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Classification of osteosarcoma by 85-Sr scintimetry

The histologic type of a classical osteosarcoma may be difficult to determine because of insufficient biopsy material and polymorphism of the tumour. Since osteoformation is directly related to the differentiation and functional capacity of the tumour cells, 85-Sr scintimetry was used to evaluate osteoid formation in 90 patients with classical osteosarcoma. Measurements over an 8-day period from isotope injection revealed a separation of the lesions into three groups, with high, medium and low activity. Compared to histologic classification into osteoblastic, chondroblastic/fibroblastic, and anaplastic variants, scintimetry revealed that only half of the 41 tumours classified as osteoblastic had a high 85-Sr uptake. The anaplastic lesions belonged to the group with low 85-Sr uptake. Scintimetric determination of the functional differentiation of tumoral cells may possibly be of prognostic value in osteosarcoma.

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Only a few of the various types of osteosarcomas can easily be classified from biopsy material. These forms include juxta-cortical and periosteal osteosarcoma, and fusiform cell sarcoma (Unni et al. 1977), and have distinct histologic and radiographic features (Dahlin 1978, Trifaud et al. 1980, Mirra 1980).

The variants of classical osteosarcoma may be difficult to recognize in biopsy material not necessarily characteristic of the tumour as a whole (Sim et al. 1979). Moreover anaplastic osteosarcoma may sometimes be difficult to distinguish from Ewing's sarcoma and Parker lymphoma (Sim et al. 1979).

In osteosarcoma the osteoid tissue formation expresses the histo-differentiation and functional capacity of the neoplastic cells. Osteoid tissue mineralization may be evaluated using 85-Sr scintimetry (Bauer et al. 1955, Bauer 1968, Reeve et al. 1976).

We investigated if 85-Sr scintimetry can be used as a quantitative parameter of cellular differentiation toward osteogenesis, and thereby be used as an aid in the classification of osteosarcoma.

Patients and methods

Ninety patients with classical osteosarcoma were examined at the Institut Curie during the period 1970–1981. The mean age was 18 (9–48) years and 49 patients were male. Eighty-eight tumours were located in the extremities, one in the pelvis, and one in the thorax. The mean tumour diameter was 12 (2–25) cm.

The tumours were radiographically classified into three groups: sclerotic 16, mixed 56, and lytic 18. Histologically, 41 lesions were osteoblastic, 32 mixed (partially osteoblastic and partially chondroblastic and/or fibroblastic) and 17 tumours were classified as anaplastic. Four teleangiectatic variants were included in the anaplastic group.

The scintimetric studies were performed either before biopsy or within 3 weeks after small biopsies. The fixation rate of 85-Sr ($E\gamma$ = 0.51 MeV, T/2 = 65 d) was evaluated over a period of 8 days by external measurement of radioactivity of both the tumoral zone and a contralateral healthy zone of reference. Adult patients were given 50 μCi (185 MBq) of 85-Sr by i.v. injection, and for children the adult dose × age of the child/20 was given. For both adults and children a maximum dose of 2 rad (0.02 Gy) was delivered for the whole body. The concentration of 85-Sr was measured with a multiprobe detection set, comprising 4γ ray detectors (3"INa) on pedestals permitting reproducible localization of probes on a rectangular system of coordinates. Each detector could carry two cylindroconic single hole collimators, wide collimator aperture 25 degrees (input diameter 40 mm), low collimator aperture 10 degrees (input diameter 20 mm); height 80 mm and minimal thickness of lead protection 50 mm. The detector with selected collimator was placed above a pre-located re-

gion, selected on the basis of 99mTc scintigraphic findings.

Most tumours extended considerably beyond the limits of the surface area projected by the low collimator aperture. The wide collimator aperture was generally used since comparative assessment with the low collimator aperture revealed no significant differences. The distance of the collimator from the skin was measured to account for the total tumoral area included in a single counting measurement.

To minimize inaccuracies in measurements associated with geometry, absorption, and metabolism, the results were expressed as the ratio of activity of the tumoral zone to that of a contralateral healthy zone. Repetition of measurements led to a sequence of counting ratios which were plotted against time.

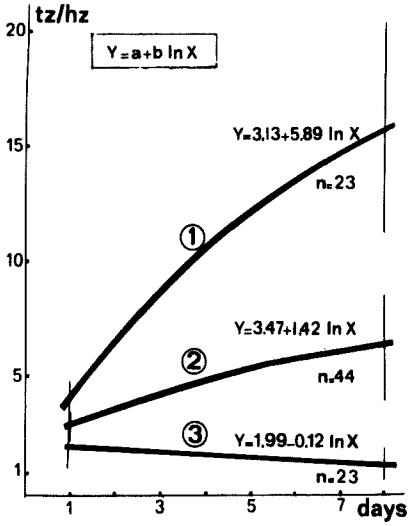

Figure 2. 85-Sr activity ratios from day 1 to day 8 plotted against time. The curves represent the means of the curves of each group.

Results

The histogram of 85-Sr activity ratios on the 8th day (R8) after isotope injection revealed that the ratios were distributed into three distinct groups (Figure 1). Group I with 23 tumours had mean R8 values of 15.9 (SD 4.5), Group II with 44 patients 6.3 (SD 0.4) and Group III with the lowest R8 activity ratios, mean 2.0 (SD 0.7) contained 23 patients. These three groups were also distinguished by different activity ratio curves from day 1 to day 8 after isotope injection (Figure 2). The mathematical formulas for the average curves are given in Figure 2.

The classification of the tumours into three groups based on the 85-Sr uptake was then compared to the histologic classification into osteoblastic, mixed (osteoblastic and chondroblastic/fibroblastic), and anaplastic variants (Table 1). The comparison revealed that the

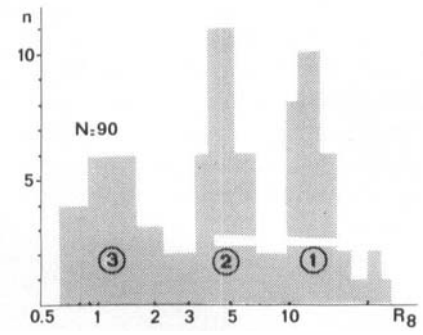

Figure 1. 85-Sr activity ratios (R8) on day 8 after isotope administration. Values are the ratio of activity in tumoral zone to a contralateral healthy zone.

Table 1. Comparison between 85-Sr scintimetric and histologic classification of 90 osteosarcomas

Scintimetry Group	Histology			Total
	Osteoblastic	Mixed	Anaplastic	
I	14	7	–	21
II	23	22	1	46
III	4	3	16	23
Total	41	32	17	90

Table 2. Comparison between 85-Sr scintimetric classification and radiographic appearance of 90 osteosarcomas

Scintimetry Group	Radiography			Total
	Sclerotic	Mixed	Lytic	
I	8	13	–	21
II	8	35	3	46
III	–	8	15	23
Total	16	56	18	90

anaplastic tumours belonged to Group III with the lowest 85-Sr activity, and the majority of the mixed tumours to Group II. Of 41 tumours classified as osteoblastic, only 21 belonged to Group I, with the highest 85-Sr activity. Four of the tumours which had an osteoblastic appearance at biopsy, actually had almost no 85-Sr uptake.

Corresponding comparison between radiographic appearance, sclerotic, mixed, or lytic, and 85-Sr activity revealed a good agreement between these two methods. Notably no lytic tumours had high and no sclerotic tumours had low 85-Sr activity ratios.

Discussion

Our study has shown that 85-Sr scintimetry provides an additional means of classifying osteosarcoma, besides histology and radiography. Based on 85-Sr activity ratios during the first 8 days after administration of the isotope, the tumours could be divided into three Groups: I (25%) with a high rate of mineral accretion, II (50%) with a medium rate, and III (25%) with a low rate of mineralization.

For each of the groups defined above, the logarithmic expression of the mean 85-Sr fixation ratios led to bi-exponential curves for the time course of the measurements. Neither the initial phase, related to dilution, nor the late ratios which were difficult to work with because of the intervention of bone clearance, were taken into account.

Osteosarcomas are generally classified histologically by the predominant type of matrix formation (osteo-, chondro-, or fibroblastic) (Dahlin 1978), and by the degree of anaplasia of the neoplastic cells, according to four grades proposed by Broders (1926). Classical osteosarcoma is highly malignant and the large majority are Grade III or IV lesions. There is, however, no prognostic difference between grades, nor does classification according to subtypes of classical osteosarcoma provide substantial prognostic information. Although classification according to type and grade is important for differential diagnostic puposes, further means of classifying osteosarcomas could be of value for prognostic purposes.

The rationale for applying 85-Sr scintimetry was that osteoid formation and mineralization are the function of specialized tumour cells. A high rate of mineralization of an osteosarcoma can thus be attributed to a relatively high degree of differentiation, whereas tumours with a low rate of mineral accretion are more anaplastic. Although osteoid content can be assessed by histologic examination, biopsy samples are not necessarily representative of the tumour as a whole, and do not give information as to the functional capacity of the osteoblastic tumour cells. Scintimetry analyses a lesion as a functional unit and classifies osteosarcoma by the capacity to form mineralized osteoid.

In our series, comparison between histology and scintimetry showed a good agreement among the highly anaplastic tumours, including the teleangietatic variants, in which the scanty areas of osteoid formation were paralleled by a low rate of 85-Sr uptake. It is interesting to note that this group accounted for as many as 20 per cent of the tumours, whereas they comprised less than 10 per cent in the literature (Dahlin 1978, Mirra 1980). On the other hand, only half of the tumours, classified histologically as osteoblastic, had a high rate of mineral accretion. It thus appears that although a lesion may be predominantly osteoblastic, the functional capacity of the neoplastic cells may be less differentiated. In osteosarcomas of chondroblastic and fibroblastic types scintimetry provides less information since these lesions may be fairly well differentiated without having a high rate of mineral accretion.

In conclusion, radionuclide scintimetry of osteosarcoma provides the possibility of measuring the rate of mineralization of osteoid and classification by their degree of osteoblastic differentiation in functional terms. Future analysis, with follow-up, may reveal whether scintimetry may be of prognostic value in osteosarcoma. Also, newer scintimetry techniques should be tested.

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