Results of Postoperative Radiotherapy of Breast Cancer observed from Lymphnodes Invasions

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乳癌術後照射におけるリンパ節転移の意義

国立がんセンター放射線

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乳癌治療成績の向上は，長年の間容易に行なわれず，高エネルギー放射線治療による期待が大きい．一方，術後照射に関しては，その有意性も問題にされ，本研究では，治療成績に最も関与するリンパ節浸潤より術後照射の評価を検討した．

1．症例は，1962年5月より1967年12月までに，国立がんセンター病院を初診例 828名，二次治療例 519名の乳癌患者が訪れ，このうち，678名に根治手術が行なわれさらに 255名に術後照射が行なわれている．術後照射の行なわれなかつた患者は腫瘍が外半側に発生し，組織学的に全摘出リンパ節の浸潤を認めなかつた早期乳癌であつた．

2．術後照射術式は，鎖骨上下および腋窩を1門に含めテレコバルトで，6週間に6000rad，胸壁および胸骨旁リンパ節領域は 180° の切線振子によつて6000rad が照射された．

3．リンパ節：手術材料より2～76コのリンパ節が摘出され平均18.2± 6.4，全例の転移陽性率は50.5%であつた．TNM分類で臨床的に N_0 と診断され組織学的なN＋であつた症例は T_1 で21.7%，T_2 で31.2%であつた．

4．再発および転移：6000rad 照射による重篤な合併症はなく術後照射による再発は，胸壁および所属リンパ節領域は少なく，胸壁では，遠隔転移の6分の1と減少し，遠隔転移での死亡は，28.5%と高かつた．

5．術後照射の有無による乳癌の5年生存率：術後照射群（リンパ節転移率96%）の5年生存率67.8%，非照射群（リンパ節転移率12%）の5年生存率89.9%，両群の計では81.5%となつた．

術後照射群中の死亡率は Biopsy より根治手術までに，1カ月以上を要したものが悪く21例中11例（52.5%）に再発および死亡が認められた．

術後照射によつてリンパ節1，2，3コ浸潤例の死亡率は，おのおの25%，31%，17%であつたが，非照射群では，リンパ節浸潤なし群で 7.5%，1コ浸潤群10%，2コ67%となり，乳癌の術後照射はリンパ節転移2コ以上の例に，有意と考えられる．

Introduction

Lymph node involment has been proved to play a significant role in the treatment of breast cancer. It is debatable whether or not the postoperative irradiation to breast cancer patients without axillary lymph node involvement results in better prognosis.

In postmastectomy radiation therapy both for radically operated primary lesions and regional lymph nodes, an analysis was made of the relationship between pathological findings of all lymph nodes in surgical specimens and prognoses of the patients.

Material and Methods

During the 5-year period, May 1962 through December 1967, we had an opportunity to treat 1368 patients with breast cancer, 482 of whom received radiotherapy (35.2%), in the Department of Radiotherapy, National Cancer Center Hospital, Tokyo.

Two hundred and twenty-three out of the 678 primary untreated patients were received radical mastectomy and postoperative irradiation (33.9%).

Of the total 1368 breast cancer patients, 828 had received no previous treatment (60.5%), 519 had receivd previous treatmet at other hospitals, and 21 were clinical shoppers. (Table 1)

Of the 828 previously untreated patients, 678 (82%) were radically operated, 489 (72% of 678) of whom were operated with classic Halsted's radical mastectomy (removal of the breast, pectoral muscles and axillary lymph tissue in continuity), while the other 189 patients (28%) had an extended radical mastectomy, in which the internal mammary lymphatics were removed in addition to the axillary nodes. Extended radical mastectomy was applied to patients with:

1. Primary tumors located in the inner-half or central portion of the breast.
2. Primary tumors located in the outer-half of the breast with metastasis in many axillary lymph nodes. The coincidence of matastases with the parasternal nodes was found to be 30% in the 189 cases.

Criteria of postoperative irradiation to the breast cancer were:

Table 1. Breast Cancer Treated in National Cancer Center Hospital
May 1962 through December 1967

	1962	1963	1964	1965	1966	1967	Total
PREVIOUSLY UNTREATED CASES	62	98	115	154	197	202	828
Extended Radical Mastectomy	15	31	38	39	36	30	189
Radical Mastectomy	47	64	75	92	119	101	489
					(3)	(1)	(4)
Radiation Therapy	0	3	2	3	1	1	10
Hormon & Chemotherapy				20	38	20	78
(Mastectomy & Radiation)	27	28	33	52	39	44	223
	(5)	(4)	(6)	(3)	(7)	(7)	(32)
PREVIOUSLY TREATED CASE	77	79	114	88	64	97	519
Surgery	32	28	37	13	4	3	117
Radiation	34	25	38	35	37	48	217
Hormon & Chemotherapy	11	26	39	40	33	45	184
CLINICAL SHOPPERS	3	4	3	7	3	1	21
Total	142	181	232	249	264	300	1368

1. No postoperative irradiation was given to patients with the tumors restricted to the outer-half of the breast and without histopathological involvement of lymph nodes.

2. Castration was not applied by radiation in young patients.

3. The postoperative irradiation consisted of gamma rays from telecobalt, 6,000 rads in 6 weeks; to the axilla-supraclavicular region with direct vertical beam and to the chest-wall including the internal mammary area with tangential rotation technique. Based on these criteria, 223 out of the total 678 radically mastectomized patients (32.9%) were treated by the postoperative irradiation and 32 with non-radical mastectomy or second primary cases were excluded from this statistical study.

4. Chemotherapy

A dose of 10 to 30 mg of Mitomycine C was intravenously injected immediatly after mastectomy in 36 postoperative irradiated patients with advanced cases.

Dose distribution of Co-60 in opposite lungs when given by the tangential rotation of 180° (90° to 90°) was 20% to 70%, (Isodose curves were taken from Toshiba film Isodose plotter, Model MRA-201-2), and leukopenia occured in 2 cases and slight radiation pneumonitis in 28 cases (12.7%). There were no serious complications such as chronic ulceration of the skin or ostitis of the under-lying bones.

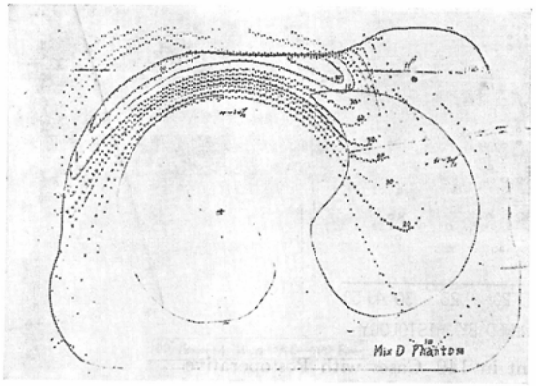

Fig. 1. Dose Distribution from Telecobalt Gamma-rays Tangential Rotation 180° (90° to 90°) Field 4 × 10cm, SAD 60 cm, 8.3 Deg.

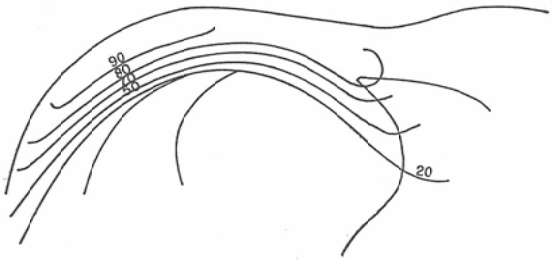

Fig. 2. Tangential Rotation 160° (90°—70°) 9.0 Deg. Co-60 γ-ray, 4 × 10 cm, SAD 60 cm

In comparison with orthovoltage roentgen irradiation, the rotation angle of the gamma rays from Co-60 could be decreased to 160 degrees without lowering the quality of the isodose curve in the chest wall and the internal mammary lesions.

Microscopic lymph node involvement according to the TNM International Classification:

For the patients with clinically negative axillary nodes, the lymph node involvement was confirmed microscopically in 21.7% of T1 cases, and in 31.2% of T2 cases. For the patients with clinically positive axillary nodes, no involvement of the axillary nodes was found microscopically in 48.9% of T1 cases and in 17.0% of T2 cases.

Axillary node involvement in the breast cancer was confirmed histopathologically in 50.5% of the total

Table 2. Lymph Node Involvement in TNM Classification

TNM		Case	Lymph node involvement N0	N+
T1	N0	207	162	45 (21.7%)
	N+	45	22 (48.9%)	23
T2	N0	205	141	64 (31.2%)
	N+	211	36 (17.0%)	175
T3	N0	20	17	3
	N+	76	7	71
T4	N0	1	1	0
	N+	13	1	12
Total	N0	433	321	112 (25.9%)
	N+	345	66 (19.1%)	281

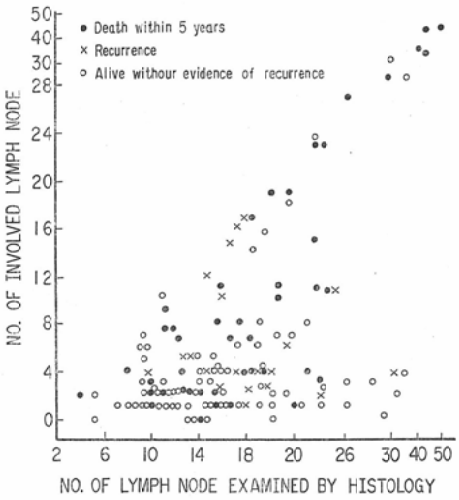

Fig. 3. Regional Lymph Node Involvement in 140 Cases with Postoperative Irradiated Breast Cancer.

778 mastectomized cases.

In the 140 patients with postoperative irradiation, 2 to 76 lymph node lesions regional to the breast were removed and they averaged 18.2 ± 6.4. The survival rate declines regularly as the number of involved lymph nodes increases. Five-year survival in the group of two lymph nodes involved was 72%, 3 involved was 78% and 4 involved was 68%.

Results

Recurrence and metastases:

Two hundred and thirty-two out of cases received mastectomy only, and 60 of the 140 cases with postoperative irradiation had recurrence and metastases within 5 years. In the postoperative irradiation group, 28.5% of the metastases ocurred at a distance, 5% in the chest wall, 4% in the supraclavicular region and 3% in others.

Table 3. Recurrence Site v.s. Ratio in the Treated Breast Cancer within 5 years

	Mastectomy only	Postoperative Irradiation
Cases	232	140
Chest wall	8 (3.5%)	7 (5%)
Axillary	0	1
Supraclavicular	3	6 (4%)
Parasternal	1	1
Opposite Supraclavivular Axillar	0	2
Distant metastases	18 (9.8%)	40 (28.5%)
Lung	8	12 (8.6%)
Plura	3	7
Bone	3	12
Liver	3	7
Others	1	2
Unknown	5	3

Table 4. Death and Recurrence in the Breast Cancer with Delayed Treatment Cases

Inteval; Biopsy to Mastectomy	within 10d.	within 30d.	more than 1 month	more than 1 year
Death	T2N2 1	T1N0 1 T2N2 1	T3N2 1	T2N0 1 T3N2 1
Recurrence	T2N1 1	T1N2 1	T2N0 1 T2N2 1	T1N1 1
Alive without evidence of recurrence	T1N0 1 T2N0 2	T1N0 1 T2N0 1	T1N0 1 T1N1 1 T2N1 2	T1N0 1

Mastectomy and Radiation 6000 rad—$\frac{\text{Death } 6 + \text{Recurrence } 5}{21 \text{ cases}}$—(52.4%)

Table 5. Survival Rate in the Breast Cancer according to Treatment

Year	No Postoperative Radiation Therapy	Postoperative Radiation Therapy	Total
1	$\frac{398}{402}$ 99.2%	$\frac{199}{223}$ 89.2%	$\frac{597}{625}$ 95.6%
2	$\frac{392}{402}$ 97.7%	$\frac{184}{223}$ 82.5%	$\frac{586}{625}$ 93.7%
3	$\frac{385}{402}$ 95.9%	$\frac{173}{223}$ 77.6%	$\frac{558}{625}$ 89.2%
4	$\frac{303}{323}$ 93.8%	$\frac{133}{183}$ 72.7%	$\frac{436}{506}$ 86.1%
5	$\frac{206}{229}$ 89.9%	$\frac{95}{140}$ 67.8%	$\frac{301}{369}$ 81.5%

Those results in which the metastases to another site was of the highest frequency may suggest that postoperative irradiation decreases local recurrence but does not decrease distant metastases.

When mastectomy did not follow biopsy within short periods, the recurrence rate increased up to 52.4% in 21 patients with postoperative irradiation. Therefore it is assumed that delayed treatment after biopsy increased the rate of recurrence and metastases.

Survival rate:

The 5-year crude survival rate was 89.9% in the cases without irradiation, and 67.8% in the 140 cases with postoperative irradiation.

The lower survival rate of the irradiated patients reflects the fact that there were histopathological lymph node metastases in 96% of the irradeated patients and in only 12% of the non-irradiated patients.

Table 6. Five-Year Survival Rate in Postoperative Irradiated Breast Cancer by Stage of Disease

UICC Classification	Cases of Postoperative Irradiation Radical Mastectomy	5-year Survival
I	40	82.5%
II	53	75.5%
III	45	44.5%
IV	2	0
Total	140	68.5%

Table 7. Five-year Results for 140 Patients with Postoperative Irradiated Breast Cancer according to Age Distribution

Age	Case	Alive without Tumore	Dead
Over 20 yrs.	5	2 (40%)	3
30 yrs.	29	20 (69%)	9
40 yrs.	48	35 (73%)	13
50 yrs.	46	30 (65%)	16
60 yrs.	10	7 (70%)	3
70 yrs.	2	1 (50%)	1
All Ages	140	95 (67..8%)	45

Table 8. Five-year Result for 140 Patients with Postoperative Irradiated Breast Cancer according to Histopathology

Histology	Alive	Dead
Non infiltrating duct carcinoma	2	0
Infiltrating duct carcinoma		
Papillary, tubular carcinoma	19	6 (4.3%)
Comedo carcinoma	13	14 (10%)
Adeno ca. scirrhosum	54	21 (15%)
Medullary carcinoma	1	1
Mucoid carcinoma	4	0
Lobular carcinoma	2	2
Special type	0	1
Total	95	45

According to the UICC International Calssification, the 5-year crude survival rate was 82.5% in 40 cases of stage I, 75.5% in stage II and 44.5% in stage III.

In regards to the age factor, the mortality rate was the highest in the twenties and then in the fifties.

In regards to histological calssification, mortality within 5 years of the patients with postoperative irradiation was 15% in infiltrating scirrhous adenocarcinomas, 10% in infiltrating comedo carcinomas and 4.3% in papillary and tubular carcinomas.

Discussion

The purpose of this study was to analyze our material so as to gain further information on the value of prophylactic radiation therapy of breast cancer in relation to lymph nodes involvement.

The harmfull effects of prophylactic radiation therapy of the breast cancer were described by Gördon-Taylor (1948), Pendergrass (1948), Garland (1958), Kaae (1962), Benninghoff (1959), Dao and Kovaric (1962) and other authors. Paterson in Manchester concluded that systematic postoperative irradiation was unnecessary, provided the patients were carefully followed and any recurrences subjected to radiotherapy.

But many other authors (Harrigton 1944, Smither 1944, Diethelm 1950, Haagensen 1951, Endler 1953, Hess 1953 and other authors) concluded that the postoperative irradiation to breast cancer is useful only for the patients with positive lymph nodes involvement. And recently Chu in Memorial Hospital has substantiated this and concluded that there was an increase of 17% in the survival rate of the irradiated patients over the non-irradiated ones when the apical axillary lymph node was involved.

Non-postoperatively irradiated breast cancer patients, all of whom had primary tumors located in the outer-half of the breast and no histopathological lymph node involvement, showed no increase in the number of recurrence or mortality rate except cases of delayed treatment after biopsy, one with breast cancer on both sides and one with highly infiltrated scirrhous adenocarcinoma.

According to Mc Whirter, a total dose of 6,000 rads of postoperative irradiation were given by telecobalt gamma ray, with no increase of serious complications compared with orthovoltage roentgen 3250 R to 3750 R.

The data in this study showed 5-year survival rates of 89.9% in non-postoperative irradiation group (12% were lymph nodes involved) and 67.8% in postoperatively irradiated group (96% were lymph nodes involved).

Table 9. Recurrence and Mortality in the Breast Cancer v.s. Lymph Node Involvement

Involved Lymph Node	Postoperative Radiation Therapy			No Postoperative Radiation Therapy		
	Total No of Patients	5 year Mortality	5 year Recurrence	Total No of Patients	5 year Mortality	5 year Recurrence
Negative Lymph Node	6	0	0	199	15 (7.5%)	12
Positive Lymph Nodes						
1	24	6 (25%)	1	20	2 (10%)	1
2	26	8 (31%)	3	6	4 (67%)	1
3	12	2 (17%)	1	2	0	1
more than 4	76	37 (49%)	13	—	—	—
Over-all	144	53 (34%)	18 (12.5%)	227	21 (9.3%)	15 (6.6%)

Murphy presented the fact that patients with one positive axillary node have about twice as large risk of recurrence after 4 years as patients with all negative nodes, and about two out of three patients with more than five positive axillary nodes have a recurrence within 4 years.

The results were then analyzed to compare the coincidence of lymph nodes involvement and mortality which occured within 5 years after the mastectomy.

In the group of mastectomy without irradiation, the mortality rate was 7.5% in cases with negative node, 10% with one positive, 67% with 2 positive.

In the postoperative irradiation group, the mortality rate was 0 in cases with negative lymph node, 25% with one postive, 31% with 2 postive, 17% with 3 postive and 49% with more than 4.

Summary and Conclusion

Improvement in treatment of breast cancer has not been easy for a long time. Today, in this respect, much is expected of the treatment by the high-energy X-ray device.

On the other hand, the significance of postoperative irradiation itself is now being questioned and for that reason efforts are concentrated in this study on the assessment of postoperative irradiation in connection with lymph node involvement which has the closest relation with the treatment performance.

1. Case:

Of the total of 1347 breast cancer patients (828 previously and 519 not previously treated respectively) whom we had an opportunity to treat at the National Cancer Center Hospital from May 1962 through December 1967, 678 underwent radical operation, 225 of whom later received postoperative irradiation. The rest who didn't receive postoperative irradiation were the patients with breast cancer in an early stage where tumors developed in the outer half and no lymph node involvement could be recognized from the histological viewpoint.

2. Postoperative irradiation:

Using a Cobalt 60 unit a total dose of 6,000 rads was given through one port covering axilla-supraclavicular region and also 6,000 rads by 180° tangential pendulum irradiation to the parasternal lymphatic glands region as well as chest wall.

3. Lymph node:

2—76 pieces of lymph node were found in the surgical specimen of the individual patient. Their number was 18.2 ± 6.4 on the average and metastasis rate was 50.5%. In cases that were diagnosed clinically negative, 21.7% and 31.2% were proved to be N^+ histologically with T1 and T2 respectively (by TNM classification).

4. Recurrence and metatasis:

No serious complication could be recognized after 6,000 rads irradiation, with recurrence rate at the chest wall being one sixth of distant metastasis rate. Mortality rate in cases of metastasis are as high as 28.5%.

5. Five-year survival rate:

Five-year survival rates of postoperatively irradiated group (lymph node metastasis rate at 96%) and the non-irradiated group (lymph node metastasis rate at 12%) were 67.8% and 89.9% respectively, with an average rate of 81.5%.

The highest mortality rate could be found in cases of long delay between biopsy and radical operation.

6. Conclusion:

The mortality rate of postoperatively irradiated cases with 1, 2 and 3 lymph node involvements were 25%, 31% and 17% respectively, while the rate of non-irradiated cases with 0, 1 and 2 lymph node involvements were 7.5%, 10% and 67% respectively.

In conclusion, postoperative irradiation of breast cancer can be considered of significant value in cases with not less than 2 lymph node metastasis.

Acknowledgement

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