

Title	High Dose Rate Intracavitary Radiotherapy Using the RALSTRON Part 2. Treatment of carcinoma of the uterine cervix under hyperbaric oxygenation
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High Dose Rate Intracavitary Radiotherapy Using the RALSTRON

Part 2. Treatment of carcinoma of the uterine cervix under hyperbaric oxygenation

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ラルストロンによる高線量率腔内照射法の研究

第2報 高圧酸素環境下に於ける子宮頸癌の治療について

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目的:

1. われわれが開発した新しい腔内照射法の至適時間的線量分布を子宮頸癌について求めること。
2. 副障害を可及的少なくすること。
3. 治療に要する総線量を可及的少なくすること。

このために酸素効果の応用と time-dose-relationship を活用した。前者のためには3気圧の高圧室において同気圧の純酸素を mask を通じ患者に呼吸せしめた。後者のために Co-60, 10 Ci-order の線源によつて1回の線量を 500rad~1,000rad の各種とし、分割照射回数を2~3回とした。

ここに行なつた治療法は高圧酸素(絶対3気圧)呼吸中における高線量率腔内照射法である。患者の高圧室に密閉されている時間は40分程度で、なお3気圧に達してより約5分後に照射を開始する。照射時間は数分程度である。

照射方法:

線源としてCo-60の10Ci-orderを用いた。tandem に5Ci(2+2+1Ci 3コ), ovoid にそれぞれ5Ciずつ、総線量計15Ciを用いた。線源配置はManchesterの一方法によつた。なお tandem, ovoid からの point A への線量寄与は Manchester

法により、tandem から $\frac{2}{3}$, ovoidから $\frac{1}{3}$ とした。これは ovoid からの照射時間を適当に調節することにより容易である。

point A での線強度は 325rad/min, point B では90rad/min であつた。

体外照射は Co-60 遠隔照射 split field method 中央部を 2×5 cmまたは3×7 cmの鉛遮蔽で行なつた。骨盤中心部で 4,000~6,000 rad の照射線量を与えた。

時間的線量配分は1週間間隔で point A に1) 2×500rad(7症例) 2) 2×725rad(11症例) または 750rad(12症例) 3) 2~3×1,000rad(18症例)の各種について行なつた。

結果:

治療後の経過が短いので早期の反応(6カ月以内の再発有無)でかりに判定するに、時間的線量分布は point A に1回に1,000radを1週間間隔で2~3回照射のものが最も良い効果を示した。

副障害については長いものは2~3年経過しているのがきわめて軽度で然も少数であつた。

酸素中毒を起こしたものは convulsion が1%程度にあつた。その他に軽度の耳痛を訴えたものが9%程度であつた。

In radiotherapy, it is desirable to reduce the total amount of radiation and the volume dose to their minimum possible level. Generally, the volume dose in the intracavitary radiotherapy is small as compared with that in the external radiotherapy. If any method of reducing the total dose becomes available, the intracavitary radiotherapy would be a treatment of choice for carcinoma of the uterine cervix. For this purpose, the application of time dose relationship is one and the increase of the radiosensitivity of tumor cells is another approach.

It is well established fact that the tumor contains populations of hypoxic or anoxic cells¹¹⁻¹³⁾. These cells are radioresistant and frequently a cause of residual disease and recurrence. The radiosensitivity of

tumor cells is influenced by the surrounding oxygen concentration or by its state of oxygenation at the time of irradiation. This is known as "oxygen effect" in radiation biology (Gray and others¹⁴⁾⁻¹⁷).

Furthermore, γ -ray of Co-60 and X-ray of betatron or linear accelerator used in radiotherapy are low in linear energy transfer. Therefore, their biological effect is influenced by the oxygen content of receptors. Thomlinson¹⁸⁾⁻¹⁹, and Powers et al.²⁰ irradiated 3,000 rad with these rays to the variously oxygenated tumor cell suspensions in vitro. The probability of cell survival was 10^{-10} , if all cells were well oxygenated. This figure became 10^{-5} if one per cent of these cells were anoxic. On the other hand, it has been postulated that the human tumor cells (squamous cell carcinoma) has at least 1% anoxic cells (Thomlinson¹⁸), Powers and Tolmach²⁰).

Based on these facts, the application of oxygen to the radiotherapy is a reasonable approach to raise the radiosensitivity of tumor cells.

Clinically, Churchill-Davidson et al.²² reported that the external radiotherapy given with high pressure oxygen in the treatment of metastatic tumors in cervical lymph nodes from squamous cell carcinoma of the head and neck led to the excellent tumor responses as compared with those treated under normal atmosphere. Van den Brenk et al.²³) and others²⁴⁾⁻²⁵) also reported similar results in the treatment of carcinomas of the head and neck. And as to carcinoma of the uterine cervix, radiotherapy under hyperbaric oxygenation has been performed in many Institutes or Hospitals in the world²⁷⁾⁻³³).

These encouraging reports led us to the application of high pressure oxygen and high dose rate to the intracavitary radiotherapy for carcinoma of the uterine cervix. For this purpose, we developed specially designed one man oxygen chamber.

In this part, we will present our clinical experiences in the treatment of carcinoma of the uterine cervix with high dose rate intracavitary radiotherapy under hyperbaric oxygenation (Fig. 2-1).

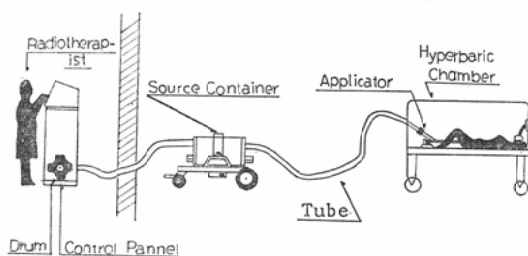


Fig. 2-1. Schematic illustration of the RALSTRON with hyperbaric chamber.

Apparatus and Procedures

A. The pressure chamber

Our specially designed "one man chamber" is shown in Fig. 2-2 A.B.C. This iron-made chamber is designed to stand with 6 atmospheric pressure (5 kg./cm² gauge pressure). A couch within the chamber can be slid outside to take films after intracavitary introduction of the applicators. Since there are microelectroswitches inside the chamber to detect the arrival of sources to the tips of applicators, the air is used for the pressurization of the chamber (Fig. 2-3 A.B.C.) and the patient breaths pure oxygen via the

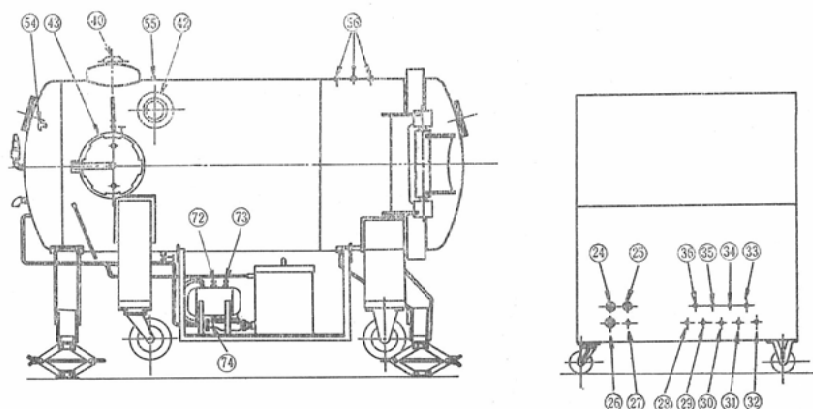


Fig. 2-2A

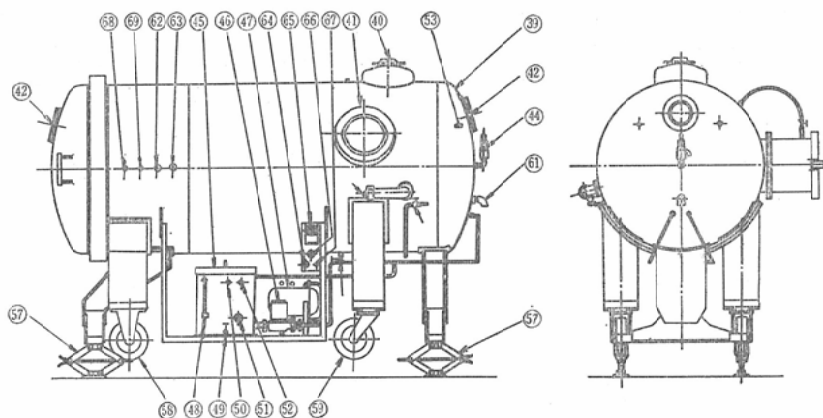


Fig. 2-2B

Fig. 2-2A, 2-2B. Diagrammatic representations of the hyperbaric chamber.

24. Connector (heater) 25. Connector (100V) 26. Connector (combined load) 27. Connector (thermal)
 28. Pipe joint (pressure water chamber's pressure gauge) 29. Pipe joint (air bleed for hospital lock)
 30. Spare nozzle 31. Pipe joint (air supply for pressure water chamber) 32. Pipe joint (sprinkler outlet panel)
 33. Pipe joint (sprinkler inlet panel) 34. Pipe joint (air bleed for hospital lock) 35. Pipe joint (air bleed for oxygen mask)
 36. Pipe joint (hospital lock pressure gauge) 39. Hospital lock 40. Lighting fixture (hospital lock)
 41. Observation window (250 mm in dia.) 42. Observation window (120 mm in dia.) 43. Medical lock 44. Safety valve 45. Water chamber (heater) 46. Circulating pump
 47. Pressure water chamber 48. Level gauge 49. Drain valve (cooling and heating) 50. Thermal gauge 51. Heater
 52. Thermal connector (cooling and heating) 53. Pipe joint (air bleed for oxygen mask) 54. Thermal connector (hospital lock)
 55. Connector (interphone) 56. Connector (wirings) 57. Jack 58. 250 mm solid wheel (fixed)
 59. 250 mm solid wheel (turning) 61. Waster nozzle (oxygen mask) 62. Spare nozzle 63. Spare nozzle
 64. Connector (combined load) 65. Thermal regulator 66. Connector (heater) 67. Thermal connector
 68. Pipe joint (air bleed for hospital lock) 69. Pipe joint (hospital lock's pressure gauge) 72. Pipe joint (air bleed for pressure water chamber)
 73. Pipe joint (pressure water chamber's pressure gauge) 74. Sprinkler pipe joint (outlet water chamber)

mask (Fig. 2-4 A.B.). In our preliminary studies, it was confirmed that the concentration of oxygen inhaled by the patient was between 90 to 95 per cent (if there were no leak, this value should be 100 per cent).

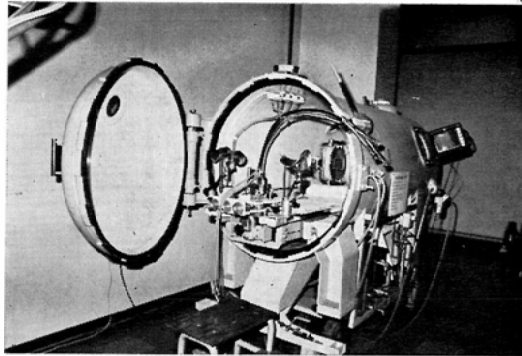


Fig. 2-2C. External view of the chamber.

The pressure of inhaling oxygen is adjusted to the same as that of inside the chamber. Expired gas is sent outside the chamber through the valve attached to the mask. The pressurization and depressurization are controlled in another room (Fig. 2-5 A.B.) and the changes of the pressure inside the chamber are recorded automatically (Fig. 2-6 A.B.). The patient in the chamber is continuously observed through the monitor T. V. in the control room (Fig. 2-7 A.B.). Speech intercommunication between patient and staffs is provided, and there is another monitor and T. V. attached to the window, through which the patient is able to talk and watch the staffs in the control room. These are helpful to relieve unnecessary apprehensions of the patient.

On the wall of the chamber near the door, three holes are made where cables for the delivery of the sources to the applicators are connected.

The applicators and their holders are fixed at one end of the couch. The connections among them are the same as described in part 1.

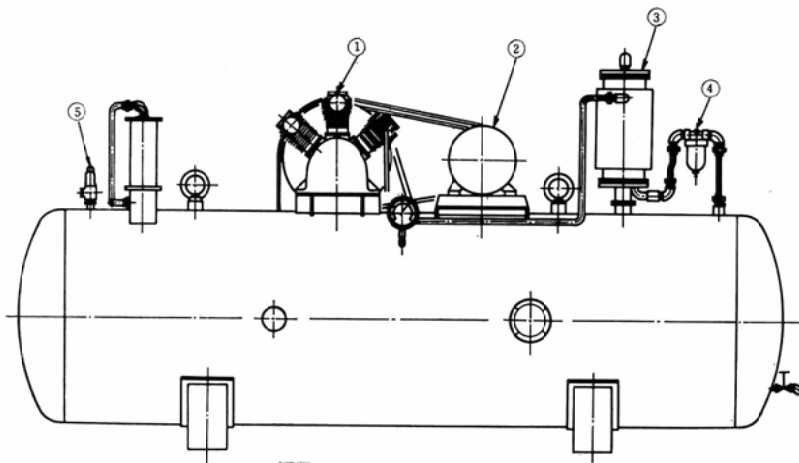


Fig. 2-3A

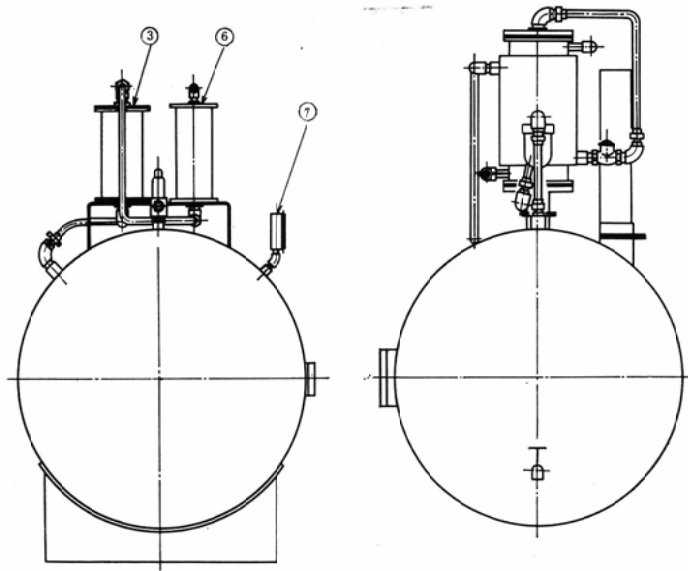


Fig. 2-3B

Fig. 2-3A, 2-3B. Diagrammatic representations of the air compressor.

1. Compressor 2. Motor 3. Air cooler 4. Air filter 5. Safety valve
6. Air filter 7. Pressure gauge

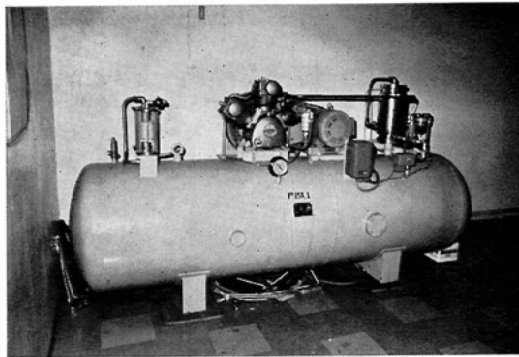


Fig. 2-3C. External view of the air compressor.

B. Sources

Co-60 is used as the source. The sources are increased 10 times of those used in the previous study (cf. part 1). They are 15 Ci in total: 5 Ci (2+2+1) for tandem and 5 Ci each for ovoids. Their specific activity is about 100 Ci/g and their dimension are the same as those in part 1. The dose rate at point A is 325 rad/minute and 90 rad/minute at point B. Therefore, with these sources, it takes 2 to 3 minutes to deliver 1,000 rad at point A (Fig. 2-8).

C. Procedures

The whole procedures are done while the patient is conscious. The orders of setting up the treatment

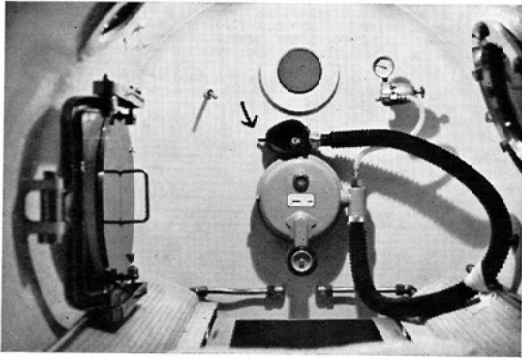


Fig. 2-4A. Internal view of the chamber.
A mask for breathing oxygen (arrow).



Fig. 2-4B. Patient breathing 100% O₂ via the mask.

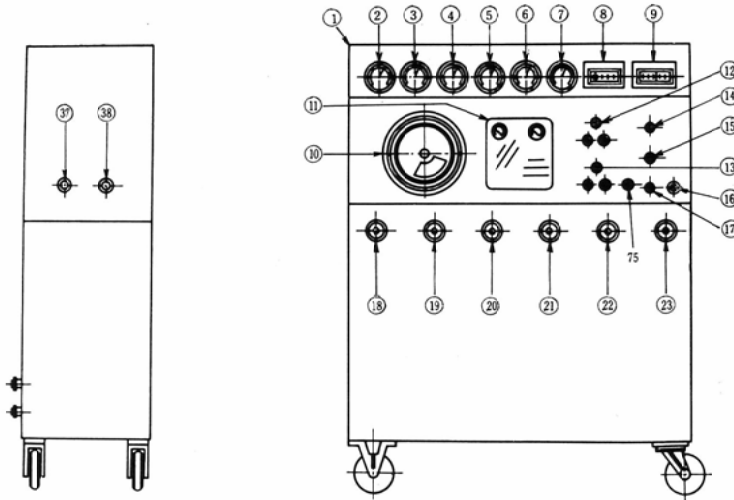


Fig. 2-5A. Diagrammatic representations of the control panel.

1. Control panel
2. Pressure gauge (primary air)
3. Pressure gauge (primary oxygen)
4. Pressure gauge (secondary air)
5. Pressure gauge (secondary oxygen)
6. Pressure gauge (hospital lock)
7. Pressure gauge (pressure water chamber)
8. Thermometer (hospital lock)
9. Thermometer (cooling and heating water)
10. Pressure recorder
11. Automatic pressure regulator
12. Switch (circulating pump)
13. Switch (heater)
14. Pilot lamp
15. Switch (thermometer)
16. Switch (hospital lock illumination)
17. Connector (interphone)
18. Air regulator
19. Oxygen regulator
20. Air supply valve (manually operated)
21. Oxygen supply valve
22. Air exhaust valve
23. Valve (pressure water)
37. Hose joint (primary air)
38. Hose joint (primary oxygen)
75. Change switch (automatic to manual)

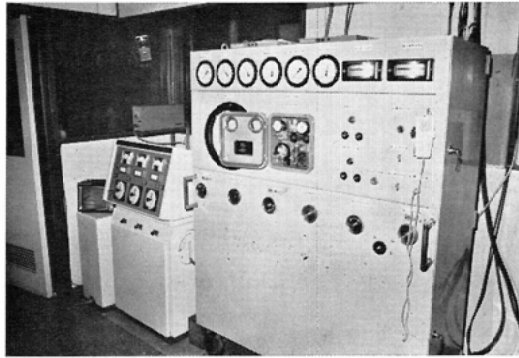


Fig. 2-5B. External view of the control panel.

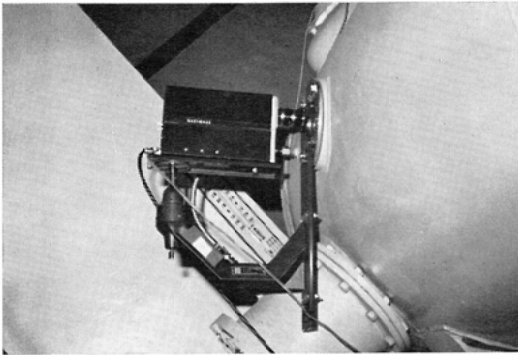


Fig. 2-7A. The patient in the chamber is observed by the monitor T. V. camera.

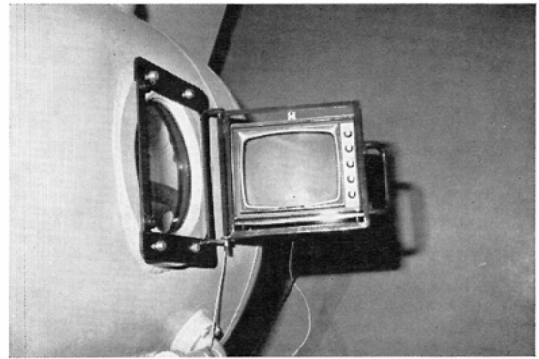


Fig. 2-7B. Another monitor T.V. attached to the window through which the patient is able to watch the staffs in the control room.

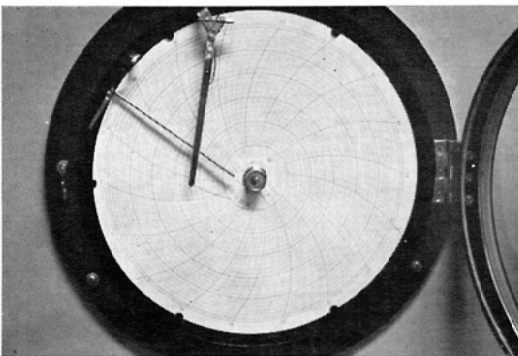


Fig. 2-6A. Pressure recording during treatment.

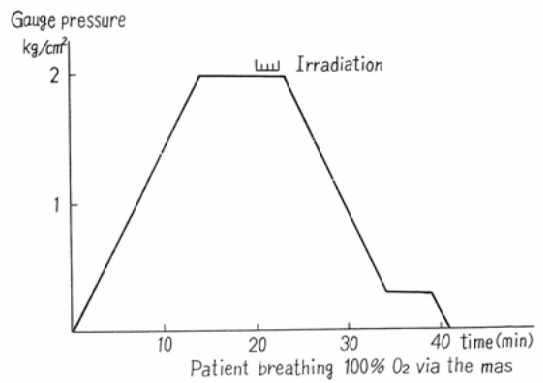


Fig. 2-6B. Irradiation is started after patient being kept under full pressure for approximately 5 minutes.

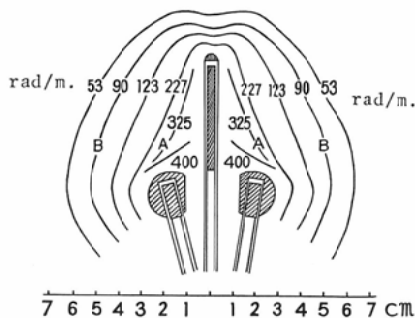


Fig. 2-8. An example of isodose distribution for tumor of the uterine cervix. The Co-60 sources are 15 Ci in total: 5 Ci (2+2+1) for intrauterine tandem and 5 Ci each for vaginal ovoids.

apparatus are as follows:

- 1) The patient lies supine on the couch.
 - 2) The catheters are inserted into the rectum and urinary bladder.
 - 3) The speculum is introduced into the vagina, and opens it in antero-posterior direction as widely as possible.
 - 4) The applicators (tandem and ovoids) are inserted and fixed.
 - 5) Small amount of contrast material is introduced into the rectum and the bladder.
 - 6) Antero-posterior and lateral films are taken (Fig. 2-9A), and relationships of the applicators in respect to the rectum and the urinary bladder are checked.
 - 7) If necessary, the position of the applicators are corrected.
 - 8) The patient is slid into the chamber with the couch.
 - 9) The delivering cables from the applicators are connected to their corresponding holes on the wall of the chamber from inside.
 - 10) The door of the chamber is closed (Fig. 2-9B), and the patient is asked to apply the mask.
- Now, the patient is ready for the pressurization and following irradiation. Usually, three atmospheres

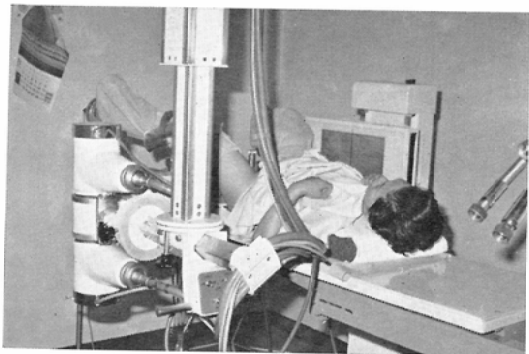


Fig. 2-9A. X-ray examination to confirm the position of the applicators.

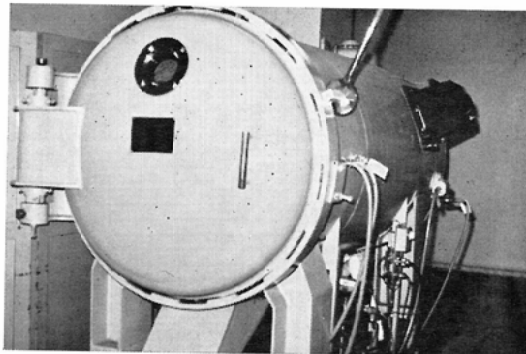


Fig. 2-9B. External view of the hyperbaric chamber.

absolute (3 ATA) (2 kg./cm² gauge pressure) is attained in 15 to 20 minutes. The patient is kept at full pressure for a period of 5 minutes to allow for the saturation. The sources are driven out of the container to their respective applicators and the irradiation is started. The distance between the container and the tip of the applicators is 7.5 meters and the sources travel this distance in 15 sec. When the predetermined time is over, the sources are drawn back to the container automatically. At the same time, depressurization is started. In 10 minutes, the pressure in the chamber is returned to the original atmosphere. Then the door is opened and the applicators are removed. The sources can also be drawn back manually to the container in the event of power failure. Usually the patient is able to walk back to the ward immediately after these procedures. It is 40 minutes in the average that the patient is kept in the chamber.

After the series of intracavitary therapy with the RALSTRON under high pressure oxygenation, the external irradiation to the pelvic cavity with Co-60 teletherapy is followed. This is done by anterior and posterior two opposing fields technique. The field of the external irradiation is designed as to include the parametria and nodes on the pelvic wall on both sides extending up to and including the iliac and presacral nodes. This field measures 14 × 14 square centimeters on the skin surface. The lead block of 2 × 5 cm² or 3 × 7 cm² is placed to shield the rectum and the urinary bladder. This is known as split field method (SP-method). Dose of 4,000 to 6,000 rad at the midplane level is delivered in about 20 fractions in the period of 30 to 40 days. It is estimated that 55.6 per cent of the midplane dose is delivered to point A with 2 × 5 cm² lead shield, and 33.3 per cent of that in case of 3 × 7 cm² lead shield (Tab. 2-1A).

By both the intracavitary and the external irradiation, 5,243 rad are delivered to point B. Over-all treatment period is 42 days in average.

Table 2-1A. Dose Contribution of Co-60 External Teletherapy to the Rectum and the Urinary Bladder*

Size of Central Shield	2 × 5 cm ²	3 × 7 cm ²
Point A	55.6%	33.3%
Rectum**	27.0%	21.0%
Bladder***	20.0%	17.0%

*Calculation made with midplane dose as 100%.

**Point 10 cm from anal opening.

***Point 10 cm from urethral orifice.

Table 2-1B. Dose Contribution of Intracavitary RALSTRON Irradiation to the Rectum and the Urinary Bladder*

	Per cent
Rectum**	29%
Bladder***	44%

*Calculation made with the dose at Point A as 100%.

**Point 9 cm from anal opening.

***Point 8 cm from urethral orifice.

Table 2-2. Post-Treatment Course in 58 Patients Irradiated under Hyperbaric Oxygenation (Oct. 1970)

Case No.	Name	Age	Stage	Duration of Post-treatment Observation				Follow-up	
				12 mos.	24 mos.	36 mos.	48 mos.		
101	M.N.	44	IIA	—	—	—	—	Alive and well	101
102	H.M.	60	IIA	—	—	—	—	Died of myocardial infarction	102
103	S.Y.	62	IIA	—	—	—	—	Alive and well	103
104	Y.A.	36	IIIB	—	—	—	—	Recurrence	104
105	S.Y.	69	IIIB	—	—	—	—	Alive and well	105
106	T.K.	56	IIA	—	—	—	—	Alive and well	106
107	H.E.	48	IIIB	—	—	—	—	Ureterocutaneousomy	107
201	E.K.	48	IIA	—	—	—	—	Alive and well	201
202	E.F.	36	IIIB	—	—	—	—	Alive and well	202
203	T.W.	58	IIA	—	—	—	—	Alive and well	203
204	F.O.	52	IIA	—	—	—	—	Alive and well	204
205	T.N.	43	IIIB	—	—	—	—	Colostomy	205
206	T.M.	43	IIA	—	—	—	—	Alive and well	206
207	H.K.	47	IIA	—	—	—	—	Recurrence	207
208	T.K.	48	IIIB	—	—	—	—	Ureterocutaneousomy	208
209	Y.K.	54	IIA	—	—	—	—	Colostomy	209
210	K.Y.	47	IIA	—	—	—	—	Died, unknown disease	210
211	H.Y.	60	IIIB	—	—	—	—	Alive and well	211
212	M.O.	57	IIA	—	—	—	—	Alive and well	212
213	K.K.	33	IIA	—	—	—	—	Convulsion similar to grand mal seizure	213
214	M.K.	51	IIA	—	—	—	—	Recurrence	214
215	Y.K.	32	IIA	—	—	—	—	Alive and well	215
216	T.O.	48	IIIB	—	—	—	—	Alive and well	216
217	K.M.	67	IIA	—	—	—	—	Alive and well	217
218	K.S.	56	IIA	—	—	—	—	Alive and well	218
219	H.K.	31	IA	—	—	—	—	Alive and well	219
220	F.M.	73	IIIB	—	—	—	—	Alive and well	220
221	M.S.	64	IIA	—	—	—	—	Alive and well	221
222	S.O.	30	IIA	—	—	—	—	Alive and well	222
223	A.H.	32	IIIB	—	—	—	—	Alive and well	223
224	T.U.	50	IIIB	—	—	—	—	Alive and well	224
225	S.K.	61	IIIB	—	—	—	—	Alive and well	225
226	M.D.	59	IIIB	—	—	—	—	Alive and well	226
227	Y.I.	63	IIA	—	—	—	—	Alive and well	227
228	S.F.	63	IIIB	—	—	—	—	Alive and well	228
229	M.S.	58	IA	—	—	—	—	Alive and well	229
230	S.E.	47	IIA	—	—	—	—	Alive and well	230
231	F.I.	67	IIIB	—	—	—	—	Alive and well	231
232	M.O.	42	IB	—	—	—	—	Alive and well	232
233	H.M.	52	IA	—	—	—	—	Alive and well	233
301	M.T.	56	IIA	—	—	—	—	Alive and well	301
302	T.K.	30	IIA	—	—	—	—	Alive and well	302
303	N.S.	73	IIIB	—	—	—	—	Alive and well	303
304	C.Y.	64	IIA	—	—	—	—	Alive and well	304
305	M.S.	42	IIIB	—	—	—	—	Alive and well	305
306	I.U.	72	IIA	—	—	—	—	Alive and well	306
307	S.S.	50	IIIB	—	—	—	—	Alive and well	307
308	H.K.	57	IB	—	—	—	—	Alive and well	308
309	T.S.	69	IA	—	—	—	—	Alive and well	309
310	H.M.	64	IIA	—	—	—	—	Alive and well	310
311	A.S.	49	IIIB	—	—	—	—	Alive and well	311
312	J.S.	40	IIA	—	—	—	—	Alive and well	312
313	T.I.	59	IIIB	—	—	—	—	Alive and well	313
314	S.K.	47	IIA	—	—	—	—	Alive and well	314
315	Y.G.	54	IA	—	—	—	—	Alive and well	315
316	S.F.	45	IIIB	—	—	—	—	Convulsion similar to grand mal seizure	316
317	T.A.	54	IB	—	—	—	—	Alive and well	317
318	Y.K.	51	IB	—	—	—	—	Alive and well	318

Clinical experiences (Tab. 2-2):

1. Two doses of 500 rad at point A with one week interval (case 101-107).

No. 101 M. N. 44 y. o. Protocol No. 139

Stage IIIA, squamous cell carcinoma

First Visit: Feb. 21, 1969

Treatment

RALS: 2 ×. 500R, 500R

External Irradiation:

SP-method 5,000R in 35 days

Total Dose (Treatment Period 49 days):

Point A 3,777R (1,000R*, 2,777R ϕ)

Point B 5,300R (300R , 5,000R)

Post-treatment Course

Alive and well at 19 months after the first visit.

Complication: none.

No. 102 H. M. 60 y. o. Protocol No. 559

Stage IIIA, squamous cell carcinoma

First Visit: July 16, 1969.

Treatment

RALS: 2 ×. 500R, 500R

External Irradiation:

SP-method 400R in 2 days

Total Dose (Treatment Period 16 days)

Point A 1,222R (1,000R*, 222R ϕ)

Point B 700R (300R , 400R)

Post-treatment Course

Died of myocardial infarct during the course of external irradiation.

Complication: none.

No. 103 S. Y. 62 y. o. Protocol No. 568

Stage IIIA, squamous cell carcinoma

First Visit: July 18, 1969

Treatment

RALS: 2 ×. 500R, 500R

External Irradiation:

SP-method 5,000R in 35 days

Total Dose (Treatment Period 49 days):

Point A 3,777R (1,000R*, 2,777R ϕ)

Point B 5,300R (300R , 5,000R)

*denotes the dose contribution from RALSTRON treatment, ϕ from the external irradiation by SP-method.

Post-treatment Course

Alive and well at 15 months after the first visit.

Complication: none.

No. 104 Y. A. 36 y. o. Protocol No. 614

Stage IIIB, squamous cell carcinoma

First Visit: Aug. 6, 1969

Treatment

RALS: 2 ×. 500R, 500R

External Irradiation:

SP-method 5,000R in 33 days

Total Dose (Treatment Period 52 days)

Point A 3,777R (1,000R*, 2,777R ϕ)

Point B 5,300R (300R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 2 ×. 500R, 500R

Local recurrence 5 months later.

Retreatment

External Irradiation: 6,000 R by whole pelvic technique.

Alive and well 14 months after the first visit.

Complication: none.

No. 105 S. Y. 69 y. o. Protocol No. 615

Stage IIB, squamous cell carcinoma

First Visit: Aug. 6, 1969

Treatment

RALS: 2 ×. 500R, 500R

External Irradiation:

SP-method 6,000R in 34 days

Total Dose (Treatment Period 48 days)

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Alive and well at 14 months after the first visit.

Complication: none.

No. 106 T. K. 56 y. o. Protocol No. 646

Stage IIIA, squamous cell carcinoma

First Visit: Aug. 18, 1969

Treatment

RALS: 2 ×. 500R, 500R

External Irradiation:

SP-method 5,500R in 39 days

Total Dose (Treatment Period 53 days)

Point A 4,055R (1,000R*, 3,055R ϕ)

Point B 5,800R (300R , 5,500R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 1 \times . 500R

Alive and well at 14 months after the first visit.

Complication: none.

No. 107 H. E. 48 y. o. Protocol No. 681

Stage IIB, squamous cell carcinoma

First Visit: Aug. 29, 1969

Treatment

RALS: 2 \times . 500R, 500R

External Irradiation:

SP-method 5,000R in 42 days

Total Dose (Treatment Period 56 days)

Point A 3,777R (1,000R*, 2,777R ϕ)

Point B 5,300R (300R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment

RALS: 1 \times . 500R

Persistent residual disease after 2 months' observation.

Retreatment

RALS: 2 \times . 1,000R, 1,000R

External Irradiation:

SP-method 5,000R

(Ureterocutaneostomy for bil. hydro. performed before the ext. irradiation.)

Died of chronic renal failure 12 months after the first visit.

Complication: none.

Seven patients were treated with this schedule. Histologically all were squamous cell carcinoma. Clinically, two were in stage IIB, 4 in stage IIIA and 1 in stage IIIB. Three patients (case 101, 103, 105) have been well with no clinical evidences of recurrences or metastasis for 17 months, 10 months and 10 months respectively after the completion of the treatment. One patient (case 102) died of myocardial infarction before the completion of the treatment. The additional treatments were necessary in the remaining three patients due to the residual disease. After that, two have been well for more than 10 months

with no clinical evidences of recurrence at present time. One patient died of the advanced disease (case 107).

2. Two doses of 725 rad or 750 rad at point A with one week interval (case 201-233).

Primarily, we attempted to deliver 1,500 rad by three sources in the present series. However, in some patients it was difficult to introduce the intra-uterine tandem due to the advanced disease: i.e., destruction of cervical canal, closure of the canal due to the infiltration etc. These patients were irradiated without the tandem source. The dosage applied in these cases were 1,450 rad at point A in two fractions by two ovoids.

A) Cases received two doses of 725 rad by ovoid sources (case 201-211)

No. 201 F. K. 48 y. o. Protocol No. 095

Stage IIIA, squamous cell carcinoma

First Visit: Feb. 8, 1969

Treatment

RALS: 2 ×. 725R, 725R

External Irradiation:

SP-method 5,000R in 32 days

Total Dose (Treatment Period 46 days)*

Point A 4,227R (1,450R*, 2,777R ϕ)

Point B 5,435R (435R , 5,000R)

Post-treatment Course

Alive and well at 20 months after the first visit.

Complication: none.

No. 202 E. F. 36 y. o. Protocol No. 111

Stage IIIB, squamous cell carcinoma

First Visit: Feb. 13, 1969

Treatment

RALS: 3 ×. 725R, 725i, 725R

External Irradiation:

SP-method 5,000R in 34 days

Total Dose (Treatment Period 55 days):

Point A 4,952 R (2,175 R*, 2,777R ϕ)

Point B 5,652.5R (652.5R*, 5,000R)

Post-treatment Course

Residual disease 2 months later.

Retreatment:

RALS: 1 ×. 725R

Intracavitary radium insertion: 1,200 mgh

Alive and well at 20 months after the first visit.

Complication: none.

No. 203 T. W. 58 y. o. Protocol No. 307

Stage IIIA, squamous cell carcinoma

First Visit: Apr. 21, 1969

Treatment

RALS: 2 ×. 725R, 725R

External Irradiation:

SP-method 5,500R in 42 days

Total Dose (Treatment Period 56 days):

Point A 4,505R (1,450R*, 3,055R ϕ)

Point B 5,935R (435R , 5,500R)

Post-treatment Course

Alive and well at 18 months after the first visit.

Complication: none.

No. 204 F. O. 52 y. o. Protocol No. 346

Stage IIIA, squamous cell carcinoma

First Visit: May 7, 1969

Treatment

RALS: 2 ×. 725R, 725R

External Irradiation:

SP-method 5,200R in 35 days

Total Dose (Treatment Period 49 days):

Point A 4,338R (1,450R*, 2,888R ϕ)

Point B 5,635R (435R , 5,200R)

Post-treatment Course

Alive and well at 17 months after the first visit.

Complication: none.

No. 205 T. N. 43 y. o. Protocol No. 363

Stage IIIB, squamous cell carcinoma

First Visit: May 13, 1969

Treatment

RALS: 2 ×. 725R, 725R

External Irradiation:

SP-method 5,200R in 28 days

Total Dose (Treatment Period 42 days):

Point A 4,338R (1,450R*, 2,888R ϕ)

Point B 5,635R (435R , 5,200R)

Post-treatment Course

Residual disease 2 months later.

Retreatment

RALS: 2 ×. 1,000R, 1,000R without hyperbaric oxygenation.

External Irradiation: 6,000R (whole pelvis)

Colostomy for severe sigmoiditis 1 month later.

Alive at 17 months with the evidence of the disease after the first visit.

No. 206 T. M. 43 y. o. Protocol No. 431

Stage IIIA, squamous cell carcinoma

First Visit: May 30, 1969

Treatment

RALS: 2 ×. 725R, 725R

External Irradiation:

SP-method 5,000R in 35 days

Total Dose (Treatment Period 49 days)

Point A 4,227R (1,450R*, 2,777R ϕ)

Point B 5,435R (435R , 5,000R)

Post-treatment Course

Alive and well at 17 months after the first visit.

Complication: none.

No. 207 H. K. 47 y. o. Protocol No. 466

Stage IIIA, squamous cell carcinoma

First Visit: June 9, 1969

Treatment

RALS: 2 ×. 725R, 725R

External Irradiation:

SP-method 5,000R in 35 days

Total Dose (Treatment Period 49 days):

Point A 4,227R (1,450R*, 2,777R ϕ)

Point B 5,435R (435R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 2 ×. 500R, 1,000R

Local recurrence and infiltration to the sigmoid 4 months later.

Retreatment:

External Irradiation: 6,000R (whole pelvis)

Alive at 16 months after the first visit.

No. 208 T. K. 48 y. o. Protocol No. 478

Stage IIIB, squamous cell carcinoma

First Visit: June 13, 1969

Treatment

RALS: 2 ×. 725R, 725R

External Irradiation:

SP-method 5,000R in 35 days

Total Dose (Treatment Period 49 days):

Point A 4,227R (1,450R*, 2,777R ϕ)

Point B 5,435R (435R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 2 \times . 725R, 1,000R

Ureterocutaneostomy for bil. hydronephroses.

Died of peritonitis carcinomatosa 5 months after the first visit.

Complication: none.

No. 209 Y. K. 54 y. o. Protocol No. 520

Stage IIIA, squamous cell carcinoma

First Visit: June 27, 1969

Treatment

RALS: 2 \times . 725R, 725R

External Irradiation:

SP-method 5,000R in 34 days

Total Dose (Treatment Period 48 days):

Point A 4,227R (1,450R*, 2,777R ϕ)

Point B 5,435R (435R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment

Retreatment:

RALS: 1 \times . 500R

Recurrence 8 months later.

Colostomy for ileus following peritonitis carcinomatosa.

Deceased 13 months after the first visit.

No. 210 K. Y. 47 y. o. Protocol No. 523

Stage IIIA, squamous cell carcinoma

First Visit: June 28, 1969

Treatment

RALS: 2 \times . 725R, 725R

External Irradiation:

SP-method 5,000R in 37 days

Total Dose (Treatment Period 51 days):

Point A 4,227R (1,450R*, 2,777R ϕ)

Point B 5,435R (435R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 1 ×. 500R

Deceased 10 months after the first visit.

No. 211 H. Y. 60 y. o. Protocol No. 855

Stage IIIB, squamous cell carcinoma

First Visit: Dec. 13, 1968

Treatment

RALS: 2 ×. 725R, 725R

External Irradiation:

SP-method 4,500R in 35 days

Total Dose (Treatment Period 49 days):

Point A 3,950R (1,450R*, 2,500R ϕ)

Point B 4,935R (435R , 4,500R)

Post-treatment Course

Recurrence 5 months later.

Retreatment:

External Irradiation: 5,000R (whole pelvis)

Ureterocutaneostomy for bil. hydronephroses.

Died of chronic renal failure 15 months after the first visit.

Eleven patients with squamous cell carcinoma, 7 in stage IIIA and 4 in stage IIIB, were treated with this regimen. Four patients died of the disease within 12 months after the completion of the treatment, and remaining four cases showed the sign of residual disease. These four received additional treatments and have been well thereafter more than 12 months. No rectal or urinary bladder injury was encountered with this treatment regimen.

B) Cases received two doses of 750 rad by a tandem and ovoid sources (case 212-233)

No. 212 M. O. 57 y. o. Protocol No. 704

Stage IIIA, squamous cell carcinoma

First Visit: Sep. 5, 1969

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,000R in 43 days

Total Dose (Treatment Period 57 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Residual disease 2 months later.

Retreatment

RALS: 2 ×. 1,000R, 1,000R

Alive and well 13 months after the first visit.

Complication: none.

No. 213 K. K. 38 y. o. Protocol No. 707

Stage IIIA, squamous cell carcinoma

First Visit: Sep. 5, 1969

Treatment

RALS: 2 ×. 750R, 750

External Irradiation:

SP-method 5,000R in 33 days

Total Dose (Treatment Period 47 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 2 ×, 500R, 500R

Alive and well at 13 months after the first visit.

Complication: Convulsion similar to grand mal seizure
during the second RALSTRON treatment under
hyperbaric oxygenation.

No. 214 M. K. 51 y. o. Protocol No. 754

Stage IIIA, squamous cell carcinoma

First Visit: Sep. 20, 1969

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,000R in 33 days

Total Dose (Treatment Period 47 days):

Point A 4,277R (1,500R* ,2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Local recurrence 6 months later.

Retreatment:

External Irradiation: 6,000R (whole pelvis)

Alive and well at 12 months after the first visit.

Complication: none.

No. 215 Y. K. 32 y. o. Protocol No. 774

Stage IIIA, squamous cell carcinoma

First Visit: Sep. 27, 1969

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,000R in 33 days

Total Dose (Treatment Period 47 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 2 ×. 500R, 500R

Alive and well at 12 months after the first visit.

Complication: none.

No. 216 T. O. 48 y. o. Protocol No. 779

Stage IIIB, squamous cell carcinoma

First Visit: Sep. 30, 1969

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,000R in 35 days

Total Dose (Treatment Period 49 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 1 ×. 500R

Alive and well at 12 months after the first visit.

Complication: none.

No. 217 K. M. 67 y. o. Protocol No. 793

Stage IIIA, squamous cell carcinoma

First Visit: Oct. 3, 1969

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,000R in 36 days

Total Dose (Treatment Period 50 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Alive and well at 12 months after the first visit.

Complication: none.

No. 218 K. S. 56 y. o. Protocol No. 815

Stage IIIA, squamous cell carcinoma

First Visit: Oct. 11, 1969

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,000R in 39 days

Total Dose (Treatment Period 53 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 1 ×. 500R

Alive and well 11 months after the first visit.

Complication: none.

No. 219 H. K. 31 y. o. Protocol No. 842

Stage IA, squamous cell carcinoma, concurrent SMON's disease

First Visit: Oct. 22, 1969

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,000R in 24 days

Total Dose (Treatment Period 38 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Alive and well at 11 months after the first visit.

Complication: none.

No. 220 F. M. 73 y. o. Protocol No. 854

Stage IIIB. swuamous cell carcinoma

First Visit: Oct. 24, 1969

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,000R in 33 days

Total Dose (Treatment Period 47 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 1 ×. 500R

Alive and well at 11 months after the first visit.

Complication: none.

No. 221 M. S. 64 y. o. Protocol No. 896

Stage IIIA, squamous cell carcinoma

First Visit: Nov. 11, 1969

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,600R in 52 days

Total Dose (Treatment Period 45 days):

Point A 4,611R (1,500R*, 3,111R ϕ)

Point B 6,050R (450R , 5,600R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 1 ×. 500R

Alive and well at 11 months after the first visit.

Complication: none.

No. 222 S. O. 30 y. o. Protocol No. 703

Stage IIIA, squamous cell carcinoma, pregnancy (first trimester)

First Visit: Sep. 5, 1969

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,000R in 36 days

Total Dose (Treatment Period 37 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 1 ×. 500R

Persistent residual disease after 2 months' observation.

Retreatment:

RALS: 2 ×. 1,000R, 1,000R

External Irradiation: 6,000R (whole pelvis)

Alive at 13 months after the first visit.

Complication: none.

No. 223 A. H. 32 y. o. Protocol No. 981

Stage IIB, squamous cell carcinoma

First Visit: Dec. 16, 1969

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,000R in 35 days

Total Dose (Treatment Period 49 days):

Point A 4,277R (1,500R*, 2,777R †)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 2 ×. 500R, 500R

Alive and well 9 months after the first visit.

Complication: none.

No. 224 T. U. 50 y. o. Protocol No. 982

Stage IIB, squamous cell carcinoma

First Visit: Dec. 16, 1969

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,000R in 27 days

Total Dose (Treatment Period 41 days):

Point A 4,277R (1,500R*, 2,777R †)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 2 ×. 500R, 500R

Alive and well at 9 months after the first visit.

Complication: none.

No. 225 S. K. 61 y. o. Protocol No. 009

Stage IIB, squamous cell carcinoma

First Visit: Jan. 7, 1970

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,300R in 35 days

Total Dose (Treatment Period 49 days):

Point A 4,444R (1,500R*, 2,944R ϕ)

Point B 5,750R (450R , 5,300R)

Post-treatment

Residual disease at the end of the above treatment.

Retreatment:

RALS: 2 \times . 500R, 500R

Alive and well 9 months after the first visit.

Complication: none.

No. 226 M. D. 59 y. o. Protocol No. 030

Stage IIB, squamous cell carcinoma

First Visit: Jan. 13, 1970

Treatment

RALS: 2 \times . 750R, 750R

External Irradiation:

SP-method 5,000R in 35 days

Total Dose (Treatment Period 49 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R*, 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 2 \times . 500R, 500R

Alive and well 9 months after the first visit.

Complication: none.

No. 227 Y. I. 63 y. o. Protocol No. 103

Stage IIIA, squamous cell carcinoma

First Visit: Feb 10, 1970

Treatment

RALS: 2 \times . 750R, 750R

External Irradiation:

SP-method 5,000R in 31 days

Total Dose (Treatment Period 45 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment

RALS: 1 ×. 1,000R

Alive and well at 8 months after the first visit.

Complication: none.

No. 228 S. F. 63 y. o. Protocol No. 114

Stage IIIB, squamous cell carcinoma

First Visit: Feb. 16, 1970

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,000R in 31 days

Total Dose (Treatment Period 45 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment

RALS: 1 ×. 1,000R

Alive and well at 8 months after the first visit.

Complication: none.

No. 229 M. S. 58 y. o. Protocol No. 116

Stage IIA, squamous cell carcinoma

First Visit: Feb. 16, 1970

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,000R in 32 days

Total Dose (Treatment Period 46 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Residual disease after the end of the above treatment.

Retreatment

RALS: 1 ×. 1,000R

Alive and well at 8 months after the first visit.

Complication: none.

No. 230 S. E. 47 y. o. Protocol No. 165

Stage IIIA, squamous cell carcinoma

First Visit: Mar. 3, 1970

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,000R in 33 days

Total Dose (Treatment Period 47 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment

RALS: 1 \times . 1,000R

Alive and well at 7 months after the first visit.

Complication: Otagia during the RALSTRON treatment under hyperbaric oxygenation.

No. 231 F. I. 67 y. o. Protocol No. 171

Stage IIB, squamous cell carcinoma

First Visit: Mar. 4, 1970

Treatment

RALS: 2 \times . 750R, 750R

External Irradiation:

SP-method 5,000R in 34 days

Total Dose (Treatment Period 48 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 1 \times . 1,000R

Alive and well at 7 months after the first visit.

Complication: none.

No. 232 M. O. 42 y. o. Protocol No. 182

Stage IB. squamous cell carcinoma

First Visit: Mar. 6, 1970

Treatment

RALS: 2 \times . 750R, 750R

External Irradiation:

SP-method 5,000R in 30 days

Total Dose (Treatment Period 44 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R*, 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 1 ×. 1,000R

Alive and well at 7 months after the first visit.

Complication: none.

No. 233 H. M. 52 y. o. Protocol No. 185

Stage IA, squamous cell carcinoma

First Visit: Mar. 10, 1970

Treatment

RALS: 2 ×. 750R, 750R

External Irradiation:

SP-method 5,000R in 35 days

Total Dose (Treatment Period 49 days):

Point A 4,277R (1,500R*, 2,777R ϕ)

Point B 5,450R (450R , 5,000R)

Post-treatment Course

Alive at 7 months after the first visit.

Complication: none.

Twenty two patients were treated with this regimen. All were squamous cell carcinoma in histological type. Their clinical stages were as follows: 2 stage IA, 1 stage IB, 1 stage IIA, 5 stage IIB, 10 stage IIIA and 3 stage IIIB. Three patients have been well with no clinical evidence of recurrence for more than 6 months. One patient showed the sign of recurrence and the remaining eighteen patients had the residual disease necessitated additional radiation treatments. These eighteen cases have been well for more than 6 months without mortality. No rectal or urinary bladder damage was noted in these cases.

There was a considerable number of cases showing the sign of residual disease in both groups received two doses of 725 rad and two doses of 750 rad. Treatment dose might have been inadequate to eradicate the disease.

3. Two or three doses of 2,000 rad or 3,000 rad at point A with one week interval (case 301-318)

No. 301 M. T. 56 y. o. Protocol No. 729

Stage IIIA, squamous cell carcinoma

First Visit: Oct. 25, 1968

Treatment

RALS: 2 ×. 1,000R, 1,000R

External Irradiation:

SP-method 4,500R in 35 days

Total Dose (Treatment Period 49 days):

Point A 4,500R (2,000R*, 2,500R ϕ)

Point B 5,100R (600R , 4,500R)

Post-treatment Course

Alive and well at 23 months after the first visit.

Complication: none.

No. 302 T. K. 30 y. o. Protocol No. 219

Stage IIIA, squamous cell carcinoma

First Visit: Mar. 24, 1970

Treatment

RALS: 2 ×. 1,000R, 1,000R

External Irradiation:

SP-method 5,000R in 37 days

Total Dose (Treatment Period 50 days):

Point A 3,875R (2,000R*, 1,875R ϕ)

Point B 5,600R (600R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 1 ×. 1,000R

Alive and well at 6 months after the first visit.

Complication: none.

No. 303 N. S. 73 y. o. Protocol No. 236

Stage IIIB, squamous cell carcinoma

First Visit: Mar. 27, 1970

Treatment

RALS: 2 ×. 1,000R, 1,000R

External Irradiation:

SP-method 5,000R in 36 days

Total Dose (Treatment Period 46 days):

Point A 3,875R (2,000R*, 1,875R ϕ)

Point B 5,600R (600R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment

RALS: 1 ×. 1,000R

Alive and well at 6 months after the first visit.

Complication: none.

No. 304 C. Y. 64 y. o. Protocol No. 290

Stage IIIA, adenocarcinoma

First Visit: Apr. 21, 1970

Treatment

RALS: 2 ×. 1,000R, 1,000R

External Irradiation:

SP-method 5,000R in 35 days

Total Dose (Treatment Period 49 days)

Point A 3,875R (2,000R*, 1,875R ϕ)

Point B 5,600R (600R , 5,000R)

Post-treatment Course

Alive and well at 5 months after the first visit.

Complication: none.

No. 305 M. S. 42 y. o. Protocol No. 361

Stage IIIB, squamous cell carcinoma

First Visit: May 19, 1970

Treatment

RALS: 2 \times . 1,000R, 1,000R

External Irradiation:

SP-method 5,000R in 42 days

Total Dose (Treatment Period 61 days):

Point A 3,875R (2,000R*, 1,875R ϕ)

Point B 5,600R (600R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment:

RALS: 2 \times . 1,000R, 1,000R

Alive at 4 months after the first visit.

Complication: none.

No. 306 I. U. 72 y. o. Protocol No. 374

Stage IIIA, squamous cell carcinoma

First Visit: May 26, 1970

Treatment

RALS: 2 \times . 1,000R, 1,000R

External Irradiation: none

Total Dose (Treatment Period 7 days):

Point A 2,000R

Point B 600R

Post-treatment Course

Alive at 4 months after the first visit.

Refused external irradiation.

Complication: none.

No. 307 S. S. 50 y. o. Protocol No. 400

Stage IIIB, squamous cell carcinoma

First Visit: June 5, 1970

Treatment

RALS: 2 \times . 1,000R, 1,000R

External Irradiation:

SP-method 2,700R in 22 days

Total Dose (Treatment Period 34 days):

Point A 2,891R (2,000R*, 891R ϕ)

Point B 3,300R (600R , 2,700R)

Post-treatment Course

Ceased external irradiation due to paralytic ileus.

Residual disease 2 months later.

Retreatment:

RALS: 3 \times . 1,000R, 1,000R, 1,000R

Alive at 4 months after the first visit.

No. 308 H. K. 57 y. o. Protocol No. 401

Stage IIB, squamous cell carcinoma

First Visit: June 5, 1970

Treatment

RALS: 2 \times . 1,000R, 1,000R

External Irradiation:

SP-method 5,000R in 43 days

Total Dose (Treatment Period 55 days):

Point A 3,875R (2,000R*, 1,875R ϕ)

Point B 5,600R (600R , 5,000R)

Post-treatment Course

Alive and well at 4 months after the first visit.

Complication: none.

No. 309 T. S. 69 y. o. Protocol No. 417

Stage IA, squamous cell carcinoma

First Visit: June 12, 1970

Treatment

RALS: 2 \times . 1,000R, 1,000R

External Irradiation:

SP-method 5,000R in 34 days

Total Dose (Treatment Period 54 days):

Point A 3,875R (2,000R*, 1,875R ϕ)

Point B 5,600R (600R , 5,000R)

Post-treatment Course

Alive and well at 4 months after the first visit.

Complication: none.

No. 310 H. M. 64 y. o. Protocol No. 459

Stage IIIA, squamous cell carcinoma

First Visit: June 25, 1970

Treatment

RALS: 3 ×. 1,000R, 1,000R, 1,000R

External Irradiation:

SP-method 5,000R in 32 days

Total Dose (Treatment Period 45 days):

Point A 4,875R (3,000R*, 1,875R ϕ)

Point B 5,900R (900R , 5,000R)

Post-treatment Course

Alive and well at 3 months after the first visit.

Complication: none.

No. 311 A. S. 49 y. o. Protocol No. 463

Stage IIIB, squamous cell carcinoma

First Visit: June 26, 1970

Treatment

RALS: 3 ×. 1,000R, 1,000R, 1,000R

External Irradiation:

SP-method 5,000R in 34 days

Total Dose (Treatment Period 52 days):

Point A 4,875R (3,000R*, 1,875R ϕ)

Point B 5,900R (900R , 5,000R)

Post-treatment Course

Alive and well at 3 months after the first visit.

Complication: none.

No. 312 J. S. 40 y. o. Protocol No. 485

Stage IIIA, squamous cell carcinoma

First Visit: July 3, 1970

Treatment

RALS: 3 ×. 1,000R, 1,000R, 1,000R

External Irradiation:

SP-method 5,000R in 32 days

Total Dose (Treatment Period 49 days):

Point A 4,875R (3,000R*, 1,875R ϕ)

Point B 5,900R (900R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment

RALS: 1 ×. 1,000R

Alive and well at 3 months after the first visit.

Complication: none.

No. 313 T. I. 59 y. o. Protocol No. 486

Stage IIB, squamous cell carcinoma

First Visit: July 3, 1970

Treatment

RALS: 3 ×. 1,000R, 1,000R, 1,000R

External Irradiation:

SP-method 5,000R in 38 days

Total Dose (Treatment Period 50 days):

Point A 4,875R (3,000R*, 1,875R ϕ)

Point B 5,900R (900R , 5,000R)

Post-treatment Course

Alive and well at 3 months after the first visit.

Complication: none.

No. 314 S. K. 47 y. o. Protocol No. 496

Stage IIIA, squamous cell carcinoma

First Visit: July 14, 1970

Treatment

RALS: 3 ×. 1,000R, 1,000R, 1,000R

External Irradiation:

SP-method 5,000R in 35 days

Total Dose (Treatment Period 54 days):

Point A 4,875R (3,000R*, 1,875R ϕ)

Point B 5,900R (900R , 5,000R)

Post-treatment Course

Alive and well at 3 months after the first visit.

Complication: none.

No. 315 Y. G. 54 y. o. Protocol No. 534

Stage IA, squamous cell carcinoma

First Visit: July 28, 1970

Treatment

RALS: 3 ×. 1,000R, 1,000R, 1,000R

External Irradiation:

SP-method 5,000R in 35 days

Total Dose (Treatment Period 49 days):

Point A 4,875R (3,000R*, 1,875R ϕ)

Point B 5,900R (900R , 5,000R)

Post-treatment Course

Alive and well at 2 months after the first visit.

Complication: none.

No. 316 S. F. 45 y. o. Protocol No. 552

Stage IIIB, squamous cell carcinoma

First Visit: Aug. 4, 1970

Treatment

RALS: 3 ×. 1,000R, 1,000R, 1,000R

External Irradiation:

SP-method 5,000R in 40 days

Total Dose (Treatment Period 49 days):

Point A 4,875R (3,000R*, 1,875R ϕ)

Point B 5,900R (900R , 5,000R)

Post-treatment Course

Alive and well at 2 months after the first visit.

Complication: Convulsion similar to grand mal seizure during the second RALSTRON treatment under hyperbaric oxygenation.

No. 317 T. A. 54 y. o. Protocol No. 563

Stage IIB, squamous cell carcinoma

First Visit: Aug. 6, 1970

Treatment

RALS: 3 ×. 1,000R, 1,000R, 1,000R

External Irradiation:

SP-method 5,000R in 43 days

Total Dose (Treatment Period 57 days):

Point A 4,875R (3,000R*, 1,875R ϕ)

Point B 5,900R (900R , 5,000R)

Post-treatment Course

Alive and well at 2 months after the first visit.

Complication: none.

No. 318 Y. K. 51 y. o. Protocol No. 602

Stage IB, squamous cell carcinoma

First Visit: Aug. 21, 1970

Treatment

RALS: 3 ×. 1,000R, 1,000R, 1,000R

External Irradiation:

SP-method 5,000R in 37 days

Total Dose (Treatment Period 57 days):

Point A 4,875R (3,000R*, 1,875R ϕ)

Point B 5,900R (900R , 5,000R)

Post-treatment Course

Residual disease at the end of the above treatment.

Retreatment

RALS: 1 × . 500R

Alive and well at 2 months after the first visit.

Complication: none.

Eighteen patients were treated with this regimen. Histologically 17 were squamous cell carcinomas and one was adenocarcinoma. Clinically, 2 were in stage IA, 1 was in stage IB, 3 were in stage IIB, 7 in stage IIIA and 5 in stage IIIB. One patient (case 306) has been well for 22 months after the completion of the treatment. Remaining 17 patients have finished their treatment course recently. The follow-up results of these cases are not available at present time.

Through these series of clinical experiences, no serious injury to the rectum and/or the urinary bladder were noted following the primary radiotherapy.

Summary

In the application of high pressure oxygen, the liability of oxygen intoxication depends on the duration of oxygenation time and the pressure used⁸⁴⁾⁻⁸⁶⁾. In the original reports of Churchill-Davidson et

Table 2-3. Summary of Data on 57 Patients Received 2 Doses of 500-1,000 Rad and 3 Doses of 1,000 Rad to Point a under Hyperbaric Oxygenation

RALSTRON Dosage (spacing, days)	No. Cases and Stage	Primary Healing	Surviving			Alive and Well	Survival Rate
			Residuum	Recurrence	Dead		
2 × 500 rad (0, 7)	6* II-2 III-4	3	3 Retreatment One died at 12 mos.	1 Retreatment	1	5/6 > 12 mos.	83%
2 × 725 rad (0, 7)	11 III-11	4	6 Retreatment Two died at 5, 10 mos.	1 Retreatment One died at 15 mos.	4**	7/11 > 12 mos.	64%
2 × 750 rad (0, 7)	22 I-3 II-6 III-13	3	18 Retreatment	1 Retreatment	0	22/22 > 6 mos.	100%
2 × 1,000 rad (0, 7)	9 I-1 II-1 III-7	6	3 Retreatment	0	0	9/9 > 3 mos.	100%
3 × 1,000 rad (0, 7, 14)	9 I-2 II-2 III-5	8	1 Retreatment	0	0	9/9 > 3 mos.	100%

*Excluded a patient died of myocardial infarction.

**Included a patient died of unknown disease.

Table 2-4. Oxygen Toxicity 192 HPO Exposures without Anesthesia in 58 Patients (1968-1970)

Average duration of each exposure at 3 ATA.....	38 minutes (range 28-59 minutes)
Convulsions	2 (1%)
Other toxicity to neuraxis.....	nil
Pulmonary damage.....	nil
Moderate otalgia.....	9%
Other tissues.....	nil
Mortality	1*

*One died of myocardial infarction after the treatment.

al.³⁷⁾, they have used 3 atmosphere absolute and the anesthesia and myringotomy were necessary to prepare the patient. Also, pure oxygen was used for both pressurization of the patient and the chamber.

In our system, 3 atmosphere absolute was used. Since microelectric switches were set inside the chamber, the air was used for the pressurization of the chamber, and the patients breathed pure oxygen via the mask. All procedures were done while the patient was conscious. Our 192 experiences on 58 patients with this hyperbaric oxygen chamber were shown in Table 2-2. In 2 out of 192 experiences (Tab. 2-4), convulsions were observed during pressurization. One of them had a probable history of convulsion in the past. Complaint of moderate otalgia was present in 9 per cent of these experiences, which subsided gradually without leaving any serious sequelae. As mentioned before, the sources were increased to 15 Ci in total. This was helpful to reduce the treatment time and at the same time, risk of oxygen intoxication. Based on these clinical experiences, it was assumed that neither anesthesia nor myringotomy was necessary to prepare the patient in our system.

As shown in Table 2-3, tumor residuals were found in more than half of the cases treated with dose regimens of 1,000 rad, 1,450 rad and 1,500 rad. These patients became free from the residual disease or recurrence after the appropriate additional radiotherapy. Van den Brenk²⁸⁾ recommended to deliver either 3,000 rad in 6 fractions or 2,900 rad in 4 fractions as the radical doses in the treatment of various kinds of cancer. Atkins et al.³⁸⁾⁻⁴⁰⁾ also reported that 2,000 rad in 2 fractions at one week interval led to the good tumor responses in the treatment of intraoral carcinomas. Considering our clinical experiences and other reports⁴¹⁾, it seemed that dosage delivered in our studies was not enough as the radical dose. We have increased the dosage further to deliver either 2,000 or 3,000 rad in 2 or 3 fractions respectively. The patients treated with these dose regimens are still in the follow-up studies at the present time. Although it is difficult to compare the present results of intracavitary radiotherapy under hyperbaric oxygenation with those under normal atmospheric conditions described in part 1, most of the patients treated under the original atmosphere showed recurrences and died of the advanced disease within one year after the treatment. On the other hand, only a few patients died within one year after the treatment with this new method. It is, however, preliminarily expected that the treatment of carcinoma of the uterine cervix with intracavitary radiotherapy under high pressure oxygen would give the better cure rate.

It is known that high pressure oxygen also increases the oxygenation of normal tissues surrounding tumors (Atkins et al.³⁸⁾⁻⁴⁰⁾ and it is possible that the radiosensitivity of these normal tissues increases as

tumor cells. Therefore, the protection of rectum and urinary bladder from the radiation injuries is the prime importance in the intracavitary radiotherapy. Special vaginal speculum was designed to increase the distance between the sources and these organs. The dose delivered to the rectum during intracavitary radiation using this speculum was 29% of that delivered to point A. In external irradiation, either $2 \times 5 \text{ cm}^2$ or $3 \times 7 \text{ cm}^2$ lead shield was used to avoid irradiation to the urinary bladder and the rectum directly. The doses delivered to the urinary bladder and the rectum were given Table 2-1A, B. The actual dosage delivered to the rectum and the urinary bladder in external radiotherapy was 1,655 rad in average. As mentioned in the clinical experiences, no serious radiation injuries of these organs were noted after the completion of the treatment at least within one year. Therefore, the dosage delivered to the urinary bladder and the rectum seemed to be in reasonable range.

In our present new regimen of radiotherapy, the over-all treatment period was 49 days in average, which could be shortened, if the external irradiation by performed during the period of intracavitary irradiation. These projects are in progress in our department.

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General Discussion

1) Comparison between Cathetron and RALSTRON:

Intracavitary radium therapy has been the most effective and established modality for the treatment of carcinoma of the uterine cervix. Since the introduction of high energy X-ray units, several attempts have been made to replace the radium therapy by external irradiation, which however ended in frequent central recurrences subsequently required to radium insertion. Even these days intracavitary radium therapy still holds the primary place for the treatment of carcinoma of the uterine cervix.

It is also true that it has several disadvantages as described in the introduction to which however little attention has been paid for the fact of remarkable result achieved by the radium treatment. Among them radiation exposure to the staff and other medical personnel will be the most serious problem which should be avoided as much as possible, especially in regards to genetic and carcinogenic effects.

To eliminate untoward exposure to the staff during the treatment, several attempts have been made, most of which have been developed independently in several countries such as Australia, Finland, Germany, Sweden, Switzerland, England, U. S. A., U. S. S. R. and Japan, utilizing the remotely controlled afterloading technique¹⁾. This new system has been introduced first by Churchill-Davidson et al. 1952^{2-A)}, Henschke^{2-B)} in 1960 and later by Martenson et al.³⁾ in 1962, Walstam⁴⁾ in 1962, Wakabayashi et al.⁵⁾ in 1965, Henschke et al.⁷⁾ in 1966, O'Connell et al.⁹⁾, Liversage et al.¹⁰⁾, Joslin et al.¹¹⁾ in 1967, and Chassagne et al.¹²⁾ in 1967. With this technique we can completely eliminate radiation exposure to the operators during the instrumentation.

However, some other problems as described in the introduction still remain to be solved. All these disadvantages of conventional radium therapy come from its long treatment time during which the patients is forced to lie in bed with radium applicator in place. Solution to these problems is to utilize stronger source and subsequently to shorten the treatment time. "Remotely controlled afterloading system with strong source" can eliminate most of the disadvantages associated with conventional radium therapy.

In table 3-1, several systems are shown along this line which have been published in the literature; Cathetron by O'Connell et al.⁹⁾⁻¹¹⁾ from Charring Cross Group Hospital in London, Gamma Med by Unérus et al.¹³⁾⁻¹⁴⁾ in Finland and Ralstron by us⁶⁾ in Japan. We have developed Ralstron since 1964 and applied it mostly to the treatment of carcinoma of the uterine cervix, the experience of which has been published in Japanese literature, RINSHO HOSHASEN in 1966⁶⁾. Regrettably enough attention has not

Table 3-1. List of Presently Available Remotely Controlled Afterloading Apparatus from the Various Medical Centers

Name	Sources	Ci-number	
GAMMAMED	Ir-192	10-150 Ci	
CERVITRON	Cs-137, Ir-192	?	(1965)
CATHETRON	Co-60	Ci order	(1966)
RALSTRON	Co-60	10 Ci order	(1965)

Table 3-2. Comparison between CATHETRON and RALSTRON

	CATHETRON	RALSTRON
Dose distribution	original Manchester method	modified Manchester method
Ci-number	ovoid	5.8, 5.5 Ci (Jan. 1968)
	tandem	5.9 Ci (Jan. 1968)
Source dimension	1.6 mm in diameter × 4.75 mm in length	1 mm in diameter × 1 mm in length
Applicators for ovoids	2.0, 2.5, 3 cm in diameter	2 cm in diameter only
Applicators for tandem	2.4, 4.25, 6.25, 8.25 cm long, 0, 20, 40, 60, 80 deg. bend	individualized, flexible
Rectal retractor	specially designed	modified Cusco's speculum
Insertion of catheters	complicated	fine adjustment possible after fixation
Treatment room	Co-60 teletherapy room	special room with hyperbaric chamber

been paid by scientists in other countries because of the language barrier.

Though Cathetron and Ralstron have been developed independently, their fundamental mechanisms are very similar. But there are several differences which are shown in table 3-2. Dose distribution of Cathetron is that of ideal Manchester system in which about two thirds of point A dose comes from tandem and the rest from both ovoids. On the other hand, dose distribution of RALSTRON was similar to that of narrow vagina in Manchester system. In our system, about one third of point A dose comes from tandem and the rest from the both ovoids.

Since 1968, old sources have been replaced by stronger ones of 10 Ci order for RALSTRON: tandem source is 5.9 Ci, two ovoid sources are 5.8 Ci and 5.5 Ci, respectively. We have also adapted an ideal Manchester method for the dose distribution.

To achieve this dose distribution, two ovoid sources are withdrawn earlier than the tandem source, that is, the tandem source is placed in position for five minutes and forty-two seconds, and both ovoid sources are placed for only one minutes and forty-eight seconds to deliver 1,000 rad at point A. The vaginal

packing is not necessary in our system to fix tandem and two ovoids in position. Therefore, the tandem tube can be moved slightly by the fine adjustment device after the fixation of all system, hereby it is possible to correct the deviated uterus to the right position. In this way, we have been able to correct the uterine position in about two thirds of cases. We have observed retroflexion of uterus in one third of cases. Cathetron has been reported to have several kinds of tandem tube with different curvature, but our Ralstron has only one kind of tandem tube with flexibility.

Cathetron treatment is carried out to the patient under the sedation, while Ralstron treatment is usually carried out without sedation. Tandem source of Ralstron is always inserted 5 cm into the uterus, if possible.

2) Discussion of high dose rate irradiation:

As described above, utilization of strong source is desirable to shorten the treatment time, hereby we are able to eliminate untoward effects to the medical personnel from radiation exposure, and able to lessen the patient's discomfort during the treatment. The intensity of source, therefore, should be increased so that one course of intracavitary application can be completed in a short time in the treatment room.

The reduction of number of fractionation is also desirable not only for the practical purposes, but also for the benefit of the patients. To achieve these purposes 2,000 rad has been given to point A in a single treatment which has been repeated two to three times with one week interval. Fifty to seventy minutes had been necessary to deliver the above dose of 2,000 rad to point A in early days when the only available Co-60 source was of 100 mCi order. In these days, stronger source with 10 Ci order has been available with hyperbaric oxygen, and treatment time has been reduced to only a few minutes to deliver the same dose. Further supplementary external irradiation has been given to the whole pelvis.

However, there arises a new problem from this high dose rate, short period treatment; enough knowledge has not been accumulated for the response of normal and malignant tissues to the large dose of 2,000 rad in a few minutes. According to Cardis¹⁵⁾, "This kind of treatment is far from our present knowledge of radiobiology". Chassagne et al.¹⁶⁾ also postulated, saying "It will take a long time before this treatment could be utilized in daily practice".

But recent achievements of radiobiology have shown some aspects of this problem. Jaslin et al.¹⁷⁾ have investigated the relationship between dose rate and lethal dose of the total body irradiation to the mouse and shown that $LD_{50(30)}$ of low dose rate exposure in 24 hours is 1,250 rad and 725 rad by high dose rate exposure in 15 minutes. Their conclusion was that the mode of death, although complicated, was mainly due to the damage of intestine and haematopoietic organs. Therefore, the radiation sensitivity of these organs increased 1.7 times due to the effect of high dose rate radiation. Liversage¹⁸⁾ also has calculated the dose rate effect of continuous exposure for 24 hours with low dose rate (of conventional radium therapy) and for 15 minutes with high dose rate (of Cathetron therapy) to estimate the optimal timedose fractionation schedule for Cathetron therapy. Elkind type recovery and cell repopulation have been taken into consideration in the above calculation. From the calculation, he has suggested that the effect of 2,000 rad continuous exposure for 24 hours is equivalent to that of 1,700 rad for 15 minutes. Enhancement of radiation sensitivity is therefore about 1.2 times from the high dose rate effect. In early days, Strandqvist¹⁹⁾ had treated successfully skin carcinoma with 2,000 rad in a single exposure. In these days, Ume-

gaki²⁰⁾ has shown good result for carcinoma of the tongue with 2,000 rad in a single electron beam exposure.

In our first clinical trial, however, we did not try to achieve the central healing of carcinoma of the uterine cervix with a single treatment. Instead two to three fractionations have been conservatively chosen because of the unknown factors involved in the high dose rate treatment. We have also received valuable suggestions from Dr. Tsukamoto and Dr. Umegaki that single exposure treatment might be dangerous and once failed there would be the high risk of fatal complications (Personal communication).

Four year result of this trial has been calculated recently which is shown in table 1-2; four year survival rate of stage II is 45% (5/11) and that of stage III is 29.4% (10/34). Similar cure rate has been reported with conventional treatment, radium application and external irradiation (Société française de Radiologie Médicale Paris, Mars. 1969, the Japanese Obstetrical and Gynecological Society 22, 1970).

Though our result is neither so satisfactory, nor so good as the results which have been reported from other institutes, better result, we believe, will be achieved through the improvement of our treatment modality.

3) Optimal dose to point A from the high dose rate intracavitary treatment:

This is another subject for discussion. Four to six thousands rad to point A has been chosen as the initial trial, however, this dosage seemed higher than the optimal dosage proposed by Strandqvist¹⁹⁾ for the treatment of squamous cell carcinoma of the skin. Recently Fowler²¹⁾ and Fowler et al.²²⁾ have proposed the table "Multiplying factor for total dose". According to this table, total dose given in three fractionations is equivalent to fifty-two per cent of the total dose in thirty fractionations. Therefore, 8,000 rad in thirty fractionations corresponds to 4,160 rad in three fractionations ($= 8,000 \times 0.52$), which is also lower than our dosage of 4,000 rad in two fractionations or 6,000 rad in three fractionations.

Animal studies show that the necessary dose to kill the well-oxygenated tumor cells is about 800 rad in one exposure^{23-A)23B)23C)}. However, anoxic portion of the tumor cells could survive with this dosage. In the majority of human tumors, especially in squamous cell carcinoma, about one week is generally considered as the period required for re-oxygenation^{24-A)24-B)24-C)}. If this is accepted, 3×800 rad (0.7th, 14th day exposures) will be the most optimal dose, which is also far lower than our dosage.

4) Radiation injury (Tab. 3-3):

This was discussed in detail in the part 1. The dose to the pelvic organs is the contribution from the Ralstron and external irradiation. Dose calculations and measurements in several patients have been

Table 3-3. Complications in 57 Patients Irradiated without Hyperbaric Oxygenation

	No. of Patients
Moderate Sigmoiditis	1
Moderate Sigmoiditis and Bladder Injury.....	5
Rectal Ulcer.....	5
Colostomy required.....	7
Colostomy and Ureterocutaneostomy required.....	3
Ureterocutaneostomy required.....	1
Total	22

done which clearly showed these organs have not been irradiated with more than the tolerable maximal dose proposed by several authors²⁵⁾⁻²⁷⁾.

However, several complications to the rectum, the small intestine and the urinary bladder have been observed due to the irradiation. These complications can be attributed to the increased sensitivity by oxygenation and especially to the high dose rate irradiation. From these experiences external irradiation has been performed with a lead block to shield midline portion of the pelvis as described in the part 2 (Split field method). Since then we have not seen the radiation injuries to the pelvic organs, though follow-up period is still short for adequate evaluation.

Therefore, we think, the pelvic organs react to the high dose rate irradiation to the almost maximal level of tolerance in some cases which can not tolerate further external radiation, although the total dose itself is within a tolerable dose range. One increment dose of 2,000 rad might be another factor for these complications, suggested by Liversage¹⁸⁾.

5) High dose rate irradiation by RALSTRON under the hyperbaric oxygenation:

The higher cure rate by irradiation can be expected by increasing the therapeutic ratio, for which the utilization of oxygen effect is most likely the best way at present time. Our next step is to introduce this oxygen effect to the high dose rate therapy by Ralstron. High dose rate intracavitary irradiation has been carried out to the patients with carcinoma of the uterine cervix under the hyperbaric oxygenation. The valuable experiences of our first trial have led us to chose smaller dose between 500 to 1,000 rad for one exposure with total dose of 1,000 to 3,000 rad to point A.

The result is shown in the table 2-3. In the first four groups, the treatment has been given in two applications with one exposure less than 1,000 rad to point A. However, a fair number of cases of residuals and recurrences have been observed in these groups who have subsequently required additional treatments. It is clear from these experiences that the dose necessary to cure the primary tumor is no less than 2,000 rad to point A in two applications, even under the hyperbaric oxygenation.

In the last group, the treatment has been given in three applications with total dose of 3,000 rad to point A. All patients have been well without evidence of the disease except one who has been treated further for the residual and been well thereafter. This fact also suggests the optimal dose to point A is not less than 3,000 rad in three applications.

Survival fractions have been calculated theoretically in the table 3-4 for which Elkind's survival theory²⁸⁾ has been taken into consideration as Van den Brenk²⁹⁾ has done before ($D_0=130$ rads, $m=2$). In the first four groups, cell survival fractions are not less than 10^{-6} which is also too large to expect good primary cure rate. On the other hand, survival fractions in the last group are small enough to anticipate better cure rate.

Though small number of patients and short period of observation do not permit to draw any definite conclusion for this treatment, the last treatment schedule 3,000 rad in 3 applications is most likely to achieve better result than the rest. Van den Brenk^{30-A)} also has reported the good tumor clearance rate 5/6 for the stage III carcinoma of the uterine cervix with the same dose schedule as we have done, which also supports our above impression. Eight thousands to nine thousands rad as the optimal dose to point A is generally accepted for the conventional radium treatment. If this dose is taken as a tissue tolerance dose for

Table 3-4. Dose-Fractionation and Iso-Effect Calculation in HPO*

Dosage (rad)	Spacing	n/no
2 × 500	0, 7 days	2.7 × 10 ⁻³
2 × 750	0, 7 days	7.0 × 10 ⁻⁵
2 × 1,000	0, 7 days	2.0 × 10 ⁻⁶
3 × 1,000	0, 7, 14 days	2.7 × 10 ⁻⁹

From Multihit formula for cell lethality

$$n/no = [1 - (1 - e^{-\frac{D}{D_0}})^m]^N$$

in where:

$$D \gg D_0,$$

$$n/no \approx [me^{-\frac{D}{D_0}}]^N$$

$$(D_0 = 130 \text{ rads}, m = 2,$$

$$N = \text{number of fractions, each } D \text{ rads})$$

*Modified from Van den Brenk et al.: Am. J. Roentgenol. 102: 8-26, 1968.

the conventional method, the therapeutic ratio of our high dose rate 3,000 rad irradiation under the hyperbaric oxygenation will be two to three times higher than the conventional treatment. This estimation would be supported by Thomlinson's experimental results^{30-B)}.

Johnson et al.³¹⁾ and others³²⁾³³⁾ have reported the increased incidences of distant metastasis with highly fractionated treatments under the hyperbaric oxygenation for the various kinds of carcinoma. Wildermuth³⁴⁾ and Evans³⁵⁾ also reported that the hyperbaric oxygen therapy increased the frequency of distant metastasis of cancer. McCredie et al.³⁶⁾ observed the growth promoting effect of hyperbaric oxygen on the mouse tumor and suggested the close relation between oxygenation and the tumor growth.

On the other hand, Churchill-Davidson³⁷⁾, and Van den Brenk³⁸⁾ denied the above views from their clinical experiences which have shown no such an oxygen effect on the metastasis. Our follow-up period is not long enough to discuss on this problem.

6) Let us now discuss about the fractionation under the hyperbaric oxygenation. Reviewing the literatures, Churchill-Davidson³⁷⁾, Van den Brenk³⁸⁾ and Bates³⁹⁾ used several fractionations. Van den Brenk used six fractionations with one dose of 500 to 600 rad to point A. Bates used six fractionations in 18 days with total dose of 3,500 rad to point A, saying this had been the best dose time schedule. However, from the clearance rate and survival fractions calculated by Van den Brenk³⁹⁾, 3 × 1,000 rad schedule seems to be the most effective and reliable treatment. Our best result is also consistent with this dose schedule.

7) Next discussion is about the time period between the fractionations. Several studies have been carried out to find the most effective timing of the second treatment after the initial irradiation. However, the reliable timing of the fractionation has not been obtained to permit the clinical application because too many different time periods have been proposed for the different tumors.

Therefore, one week interval has been chosen for our spacing of the fractions as Van den Brenk³⁸⁾ has done.

8) Finally, let us discuss about the clinical application of the oxygen effect. Oxygen enhancement

ratio (O. E. R.) in the radiobiology has been experimentally shown to be two to three by many authors, first by Gray⁴⁰⁾. However, O. E. R. obtained from the clinical studies has not been consistent with this value (Churchill-Davidson³⁸⁾, Van den Brenk³⁹⁾. It is generally accepted that oxygenation takes place in the tissue by the diffusion within the distance of 150 μ from the capillary beyond this range oxygen can not diffuse (Warburg⁴¹⁾. Therefore, oxygen effect can be expected only in the area within 150 μ from the capillaries. We think, however, that the tumor cells in this range are possibly influenced effectively by hyperbaric oxygenation by which more death of tumor cells will occur than in normal atmosphere.

Furthermore revascularization⁴²⁾⁻⁴⁶⁾ takes place during the period between two fractions, subsequently the resistant anoxic cells can reach near the capillaries. Consequently, a proportion of the initially hypoxic cells in a tumor becomes re-oxygenated and more radiosensitive⁴⁷⁾⁻⁵²⁾. These newly oxygenated cells now can show better response to radiation particularly under hyperbaric oxygen. Our experiences as well as the others, including Churchill-Davidson³⁷⁾, Van den Brenk³⁸⁾ and Bates³⁹⁾, also support this evidence to expect the oxygen enhancement effect in the clinical treatment. O. E. R., however, can not be calculated from our experiences which include two different factors, oxygen effect and high dose rate effect. Therefore, it is impossible to say how much has contributed to the over-all results from the oxygen effect and how much from the high dose rate irradiation.

However, we believe that the above evidence and analysis show the effectiveness of RALSTRON treatment under the condition of hyperbaric oxygen of 3 ATA.

It is also true that our treatment has several disadvantages as described in the part 1 and 2.

These are:

- 1) Complicated instrumentation
- 2) Limitation in the number of patients treated (Average 4 to 5 patients in a day)
- 3) Oxygen intoxication 1%
- 4) Otagia 9% of all patients

From this experience we strongly feel that the patients should be closely observed during the treatment under the hyperbaric oxygenation.

Recently it has been said that a similar effect can be expected by the irradiation under the conditions of the mixed gas of 95% oxygen and 5% carbon dioxide, and the hyperbaric oxygen. Using RIB₅ tumor, Watanabe et al.⁵³⁾ have studied the radiation response with 500–2,000 rad in one exposure under the condition of 1 ATA oxygen, 3 ATA oxygen and the above mixed gas. Their study showed that the mixed gas was more effective than the oxygen of 1 ATA, though the oxygen of 3 ATA was shown to be more effective than the mixed gas. They, therefore, advocated the irradiation under the mixed gas in the views of safety, easy handling and its effectiveness in place of hyperbaric oxygen. We have also had a few experiences of this mixed gas, however, small number of patients does not allow to present the result at this time.

General Conclusion (Part 1 and 2)

- 1) RALSTRON has been developed by us for the high dose rate intracavitary treatment of carcinoma of the uterine cervix.
- 2) Comparison of RALSTRON with similar mechanical device "Cathetron" was made.
- 3) Fifty-seven patients have been treated with RALSTRON and been followed for four years.

4) Four year survival rate of stage II and that of stage III carcinoma of the uterine cervix were 45% and 29.4% respectively, after the treatment with $3 \times 2,000$ rad to point A from RALSTRON, followed by external irradiation of 4,000 to 5,000 rad to the pelvis.

5) Several radiation injuries to the intestine and a few to the urinary bladder were observed after the above treatment.

The main cause of these injuries is thought to be the high one increment dose from external irradiation.

6) RALSTRON therapy has been carried out to the patients being placed under 3 ATA air and breathing pure oxygen of same pressure via the mask.

Four dose schedules of RALSTRON treatment have been done with 2×500 rad (0, 7th day exposures), 2×750 rad (0, 7th day exp.), $2 \times 1,000$ rad (0, 7th day exp.) and $3 \times 1,000$ rad (0, 7th, 14th day exp.) to point A.

These intracavitary treatments have been followed by external irradiation to the pelvis with the same dose as described in part 1, but midline portion the pelvis has been shielded (Split field method).

The best result was obtained in the last group received $3 \times 1,000$ rad to point A followed by external irradiation, judging from the primary healing. Cell survival fractions of this group were calculated theoretically which showed the extremely low value of 10^{-9} . No radiation injury has been observed in this group for a short period of one year.

7) If the above dose of $3 \times 1,000$ rad is taken as an optimal dose for the high dose rate treatment, this dose corresponds one-half to one third of the dose for the conventional radium treatment. Therefore, the therapeutic ratio of the above treatment will be two to three times higher than that of conventional radium treatment.

8) One per cent of oxygen intoxication and 9 per cent of moderate otalgia were observed.

9) Several problems arising from RALSTRON treatment and hyperbaric oxygen therapy were discussed.

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