Journal of Korean Medical Science
Vol. 8, No. 2, 121-126 April 1993

Pathological Responses to Preoperative High-Dose Methotrexate Chemotherapy in Osteosarcoma

— Experience in Korea Cancer Hospital —

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During the last decade, many clinical investigators at various cancer centers have reported the efficacy of various chemotherapeutic agents in the treatment of osteosarcoma.

The regimens using high-dose methotrexate (HDMTX) with citrovorum factor rescue are now considered to be one of the most effective treatments of choice. From December 1989 to May 1991, sixteen patients with Enneking's stage (Enneking et al., 1980) IIB osteosarcoma of the extremities were treated with a high-dose methotrexate regimen. After two cycles of preoperative chemotherapy, an operation was performed; either limb salvage or amputation. The resected lesions were examined pathologically and classified according to Huvos' criteria. On pathological examination, 8 (50%) cases showed Grade IV; 1 (6.25%) Grade III; 4 (25%) Grade II; and 3 (18.75%) Grade I. The types of surgery performed were tumor prosthesis replacement (11); wide resection with or without reconstruction (2); resection and arthrodesis (1); and amputation (2).

Key Words: *Osteosarcoma, stage IIB, preoperative chemotherapy, high-dose methotrexate, pathological response*

INTRODUCTION

Since Rosen et al. (1982) reported excellent results in the treatment of osteosarcoma using high-dose methotrexate (MTX) and "tailored" chemotherapy, the combination regimen with high-dose MTX has become the most popular chemotherapeutic treatment for osteosarcoma.

In many cases, following intensive preoperative chemotherapy, the pathological examination of surgically removed osteosarcoma specimens revealed substantial necrosis and reduction of the tumor mass. If necrosis of the tumor was total or near complete, then the same regimen that was performed preoperatively should be continued postoperatively. However, if the necrosis of the tumor was not remarkable, then the postoperative chemotherapy should be changed to a different regimen. Thus the patient is given an additional chance at assessing their tumors in vivo chemosensitivity. This is called "tailored" chemotherapy.

The purposes of this study are to present our protocol for treating osteosarcoma, to analyze the rate of necrosis of the mass after preoperative chemotherapy using high-dose MTX, and to present our method of pathological examination of the specimen.

MATERIALS AND METHODS

Patients characteristics (Table 1)

From December 1989 to May 1991, sixteen patients with Enneking's stage (Enneking et al., 1980) IIB os-

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Table 1. Characteristics of Cases

Case Number	Age/Sex	Location	Pathologic Subtype	Type of Surgery	Necrosis rat (%)
1	14/F	Distal Femur	Chondroblastic	AK amputation	100
2	17/M	Distal Femur	Osteoblastic	Tumor Prosthesis	100
3	14/F	Proximal Tibia	Osteoblastic	Tumor Prosthesis	100
4	11/M	Proximal Humerus	Osteoblastic	Wide Resection and Living Fibular Graft	100
5	16/M	Distal Femur	Osteoblastic	Tumor Prosthesis	100
6	14/M	Distal Femur	Osteoblastic	AK amputation	100
7	20/M	Proximal Femur	Osteoblastic	Tumor Prosthesis	100
8	23/F	Distal Femur	Osteoblastic	Tumor Prosthesis	100
9	11/G	Distal Femur	Osteoblastic	Resection and Arthrodesis	97.5
10	15/F	Proximal Tibia	Chondroblastic	Tumor Prosthesis	78
11	18/M	Proximal Tibia	Osteoblastic	Tumor Prosthesis	80
12	16/M	Proximal Fibula	Osteoblastic	Wide Resection	20
13	14/F	Distal Femur	Osteoblastic	Tumor Prosthesis	44
14	19/M	Distal Femur	Osteoblastic	Tumor Prosthesis	81.7
15	16/M	Distal Femur	Osteoblastic	Tumor Prosthesis	10
16	17/M	Distal Femur	Osteoblastic	Tumor Prosthesis	72

teosarcoma of the extremities were treated with a high-dose methotrexate regimen. Before preoperative chemotherapy, all of the patients were biopsied but received no other treatment. The staging work-up included; computed tomograms (CT) of the chest and the lesion site, bone scans,angiograms and simple X-rays. Magnetic resonance imaging (MRI) and ultrasound were performed on some of the patients. Of the 16 patients, ten were male and six were female. The patient's ages ranged from 11 to 23, the average being 16. The locations of the lesions were as follows; distal femur (10); proximal tibia (3); proximal humerus (1); promimal femur (1); and proximal fibula (1). Histologically, 13 cases were osteoblastic type and three were chondroblastic.

Treatment protocol

Preoperatively, all of the patients received 2 cycles of chemotherapy. Each cycle consisted of two administrations of high-dose MTX (8gm/m^2) with citrovorum factor rescue given at one week interval; adriamycin (ADR, 30mg/m^2/day for 2 days) and cisplatin (CDDP, 100mg/m^2) were administered one week later. This cycle was repeated three later. The schedule of preoperative chemotherapy is illustrated in Fig. 1.

Surgery

Two types of surgery were performed: 1) the limb-salvage procedure and 2) the ablative procedure including amputation and disarticulation. The indications for either of the above, were based mainly on the neurovascular involvement and the extent of the disease. We performed limb salvage operations when the major neurovascular structures were spared and the tumor had not passed through the periosteum even when the cortex was destroyed. Among the sixteen patients, two underwent amputations (AK amputation) and 14 received limb-salvage operations. Of the limb-salvage procedures, 11 were tumor prosthesis replacement; one was a wide resection and living fibular graft; one was a resection and arthrodesis; and one was a wide resection.

Postoperative chemotherapy

The postoperative chemotherapy was divided into two groups based on the pathological response. If the

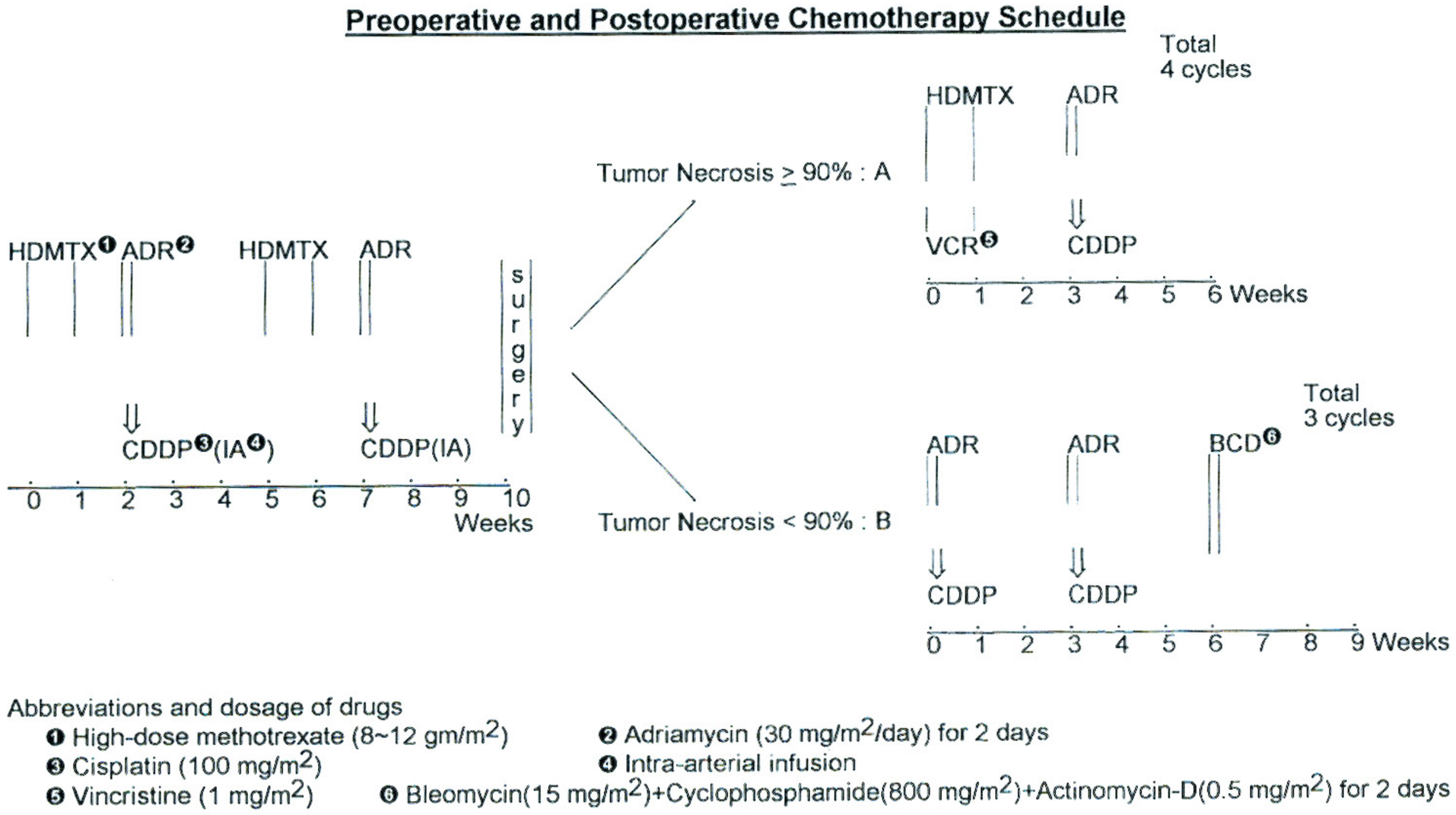

Fig. 1. Schedule of chemotherapy. All of the patients with stage IIB receive the entire 10 weeks of preoperative chemotherapy. The postoperative regimen is determined by the tumor necrosis rate assessed by pathological examination of the surgical specimen.

tumor necrosis was greater than 90% (Grade III or IV), then patients were treated with drug regimen A; if less than 90% of the tumor had necrosed, then the patients were treated with drug regimen B. The postoperative chemotherapy schedule and the dosage of each drug are illustrated in Fig. 1. In regimen A, the chemotherapy schedule was the same as the preoperative chemotheraphy except that vincristine (VCR, 1.5mg/m²) was added 30 minutes prior to each MTX infusion. This use of vincristine was based upon reports that it promotes the uptake of MTX by tumor cells (Goldman, 1987; Zager et al., 1981). This postoperative chemotherapy was repeated for three more cycles, with 3 weeks interval between each cycle. In regimen B, adriamycin and cisplatin were administered at 3 weeks, and then bleomycin (Bleo), cyclophosphamide (CTX) and actinomycin-D (Act-D) were administered 3 weeks later.

Histologic grading of the effects of preoperative chemotherapy

The specimen was sectioned sagittally by motor saw, along the plane of the largest diameter of the main tumor mass (Fig. 2 A). The cut surface of the tumor was copied onto the grid paper. Once again the specimen was cut sagittally into about 5mm thickness slice, this slice was cut into 1×2cm block to demineralize, and each demineralized block was processed to microscopic slide. Pathologist searched each slide for necrosis rate, and mapping was made on the grid paper (Fig. 2, B). Total necrosis rate was calculated by summing-up the necrosis rate of each slide.

The criteria for the histologic grading to determine the effectiveness of preoperative chemotherapy on the primary tumor were based on Huvos' grading system (Huvos, 1991): Grade I, little or no effect of chemotherapy noted; Grade II, partial response with more than 50% tumor necrosis; Grade III, more than 90% tumor necrosis, and Grade IV, no viable cells in any of the histologic sections (Fig. 3 A, B, C, and D).

RESULTS

Of the 16 patients, eight showed complete (100%) necrosis: one was 97.5%; four were approximately 80%; one was 44%; and to were 10% (Table 1). The average necrosis rate was 80.2%. According to Huvos' grading (Huvos, 1991), 50% (8/16) were Grade IV; 6.25 (1/16) were Grade III; 25% (4/16) were Grade II; and 18.75% (3/16) were Grade I.

DISCUSSION

Jaffe (1972) suggested that conventional doses of MTX lacked efficacy in unresectable or advanced osteosarcoma. However, subsequent studies using high-dose MTX have shown a 30% to 40% response rate in this disease (Pratt et al., 1980). In the past decade, many authors have reported between 38% and 89%

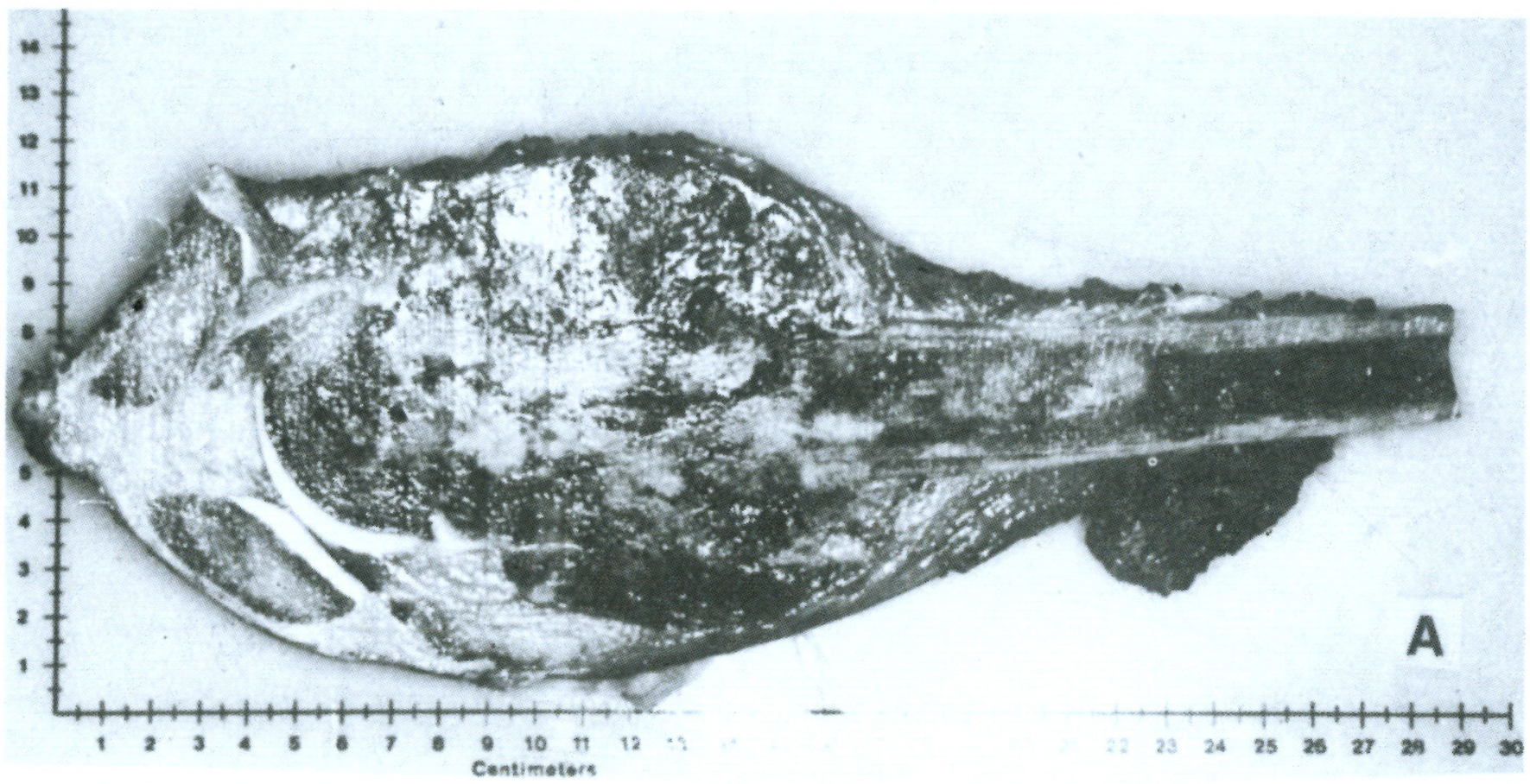

Fig. 2. Pathologic examination of the specimen. The specimen was cut along the maximal diameter of the mass (A). This cut surface was copied on to tracing paper. Total necrosis rate of the tumor was determined by a pathologist (B).

metastasis-free survival rates using high-dose MTX combined with other drugs (Goorin et al., 1987; Rosen et al., 1982; Weiner et al., 1986; Winkler et al., 1984). So it is widely accepted that combined high-dose MTX therapy is one of the most effective regimens in the treatment of osteosarcoma. Because the responses to high-dose MTX therapy are thought to be dose related, Rosen et al. (1982) and Jaffe et al. (1983) attempted to obtain maximum concentrations using 12.5 grams per square meter of body surface. But the careful monitoring of plasma level to prevent irreversible severe toxicities is an essential component of using this high-dose MTX therapy (Baek et al., 1990). Though there have been many protocols presented for the use of high-dose MTX in combination with other drugs, we designed our protocol by modifying that of Rosens' T-10 (Rosen et al., 1982).

The use of preoperative chemotherapy in patients with osteosarcoma, and the individualized approach to postoperative chemotherapy based on the patient's response to preoperative chemotherapy, offers many advantages. Actually, this approach is a kind of "in vivo chemosensitivity". If a patient had a poor response to preoperative chemotherapy, he or she could have an additional chance at survival by changing the postoperative chemotheraphy regimen from the preoperative one. Rosen et al. (1982) obtained results using this "tailored" chemotherapy (T-10 protocol) in which the disease-free survival after 20 months follow-up was 93%. Forty nine percent of the patients in Rosen's series showed a good response (Grade III or IV) to the T-10 protocol (Rosen et al., 1982). It is widely

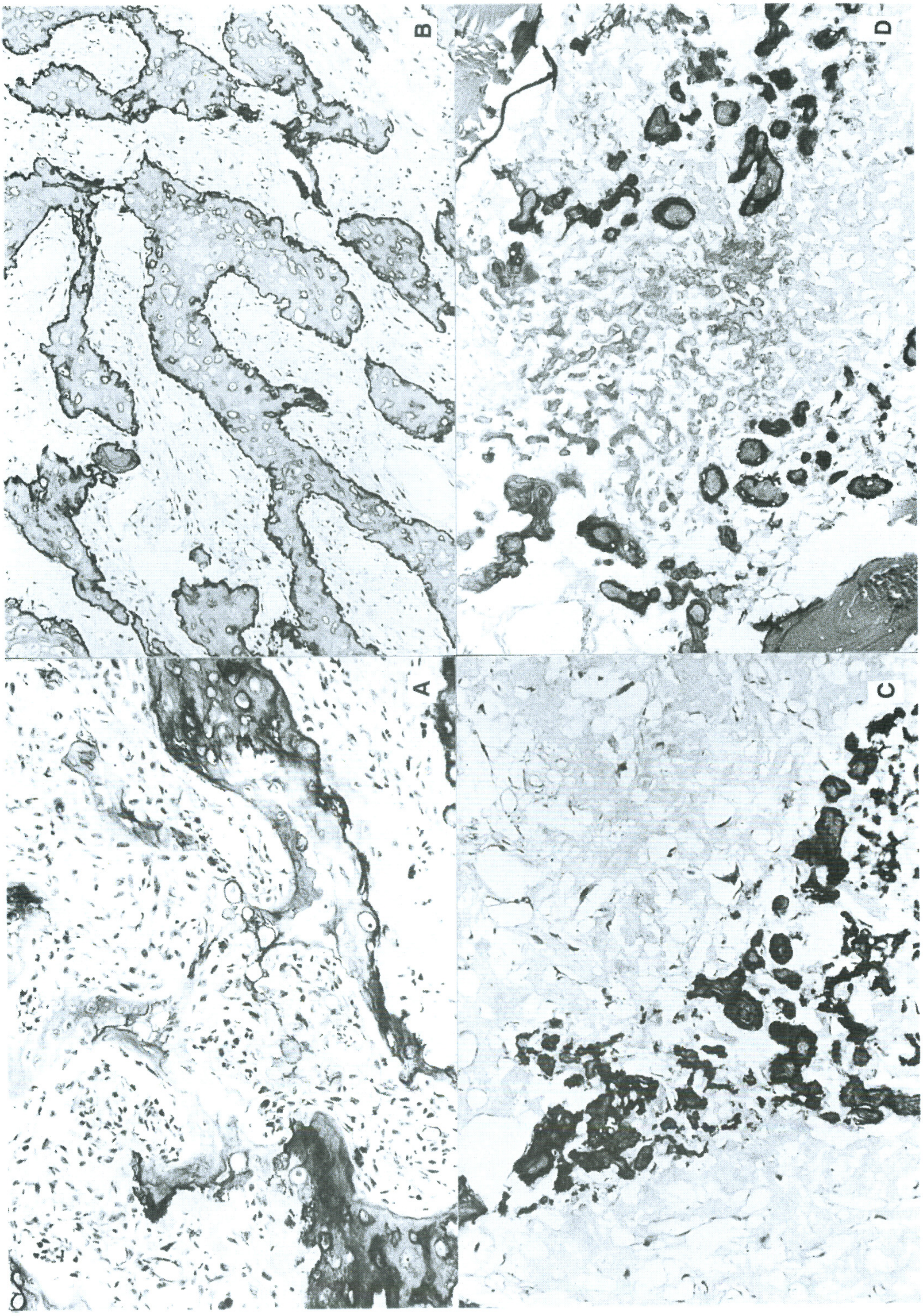

Fig. 3. Pathologic findings according to Huvos' criteria. (A) Grade I, (B) Grade II, (C) Grade III, and (D) Grade IV.

accepted that the good responders (Grade III or IV) have a better prognosis than the poor responders (Grade I or II) in spite of the tailored chemotherapy. Rosen's results were similar to ours, in that a good response was noted 56.3% of the patients in our study. Although the duration of our postoperative follow-up was short (3 to 20 months, 9.5 months; average), there has been no local recurrence or distant metastasis in any of the patients in our study. However, one patient died because of graft-versus-host reaction during a blood transfusion to correct thrombocytopenia.

Considering the 56.3% rate of good response to tailored postoperative chemotherapy, the results of our protocol seem promising.

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