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About the Destiny of Transplanted Tissues and Their Process at Individuals Therapeutically Implanted with Extirpated Cancer Tissues

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摘出癌組織を治療的に移植した個体に於ける経過
並に移植組織の運命について

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曩きに癌組織の治療的移植による癌の治療法についてと題して報告し、特にその理論的根拠と術式を解説したが、その後各症例について5カ年間の治療計画を樹て、実施し、目下症例を重ねると共に経過追及中である。

本論文に於ては移植を受けた個体の経過と移植

組織の状態について報告し度いと思う。移植組織は或る間隔を置いて剔出し、その組織像について検討を加え、その所見並に臨床上の所見に従つて移植組織は近接照射によつてその発育を調整し成果を挙ぐ。

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CHAPTER I. FOREWORD

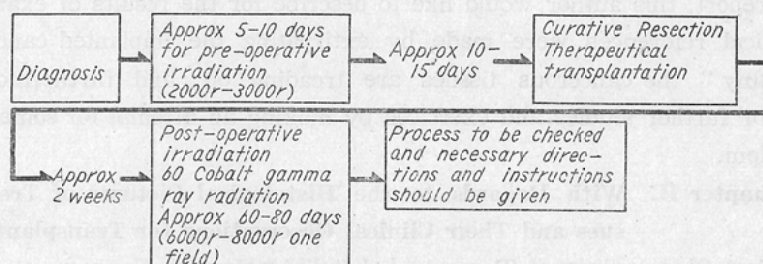
This author had already explained in my earlier report, Report No. 4, relating this study, particularly about the method and its theoretical ground under the subject of "About the Treatment of Cancer by Therapeutic Transplantation of Cancer Tissues".

Afterwards, a treatment schedule was established in each case as to make an attempt for close investigation and its process extending over five years, and thus, it has come to the present. In this report, this author intend to make a further investigation about the

clinical process of individuals transplanted and the histological pictures of implanted tissues which are to be removed by leaving some intervals.

At first, the treatment schedule must be understood as to know how the therapeutic transplantation of extirpated cancer tissues are to be exercised. Figure 1 is for its schedule. Primarily, about 5 to 10 g. of extirpated cancer tissues should be implanted subcutaneously and remaining tissues should be preserved in a dried-frozen state for further implantation inoculation at two months intervals.

Fig. 1.



However, we conducted the following observations to try to ascertain clinically for the degree of so-called "remote effect" which was confirmed in the experimental examination of "energy" metabolism of tumor tissues (tissue respiration and glycolysis). That is, among the cancer patients which we treated, the Virchow gland in the patients with gastric cancers and the metastasis of associated lymphatic gland in uterus and breast cancers were irradiated prior to the treatment of primary cancer, and thus, we examined how they affect to the whole body of individual with cancer and how they react to the primary cancer. For example, in this observation, we realized not only the subjective symptoms of primary cancer but the improvement of symptoms in whole body about time (approx of 10 to 15 days) the metastatic lymphatic node, about the size of thumb-tip or a pigeon-egg, was completely absorbed by a close irradiation of 3,000r to 4,000r, and this fine progress had been maintained in clinically at least of 4 to 5 consecutive weeks. That is, we had confirmed clinically the powerful remote-effect which is the fact that we experimentally experienced as aforementioned. However, the metastatic focus was conversely influenced favourable effect by irradiation of primary cancer and its softening and reduction upon palpation was confirmed. Although an essentiality in considering these facts is the reaction to the surrounding tissues affects at irradiation, a strict preventive measure is being devised as plainly stated in my earlier report. Consequently, nothing is to be considered except cancer necrohormone which plays an important role for the remote-effect.

Upon considering the above experiments and several facts of clinical observations we, at first, contemplated to utilize its absorption and resolution of cancer tissue for anti-

cancerous purpose by obtaining the tissue, about a size of thumb-tip or pigeon-egg, as for the amount of transplantation and implant it subcutaneously as aforementioned, and further expected to complete the cancer immunity by living cancer tissues.

As previously introduced, I have some degree of experience in the experiment of animals with cancers in regards with the dangerous of applying the method of cancer immunity devised by Ehrlich and his disciples. Consequently, we had devised various methods for transplantation such as to use the irradiated cancer tissues or sometimes the instantaneous heat processing undertaken to this, or non-irradiated cancer tissue is to be implanted by undertaking the heat processing, and so on.

In this report, this author would like to describe for the results of examinations since the histological references were made by extirpating the implanted cancer tissues and what "destiny" the cancerous tissues are treading on, and furthermore, I wish to contribute for further studies and exercises by making an attempt for some considerations to this problem.

Chapter II. With Regards to the Histological Pictures of Transplanted Tissues and Their Clinical Observations for Transplanted Individuals

1. Clinical Observations of Transplanted Individuals with Cancers.

Upon the completion of complete extirpation of cancerous tumor and an operation of lymphatic gland, a part of extirpated cancer tissues were shallowly implanted subcutaneously by the method as stated in Chapter 1.

Although some absorptions or the process of increase were observed by leaving a certain intervals after implantation, no suppurations were noted except a case of some mucous membranes were adhered in the implanted pieces. Naturally, it must be said that so-called "bedded-on condition" was fine. At the cases which had gone through the favourable progress, the implanted pieces had begun its absorption approximately from third week and there was almost no palpation at the time between seventh and tenth week. Contrarily, at the cases which showed a poor absorption, the hardness has increased and bulged as a tumor state and was remained in the site of implantation. Although there was only a single case which apparently showed an abominable condition so-called "success of complete transplantation" by enlarging its implanted piece and increasing its hardness, it has softened and disrupted and finally undergone the suicidal destiny by the close irradiation of 6,000r. In this case, we were much amazed to see the improvement of general clinical symptoms (especially subjective symptoms) by X-ray irradiation of transplanted tumor. A part of the said cases will be shown in a column of histological findings.

2. About the Histological Pictures of Transplanted Cancer Tissues.

The transplanted cancer tissue is the same tissue as was examined the histological finding of pre-operative irradiation in the previous report, and we were able to obtain the following findings (as shown in Fig. 2) by immediate implantation of its tissue.

Fig. 2

Case No.	Name	Age	Name of disease	Implanted tissues	Heat process	Postoperative irradiation	No. of days required till re-explantation	Pathological findings of extirpated/implanted tissue	Brief opinions made by Prof. Takizawa for extirpated/implanted tissue
1	Kawamoto	52	Gastric cancer	Gastric cancer tissue	+	+	46	Cancerous cells(—)Reaction of alien substance (+)	A sedimentation of Hemosiderin is only recognized by bleeding at the time of implantation
2	Fujita	67	-ditto-	-ditto-	—	+	41	-ditto- (+)	A fibroma and an alien substance which surrounding silk thread at the time of operation is to be observed
3	Ueda	46	Rectum cancer	Rectum cancer	—	+	38	-ditto- (+)	A fibrous granula tissue is only observed. A massive tissue is to be situated, but hard to recognize as cancer tissue
4	Sasaki	56	Gastric cancer	Gastric cancer tissue	—	+	36	-ditto- (+)	Muscle tissue is to be observed. (May be the remainder of gastric tissue)
5	Nakami	63	Reccurrence of gastric cancer	Metastatic lymphatic gland	+	+		-ditto- (+)	A substance which is to be considered as denaturalized cancerous tissue is observed in fibrous tissues
6	Abe	57	Gastric cancer	Gastric cancer tissue	—	+ — Incomplete	19	-ditto- (+)	Proliferation of cancerous tissue is recognized in subcutaneous tissue. The nuclear division is observed. A danger of proliferation is recognized.
7	Shinsaku	67	-ditto-	-ditto-	—	+	17	-ditto- (+)	A node which has cancerous cells enveloped by fibrous tissues is observed
8	Takamura	64	-ditto-	-ditto-	+	+		-ditto- (+)	Completely absorbed at two months after the completion of operation

In these days, the cases reported are still few, however, we are hinted many things by observing them in detail. First of all, we have learned from Prof. Takizawa's instruction that the problem so-called the "recurrence of transplanted cancer" is quite important prior to expect the therapeutical effect of implanted tissues. Prof. Takizawa had pointed out as follows, that is,

"The Case No. 5, 6 and 7 would be a subject of danger of recurrence of transplanted cancer. These three cases, the cancer tissues were observed in transplanted skin, particularly the Case No. 6 has a danger of recurrence since the infiltrative proliferation of cancer tissues have been observed. Although the cancerous cells were observed in Case No. 7, they had been enveloped and has no danger. The Case No. 5 had a minor cancerous cells but it was also hard to anticipate the recurrence. In other cases, at least

no cancerous tissues were visible in transplanted sites. However, I cannot say definitely that there were no cancerous cells only by these occasions". To the fact that he added a proviso "only invisible" has suggested that we should be very cautious about this problem and this author was deeply impressed.

In case, we make more close observation for the above three cases, the implanted tissues shown in Case No. 5 was a metastatic lymphatic node which had been removed and gone through the examination at 14 days intervals upon a completion of transplantation by instantaneous heat processing due to the pre-operative irradiation had not been applied. Accordingly, it could be considered that there might be existed some point of difference which differ from a part of extirpated cancerous tumor. Both case No. 6 and No. 7 were the tissues extirpated while on the post-operative irradiation, for which the pre-operative irradiation was applied and implanted without taking any preliminary transactions. The Case No. 6 showed a strong reaction to the ^{60}Co gamma rays and was forced to apply only a few times of post-operative irradiation due to impossibility of continual irradiation. Consequently, the length of time between transplantation and extirpation of implanted cancerous tissue was not adequate. Although the two pieces of cancerous tissues were implanted for purpose of making an investigation of transplanted tissues for Case No. 6, a remaining piece of transplanted tumor was clearly augmented and increased its hardness which was impressed as infiltrative augmentation in appearance.

It was, therefore, the patient of said case was explained about an importance of the post-operative irradiation and the doses of 6,000 r were applied by body cavity tube for the remaining implanted tissues. As soon as this was done, the hardness of tumor was suddenly reduced and withered, and finally self-destroyed and absorbed. For Case No. 7, the remaining of the enveloped cancerous cells was to be considered very natural since the time of extirpation seemed to be a premature, and it was further to be considered that it would be absorbed without having any risk by gaining effect of the post-operative irradiation.

Chapter III. Summary and Discussion

In regards with the therapeutic transplantation of cancer tissues, we are aware of results of Prof. Sachio Ishihara. When this author had presented him one of my humble writings and asked for his opinion, he instructed me that the transplantation of living cancer cells is most effective for auto-immunity. In view of the fact that we also consider the same, we had been cudgeling our brains to put the living cancer tissues into practical use for clinical purpose by implanting them at harmless condition.

It is believed that anyone whoever observes the result of experimental studies exercised by Ehrlich and his disciples and has interest in this field, would have once considered to this problem.

However, as aforementioned, this author was unable to step out easily for the transplantation of living cancer tissues even how effective it would be since I have experienced

at several occasions about active metastasis, proliferation and power of bedding-on of the transplantable rabbit sarcoma at my experimental studies and, in clinically, I have gone through the fearfulness of sowing which lately accidentally happen at the time of surgical operation.

While the time was going by in considering this and that, I have come to realize an essentiality of maintenance of cancer necrohormone in body after operation, upon a concrete theory of pre-operative irradiation, and finally, it has developed to the therapeutical transplantation of irradiated cancer tissues and subsequently, to the transplantation of living cancer tissues by instantaneous heat processing method. It is needless to say that this ideology had been urged from time to time as pivoting the irradiation treatment.

As it is evident in my previous report, the cancer tissues which we have transplanted are to be considered as X_1 according to the irradiation effectiveness judging criterion, and their histological pictures are the tissues which are suffered from the disorders such as some degree of proliferation picture is still observed in cancer cells. Accordingly, they are the cancer tissues almost same as "crude" which is so to speak, slightly controlled its development and proliferation. Consequently, if the tissues are unfortunately bedded-on, then, it is possible to be a source of recurrence and/or metastasis as directed by Prof. Takizawa. Although the living cancer tissues underwent the heat processing are free from danger since outer part of the tissues are surrounded by denaturalized cell-layers, there is also a fear of metastasis if a section of membrane become disrupted and absorbed. Thereupon, the cancerous cells were implanted subcutaneously as to observe their state easily, and a proper dose of 2,000 r to 6,000 r had been applied by close-irradiation method as occasion demands, and thus, the recurrence and metastasis had been avoided which we were apprehended. The remaining implanted tumor in Case No. 6 as described above, was retarded its infiltrative growth by this irradiation and was finally self-destructed and absorbed.

However, to reflect on the histological pictures of transplanted cancer tissues, a normal absorption and progress was visible as we expected. That is, an amount of 5 to 10g. of the tissues of implanted pieces which we computed from our clinical and experimental experiences was completely absorbed within about two months or it has denaturalized and/or remained fibrous tissues owing to the reaction of foreign body and had proved as out of danger.

Accordingly, we are practising today the therapeutical transplantation as scheduled and gaining the number of cases day after day.

Considering the results of above studies we are intending to exercise our scheme, in future, by attending the following points.

1. The cancer tissue awaiting for transplantation has a great concern with the irradiation dose since it is completed with the pre-operative irradiation. That is, a proper dosage of pre-operative irradiation is between 2,000 r and 3,000 r as we fixed, and it is the degree of X_1 according to the Prof. Takizawa's effective judging criterion. However, we consider

that this dosage is rather satisfactory.

2. Approximately from 5 to 10 g. of extirpated cancer tissue, which is suffered from disorder degree of X_1 should be implanted subcutaneously extremely shallow. However, in case the tissue is unsanitary or non-applied of pre-operative irradiation, it will be safe to undertake a heat processing.

3. About two weeks after the implantation which is about same time as the beginning of post-operative irradiation, even this implanted cancerous tissue is need of the post-operative irradiation. However, the irradiation dosage should be determined by the condition of implanted tumor, and the doses between 2,000 r and 6,000 r should be applied appropriately.

4. In primary transplantation, it is possible to implant the living cancer tissue immediate after the operation which is also ideal theoretically as auto-immunity method, however, a preserved tissue in frozen/dried state should be used at the second and third implantation. The implantation should be performed at about two months intervals and should be continued as long time as possible.

5. Although the above stated was conceived in accordance with the results of this study, this author further intend to put forward for the study concerning the transplantation of harmless living cancer tissues.

However, as long as the treatment is to be carried out, both subjective and objective symptoms of individual with cancer must be improved by irradiation. According to the literature reports, no clinical improvement is observed whatsoever between 70% and 80% of the cases in the most important pre-operative irradiation, however, the many have complain of debilities. It should be always kept in mind that however the tumor being reduced may be, the experience of clinicians has a great weight in conducting the irradiation so as not to play the foolishness as "being worse than the evil it was supposed to correct".

It is therefore, try to be free from the kind and dosage of irradiation though they are fixed in the treatment schedule, and to lay emphasis on the improvement of symptoms for individual with cancer. While in time of treatment, the utmost care should be taken such as to give the high calories of food and efficacious remedies, otherwise, the effects cannot be expected. Contrarily, in the cases that the implanted cancerous tissue does not show any sign of favourable absorption or peculiarly shows a tendency to increase, then, it is needless to say that immediate action should be taken such as the irradiation or the extirpation should be conducted by carrying out a histological examination in appropriate time.

When the examination was made in detail for the results of above observation, it became apparent that there would be no danger as we feared, and this is the reason why we are intending to obtain the constant result as pivoting the pre-and post-operative irradiation according to our established treatment program.

Anyway, the remarkable effect of transplantation may be established both theoretically

and therapeutically, or furthermore, the favourable result may be already produced experimentally, it should be extremely deliberate and cautious about using them for clinical purpose as we experienced until today. Much more, in determining the effect of this new therapeutical method, the matter should be depended on the future observations and studies extends for many years to come.

As a matter of fact, we have encountered with the difficulty how to determine the immunity effect of cancer by transplantation in accordance with the progress of pre-operative irradiation, the surgical intervention, and further to the therapeutical implantation of cancer tissues at the stage of therapeutical treatment as for synthetic effect.

We realize so keenly that much more to be done and strive ourselves to solve the many problems which still remained unsolved.

— 15/10/1961 —

Upon a conclusion of this manuscript, I wish to express my deepest appreciation to Professor Takizawa of Chiba University who had given to me the special directions and instructions.

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