特別掲載

Radiosensitizing Action of Ametohepazon on the Irradiated Tumor Tissues
II. Preliminary clinical report

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Ametohepazon の放射線増感作用について
II. 悪性腫瘍患者に対する併用療法（予報）

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悪性腫瘍の放射線療法に際して，放射線増感剤との併用が盛んに試みられている．しかし，現在知られている増感剤のほとんどに共通する特徴は，増感剤の単独投与によつても抗腫瘍作用があることで，そのため，副作用も強く全身状態の悪化は避け難いものである．ところで，1報において報告したAmetohepazonには，単独では抗腫瘍作用がなく，放射線と併用してはじめて増感効果を発揮するもので，認むべき副作用はなかつた．

そこで，当科に入院した悪性腫瘍患者11名（局所投与7名，全身投与4名）につき，放射線との併用療法を行なつた．

同一人で併用療法と放射線だけの照射療法をうけた患者は6名あつたが，併用療法が単独照射療法に劣る例は1例もみられなかつた．6例中5例においては，併用療法の方が明らかに良いと思われる結果が得られた．

Ametohepazon と照射との併用療法を行なう際，効果判定で注意すべきことは，肉眼的には効果がないように見える場合においても，組織学的には，線維化，凝固壊死巣など効果が著明に認められる場合があることである

投与方法による差異については，更に例数を重ねる必要があるが，静脈内投与が可能であり，かつ，有効であつた．

副作用としては，局注例の局所に発赤と軽い疼痛が認められたが，治療を中止するほどのものではなかつた．むしろ，Ametohepazon は鎮痛，消炎剤として開発されたもので，持続した微熱患者には軽度の解熱効果があり，食慾増進など一般状態の改善が認められたものがあった．

A difficult problem which is often encountered in radiotherapy of malignant tumors is the presence of resistant cells to radiation. To solve this, the improvement of various physical factors and of irradiation method from biological viewpoint, and combination therapy with various agents have been attempted intensively. Especially in recent years, attempts with radiosensitizer have become remarkable. There are various agents[1-7], for example, Oxygen, 5-FU, BUdR, Radioplex, Actinomycin D, Methotrexate, which are known to have radiosensitizing effect. But a common feature, which is shared by nearly all of them, is that they exert anti-cancer action even when applied alone. It is subsequently difficult with any of them to avoid systemic disorder and impairment of the health, which is a greatest barrier in the chemotherapy of cancer. It was against this background that Ametohepazon, a seven-membered ring compounds[8] developed by the Central Research Laboratories of Sankyo Co., was reported by Hayashi[9] to have radiosensitizing effect but scarcely any side action. We were strongly interested in this scarcity of side action, and performed investigation on the action mechanism of Ametohepazon using experimental tumor as reported in the previous paper[10]. At the same time, we tentatively applied it with radiation to 11 patients of malignant tumors hospitalized in this department (topically to 7, and sistemicly to 4). It is sufficiently difficult to give objective assessment of the effect of the combination therapy. But so far as ours hort term observation has revealed to date, Ametohepazon has an action as radiosensitizer on human cancer as well. The object of this paper is to report on it.

Procedure

1. Subjects of investigation

The subjects are 11 patients with malignant tumors who have been admitted in the department of radiology of Gunma University hospital since March 1967. The tumors were recognized either macroscopically or by rentgenography. Diagnosis of malignant tumor had been established histologically or cytologically for all the cases.

2. Ametohepazon; method of its administration

Ametohepazon is a product of the Central Research Laboratories of Sankyo Co, and one ampoule of 1 ml contains 50 mg of Ametohepazon. It is adjusted to pH 6.4. It was injected either topically or intravenously 30 minutes before irradiation. In the former Ametohepazon alone was given, while in the latter it was given with a 20% glucose solution.

3. Apparatus of irradiation

^{60}Co irradiation was made with the Shimazu's RT-10,000, and X-ray irradiation with the Toshiba's KXC-18.

Report of Cases

Case 1. I.Y. Aged 64. A female.

Primary pulmonary cancer in the left upper lobe. There were already extensive metastases in the brain, left supraclavicular and left axillary lymph nodes. Treatment was started on February 20, 1967 by irradiation with ^{60}Co to the primary focus, in the total dose of 6,000 R by March 30. Combination therapy with intratumor injection of Ametohepazon and ^{60}Co radiation was performed to a fist-sized left axillary tumor from March 6 to 18. The total dose of Ametohepazon during this period was 500 mg,

and that of the radiation 2,000 R. Pain by topical Ametohepazon injection was slight, but on the 6th day of the treatment, pain, redness and swelling were noted on the site of the injection. She died on April 1 owing to exacerbation of the brain symptom without showing any remarkable change in the size and consistency of the irradiated tumor.

Autopsy confirmed the brain metastasis as the cause of death. The left axillary tumor mostly underwent coagulation necrosis, and was wrapped by fibrous connective tissue which was so deep as to attain the subcutaneous adipose tissue. Between these connective and necrotic tissues were seen a small number of tumor cells with increased polymorphism. The primary focus which had received 6000 R irradiation showed a polymorphocellular carcinoma-like picture, which was distinguishable from the finding of the typical papillary adenocarcinoma in the non-irradiated part as well as from that in cytological examination of sputum collected before irradiation, thus demonstrating the effect of radiation. But a considerable number of tumor cells were still found surviving. (Plates 1—4).

Case 2. N.S. A 47 year female. On September 29, 1966, she received radical operation of the left mammary cancer, and then postoperative irradiation to the thoracic wall and the right axilla from December 1966 through February 1967. But in early April a pea-sized tumor was found in the right axilla and in the left thoracic wall. These were rapidly enlarged, and both became fist-sized in late April. From April 21 to May 20, 3000 R ^{60}Co irradiation was made to the right axillary tumor without obtaining any regression. On June 6, the tumor was removed for histological investigation, which disclosed remarkable giant cell carcinoma which was appreciably different from adenomatous cancer before the irradiation, thus indicating the effect of the radiation. But nevertheless the presence of numerous mitotic figures demonstrated the lack of the inhibitory effect. On the tumor of the left thoracic wall, combination therapy with Ametohepazon and X-ray was started on May 9, and several days later, swelling and redness were observed on the irradiated area. About the 10th day of the therapy, the Ametohepazon injected-site became yellowish gray and tender, indicating softening of tumor tissue. There were erosion on the surface and tendency of regression in size. On June 3, X-ray irradiation was stopped (the total dose 4,000 R), but the topical injection of Ametohepazon was still continued until June 23 (the total dosage 1,800 mg). The size of the tumor continued to diminish after the termination of Ametohepazon administration (Fig. 1 and Plates 5—7).

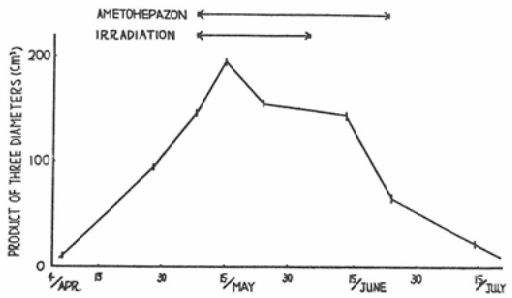


Fig. 1 Regression curve of case 2

Case 3. T.F. A 60 year male.

A chestnut-sized tumor on the left side of the root of the tongue. Histological examiniation revealed it to be squamous-cell carcinoma. Combination therapy of intratumorous injection of Ametohepazon and deep X-ray irradiation was started on May 27, 1967. In the first 3 weeks of the therapy there was little tendency of regression of the tumor, but later it diminished rapidly, and became scarcely discernible on June 26 when it was completed. The total dose of X-ray was 6,000 R, and that of Ametohepazon 1,250 mg.

On June 28 the site of the tumor was examined histologically, but no tumor cells were detected.

Case 4. S.O. A 77 year male.

A patient with metastatic skin cancer. Several tumors, larger ones thumb-tip-sized, were found subcutaneously in the abdomen. One of them was treated by topical injection of 250 mg/5 days of Ametohepazon plus 1,200 R/5 days of ^{60}Co irradiation, and at 2 days after the completion of the therapy, the tumor was excised. Macroscopically, there was no remarkable change in the excised tumor except slight increase in consistency. But microscopically proliferation of fibers was observed, and though the tumor retained the same structure of squamous-cell carcinoma as in the non-irradiated ones, the tumor focus was diminished as a whole, and also individual cells showed degenerative picture. The site of Ametohepazon injection partly became edematous and partly vesicular, indicating transition to fibrosis. (Plates 8, 9)

Case 5. Y.H. A 14 year female.

She received 3,000 R/37 days of ^{60}Co irradiation to malignant thymoma. And X-P showed disappearance of shadow of the mediastinal tumor. But 2 months later, that is, in the end of February 1967 the shadow of a mediastinal tumor reappeared, and at the same time, metastasis in the left thoracic wall and deposition of pleural fluid were detected. The pleural fluid contained numerous metaplastic lymphocyte-like cells, and also sporadically showed mitotic figures. Thereupon, the pleural cavity was irradiated 3 times with 100 R (air dose) of ^{60}Co to the area of 11 × 11, but neither pleural fluid nor tumorous cells diminished. In view of this, Ametohepazon was intrapleurally injected every other day in addition to ^{60}Co irradiation from March 6 to 30. And in March 8, when 100 R (air dose) of ^{60}Co alone was given, pleural fluid demonstrated red cells but not any nucleated cells. Also the deposition of pleural fluid remarkably diminished. The total dossage of Ametohepazon given in this period was 500 mg, and that of ^{60}Co 1,000 R. But the patient developed heart failure owing to the general metastases, and died on May 9. Autopsy disclosed tumor infiltration in myocardium, which became the primary cause of her death. The noteworthy feature in the present case was fibrous thickening of the pleura and its strong adhesion. Histological diagnosis of malignant lymphatic thymoma, lymphosarcoma, was made. (Plates 10, 11 12)

Case 6. K.T. A 41 year male.

A patient with post-burn skin cancer. At the site of the cancer there was ulcer of 40 × 40 cm^2, and in its periphery was noted tumorous elevation about 0.5 cm high. Histological examiniation of this site gave diagnosis of squamous-cell carcinoma. From March 3 to 24, 1967, 100 mg of Ametohepazon was topically applied with gauze in addition to ^{60}Co irradiation. Remarkable regression of the tumor was brought about by total dose of 1,100 mg of Ametohepazon and total dose of 2,200 R of ^{60}Co. But in May the tumor was again enlarged, filling the depression produced by ulcer, and once more forming the peripheral elevation. Thereupon, 2,200 R of ^{60}Co irradiation was given alone from May 18 to June

9, but the tumor, instead of regressing, conversely grew larger. It was consequently to place the patient again in the combined therapy. But this was given up owing to private reason on the part of the patient.

Case 7. S.S. A 62 year male.

In September 1966, irradiation with 9,000 R of ^{60}Co produced regression in primary squamous-cell carcinoma which developed on the soft palate. In May 1967, the cancer relapsed, forming tumorous ulcer of 3 × 2 cm^2. From May 26 to June 8, combination therapy with Ametohepazon and ^{60}Co was performed, the former being topically given through a catheter inserted into A facialis, but without any diminishing effect. The total dose of Ametohepazon in this therapy was 650 mg, and that of ^{60}Co 3,900 R. But after the termination of the therapy, the regression of the tumor was detected, and on June 28, tumorous elevation in the periphery of the ulcer completely disappeared, and histological examination could not found any intact tumor cells in the ulcer.

Case 8. M.S. A 57 year male.

A patient with postoperative recidivation of rectal cancer. On March 7, 1967, systemic administration of Ametohepazon by intravenous route was attempted, and as the result, persistent febricula disappeared, and appetite increased. No change was observed in blood picture and hepatic function. In view of this, without stopping the intravenous injection, irradiation was performed with 3,000 R to a super fist-sized tumor in the anus from March 20 to April 7, and with the same dose to chestnut-sized tumor in the left lower pulmonary lobe from March 28 to April 24. Either of them did not show any tendency of regression, nor any growth, and white blood cell count maintained the order of 4,000. There was no side effect, and improvement was seen in appetite and other general conditions. About April 25, however, the exacerbation of atelectasis in the right lung produced cor pulmonale and obstruction of the ureter, and the patient died on April 30. The total dose of Ametohepazon was 2,350 mg. Aside from this, 5,200 R irradiation was given to anal tumor, and 1,800 R to left pulmonary tumor in October 1966. The present treatments were the second ones to their recidivations.

At autopsy, typical papillary adenocarcinoma was histologically confirmed in the non-irradiated part, but the irradiated part underwent complete fibrosis, showing only scattered small aggregations of tumor cells. Also the whole of the tumor of the left lower pulmonary lobe underwent necrosis. So far as the present examination revealed, there were no abnormal findings which could be ascribed to harmful effect of Ametohepazon. (Plates 13—15)

Case 9. S.Y. A 79 year female.

In November 1965, with diagnosis of left maxillary cancer, she received irradiation of 5,800 R ^{60}Co, and remarkable regression in the tumor was obtained. In April 1967, tumor reappeared on the left maxilla, and she was placed on irradiation with 4,000 R in total of ^{60}Co plus intravenous injection of 900 mg in total of Ametohepazon. As the result, the maxillary tumor completely disappeared, and also stuffy nose, which persisted until then, was simultaneously cured. The tumor was histologically diagnosed as squamous-cell carcinoma.

Case 10. M.F. A 73 year male.

The right orbit was remarkably protruded owing to reticulosarcoma which originated in the right orbit. Besides was seen a metastatic focus of 5.5 × 5.5 cm on the right side of the neck. On April 26, 1967, combination therapy was started with Ametohepazon and ^{60}Co, and on the 3rd day, remarkable regression was seen in the both tumors. Several days later, cervical tumor disappeared, and the right exophthalmus returned to the normal. The combination therapy was continued until May 22, and the

total dose of ^{60}Co irradiation in this therapy was 3,800 R and that of Ametohepazon 900 mg. (Plates 16, 17)

Case 11. K.I. A 70 year male.

Since February 1966, he received treatment of pulmonary tuberculosis (culture gave one plus of tuberculous bacilli). In early March 1967, a circular shadow of 8.0 × 6.7 cm² was seen in the right lower pulmonary field, superimposing the calcified focus of tuberculosis. In late April, cytological examination of sputum found tumor cells. Thereupon, combination therapy was performed by ^{60}Co irradiation and intravenous administration of Ametohepazon from May 10 until June 10, when it was discontinued owing to hemoptysis. X-ray picture disclosed formation of a cavity of 3.0 × 3.0 cm² in the center of the tumor. Also the size of the tumor itself was reduced to 6.5 × 6.0 cm². The total doses were 5,000 R of radiation and 1,300 mg of Ametohepazon.

Comment

The results of combination therapy with Ametohepazon and radiation on 11 patients as of July 1967 are summarized in Table 1.

Table 1 Summary of combination therapy with ametohepazon and radiation on 11 parients

Case	Clinical diagnosis	Histological diagnosis	Irradiated portion	Exposure dose	Over all time	Ameto-hepazon	Route	Effect macro.	Effect micro
1	bronchial cancer	adeno-carcinoma	1 axilla 2 lung	2000R 6000R	13 days 39 days	500mg —	local —	± ±	++ +
2	breast cancer	adeno-carcinoma	1 breast 2 axilla	4000 3000	26 30	1800 —	local —	++ ±	 +
3	tongue cancer	squamous-cell carcinoma	tongue	6000	29	1250	local	++	+++
4	bronchial cancer	squamous-cell carcinoma	abdominal wall	1200	5	250	local	±	++
5	thymoma	lympho-sarcoma	1 pleural 2 cavity	1000 300	25 3	500 —	local —	+ —	++ —
6	skin cancer	squamous-cell carcinoma	1. skin 2. skin	2200 2200	22 23	1100 —	local —	++ —	
7	palate cancer	squamous-cell carcinoma	1. palate 2. palate	9000 3900	44 14	— 650	— i.a.	++ +++	 +++
8	rectum cancer	adenocarcinoma	1. anus 2. lung	3000 3000	19 28	2350	i.v.	± ±	++ ++
9	maxilla cancer	squamous-cell carcinoma	1. maxilla 2. maxilla	5800 4000	32 29	— 900	— i.v.	++ ++	 +++
10	orbit sarcoma	reticulum-cell sarcoma	1. orbit 2. neck	3800 3800	27 27	900 900	i.v.	+++ +++	
11	bronchial cancer	class 5	lung	6000	32	1300	i.v.	+	++

1. Comparison between combined and single (radiation) therapy

It was cases 1, 2, 5, 6, 7 and 9 that individually received both the combined and the single therapy. Comparison of the effect between them revealed that in none of them the former was inferior to the latter. Especially in 5 cases, that is, in all except case 9, the combination was far better than the single. Of course, the comparison was made inclusively with all sorts of cancer as a whole, irrespective of its site or of whether it was primary or metastatic. So we do not pretend to have decisively established the radiosensitizing effect of Ametohepazon. Our results, however, will suggest it worthwhile to repeat investigation on it with increased number of cases.

CASE 1

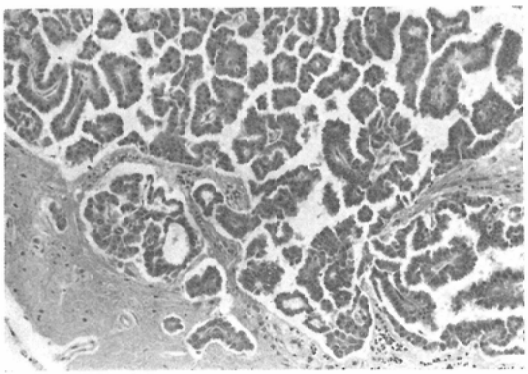


Plate 1 At autopsy. Non-irradiated metastatic tumor of the brain. Typical adenocarcinoma.

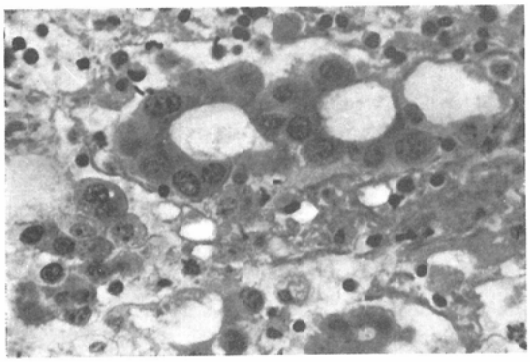


Plate 2 Sputum collected before irradiation. Typical adenocarcinoma.

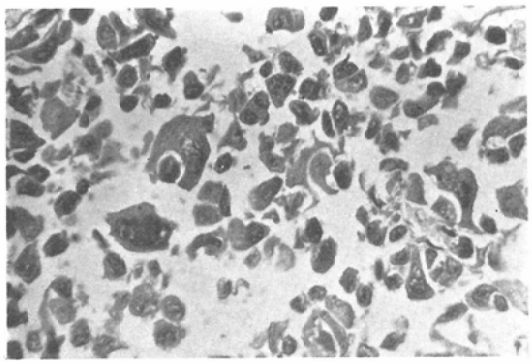


Plate 3 At autopsy. The primary tumor irradiated with 6000R. Polymorphocellular carcinoma like tumor cells.

CASE 1

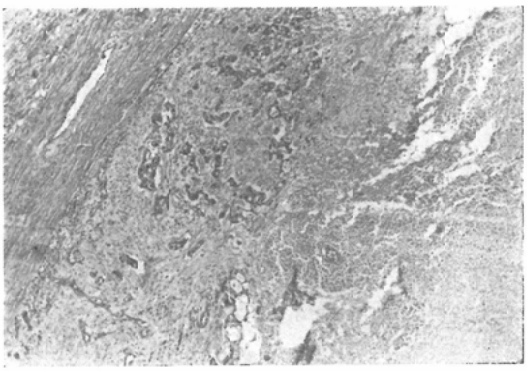


Plate 4-a At autopsy. The axillary metastatic tumor recieved irradiation of 2000R with Ametohepazon. Coagulation necrosis and connective tissues are seen remarkable.

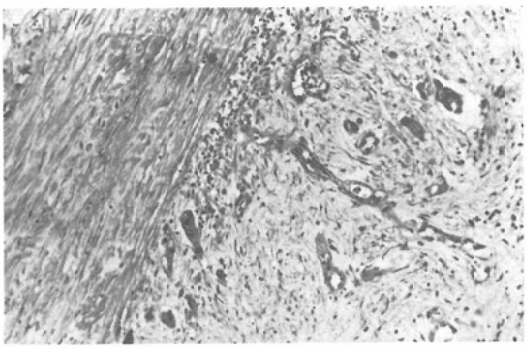


Plate 4-b The same as above, high power.

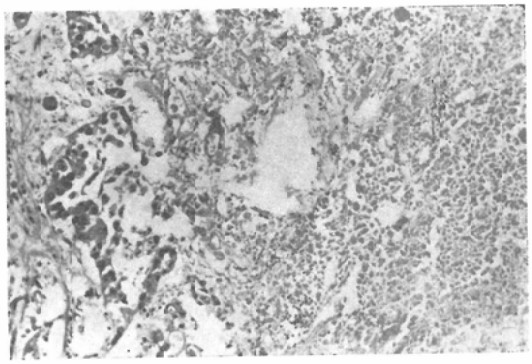


Plate 4-c The same as plate 4-a, high power.

CASE 2

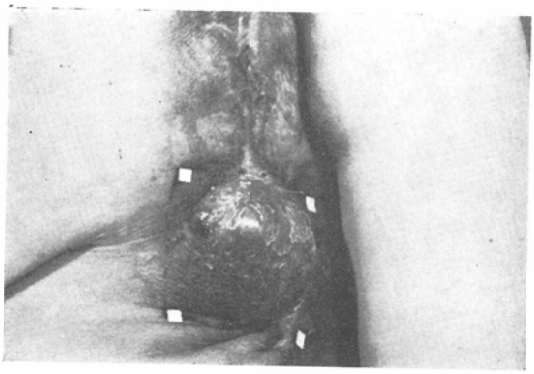


Plate 5 Just before combined therapy.

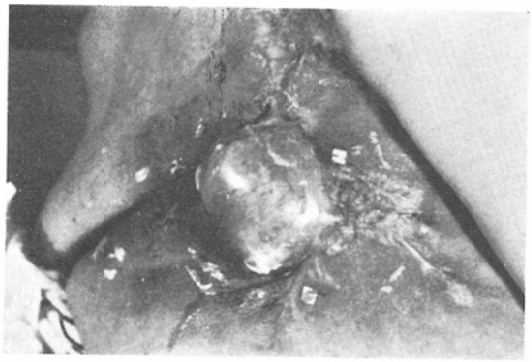


Plate 6 The 10th day of the therapy. Ametohepazon injected-site become yellowish grey and tender.

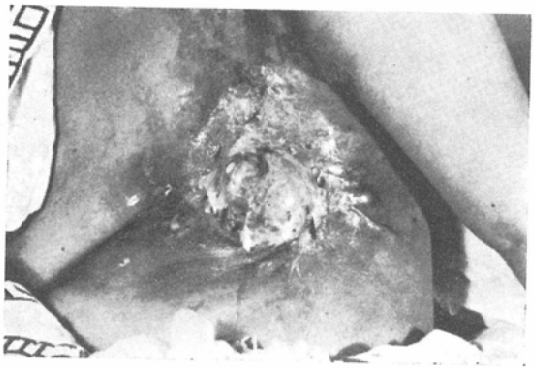


Plate 7 Just after the termination of Ametohepazon administration.

CASE 4

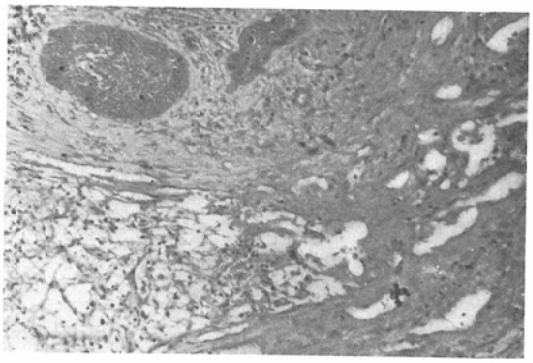


Plate 8-a Early effect of the combined therapy. The site of Ametohepazon injection become edematous and fibrous changes of the tumor tissue.

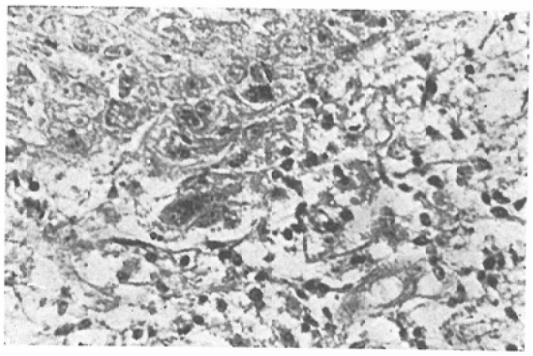


Plate 8-b The same as above, high power.

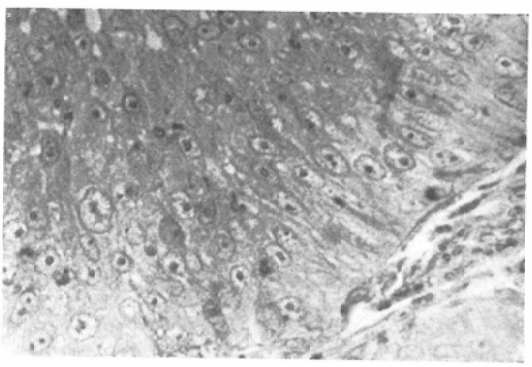


Plate 9 Non-irradiated part.

CASE 5

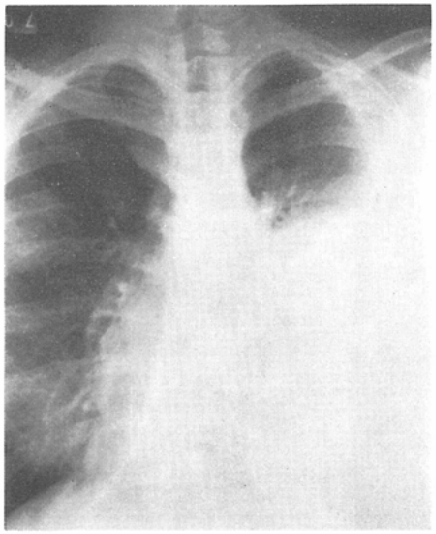


Plate 10 Just before combination-therapy. Fluid of the left pleural cavity is marked.

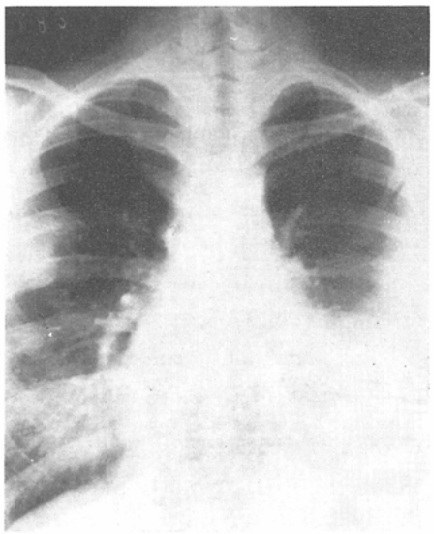


Plate 11 The 8th day after start of combined therapy. Fluid is remarkably diminished.

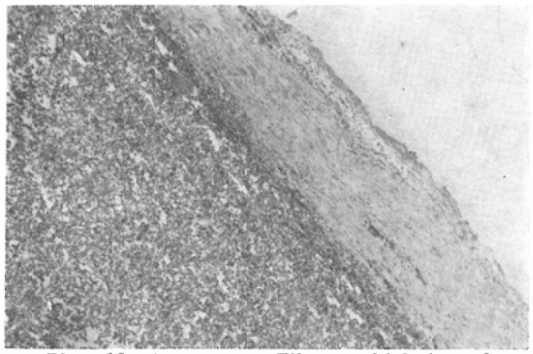


Plate 12 At autopsy. Fibrous thickning of the pleura is remarkable.

CASE 8

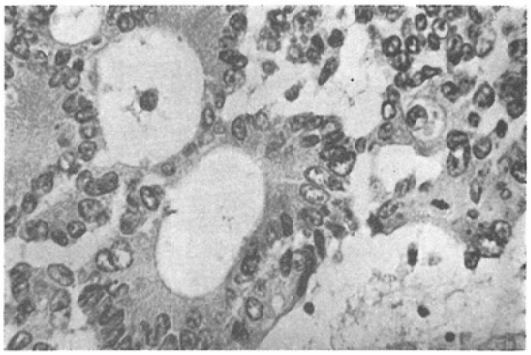


Plate 13 At autopsy. The tumor of the left lower pulmonary lobe non-irradiated shows typical adenocarcinoma.

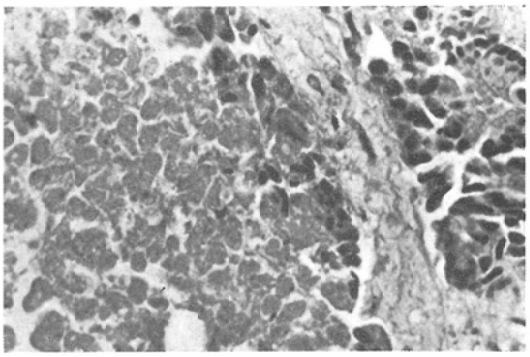


Plate 14 At autopsy. The greater part of the tumor of the left lower pulmonary lobe irradiated with 3000R undergoes necrosis.

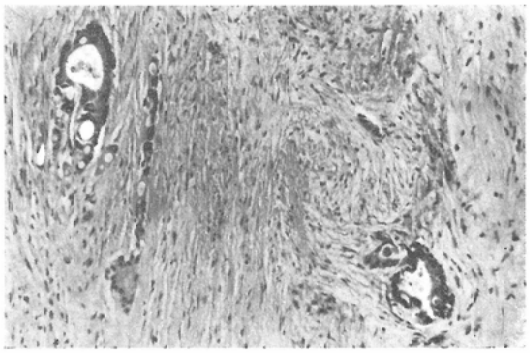
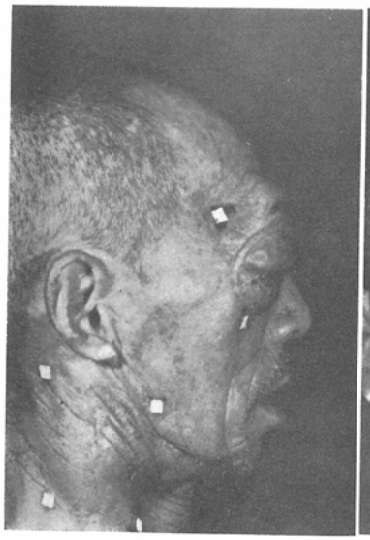
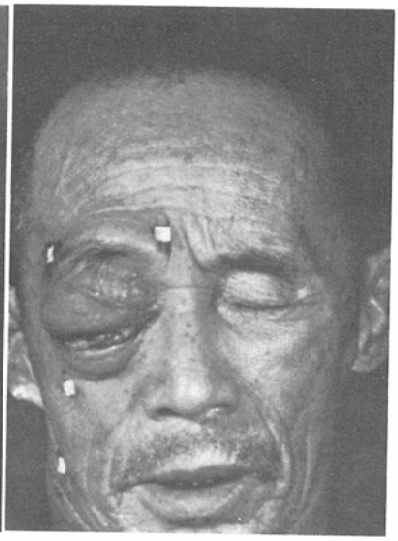


Plate 15 At autopsy. The irradiated rectal tumor undergoes complete fibrosis, showing only scattered small aggregation of tumor cells.

CASE 10





Plates 16-a,b The right orbit and the right side of the neck is remarkably protruded owing to reticulosarcoma.

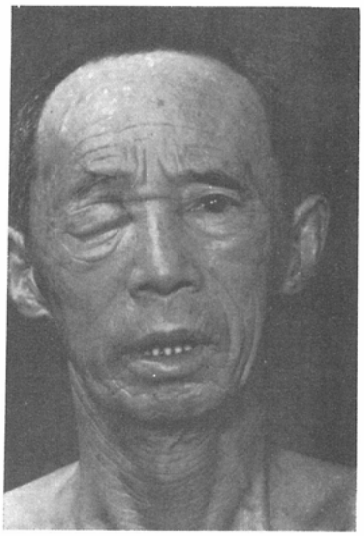


Plate 17 Several days after start of combined therapy, cervical tumor disappears and the right exophthalmus returns to the normal.

2. Characteristic features in the combination therapy

a) As exemplified in cases 1 and 8, the effect was not manifested during their lifetimes, but found only in autopsy by histological examination as remarkable degeneration, necrosis or fibrosis of the tumor. Also in cases 2, 3, 7 and 9, it was after the termination of the therapy that tendency of remarkable regression was observed. In this way there was divergence between macroscopical and microscopical findings. Table 2 gives both macroscopical and microscopical findings in 8 cases (9 tumors) which permitted histological investigation. It can be seen herein that numerous cases which failed macroscopically to show remarkable effect exhibited it histologically. This will have important significant in clinical evaluation of the effect.

Table 2 Divergence between macroscopical and microscopical findings

effect of combined theray		macro findings	micro. findings
disappeared	##	1 cases	3 cases
remarkable regression or degeneration	#	2	6
mild regression or degeneration	+	2	0
unchanged	±	4	0
aggravation	−	0	0
total		9	9

b) Response in the periphery of tumor: Remarkable swelling and redness were produced (cases 1, 2 and 9). They appeared too early to be considered as erythema due to radiation. On account of strong swelling it is assumed to be an inflammatory picture principally resulting from circulatory dis-

turbance. This finding resembles the swelling around the tumor which was produced in animal experiment on the 2nd day of irradiation as reported in the previous paper[10]. In the animal, however, the tumor tissue assumed a yellowish grey tint, scarcely reddish, different from that in the human subject. At any rate it is of interest that in both, a circulatory disturbance can be inferred as the cause of the topical swelling.

c) Topical injection produced softening and yellowish grey tint at the site of the injection as seen in case 2. The same was produced also when topical Ametohepazon injection was continued after termination of irradiation. This makes us estimate the possibility of celldamaging effect of Ametohepazon. But this possibility seems very small when we consider the findings in our present animal experiment, reports by Hayashi *et al*[9], and observations of patients who were given Ametohepazon as antalgic or antiphlogistic. It is rather more probable that Ametohepazon may exert its effect only on such cells as have already been damaged by irradiation.

d) Histological findings as observed in autopsy and exploratory excision after the combination therapy were scarcely different qualitatively from those after irradiation alone. The difference was only quantitative in number of tumor cells or extent of fibrosis. This may be ascribed to the fact that it was difficult to find early change produced by the combination therapy, since the samples were made available for histological examination long after the termination of the therapy. In samples from cases 4, which were prepared 2 days after irradiation for the object of examining the early effect, there were findings similar to those in animals in which Yoshida sarcoma was transplanted into the femur, that is, edematous change, cellular infiltration, softening necrosis and fibrosis at the site of Ametohepazon injection. These are considered to be some of the early effects of the combination therapy.

What interested us especially is the focus of coagulation necrosis found in the pulmonary tumor of case 8 and in the axillary tumor of case 1. From this we may infer the presence of lesion resulting from vascular disturbance. For the moment, however, we have no positive evidences in support of this inference.

3. Method of administration

The systemic administration was made by the intravenous route, and the topical administration by the injection into the tumor, and by intraarterial and intrapleural injection, and also by direct application on the site. The effect was visible in all of them. It seems, however, necessary to make the comparative study with a greater number of cases to find out difference in effect by the method of administration.

As for the temporal relation between irradiation and Ametohepazon administration, the latter was given, as a rule, 30 minutes before the former in the present experiment. But the effect was visible also in an exceptional case 2, in whom the topical injection of Ametohepazon was continued after the termination of the irradiation. It seems therefore that Ametohepazon may be effective even when it is given after irradiation unless the tumor cells are recovered from damage of irradiation.

4. Side action

As afore mentioned, pain and redness were noted at the site of the topical injection in some cases, but they were not so significant as to necessitate the discontinuation.

As for laboratory data such as white blood cell count and hepatic function, there were nothing indicative of damage by Ametohepazon. It was rather found that general improvement such as removal of febricula and increased appetite resulted from the administration of Ametohepazon, which was initially developed as analgensic and antiphlogistic.

Summary

Combination therapy with Ametohepazon and radiation was attempted on 11 patients of malignant tumor, and the early effects as observed to date were commented.

It is true that clinical observation, in which it is difficult to use the appropriate control, is open to criticism of lack of objectivity. But at any rate we could confirm effect of Ametohepazon which can be considered as radiosensitizer. Side effect or the like has been found in none to date. Some patients rather showed general improvement. We want to continue the investigation further with increased number of cases.

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