Experiences in the treatment of Osteosarcoma in Ramathibodi Hospital

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Abstract:

One hundred thirty cases of osteosarcoma were enrolled to the multidisciplinary treatment. The 9 years survival probability was 55% and the survival was stable after 4.4 years. Local irradiation of the primary tumor was proved to increase chance of limb salvage surgery ($p = 0.007$) and provided more tumor response as compare to the control patients ($p = 0.14$). The 9 years survival in the patients with local radiation was 70% and dropped to 45% in the non radiation. (log-rank = 0.01). Prophylactic whole lung irradiation also beneficially decreased the incidence of lung metastases ($p = 0.0009$) and the 9 years survival was 70% versus 46% in PLI and non PLI patients (log-rank = 0.05).

Introduction

Osteosarcoma is a rare tumor. The incidence in Thai people is 1.3 cases per million per year according to the incidence of the National Cancer Institute(1). In Ramathibodi Hospital, there was 20 cases of osteosarcoma out of 1985 malignant tumor (0.01%) in the year 1993.(2)

Although it was a rare tumor but the cure rate was so poor. Before 1972, 20% of osteosarcoma survived for five years after diagnosis and after the introduction of intensive chemotherapy especially with high dose methotrexate, doxorubicin, cisplatin or ifosfamide, the long term survival was improved to 55-75% range. (3) Chemotherapy was claimed to able to control micrometastases included skip lesion and feeling that neoadjuvant chemotherapy might reduce soft tissue infiltration, leading to limb salvage surgery. (3) Because of effective prophylactic or treatment of metastases with chemotherapy, radiation has since been replaced and radiation therapy was omitted, and only used as palliative purpose or radiated the rarer location in spine, base of skull or pelvis. (7,8)

Yamamuro described the technique of intraoperative radiotherapy with a single electron dose of 50-60 Gy and subsequent adjuvant therapy and provision of a prosthesis after 3 months. Only 1 out of 32 patients developed local recurrence with 78% 5 years survival. Bleher mentioned about the report from Takada (7) treated 38 osteosarcoma patients with fast neutron radiotherapy, systemic chemotherapy and limb salvage surgery. Thirty-five of 38 cases underwent en bloc resection. Only one had evidence of local tumor recurrence. Other 31 cases were alive without distant metastases after 9-120 months. Hug (8) in 1995 gained overall survival of 44% at 5 years in axial skeletal disease treated by combined proton and photon radiation therapy. In the situation of Thai people when percutaneous photon therapy is the only practical way in treating osteosarcoma, local irradiation combined with chemotherapy still the most optimal treatment. So radiation treatment may be still have some role in the treatment of osteosarcoma However, despite aggressive primary treatment, 30-40% of the patients still relapse, mostly from pulmonary metastases. Surgical resection of the pulmonary nodule had been attempted with curative intent by several centers in the world literature with 30-40% long term survival. (3) But surgical resection in pulmonary metastases was a limited procedure in Thai patients due to very advance both primary and pulmonary disease and nonavailable adequate chemotherapy so pulmonary resection in this country was not worth-while. So pulmonary irradiation may be another way to prevent and control pulmonary metastases.

The purpose of this study was to demonstrate the efficacy of various roles of radiation in the treatment of osteosarcoma included local irradiation and prophylactic whole lung irradiation.

Materials and Methods

From 1986 to 1995, 130 cases of primary osteosarcoma were enrolled to the prospective multidisciplinary treatment in Faculty of Medicine, Ramathibodi Hospital, Mahidol University. Seventy three percent of the patients were refered from other hospitals included both in Bangkok and provincial hospitals. The treatment consisted of 2-6 courses of intraarterial chemotherapy of 100 mg/m2 in day 2 or epirubicin 20 mg/m2 day 2,3,4, or 60 mg/m2 3,4 of etoposide based on the simple randomization.

Fifty one cases were locally irradiated at the primary site while other 79 were not. The radiation port only included the gross disease that was seen in the angiography without any safety margin, due to the assumption that microscopic lesion even skip lesion can be destroyed by intraarterial and intravenous chemotherapy and to minimize the radiation effect on the soft tissue in the cases of limb salvage surgery. Surrounding soft tissue as much as possible was spared for avoiding radiation injury and cause problem on the wound healing when the limb was salvaged. The total dose was 30 Gy in the period of 2 weeks. In the group of patients with local irradiation (local RT), the surgical treatment were delayed for another 2 weeks. After surgery, all the patients after June 1989, had

prophylactic whole lung irradiation (PLI). The treatment was from Co-60 machine or 6 MV linear accelerator, without any lung correction for the lesser absorption in the air containing lung. The dose was 2250-2700 cGy, mean 2486.67±151.22, median 2510 cGy with the daily dose of 150 cGy on every other days. The total treatment time ranging from 6-16 weeks with the median of 8 weeks. The criteria for selection of PLI modified from Breur et al (10) included.

1) age under 50 years
2) primary tumor must be high to moderate grade histology of osteosarcoma
3) tumor located in one limb only
4) absence of clinically detectable metastases.

In the total of 130 cases, 63 (49.5%) were completed the treatment while other 67 the treatment was terminated before completed the scheme, 17 due to initial lung metastases, 4 refused to have any treatment, other 46 lost before treatment ended, 31 out of 46 lost after good response to neoadjuvant treatment and refused to be amputated. The follow up time ranging from O to 116.3 months with mean ±SD and median = 26.1 ±26.3 months and 15.45 months respectively.

Results

There were no statistical different in the patients' profile between local RT and non local RT or patients with PLI and non PLI as shown in Table I, II.

Fifty one cases who received local RT, had further surgery other 6 lost. Twenty out of 45 or 44.4% can salvage the limb, 5 had various type of surgery included 4 disarticulation and one pelvic bone resection, other 20 cases (44.4%) had amputation. Six cases who had local RT and lost to follow up, two had local RT of 600 cGy and 150 cGy then lost, one returned to the hospital again and died with lung metastasis 24 months after diagnosis while the other suspected dead due to her poor condition. She had very high serum AP of 1350 U/L and the level never decrease after 4 courses of intraarterial and intravenous chemotherapy. The other 4 had 3000 cGy local RT and all refused amputation after good response to neoadjuvant treatment. One developed lung metastasis and dead 14 months after initial diagnosis. The other 3 was lost.

In 79 cases of non local RT patients 37 cases had further surgery, 6 out of 37 (16.2%) can preserve the limb and other 23 (62.2%) had amputation.

Twenty one out of 40 evaluated patients with local irradiation had 100% tumor necrosis while the non local RT group, 8 out of 24 (33.3%) had the 100% tumor response after neoadjuvant treatment ($p = 0.14$). The survival in the local RT was 70% and dropped to 45% in the patients without local irradiation (log-rank $p = 0.01$).(Table III, Fig I)

Evaluation of complication from local RT there were 4 out of 7 cases of tibia lesion with local RT had chronic discharge from the sinus tract after limb salvage surgery, while there was only one cases of tibia lesion without local RT had limb salvage surgery and unfortunately, this case developed local recurrence at 12 months after surgery. Other complications such as

one delay calcification and another foot drop were found in local RT patients. Other 11 limb salvage patients had no surgical complication. In the group of non local RT, 6-limb salvage surgery were achieved without any complication accept one local recurrence as mentioned before. (Table IV) There were 5 local recurrence, 3 belonged to the local RT group and 2 in the non local RT. (Table V).

In the point of view of the prophylactic whole lung irradiation, there were 6 in 36 cases (16.7%) developed lung metastases while 39 out of 79 (49.4%) in non PLI group had lung disease (p = 0.0009). The patient with local RT combined with PLI had lower incidence of lung metastasis as compared to the local RT without PLI. (Table VI) The 9-years survival of the PLI patients were 70% as compared to the non PLI was 46% (log-rank p = 0.05) (Fig II).

Table I Initial profile of the patients with local RT and non local RT

Profile	control (non local RT) N %	local RT N %	p value X^2
Age (mean)	18.2 yrs.	17.4 yrs.	NS (0.56)
Sex			
male	44 (55.7)	28 (54.9)	NS (0.93)
female	35 (44.3)	23 (45.1)	
Bone position			
femur	43 (54.4)	24 (47.1)	NS (0.33)
tibia	19 (24.1)	16 (31.4)	
Sign duration			
≥ 2 mos	22 (28.2)	10 (19.6)	NS (0.26)
≥ 3 mos	17 (21.8)	14 (27.5)	
-Chief complaint			
mass	16 (28.3)	14 (27.5)	NS (0.34)
mass + pain	60 (75.9)	35 (68.6)	
Trauma -ve	37 (46.8)	23 (45.1)	NS (0.82)
+ve	40 (50.6)	27 (52.9)	
Fracture -ve	59 (74.7)	47 (92.3)	0.017*
+ve	19 (20.1)	4 (7.8)	
Pathology			
osteoblastic	30 (38.0)	19 (37.3)	NS (0.46)
chondroblastic	10 (12.7)	12 (23.5)	
telangiectasia	9 (11.4)	7 (13.7)	
Chemotherapeutic agent			
doxorubicin	18 (22.8)	21 (41.2)	NS (0.10)
epirubicin	50 (63.3)	26 (51.0)	
etoposide	9 (11.4)	4 (7.8)	

Table II Initial profile of the patients with Non PLI and PLI

Profile	control (non local RT) N %	local RT N %	p value X^2
Age (mean)	18.3 yrs	17.2 yrs	NS (0.61) (t-test)
Sex			
male	42 (53.2)	19 (52.8)	NS (0.97)
female	37 (46.8)	17 (47.2)	
Bone position			
femur	42 (51.9)	18 (50.0)	NS (0.56)
tibia	24 (29.6)	6 (16.7)	
Sign duration			
2 mos	19 (29.2)	10 (20.4)	NS (0.56)
3 mos	12 (18.5)	15 (30.6)	
Chief complaint			
mass+ pain	43 (65.2)	32 (64.0)	NS (0.78)
mass	8 (12.1)	7 (14.0)	
+ve	38 (46.9)	20 (55.6)	
Fracture -ve	59 (74.7)	30 (83.3)	NS = 0.87
+ve	14 (17.7)	6 (16.7)	
Pathology			
osteoblastic	26 (32.1)	17 (47.2)	NS (0.26)
chondroblastic	15 (18.5)	5 (13.9)	
Chemotherapeutic agent			
epirubicin	50 (63.3)	28 (77.8)	NS (0.63)
etoposide	6 (7.4)	6 (16.7)	

Table III Local RT related to type of surgery and result

	local RT		
	+	-	p value
Type of Surgery			
limb salvage	20/45	6/37	$X^2 = 0.01$
amputation	20/45	23/37	
Residua tumor			
tumor = 0	21/29	8/29	$X^2 = 0.05$
tumor > 0.99 <9.99%	0/2	2/2	
tumor ≥10≤49.99%	16/24	8/24	
tumor > 50%	3/9	6/9	
9 - year survival	70%	45%	log-rank p = 0.01

Fig I Survival probability of local RT and non local RT patients

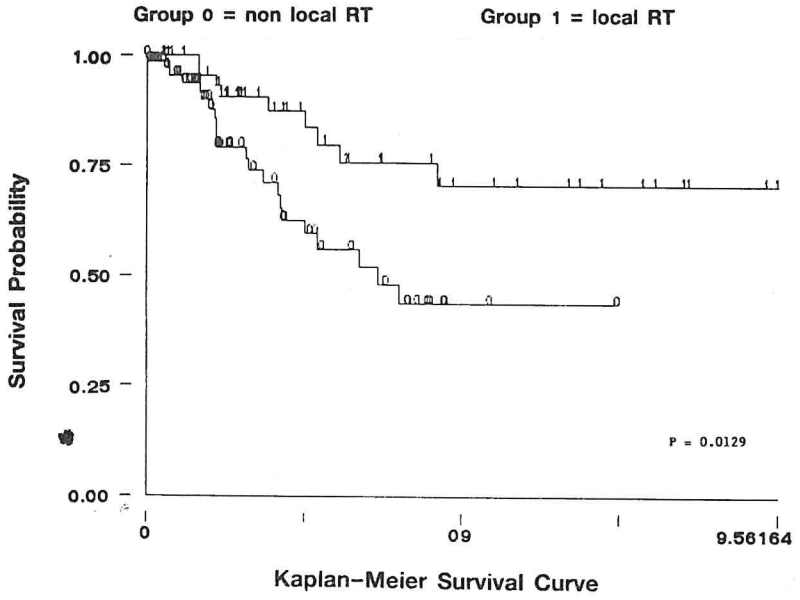
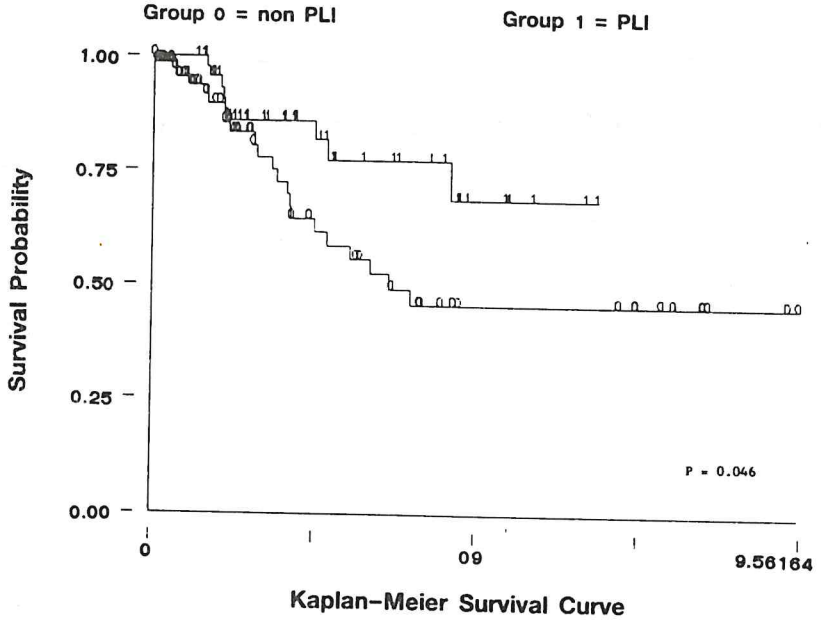


Fig II Survival probability of PLI and non PLI patients



Discussion

Radiation response of osteosarcoma is a rather limited role due to the relatively radioresistant tumor with high capacity to repair the sublethal damaged cell (11-12) and very rapidly growth with 34 days to doubling the tumor cells.(3) So by conventional way of treatment, radiation therapy was ignorant since various chemotherapy was introduced in 1970. High dose methotrexate and doxorubicin found to be very effective in controlling metastases and leading to limb salvage surgery after neoadjuvant therapy. Multidrug neoadjuvant therapy showed a significant favorable impact on disease free survival and drug might reduce soft tissue infiltration by tumor cell, also the intramedullary spread and skip lesion. (3-7,11-14)

Limb sparing resection was originated in 1970 (3) and in Ramathibodi Hospital in 1986.(15- 21) We combined intraarterial cisplatin, intravenous doxorubicin, epirubicin or etoposide to local irradiation by simple randomization. The group with local RT achieved more limb salvage surgery and more tumor necrosis (log-rank p = 0.009) and had higher survival probability. (log-rank p = 0.01) Although in the local RT had more local recurrence, the reason might due to more limb salvage surgery was achieved while the patients without local RT had amputation. The histological subtype might be an other reason, chondroblastic cell trend to have worse response to neoadjuvant therapy as compare to other subtype, there were 40, 80% tumor left after local RT combined with chemotherapy. Telangietatic subtype had 100% tumor necrosis after local RT and chemotherapy. Osteoblastic had 10, 100% tumor left when only chemotherapy was implemented. (Table IV). The cause of local recurrence included limb salvage procedure in the fractured limb, we had a case of 6 years old girl with 100% tumor necrosis of fractured humerus and the surgical procedure had no any postoperative complication, her disease recurred at 13 months and lung disease was so delay and still had long survival, these might be due to she had PLI after surgery. In the patients with PLI we had proved that only 16.7% of PLI group had better survival probability with log-rank p value = 0.05. The failure of PLI might be suboptimal treatment time. We irradiated the lung at the same time of post-operative chemotherapy, so every patients had WBC dropped and poor condition, high dose medroxy-progesterone acetate had been proved to be benefit in these patients and will be reported elsewhere. Some patients finished the PLI after 8 weeks period. Conventional dose for whole lung irradiation of 2500 cGy is just 3 weeks but only 70% of the cases could finish the radiation less than 8 weeks other 30% had prolong irradiation up to 16 weeks. So this might be the main reason of PLI failure.

We had a patient with 2.5 cm soft tissue nodule a distance far from the biopsy scar and local RT was skip this lesion due to we believed that intraarterial and intravenous chemotherapy could sterile the soft tissue infiltration and we wanted not the cover the whole circumference in the radiation port. This patients had 100% tumor necrosis on limb salvaged bone but the soft tissue still had viable tumor so she was amputated immediately and still in good health for more

than 90 months now. So we assumed that gross soft tissue lesion had to combined with local RT, not only adjuvanted with chemotherapy.

Conclusion

In a part of multidisciplinary approach in the treatment of osteosarcoma, local irradiation had a definite role to produce more possibility of limb salvage surgery and more survival with acceptable complication. Prophylactic whole lung irradiation was another way for preventing or controlling lung metastases. Further research question was whether prophylactic whole lung radiation had a role in other microscopic metastatic lung disease, not only in osteosarcoma.

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