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Spontaneous necrosis in osteosarcomas

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Summary. In the treatment of osteosarcoma pre-operative chemotherapy has assumed considerable importance in helping improve survival, and enabling limb-sparing procedures. The quantitative assessment of tumour necrosis in the resected specimen by morphological means has become a significant step in judging therapeutic response and in helping determine post-operative management. Different systems of grading tumour regression have been proposed. Little is known, however, about the morphology or degree of spontaneous necrosis in osteosarcomas, in particular to what extent necrosis can be considered to be due to cytotoxic treatment. For this purpose, 13 osteosarcomas, taken from patients treated by surgery alonge, were examined by the same method we routinely employ in assessing chemotherapeutic response. The results demonstrate that the extent of spontaneous necrosis does not approach that achieved in response to chemotherapy. Sub-total necrosis may be due to spontaneous regression, inadequate therapeutic response, or to a combination of both. Hence, only two categories of response, good and poor, appear relevant and these terms should be used in preference to good, intermediate and poor.

Key words: Osteosarcoma – Necrosis – Surgery, operative – Drug therapy, chemotherapy

Introduction

In the treatment of osteosarcoma pre-operative chemotherapy has gained considerable importance in helping improve survival and enabling limb-sparing procedures (Eilber et al. 1984; von Hochstetter, in preparation; Lane et al. 1986; Rosen 1986; Winkler et al. 1986). Its effectiveness, judged first by the clinical response, is assessed later by the extent of tumour destruction in the resected specimen (Honegger et al. 1984). The measurement of tumour necrosis by morphological means has come to play a significant part in judging therapeutic response and thus in helping to determine post-operative management (Honegger et al. 1984; Lane et al. 1986; Rosen et al. 1979; Winkler et al. 1986). While the aim of effective therapy remains total tumour necrosis, the response may be sub-total or less than this. In these circumstances it is not known to what extent tumour necrosis is due to treatment or to spontaneous events. Very little, in fact, is known about the extent of spontaneous necrosis in osteosarcoma, all the more as it is increasingly difficult to obtain entire specimens that have not been exposed to adjuvant treatment. Hence, we subjected 13 specimens of osteosarcoma of the extremities treated by surgical means alone to the same procedure of quantifying necrosis that we use routinely on specimens from our patients treated by pre-operative chemotherapy.

Materials and methods

Our osteosarcomas were taken from our collection of wet specimens, preserved over many years in fixative. Clinical information in all cases indicated that there had been no adjuvant therapy. The quality of tissue preservation was excellent.

Our method of assessing the degree of tumour destruction by light microscopic means has been described elsewhere (von Hochstetter et al. 1983; Honegger et al. 1984). Essentially, an entire cross-sectional tumour surface is screened at low to medium magnification and the amount of necrosis in each visual field plotted on a grid overlying a polaroid composite photomosaic which reproduces the topography of the specimen.

Several systems of classifying the amount of necrosis have been described (Fig. 1). Ours uses the original categories of "absent, partial, predominant, and total tissue necrosis", defining the two middle categories as necrosis of less and of more than 50% of the tumour cell population per visual field. The resultant figures express the percentage of the cross-sectional tumour surface that is totally or largely necrotic, or vital (Figs. 2, 3).

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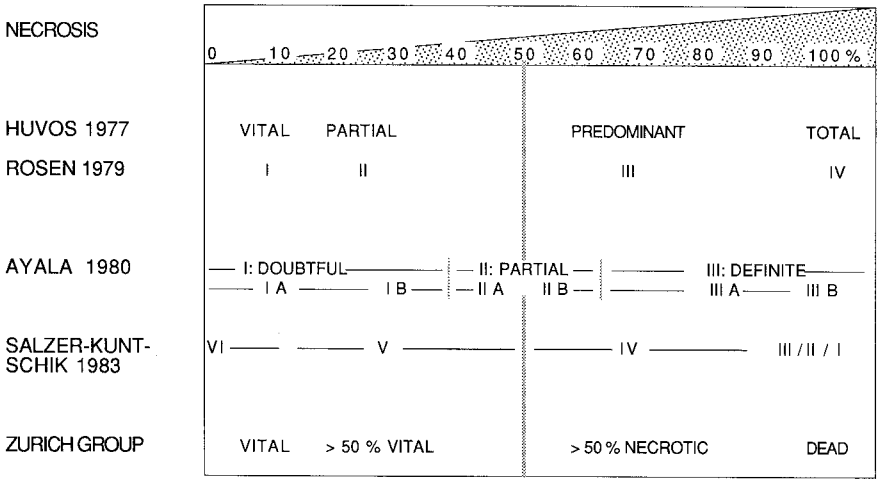

Fig. 1. Comparison of various systems used in quantifying tumour necrosis morphologically, through the definition of categories (grades of regression) and their ranges

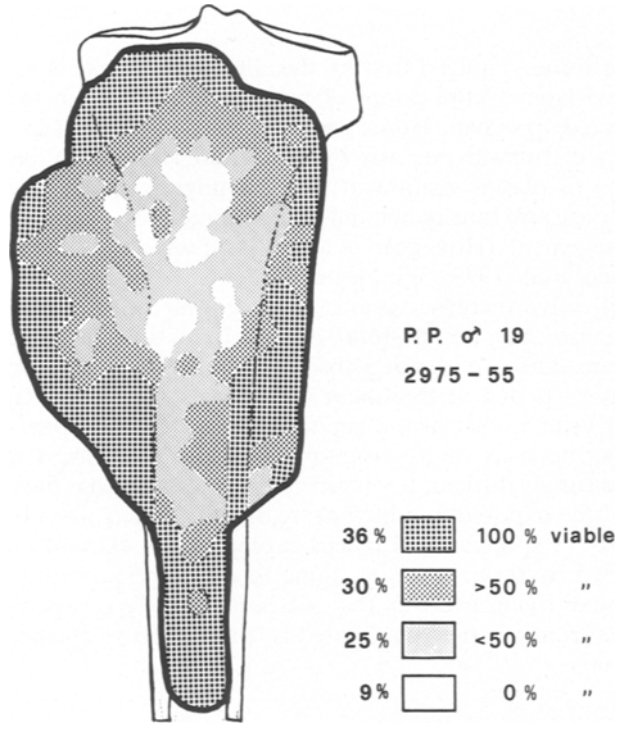

Fig. 2. Nineteen-year-old male. Osteosarcoma of the tibia. In all, 34% of the tumour surface is totally or largely necrotic. These zones are located centrally, about the epicentre of the tumour

Results

Our specimens were derived from eight male and five female patients, aged 9–31 years, with an average and median of 17 years. Five tumours each were located in the femur and tibia, two in the humerus, and one in the fibula. There was one parosteal and one periosteal osteosarcoma, both in the distal femur. The tumour in the fibula was of the telangiectatic type.

Histologically, there were eight osteoblastic tumours, one of which was largely telangiectatic in appearance. Three were chondroblastic, including the periosteal lesion, and two other were largely fibroblastic, including

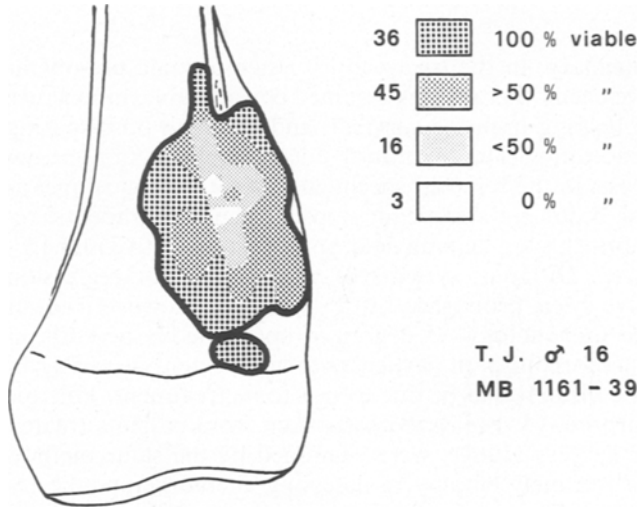

Fig. 3. Sixteen-year-old male. Osteosarcoma of the distal femur in a typical excentric location. Zones of total or predominant necrosis are located near the epicentre of the tumour, about the metaphyseal cortex

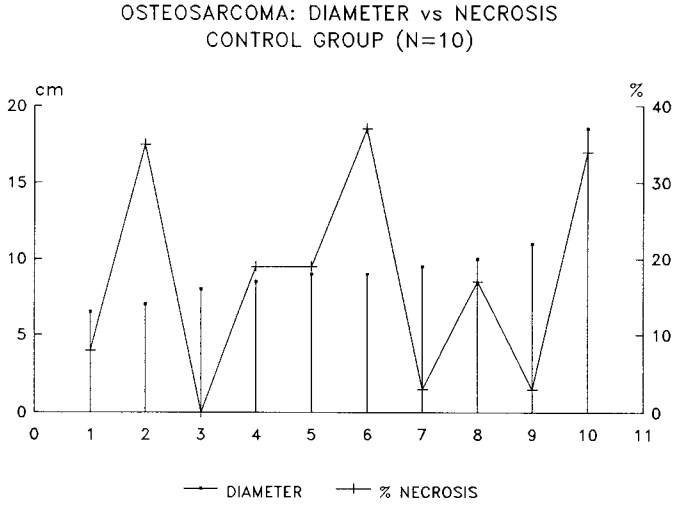

Fig. 4. Tumour diameter vs spontaneous necrosis in ten osteosarcomas. Periosteal, parosteal and telangiectatic forms are not included

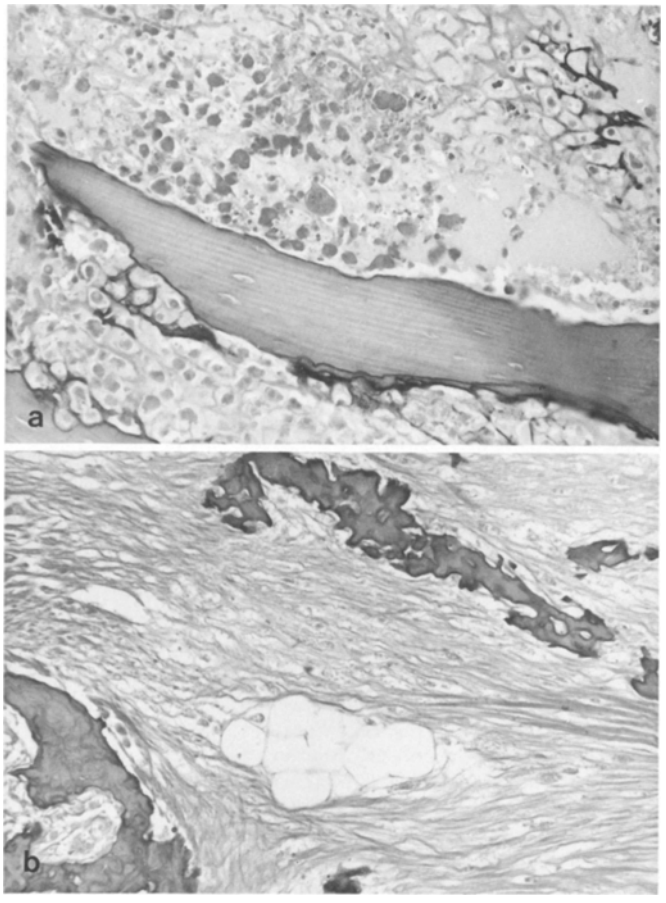

Fig. 5A, B. Tumour necrosis in osteosarcoma treated by surgery alone. **A** Coagulation type: eosinophilic mass lacking structure; **B** depopulation type: structural elements remain but cellular population has disappeared. Note that the fat cells are not necrotic. **A, B** H & E × 160

the parosteal tumour. The diameters ranged from 5 to 18.5 cm, with an average and median of about 9 cm. The extent of necrosis was not found to relate to diameter, even when the variant forms were excluded (Fig. 4). Necrosis was about equally of the coagulation and depopulation types (Fig. 5). The type of necrosis did not correlate with a particular histological type, but rather with the amount of intercellular substance present: densely cellular areas displayed coagulation necrosis, while those rich in fibres, osteoid or bone manifested depopulation. Necrosis was more pronounced in central portions of the tumour (Figs. 1, 2), regardless of whether the epicentre lay centrally or excentrically in relation to the topography of the bone.

In all tumours considered, necrosis ranged from 0 to 37% of cross-sectional tumour surface (Fig. 6). In the group of osteoblastic tumours the median was 19%, the average 18%. Spontaneous necrosis in endosteal/central osteosarcoma averages around 20%. In comparison, a series of tumours from patients who had undergone pre-operative chemotherapy manifested an average extent of necrosis just over 70%, with a median in the osteoblastic group of 90% (Fig. 6) (von Hochstetter, in preparation).

Discussion

Several methods of evaluating treatment response morphologically in osteosarcomas have been proposed (Ayala et al. 1980; von Hochstetter et al. 1983; Huvos et al. 1977; Salzer-Kuntschik et al. 1983). Common to all is the attempt to assess the amount of necrosis in the resected lesion. They differ in method, terminology and precision. We have found it impossible in practice to discern intermediate measures of necrosis (e.g. 30%, 40%, 60%) with any degree of assurance. Our method has the advantage of establishing four easily applicable categories expressing percentage of total tumour surface that is largely necrotic or largely vital.

The results on 13 osteosarcomas treated by surgery alone reveal a far lesser degree of necrosis than we have found in our patients treated with adjuvant chemotherapy. In the central tumours, largely necrotic areas covered about 20% of the cross-sectional surfaces. The greatest single figure was 37%, whereas one tumour was essentially vital throughout. Whether the amount of necrosis depends on the histological type is questionable. In particular, two chondroblastic tumours were more necrotic than the average. The parosteal fibroblastic tumour was

Topography	Histological type	Control group ($N=13$)			Chemotherapy Group ($N=21$)		
		N	%	Necrosis*	N	%	Necrosis*
Endosteal		13	18		18	72	
	Osteo	7		18 (19/0–35)	11		73 (90/16–100)
	Chondro	2		20 (3–37)	2		75 (46–84)
	Fibro	1		17	3		67 (67/37–100)
	Telang	1		22	2		?
Periosteal	Chondro	1	25		1	26	
Parosteal	Fibro	1	6		2	30 (12–48)	

* Figures in parentheses are: mean/range

Fig. 6. Results of semiquantitative assessment of tumour necrosis in 13 osteosarcomas treated by surgery alone in comparison with 21 tumours from patients treated with preoperative chemotherapy (3)

well below average, however, possibly due to fewer vascular accidents during the slow growth of such lesions.

To our knowledge, only one other study has reported on spontaneous necrosis in osteosarcomas of the extremities (Misdorp 1986). The results were generally higher, ranging from 10% to 90% with an average of 50%, but unfortunately neither methodology nor histological subtypes are described.

The tendency for central regions to become devitalized is in keeping with necrosis in other malignant tumours and probably relates to the mechanisms of vascular supply. That the same configuration, although greatly increased in extent, is found in tumours following chemotherapy, cannot be explained on grounds of vascular supply alone since exposure to cytostatic substances should be less in the central portions of the tumours. (Picci et al. 1986; von Hochstetter, in preparation).

The long-term results of several groups of clinical researchers have shown that the watershed between a good and a lesser response is around 90% necrosis (Rosen 1986; Picci et al. 1988; von Hochstetter, in preparation). Since spontaneous necrosis can account for devitalization covering about half the cross-sectional tumour surface, a category for an intermediate response, e.g. 60–90%, appears superfluous. On morphological grounds, response to treatment can be considered either manifest (>90%) or not.

References

Ayala AG, Mackay B, Jaffé N, Sutow WW, Benjamin R, Murray JA (1980) Osteosarcoma: The pathological study of specimens from en bloc resection in patients receiving preoperative chemotherapy. In: van Eys J, Sullivan MP (eds) Status of the curability of childhood cancers. Raven Press, New York, pp 127–144

Eilber FR, Eckardt J, Mirra J, Caulkins E, Weisenburger T (1984) Osteosarcoma: experience at the University of California at Los Angeles. In: Uhthoff HK (ed) Current concepts of Diagnosis and treatment of bone and soft tissue tumours. Springer, Berlin Heidelberg New York, pp 377–382

Hochstetter AR von, Cserhati M, Honegger HP, Grosscurth P, Hofmann V (1983) Zurich bone sarcoma study. II. Histomorphologic analysis of bone sarcomas following treatment with preoperative chemotherapy (abstract). Verh Dtsch Ges Pathol 4:783

Hochstetter AR von (1990) Morphologische Untersuchungen an menschlichen Osteosarkomen – Vergleich von spontanen mit zytostatisch induzierten Nekrosen und ihre prognostische Bedeutung. Habilitationsschrift. Universität Zürich

Honegger HP, Hochstetter AR von, Groscurth P, Hofmann V, Cserhati M (1984) The effect of chemotherapy on human bone sarcomas: a clinical and experimental study. In: Recent results in cancer research, vol 94. Springer, Berlin Heidelberg New York, pp 66–75

Huvos AG, Rosen G, Marcove RC (1977) Primary osteogenic sarcoma: pathologic aspects in 20 patients after treatment with chemotherapy, en bloc resection, and prosthetic bone replacement. Arch Pathol Lab Med 101:14–18

Lane JM, Hurson B, Boland PJ, Glasser DB (1986) Osteogenic sarcoma. Clin Orthop 204:93–110

Misdorp W (1986) The assessment of necrosis in osteosarcoma. In: van Oosterom AT, van Unnik JAM (eds) The management of soft tissue and bone sarcomas. Raven Press, New York, pp 241–243

Picci P, Bacci G, Campanacci M, Gasparini M, Gherlinzoni F, Calderoni P, Pilotti S, Cerasoli S, Campanna R (1986) Evaluation of necrosis in 42 patients with osteosarcoma of the extremities treated by preoperative chemotherapy. In: van Oosterom AT, van Unnik JAM (eds) management of soft tissue and bone sarcomas. Raven Press, New York, pp 245–251

Picci P, Bacci G, Capanna R, Madon E, Paolucci G, Marangolo M, Avella M, Baldini N, Mercuri M, Campanacci M (1988) Neoadjuvant chemotherapy for osteosarcoma – results of a prospective study. In: Ryan JR, Baker LO (eds) Recent concepts in sarcoma treatment. Kluwer, Dordrecht, Boston, pp 291–296

Rosen G (1986) Role of chemotherapy in the treatment of primary osteogenic sarcoma: a five year follow-up on T10 neo-adjuvant chemotherapy. In: Kimura K, Wang YM (eds) Methotrexate in cancer therapy. Raven Press, New York, pp 227–238

Rosen G, Marcove RC, Caparros B, Nirenberg A, Kosloff C, Huvos AG (1979) Primary osteogenic sarcoma: the rationale for preoperative chemotherapy and delayed surgery. Cancer 43:2163–2177

Salzer-Kuntschik M, Brand G, Delling G (1983) Bestimmung des morphologischen Regressionsgrades nach Chemotherapie bei malignen Knochentumoren. Pathologe 4:135–141

Winkler K, Beron G, Kotz R, Salzer-Kuntschik M (1986) The COSS Study Group. In: van Oosterom, van Unnik (eds) Management of soft tisue and bone sarcomas. Raven Press, New York, pp 275–288