Osteosarcoma : A Study of 130 Cases

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Abstract

Multidisciplinary treatment of osteosarcoma in the Faculty of Medicine Ramathibodi Hospital, Mahidol University, using preoperative intraarterial and postoperative chemotherapy, with or without local irradiation, combined with surgery and prophylactic lung irradiation provided an excellent 5 years' survival of 55 per cent, the same rate as the 9 years' survival. The survival was stable after 4.4 years. The patients with local irradiation had more tumor destruction apparent on the surgical specimen. The administration of prophylactic whole lung irradiation provided an outcome without any undesirable complication. Sixteen per cent of the cases with PLI developed lung metastasis compared to 48 per cent without PLI. The most important prognostic factor was low level of serum lactic acid dehydrogenase. The unanswered question is what is the optimal treatment for osteosarcoma?

Osteosarcoma is the most common bone tumor in Thailand[1,2]. The incidence at the National Cancer Institute from 1988 to 1993 was 1.3 cases per million per year[3] and it was 1.01-2.2 per cent of all malignant diseases in Ramathibodi Hospital[4,5] or 39.9 per cent of all bone tumors.

Osteosarcoma is well known as an aggressive disease and is claimed to be a relatively radioresistant tumor. In the early years, surgery played an important role in the treatment of this tumor but the results were rather disappointing. Local recurrence with distant metastasis especially in the lung

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were the important cause of death after surgery. Recently, a multimodality approach by using intra-arterial and systemic chemotherapy combined with radiation and limb salvage procedure has introduced a new era for treating osteosarcoma due to the definite synergism of radiation and chemotherapy. Like other aggressive tumors, the osteosarcoma grows very rapidly, the tumor doubling time is just 34 days[6]. Gross metastases in the lung or even in the bone were present at diagnosis in 10-20 per cent of all patients with osteosarcoma. In previous experience, relapse after treatment occurred mainly in the first year and rarely after the second year. Half of the patients had pulmonary metastasis by the fifth month after operation, and thirty months after amputation, the risk of recurrence and death had considerably diminished. About 90 per cent of relapses occur within the first year. Chemotherapy alone cannot eradicate bulky disease but can effect micrometastasis and delay the lung metastasis. Jaffe et al stated the incidence of pulmonary metastasis in patients who had adjuvant chemotherapy which occurred later and were fewer in number per lung when compared to the previous group. Chemotherapy had increased the survival rate in the non-metastatic group from 20 per cent to 60-80 per cent in the year 1985[6]. Sutow questioned the late metastases after more effective chemotherapy and warned about the premature interpretation of the survival. In his experience the risk of metastasis was 20 per cent between 12-24 months and 5 per cent between 24-36 months among the patients at risk[7].

The purpose of the study was to present the results of a multidisciplinary approach in treating osteosarcoma and establish the value of radiation both for controlling local disease as well as preventing pulmonary metastasis. For statistical consideration, log-rank test and Chi-square were used for comparison. The disease free survival rate was calculated by Kaplan-Meier method.

MATERIAL AND METHOD

From 1986 to 1995, 130 cases of osteosarcoma were enrolled in the prospective study of multidiscisplinary treatment at the Faculty of Medicine, Ramathibodi Hospital, Mahidol University. Seventy three per cent of the cases were referred from other hospitals throughout the country.

There were 72 males and 58 females with the mean age of 17.9±7.23 and a range of 4 to 50

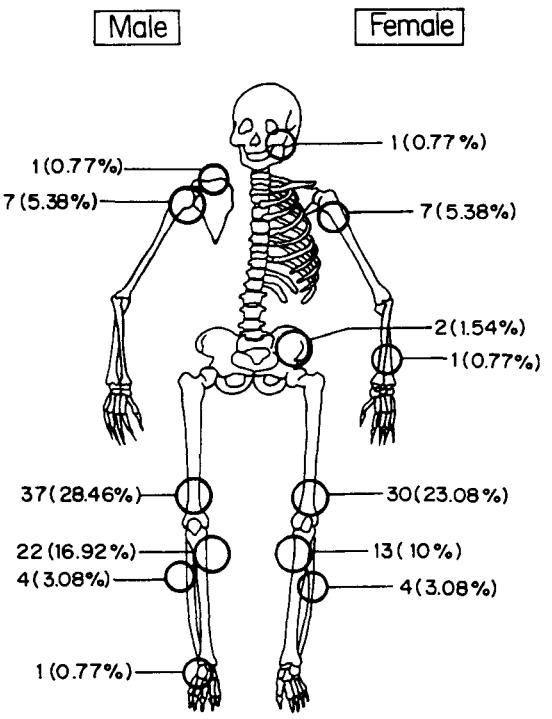

Fig. 1. The skeletal distribution of 130 cases.

years old. The skeletal distribution was found in the following locations : femur (67), tibia (35), humerus (14) and 14 cases at other sites as shown in Fig. 1. The pathological subtype of the disease and the site of bone position are shown in Table 1. About 60 per cent of the patients had the disease diagnosed in the first 3 months ranging from 1-36 months, a mean of 4.21±4.001 months, median 3 months. Only two cases needed medical treatment for 14 and 36 months after the first symptoms. Sixty seven patients had a history of trauma before the disease was detected. Twenty three cases had pathological fracture and 17 cases had developed lung metastasis by the initial diagnosis. The treatment consisted of 2-6 courses of preoperative intra-arterial cisplatin of 100 mg/m^2 body surface on day 1. Intravenous 50 mg/m^2 of doxorubicin on day 2 was administered in 39 cases, 20 mg/m^2 on days 2, 3, 4 of epirubicin in 76 cases and etoposide of 60 mg/m^2 on days 3, 4 in the other 13 cases according to the randomization. Local radiation was given to 51 cases. Surgical treatment included limb

Table 1. Number of patients according to pathological subtype and bone site.

Subtype	Bone site					Total
	Femur	Tibia	Fibula	Upper limb	Other	
Osteoblastic	25	12	5	5	2	49
Chondroblastic	11	4	2	4	1	22
Telangiectatic	8	4	1	3	-	16
Fibroblastic	3	6	-	1	-	10
Mixed form	5	4	-	-	1	10
Other	15	5	-	2	1	23
Total	67	35	8	15	5	130

preservation or amputation in 82 cases. After June 1989, all the cases had prophylactic whole lung irradiation (PLI) of about 2550 cGy, 150 cGy/d in a 6-16 weeks period with the mean of 8.47±1.86 from the Co-60 machine or 6 MV linear accelerator without any lung correction. At the same time as PLI, they had postoperative chemotherapy of the same regimens as the previous treatment for a total of 8 courses (Fig. 2). In these 130 cases, there were 63 cases (48.5%) who finished all the treatment while the other 67 cases (51.5%) were incomplete. Of these 67, 17 had initial lung metastases, 4 refused all treatment and 46 were lost to follow-up before the treatment ended, most of them, 31 were lost after good response of preoperative treatment but refused further amputation.

The mean follow-up time was 78.28 days with SD of 787.96 days, while the median was 463.5 days.

RESULTS

The overall 5 years' survival rate for the whole group was 55 per cent, the same rate as the 9 years' survival (Fig. 3). Among 63 who completed the treatment, 20 died (31.7%) from lung metastasis, compared to the group with incomplete treatment of whom 32/67 (47.8%) died from lung disease, another 3 cases in the complete treatment group died from bone metastasis, 1 had combined lung and bone disease. Three with lung disease had either combination of bone, liver and pericardium, or brain metastasis.

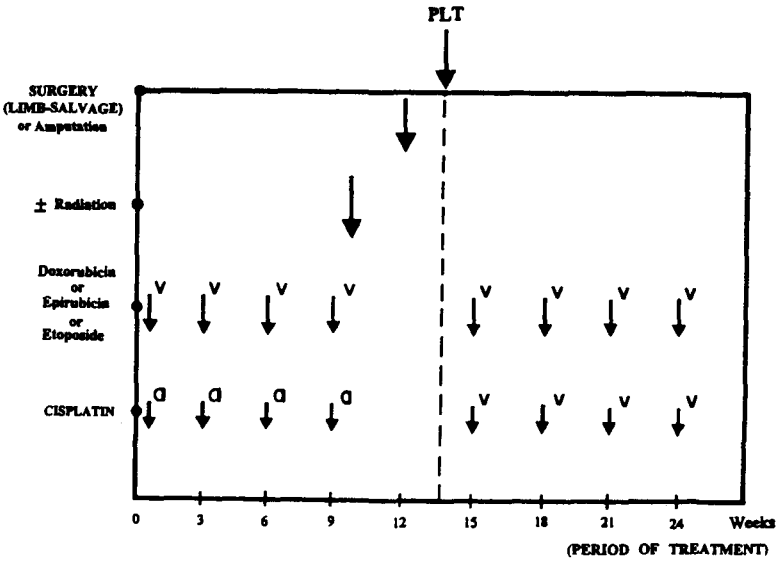

Fig. 2. Schedule of treatment.

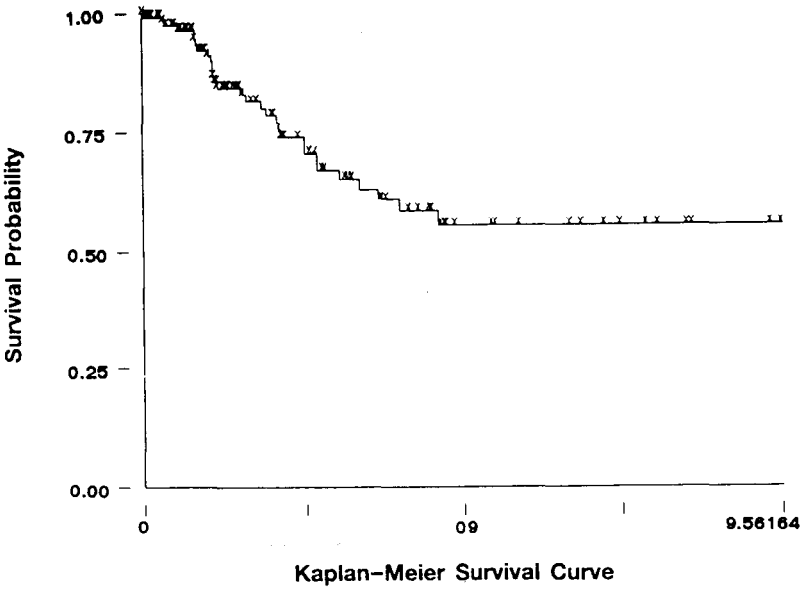

Fig. 3. The survival rate of 130 cases.

Of the 17 patients with initial lung metastasis, 4 had combined treatment, only 2 survived for 86 and 10 months with very good health, two had progressive disease of the nonirradiated lung with stable disease of the radiated site and were still alive after 15 and 7 months. Another 4 had already died with 9 lost to follow-up but were suspected to have died because of moribund state. In the group of 67 with incomplete treatment some returned to the hospital within one year with 2 local recurrences. Thirty two (47.8%) died from lung metastases. Twenty were definitely lost.

The outcome of various chemotherapies in the group of 39 with doxorubicin combined with cisplatin, 8 (20.51%) are still alive and 9 have died (23.08%). While 27 of 76 (35.53%) with epirubicin are still alive and 21 (27.63%) have died. The group with etoposide 7/13 (53.85%) are still alive. The different results of treatment with various types of chemotherapy have a significant outcome with p-value of 0.01.

From the point of view of effectiveness of local irradiation, there were 21 cases out of 29 with 100 per cent tumor necrosis in the local radiated group, while 8 who had no radiation had zero residual tumor in the surgical specimens (p = 0.001). The degree of tumor necrosis is strongly related to the outcome of disease in log-rank test. The survival time in each group of tumor necrosis is shown in Table 2. The patients with local radiation at the primary site had better survival at 9 years (70% *vs* 45% p = 0.01).

Table 2. The relation between residual tumor and survival.

	residual tumor %	5, 9 year survival %	Log-rank test p value
grade I	≥ 50	40	0.009
grade II	$\geq 10 \leq 49.99$	75	
grade III	$\geq 0.99 \leq 9.99$	100	
grade IV	$= 0$	70	

In the first period of the study, from March 1986 to May 1989, 10/49 patients (20.4%) survived, 24 (48.98%) had lung metastases while 3 cases developed bone disease, one brain metastasis, the others maxilla and pelvic osteosarcoma died from disease progression, 9 were lost to follow-up. When prophylactic lung irradiation was started in June 1989, 36 cases with PLI, 6 (16.67%)

developed lung metastases while 79 cases without PLI, 38 (48.10%) had lung disease (p = 0.0014). The 9 years' survival rate in PLI and non patient PLI was 70 per cent *vs* 46 per cent respectively (p = 0.046).

Cases with high dose medroxy-progesterone acetate. Even their leucopenia still occurred during the course of treatment. However, they seem to have had better tolerance with not so much weight loss as well as a better sense of well being. The result of the treatment will be reported separately elsewhere.

DISCUSSION

Neoadjuvant chemotherapy has opened a new era in the treatment of osteosarcoma. The 5 years' survival increased from 20 per cent to 60-80 per cent in the years after 1985[6] chemotherapy combined with local irradiation and prophylactic whole lung irradiation. Munzenrider et al and Neff & Enneking stated that local preoperative irradiation would traumatize the tumor and prevent surgical seeding and also provoke an immune response by the previously sensitized irradiated lesion[8,9]. O'hara et al claimed that radiotherapy may cause devitalization of the osteoblasts measured by the significant decrease in alkaline phosphatase level both in serum and in the tumor after radiation[10]. In this study, we have proved the efficacy of preoperative intraarterial and intravenous[11-16]. The 9 years' survival rate after 8 courses of chemotherapy was 55 per cent. The survival rate reached a plateau after 4.4 years. In cases with local irradiation at the primary site we found better survival, 70 per cent *vs* 45 per cent (p = 0.0129) but we failed to demonstrate the efficacy of local RT to prevent lung metastases, however, in the group with PLI it proved to be effective in prevention of lung metastases. In the group with prophylactic irradiation we had better 9 years' survival 70 per cent *vs* 46 per cent (p = 0.046) and no patient had lung complications. So the PLI of about 2550 cGy may be enough to destroy the micrometastatic lesions in the lung and produce less lung metastasis (16.67% *vs* 48.10%).

The difference between the group of various chemotherapies was statistically significant (p = 0.01). However, this may be questionable because the number in each group was not equal. We changed doxorubicin to epirubicin for the reason of less cardiotoxicity. We have changed again to etoposide, after preliminary evaluation that we still loose some patients after completion of all the regimens by metastatic disease. Etoposide had the history of good response in soft tissue sarcoma and with minimal side effects as well as being less expensive. We continue to randomize the patients into groups of epirubicin and etoposide and look forward to presenting the efficacy of each group in the near future. As regards the prognostic factors of these 130 cases, only minimal levels of serum lactic acid dehydrogenase (under 300 U/L) showed a significantly by better outcome in multivariated analysis (p = 0.01). The various prognostic factors were presented elsewhere.

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การศึกษาในผู้ป่วยออสตีโอซาร์โคมา 130 ราย

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การรักษาโรคออสตีโอซาร์โคมาในคณะแพทยศาสตร์โรงพยาบาลรามาธิบดี ได้ใช้วิธีผสมผสานโดยการให้สารเคมีทางหลอดเลือดแดงก่อนผ่าตัดร่วมกับการสุ่มตัวอย่างเพื่อฉายรังสีบริเวณปฐมภูมิ และมีการฉายรังสีบริเวณปอดทั้ง 2 ข้าง เพื่อป้องกันโรคกระจายมายังปอดหลังผ่าตัด ตามด้วยการให้สารเคมีบำบัดทางหลอดเลือดดำ พบว่ามีอัตราการอยู่รอดที่ 5 ปี และ 9 ปี เท่ากับร้อยละ 55 โดยอัตราการอยู่รอดไม่เปลี่ยนแปลงหลังปีที่ 4.4 ผู้ป่วยที่ได้รับการฉายรังสีในมะเร็งปฐมภูมิมีการทำลายของเซลล์มะเร็งมากกว่าผู้ป่วยที่ไม่ได้รับการฉายรังสีและผู้ป่วยที่ได้รับการฉายรังสีบริเวณปอดจะมีอัตราการลุกลามของโรคไปปอดน้อยกว่ากลุ่มที่ไม่ได้ฉาย การพยากรณ์โรคที่ดี ซึ่งสำคัญที่สุดขึ้นอยู่กับระดับต่ำสุดของ serum lactic acid dehydrogenase ในผู้ป่วยรายนั้น ๆ ปัญหาที่ยังต้องการคำตอบคืออะไรเป็นการรักษาที่พอเหมาะสำหรับผู้ป่วยเหล่านี้

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