Effect of Radiotherapy on Chromosomal Aberration in Cancer Patients

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We evaluated frequency and types of chromosomal aberrations by ionizing radiation in cancer patients treated with radiotherapy in our institution. Twenty-five patients with various types of carcinomas such as lung, uterine cervix, esophagus, rectum, head and neck and pancreatic cancers were studied immediately before and after external beam radiotherapy. The frequency of aberrant metaphase prior to treatment was 4.93%, which was higher than that of control group. Especially in lung cancer, the freuqency of aberrant metaphase was three times higher than control group. A comparison of chromosomal abnormalities observed before and after radiotherapy demonstrated that proportion of aberrant metaphases was significantly inreased to 22.13%. Major chromosomal aberrations like structural abnormalities showed remarkalbe increase from 65.45 to 88.45% after the treatment. Also the numbers of chromosomal alterations per cell were increased by a factor of 6.5. Aberrations with two or more break points were more prominently increased, compared with aberrations with single break point. The number of chromosomal break points was noted to be higher than expected value in No. 1, 3, 8 and 11 chromosomes and lower in No. 13, 15, 17 and 21 chromosomes. Based on this study, we believe that the distribution of chromosomal breakage is related with gene and chromosomal rearrangement which could result in the development of cancers.

Key Words: Cancer, Radiotherapy, Chromosome

INTRODUCTION

Since the study method of chromosomes in human being has been developed by Tijo and Levan in 1956[1], approximately seven hundred chromosomal aberrations were reported thus far[2]. Precipitating factors for chomosomal aberrations include viral infections, chemical materials causing mutation and exposure to radiation. Of these, radiation is thought to be the cause of chromosomal abnormalities. This has been shown by the fact that normal blood cells develop chromosomal aberrations after radiation therapy in vitro test[3~6]. However, in vivo study of chromosomal aberrations after irradiation has been rare. Those in vivo studies reported were studies such as radiation accident for general population, occupational exposure and types and freqency of chomosomal aberrations for population exposed to atomic bomb[7~14] Study of chromosomal abnormalities due to irradiation could implicate the radiation dose exposed and supply a good information on radiation protection and medical utilization. Several studies reported chromosomal abnormalities after radiotherapy in cancer patients and types and freqency of chromosomal aberrations were reported also[15~19]. However, studies with G-band analysis were rare[19].

Irradiation is well known to be a cause of mutation and carcinogenesis. Thus, the distribution of break points for chromosomal aberrations in cancer patients has been thought to be related with that for chromosomal aberrations after radiotherapy[3,6,20]. Also, the distribution of break points is noted to be related to carcinogenic gene locations such as fragile site of chromosome and protooncogene[21~26]. We analyzed chromosomal aberrations before and after radiotherapy through lymphocyte culture and report chromosomal abnormalities and distribution of break points after radiotherapy.

MATERIALS AND METHODS

Total of 25 patients with cancer treated in Dept. of Radiation Therapy were evaluated between May, 1991 and Nov. 1991. As shown in Table 1, there were 11 lung cancer, 6 uterine cervix cancer, 2 esophageal cancer, 2 rectal cancer and 4 other cancers (3 head and neck and 1 pancreas). Patients with history of previous chemotherapy were excluded from the study because of possible

Table 1. Clinical Data and Radiotherapy Doses of the Patients

Case	Sex/Age	Neoplasia	FA	OEM	Dose (rad)/weeks
1	f/45	Cervix	None	None	7,000/7
2	m/60	Nasopharynx	Yes	None	7,000/7
3	m/65	Nasopharynx	None	None	7,000/7
4	m/56	Esophagus	None	None	5,000/5
5	f/72	Cervix	None	None	6,600/6.5
6	f/59	Cervix	Yes	None	4,400/4.5
7	f/39	Cervix	None	None	5,100/5.5
8	f/72	Lung	Yes	None	5,000/5
9	m/59	Esophagus	Yes	None	6,000/6
10	f/33	Cervix	None	None	5,000/5
11	m/72	Lung	Yes	None	6,500/5.5
12	m/48	Lung	None	None	6,000/6
13	f/76	Lung	None	None	5,000/5
14	m/66	Lung	None	None	5,400/5.5
15	m/63	Lung	Yes	None	6,000/6
16	m/48	Rectum	None	None	5,600/5.5
17	m/53	Pancreas	Yes	None	4,000/4
18	m/57	Rectum	Yes	None	5,500/6
19	m/55	Larynx	None	None	6,400/6.5
20	f/59	Lung	Yes	None	5,000/5
21	m/59	Lung	Yes	None	6,300/5.5
22	f/45	Lung	Yes	None	6,000/6
23	m/73	Lung	None	None	5,400/5.5
24	f/32	Cervix	None	None	5,000/5
25	m/63	Lung	Yes	None	5,000/5

FA: familial antecedents of neoplasia
OEM: occupational exposure to mutagens

chromosomal changes due to chemotherapeutic agents. All of the patients received radiotherapy with radical aim and those treated with palliativve radiotherapy were excluded also. Radiation dose delivered was ranged from 40 to 70 Gy.

Two peripheral blood samples were obtained in heparin containing tube: one immediately before treatment started, and the other immediately after the end of partial body radiotherapy. Lymphocyte culture was done with macromethod for short-term lymphocyte culture and Arakaki and Sparkes' micromethod[27,28]. Blood samples were cultured for 72 hours at 37 C in HAM's F-10 media (GIBCO), supplemented with 20% fetal bovine serum and phytohemagglutinin. Colcemid (0.1-0.2 ug/ml) was added to obtain the metaphases, one hour before the end of culture. After the culture, sample was centrifused at 1000 rpm and cultured lymphocytes were extracted. Hypotonic shock was done with potassium chloride (0.075 M) for 15 minutes at 37 C. The sample was recentrifused and prepared with Carnoy's fixative (absolute methanol: glacial acetic acid=3 : 1). One to two drops of diluted cells was refriegerated and airdried. Finally chromosome slides were obtained. Chromosome slide which was put in slide chamber at 60 C overnight was prepared for G-band analysis, according to Seabright's method[29]. Hydrogen peroxide (50%) was added on the slide and diluted with normal saline after 10 minutes. Dried slide was treated with 0.025% trypsin and stained with Giemsa solution. Thirty metaphases were evaluated for each slide under the microscope and aberrant metaphase was photographed and enlarged for the evaluation of break points. Expression of chromosomal abnormalities was based on ISCN[30].

RESULTS

We evaluated total of 1500 metaphases: 30 metaphases for total of 25 patients before and after radiotherapy. Observed aberrant metaphases for each patient were 1 to 3 before the treatment and 5 to 10 after the treatment as shown in Table 2. Types and frequency of chromosomal aberrations observed in pre-radiotherapy are shown in Table 3.

Table 2. Total Number of Aberrant Metaphase Observed Pre and Post Radiotherapy

Case	Sex/Age	Neoplasia	Aberrant metaphases /Total metaphases	
			Prior Tx	After Tx
1	f/45	Cervix	1/30	5/30
2	m/60	Nasopharynx	2/30	6/30
3	m/65	Nasopharynx	1/30	7/30
4	m/56	Esophagus	3/30	8/30
5	f/72	Cervix	2/30	5/30
6	f/59	Cervix	1/30	6/30
7	f/39	Cervix	0/30	5/30
8	f/72	Lung	2/30	8/30
9	m/59	Esophagus	0/30	6/30
10	f/33	Cervix	1/30	5/30
11	m/72	Lung	2/30	7/30
12	m/48	Lung	1/30	9/30
13	f/76	Lung	1/30	8/30
14	m/66	Lung	3/30	10/30
15	m/63	Lung	3/30	8/30
16	m/48	Rectum	2/30	8/30
17	m/53	Pancres	1/30	6/30
18	m/57	Rectum	1/30	7/30
19	m/55	Larynx	1/30	6/30
20	f/59	Lung	3/30	8/30
21	m/59	Lung	2/30	7/30
22	f/45	Lung	0/30	6/30
23	m/73	Lung	1/30	7/30
24	f/32	Cervix	1/30	8/30
25	m/63	Lung	2/30	7/30

Frequency of aberrant metaphase was 4.93% (37/750 observed metaphases) and this was higher than that of normal control 2% (3/150 observed metaphases $p<0.05$). Also, each group of cancer showed higher frequency than normal control. Especially lung cancer (6.1%) showed three times higher than normal control.

Types and frequency of chromosomal aberrations observed in post-radiotherapy are shown in Table 4. Compared with pre-radiotherapy, frequency of aberrant metaphases was increased to 22.13% (166/750 observed metaphases $p<0.001$). The mean number of chromosome anomalies per aberrant metaphase was 1.49 (55 anomalies/37 aberrant metaphases) prior to treatment, and 2.14 (355 anomalies/166 aberrant metaphases) after radiotherapy. This indicates that ionizing radiation not only increases the number of aberrant metaphases, but also the number of chromosome abnormalities per metaphases.

As shown in Table 3 and 4, frequency of major chromosomal aberration, especially structureal abnormalities, was increased from 65.45% to 88.45% following the radiotherapy. However, frequency of minor structural abnormalities such as chromosome breakage and numerical abnormalities was decreased after treatment. Aberrations with 2 or more break points (translocations, ring chromosomes, inversions) were more prominently

Table 3. Types and Frequencies of Chromosomal Aberrations Obseved in Pre-radiotherapy

Neoplasia	Lung	Cervix	Esophagus	Rectum	Others	Total
Metaphases analysed	330	180	60	60	120	750
Aberrant metaphases	20 (6.1)	6 (3.3)	3 (5.0)	3 (5.0)	5 (4.2)	37 (4.93)
Total abnormalities	32	9	5	3	6	55
A. Structural abnormalities						
Translocations	3 (9.38)	1 (11.11)	—	—	1 (16.67)	5 (9.09)
Dicentric translocations	4 (12.5)	—	—	—	—	4 (7.27)
Deletions	3 (9.38)	3 (33.33)	1 (20.0)	1 (33.33)	1 (16.67)	9 (16.36)
Inversions	—	—	—	—	1 (16.67)	1 (1.82)
Acentric fragments	7 (21.86)	1 (11.11)	1 (20.0)	—	1 (16.67)	10 (18.18)
Rings	—	—	1 (20.0)	—	—	1 (1.82)
Markers	5 (15.63)	1 (11.11)	—	—	—	6 (10.91)
Subtotal	22 (68.75)	6 (66.67)	3 (60.0)	1 (33.33)	4 (66.67)	36 (65.45)
Chromosome gaps	2 (6.25)	1 (11.11)	—	—	1 (16.67)	4 (7.27)
Chromosome breakages	6 (18.75)	1 (11.11)	1 (20.0)	1 (33.33)	—	9 (16.36)
Subtotal	8 (25.0)	2 (22.22)	1 (20.0)	1 (33.33)	1 (16.67)	13 (23.64)
B. Numerical abnormalities						
Aneuploids	1 (3.13)	1 (11.11)	—	1 (33.33)	1 (16.67)	4 (7.27)
Polypoids	1 (3.13)	—	1 (20.0)	—	—	2 (3.64)
Subtotal	2 (6.25)	1 (11.11)	1 (20.0)	1 (33.33)	1 (16.67)	6 (10.91)

Table 4. Types and Frequencies of Chromosomal Aberrations Observed in Post-Radiotherapy

Neoplasia	Lung	Cervix	Esophagus	Rectum	Others	Total
Metaphases analysed	330	180	60	60	120	750
Aberrant metaphases	78 (24.64)	34 (18.89)	14 (23.33)	15 (25.00)	25 (20.83)	166 (22.13)
Total abnormalities	196	52	31	30	46	355
A. Structural abnormalities						
Translocations	35 (17.86)	5 (9.62)	7 (22.58)	5 (16.67)	5 (10.87)	57 (16.06)
Dicentric translocations	58 (29.59)	9 (17.31)	6 (19.35)	9 (30.0)	10 (21.74)	92 (25.92)
Deletions	18 (9.18)	1 (1.92)	3 (9.68)	3 (10.0)	2 (4.35)	27 (7.61)
Inversions	3 (1.53)	—	—	—	1 (2.17)	4 (1.13)
Acentric fragments	30 (15.31)	12 (23.08)	5 (16.13)	6 (20.0)	11 (23.91)	64 (18.03)
Rings	17 (8.67)	2 (3.85)	1 (3.23)	4 (13.33)	2 (4.35)	26 (7.32)
Markers	22 (11.22)	6 (11.54)	6 (19.35)	1 (3.33)	5 (10.87)	40 (11.27)
Insertions	2 (1.02)	—	—	1 (3.33)	1 (2.17)	4 (1.13)
Subtotal	185 (94.39)	35 (67.31)	28 (90.32)	29 (96.67)	37 (80.43)	314 (88.45)
Chromosome gaps	1 (0.51)	3 (5.77)	—	—	2 (4.35)	6 (1.70)
Chromosome breakages	2 (1.02)	3 (5.77)	1 (3.23)	—	2 (4.35)	8 (2.25)
Subtotal	3 (1.53)	6 (11.54)	1 (3.23)	—	4 (8.70)	14 (3.94)
B. Numerical abnormalities						
Aneuploids	3 (1.53)	3 (5.77)	2 (6.45)	1 (3.33)	2 (4.35)	11 (3.10)
Polypoids	3 (1.53)	4 (7.69)	—	—	1 (2.17)	8 (2.25)
Subtotal	6 (3.06)	7 (13.46)	2 (6.45)	1 (3.33)	3 (6.52)	19 (5.35)
Tetraradials	2 (1.02)	4 (7.69)	—	—	2 (4.35)	8 (2.25)

Table 5. Frequencies of Chromosomal Aberrations Per Cell Pre and Post-radiotherapy

Type of chromosomal aberrations	Prior Tx	After Tx	X
Total aberrations/cell	0.0733	0.4733	6.5
Translocations/cell	0.0067	0.076	11.34
Dicentric translocations/cell	0.0053	0.1227	23.14
Deletions/cell	0.012	0.036	3
Inversions/cell	0.0013	0.0053	4.1
Acentric fragments/cell	0.0133	0.0853	6.4
Rings/cell	0.0013	0.0347	26.69
Markers/cell	0.008	0.0533	6.66
Gaps+Breakages/cell	0.0173	0.0187	1.08
Numerical aberrations/cell	0.008	0.0253	3.16

X: increase factor.

increased, compared with aberrations wuth single break point. Also, asymmetrical aberration was more increased after treatment than symmetrical aberration.

Frequencies of chromosomal aberrations per cell pre and post radiotherapy are shown in Table 5. Total aberrations per cell was increased by a factor of 6.5 after the treatment. Reciprocal translocation, Robertsonian translocation and ring chromosome were increased 11.34, 23.14 and 26.69 times, respectively. However, breakage and numerical aberrations were not markedly increased. Fig. 1 showed breakage point distribution of radiation induced chromosome alterations. Breakages were located at all chromosomes except Y chromosome and total number of breakages was 240. Number of break points was noted to be higher than expected value in No. 1, 3, 8 and 11 chromosomes and lower in No. 13, 15, 17 and 21 chromosomes as shown in Table 6.

DISCUSSION

Although our study demonstrated higher frequency of chromosomal anomalies prior to treatment than that of normal control in each group of cancer patients, this was lower than results reported by others[19,31,32]. Also compared with study done by Barrios et al, the frequency of chromosomal anomalies after the treatment was lower[19]. This was probably due to the difference of type of cancer and in vitro chromosomal production and disappearance during the lymphocyte culture[33,34]. Also, our results are biased on the low side, because some unstable chromosome abnormalities may have been eliminated by 50% during the

Table 6. Observed and Expected Distribution of Chromosomal Breakpoints among Chromosome after Radiotherapy

Chromosome No.	Relative length[a]	Observed number	Expected number	Chi-square	p
1	8.44	45	19.50	33.35	<0.001
2	8.02	20	18.53	0.12	NS
3	6.83	24	15.78	4.28	$0.025<p<0.05$
4	6.30	14	14.56	0.02	NS
5	6.08	11	14.05	0.68	NS
6	5.90	11	13.63	0.51	NS
7	5.36	12	12.39	0.01	NS
8	4.93	20	11.39	6.51	$0.01<p<0.025$
9	4.80	13	11.09	0.33	NS
10	4.59	9	10.61	0.24	NS
11	4.61	19	10.65	6.55	$0.01<p<0.025$
12	4.66	10	10.77	0.06	NS
13	3.74	2	8.64	5.10	$0.01<p<0.025$
14	3.57	6	8.25	0.61	NS
15	3.46	1	8.00	6.13	$0.01<p<0.025$
16	3.36	4	7.76	1.45	NS
17	3.25	1	7.51	5.64	$0.01<p<0.025$
18	2.93	4	6.77	1.13	NS
19	2.67	4	6.77	1.13	NS
20	2.56	3	5.92	1.44	NS
21	1.90	0	4.39	4.39	$0.025<p<0.05$
22	2.04	3	4.71	0.62	NS
X	2.96	4	6.84	1.18	NS
Y	0.90	0	2.08	2.08	NS

a: Lubs *et al.* (1978) (38)

Table 7. Chromosomes More Frequently Implicated in Radiation-induced Alteration

Chromosomes	Irradiation	References
1, 5	*in vitro*, X-ray	Bauchinger and Gotz (1979)
1, 7, 12	*in vitro*, gamma-ray	Lee and Kamra(1981)
11,12,14,20	*in vitro*, gamma-ray	Dutrillaux *et al.*(1983)
	in vitro, gamma-ray	
15	*in vitro*, gamma-ray	Dutrillaux *et al.*(1981)
1	*in vitro*, X-ray	Kano and Little(1986)
9,10,14,15	*in vitro*, X-ray	Buckton (1983)
8,15,18,22	*in vitro*, gamma-ray nentrons	Tanaka *et al.* (1983)
1, 3, 7	*in vitro*, gamma-ray	Barrios *et al.* (1989)
1, 3, 8, 11	*in vitro*, gamma-ray	Present Study

72 hour culture. However, cellular growth was quite deficient at 48 hour culture, and to obtain a sufficient number of analyzable G-banded metaphases, a 3-day culture protocol was chosen.

Compared with prior to treatment, the frequency of aberrant metaphases was significantly increased from 4.93 to 22.13%. This was increased in all types of cancer after the treatment with slight discrepancy. This was belived to be due to the fact that cancer cells have more latent chromosomal instability than normal cells and can be easily broken by physical stimulus like irradiation[19]. Studies reported thus far regarding the increase of frequency of chromosomal abnormalities after the radiation have had a limitation of short numbers in the study and were not compared with adequate normal control. Thus above mentioned conclusion can not be definitely made.

Our study showed that aberrations with two or more break points (translocation, ring chromosomes, inversions) were more prominently increased after the treatment, compared with aberrations with single break point. Also the ratio of asymmetrical aberration versus symmetrical aberration was different from expected 1:1 ratio[14,35]. This result was similar to that of Barrios et al. This was thought to be the result of simultaneous appearance of two or more chromosomal break points after radiation and position exchange of those break points. However, the reason for increase of asymmetrical aberration should be

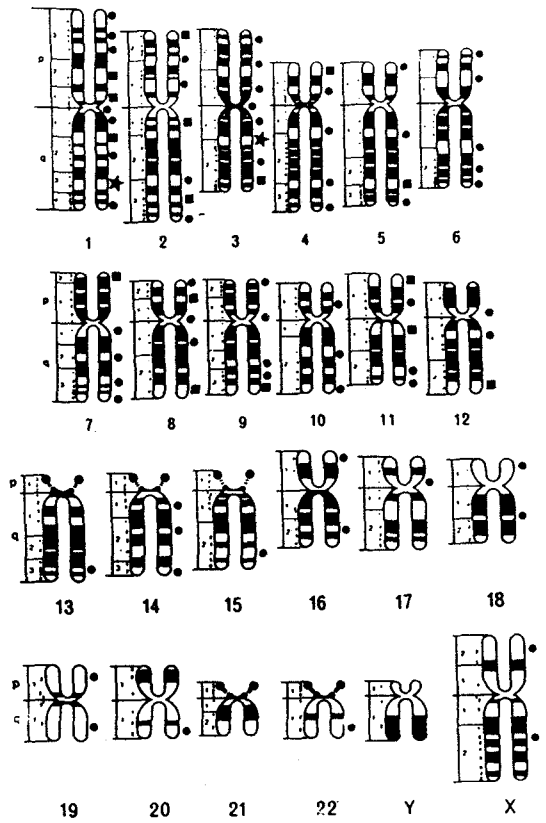

Fig. 1. Breakpoint distribution of radiation-induced chromosome alterations. ★, above 10 breakpoints; ■, from 5 to 10 breakpoints; ●, below 5 breakpoints.

investigated further in the future.

Distribution of break points revealed the increase of number of break points in No. 1, 3, 8 and 11 chromosomes. Especially No. 1 chromosome showed remarkable increase with p-value <0.001. As shown in Table 7, distribution of break points after radiation is somewhat different depending on studies reported. However, many studies showed the increase of break points in No. 1 chromosome as we did[5,20,36]. Abnormalities in No. 1 and 3 chromosomes were thought to be one of the mutations which can be found in cancer cells[25,37]. Also other studies reported that the increase of break points in No. 8 and 11 chromosomes is related with development of cancer[10,13]. These results are correlated with increase of break points after the radiation in our study. Except for No. 17 chromosome, No. 13, 15 and 21 chromosomes with decrease of break points are noted to be rare chromosomal abnormalities in cancer patients.

Based on this study, we believe that the distribution of chromosomal break points is related with gene and chromosomal rearrangement which could result in the development of cancer.

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= 국문초록 =

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방사선에의 노출은 염색체 이상을 유발하는 원인으로 널리 인식되고 있으나 *in vivo* 상태에서 방사선 조사 후 발생되는 염색체 이상의 종류와 빈도 규명은 드물었다. 이에 본 연구에서는 암 환자에서 방사선 치료 전 및 후에 말초혈액 임파구의 염색체 변이를 비교 관찰하고 방사선 조사에 의해 암 환자 세포에서 나타나는 염색체 이상에서 절단점의 분포가 암 발생과 밀접한 연관이 된 유전자 및 염색체의 재조합이 자주 일어나는 부위와 연관관계가 있음을 규명하고자 하였다.

25예의 암 환자에서 방사선 치료가 시작되기 전과 4000~7000 cGy의 근치적 방사선치료가 끝난 직후 말초 혈액을 채취하여 임파구를 배양후 G-분염법을 이용하여 염색한 후 환자마다 방사선치료 전후로 각각 30개씩의 증기상을 관찰하였다.

치료전에 염색체 이상을 나타낸 세포 분열 증기상의 빈도는 4.93%로 정상 대조군 집단의 빈도 2%보다 높았다($p<0.05$). 방사선 치료후 염색체 이상 세포의 빈도는 22.13%로 치료전에 비해 매우 증가되었다($p<0.01$). 또한 세포 증기상당 이상 염색체의 수도 치료전과 후가 각각 1.49 및 2.14로 치료후 증가 되었다($p<0.05$).

염색체 이상의 종류는 major chromosomal aberration 특히 구조적 이상의 빈도가 치료전보다 후에 65.45%에서 88.45%로 증가되었고 minor structural abnormality와 수적 변이의 빈도는 감소되었다. 방사선 치료 후 염색체 절단점의 수가 2개 이상인 경우가 단일 절단점을 가진 이상에 비해 증가되었다. 절단점의 분포에 있어서는 암 세포에서 가장 흔한 이상을 나타내는 1번 및 3번 염색체와 절단점의 증가가 암 발생관 연관된다고 보고된 8번 및 11번 염색체에서 본 연구결과 기대치 이상의 절단점의 분포를 보이고, 암 세포에서 드물게 이상을 나타내는 13, 15 및 21번 염색체에서는 기대치 보다 감소된 절단점의 분포를 보였다.

따라서 방사선 치료 후 염색체 이상의 빈도는 증가되었으며 방사선 조사에 의해 나타나는 염색체의 절단점의 분포는 암 발생과 밀접한 연관이 된 유전자 및 염색체의 재조합이 자주 일어나는 부위와 밀접한 연관 관계가 있음을 보여 주었다.