	10
Primary Site	
Femur	57
Tibia	32
Humerus	8
Other Extremity Bone	3
Nonextremity Bone	9
Stage*	
IIA	3
IIB	90
III (metastatic)	16
Histology	
Osteosarcoma	99
MFH	10

tients to remain at home or attend school or work as tolerated. Each 24-hour aliquot was mixed in 250–500 mL of dextrose 5% in water with 0.45% sodium chloride and infused through a small portable pump. Most patients also had an antiemetic agent (ondansetron or granisetron) added to the infusion.

After completion of the IV infusion, overnight inpatient hydration consisting of dextrose 5% in water with 0.45% sodium chloride plus 20 mEq/L KCl and 1g/L of MgSO<sub>4</sub> infused at a rate of 150 mL/m<sup>2</sup>/h was given in preparation for the arteriogram and subsequent IA chemotherapy the following day.

Patients were brought to the interventional radiology suite for arteriography. General anesthesia was administered for patients 12 years of age and younger. For patients at least 15 years of age, local anesthesia and IV-assisted conscious sedation was used. Those between ages 12 and 15 were individually evaluated and appropriately sedated or anesthetized. A Foley catheter was placed in the majority of female patients to decrease motion and improve ease of urination. Male patients were able to use a urinal with minimal motion and did not require this intervention. The appropriate

common femoral access site was prepared and draped in a sterile fashion. In most cases, the entry site for the initial diagnostic arteriography and IA cisplatin infusion was via the contralateral groin for pelvic, hip, and femoral tumors. When anatomically and physiologically feasible (all tumor blood supply via the superficial femoral artery or distal), subsequent arteriography and IA cisplatin infusions were performed with an antegrade femoral approach.

Femoral artery access was achieved with a single-wall technique with use of a 21-gauge needle and 4-F or 5-F micropuncture system (Cook, Bloomington IN). Vascular sheaths were rarely used unless oozing at the procedural puncture occurred. Variably shaped 4-F and occasionally 5-F end hole catheters were used for diagnostic arteriography. Detailed studies of the tumor-bearing region were then carried out to ascertain the arterial trunk source of all the feeding branches and to record TNV. Subselective arteriography of potentially contributing trunk vessels (internal/external iliac arteries for pelvic tumors, superficial/deep femoral arteries for thigh tumors) was performed, including contralateral studies for nonextremity tumors approaching the midline. When the target trunk vessel providing the tumoral arterial supply was identified, the catheter was placed and anteroposterior and lateral orthogonal arteriograms of the tumor were obtained.

The contrast agents used in the study period evolved from ionic Conray 60 (Mallinckrodt Medical, Hazelwood, MO) to nonionic Isovue 300 (Amersham, Piscataway, NJ) and, after 1995, to low-osmolar, water-soluble, ionic Visipaque 320 (Amersham). Injection volume and rate were robust to enhance opacification and visualization of the TNV. Flow rates varied depending on vessel size. For example, the flow rate for the common or external iliac artery was 24 mL at 8 mL/sec, and for the common femoral or large superficial femoral artery, it was 21 mL at 7 mL/sec. Injection duration was strictly limited to 3 seconds to provide a tight arterial bolus. Before 1999, the majority of studies were performed with use of Schoenander 14-inch × 17-inch cut radiographs with hand subtractions. Since then, a Flu-

oricon AFM or LUA imaging system (GE Medical Systems, Milwaukee, WI) has been used for digital subtraction. Imaging runs were obtained at two films per second.

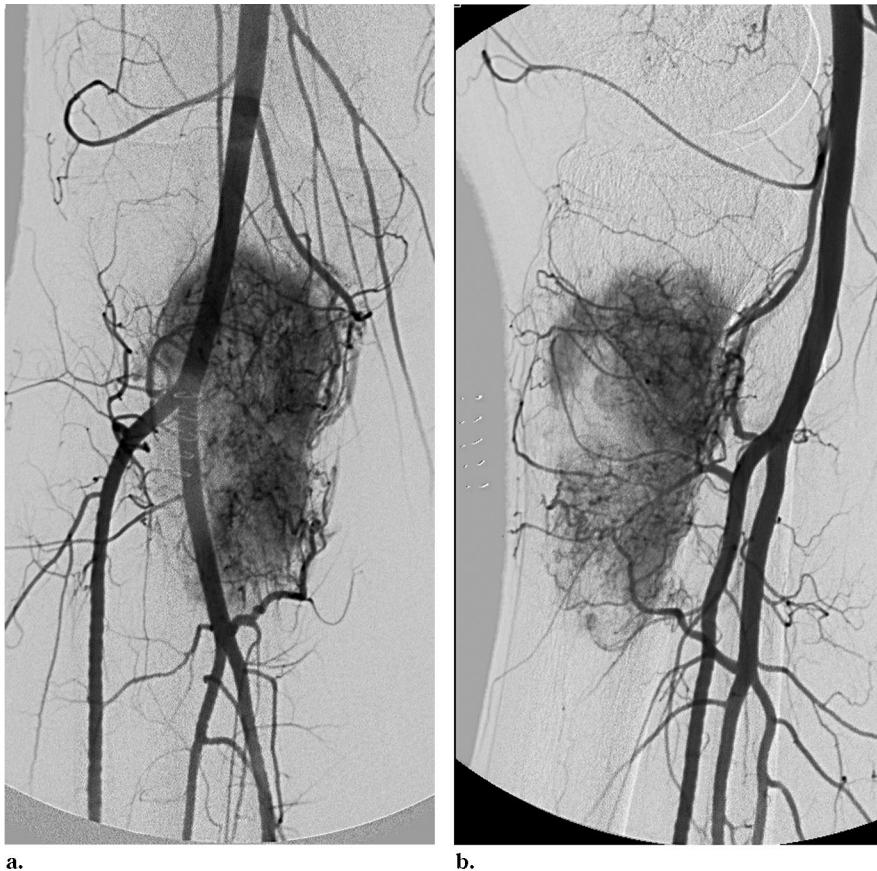
In an effort to eliminate artifactual changes from study to study, all imaging and injection parameters selected at the initial examination (eg, catheter location, magnification factor, table location, tube angulation, subtraction techniques, contrast agent type, volume, and rate) were meticulously recorded and reproduced at each succeeding study. The infusion catheter (initially 5-F end hole and, since 1997, straight 4-F, six-side hole for lower extremity/pelvic and H1 4-F end hole for upper extremity tumors) was then positioned in the target trunk artery and fixed in place.

Because infusion catheter tip proximity to non-tumor supplying musculocutaneous branch artery origins appears to be the chief determinant in the development of localized chemotoxic soft-tissue necrosis, every effort was made to position the catheter tip at the upper end of the longest branch-free segment of the target trunk vessel. This was achieved by slowly pulling the catheter back under continuous fluoroscopy with gentle hand injections. A digital subtraction imaging run with gentle hand injection of contrast material was then obtained to document final catheter position. If no localized chemotoxic event developed after the initial cisplatin infusion, subsequent infusions were performed from the same location. After catheter fixation at the femoral insertion site with built-in catheter redundancy, dressing placement, and surgical drape removal, catheter tip position and stability were reconfirmed with fluoroscopy immediately before cart transfer. All arterial infusions of cisplatin in this study were performed with use of rapid pulsatile jet infusion made possible by a Gianturco-Wallace Chemo-Pulser Pump (Cook), which was attached to the arterial catheter tubing in the interventional radiology suite. Catheter patency was maintained with an infusion of dextrose 5% in water with heparin 3000 U per 500 mL delivered via IVAC pump (Alaris Medical Systems, San Diego, CA) at 60 mL/h. The patient was returned to the appropriate oncology unit and IA cisplatin infusion was initiated. All pa-

tients were strictly limited to bed rest after placement of the arterial catheter. The urinary catheter remained in place until the IA chemotherapy was completed. Infusion of cisplatin into a large artery should not be perceptible to the patient. If pain or paresthesias developed with initiation of the infusion, the patient was returned to the interventional radiology suite for catheter position check and repositioning if necessary.

IA cisplatin was administered as a 6-hour infusion at a dose of 120 mg/m<sup>2</sup> for primary tumors no larger than 10 cm in the largest dimension. For primary tumors larger than 10 cm or for patients with metastatic disease, a 24-hour infusion at a dose of 160 mg/m<sup>2</sup> was given. The 6-hour standard dose infusion was mixed in 3% (hypertonic) normal saline solution to a total volume of 300 mL and was infused at 50 mL/h for 6 hours. The high-dose infusion (3% normal saline solution) was mixed to a total volume of 1,000 mL and infused at 40 mL/h for 24 hours. Mannitol was not used with either infusion; however, patients received a single dose of furosemide (0.5 mg/kg) before initiation of the infusion. Two times maintenance IV fluids, with use of the same fluid used for the prehydration, were continued after cisplatin infusion. After the cisplatin infusion was completed, the same IV fluids were continued at the rate equal to two times the calculated maintenance requirement for each patient. Volume adjustments were made in the rare cases of children who weighed less than 30 kg.

All patients were monitored closely for decreased urine output, diminished pedal pulses, diastolic hypertension, hematoma at the arterial catheter site, and evidence of arterial spasm. The arterial catheter was removed promptly at the completion of the chemotherapy infusion by a member of the interventional radiology staff. Most pediatric patients received a single dose of morphine or fentanyl before removal of the arterial catheter. During the cisplatin infusion, furosemide was administered in the event that urine output did not meet the calculated expectation. Antiemetic agents were continued and the patients received fluids at twice the maintenance rate until discharge. Laboratory evaluations, consisting of a comprehensive



**Figure 1.** Last full-column images of (a) anteroposterior and (b) lateral views of the baseline arteriogram of a patient with osteosarcoma of the proximal tibia.

metabolic panel, including calcium and magnesium, were performed daily.

Criteria for discharge included stable metabolic parameters, demonstrated ability to take and retain oral fluids, appropriate urine output, and no evidence of complications after arteriography. Patients were followed closely as outpatients and received additional supplementary IV hydration as needed.

Preoperative chemotherapy cycles were administered at 21-day intervals. Hematologic recovery, defined as an absolute neutrophil count greater than 1,000 and a platelet count greater than 100,000, was required before each cycle, which occasionally resulted in a prolonged interval. The majority of patients received adjuvant hematopoietic growth factors (granulocyte or granulocyte-macrophage colony-stimulating factors) after these became commercially available. A minimum

of three and a maximum of five neoadjuvant chemotherapy cycles were administered.

#### Arteriographic Interpretive Methods

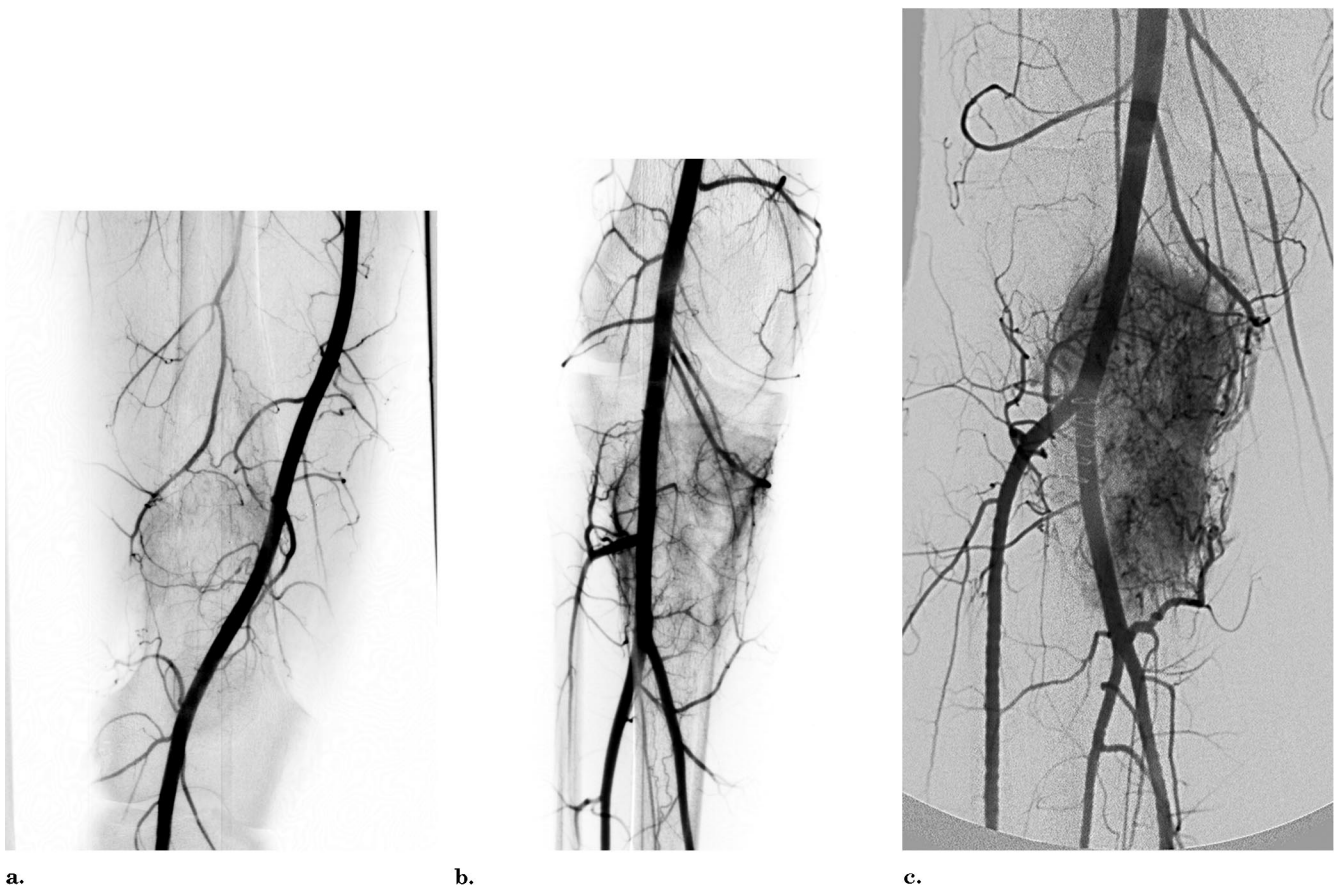
Arteriograms were obtained before the administration of each dose of cisplatin. The last anteroposterior and lateral images in the arteriographic sequence, which demonstrated full contrast agent filling of the target trunk vessel (ie, last full column), were chosen from each imaging run for interpretation and comparison with future studies (Fig 1).

The volume and intensity of TNV on the baseline arteriogram was assessed and scored by an interventional radiologist as: 1+ (mild), 2+ (moderate), or 3+ (marked or prominent) TNV (Fig 2). Subsequent arteriograms were compared with the baseline study to assess change in TNV as an indicator of tumor response. IA che-

motherapy cycles were continued until one of three arteriographic criteria were met: (i) virtually complete (>90%) disappearance of TNV, (ii) initial response followed by plateau of effect, or (iii) no response or progressive disease. A plateau of effect was defined as no further decrease in TNV on a subsequent arteriogram after an initial decrease had been observed. Concomitant with arteriography demonstrating more than 90% response, each patient received a final dose of IA cisplatin. No further arteriography was performed and preoperative therapy was then deemed complete. Arteriograms were interpreted prospectively by the interventional radiologist performing the infusion. Arteriograms were presented at a weekly multidisciplinary conference. The study interventional radiologist (B.A.J. or S.L.S.), the oncologist, and the orthopedic oncologist agreed on the final arteriographic response before proceeding to definitive surgery.

#### Surgical Methods

Local surgical control was considered only after maximum arteriographic response was achieved prospectively as determined by the multidisciplinary team. An optimal "window" for definitive surgery was planned (usually 3–4 weeks later). The type of surgical procedure was determined by assessment of the neurovascular bundle involvement on the initial and most recent magnetic resonance (MR) imaging scans of the primary tumor. If the neurovascular structures appeared to be free of tumor and the patient was predicted to retain adequate limb function, a limb preservation procedure was planned. In addition, the advance knowledge of whether a patient was responding to chemotherapy was an important factor in surgical planning. Computed tomography (CT) of the chest, plain radiography, and bone scan were repeated before surgery. If limb preservation surgery was planned, the type of reconstruction (endoprosthesis, allograft reconstruction, or allograft prosthetic composite) was determined by location and extent of the tumor, patient age, and activity expectations. Amputation was recommended for patients who were believed to be at high risk for local recurrence as a re-



**Figure 2.** Examples of baseline arteriograms demonstrating TNV scores include (a) minimal (1+); (b) moderate (2+); and (c) marked or prominent (3+).

sult of previous excisional biopsy, involvement of the neurovascular bundle, or poor arteriographic response.

#### Pathologic Methods

The diagnosis of high-grade osteosarcoma or MFH of bone was confirmed by needle or open biopsy. Postoperative assessment of overall percentage of tumor necrosis was performed according to the method described by Huvos et al (10). To summarize, longitudinal sections of the specimen were obtained at 3-mm intervals and examined grossly. Multiple representative sections from central and perimeter areas of the neoplasm were submitted for histologic examination after decalcification. Estimation of the overall percentage of tumor necrosis was performed microscopically, with at least 90% necrosis defined as a good response and less than 90% necrosis defined as a poor response.

#### Statistical Methods

Correlation was made between TNV decrease of at least 90% by arteriography and at least 90% tumor necrosis by histologic examination. Sensitivity and specificity of arteriographic prediction of necrosis were calculated according to the typical formulas. Histology was assumed to represent the “gold standard” and the arteriogram was assumed to represent the experimental test. Accuracy was defined as the percentage of patients for whom there was agreement between histologic and arteriographic findings. Univariate analysis was performed to determine if factors could be identified that would influence the sensitivity, specificity, or accuracy of the arteriogram in predicting a good histologic response. The following factors were evaluated: the study time period, patient age, presence of pathologic fracture at diagnosis, tumor site, tumor size, disease stage, tumor histo-

logic type, degree of initial TNV, and number of neoadjuvant IA cycles administered. The study was divided into three time periods according to date of patient enrollment: 1987–1991, 1992–1996, and 1997 to the conclusion of enrollment in January 2003. Patient age was divided into the following groups: 0–19, 20–29, 30–39, 40–49, and 50–77. In addition, patients younger than 20 years of age were compared with patients aged 20 years and older. The presence or absence of pathologic fracture was assessed. Tumor site was analyzed several different ways: extremity versus nonextremity, upper versus lower extremity, and specific bone involvement (ie, femur, humerus). Tumor size less than or equal to 10 cm versus greater than 10 cm was analyzed as well. Stage was evaluated by the presence or absence of metastasis at presentation. MFH and osteosarcoma were separately analyzed and compared with the group as a whole. The degree of initial TNV

was divided into two groups: mild/moderate versus marked/prominent. Statistical comparisons were based on the use of a two-sided Fisher exact test. Statistical significance was assumed for *P* values less than .05 and all analyses were performed with use of SAS software (SAS, Cary, NC).

## RESULTS

A total of 109 patients underwent 408 arteriography procedures followed by an IA infusion of cisplatin. Two hundred seventy treatments were infused over 6-hour periods and 138 were infused over 24-hour periods. Forty-two patients received the minimum three cycles, 53 required four, and 14 received five neoadjuvant cycles. Tumor neovascularity was decreased by at least 90% in 88%, 89%, and 71% of patients who received three, four, and five cycles, respectively. Fifteen patients did not exhibit a good arteriographic response. Examples of good and poor arteriographic responses are demonstrated in **Figures 3 and 4**, respectively.

There were three minor complications and no major complications related to arteriography (among 408 cases; 0.7%). One patient experienced painful arterial spasm, which resolved with nominal therapy. Two patients developed minor hematomas at the arterial puncture site that did not require intervention beyond local pressure.

The cisplatin infusion was associated with soft-tissue necrosis in seven instances (1.7%). These patients required pain medication but no further intervention. No patient experienced a second episode of necrosis with subsequent infusions and no one was removed from the protocol as a result of these complications. The area of necrosis was usually excised at the time of the definitive surgery and a separate surgical procedure was not required as a result of the necrosis.

In addition, seven episodes of deep vein thrombosis (1.7%) occurred in the same extremity as the IA infusion within 10 days of IA therapy. None of these were associated with pulmonary embolism. All were treated successfully with anticoagulation therapy. It is unclear whether these complications were related to the IA procedure.

Initial arteriograms showed mildly

increased TNV in nine patients and moderate to marked TNV in 100 patients. A good radiographic response, defined as at least a 90% decrease in TNV, was achieved in 94 patients (86%). A good histologic response, defined as at least 90% tumor necrosis, was achieved in 82% of tumors. The arteriogram correctly predicted a good histologic response in 86 of 89 patients, yielding a sensitivity of 97%. In addition, the arteriogram correctly predicted a poor histologic response in 12 of 20 patients, for a specificity of 60%. The overall accuracy of predicting the histologic response by evaluating the decrease in TNV on serial arteriograms was 90% (98 of 109).

Univariate analysis to determine impact of prognostic factors on arteriographic prediction of necrosis demonstrated no statistical differences for the parameters tested except the number of IA cycles administered per patient. The prediction of necrosis by arteriography was less sensitive (*P* = .03) and less accurate (*P* = .02) after five neoadjuvant cycles than after three or four cycles. There was no significant difference for specificity based on the number of IA cycles administered.

Limb preservation surgery was performed in 91% of patients (99 of 109). Ten amputations were performed at the time of definitive surgery and seven amputations (6%) were required secondarily. The most common primary surgery was wide local resection with endoprosthetic replacement (*n* = 52). Later in the series, skeletally immature children estimated to have greater than 4.0 cm of remaining extremity growth underwent reconstruction with a "growing prosthesis" (*n* = 3; Repiphysis; Wright Medical Technology, Arlington, TN). Other reconstructions included a structural osteochondral (*n* = 8) or intercalary allograft (*n* = 14), allograft prosthetic composite (*n* = 9), and resection with soft-tissue reconstruction only (*n* = 4). A secondary amputation was required in six patients: four for uncontrolled infection of the prosthesis or allograft after the completion of postoperative chemotherapy and two for progressive disease.

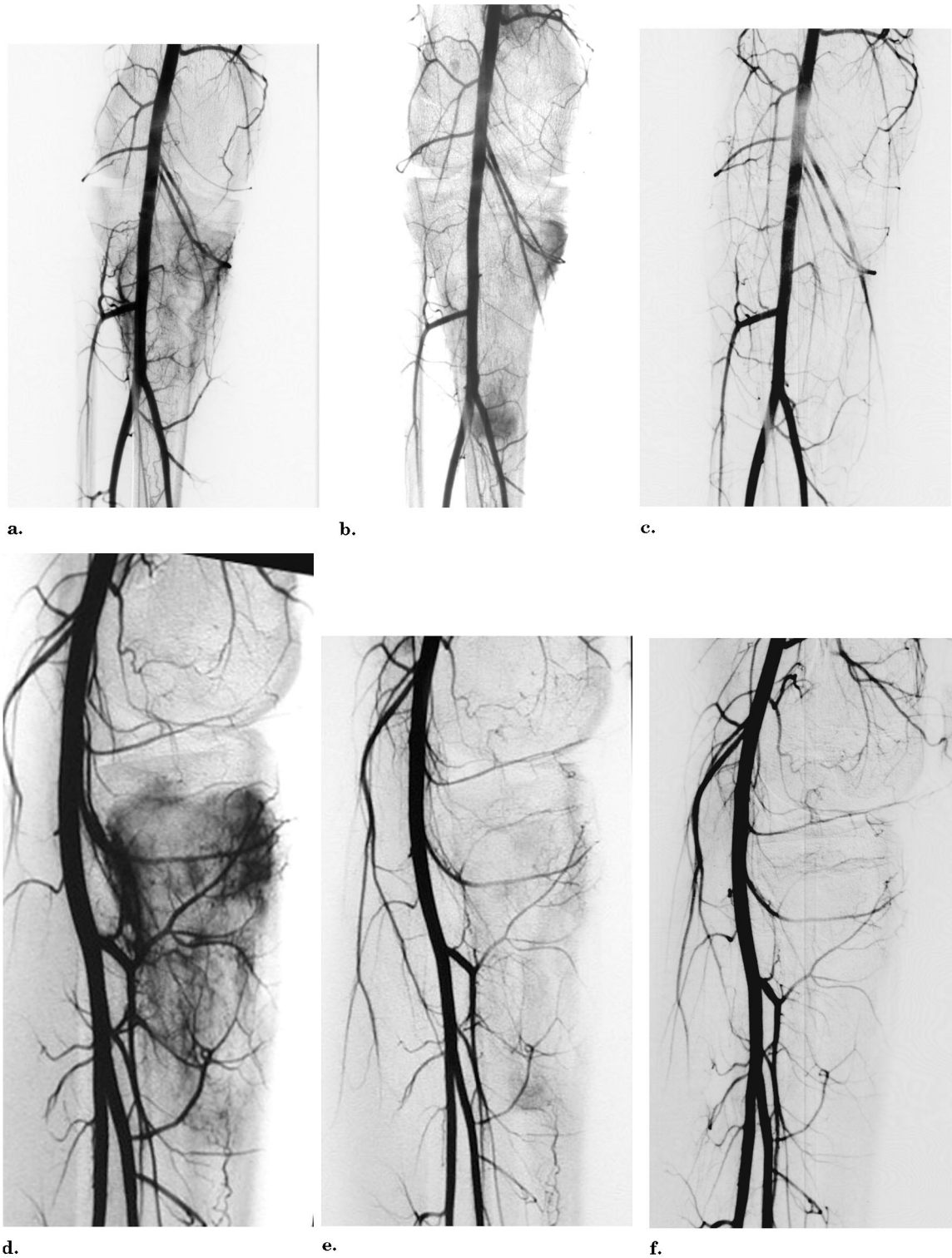
Seven patients had tumors located in the pelvis, ilium, or acetabulum and were treated with internal hemipelvectomy. The two patients with scapular lesions underwent resection and

primary soft-tissue reconstruction; however, one of these patients later required forequarter amputation as a result of progressive disease.

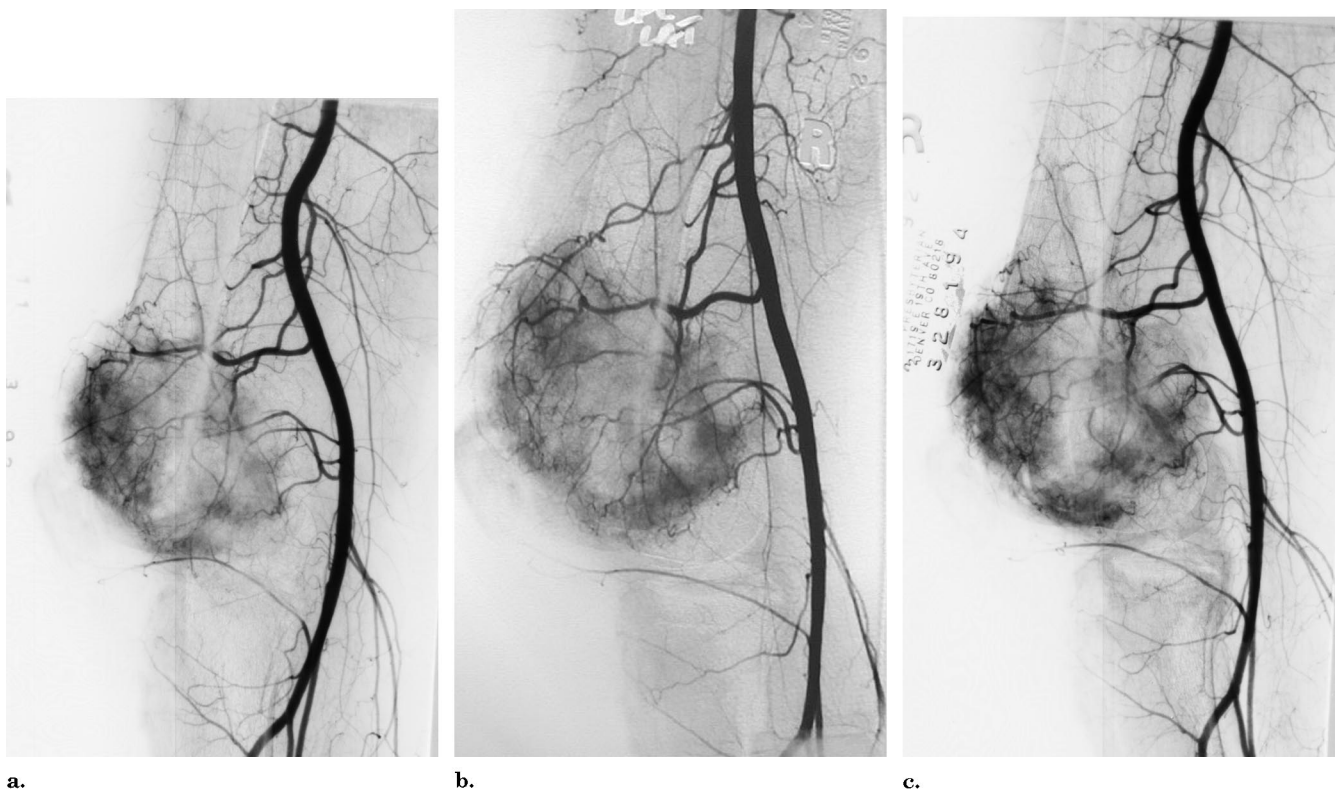
Primary amputations in extremity lesions were necessitated by the location of the tumor involving the neurovascular bundle (*n* = 7), presence of a skip lesion (*n* = 2), and previous treatment for fibrous dysplasia of the same bone (*n* = 1).

## DISCUSSION

The histologic response to neoadjuvant therapy is one of the most important prognostic factors for long-term survival in nonmetastatic osteosarcoma (11). In a multivariate analysis of 1,702 patients, Bielack et al (12) found that histologic response was the most important prognostic factor for osteosarcoma of the extremity (*P* < .0001). Provisor et al (13) reported 8 year event-free survival and overall survival rates of 81% and 87%, respectively, for cases with good response, versus 46% and 52%, respectively, for poor response (*P* < .0001). Unfortunately, only 28% of patients exhibited a good histologic response in that study. The ability to accurately assess preoperative tumor response would allow treatment individualization to achieve maximum response to neoadjuvant chemotherapy and limit therapy-related toxicity. Adjustments to neoadjuvant therapy might entail (i) continuing until the desired response was achieved, (ii) intensifying the dose or duration if response was slow, or (iii) discontinuing therapy and proceeding to definitive surgery without further delay. Reasons for proceeding to definitive surgery would include achievement of at least 90% TNV, an initial response followed by plateau of effects, or a failure to respond. All the modalities used to image bone neoplasms, including plain radiography, CT, scintigraphy (thallium, technetium, or gallium), dynamic MR imaging, MR arteriography, positron emission tomography (PET), and arteriography, have been evaluated for their ability to preoperatively predict tumor necrosis. Holscher et al (14) demonstrated that changes on plain radiographs during or after neoadjuvant treatment failed to predict or correlate with tumor necrosis. Liszka et al (15) concluded that CT was not a suit-



**Figure 3.** To accurately assess response on serial arteriograms, it is important to evaluate anteroposterior (a,b,c) and lateral views (d,e,f). Baseline anteroposterior and lateral arteriograms (a,d) demonstrate moderate (2+) TNV. Second anteroposterior and lateral arteriograms (b,e) show a significant progress, and the third arteriographic views (c,f) show at least 90% reduction of TNV. This was concordant with histopathologic necrosis.



**Figure 4.** A poor response to neoadjuvant chemotherapy is depicted. **(a)** Lateral view (2+) arteriogram of distal femur with osteosarcoma. **(b)** Second arteriogram demonstrated a mild decrease in TNV and significant decrease in mass effect on the popliteal artery. **(c)** The final arteriogram demonstrated TNV greater than seen at baseline, which was judged to represent progression of disease. The decision was made to discontinue neoadjuvant therapy and the patient underwent surgery. Surprisingly, histopathologic necrosis was 65%.

able tool for assessment of tumor response and Wellings et al (16) determined that CT evaluation of tumor cross-sectional area and volume were poor predictors of histologic change. Ramanna et al (17) found thallium 201 to be superior to gallium or technetium serial scintigraphy in bone and soft tissue sarcomas. Sanchez et al (18) determined that nonenhanced MR was inadequate in predicting tumor necrosis as a result of overlap of signal intensity in areas of viable and necrotic tumor, edema, hemorrhage, and fibrosis. Data from various published reports evaluating the predictive ability of the remaining imaging modalities (scintigraphy [19–22], MR [19, 23,24], and PET [22,25,26]) in osteosarcoma are summarized in **Table 2**. Kawai et al (19) concluded that dynamic MR imaging was best after comparing it with digital arteriography and  $^{201}\text{Th}$  scintigraphy.

Because PET scanning with [ $^{18}\text{F}$ ]fluorodeoxyglucose allows quantitative metabolic imaging, it seems ideally

**Table 2**  
**Imaging Methods to Predict Tumor Necrosis in Osteosarcoma (19–22,24–26)**

Imaging Method (Reference)	No. of Pts.	Sensitivity (%)	Specificity (%)	Accuracy (%)
Technetium Scintigraphy (20)	26	94	100	96
Technetium Scintigraphy (22)	11	33	100	45
Th-201 Scintigraphy (19)	11	75	86	82
Th-201 Scintigraphy (21)	19	88	100	95
Dynamic MR (19)	10	100	86	90
MR angiography (24)	8	100	100	100
PET (25)	27	100	80	92
PET (26)	16	87	100	94
PET (22)	11	33	100	45

suited for evaluating tumor viability. However, there was no consistency in the reporting parameters. Nair et al (26) reported high levels of accuracy with use of direct tumor/background ratio (TBR) with a good/poor response cutoff value of 1.4, but only 50% accuracy with percent change in TBR on serial images. Franzius et al (22) achieved their best results report-

ing percent change in the TBR between pre- and posttreatment studies. However, when the 1.4 cutoff value of Nair et al (26) was applied to the direct TBR data for osteosarcoma reported by Franzius et al (22), the accuracy rate decreases to 45%. Schulte et al (25) reported 100% sensitivity in a retrospective analysis with a cutoff point of a 0.6 ratio (final to initial TBR). With

**Table 3**  
**Use of Arteriography to Predict Tumor Necrosis in Osteosarcoma**

Reference	No. of Pts.	Sensitivity (%)	Specificity (%)	Accuracy (%)
Chuang et al, 1982 (27)	42	94	88	90
Kumpan et al, 1986 (29)	22	100	100	100
Carrasco et al, 1989 (31)	81	91	50	74
Kawai et al, 1997 (19)	12	100	57	75
Kunisada et al, 1998 (21)	19	88	73	79
Present study	109	97	60	90
Total	285	95	67	85

the final TBR and the 1.4 cutoff value of Nair et al (26), the sensitivity decreases to 12%. Therefore, although each retrospective study was able to determine a best fit yielding a high accuracy rate for their data sets, prospective analysis according to percent change or final TBR has not been reported.

The accuracy of scintigraphy, MR imaging, and PET scanning appeared promising in the evaluation of response to neoadjuvant therapy for osteosarcoma. However, the number of patients in each series was small and all studies were retrospective. No modality has previously been used prospectively to determine duration of neoadjuvant chemotherapy.

Assessment of change in TNV by arteriography is subjective. Therefore, a certain amount of skill and experience are required. However, in our study, the arteriograms were obtained and interpreted by 14 different interventional radiologists. Consistency was provided by the two study interventional radiologists (B.A.J., S.L.S.) and the protocol's multidisciplinary team. Our results did not change nor improve over time during the conduct of the study: consistent results were maintained in terms of sensitivity, specificity, and accuracy during all time periods of the study (1987–1991, 1992–1996, and 1997–2003). In addition, this technique has yielded similar results in other smaller studies. The ability to predict necrosis with arteriography was reported as early as 1982 (27). At least six groups have published results of arteriographic prediction of necrosis (19,21,27–30). Sensitivity and specificity were reported in five of these six studies and are summarized along with the results of our study in **Table 3**. The accuracy

and sensitivity rates in our series of 109 patients were 90% and 97%, respectively. A review of the worldwide literature yielded a total of 285 patients who had been assessed preoperatively with arteriography, for a composite accuracy rate of 85% and sensitivity of 95%. This was true regardless of whether the neoadjuvant chemotherapy was solely IV, a combination of IV and IA, or single-agent IA cisplatin. Administering IV doxorubicin and IA cisplatin, Carrasco et al (31) varied the duration of neoadjuvant chemotherapy. Patients received two to eight cycles of therapy (median, 4), but the indication for proceeding to surgery was not specified. Histopathologic correlation demonstrated that 91% of good responders could be identified by arteriography. In our study, the duration of neoadjuvant chemotherapy was determined by the arteriographic response. Patients proceeded to undergo surgery when arteriography demonstrated one of the following: (i) at least 90% decrease in TNV, (ii) initial response followed by plateau of effect, or (iii) no response or progressive disease.

An ideal positive preoperative therapeutic response demonstrated a decreasing tumor blush and neovascularity at each serial arteriogram to an endpoint at which there is essentially no remaining abnormal TNV ( $\geq 90\%$  decrease in TNV). The last full-column image depicts late arteriolar and early capillary filling. This point in the arteriographic sequence best represents the TNV. Images later in the venous phase are not as indicative of TNV. This protocol and technique was based on earlier work by Carrasco et al (31) with some modifications, ie, the duration of IV doxorubicin infusion was shortened from 96 hours to 48–72

hours, course cycle time was shortened from 28 days to 21 days, and the range of the number of courses was reduced from two to eight courses to between three and five courses. Because the majority of cases of high-grade osteosarcoma and MFH of bone lesions demonstrate some degree of TNV on arteriography, are isolated to an extremity, and are not associated with a pathologic fracture, the majority of our cases were straightforward and showed steady progression to a finite arteriographic endpoint on which everyone could agree. Tumors that were axial, had pathologic fractures, or had minimal TNV presented additional challenges. Other problems encountered in predicting necrosis included increased TNV after the first cycle and the development of soft-tissue hyperemia.

Axial lesions had the added potential of bilateral arterial supply and simply perfusing the aorta was deemed to have too high a dilutional effect. In those cases of large, predominantly unilateral torso lesions (ie, iliac wing, ischial lesions) extending to or beyond the midline, any demonstrable contralateral arterial supply was permanently coil-embolized at the first arteriography procedure to allow for unilateral infusions that would achieve cisplatin concentrations reached in the extremity lesions. True midline lesions (ie, sacral or pubic symphysis lesions) with symmetric, bilateral iliac supply were treated with sequential unilateral internal iliac infusions of half the dose at the full calculated rate into each feeding artery. It was elected not to perform dual simultaneous bilateral infusions.

Virtually all the patients who presented with pathologic fractures showed progressive healing with formation of hyperemic callus and periosteal new bone during the preoperative chemotherapy period. Arteriographically, this potentially presented the problem of differentiating between diminishing TNV and the increasing hypervascular blush of healing callus and new bone, and could have made it more difficult to determine the arteriographic endpoint. Two arteriographic features of healing bone helped with this differentiation. Tumor neovascularity was characterized by an angular, nodular, coarse, and blotchy appearance whereas heal-

ing bone hypervascularity has a smoother, more homogeneous, bland appearance. At initial arteriography, all tumors had remarkably variable TNV, from foci of intense enhancement to areas of complete avascularity within the tumor. In our experience, healing hypervascular new bone formed at the periphery and in areas of the tumor which, on the initial arteriograms, were hypovascular or avascular. Also, poor arteriographic responses presented as persistence of the initial areas of TNV, not as new areas. Development of curvilinear areas of bland, homogeneous hyperemic stain in areas of initial hypovascularity or avascularity reliably represented healing bone in cases presenting with pathologic fracture. **Figure 5** depicts a patient who presented with a pathologic fracture through the tumor, but serial arteriograms clearly show progression to a good response.

In cases in which the initial arteriogram showed minimal TNV, it was difficult to identify the arteriographic endpoint for neoadjuvant chemotherapy. These cases were much more susceptible to and influenced by technical artifacts such as subtraction motion and patient position. This difficulty with quantifying an arteriographic change in TNV was initially disconcerting. Serial treatments were continued, however, based on clinical improvement (eg, reduced pain, increased range of motion, decreased tumor size) and the lack of tumor progression evidenced by arteriography. Arteriographic evaluation of minimally vascular tumors is enhanced by robust contrast medium injection rates and volumes and requires meticulous attention to technical details.

Increased TNV occasionally occurs after the first cycle of IA cisplatin administration. It is important to avoid misinterpreting this blush as tumor progression. In most cases, this increased blush was followed by a progressive decrease in TNV to complete response with continued IA cycles (**Fig 6**). Persistence of increased TNV was indicative of a poor response (**Fig 4**) and resulted in termination of neoadjuvant therapy and scheduling of resection.

Development of small (1–2 cm) foci of relatively intense hyperemia in the soft tissues around the tumor (usually proximal to the tumor) was occasion-

ally seen on serial arteriography after initial treatment. This was a possible sign of tumor progression with development of satellite lesions. These foci were not in the usual (groin/axillary) lymph node-bearing areas. Initially, these cases were reevaluated with repeat CT/MR imaging studies, which proved uniformly negative, and the foci always disappeared on subsequent arteriograms during continued treatment. We suspect that these foci represented a localized hypervascular response to direct arteriolar/capillary cisplatin toxicity that has proved to be clinically inconsequential.

All these challenges were ultimately surmountable, did not preclude successful treatment, and proved to be statistically inconsequential. In addition, our study showed that numerous other factors (study time period, patient age, tumor site, size, stage, histologic findings) did not adversely affect the ability to predict necrosis with serial arteriography. Although the prediction of necrosis after five IA cycles of cisplatin was statistically less sensitive and less accurate, this could be at least partially explained by the fact that a sixth arteriogram was not obtained to substantiate the impact of the final treatment before surgery for this group of 14 patients.

The IA infusion of cisplatin was associated with seven episodes of myocutaneous inflammation among 408 procedures. This represented 1.7% of infusions and 6.4% of patients (seven of 109). This compares favorably with the 8.4% rate reported by Tsuchiya et al (32) with use of IA cisplatin in 107 patients with bone and soft-tissue sarcomas of the extremity. Although painful, these lesions were medically managed and did not disrupt neoadjuvant therapy. Our patients did not require additional surgical procedures or have poorer functional outcomes as found in the use of IA doxorubicin reported by Bezwada et al (33). The area of inflammation was excised at the time of definitive surgery in six of seven cases. One of the seven episodes of myocutaneous inflammation involved the abdominus rectus and the patient presented with acute abdominal pain. Two similar cases were reported by Cheon et al (34) and attributed to infusion catheter proximity to the inferior epigastric artery origin. As

in the cases of Cheon et al (34), our patient underwent conservative management and the symptoms resolved without surgical intervention. The occurrence of myocutaneous inflammation did not impact our ability to perform limb-preservation surgery.

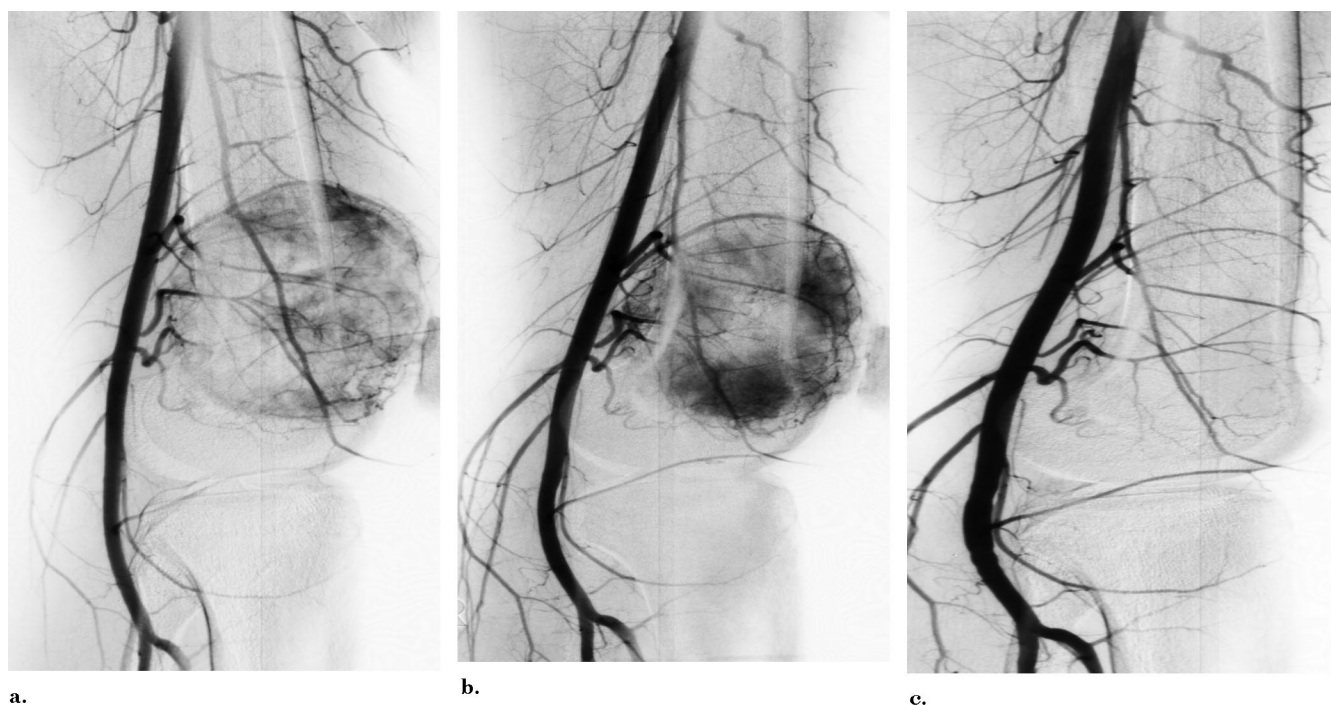
The seven cases of deep vein thrombosis did not impact the therapeutic regimen. It was uncertain whether they were secondary to venous intimal injury from the higher concentration of cisplatin returning through the venous system, the immobilization required during the arterial infusion, the inherent hypercoagulability of patients with malignancy, or a combination of these factors.

The use of the IA route of administration of cisplatin allows the dose of drug delivered to the tumor to be increased by as much as fivefold compared with the IV route without increasing the systemic concentration, effect, or toxicity (5,35). Adjusting the dose to 160 mg/m<sup>2</sup> over 24 hours for patients with tumors greater than 10 cm in largest dimension (compared with 120 mg/m<sup>2</sup> over 6 hours for smaller tumors) further increased the dose delivered to the tumor.

Results of this study differ from previously reported results of the use of IA cisplatin in at least four significant ways. First, the therapy used only two drugs repetitively. There was no interruption to administer methotrexate or ifosfamide. Second, the chemotherapeutic agent (cisplatin) was delivered in a pulsatile jet fashion with use of a Wallace-Gianturco pump. This was an attempt to achieve more homogenous distribution of drug throughout the tumor, as demonstrated by Nishimura et al (36) with pulsatile jet hepatic artery infusions. Third, the dose of cisplatin was increased with large tumors (>10 cm) by 33% and the duration of infusion lengthened from 6 to 24 hours. Fourth, the number of neoadjuvant cycles administered was individualized based on each patient's response as judged by decreased TNV on serial arteriograms. Although the claim has been made that the good histologic response rate can be improved with prolonged neoadjuvant therapy, this has not been shown to be true. In addition, prolonging neoadjuvant therapy only for cases of slow responses decreases



**Figure 5.** Images from an 18-year-old male patient who presented with osteosarcoma of the proximal tibia and pathologic fracture. **(a)** Lateral baseline arteriogram depicts a large (>10 cm) prominently hypervascular (3+) lesion. **(b)** A second arteriogram shows significant decrease in TNV, especially anteriorly, with reduction in size of mass and less bulging of vessels. **(c)** The third arteriogram shows further decrease in TNV centrally and posteriorly, but less than the desired goal of 90%. **(d)** Fourth and final arteriogram demonstrates complete resolution of TNV and a good response ( $\geq 90\%$ ), which correlated with pathologic necrosis.



**Figure 6.** Images from a patient with 2+ TNV on the initial arteriogram (a) shows apparent increased hyperemia on the second arteriogram (b). (c) The third and final arteriogram demonstrates almost complete resolution of TNV, which was concordant with tumor necrosis.

the likelihood of overtreating early or rapid responders.

Assessment of serial arteriograms at the time of catheter placement before each IA cycle allowed therapy to be individualized for each patient. Not only was the arteriogram valuable as an endpoint to proceed with surgery, but poor arteriographic responders (<90% decrease in TNV) underwent early definitive surgery and were switched to receive an alternative therapy if tumor necrosis proved to be less than 90%. Additionally, arteriography was successful in individualizing the duration of therapy based on response. If the protocol had empirically mandated three neoadjuvant cycles, 67% of patients may have been undertreated and had a poor response. Conversely, empirical administration of four neoadjuvant cycles would have resulted in overtreatment of 33% of patients and undertreatment of 22%. Finally, administration of five neoadjuvant cycles regardless of response would have overtreated at least 72% of patients. It appears that duration of neoadjuvant therapy can be based on response. This improves the chances of achieving a good histologic re-

sponse and avoids unnecessary toxicity for rapid responders.

In our previous report of patients younger than 22 years of age with nonmetastatic osteosarcoma of the extremity treated on this protocol, 86% of patients exhibited a good histologic response (30). In addition, this good response rate translated to improved long-term survival rates. The Kaplan-Meier actuarial survival rate was 92% and the event-free survival rate was 84% at 10 years, with a median follow-up in excess of 7 years. For good responders, the 10-year survival and event-free survival rates were 93% and 86.5%, respectively. The overall and event-free survival rates for poor responders were 80% and 62.5%, respectively. The poor responders received more intense postoperative therapy for a longer duration and with different drugs. To our knowledge, these treatment results are the best reported to date for osteosarcoma.

These data suggest that the use of serial arteriograms to predict tumor necrosis allows the duration of neoadjuvant therapy to be individualized according to patient response and assists in achieving the excellent rate of good

histologic response. Because the IA therapy and arteriographic interpretations were performed at a single institution, further studies are needed in a multiinstitutional setting to confirm our results.

#### References

1. Bacci G, Ferrari S, Tienghi A, et al. A comparison of methods of loco-regional chemotherapy combined with systemic chemotherapy as neoadjuvant treatment of osteosarcoma of the extremity. *Eur J Surg Oncol* 2001; 27:98-104.
2. Benjamin RS, Chawla SP, Carrasco CH, et al. Preoperative chemotherapy for osteosarcoma with intravenous adriamycin and intra-arterial cis-platinum. *Ann Oncol* 1992; 3(suppl 2):3-6.
3. Ferrari S, Mercuri M, Picci P, et al. Nonmetastatic osteosarcoma of the extremity: results of a neoadjuvant chemotherapy protocol (IOR/OS-3) with high-dose methotrexate, intra-arterial or intravenous cisplatin, doxorubicin, and salvage chemotherapy based on histologic tumor response. *Tumori* 1999; 85:458-464.
4. Fuchs N, Bielack SS, Epler D, et al. Long-term results of the cooperative German-Austrian-Swiss osteosarcoma study group's protocol COSS-86 of intensive multidrug chemotherapy and

- surgery for osteosarcoma of the limbs. *Ann Oncol* 1998; 9:893-899.
5. Jaffe N, Knapp J, Chuang VP, et al. Osteosarcoma: intra-arterial treatment of the primary tumor with cis-diammine-dichloroplatinum II (CDP). *Cancer* 1983; 51:402-407.
  6. Jaffe N, Raymond AK, Ayala A, et al. Effect of cumulative courses of intraarterial cis-diamminedichloroplatin-II on the primary tumor in osteosarcoma. *Cancer* 1989; 63:63-67.
  7. Rha SY, Chung HC, Gong SJ, et al. Combined preoperative chemotherapy with intra-arterial cisplatin and continuous intravenous adriamycin for high grade osteosarcoma. *Oncol Rep* 1999; 6:631-637.
  8. Winkler K, Bielack S, Delling G, et al. Effect of intra-arterial versus intravenous cisplatin in addition to systemic doxorubicin, high-dose methotrexate, and ifosfamide on histologic tumor response in osteosarcoma (Study COSS-86). *Cancer* 1990; 66:1703-1710.
  9. Enneking WF, Spanier SS, Goodham MA. A system for the surgical staging of musculoskeletal sarcoma. *Clin Orthop* 1980; 153:106-120.
  10. Huvos AG, Rosen G, Marcove RC. Primary osteogenic sarcoma: pathologic aspects in 10 patients after treatment with chemotherapy, en bloc resection, and prosthetic bone placement. *Arch Pathol Lab Med* 1977; 101:14-18.
  11. Bielack SS, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. *J Clin Oncol* 2002; 20:776-790.
  12. Davis AM, Bell RS, Goodwin PJ. Prognostic factors in osteosarcoma: a critical review. *J Clin Oncol* 1994; 12: 424-431.
  13. Provisor AJ, Ettinger LJ, Nachman JB, et al. Treatment of nonmetastatic osteosarcoma of the extremity with preoperative and postoperative chemotherapy: a report from the Children's Cancer Group. *J Clin Oncol* 1997; 15: 76-84.
  14. Holscher HC, Hermans J, Nooy MA, et al. Can conventional radiographs be used to monitor the effect of neoadjuvant chemotherapy in patients with osteogenic sarcoma? *Skeletal Radiol* 1996; 25:19-24.
  15. Liszka G, Szendroi M, Szanto J. Response to COSS-86 neoadjuvant therapy assessed by computed tomography and histology. *Acta Chir Hung*. 1992-93; 33:109-116.
  16. Wellings RM, Davies AM, Pynsent PB, Carter SR, Grimer RJ. The value of computed tomographic measurements. *Clin Radiol* 1994; 49:19-23.
  17. Ramanna L, Waxman A, Binney G, et al. Thallium-201 scintigraphy in bone sarcoma: comparison with gallium-67 and technetium-MDP in the evaluation of chemotherapeutic response. *J Nucl Med* 1990; 31:567-572.
  18. Sanchez RB, Quinn SF, Walling A, Estrada J, Greenberg H. Musculoskeletal neoplasms after intraarterial chemotherapy: Correlation of MR images with pathologic specimens. *Radiology* 1990; 174:237-240.
  19. Kawai A, Sugihara S, Kunisada T, Uchida Y, Inoue H. Imaging assessment of the response of bone tumors to preoperative chemotherapy. *Clin Orthop* 1997; 337:216-225.
  20. Knop J, Delling G, Heise U, Winkler K. Scintigraphic evaluation of tumor regression during preoperative chemotherapy of osteosarcoma. Correlation of 99mTc-methylene diphosphonate parametric imaging with surgical histopathology. *Skeletal Radiol* 1990; 19: 165-172.
  21. Kunisada T, Ozaki T, Kawai A, et al. Imaging assessment of the responses of osteosarcoma patients to preoperative chemotherapy: angiography compared with thallium-201 scintigraphy. *Cancer* 1999; 86:949-956.
  22. Franzius C, Sluk J, Brinkschmidt C, Jurgens H, Schober O. Evaluation of chemotherapy response in primary bone tumors with F-18 FDG positron emission tomography compared with histologically assessed tumor necrosis. *Clin Nucl Med* 2000; 25:874-881.
  23. Dyke JP, Panicek DM, Healey JH, et al. Osteogenic and Ewing sarcomas: Estimation of necrotic fraction during induction chemotherapy with dynamic contrast-enhanced MR imaging. *Radiology* 2003; 228:271-278.
  24. Lang P, Grampp S, Vahlensieck M, et al. Primary bone tumors: value of MR angiography for preoperative planning and monitoring response to chemotherapy. *AJR Am J Roentgenol* 1995; 165:135-142.
  25. Schulte M, Brecht-Krauss D, Werner M, et al. Evaluation of neoadjuvant therapy response of osteogenic sarcoma using FDG-PET. *J Nucl Med* 1999; 40:1637-1643.
  26. Nair N, Ali G, Green AA, et al. Response of osteosarcoma to chemotherapy. Evaluation with F-18 FDG-PET scans. *Clin Positron Imaging* 2000; 3:79-83.
  27. Chuang VP, Benjamin R, Jaffe N, et al. Radiographic and angiographic changes in osteosarcoma after intraarterial chemotherapy. *AJR Am J Roentgenol* 1982; 139:1065-1069.
  28. Bilbao JI, Algarra SM, de Negri JM, et al. Osteosarcoma: Correlation between radiological and histological changes after intra-arterial chemotherapy. *Eur J Radiol* 1990; 11:98-103.
  29. Kumpan W, Lechner G, Wittich GR, et al. The angiographic response of osteosarcoma following preoperative chemotherapy. *Skeletal Radiol* 1986; 15:96-102.
  30. Wilkins RM, Cullen JW, Odom L, et al. Superior survival in treatment of primary nonmetastatic pediatric osteosarcoma of the extremity. *Ann Surg Oncol* 2003; 10:498-507.
  31. Carrasco CH, Charnsangavej C, Raymond AK, et al. Osteosarcoma: angiographic assessment of response to preoperative chemotherapy. *Radiology*. 1989; 170(3 Pt 1):839-842.
  32. Tsuchiya H, Morinaga T, Taki J, et al. Effect of myocutaneous inflammatory changes caused by intra-arterial chemotherapy on the outcome of patients who undergo limb-saving surgery. *Cancer* 2001; 91:2447-2453.
  33. Bezwada HP, Granick MS, Long CD, et al. Soft tissue complications of intra-arterial chemotherapy for extremity sarcomas. *Ann Plast Surg* 1998; 40:382-387.
  34. Cheon JE, Kim IO, Kim WS, et al. Abdominal-wall myositis secondary to intra-arterial chemotherapy for femoral osteosarcoma. *Pediatr Radiol* 1999; 29: 546-548.
  35. Stewart DJ, Benjamin RS, Zimmerman S, et al. Clinical pharmacology of intraarterial cis-diamminedichloroplatinum(II). *Cancer Res* 1983; 43:917-920.
  36. Nishimura Y, Yoshimura H, Iwata K, et al. Distribution of pulsed intra arterial infusion chemotherapy in hepatic carcinomas [Japanese]. *Gan To Kagaku Ryoho*. 1989; 16(suppl):2991-2994.