The Role of Radiation Therapy in Management of Wilms' Tumor

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Treatment results of 28 patients with Wilms' tumor who received radiation therapy at the Department of Therapeutic Radiology, Seoul National University Hospital from 1979 to 1988 were analyzed. The median follow-up period for the survivors was 40 months.

The local control and overall survival rate at 3 years were 78.1% and 67.4%, respectively. The local control was not affected by age. The local control rates for favorable histology (FH) and unfavorable histology (UH) were 83.3% and 62.5%, respectively. In FH, the local control rates of stage II and III were not different (83.3% vs 100.0%). In UH, the control rates of stage I/II and stage III were 83.3% and 0%, respectively. Poor local control was correlated with involvement of lymph node (50.0% vs 87.5%). Radiotherapy delayed 10 or more days after operation resulted in poorer local control than that without delay ($p<0.05$).

Thus radiotherapy contributed to reduction of local recurrence in patients with high risk factor without increased severe complication. It is suggested that bulky unresectable mass might need a more intensified treatment.

Key Words: Radiation therapy, Wilms' tumor, Local control

INTRODUCTION

One of the most dramatic successes in the oncology fields has been the progressive improvement in the survival of infants and children with Wilms' tumor. Gross and Nauhauser[1] reported that the 2-year survival rate after treatment was 32% in the 1930s. The addition of postoperative radiation therapy to tumor bed as a routine in the 1940s appeared to improve the survival rate up to 47%. Recently, with the use of chemotherapy and multidisciplinary treatment, the cure rate for all stages of Wilms' tumor is predictively over 80%, which could be achieved mainly by the continued efforts of group-wise prospective studies such as National Wilms' Tumor Study (NWTS).

In Korea, no study has ever been done concerning local control and survival of Wilms' tumor by treatment modality. In order to analyze these factors, radiotherapy results of Wilms' tumor during last nine years were analyzed.

MATERIALS AND METHODS

From 1979 to 1988, 38 patients with Wilms' tumor were treated at the Department of Therapeutic Radiology, Seoul National University Hospital. Eleven patients were excluded from this analysis because of incomplete radiotherapy, pathologically proven rhabdoid type, or recurrent disease. Two patients received lung and abdominal irradiation after lung metastais or local relapse. They were included in the analysis of lung irradiation but excluded from analysis of the local control. Eight cases were referred for radiation therapy from outside hospital after nephrectomy.

This work was partly supported by SNUH 1990 Clinical Research Fund.

The patients were infants and children with median age of 30 months and their age ranged from 5 to 84 months. The sexes were evenly distributed (Table 1).

Pathoiogic slides were reviewed for confirmation of histology grade by the criteria of NWTS[2]. In one patient, the histology grade was not defined because of absence of pathologic information. Sixteen patients had favorable histology (FH). Among the 11 patients with unfavorable histology (UH), three patients had diffuse sarcomatous features and eight patients had focal or diffuse anaplasia (Table 2).

Surgical removal was tried at first in all patients after inital evaluation. Extent of tumor resection was complete in 25 patients and incisional biopsy only was done in three patients due to unresecable bulky mass. There was tumor spillage during surgery in five patients. The distribution of histology and staging by NWTS-III[3] is summarized in Table 2.

Radiation therapy was delivered with a Co-60

Table 1 Characteristics of Patients

Characteristics	No.	%
Age (month)		
– 12	2	7.1
13 – 24	9	32.1
25 – 36	5	17.9
37 – 48	5	17.9
49 – 60	4	14.3
61 – 72	2	7.1
73 – 84	1	3.6
Sex		
Male	16	57.1
Female	12	42.9
Total	28	100.0

Table 2. Distribution of Stage and Pathology

Stage	FH*	UH#	Total (%)
I	–	2	2 (7.4)
II	8	5	13 (48.2)
III	7	3	10 (37.0)
IV	1	1	2 (7.4)
Total(%)	16 (59.3)	11 (40.7)	27 (100.0)

* FH ; Favorable Histology
\# UH ; Unfavorable Histology

teletherapy unit by anterior-posterior opposing port. The portal included the limits of the tumor bed and its medial margin extended across the midline to encompass the entire width of vertebrae at the relevant levels. No patient was treated by whole abdominal irradiation. The dose was determined according to age, stage, operative finding, and histology. The radiation dose of 1,080~3,960 cGy was delivered to the tumor bed. The whole lung irradiation was done in five patients who had initial lung metastasis (two cases) or lung relapse (three cases). In the patients with lung metastasis, 1,200 ~1,500 cCy was delivered to whole lung and boost dose of 200~1,000 cCy was added to the metastatic foci (Table 3). Radiation therapy started within 9 days after surgery in 10 patients while in 16 patients the interval was more than 9 days. The survival and the local control rates were calcuated by the life table method and comparisons were performed by log rank test[4].

RESULTS

The survival rate and the local control rate at 3 years were 67.4% and 78.1%, respectively (Fig. 1). The local control rate was analyzed according to the various factors known to affect the outcomes of Wilms' tumor. The local control rate at 2 years was not affected by age (Table 4).

The local control rates of FH and UH were 83.3% (10/12) and 62.5% (5/8), respectively (Table 5). In FH, the local control rates of stage II and III were

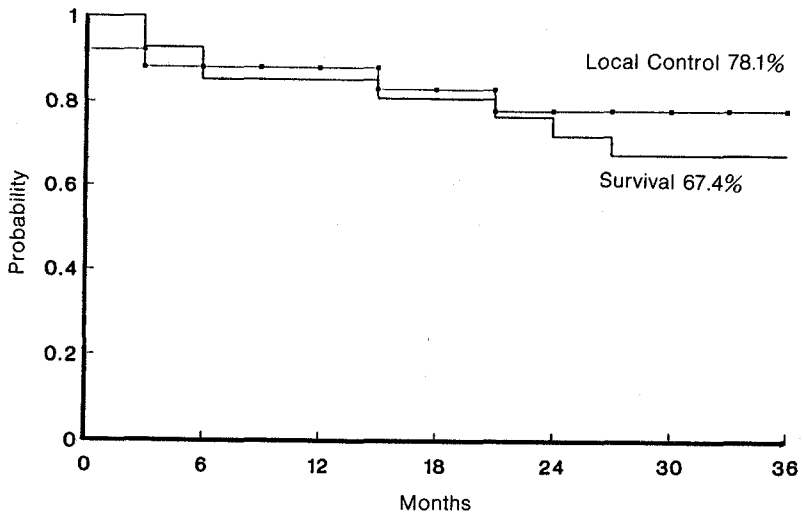

Fig. 1. Actuarial local control and overall survival.

not different (83.3% vs 100.0%). But in UH, the local control rates of stage I/II and stage III were 83.3% (5/6) and 0% (0/2), resptively. One patient with undefined histology has been in locally controlled state.

Table 3. Methods of Radiation Therapy

Site	Dose (cGy)
Tumor bed	
FH*	1,080 – 3,960
UH#	1,500 – 3,600
Lung	
Whole lung	1,200 – 1,500
Boost	200 – 1,000

* FH ; Favorable Histology
\# UH ; Unfavorable Histology

Table 4. Local Control at 2 Year by Age

Age (Month)	Local Control
– 12	2/2
13 – 24	3/4
25 – 36	3/4
37 – 48	3/4
49 – 60	2/3
61 – 72	1/3
73 – 84	1/1

The local control rate of tumors with involvement of lymph nodes was poorer (50.0% vs 87.5%) than that of tumors without involvement of lymph nodes microscopically or grossly (Table 6). But the difference was not significant. In cases with tumor spillage, the local control was not poor (Table 6).

The local control rate was significantly influen-

Table 5. Local Control at 2 Year by Histology and Stage

Type	Stage				Total
	I	II	III	IV	
FH*	–	5/ 6	5/5	0/1	10/12
UH#	2/2	3/ 4	0/2	0/0	5/ 8
Total	2/2	8/10	5/7	0/1	15/20

* FH ; Favorable Histology
\# UH ; Unfavorable Histology

Table 6. Local Control at 2 Year by Operative Findings

Finding	Local Control	p Value
LN Involvement		
Absent	14/16	
Present	2/ 4	>0.05
Tumor Spillage		
Absent	12/17	
Present	4/ 4	>0.05

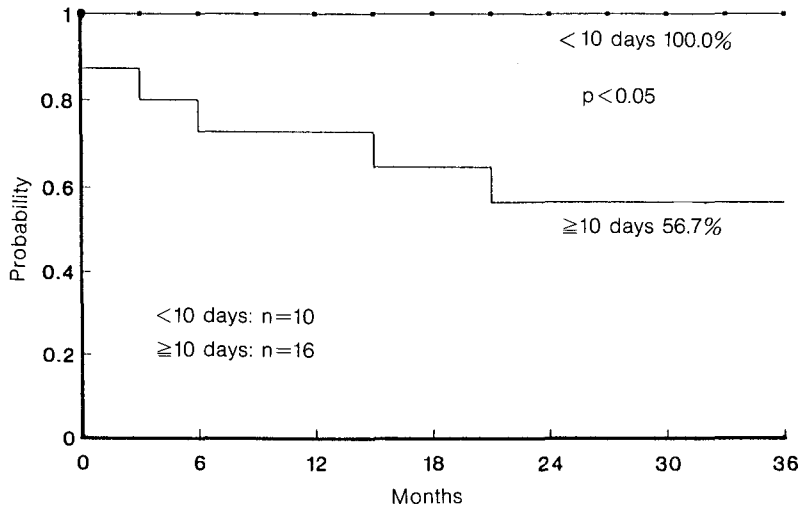

Fig. 2. Local control by interval between operation and radiotherapy.

Table 7. Characteristics of Locoregional Failure After Radiotherapy in Five Patients Who All Received Actinomycin-D + Vincristin + Adriamycin

No.	Age*/Sex	Stage	Histology	RT Dose (cGy)	OP	Distant Failure	Survival#
1	56/F	IV	FH	2,400	TR	Lung	29
2	61/F	II	FH	2,550	TR	Lung, Inguinal LN	9
3	20/M	III	Ana	2,400	Bx	None	4
4	60/M	II	Ana	2,000	TR	Liver, Lung, Bone	23
5	40/F	III	Ana	1,980	Bx	None	3

*, # : Month, FH : Favorable Histology, Ana : Anaplasia, TR : Total Removal, Bx : Biopsy only

ced by the starting time radiotherapy after operation (Fig. 2); 100.0% and 56.7% with radiotherapy started before 10 days and at 10 or more days, respectively ($p<0.05$).

The treatment failure was identified in six patients. One patient died of unknown cause without disease. Two patients had locoregional failure, one had distant failure (lung) only, and three patients had both. The general features of the local relapse after radiotherapy are shown in Table 7.

Of the five patients who were irradiated to the metastatic lung lesions, one patient had complete response and four patients had partial response. One patient with complete response died of uncontrolled primary tumor.

Among long-term survivors, there was no complication induced by radiotherapy such as scoliosis.

DISCUSSION

Increasingly better survival rate had been obtained in children with Wilms' tumor over the several decades since 1930s. Efforts are continuing to further improve the surival of patients with advanced disease or unfavorable histology and to scale down the therapy for patients with early stage tumor to minimize sequelae.

By NWTS-III, two drug combination chemotherapy (AMD+VCR) without irradiation was selected as the standard regimen for stage II/FH tumors because neither postoperative radiation therapy nor addition of adriamycin was found to yield the better results. In patients with stage III/FH, there was no difference in the relapse free survival and the death rate whether the patients were given 1,000 cCy or 2,000 cCy postoperatively with three drug combination chemotherapy (AMD+VCR+ADR). Stage IV/FH children treated with three drug combination chemotherapy (AMD+VCR+ADR) and pulmonary irradiation (1,200 cCy) had excellent survival[3].

Prognosis for Stage I anaplastic tumors was as good as their FH counterparts and thus actinomycin-D plus vincristin without postoperative radiation therapy was sufficient. Children with stage I, III, and IV anaplastic tumors perhaps got benefit from the addition of cyclophosphamide to the other three drugs[3].

The 2-year relapse free survival and the overall survival were 81.5% and 88.6%, respectively in 524 children randomized in NWTS-II[5]. Those of 1,439 NWTS-III children were 85.3% and 92.4%, respectively[3]. Thus the excellent outlooks for children with Wilms' tumor have been sustained despite of the decrease in the intensity of therapy. Conversely more intensive treatment has improved results for some of high risk subsets, notably for children with stage III and IV tumors with favorable histology and for those with clear cell sarcoma of any stage.

In our study, the local control rate and the overall survival rate were 78.1% and 67.4%, respectivey. In FH only, the local control rates of stage II and III were similar (83.3% vs 100.0%). This result suggested that patients with stage III/FH benefited by radiation therapy in diminishing local relapse comparable to that of patients with stage II/FH. NWTS-III reported that 2-year relapse free survival rate for stage III/FH children was not as good as that for their stage II/FH (79.7% vs 90.4%).

Two patients with stage I/UH have survived without relapse. Their pathology subsets were focal anaplasia and sarcomatous feature respectively. NWTS-III reported that the local relapse free survival of stage I anaplastic tumor was as good as their favorable counterparts (over 90% survival rate).

In our study, stage II/UH patients had good results, while all three patients with stage III/UH

expired. Among them, two patients received incisional biopsy only because of massive unresectable tumor. To reduce the bulk of tumor, chemotherapy and radiation therapy were done but reduction in tumor size was not achieved. These patients died with locoregional failure only. Past experiences in NWTS-I and the studies conducted by the International Society of Pediatric Oncology (SIOP) have shown that pretreatment with chemotherapy almost always reduces the bulk of the tumor, and renders it resectable[6,7]. This method, however, did not result in the improvement of survival. These inoperable patients should be treated initally with chemotherapy. If tumor size was not reduced radiation theray was begun. Nephrectomy should be performed with minimal risk as soon as sufficient shrinkage has occurred. In general, the operative procedure can be performed with six weeks of diagnosis.

Among two stage IV patients, one had FH and the other had diffuse sarcomatous feature (UH). They died due to combined failure. According to NWTS-III, in stage IV/FH patients four-year survival rate was over 70%[3].

By operative finding, spread to lymph nodes and tumor spillage during operation significantly altered the prognosis in patients with Wilms' Tumor[8~10]. By Breslow's multivariate analysis, operative spillage was not a contributing factor in relapse[11]. In our analysis, lymph node involvement was a risk factor of local relapse but operative spillage was not.

In our study, six patients had relapses. These patients were not salvaged by chemotherapy and radiation therapy. Grandy, et al reported that 3-year post-relapse survival for all 367 patients was 30·3%[12]. The patient with UH was predicted a very poor outcome regardless of relapse site. For FH cases only, relapse confined to the lungs was associated with a significantly better 3-year post-relapse survival than abdominal recurrence or relapse at other sites (44±5% vs 28±7% vs 11±10% respectively, $p<0.005$). By Breslow[9], the long term survival rate for patients with tumors of FH who developed metastasis after treatment (47.0% at 5 years) was substantially worse than that for those with metastatic disease at diagnosis (72.7%) ($p<0.0001$). For UH patients, the survival was poor regardless of time of the detection of metastasis[9] (10.8% and 17.2% at 5 years for relapsed stage I-III and stage IV)

A reported[13] control rate (50%) of thoracic disease by whole lung irradiation was somewhat higher than that of our result of 20%, In NWTS-III, diffuse interstitial pneumonitis was reported in 13.0% of patients treated with whole lung irradiation[14]. Eleven of them (57.8%) died with pneumonitis of unknown etiology. The later complication of whole lung irradiation is reduction in both lung volume and dynamic compliance[15,16]. In contrast to adults, these effects resulted from impaired chest wall growth and failure of alveolar multiplication[15]. In Pediatric Oncology Nephroblastoma Trial and Study Committee, only four of 36 patients with pulmonary metastsis at diagnosis received whole lung irradiation[17]. The others were treated by chemotherapy with or without metastatectomy. Disease free survival and actuarial survival rate are 83% with a mean follow-up of four years. This report provided further questions regarding the routine use of whole lung irradiation in Wilms' tumor with metastatic lung lesion.

Radiation related acute toxicities in NWTS-I were developed in 7.2% of randomized patients (26/359) and three patients died, two of pulmonary fibrosis and one of cardiotoxicity[18]. That of NWTS-II was very similar (23/303). Five (1.6%) fatalities were recorded[19].

Later effects such as musculoskeletal abnormalities and second cancer were demonstrated[20,21]. In our study, specific radiation therapy related complication was not detected.

As the role of chemotherapy increases, considerable controversy exists regarding the role of radiation therapy. There were a few reports about radiation therapy only. By a review of 250 patients enrolled in the NWTS-I and II[22], delay in initiating post operative radiation therapy, dose, and field size were the important factors for the radiotherapy. They reported that significantly more local relapse was found when radiotherapy was delayed days after operation. But when histologic grade was considered, the delay alone was not a contributing factor in the local relapse. Relapsed patients did not differ from relapse-free patients with respect to field size or median dose. In our study, radiotherapy delayed 10 or more days after operation had poorer result than that without delay, although the stage and histology were comparatively evenly distributed between two groups. This result suggested that radiation therapy should start within 9 days after surgery.

Intensive multiple agent chemotherapy contributed to control of local as well as remote diseases and they substituted in some measure tumor bed radiation therapy[23]. But radiation therapy had the role of diminishing abdominal relapse

in patient with high risk of local relapse. SIOP identified several factors that raised abdominal recurrence such as large tumor size, incomplete excision, peritoneal adhesion, or tumor extending to renal vein or vena cava[24]. A tumor rupture increased the chance of abdominal recurrence, especially if appropriate radiotherapy was not given. Although the risk of an abdominal relapse after treatment of Wilms' tumor was fortunately rare, it carries a high risk of killing the patients. These patients who relapsed in abdomen had 3-year survival rate of 28%[12].

In summary, radiation therapy contributed to reduce local recurrence in patients with high risk factor without severe complication. It is suggested that bulky unresectable mass might need a more intensified treatment.

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국문초록 =

Wilms씨 종양에서 방사선 치료의 역할

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김 미 숙·김 일 한·윤 형 근

1979년부터 1988년까지 서울대학교병원 치료방사선과에서 방사선 치료를 받았던 Wilms씨 종양 환자 28명의 치료성적을 분석하였다. 평균 추적관찰기간은 40개월이었다. 3년 국소 치유율 및 생존율은 각각 78.1%와 67.4%이었다. 연령에 따른 국소치유율의 차이는 없었다. Favorable histology와 Unfavorable histology 유형의 국소치유율은 각각 83.3%와 62.5%이었다. Favorable histology 유형의 II기와 III기 종양의 국소치유율 간에는 차이가 없었다(83.3% vs 100.0%). Unfavorable histology 유형의 I/II기와 III기 종양의 국소치유율 간에는 유의한 차이가 있었다(83.3%:0%). 임파절 침윤이 확인된 경우에서의 국소치유율은 불량하였다(50.0% vs 87.5%). 방사선치료를 수술 후 10일 이후에 개시한 경우에서의 국소치유율과 수술 후 9일 이내에 개시한 경우에서의 국소치유율 간에는 유의한 차이가 있었다($p<0.05$). 따라서 방사선치료는 국소치유율을 향상시키는데 유용하였으나 수술적 절제가 불가능한 종양에 대하여는 치료방법의 강화가 필요하다고 판단된다.