Med. J. Malaysia Vol. XXXII No. 3, March, 1978

A REVIEW OF CASES OF OSTEOSARCOMA ADMITTED TO THE UNIVERSITY HOSPITAL KUALA LUMPUR

by *J. Francis Silva*
AM, MD, FRCS, FRACS, FACS, FICS

and *Teo Wee Sin*
MBBS

Department of Orthopaedic Surgery,
Faculty of Medicine,
University of Malaya,
Kuala Lumpur, Malaysia

IT WAS Samuel Gross (1879) who first described the differentiation between bone sarcoma and metastatic carcinomas. Even at that time he stressed the futility of local excision and recommended ablation inspite of its high mortality of thirty percent.

During the recent years three facts have evolved about the relentless course of this tumour from clinical, radiological and pathological material.

These are firstly, the situation of the tumour in the metaphysis of long bones, secondly the metastatic spread to the lungs which manifest only too late, and thirdly the metastatic spread to other parts of the body, (Enneking, 1975; Dahlin, 1975).

The possible etiology has been an enigma over the many years of its study. Chemical, viral and radiation carcinogenesis have been studied as possibilities (Pritchard *et al.*, 1975).

Clinically possibilities have evidenced themselves in its association with Pagets disease, induction by radiotherapy, possible epidemiologic grouping and hormonal relationships.

The traditional treatment of osteosarcoma has been amputation. In doing so, one hopes for the absence of micrometastasis. The five year survival rate after such treatment has been very unsatisfactory. It may well be that open biopsy followed by amputation or disarticulation would possibly provoke metastasis, but even with frozen section and immediate ablation the results are not significantly different.

Many studies and trials in management of this unfortunate illness which often affects the younger age groups are being carried out in many countries. These will be discussed later in this paper.

The present series of patients treated at the University Hospital consists of twenty-one patients and is the basis for the present retrospective study.

CLINICAL MATERIAL

During the period under review there have been twenty-one patients with osteosarcoma admitted for treatment. Seven of these patients have been from the state of Selangor, three from Negri Sembilan, four from Johore, three from Perak, two from Malacca, one each from Trengganu and Sarawak. This distribution is not statistically significant to ascertain whether there is a rural or urban distribution. In a previous study, Bovill, Silva and Subramanian (1972) showed an indication that in both the Malay and Chinese ethnic groups there was a higher incidence in the urban dwellers. Table I shows the analysis of the present series.

The ethnic distribution

The ethnic groups most commonly affected were the Chinese, there being sixteen patients, while only three patients were Malays and one an Indian. In the earlier study of both East and West Malaysia there were thirty-four Chinese as opposed to twenty-two Malays.

This tumour thus appears to afflict the Chinese community more than the Malays while the Indian race seems to be the least involved.

Table I showing analysis of patients with osteosarcoma

Case No.	Age (yrs)	Sex	Ethnic Group	Duration of Symptom at 1st Visit (mths.)	Site of Lesion	Histology	Previous Treatment	Present Treatment	Follow/ Up (mths)	Duration at Time of Study
1.	42	F	Indian	2½ – ulcer	(L) Ulna	Osteosarcoma	Nil	Above-elbow amputation	3	Lost to follow-up
2.	19	M	Indian	4 – pain	(R) Fibula head	Osteosarcoma	Nil	Above-knee amputation with deep x-ray therapy	21	Died – pulmonary metastasis
3.	4	F	Chinese	6 – pain	(L) Lower 2/3 Tibia	Osteosarcoma	Biopsy G.H. Ipoh	Above knee amputation with deep x-ray therapy	3	Died – Localised metastasis
4.	16	M	Chinese	2½ – pain	(L) Upper 1/3 Femur	Osteosarcoma (x-ray)	Nil	Referred for deep x-ray therapy	Died	Died in hospital – pulmonary metastasis
5.	13	M	Chinese	4 – Pain	(L) Lower 1/3 Femur	Osteosarcoma (x-ray)	Sinseh	–	Died	Died – Pulmonary metastasis
6.	13	F	Chinese	1½ – Pain	(L) Fibula head	Osteosarcoma	Nil	Excision biopsy with deep x-ray therapy	4	Defaulted – mass recurred.
7.	16	M	Malay	2 – Pain	(R) Upper 1/3 tibia	Osteosarcoma (x-ray)	Nil	–	Nil	Lost to follow-up – Pulmonary metastasis
8.	21	M	Chinese	2½ – Pain	(R) Upper Humerus	Osteosarcoma	Nil	Advised deep x-ray therapy	Nil	Defaulted
9.	15	M	Chinese	3 – Mass	(R) Shaft Femur	Osteosarcoma	Nil	Subtrochanteric amputation with deep x-ray therapy	20	Alive and well – no metastasis
10.	19	M	Malay	8 – Pain	(R) Upper end tibia	Osteosarcoma	Deep x-ray therapy – G.H., K.L.	Deep x-ray therapy	Nil	Lost to follow-up
11.	12	M	Chinese	5 – Pain & Swelling	(R) Upper Humerus	Osteosarcoma	Nil	Deep x-ray therapy	Died	Died – pulmonary metastasis
12.	22	F	Chinese	4 – Pain & Swelling	(L) Lower Femur	Osteosarcoma	Nil	Deep x-ray therapy, above knee amputation chemotherapy	9	Lost to follow-up – pulmonary metastasis
13.	9	M	Chinese	3 – Pain & Swelling	(R) Upper Fibula	Osteosarcoma	Nil	Advised deep x-ray therapy	Died	Died – pulmonary metastasis
14.	21	M	Malay	3 – Pain	(L) Lower Femur	Osteosarcoma	Nil	Disarticulation (L) hip with deep x-ray therapy	13	Died – pulmonary metastasis
15.	22	M	Chinese	5 – Swelling	(R) Lower Femur	Osteosarcoma	Nil	–	Nil	Died – Refined surgery
16.	7	M	Chinese	2 – Pain & Swelling	(R) Lower Femur	Osteosarcoma	Sinseh	Advised deep x-ray therapy	Defaulted	Died
17.	16	M	Chinese	4 – Swelling	(L) Pubic bone	Osteosarcoma	Nil	Deep x-ray therapy	Nil	Died – multiple metastasis
18.	18	M	Chinese	6 – Swelling	(R) Upper tibia	Osteosarcoma	Sinseh	Subtrochanteric amputation with chemotherapy	5	Died – multiple metastasis
19.	16	M	Chinese	3 – Pain & Swelling	(L) Lower Femur	Osteosarcoma (x-ray)	Deep x-ray therapy	–	Nil	Transferred to G.H., K.L.
20.	15	F	Chinese	3 – Pain & Swelling	(R) Shaft Femur	Osteosarcoma	Nil	Deep x-ray therapy	Nil	Referred to G.H., K.L.
21.	21	M	Chinese	7 – Pain & Swelling	(L) Upper Tibia	Osteosarcoma	Nil	Above knee amputation and chemotherapy	12	Died – pulmonary metastasis

Sex

In this study there were sixteen males as compared to five females showing a male preponderance. In the earlier study concluded for Malaysia, a similar trend was seen there being forty males and twenty-eight females. Figure 1 shows the ethnic and sex distribution in the present study.

The age group most affected in the present series was the second decade there being twelve patients. This is the unfortunate significance of osteosarcoma, in that it affects the flower of youth. In the 1969 – 1972 study the same age group was again the most commonly involved. Figure 2 shows the age distribution in the present series.

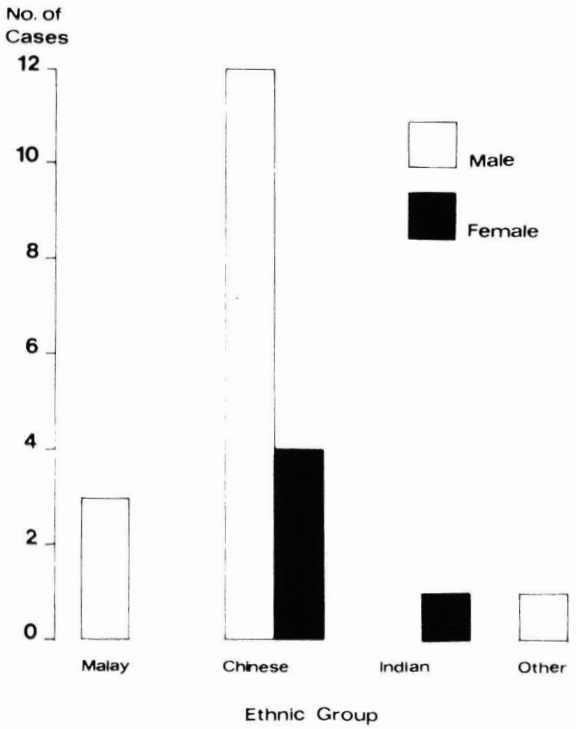

Figure 1. shows the ethnic and sex distribution of 21 cases of osteosarcoma.

The sites of the lesion

Figure 3 shows the sites of the lesion in this study. Fourteen of the patients had the neoplasm around the knee joint, thus conforming to the general pattern of this tumour. The lower femur was involved in six cases, the upper tibia in five and the fibula in three. Of the remaining seven, three were in the upper femur.

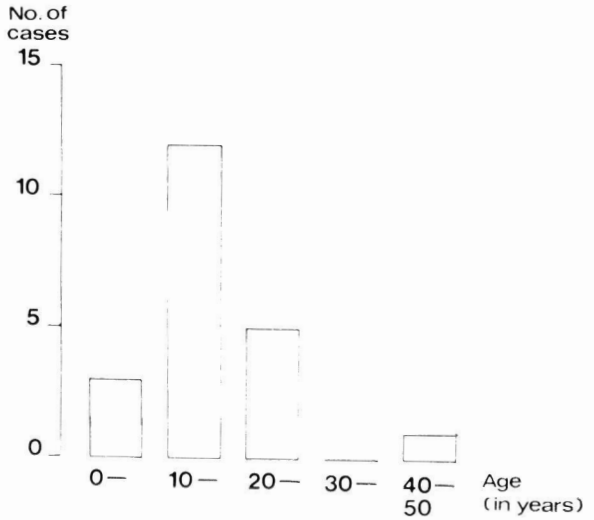

Figure 2. shows the age distribution of 21 cases of osteosarcoma.

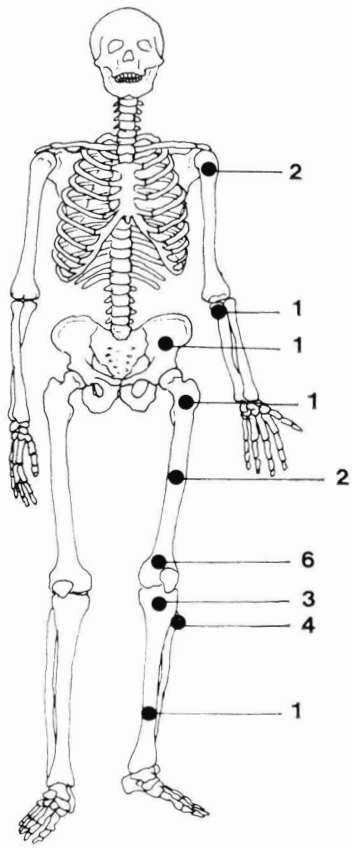

Figure 3 shows the sites of the lesion.

Metastasis

Seven patients had pulmonary metastasis. Three patients have had metastasis in under three months while three have developed this complication in seven, eight and nine months respectively.

Three cases had metastasis in the lungs when they were first seen at the University Hospital.

One patient was alive and well with no pulmonary metastasis at twenty months.

In eight patients there was no follow up possible on a written questionnaire.

Three patients had generalised metastasis and in one there was a local recurrence. (Table II).

Table II

Condition of patient at time of study

Condition	Number of patients
Death with pulmonary metastasis	7
Death with localised or multiple metastasis	3
Death – condition unknown	2
Alive and well	1
Lost to follow-up	8
Total:	21

Duration of symptoms

The duration of symptoms in patients with this neoplasm is significant from the point of view of survival. In a tumour with such a poor prognosis early admission is vital, to have a high percentage of five year survivals even with the most modern forms of combined therapy.

In the present series seven cases have had symptoms for two months, thirteen for three months and five for four months.

Management

The management of these patients has been a problem, in that neither the patients nor their relative favour radical surgery.

Under these circumstances seven patients discharged themselves against medical advice and six patients had only a course of deep x-ray therapy. These thirteen patients however were lost to follow up.

Four patients had deep x-ray therapy followed by radical surgery. Of these one patient was lost to follow up. Two were dead with metastasis while one is alive at twenty months. Three patients had adjuvant chemotherapy in addition to surgery, one of whom was lost to follow up. One patient had only an amputation as a palliative procedure to make life tolerable in the terminal stages.

Table III shows the analysis of the treatment given in the present series. Figure 4 shows the level of the lesions and site of ablation in the patients who consented to surgery.

Tibial lesions have had above knee amputation thus leaving a joint intervening between the lesion and the amputation. In the femoral lesions however one has had a high amputation, another a disarticulation while the others have had amputations above the level of the lesion.

Here again the problem to some extent has been the reluctance of patients to have a radical procedure while in others the surgery has been for the sole purpose of excision a fungating mass.

Table III

Types of treatment given to patients with osteosarcoma

Type of treatment	Number of cases
Deep x-ray therapy	7
Deep x-ray therapy with amputation	4
Deep x-ray therapy with amputation and chemotherapy	1
Amputation and chemotherapy	2
Amputation	1
Defaulted	6
Total:	21

DISCUSSION

The surgical management of osteosarcoma involves either a biopsy which may be open or needle followed by amputation. In the alternative, the amputation is done if the patient is free of metastasis six months after a course of radiotherapy (Cade, 1947, Cade, 1955).

The advantage of such a regime is that fewer patients are subjected to radical surgery. Further the survival rate of those operated on is improved (Sweetnam, 1975). As for biopsy which could be open or a drill biopsy there is no advantage in

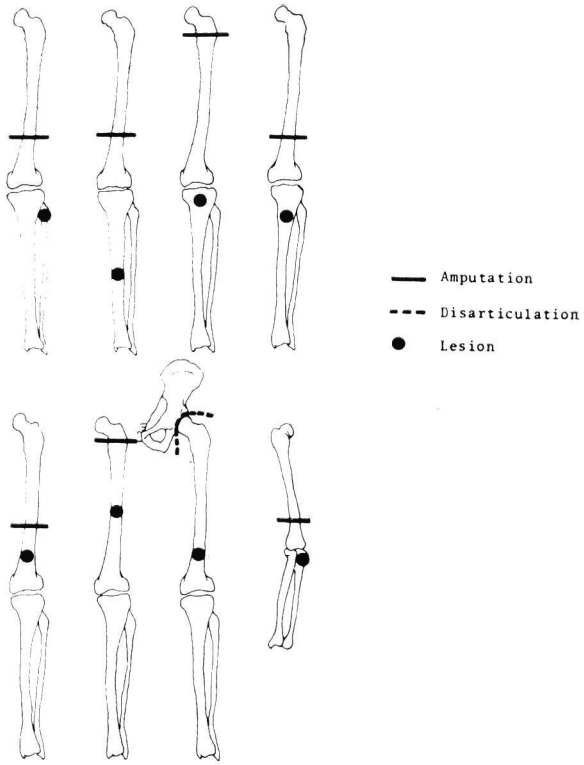

Figure 4 shows the sites of lesion and level of amputation or disarticulation.

avoiding it. In a series of nineteen patients operated without biopsy only two survived (Sweetnam, 1969). For biopsy an open technique is preferable as drill biopsy does not give adequate tissue for study.

There does not appear to be a real difference between primary ablation and that after radiotherapy. In either case the metastasis appear after an interval of ten months. The disadvantages of following the routine of radiotherapy and delayed amputation as advised by Cade (1955) are the problems that arise in the terminal stages of the disease such as pain, fungation and even a pathological fracture. In the present series the patients did not report as early for treatment as one would like. Hence the chances of these complications are much more likely.

In the present series only one case was subjected to amputation after radiotherapy while deep x-ray therapy alone was offered to six patients and one patient had only an amputation while another had chemotherapy as an adjuvant.

There is no proof that disarticulation is better than high amputation, there being no adequate study to prove that the one is better than the other.

However should recurrence appear in a stump it would lead to intolerable suffering. Hence disarticulation may be considered the better procedure. Dahlin and Coventry (1967) recommend through femur amputation. They had ten stump recurrences.

Pulmonary metastasis

The current trend is to treat the pulmonary metastasis aggressively (Martini *et al.*, 1971). In patients treated by multiple wedge resections the five year survival rate went up to forty-five per cent at a three year follow up, while it was only five percent without (Marcove *et al.*, 1975). At five years, fifteen were alive with disease and twelve with disease elsewhere. This latter factor is what causes failure after multiple thoracotomies.

However in an untreated series with pulmonary metastasis, fifty percent were dead at the end of the first year (Marcove *et al.*, 1973). The important criterion is the early detection of the pulmonary tumour and if possible to know when it started.

Bilateral staged thoracotomies followed by immunotherapy and chemotherapy would be the answer provided there was no involvement of the myocardium, the bronchial tree or a blood stained pleural effusion. In this series one patient had a pneumonectomy for secondaries. None were subjected to multiple thoracotomies.

Radiotherapy

Irradiating the tumour and delaying ablative surgery for six months meant that fewer patients came to surgery and hence a longer survival rate in those subjected to it (Poppe *et al.*, 1968; Sweetnam *et al.*, 1971). Irradiation of the lung with 1700 rads in ten fractions is claimed to improve the survival rate at twenty-four months to sixty per cent in the treated group, whereas it was thirty percent when the lungs were not radiated (Suit & Phil, 1975). None of the patients in this series were offered this routine largely owing to their late presentation.

The host immune response

Statistical projections based on the known rate of mitosis and gene replication show 10,000 mitotic errors to occur daily in man (McMaster *et al.*, 1975). Although most cells are non viable, the low incidence of neoplasia in humans suggest the possibility of the existence of a system to eliminate these aberrant cells after their identification.

Thus a cellular immunity may be responsible for cancer surveillance (Weinert *et al.*, 1974).

Foreign cell membranes are distinct from host cells antigenitically and could so produce a lymphocyte medicated hypersensitivity leading to their ultimate rejection.

A failure on the part of lymphocytis to recognise these cells could well be the factor responsible for neoplasm production.

Hence adjuvant immunotherapy is useful to increase the five year survival of osteosarcoma.

BCG and allogenic sarcoma tumour cell vaccine are two possibilities. One ampoule of B.C.G. should be given intradermally at weekly intervals into the groin or axilla.

Allogenic sarcoma cell vaccine 1×10^7 tissue culture cells was given once a week for three months and there after every two weeks for three months.

The sarcoma cells are now prepared from several tumours (Eilber *et al.*, 1975; Jaffe *et al.*, 1969). Immunotherapy however does not increase the response to chemotherapy. It is an additional mode of independent attack on the tumour. The time of death was the same in patients who received chemotherapy alone and those that were given both immunotherapy and chemotherapy. Hence it seems advisable to give chemotherapy immediately after surgery to reduce the tumour cell population in the patient. Immunotherapy could possibly then reinforce the action by stimulating an immense response in the host. The latter action is still not conclusive.

Chemotherapy

In the past, the cure rate for osteosarcoma was 10 – 20 per cent. The interval between diagnosis and metastasis was ten months, and death occurred about six months after the appearance of the first metastatic deposit (Sinks *et al.*, 1975). Chemotherapy has improved this situation. A choice of several combinations of chemotherapy are available either Adriamycin alone, 30 mg/M^2 daily for four to six weeks after amputation or a combination of more than one drug. Jaffe *et al.* (1974) suggested methotrexate with citrovorum rescue and incristine. A multi drug regime commonly used and efficacious is Cyclophosphamide, Vincristine, L-Phenylalanine Mustard and Adriamycin, known as Conpadri I (Sutow *et al.*, 1974). With this treatment they had a 55 per cent two year survival. Adding a high dose of methotrexate (Conpadri II) to the above has also been tried out, (Sinks & Mendell, 1975). The toxic effects of these drugs should however be appreciated such as haemopoetic depression, gastro-intestinal ulceration and alopaecia but with their use, surgical removal of pulmonary metastasis have been made possible thereby prolonging life.

Thus what one has to decide in which is the most useful combination of drug therapy and in this light which is the most useful surgical approach. Reinforcement of these modalities of treatment with immunotherapy and deep x-ray therapy to the lung fields will probably help in the long term survival rate.

Perfusion of the osteosarcoma has also been tried and is claimed to help in prolonging life (Tateishi & Sekine, 1976).

This multifaceted approach which also must be multi displinary will help our patients, who generally come late for treatment.

SUMMARY

The management of osteosarcoma is indeed a sad and difficult task. This is more so when patients present themselves late for treatment. This has been evident in the present series.

This paper is a retrospective study of patients with osteosarcoma admitted to the University Hospital. In evaluating their management, the current trends in treating this unfortunate disease have been discussed and the newer approaches highlighted. In so doing the improved techniques available to prolong the life of patients with osteosarcoma have been stressed. To achieve this end the need for a combined therapeutic approach using all the modalities of treatment available at present, has been suggested as the most plausible way to achieve the longest possible survival rates.

REFERENCES

Bovill, E.G., Silva, J.F. and Subramanian, N. (1974): An epidemiologic study of osteogenic sarcoma in Malaysia, *Clin. Orthop.* and *Related Research,* **113,** 119.

Cade, S. (1947): Primary malignant tumour bone (symposium), *Br. J. Radiol.* n.s. **20,** 10.

Cade, S. (1955): Osteogenic sarcoma, *J. Royal College Surg. Edinburgh,* **1,** 79.

Dahlin, D.C. and Coventry, M.B. (1967): Osteogenic sarcoma, *J. Bone* and *Jt. Surg.* **49A,** 101.

Dahlin, D.C. (1975): Pathology of osteosarcoma, *Clin. Orthop. and Related Research,* **111,** 23.

Eilber, F.R., Townsend, C. and Morton, D.L. (1975): Osteosarcoma – results of treatment employing adjuvant immunotherapy, *Clin. Orthop. and Related Research,* **111,** 94.

Enneking, W.F. (1975): Osteosarcoma, *Clin. Orthop. and Related Research,* **111,** 2.

Gross, S.W. (1879): Sarcoma of long bones, *Am. Med. Sc.* n.s. **78:** 17–57, 338–377.

Jaffe, N., Malmgren, R.A. and Hall, W.T. (1969): Immunologic and virus studies with human sarcomas, *Surg.* **66,** 152.

Jaffe, N., Frei, E., Traggis, D. and Bishop, Y. (1974): Adjuvant methotrexate and citrovorum-factor treatment of osteogenic sarcoma, *N. Engl. J. Med.* **291,** 994.

Marcove, R.C. and Lewis, M. (1973): Prolonged survival in osteogenic sarcoma with multiple pulmonary metastasis, *J. Bone Jt. Surg.* **55A,** 1516.

Marcove, R.C., Martini, N. and Rosen, G. (1975): The treatment of pulmonary metastasis in osteogenic sarcoma, *Clin. Orthop. and Related Research,* **111,** 65.

Martini, N., Huvos, A.G., Mike, V., Marcove, R.C. and Beattie, E.E. Jr. (1971): Multiple pulmonary resections in the treatment of osteogenic sarcoma, *Ann. Thorac. Surg.* **12,** 271.

McMaster, J.H., Scranton, P.E. Jr. and Drash, A.L. (1975): Growth and hormone control mechanisms in osteosarcoma – evidence for a new therapeutic approach, *Clin. Orthop. and Related Research,* **106,** 366.

Poppe, L.K. and Efskind, J. (1968): Osteosarcoma, *Acta Chir. Scand.,* **134,** 549.

Pritchard, D.J., Finkel, M.P. and Reilly, C.A. (1975): The etiology of osteosarcoma – A review of current considerations, *Clin. Orthop. and Related Research,* **111,** 14.

Sinks, L.F. and Mindell, E.R. (1975): Chemotherapy of osteosarcoma, *Clin. Orthop. and Related Research,* **111,** 101.

Suit, H.D. and Phil, D. (1975): Radiotherapy in osteosarcoma, *Clin. Orthop. and Related Research,* **111,** 71.

Sutow, W.W., Sullivan, M.P., Fernbach, D.J., Cangir, A. and George, S.L. (1974): Adjuvant chemotherapy in primary treatment of osteogenic sarcoma, Proceedings, AACR.

Sweetnam, D.R. (1969): Osteosarcoma, *Ann. Royal College Surg.* **44,** 38.

Sweetnam, D.R., Knoweldon, J. and Seddon, H.J. (1971): Bone sarcoma – treatment, irradiation, amputation or a combination of the two, *Br. Med. J.* **2,** 363.

Sweetnam, D.R. (1975): The surgical management of primary osteosarcoma, *Clin. Orthop. and Related Research,* **111,** 57.

Tateishi, A. and Sekine, K. (1976): Perfusion chemotherapy of osteosarcoma – A clinical study on 75 cases, *Panminerva Medica,* **18,** 22.

Weinert, C.R. Jr., McMaster, J.H. and Ferguson, R.J. (1974): Immune response to sarcomas – A review, *Clin. Orthop. and Related Research,* **102,** 207.