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Histopathological predictive factors in Ewing's sarcoma of bone and clinicopathological correlations

A retrospective study of 261 cases

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Summary. A retrospective multifactorial analysis on 261 previously untreated patients with Ewing's sarcoma (Es) of bone has been carried out in order to ascertain the prognostic value of several histological variables on survival. Among those cases accepted as Es, 208 (80% of the patients) were considered to be "typical Es", while 40 (15%) displayed a large cell predominance, being subclassified as "atypical large cell Es". Furthermore, 13 patients (5%) possessed tumours of endothelial-like appearance. Eleven cases which displayed a mixed histological configuration were finally included within one of the three previous groups according to their predominant histological pattern.

After adjustment for therapeutic regimens and initial location of the tumour, only two histological characteristics remain significant; i.e. the presence of necrosis ($p=0.002$) and, to a lesser degree, the presence of filagree "en damier" pattern ($p=0.08$), both of which are of poor prognostic value. From this study, it can be assumed that the morphological (and possibly histogenetical) heterogeneity of Es of bone has no prognostic influence on survival.

Key words: Ewing's sarcoma – Bone – Histology – Prognosis

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Introduction

Certain factors seem to display prognostic significance in Ewing's sarcoma (Es) of bone and in recent years, several publications have dealt with these clinicopathological features. Among them, metastatic disease at time of diagnosis, central osseous location, and soft-tissue extension of the neoplasm at primary sites are correlated with a reduced survival rate (Johnson and Pomeroy 1975; Pomeroy and Johnson 1975; Perez et al. 1977; Glaubiger et al. 1980; Pilepich et al. 1981; Mendenhall et al. 1983).

There is, however, little information about the prognostic significance of diverse histological variables in this neoplasm. In 1983, Kissane et al. observed that the existence of an organoid inter-anastomosing filagree pattern was associated with a lower survival rate in patients of the Intergroup Ewing's Sarcoma Study (IESS) and, in 1984, Stefani et al. showed that the presence of histologically marked necrosis within the tumour is strongly connected with a reduced survival rate.

A number of authors, ourselves included (Pritchard et al. 1975; Llombart-Bosch et al. 1978, Llombart-Bosch et al. 1980; Nascimento et al. 1980; Llombart-Bosch et al. 1982), have postulated the existence of numerous histological variants of Es of bone. This has been confirmed with transmission electron microscopy (TEM), scanning electron microscopy (SEM), and in vitro culture techniques; but their importance regarding prognosis remains uncertain. Meanwhile a dramatic improvement in Es survival rate has been reached in recent years, thanks to the efficacy of multiple-drug chemotherapy in conjunction with radiotherapy as an adjuvant treatment for this tumour (Rosen et al. 1978; Nesbit et al. 1981; Rosen et al. 1981, Thomas et al. 1983; Zucker et al. 1983; Deméocq et al. 1984a; Deméocq et al. 1984b; Oberlin et al. 1985).

In the present study, multifactorial analyses were carried out on a cohort of 261 patients to ascertain the value of a number of histological variables present in this tumour which could be clinicopathologically correlated with survival.

Patients and methods

The present study was initiated with 309 cases of previously untreated primary bone tumours which had earlier been diagnosed as Es or "round cell sarcoma of bone, Es". Of all these tumours, 234 were seen and treated at the Institut Gustave Roussy (Villejuif, France) from 1962 to 1983; a further 49 cases were obtained from various oncological centers in France in a joint study undertaken by the SFOP (Société Française d'Oncologie Pédiatrique); and the remaining 26 cases were collected in Spain (Department of Pathology, University of Valencia Medical Center).

Following review of all the slides available by three of us simultaneously, 48 cases (16%) were excluded from the present analysis: 15 cases were considered to be inappropriate for diagnosis because of technical inadequacy, or an insufficient number of slides and lack of wet tissue or paraffin-embedded material; 10 cases in which the diagnosis was made on metastatic material (3 cases) or after treatment (7 cases); and 23 cases because of failure in agreement among the three observers on a histological diagnosis of Es of bone (neuroblastoma: 6 cases, malignant non-Hodgkin's lymphoma, small and large cell variants: 9 cases, microcellular anap-

lastic (small cell) osteosarcoma: 4 cases, granulocytic sarcoma: 1 case, rhabdomyosarcoma: 2 cases, and metastatic clear cell carcinoma of kidney: 1 case).

Original biopsy specimens were stained with hemateine-erythrosine-safranin (HES), periodic-acid-Schiff (PAS), and Best's carmine for glycogen and Wilder or Gomori for reticulin stains. Electron microscopical diagnosis was performed on 61 cases to enhance diagnostic accuracy, and to clarify the histogenesis of the neoplasm, as well as to differentiate the types of cells present. Unfortunately, histochemical analysis of the biopsy specimens could not be performed because paraffin embedded blocks were not available for 56% of the cases. Based upon such studies, three subtypes of Es of bone were detectable, as previously published (Llombart-Bosch et al. 1982): "typical Es", "large cell Es", and "atypical Es with endothelial differentiation".

The degree of histological accuracy in each tumour type was estimated on a scale of one to three points; when all the previously indicated histological techniques were present, and agreement on all the histological variables reached, the degree of histological accuracy was 3. However, if some disagreement existed because of minor technical features, or failure to agree by one of the three observers, the histological accuracy in diagnosis was set at 2 or 1, depending upon the extent of disagreement. This scheme of pathological diagnosis is somewhat similar to that proposed by Kissane et al. (1983), such as: "Ewing's sarcoma" (which should be comparable to our histological accuracy, type 3); "consistent with Es" (equiparable to our type 2); and "malignant tumour, related to Es, undetermined" (equivalent to our type 1).

Furthermore, a number of histological and cytological variables have been introduced as analytical factors of possible prognostic value, which are briefly described as follows.

Es of bone is generally considered to possess a structureless pattern which adopts variable features depending upon the extent of infiltration into the bone marrow, cortical bone, periosteal dense fibrous connective tissue, or adjacent soft-tissues, mainly muscle and fibrous connective tissue. Nevertheless, when carefully and comparatively observed, the cells of Es show some degree of architectural pattern, which were thus classified into:

a) A "Cohesive type" – in which the cells adopt a dense, homogeneous pattern of broad fields of tumour, devoid of any particular structure.

b) A "Dissociate type" – with presence of cell aggregates, separated by fibrous septae or vessels. The individual clumps of tumour cells appear quite isolated from one another.

c) The "En damier (chessboard) type" – cell proliferation is cohesive, but in small aggregates isolated by fine, fibro-vascular septae and occasional reticular fibres which in turn encircle groups of cells, giving an "en damier" appearance (Fig. 1a). This type could be considered similar to the "filagree type" proposed by Kissane et al. (1983).

d) A "Pseudo-rosette type" – the presence of rosette-like structures, rather similar to those seen in neuroblastomas (Homer-Wright rosettes), is not uncommon in Es tumours. This pattern frequently raises the issue of differential diagnosis, and even histogenesis among these "round cell" tumours.

e) A "Reticular network" – A reticular network may be completely absent (0), or acquire progressive density (1 to 2). These reticular fibres never isolate cells from one another, as is the case in so-called "reticulum cell sarcoma of the bone".

The segregation of the diverse architectural types is not absolute; this should mean that, within a given neoplasm, and in different histological sections, a given pattern may be predominant. Therefore, the patterns are not considered mutually exclusive, but rather independently and concurrent with one another. For instance, a given neoplasm may show a predominantly cohesive pattern in some fields, while in others, a minor "en damier" pattern or it might even be associated with the presence of some pseudo-rosettes.

Different cell types were present in Es, independent of ultrastructural, histochemical, or immunohistochemical considerations which could influence this cell-typing. These included:

a) "Small round blue (SRB) cells" – this cell type is the most characteristic of Es (Fig. 1b), possessing small, round or elongated nuclei, finely dispersed chromatin, and one or two inconspicuous nucleoli. Cell contour

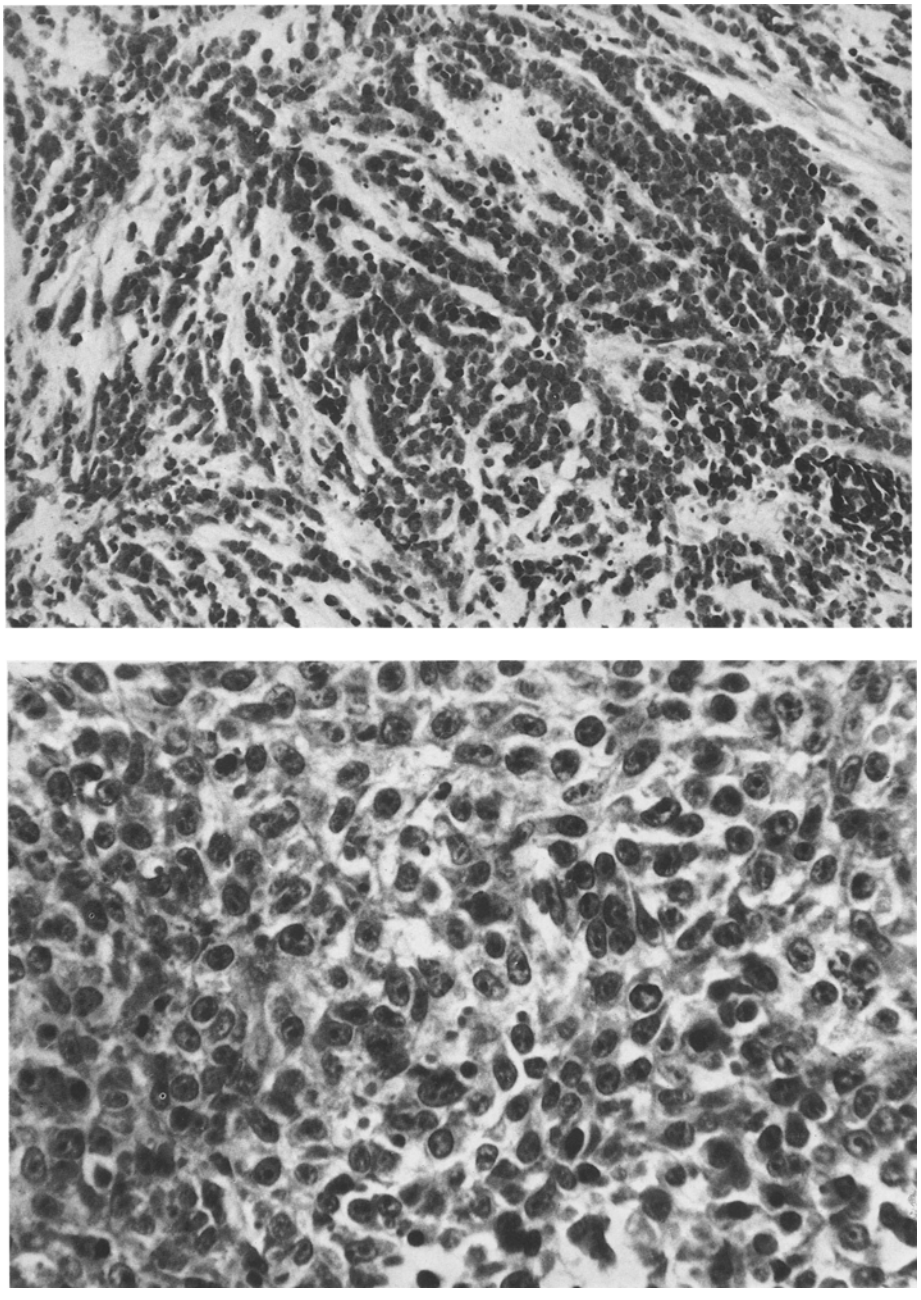
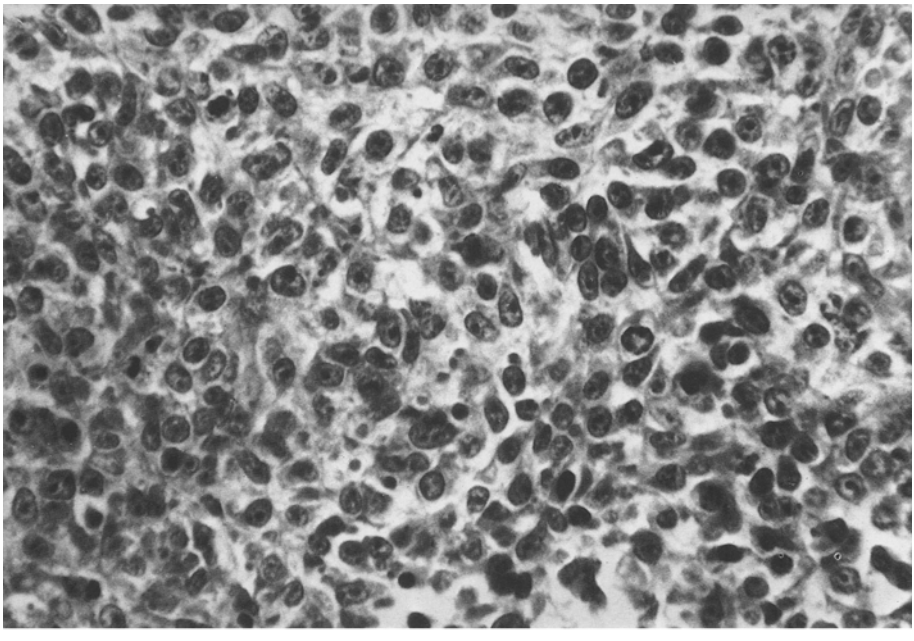


Fig. 1. **a** Ewing's sarcoma: filagree "en damier" pattern (Hematein-Erythrosine-Safranin ×200). **b** Typical Ewing's sarcoma with large necrosis area (Hematein-Erythrosine-Safranin ×200). **c** Atypical "large cell" Ewing's sarcoma (Hematein-Erythrosine-Safranin ×400). **d** Atypical Ewing's sarcoma with endothelial differentiation (Gordon, Sweet & Wilder ×200)



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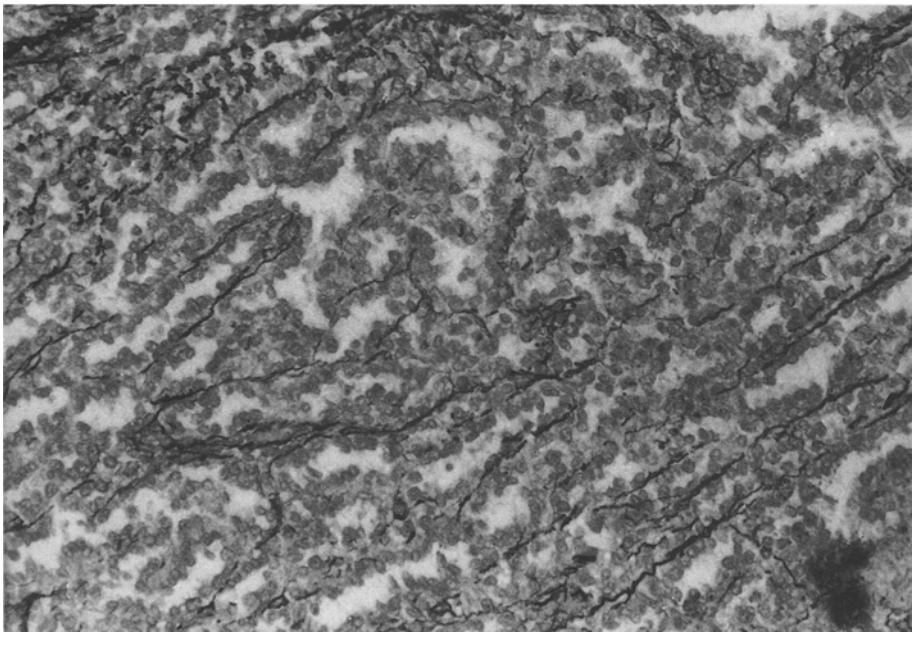

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is poorly delimited, and the cytoplasm is usually barely visible and often vacuolated (glycogen). Cell size averages 12–14 microns in sections, but sometimes isolated larger cells are also seen. Mitotic activity is highly variable in amount and distribution.

b) "Degenerative cells" – these are "dark cells" because of their denser and more elongated nuclear contours, unidentifiable nucleoli, and tendency to cell-to-cell crowding. No mitotic activity is seen. This cell type is considered involutionary, and in fact transitional forms between these and the SRB cells exist.

c) "Mesenchymal-appearing cells" – these are fusiform tumour cells, somewhat elongated in contour, which should not be confused with the stromal fibroblasts which are also present in the septae as a reactive phenomenon. They appear isolated or intermingled with SRB cells and in cases, show close continuity with the latter.

d) "Large cells" – this cell type, when present, lends a "histiocytoid" appearance to the tumour cells. The tumour cells look like SRB cells, but their nuclei are larger and the chromatin less condensed (Fig. 1c). Nucleoli are prominent (one or two), and the cytoplasm is more acidophilic, with better delineated cell contours. Cell size varies from 14 microns to 20–24 microns.

e) "Endothelial-looking cells" – have been observed in some cases as a component of the tumour, not reactive in nature. They appear isolated, or else constitute more extensive areas of the neoplasm (Fig. 1d). These cells show a round-to-elongated nucleus which is poor in chromatin and possesses one to two nucleoli; cell size varies from 14–18 microns, and the cytoplasm is extensive being partially vacuolated, due to the presence of glycogen and hydropic vacuoles. These cells attach to one another intimately and delimit empty spaces which look like vascular spaces.

The presence of glycogen aggregates within the tumour cell cytolplasm is one of the most outstanding features in the diagnosis of Es of bone. Other tumours may also possess a high glycogen content although generally less frequently or extensively (Triche and Ross 1978; Triche and Askin 1983). Three values were used: (0) when glycogen was completely absent; (1) when some traces were seen in isolated cells; and (2) when large amounts of glycogen were present in several fields, whether intracytoplasmic or extracellular.

Most of our material was buffered formalin fixed; but owing to the heterogeneity of its origin (several laboratories), no special precautions could be taken to ensure a better preservation for the glycogen (similar problems were encountered in the IESS material).

Embolism was a common feature in Es of bone, mainly in those fields where the neoplasm invaded the bone marrow. Small clumps of cells appeared, either isolated within the vascular sinuses or located between haematopoeic cells.

Necrosis was also a common feature frequently present in our cases, mainly when the tumour infiltrated soft tissues (Fig. 1b). Therefore, the evaluation of necrosis was undertaken only with consideration of all fields

reviewed in the histological slides, giving them a scale of values extending from total absence (0), to its presence in less than 25% of all the histological fields (1), to a larger extension in over 25% of the histological fields present in the slide (2).

Apart from an apparent vasoformative potentiality of some Es cells in isolated cases, a prominent vascular reaction was generally seen within the tumour, especially when the neoplastic cells infiltrated soft tissues or muscle. The degree of vascular reaction also varied greatly from one tumour to another; thus, cases ranged from those with a complete absence of neoformed vessels (0) to those with several fields with a prominent reactive vessel proliferation (2).

As previously mentioned, several groups of patients from diverse centers in France and Spain are included in this retrospective study. We have divided them into two groups. First, 87 patients (the historical ones), were treated with either surgery or radiotherapy, plus monodrug chemotherapy (Zucker and Henry-Amar 1977). The second group comprised 167 patients, submitted to various protocols in which intensive systemic multidrug chemotherapy was employed in association with radiotherapy or, in some cases, surgery (Zucker et al. 1983; Deméocq et al. 1984a; Deméocq et al. 1984b; Oberlin 1985). Seven patients were excluded from the prognostic factor study because of the absence of detailed information on therapy or follow-up.

Relationships between histological characteristics and clinico-pathological correlations were estimated using the Pearson chi-square, the Fisher *t*-test, the Wilcoxon *W*-test and the analysis of variance, as appropriate.

As the prognosis strongly depends upon the treatment administered (i.e., no polychemotherapy or polychemotherapy) or depends upon the presence or the absence of metastases at onset, the proportional hazard Cox's model was used in stepwise fashion to assess the prognostic value of each variable considered in the model (Cox 1972; Breslow 1979).

Data were stored and analysed in the Institut Gustave Roussy Medical Statistics Department, using a general database management system (Wartelle et al. 1983) and the BMDP statistical package for multivariate analyses (Dixon et al. 1981).

Results

Among the 261 cases definitely accepted as Es of bone in this study, 208 (80% of the patients) were considered to be "typical Es" (group 1) while 40 (15%) were subclassified as "atypical large cell Es" (group 2). Only 13 patients (5%) possessed neoplasms with an endothelial-like appearance (group 3).

Eleven cases displayed a mixed histological configuration that implied the presence of SRB cells in association with large cell conglomerates (3 cases), or with some endothelial features (6 cases). Finally, it was decided to include each of these cases according to its predominant histological pattern within one of the three previously considered groups.

In reference to the architectural pattern and the distribution of the histo-

logical structures analysed variable by variable, the following observations were made: The "cohesive type" of structure was the most frequently observed (200 tumours possessed this type of histological configuration), while a dissociated type of morphology appeared in 171 tumours; and the so-called "chessboard type" ("en damier") predominated in only 76 cases. "Pseudo-rosette" images were also found in 54 cases, always being intermingled with any of the other previously described structures.

The reticular network was absent in 175 cases, or else limited to a fine perivascular rim. Sparse nests of reticular fibres were found in 63 tumours, while a more abundant and well-developed reticular network, mainly of a wicker-basket ("en panier") configuration, was seen in only 12 tumours, mainly of the large cell variant.

The number of reactive vessels was small in 126 cases and large in 84 cases. Embolism was histologically confirmed in 148 cases. Nevertheless, these two variables (number of vessels and embolism) were not correlated. Therefore, greater vascularization of Es is not correlated with increased number of emboli.

Regarding cell types, the cell most frequently seen (246 cases) was the so-called principal or SRB type, which is considered to be the stem cell of all three neoplasms. Degenerative (dark) cells were also seen quite frequently (237 cases), in close association with the former. Larger cells were present in 27 cases, being related to the group of "atypical large cell variant of Es". Endothelial, large, clear cells were also seen within the context of the "endothelial variant of Es".

Large amounts of glycogen with either PAS or Best's carmine were present in 47% of the 134 cases in which these techniques were available. In contrast, glycogen was completely absent with both techniques in 19%.

Necrosis is very common in this type of sarcoma, independent of cytological type. Only 15 cases displayed no necrosis, while small amounts of necrotic tumour (less than 25% of the total material included within the histological slide) was seen in 150 cases; a further 96 cases showed extensive fields of necrosis.

An analytical study was performed on the four previously described architectural and cytological variables, in comparison with one another. From this series the cohesive and dissociated architectural patterns appeared closely intermingled within the same tumour ($p < 0.001$), and pseudo-rosettes were also frequently associated with both ($p < 0.005$). Only the "en damier" (chessboard-like) pattern showed no association with the other 3 patterns. In these cases, embolism was common ($p < 0.05$). The "dissociated" architectural pattern was associated with the extent of necrosis ($p < 0.05$), while the "en damier" pattern was also associated with an extensive reactive vascular proliferation ($p < 0.01$). A relationship between the amount of reticular network and degree of necrosis was also seen ($p < 0.05$).

The SRB cells were closely correlated with the degenerative (dark) ones ($p < 0.001$), as well as with those cells of histiocytic ($p < 0.001$) and endothelial ($p < 0.001$) appearance. This suggests a common histogenesis of these cell types, and, therefore, of these three variants of Es. The same observation

was true of the so-called degenerative (dark) cell, present not only in close association with tumours composed of principal SRB cells alone ($p<0.001$), but also in tumours of large ($p<0.001$) and endothelial cells ($p<0.01$).

A male predominance was detected within the total group of patients, with a sex ratio of 1.51, with no differences by histological variant. In this series, the mean age was 12.4 years (SD 6.4 years). The youngest case was under one year, and the oldest, almost 40 years. Mean age showed no difference by sex. In connection with the three tumour types, some differences could be observed: the typical Es occurred in the youngest patients (mean age = 11.6 years), while large cell Es (14.9 years) and the endothelial variant (16.3 years) appeared somewhat later ($p<0.001$).

Five groups of anatomical locations were distinguished: long bones (with proximal tumour location), bones with distal location, trunk, pelvis, and "others". The most common anatomical locations were pelvic girdle and trunk (38%), followed by distal locations (25%) and those located in long bones, but which were clinically considered to be proximals (25%). No differences in anatomical distribution appeared when comparing typical Es to its atypical variants. The most common locations of large cell Es were trunk and pelvis (20 cases), while the distribution of the endothelial variant was quite homogeneous throughout the skeleton.

With regards to the presence of heavy soft-tissue tumour, only the "en damier" (chessboard) type was highly correlated ($p<0.001$).

Of the 261 patients included in the study, 254 have been studied prospectively. Of them, 47 (19%) had metastatic disease at onset. They were excluded from the prognostic study as metastases were known to indicate a very poor prognosis when compared with non metastatic patients ($p<0.001$), whatever the treatment.

A prognostic study was then carried out on the 207 remaining non metastatic patients at onset. Variables considered in the proportional hazard Cox' model were those which were found to be of prognostic value in a univariate analysis, i.e. treatment category ($p=0.002$), initial location of the tumour ($p=0.002$), "en damier" (chessboard) type ($p=0.02$) and necrosis ($p=0.07$). When the last variable was taken into consideration no difference in term of survival rate, whether the necrosis was slight or marked on the slide, was observed. Necrosis was then considered to be absent or present. While age, sex and two cytological variables (i.e., presence or absence of SRB cells, presence or absence of large cells) did not correlate with survival in the univariate analysis, they were included in the final run since other analyses had shown them to be of prognostic value. Treatment categories were grouped in those with no polychemotherapy and those with polychemotherapy. Anatomical location of the tumour was used first in four categories, i.e. long bones proximal, distal bone location, trunk and pelvic girdle. In a second analysis, they were grouped in two categories, distal bone location and other locations, as long bones (proximal), trunk and pelvic girdle presented no different survival prognostic influence.

The results of the stepwise regression are summarized in Table 1. Variables are listed in the order of selection by the stepwise process. The initial

Table 1. Stepwise regression (Cox model) on survival: coefficient of risk (β) and relative risks. Non-metastatic patients at onset only

Variables	Regression coefficient		Relative risks $RR = \exp(\beta)$	Maximized log-likelihood	Significant level at entry
	β	(SD)			
None	0			−469.9	
Location:					
no distal/distal	0.85	(0.26)	2.33	−491.8	0.001
Treatment:					
poly-CT/no poly-CT	−0.66	(0.20)	0.52	−486.4	0.001
Histological char.					
necrosis (+)/(−)	1.54	(0.59)	4.65	−481.5	0.002
"en damier" (+)/(−)	0.38	(0.21)	1.46	−479.9	0.08

(SD) = standard deviation; (−) = absence; (+) = presence

location of the tumour, the first variable selected, provided the best individual fit to survival. The treatment category, the second variable selected, provided a similar individual fit to survival. The absence of necrosis also had a prognostic significance on survival but the number of cases without necrosis was very low (6%). The "en damier" type had a little influence on survival; the other histological variables, plus sex and age had no prognostic influence.

Discussion

This retrospective review of 261 cases of Es of bone by routine microscopical methods emphasizes the presence of heterogeneous patterns within this tumour entity, with the existence of atypical variants. Among those the large cell pattern (Pritchard et al. 1975; Llombart-Bosch et al. 1982) and the endothelial-like tumour (Llombart-Bosch et al. 1980; Llombart-Bosch et al. 1982) are the most outstanding patterns. Other malignant tumours, composed of SRB cells, and segregated from the Es, are considered to be different entities (Askin et al. 1979; Martin et al. 1982) such as neuroectodermal tumours of bone (Gonzales-Crussi et al. 1984; Jaffe et al. 1984) and primitive mesenchymal tumour of bone (Perez et al. 1977; Llombart-Bosch 1983). They are therefore excluded from this study.

Even if the morphology of Es of bone and its variants is well-known through the use of modern morphological and biological approaches (Triche and Askin 1983; Llombart-Bosch 1983) its prognostic significance remains unclear. Nascimento et al. (1980) have reviewed the clinico-pathological pattern of 20 large cell Es of bone. In their series the tumour follows a rapid course, but no definite conclusions can be drawn from this study. Furthermore, little information is available about the existence of prognostic histo-

logical factors in this tumour, unlike those accepted for osteosarcoma (Rosen et al. 1982; Apel et al. 1985) or soft-tissue sarcomas (Costa et al. 1984; Trojani et al. 1984). The microscopical structures which seem to express a poor prognosis in Es of bone are the presence of a filagree "en damier" pattern (Kissane et al. 1983) and large necrotic areas (Stefani et al. 1984).

The atypical variants of Es of bone account for up to 20% of all cases in our material; 15% of cases with predominance of large cells and 5% with endothelial-like cells. However, cases with a mixed histological pattern have also been found, intermingled with the conventional Es. This fact lends support to the presence of mixed cellularity outlined in the discriminant analysis which has been made, when compared with homogeneous structures which characterize the typical Es. The main result of this study is that histological variability in Es is not correlated with survival. Nevertheless these histological variants are correlated with the age of the patients, but not with the anatomical location of the tumour. Another finding shows that the large cell Es of bone is, to a considerable extent prone to soft-tissue infiltration, as observed by others (Nascimento et al. 1980) but when submitted to a mono- or multiagent chemotherapy, this circumstance has no influence on prognosis. A decrease in survival of Es of bone with soft-tissue extension, independent of the primary site, resulted from an increase in the distant metastases in the 28 cases reported by Mendenhall et al. (1983). Unfortunately, this observation has not been studied in this retrospective series.

Several other histological variables (i.e., cytological type, presence of glycogen, extent of the reticular network, vascular reaction within the tumour and presence of tumour embolism) have not demonstrated prognostic value when the patients were submitted to an adjuvant multiagent chemotherapy protocol. Moreover, no correlations were found in any of these morphological variables with either the presence or absence of metastases at initial diagnosis.

Our results are therefore in accordance with the earlier clinical trials of the IESS Group (Nesbit et al. 1981), the NCI Study group (Kinsella et al. 1984; Miser et al. 1985) as well as with some of our own (Zucker et al. 1983; Deméocq et al. 1984a; Deméocq et al. 1984b; Oberlin et al. 1985) confirming that the major predictive outcome for non metastatic Es of bone is the primary anatomic location of the tumour.

The presence of necrosis, little or abundant, seems to have a poor prognosis in our series but referred only to those cases without metastasis at time of diagnosis. The amount of necrosis held no significance when related to the anatomical location or to the type of treatment.

The multifactorial analysis performed shows that only two histological factors, necrosis and filagree "en damier" pattern, have an independent prognostic value seems to confirm to some extent a previous publication (Kissane et al. 1983).

From the present study it can be concluded that, among the histological variables analysed in Es of bone, including its atypical variants, only necrosis

has a significant influence on survival, and, to a lesser degree, filagree "en damier" pattern which is related to soft-tissue extension of the tumour. Other clinical factors such as age and sex are devoid of prognostic significance in this series when taking into account the anatomical location of the tumour and the therapy. These last two variables, in the absence of metastasis at initial diagnosis, remain the best prognostic factors for survival in Es of bone.

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