

Bulletin of the
**University of Minnesota Hospitals
and
Minnesota Medical Foundation**



**Role of X-Ray Therapy
In Breast Carcinoma**

BULLETIN OF THE
UNIVERSITY OF MINNESOTA HOSPITALS
and
MINNESOTA MEDICAL FOUNDATION

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I. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

March 6 - 12, 1949

No. 238

Sunday, March 6

9:00 - 10:30 Surgery Grand Rounds; Station 22, U. H.

10:30 - 11:00 Synoviomias; I. Ariel; Rm. M-109, U. H.

Monday, March 7

8:00 - Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; M-109, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:00 - 11:50 Roentgenology-Medicine Conference; Staff; Veterans Hospital.

11:00 - 11:50 Physical Medicine Seminar; Involvement in Polio; James Bosma; E-101, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.

12:00 - 1:00 Physiology Seminar; Subject to be announced; John J. Bittner; 214 M. H.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - 1:20 Pathology Seminar; Osteofibroma of the Mandible; J. C. Tam; 104 I. A.

12:30 - 1:30 Surgery Problem Case Conference; A. A. Zierold, C. Dennis and Staff; Small Class Room, Minneapolis General Hospital.

1:30 - 2:30 Surgery Grand Rounds; A. A. Zierold, C. Dennis and Staff; Minneapolis General Hospital.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

*4:00 - 6:00 Kellogg Lecture; Virus Infections of the Respiratory Tract; John H. Dingle, Western Reserve University, Cleveland, Ohio; Powell Hall Amph.

* Indicates special meeting. All other meetings occur regularly each week at the same time on the same day. Meeting place may vary from week to week for some conferences.

- 4:00 - Pediatric Seminar; Studies of Porphyria; Robert Aldrich; 6th Floor, Child Psychiatry, U. H.
- 5:00 - 5:50 Clinical Medical Pathologic Conference; Todd Amphitheater, U. H.
- 5:00 - 6:00 Urology-Roentgenology Conference; D. Creevy and H. M. Stauffer and Staffs; M-109, U. H.

Tuesday, March 8

- 8:00 - 9:00 Fracture Conference; Auditorium, Ancker Hospital.
- 8:30 - 10:20 Surgery Seminar; Anomalies of the Gallbladder and Bile Ducts; Frank E. Johnson; Small Conference Room, Bldg. I, Veterans Hospital.
- 9:00 - 9:50 Roentgenology Pediatric Conference; L. G. Rigler, I. McQuarrie and Staff; Todd Amphitheater, U. H.
- 10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and Robert Hebbel; Veterans Hospital.
- 12:30 - Pediatric-Surgery Rounds; Sta. I, Minneapolis General Hospital; Drs. Bosma, Wyatt, Chisholm, McNelson and Dennis.
- 12:30 - 1:20 Pathology Conference; Autopsies; Pathology Staff; 102 I. A.
- 1:00 - 2:30 X-ray Surgery Conference; Auditorium, Ancker Hospital.
- 2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans Hospital.
- *2:00 - 4:00 Kellogg Lecture; Chemotherapeutic Agents and Antibiotics; Wallace E. Herrell, Mayo Clinic; Todd Amphitheater, U. H.
- 3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.
- 3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans Hospital.
- 4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.
- 5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Todd Amphitheater, U. H.
- 5:00 - 6:00 X-ray Conference; Drs. Fink, O'Loughlin and Staff; Veterans Adm. Hospital; Powell Hall Amphitheater.

Wednesday, March 9

- 8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515, U. H.
- 8:30 - 9:30 Clinico-Pathological Conference; Auditorium, Ancker Hospital.
- 8:30 - 10:00 Orthopedic-Roentgenologic Conference; Edward T. Evans; Room 1AW, Veterans Hospital.
- 8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker and Joe R. Brown; Veterans Hospital.
- 11:00 - 12:00 Pathology-Medicine-Surgery Conference; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.

- 12:00 - 12:50 Radio-Isotope Seminar; Blood Volume and Tissue Volume Studies with Radio-Sodium and Radio-Chlorine; J. C. Wang; Rm. 212 Hospital Court, Temporary Bldg.
- 3:30 - 4:30 Journal Club; Surgery Office, Ancker Hospital.
- 4:00 - 5:00 Infectious Disease Rounds; Main Lecture Room, Minneapolis General Hospital.

Thursday, March 10

- 8:15 - 9:00 Roentgenology-Surgical-Pathology Conference; Craig Freeman and H. M Stauffer; M-109- U. H.
- 8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans Hospital.
- 9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-109, U. H.
- 10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.
- 10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans Hospital.
- 11:00 - 11:50 Urology Seminar; Urinary Incontinence; J. L. McKelvey; E-101, U. H.
- 11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.
- 11:30 - 12:30 Clinical Pathology Conference; Steven Barron, C. Dennis, George Fahr, A. V. Stoesser and Staffs; Large Class Room, Minneapolis General Hospital.
- 12:00 - 1:00 Physiological Chemistry Seminar; Chemistry of Streptomycin; Clay Branden; 214 M. H.
- 1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.
- 2:00 - 3:00 Errors Conference; A. A. Zierold, C. Dennis and Staff; Large Class Room, Minneapolis General Hospital.
- 4:00 - 5:00 Bacteriology and Immunology Seminar; 214 M. H.
- 4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.
- 5:00 - 6:00 X-ray Seminar; Presentation of Cases from Miller Hospital; Drs. Peterson and Miller; Todd Amphitheater.

Friday, March 11

- 8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.
- 9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.
- 10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.
- 10:30 - 11:20 Medicine Grand Rounds; Staff; Veterans Hospital.
- 10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.
- 11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, O. S. Wyatt, A. V. Stoesser and Staffs; Minneapolis General Hospital.

- 11:30 - 12:50 University of Minnesota Hospitals General Staff Meeting; Some Preliminary Findings from the Research Program on Cardiovascular Degeneration at the Laboratory of Physiological Hygiene; Ancel Keysl Powell Hall Amphitheater.
- 12:00 - 1:00 Surgery Clinical Pathological Conference; Clarence Dennis and Staff; Large Classroom, Minneapolis General Hospital.
- 1:00 - 1:50 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.
- 1:00 - 3:00 Pathology-Surgery Conference; Auditorium, Ancker Hospital.
- 1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.
- 4:00 - 5:00 Electrocardiographic Conference; George N. Aagaard; 106 Temp. Bldg., Hospital Court, U. H.

Saturday, March 12

- 7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; Station 20, U. H.
- 8:30 - 9:30 Surgery Conference; Auditorium, Ancker Hospital.
- 8:00 - 9:00 Pediatric Psychiatric Rounds; Reynold Jensen; 6th Floor, West Wing, U. H.
- 8:00 - 9:00 Surgery Literature Conference; Clarence Dennis and Staff; Minneapolis General Hospital, Small Classroom.
- 9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-101, U. H.
- 9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.
- 9:00 - 11:30 Surgery-Roentgenology Conference; Injuries of the Hand; Roscoe Webb; Todd Amphitheater, U. H.
- 9:00 - 12:00 Psychiatry Conference; Veterans Hospital Annex, Fort Snelling.
- 10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.
- 10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

II. CARCINOMA OF THE BREAST: AN ANALYSIS OF 626 CASES REFERRED FOR X-RAY THERAPY

Harvey W. Stone
Halvor Vermund

Introduction

Carcinoma of the breast represents one of the major problems in cancer management. Statistics reported by the Metropolitan Life Insurance Company covering the years 1936-1945 indicated that there were 19,197 deaths per year from this disease. This represented 11.2% of the total cancer mortality and about one-sixth of all cancer deaths among women. Cancer of the breast in females is second in frequency only to cancer of the uterus.

No great advances in the treatment of breast cancer were made until 1894 when Halstad¹⁴ published the first group of cases treated by radical mastectomy. In his group, 38.3% were free from recurrence or known metastases after 3 years. Following this, rapid strides were made in the surgical management of this disease. Later, radiation therapy assumed increasing importance, and now, it is being used extensively in inoperable cases, even though hormone therapy has most recently come into prominence in the treatment of certain far-advanced stages of breast cancer.

During the years of progress in the management of carcinoma of the breast, some principles have become generally accepted.

- (1) Early diagnosis and early radical treatment offers the best prognosis.
- (2) Radical surgery is the primary treatment of choice in operable carcinoma of the breast. This assumption has, however, been challenged by some investigators and the determination of operability of the tumor has been a much debated issue.

- (3) Radiation therapy is the treatment of choice in inoperable and recurrent carcinoma of the breast. In this group, there is evidence³³ that palliative therapy is of definite value in increasing the length of survival as well as relieving symptoms. Hormone therapy may also be used in certain selected cases of far-advanced breast cancer.

Radiation therapy was first used for carcinoma of the breast in the early part of this century. Since that time, many have strongly advocated, and others as strongly opposed, its use in operable breast cancer. In the United States, a swing towards more reliance on surgery in these cases has been noticed in the last few years. This has been particularly advocated by Haagensen^{10,11} at the Presbyterian Hospital, New York, and Simmons and Taylor^{29,30} at Boston. However, elsewhere, the swing has been in the opposite direction. McWhirter^{7,19} in Scotland advocates simple mastectomy followed by adequate post-operative irradiation. The reasoning here is that surgical trauma in the axilla leads to distant dissemination of tumor; therefore, since adequate irradiation can destroy tumor in axillary lymph nodes, radical surgery should not be used. At a few other centers (Keynes in England), radium and x-ray therapy without surgery has been used in an attempt to cure carcinoma of the breast.

Many^{10,11,21,22} who feel that radiation therapy has no place in the management of operable carcinoma of the breast argue as follows:

- (1) Adequate radical surgery has given better results in their material than surgery plus irradiation.
- (2) Pre-operative irradiation leads to needless delay of the curative surgical procedure. Metastases may occur during this delay.
- (3) Post-operative irradiation is useless as it fails to destroy tumor

cells, and, therefore is an unnecessary discomfort for patients.

Those^{5,13,19,24} who feel that radiation therapy is of definite value argue that:

- (1) Radical surgery plus adequate irradiation has given better results in their material than surgery alone.
- (2) Pre-operative irradiation destroys the sensitive cells and renders normal tissues less receptive to implantation. Surgery should follow within 2-3 weeks after x-ray therapy^{13,24}. A delay of more than 4-6 weeks leads to regrowth of the surviving tumor cells. Most of those who have obtained poor results with pre-operative irradiation have delayed surgery more than 6 weeks.
- (3) Adequate post-operative irradiation destroys remnants of tumor which may not have been removed at surgery. This reduces the number of local recurrences and increases the number of survivals.

We are in accord with those^{8,31} who feel that irradiation is of definite value in the treatment of operable carcinoma of the breast in which there is extension beyond the freely movable primary mass.

The Case for Irradiation in Operable Carcinoma of the Breast

The histologic changes in irradiated tumors have been well summarized by Halley and Melnick¹³. With specific reference to human breast tumors, these authors have drawn the following conclusions in cases given a pre-operative tumor dose ranging from 1200-4500 r by fractional methods followed by surgery 1-45 days after the end of treatment.

- (1) Irradiation by fractional methods produces, early, a simple radionecrosis of sensitive cells.
- (2) After 3 weeks, the tumor shows extensive radiation changes with

almost complete transition of the surviving tumor cells to large giant forms.

- (3) Further regrowth of surviving cells appears 4-6 weeks after the end of therapy. Therefore, the optimal time for surgery after pre-operative irradiation is 2-3 weeks.

Pfahler^{23,24} advocates the use of pre- and post-operative x-ray therapy. He states that pre-operative radiation tends to devitalize or destroy the more malignant types of cells and renders normal tissues less receptive to implantation. In support of the latter statement, he quotes Russ and Scott who exposed two opposing quadrants of a circle of skin in mice to irradiation (50-100% erythema dose), protecting the central portion. They then implanted malignant disease in the unexposed center; and in all instances, the tumor tissue grew only into the unirradiated areas. Pfahler further advocates post-operative therapy for the following reasons:

1. It destroys malignant cells that may have been transplanted during the operation.
2. It destroys microscopical remnant of cancerous tissue which the surgeon may have missed.
3. It renders normal tissue more resistant to cancerous growth.

He states, "It is our impression that remnants of cancerous tissue left behind are rendered more malignant and also more radiosensitive by the congestion and traumatism of operation. Since almost everyone recognizes that roentgen therapy is of value in the treatment of recurrent cancer, and since recurrent cancer is proof that cancer cells were left behind at the time of operation, it is reasonable to assume that the same irradiation given while the disease is only microscopic and the cancer cells not yet well nourished and adapted to their surroundings, will produce even a better chance of destroying the disease."

Engelstad⁵ states that the destruction of tumor cells in areas inaccessible to surgery, that is, in the supra-clavicular and deep fascial lymphatics, and lymphatics inside the chest wall is the most important task of irradiation. He feels that radiation therapy should be given post-operatively in one series and with large doses, for the following reasons:

1. Conditions are rendered favorable for an homogeneous irradiation with the largest possible doses.
2. Access is rendered easier to the very lymphatics that most need the radiation treatment and that are inaccessible to surgery.
3. Needless delay of the radical operation of a tumor that is only slightly radiosensitive, or even entirely radioresistant is avoided.

McWhirter^{7,19} reports a marked reduction in the incidence of recurrence and a definite increase in the 5-year survival rates when post-operative irradiation was added to the radical surgical treatment. In operable cases treated with radical surgery alone, the 5-year recurrence rate was 40% and the 5-year survival rate was 37%. Whereas, in operable cases treated with surgery and post-operative irradiation, the 5-year recurrence rate was 14% and the 5-year survival rate was 51%. He feels that the reduction in the recurrences when post-operative irradiation is used is related to the destruction of tumor not removed by radical surgery.

In the consideration of tissue reactions to irradiation, it is clear that a tumor dose could be delivered which could completely destroy the tumor in all individuals. However, due to the biologic variations of individuals, it is equally clear that doses smaller than this maximal dose may completely destroy all tumor cells in some individuals. Therefore, even if the maximal tumoricidal dose is not delivered, complete destruction of the small tumor remnants remaining after radical mastectomy may be accomplished in

some cases.

Materials

This study includes 626 cases of carcinoma of the breast referred for radiation therapy to the University of Minnesota Hospitals during the seven years from January 1, 1939 to December 31, 1945. The policy for patients treated surgically at the University Hospitals or elsewhere was to refer for irradiation only those with extension beyond a freely movable mass and particularly with proved axillary metastases. However, in the earlier years of this study (1939-1941), more cases without axillary metastases were given post-operative irradiation. (Table I)

Classification of patients

The classification of patients is one of the most important tasks in the statistical analysis of results in cancer studies. It is chiefly by this means that the results of therapy used at various centers can be compared. Unfortunately, no standardized clinical classification of carcinoma of the breast has been generally accepted. In addition, pertinent information necessary for the use of many of the classifications which have been suggested is often lacking. Therefore, we have used groupings which include as much of the clinical and pathological material as was available.

Table I indicates the classification of our patients into groups with the number referred for treatment each year during the period 1939-1945. There were 314 patients (50.1%) who were considered operable and were referred for post-operative deep roentgen therapy following surgery. Of this number, 195 patients (62.4%) had proved axillary metastases; and 50 patients (17.2%) were proved to be free of axillary metastases. Considering that 24 patients (7.6%) had had previous simple mastectomy and 45 patients (15.6%) had inadequate histopathologic examinations of the axillary contents, it seems likely that over 70% of our operable cases had

These groups are not to be confused with the classes used by other authors.

Table I

Classification of Patients in Groups with Number of Patients Referred for Treatment Each Year in the Period 1939-1945

Year	Group I	Group II	Group III	Group IV	Group V	Group VI	Group VII	Total
1939	10	32	9	2	21	28	3	105
1940	13	29	10	2	26	18	4	102
1941	12	27	10	8	21	19	4	101
1942	5	30	5	5	30	20	3	98
1943	4	23	6	5	25	17	3	83
1944	4	26	4	1	12	21	2	70
1945	2	28	1	1	14	19	2	67
Total	50	195	45	24	149	142	21	626
Percentage	8	31.1	7.2	3.8	23.8	22.7	3.4	100
	Operable: 314 or 50.1%							

Group I: This includes cases with carcinoma limited to the breast. Radical mastectomy was performed in all cases in this group, and the axillary contents proved negative to histologic examination. Post-operative deep roentgen therapy was started usually within 30 days after surgery. No evidence of recurrences or metastases were noted at the beginning of irradiation.

Group II: This includes cases of carcinoma of the breast with histologically proved axillary metastases. Radical mastectomy was performed in all cases, and deep roentgen therapy was started usually within 30 days after surgery. No recurrences or metastases were noted at the beginning of irradiation.

Group III: This includes cases of carcinoma of the breast in whom incomplete data concerning the histology of the primary lesion or the axillary contents were available. Radical mastectomy preceded post-operative therapy in all cases usually by more than 30 days. No recurrences or metastases were noted at the beginning of irradiation.

Group IV: This includes all cases of carcinoma of the breast treated by simple mastectomy followed by post-operative irradiation. Radical mastectomy was not performed because these patients were poor operative risks due to advanced age, heart disease, diabetes or other contraindications. Therapy was usually started more than 30 days after surgery.

Group V: This includes cases of carcinoma of the breast which were considered inoperable on the basis of local unresectability and/or distant metastases. This group includes 21 cases of inflammatory carcinoma of the breast. None of these patients had had any type of therapy previously. Treatment was palliative.

Group VI: This includes all cases of recurrences or distant metastases follow-

ing previous treatment. None of these cases had been previously treated by irradiation at the University Hospitals.

Group VII: This includes all bilateral double primary carcinoma of the breast.

axillary metastases. 149 patients (23.8%) were inoperable; 142 patients (22.7%) were treated for recurrent or metastatic disease; 21 patients (3.4%) had bilateral double primary carcinoma of the breast.

It is interesting to note the decrease in recent years in the number of patients without axillary metastases who were referred for x-ray therapy.

Sex and Age

In our series of 626 cases, 622 (99.3%) were females and 4 (0.66%) were males. Carcinoma in the male breast in our series is well within the range reported by others^{16,20,28}. Sachs²⁷ reports a range of 0.08-3.0% in the ratio of male to female breast carcinoma, with a mean average of 1.16%.

Table II

Age Incidence by Decades for 617 Patients with Carcinoma of the Breast

Age	Cases	Per Cent
20-29	4	0.65
30-39	63	11.0
40-49	153	25.0
50-59	153	25.0
60-69	148	24.0
70-79	86	14.0
80-89	9	1.45

Table II indicates the age incidence of carcinoma of the breast in our series divided into decades. Fifty per cent occurred between 40 and 59 years, and 88% occurred after the age of 40. The youngest patient was 25, the oldest, 83.

The incidence of carcinoma of the breast in our group between the ages of 40 and 49 (50%) is somewhat lower than that reported by Harrington¹⁵, 61% of 5,026 cases; and Schreiner and

Stenstrom²⁸, 58% of 563 cases. The incidence of cases over 40 (88%) agrees with Marshall and Forney²⁰ who report 90% of 300 cases over forty; but is higher than the figures given by Kaplan and Rosh¹⁶ who report 80% of 661 cases over 40, and Lewis and Reinhoff¹⁷ who report 81% of 950 cases over 40.

Signs and Symptoms

Table III indicates the symptoms noted by patients in our series. It is apparent that, in a vast majority of cases (81%), the first manifestation of breast cancer was a mass in the breast. Pain, as a first symptom was fairly uncommon (4.5%). It is interesting to note that the first sign in 14 cases (20.2%) was a mass in the axillary region. This is explained either by the fact that breast tissue may be misplaced in axilla; or by the fact that the primary breast tumor is too small to palpate and presents first as metastatic tumor in axillary lymph nodes. It is also interesting that in 16 cases there was diffuse swelling and in 18 cases there was local warmth and redness without a definite mass. Probably, a majority of these cases represented the acute inflammatory type of carcinoma of the breast. The other findings agree well with those noted by other authors^{10,15,20,25}

Table IV indicates the duration of carcinoma of the breast before surgery in 313 cases. The shortest duration before surgery was 1 day, the longest 20 years. Seventy-five per cent were treated within one year after onset, and almost one-fourth were delayed more than one year before surgery.

Pregnancy and Lactation

The occurrence of carcinoma of the breast during pregnancy or lactation

Table III

Signs and Symptoms

	Observed by Patient as First Symptom	
	No.	%
1. Mass in breast	508	81.
2. Pain in breast	28	4.5
3. Diffuse swelling of breast without definite mass	16	2.6
4. Mass in axilla	14	2.2
5. Redness of skin and local warmth	18	2.9
6. Retraction of nipple	10	1.6
7. Blood from nipple	7	1.1
8. Discharge from nipple	3	0.5
9. Erosion of nipple	3	0.5
10. Dimpling of skin	2	0.3
11. Ulceration	1	0.2
12. Lymphedema of arm	1	0.2
13. Mass in neck	1	0.2
14. Trauma	20	3.2

Table IV

Duration from Onset of Symptoms to Surgery: 313 Cases

Duration	No. Cases	%
Less than 1 week	15	4.8
1-4 weeks	53	16.9
1-3 months	62	19.8
4-6 months	49	15.8
7 months-1 year	57	18.3
More than 1 year	77	24.4
Total	313	100.

exerts an unfavorable influence on the prognosis^{6,11,15}. In our series, 10 cases (1.6%) occurred during pregnancy or lactation. Four cases were classified as inoperable (Group V) as all of these had inflammatory carcinoma of the breast. Two cases were recurrences following previous radical mastectomies, three were treated as operable cases with radical mastectomy followed by post-operative x-ray therapy, and one had a simple

mastectomy followed by post-operative x-ray therapy. All of these patients died within 2 years, except one who survived 4 years.

Haagensen and Stout¹¹ report on 29 cases of carcinoma of the breast developing during pregnancy. Twenty cases were treated by radical mastectomies with no permanent cures. Three, or 15%, were alive with disease after 5 years. These authors further state that 19 of 20 cases (95%) had axillary metastases. Harrington¹⁵ reports a similar experience with 78 cases: 84.8% had axillary metastases and only 7.7% survived 5 years.

However, Engelstad⁵ suggests that if these cases can be diagnosed early enough, the chance for recovery is not essentially different from other groups. He cites his experience with 24 cases of carcinoma of the breast developing during pregnancy and lactation, in which 10 cases (41.6%) were symptom-free over 5 years following radical mastectomy and post-operative irradiation. All 10 of these cases were classified in the operable group of which there were 13. No 5-year survivals were obtained from the 11 cases in the inoperable group.

Heredity

In our series, data related to the history of cancer in the family was available in 456 cases. Of this group, cancer of some type was reported in the family of 149 patients, a familial incidence of 33%. Carcinoma of the breast occurred in the family of 34 of these patients, an incidence of 7.4%. Other authors^{18,20,28} have reported similar figures.

Location

Carcinoma of the breast has been reported as occurring more commonly on the left^{25,28} and most frequently in the upper, outer sector^{11,25}. In our series, 290 occurred in the right breast, 315 in the left breast, and 21 were bilateral.

In a series of 57 cases treated exclusively at the University Hospitals by

radical mastectomy followed by post-operative irradiation between 1939 and 1942, the 5-year survival was determined as related to the location of the tumor in the breast. Of 22 patients having the primary tumor located in the medial aspects of the breast, 12 or 55% lived 5 years or more. In the remaining 35 cases with tumors located in the lateral aspects of the breast 17 or 49% survived 5 years or more. Although the series is small, these figures would tend to indicate no definite correlation between survival and the location of the tumor in the breast.

Histology

The classification of histological types of carcinoma of the breast followed that outlined by Bell². However, some of our reports were made by outside pathologists so that complete uniformity does not prevail. As seen in Table V, the great majority (298 cases or 75%) of tumors were scirrhous carcinomas.

Table V
Histology of 399 Breast Tumors

	<u>No.</u>
1. Scirrhous carcinoma	298
2. Adenocarcinoma	43
3. Medullary carcinoma	26
4. Gelatinous carcinoma	8
5. Comedo-carcinoma	7
6. Carcinoma simplex	6
7. Paget's carcinoma of the nipple	4
8. Undifferentiated carcinoma	3
9. Diffuse duct carcinoma	2
10. Papillary cystadenocarcinoma	2

No attempt was made to grade these tumors as to the degree of malignancy. Harrington¹⁵ states that his series indicates a much better survival for less histologically malignant tumors. Simmons, Taylor, and Welch²⁹ find that the poorer prognosis in women under 40 is related to the fact that they have tumors of higher degrees of malignancy. However, Daland⁴ states: "We were unable to demonstrate any longer life in un-

treated cases of lower than of higher malignancy."

Other Diseases and Malignancies

Second primary malignancies occurred in 21 patients (3.4%). Of these, 7 patients developed carcinoma of the uterus, 4 carcinoma of the stomach, and 1 carcinoma of the colon. Other malignancy neoplasms developed were hypernephroma, lymphosarcoma, basal cell carcinoma, malignant melanoma, etc. This does not include the group of double primary breast carcinoma. Pendergrass and Kirsh²⁰ report that 4.9% of 406 cases of carcinoma of the breast had a malignant neoplasm previously or developed one subsequently. These authors quote Warren and Ehrenrich who found multiple cancers in 6% of 3,907 cancer autopsies.

Diabetes mellitus was present in 6 cases, non-toxic goiters in 2 cases, hyperthyroidism in 4 cases, and myxedema in 2 cases in our series. Five patients had central nervous system syphilis, and one had leptic aortitis; one patient had diffuse neurofibromatosis one had pernicious anemia; and one had pulmonary tuberculosis. In addition, cardiovascular disease was prominent, but this is not surprising in view of the age group we are dealing with.

Metastases

Carcinoma of the breast may metastasize to practically any organ in the body. Frequent sites are given in Table VI. These include bones (212 cases), lungs and pleura (174 cases), liver (38 cases), and nervous system (21 cases). These findings are consistent with those of most other observers^{2,6,8,29}. Metastatic carcinoma to the opposite breast occurred in 21 cases (3.4%).

It is interesting to note that metastasis to the homolateral supra-clavicular lymph nodes is a relatively common occurrence (126 cases). Thirty-one of these cases occurred in the operable group subsequent to treatment

an incidence of 10% of 314 cases. Other lymph node areas involved include the mediastinum, contralateral supraclavicular area, and contralateral axilla. In addition, the site of metastasis was the eye in 2 cases and the cervix uteri in one case.

Table VI

Site of Metastases from Carcinoma
of the Breast: 626 Cases

Site	Incidence
Local recurrence (in treated area)	70
Supraclavicular lymph nodes (homolateral)	126
Lung and pleura	174
Bones	212
Skin	130
Nervous system	21
Liver	38
Opposite breast	21
Other lymph nodes	60
Other regions	19

The status of the axillary lymph nodes is one of the most important prognostic signs in operable carcinoma of the breast. Metastases occur in axillary nodes in 50-75% of cases in most series^{2,15,20,25}. In our analysis, we have utilized the 245 cases in Groups I and II in which there was histological examination of the axillary contents.

Table VII

Axillary Lymph Node Metastases in 245 Cases
of Carcinoma of the Breast: Groups I and II

Clinical	Cases	Histological			
		Positive		Negative	
		No.	%	No.	%
Axillary nodes palpable	111	106	95.5	5	4.5
Axillary nodes not palpable	87	55	63.5	32	36.5
Not stated	47	34	72.5	13	27.5
Total	245	195	79.5	50	20.5

metastases and to the wellknown occurrence of late recurrences^{2,6,30}. Survival was computed from the date of

Table VII presents an evaluation of the clinical appraisal of axillary lymph nodes. Axillary nodes were definitely palpable in 111 cases, and the great majority of these (106 cases or 95.5%) proved to have histological evidence of metastatic disease. In 5 cases (4.5%) palpable lymph nodes proved benign. However, of 87 cases where axillary nodes were not palpable, 55 cases (63.5%) were proved to contain metastases. Therefore, clinical appraisal was inaccurate in 30% (60 of 198 cases) of operable carcinomas of the breast. This is substantiated by Taylor and Bruce³² who found the clinical appraisal in error in 28% of cases, and by others^{10,22,29}.

Table VII also indicates that 195 or 245 cases (79.5%) in Groups I and II had axillary metastases proved histologically. All the operable Groups (I,II,III,IV) taken together constitute 314 cases of which 195 (62%) had proved axillary metastases. However, it is likely that if the number of axillary metastases in Groups III and IV could be definitely determined, the percentage of the operable groups with axillary metastases would be well over 70%.

Results

In this study, the term "survival" was used rather than "cure" to indicate the results of therapy. This was deemed advisable due to the difficulty of definitely determining the presence of

the first x-ray treatment here.

All 626 patients, except for 29

(4.6%) were followed up to 1947. Untraced patients were considered as dead from carcinoma of the breast on the date of the last follow-up. Patients dying of intercurrent diseases with no evidence of recurrence were counted as cancer deaths as the cause of death was not considered in this statistical analysis.

Operable cases: Table VIII presents the results in 50 cases in Group I treated post-operatively with x-ray therapy. 28 of 40 patients or 70% survived 5 years or more. Of this group, 23 patients were referred for radiation therapy after radical mastectomy at the University Hospitals, and 27 patients were referred to us by outside surgeons. It is apparent from the table that the numbers in this group have been reduced markedly in recent years.

It is concurrent with our feeling that surgery alone in this group can achieve results at least equal to that of surgery plus post-operative irradiation. Adair¹ reported a 5-year survival of 74.2% in cases without axillary metastases treated by surgery alone. Cade³ and others^{10,23,29} substantiated these observations.

Table IX presents the results in 130 cases in Group II treated by post-operative irradiation following radical mastectomy at the University Hospitals: 33 of 78 patients or 42% survived 5 years or more. Table X indicates the results in 65 patients previously operated upon by surgeons outside the University Hospitals: 13 of 40 patients or 33% survived 5 years or more. The improvement in 5-year survival in the series oper-

Table VIII

Survival of Patients in Group I with Carcinoma of the Breast without Axillary Metastases by Histological Examination of Specimen Removed by Radical Mastectomy and No Other Signs of Metastases, Treated by Irradiation Following Radical Surgery. The Entire Group.

Year	No. of Cases	Number of Years							
		1	2	3	4	5	6	7	8
1939	10	10	10	7	7	6	5	5	5
1940	13	13	12	12	12	11	10	7	
1941	12	11	10	10	8	8	7		
1942	5	5	5	4	4	3			
1943	4	4	4	3	3				
1944	4	4	3	2					
1945	2	2	2						
Total	50	50	50	48	44	40	35	23	10
Living		49	46	38	33	28	22	12	5
Percentage Living		98	92	79	75	70	63	52	50

ated at the University Hospitals may be related to more complete surgery; or, to the fact that the great majority of patients (72%) operated at the University Hospitals were started on post-

operative therapy usually 10-14 days after surgery; whereas, of those operated by outside surgeons, 56% were started on radiation therapy more than 30 days after operation.

Table IX

Survival of Patients in Group II with Carcinoma of the Breast Treated Postoperatively by Irradiation Following Radical Mastectomy at the University Hospitals.

Year	No. of Cases	Number of Years					
		1	2	3	4	5	6 or more
1939	22	22	17	14	13	11	10
1940	26	22	17	16	13	12	12
1941	15	12	10	8	5	4	4
1942	15	15	9	8	7	6	
1943	13	11	11	8	7		
1944	21	17	13	10			
1945	18	16	13				
Total	130	130	130	112	91	78	63
Living		115	90	64	45	33	26
Percentage Living		89	69	57	49	42	41

Table X

Survival of Patients in Group II with Carcinoma of the Breast Treated Postoperatively by Irradiation Following Radical Mastectomy Outside the University Hospitals.

Year	No. of Cases	Number of Years					
		1	2	3	4	5	6 or more
1939	10	10	9	5	4	4	4
1940	3	3	3	1	1	1	0
1941	12	10	7	5	4	4	3
1942	15	15	12	9	8	4	
1943	10	10	8	7	6		
1944	5	5	5	4			
1945	10	9	5				
Total	65	65	65	55	50	40	25
Living		62	49	31	23	13	7
Percentage Living		95	75	56	46	33	28

Table XI covers all the cases in Group II (195 cases): 46 of 118 patients or 39% survived 5 years or more. In this group, 2 patients treated in 1939 and 1941, respectively, were well when last seen 2 and 3 years, respectively, after treatment. In addition, 2 patients treated in 1940 died of heart disease with no evidence of recurrence after less than 1 year survival; one treated in 1941 died after 1 year of a stroke; and the last,

treated in 1942, died after 3 years of chronic myelogenous leukemia with no evidence of recurrence at autopsy. If these patients were excluded from the statistics the five-year survival would increase to 41%. This compared favorably with statistics offered by Cade³; 29% 5-year survivals after surgery alone and 35% 5-year survivals after surgery plus postoperative irradiation. Gylstorff-Peterson⁹ obtained 27% 5-year survivals in 340 cases with surgery

and post-operative irradiation. Haagen-
sen¹⁰ reported 28.2% 5-year survivals
in 154 patients treated with surgery
alone; and 36% 5-year survivals in 143
patients treated with surgery and post-
operative irradiation.* Stenstrom
and Baggenstoss³¹ state that post-
operative radiation therapy has consist-
ently improved the results in carcinoma
of the breast with axillary metastases.
These authors obtained 41% 5-year sur-
vival in 110 patients with proved axil-

lary metastases. Engelstad⁵ reported
52.8% 5-year survivals in 494 patients
with the use of post-operative irradia-
tion.

The survival of all patients in Groups
I and II operated at the University Hos-
pitals is shown in Table XII: 48 of 98
patients or 49% survived 5 years or more.
In these groups, operated outside the
University Hospitals, 26 of 60 patients
or 43% survived 5 years or more.
Table XIII.

Table XI

Survival of Patients in Group II with Carcinoma of the Breast and Axil-
lary Metastases proven by Histological Examination of Specimens Removed
by Radical Mastectomy, But with No Other Signs of Metastases. Treated
by Postoperative Irradiation Following Radical Surgery. The Entire Group.

Year	No. of Cases	Number of Years							
		1	2	3	4	5	6	7	8
1939	32	32	26	19	17	15	14	12	9
1940	29	25	20	17	14	13	12	7	
1941	27	22	17	13	9	8	7		
1942	30	30	21	17	15	10			
1943	23	21	19	15	13				
1944	26	22	18	14					
1945	28	25	18						
Total	195	195	195	167	141	118	88	61	32
Living			177	139	95	68	46	33	19
Percentage Living			91	71	57	48	39	38	31

Table XII

Survival of Patients in Group I and II Treated by Postoperative Irra-
diation Following Radical Mastectomy at the University of Minnesota.

Year	No. of Cases	Number of Years							
		1	2	3	4	5	6	7	8
1939	29	29	24	20	19	16	14	13	12
1940	33	29	24	23	20	19	18	12	
1941	19	16	13	11	7	6	6		
1942	17	17	11	9	8	7			
1943	15	13	13	9	8				
1944	22	18	14	11					
1945	18	16	13						
Total	153	153	153	135	113	98	81	62	29
Living			138	112	83	62	48	38	25
Percentage Living			90	73	61	55	49	47	40

*These are the corrected figures for 5-year survival given by Stenstrom
and Baggenstoss³¹.

Table XIII

Survival of Patients in Group I and II Treated by Postoperative Irradiation Following Radical Mastectomy Outside the University Hospitals.

Year	No. of Cases	Number of Years							
		1	2	3	4	5	6	7	8
1939	13	13	12	6	5	5	5	4	2
1940	13	13	12	10	8	8	7	2	
1941	17	14	11	9	8	8	5		
1942	17	17	14	11	10	5			
1943	12	12	10	9	8				
1944	8	8	7	5					
1945	12	11	7						
Total	92	92	92	80	72	60	43	26	13
Living		88	73	50	39	26	17	6	2
Percentage Living		96	79	63	54	43	40		

Table XIV

Survival of Patients in Group III with Carcinoma of the Breast Having Incomplete or no Record of the Pathological Diagnosis Treated by Postoperative Irradiation Following Radical Mastectomy, All Operated Outside University Hospitals.

Years	No. of Cases	Number of Years							
		1	2	3	4	5	6	7	8
1939	9	6	5	5	5	4	4	3	1
1940	10	9	8	7	6	5	4	0	
1941	10	8	7	5	5	3	0		
1942	5	4	4	3	3	2			
1943	6	6	4	2	1				
1944	4	4	4	4					
1945	1	0							
Total	45	45	45	44	40	34	29	19	9
Living		37	32	26	20	14	8	3	1
Percentage Living		82	71	59	50	41	28	16	11

Table IV reveals the results in those cases where inadequate pathological reports were available but who had operable carcinoma of the breast (Group III). In this group of 45 patients, 14 of 34 (41%) survived 5 years or more. This parallels the results in Group II so closely that it is likely that most, if not all, of these patients had axillary metastases. The results in Group IV (24 patients) are shown in Table XV: 10 patients (59%) of 17 survived 5 years

or more. In this group, simple mastectomy rather than radical mastectomy was performed because of advanced age or poor general condition of the patient, not because of inoperability of the lesion.

The results in the entire operable group (314 cases) are summarized in Table XVI: 98 of 209 patients or 47% survived 5 years or more. This is somewhat lower than the figure obtained by

Table XV

Survival of Patients in Group IV with Carcinoma of the Breast Treated with Simple Mastectomy and Postoperative Irradiation

Year	No. of Cases	Number of Years							
		1	2	3	4	5	6	7	8
1939	2	2	1	1	1	1	0	0	0
1940	2	2	1	1	1	1	1	1	
1941	8	7	6	6	6	5	4		
1942	5	4	4	3	3	3			
1943	5	5	4	3	2				
1944	1	1	1	0					
1945	1	1	1						
Total	24	24	24	23	22	17	12	4	2
Living		22	18	14	13	10	5	1	0
Percentage Living		92	75	61	59	59			

Gratzek and Stenstrom⁸ in a previous study at this institution: 129 cases (51%) of 254 survived 5 years or more. Engelstad⁵ obtained a 5-year survival of 63% in 768 operable cases treated with surgery plus post-operative irradiation.

Inoperable cases: In this group of 149 cases (Group V) only 4 of 98 patients or 4% survived 5 years or more (Table XVII). In further breaking down this

group, 84 cases had distant metastases and only 1 of these survived 5 years; 7 cases were inoperable on the basis of poor general condition and none survived more than 3 years; 37 were locally inoperable and 3 of these survived more than 5 years (6,7,7 years (6,7,7 years respectively): 21 were acute inflammatory carcinomas and none lived over 3 years.

Table XVI

Survival of Patients in Groups I, II, III and IV with Operable Carcinoma of the Breast without Distant Metastases Treated with Postoperative Irradiation Following Surgery

Year	No. of Cases	Number of Years							
		1	2	3	4	5	6	7	8
1939	53	50	42	32	30	26	23	17	15
1940	54	49	41	37	32	30	27	15	
1941	57	48	40	34	28	24	18		
1942	45	43	34	27	25	18			
1943	38	36	31	23	19				
1944	35	31	26	20					
1945	32	28	21						
Total	312	312	312	282	247	209	164	107	53
Living		285	235	173	134	98	68	32	15
Percentage Living		91	75	61	54	47	41	30	28

Table XVII

Survival of Patients in Group V - Entire Group
Consisting of Inoperable Patients Treated for Palliation Only

Year	No. of Cases	Number of Years							
		1	2	3	4	5	6	7	8
1939	21	9	4	2	1	0			
1940	26	14	8	7	4	4	3	2	
1941	21 ^x	7	4	1	1	0			
1942	30	13	8	5	4	0			
1943	25 ^x	8	1	0					
1944	12	6	4	0					
1945	14	4	2						
Total	149	149	149	135	123	98	68	47	21
Living		61	31	15	10	4	3	2	0
Percentage Living		41	21	11	8	4	4	4	0

^x 1 male

Recurrent and Metastatic Cases

In this group of 142 cases (Group VI) 12 of 85 patients or 14% survived 5 years or more (Table XVIII). Local recurrence was treated by irradiation only in 56 patients: 5 of 39 patients or 13% survived 5 years or more. In 20 patients, the local recurrence was removed surgically followed by irradiation: 3 of 5 patients lived 5 years or

more. Sixty-six patients had distant metastases and were treated by irradiation to symptomatic areas: 3 out of 40 patients survived 5 years or more. In the entire group, the average minimal duration of the tumor before the first treatment here was 3.8 years. Therefore, it seems probable that the 2-year survival of 36% we obtained would be equivalent to the 5-year survival of these patients from onset of symptoms.

Table XVIII

Survival of All Recurrent Cases Treated with Irradiation
At the University of Minnesota: Group VI

Year	No. of Cases	Number of Years							
		1	2	3	4	5	6	7	8
1939	28	12	8	7	4	4	3	2	0
1940	18	11	6	5	4	4	3	3	
1941	19	8	3	3	2	2	2		
1942	20	17	11	7	6	2			
1943	17	10	9	9	7				
1944	21	12	7	4					
1945	19	10	7						
Total	142	142	142	123	102	85	65	46	28
Living		80	51	35	23	12	8	5	0
Percentage Living		56	36	28	23	14	12	11	0

Bilateral Breast Cancer

Twenty-one patients or 3.4% of the entire group had bilateral double primary carcinoma of the breast (Group VII). Eight cases occurred simultaneously. Three patients in this group had bilateral radical mastectomy followed by post-operative irradiation: one lived 5 years and died of metastases, and the others died after one year. Four patients received irradiation only to both breasts and none survived more than 3 years. One patient had bilateral simple mastectomy followed by irradiation in 1944; this patient was well on the last follow-up in 1948.

Thirteen patients developed carcinoma in the second breast at a later date. Eleven patients in this group had had previous radical mastectomies, and 6 were again subjected to radical mastectomy for the second primary breast carcinoma followed by postoperative irradiation. The survivals after the first and second operations were as follows: Case 1, 16 and 5 years; Case 2, 7 and 4 years; Case 3, 15 and 0 years; Case 4, 5 and 4 years; Case 5, 6 and 1 years; Case 6, 5 and 0 years. Two patients are still living and well 4 years after treatment of the second primary.

Five of the eleven patients with previous radical mastectomy were considered inoperable when seen with the second breast cancer. Simple mastectomy followed by irradiation in 2 cases and irradiation alone in 3 cases were the methods of treatment. The survivals from the first operation and from the second operation or the start of x-ray therapy were as follows: Case 1, 2 and 0 years; Case 2, 6 and 1 years; Case 3, 1 and 0 years; Case 4, 2 and 1 years; Case 5, 3 and 0 years. None of these patients survived more than one year from the treatment of the second primary.

In addition, two patients had had a previous simple mastectomy and were now treated by radical mastectomy plus postoperative irradiation for the second primary. Survival from the two series

of treatments was as follows: one case, 8 and 1 years (this patient is alive and well); one case, 10 and 2 years (this patient was last seen in 1946).

The time interval between the first and second primary breast tumors shows a wide range of variation. Six patients developed second primaries within 3 years; 5 patients between 5-8 years; one within 11 years and one within 13 years. Great difficulty may be encountered in differentiating primary from metastatic disease in the second breast. However, the absence of local recurrences and distant metastases will usually make the differential diagnosis apparent.

All Groups

Table XIX summarizes the entire series of 626 cases of carcinoma of the breast, irrespective of the stage of the disease, referred for x-ray therapy to the University Hospitals. One hundred and twenty patients out of 406 or 30% survived 5 years or more. In the previous study at this institution⁸, very similar results were obtained: 158 of 587 patients or 27% survived 5 years or more. Engelstad⁵ reports a 5-year survival of 37.8% (520 of 1377 patients) in his entire group.

A further study of 153 operable cases in Groups I and II treated by radical mastectomy and x-ray therapy exclusively at the University Hospitals was made to evaluate the results using Haagensen's^{11, 12} criteria of operability. According to these criteria, all cases of carcinoma of the breast whose general physical condition permits major surgery, whatever their age, and even though the lesion is bilateral, should be treated by radical mastectomy except:

1. When the tumor develops during pregnancy or lactation.
2. When inflammatory carcinoma of the breast is present.
3. When there is extensive edema over the breast (more than one-third of skin affected).
4. When there are satellite tumor nodules in or beneath the skin over the breast or adjacent chest wall.

5. When there are intercostal or parasternal tumor nodules.
6. When there is edema of the arm.
7. When there are any two or more of the following signs of locally advanced breast carcinoma:
 - a. Ulceration of the skin.
 - b. Edema of the skin over the breast of limited extent (less than one-third of the skin affected).
 - c. Fixation of the tumor to the chest wall.
 - d. Fixation of the axillary lymph nodes to the skin or the deeper structures of the axilla.
 - e. Axillary lymph nodes measuring 2.5 cm. or more in transverse diameter.
8. Proved or clinically unquestionable supraclavicular metastases.
9. Distant metastases to contralateral axilla, lungs, bones, liver, or elsewhere.

Haagensen¹² stated that if these criteria had been rigidly followed in their series of 640 radical mastectomies, 109 of the patients would not have been operated upon. Yet the number of patients permanently cured would not have decreased by a single one.

In our series of 153 cases, 95 (62%) were classified as operable (Table XX) according to Haagensen's criteria. Of these, 38 patients out of 63 or 60% sur-

Table XIX

Survival of All 626 Patients with Carcinoma of the Breast Treated with Irradiation Therapy at the University of Minnesota

Year	No. of Cases	Number of Years							
		1	2	3	4	5	6	7	8
1939	105	74	57	43	36	31	27	20	16
1940	102	77	58	52	43	41	35	21	
1941	101	66	47	38	31	26	20		
1942	98	76	61	41	37	22			
1943	83	57	44	34	27				
1944	70	51	39	28					
1945	67	43	30						
Total	626	626	626	559	489	406	308	207	105
Living		444	336	236	174	120	82	41	16
Percentage Living		71	54	42	36	30	27	20	15

vived 5 years. Twenty patients (13%) were classified as inoperable. (Table XXI) Of these, 4 out of 14 patients or 28% survived 5 years or more (one 8 years and two, 7 years). In thirty-eight (25%) insufficient data was available for adequate classification. (Table XXII) However, the survival in this latter group was identical (6 patients of 21 or 28%) to that of the inoperable group. Adding the last two groups together, the result is that 10 patients of 35 or 28% survived 5 years or more.

Recurrences in Operable Cases.

The numerical incidence of local recurrences and distant metastases is shown

in Table XXIII. The total number developing local recurrences and distant metastases is 160 of 314 patients (51%). Local recurrence in the operative site (i.e., anterior chest wall and axilla) was noted in 45 instances or 14.3% of 314 cases. Recurrences in the various groups was as follows: 6 of 50 cases (12.0%) in Group I; 30 of 195 cases (15.4%) in Group II; 7 of 45 cases (15.4%) in Group III; and 3 or 24 cases (12.5%) in Group IV. Recurrences occurred in the skin of the operative site in 18 patients; in the scar in 17 patients; and in the axillary area in 20 cases. It is interesting that, up to 1942, the recurrence rate was 18.5% (33 recurrences in 173 patients,

Table XX

Survival of Patients in Groups I and II with Carcinoma of the Breast Considered Operable by Haagensen's Criteria Treated with Postoperative Irradiation Following Radical Mastectomy at the University Hospitals

Year	No. of Cases	Number of Years							
		1	2	3	4	5	6	7	8
1939	19	19	17	15	15	12	11	10	9
1940	20	19	15	15	15	15	14	10	
1941	10	10	9	9	6	5	5		
1942	14	14	9	7	6	6			
1943	6	6	6	6	6				
1944	13	11	10	9					
1945	13	13	11						
Total	95	95	95	82	69	63	49	39	19
Living			92	77	61	48	38	30	20
Percentage Living			97	81	74	70	60	61	51

Table XXI

Survival of Patients in Groups I and II with Carcinoma of the Breast Considered Inoperable by Haagensen's Criteria Treated Post-operatively by Irradiation Following Radical Mastectomy at the University of Minnesota

Year	No. of Cases	Number of Years							
		1	2	3	4	5	6	7	8
1939	4	4	3	3	2	2	1	1	1
1940	6	4	4	4	2	2	2	2	
1941	3	3	2	1	0	0	0		
1942	1	1	0	0	0	0			
1943	1	0	0	0	0				
1944	3	3	2	2					
1945	2	1	1						
Total	20	20	20	18	15	14	13	10	4
Living			16	12	10	4	4	3	1
Percentage Living			80	60	56	27	28	23	25

Since 1942 with the use of slightly greater total x-ray dose to the anterior breast region, the recurrence rate has fallen to 7.5% (7 recurrences in 92 patients). This compared favorably with Haagensen's personal series of carefully selected cases in which the recurrence rate was 12.5% (12). In a previous publication by Haagensen¹⁰, the

recurrence rate had been 22.8%. Rodman²⁶, using radical mastectomy alone, reports only 2.2% local recurrences in 132 cases. He cites the recurrence rates obtained by White as 22.6% and Lewis and Reinhoff as 19.6% without post-operative radiation.

Table XXII

Survival of Patients in Group I and II with Carcinoma of the Breast Indeterminable Due to Incomplete Information as to Haagensen's Criteria, Treated Post-operatively by Irradiation Following Radical Mastectomy at the University of Minnesota

Year	No. of Cases	Number of Years							
		1	2	3	4	5	6	7	8
1939	6	6	4	2	2	2	2	2	2
1940	7	6	4	4	3	2	2	0	
1941	6	3	2	1	1	1	1		
1942	2	2	2	2	2	1			
1943	8	7	7	3	2				
1944	6	4	2	0					
1945	3	2	1						
Total	38	38	38	35	29	21	19	13	6
Living		30	22	12	10	6	5	2	2
Percentage Living		79	58	34	34	28	26	15	

Table XXIII

Site of Metastases and Recurrences Developed After Treatment of 314 Operable Patients

	Operated at University Hospitals (153 cases)	Operated Outside (161 cases)	Total
Total recurrences and distant metastases			160
Local recurrence in operative site			45
Local recurrence in treated area of skin	9	9	18
Local recurrence in scar after operation	7	10	17
Local recurrence in homolateral axillary nodes	10	10	20
Local recurrence in homolat. supracl. nodes	17	14	31
Local recurrence in homolat. cervical nodes	5	3	8
Recurrence in contralateral axillary nodes	3	3	6
Recurrence in contralateral supracl. nodes	2	1	3
Recurrence in contralateral cervical nodes	3	0	3
Recurrence in skin outside treated area	3	2	5
Recurrence in opposite breast	5	3	8
Distant metastases: Bones	39	26	65
Lungs and mediastinum	20	22	42
Pleural effusion	13	13	26
Nervous system	5	3	8
Liver	6	9	15
Other organs	5	10	15
Recurrence without definite statement of location		2	2

Technique of Therapy

1. Postoperative Irradiation in Operable Cases: Postoperative therapy was as a rule started within 30 days in patients operated at the University Hos-

pitals (usually 10-14 days) and after 30 days in patients operated on outside.

a. 1939-1942: 200 KVP., 30 ma., 0.25 mm. Cu and 1 mm. Al filter (H.V.L.)

0.6 mm. Cu), focal skin distance 70 cm. The field included the anterior breast region, anterior supraclavicular, cervical and axillary regions, the midline medially and the inferior end of the mastectomy scar. The dose was 200 r (in air), given every other day for 6 treatments (total 1200 r in air) - delivering about 1800 r to the skin over a period of around 14 days.

In addition, the axilla and the supraclavicular regions were given from 200-600 r in air to an anterior field and from 600-900 r in air to a posterior field with 0.5 mm. Cu and 1 mm. Al filter (H.V.L. 0.9 mm. Cu) at 60 cm. F.S.D. over the same period of time, 300 r in air being given to each field at a time and the supraclavicular and axillary regions being treated separately and alternately.

b. 1942: 140 KVP with 0.25 mm. Cu and 1 mm. Al filter (H.V.L. 0.56 mm. Cu) was used for the large anterior breast field at 70 cm. target skin distance and the other fields were treated with 220 KVP with 0.5 mm. Cu and 1 mm. Al filter (H.V.L. 1.35 mm. Cu) at 60 cm. focal skin distance. The same doses were given over the same period of time.

c. Since 1942 additional treatments to tangential, medial and lateral fields of the anterior chest were given using 220 KVP 0.5 mm. Cu and 1 mm. Al (H.V.L. 1.3 mm. Cu) at 60 cm. F.S.D. and giving 300 r in air to each field. The dose to the axilla and supraclavicular regions was also somewhat increased up to 1200 r in air to the posterior fields - later the anterior fields to the axilla and supraclavicular regions were omitted except in heavy patients.

2. Inoperable Cases: In this group of patients the involved breast was treated in quadrants with the beam directed tangentially through the

breast. The breast is divided into a superior, inferior, medial and lateral triangular quadrant, and the patient placed in such a position as to minimize the amount of radiation striking the lung parenchyma. The anterior supraclavicular region is included in the upper breast quadrant and the axilla in the lateral quadrant. In some obese patients the supraclavicular field was treated separately. Each field was treated by the fractional dose method so that the total dose to each field amounted to between 1000 and 1500 r (in air) with 200-300 r (in air) as the maximum daily dose to one quadrant. The posterior axilla and supraclavicular areas received supplementary treatment with 600 to 1200 r (in air) each. The factors used were 200-220 KVP 60 cm. F.S.D. 0.5 mm. Cu + 1 mm. Al filter (H.V.L. 0.9 and 1.3 mm. Cu).

3. Recurrent and Metastatic Cases: No routine method of treatment was used in these cases, and the great majority was treated for palliation only. Local recurrent skin nodules were often treated with soft irradiation 100-140 KVP with 0.25 mm. Cu + 1 mm. Al or without filter, the size of the field being limited to the recurrent lesions. The bone metastases were treated for relief of pain and the amount of irradiation differed in each individual case depending on the subjective effect of the therapy. On the average 1000 tissue roentgens were given. Very rarely irradiation therapy was applied to metastases in central nervous system and lymphogenous metastases of the lungs.

Complications of Treatment

Lymphedema of the arm and lung fibrosis are commonly mentioned complications of x-ray treatment in carcinoma of the breast. In our series 41 cases or 6.7% developed lymphedema of the arm. Of these, 20 patients were in the inoperable groups and 21 were in the operable groups. Four cases had edema before x-ray therapy. Pendergrass and Kirsh²² report lymphedema in 34 or 18%

of operated cases who received radiation and in 25 or 16% of those who did not receive radiation. It seems likely that this was due to surgery, not radiation.

Pulmonary fibrosis is very frequently difficult to distinguish from lymphogenous pulmonary metastases. In our series, 37 cases or 6% had x-ray evidence of pulmonary fibrosis after radiation treatment. Very few of these patients noticed any symptoms.

Summary

1. A brief review of the literature on carcinoma of the breast is presented. A lack of standardization of treatment in operable cases is noted.
2. Six hundred and twenty-six patients with carcinoma of the breast were referred for deep roentgen therapy to the University Hospitals from January 1, 1939 to December 31, 1945.
3. Six hundred and twenty-two patients were females and 4 were males. Fifty per cent were 40-49 years of age, while 88% were over 40.
4. Survival was computed from the date of the first x-ray treatment at this institution.
5. Three hundred and fourteen or 50.1% were operable. These were treated by surgery followed by post-operative irradiation: 98 of 209 patients or 47% survived 5 years or more. Axillary lymph node metastases occurred in over 70% of cases.
6. One hundred and forty-nine or 23.8% were treated for inoperable tumors: 4 of 98 patients or 4% survived 5 years or more. One hundred and forty-two or 22.7% were treated for recurrences or distant metastases following previous treatment elsewhere: 12 of 85 patients or 14% survived 5 years or more.

7. The use of Haagensen's criteria of operability in 153 cases was evaluated: 28% of these considered inoperable survived 5 years or more.

8. Local recurrences in the operative site occurred in 13.4% (45 of 314 cases) of the operable group. Since 1942, this has been reduced to 7.5% (7 of 92 cases).

Conclusions

Many investigators have tried to analyze results of different treatments used for mammary carcinoma in order to determine the best method or combinations of methods available.

It has been generally agreed that hormone therapy should be used for selected cases with inoperable carcinoma and that irradiation therapy is the method of choice for most of these patients. Both palliation and prolongation of life has been obtained. Occasionally addition of surgical removal of the breast or an ulcerating mass is indicated.

In studies dealing with operable cases, as defined by individual investigators, the problem of management runs the gamut from the use of surgery alone to the use of x-ray therapy and/or radium alone. Each extreme has its adherents. However, the mass of investigators range somewhere in between these extremes. It is felt by most of this group that radical surgery with added irradiation offers the best chance for completely irradiating the disease.

It is apparent that early diagnosis before the lesion has become locally inoperable or has metastasized beyond the axillary nodes is essential if the mortality rate is to be reduced. We feel that radical surgery followed by post-operative irradiation in operable lesions with extension beyond the freely movable mass is the treatment of choice. Comparison of statistics from various clinics confirms the impression that this combination is superior to surgery

alone in this group.

Ann.Surg.118:859-870 and 1032-1051,
'43.

References

1. Adair, F. E.
The Role of Surgery and Irradiation in Cancer of the Breast.
J.A.M.A. 121:553-559 (Feb.20) '43.
2. Bell, E. T.
Textbook of Pathology. Philadelphia. Lea and Febiger, 6th ed.
p. 387, '47.
3. Cade, S.
Carcinoma of the Breast.
J.A.M.A.138:1083-1087 (Dec.11)'48.
4. Daland, E. M.
Untreated Cancer of the Breast.
Surg.,Gynec.& Obst. 44:264-268, '27.
5. Engelstad, R. B.
Surgical and Radiation Treatment of Cancer of the Breast.
Am.J.Roent.60:776-787, '48.
6. Geschickter, C. F.
Diseases of the Breast.
Philadelphia, J. B. Lippincott Co.,
2nd ed., 394, '45.
7. Gordon-Taylor, G.
Discussion: The Treatment of Cancer of the Breast. (Abridged).
Proc.Roy.Soc.of Med.41:118-132
(Feb.) '48.
8. Gratzek, F. R. and Stenstrom, K. W.
Roentgen Therapy of Mammary Carcinoma: Survival Based on 731 Cases.
Radiol.44:44-57, '45.
9. Gylstorff-Peterson, H.
Roentgen Treatment of Carcinoma of the Breast.
Acta Radio.25:1-12, '44.
10. Haagensen, C. D. and Stout, A. P.
Carcinoma of the Breast: I, Results of Treatment.
Ann.Surg.116:801-815, '42.
11. Haagensen, C. D. and Stout, A. P.
Carcinoma of the Breast: II, Criteria of Operability.
12. Haagensen, C. D.
Carcinoma of the Breast.
J.A.M.A. 138:279-292 (Sept.) '48.
13. Halley, E. P. and Melnick, P. J.
Preoperative Irradiation in Carcinoma of the Breast.
Radiol.35:430-438, '40.
14. Halsted, W. S.
The Results of Operations for the Cure of Carcinoma of the Breast.
Ann.Surg.20:497, 1894.
15. Harrington, S. W.
Results of Radical Mastectomy in 5026 Cases of Carcinoma of the Breast.
Pennsylvania M.J. 43:413-427, '40.
16. Kaplan, I. I. and Rosh, R.
Cancer of the Breast.
Radiol.47:583-592 (Dec.) '46.
17. Lewis, D. and Reinhoff, W. F.
A Study of the Results of Operations for the Cure of Cancer of the Breast.
Ann.Surg.95:336-400, '32.
18. MacDonald, I.
Mammary Carcinoma: A Review of 2636 Cases.
Surg.,Gynec.,Obst.,74:75-82 (Jan.) '42.
19. McWhirter, R.
The Value of Post-Operative Radiotherapy in Carcinoma of the Breast.
Edinburgh M.J. 50:193-207 (April)'43.
20. Marshall, S. F. and Forney, J.
Carcinoma of the Breast: An Analysis of 300 Cases.
Surg. Clin.N.Am.26:723 (June) '46.
21. Pendergrass, E. P. and Hodes, P. J.
Some Observations on Cancer of the Breast.
Am.J.Roentgenol.39:397-406, '38.
22. Pendergrass, E. P. and Kirsh, D.
The Role of Irradiation in the Management of Carcinoma of the

- Breast.
Radiol. 51:767-778 (Dec.) '48.
23. Pfahler, G. E.
The Treatment of Carcinoma of the Breast.
Am.J.Roent. 39:1-18 (Jan.) '38.
24. Pfahler, G. E. and Keefer, G. P.
The Object, Value, and the Technique of Preoperative and Post-operative X-ray Treatment in Carcinoma of the Breast.
Surg., Gynec., and Obst., 85:35-46, '47.
25. Putzki, P. S. and Scully, J. H.
205 Cases of Cancer of the Breast Treated by Radical Mastectomy.
Surg., Gynec., and Obst., 83:751-760, (Dec.) '46.
26. Rodman, J. S.
Skin Removal in Radical Breast Amputation.
Ann.Surg., 1182:694-705, '43.
27. Sachs, M.D.
Carcinoma of the Male Breast.
Radiol. 37:458-467 (Oct.) '41.
28. Schreiner, B. F. and Stenstrom, A. T.
End-Results in 563 Cases of Breast Cancer.
Surg.,Gynec.& Obst., 44:608-612, '27.
29. Simmons, C. C., Taylor, G. W., and Welch, C. E.
Carcinoma of the Breast. End-Results: Mass. General Hospital 1930, 1931 and 1932.
Surg., Gynec., and Obst., 69:171-177 (Aug.) '39.
30. Simmons, C. C.
Cancer of the Breast: Ten Year End-Results.
Surg.,Gynec.,& Obst., 74:763-765, '42.
31. Stenstrom, K. W., and Baggenstoss, O. J.
Results of Surgery and Radiation for Carcinoma of the Breast with Axillary Metastases.
Acta Radiol. 28:623-632, '47.
32. Taylor, G. W. and Bruce,
Prognostic Factors in Carcinoma of the Breast.
New Eng.J.Med., 222:790-792, '40.
33. Wade, P.
Untreated Carcinoma of the Breast.
Brit.J.Radiol.19:272-280, (July) '46.

III. MEDICAL SCHOOL NEWS

Minnesota Medical Foundation News

Gifts are still being sought by the Minnesota Medical Foundation in its drive to memorialize Dr. Jennings Crawford Litzenberg, beloved professor of Obstetrics and Gynecology.

It was hoped that the memorial fund might be used to establish a fellowship in obstetrics or maternal welfare. All of Litz's former students will remember how interested he was in the problem of maternal mortality. His personal crusade against causes of maternal death was an important factor in bringing about safer delivery for mothers and babies here in Minnesota.

Although substantial gifts have already been received, much remains to be done if a fellowship is to be established in Litz's name. His friends and former students are invited to participate in this memorial.

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Progress Note

Alumni and friends of the Medical School will be happy to learn that construction is proceeding on the Variety Club Heart Hospital. Excavation has almost been completed, the wooden forms are being built, and very shortly concrete will be poured.

Kellogg Foundation Lectures

The following lectures will be given during the week of March 7. All medical students, interns, nurses, technicians, dietitians, and physicians are cordially invited to attend these lectures. A special invitation is extended to University Fellows.

Dr. John H. Dingle (Western Reserve Univ., Cleveland, Ohio)	"Virus Infections of the Respiratory Tract"	Monday, March 7, 4:00-6:00 p.m. Powell Hall Amphitheater
Dr. Wallace E. Herrell (Mayo Clinic)	"Chemotherapeutic Agents and Antibiotics"	Tuesday, March 8, 2:00-4:00 p.m. Todd Amphitheater, U. H.

Dr. Bell Speaks in Durham, No. Carolina

Dr. E. T. Bell, Professor and Head of the Department of Pathology, participated in the annual Watts Hospital Clinical Conference in Durham, North Carolina, on February 16 and 17. The conference was attended by more than 300 doctors from North Carolina. The entire conference centered around the problem of heart disease.

Other distinguished physicians who participated in the conference along with Dr. Bell were Dr. Paul White and Dr. Robert Gross of Boston and Dr. Hugh Butt of the Mayo Clinic.

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New Minn. Medical Foundation Members

Dr. Lawren B. Nasset, 2929 Bloomington Ave., Minneapolis
 Dr. Elizabeth Troxil, 4628 LaSalle Bldg., Minneapolis
 Dr. Ivar Sivertsen, 500 LaSalle Bldg., Mpls
 Dr. H. F. Schroeckenstein, 656 Chippewa Ave., St. Paul
 Dr. C. H. Coombs, Cass Lake
 Dr. Arthur Thompson, Cokato Hospital, Cokato
 Dr. A. D. Rydland, Northwestern Clinic, Crookston
 Dr. J. C. Klein, Shakopee
 Dr. M. Westby, Madison