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OSTEOSARCOMA

A Multifactorial Clinical and Histopathological Study with Special Regard to Therapy and Survival

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A multifactorial analysis was performed on all 153 unequivocal cases of genuine osteosarcoma recorded in the Swedish Cancer Registry for the years 1958 through 1968. Cases of so-called parosteal osteosarcoma, soft-tissue osteosarcoma and osteosarcoma secondary to Paget's disease of bone were not included. The osteosarcomas were subclassified as follows: osteoblastic (69 per cent), chondroblastic (19 per cent) and fibroblastic (12 per cent). The overall 5-year survival rate was 22 per cent; 55 per cent for those who had undergone amputation above the joint proximal to the involved skeletal part, 22 per cent for those amputated on the involved skeletal part, 11 per cent for those treated with local extirpation of the tumor, and 1 per cent in cases in which the lesion was not radically removed. Tumors of the femur, humerus and scapula were as malignant as axial tumors. The former carried a 5-year survival rate of 13 per cent, regardless of whether the patients had been treated with exarticulation or amputation on the involved skeletal part. Patients with axial tumors showed a 5-year survival rate of 15 per cent. These survival data suggest that proximal amputation alone might suffice for lesions situated distally to the knee and elbow joints, while tumors in the humerus and femur should be treated with amputation combined with multicytostatic treatment or immunotherapy and axial tumors with local resection and multicytostatic or immunologic treatment.

Key words: osteosarcoma; therapy; histopathological study

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Despite several reports in the medical literature of large series of genuine osteosarcoma, there is still some controversy as to the overall prognosis. In earlier reports, the estimated 5-year survival rate ranged from about 5 to over 30 per cent (Simmons 1939, Jaffe & Selin 1951), while in later series it ranges from 10 to 20 per cent (McKenna et al. 1964, Dahlin & Coventry 1967). However, the patient populations have been influenced by selection to a varying degree (McKenna et al. 1964). The results might also have been influenced by improvements in diagnostic and treatment efficiency over the years.

The present investigation represents a combined clinical and histopathological analysis of osteosarcomas collected from those recorded in the Swedish Cancer Registry during the 11-year period from 1958 through 1968. The overall 5-year survival rate was determined, and also the survival in

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relation to various factors such as tumor site and kind of treatment. Primary attention was thus paid to factors which have been considered to influence the survival rate, such as histopathological type of tumor, site and size of tumor, rapidity of tumor growth and soft-tissue involvement, diagnostic measures, presence or absence of fracture, age and sex, and mode of therapy. This information may provide a basis for the indications for primary ablative surgery, either alone or in combination with adjunctive chemotherapy or immunotherapy, and also for evaluation of the results which may be achieved with new therapies for osteosarcoma, e.g. chemotherapeutics such as methotrexate or adriamycin (Editorial 1974, Cortes et al. 1974, Pratt et al. 1974, Sutow et al. 1974, Campbell et al. 1975) immunotherapeutics such as intravenous transfer of sensitized lymphocytes (Southam et al. 1973, Editorial 1974, Neff & Enneking 1975), or interferon administration (Nilsonne et al. 1975).

MATERIAL AND METHODS

Since 1958 all cases of clearly malignant and possibly malignant tumors diagnosed in Sweden have been reported to the Cancer Registry by a very efficient system (Larsson 1971) of double reporting throughout the country from clinicians on one hand, and pathologists and/or cytologists on the other hand. The reliability of the data was discussed in a report from the Swedish National Board of Health and Welfare 1974. Two hundred and forty-two patients were reported with a diagnosis of osteosarcoma during the years 1958 through 1968.

The histopathological re-examination was carried out by one of the authors (L.B.). The original slides were re-examined and new sections were prepared and stained with hematoxylin and eosin, van Gieson's stain, periodic acid-Schiff, phosphotungstic acid hematoxylin, and Laidlaw's silver impregnation. Only those cases were accepted for further study in which we could prove a definite diagnosis of genuine osteosarcoma and in which *complete* clinical records and biopsy material were available to allow a multifactorial analysis. Cases were thus excluded in which the diagnosis of osteosarcoma had been made primarily but could not be finally proved because of a lack of adequate histopathological material for thorough re-examination. This means that the number of patients accepted for the present analysis was smaller than the total number of recorded cases used in preceding incidence and geographical studies (Larsson & Lorentzon 1974a and b). The present series of unequivocal osteosarcoma cases thus had to be selected to enable an analysis as complete and representative as possible without limitation of the significance of the study (Lockshin & Higgins 1968).

The possible influence of various factors, such as tumor localization and type of treatment, upon the prognosis, was subjected to statistical analysis using a chi-square test. When testing the possible simultaneous influence upon the prognosis of various factors, such as the type of diagnostic procedure used, a multiple regression analysis was performed (Angsmark 1969, Cramer 1954). All hypotheses were tested at the 1 per cent level of significance.

RESULTS

Histopathological study

The histopathological diagnosis was osteosarcoma in all 242 cases recorded in the Cancer Registry but owing to the described criteria for our re-examination, the present series consisted of only 153 proven genuine osteosarcomas. A total of 23 cases represented either parosteal or extraosseous osteosarcomas, or were secondary to Paget's disease of bone. These cases were not included. Thirty cases could not be fully proven to represent genuine osteosarcoma from the available material, and a few cases with unrelated malignancies had wrongly been registered as osteosarcoma. These cases had lesions with central locations, predominantly. In 26 cases sufficient specimens and clinical records could not be obtained for a complete analysis, and six cases were excluded because their initial symptoms appeared the year before the time period covered by our study.

Histopathologically, the genuine osteosarcomas were subclassified as predominantly osteoblastic in 69 per cent of the cases, as chondroblastic in 19 per cent, and as

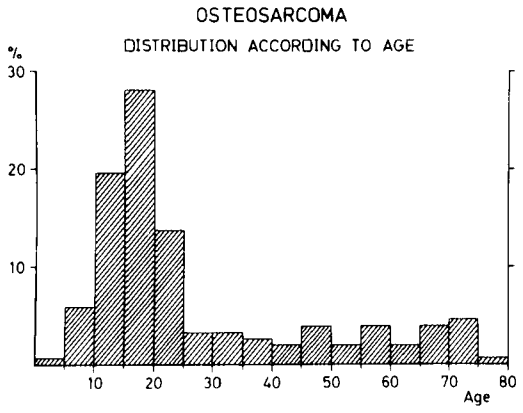

Figure 1. Distribution of primary osteosarcoma according to age.

fibroblastic in 12 per cent. This subclassification was found to have no prognostic value; nor did assessment of the degree of malignancy according to Broder's grading (Jaffe 1958, Price 1961) have any prognostic significance.

Age and sex

The age distribution of the genuine osteosarcomas is shown in Figure 1. One peak was obtained for the adolescent ages, two-thirds of the neoplasms occurring in persons below 23 years of age. An even distribution of the tumors was found for the adult ages. A similar age distribution was found for males and females, apart from the fact that the peak incidence occurred at a mean age of 12 years in girls and 16 years in boys, as previously reported (Larsson & Lorentzon 1974b). The adolescent incidence peak was caused by tumors localized to the long bones of the lower limbs. The genuine osteosarcomas showed a predilection for males, giving the following ratios for males to females: for all ages together 1.47 to 1, in the ages below twenty-three 1.72 to 1 and in the ages above twenty-three 1.11 to 1. Age was found not to influence the prognosis in the present series. Females had a slightly better prognosis than males, the 5-year-survival rates were 23 and 21 per cent, respectively.

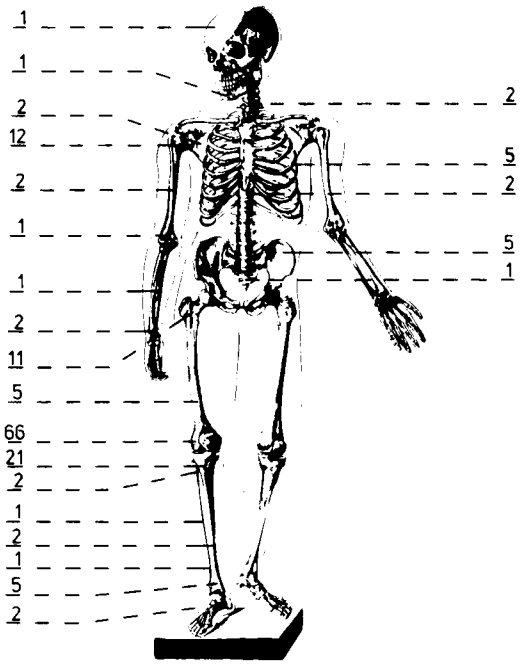

Figure 2. Skeletal distribution of primary osteosarcoma.

Tumor location, and clinical and roentgenological findings

The skeletal distribution of the genuine osteosarcomas is shown in Figure 2. Forty-three per cent affected the lower portion of the femur, 14 per cent the upper part of the tibia, and 7 per cent each the upper metaphyseal region of the femur and humerus. No patient initially had more than one tumor.

Twenty-four per cent of the neoplasms had a peripheral localization, i.e. distal to the knee and elbow joints (site 1); 65 per cent were located within the femur, humerus and scapula (site 2), and 11 per cent within the pelvis, spine, sacrum, ribs, mandibula and skull (site 3).

The most frequent symptom on admission was local pain noted in 91 per cent of the patients. Local swelling was present in 81 per cent; limitation of motion of the adjacent joint in 45 per cent; pathological fracture in 14 per cent; a general feeling of sickness in 10

per cent; and neurological symptoms in 7 per cent of the patients.

The most characteristic roentgenological appearance of the lesions was an expanded, osteolytic destruction of the affected bone, with areas of calcification often with visible bony structures, and periosteal new bone formation. The majority of the cases presented with advanced lesions showing destruction of cortical bone and a relatively high frequency of pathological fractures (see above). Periosteal bone formation with spiculae and Codman's triangles was a prominent feature. The neoplasms affected roentgenologically the metaphysis of a long bone in 61 per cent of the cases, the diaphysis in 7 per cent, the metaphyseal-diaphyseal border in 21 per cent, and a flat bone in 11 per cent of the patients.

Gross appearance

Some of the tumors were soft with areas of necrosis and cyst formation, while others were firm with chondromatous or ossified areas and central sclerosis.

The tumor size was estimated on roentgenograms and in some cases also on gross examination of the removed specimen. Tumors larger than 10 cm in diameter were found in 44 per cent of the patients; tumors 5–10 cm in diameter were also found in 44 per cent; tumors 2–5 cm in 11 per cent; and tumors smaller than 2 cm in 1 per cent of the cases. The peripheral lesions, i.e., those situated distally to the knee and elbow joints (site 1) were somewhat smaller (Table 1) than those in the femur, humerus and scapula (site 2) and the axial ones (site 3).

Table 1. The percentage distribution of genuine osteosarcoma according to tumor size on admission and primary localization.

Tumor diameter in cm	Site 1	Site 2	Site 3
< 2	2.7	0	5.9
2–5	21.6	8.2	5.9
5–10	51.4	42.3	35.3
> 10	24.3	49.5	52.9
	100.0	100.0	100.0

Site 1 = radius, ulna, tibia, fibula and foot skeleton.
Site 2 = humerus, scapula and femur.
Site 3 = rib, mandible, skull, spine, sacrum and pelvis.

Soft-tissue involvement and joint penetration was determined roentgenographically, at surgery, and at examination of the removed specimen. Involvement of the surrounding soft tissues by the tumor had occurred in 82 per cent of the cases and penetration into the adjacent joint cavity in 12 per cent of the patients.

Duration of symptoms before admission and "doctor's delay"

Thirty-nine per cent of the patients had experienced symptoms for less than 1 month before admission, 23 per cent complained of symptoms with 1 to 2 months duration and 26 per cent with 2 to 6 months duration.

The time which elapsed between the first contact with the physician and the initiation of treatment ("doctor's delay") was less than 1 month in 50 per cent of the cases, 1 to 2 months in 20 per cent, and 2 to 4 months in 16 per cent of the patients. No difference was found between the different tumor sites as to the time elapsed from the occurrence of symptoms until the institution of treatment.

Treatment

Local resection of the lesion was performed in seven patients (5 per cent) as shown in Table 2; local resection with inlay of bone graft in six (4 per cent); amputation on the skeletal part harboring the lesion in 39 (26 per cent); amputation through a proximally situated skeletal part in 26 (17 per cent); amputation by exarticulation of the proximal joint in 25 (16 per cent); hemipelvectomy in two (1 per cent) and forequarter amputation in four patients (3 per cent). The neoplasm was not macroscopically removed in 44 patients (29 per cent).

Table 2. The distribution of the patients with genuine osteosarcoma according to treatment, primary tumor localization and survival.

Type of treatment	Site 1	Site 2	Site 3	Survival
Local resection	3	1	3	See Figure 5
–"– + bone grafting	1	3	2	
Amputation on the involved skeletal part	0	38	0	See Figures 5 and 6
–"– + extirpation of lymph nodes	0	1	0	2 months
Amputation on the proximal skeletal part	25	0	0	See Figures 5 and 6
–"– + extirpation of lymph nodes	1	0	0	8 months
Exarticulation	2	23	0	See Figure 6
Forequarter amputation	0	4	0	4, 7, 9 and 151 months
Hemipelvectomy	0	2	0	11 and 18 months
Not macroscopically removed	5	27	12	See Figure 5
	37	99	17	

Chemotherapy was instituted primarily in 14 per cent of the patients and palliatively in patients with pulmonary metastases in 14 per cent. Combined chemotherapy and radiation treatment was given in 1 per cent of the patients.

Treatment according to Cade (1947), i.e. primary high-dose radiation treatment followed by amputation 6 months later in patients without pulmonary metastases, was performed in 18 per cent of the patients. Radiation treatment alone was given in 22 per cent of the cases; almost all of these were initially planned to receive a complete Cade treatment but succumbed with pulmonary metastases before ablative surgery could be undertaken. In 12 per cent of the patients, radiation treatment was given post-operatively.

Prognosis in relation to tumor localization and treatment

The overall survival rate for all genuine osteosarcoma patients differed significantly from that obtained for patients grouped with respect to tumor localization and kind of treatment. The overall 2-year survival rate was 31 per cent, and the overall 5-year survival rate was 22 per cent (Figure 3).

Patients with a peripheral localization of the neoplasm (Figure 4, site 1) had a significantly better prognosis than those with more centrifugal tumors (sites 2 and 3). The 5-year survival rate for patients with site 1 tumors, i.e. lesions located distally to the knee and elbow joints, was 47 per cent; that for patients with site 2 tumors, i.e. lesions in the

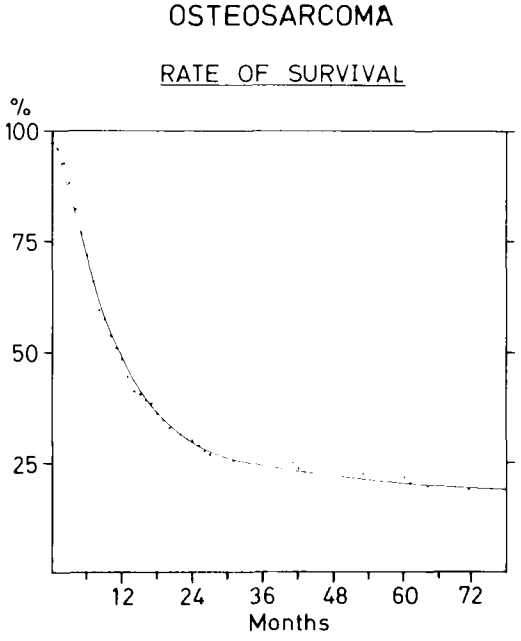

Figure 3. Rate of survival of all 153 patients with histopathologically verified primary osteosarcoma recorded in the Swedish Cancer Registry for the years 1958 through 1968.

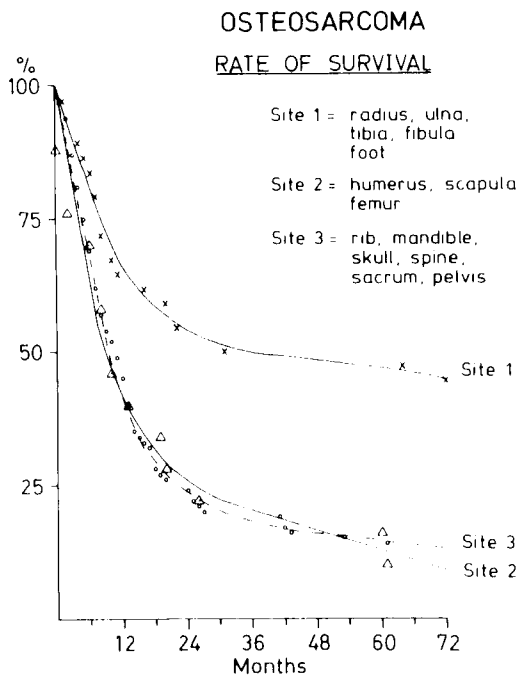

Figure 4. Rate of survival of the osteosarcoma patients according to tumor site. Patients with peripheral tumors (site 1) had a significantly ($P < 0.001$) *better survival rate than those with tumors of the femur, humerus and scapula (site 2) or axial tumors (site 3). The symbols indicate survival percentage at each point of analysis (the same as in Figures 6 and 7).*

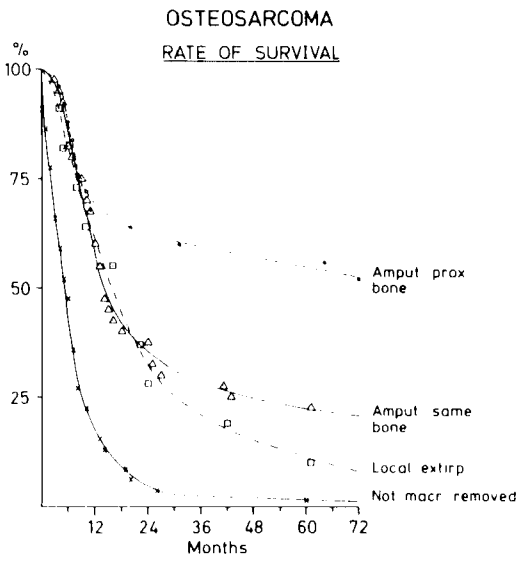

Figure 5. Rate of survival of the osteosarcoma patients according to the extent of surgical treatment performed. Patients amputated above the joint to the involved skeletal part had significantly ($P < 0.001$) *better survival rates than those treated with amputation on the involved skeletal part or local extirpation of the bone, or those who did not have their tumor macroscopically removed.*

humerus, scapula and femur 13 per cent; and that for site 3 tumors, i.e. lesions in the ribs, mandible, skull, spine, sacrum and pelvis, 15 per cent. While the better prognosis of site 1 tumors in relation to that of site 2 and site 3 tumors was statistically highly significant ($P < 0.001$), no significant difference was found between site 2 and site 3 tumors. The 2-year survival rates for patients with the three different tumor localizations were 54, 25 and 24 per cent, respectively. Although the tumors of site 1 were somewhat smaller than those of sites 2 and 3, the different prognoses were apparently associated with the type of treatment used and not so much with differences in tumor aggressiveness.

When the prognosis was related to the kind of treatment instituted (Table 2, and Figures 5 and 6), amputation on the skeletal part proximal to that harboring the neoplasm was associated with a significantly better prognosis than other kinds of treatment (Figure 5). Thus, patients who had undergone amputation above the joint proximal to the involved skeletal part showed a 5-year survival rate of 55 per cent (site 1 tumors), those amputated on the involved skeletal part 22 per cent (site 2 tumors), those treated with local extirpation of the tumor 11 per cent, and those in whom the lesion was not macroscopically removed 1 per cent. The 2-year survival rates were 62, 35, 32 and 5 per cent, respectively. Thus, ablative surgery and also local extirpation of the tumor was associated with a definitely better prognosis than non-operative treatment. The better prognosis for patients treated with high amputation (site 1 tumors) than for those amputated on the involved skeletal part (site

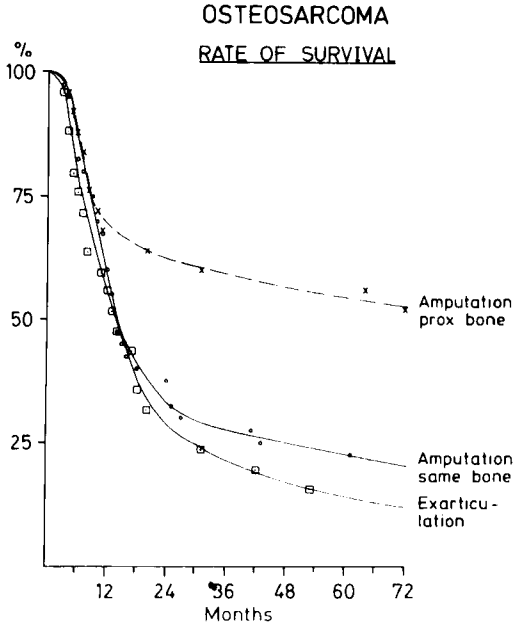

Figure 6. Rate of survival of the osteosarcoma patients in relation to the level of the ablative surgery performed. Patients amputated above the joint proximal to the involved skeletal part had significantly ($P < 0.001$) *better survival rates than those treated with amputation on the involved skeletal part or exarticulation. Patients who had undergone hip exarticulation did not have a better prognosis than those amputated on the involved skeletal part.*

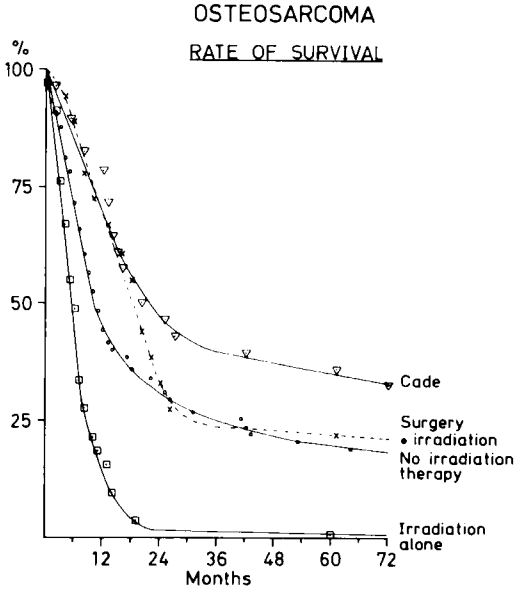

Figure 7. Rate of survival of the osteosarcoma patients in relation to radiation treatment given. Patients who received no radiotherapy were treated surgically. The majority of the patients treated with irradiation alone were scheduled to undergo treatment according to Cade but succumbed with pulmonary metastases before ablative surgery could be undertaken. Patients who had received a complete Cade treatment had survival rates comparable to those treated with primary ablative surgery alone.

2 tumors) was statistically highly significant ($P < 0.001$). Patients who had undergone amputation on the involved skeletal part had a significantly ($P < 0.001$) better prognosis than those who had received non-operative treatment.

The prognosis in relation to the level of ablative surgery performed is shown in Figure 6. While patients who had undergone a high amputation (site 1 tumors) showed a significantly better prognosis than those treated with amputation on the involved skeletal part (site 2 tumors), exarticulated patients (with site 2 tumors, predominantly) were found to have a bad prognosis. The 5-year survival rates for these categories of patients were 55, 22 and 14 per cent, respectively.

Patients who had received radiation treatment alone showed a very poor prognosis (Figure 7); the 5-year survival rate was less than 1 per cent. Some patients in this group had very advanced tumors already at the time of diagnosis. This group also included cases who initially were scheduled to receive treatment according to Cade, but pulmonary metastases occurred before surgery could be instituted. Patients who had undergone a complete Cade treatment showed a 5-year survival rate of 35 per cent. The corresponding figure for those primarily treated with ablative surgery was 21 per cent. The combined group of patients consisting of those who had undergone a complete Cade treatment and those who had received radiation treatment alone showed a

significantly lower 5-year survival rate than those who primarily were treated surgically.

Chemotherapy with cyclophosphamide was given as an adjuvant after amputation in a limited number of patients. Although the data did not demonstrate a significant effect of this treatment upon the prognosis, a slight tendency towards an improved prognosis was found. Ten patients received local perfusion of the involved extremity with very high doses of cyclophosphamide prior to amputation. Three of these patients survived for more than 5 years.

Influence of diagnostic procedure upon prognosis

The various diagnostic procedures used in the present series were found not to exert any statistically significant effect upon the prognosis. Using multiple regression analyses it was not possible to demonstrate any significant influence, upon the prognosis, of the different diagnostic procedures used, e.g. frozen section and surgery primarily; biopsy and surgery secondarily in a bloodless field; biopsy and surgery secondarily without a bloodless field; and surgery primarily without biopsy.

DISCUSSION

The 5-year survival rate of 22 per cent in all genuine osteosarcomas of the present series corresponds very well with the 23 per cent survival rate in the Mayo Clinic series (Dahlin & Coventry 1967), but is lower than the 28 per cent reported for the series from South-West England (Price 1962) and the 34 per cent recorded in an early American series (Coley & Pool 1940). However, the 5-year survival rate in our series is definitely higher than the 11 per cent recorded at the Memorial Centre for Cancer in New York between 1925 and 1955 as reported by McKenna and his colleagues (1966) who excluded patients dying after 5 years follow-up, and the 15 per cent survival rate recorded at the Massachusetts General Hospital from 1920 to 1962 (Weinfeld & Dudley 1962).

Patients with small tumors had a somewhat better prognosis than those with large ones. However, the majority of the patients had large tumors on admission; only 12 per cent presented with lesions less than 5 cm in diameter. Involvement of the surrounding soft tissues by the tumor had a marked effect upon the prognosis; patients with soft-tissue involvement had a 5-year survival rate of only 18 per cent compared with 39 per cent in patients who had no soft-tissue involvement. However, the latter group of patients constituted only 18 per cent and the former 82 per cent, indicating that the vast majority of the patients had advanced neoplasms on admission, although 61 per cent had experienced symptoms for less than 2 months. Nevertheless, the prognosis may improve if diagnosis can be made at an earlier stage of the disease. The 5-year survival rate was found to be somewhat better in patients with a long rather than a short duration of symptoms indicating differences in tumor aggressiveness, although histopathological grading had no prognostic value. The groups of patients with respectively good and poor prognoses showed no differences with respect to frequency of symptoms such as local pain, swelling, neurological disturbances, or history of antecedent trauma, nor with respect to routine laboratory data and blood sedimentation rate which showed wide variations in both categories.

The prognosis was not significantly affected by the various diagnostic procedures applied. It was not possible to demonstrate any positive effect upon the 5-year survival rate of primary surgical treatment subsequent to freeze-section diagnosis in comparison with biopsy and secondary surgical treatment after definite histopathological diagnosis had been obtained. It has been recommended that biopsy of suspected lesions should be performed without tourniquet to avoid flushing of the tumor cells from the marrow cavity (Allen & Stevens 1973).

Readily accessible osteosarcomas suitable for surgical treatment, e.g. peripheral tumors, are generally considered to carry a better prognosis than non-excisable, e.g. axial tumors (Lockshin & Higgins 1968). The skeletal distribution of osteosarcoma is similar in different reports and that of the present series does not deviate markedly. Thus, 43 per cent of the tumors were located in the distal femur and 14 per cent in the proximal tibia. The peripheral tumors situated distally to the joints of the knees and elbows carried a significantly better prognosis than those situated in femur, humerus and scapula; the 5-year survival rates being 47 and 13 per cent, respectively. On the other hand, the corresponding figure of 15 per cent obtained for the axial tumors did not differ significantly from that of the tumors situated within the femur and humerus. Although surgically accessible, the latter osteosarcomas thus carried as poor a prognosis as did the axial tumors. The two categories of lesions showed no difference with regard to parameters such as tumor size and duration of symptoms on admission.

The 47 per cent 5-year survival in osteosarcomas situated distally to the joints of the knees and elbows is better than the corresponding figure of 36 per cent reported for the Mayo Clinic series which showed a 10-year survival rate of 27 per cent (Dahlin & Coventry 1967). The peripheral tumors of the present series also showed a better prognosis than that reported earlier for tumors of the tibia (Coley & Pool 1940, Dahlin & Coventry 1967, McKenna et al. 1966, Price 1966, Weinfeld & Dudley 1962). On the other hand, the 5-year survival rate of 13 per cent for the osteosarcomas of the femur and humerus in the present series is less than the 16 to 21 per cent rate reported in the studies cited above. For the axial tumors, the survival rate of 15 per cent is somewhat higher than the 5 to 13 per cent rate recorded in the earlier series. Apparently, the neoplasms of the femur and humerus of the present series were more malignant than earlier considered.

It is evident from the data of the present study that primary amputation above the joint proximal to the involved skeletal part is the best treatment for tumors situated distally to the joints of the knees and elbows, i.e. site 1 tumors, giving a 5-year survival rate of 55 per cent. This unexpectedly high survival rate makes the rationale of using combined primary chemotherapy with drugs like adriamycin, methotrexate, cyclophosphamide, vincristine and 1-phenylalanine mustard questionable for patients with these peripheral lesions, when the serious toxic effects of these agents are taken into consideration. In addition, chemotherapy does not seem to prevent the late occurrence of metastases. For tumors of the femur and humerus (site 2) and for axial tumors (site 3), primary multi-cytostatic treatment appears to be indicated because of the minor effect upon the prognosis resulting from surgical treatment alone. The results of our series indicate that amputation or exarticulation as well as hemipelvectomy or forequarter amputation, offer relatively little to the final outcome in these patients, except for some palliation. It has not been shown earlier whether disarticulation at the hip is preferable to amputation through the upper part of the femur for osteosarcomas of the distal portion of the femur (Dahlin 1967). Our data indicate that the more mutilating hip disarticulation does not give a better prognosis than amputation on the proximal femur. The possibility of spread of osteosarcoma in the bone marrow must then be checked carefully. In the present series, 6 per cent of all patients had local recurrence of the tumor. Perfusion of the involved extremity with high doses of cytostatic agents prior to amputation might improve prognosis, as suggested by our data. Radical local excision should be employed whenever possible only for tumors not localized to the extremities. Radiation therapy did not affect the prognosis favorably in the present series. Consequently, treatment according to Cade (Cade 1947) cannot be recommended. Ten patients of our series had undergone pulmonary resection because of metastases occurring after the primary

neoplasm had been treated. The results obtained supported the view that this kind of treatment is indicated in cases with solitary metastases appearing 1 year after radical treatment of the primary lesion. The possibility of metastatic spread of osteosarcoma to other locations in the skeleton should then be examined thoroughly. This occurred in 14 per cent of all patients of our series; in the majority of the patients later than 6 months from the time of diagnosis.

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