Determining Growth Rates of Focal Lesions of Bone from Radiographs[1]

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Rate of growth divides focal lesions of bone into two classes which are largely mutually exclusive. Not all focal lesions require biopsy, and grading is especially helpful in deciding which should be biopsied and which may be safely followed. The statistical proof and logic of grading as an expression of growth rate are presented with a set of rules establishing each of the five grades in the presence of bone destruction. The radiologic signs necessary to establish rates are described and illustrated.

INDEX TERMS: Bone neoplasms, diagnosis • (Skeletal system, error in diagnosis, 4[0].940) • (Skeletal system, fundamental observation, 4[0].910)

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Radiographs of most focal lesions of bone permit determination of rate of growth in a single frame in time. This is important for both diagnosis and establishment of a rational plan of management. Over a period of years, an increasing number of cases of focal bone lesions submitted to the Mid-America Bone Diagnostic Center for consultation has been successfully managed without biopsy. Grading has been an essential element of the decision process which permits our staff to make this recommendation with confidence. In this paper, the methodology and proof of the grading concept are presented. In the paper which follows (p. 585), the experiences of four readers who applied the grading concept to a test library of 223 cases are analyzed, and the results of the study used to eliminate major sources of error.

BACKGROUND

The concept of estimating rate of growth from radiographs of focal lesions in bone arose as the result of an analysis of cases from the Bone Sarcoma Registry of the American College of Surgeons, now a part of the Codman Bone Sarcoma Registry at the Armed Forces Institute of Pathology. This unique collection contains extensive clinical, histologic and radiographic information about more than 2,000 cases, including survival time. One of the authors (G.S.L.) reviewed the collection to gather sufficient clinical, radiographic, and histologic information to be able to establish a significant relationship of radiologic signs to diagnosis. Radiographic images were analyzed according to a protocol which includes skeletal location and size of tumor, patterns of bone destruction, reactive changes in bone, and tumor matrix mineralization. The initial insight into the prognostic (and rate) significance of different radiographic patterns resulted from an experiment with fibrosarcomas of bone: cases were divided into three

Fig. 1. Geographic destruction: radiographic appearance of a single or confluent hole in bone in which destruction is complete. If geographic is the only visible pattern of destruction, the edge of the destroyed area can be found to vary from sharp (see inner surface of cortex) to ill-defined (see edge in cancellous bone). The structure of bone adjacent to the destroyed area is uninvolved. [Bone cyst, Grade IB.]

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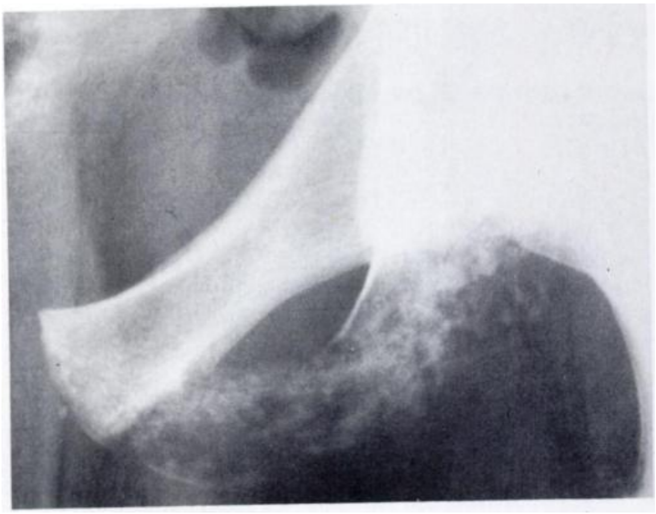


Fig. 2. Moth-eaten destruction: radiographic pattern of a poorly circumscribed focal lesion which shows multiple, apparently randomly distributed holes which destroy the structural integrity of bone. The holes lack uniformity of size, ranging from those large enough to destroy the total thickness of cortex to those small enough to resemble those of permeated destruction. The pattern is extensively destructive and often responsible for pathologic fracture. [Osteomyelitis, Grade II.]

Fig. 3. Permeated destruction: multiple uniformly small holes in a poorly circumscribed area. The holes are so small that they do not destroy structures but rather leave their outlines essentially intact. Their locations conform to the osteone systems, and often they are larger and more numerous in the center of a lesion than at its edge. The appearance is very much like that of osteoporosis. Permeated destruction is more difficult to detect in spongy bone in which the cortex is thin. [Reticulum cell sarcoma, Grade III.]

sets according to whether the pattern of destruction was basically geographic (Fig. 1), moth-eaten (Fig. 2) or permeated (Fig. 3) (1). The set characterized by permeated destruction had few five-year survivors, while that with geographic destruction had many. The set with moth-eaten destruction had an intermediate number of survivors.

With this basic information and through detailed observation of radiographic patterns of tumor behavior at various levels of malignancy, a concept arose of estimating probability of survival from radiographs as a set of five grades: 1A, 1B, and 1C having predominantly geographic destruction, II moth-eaten destruction, and III permeated destruction.

This has been experimentally tested on data from six classes of tumors from the Codman Registry. Because of the massive volume of materials, computer processing was employed using a grading algorithm[3] nearly identical to that illustrated in TABLE VIII. Applying the grading concept to radiographs of 143 fibrosarcomas, 119 chondrosarcomas, 182 osteosarcomas and 161 Ewing sarcomas (TABLES I–IV) resulted in effective separation of tumors into spectra revealing progressively smaller numbers of five-year survivors from Grade IA to Grade III. Two other important features were demonstrated. First, the biologic

[3] Algorithm: A set of well-defined rules for the solution of a problem in a finite number of steps. The term is derived from *al-Hwa-rizmi* (Muhammed Ibn Musan), a nineteenth century Arab mathematician.

TABLE I: DISTRIBUTION OF 143 CASES OF FIBROSARCOMA BY RADIOLOGIC GRADE

FIBROSARCOMA		IA	IB	IC	II	III
	50—					
Distribution of graded tumors	30—	19	15	50	32	27
Average delay in diagnosis (months)	20—	50.0	15.3	15.2	14.2	6.6
Absolute 5-year survival (%)	10—	52.6	46.7	36.0	15.6	7.4

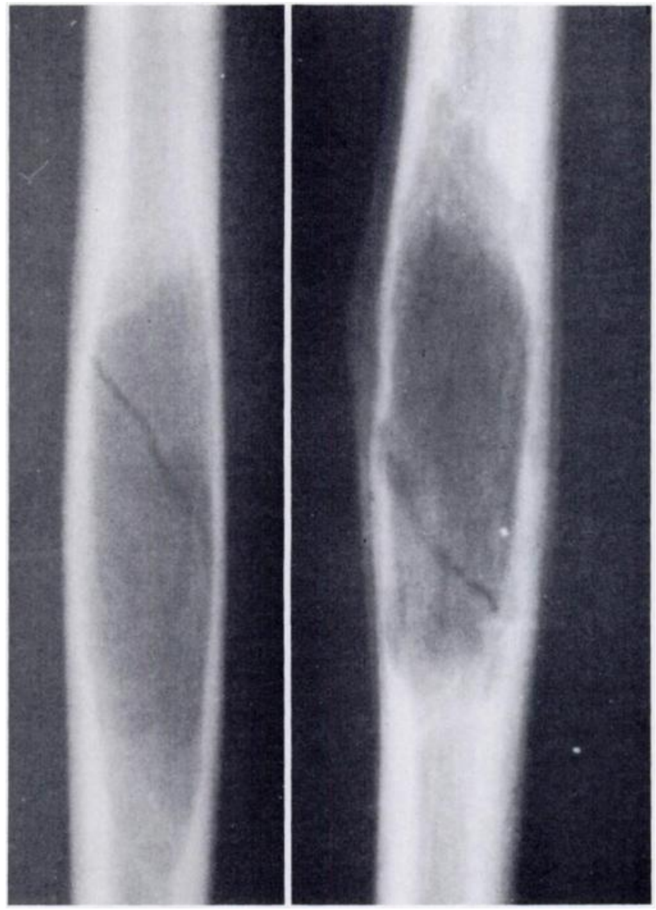
Graph indicates the numerical incidence by grade. Probability that survival incidence is due to random distribution: $\chi^2 p = <0.01$.

TABLE II: DISTRIBUTION OF 119 CASES OF CHONDROSARCOMA BY RADIOLOGIC GRADE

CHONDROSARCOMA		IA	IB	IC	II	III
	30—					
Distribution of graded tumors	20—	29	25	26	17	22
Average delay in diagnosis (months)	10—	25.8	28.7	22.6	8.8	7.5
Absolute 5-year survival (%)	0—	44.8	32.0	34.6	23.5	22.7

Graph indicates numerical incidence by grade. The probability of observed decline in elapsed time between first symptoms and actual diagnosis as the result of random distribution is $\chi^2 p = <0.001$.

Fig. 4. Total penetration of cortex: geographic destruction of bone by a lesion centered in the cortex, extending into the medullary canal and outward into soft tissues. The lesion is partially enveloped by a reactive barrier of sclerosis within and an incomplete shell externally. The central densities are ossifying tumor matrix. [Osteoblastoma, Grade IC.]



5a,b

Fig. 5. **a.** Partial penetration of cortex: geographic destruction, pathological fracture. The cortex is uniformly thinned from within and is slightly expanded. Contour of edge is regular.

b. One month later, with the arm at rest, disuse osteoporosis is apparent, and the contour of the inner surface has been modified by multicentric foci of osteoclastic activity. Note resemblance of osteoporosis to permeated destruction. [Benign bone cyst, Grade IB.]

behavior of fibrosarcomas and chondrosarcomas results in different distributions from those of osteosarcomas and Ewing sarcomas, the latter two being numerically more concentrated at the highly malignant end of the spectrum, and the other two more evenly distributed through the total range of biologic behavior. Still, there are a few cases of osteosarcoma and Ewing sarcoma to be found in the Grade IA high survival group. Secondly, as five-year survival diminishes, there is also a trend for the duration of symptoms between onset and diagnosis to diminish.

In order to improve the statistical confidence of the first four tables, all cases are combined into a single graph (TABLE V) depicting declining survival by grade. This table confirms a highly valid relationship between radiological grade and five-year survival. However, the slope of the curve is not uniform, and shows the most striking differences in survival occurring between Grades IA and IB and between Grades IC and II (TABLE VI).

Finally, TABLE VII depicts two primary neoplasms of

TABLE III: DISTRIBUTION OF 182 CASES OF OSTEOSARCOMA BY RADIOLOGIC GRADE

OSTEOSARCOMA		IA	IB	IC	II	III
Distribution of graded tumors	110— 100—	4	1	16	50	111
Average delay in diagnosis (months)	50—	8.7	12.0	15.7	6.0	3.5
Absolute 5-year survival (%)	0—	50.0	0.0	25.0	8.0	5.4

The number of survivors in the individual grades is too small for application of the χ^2 test. Results are calculated according to Hald's binomial test using totals of Grade I and combined Grades II and III. Probability that the relative frequencies are equal is <0.01.

TABLE IV: DISTRIBUTION OF 161 CASES OF EWING SARCOMA BY RADIOLOGIC GRADE

EWING SARCOMA		IA	IB	IC	II	III
Distribution of graded tumors	125— 100—	6	10	12	11	122
Average delay in diagnosis (months)		6.5	16.4	10.1	5.3	8.6
Absolute 5-year survival (%)	50—	16.7	30.0	41.7	0.0	10.7
IA, B, & C combined			32.1			
II & III combined	0—					9.8

The number of survivors in the individual grades is too small for application of the χ^2 test. Results are calculated according to Hald's binomial test using totals of Grade I and combined Grades II and III. The probability that the relative frequencies are equal is <0.01.

6a,b

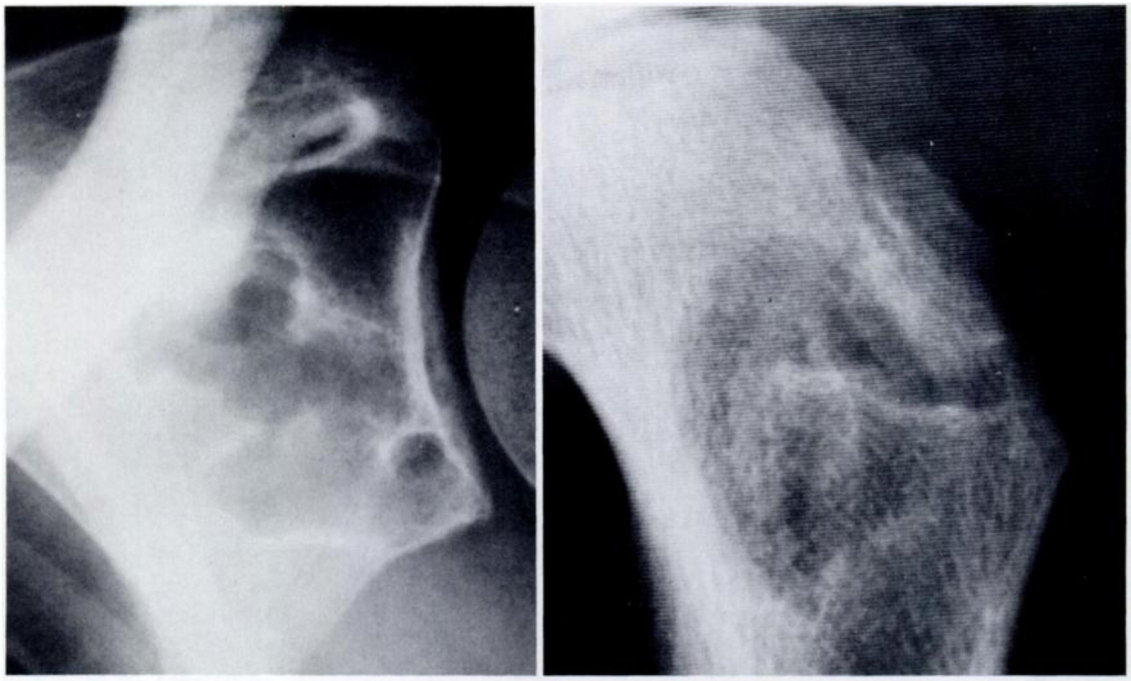


Fig. 6. **a**. Sclerotic rim: geographic destruction. Clearly defined narrow zone of reactive new bone coincides with the edge of the destroyed area. Destruction is "geographic" in the sense that the details of its outline are as if shown on a map. [Benign cyst, Grade IA.]
b. Absence of sclerotic rim: geographic destruction. There is no visible formation of new bone at the edge of the destroyed area. [Benign bone cyst, Grade IB.]

bone found at the high survival ends of the spectrum. Chondroblastoma, almost always benign, falls largely within Grade IA, while the more aggressive giant cell tumor peaks in frequency at Grade IC. However, with the exception of one giant cell tumor in Grade II, both are confined to the Grade I compartment.

With time, grade as a concept of degree of malignancy has been replaced by grade as a concept of rate of growth, since it is apparent that the patterns of destructive and reactive behavior originally studied in neoplastic diseases are common to all disease classes in bone, and these patterns reflect the dynamic behavior of disease in bone first, and prognosis only as it relates to behavior.

LOGIC AND METHODOLOGY OF GRADING

Estimation of rate of growth from the radiographic image of a bone tumor is possible in part because the richness of detail and contrast provides the best representation of gross morphology short of removal and examination of the lesion. Not only is the manner in which bone is destroyed of behavioral significance, but also the interface zone

TABLE V: SURVIVAL OF 605 PATIENTS WITH PRIMARY BONE SARCOMA BY RADIOLOGICAL GRADE

Distribution of graded tumors	50—	58	51	104	110	282
Absolute 5-year survival (cases)	25—	26	18	36	13	26
Absolute 5-year survival (per cent)	0—	44.8	35.3	34.6	11.8	9.2

Graph depicts declining survival by grade. Probability that survival distribution is random: $\chi^2 = 53.16$ $p = <0.001$.

TABLE VI: CRITICAL DECISION LEVELS IN RADIOLOGICAL GRADING OF 605 PRIMARY BONE SARCOMAS

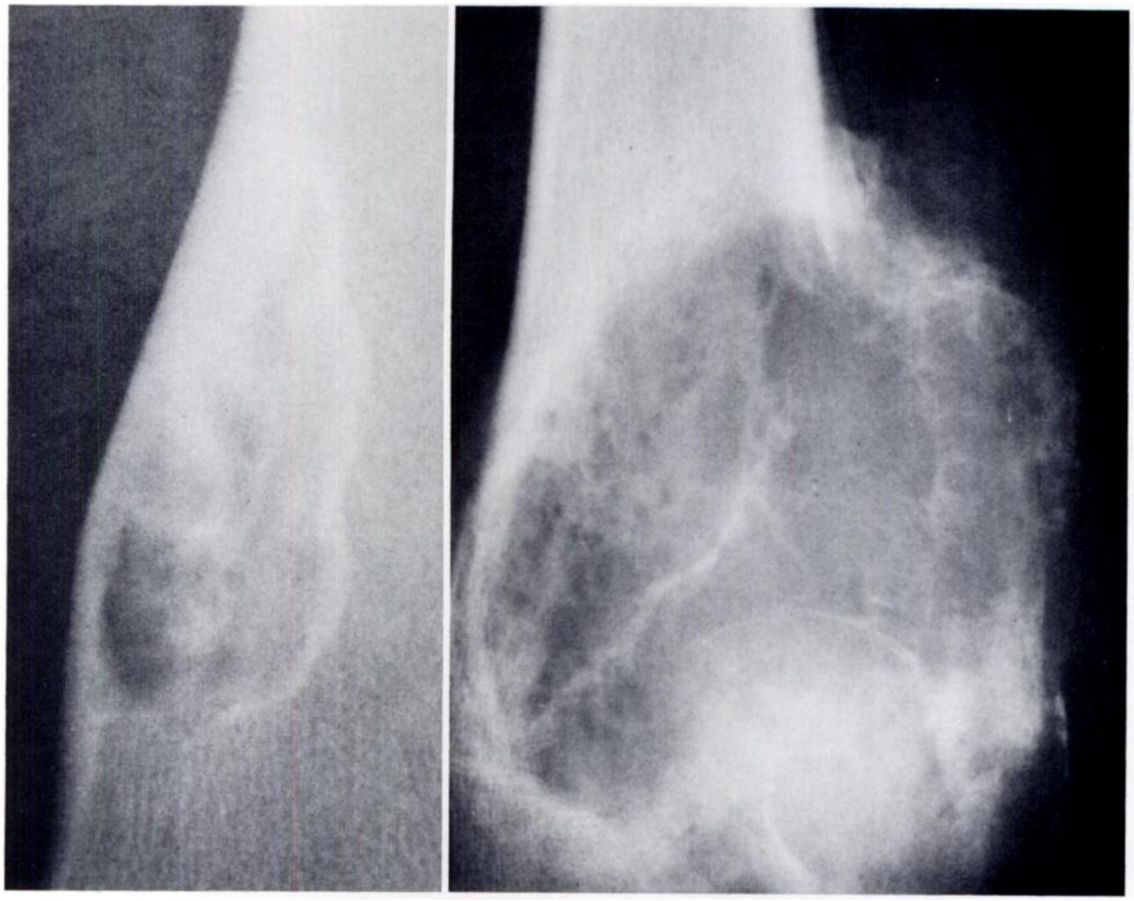
IA		IB		IC		II		III
	← 9.5% →		← 0.7% →		← 22.8% →		← 2.6% →	

In composite statistics for four types of tumors, the greatest decline in five-year survival occurs between Grades IA and IB, and between Grades IC and II.

TABLE VII: DISTRIBUTION OF 51 CHONDROBLASTOMAS AND 155 GIANT CELL TUMORS BY RADIOLOGIC GRADE

CHONDROBLASTOMA		IA	IB	IC	II	III
Distribution of graded tumors	40—	37	5	9	0	0
Average delay in diagnosis (months)	20— 0—	11.6	12.8	21.6	...	...
GIANT CELL TUMOR	70—					
Distribution of graded tumors	35—	27	57	68	2	0
Average delay in diagnosis (months)	0—	17.8	18.4	8.8	6.5	-

Graph indicates numerical incidence by grade. The probability that this incidence is the result of random distribution is
Chondroblastoma $\chi^2 p = <0.001$.
Giant Cell Tumor $\chi^2 p = <0.001$.



7a,b

Fig. 7. **a**. Expanded shell: less than 1 cm, geographic destruction, sclerotic rim. Expanded shell is a simple term to describe a more complex phenomenon, wherein the inner surface of the cortex is either dynamically thinned by a lesion or maintained in an established location while the cortex is modeled around it. In either circumstance new bone laid down by periosteum fuses with existing bone to form the shell. [Fibroxanthoma, Grade IA.]

b. Expanded shell, greater than 1 cm: geographic destruction with a narrow moth-eaten zone. To measure expansion, the normal contour of cortex is projected to its former location, and the difference between the two measured on a perpendicular line. There is at least one hole in the periosteal shell. [Giant cell tumor, Grade IC.]

between the lesion and bone or periosteum accurately reflects growth behavior and host response.

Grading can be accomplished effectively whenever there is destruction of bone. In order to reach a consistent grading conclusion, specific signs must be considered in a definite order of priority:

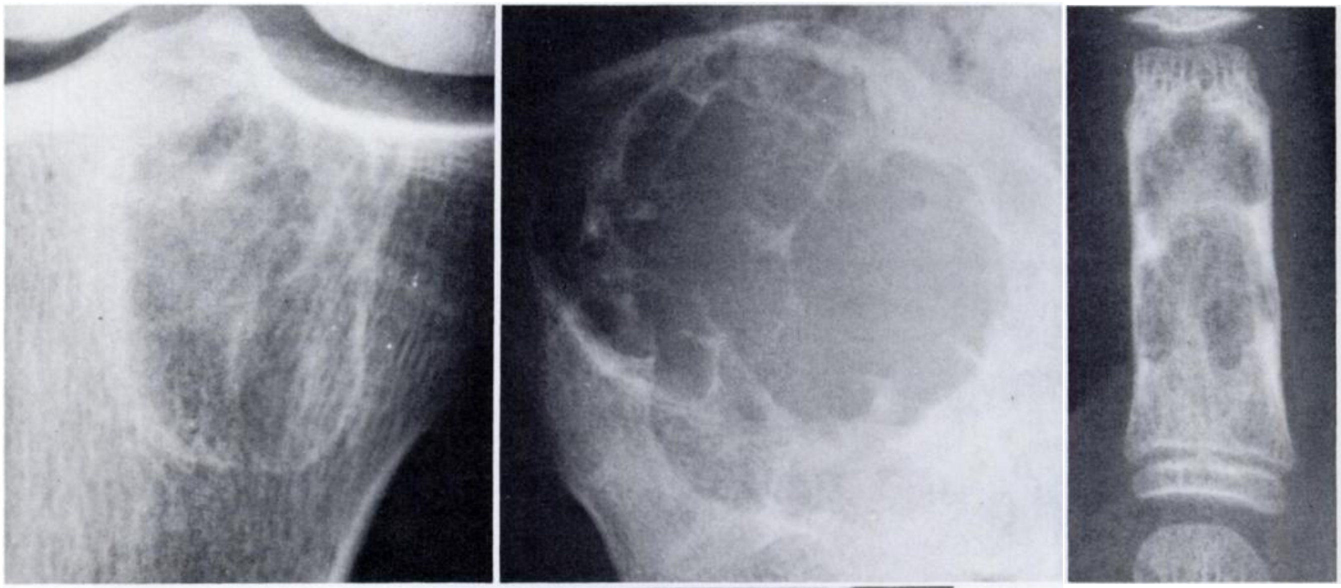
1. Pattern of destruction; if geographic, also the configuration of the marginal interface zone
2. Whether the lesion has resulted in penetration of the cortex
3. Presence or absence of a sclerotic rim
4. Presence and extent of expanded cortical shell.

The ordered priority of specific radiological signs comprises a grading algorithm which is easily applied in the clinical setting, yet is easily programmable for experimental analysis by computer (TABLE VIII). The ordered logic is such that human *failure* to observe specific findings, particularly edges, sclerotic margins and encapsulating shells, results in selection of grades biased toward the more rapidly growing end of the rate spectrum. The logic of this grading order is based upon the observations that in bone:

1. The basic patterns of destruction, specifically geographic and moth-eaten/permeated, are fundamentally different from each other, and not merely different stages in the evolution of a common kind of destructive process, although combinations of patterns are common.
2. Lesions which are static or which grow most slowly are well circumscribed, remain confined within bone, and by and large are not in direct contact with soft tissues.
3. As the rate of growth increases, there is less evidence of circumscription and more vigorous destruction of cortical bone, until ultimately the barriers between the lesion and soft tissues are penetrated.

The rules for the radiographic interpretation of this finding are that total penetration of cortex is assumed with permeated and moth-eaten patterns of bone destruction in any combination. Otherwise, the cortex is assumed to be totally penetrated where in profile the total thickness of cortical bone or expanded shell is destroyed, as represented by a discontinuity (Fig. 4) or by direct evidence

8a–c



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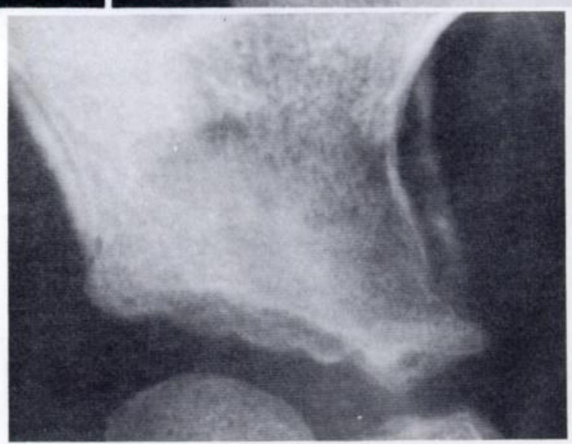

Fig. 8. **a**. Regular margin: geographic destruction. The outline of the destroyed area, with its visibility enhanced by sclerosis, is smooth, without irregularity or scalloping. [Cyst of bone, Grade IA.]

b. Lobulated margin: geographic destruction. The outline of the destroyed area, enhanced by sclerosis, consists of multiple curves of similar size which intersect each other. "Lobulated" infers that an outline such as this would be produced by a lobulated tumor. [Chondrosarcoma, Grade IB.]

c. Multicentric margin: geographic destruction. The outline of the destroyed area, while smooth, follows a course of many curves of unequal size, suggesting multiple foci of activity. This pattern is seen most often in tumors which contain slowly growing cartilage. [Enchondroma, Grade IA.]

d. Ragged or poorly defined margin: geographic destruction. The density change between destroyed bone is abrupt, but the edge is irregular and ill defined. [Eosinophilic granuloma, Grade IC.]

of extension through the cortex, as by an invasion of soft tissues. Partial penetration is defined as erosion or localized thinning of either surface or cortical bone (Fig. 5), always present when the cortex is expanded and not totally penetrated.

4. Host response to slow growth is usually to surround the lesion with reactive bone; within spongy bone by means of an enveloping sclerosis (Fig. 6), and in the cortex by deposition of a shell of new bone by the periosteum (Fig. 7).
5. As rate of growth increases, envelopment by sclerosis becomes less well organized and less effective.
6. Six different marginal patterns are associated with geographic destruction of bone. Three of these are essentially sharp edges of differing contour, regular (Fig. 8a), lobulated (Fig. 8b) and multicentric (Fig. 8c). A fourth is ill-defined or ragged contour (Fig. 8d). The remaining two represent marginal zones of moth-eaten destruction of differing widths, one less than or equal to one centimeter, and the other greater than one centimeter. These descriptive signs are important because they represent the interface between the lesion and uninvolved bone, and to a limited extent the rate with which bone is being destroyed. They also have diagnostic significance.

TABLE IX shows how these 14 descriptive variables are used to describe and define the radiological patterns for each of the five grades.

CONCLUSIONS

1. The use of radiographs to estimate rate of growth of focal lesions in bone is a statistically valid and useful concept in clinical practice.

2. The rules for establishing grade are natural and easily followed, requiring a search of the radiograph for no more than five descriptive signs.

3. Recognition of rate of growth rationalizes the approach to management even when the exact class of disease is not known.

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TABLE VIII: ALGORITHM FOR GRADING IN THE PRESENCE OF BONE DESTRUCTION

	IA	IB	IC	II	III
1. BONE DESTRUCTION PATTERN					
1. Absent	1	1	1	1	1
2. Geographic with regular margin	1	1	1	0	0
3. Geographic with lobulated margin	1	1	1	0	0
4. Geographic with multicentric margin	1	1	1	0	0
5. Geographic with ragged or poorly defined margin	0	1	1	0	0
6. Geographic with moth-eaten margin ≤ 1 cm	0	0	1	0	0
7. Geographic with moth-eaten margin > 1 cm	0	0	0	1	0
8. Moth-eaten	0	0	0	1	0
9. Permeated included	0	0	0	0	1
2. PENETRATION OF CORTEX					
1. Absent	1	1	0	0	0
2. Partial	1	1	0	0	0
3. Total	0	0	1	1	1
3. SCLEROTIC RIM					
1. Present	1	1	1	1	1
2. Absent	0	1	1	1	1
4. EXPANDED SHELL					
1. Absent	1	0	1	1	1
2. ≤ 1 cm	1	0	1	1	1
3. > 1 cm	0	1	1	1	1

This is the logic employed by the computer for determining radiologic grade and expresses essentially the same information found in TABLE IX. The computer considers the diagnostic signs in numerical sequence. As each sign is examined, the zeros eliminate grades from further consideration until a single grade remains. At this point, the grade is selected, and no further signs are considered.

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TABLE IX: GRADING WITH DESTRUCTION OF BONE

Radiographic Pattern	IA	IB	IC	II	III
Destruction	Mandatory Geographic	Mandatory Geographic	Mandatory Geographic	Moth-eaten or Geographic	Mandatory Permeated
Edge characteristic	(One of 3 patterns) 1. Regular or 2. Lobulated or 3. Multicentric	(One of 4 patterns) 1. Regular or 2. Lobulated or 3. Multicentric or 4. Ragged/poorly defined	(One of 5 patterns) 1. Regular or 2. Lobulated or 3. Multicentric or 4. Ragged/poorly defined 5. Moth-eaten, 1 cm or less	If Geographic, mandatory moth-eaten edge greater than 1 cm	Any edge
Penetration of cortex	None or partial	None or partial	Mandatory Total	Total by definition	Total by definition
Sclerotic rim	Mandatory	Optional	Optional	Optional but unlikely	Optional but unlikely
Expanded shell	Optional only 1 cm or less	If sclerotic rim present, expanded shell must be greater than 1 cm	Optional	Optional but unlikely	Optional but unlikely

The rules used both by radiologists and the computer to determine radiographic grade.
(Ruled line indicates level at which decision has been made.)
Mandatory = Essential to the grade.
Optional = May or may not be present.