Results of Radiation Treatment of Malignant Lymphoma

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悪性リンパ腫の放射線治療成績

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1957～1961の5年間に癌研放射線科において166例の悪性リンパ腫患者が放射線治療を受けた．細網肉腫は137例あり全体の83%を占め，リンパ肉腫7，巨大濾胞性リンパ腫1，ホジキン病6および分類不能が15であつた．全例の5年生存率は19%で，細網肉腫のそれも19%であつた．ホジキン病には5年生存者はなかつたが，半数は比較的経過の長いものであつた．

悪性リンパ腫の男女比は2：1で，5年生存率は同率であつた．進行度は山下教授を中心としたTNM分類日本小委員会案を用いた．TN1M0，TN2M0およびTN3またはM1に分けて5年生存率を求めるとそれぞれ58%，21%，4%であつた．大部分の症例は深部治療で，1960から一部にTelecobalt，Telcesium治療が行なわれた．腫瘍線量は3,000～5,000Rを3～5週間に与えるのが普通であつた．average time-dose curveを求めると，$D = 1{,}750R \times t^{0.30}$となつた．また．腫瘍の大きさ（V）と4週間線量（$D_{4w}$）との関係は，$D_{4w} = 4{,}000R \times V^{0.04}$であつた．腫瘍が小さい場合の方が早く消失する傾向があるが必要線量が与えられているので上記の曲線の傾斜は有意でなかつた．今後，更に検討したい（本論文の主旨は第4回日本医学放射線学会シンポジウム部会，1967年9月福島において述べられたものである）．

Results of radiation treatment of malignant lymphoma at our hospital* between 1946 and 1956 have been reported in 1963 by Kaneta & Yamashita[1]. The results of the succeeding period between 1957 and 1961 will be reported in the present paper. The radiobiological study to conduct the time-dose relationship or time-dose-volume relationship in the treatment also attempted.

1. Number of cases and their histological classification

A Total of 66 cases is shown with histological classifications and five-year survival rates in Table 1. The proportion of histological type is the same as reported in the previous paper.

2. Age and sex

The distribution of cases in both sexes is shown in Figure 1, with the number of five year survivors, respectively. The ratio of male to female was 2 : 1, with equal rates of five-year survivors, as shown in

*Hospital of Japanese Foundation for Cancer Research.

Table 1. Histological classification of our cases with malignant lymphoma and their five-year survival rates

Classification	No. of cases	No. of five-year survivors(%)
Reticulum cell sarcoma	137	26 (19%)
Lymphosarcoma	7	1
Giant follicular Lymphoma	1	1
Hodgkin's disease	6	0
Malignant lymphoma not specifiable	15	3
Total	166	31 (19%)

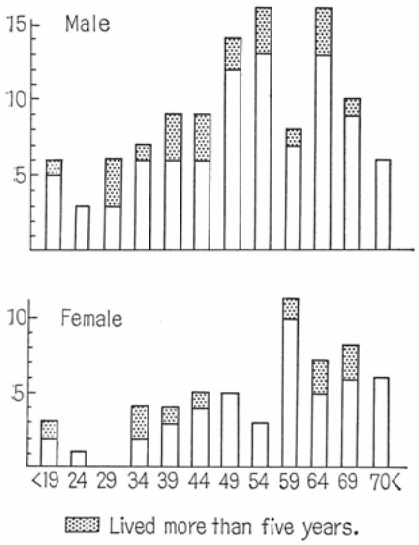

Fig. 1. Age distribution and number of five-year survivors of malignant lymphoma cases.

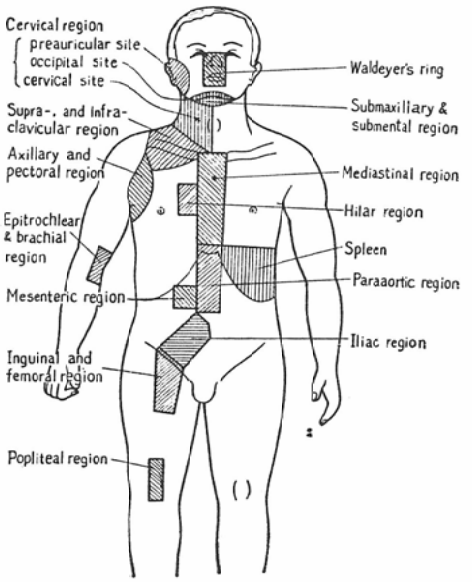

Fig. 2. Anatomical lymphatic region (Japanese Subcommittee, 1967).

Table 2. The ocurrance of cases is more dominant in rather old age groups regardless of sexes. The number of five-year survivors is found to distribute almost uniformely among various age groups and sexes.

3. Localisation and stage

Recently, the Japanese subcommittee, proposed the stage classification of Lymphoadenoma-Hodgkin's disease, as suggested by UICC TNM staging committee, as follows by Yamashita and Matsubayashi[2] in 1867.

TN1: Disease limited to one anatomical region

TN2: Disease limited to two contiguous anatomical regions

TN3: Disease limited to more than two anatomical regions or in two non-contiguous regions

M0: No involvement of other tissues or organs beyond anatomical regions

M1: Involvement of other tissues or organs

Table 2. Sex and five-year survivors

Sex	No. of cases	No. of five-year survivors
Male	109	21
Female	57	10

Table 3. Localization and clinical staging of malignant lymphoma cases and their five-year survivors by radiation treatment

Primary	TN1M0	TN2M0	TN3 or M1	Total
Waldyer's ring	9/17	7/23	2/52	18/92
Maxillary antrum or nasal cavity	1/2	0/2	0/2	1/6
Cervical or supraclavicular lymph node	8/14	0/7	1/12	9/33
Axilla	0/1	—	0/2	0/3
Cubital	1/1	—	—	1/1
Shoulder	1/1	—	—	1/1
Anterior chest wall	—	—	0/1	0/1
Mediastinum	—	—	1/1	1/1
Esophagus	—	—	0/1	0/1
Stomach	—	—	0/2	0/2
Small intestine	—	—	0/1	0/1
Colon	—	—	0/2	0/2
Retroperitoneal	—	—	0/3	0/3
Inguinal	0/1	0/1	0/1	0/3
Bone	—	—	0/1	0/1
Femoral	—	—	0/1	0/1
Unkown	—	—	0/14	0/14
Total	20/37	7/33	4/96	31/166
%	58%	21%	4%	19%

Our cases were classified into TN1M0, TN2M0, TN3M0 or M1 groups. Decreasing rate of five-year survivors for increasing stages is shown clearly in Table 3, irrespective of the origin.

Regarding to the staging, TN1M0 in our classification is the same as stage 1 or stage 1-1 described by Peters & Middlemiss[8], Kaplan[4] and Rye conference[5] and TN2M0 is practically comparable to stage 2 or stage 1-2 of the above authors. When tumor involvement extends to 3 or more anatomical regions in either side of the diaphragm, their classification is stage 2, while our classification is TN3. Thus, our 4 five-year survivors in TN3M0 cases should be included in stage 2 according to the previous classification, because their diseases were limited to the upper half of the body.

4. Method of treatment

Treatment policy was not changed much from the previous report[1]. Main changes are: 1) the adoption of prophylactic irradiation covering the surrounding areas of lymphatic drainage since 1959, and 2) changing modalities from conventional X-ray to cobalt 60 and cesium 137 γ-rays since 1960.

Usually rectangular treatment fields of small to medium size ($6 \times 8 - 10 \times 15\ cm^2$) were used to restricted areas of the primary tumor with reasonable margine.

Tissue dose to the tumor bearing area was 3000–5000 R in 3–5 weeks. A booster dose of 1000–2000 R

was administered to the limited spot where remaining irradiated tumor was suspected active. For the prophylactic irradiation, a dose of 3000–4000 R was administered to the adjucent lymph node area after the completion of irradiation to the primary area. "Mantle field" (Kaplan)[6] or "extended field" (Fuller)[7] was not used in this period.

When the disease is generalized, multiple separated fields were employed routinely.

5. Results of treatment

Five-year survival rates for each histological classification were shown in Table 1. Among 37 cases of TN1M0, 20 cases survived more than five years, and among 33 cases of TN2M0, 7 cases survived more than five years, while only 4 cases survived more than five years ovt of 96 cases of T3M0 or M1 (Table 3).

Among 31 five-year survivors, 28 cases originated from head and neck region 1 from shoulder area 1 from cubital area and the last one from mediastinal area two cases whose primary regions were either shoulder area or cubital node received surgical removal followed by irradiation. The last one case revealed non-resectable mediastinal malignant lymphoma with hilar and peri-pleural spread at exploratory thoracotomy. This patient received post-surgical irradiation of 6000 R in 2 series during 70 days.

Primary lesions were locally well controlled by primary treatment more than for 6 months in 31 cases, of TN1MO 24 of which survived for more than five years without disease, but remaining 7 died within five years probably due to the exacerbation and 5 cases out of 23 TN2 originated in Waldyer's ring has developed residual nodes inside irradiation field, even though the primary lesion had been well controlled. (Table 4).

Table 4. Local conditions or primary site of exacerbation following radiation treatment

Stage ／	Post-treatment condition／Primary	Waldyer's ring	Cervical node	Total
TN1M0	well controlled*	10	8	18
	Residual	0	1	1
	Recurrence	0	1	1
	Extension to distant area	1	1	2
	Died of other disease	0	1	1
	Uncertain	6	2	8
	Total	17	14	31
TN2M0	Well controlled*	10	3	13
	Primary well with residual node(s)	5	0	5
	Recurrence	1	0	1
	Marginal extension	1	1	2
	Extension to distant area	1	0	1
	Uncertain	5	3	8
	Total	23	7	30

*"well controlled" in this table means no recurrence inside radiation field.

Median survival time was 1.2 years for 40 cases of TN1M0 and TN2M0 originated in the Waldyer's ring, and 1.8 years for 21 cases of the same stage originated in the neck, the five-year survival rates in each group were 40%, and 37%, respectively (Figures 3, 4 and 5).

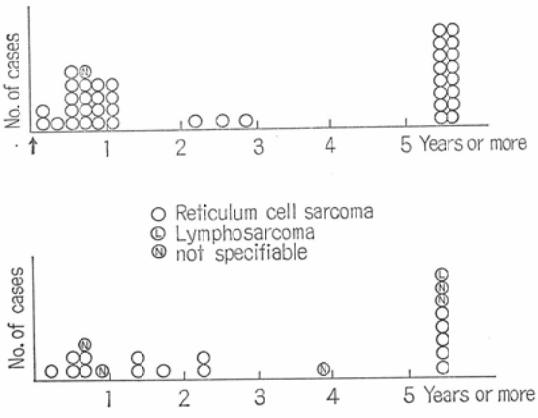

Fig. 3. Survival time after initiation of radiotherapy of TN1 or TN2M0 cases of the Waldyer's ring origin (above) and of cervical node origin (below) (○ represents each case).

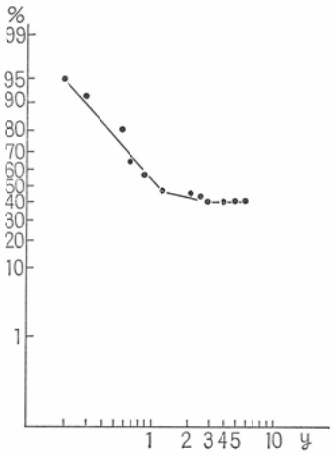

Fig. 4. Survival rate after the initiation of radiotherapy for TN1 or TN2 cases of Waldyer's ring origin.

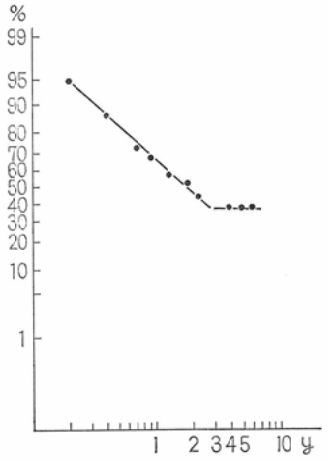

Fig. 5. Survival rate after initiation of radiotherapy for TN1 or TN2 cases of cervical origin.

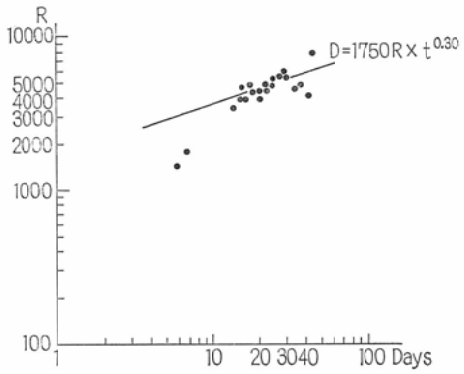

Fig. 6. Average time-dose relationship for 21 five-year survivors of TN1M0 or TN2M0 stages, whose primary sites were either in the Waldyer's ring or the cervical region.

6. Time-dose relationship

Most patients, who belonged to TN1M0 and TN2M0 stages of the Waldyer's ring or the cervical region, received tumor doses from 4000 to 5000 R in 3 to 5 weeks and they Figure 6 shows the distribution of the time-dose relationship without regarding the volume of the tumor in 21 patients, whose five-year follow up was established to be free from disease after primary radiotherapy. Tentative time dose curve was drawn by free hand in Figure 6, which was calculated as $D = 1750\ R \times t^{0.30}$, where D is the average tumor dose delivered in over-all t days.

7. Time-dose-volume relationship

Equivalent 4 weeks tumor doses were plotted against tumor volume, as in Figure 7, by computing the tumor dose using the recovery factor of 0.25 (Friedman)[6]. Ten double round circles represent the

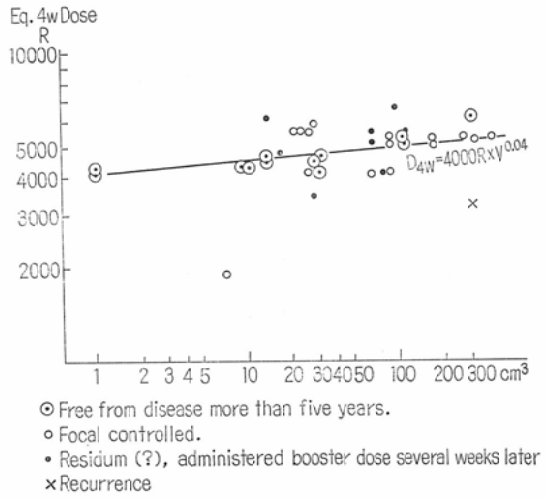

Fig. 7. Volume of involved lymph nodes in the cervical region and equivalent 4 week's dose.

Table 5. Rate of tumor disappearance following graded doses of irradiation

Dose in 4 weeks \ Size of tumor	< 9.9 cm³	10–49 cm³	< 50 cm³	Total
> 5000 R	1/1	4/5	10/14	15/20
4999–4000 R	3/3	6/7	2/3	11/13
3999–3000 R	0	0/1	0/1	0/2
< 3000 R	1/1	0	0	1/1
Total	5/5	10/13	12/18	27/36

successful doses which produced complete regression without exacerbation for more than five years, 17 round circles represent the doses for complete regression for more than 6 months, 8 solid dots represent the tumors which required a booster dose several weeks later and one recurrence is signified by cross sign. The relative biological effectiveness (RBE) is not considered here. The straight line is drawn by free hand to demonstrate time-dose-volume relationship, as $D_{4w} = 4000\,R \times V^{0.04}$, where $D_{4w}$is the tumor dose in 4 weeks and V is the volume of the individual tumor. The slope of 0.04 indicates that no significant dose-volume lationship could be found clinically.

Above 36 dose points in Figure 7 were divided into 12 groups according to 4 dose levels against 3 levels of tumor volume as tabulated in Table 5. For example, small tumors of less than 9.9 cm³ in volume regressed completely at all dose levels, while 4 tumors of more than 50 cm³ could not be controlled by dosis well above 5000 R. Thus, when the involved lymph nodes are smallerin, they tended to disappear earlier and can be more easily controlled.

8. Prophylactic irradiation

Among 23 cases of cervical origin of TN1 and TN2M0 stages, 11 received prophylactic irradiation to both axilla and mediastinum. No significant difference was observed in five-year survival between

the results with or without prophylactic irradiation.

9. Hodgkin's disease

There were only 6 cases of Hodgkin's disease among 166 malignant lymphoma cases in this series. There was no five year survivor, but 3 cases survived for rather long time.

Discussion

It is to be noted, first of all, that the great difference exists in relative incidence of so-called malignant lymphoma between Japan and U.S.A. In the present series, relative incidence of reticulum cell sarcoma, lymphosarcoma and Hodgkin's disease were 82%, 4% and 3.5%, respectively, which is almost the same as reported in our previous paper[1]. Low incidence of Hodgkin's disease is also reported as of 5.8% by Yasukōchi, Iino and Watanabe[9] from the Tokyo University Hospital. The major sites of exacerbation in reticulum cell sarcoma is either paraaortic, iliac or inguinal nodes or distant extranodal extension. We are now trying to deliver prophylactic irradiation to the main drainage of the retroperitoneal lymph nodes besides axillary and mediastinal region for reticulum cell sarcoma of head and neck origine, to improve our present results.

As to the tumor dose for Hodgkin's disease, Kaplan[4] reported that there are practically no recurrence following irradiation of 4000 rads in 4 weeks. Friedman[8] reported a equivalent single dose of 1750 R and the recovery factor of 0.25 for this disease. Scott & Brazil[11] described the time-dose relationship is given by the formula of $D = 1400\ R \times t^{0.29}$ for supervoltage radiotherapy, and $920\ R \times t^{0.38}$ for orthovoltage radiotherapy, indicating larger dose must be given with supervoltage X-rays.

As to the tumor dose for reticulum cell sarcoma, Kaplan[4] reported that higher radiation dose than Hodgkin's disease i.g. 5000 rads in 4 weeks is required for some cases, while Miyakawa[10] et al. administered at least 4000 R in 4 weeks. Our proposed tumor dose ranged 4000–5000 R in 3–4 weeks. The time-dose relationship for the reticulum cell sarcoma was calculated by the formula, $D = 1750\ R \times t^{0.30}$. Clinical trial to derive relationship between tumor dose and tumor size failed to show any significancy, but possible relationship should be studied extensively. A lower dose might be sufficient for small tumors and prophylactic treatment, but its magnitude could not be estimated from our data. Other modifying factors, e.g. histology and individual sensitivity which is difficult to be estimated at present should be ako considered more carefully.

Summary

During the interval between 1957 and 1961, 166 malignant lymphoma patients received radiation treatment at the Hospital of Japanese Foundation for Cancer Research. The frequency of reticulum cell sarcoma, lymphosarcoma, Hodgkin's disease and unclassified malignant lymphoma was 82.5%, 4.2%, 3.6% and 9%, respectively, and one case of giant follicular lymphoma was included in this series.

Over-all five-year survival rate of malignant lymphoma was 19%. Five-year survival rate of all reticulum cell sarcoma was 19%, which is almost the same as reported in many western literatures[12]. Patients were divided into 3 stages, i.e., TN1M0,TN2M0, TN3M0 or TN1-3M1, according to the staging of the japanese subcommittee for TNM system. Five-year survival rates for TN1M0, TN2M0, TN3M0 or TN1-3M1 weres 58%, 2I% and 4%, respectively.

For Hodgkin's disease, its occurrence in Japan is too small to draw any conclusion, but its nature seems to be more vigorous than that in western countries considered from our poor result.

Were studied on malignant lymphoma cases originated in head and neck region Pthe time-dose relationship and time-dose-tumor volume relationship. Proposed tumor dose is found to be 4000–5000 R in 3 to 4 weeks. Average time-dose curve was calculated as $D = 1750\,R \times t^{0.30}$.

Average volume-dose curve was calculated as $D_{4w} = 4000\,R \times V^{0.04}$, indicating no significance, bet ween volume and dose.

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