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Van de Graaff Neutrons for Superficial Tumor Therapy

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表在治療用バンデ・グラーフ中性子線

放医研・物理

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バンデ・グラーフ型加速器による 2.8MeV 重陽子をベリウム・ターゲットに入射してえられる平均1.9MeV 中性子線は，LET が高く，表在の抵抗性癌治療に有利であり，この適用の際の主として物理的諸データを実験的に求めた．また，深部線量を改善すべくリチウム・ターゲットを用いれば，平均 5.9MeV 中性子線がえられることを示した．測定された中性子線エネルギー分布にもとづき，電離法による線量測定パラメータを求め，ポリエチレン・コリメーターによる照射野形成，深部線量分布および，γ線混在度につき結果をえた．また，中性子線コリメーションが x, γ線に比較して困難であることから，積分線量の推定・記録が重要と考えて，これを治療患者の放射化データより推定する方法を示した．全身平均線量の推定に染色体異常のデータを採用した．

Summary

Neutron beams produced from beryllium and lithium target, bombarded by 2.8 MeV deuterons of a Van de Graaff accelerator, have been studied and applied for the purpose of superficial radio-resistant tumor therapy. Neutron spectra were determined, and the average energies of the foreward neutrons from beryllium and lithium target were 1.9 and 5.9 MeV, respectively. The kerma rates for 6 cm diameter collimator at 25 cm distance from the target were 12 and 17 rad per minute per 200 μA deuteron incidence on beryllium and lithium targets, respectively. Integral dose for each treatment was estimated by the whole body counting of neutron induced activities and also by the observation of chromosome aberrations in small lymphocytes in the blood of patient.

1. Introduction

Clinical trials were started in 1968 for investigating the therapeutic effectivenesss of 1.9 MeV neutron in average produced by a 3MeV Van de Graaff generator[1], based on the physical and biological data[2][3][4] obtained by preliminary studies. Due to the quick attenuation of the neutron beam in tissue, superficial tumors suuh as metastatic skin tumor or metastatic lymph nodes were included in this trial. However, the main parts of the patients (25/30) included bore radioresistant tumors, such as melanoma and parotid tumor of fibrosarcoma. The results in those clinical trials suggested that malignant melanoma could be sufficiently controlled by the present neutron irradiation and that adenocarcinomas, such as breast and parotid tumor, were also controlled within the tolerance limit for normal tissue[5]. These results indicated the possibility that the therapeutic application of the 1.9 MeV neutron is more feasible than that of cyclotron neutron especially for superficial radiotherapy.

This paper describes the physical problems experienced with the Van de Graff neutron beam applied for radiotherapy.

2. Neutron source

Van de Graff accelerator used in this study was horizontally mounted machine, manufactred by High Voltage Engineering Corp. (USA) and its maximum voltage was 3 MeV. One of the beam ports (a straight beam course) has been used for therapy. Two types of thick metal target were used at the end of the beam port for (d,n) neutron production. One was beryllium metal disk pressed on an aluminum metal backing holder with water cooling. This target assembly was tolerable for the incident beam up to 200 μA defocused in 1.5 cm diameter at 2.8 MeV. The neutron yield of this target was on the 15% decrease after 1000 hrs under $2-5\times10^{-6}$

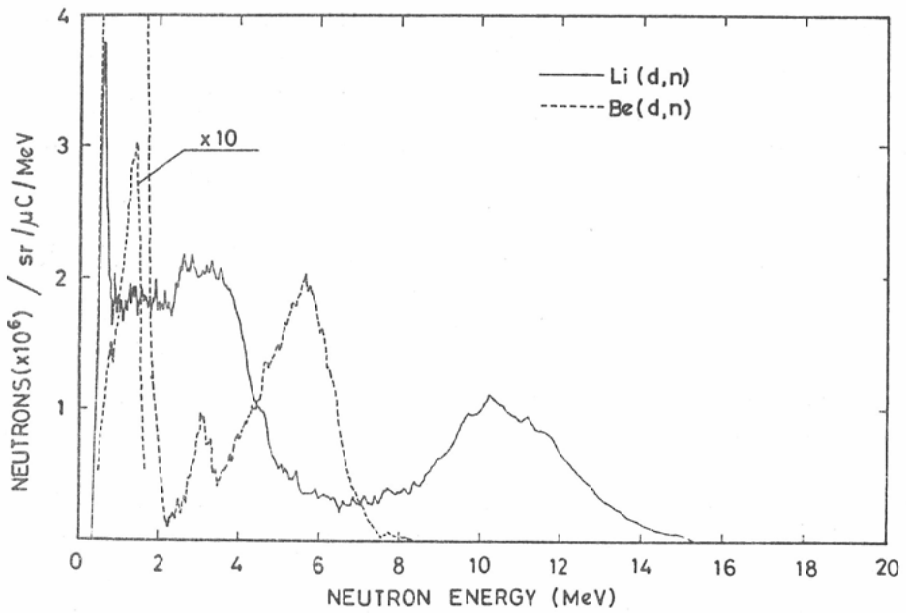

Fig. 1. Energy spectra of foreward neutrons from thick beryllium and lithium (d,n) reactions at 2.8 MeV.

torr vacuum. Second type was the thick target of unseparated lithium metal which was prepared by metal-coating method[6] on to an aluminum cup. The incidence of 2.8 MeV deuteron beam of 1.5 cm diameter on the water cooled target was possible up to 200 μA. The surface of lithium metal target was kept unhydrogenized even after 480 hrs storage in 10^{-3} torr vacuum at the beam port within around 4% decrease in the neutron output. This type of lithium target was fabricated for every period of use.

Fig. 1 shows the energy spectra of foreward neutrons from beryllium and lithium (d,n) reactions at 2.8 MeV, obtained by the time-of-flight method[2]. The ordinate represents the number of neutrons versus neutron energy. The average energies of neutrons from beryllium and lithium targets were 1.9 and 5.9 MeV, respectively.

3. Dosimetry

A pair of 3 cm^3 ionization chambers was used in this work and it was cyrindrical type connected to a gas flow system. The tissue equivalent plastic material (TEP)[7] was used for the wall of neutron sensitive chamber which was filled with tissue equivalent gas (TEG)[8]. The neutron less sensitive chamber was walled by teflon mixed with 20% carbon, and filled with CO_2 gas. The sensitivities of these chambers to neutrons and gamma rays were estimated based on the energy distributions shown in Fig. 1. The stopping power S_n was taken as to the recoil protons with the energy of one-fourth of the incident neutron, and S_B for the Compton electron with average initial energy. The ratios of mean ionizing energy for tissue equivalent gas and CO_2 gas were taken as $(\bar{W}_n/\bar{W}_B)_{TEG}=1.055$ and $(\bar{W}_n/\bar{W}_B)_{CO2}=1.036$. The resultant parameters used in this chamber system are $k_T=1$, $k_u=0.12$ and 0.17 for beryllium and lithium (d,n) neutrons, respectively.

4. Dose distribution

4—1. Field definition

A therapeutic set-up of the target and collimator assembly is schematically illustrated in Fig. 2. The small SSD value (25 cm) was taken for the present neutron beam to maintain the dose rate around 10 rad per minute.

Polyethyrene collimators were used as the inserted plugs with conical hole of several diameter. The

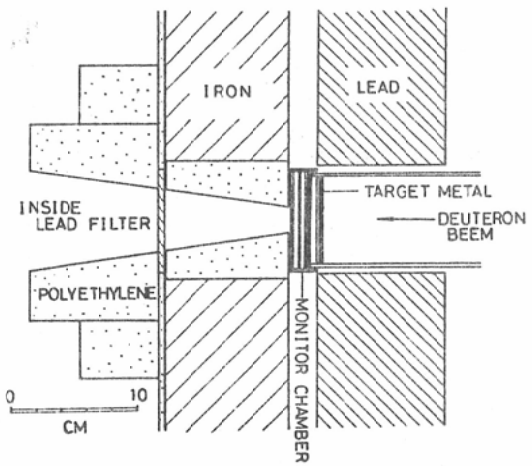

Fig. 2. Therapeutic arrangement of target and collimator assembly.

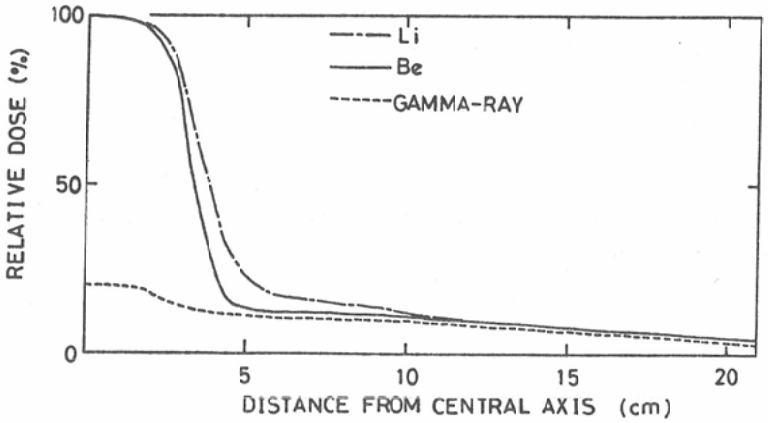

Fig. 3. Lateral dose distributions for neutrons from beryllium and lithium (d,n) reactions at 2.8 MeV, defined by a collimator of 6 cm diameter. Distribution for gamma-ray dose is given by broken curve.

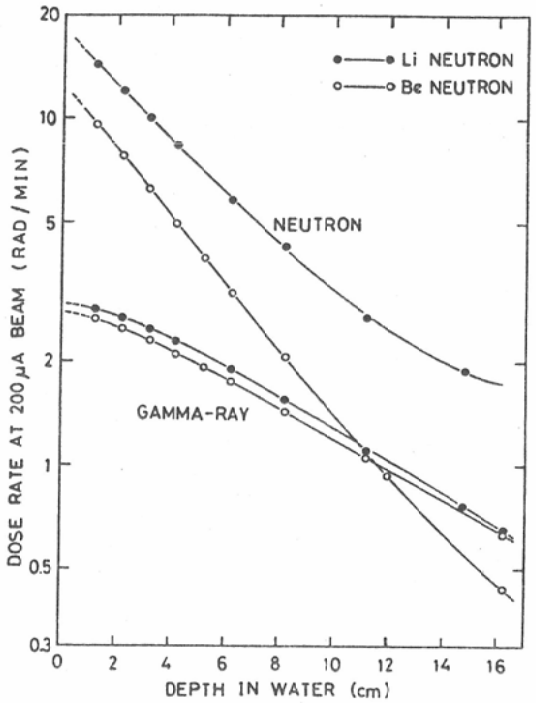

Fig. 4. Depth dose distributions for neutrons and gamma-rays from beryllium and lithium (d,n) reactions at 2.8 MeV.

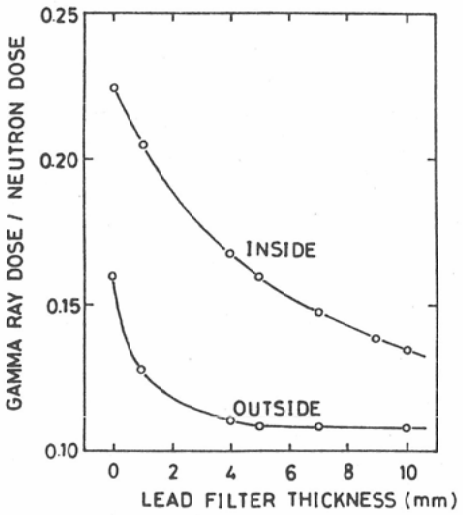

Fig. 5. Gamma-ray dose relative to neutron dose as a function of lead filter thickness. "Inside" and "Outside" denoted in the figure indicate lead filters set inside and outside the collimator, respectively.

transmission experiment revealed that the neutron dose was effectively attenuated by polyethyrene and, by the use of 20 cm thick polyethyrene slab, the total dose was attenuated below 10%, somewhat depending on the field size.

The lateral dose distributions of the field defined by the collimator assembly are shown in Fig. 3 for an inserted collimator of 6 cm diameter. When compared with the other usual teletherapeutic irradiation field, the present assembly defined the moderately clear periphery of radiation field.

4—2. Depth dose distribution

Depth dose distribution in water was measured by the paired ionization chamber for neutrons and gamma rays from thick target beryllium and lithium (d,n) reactions at 2.8 MeV. The typical results obtained for the field formed by a 6 cm diameter collimator are illustrated in Fig. 4.

4—3. Gamma ray contamination

Gamma rays were induced more or less from three sources: 1) from Van de Graaff accelerator and neutron target, 2) from inserted collimator and 3) from patient under treatment. The last component from patient was estimated to be less than 6% of the neutron dose at the surface of patient and was hard to be removed. In the therapeutic set-up illustrated in Fig. 2, a lead disk named inside filter was installed, in the middle of the inserted eollimator. The attenuation of gamma ray dose with this filter is given by the curve denoted as INSIDE in Fig. 5, in which the ratio of gamma dose to neutron dose for beryllium (d,n) neutron is given as the function of filter thickness.

In the present work, the inside filter thickness was taken to be 5 mm and an additional lead plate, named outside filter, was placed outside the collimator only when necessary in order to avoid the neutron dose attenuation caused by this extra lead filter. The curve denoted as OUTSIDE in Fig. 5 shows the effect of gamma dose attenuation by the use of filter. From this result, an outside filter of 4 mm thick lead plate was installed to suppress the gamma dose contamination within 11%. This figure seems to be twice as that of cyclotron neutron field.

The similar remarks could be made for the neutron field from lithium target, except for nearly 2% decrease in the ratio of gamma to neutron dose.

5. Estimation of integral dose (mean energy imparted)

After the neutron irradiation, certain amount of activity was induced in the patient, which was not too high to be significant dose but presumably relevant to estimate the neutron integral dose. Before and 30 minutes after the neutron treatment, the activity of the patient was measured by a whole body counter for 30 minutes. The detection efficiency of the counter for gamma rays of ^{24}Na distributed uniformly in human body was calibrated by a phantom. A typical pulse height spectrum of gamma rays from neutron induced activity in the patient is shown in Fig. 6, for the counting after the treatment on parotid gland with the surface dose of 155 rad in 6 cm diameter field. The gamma ray counts at 2.75 MeV was summed up as the exemplary value ^{24}Na activities, because the half-life of ^{24}Na was adequate for counting and 2.75 MeV peak was almost free from the counts due to the other gamma rays.

Fig. 7 shows the induced activities per unit neutron dose and per unit field area geometrically defined, for the various treatment position of the patient whose weight was normarized to 50 kg, versus the diameter of circular field. This quantity should be nearly constant for each treatment position, if the radiation level outside the field is negligibly low. However, the result of Fig. 7 indicate that the quantity increases significantly for the

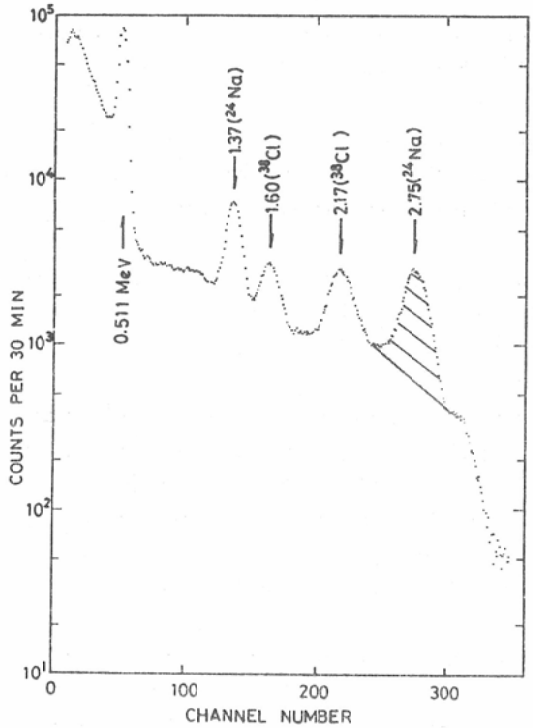

Fig. 6. A typical pulse-hight spectrum of gamma-rays from induced activities on a patient, obtained, by a 8 in. dia. ×4 in. long NaI scintillator in NIRS whole body counter.

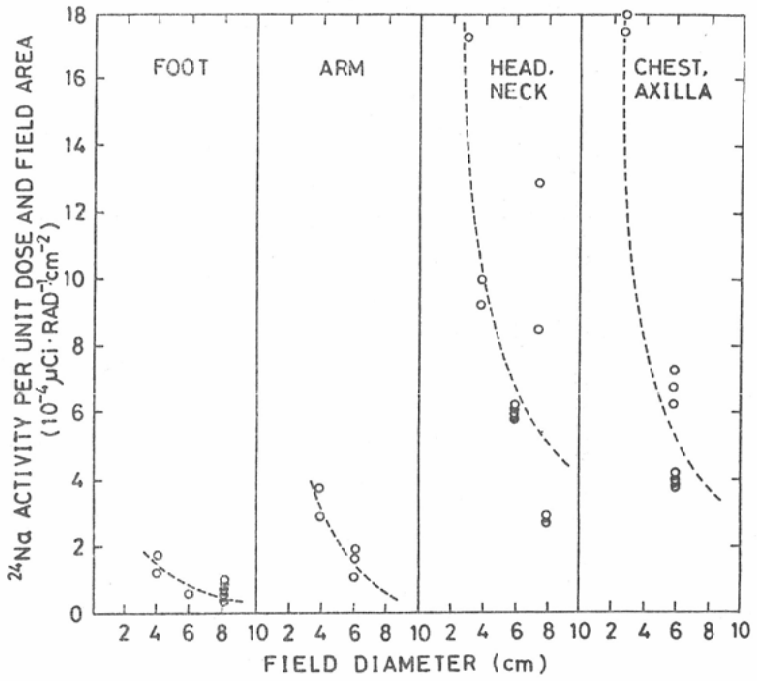

Fig. 7. Induced activities per unit neutron dose and per unit field area defined geometrically at various treatment position of the patient of 50 kg weight, versus the geometrical field size.

smaller field. ^{24}Na is produced by ^{23}Na(n_{th},γ) ^{24}Na reaction. So, the distribution of thermal neutron in the patient must be discussed for various field sizes. Therefore, it was complicated to estimate the integral dose in the case of neutron therapy when the radiation level was not negligible outside the field.

In the present work, the following biological procedure was utilized to estimate the relation between the integral dose for total body and the induced activity of ^{24}Na. A blood examination was made for every patient before and after the neutron therapy. The radiation induced chromosome aberrations (dicentrics and rings) in small lymphocytes in blood, which was assumed to be circulating uniformly throughout the body, were observed by Ishihara et al.[9] Results with the irradiated patients were plotted against ^{24}Na activity as shown in Fig. 8. The dose-response relation on chromosome aberration was obtained for the present neutron field by Sasaki[10] earlier as in the foam;

$$m=5125.36\times10^{-6}.D^{1.09}$$

where m is the number of dicentrics and rings per cell observed in the first cell division after the commencement of phythemagglutinin culture and D is the dose in rad. Hence, we can convert the ordinate of Fig. 8 in terms of dose. The relation between ^{24}Na activities(A) and average dose(D) can now be written as in foam;

$$D(rad)=1.3\ A(\mu Ci).$$

From the present procedure, it could be derived that the integral dose for total body of a 50 kg weight patient who received the dose of 100 rad in 6 cm diameter field is estimated to be 50 kg•rad and 150 kg•rad in the case of foot and chest treatment, respectively.

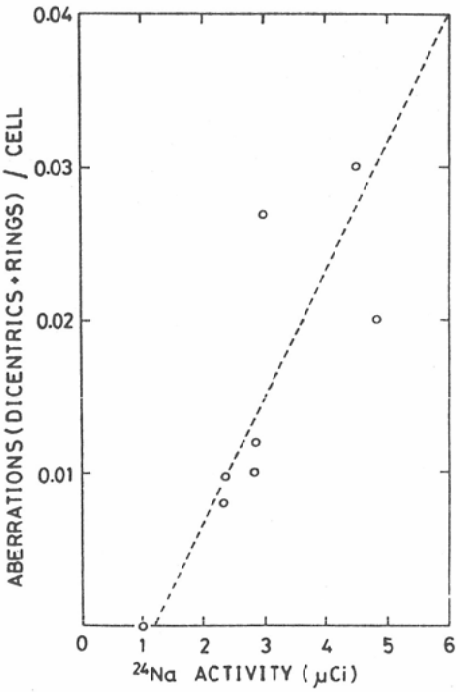

Fig. 8. Relation between chromosome aberration and ^{24}Na activity induced by neutron irradiation.

6. Discussion

6—1. Neutron source improvement

Van de Graaff neutron might better control the resistant tumour cells for its high LET[11], which is mainly characterized by low energy protons recoiled by neutron of 1.9 MeV on an average. However, such low energy neutron beam attenuates quickly in soft tissue due to the short SSD and the high interaction cross section. The use of neutrons produced by lithium (d,n) reactions instead of beryllium (d,n) reactions could be a practical improvement in the depth dose distribution.

Moreover, any other procedure to increase in source intensity will be a practical improvement for such high LET neutron therapy. At present the insulating gas in Van de Graaff tank of our institute is under replacement from N_2-CO_2 mixture to N_2-SF_6 mixture. This procedure will make the accelerating voltage higher up to 3.3 MeV and increase the depth dose rate. There are two other possible ways of the improvement. One is to develope a rotating target for allowing the more intence beam incidence. Our Van de Graaff has the capability to accelerate deuteron beam current up to 400 μA which are twice as intense as that of the present beam. The usual static metal target can not tolerate such high beam intensity even with forced water cooling. The rotating target assembly, in which a beryllium disk rotates and is effectively cooled like as a rotating anode X-ray tube, will be useful for the present purpose. Such trial has been made for the tritium target in D-T generator, but not for thick metal target yet.

The radiological properties of the fast neutrons of the mean energy of 0.85 MeV are being investigated at JANUS reactor, Argonne National Laboratory, using V-79 Chinese hamster cells in culture, that is relevant to

radiation therapy[11]. In Japan, we have started a project on the application of the fast column neutron beam at YAYOI reactor, University of Tokyo, for biomedical researches. The mean energy of the fission neutrons from this fast neutron source reactor could be around 0.9 MeV[12], but the more intense beam than that of Van de Graaff neutrons will make it possible to adapt the larger SSD and the longer collimator for improving the field definition.

6—2. Validity of integral dose estimation

One of the undesirable situations in neutron therapy is the considerably higher dose outside the field defined, than that for X- or gamma-rays, while the effect induced by neutron might be a serious problem in future. The estimation and record of the integral dose, therefore, could be important in neutron therapy, including the cases using neutron sources other than Van de Graaff neutrons.

The first and common method to estimate the integral dose is due to the calculations based on the depth dose distributions of the entire body for neutrons and gamma-rays. The radiations in the body are consisted of the incident radiations and the thermal neutron-captured gamma-rays of 2.2 MeV. The field definition in this work was less clear as shown in Fig. 3, and it was noticed to be neither certain nor practical for the present purpose to estimate the entire dose distribution of the patient under such complex situation. The present method, which only needs the whole body counting of ^{24}Na activity, seems to afford a practical solution to this problem.

The validity of this procedure is based on the assumption that the responce of small lymphocytes is proportional to the integral dose. The assumption was verified to be correct on a patient treated by ^{60}Co gamma-rays. Using the dose-response relation obtained also by Sasaki[10] as;

$$m=25.50\times10^{-6}.D^{1.78}$$

the integral dose for a 50 kg weight patient was estimate as 310 kg•rad per 100 rad irradiation which was delivered in the well defined field of 100 cm^2. The integral dose obtained by the observation of the chromosome abberations by Ishihara et al.[9] on a patient treated by ^{60}Co gamma-rays was in good agreement with the integral dose calculated by Mayneord's formulae.

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