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RADICAL IRRADIATION IN THE PRIMARY MANAGEMENT OF LOCALIZED BREAST CARCINOMA

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The role of radiation therapy in the management of breast carcinoma has undergone many changes over the last decade. Although in other countries, radiation therapy has played a major role in the primary management of patients with early breast carcinoma, it was rarely used in the USA except where surgery was refused or not possible. A number of articles have been published that show comparable survival to surgery when radiation is used as the primary treatment modality, not only for locally advanced breast neoplasm, but also for operable lesions, i.e. stages I and II (PORRITT 1964, WISE et coll. 1971, ATKINS et coll. 1972, FLETCHER 1972, MUSTAKALLIO 1972, PROSNITZ & GOLDENBERG 1975, FLETCHER et coll. 1976, LEVENE et coll. 1977, PROSNITZ et coll. 1977, SPITALIER et coll. 1977, ALPERT et coll. 1978, CALLE et coll. 1978). In these series, primary irradiation was given after either lumpectomy, partial mastectomy, incisional biopsy or needle biopsy.

The present report presents the results of the experience at this University Hospital in the use of radiation as the primary treatment for stages I–III breast carcinoma. Part of the data has been used in a previous report on the results of treatment for stage I and II lesions, based on data collected from 4 different institutions (PROSNITZ et coll.). The present data represent an update of the long term results of treatment and follow-up of the stage I–III cases.

Materials and Methods

The records of 119 patients with stage I–III breast carcinoma treated between August, 1956 and December, 1976 were reviewed. Six patients were excluded because of incomplete treatment records as well as one male patient, thus 112 females remained. The age range was 28 to 84 years, with both the median and mean age at 56. All patients had proven adenocarcinoma of the breast. Staging was done at the time of treatment; however, for the purpose of the present report, staging was done retrospectively using the TNM system of the Union Internationale Contre le Cancer (UICC). The distribution of these patients by stage appears in Table 1. In stage I and II patients, the pathologic specimen was obtained by needle, incisional, excisional biopsy or partial mastectomy; incisional biopsy being performed in 13 per cent (6/45) and needle biopsy in the same number. In stage III needle biopsy was done in 40 per cent and incisional biopsy in 43 per cent. Excisional biopsy, supraclavicular node biopsy and smear from an ulcerative lesion accounted for the rest of the histopathologic confirmation in this group.

Treatment was administered by megavoltage equipment to 92 per cent (103/112) of the patients.

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Table 1

Distribution of patients by stage

Stage I	
T1N0	17
Stage II	
T1N1	0
T2N0	19
T2N1	9
Subtotal	28
Stage III	
T2N2–3	5
T3N0–3	26
T4N0–3	36
Subtotal	67
Total	112

Between 1956 and 1958 9 patients were treated with 250 kV roentgen rays. Initially, the so-called five-field technique was used, wherein the breast was irradiated with opposing medial and lateral tangential fields; the internal mammary nodes with a single anterior field; the supraclavicular and axillary areas with opposing antero-posterior fields. In later years, the internal mammary, supraclavicular and axillary areas were included in a single 'hockeystick' shaped field and the axilla was boosted at midplane with a small posterior field measuring 6 cm × 6 cm to 8 cm × 8 cm. The medial tangential field overlapped the lateral border of the internal mammary field by 0.5 cm in order to minimize the cold spot on the chest wall at this junction. Wedges were used with the tangential fields when applicable to insure homogeneity of the dose to the breast and underlying chest wall. During the latter years of the period, the thickness of the breast and chest wall was measured by ultrasound to allow a more accurate calculation of the doses to these areas and underlying lung. Bolus was used during the first half of the treatment to raise the skin dose to at least 45 Gy. The dose to the internal mammary and supraclavicular nodes was calculated at 3 cm depth while the dose to the axilla was calculated at the midplane. The daily dose was 1.8 to 2 Gy at 5 fractions per week. If a treatment plan was done the dose was 1.8 Gy to the tumor volume which was included in the 90 per cent isodose. The treatment was interrupted for 1 to 2 weeks if moist skin reaction developed.

The distribution of the patients as to dose received is given in Table 2. The patients treated with 250 kV roentgen rays received doses of 40 to 50 Gy to the breast and lymphatic areas. Four of these 9 patients received a boost to their breast masses, 2 with 8 Gy and another 2 with 10 Gy each. All but one of the patients treated with megavoltage beams received a minimum dose of 50 Gy to the breast, chest wall and lymphatic areas. The mass or its site (in patients who had excisional biopsy or partial mastectomy) received a boost of 10 to 20 Gy. In most cases, the boost was given using megavoltage photons, with reduced tangential fields over the mass or excision site. Nine cases (3 stage I, 1 stage II, and 5 stage III) were boosted with a single field using 5 to 15 MeV electrons. Two patients had ^{192}Ir implants for the boost. The implant dose in each case was 30 Gy. The patients were usually given a 2-week break before the boost was given. Except for 3 stage III patients, all the other patients had no adjuvant chemotherapy or hormonal therapy. They were, however, placed on either treatment when they relapsed. In one patient oophorectomy was also carried out before the radiation therapy.

Results

All patients alive at the time of review had a median follow-up of 6 years. The longest follow-up was 19 years. Of those who died, adequate information was obtained as to the cause of death and the presence or absence of local or distant disease. One patient was lost to follow-up.

Local recurrence developed in 26 (23%) of the 112 patients. One (6%) of the 17 stage I patients developed local recurrence 2 years after treatment. This was associated with lung metastases. Of the 28 stage II patients, 4 (14%) developed local recurrence, 3 occurring within 3 years after treatment. One of these patients was cured by simple mastectomy and had no evidence of disease 2 years later. A fourth patient developed local recurrence 2 years after treatment.

The local recurrence in the stage I and II groups did not appear to be due to inadequate doses as all 5 patients had excision of the primary tumor and each received at least 50 Gy to the breast. This dose has been shown to be adequate for control of subclinical disease (FLETCHER 1972). The unfavorable effect of incomplete excision of the primary on local control of T1 and T2 lesions observed by LEVENE et coll., was not evident in the present series. In 12 patients with T1 or T2 lesions either needle or incisional biopsy was performed and not one developed local failure.

Table 2

Distribution of patients by total dose received

Stage	45 Gy or less	46–50 Gy	51–55 Gy	56–60 Gy	61–65 Gy	66–70 Gy	>70 Gy
I	–	2	1	2	1	10	1
II	1	5	2	5	1	14	–
III	4	9	6	9	4	34	1

Table 3

Local recurrence related to tumor size and nodal status in stage III patients

Stage	No. of patients	Local recurrence		Avg. time of recurrence
T2N2	4	2		8 months
T2N3	1	0	40%	
Subtotal	5	2		
T3N0	9	2		
T3N1	8	3		18.6 months
T3N2	6	1	27%	
T3N3	3	1		
Subtotal	26	7		
T4N0	7	4		
T4N1	14	3		16.8 months
T4N2	9	2	33%	
T4N3	6	3		
Subtotal	36	12		
Total	67	21	31%	16.1 months

Table 4

Incidence of distant metastases and time of occurrence of first metastatic lesion

Stage	No. of patients involved		Average time of first metastasis (months)
I	4/17	(24%)	48
II	9/28	(32%)	54.7
III			
T2N2–3	3/5	(60%)	19.5
T3N0–3	20/26	(77%)	20.6
T4N0–3	28/36	(78%)	14.2
Total stage III	51/67	(76%)	17.0

In the stage III group, 31 per cent (21/67) had local recurrence (Table 3). Most of the local failures were due to the advanced status of the primary lesion. As was observed in the stage I and II groups, all the local recurrences in the stage III patients occurred first at the primary site. Nodal status at diagnosis did not appear to influence the incidence of local recurrence. Doses of 60 to 70 Gy to the breast appeared to be inadequate in a majority of those patients who failed locally. Except for 2 patients who received 40 Gy with orthovoltage equipment and 2 others who received 50 Gy, the rest of the group with local failures received at least 60 Gy to the whole breast. Nine patients actually received 70 Gy to the area of primary lesion. Only 2 patients in the stage III group had mastectomy following radical irradiation because of a persistent mass. This operation did not prevent local recurrence in either case.

The average time interval from initial treatment to local recurrence for the stage III group was 16.1 months. The longest interval was 5 years. Seventy-one per cent of these patients died within one year from appearance of their recurrent lesions. All patients in this group had distant metastases at the time of local recurrence.

Table 4 shows the incidence of distant metastases in the 3 different stages in relation to the time of appearance of the first metastatic lesion. Distant metastases occurred earlier and with greater frequency in the patients with stage III disease than in the stage I and II patients. Bone and lung were the most common sites first involved by metastatic spread.

The acute and late complications observed appear in Table 5. Moist skin reaction developed in most patients although only a small number of those in the stage I and II groups had the reaction severe enough to cause interruption of treatment for a week or more. Severe skin reaction, however, was observed in 33 per cent (22/67) of the stage III cases.

The delayed complications centered mostly on the irradiated breast. Mild fibrosis usually developed at the junction of the tangential fields with the internal mammary and supraclavicular fields. Moderate fibrosis appeared at the site of lumpectomy, or the primary tumor if it was not resected. In 5 stage III cases, this localized fibrosis was suggested to be residual disease in the early follow-up period but this was ruled out on subsequent visits. Severe fibrosis involving the whole breast occurred in one stage II and one stage III patient. Breast atrophy which caused obvious asymmetry of the breasts was noted in 3 stage I, 3 stage II, and 10 stage III cases. Marked telangiectasia developed in patients who

Table 5

Acute and delayed complications of primary irradiation for breast carcinoma

	Stage			Total
	I	II	III	
Acute				
Moist skin reaction (requiring one week rest)	3	4	22	29
Dysphagia		3	3	6
Nausea/vomiting	1	4	3	8
Pneumonitis	1		1	2
Subtotal	5	11	29	45
Delayed				
Breast fibrosis				
Mild	3	6	3	12
Moderate		1	10	11
Severe		1	1	2
Breast atrophy	3	3	10	16
Telangiectasia	3	1	4	8
Breast pain		1	1	2
Breast edema	1			1
Breast abscess/cellulitis		1	1	2
Breast necrosis (skin)			1	1
Fat necrosis (breast)		1		1
Rib fracture		1	3	4
Frozen shoulder	1		2	3
Lung fibrosis (apex)		2	3	5
Nerve injury			1	1
Lhermitte's syndrome		1	1	2
Subtotal	11	19	41	71
Total	16	30	70	116

were treated with 250 kV roentgen rays. Other complications related to the breast in the form of pain, edema, abscess, cellulitis or skin necrosis occurred in individual cases. In these cases, there was no tumor in the breast when the complications occurred. These responded well to medical management. Asymptomatic rib fractures were observed on chest films of one stage II and 3 stage III cases with no evidence of disease. The relationship of these fractures to the radiation dose was unclear since the estimated dose received by the affected rib in these cases varied from 45 to 70 Gy. Asymptomatic apical fibrosis on the treated side was noted on the chest films of 2 stage II and 3 stage III patients. The 3 patients who developed a 'frozen' shoulder received from 40 to 50 Gy to the supraclavicular and axillary areas. These patients actually had very mild limitation of motion. Brachial plexus injury was suggested in a stage III patient who developed weakness and numbness of the right arm one year after treatment; no tumor was found on surgical exploration of the supraclavicular area. This patient had received 48 Gy to the supraclavicular area.

Two patients developed Lhermitte's syndrome 6 months and one year after irradiation, respectively. In both cases the internal mammary nodes had received 50 Gy/5 weeks with ^{60}Co at 3 cm depth through a single anterior field. The Lhermitte's syndrome disappeared after 3 to 6 months without serious sequelae.

The survival of these patients calculated by the life-table method (BERKSON & GAGE 1950) is shown in Figs 1 and 2. The cumulative 5-year survival for the stage I cases was 83 per cent and the 10-year survival was 62 per cent. Disease-free survival was 77 per cent at 5 years and 58 per cent at 10 years. The stage II group showed a cumulative survival of 82 and 74 per cent at 5 and 10 years, respectively. Disease-free survival was 77 per cent at 5 years and 70 per cent at 10 years. The longest survivor in this group is a 67-year-old patient who has remained disease-free 18 years after radiation therapy.

Combining the stage I and II patients, cumulative survivals of 82 per cent at 5 years and 70 per cent at 10 years were obtained. Disease-free survival of this combined group was 78 per cent at 5 years and 66 per cent at 10 years. The survival of stage III patients was quite dismal. Only 25 per cent were alive without disease after 5 years. Disease-free survival at 10 years was 5 per cent. Cumulative survivals of 31 per cent at 5 years and 8 per cent at 10 years were obtained. The median survival in this group was 20 months.

Discussion

Data concerning the effectiveness of radiation therapy as the primary modality in the curative management of early breast carcinoma continue to accumulate. Most of the published results were retrospectively obtained on patients who were irradiated because of medical contraindications to surgery, patient's refusal of surgery, or physician's preference. These reports showed 5-year survival rates of 65 per cent (PORRITT) and 95 per cent (FLETCHER et coll.) for early stage breast carcinoma. PETERS (1967) and CALLE et coll. reported 10-year survival rates of 44.5 and 51 per cent, respectively. In the present series 5- and 10-year disease-free survivals were 78 and 66 per cent, respectively, with stage I and II combined which compare well with the results men-

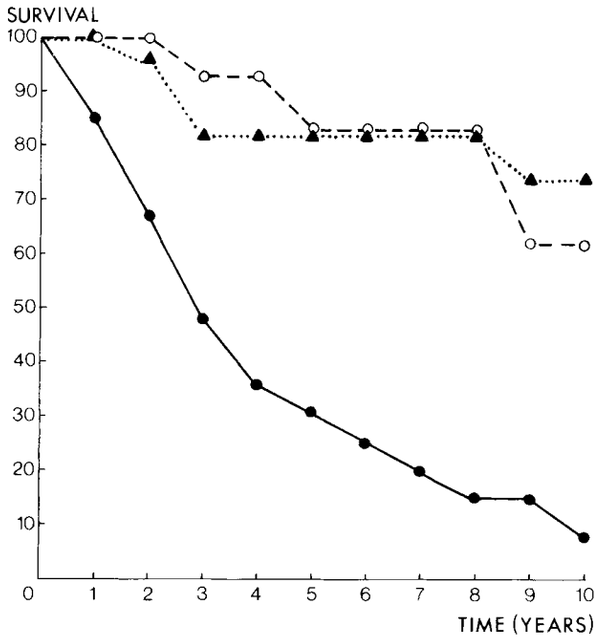

Fig. 1. Cumulative survival (in per cent) for patients stage I (○), stage II (▲) and stage III (●).

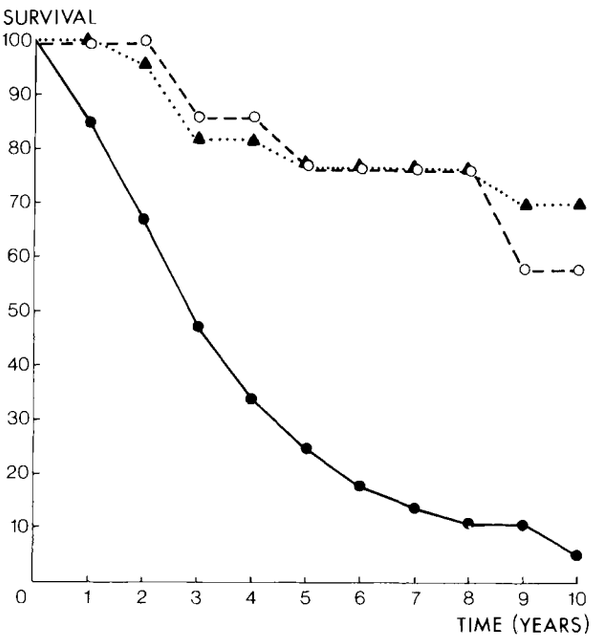

Fig. 2. Disease-free survival (in per cent) for patients stage I (○), stage II (▲) and stage III (●).

tioned. Despite these findings the shortcomings of a retrospective review are clear when compared with other equally uncontrolled series. Nevertheless, the results seem to support the contention that the conservative approach does not compromise the patient's chances of survival from this disease. Obviously, most of the doubts concerning the efficacy of the conservative approach would be cleared up only with well controlled randomized clinical trials comparing these procedures.

The randomized series of ATKINS et coll. comparing 'extended tylectomy' and radical mastectomy, both followed by irradiation, has shown comparable 10-year survival rates for stage I cases in both groups but for stage II cases, the survival was significantly lower with the 'extended tylectomy' group. Local recurrences were significantly higher in both stages I and II of this conservatively treated group, with most of the recurrences occurring in the axilla. In the stage II 'extended tylectomy' group the local recurrence rate was up to 70 per cent. This finding, in addition to the significant difference in survival between the 2 stage II groups has led to the termination of this part of the trial in favor of the radical mastectomy for stage II disease. However, it is well recognized that the radiation dose was much lower than what is currently considered optimum for local control of breast carcinoma (FISHER 1973, PROSNITZ & GOLDENBERG, FORREST 1977). To this effect, it appears that the results of that trial are less than conclusive concerning the superiority of radical surgery over 'extended tylectomy' for stage II disease. In a summary of the results of other retrospective reviews, PROSNITZ & GOLDENBERG showed better survivals and less local recurrences for stage II disease than that shown by ATKINS et coll. This was attributed to the use of higher radiation dosages. The present results with stage II cases support the observations made by PROSNITZ & GOLDENBERG and these parallel the findings of ATKINS et coll., using radical mastectomy and irradiation (Table 6).

In the stage III group, a 5-year disease-free survival of 25 per cent was observed. This compares well with the results of other authors (FLETCHER 1973, ZUCALI et coll. 1976, LEVENE et coll.), but it remains disappointingly poor. In the present series, the incidence of distant metastases was about the same with T3 and T4 lesions, although an earlier occurrence of metastases was apparent in the T4 group. A slightly higher local recurrence rate was also associated with T4 lesions. Since mastectomy after irradiation was performed in only 2 patients in this group, no conclusion could be drawn as to the effect of this added procedure to the control of the patients' disease. SPITALIER et coll. found that irra-

Table 6

Comparison of the present results using excision and irradiation with the results of Atkins et coll. using radical mastectomy and irradiation for stage II cases

Series	No. of patients	Local recurrence (per cent)	Distant recurrence (per cent)	Five-year survival (per cent)
Atkins et coll. (Radical mastectomy + irradiation)	80	15	30	70
This series (Excision + irradiation)	28	14	32	77

diation after mastectomy was ineffective in improving survival. However, FLETCHER (1973) and ZUCALI et coll. have observed a higher 5-year survival in patients with locally advanced carcinoma who had mastectomy carried out after irradiation. ZUCALI et coll. noted that radiation alone was able to sterilize only about 10 per cent of breast lesions on the histopathologic level. They observed that about half of their patients showed local or distant relapse within 2 years. They concluded that 'radiotherapy alone offers a satisfactory long-term control only in a minority of patients presenting with T3–T4 mammary carcinoma'. They recommended combination chemotherapy to supplement radiation therapy, with the purpose of controlling distant metastases which may even have started at the time of local treatment.

DE LENA et coll. (1978) made an investigation in the same institution as ZUCALI et coll., giving Adriamycin and Vincristine before radiation therapy and randomizing the patient to either maintenance chemotherapy or no further treatment after irradiation. They found that 82.7 per cent of patients who responded to induction chemotherapy obtained complete response after irradiation. Maintenance chemotherapy prolonged the median disease-free interval to 19 months versus 11 months for those who had no maintenance chemotherapy. This does not mean very much in a disease in which an 8-month difference in survival is of no consequence. Also, the incidence of distant metastases was not affected; thus the chemotherapy had no effect on the metastases which was the reason it was given. The 3-year survival in the present series was 52.8 per cent, which was similar to that obtained with irradiation plus surgery in the series of ZUCALI et coll. In effect, it appears that combination chemotherapy only achieved the results that were earlier observed with post-irradiation mastectomy. Since 24.3 per cent of the patients with maintenance chemotherapy still developed local recurrence, it may be speculated as to how much a subsequent mastectomy would have contributed to their local control. A randomized series to evaluate post-irradiation surgery or chemotherapy, or a combination, would be of interest.

The incidence of complications with radical irradiation varies from institution to institution. WISE et coll. reported 'virtually no complications' in their patients treated with local excision and irradiation. CALLE et coll. observed minimal and moderate sequelae of 28 and 27 per cent, respectively, in patients who had lumpectomy and irradiation. No severe sequelae were observed. Their patients given exclusive irradiation developed more severe sequelae then those who had lumpectomy and irradiation. Obviously, maintenance of a good cosmetic appearance of the irradiated breast is an important goal for most authors since this is one of the major reasons for advocating conservative surgery and irradiation over radical mastectomy. The general observation is that good cosmesis is maintained in at least 85 per cent of cases (LEVENE et coll., PROSNITZ et coll., CALLE et coll.). Conflicting observations exist as to the relationship of breast size to the cosmetic results. PROSNITZ et coll. suggested that large pendulous breasts would be more difficult to treat and would tend to develop fibrosis, resulting in poor cosmesis. ATKINS et coll. observed poor cosmetic results in patients who had large tumors and small breasts. The latter results are partly due to the removal of at least 3 cm of normal breast around the tumor. These findings obviously call for selection of the patients that would benefit best from this treatment.

In the present series, most of the complications related to the breast itself occurred in the stage III patients. This was probably due to the size of the

lesions, requiring wider fields to be given a higher dose. LEVENE et coll. made the same observation and suggested the use of interstitial implants after 40 Gy of external beam irradiation. In general, the complications in the present series were well tolerated and most of them responded to conservative treatment. Interestingly, no arm edema was observed in any of the patients who were disease-free. ATKINS et coll. noted slight lymphedema in 57 per cent of their patients in the 'extended tylectomy' group 15 months after treatment. They attributed this to the axillary irradiation. Since a considerable number of their patients had axillary recurrence, it may be questioned if some of the cases of lymphedema could have been due to persistent axillary disease rather than radiation-induced fibrosis.

There are many factors that need to be understood in the primary irradiation management of breast carcinoma. Just as there are many variations in the surgical procedures for this disease, different techniques are also utilized in radiation therapy (MANSFIELD et coll. 1979). A selective combined approach needs to be established in order to attempt to improve survival and decrease recurrences. This can be established through cooperation rather than competition among the different disciplines involved in the management of this puzzling disease.

SUMMARY

One hundred-twelve females with stage I–III breast carcinoma were treated primarily with radical megavoltage irradiation. The loco-regional area received 50 Gy/5 weeks with a boost to the primary site of 10 Gy/1 week to 20 Gy/2 weeks. Local control rates were as follows: 94 per cent in stage I, 86 per cent in stage II and 69 per cent in stage III. Survival rates were comparable to those reported by other authors. Complications correlated with disease stage and extent of radiation fields.

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