Postoperative Radiotherapy in the Treatment of Breast Cancer:

Results of the NSABP Clinical Trial

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AFTER three-quarters of a century there remains uncertainty concerning which type of surgery is best for treatment of breast cancer, as there is doubt concerning the merit of radiotherapy as an adjunct to surgery. Evidence has been published to suggest that postoperative irradiation when combined with radical mastectomy provides the best results in the treatment of such primary neoplasms.[1, 10, 13, 15, 20] Others have reported no advantage in its use [2, 3, 4, 7, 12, 14, 16, 18, 19] and several have suggested that radiotherapy may actually be harmful.[5, 6]

Prompted by this therapeutic uncertainty, the National Surgical Adjuvant Breast Project (NSABP) * in October, 1961, initiated a randomized prospective clinical trial to assess the worth of postoperative irradiation in the treatment of breast cancer. This report presents data from this study which have accumulated to the present time.

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* National Surgical Adjuvant Breast Project.

Procedure

All data in this report come from women who underwent surgical treatment in 25 institutions which participated in the trial (see Addendum). A detailed explanation of the group organization, method of data collection, follow-up studies, criteria of patient eligibility, and methods of statistical analyses have been published.[8] Only those facets particularly germane to this study will be described in detail. All women who fulfilled the criteria of eligibility as outlined in the protocol were treated by conventional radical mastectomy which consisted of *en bloc* removal of breast, pectoral muscles and axillary contents. Patients with intact ovaries and less than 50 years of age were considered premenopausal.

Throughout the study patients were randomly assigned by the statistical center to one of the following treatment categories. At its inception, all premenopausal women were randomized so that one-half were recipients of radiotherapy; one-quarter received a placebo; and one-quarter were given triethylenethiophosphoramide (TSPA). The drug was administered intravenously on the day of operation (0.4 mg./Kg.) and on each of the next 2 days (0.2 mg./Kg./day). Postmenopausal women were randomized according to one of two options in which a particular institution

participated. In one option ("E") patients, regardless of their nodal status, were randomized the same as the premenopausal women. In the other ("F"), only positive node patients were similarly randomized. Patients with negative axillary nodes received no radiotherapy but were randomized equally between TSPA and 5-FU. In May, 1967, when the results of another NSABP study suggested that premenopausal women with four or more positive nodes treated with TSPA were at advantage over placebo-treated patients, the protocol was altered. In the premenopausal category the placebo was eliminated and patients were randomized so that for each two that received radiotherapy, one was given TSPA. A change in randomization occurred in postmenopausal Option E so that for each two that received radiotherapy, one patient was untreated. Positive node patients in Option F were also similarly randomized. Those with negative nodes in Option B were no longer entered in the study. Patient entry was terminated in August, 1968.

Simultaneous with this study another clinical trial was carried out by the NSABP to evaluate postoperative oophorectomy as an adjuvant to radical mastectomy.[17] In that study similar premenopausal patients were at first randomized so that one-half received postoperative radiotherapy, one-quarter were given a placebo and one-quarter were recipients of TSPA. Just as described in the radiotherapy control randomization, in 1967 the placebo group was eliminated and patient allocation was such that two-thirds underwent oophorectomy and one-third TSPA. Careful scrutiny of the premenopausal control patients in the oophorectomy study revealed that their average age, total recurrence and survival experience was entirely comparable to that found in the radiotherapy controls. Consequently, in this report the results obtained from the oophorectomy controls (87 recipients of TSPA and 55 of placebo) are added to those from the radiotherapy study. Their inclusion enhances the reliability of the data in certain subsets of patients whose numbers are otherwise too small for valid interpretation. Exclusion, however, would not alter the overall conclusions of this study.

The aim of this study was to administer a therapeutic dose of irradiation to those regions adjacent to the surgically extirpated area which might harbor residual tumor. These included the internal mammary chain of nodes, the apex of the axilla, and the supraclavicular region. The chest wall and the axilla as a whole were not irradiated. To facilitate standardization of a postoperative technic of radiotherapy, it was required that the equipment used be at least 200-KV and the radiation be no less than half-value-layer 1.0 mm. Cu. Radiotherapy was delivered to a long, narrow parasternal field centered 1 cm. lateral to the border of the sternum extending from the first to the seventh interspace and to another field covering the apex of the axilla and the supraclavicular region. Exact field size was left to the judgment of the therapist.

A minimum total tissue dose of 3,500 roentgens in no more than 3 weeks or 4,500 roentgens in no more than 5 weeks was required. The dose was calculated 2 cm. below the skin for the parasternal field, and at the junction of the anterior third and posterior two-thirds of the supraclavicular region. The latter was with the arm extended and at the level of the medial third of the clavicle. Both areas were irradiated concurrently no less than four times a week, with equal daily dosage throughout the treatment period. Treatment was started at the discretion of the surgeon and the therapist as soon as feasible following mastectomy, but no more than 30 days postoperatively. Approximately 75% of the 470 radiotherapy patients were recipients of supervoltage irradiation. There was no uni-

TABLE 1. *Disposition of Patients Entered into the Three Adjuvant Treatment Series*

Group	Entered	Ineligible	Excluded Incomplete Data	% Withheld	Eligible for Analysis
Radiotherapy	915	331	114	48.6	470
Controls	967	238	96	34.5	633
TSPA	454	110	28	30.4	316
Placebo	513	128	68	38.2	317
Total	1,882	569	210	41.4	1,103

formity from institution to institution relative to the type of equipment employed. Aside from Co^{60}, institutions utilized Cesium 137, the Van de Graff linear accelerator, Maxitron 1000, Varian Clinac, Westinghouse 250, Picker 250, GE 250 Maxima and other equipment. Several treated their patients with orthovoltage equipment at the beginning of the study and after acquiring the facility for supervoltage therapy, switched to its use.

No other adjuvant treatment for breast cancer was permitted. This precluded use of hormones, radiation or chemotherapy until there was definite evidence of tumor recurrence.

Data relative to the disease status of patients (i.e. local or regional recurrence or distant metastases) come from all acceptable patients followed for longer than 18, 36, or 60 months and survival rates from those on the study for longer than

TABLE 2. *Reasons for Exclusion of Patients Treated with Radiotherapy, TSPA or Placebo*

	Radiotherapy	TSPA[a]	Placebo[b]	Total
1. Benign lesions	43	39	45	127
2. Ineligible according to protocol	54	24	36	114
3. Adjuvant therapy refused by patient	30 (13+, 12−, 5?)*	8	1	39
4. Surgical procedure[c]	15	5	9	29
5. Grossly inadequate dosage	24 (14+, 10−)	5	4	33
6. Adjuvant therapy started too late	16 (8+, 8−)	3	1	20
7. No reason for not giving	2 (1+, 1−)	2	0	4
8. Administrative error	8 (5+, 3−)	2	2	12
9. Physician chose not to give adjuvant therapy	13 (2+, 11−)	2	5	20
10. Complications of surgery preventing initiation of adjuvant therapy according to protocol	98 (59+, 39−)	2	4	104
11. Prophylactic therapy other than in protocol	0	8	8	16
12. Post-adjuvant therapy without recurrence or metastases	3	5	6	14
13. Miscellaneous	25 (14+, 11−)	5	7	37
	331	110	128	569

[a] Does not include TSPA treated patients from options where the randomization was between TSPA and 5-FU.
[b] Includes 5 patients entered after the design change where instead of a placebo, no adjuvant therapy (controls) was given.
[c] Other than the standard Halsted procedure was performed.
* Nodal status.

TABLE 3. *Disease Status* after 18, 36 and 60 Months for All Patients on Study at Least as Long as These Intervals*

	Radiotherapy		TSPA		Placebo		All Controls	
	# Pts.	% of Total pts. Followed	# Pts.	% of Total pts. Followed	# Pts.	% of Total pts. Followed	# Pts.	% of Total pts. Followed
	18 months after surgery (pts. entered ≥ 18 mo.)							
No evidence of disease	320	78.8	226	81.0	216	80.3	442	80.7
Recurrence—local[a]	18	4.4	10	3.6	21	7.8	31	5.7
Recurrence—regional[b]	3	0.7	12	4.3	7	2.6	19	3.5
Distant metastasis	65	16.0	31	11.1	25	9.3	56	10.2
Recurrence—site unknown	0	0.0	0	0.0	0	0.0	0	0.0
Total failed	86	21.2	53	19.0	53	19.7	106	19.3
Patients followed	406		279		269		548	
	36 months after surgery (pts. entered ≥ 36 mo.)							
No evidence of disease	185	61.1	147	67.7	130	66.0	277	66.9
Recurrence—local	24	7.9	13	6.0	23	11.7	36	8.7
Recurrence—regional	4	1.3	14	6.5	7	3.6	21	5.1
Distant metastasis	87	28.7	41	18.9	37	18.8	78	18.8
Recurrence—site unknown	3	1.0	2	0.9	0	0.0	2	0.5
Total failed	118	38.9	70	32.3	67	34.0	137	33.1
Patients followed	303		217		197		414	
	60 months after surgery (pts. entered ≥ 60 mo.)							
No evidence of disease	91	50.6	60	50.8	58	49.6	118	50.2
Recurrence—local	14	7.8	7	5.9	18	15.4	25	10.6
Recurrence—regional	1	0.6	10	8.5	4	3.4	14	6.0
Distant metastasis	72	40.0	39	33.1	37	31.6	76	32.3
Recurrence—site unknown	2	1.1	2	1.7	0	0.0	2	0.9
Total failed	89	49.4	58	49.2	59	50.4	117	49.8
Patients followed	180		118		117		235	

* All evidence of disease is that first reported.
[a] Local chest wall or scar.
[b] Regional—axilla, supraclavicular or parasternum.

36, 48, or 60 months. There were 1,882 patients assigned to the three treatment groups (Table 1). Of this number, 569 (30%) were excluded for failure to meet protocol requirements. Another 210 were excluded because of incomplete data. Of the 1,103 remaining patients, 470 were recipients of radiotherapy, 316 received TSPA and 317 were given a placebo. Reasons for ineligibility varied (Table 2). Because of the larger number in the radiotherapy group than in the control group—particularly in certain categories—it is deemed important to document the reasons so as to eliminate any suggestion that bias dictated such exclusions or entered into conclusions. There was a large number of benign lesions in all treatment groups because in the early phase of the study all patients with breast lesions were registered with the statistical center upon admission to hospital and prior to complete evaluation relative to their acceptability. Those patients designated as "ineligible according to protocol" consisted of patients with bilateral malignancy, previous or concomitant malignancy, palpable supraclavicular nodes, biopsies done more than 14 days prior to surgery, etc. Such patients should never have been registered in the study. There were almost an equal number of exclusions in the radiotherapy and control

groups for this reason. More patients refused to be treated with x-ray than refused TSPA. In view of time of administration of therapy relative to surgery and the short dosage regimen of the chemotherapy as compared with the radiotherapy, such a difference seems reasonable. It is of interest that of those patients refusing irradiation, 13 of the 25 whose nodal status was known had positive axillary lymph nodes—a distribution which was not appreciably different from the nodal status of all patients in the study. An equivalent number of patients in control and radiotherapy groups were removed because surgical procedures other than the standard Halsted radical mastectomy was performed.

Twenty-four of the radiotherapy patients were excluded because of "inadequate dosage." Such dosage was markedly less than required by the protocol or it was administered over too prolonged a period of time. Only two of the patients were given the required dosage in a time which exceeded the prescribed limit by a few days (38 and 37 days instead of 35 days) and could have perhaps been included in the study. One had positive axillary nodes and the other negative nodes. In this group of patients 14 had positive nodes, again a nodal distribution in keeping with that of patients in the study.

Irradiation was started too late (more than 30 days postoperatively) in 16 patients. In most, this time lapse was several weeks or longer. Of this group eight had positive nodes. Two patients did not receive radiotherapy for which no reason was documented. Eight patients were listed as "administrative errors"; due to lack of communication, patients were not informed that they were to receive such therapy. Five of these patients had positive lymph nodes in their surgical specimens. There were 13 patients from five institutions in which the surgeon chose not to use radiotherapy despite their randomization into such a category in definite violation of the study. Eleven of the patients had negative axillary nodes suggesting bias in such deletions. All of the data from the one institution which treated six of the patients were analyzed so as to compare treatment failure and survival rates at that institution with the findings as a whole. It was found that the institution had a higher proportion of patients with negative nodes in their series than did all other institutions suggesting that possibly no bias was introduced by their patient exclusions. Moreover, the data (treatment failure and survival) were not significantly different from that obtained from all of the other institutions.

Complications of surgery prevented initiation of adjuvant therapy according to the protocol in 98 radiotherapy patients and only in six of the control groups. Such a disproportionate number of patients may be the subject of suspicion. Careful scrutiny of records revealed that almost all of those which failed to receive irradiation did so because of surgical wound complications. Large sloughing ulcers, failure of skin grafts to heal, persistent seromas, wound dehiscence, etc., restrained the surgeon from referring such patients to the radiotherapist despite the fact that irradiation was not (according to the protocol) to be given to the region of the wound. Patients receiving TSPA or placebo also suffered such complications—but subsequent to the administration of such therapy. Thus, the discrepancy in exclusions between the irradiated and control groups may be readily explained. Of interest was the finding that in this group of 98 patients 59 had positive nodes which was again comparable to the nodal status of all eligible patients. Of those who did not receive radiotherapy and were categorized as "miscellaneous" exclusions (25), seven died before therapy could be given, two had cardiac problems, one septicemia, two received postoperative

TABLE 4. *Location of First Evidence*

Location of Failure (F)	Radiotherapy								TSPA							
	18 Months[a]		3 Years[b]		5 Years[c]		All[d]		18 Months		3 Years		5 Years		All	
	# F	% Total F	# F	% Total F	# F	% Total F	# F	% Total F	# F	% Total F	# F	% Total F	# F	% Total F	# F	% Total F
Local recurrences																
Chest wall	14	16.3	20	16.9	13	14.6	23	15.8	5	9.4	8	11.4	5	8.6	12	13.0
Scar	4	4.6	4	3.4	1	1.1	5	3.4	5	9.4	5	7.2	3	5.2	8	8.7
Sub total	18	20.9	24	20.3	14	15.7	28	19.2	10	18.8	13	18.6	8	13.8	20	21.7
Regional recurrences																
Tissue of axilla	2	2.3	3	2.5	1	1.1	3	2.1	1	1.9	1	1.4	0	0.0	1	1.1
Supraclavicular	1	1.2	1	0.8	0	0.0	2	1.4	9	17.0	12	17.2	9	15.6	13	14.1
Parasternum	0	0.0	0	0.0	0	0.0	0	0.0	2	3.8	1	1.4	0	0.0	2	2.2
Sub total	3	3.5	4	3.4	1	1.1	5	3.4	12	22.7	14	20.0	9	15.6	16	17.4
Distant metastases																
Skeletal	27	31.4	37	31.4	32	36.0	47	32.2	9	17.0	16	22.9	16	27.6	20	21.7
Respiratory	20	23.3	31	26.3	26	29.2	41	28.1	13	24.5	16	22.9	18	31.1	25	27.2
Hemic & lymphatic	3	3.5	3	2.5	2	2.2	3	2.1	4	7.5	4	5.7	1	1.7	4	4.3
Digestive	9	10.4	7	5.9	7	7.9	12	8.2	3	5.7	2	2.8	2	3.4	3	3.3
Genital	1	1.2	2	1.7	1	1.1	2	1.4	0	0.0	0	0.0	0	0.0	0	0.0
Nervous	1	1.2	2	1.7	1	1.1	2	1.4	1	1.9	0	0.0	0	0.0	1	1.1
Miscellaneous	4	4.6	7	5.9	3	3.4	6	4.1	1	1.9	4	5.7	2	3.4	3	3.3
Sub total	65	75.6	89	75.4	72	80.9	113	77.4	31	58.5	42	60.0	39	67.2	56	60.9
Site unknown	0	0.0	1	0.8	2	2.2	0	0.0	0	0.0	1	1.4	2	3.4	0	0.0
Total failures	86		118		89		146		53		70		58		92	
Patients followed	406		303		180		406		279		217		118		279	

[a] Failures occurring $\leq$ 18 months in all patients followed $\geq$ 18 months.
[b] Failures occurring $\leq$ 3 years in all patients followed $\geq$ 3 years.
[c] Failures occurring $\leq$ 5 years in all patients followed $\geq$ 5 years.
[d] All failures occurring at any time for all patients followed $\geq$ 18 months.

steroid therapy, two had subsequent second primary tumors, two were psychiatric problems, one had severe thrombophlebitis requiring anticoagulants which resulted in further complications preventing irradiation. The others received Dakins solution at operation, were placed in the wrong treatment options or had other surgical treatment in the postmastectomy period. Of this group 14 had positive axillary lymph nodes.

Local recurrence is defined in this study as reappearance of disease within the area of operation—namely the scar and chest wall. Regional recurrence is defined as reappearance of disease within the area of irradiation—namely the axilla, supraclavicular and parasternal region of the side under treatment. Distant metastasis is defined as that disease which occurred elsewhere. In this report, all reference to recurrence or metastasis means only that which was *first* reported.

Results

Disease Status. A comparison of the disease status of patients receiving radiotherapy with that of controls (TSPA and Placebo) was made 18, 36 and 60 months after operation (Table 3). Patients were categorized into those free of disease and those having local recurrence, regional recurrence or distant metastases. The distribution of disease status for radiotherapy patients was significantly different than that for TSPA or placebo-treated women at all follow-up periods. At each time the proportion of women in all groups showing no evidence of disease was almost identical. Conversely the number *with* dis-

of Treatment Failure

Placebo								All Controls							
18 Months		3 Years		5 Years		All		18 Months		3 Years		5 Years		All	
# F	% Total F	# F	% Total F	# F	% Total F	# F	% Total F	# F	% Total F	# F	% Total F	# F	% Total F	# F	% Total F
12	22.6	13	19.4	6	10.2	16	16.0	17	16.0	21	15.3	11	9.4	28	14.6
9	17.0	10	14.9	12	20.3	14	14.0	14	13.2	15	10.9	15	12.8	22	11.4
21	39.6	23	34.3	18	30.5	30	30.0	31	29.2	36	26.2	26	22.2	50	26.0
2	3.8	2	3.0	0	0.0	2	2.0	3	2.8	3	2.2	0	0.0	3	1.6
5	9.4	5	7.4	4	6.8	10	10.0	14	13.2	17	12.4	13	11.1	23	12.0
0	0.0	0	0.0	0	0.0	0	0.0	2	1.9	1	0.7	0	0.0	2	1.0
7	13.2	7	10.4	4	6.8	12	12.0	19	17.9	21	15.3	13	11.1	28	14.6
14	26.4	19	28.4	17	28.8	32	32.0	23	21.7	35	25.5	33	28.2	52	27.1
6	11.3	10	14.9	13	22.0	15	15.0	19	17.9	26	19.0	31	26.5	40	20.8
2	3.8	3	4.5	3	5.1	3	3.0	6	5.7	7	5.1	4	3.4	7	3.6
2	3.8	4	6.0	3	5.1	5	5.0	5	4.7	6	4.4	5	4.3	8	4.2
0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
1	1.9	1	1.5	1	1.7	1	1.0	2	1.9	1	0.7	1	0.9	2	1.0
0	0.0	0	0.0	0	0.0	2	2.0	1	0.9	4	2.9	2	1.8	5	2.6
25	47.2	37	55.3	37	62.7	58	58.0	56	52.8	79	57.7	76	65.0	114	59.4
0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.7	2	1.7	0	0.0
53		67		59		100		106		137		117		192	
269		197		117		269		548		414		235		548	

ease was similarly proportioned for each series. For example, 5 years after operation 49.4% of the 180 patients receiving radiotherapy, 49.2% of those who were recipients of TSPA and 50.4% of those given a placebo had evidence of disease. The proportion of treatment failures (i.e. first recorded) that were due to local recurrences was similar for radiotherapy and TSPA groups and was slightly greater in placebo patients at each of the times considered, e.g. 7.8%, 5.9% and 15.4%, respectively, at 5 years. The proportion of treatment failures due to regional recurrences was lower at each time for irradiated patients than for TSPA or placebo-treated women. At all three time periods, this difference was greater between the radiotherapy and TSPA-treated women than between radiotherapy and the placebo groups (0.6% for radiotherapy, 8.5% for TSPA, 3.4% for placebo at 5 years). There was, however, a higher proportion of patients with distant metastases (as first reported evidence of disease) in the radiotherapy group than in the other groups. Whereas at 5 years there were 40.0% of those irradiated with such lesions, they were present in 33.1% and 31.6% of patients receiving TSPA or placebo, respectively.

A more precise listing of the areas involved at first evidence of treatment failure in the three groups at the various times recorded in Table 3 is presented in Table 4. In addition, location of all failures occurring at any time for all patients followed $\geqslant$18 months is shown. From these data the proportion of all of the failures occurring at the various locations was deter-

TABLE 5. *Disease Status* of Patients with Negative Axillary Nodes*

	Radiotherapy		TSPA		Placebo		All Controls	
	#	% of Neg. Node Pts.	#	% of Neg. Node Pts.	#	% of Neg. Node Pts.	#	% of Neg. Node Pts.
	At 3 years for patients entered 3 or more years							
Patients followed	109		95		87		182	
No evidence of disease	94	86.2	83	87.4	78	90.0	161	88.5
Recurrence—local	4	3.7	2	2.1	2	2.3	4	2.2
Recurrence—regional	0	0.0	0	0.0	2	2.3	2	1.1
Distant metastasis	11	10.1	10	10.5	5	5.7	15	8.2
Recurrence—site unknown	0	0.0	0	0.0	0	0.0	0	0.0
Total failed	15	13.8	12	12.6	9	10.3	21	11.5
	At 5 years for patients entered 5 or more years							
Patients followed	56		44		52		96	
No evidence of disease	44	78.6	36	81.8	37	71.2	73	76.0
Recurrence—local	5	8.9	0	0.0	2	3.8	2	2.1
Recurrence—regional	0	0.0	0	0.0	2	3.8	2	2.1
Distant metastasis	7	12.5	7	15.9	11	21.2	18	18.8
Recurrence—site unknown	0	0.0	1	2.3	0	0.0	1	1.0
Total failed	12	21.4	8	18.2	15	28.8	23	24.0

* All evidence of disease is that first reported.

mined. Findings were essentially similar to those obtained (Table 3) when results relative to disease status were presented as proportions of all patients followed. It was observed, for example, that of all failures occurring at any time in patients followed $\geqslant$18 months only 3.4% were regional in patients receiving irradiation whereas there were 17.4% and 12.0% in the TSPA and placebo groups, respectively. Of significance in this regard was the marked reduction of supraclavicular nodal involvement in the irradiated group. In the group receiving radiotherapy 19.2% of first reported failures were local, whereas 26.0% of all failures in control patients were in that category. Of interest was the observation that the incidence in the scar was lower in those who were irradiated (3.4% versus 11.4% for all controls). The proportion of failures which were reported as distant metatstases was significantly greater in irradiated patients at any period. In all groups a preponderance of such failures were found in the skeletal and respiratory systems. Twenty-eight per cent in the irradiated groups occurred in the latter, i.e., lungs, pleura and mediastinum, whereas only 15.0% in the placebo group had involvement in those locations. In TSPA treated patients 27.2% of all first failures were related to the respiratory system.

The disease status of patients was determined according to their axillary nodal involvement at time of operation. Of those with negative nodes who received radiotherapy, 13.8% and 21.4% had evidence of disease at 3 and 5 years, respectively, whereas 11.5% and 24.0% of all controls were similarly categorized (Table 5). Subdividing these treatment failures (first reported) according to their locations resulted in information which, because of the too few patients involved, can only be suggestive rather than definitive. There seemed, however, to be no trend to indicate that radiotherapy significantly reduced the number of failures at any loca-

tion in patients so treated. Of women with positive nodes (Table 6) who were subjected to irradiation, 53.1% and 62.1% demonstrated evidence of disease at 3 and 5 years, whereas 50.0% and 67.6% of all controls at these times represented treatment failures—not a statistically significant difference between the groups. While patients with 4+ positive nodes who received radiotherapy seemingly had a lower total failure rate 5 years after operation than did those who received TSPA (71.6% versus 85.0), they differed less from the placebo group (78.1%), and none of the differences achieved statistical significance. Further examination of treatment failures according to their locations at 3 and 5 years in all positive node patients revealed that local recurrence rates were lower in irradiated patients (both with 1–3 and 4+ positive nodes) than in those who were recipients of a placebo, but were more similar to TSPA treated women. Regional recurrences were likewise less in the irradiated group (0.8% at 5 years) than in the placebo group (3.1%) and markedly lower than in the TSPA group at that time (13.5%). Whereas 52.4% of positive node patients treated with irradiation exhibited distant metastases at 5 years, 43.2% of the TSPA group and 40.0% of those in the placebo group had such evidence of disease. Both patients with 1–3 or 4+ positive nodes demonstrated greater proportion of distant metastases when administered radiotherapy.

When disease status was determined 3, 4 and 5 years after operation in patients according to their menopausal classification, no advantage could be ascertained for those who received radiotherapy (Table 7). It was observed, for example, that 50% of postmenopausal women who were irradiated and 50% of those who served as controls had evidence of disease at 5 years.

Further confirmation of the findings relative to disease status was obtained from life table plots utilizing *all* patients with follow-up data. When such curves were prepared according to the menopausal and /or nodal status of patients, no significant difference was observed between the irradiated and control groups. Findings are exemplified by those obtained for all positive node patients in the TSPA, placebo and radiotherapy groups (Fig. 1).

Curves were prepared to demonstrate the cumulative frequency distributions of times to first evidence of treatment failure (i.e., disease) according to location of such failures in all patients followed $\geqslant$18 months. It was found (Fig. 2) that the curves prepared from local and regional failures for irradiated and control (TSPA and placebo combined) patients were superimposed on each other. The curves indicating distant metastases were not significantly different but suggested that disease occurred earlier in the irradiated group than in the control patients. "Local and regional" failures were listed in separate categories in one series that was too small to evaluate (radiotherapy-regional with five patients). The cumulative frequencies for "local" in both series were very similar so that a plot of values were superimposed upon each other.

Survival. Survival of patients was determined 3, 4 and 5 years following operation regardless of their nodal or menopausal status. At each time, survival of those irradiated was slightly less than in the control patients (Table 8). When data were subgrouped according to nodal status, i.e. positive or negative, no advantage was ascertained for those who were recipients of radiotherapy (Table 9). The 5-year survival for negative node patients so treated was 74% and was 79% for controls. Women with positive nodes who received irradiation had a 47% survival at that time whereas the survival for combined control groups was 49%. Survival was related to the number of positive nodes present, and

TABLE 6. *Disease Status* of Patients with Positive Axillary Nodes*

	Radiotherapy		TSPA		Placebo		All Controls	
	#	% of Pos. Node Pts.	#	% of Pos. Node Pts.	#	% of Pos. Node Pts.	#	% of Pos. Node Pts.
At 3 years for patients entered 3 or more years								
Patients followed	194		122		110		232	
1–3	90		61		49		110	
4+	104		61		61		122	
No evidence of disease	91	46.9	64	52.5	52	47.3	116	50.0
1–3	51	56.7	43	71.7	28	57.1	71	65.1
4+	40	38.5	21	33.9	24	39.3	45	36.6
Recurrence local	20	10.3	11	9.0	21	19.1	32	13.8
1–3	7	7.8	4	6.7	7	14.3	11	10.1
4+	13	12.5	7	11.3	14	23.0	21	17.1
Recurrence regional	4	2.0	14	11.5	5	4.5	19	8.2
1–3	2	2.2	3	5.0	2	4.1	5	4.6
4+	2	1.9	11	17.7	3	4.9	14	11.4
Distant metastasis	76	39.2	31	25.4	32	29.1	63	27.2
1–3	29	32.2	11	18.3	12	24.5	23	21.1
4+	47	45.2	20	32.3	20	32.8	40	32.5
Recurrence—site unknown	3	1.5	2	1.6	0	0.0	2	0.9
1–3	1	1.1	0	0.0	0	0.0	0	0.0
4+	2	1.9	2	3.2	0	0.0	2	1.6
Total failed	103	53.1	58	47.5	58	52.7	116	50.0
1–3	39	43.3	18	28.3	21	42.9	39	34.9
4+	64	61.5	40	66.1	37	60.7	77	63.4
At 5 years for patients entered 5 or more years								
Patients followed	124		74		65		139	
1–3	57		34		33		67	
4+	67		40		32		72	
No evidence of disease	47	37.9	24	32.4	21	32.3	45	32.4
1–3	28	49.1	18	52.9	14	42.4	32	47.8
4+	19	28.4	6	15.0	7	21.9	13	18.0
Recurrence local	9	7.3	7	9.5	16	24.6	23	16.5
1–3	3	5.3	4	11.8	7	21.2	11	16.4
4+	6	9.0	3	7.5	9	28.1	12	16.6
Recurrence regional	1	0.8	10	13.5	2	3.1	12	8.6
1–3	0	0.0	2	5.9	1	3.0	3	4.5
4+	1	1.5	8	20.0	1	3.1	9	12.5
Distant metastasis	65	52.4	32	43.2	26	40.0	58	41.7
1–3	25	43.9	10	29.4	11	33.3	21	31.3
4+	40	59.7	22	55.0	15	46.9	37	51.4
Recurrence—site unknown	2	1.6	1	1.4	0	0.0	1	0.7
1–3	1	1.8	0	0.0	0	0.0	0	0.0
4+	1	1.5	1	2.5	0	0.0	1	1.4
Total failed	77	62.1	50	67.6	44	67.7	94	67.6
1–3	29	50.9	16	47.0	19	57.6	35	52.2
4+	48	71.6	34	85.0	25	78.1	59	81.9

* All evidence of disease is that first reported.

TABLE 7. *Disease Status* Related to Menopausal Classification*

Menopausal Status	Years Post Surgery	Radiotherapy			TSPA			Placebo			All Controls		
		#Pts.	#F[a]	%R	#	#F	%R	#	#F	%R	#	#F	%R
Pre	3	48	21	44	75	27	36	63	23	37	138	50	36
	4	37	19	51	61	28	46	52	19	37	113	47	42
	5	23	10	43	43	21	49	35	17	49	78	38	49
Post	3	255	97	38	142	43	30	134	44	33	276	87	32
	4	213	100	47	111	43	39	110	53	48	221	96	43
	5	157	79	50	75	37	49	82	42	51	157	79	50

* All evidence of disease is that first reported.
[a] F = treatment failures, i.e. patients with disease.

again, no significant advantage for irradiated patients existed (Table 10). Likewise, when survival rates were categorized according to menopausal status (Table 11) or to menopausal *and* nodal status (Table 12) at no time did those treated with radiotherapy demonstrate an advantage. Survival rates were obtained 3 years after operation from positive node patients grouped according to their menopausal status *and* numbers of nodes involved. While the number of patients in some subsets were too small for reliable evaluation, there was no trend to suggest a favorable response to irradiation (Table 13).

Life table plots of survival were made utilizing all of the patients with follow-up information. In no circumstance did such analysis, as is exemplified by that for all positive node patients (Fig. 3), reveal any significant difference between the irradiated and control groups.

Discussion

Evidence to support the worth of postoperative irradiation as an adjunct to primary surgical treatment of breast cancer is tenuous. Frequently information has been obtained from retrospective analyses of heterogeneous groups of case records and by comparisons of data obtained from divergent series of patients. In 1943 Adair concluded from such a study of 3,535 patients that the preferable method of treating operable breast cancer was radical mastectomy combined with postoperative ir-

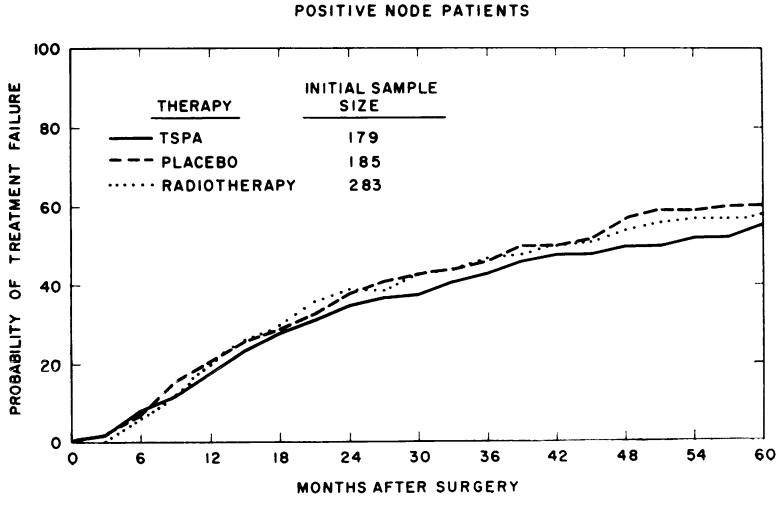

FIG. 1. Evidence of disease following radiotherapy.

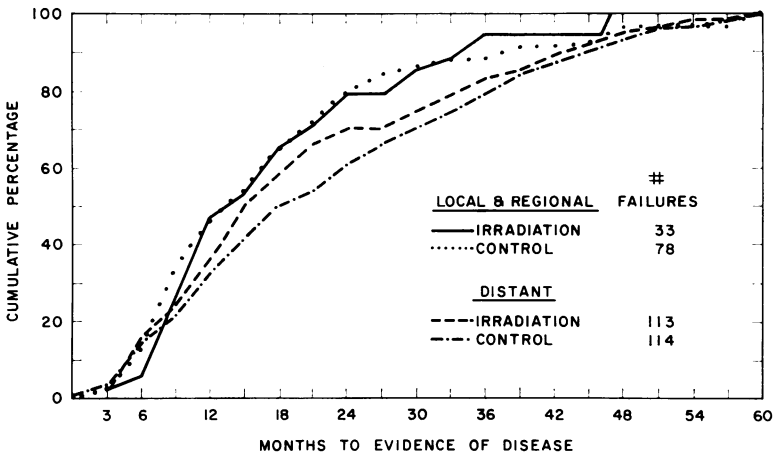

FIG. 2. Distribution of months to first evidence of treatment failure according to location.

radiation.[1] With such therapy, 5-year survival was 76.8% for women having no axillary node involvement and 41.8% when nodes contained tumor. Unfortunately, no group of patients treated by surgery alone was present for comparison. Adair's contention was supported by Marshall and Hare (1947) who reported that surgical removal of breast carcinoma followed by irradiation "appears to improve statistical results in cancer of the breast and offers the best possibility for prolongation of life."[15] In a series of 238 patients so treated, 52% were alive 5 years or longer without evidence of recurrence. A comparison of these results with those obtained from non-irradiated patients at other institutions led them to this conclusion. Harrington (1953) likewise favored irradiation, reporting that the 5-year survival rate of patients with or without axillary node involvement was enhanced by 5% when irradiation was added to surgery.[13] One of the most ardent advocates of radiotherapy in the treatment of primary operable breast carcinoma has been Guttmann. In 1963 she reported results from patients who, while meeting all other criteria of operability, were considered inoperable because "double" or "triple" biopsies demonstrated tumor in the highest axillary node and/or an internal mammary node.[10] Such patients were given supervoltage irradiation to the supra- and infraclavicular areas, the axilla and the internal mammary lymph nodes. Of 67 patients receiving such treatment and followed for 5 years, the survival rate varied between 47 and 60 per cent (average 50%) according to the lymph node involvement. Guttmann was of the opinion that the findings confirmed her previous observations reported in 1958 that it is possible by radiotherapy to sterilize metastatic lymph nodes.[9] In 1967 she concluded that

TABLE 8. *Survival Rates—All Patients**

Years Post Surgery	Radiotherapy			TSPA			Placebo			All Controls		
	#	#S†	%S	#	#S	%S	#	#S	%S	#	#S	%S
3	318	224	70	218	172	79	194	150	77	412	322	78
4	259	158	61	176	122	69	163	112	69	339	234	69
5	195	109	56	120	74	62	113	70	62	233	144	62

* Without regard for nodal or menopausal status.
† S = survival.

TABLE 9. *Survival Rates Related to Nodal Status*

Years Post Surgery	Nodal Group	Radiotherapy			TSPA			Placebo			All Controls		
		#	#S	%S	#	#S	%S	#	#S	%S	#	#S	%S
3	Neg.	115	101	88	96	85	89	89	81	91	185	166	90
	Pos.	203	123	61	122	87	71	105	69	66	227	156	69
4	Neg.	88	71	81	75	60	80	72	64	89	147	124	84
	Pos.	171	87	51	101	62	61	91	48	53	192	110	57
5	Neg.	62	46	74	47	37	79	50	40	80	97	77	79
	Pos.	133	63	47	73	37	51	63	30	48	136	67	49

irradiation "has an undisputed place in the management of patients with carcinoma of the breast as well as the primary treatment and as an adjunct to surgery."[11] Her conclusions were supported the same year by Watson[20] who wrote that "proper" postoperative irradiation when combined with radical mastectomy should produce the best possible results in the treatment of breast cancer.

Other investigators have, however, failed to observe an advantage in the use of such therapy. Treves and Holleb,[19] in a study of breast cancer in women 35 years of age or younger, reported that postoperative x-ray therapy, regardless of axillary node involvement had no influence on the clinical cure rate. Butcher *et al.*[2] observed that irradiation therapy to the supraclavicular and parasternal areas after radical mastectomy did not influence subsequent survival. In their study, 249 women were treated randomly by radical mastectomy alone or by radical mastectomy and postoperative irradiation using orthovoltage equipment. In a study comparing the long-term results in patients who were not randomized but who were in the same stage of disease, Robbins *et al.*[18] found no significant difference in cure rates between such groups of patients. There was no difference in results whether axillary nodes were free of cancer or had metastases. Nor was there a difference when those with axillary involvement were compared as a whole or by level of node involvement. As in the present study, there was a significantly lower rate of metastases in the supraclavicular area of those patients receiving x-ray therapy. Others such as Haagensen and Stout[12] and Hickey *et al.*,[14] found no advantage, in terms of first recurrence or survival, to postoperative radiotherapy in their series of patients.

TABLE 10. *Survival Rates Related to Number of Positive Nodes*

No. Pos. Nodes	Years Post Surgery	Radiotherapy			TSPA			Placebo			All Controls		
		#	#S	%S	#	#S	%S	#	#S	%S	#	#S	%S
1–3	3	89	64	72	60	50	83	46	35	76	106	85	80
	4	72	47	65	47	37	79	41	26	63	88	63	72
	5	59	35	59	35	26	74	31	20	65	66	46	70
4+	3	114	59	52	62	37	60	59	34	58	121	71	59
	4	99	40	40	54	25	46	50	22	44	104	47	45
	5	74	28	38	38	11	29	32	10	31	70	21	30

TABLE 11. *Survival Rates Related to Menopausal Status*

Menopausal Status	Years Post Surgery	Radiotherapy			TSPA			Placebo			All Controls		
		#	#S	%S	#	#S	%S	#	#S	%S	#	#S	%S
Pre	3	58	38	66	73	56	77	58	46	79	131	102	78
	4	43	23	53	61	41	67	51	38	75	112	79	71
	5	30	16	53	42	27	64	34	21	62	76	48	63
Post	3	260	186	72	145	116	80	136	104	76	281	220	78
	4	216	135	63	115	81	70	112	74	66	227	155	68
	5	165	93	56	78	47	60	79	49	62	157	96	61

A study most frequently referred to when evaluating postoperative irradiation is that of Paterson and Russell [16] who analyzed results from 1,461 instances of breast cancer treated between 1949 and 1955 at the Christie Hospital in Manchester, England. Approximately one-half of the patients in the series were treated with immediate irradiation following radical mastectomy and the rest were treated only when the need arose. The purpose of the study was not to evaluate the results of prophylactic radiotherapy and no radiotherapy, but to compare the effects of radiotherapy given immediately after operation with that administered when recurrence appeared. No significant difference in the crude mortality rate was observed between the two groups. Paterson concluded that irradiation did what was expected of it—it prevented recurrence in the irradiated areas, but if treatment was delayed until recurrences appeared, they could be controlled equally as well. A possible increase in the incidence of liver metastases in the prophylactically irradiated cases was commented upon. Since only one-third of the "watched" patients required treatment at a later time for local recurrence, two-thirds of the patients were spared unnecessary treatment.

The rationale for the employment of postoperative irradiation is worthy of consideration. Since such therapy is considered to be "regional" it seems inappropriate to anticipate that its use should enhance the curability of surgery in the large group of patients who already have distant dissemination at the time of operation and/or irradiation. Similarly, those women in whom surgery has eradicated all of the tumor could not be expected to demonstrate an improved survival; for, there having

TABLE 12. *Survival Rates Related to Nodal and Menopausal Status*

Nodal Status	Menopausal Status	Years Post Surgery	Radiotherapy			TSPA			Placebo			All Controls		
			#	#S	%S	#	#S	%S	#	#S	%S	#	#S	%S
Negative	Pre	3	23	22	96	36	30	83	29	28	97	65	58	89
	Post	3	92	79	86	60	55	92	60	53	88	120	108	90
		4	71	57	80	47	39	83	46	40	87	93	79	85
		5	50	37	74	28	22	79	33	27	82	61	49	80
Positive	Pre	3	35	16	46	37	26	70	29	18	62	66	44	67
	Post	3	168	107	64	85	61	72	76	51	67	161	112	70
		4	145	78	54	68	42	62	66	34	52	134	76	57
		5	115	56	49	50	25	50	46	22	48	96	47	49

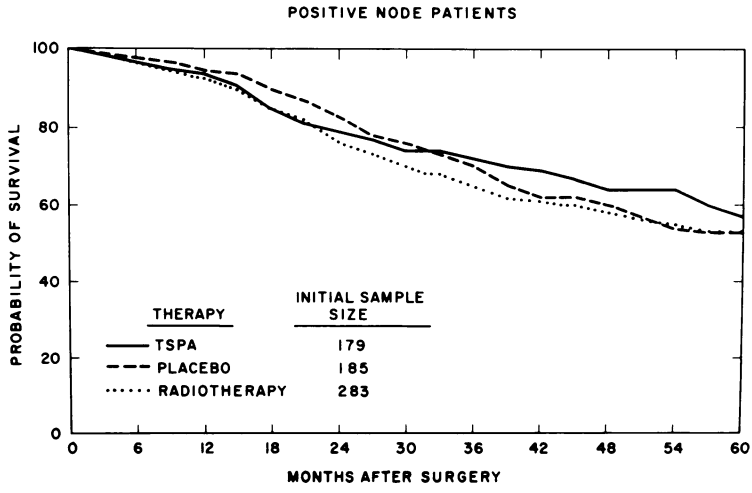

FIG. 3. Survival following radiotherapy.

been no spread to unremoved areas, total curability should have been effected by operation alone. Consequently, irradiation might exert its benefits only on a small number of women who, following operation, have residual tumor in locations accessible to regional irradiation but in no other place (i.e., distant), and by the eradication of such tumor with radiotherapy the development of metastases (distant) from metastases (regional) could be prevented. It may well be that the sample size, duration of follow-up and other factors indigenous to the present study are inadequate to permit demonstration of the worth of radiotherapy on this small but critical group of patients. It is unlikely, unfortunately, that even further evaluation of the data from this study in the future will satisfactorily provide answers in this regard. Further clinical trials may be needed for this. Other findings suggest, however, that if such an advantage for radiotherapy could be revealed in that group (by accumulation of an exceedingly larger sample size) it possibly may be nullified by the greater incidence of distant metastases in other patients.

The data accumulated in this study have, to the present time, demonstrated that the proportion of patients who are treatment failures because of new evidence of tumor for which they were operated is similar for the radiotherapy and control groups. Further examination of patients who were failures at 5 years, for example, has revealed, however, that radiotherapy *did* effectively reduce the proportion of women whose failures were regional in location (0.6% versus 8.5% and 3.4% in TSPA and placebo groups). Moreover, the proportion of patients whose failures were local was less in the irradiated group (7.8%) than in the placebo group (15.4%), but was similar to

TABLE 13. *Survival Rates Related to Menopausal Status and Number of Positive Nodes—3 Years*

Menopausal Status	Number Positive Nodes	Radiotherapy			TSPA			Placebo			All Controls		
		#	#S	%S	#	#S	%S	#	#S	%S	#	#S	%S
Pre	1–3	8	4	50	17	13	76	8	6	75	25	19	76
	4+	27	12	44	20	13	65	21	12	57	41	25	61
Post	1–3	81	60	74	43	37	86	38	29	76	81	66	81
	4+	87	47	54	42	24	57	38	22	58	80	46	58

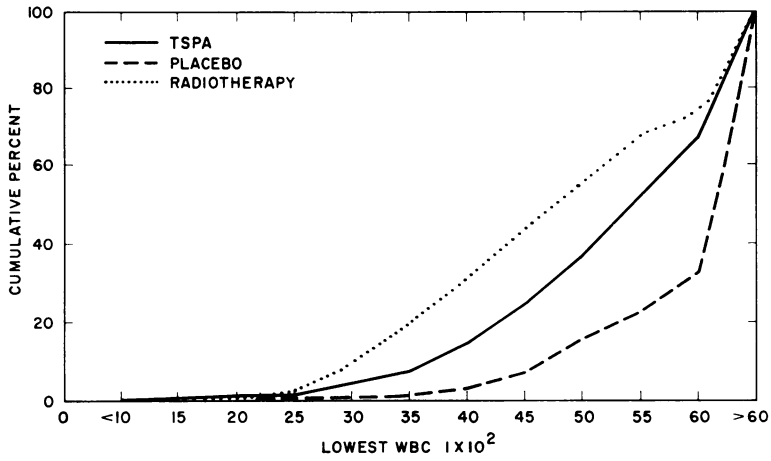

FIG. 4. Distributions of lowest WBC for each therapy.

that in the TSPA (5.9%) group. Because, however, the proportion of patients having distant metastases was sufficiently greater in the radiotherapy group (40.0%) than in either of the control groups (33.1% for TSPA patients and 31.6% for those getting placebo) there was the similarity in the proportion of total patient failures in the three groups.

Because of concern that the larger proportion of patient exclusions in the radiotherapy group might be construed as a possible mechanism of bias against irradiation, such exclusions were carefully reviewed. The large number of patients who developed local surgical complications preventing institution of irradiation within the specified time of the protocol was entirely in keeping with findings from a previous NSABP study,[8] where it had been demonstrated that approximately one-third of patients developed such undesirable sequelae subsequent to operation. Such complications were randomly distributed through all participating institutions, and surgeons were reluctant to expose their patients to irradiation as long as such complications were present even though irradiation was not directed to the chest wall.

Attention is directed toward the 13 patients whose physicians chose not to administer radiotherapy after their randomization into that category. All but two of the patients had negative axillary nodes. One had 13 of 16 positive nodes and the other three of nine were positive. If the 11 with negative nodes had been kept on study, six would have been followed 5 or more years at this time. The two patients with positive nodes would also have been on study for 5 or more years. If such patients (8) had all benefited by radiotherapy had it been given, so that none had evidence of disease by 5 years, to what extent would their inclusion in the study have altered the findings? Instead of 50.6% of patients in the study reported free of disease at 5 years, there would have been 52.7% of such women disease free. When compared with the 50.2% of control patients without disease, the difference does not become significant by their inclusion.

The observance of more frequent distant metastases in the group treated with regional irradiation seems to indicate that dissemination and lodgment of tumor cells may have occurred more frequently than did metastases. Perhaps only when host-tumor cell relationships were altered did they become overt metastases. That local irradiation may have resulted in systemic effects is suggested by observations relative to white blood counts of women receiving irradiation. Such counts were performed weekly for 4 weeks postoperatively on all patients. Distributions of lowest counts re-

corded demonstrated that while "severe" depression of leukocytes (<2,500) was rare, nearly ⅓ of women who received irradiation demonstrated leukopenia (<4,000) (Fig. 4). Unfortunately, lymphocyte counts and the duration of the leukocyte depression were not evaluated. The relevance of these findings with particular regard to the depression of systemic immunity warrants further investigation.

Controversy may exist relative to whether there truly was an increase in distant metastases following irradiation. The conclusion may be reached by some (P. J. C.) from the data that since the proportion of first failures which were due to regional and local recurrences decreased by the irradiation, then it necessarily follows that the proportion which were distant must increase. Others (B. F.) may interpret the data as indicating an increase in such metastases since the proportion of all patients who were free of disease was not increased following irradiation despite the decrease in regional recurrences.

The possible inadequacies of radiotherapy employed in this study may be criticized. A variety of equipment was employed and no attempts were made to monitor the uniformity of irradiation administered from institution to institution, or within institutions. Since, however, the present information was obtained from a variety of reputable institutions it has the virtue of probably being representative of the type of radiotherapy used at that time throughout the country. Consequently, to relate therapeutic ineffectiveness to methodology and technics of administration would be deplorable considering the number of women subjected to such treatment with the conviction that they were being benefited.

Again, it may be reiterated that a small group of women could have possibly been benefited by irradiation but have escaped notice because of certain limitations of the present study. This study, which was one of the first cooperative undertakings of its kind in this country, has had shortcomings which by today's sophistication is vulnerable to criticism. Over the years much has been learned from the NSABP relative to the trials and tribulations of such an endeavor. Nevertheless, it is to be emphasized that difficulties encountered have had no relevance to the results of this study.

From the data available it would seem that the use of postoperative irradiation has provided no discernible advantage to patients so treated in terms of increasing the proportion who were free of disease for as long as 5 years. While its use (as employed here) *did* decrease regional recurrence, the apparent increase of failure due to distant metastases as first evidence of disease and the lack of increase in survival rates fails to support the use of irradiation as an adjuvant to surgery in the treatment of operable breast cancer. Follow-up of patients will be continued to determine whether or not an advantage to irradiation becomes apparent.

Summary

In 1961, the National Surgical Adjuvant Breast Project (NSABP) initiated a randomized prospective cooperative trial with a specific protocol to resolve the uncertainty concerning the worth of postoperative irradiation as an adjunct to radical mastectomy in the treatment of operable breast cancer. Information was obtained from 1,103 acceptable study patients contributed by 25 institutions. Of this number, 470 women were recipients of postoperative parasternal, axillary, and supraclavicular irradiation and 633 served as controls receiving either TSPA (316 patients) or a placebo (317 patients).

Disease status and survival rates were determined for all patients 3, 4, or 5 years after operation. No significant difference in these parameters existed at any time between all patients who received radiotherapy and those who served as controls.

At 5 years, for example, 50.6% of patients who were recipients of radiotherapy were free of disease whereas 50.2% of all controls were in this category. Survival rates were 56% and 62%, respectively.

It was observed, however, that only 0.6% of the irradiated patients exhibited regional recurrences as *first* evidence of disease at 5 years whereas 8.5% of TSPA and 3.4% of placebo patients demonstrated such recurrence, indicating that irradiation effectively decreased the incidence of regional recurrences in areas irradiated. Likewise, local recurrences were decreased in the radiotherapy group (7.8%) when compared to placebo treated patients (15.4%) but not when compared to TSPA controls (5.9%). The proportion of patients whose treatment failures were due to distant metastases as *first* evidence of disease was greater following irradiation than in all controls (40.0% versus 32.3%).

Examination of data relative to axillary nodal (positive or negative) or menopausal status failed to demonstrate a clear advantage for the radiotherapy group either in terms of disease status or increased survival.

Cumulative percentage plots of times when disease again became evident following operation (treatment failures) revealed that those prepared from regional and local recurrences were almost identical in irradiated and control patients. Those from distant metastases demonstrated a slight delay in such lesions in control patients when compared with those irradiated.

As a consequence, it is concluded that this study to the present time has failed to clearly demonstrate the advantage of postoperative irradiation as an adjuvant to surgery in the treatment of operable breast cancer when considered in terms of disease free status and survival of patients. Observations of patients will continue to determine whether or not an advantage to irradiation occurs after a more prolonged follow-up.

Addendum

Administration of the National Surgical Adjuvant Breast Project was composed of:

Executive Committee. Bernard Fisher, M.D., Chairman, Pittsburgh; George E. Moore, M.D., Ph.D., Past Co-Chairman, Buffalo; Rudolf J. Noer, M.D., Past Co-Chairman, Louisville; Patrick J. Cavanaugh, M.D., Durham; Isidore Cohn, Jr., M.D., New Orleans; Lewis W. Guiss, M.D., Los Angeles; Edward F. Lewison, M.D., Baltimore; James J. Nickson, M.D., Chicago; Robert G. Ravdin, M.D., Philadelphia; Louis M. Rousselot, M.D., Washington, D. C.; Robert Robbins, M.D., Philadelphia.

Statistical Service. Roswell Park Memorial Institute, Buffalo; Irwin D. J. Bross, Ph.D., and Nelson H. Slack, Ph.D.

Radiotherapy Subcommittee. Juan A. del Regato, M.D., Colorado Springs; David L. Benninghoff, M.D., Brooklyn; Luther Brady, M.D., Philadelphia; Patrick J. Cavanaugh, M.D., Durham; Walter Murphy, M.D., Buffalo.

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University of Pittsburgh *	Bernard Fisher, M.D. Raul Mercado, M.D.
University of Puerto Rico	Luis A. Vallecillo, M.D. Victor Marcial, M.D.
University of Southern California *	Lewis W. Guiss, M.D. Frederic W. George, III, M.D.
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Discussion

Dr. Charles Eckert (Albany): [Slide] This slide shows our cumulative survival statistics for patients having postoperative irradiation therapy compared with those having radical mastectomy alone and the survival curves are almost identical. This study is in agreement with the results reported by Dr. Fisher and his co-workers.

Our numbers were not as great as in this large cooperative study; however, our study has some merit because although we did not classify our groups as finely as Dr. Fisher in trying to assess local recurrence, etc., choosing survival as our principal criterion of effectiveness, we did expend considerable effort to see whether the treated and control groups were indeed comparable. From this standpoint, we did find that for most of the parameters in which the prognosis of mammary cancer was based, they were indeed very similar. For this reason, we thought our results were valid.