Results of Radiation Therapy of Malignant Lymphomas, Especially of Reticulum Cell Sarcoma(1946–1963)*

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Research field code	Key Words
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悪性リンパ腫の放射線治療，特に細網肉腫について

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1946—1963の間に癌研放射線科において治療された悪性リンパ腫の患者は423例ある．細網肉腫が88%を占め，リンパ肉腫5%，ホジキン病2%，巨大濾胞性リンパ腫1%，分類不能が4%であつた．特に細網肉腫について年令，性別，部位，ひろがり，発病より治療までの期間，照射の方法などが予後に及ぼす影響を調べた．頭頸部原発のものが88%を占めているが，この部のものは他の部のものに比して予後が良かつた．頭頸部の一領域のみに限局している場合の5年生存率は44%で，次の一領域に進展した場合は36%であつた．頭頸部原発で同じStageと判定されたものでも鎖骨上窩リンパ節にまで進展していたものは予後がわるかつた．リンパ節原発の細網肉腫よりも所謂Extra-nodal originの方が予後が良かつた．頭頸部原発で二つの領域に進展していた症例の一部に対して腋窩，縦隔洞に予防照射が行なわれたが有効であつたとはいえなかつた．

治療終了後の再燃をみると照射野内に起るものよりも照射野周辺および遠隔の部に起るものの方が頻度が高かつた．ちなみに，62例の5年以上生存者のうち11例は第1回の治療終了後に再燃をおこしたが，再治療で長期生存を得られたものである．本症のなかには進行のおそいものもあることが推察される．このことは治療までの期間と予後との関係を調べた結果からも推察された．

（本報告は第12回ICR，1969のシンポジウムで述べたものである．）

During the period from 1946 to 1963, radiation therapy was given to 423 patients with malignant lymphoma as primary treatment at the Cancer Institute Hospital,** Tokyo. The present report describes

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the prognosis of these cases by age, sex, site, extent of tumor, duration of symptoms and modality of radiation therapy. As the relative incidence of reticulum cell sarcoma is the highest among lymphomas in Japan, attention was focussed primarily on reticulum cell sarcoma with brief mention of other diseases.

MATERIAL

Histological diagnosis of reticulum cell sarcoma was established in 374 cases or 88% of all malignant lymphoma cases. Other types including lymphosarcoma, giant follicular lymphoma and Hodgkin's disease were found in a small number of cases as shown in Table 1.

The distribution of malignant lymphomas by age and sex is shown in Table 2 and Fig. 1. The ratio of male to female of reticulum cell sarcoma was 1.5 : 1. Age of onset showed a wide range, but the proportion was high in the 41–70 age group for males and in the 31–70 age group for females. All cases of Hodgkin's disease were males. The age distribution of lymphosarcoma was similar to that of reticulum cell sarcoma.

Table 1. Histological classification

	No. of cases	%	Remarks
Reticulum cell sarcoma	374	88	
Lymphosarcoma	22	5	
Giant follicular lymphoma	3	1	
Hodgkin's disease	7*	2	* 1 Paragranuloma type**
			4 Granuloma type
Unclassifiable	17	4	1 Sarcoma type
			1 Uncertain type
Total	423	100	

**Jackson and Parker's classification. One case of granuloma type changed to sarcoma type when extension developed. Lukes and Buttler's classification was not applied here.

Table 2. Distribution of malignant lymphoma cases by age and sex

Age		< 10	11–20	21–30	31–40	41–50	51–60	61–70	> 71
Reticulum cell sarcoma	Male	3	8	27	28	45	60	49	11
	Female	5	7	12	25	31	30	24	9
Lymphosarcoma	Male				2		3	3	
	Female	1	2		2	4	1	3	1
Giant follicular lymphoma	Male			1		2			
	Female								
Hodgkin's disease	Male	1		1	1	1	3		
	Female								

As the staging of malignant lymphoma has not yet been established by UICC, the stage classification proposed for Hodgkin's disease at the Paris Conference and the Rye Conference[10] was applied:

Stage 1-1.....Disease limited to one anatomic region or site.

Stage 1-2.....Disease limited to two contiguous regions.

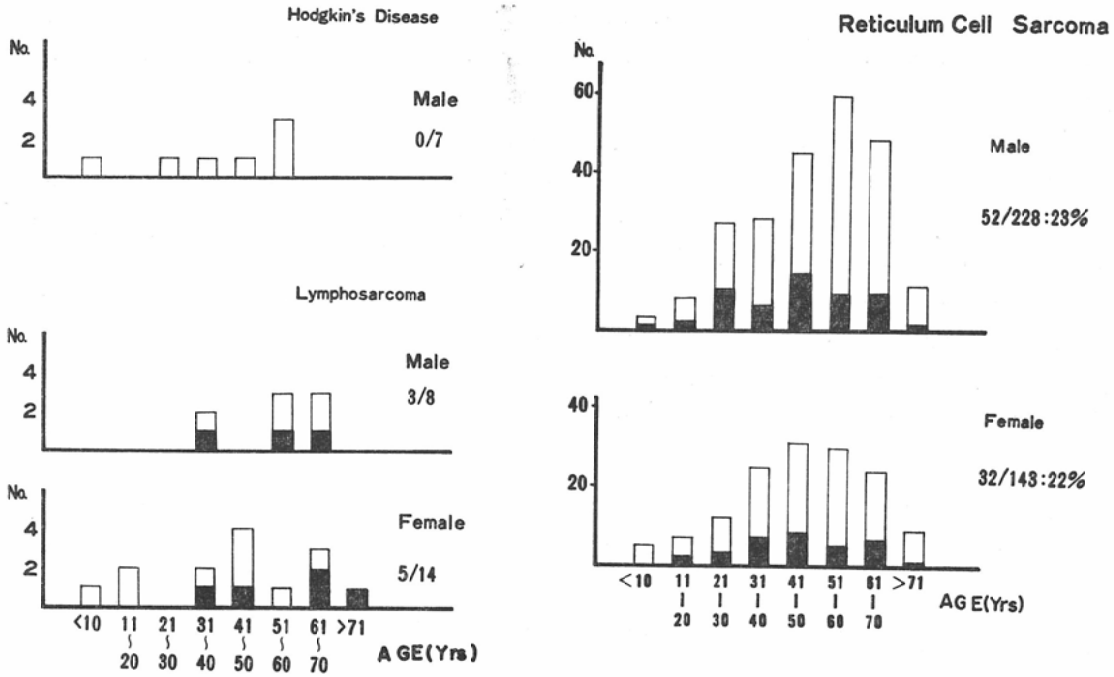

Fig. 1. Age distribution of all cases and 5-year survivors (dark area).

Stage 2.....Disease in more than two anatomic regions on one side of the diaphragm.

Stage 3.....Disease on both sides of the diaphragm.

Stage 4.....Involvement of the bone, bone marrow, lung parenchyma, pleura, liver, and any tissue or organ in addition to lymph nodes, spleen, and Waldyer's ring.

At the Rye Conference the spleen and Waldyer's ring were designated as separate anatomic sites for the staging of Hodgkin's disease. As it is not uncommon for reticulum cell sarcoma to develop in not only these two sites but also in extra-nodal tissues such as the nasal cavity, maxillary antrum and thyroid, the latter tissues were used as the sites for the staging.

As general symptoms or signs were rarely observed in our cases, the subclassification of A or B was not used to indicate the presence or absence of general symptoms.

Modalities of Radiation Therapy

Conventional X-ray therapy was chiefly applied during 1946–1960 period. Telecobalt and telececium units became available since 1957, and 4.3 MeV linear accelerator (Mullard) was installed in 1964. Results of linear accelerator radiotherapy will be reported at a future date.

In conventional X-ray therapy, the field size ranged from 6 × 8 to 10 × 15 cm^2 depending on the extent of the disease. Treatment factors were 180 kVp, HVL 1.0 mm Cu, and FSD 40 cm. For the head and neck region, irradiation was given unilaterally or bilaterally by case. Average tumor dose was generally aimed at 3000–4000 rads in 3–4 weeks and wait-and-see policy was used in most of the cases. For residual tumors, radon seed implantation or booster dose of 1000–2000 rads was given subsequenthy.

The technique employed in telecobalt therapy was almost the same as that of conventional X-ray therapy, and prophylactic irradiation has not been routinely used until 1959. Prophylactic irradiation with a dose of 3000 rads was delivered to the contiguous region only in a small number of cases. Mantle technique[6] or extended field technique has been applied routinely since 1964.

Results

The 5- and 10-year crude survival rates of reticulum cell sarcoma were 22% (84 out of 374 cases) and 21% (53 out of 252 cases), respectively (Table 3). When the figures were corrected for life expectation, the 5- and 10-year survival rates became 26% and 28%, respectively. When the tumor was confined to the head and neck region, the prognosis was considerably better than that from other origins. The 5-year survival rate of reticulum cell sarcoma originating in the head and neck was 80 out of 328 cases or 24%, as shown in Table 4. On the contrary, there were only 4 cases of 5-year survival from other origins, such as hilar, retroperitoneal, and shoulder area, tonsil and mesenteric lymph nodes.

When the tumor was confined to a single anatomic region or site (Stage 1-1), the 5-year survival rate

Table 3. Histological calssification of malignant lymphoma cases and their 5- and 10-year survival rates

	No. of cases	No. of 5-year survivors	Survival rate (%) 5 years	10 years
Reticulum cell sarcoma	374	84	22 (26)*	21 (28)*
Lymphosarcoma	22	7	32	
Giant follicular lymphoma	3	3	100	
Hidgkin's disease	7	0	0	
Unclassifiable	17	3	18	
Total	423	97	23	

*Relative survival rate is indicated in parentheses.

Table 4. Stage and 5-year survival rate of reticulum cell sarcoma cases

Primary site	Stage 1–1	1–2	2	3	4	Total (%)
Head and neck	32/73	41/114	7/92	0/46	0/3	80/328 (24%)
Axilla	0/2					0/2
Hilum			1/2			1/2
Retroperitoneal region	1/2					1/2
Inguinal region	0/1		0/1			0/2
Stomach and intestine					0/9	0/9
Others	1[a]/3[b]			1[c]/1	0/4[d]	2/8
Uncertain				0/13	0/8	0/21
Total (%)	34/81 42%	41/114 36%	8/95 9%	1/60	0/24	84/374 23%

a) shoulder area. b) solitary subcutaneous tumor in 2 cases. c) mesenteric nodes and tonsil. d) bone (one case)., pancreas (one case), and subcutaneous tissue (2 cases).

Table 5. Stage and 5-year survival rate in reticulum cell sarcoma originating in head and neck

Primary site	Stage 1–1	Stage 1–2	Stage 2 above clavicle	Stage 2 below clavicle	Stage 3 and 4
Nodal origin					
Cervical node(s)	8/25	—	0/8	0/7	0/16
Extra-nodal origin					
Waldyer's ring					
Epipharynx	7/17	12/19	1/19	0/3	0/9
Tonsil	9/19	26/76	5/36	0/9	0/21
Base of tongue	1/1	0/2	0/3	0/1	—
Nasal cavity or maxillary antrum	7/10	3/7	0/5	—	0/3
Cheek	0/1	—	—	—	—
Thyroid	—	—	1/1	—	—
Total	32/73	41/114	7/72	0/20	0/49
(%)	(44%)	(36%)	(10%)		

was 42% (34 out of 81 cases), as shown in Table 4. When the tumor extended to both sides of the diaphragm, skin, bone, bone marrow, or liver (Stage 3 or 4), the prognosis was very poor with only one case surviving over 5 years. Table 5 summarizes the 5-year survival rates of reticulum cell sarcoma originating in the head and neck of different stages. Five-year survival rate was 44% (32 out of 73 cases) for stage 1-1 and 36% (41 out of 114 cases) for stage 1-2.

Involvement of supraclavicular lymph node(s): Of 25 cases of reticulum cell sarcoma originating in the neck of stage 1, 8 cases survived over 5 years (Table 6). Of these 25 cases, supraclavicular node involvement was found in 5 cases and none survived over 5 years. Of 97 cases originating in Waldyer's ring of stage 1-2, 38 cases survived over 5 years. The involvement of the supraclavicular node was found in 9 cases and only 1 case survived over 5 years. The prognosis of stage 1 with involvement of the supraclavicular node was as poor as that of stage 2.

Table 6. Five-year survival rate and involvement of supraclavicular lymph node (s) in cases of reticulum cell sarcoma originating in head and neck

	Involvement of supraclavicular node(s)			
	+		−	
Cervical node origin in stage 1–1	0/5		8/20	
Waldyer's ring origin in stage 1–2				
Epipharynx	0/1	1/9	12/18	37/88
Tonsil	1/8		25/68	
Base of tongue	–		0/2	

When stage 2 cases were classified into two subgroups ("above clavicle" and "below clavicle") according to the extent of the disease, 5-year survival rates became 10% and 0%, respectively (Table 5). It is noteworthy that the prognosis became extremely poor when the disease extended beyond the clavicular region.

Extra-nodal type (Waldyer's ring, nasal cavity, and maxillary antrum) showed a better response than the nodal origin (Table 5). However, it should be added that 7 cases out of 8 five-year survivors of the cervical origin had received irradiation after adenectomy.

Among 25 cases of reticulum cell sarcoma confined to the unilateral cervical lymph node region, 8 cases survived over 5 years. When the tumor of the neck extended to the supraclavicular region, none survived over 5 years even though 3 out of 5 cases received prophylactic irradiation to both axilla and mediastinum (Table 7).

The relationship between 5-year survival rate and the duration of symptoms prior to treatment is shown in Table 8. No difference was observed in 5-year survival rates between the cases receiving radiation therapy within one month and over 6 months. This suggests a great individual difference in the natural tendency for tumor growth.

Table 7. Number of cases receiving prophylactic irradiation
(Reticulum cell sarcoma originating in neck)

Localization		Prophylactic irradiation		
		Axilla	Axilla and mediastinum	Not given
Unilateral cervical region without supraclavicular node involvement	Surviving over 5 years	3	0	5
	Died within 5 years	2	0	10
Unilateral cervical region with supraclavicular node involvement	Surviving over 5 years	–	–	–
	Died within 5 years	1	3	1

Table 8. Five-year survival rate in relation to duration of symptoms prior to treatment in early cases of reticulum cell sarcoma without supraclavicular node involvement

Localization \ Duration of symptoms (months)	< 1	1–3	3–6	> 6
Epipharynx alone	2/4	4/8	1/1	0/4
Tonsil alone	1/2	3/5	4/9	1/2
Unilateral cervical region alone	2/4	1/7	4/7	1/2
Epipharynx and its regional lymph node(s)	2/5	3/6	2/7	5/10
Tonsil and its regional lymph node(s)	6/17	10/29	3/9	7/12
Total	13/32	21/55	14/33	14/30
(%)	(41%)	(38%)	(43%)	(47%)

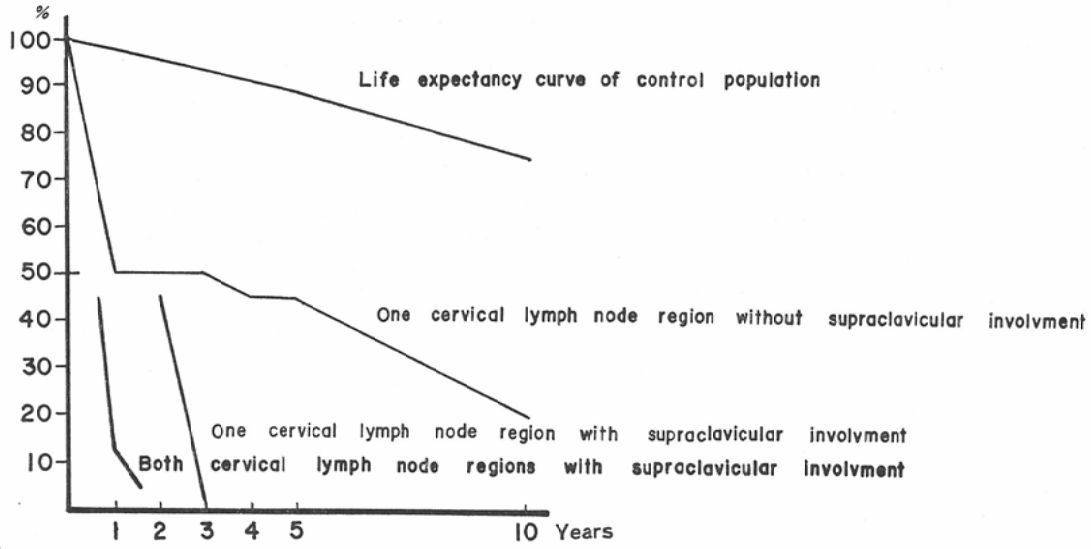

Fig. 2. Percentage survival correlated with the extent of the disease, in reticulum cell sarcoma cases originated in neck.

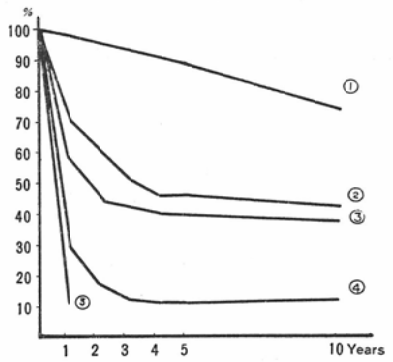

Fig. 3. Percentage survival correlated with the extent of the disease, in reticulum cell sarcoma cases originated in Waldyer's ring.

① Life expectancy of control population of the same age distribution
② Involvement of Waldyer's ring only
③ Involvement of Waldyer's ring and one regional node region. Cases of supraclavicular node involvement are excluded.
④ Involvement of Waldyer's ring and one regional node region. Cases of supraclavicular node involvement are included.
⑤ Waldyer's ring origin with extension below the clavicle but not beyond diaphragm.

The percentage survival in reticulum cell sarcoma originating in the neck and having a different extent is graphically shown in Fig. 2. When the tumor was confined to unilateral lymph node region, the percentage survival curve became almost parallel to that of life expectation one year after treatment. One the contrary, the curve fell sharply for advanced stages. Fig. 3 shows the same tendency observed

for cases originating in Waldyer's ring.

Exacerbation*: The frequency of primary type of exacerbation was studied for cases in early stages originating in the epipharynx, tonsil, and cervical lymph node (Table 9). Recurrence was noted in 14 out of 69 cases or 20%, while marginal extension was observed in 23 cases or 33% and abdominal extension in 21 cases or 31%,

The interval from initial treatment to abdominal extension measured less than 5 months in 10 cases and over 6 months in 11 cases. Among 62 five-year survivors of reticulum cell sarcoma, 11 had exacerbation, and 10 of which could be controlled by repeated irradiation (Table 9). Most cases with exacerbation died within a short period of time, indicating the rapid spread of this disease, while some cases showed better prognosis.

Table 9. Primary type of exacerbation (new manifestation) of reticulum cell sarcoma originating in epipharynx, tonsil, and cervical region

	5-year survival rate	Surviving without exacerbation	recurrence	Marginal extension	Mediastinal extension	Abdominal extension	Multiple	Others	Unknown
Epipharynx									
Without node involvement	7/17	7	3	3	–	1	–	–	3
With involvement of one regional lymph node region**	12/28	8	2	8	–	3	–	–	7
Tonsil									
Without node involvement	9/19	7	1	2	–	3	–	–	6
With involvement of one regional lnymph node region**	26/68	24	7	9	–	11	3	5	9
Unilateral cervical region**	8/20	5	1	1	1	3	2	–	7
Total	62/152	51	14	23	1	21	5	5	32

**Cases with involvement of supraclavicular node(s) were excluded

Tumor dose: The median dose of 3500–5000 rads was delivered in 3–6 weeks in most cases. Scatter diagram of doses against time is shown for 30 cases originating in Waldyer's ring with or without involvement of one regional lymph node (Fig. 4). These cases were selected from those treated successfully. Solid circles indicate conventional X-ray therapy and open circles telecobalt or telececium therapy. The isoeffect curve was drawn by free hand. Tentative time-dose relationship is expressed by $D = 1750 \text{ rads} \times t^{0.30}$, where D is the median tumor dose and t is day, and the recovery factor is 0.30.

The results of radiation therapy for lymphosarcoma and Hodgkin's disease will be mentioned briefly.

*Exacerbation implies recurrence as well as extension.

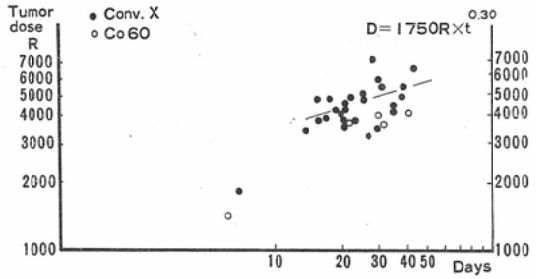

Fig. 4. Time-dose relationship for long-term local control. The RBEs of conventional X-ray and ^{60}Co γ-ray were not considered.

The 5-year survival rate of lymphosarcoma was 36% or 8 out of 22 cases as shown in Table 10. The prognosis of stage 2 seemed slightly better than that of reticulum cell sarcoma. It should be noted, however, that 2 outof 3 lymphosarcoma cases below the age of 20 developed lymphatic leukemia soon after radiation treatment.

Hodgkin's disease was seen only in 7 cases, dying all within 5 years following radiation therapy (Table 11). The cause of death was the generalization of the disease.

Table 10. Stage and 5-year survival rate in lymphosarcoma

Primary \ Stage	1–1	1–2	Stage 2	Stage 3	Stage 4	Total
Head and neck	4/5	1/2	2/4	0/2	0/2	7/15
Inguinal	0/1	1/1	–	–	–	1/2
Intestine	–	–	–	–	0/2	0/2
Unknown	–	–	–	0/3	–	0/3
Total	4/6	2/3	2/4	0/5	0/4	8/22

Table 11. Stage and 5-year survival rate in Hodgkin's disease

Primary \ Stage	1–1	1–2	Stage 2	Stage 3	Stage 4	Total
Head and neck	0/1	–	–	0/2	0/1	0/4
Axilla	–	–	–	0/1	–	0/1
Inguinal	0/1	–	–	–	–	0/1
Unknown	–	–	0/1	–	–	0/1
Total	0/2	–	0/1	0/3	0/1	0/7

Discussion

It is generally believed that reticulum cell sarcoma of extra-nodal origin of the head and neck is less vigorous than that of nodal origin.[9,18] According to our experience, reticulum cell sarcoma in stage 1 originating in Waldyer's ring showed a fairly good prognosis by small field irradiation. When the tumor was confined to unilateral cervical lymph node region, the prognosis was also favorable. On the con-

trary, when the disease extended below the clavicle, the prognosis suddenly became poor and none survived over 5 years.

The importance of prophylactic irradiation to the lower neck region in early cases of Waldyer's ring origin has been stressed.[14,15] Some authors[5,9,13] reported that systemic prophylactic irradiation might be worth while, especially for reticulum cell sarcoma of the head and neck origin, while Peters[10] and Rosenberg and Kaplan[12] reported negative results.

As to the location of exacerbation after the primary treatment, Wang[15] and Tikka and Malmio[14] have indicated mainly the contiguous lymph node region. Rosenberg and Kaplan,[12] however, stated that the development of reticulum cell sarcoma is more haphazard and often not orderly than that of Hodgkin's disease. It is conceivable that the "multi-target" theory of this disease might have been derived pathologically from this aspect. The results of our study clearly indicate that, 33% of the cases in early stage of reticulum cell sarcoma originating in the head and neck region had marginal extension as the initial type of exacerbation, 31% developed a distant extension, while only 20% had local recurrence within the irradiated field.

Above findings suggest that the adoption of systemic prophylactic irradiation to the main lymphatic regions such as axillary, mediastinal, para-aortic, iliac, and inguinal regions in cases of reticulum cell sarcoma originating in the head and neck region might be worth while. As we could not obtain any significant results sofar due to small number of cases, future continued study seems necessary to get more definite evaluation.

Average tumoricidal dose for reticulum cell sarcoma originating in the head and neck region is to be 4000 rads in 4 weeks, although additional booster dose of 1000–2000 rads might be required to remaining tumor in some cases.

Fuller[8] and Kaplan[7] believe that tumoricidal dose for reticulum cell sarcoma should be higher than that of Hodgkin's disease being 5000 rads in 5 weeks in megavoltage therapy or 5000 rads with a weekly dose of 750 rads in orthovoltage therapy. Hansen[4] reported that the average tumor dose for reticulum cell sarcoma patients surviving over one year was 2800 R in 33 days with a recovery factor of 0.45. Our experience indicates that the tumor of less than 50 cm^3 in size could be controlled permanently with 4000 rads in more than 90%.

Newall *et al.*[9] reported that both radioresistant and radiosensitive tumors may appear according to the location of reticulum cell sarcoma in the body. Reticulum cell sarcoma originating in the bone is most radioresistant, requiring 5000–6000 rads in 20–25 days, but the tumors originating in the lymph nodes of the head and neck are almost always radiosensitive and curable, although requiring 4500–5000 rads in 25–35 days. No comments can be made here, as the incidence of reticulum cell sarcoma arising in bone is rare in Japan.

Natural tendency of the generalization of this disease varies considerably by cases. As little histological information was available at present, the relationship among histological malignancy, radiosensitivity, radiocurability and predictable clinical course can not be reported. We are now trying to deliver prophylactic irradiation to the main drainge of axillaryt, mediastinal and para-aortic lymph nodes using linac large-field technique to improve our results.

The reported 5-year survival rate for stage 1 reticulum cell sarcoma ranges from 68% to

40%.[1,4,5,10,13] The 5-year survival rate of this disease originating from Waldyer's ring without nodal extension was reported as 79% by Wang.[15] These figures are in good agreement with our results.

According to the japanese and western pathologists, the ratio of occurrence of reticulum cell sarcoma and lymphosarcoma versus Hodgkin's disease in Japan is roughly 80 to 20, differing markedly from that in western countries, and thus the racial difference should be stressed.

Summary

Results of radiotherapy of 423 malignant lymphoma cases at the Cancer Institute Hospital in Tokyo during the 18-year period from 1946 to 1963 were reviewed. As the frequency of reticulum cell sarcoma was 88% of all cases, attention was focussed mainly on this disease.

Five-year survival rate of reticulum cell sarcoma was 42% for stage 1-1, 36% for stage 1-2, 9% for stage 2, 1.6% for stage 3 and 0% for stage 4, averaging 23% for total cases.

Five-year survival rates were further correlated with age, sex, site and extent of tumor, duration of symptoms, and the modality of treatment. Relatively favorable results were obtained in cases of reticulum cell sarcoma originating in the head and neck region, with an average tumor dose of 4000 rads in 4 weeks. Not only the staging of this disease but also the extension either to supraclavicular region or below the clavicle was found very important in evaluating the prognosis. The primary type of exacerbation (new manifestation) was encountered more frequently in both marginal and distant nodal regions than local recurrence. Effective method for controlling subsequent spread should be studied in the future to increase the over-all curability.

Our results of radiation therapy of lymphosarcoma and Hodgkin's disease were also briefly described.

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