

**METASTASES TO THE SKELETON, BRAIN AND SPINAL
CORD FROM CANCER OF THE BREAST AND THE
EFFECT OF RADIOTHERAPY**

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THE clinical course and response to therapy of metastases from cancer of the breast may best be studied in patients whose histories are known from the time of discovery of the tumor to the time of death. Patients alive when they are investigated or those dying accidentally or from intercurrent diseases, illustrate only single chapters in the life history of the cancer and do not give a true picture of the disease as a whole.

The greater number of patients with cancer of the breast admitted to the Radiotherapeutic and Surgical Services of the Montefiore Hospital of New York during the past ten years, reached the hospital in the terminal stage of the disease. They died shortly after, either in the hospital or at home while under direct or indirect supervision of the medical staff of these services. The clinical course of the earlier phases of the disease had to be reconstructed in most cases from the history as given by the patient or from records of other hospitals. Through the coöperation of the departments of pathology of Montefiore Hospital and several other hospitals, histological studies on the original tumor and its metastases were made possible in nearly four-fifths of the cases.*

Material.—One hundred and sixty-eight cases of carcinoma of the breast with metastases to various parts of the body were studied from the time of the discovery of the tumor to the time of death. Nearly half (eighty-one cases) had skeletal metastases, proven röntgenographically or at autopsy. More than half of these had involvement of the lumbosacral spine and about one third of the skull. Of the latter, more than half gave neurologic signs

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of brain involvement and of the former, thirteen cases were thought to have spinal-cord metastases. No cases of spinal-cord involvement were observed in the absence of evidence of the disease in the lumbosacral spine. It is doubtful whether true metastases to the spinal cord occurred, in as much as autopsy of four of the thirteen showed, in three only compression of and in one an extension into the cord. A similar problem arose with regard to brain involvement: in nine autopsies, extension from the calvarium to the dura was found in one, extension from the calvarium through the dura to the brain in three, and multiple metastases apparently spread by the blood-stream in five. It can thus be seen that clinical differentiation of compression, extension and true metastases from carcinoma of the breast in the central nervous system is difficult if not impossible. Of the eighty-five cases of metastases to the skeleton and central nervous system, sixty-seven were verified histologically; thirty-two of these were examined post-mortem. Sixty cases of the eighty-five could be grouped according to histological evidence of malignancy, into Grade I, or least malignant, Grade II, or moderately malignant, and Grade III or most malignant. Of the eighty-five cases nearly 66 per cent. (fifty-six cases) had radical mastectomies; 15 per cent. (thirteen cases) were not operated upon; 8 per cent. (seven cases) had simple mastectomies, and 6 per cent. (five cases) had only biopsies. Many cases were so far advanced when admitted to the Montefiore Hospital that radiotherapy was withheld, or one X-ray treatment given for psychological reasons. These latter cases have not been used in evaluating the efficiency of radiotherapy.

Definitions.—The term of life of the patient, from the time of the discovery of the primary tumor to death, was divided into two periods. The last third was designated as terminal in contrast to the earlier two-thirds or pre-terminal. An exception was made in the case of patients who lived over three years. In these, the last year of life was looked upon as the terminal stage. It was found that at least 55 per cent. of the cases of skeletal metastases occurred during the pre-terminal period of the disease, and that survival in this group after the appearance of clinical evidence of skeletal metastases varied from a few months in fulminating cases to four and two-thirds years in the slowly advancing carcinomas.

Our criterion for clinical evidence of skeletal metastases was pain or tenderness localized in a part of a bone which later showed the typical röntgenographic picture of metastasis, or in which cancer was found at autopsy. All of the cases quoted in this paper as skeletal metastases have been thus verified. The clinical diagnosis of brain and cord involvement was based on symptoms of increased intracranial pressure or neurologic signs of localized cerebral, cerebellar, brain stem or cord involvement. The difficulty of differentiating between compression, extension and true metastases in this connection has already been mentioned. Clinical diagnosis of pulmonary and pleural metastases was made on subjective symptoms or physical signs of a process in the lungs which could not be explained on other grounds, and in which later, röntgenographic or post-mortem evidence of cancer was found.

Under skin metastases, were included typical cutaneous and subcutaneous nodules in or near the operative scar, or related to a carcinomatous ulcer. Direct extension from a broken-down carcinomatous ulcer of the skin was excluded, as it was felt that this was not a true metastasis. In spite of probable errors and the incompleteness of individual case histories, it is believed that the sum total of information gathered allows certain general conclusions which hold true for the average case of carcinoma of the breast with metastases to the skeletal and central nervous systems.

Sex, Age, Location of Primary Tumor.—Of the eighty-one cases with skeletal metastases, eighty were in women and one was in a man.

The age of the patients when the tumor was first noted, varied from twenty-two to seventy-five years. As seen from Table I the greatest number of cases occurred between the ages of forty and fifty years. A definite relationship between age and duration of life following the discovery of the tumor could not be established. Several of our youngest patients were among those who lived for a long period while some of the oldest patients died soon after the discovery of the tumor.

TABLE I
Age When Tumor Was Noted—81 Cases

Age Groups	Per cent. of cases
Under 30	5
30-40	30
40-50	37
50-60	19
60-70	8
Above 70	1

The primary tumor arose in the right breast in forty-three cases and in the left breast in thirty-eight cases. Data giving more exact localization of the tumor in the breast were too incomplete to be of much value. Information regarding clinical or microscopical involvement of axillary lymph-nodes was frequently so unsatisfactory that it was decided to leave this factor also out of consideration.

Anatomical Distribution of Skeletal Metastases.—Among the eighty-one patients there were only 16 per cent. (thirteen cases) that apparently had metastases to the skeleton alone. In the rest, *i.e.* 84 per cent. (sixty-eight cases) skeletal invasion was associated with metastases to one or several of the other body systems. The distribution of these metastases in eighty-one cases was as follows: lungs 52 per cent. (forty-two cases), skin 36 per cent. (twenty-nine cases), brain 21 per cent. (seventeen cases), spinal cord 16 per cent. (thirteen cases).

Most of the skeletal metastases were multiple. Of the eighty-one cases only fourteen showed involvement of a single bone, and even in these it may be questioned whether some other metastasis was not overlooked.

The regional distribution of the metastases was investigated, first as to

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general distribution, and secondly as to the site of the first localization. The latter study probably gives a truer picture of the predilection of the metastatic process for certain bones especially if the pre-terminal cases are considered separately.

TABLE II
*Anatomical Distribution in 81 Cases of Skeletal Metastases**

General localization	Per cent.	No. of cases	Specific localization	Per cent.	No. of cases	Homolateral† Heterolateral Bilateral
Pelvis.....	62	51	Ischium..	37	19	
			Ilium....	58	30	
			Pubis....	56	29	
Spine.....	59	48	Cervical..	13	8	
			Dorsal...	40	24	
			Lumbar..	57	34	
			Sacral....	38	23	
Femur.....	54	44				Bilateral..... 31 Heterolateral.. 8 Homolateral.. 5
Ribs.....	39	32				Bilateral..... 20 Heterolateral.. 5 Homolateral.. 7
Skull.....	35	29				
Humerus.....	27	22				Bilateral..... 11 Heterolateral.. 5 Homolateral.. 6
Scapula.....	16	13				Bilateral..... 8 Heterolateral.. 4 Homolateral.. 1
Clavicle.....	14	12				Homolateral.. 1 Bilateral..... 5 Heterolateral.. 6
Tibia.....	3	3				Homolateral.. 2 Heterolateral.. 1
Sternum.....	I	I				
Radius.....	I	I				
Ulna.....	I	I				
Hands.....	I	I				
Fibula.....	I	I				
Bones of Feet.....	I	I				

NOTE.—* Most of the cases had multiple metastases, so that the same case may appear under several headings. A clearer picture of the relative frequency may be obtained from Table III.

† "Homolateral" designates occurrence on the same side as the primary growth in the breast: e.g. right breast and right femur; "Heterolateral" on the opposite side.

Of the forty-five cases of skeletal metastases occurring in the pre-terminal stage the skeleton was the primary localization in 82 per cent. (thirty-nine cases). In only six cases did röntgenographic or clinical evidence of other metastases precede skeletal invasion; in three these were pulmonary and in three cutaneous metastases. The metastases however did not remain localized

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TABLE III

The First Site of Involvement as Suggested by Pain and Later Confirmed Röntgenographically.
75 Cases

	Per cent.	No. Cases
Sacro-lumbar spine.....	37	28
Femur.....	16	12
Pelvis.....	14	11
Skull.....	13	10
Dorsal spine.....	5	4
Ribs.....	5	4
Humerus.....	4	3
Scapula.....	2	2
Clavicle.....	1	1
Tibia.....	1	1

to the skeleton. In 80 per cent. (thirty-six cases) they were complicated by metastases to other parts of the body. In ten the skeletal metastases were followed by pulmonary and in ten others by cutaneous invasion. The relationship between the time of onset of skeletal and other metastases could not be determined in the remaining cases. The regional distribution of the first localization in the forty-five cases occurring in the pre-terminal stage is given in Table IV.

TABLE IV

First Localization in the Skeleton of Cases in the Pre-Terminal Stage, 45 Cases

Region	Per cent.	No. of Cases
Lumbo-sacral spine.....	39	17
Femur.....	18	8 {heterolateral, 7 homolateral, 1
Pelvis.....	16	7
Skull.....	8	4
Dorsal spine.....	7	3
Ribs.....	4	2
Scapula.....	4	2 {homolateral, 1 heterolateral, 1
Humerus.....	2	1 heterolateral

The anatomical distribution of metastases as given in Table IV corresponds to the finding of Lee,²¹ Semken,³⁰ and others, and differs somewhat from that quoted by Handley,¹³ and more recently by Carnett and Howell.³ While the figures on the frequency of involvement of the sternum and ribs quoted by Handley are probably nearer the truth than those given here, metastases to the lumbosacral spine, pelvis, and femur, surely occur more often than it would appear from the tables of this author. The discrepancy may be due to the fact that the criterion for localization of skeletal metastases in this series was pain and later a positive röntgenogram, whereas Handley's statistics are based on autopsy findings. It is well known that röntgenographs of metastases in the sternum and the adjacent portion of the ribs are rarely satisfactory.

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Histological Grading of Malignancy and Its Bearing on the Survival Period Following Discovery of the Tumor, the Metastases, and the Time Interval between These.—The microscopic structure of the primary tumor, or the metastases or both were investigated and an attempt was made in fifty-seven cases of skeletal metastases to grade the tumor according to the histological evidence of malignancy without reference to the clinical history. Variation in size and staining qualities of the cells and nuclei, frequency of mitotic figures, secretion vacuoles, glandular differentiation, connective tissue reaction, round-cell infiltration, and necrosis were studied. The order of importance of these factors in determining the degree of malignancy, is that just given. Grouping into Grade I and III was comparatively easy. Grouping of cases into Grade II on the other hand was difficult, as the histological characteristics in many cases approached either Grade I or III. This is illustrated in the following case.

B.G., with a primary inoperable carcinoma of the left breast, had a biopsy done and three years later died of broncho-pneumonia. The histological picture of the original tumor showed extreme variation in the size and staining qualities of cells and nuclei, two to three mitotic figures per high power microscopic field, no secretion vacuoles or attempt at glandular differentiation. Specimens obtained at post-mortem examination from skull, dura, brain and adrenals, on the other hand, showed slight to moderate variation in the size and staining qualities of cells, practically no mitotic figures, no secretion vacuoles, but a slight attempt at glandular differentiation. Our classification based on sections of the original tumor would have been Grade III, on sections from the autopsy material, Grade I. After seeing both we grouped the case as belonging to Grade II.

Of the fifty-seven cases twenty-six were thus classed in Grade I, twenty-six in Grade II, and five in Grade III. While inaccuracies in grading occurred, the general clinical value of this histological grading is supported by a study of the survival period after the discovery of the tumor as illustrated in Table V. It is interesting to note that five cases of Grade I with marked

TABLE V
Survival Period According to Histological Grading, 57 Cases

Grade	No. of Cases	Average duration of life in months
I.....	26	50.2
II.....	26	23.5
III.....	5	17.3

glandular differentiation had an average survival period of 71.1 months as compared to an average survival period of forty-five months for the twenty-one other cases which did not show this histologic characteristic.

Cases with marked connective tissue reaction (scirrhous cancer) showed somewhat increased survival periods for Class II and III, not for Class I. The significance of this finding may be questioned.

There were thirty-nine cases in which a radical amputation of the breast was done and six non-operated cases which could be graded according to the histological evidence of malignancy. The survival period varied with the histological grading and appeared to be somewhat shorter in the non-operated

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TABLE VI

Survival Period in Cases with Marked Connective Tissue Reaction, 16 Cases

Group	No. of Cases	Survival period in months
I.....	6	49.4
II.....	8	32.3
III.....	2	20

series. However, definite conclusions cannot be drawn on this last question on account of the marked numerical divergence of the two series. It might be interesting to mention, that the only three patients of the radically operated Grade I group that survived a year or less after the tumor was noted, were patients who showed pain and tenderness in bones before the operation, and post-operatively showed röntgenographic evidences of skeletal metastases. Whether this is a coincidence in patients operated upon when they were nearing their terminal stage, or whether the operative interference so lowered their resistance as to accelerate the approach of death offers interesting material for speculation.

TABLE VII

Duration of Life Arranged According to Histological Grading—46 Cases

Group	Cases with radical amputation of the breast		Non-operated cases	
	No. of cases	Survival period discovery of tumor to death (months)	No. of cases	Survival period discovery of tumor to death (months)
I.....	22	53.6	1	30
II.....	14	41.2	4	27.7
III.....	3	20	2	13.5

The influence on the survival period of the pre-operative duration of a palpable tumor in cases subjected to radical amputation of the breast was studied, but no definite conclusions could be arrived at, perhaps on account of lack of sufficient material. It seemed however that patients in whom the rate of growth of the tumor was slow²³ and who therefore visited the surgeon and were operated upon late did better than those in whom the rate of growth was rapid, caused discomfort and who were operated upon earlier. This in no way affects the advisability of early operation, but is the probable explanation of this unexpected finding. For instance, in three Grade III cases a radical mastectomy had been performed three months after the tumor was noted. The average survival period in these was only seventeen and one-third months. On the other hand in four cases of Grade I in whom the tumor had been noted for more than a year prior to the time of mastectomy the survival period was 47.6 months.

Our data was insufficient to form conclusions as to the possible influence of castration on the occurrence of skeletal metastases.

The time interval between the discovery of the primary breast tumor and

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TABLE VIII

Interval Between Discovery of Tumor and Onset of Skeletal Metastases—43 Cases

Group	Radically operated cases		Non-operated cases	
	No. of cases	Interval between discovery of tumor and onset of metast. (months)	No. of cases	Interval between discovery of tumor and onset of metast. (months)
I.....	19	46.5	1	29
II.....	14	29.1	4	21.1
III.....	3	10	2	6

the onset of symptoms of skeletal metastases as seen from Table VIII also seem to depend greatly on the histological grading of the tumor.

Survival after the onset of skeletal metastases varied from three months to four years and eight months. The combined terminal and pre-terminal, and then the latter alone were studied and graded histologically in Tables IX and X.

TABLE IX

Survival After Onset of Skeletal Metastases, 50 Cases

Grade	No. of Cases	Survival period in months
I.....	23	15.1
II.....	22	8
III.....	5	9

TABLE X

Survival of Pre-Terminal Cases After Onset of Skeletal Metastases, 32 Cases

Grade	No. of Cases	Survival period
I.....	15	19.7
II.....	13	16.2
III.....	4	10

The slightly longer survival period in the pre-terminal group as compared with the general group is naturally what one would expect.

Clinical Symptomatology of Metastases to the Skeleton.—Pain^{11, 24} and less frequently bony tenderness on direct pressure or percussion are usually the first symptoms of invasion of the skeletal system by metastases from cancer of the breast. In 75 per cent. *i.e.*, sixty-one of the eighty-one cases, attention was drawn to the presence of bony metastases through the fact that the patient complained of localized pain. This was usually at the site of the metastases, occasionally, however, over the area of distribution of the nerve immediately adjacent to the metastases. In 17 per cent. (fourteen cases) pain occurred at about the same time as röntgenographic corroboration was obtained and in only 7 per cent. (six cases) were metastases discovered incidentally when röntgenographs were made as a routine measure, the patient not complaining of any pain. In nine cases it was possible to follow the gradual appearance of definite röntgenographic evidence of skeletal metastases in places where the patient complained of pain from one-half to twelve months

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prior to positive röntgenograms. In these cases röntgenographs were made at frequent intervals until they became positive. In six of the cases the skeletal metastasis was the first point of localization; in three, involvement of other parts of the skeletal system had been diagnosed röntgenographically and attention to the new invasion was drawn by the patient's complaints. A table of the nine cases follows:

Interval between onset of pain and positive Röntgenographs	Clinical symptoms	Röntgenographs
½ mo.	F. H.—Severe pain sternal end of left clavicle 18½ months after discovery of tumor.	18½ mos. P.T.* Clavicles negative. 19 mos. P.T. Path. fracture 2" from sternal end of left clavicle.
3½ mos.	A. B.—When tumor discovered, pain in lumbar and sacral regions radiating anteriorly. Pain continued following operation 2 mos. later.	2 mos. P.T. Lumbar spine negative. 3½ mos. P.T. Slight narrowing of body of 1st L.V. Small area of bone absorption in left wing of sacrum.
3 mos.	C. T.—14 mos. P.T. Pain and tenderness 2nd left rib anteriorly.	14 mos. P.T. Chest and shoulders negative. 19 mos. P.T. Metastases 6, 7th right ribs 7th left rib. 22 mos. P.T. Metastases in practically all the ribs.
5 mos.	R. K.—7 mos. P.T. Pain in left hip and crest of ilium. 9 mos. P.T. Tenderness in lumbar spine and left hip. 12 mos. P.T. Pain in left hip radiating to ankles, right hip and also right shoulder.	9 mos. P.T. Pelvis and upper third of femora negative. 12 mos. P.T. Small area of rarefaction in left pubic bone. Femora negative. 17 mos. P.T. Area of bone destruction and sclerosis in descending ramus of right ischium. Metastases in left os and descending ramus of left pubis.
6 mos.	H. F.—9 yrs. 9 mos. P.T. Pain right foot. Pain in right foot persisted.	9 yrs. 9 mos. P.T. Right foot negative. 10 yrs. 3 mos. P.T. Metastasis to right cuneiform bone.
7 mos.	R. T.—16 mos. P.T. Severe pain in dorsal region.	16 mos. P.T. Dorsal region negative. 23 mos. P.T. Multiple metastases in dorsal vertebræ.
7 mos.	S.—27 mos. P.O. Pain in both shoulders radiating down the arms. Pain persisted.	27 mos. P.O. Shoulders negative on numerous chest films taken before and following this date. 34 mos. P.O. Metastasis to head of right humerus.
8 mos.	R. K.—34 mos. P.T. Pain right leg. 36 mos. P.T. Pain and tenderness right lower tibia. 38 mos. P.T. Marked tenderness over tibia. 42 mos. P.T. Swelling and tenderness right ankle.	34 mos. P.T. Right leg and foot negative. 37 mos. P.T. Right ankle and leg negative. 39 mos. P.T. Right tibia negative. 42 mos. P.T. Few areas of bone destruction lower end of right tibia and fibula; röntgenographic appearance suggestive of metastases.

* P.T. after discovery of tumor; P.O. after operation.

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Interval between onset of pain and positive Röntgenographs	Clinical symptoms	Röntgenographs
11 mos.	C. T.—16 mos. P.T. Pain and tenderness both scapulæ.	16 mos. P.T. Shoulders negative. 19 and 22 mos. P.T. Chest X-rayed for ribs—negative. 28 mos. P.T. Multiple metastases in scapulæ.
12 mos.	R. B.—16 mos. P.T. Onset of pain and bony tenderness right ribs.	10 to 16 mos. P.T. Röntgenographs of chest during this period were negative for rib metastases. 22 mos. P.T. Metastasis to 2nd right rib.
12 mos.	R. S.—7 mos. P.T. Pain in back. 11 mos. P.T. Radical mastectomy. Pain in back persisted post-operatively. 18 mos. P.T. Pain in back became very severe and started to radiate down the thighs.	11 mos. P.T. Lumbo-dorsal spine negative. 13¼ mos. P.T. Pelvis negative. 19 mos. P.T. Extensive metastases to 4th and 5th lumbar vertebræ 21 mos. P.T. Metastases to all lumbar vertebræ and pelvis.

Pain apparently is earliest and most pronounced where pressure due to natural body weight or muscular tension is greatest. Thus, for instance, pain due to invasion of the lumbar spine or sacro-iliac region is usually present early, whereas pain due to invasion of the vault of the skull is commonly not complained of until late in the course of this metastasis, when it has either reached a considerable size or is producing increased intra-cranial pressure. While pain and bony tenderness usually indicate the presence of skeletal metastases, this diagnosis can only be made on the basis of röntgenographic evidence or microscopical examination. Indirect symptoms of skeletal metastases such as cachexia and unusual blood findings such as mentioned by Piney²⁷ were not carefully studied in this series. It was found, however, that cachexia did not seem to be an important symptom except in the terminal stage of the disease.

Röntgenographic Corroboration.—Before the advent of recent improvements in röntgenographic technic² and the recognition of the frequency of skeletal metastases, many cases were missed. At present, however, many more metastases are recognized. The röntgenographic characteristics of skeletal metastases from cancer of the breast closely correspond to the pathological findings. The lesions may be circumscribed or diffusely infiltrating. They are generally of the osteoclastic type (77 per cent. in this series) and less frequently a mixture of osteoclastic and osteoblastic types with the one or the other predominating (23 per cent. in this series). In some cases the amount of new bone laid down is so great that the areas involved become very dense and röntgenographically give an almost ivory-like appearance. The extensive, infiltrating types of skeletal metastases are the ones most likely to show osteosclerosis. Small localized areas of bone sclerosis are

occasionally seen especially near the sacro-iliac joint. These areas may be benign, but require repeated röntgenographic check-up in order to avoid overlooking the development of early metastases. The same caution should be exercised in interpreting the significance of röntgenographic evidence of spondylitis. This may often mask an early metastasis.

Pathological Fractures.—Pathological fractures of one or more of the long or flat bones were encountered in 26 per cent. of the cases (twenty-one of eighty-one). They occurred only in the terminal stage of the disease. Fractures were observed in the femur (nine cases), humerus (nine cases), ribs (two cases), and clavicle (one case). The fractures of the ribs were probably much more numerous, but were missed on account of the difficulty of the röntgenographic diagnosis of rib involvement.

Effect of Radiotherapy.—In considering the possible benefits from radiotherapy in skeletal metastases it should be remembered that the greater number of patients were admitted to the Radiotherapy Department of Montefiore Hospital during the terminal stage of the disease. In only thirty-one of the eighty-one cases was it possible to evaluate the results of radiotherapy. The number of treated cases in each of the histological grades was insufficient to permit any definite conclusion on this question. The metastases were usually so widespread that only mild palliation was attempted. In three cases the metastases seemed to be localized to a single bone. Two of these improved in spite of the fact that they were in the terminal stage of the disease. In nineteen cases treated during the terminal stage of the disease, ten showed clinical improvement and nine remained unimproved. Of twelve cases treated in the pre-terminal stage, all were markedly improved by therapy. The duration of improvement varied from a few weeks to three years. It was manifested in relief of pain within twenty-four to forty-eight hours after the first X-ray treatment; and there was progressive improvement in many cases. The clinical improvement was at times striking. Thus we had two patients that were admitted as apparently hopeless and moribund, who were able to leave the hospital walking after they had received a series of X-ray treatments. They remained clinically well for twenty-seven and thirty-six months respectively. One of them, a milliner, was able to follow her regular occupation during a period of over three years.

Bone sclerosis following X-ray therapy occurred in fourteen of thirty-one cases. In ten this had not been present prior to irradiation, in four the metastases were osteoblastic before irradiation and the bone sclerosis was somewhat increased in density following the treatment. The dosage apparently was not the determining factor in producing the improvement. Most of the cases were treated with X-rays with the following factors: 200 KV, 0.5 millimetre copper filter, 50 centimetre target skin distance, and moderately sized fields. A few cases were treated with radium packs at a distance of two to three centimetres (this was done before our association with the department). A "series" of treatments consisted of the total amount of

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radiation given within a period of about two months. The administration of more than two erythema doses to the skin over one area in a series was considered a large dose; one or two erythema doses as a moderate; and less than one erythema dose as a small dose. It was found that those cases which improved did so with small or moderate amount of irradiation. In twenty-one cases in which clinical improvement occurred following the treatment with X-ray and radium, the dosage was small in seven, moderate in thirteen, and large only in one case.

Radiotherapy of pathological fractures could be evaluated in seven cases. Four fractures did not unite. Three of these had very little and one a large amount of irradiation. A fracture of the middle third of the humerus showed marked callus formation after two small X-ray treatments. Bone sclerosis, but no union, followed the administration of moderate amounts of X-ray treatment to a fracture of the surgical neck of the femur. Complete bony union of a fracture of the left clavicle was noted following very small radiation doses from a 3-centimetre radium pack. Union of pathological fractures in several cases of cancer of the breast has been observed without any treatment (Harold Neuhof, personal communication).

A remarkable case not included in this series should be mentioned in this connection. It is a case of generalized skeletal metastases from a carcinoma of the breast with involvement of the skull, the spine, the pelvis, *etc.* The various skeletal metastases were irradiated with small doses of X-rays and improvement followed. The skull was not exposed to X-rays, yet comparison röntgenographs showed marked diminution in the size and number of the osteoclastic metastases in the skull. Evidently something more than local X-ray effect took place in this case.

Metastases to the Central Nervous System.—It was mentioned in the beginning of this paper that clinical differentiation of compression, extension, and metastases in the central nervous system from cancer of the breast is difficult if not impossible. Since only nine of the twenty-five cases suspected of brain metastases and four of the thirteen cases diagnosed as spinal-cord metastases were examined post-mortem, our figures as to frequency of occurrence of metastases into the central nervous system are not quite accurate. As a matter of fact, it may be questioned whether true metastases occurred in the spinal cord or whether all cases with cord symptoms were either compression by, or extension from a metastatic focus in the corresponding vertebræ. Symptoms of metastases to the central nervous system occurred in nearly 21 per cent. of the 168 cases investigated. Sixty-eight per cent. of the cases (seventeen of eighty-one) with neurologic evidence of brain involvement also showed positive röntgenographs of skull metastases. *Vice versa*, 68 per cent. of the patients with röntgenographic evidences of metastases to the skull also showed definite symptoms of brain invasion.

The symptoms of the onset of the brain invasion varied. They can be divided into three groups:

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- A. Cases showing signs of gradually increasing intracranial pressure (three cases).
- B. Cases with signs of increasing intracranial pressure and localizing neurologic signs of cerebral, cerebellar or brain stem involvement (eleven cases).
- C. Cases showing neurologic signs of cerebral, cerebellar and brain stem invasion without increased intracranial pressure (ten cases).

In 68 per cent. (seventeen of twenty-five) of the brain metastases and in 70 per cent. (nine of thirteen) of spinal-cord cases, the involvement occurred during the terminal stage of the disease. The survival period after the appearance of neurologic evidence of involvement in the eight pre-terminal brain cases varied from seven to twenty months, and in the four cord cases from five to thirty-one months. The effect of radiotherapy could be evaluated in five pre-terminal brain cases and in three pre-terminal cord cases. Three of the brain cases had shown early signs of increasing intracranial pressure. In one case, as a result of moderate X-ray therapy, headache disappeared for a period of four months, then re-appeared and was again relieved for a short time, then the patient succumbed to brain stem involvement. In another, headache was relieved for six months then recurred as a terminal feature. At autopsy extensive involvement of the dura without invasion of the brain was found. In the third case headache, vomiting, and convulsions of the right upper extremity disappeared following a small radium application and little X-ray treatment to the opposite side of the brain. The survival period in these three cases after the onset of clinical evidence of brain metastases were eleven, eighteen, and twenty months respectively. It is noteworthy that the generalized skeletal metastases in these patients also responded well to the X-ray therapy which they received. Of the two cases which gave neurologic signs of localized involvement of the brain, one improved following a small radium pack, while no improvement was noted in the other, after apparently well-placed, moderate X-ray therapy. Several other cases are not quoted in detail as they occurred in the terminal stage. They showed temporary regressions of headache, and diplopia, and disappearance of facial palsy for periods varying from a few weeks to three months. Of the three cord cases, two showed definite relief of pain from moderate X-ray dosage. No beneficial effect was seen in the third case.

SUMMARY

One hundred and sixty-eight cases of metastases to various body systems from carcinoma of the breast were studied from the time of discovery of the tumor to the time of death. Forty-eight per cent. had skeletal metastases, 15 per cent. showed brain metastases, and 8.7 per cent. spinal cord-involvement.

Of the eighty-five cases of metastases to the skeleton and central nervous system thirty-two were examined post-mortem, sixty-seven were corroborated histologically, and sixty were graded according to the histological evidence of

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malignancy into three groups: Grade I or least malignant, Grade II or moderately malignant, Grade III or most malignant.

It was found that three time factors varied in direct relation with this grading: *a*, the time interval between the discovery of the tumor and the onset of symptoms of skeletal metastases; *b*, the survival period after discovery of the tumor; and *c*, after symptoms of skeletal metastases. These three periods were markedly shortened with increasing malignancy; thus the average interval between the discovery of the tumor and the onset of metastases was 46.5 months for Grade I, 29.1 months for Grade II, and 10 months for Grade III. The survival period after the discovery of the tumor for cases in Grade I was 50.2 months, Grade II 23.5 months, and Grade III 17.3 months. The survival period of pre-terminal cases after the onset of skeletal metastases was 19.7 months for cases in Grade I, 16.2 months for those of Grade II, and 10 months for those of Grade III. The survival of cases with marked glandular differentiation was somewhat longer than those which did not show this characteristic.

The term of the patient's life following the discovery of the tumor was divided into two periods, a terminal period, that is the last third or in cases lasting more than three years, the last year of life, and pre-terminal or earlier period; 55 per cent. of the skeletal metastases occurred in the pre-terminal period.

Age apparently had no influence upon the survival period and most cases occurred between the ages of forty and fifty.

The primary tumor arose in the right breast in forty-three and the left breast in thirty-eight cases.

Of forty-five cases occurring in the pre-terminal stage, the skeleton was the primary localization in 82 per cent. However in only 16 per cent. did it remain limited to the skeletal system. In the rest it was associated with metastases to other parts of the body.

The most frequent localization in the skeleton of the pre-terminal cases was the lumbo-sacral spine, the femur, pelvis, dorsal spine, skull, ribs, scapula, and humerus, in the order mentioned.

Pain was the first sign to call attention to skeletal metastases in 75 per cent. of the cases. The time interval between the first complaint of pain and the appearance of definite röntgenologic evidence of skeletal metastases was followed carefully in nine cases. It was found to vary from a few weeks to one year.

Pathologic fractures occurred as a terminal manifestation of the disease and were encountered in 26 per cent. of the cases. Of seven treated pathologic fractures only one united after a radium application.

X-ray and radium therapy were very useful agents in control of pain. They caused diminution and at times marked temporary regression of the clinical and röntgenographic signs of skeletal metastases. Clinical improvement started twenty-four or forty-eight hours after the first treatment and

lasted from a few weeks to three years. Moderate dosage seemed to be sufficient and sclerosis of the radiated bone was observed in several cases.

Clinical signs suggesting metastases to the central nervous system occurred in 21 per cent. of the one hundred and sixty-eight cases investigated and were usually a terminal manifestation. Clinical differentiation between compression, extension and true metastases into the central nervous system was impossible. Sixty-eight per cent. of the cases diagnosed as brain involvement showed positive röntgenograms of skull metastases and all cases diagnosed as spinal-cord metastases showed röntgenographic evidence of a preceding metastasis to the lumbar vertebra at the same level. In a few cases temporary regression of signs of increased intracranial pressure and localized brain involvement occurred following moderate dosage of radiotherapy.

CONCLUSIONS

The prognosis of skeletal metastases from cancer of the breast varies with the histological character of the primary tumor or its metastases. This influences the survival period after the discovery of the tumor and after the onset of the metastases, and has a bearing upon the time interval between the discovery of the tumor and the onset of skeletal metastases.

Pain usually precedes positive röntgenographs of skeletal metastases and is the most important symptom of skeletal invasion.

Clinical signs suggesting metastases to the central nervous system from cancer of the breast occurred in about one-fifth of the cases investigated. In more than half of the brain cases there were associated metastases in the skull and in all of the spinal cord cases there were metastases in the corresponding vertebræ.

Radiotherapy relieves pain in a great number of cases of skeletal metastases. In a few cases of skeletal metastases it produced a remarkable temporary regression and in a few cases of invasion of the central nervous system it also caused palliation.

REFERENCES

- ¹ Appclrath, H.: Ein Vorschlag für eine rationelle Methode der post operativen Bestrahlung der Mammakarzinome. *Strahlentherapie*, vol. xiii. pp. 611-617, 1922.
- ² Bendick, A. J.: Importance of a Pelvic Roentgenogram in Treatment of Mammary Carcinoma. *Am. J. Roent. and Rad. Therapy*, vol. xviii, pp. 244-246, September, 1927.
- ³ Carnett, J. B., and Howell, J. C.: Bone Metastases in Carcinoma of the Breast. *ANNALS OF SURGERY*, vol. xcl, pp. 811-832, June, 1930.
- ⁴ Delbet, P., and Mendaro: *Les Cancers du Sein*. Masson & Cie, Paris, 1927.
- ⁵ Dalland, E. M.: Untreated Carcinoma of the Breast. *Surg., Gynec., and Obstet.*, vol. xlv, pp. 264-268, February, 1927.
- ⁶ Ewing, James: *Neoplastic Diseases*. Third edition, W. B. Saunders Company, Philadelphia, 1928.
- ⁷ Finzi, N. S.: X-rays and Radium in the Treatment of Carcinoma of the Breast. *Brit. Med. Jour.*, vol. ii, p. 728, October, 1927.
- ⁸ Gerota, D.: Nach Welchen Richtungen Kann Sich der Brustkrebs Weiter Verbreiten. *Arch. f. Klin. Chir. Berl., Bad liv*, pp. 280-288, 1897.

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- ⁹ Gottesmann, J.: Carcinoma of the Breast. *Surg. Cl. of North Amer.*, vol. viii, pp. 421-431, April, 1928.
- ¹⁰ Greenough, R. B.: Varying Degrees of Malignancy in Carcinoma of the Breast. *Jour. Ca. Res.*, vol. ix, pp. 453-463, 1925.
- ¹¹ Ginsburg, Solomon: Pain in Cancer of the Breast. Its Clinical Significance with Special Reference to Bone Metastases. *Amer. Jour. Med. Sci.*, vol. clxxi, p. 520, April, 1927.
- ¹² Ginsburg, Solomon: Osteoplastic Skeletal Metastases from Carcinoma of the Breast. Report of an Unusual Case. *Arch. of Surg.*, vol. xi, August, 1925.
- ¹³ Handley, W. S.: Cancer of the Breast and Its Treatment. Second edition, P. B. Hoeber, New York, 1922.
- ¹⁴ Jentzer, A.: Contribution à l'Etude du Cancer du Sein. *Schweiz. Med.*, vol. iii, pp. 908-911, Basel, 1922.
- ¹⁵ Kaufmann, E.: Lehrbuch der Speziellen Pathologischen Anatomie, Verein. Wiss. Verl., Berlin, 1922.
- ¹⁶ Knox, Leila C.: Radio Sensitivity and Tumor Morphology. *Radiology*, vol. xi, pp. 229-239, September, 1928.
- ¹⁷ Lane-Clayton, J. C.: Cancer of the Breast and Its Surgical Treatment. Reports on Public Health and Medical Subjects. No. 28, London, 1924.
- ¹⁸ Lane-Clayton, J. C.: A Further Report on Carcinoma of the Breast with Special Reference to Its Associated Antecedent Conditions. Reports on Public Health and Medical Subjects. No. 32, London, 1926.
- ¹⁹ Lane-Clayton, J. C.: Report on the Late Results of Operation for Cancer of the Breast. Reports on Public Health and Medical Subjects. No. 51, London, 1928.
- ²⁰ Lancaster, E. H.: Metastases in Bones Following Carcinoma of the Breast. *Med. Rec. and Ann.*, vol. xxiii, pp. 433-435, November, 1929.
- ²¹ Lee, B. J.: Discussion of an Article by Carnett and Howell. Bone Metastases in Carcinoma of the Breast. *ANNALS OF SURGERY*, vol. xcl, pp. 942-944, June, 1930.
- ²² Lee, B. J., and Tannenbaum: Recurrent Inoperable Carcinoma of Breast. An Analysis of 363 Cases Treated by Radium and Roentgen Rays. *Jour. A. M. A.*, vol. 86, pp. 250-256, January 23, 1926.
- ²³ Lee, B. J., and Stubenbord, J. J.: A Clinical Index of Malignancy for Carcinoma of the Breast. *Bull. N. Y. Acad. Med.*, vol. v, pp. 188-195, 1929.
- ²⁴ Levine, I.: The Prognostic and Therapeutic Significance of Skeletal Metastases in Carcinoma of the Breast. *ANNALS OF SURGERY*, vol. lxxv, pp. 326-340, March, 1917.
- ²⁵ Liek, E.: Hartnäckige Kreuzschmerzen als Erstes Zeichen Eines Brustkrebses. *Zentralblatt f. chir.*, vol. liiii, pp. 3212-3213, December 18, 1926.
- ²⁶ Patey, D. H.: Clinical Features and Distribution of Secondary Deposits in Bone. *Brit. Jour. Surg.*, vol. xv, pp. 182-192, October, 1927.
- ²⁷ Piney, A.: Recent Advances in Hematology, pp. 145-152, J. A. Churchill, London.
- ²⁸ Proust, R.: Le Traitement Radiothérapique des Métastases Osseuses du Cancer du Sein. *Strasb. Med.*, vol. lxxxix, pp. 77-79, February 20, 1929.
- ²⁹ Regaud, C.: Carcinoma of the Breast from a Radiotherapeutic Standpoint. *Arch. Inst. du Podin de l'Univ. de Paris*, vol. i, pp. 443-460, 1929.
- ³⁰ Semken, George: Discussion of an Article by Carnett & Howell. Bone Metastases in Carcinoma of the Breast. *ANNALS OF SURGERY*, vol. xcl, pp. 942-944, June, 1930.
- ³¹ Smith, G. V. S., and Bartlett, M. K.: Malignant Tumors of the Female Breast. *Surg., Gynec. and Obstet.*, vol. xlvi, pp. 314-320, 1929.
- ³² Thorne, M.: Theories with Regard to Secondary Growths in Carcinoma of the Breast. *Brit. Med. Jour.*, vol. ii, pp. 1745-1747, 1912.
- ³³ Webster, J. H. D.: Radiology and Surgery in Carcinoma of the Breast and in Chronic Mastitis. *Lancet*, vol. ii, pp. 63-65, July 14, 1929.
- ³⁴ Wolff, J.: Die Lehre von der Krebskrankheit. First edition, vol. ii, pp. 387-392, Gustave Fischer, Jena, 1911.