# ADJUVANT CHEMOTHERAPY FOR OSTEOSARCOMA AT THE SINGAPORE GENERAL HOSPITAL

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## SYNOPSIS

**The management of patients with osteosarcoma in Singapore has for many years been an unrewarding task for the attending physicians.**

**Encouraged by reports of long-term survivals with adjuvant cytotoxic chemotherapy appearing in 1975, orthopaedic surgeons and radiation therapists at the Singapore General Hospital undertook a program of chemotherapy in moderate doses for osteosarcoma patients with localised disease treated by ablative surgery. A few who refused surgery had irradiation of the primary tumour.**

**The first 25 consecutive cases given this treatment are reported on. Three of these were subsequently excluded. Five of the remaining 22 cases failed to complete the chemotherapy. Four patients refused ablative surgery as primary treatment and had instead high-dose irradiation to the primary. 14 of the 22 cases (63.6%) were alive when last seen at periods ranging from 7 months to 72+ months post-diagnosis.**

**8 patients were known to have died from disease between 5 months and 41 months post diagnosis.**

**The actuarial survival rates at 5 years were 60.3% for the 17 patients adhering to the adjuvant chemotherapy regime and 54% for all 22 cases.**

**The survival curves show a flattening from the 4th year after diagnosis and justify optimism that a number of long term survivals may be cured.**

## INTRODUCTION

It had been the clinical impression of surgeons and radiotherapists that the results of treatment for osteosarcoma in Singapore were dismal — well below the average 5 year survival rate of about 18% in series reported in Europe and North America (1, 2, 3, 4, 5, 6). This was confirmed by a retrospective study of osteosarcoma patients diagnosed between January 1972 and October 1975 and treated by surgery, radiotherapy or a combination of both. Only one of the twenty-three patients survived 5 years and this was a patient with Paget's sarcoma of the calvarium (7). Excluding this extraordinary case, all patients had died before the fifth anniversary of diagnosis and only two of the remaining 22 cases (9.1%) survived beyond 2 years.

When reports of improved survival with adjuvant chemotherapy appeared in 1974-75 (8, 9, 10), it was decided to add adjuvant chemotherapy after ablative surgery (or high-dose irradiation for these who refused surgery) for patients with clinically localised osteosarcoma. As the results of "classical" therapy were so poor, it was considered unethical to withhold adjuvant chemotherapy from any suitable patient which a controlled trial would demand.

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TABLE 1

**ADJUVANT CHEMOTHERAPY FOR OSTEOSARCOMA PATIENTS BY AGE & SEX**

| Age in Years | Males | Females | Total |
|---|---|---|---|
| 6 | — | 1 | 1 |
| 10 | 1 | 1 | 2 |
| 11 | 1 | — | 1 |
| 13 | 2 | 1 | 3 |
| 15 | — | 1 | 1 |
| 16 | — | 1 | 1 |
| 17 | 3 | — | 3 |
| 18 | 1 | 2 | 3 |
| 19 | 1 | 2 | 3 |
| 20 | 1 | 1 | 2 |
| 21 | 1 | — | 1 |
| 23 | — | 1 | 1 |
| All Ages | 11 | 11 | 22 |

**M: F Ratio = 1 : 1**
**Mean Age = 16 years**
**Median Age = 17 years**

TABLE 2

**ADJUVANT CHEMOTHERAPY FOR OSTEOSARCOMA SITE OF PRIMARY TUMOUR**

| | Right | Left | Total |
|---|---|---|---|
| Lower Femur | 9 | 5 | 14 |
| Upper Tibia | 2 | 2 | 4 |
| Upper Fibula | 1 | 1 | 2 |
| Upper Humerus | — | 1 | 1 |
| Other Sites | — | 1 | 1 |
| All Sites | 12 | 10 | 22 |

## MATERIAL AND METHODS

A report of the first 20 consecutive patients with osteosarcoma given adjuvant chemotherapy at the Department of Therapeutic Radiology, Singapore General Hospital, has been published (11). The present report includes an additional five patients, bringing the total to 25. They were diagnosed between November 1975 and September 1980 and the results analysed at June 1982. All cases had histologically confirmed diagnosis. Three were excluded from further analysis — one because of divided opinion on the histology (osteosarcoma or reticulum cell sarcoma), the second had a parosteal sarcoma and the third patient had lung metastases at presentation on review of her chest x-ray films.

Tables 1 and 2 show the analysis of patients by age, sex and site of primary tumour, all of which are unremarkable and in keeping with other series.

### Chemotherapy

Adjuvant cytotoxic chemotherapy was given post-operatively. Electro-cardiogram was ordered before commencing therapy and full blood counts done before each injection. Follow up chest films were done at average intervals of three months for the first three years and six monthly to five years post diagnosis.

Details of the quadruple combination therapy used appear in the earlier report. Briefly, 4 drugs (Vincristine 1.0mg/M², Methotrexate 20mg/M², Cyclophosphamide 300mg/M² and Adriamycin 40mg/M²) were cycled over a 2 week period, 6 cycles being given with resting intervals of 2-3 weeks, 4 further cycles at intervals of 3 months and the final 2 cycles at 6 monthly intervals. The total of 12 cycles were thus adminstered over a period of about 2 years 8 months. Only one patient required admission for the chemotherapy for the first six cycles, receiving the subsequent treatment as an outpatient. Five patients failed to complete chemotherapy. Temporary alopecia, nausea and vomiting up to 48 hours after cytotoxic injections were experienced by almost all patients. Nausea was usually accompanied by a heightened sense of smell, especially to "antiseptic" odours reminiscent of hospitals. Haematological depression was uncommon.

After some four years' experience with the quadruple combination chemotherapy it was clear that a number of patients would not accept prolonged therapy. This, coupled with Cortes' experience (8) showing that the use of Adriamycin as a single agent was as effective as combination chemotherapy, led to an alternative regimen being used from 1980. I/V Adriamycin 60mg/M² used singly, was given every 3 weeks for 8 doses. It is likely that with the much shortened duration of chemotherpay of about five to six months, the compliance rate would be higher.

## RESULTS

Fourteen of the 22 cases (63.6%) were alive when last seen at periods ranging from 7 months ot 72+ months post diagnosis. Twelve of the 22 were disease free (54.5%) and 3 patients have survived beyond 5 years. Figure 1 shows the results of the various therapy "sub-sets". The number of patients in each group are too few for valid comparisons to be made. Four patients refused ablative surgery and were treated by external beam irradiation to the primary lesion and adjuvant chemotherapy. Two of these adhered to the adjuvant cytotoxic regimen and are alive and well at 27 months and 72+ months after diagnosis.

Eight patients died of their disease between 5 months and 41 months from diagnosis. Five had died by the second year and seven by the third completed year. The patient who died at 41 months was the only one of the deaths to have completed adjuvant chemotherapy (at 35 months). Clinical details were available at the time of death for seven fo the eight cases — all seven had pulmonary metastases, two of whom also had stump recurrence of tumour and one had in addition metastases to other long bones. Recrudescence of disease was seen early in the clinical course, six of the eight patients who have died having active disease within 10 months of diagnosis. One patient died at 26 months with no clinical details of death available; one had massive haemorrhagic right pleural effusion at 40 months post diagnosis and died a month later. Late recurrence was seen in one patient at 52 months when a radionuclide bone scan showed multiple skeletal metastases. This patient was still alive with disease at 59 months when he was last seen at follow up. Another patient last seen alive with disease had a pleural effusion at 11 months from diagnosis.

Actuarial survival rates were computed for the patients adhering to the chemotherapy regimen and for all 22 patients in this series (Figs 2 and 3). The 3 year survival rates were 68.9% and 61.7% respectively. The 4 and 5 year rates were similar for each of the groups at 60.3% (compliance group) and 54% (overall).

## DISCUSSION

These results justify optimism that the long-term survivors may be cured of their disease, rather than merely having delayed appearance of recurrences or metastases. The majority (7/11) of failures in tumour control appeared by the eleventh month.

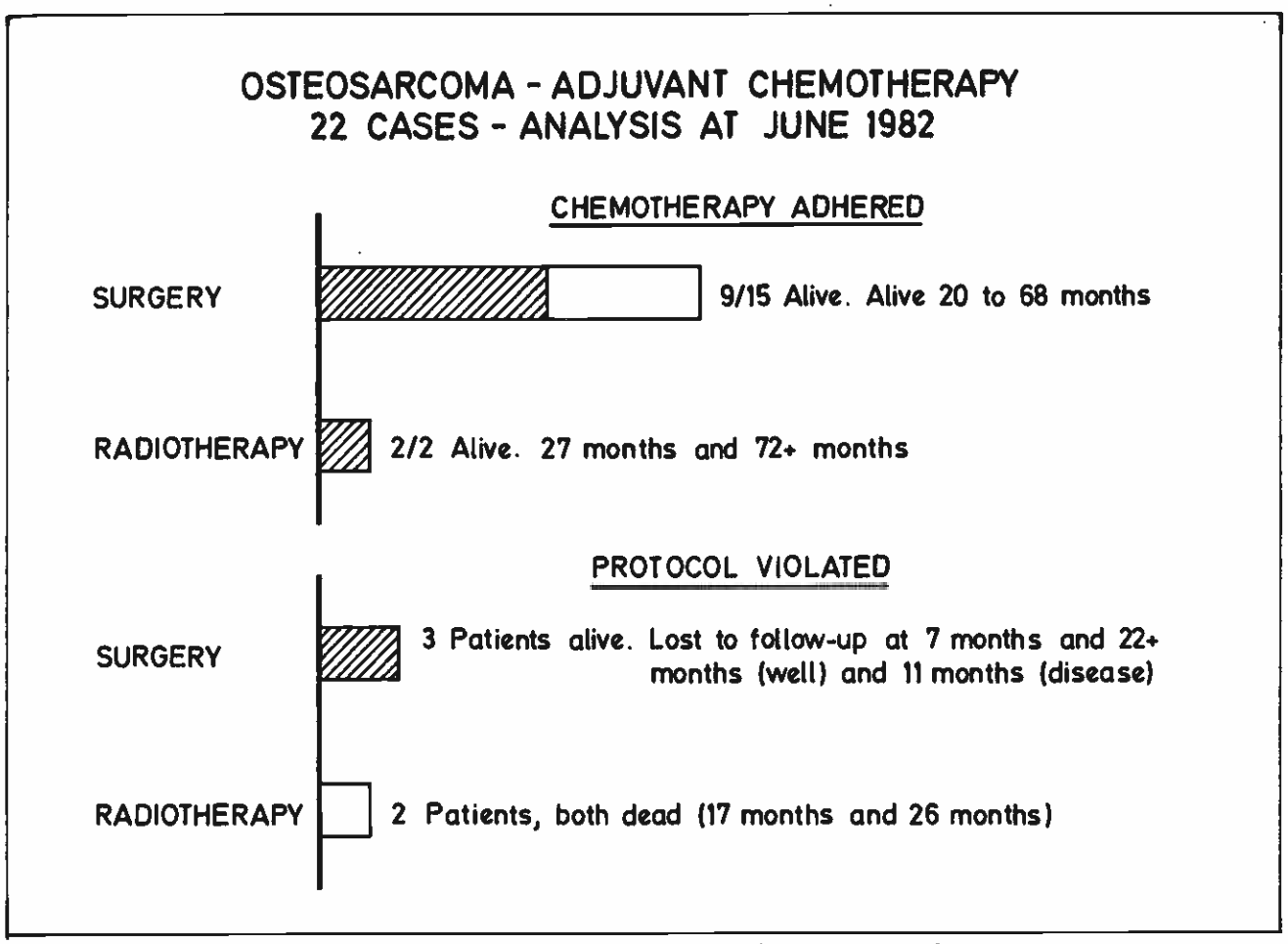



Fig 1 Adjuvant Chemotherapy for Osteosarcoma. Therapy details and results.

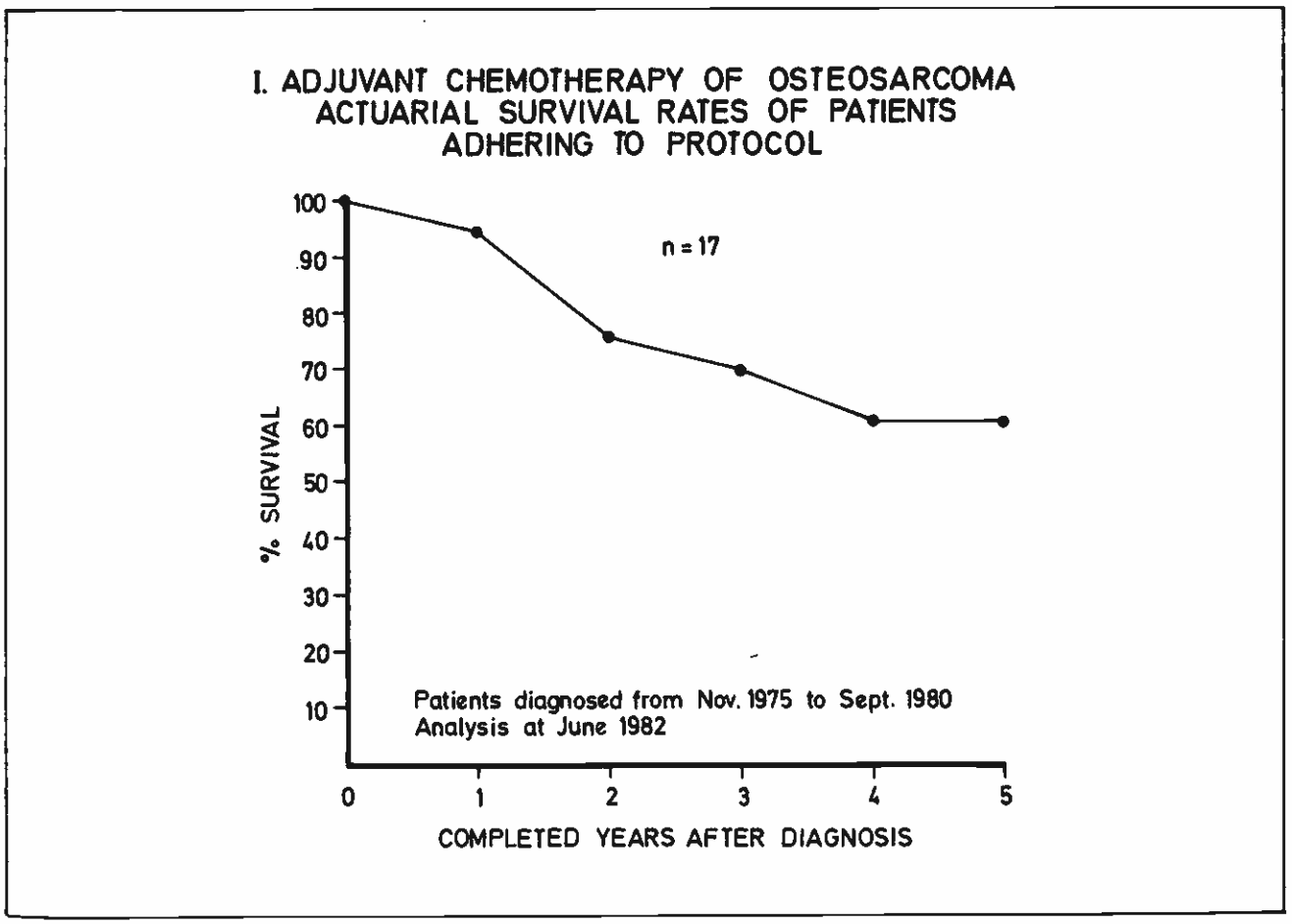
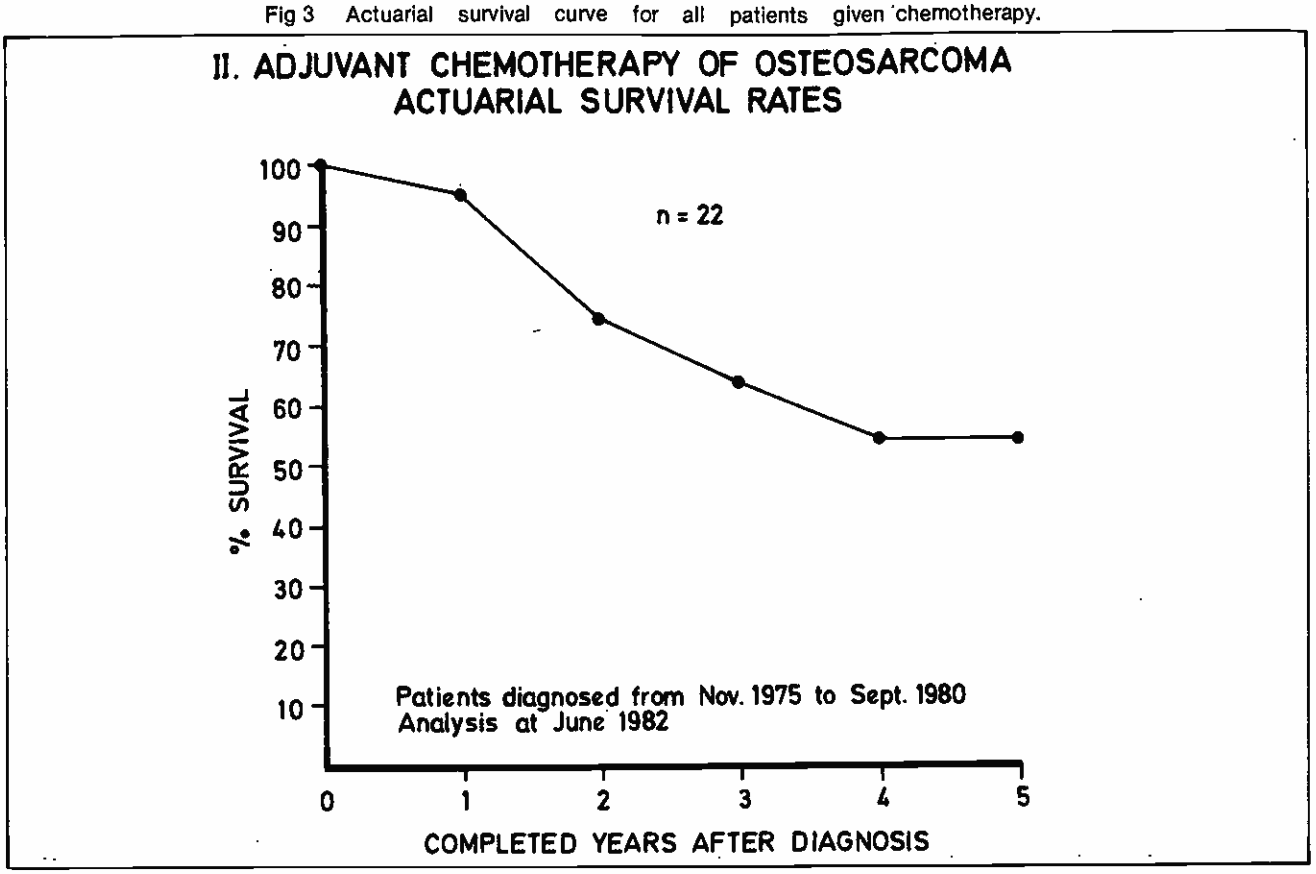



Fig 2 Actuarial survival curve for patients adhering to chemotherapy regimen.

Fig 3 Actuarial survival curve for all patients given chemotherapy.




The improvement in survival when compared with the immediate pre-adjuvant therapy period (historical controls) is remarkable.

While the Mayo Clinic workers (12) have shown a significant improvement in their 3 year survival rates before and after 1972 from surgery alone, few other groups have shown a similar improvement without adjuvant chemotherapy. Bleyer et al (13) suggest that adjuvant therpay might have further improved the survival figures at the Mayo Clinic.

Our results also support the Bologna experience (14) that medium dose adjuvant chemotherapy, given in the main on an outpatient basis with attendant advantages in lower toxicity and costs are as effective as more complex or toxic high-dose regimens. Tatezaki (15) for example, reported on 24 patients treated with pre-operative intra-arterial cytotoxic infusion and fast neutron irradiation followed by post-operative intensive systemic chemotherapy with multiple drugs including adriamycin and high-dose Methotrexate. His results show 13/24 (54.2%) patients alive without disease from 5 to 38 months, no superior to those from Bologna (26 disease-free survivors of 55 patients, 30 to 78 months after operation) nor from this report.

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