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# Localized Ewing's Sarcoma of Bone: Ten Years' Experience at the Istituto Ortopedico Rizzoli in 124 Cases Treated with Multimodal Therapy*

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**Abstract**—*The results obtained in the treatment by multimodal therapy (surgery, radiation therapy and chemotherapy) of 124 cases of Ewing's sarcoma are presented. At a medium follow-up of 65 months 48% of the patients are disease-free. One patient died of leukemia and two patients developed an irradiation-induced sarcoma. Analysing the data, three factors seem to be correlated to prognosis: location of the initial lesion outside the pelvis and sacrum, a four-drug chemotherapy protocol and the use of surgery in the treatment of the initial lesion seem to give better results.*

## INTRODUCTION

EWING'S tumor is unanimously considered the most lethal of all bone tumors. In fact, when diagnosis is made about 20% of the patients already show metastatic dissemination. Even in 'apparently localized' cases the cure rate achieved with only local treatment (radiation therapy or surgery) is very poor (about 5% in our experience concerning 83 patients treated between 1950 and 1970 [1]).

During the past 15 yr, adjuvant chemotherapy (AC) has considerably improved the prognosis of this tumor, increasing the percentage of long-term disease-free survivors from 5 to 35–75% [2–10]. This rise in prognosis puts in evidence certain facts which in the past were disguised by the early death of these patients. In particular, the usefulness of radiation therapy, which was considered for years the local treatment of choice in this tumor, has been questioned and the role of surgery has been reconsidered [11–13].

Recently preliminary good results of new protocols (surgery, radiation therapy and chemotherapy, sometimes used also as initial treatment) have been reported [13, 14]. However, because Ewing's tumor is a rare disease and can initially occur in almost any bone, the number of patients with the same characteristics and risks and treated with the same therapy is too small to establish which is today the best method of treatment.

During 1972–1981 124 consecutive cases of localized Ewing's sarcoma were treated with multimodal therapy at the Bone Tumor Center of the Istituto Ortopedico Rizzoli. The treatment of the primary lesion, clearly individualized, was performed with surgery, radiation therapy or both.

AC was performed with two different protocols activated successively at a later date. The preliminary results obtained in 80 patients with the first, three-drug protocol have been reported in a previous paper [1]. This study includes a longer follow-up of those patients as well as information on 44 more recent cases treated with the second, four-drug protocol.

## MATERIALS AND METHODS

### *Patient selection and follow-up*

In this study only previously untreated patients with typical histological features of Ewing's sarcoma were considered. The tumor had to be localized in the bone in a patient free of

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demonstrable metastases. Histological slides were examined by three pathologists with special expertise in orthopedic pathology. The pathologists also had the radiographs at their disposal, and any debatable case was excluded. In the last 10 cases, light microscopic findings were confirmed by electron microscope.

Out of 181 cases of histologically confirmed 'malignant round cell tumors' of the bone observed between April 1972 and September 1981 (Table 1), 153 (84%) were Ewing's sarcoma.

Before entering the study, routine history, physical examination, hematological and serum chemical analyses and ECG were performed on all patients. The same tests were performed before each cycle of cytotoxic drugs and were repeated at 3-month intervals for 1 yr after the end of chemotherapy.

Diagnostic procedures to exclude the presence of metastatic disease varied during the 10 yr of the study. For the first 43 patients, observed before July 1976, these procedures included radiographs of the chest, bone marrow examination, urinary cathecolamines, radiographs of the primary lesion and, from clinical indication, also radiographs of other bones. In the 110 cases observed after July 1976 other tests were added: full-chest tomograms, total-body scans and lymphangiograms. This last examination was performed only in 29 cases of primary lesions located in the pelvis or lower limbs. In addition to these tests, the last 30 patients had a CT scan of the primary lesion.

Of the 153 patients, 29 showed one or more metastases. Metastases were detected by chest X-rays (18 cases), full-chest tomograms (two cases), total-body scans (five cases), lymphangiograms (four cases) and radiographs of other bones from clinical indication (six cases). No metastases were detected by bone marrow examination. These 29 metastatic cases were excluded from the study. The pertinent clinical data of the 124 patients with localized Ewing's tumor who entered the study are reported in Fig. 1 and Table 2.

*Table 1. Cases of malignant round-cell tumor observed between April 1972 and September 1981 at IOR Bone Tumor Center*

| | Classic Ewing's tumor | | Atypical Ewing's tumor | | Primary non-Hodgkin's lymphoma of bone |
|---|---|---|---|---|---|
| | Local. | Metast. | Local. | Metast. | |
| 1972-1978 | 80 | 16 | 4 | 2 | 15 |
| 1979-1981 | 44 | 13 | 1 | - | 6 |
| Total | 124 | 29 | 5 | 2 | 21 |

*Table 2. Patient characteristics*

| | Protocol 1 (80 cases) | Protocol 2 (44 cases) | Total (124 cases) |
|---|---|---|---|
| Age | 4-43 ($\bar{x}=16$) | 1.5-50 ($\bar{x}=16$) | 1.5-50 ($\bar{x}=16$) |
| Sex | | | |
| Male | 45 (56%) | 29 (66%) | 74 (60%) |
| Female | 35 (44%) | 15 (34%) | 50 (40%) |
| Site | | | |
| Pelvis and sacrum | 19 (24%) | 7 (16%) | 26 (21%) |
| Extremities | 48 (60%) | 27 (61%) | 75 (60%) |
| Other sites | 13 (16%) | 10 (23%) | 23 (19%) |
| Local treatment | | | |
| Surgery alone | 4 ( 5%) | 5 (11%) | 9 ( 7%) |
| Surgery plus RXT* | 28 (35%) | 19 (43%) | 47 (38%) |
| RXT alone | 48 (60%) | 20 (46%) | 68 (55%) |
| Local extension | | | |
| Intra-osseous | 14 (18%) | 7 (16%) | 21 (17%) |
| Extra-osseous | 66 (82%) | 37 (84%) | 103 (83%) |

*RXT = radiation therapy.

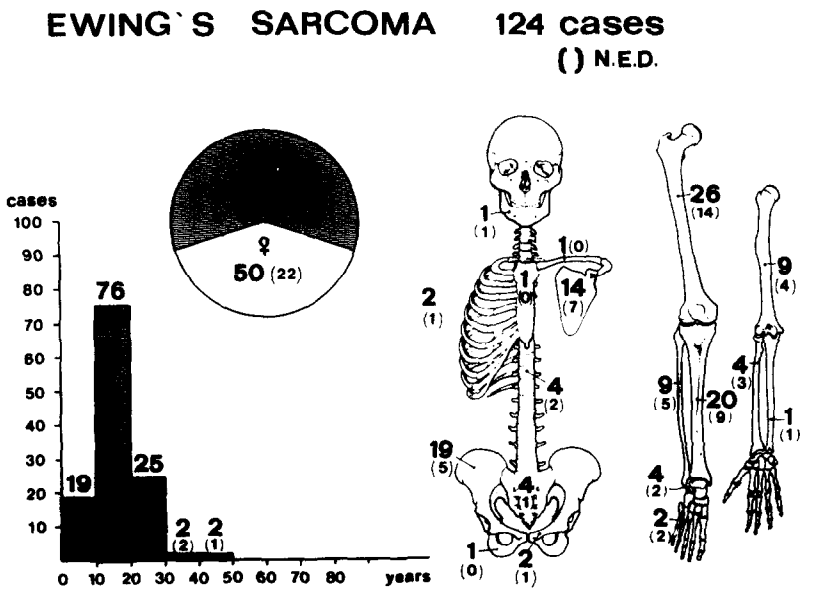


*Fig. 1. Age, sex and site of primary lesion. The number of disease-free patients is given in parentheses.*

Clinical examinations, to detect progression of disease or delayed complications of therapy, were performed every 3 months and subsequently every 6 months. These examinations included radiographs of the primary skeletal lesion and of the chest, lab. tests and ECG. Other tests or biopsies to rule out metastases or local recurrences (LR) were performed only according to clinical indications.

The treatment efficacy was evaluated by the percentage of patients continuously disease-free and the duration of the disease-free interval in cases of relapse. The patients' survival has also been evaluated but the relative figures are to be considered with caution. In fact, after a patient's relapse with metastatic disease no homogeneous treatment could be performed because several patients moved to other institutions, where they were treated with different protocols. We therefore know the date of death of these patients but not the treatment applied in the interval between the appearance of metastases and death.

*Radiation therapy*

Radiation therapy was used alone in 68 cases and associated to surgery in another 47 patients. The total dose delivered varied between 3500 and 6000 rad according to the site and volume of the tumor, the possible previous surgery, the patient's age and the presence of severe soft tissue reactions. Radiation therapy was started approximately 7 days after biopsy. In the case of conservative surgery it was delayed 15-21 days.

*Surgery*

Amputation was performed in nine cases. This decision was due to the large extension of the tumor (three cases) or to the age and location (young children with a tumor in the distal lower extremity, six cases). In the latter cases radiation therapy would have probably caused a functional deficit greater than amputation.

Conservative surgery was carried out in 47 patients. The indication was based on the following main factors: (a) resectability of the tumor, even if with a marginal margin; (b) location in an expendable bone, that is, a skeletal segment where resection does not imply severe functional impairment and/or does not need an substitutive reconstruction (i.e. scapula, rib, fibula, part of the pelvis); and (c) location in a skeletal articular segment where resection can be repaired with an endoprosthesis.

Of these 47 patients treated by conservative surgery, the surgical margins, according to the Surgical Staging System of Enneking *et al.* [15], were considered wide in ten, marginal in 11 and intralesional in 26.

*Adjuvant chemotherapy*

Adjuvant chemotherapy (AC) was given according to two different protocols activated in different periods.

The first protocol was used in the 80 patients treated between 1972 and 1978. It consisted of a three-drug regimen (vincristine, adriamycin and cyclophosphamide) delivered in 24 months, as shown in Fig. 2. In this protocol chemotherapy was started together with radiation therapy or given 4-8 days after ablative surgery.

In the 44 cases treated between 1979 and 1981 we used a second protocol. Four drugs (the same as the first protocol plus actinomycin D) were delivered over a period of 18 months, as shown in the table in Fig. 3.

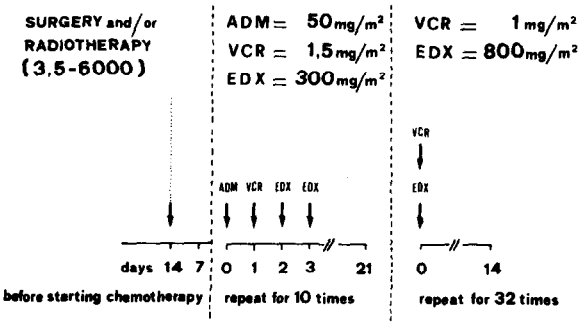


*Fig. 2. Adjuvant chemotherapy protocol employed between 1972 and 1978.*

With the first protocol we observed a poor prognosis in patients with pelvic lesions; thus, in the second study those patients were treated by a 9-week course of high intermittent chemotherapy followed by surgery when feasible, as illustrated in Fig. 4. After surgery, or if surgery was not attempted, the patients received radiation therapy (4500-5500 rads) on the area of the primary lesion in addition to intermittent chemotherapy following the regimen used for extrapelvic site. If surgery was performed, radiation therapy and chemotherapy were delayed for 3-4 weeks.

## RESULTS

All 124 patients completed the planned chemotherapy program with the exception of 38 patients who relapsed during the adjuvant treatment

As of September 1983, the follow-up range from 24 to 140 ($\bar{x}=65$). Seventy-one of these patients (61%) were followed for more than 5 yr and 92 (74%) for more than 4 yr.

*Disease-free survival*

Of the 124 patients (48%) 60 are continuously disease-free 24-124 months ($\bar{x}=66$ months) from the beginning of treatment. Sixty-three patients (51%) relapsed, 38 with metastatic disease, three with local recurrence (LR) and 22 with both (Table 3).

Lesions arising in the pelvic bones presented a

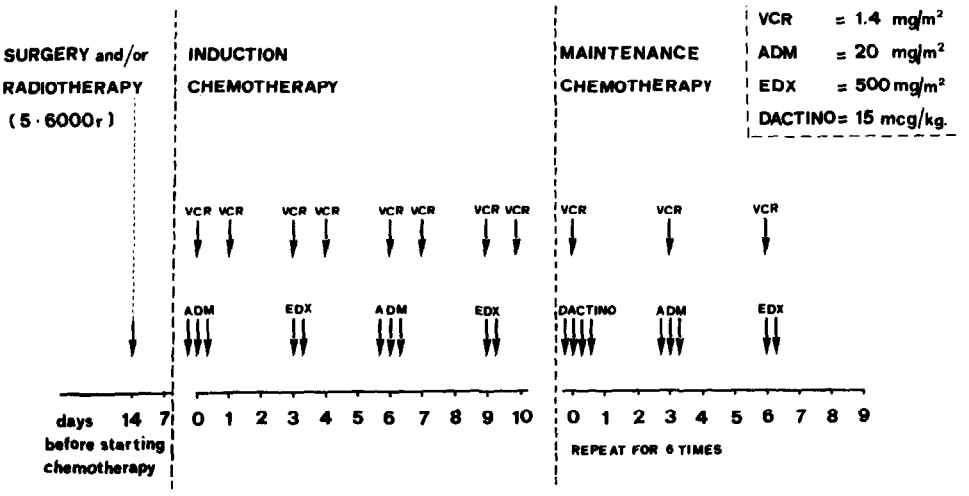


*Fig. 3. Adjuvant chemotherapy protocol for non-pelvic lesions employed from 1979.*

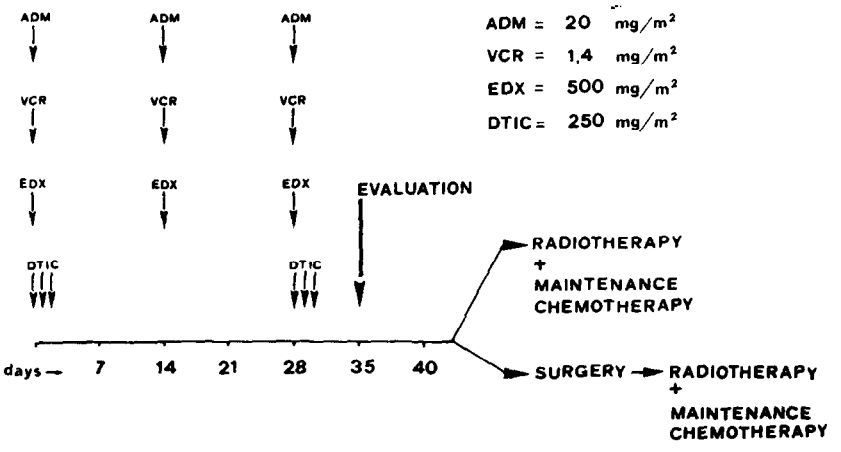


*Fig. 4. Adjuvant chemotherapy protocol for pelvic lesions employed from 1979.*

*Table 3. Overall results*

| | Protocol 1 (80 cases) | Protocol 2 (44 cases) | Total (124 cases) |
|---|---|---|---|
| Follow-up (months) | 54-140 ($\bar{x}=81$) | 24-57 ($n=37$) | 24-140 ($\bar{x}=65$) |
| Disease-free patients | 29 (36%) | 31 (70%) | 60 (48%) |
| Metastases* | 48 (60%) | 12 (27%) | 60 (48%) |
| Local recurrences* | 20 (25%) | 5 (11%) | 25 (17%) |
| Deaths† | 47 (59%) | 12 (27%) | 59 (41%) |

*22 patients presented both metastases and local recurrence.
†Including the patient who died of leukemia.

*Table 4. Patients continuously disease-free in terms of site and treatment of the primary lesion*

| | Surgery alone | Surgery plus RXT | RXT alone | Total |
|---|---|---|---|---|
| Sacrum and pelvis | - | 4/12 (33%) | 3/14 (21%) | 7/26 (27%) |
| Extremities | 6/9 (67%) | 18/23 (78%) | 18/43* (44%) | 42/75* (56%) |
| Other sites | - | 10/12 (83%) | 1/11 ( 9%) | 11/23 (48%) |
| Total | 6/9 (67%) | 32/47 (68%) | 22/68 (31%) | 60/124 (48%) |

*Including the two patients who developed an irradiation-induced sarcoma, considering them disease-free for Ewing's tumor.

*Table 5. Patients continuously disease-free in terms of irradiation dose*

| | RXT alone | | Surgery plus RXT | |
|---|---|---|---|---|
| | NED | F-U | NED | F-U |
| 3500-4000 rads | 2/8 (25%) | 90 (48-140) | 7/12 (58%) | 74 (36-134) |
| 4500-5000 rads | 9/29 (31%) | 80 (36-140) | 24/33 (72%) | 56 (30-134) |
| 5500-6000 rads | 11/31 (35%) | 54 (24-78) | 1/2 (50%) | 36-44 |
| Total | 22/68 (32%) | 67 (24-140) | 32/47 (68%) | 60 (30-134) |

worse prognosis than lesions arising in other anatomic sites (Fig. 5). Relapse occurred significantly sooner for those patients with pelvic tumors ($\bar{x}=12$ months). No differences were observed in the time to relapse for the other two groups: 'extremities' ($\bar{x}=23$ months) and 'other sites' ($\bar{x}=22$ months).

In terms of local treatment modalities, the percentage of patients continuously disease-free seems to be higher when the primary lesion was treated by surgery plus radiation therapy (68%, 32/47) than when radiation therapy alone was used (31%, 22/68) (Table 4, Fig. 6).

No definite correlation seems to exist between the percentage of disease-free patients and the doses of radiation therapy used for the treatment of the initial lesion (Table 5).

One patient was not evaluable because he died of an acute lymphoblastic leukemia which appeared 13 months after the beginning of treatment. Two patients whom we considered disease-free for Ewing's tumor developed a secondary bone tumor detected 7 and 8 yr respectively after the beginning of therapy. Both of these patients were locally treated by radiation therapy (4600 and 6500 rads) and had had

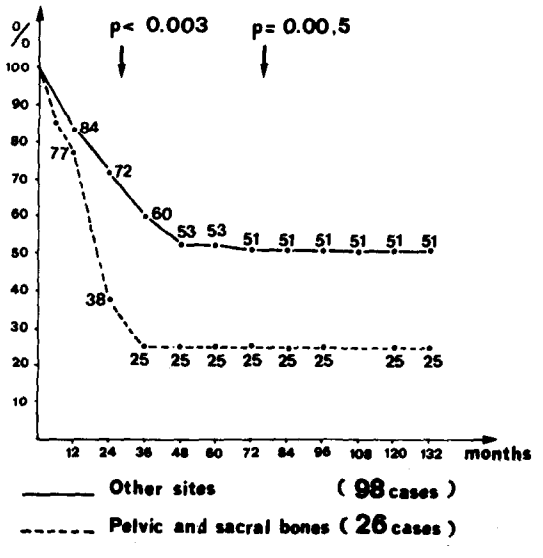


*Fig. 5. Disease-free survival curves for prognosis by site (Cutler and Ederer method).*

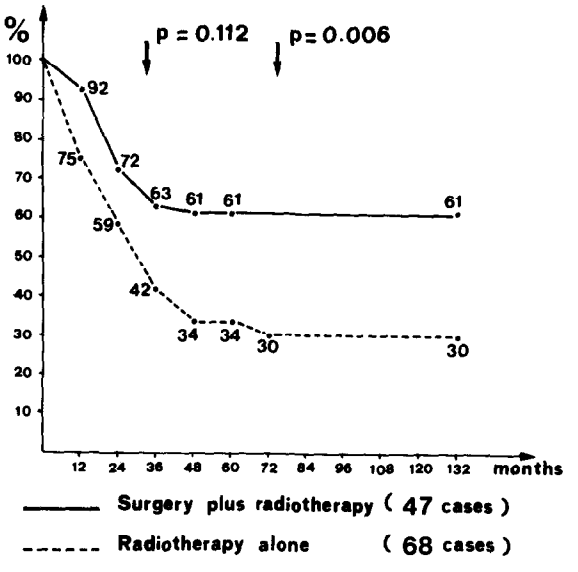


*Fig. 6. Disease-free survival curves for prognosis by type of local treatment (Cutler and Ederer method).*

adjuvant chemotherapy according to the first protocol. The second tumor, respectively a malignant fibrous histiocytoma and an osteosarcoma, in both cases arose in the field of irradiation. These two patients are both disease-free 14 and 10 months respectively after wide surgery was performed for the second tumor.

In terms of adjuvant chemotherapy the first protocol (three-drug regimen for 24 months) does not seem to be as effective as the second protocol (four-drug regimen for 18 months). This appearance is not completely due to the longer follow-up of the patients in the first group; this trend is confirmed by comparing the groups at the same follow-up of 2 yr (Table 6, Fig. 7). This may not be significant because the two groups taken into consideration were not exactly superimposable for the number of cases located in the pelvis and for the number of patients treated with radiation therapy alone (Table 2).

*Local recurrence (LR)*

Local recurrence (Table 7) occurred in 25 (20%) cases, from 4 to 57 months after the onset of therapy ($\bar{x}=20$ months). In four cases LR appeared after 48 months or more from the beginning of therapy. In three of these patients LR was detected only by clinical and radiographic examination, thus we can not exclude the possibility of a post-irradiation sarcoma.

In 22 patients metastases were associated with an LR. In five of these cases metastases developed 3–12 months before the local recurrence became evident. For these five patients it was impossible to discover whether the tumor was a true LR or represented a 'reseeding' from a systemic source. Three patients had LR without apparent metastases. One of these patients died from local invasion of the pelvis and subsequent renal failure. The other two patients are disease-free 1 and 6 yr respectively after a wide surgical resection with prosthetic replacement of the proximal humerus in one case and of the proximal femur in the other. In both of these patients Ewing's tumor was initially treated only with radiation therapy and the LR appeared after 42 and 38 months respectively.

The incidence of LR seemed to be related to the primary location, with a higher incidence in the pelvis (Table 7). In this site surgery does not seem to modify the high rate of LR (43% with radiation therapy alone vs 33% adding surgery).

In those patients with Ewing's tumor located in

*Table 6. Comparison between the two protocols at 2 yr follow-up*

| | Protocol 1 | Protocol 2 | Total |
|---|---|---|---|
| Sacrum and pelvis | 7/19 (37%) | 4/7 (57%) | 11/26 (42%) |
| Extremities | 28/48 (58%) | 24/27 (89%) | 52/75 (69%) |
| Other sites | 6/13 (46%) | 8/10 (80%) | 14/23 (61%) |
| Total | 41/80 (51%) | 36/44 (82%) | 77/124 (62%) |

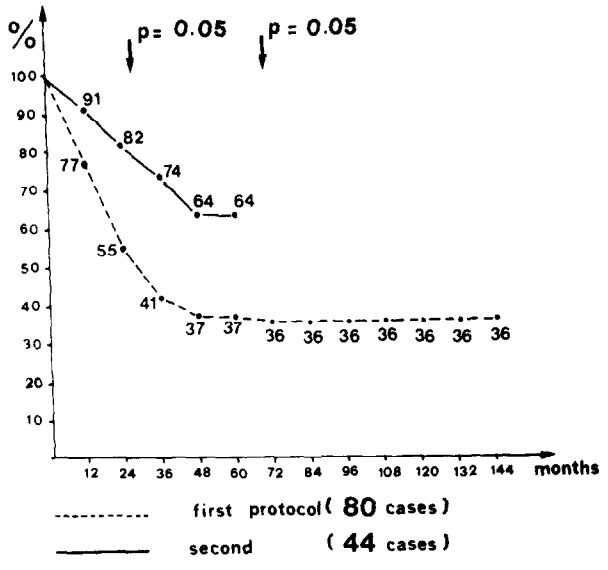


*Fig. 7. Disease-free survival curves for prognosis by type of adjuvant chemotherapy (Cutler and Ederer method).*

the extremities or in the 'other bones' (or axial skeleton) we did not observe any local recurrence when the tumor was locally treated by surgery plus radiation therapy. The incidence of LR in the extremities was 30% and in other sites 18% when the treatment received was radiation therapy alone (Table 7).

If we consider the cases treated by radiation therapy alone, there is no strict correlation between radiation dose and local control or between radiation dose and median time to local recurrence (Table 8).

*Metastases*

Sixty patients (48%) developed metastases 2-64 months ($\bar{x} = 19$) after the beginning of treatment. In 36 patients the metastases appeared during the adjuvant treatment; in the remaining 24 patients the metastases appeared 3-40 months after the end of chemotherapy. The initial metastatic sites were lungs (28 cases), bones (27), skin (two) and multiple sites (one). In the remaining two patients, the first sign of generalized disease was early spinal cord compression due to epidural tumor growth, with no radiological evidence of metastatic vertebral involvement. This symptom appeared after 2 and 4 months respectively from the beginning of treatment. The incidence of metastases was 46% (22/47) for those patients whose initial lesion was treated by surgery and 66% (45/68) for the patients treated by radiation therapy alone.

No correlation was found between the site of metastases and site of the initial lesions, local treatment and adjuvant chemotherapy protocol. No patient with metastases was rendered disease-free for a long period. Fifty-seven of these patients died 4-61 months after the beginning of therapy ($\bar{x} = 29$ months); the other three patients are alive with uncontrolled disease 42, 54 and 58 months after the onset of treatment.

*Toxicity and systemic complications*

Toxicity with both protocols was minimal. It included non-life-threatening leukopenia, neurotoxicity and enhanced cutaneous reactions with dactinomycin.

*Table 7. Local recurrences in terms of initial lesion site and local treatment*

| | Surgery alone | Surgery plus RXT | RXT alone | Total |
|---|---|---|---|---|
| Sacrum and pelvis | - | 4/12 (33%) | 6/14 (43%) | 10/26 (38%) |
| Extremities | 0/9 | 0/23 | 13/43 (30%) | 13/75 (18%) |
| Other sites | - | 0/12 | 2/11 (18%) | 2/23 ( 9%) |
| Total | 0/9 | 4/47 ( 9%) | 21/68 (31%) | 25/124 (20%) |

*Table 8. Local recurrences in terms of irradiation dose in those patients locally treated by radiation therapy alone*

| | Total local recurrences | Median months to local recurrence |
|---|---|---|
| 3000-4000 rads | 4/8 (50%) | 18 (4-32) |
| 4500-5000 rads | 10/29 (34%) | 23 (4-48) |
| 5500-6000 rads | 7/31 (22%) | 15 (4-42) |
| Total | 21/68 (31%) | 20 (4-48) |

With the first regimen in only seven patients were some small protocol deviations necessary because of pronounced leukopenia or delayed restoration of the blood counts. With the second protocol vincristine was omitted for some cycles (3/5) because of neurotoxicity in about one-half of the patients at the end of the 'induction' cycles. In only five patients was the programmed chemotherapy reduced because of the toxicity produced by the other three drugs.

The role of AC in the development of leukemia, observed in one of our patients, and of irradiation-induced sarcomas, observed in two other patients, has already been widely discussed and reported [16, 17]. In the first protocol two important infections were also observed: one patient developed Herpes zoster infection at the end of treatment, but subsequently healed spontaneously. Miliary pulmonary tuberculosis developed in another patient after 20 months of chemotherapy. Chemotherapy was thus discontinued and the tuberculosis responded well to the appropriate medications.

There was universal, but reversible, alopecia, transient jaw pain and transient depression or abolition of patellar and calcaneal reflexes. Approximately 80% of the patients had nausea and vomit limited to the days of treatment. No cardiac toxicity, clinical or electrocardiographic, was observed, although the overall dose of adriamycin was 500 mg/m$^2$.

*Local and functional effects*

Among the patients treated with radiation therapy alone two presented severe leg shortening. These patients were treated with 5000 and 6000 rads respectively.

We also observed six pathological fractures, which appeared from 4 to 39 months ($\bar{x} = 18$ months) after radiation therapy. Two of these patients were treated by plaster and the fractures healed in 45 and 60 days respectively; two patients were treated by internal fixation with Kuntschner rods and the fractures healed in 4 and 6 months respectively; because of systemic metastases, the last two patients were treated by orthopedic devices and without weight-bearing. Minor local complications were slight edema and induration in the irradiated limb (three cases) and inflammation at the biopsy site (three cases). Amongst the patients treated by local resection plus radiation therapy the major local complications were one paresis of the popliteal nerve, now in regression, and two severe wound infections.

## DISCUSSION

Out data, based on a large and homogeneous case load from a single institution, confirm that adjuvant chemotherapy is effective in localized Ewing's tumor, increasing the length of disease-free survival and, probably, the cure rate.

The overall disease-free survival observed in our study (46%) is less than that observed in other studies of adjuvant chemotherapy for this tumor [3-5, 8, 9, 14]. We cannot establish if this difference is due to our chemotherapy protocol or to the fact that our follow-up ($\bar{x} = 65$ months) is longer than that of other series.

Three factors seem to have influenced the prognosis in our study: (1) the initial location of the tumor; (2) the treatment of the initial lesion; and (3) the chemotherapy protocol used.

(1) *Initial location of the tumor*

Previous reported studies [4, 6, 8, 9, 13] concerning adjuvant chemotherapy in Ewing's tumor have confirmed that lesions arising in the pelvic bones have a worse prognosis than lesions arising in other sites. Our data also confirmed this observation. In fact, in our study 73% (19/26) of the patients with pelvic and sacral lesions relapsed, compared to 48% (47/98) of the patients with primary lesions elsewhere (Table 4, Fig. 5).

The poor prognosis for these lesions does not seem to vary significantly with a more aggressive local treatment (adding surgery to radiation therapy) (Table 4) or with a more aggressive chemotherapy protocol (adding actinomycin-D) (Table 6). Moreover, in seven cases we gave aggressive chemotherapy prior to any other local treatment, and this too did not seem to improve prognosis.

(2) *Treatment of the initial lesion*

In extrapelvic sites the multimodal approach has significantly improved the disease-free status and the survival. In fact, in our study the patients treated by surgery plus radiation therapy had a better disese-free survival percentage than those treated by radiation therapy alone.

Radiation therapy has been considered for years the best treatment for Ewing's tumor. Although most patients showed a striking volumetric reduction of their lesion, in the past they died of widespread dissemination. These early deaths did not allow a good evaluation of the effects of the radiation therapy.

The use of AC sufficiently increased the number of long-term survivors, thus showing several limits of the radiation therapy: a high percentage of late local recurrence, severe functional deficit and the development of irradiation induced sarcomas.

Although some studies [2, 3, 18, 19] have indicated that adding AC to radiation therapy significantly increases the local control of

Ewing's tumor, in our experience this is not confirmed. In fact, the incidence of local recurrence is again greater than 30% for the patients locally treated by radiation therapy alone but decreases to 9% when surgery is added or is preferred to radiation therapy for local treatment. We do not believe that this disturbingly high incidence of LR is entirely due to the lower doses of irradiation used in our patients compared to those used in other institutions. In fact, Rosen *et al.* [9, 13], with more aggressive radiation therapy (6000-7000 rad) and simultaneous chemotherapy, reported in 34 cases a similar local recurrence rate. On the other hand, in the large series of the IESS at short follow-up ($\bar{x} = 30$ months) the percentage of LR after radiation therapy was about 15% [20]. The incidence of LR tends to increase with a longer follow-up (20% of our local recurrence appeared after 30 months), thus this percentage will probably increase.

In Ewing's tumor the problem of LR is crucial. In our experience it is a very ominous sign; almost always an LR is associated with or followed by the appearance of distant metastases. Also, in the IESS study the appearance of LR had the same unfavorable prognosis, and was related to the development of metastatic disease [21].

In our study it appeared that resection, whether wide or marginal, followed by radiation therapy seemed more effective than radiation therapy alone, not only in reducing the percentage of LR but also in preventing metastatic disease. This trend has also been reported in other series [3, 9, 13]. It is possible that incomplete eradication of the primary tumor with radiation therapy could be responsible in some patients for metastatic seeding in distant sites before or without the clinical evidence of local recurrence. The possibility that residual tumor cells continue to exist after radiation therapy without any clinical or radiographic signs of LR was demonstrated by Telles *et al.* [22]. These authors, in an autopsy study of Ewing's sarcoma treated by multimodal therapy, found microscopic evidence of residual tumor at the irradiated primary site in 13 of the 20 cases in which the site was examined. In these cases there was no clinical nor radiological evidence of tumor persistence or reactivation.

In recent years many authors [2, 4, 8, 9, 13, 14] have also observed irradiation-induced sarcomas after radiation therapy was delivered in association with adjuvant chemotherapy to patients with localized Ewing's tumor. In our study we observed two cases of sarcoma developed within the field of irradiation. The exact incidence of this complication as well as the role of chemotherapy in determining it is not known. However, if we consider that many years are necessary for the development of irradiation-induced sarcomas, we have reason to believe that with the increased survival rate other cases of irradiation-induced sarcomas are to be expected.

Finally, the use of high-dose radiation therapy plus chemotherapy for Ewing's tumor of the lower extremities is often complicated by severe morbidity and may produce a functional deficit sometimes greater than amputation. The incidence of these complications in our study was less than that of other studies [10, 23-25]. This was probably due to the less aggressive radiation therapy used and because in our series local treatment for Ewing's tumor of the lower limb in young children was generally amputation.

From these considerations it derives that in planning future therapeutic trials for localized Ewing's sarcoma the local management of the primary site is a major problem. We believe that because of the questionable effectiveness of radiation therapy in controlling the primary lesion, its undesirable side effects and its complications, the role of surgery in conjunction with AC for treatment of the disease should be reconsidered.

Generally, the surgery proposed for Ewing's tumor is either ablation of the involved limb in a few selected cases (a large lesion with an irreparable pathologic fracture; lesions in the distal lower extremity in young children) or, more often, complete resection of the entire tumor with the surrounding normal tissue. Ewing's tumor, though, is rarely confined to the bone when diagnosis is made. In our series soft tissue extension was present in over 80% of the cases. Uncontaminated wide or radical resection is therefore difficult and not often possible. In our study, and also in the experience of other groups [3, 9, 13, 14, 26], even incomplete resection (marginal or intralesional) followed by radiation therapy seemed to produce a favorable influence on prognosis and to be more effective than radiation therapy alone in preventing both local recurrence and metastatic disease. It is possible that the removal of the tumor core makes subsequent radiation therapy more effective.

We also believe that because of cellular kinetics, debulking makes chemotherapy more effective locally. Although our study is not a randomized trial (between surgery and radiation therapy vs radiation therapy alone) and we cannot exclude with certainty that patients treated with resections had been unintentionally selected, our results suggest expanding the role of surgery in this tumor even when the tumor cannot be completely and clearly excised.

(3) *The chemotherapy protocol used*

The patients who received the four-drug

regimen (VCR, ADM, EDX, DACT) had a significantly better disease-free percentage than those receiving the three-drug regimen (VCR, ADM, EDX). The two groups of patients, although treated in different periods, were essentially superimposable for age, serum LDH value at presentation, tumor site and type of local treatment. This fact confirms the results reported by the IESS [8], where another three-drug protocol (VCR, EDX, DACT) gave worse results than a four-drug protocol including the same drugs we employed in our four-drug protocol.

It remains to be evaluated whether chemotherapy should be given also prior to the local treatment as performed recently in some institutions [13, 14].

In spite of the fact that in our experience in the pelvis area this new procedure has not had good results, we feel that for other sites pre-operative chemotherapy could give certain advantages. The often dramatic reduction of the tumor size and the induration of the tumor by chemotherapy could permit or facilitate a wide uncontaminated resection of the involved bone. Moreover, chemotherapy given prior to local treatment could allow for lower doses of irradiation, consequently minimizing the incidence of functional deficit and the risk of 'secondary malignant neoplasm'.

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