# DEOXYGENATION RADIOTHERAPY

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# 低酸素圧放射線治療の研究

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所謂酸素効果を放射線治療に応用する方法については従来高圧酸素を吸入せしめる酸素加圧法が行われていた．しかし，この方法では腫瘍内酸素圧の上昇は期待程ではなく，又正常組織の感受性を増強し，かえつて治療比を低下せしめる可能性のあることが明らかとなつた．著者等は逆に低酸素圧下に照射することにより正常組織の放射線感受性を低下せしめて相対的に治療比を改善しようと考え，基礎的研究を行つた．ラッテのロダミン肉腫について行つた低酸素圧放射線治療の成績は優秀で，著明な治療比の改善を示した．低酸素状態を安全に維持するためには低体温法が最もよく，これにより正常組織の放射線感受性を約1/2に低下させることが出来る．以上の研究結果から臨床的にも好い結果が期待せられ，実際の治療に応用を始めている．

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It is well known fact that the radiosensitivity of a cell is markedly influenced by the oxygen tension of its environment. Clinical applications of this so-called oxygen effect have been tried and brought into practice chiefly by British radiotherapists. Several papers were published already. Up to now the so-called oxygenation therapy was thought to be only one practical way to approach. The essential point of this method is to raise up the oxygen tension within a tumor by means of the high pressure oxygen inhalation and to improve the therapeutic ratio. The theoretical basis of the high pressure oxygenation therapy was shown by Gray as Fig. 1.

We, however, have some doubts about this assumption. The oxygen tension in the normal tissue is not always so high as shown in Fig. 1. Fig. 2 shows the effect of oxygen inhalation on the oxygen tension in normal and tumor tissues. Measurements were done with the oxygen polarogragh improved in our laboratory. The extent of rise up in

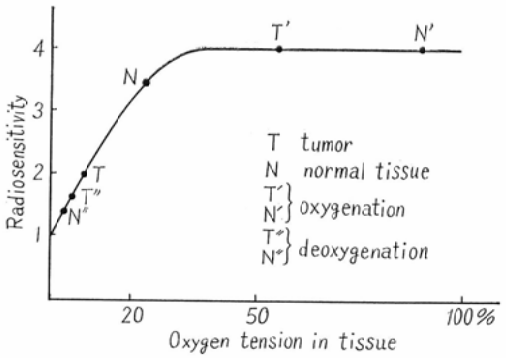


Fig. 1 Oxygen tension and radiosensitivity of cells. Theoretical basis of oxygenation and deoxygenation radiotherapy.

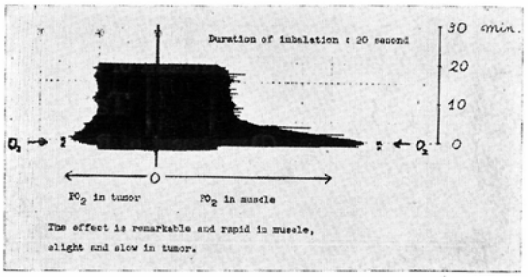


Fig. 2 The effect of oxygen inhalation on $PO_2$ in muscle and tumor

the normal tissue is 5-6 times in usual and often up to 10 times. Su h a high rise up of oxygen tension means that the oxygen tension in normal tissues is far below saturation, and the oxygen inhalation may considerably enhance its radiosensitivity. Evidently the rise up in the tumor is markedly less and slower than in the normal tissue. The extent of rise up within tumors is 1.2-1.5 times in moderate size, but quite small at the center of large sized tumor. Therefor the improvement of therapeutic ratio may not always be expected and in unfavourable cases even the fall down may be possible.

Oxygenation, we consider, is not a sole method to apply the oxygen effect to clinical therapy. Look at the Gray's curve again. If we can decrease the oxygen tension in the normal tissue below the tumor, then the improvement of therapeutic ratio will be definite. However, the extreme decrease of oxygen tension or anoxia is too dangerous to introduce it as a routine clinical procedure. Recently it has been a topic in the field of surgery and anesthesiology how to avoid damages of brain tissue due to anoxic conditions. General or local hypothermia under adequately controled anesthesia was proved to be the best way to overcome this difficulty.

Fig. 3 shows the change of oxygen tension under the oxygen poor inhalation. Oxy-

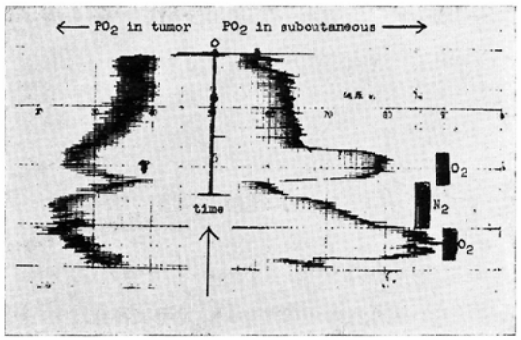


Fig. 3 The effect of oxygen and nitrogen inhalation on the oxygen tension in tissue

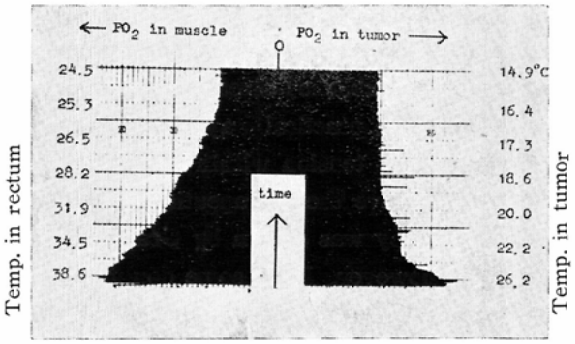


Fig. 4 The effect of hypothermia on the oxygen tension in normal and tumor tissue

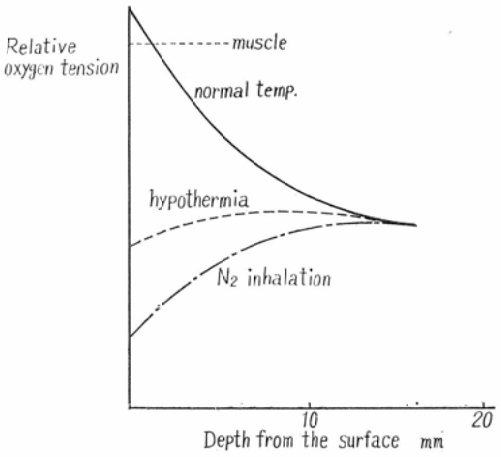


Fig. 5 The oxygen tension at the different depth in a rat's Rhodamin sarcoma under $N_2$ inhalation or hypothermia

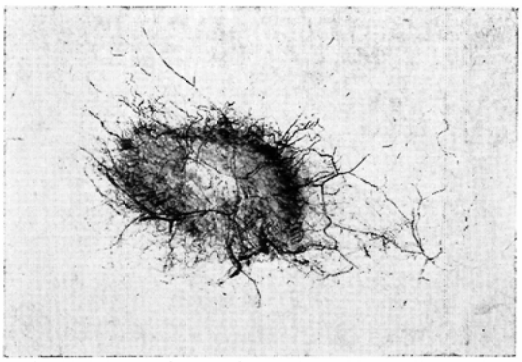

Fig. 6 The microradiography of a Rhodamin sarcoma. This shows the marked vascularization at the periphery of tumor and very poor vascularization within the tumor. At the center almost no blood vessels can be seen. (2×)

gen tension in the normal tissue is higher than in the tumor before inhalation, but at the moment of extreme hypoxia the condition is just reversed. Although such an extreme hypoxia is very dangerous and impractical at the normal temperature, we can minimize damages with the hypothermic anesthesia. Actually the hypothermia only without inhalation will be sufficient to reduce the oxygen tension.

Fig. 4 shows the effect of hypothermia on the oxygen tension in tumor and normal muscle. The oxygen tension in the normal muscle falls down to about 1/3 of the value before cooling. We consider that the reduced blood flow under the hypothermia is the main cause of this fall down. The nearer the distance from capillaries is, the greater the extent of the fall down.

Fig. 5 shows the relation of the oxygen tension at the center of the tumor to the diameter of tumor. Regarding this experimental rat tumor -Rhodamin sarcoma -, the oxygen tension at the center of tumor larger than 3 cm in diameter is constantly low inspite of inhalation or hypothermia. The distance of diffusion from capillaries seems to be less than 1 cm. Fig. 6 shows a microangiography of subcutaneously implanted Rhodamin sarcoma. These results suggest the difficulty in the oxygenation therapy and the prospect of the deoxygenation therapy.

Fig. 7 shows the uptake and excretion curve of $I^{131}$ rosebengal by a rabbit liver. Under the hypothermic anesthesia, a strange two phased curve is seen. The first wave corresponds to the extremely retarded passage of rose-bengal through the liver. The second wave corresponds to the uptake by liver cells which is not seen until the temperature rise up over 26°C.

Fig. 8 shows the similar curve obtained with $I^{131}$ hippuran measured on rabbit kidneys. We believe such a condition of standstill will significantly reduce the radiosensitivity of these organs.

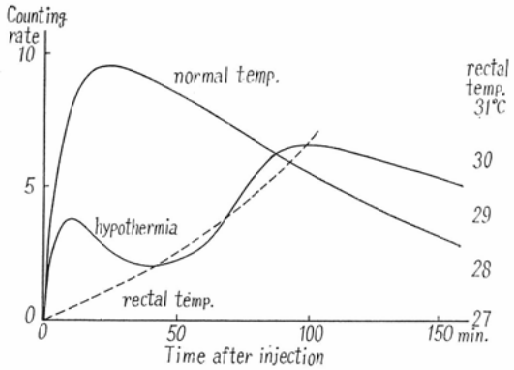


Fig. 7 Liver function test under the hypothermic anesthesia
Material: rabbit
Method: external counting on the liver after the injection of $I^{131}$ rose bengal

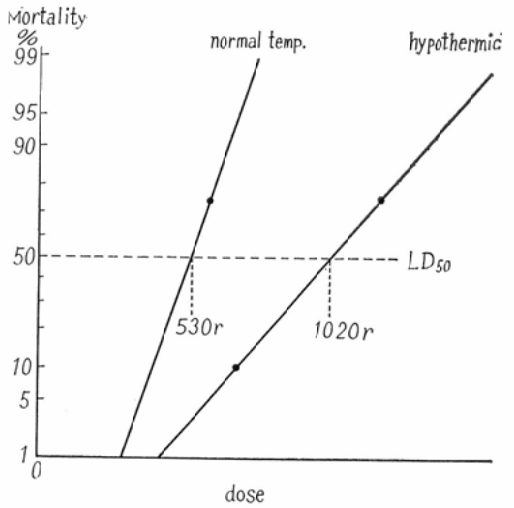


Fig. 9 Mortality by total body irradiation
Material: mice

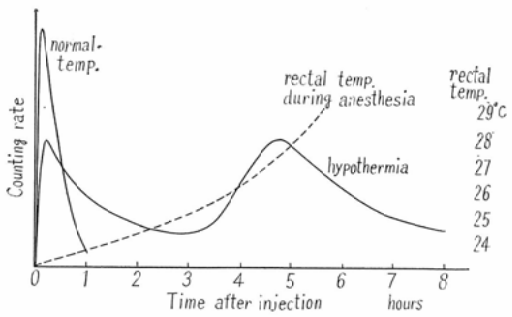


Fig. 8 Renal function test under the hypothermic anesthesia
Material: rabbit
Method: external counting on the kidney after the injection of $I^{131}$ hippuran

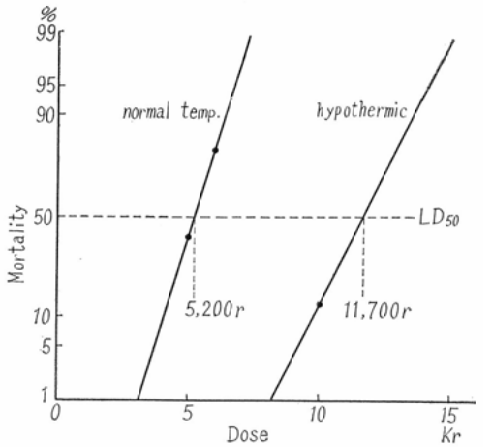


Fig. 10 Mortality by local irradiation
Material: dogs, irradiated immeadiately after the gastrectomy and the anastomosis with small intestine.
Site of irradiation: surroudings of anastomosis.
Field size: 2.5×6 cm

Fig. 9 shows the increase of $LD_{50}$ of mice by the hypothermia. Mice recieved the total body irradiation. Here the factor of protection is about 2. Fig. 10 shows the increase of $LD_{50}$ of dogs also by the hypothermia. This time the irradiation was done locally on anastomosed wounds immeadiately after the partial gastrectomy. Here the factor of protection is about 2 also.

Fig. 11 shows the increase of $LD_{50}$ of rats irradiated on their backs. Again the factor is about 2. There is a tendency that the protection effect is more marked in the total body irradiation or abdominal irradiation than in the peripheral irradiation. In spite of these remarkable protection effect on the normal tissues, $LD_{50}$ of the implanted

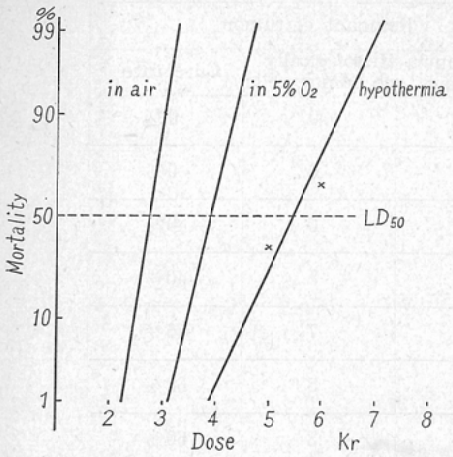


Fig. 11 Mortality by local irradiation
Material: rats
Site of irradiation: back
Field size: 2 cm diameter

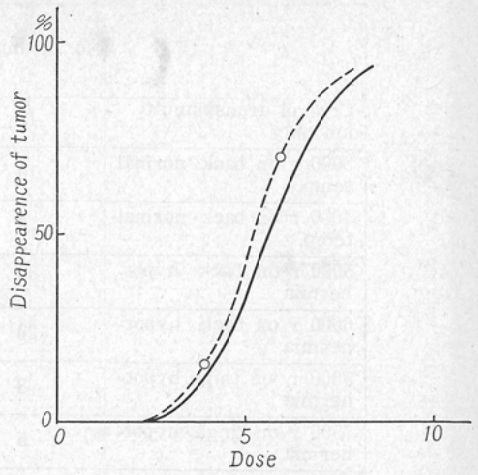


Fig. 12 Lethal dose of Rhodamin sarcoma estimated from clinical and histological datas
——irradiated under normal temp.
·····irradiated under hypothermia

| | No. of animals | Cured | Died from tumor | radiation damage | Cure rate |
|---|---|---|---|---|---|
| Control transplantation only | 13 | 0 | 13 | 0 | 0% |
| 3000 r on back normal temp. | 10 | 0 | 0 | 0 | 0% |
| 4000 r on back normal temp. | 8 | 0 | 0 | 8 | 0% |
| 5000 r on back hypothermia | 20 | 5 | 8 | 7 | 25% |
| 6000 r on back hypothermia | 20 | 3 | 4 | 13 | 15% |
| 5000 r on thigh hypothermia | 8 | 2 | 3 | 3 | 25% |
| 7500 r on thigh hypothermia | 5 | 3 | 0 | 2 | 60% |
| Irradiated under normal temp. | 18 | 0 | 0 | 18 | 0% |
| Irradiated under hypothermia | 53 | 13 | 15 | 25 | 24.5% |

Fig. 13 Clinical cure rate of Rhodamin sarcoma by the hypothermic deoxygenation radiotherapy

Rhodamin sarcoma of rat shows only slight decrease by the hypothermic irradiation. From our results the factor of protection on the tumor was estimated as about 1.1. Consequently the improvement of the therapeutic ratio in the radiotherapy of Rhodamin sarcoma is near to two. Originally the Rhodamin sarcoma is a kind of fibrosarcoma and one of the most radioresistent tumors. It requires over 4000 rads in single exposure to eradicate. Tumor bearing rats on their backs cannot tolerate to such a high dose. All

| | No. of animals | Remnant of tumor | | |
|---|---|---|---|---|
| | | Clinical remnant of tumor | Histologically no tumor cells | Cure rate |
| Control transplantation only | 13 | 13 | 0 | 0% |
| 3000 r on back normal temp. | 10 | 10 | 0 | 0% |
| 4000 r on back normal temp. | 8 | 8 | 0 | 0% |
| 5000 r on back hypothermia | 20 | 12 | 8 | 40% |
| 6000 r on back hypothermia | 20 | 13 | 7 | 35% |
| 5000 r on thigh hypothermia | 8 | 3 | 5 | 62% |
| 7500 r on thigh hypothermia | 5 | 2 | 3 | 60% |
| Irradiated under normal temperature | 18 | 18 | 0 | 0% |
| Irradiated under hypothermia | 53 | 30 | 23 | 42.8% |

Fig. 14 Histological cure rate of Rhodamin sarcoma by the hypothermic deoxygenation radiotherapy

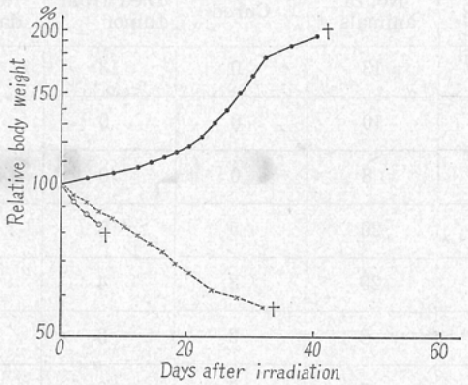


Fig. 15 Relative body weights of tumor bearing rats after the irradiation on back under normal temperature.
Rhodamin sarcoma transplan
Rhodamin sarcoma transplanted on back
3000 r- 4000 r in single dose on back
●——● Control: 13 animals. All died from the tumor.
○·····○ 4000 r : 8 animals. All died from acute radiation damaged
×·····× 3000 r :10 animals. All died from acute radiation damages

animals irradiated with tumor lethal dose died from acute abdominal radiation damages. Only the irradiation under the hypothermic anesthesia succeeded to cure them. Fig. 13 shows the results of radiotherapy of Rhodamin sarcoma. Although the cure rate is low in the group rats bearing tumors on their backs, this is the definite proof of the superi-

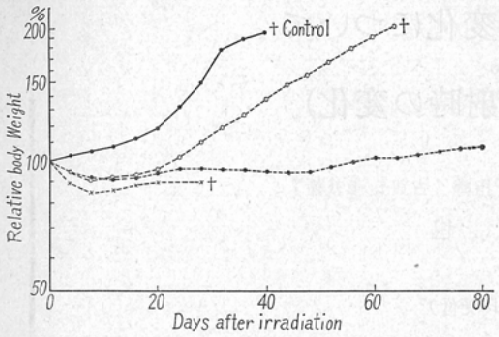


Fig. 16 Relative body weights of tumor bearing rats after the irradiation on back under hypothermia.
Rhodamin sarcoma transplanted on back.
5000 r in single dose on back.
●·····● Cured: 5 animals
○·····○ Recurred and died from the tumor: 8 anima
×·····× Died from radiation damages: 7 animals

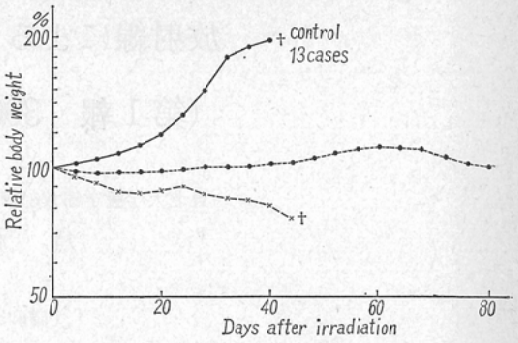


Fig. 17 Relative body weights of tumor bearing rats after the hypothermic irradiation.
Rhodamin sarcoma transplanted on thigh.
7500 r in single dose on thigh.
●·····● cured: 3cases
×·····× died from radiation damage: 2 cases

ority of deoxygenation radiotherapy. In the group of rats bearing tumors on their thigh, the cure rate is higher. Some of the latter group lost their legs but maintained good health. Fig. 14 shows the histological examination. Fig. 15–17 shows the body weights of animals after the beginning of irradiation. Here you will see 4 types of curve. The body weight of the control group which received no treatment shows constant increase due to the growth of tumor until their death. Radiation death group showed constant decrease until their death. Cured group showed only a small decrease at first but restored soon. Recurrent group showed a similar tendency as cured group at first then turned to rise up just similar as control group.

Encouraged from these experimental datas, we decided to apply this deoxygenation therapy to clinical practice. Up to now we have treated more than 10 cases. All of them are cases of advanced cancer. They were irradiated under hypothermic anesthesia about 27°C to 30°C. 2000–3000 rads were given in single exposure to tumors. The impression from our clinical experience is its extremely slight side effect. In spite of these massive irradiation the radiation sickness was almost negligible. Certain degree of protection effect was seen on the skin. It seems too early to discuss the effect on the tumor clinically, but we believe it is very promising.