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Morphological Grades of Regression in Osteosarcoma after Polychemotherapy – Study COSS 80

M. Salzer-Kuntschik[1], G. Delling[2], G. Beron[3], and R. Sigmund[4]

[1] The Vienna Bone Tumor Registry (Head: Prof. Dr. M. Salzer-Kuntschik) at the Pathologic Institute (Head: Prof. Dr. J. H. Holzner) of the University of Vienna, Spitalgasse 4, A-1090 Vienna, Austria
[2] The Pathologic Institute (Head: Prof. Dr. G. Seifert) of the University of Hamburg, Martinistraße 52, D-2000 Hamburg, Federal Republic of Germany
[3] The Department of Blood Coagulation Research and Oncology (Head: Prof. Dr. K. Winkler) at the Pediatric Clinic (Head: Prof. Dr. G. Landbeck) of the University of Hamburg, Martinistrasse 52, D-2000 Hamburg, Federal Republic of Germany
[4] The Orthopedic Clinic (Suppl. Head: Prof. Dr. F. Meznik) of the University of Vienna, Garnisongasse 9, A-1090 Vienna, Austria

Summary. The histologic grade of regression of 50 osteosarcomas after polychemotherapy – according to the protocol study, COSS 80 – was classified on a six-stage regression scale; 56% of all patients responded well to chemotherapy regression grades I, II, and III and no significant difference between BCD- and CPL-treated patients could be found. Tumors under 10 cm in length responded better to chemotherapy than those of greater length and there was a good correlation between the clinical estimation of tumor regression and progression and the histologic grade of regression.

Key words: Osteosarcoma – Chemotherapy – Histologic grades of regression

Partial or even complete regression of osteosarcomas can be achieved with high-dose polychemotherapy (Huvos et al. 1977; Kotz 1978; Rosen et al. 1976 and 1982). Thus, it has become possible to carry out limb-salvaging resections instead of amputations and enucleations as formerly. The extent of tumor regression through chermotherapy applied after biopsy and before definite surgical treatment is decisive for postoperative chemotherapy (Rosen et al. 1982). For this reason the grade of regression has to be given with utmost care by pathologists. In the following, the results of the regression of 50 osteosarcomas after chemotherapy are presented according to the COSS 80 study (Winkler 1982).

Materials and Methods

Fifty osteosarcomas from the COSS 80 study were examined and analyzed. After diagnosis had been verified by biopsy, the patients were treated with different chemotherapy regimes – which are presented earlier in this symposium (Winkler 1982) – before definite surgery. Operation specimens were analyzed histologically in at least two longitudinal sections and furthermore in various transversal sections by two pathologists (Delling and Salzer-Kuntschik). One half of an operation specimen was cut into 2-cm blocks and treated according to the paraffin method. The other half was split into 7 × 5-cm blocks for undecalcified, metacrylate embedded slides (Delling 1972). The proportions of vital, devitalized, and organized tumor parts from the paraffin slides were transferred onto life-sized photographs of the operation specimens. Thus, the percentage of vital tumor parts of the whole tumor area could be estimated (Salzer-Kuntschik et al., 1983). The proportions of vital and devitalied tumor areas of the undecalcified slides were measured with an electron image-analyzing system

Offprint requests to: Prof. Dr. M. Salzer-Kuntschik (address see above)

Table 1. Osteosarcoma. Histologic grade of regression by chemotherapy

Salzer-Kuntschik Wien		Huvos New York	
I	No viable appearing tumor cells		IV
II	Single vital tumor cells or one vital cell cluster < 0.5 cm	Foci of Viable tumor < 10%	III
III	Vital tumor < 10%		
IV	Vital tumor 10–50%	Tumor necrosis > 50%	II
V	Vital tumor > 50%	Little or no effect of chemotherapy	I
VI	No effect of chemotherapy		

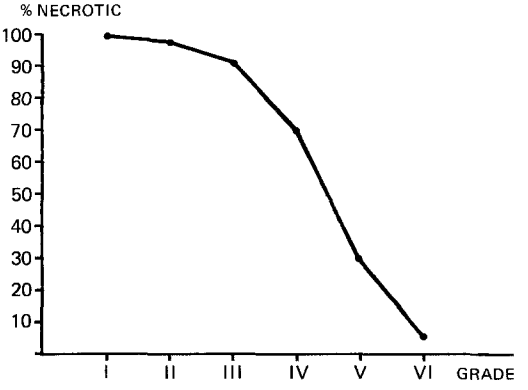

Fig. 1. Histologic grading of preoperative chemotherapy effect as defined by proportion of necrotic tumor

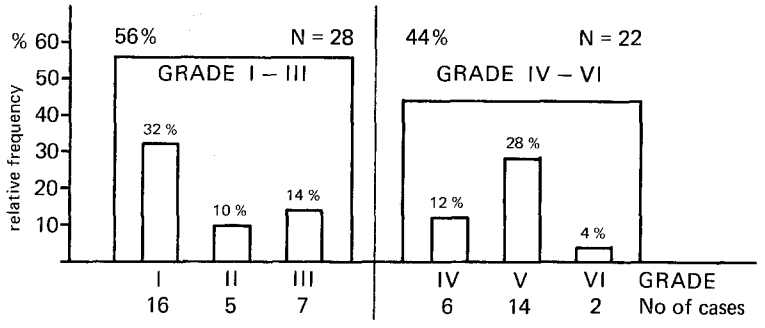

Fig. 2. Distribution of histologic tumor regression in 50 patients after preoperative chemotherapy

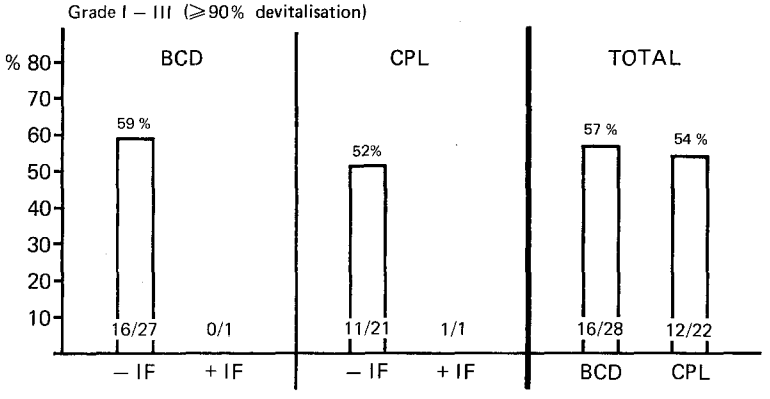

Fig. 3. Relative frequency of favorable histologic response by branches of chemotherapy

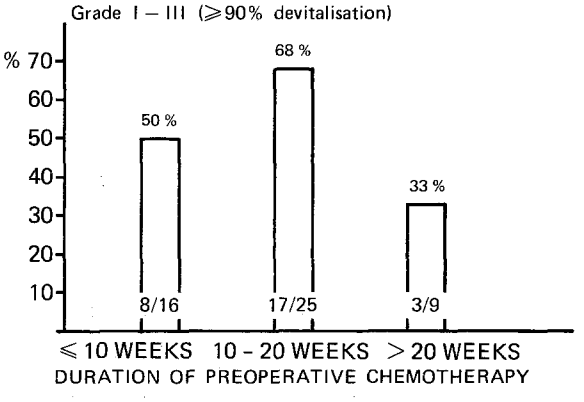

Fig. 4. Relative frequency of favorable histologic response and duration of preoperative chemotherapy

(Delling et al., to be published). The grade of regression was classified according to the six-stage scale, which has been used in the Vienna Bone Tumor Registry since 1977 (Table 1, Fig. 1, Salzer-Kuntschik et al., 1983). The grades of regression were evaluated as good (grades I, II, III) and bad response to chemotherapy (grades IV, V, VI).

Results

Twenty-eight (56%) of 50 osteocarcomas responded well to chemotherapy (Fig. 2) and 16 (57%) of the 28 patients treated with BCD and 12 (54%) of the 22 that were treated with CPL showed good response to chemotherapy (Fig. 3). Sixteen (59%) of 27 BCD-treated patients operated up to the 20th week of therapy who had not received interferon responded well. Poor response to chemotherapy could be observed in one further patient on the BCD regimen, who had received interferon and in whom surgery was performed after the 20th week (Fig. 3). Eleven (52%) of 21 CPL-treated patients who had not recieved interferon and were operated up to the 20th week of therapy responded well (Fig. 3). Two patients on the CPL regimen who had recieved interferon additionally showed a good and a bad response (Fig. 3). Eight (50%) of 16 patients on both chemotherapy regimens operated up to the 10th week of therapy and 17 (68%) of 25 patients operated between week 10 and 20 responded well (Fig. 4).

Osteosarcomas of the tibia showed somewhat better regression than those of femur and humerus (Fig. 3). Osteosarcomas which were under 10 cm in length responded well in 71% of all cases, where as only 37% of tumors over 10 cm in length showed equally good results. The majority of the histologic nonresponders clinically also gave the impression of tumor progression or poor response. None of the cases which responded well histologically showed signs of progression clinically. On the otherhand 2 cases that had seemed to be non-responders clinically, proved to be responders histologically. Ten of 35 cases showed signs of regression clinically, but did not respond well histologically (Fig. 4).

Discussion

The histologic examination and analysis of both halves of the specimens in at least one longitudinal and several transversal sections has proved necessary for an accurate evaluation of the grade of regression. In 25% of all cases, grading differed by one grade in the two halves. This was not due to misinterpretation, but to the fact that regression was actually different in the two halves of the specimen (Salzer-Kuntschik et al., 1983). In two cases, there was uncertainty concerning the grading on the part of one of us. Definite grading was achieved after cooperative examination of the slides. The six-stage regression scale that was used is comparable to the four-stage scale of Huvos (Table 1; Rosen et al. 1982). Good response to chemotherapy corresponds to grades I, II, and III, which tally with Huvos' grades IV and III.

In this study, 22 (56%) of 50 patients were histologically good responders to chemotherapy (Fig. 2). In the study of Rosen et al. (1982), 22 of 57 cases responded well. There was no significant difference of regression between chemotherapy regimens BCD and CPL (Fig. 3). With the limited number of patients (there were only three) who had received interferon additionally, it is not possible to make comment on an interferon effect. Among the patients who were operated up to the 10th or between the 10th and 20th week of therapy there were more good responders (25 of 41) than among patients operated after the 20th week of therapy (three of nine; Fig. 4).

Osteosarcomas up to 10 cm in length showed good regression in 15 of 21 cases, whereas the same positive development could be observed in only 6 of 16 tumors with a length over 10 cm (Table 2). There was good correlation between the clinical estimation of tumor re-

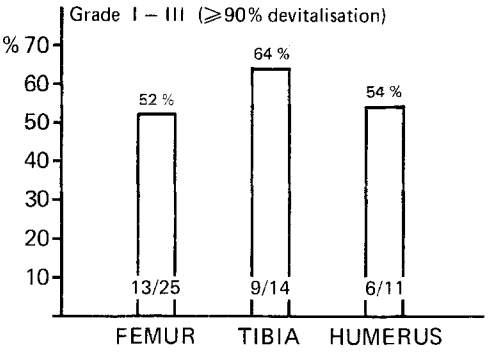

Fig. 5. Relative frequency of favorable histologic response and tumor site

Table 2. Histologic grade of regression tumor site/morphologic tumor length

Tumor site	Morphologic length cm	N	Grade I–III ≧90% devitalisation	Grade IV–VI <90% devitalisation
Femur		17		
	<10	9	6	3
	>10	8	3	5
Tibia		10		
	<10	9	7	2
	>10	1	0	1
Humerus		10		
	<10	3	2	1
	>10	7	3	4
Total		37		
	<10	21	15 (71%)	6 (29%)
	>10	16	6 (37%)	10 (63%)

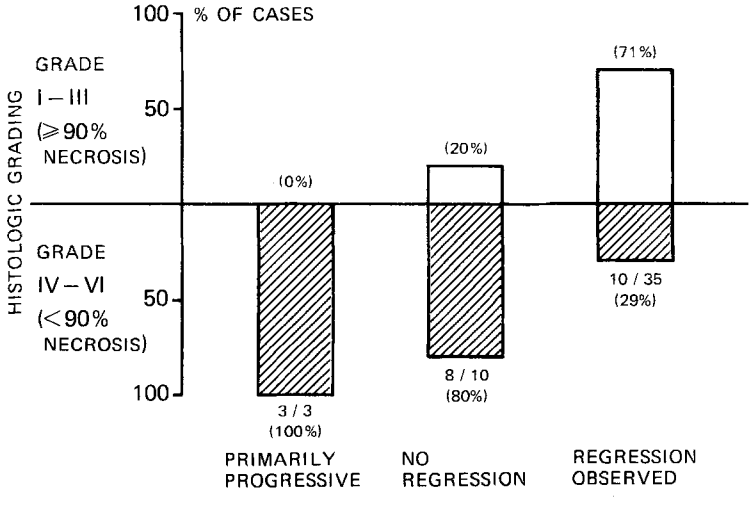

Fig. 6. Clinical evaluation of tumor development. Adjuvant chemotherapy in osteosarcoma; clinical tumor development and histologic grading of chemotherapy effectiveness

gression and tumor progression and the histologic grades of regression (Fig. 6).

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