SURVIVAL IN BONE SARCOMA

By

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INTRODUCTION

The sarcomas of bone have for many years been regarded as amongst the most lethal forms of malignant disease. This is still true and the outlook in general remains grave. But recent analyses of survival periods after ablation of the tumours by operation or irradiation, have dispelled some of the extreme pessimism which has long surrounded this problem. Much of our information comes from the United States of America where during the past generation large collections of documented material relating to bone tumours have been concentrated in a relatively few centres. The standards of five and ten year survival periods have been used as in other forms of malignant disease. *(Geschickter & Copeland* 1931; 1949; *B. L. Coley et al.* 1949; *Coventry & Dahlin,* 1957).

PERSONAL MATERIEL

Classification. My own fully documented collection of bone sarcomas covering the period 1920 to 1961 comprises 256 tumours.

TABLE I

	Total.	Operable Tumours.
Osteogenic Sarcoma.	151	124
Extra-Periosteal Sarcoma.	39	29
Ewing's Tumour.	30	21
Malignant Giant-Cell Tumour.	5	4
Sarcoma in Abnormal Bones.	31	24
	256	202

Number of five-year survivals – 58 – (21 %)

The classification adopted in the above table is used for the purpose of introducing the broad clinical picture of this field of malignant disease. But for many years in both undergraduate and postgraduate teaching I have found it convenient to adopt a simple classification of primary malignant tumours of bone based on the recognition of the tumours as anatomical and clinical entities. In this, two main categories of tumour are distinguished – the *extra-osseous* tumours, and the *intra-osseous* tumours. *(Platt* 1951.)

TABLE II

Extra-Osseous Group.	Osteogenic Sarcoma –	Sclerosing.
		Osteolytic.
		Chondro-sarcoma.
	Ewing's tumour.	
	Extra-periosteal sarcoma.	
Intra-Osseous Group.	Chondro-myxo-sarcoma.	
	Endotsteal fibro-sarcoma.	
	Malignant giant-cell tumour.	
	Haemopoietic tumours.	
	Adamantinoma.	

It will be noted that I have retained the extra-osseus chondro-sarcoma tumours within the osteogenic sarcoma class. This is for convenience in clinical diagnosis. The intra-osseous chondro-sarcomas, like other primary malignant intra-osseous tumours, are relatively uncommon – in my series 10 out of 44 tumours of the malignant cartilaginous group.

Survival Periods.

Osteogenic Sarcomas – 151 cases. Males 95. Females 56.

Osteolytic type 78
Chondro-myxo-sarcoma type 44
Sclerosing type 29

In this group 30 patients have survived 5 years and over since eradication of the tumour, with 15 of these surviving beyond the 10 year follow-up period. In 121 operable tumours this represents an over-all survival rate of 24 %. (1) Of these thirty "long" survivors, 15 are *chondromyxomas,* 7 of whom lived beyond the ten-year period, with the longest survivor still alive seventeen years following a disarticulation at the shoulder joint. (2) 12 are *osteolytic sarcomas* with 6 survivals over ten years, and with the longest survivor alive and well twenty-one years after a mid-thigh amputation; (Figs. 1, 2 and 3). (3) Three are *sclerosing sarcomas.*

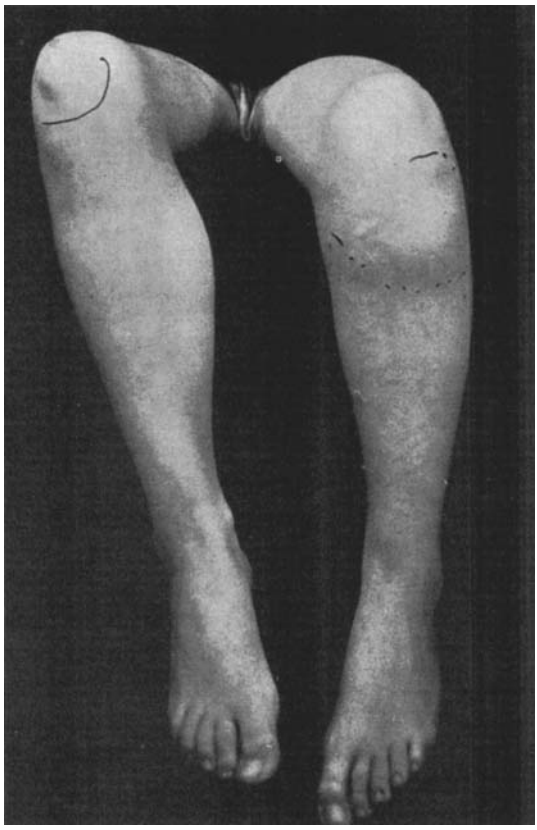

Fig. 1.
Male. Age 11. Osteogenic Sarcoma Tibia Upper End. (L). (Osteolytic type).

The mortality rate within the three year period (short survivals) following ablation of the tumour was a little over 50 % in the chondro-myxo-sarcomas, 70 % in the osteolytic tumours, and 90 % in the sclerosing tumours. These facts give us a crude picture of the relative malignancy of these three types of osteogenic sarcoma.

Extra-Periosteal Sarcomas. 39 cases (operable 29.) { Females 25. Males 14

In this group there are 11 five year survivors, 9 of them alive over ten years from the date of removal of the tumour. By contrast 12 patients died within the three year period with one of them surviving less than one year. Thus this small series contained a high proportion of lethal tumours.

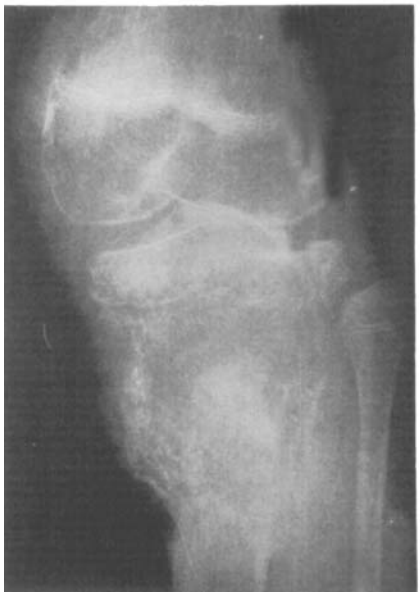

Fig. 2.
Same case. Pre-Operative X-ray. *Histology* – spindle cell Sarcoma with numerous mitoses and some bone formation.

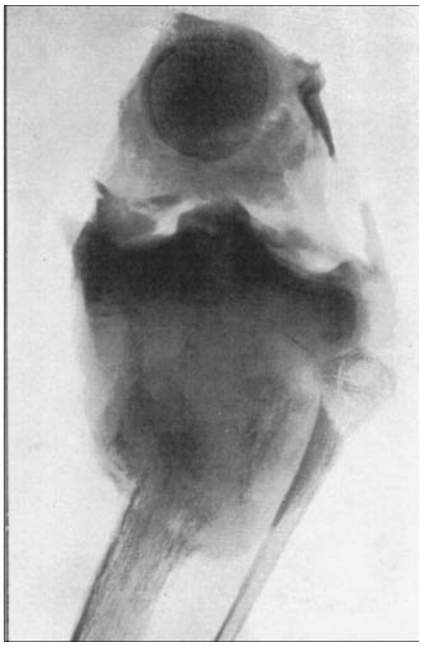

Fig. 3.
Same case. X-ray of amputation specimen. Patient alive and well 21 years after mid-thigh amputation

Ewing's Tumours. This type of bone sarcoma has long been regarded as the most deadly of the primary malignant tumours of bone, although in 135 such tumours in the collection of *Geschickter & Copeland* (1949) there was a five year survival rate of 19 %. My own limited experience of this uncommon lesion illustrates the fallacies involved in the estimation of survival periods at any given time. In 1950, out of 23 Ewing's tumours (16 operable) I could record no five year survivors. But by 1961, in 30 cases, there were now 8 five year survivors, five of whom had lived over ten years! Nevertheless, over two-thirds of my patients had died within two years from the time of the ablation of the tumour. The comment may be made that this series of Ewing's sarcomas could include tumours which in the opinion of some authorities would be regarded as reticulum-cell sarcomas – tumours which are believed to offer a more favourable prognosis than the classical Ewing's sarcoma.

Sarcoma in Abnormal Bones. This group of 31 sarcomas includes 18 *fibroblastic sarcomas* arising in Paget's disease; 2 such tumours in

Fig. 4.
Male. Age 48. Chondrosarcoma Scapula (L). Specimen after total excision of scapula. Period of survival 9 years following operation. Pulmonary metastases at the time of follow-up.

osteodystrophia fibrosa; and *11 chondro-sarcomas* representing malignant "transformation" in *benign chondromas* of long standing. The Paget sarcomas, which may have a multifocal origin, are in general highly lethal, although two of my patients survived for five and six years respectively. Of the two tumours arising in bones affected by osteodystrophia fibrosa, one patient lived for six years and the other for nine years. This is perhaps not an unexpected behaviour pattern, but the number of examples of this sequence of events is too few to justify any generalisations.

The advent of malignant change in a *benign osteochondroma*, more

particular in tumours which have grown to large size, has always presented a difficult diagnostic problem. As *Bradley Coley* (1960) has pointed out, the histological picture is not always a reliable guide, and he emphasises the need for early radical extirpation of all doubtful tumours, a procedure which I have long advocated (*Platt* 1935: 1951). Here again, the outlook for survival should be at least as favourable as in the socalled primary chondromas. Five out of eleven patients in this very small series passed the five year period.

Malignant Giant Cell Tumours. In my very small series, 5 cases in all, 4 patients died within a year, and one survived for just over three years.

FACTORS IN PROGNOSIS

The broad picture of potential survival rates in the various categories of bone sarcoma presented by the analysis of my own material, is in accordance with the findings of others who have investigated this problem in much larger collections of tumours. These fact cannot, however, be used without reservations in any attempt to predict the statistical changes of long or short survival in individual tumours. The problem is one of practical importance in the not uncommon tumours of the osteogenic sarcoma group. From time to time attempts have been made to assess the significance of factors which either singly or in combination might be concerned in determining lengths of survival. – *Bradley Coley & J. L. Pool* (1940); *A. B. Ferguson* (1940); *MacDonald & Budd* (1943) and *Bradley Coley & C. C. Harrold* (1950). More recently the results of important studies have come from the Argentine – under the guidance of *José Valls.* (*Mondolfo, Schajowicz & Derqui* 1960); from the Mayo Clinic (*Coventry & Dahlin* 1957; *Troup & Bickel* 1960); and in Great Britain from *Price* (1961). The many contributions to this problem over a long period by *Geschickter & Copeland* have also been invaluable.

Factors subjected to scrutiny as potentially significant, have been age; sex; duration of symptoms before treatment of the tumour; site of origin; periodicity in tumour growth; histological grading; and methods of treatment. It should be said at once that the findings of different observers in relation to the apparent rôle of many of these factors are conflicting.

Take for example the *age* groups in the osteogenic sarcomas. *Bradley Coley & Pool* (1940) found the prospects of long survival less favourable under the age of 10 and over the age of 40. In my own series, by

contrast, a substantial proportion of the short survivals fall into the age period 10–20, whereas the majority of the three year and over survivals (which include the long survivals of five years and over) have been found in the 20–30 age period, or in the over 40 age period. From the records of the General Register Office (Great Britain) during the period 1951–1953, the age period of maximum mortality in primary malignant bone tumours in the limbs was 15–19; the mortality rate fell between the ages of 20–34, but rose from 40 onwards due to the incidence of Paget's Sarcoma.

In 353 osteogenic sarcoma patients whose fate was known, analysed by *Coventry & Dahlin*, there was an over-all 5 year survival rate of approximately 19.3 %, and a 10 year survival rate of 15.3 %; in patients under 30 21.2 %; 30 years and over 14.3 %. The 10 year survival rate in these two age groups was 17.7 % and 8.1 % respectively.

Sex incidence has no relevance to prognosis. As regards the *sites* of tumours, *Coley & Pool* found that in tumours in the distal parts of the limbs there were more five year survivals than in the upper end of the femur. *Coventry & Dahlin* (loc. cit.) found that in osteogenic sarcomas below the upper end of the femur the long survival rates were 22.8 % (5 year survivals) and 17.6 % (10 year survivals). In osteogenic sarcomas involving the upper end of the tibia there was a substantially larger 5 year survival rate (34.6 %). It is clear however that this factor cannot be considered in isolation from the question of the ease of accessibility of the tumour to operative attack. Similarly, periods of *duration of symptoms* do not necessarily give an accurate estimate of the "age" of these tumours. It would be natural to expect that the prompt ablation of an osteogenic sarcoma discovered by accident in its earliest stage, might guarantee a longer survival than a rapidly growing tumour discovered at a time when its clinical features were unmistakeable. But even such a sweeping generalisation could prove to be fallacious.

In the course of the analysis of survival rates by *A. B. Ferguson* (loc cit.) by *Bradley Coley & Pool* (loc. cit.) and by *MacDonald & Budd* (loc. cit.) evidence emerged which suggested that some malignant bone tumours exhibited alternate periods of activity and regression. This led to the conclusion that a better prognosis would follow a policy of deliberate delay in extirpating the tumour after the diagnosis had been established. The majority of surgeons with a large experience in this field have not been convinced that such a policy is justifiable.

We are thus left with two factors which merit more detailed con-

sideration – (1) the histological grading of tumours; and (2) methods of treatment.

HISTOLOGICAL GRADING

The cytological grading of malignant tumour cells has been based either on the degree of anaplasia, or on quantitive estimation of mitotic phenomena. The ideal would be to establish a relation between the mitotic ratio and the length of survival in any given tumour. *Price* (1961) claims to have demonstrated such a positive correlation in osteogenic sarcomas. In the three grades of tumour adopted in this investigation, the 5 year survival rate was 61 % in Grade I; 15 % in Grade II; and nil in Grade III. In the whole series the average survival from the appearance of symptoms to the time of death was thirty-six months. *Schajowicz et al* (1960) on the contrary find that whereas a correlation between histological grading and clinical behaviour holds in the chondro-sarcomas, there is no correlation in the osteogenic sarcomas. These contradictory results should stimulate further investigations into what might prove to be a valuable aid in prognosis and a useful guide in treatment in this tragic field of malignant disease.

METHODS OF TREATMENT

In the choice of method of extirpating a primary malignant bone tumour the aim should be two-fold; (1) a technique best calculated to avoid the risk of local recurrence, and if convincing evidence be available, to offer the best chance of long survival; and (2) a method which involves as little mutilation as possible, which can be speedily completed, and which offers a short convalescence and so enables the patient to resume useful activities during whatever period of survival may be vouchsafed to him. This is the human and social aspect of the choice of method, and in certain circumstances it may be in conflict with more strictly scientific arguments in favour of one particular method or another.

In the treatment of the sarcomas of bone I remain a consistent advocate of the policy of extirpating all accessible tumours by appropriate *surgical* measures. In the majority of operable tumours in the limbs this implies amputation or disarticulation. The advantages of amputation are that the risks of local recurrence are negligible, the convalescence is short, and the patient can resume many forms of activity even before he has learnt to manipulate an artificial limb.

As an alternative, in certain sites, resection of the tumour area is

practicable, and this more conservative technique has been increasingly used in recent years. Where the gap following resection can be filled by a prosthesis (plastic or metal) as in the upper end of the humerus or upper end of the femur, a useful limb can be preserved. In the knee region – a favourable site for bone sarcoma – wide resection demands the use of massive bone grafts in order to secure an arthrodesis – a procedure which necessitates a long period of immobilisation of the operation area. Experience has shown that failure to achieve solid fusion is by no means uncommon. Similarly, in tumours of the shafts of long bones, which embrace the Ewing's tumours, wide resection involves bridging the gap by a substantial graft. In certain uncommon sites, for example the ulna or fibula, the gap can be left unfilled without any appreciable loss of function in the limb.

Tumours of the *scapula* offer almost ideal anatomical conditions for local resection with the preservation of a useful upper limb, even after total excision of the shoulder blade. In my own series of nine scapular tumours there are three long survivors – (1) an osteolytic sarcoma treated by excision of the lower third of the bone (15 year survival); (2) a chondrosarcoma surviving 9 years after total excision; and (3) (Fig. 4) an extraperiosteal sarcoma surviving 16 years after total excision.

I have no doubt, however, from my own experience that resection in tumours of the long bones carries a definite risk of local recurrence, both in the highly malignant and less malignant types of tumour.

This liability has been recognised by others (*Mondolfo et al 1960*). The practice of ablating primary malignant tumours of bone by radical surgical measures (disarticulation; amputation; or local resection) still holds the alliegance of the majority of surgeons who are continuously occupied in the diagnosis and treatment of these tumours.

If amputation be accepted as the surgical method of choice in tumours where for anatomical reasons local resection is impracticable, the question arises whether or not the level of the amputation has any influence on the length of survival. It was *Joseph Bloodgood*, a pioner in the study of bone tumours, who long ago taught that amputation at levels well above the limit of the tumours is all that is required.

From the Mayo Clinic, (*Troup & Bickel* 1960) come the results in terms of survival in 264 patients treated by hindquarter amputation; disarticulation of the hip; and forequarter amputation.

In this series, the level of ablation per se would seem to have no specific determining influence on survival rates.

The rôle of irradiation in the treatment of primary malignant tumours of bone has been much debated for more than a quarter of a century. When it became apparent that the Ewing's tumour was highly radio-sensitive, irradiation was advocated as the therapy of first choice in tumours whether accessible or inaccessible to operative attack. Nevertheless, when local recurrence followed a period of apparent obliteration of the tumour – a not uncommon event – resection or amputation had now to be carried out. For this reason many surgeons have always preferred to treat Ewing's tumours by radical surgical measures without delay. In the majority of the centres in the United States, to which large numbers of bone tumours began to gravitate, irradiation became reserved for inoperable tumours, or as a preliminary to surgical ablation. At the New York Memorial Hospital pre- operative irradiation was given a prolonged trial in tumours known to be radio-resistant – e.g. osteogenic sarcomas and extra-periosteal sarcomas; but this procedure was ultimately discarded in common with the use of Coley's toxins (*Bradley Coley & Harrold* 1950).

Striking advances in radiotherapeutic technique have been made since those earlier years, and it is now claimed that the question of relative radio-sensitivity is no longer all-important. Thus, in 9 patients with osteogenic sarcoma treated by heavy radiation (*Tudway 1961*) five survived for 3–14 years. The conclusions drawn from these observations, however, were that the method should be used in the upper limb tumours only.

But even in the upper limb, the arguments in favour of abandoning surgical ablation of the tumour will carry little weight where conservative resections are feasible. Indeed, in extensive tumours of the shoulder region, a more radical resection technique is available as a means of avoiding forequarter amputation. This consists of removal of the scapula; excision of the clavicle (partial or complete); the upper end of the humerus, with the sourrounding soft tissues. This type of resection of the shoulder girdle was apparently first practised over fifty years ago in Russia, and has been called the Tikhor-Linberg Resection (*Pack & Crampton* 1961).

In my judgement, the case for the substitution of irradiation for surgical therapy as the first choice in operable tumours in both the osteogenic sarcomas and Ewing's tumours remains unproven. Is there a place for a preliminary "destruction" of the tumour, to be followed by surgical extirpation: (*Cade* 1955)? I can find no convincing evidence that much longer survival periods follow the adoption of this

plan of action. This being so, I come back to the human and social aspects of the problem of the choice of treatment – to me, the disturbing situation by any deliberate policy of delay once a diagnosis has been established. Following irradiation, the chances of local recurrence or reactivation of the tumour cannot be ignored. In such a sequence of events, as I know from my own experience, the surgeon is confronted at a later stage by the necessity of performing a more extensive local resection than would have been required at an earlier stage; or he may be compelled to ampute or disarticulate a limb which could have been preserved. After a long experience in this field of malignant disease, my attitude towards the treatment of operable primary malignant tumours of bone remains unchanged; for me the attacking policy is "once for all". The surgical removal of these tumours, no matter how radical the technique may be, is in the last analysis an act of mercy. Long or short survivals depend on others factors – some known, others unknown. In the latter category lies the mystery of the existence in some individuals of an immunity factor which calls a halt to the metastasising sarcoma cells. Assuming that there has been no mistake in diagnosis, how else can we explain on the one hand very short survivals, and on the other survivals of over twenty years, in tumours belonging to the highly lethal categories?

SUMMARY

(1) In the writer's fully documented collection of 256 bone "sarcomas" the overall five-year survival rate was 21 %.

(2) In 121 operable tumours of the *osteogenic sarcoma* group, the overall survival rate was 24 %. In 30 long survivors, (a) 15 were tumours of the *chondro-sarcoma* type, with 7 patients surviving over 10 years; (b) 12 were osteolytic sarcomas, with 6 surviving over 10 years; and (c) 3 only belonged to the sclerosing sarcoma type.

(3) In 39 *extra-periosteal sarcomas* there were 11 five year survivals (9 living over the 10 year period); but this small series contained a high proportion of lethal tumours.

(4) In 30 *Ewing's sarcomas* there were 8 five year survivals, with 5 patients living beyond the 10 year period.

(5) In 31 *"sarcoma" arising in abnormal bones* – a clinical group dominated by Paget's disease – the Paget's sarcomas were highly lethal, although 2 patients out of 18 survived over 5 years. In the "secondary" chondro-sarcomas (malignant transformation in be-

nign osteochondromas) and the few sarcomas in osteodystrophia fibrosa, the prognosis was more favourable.

(6) The *malignant giant-cell tumours* (5 cases only in the collection) were all highly lethal.

(7) The broad picture of relative malignancy in the various categories in bone sarcoma is well established. A scrutiny of factors which might possibly be significant in determining prognosis in any given tumour affords little evidence which can be regarded as significant. More exact prediction may come from a detailed study of cytological grading.

(8) In the treatment of bone sarcomas the writer is a convinced advocate of early extirpation of the tumours by surgical methods (resection or amputation). In the last analysis, however, the fate of the patient, i.e. the early or remote appearance of pulmonary metastases, does not depend on the method of treatment. Survival rates were most probably related to the existence or non-existence of an immunity factor which inhibits the spread of metastasising sarcoma cells.

RESUME

(1) Dans le collection de 256 «sarcomes» osseux, entièrement documentée par l'auteur, le pourcentage de survie pour une période de cinq ans a été de 21 %.

(2) Dans 121 tumeurs opérables du groupe des *sarcomes ostéogéniques*, le pourcentage de survie a été dans l'ensemble de 24 %. Dans 30 cas de longue survie (a) 15 étaient des tumeurs du type *chondrosarcome*, avec 7 malades ayant survécu pendant 10 ans et (c) 3 seulement appartenaient au type du sarcome sclérosant.

(3) Dans 39 *sarcomas extra-périosteal*, il y eut 11 cas de survie de 5 ans (9 ayant vécu pendant la période de 10 ans); mais il y avait dans cette petite série un pourcentage élevé de tumeurs létales.

(4) Dans 30 *sarcomes Ewing*, il y eut chez 8 malades une survie de cinq ans avec 5 malades au-delà de la période de 10 ans.

(5) Dans 31 *«sarcomes» survenus dans des os anormaux* – un groupe clinique dominé par la maladie de Paget – le sarcome de Paget entraîna une létalité elevée, seulement 2 malades sur 18 ayant survécu pendant 5 ans. Dans les chondrosarcomes «secondaires» (transformation maligne d'ostéochondromes bénins) et les rares sarcomes de fibrose ostéodystrophique, le prognostic fut plus favorable.

(6) Les *tumeurs malignes à cellules géantes* (5 cas seulement de la série) ont donné un pourcentage élevé de létalité.

(7) Le tableau de la malignité relative des différentes catégories de sarcomes osseux est bien établi. Une étude des facteurs qui ont peut-être une importance décisive pour le pronostic de chaque catégorie de tumeur ne semble pas apporter de données décisives. Des prévisions plus exactes peuvent découler d'une étude détaillée du degré cytologique.

(8) Dans le traitement des sarcomes osseux, l'auteur est partisan convaincu d'une extirpation précoce des tumeurs par intervention chirurgicale (résection ou amputation). L'analyse du sort du malade montre que l'apparition précoce ou tardive de métastases pulmonaires ne dépend pas de la méthode de traitement. Le pourcentage de survie est plus probablement lié à un facteur d'immunité qui empêche la propagation des cellules métastatiques du sarcome.

ZUSAMMENFASSUNG

(1) In der vom Verfasser authentisch belegten Sammlung von 256 Knochensarkomen war die gesamte Überlebungszahl nach fünf Jahren 21 %.

(2) Bei 121 operablen Tumoren der *osteogenetischen* Sarkomgruppe war die Gesamtzahl der Überlebenden 24 %. Bei 30 lang Überlebenden (a) handelt es sich in 15 um Tumoren der *Chondrosarkom*-Type, von denen 7 Patienten länger als 10 Jahre lebten, (b) 12 waren osteolytische Sarkome, davon 6 mehr als 10 jahre überlebend, und (c) nur 3 gehörten zur sklerosierenden Sarkomtype.

(3) Von 39 *extraperiostalen Sarkomen* überlebten 11 die Fünfjahrsperiode (9 leben noch nach 10 Jahren). Aber diese kleine Reihenfolge enthält eine hohe Anzahl von tötlichen Tumoren.

(4) Von 30 *Ewings Sarkomen* überlebten 8 die Fünfjahrsperiode, davon lebten 5 Patienten über 10 Jahre.

(5) Bei 31 *„Sarkomen" die von abnormen Knochen ausgingen* – einer klinischen Gruppe, die von der Paget-Erkrankung beherrscht wird – waren die Paget-Sarkome äusserst lethal, obwohl von einer Gruppe von 18 Patienten 2 mehr als 5 Jahre überlebten. Bei den „sekundären" Chondrosarkomen (maligne Entartung bei gutartigen Osteochondromen) und bei den wenigen Sarkomen in Fällen von Osteodystrophia fibrosa war die Prognose günstiger.

(6) *Die bösartigen Riesenzellengeschwülste* (nur 5 Fälle in dieser Sammlung) waren alle äusserst lethal.

(7) Das Bild der verhältnismässigen Bösartigkeit der verschiedenen Kategorien von Knochensarkom ist wohl bekannt. Eine Prüfung von Faktoren, die möglicherweise bezeichnend für die Bestimmung der Prognose eines gegebenen Tumors sein könnten, liefert wenige Beweise, die als charakteristisch angesehen werden können. Eine genauere Voraussage kann vielleicht durch eingehendes Studium der cytologischen Abstufungen möglich gemacht werden.

(8) In der Behandlung der Knochensarkome ist der Verfasser ein überzeugter Fürsprecher der frühzeitigen Exstirpation des Tumors mit chirurgischen Methoden (Resektion oder Amputation). In der Endanalyse jedoch hängt das Geschick des Patienten, d. h. das Früh – oder Spätauftreten von Lungenmetastasen, nicht von der Behandlungsart ab. Die Überlebungszahl steht wahrscheinlich in Beziehung zu einem vorhandenen oder nicht vorhandenen Immunitets faktor, der die Ausbreitung von metastasierenden Sarkomzellen verhindert.

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