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THE VALUE OF POST-OPERATIVE RADIOTHERAPY IN CARCINOMA OF THE BREAST *

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CARCINOMA of the breast is a comparatively common disease and, in women, accounts for approximately one-fifth of all the deaths from cancer. This figure is all the more remarkable in view of the fact that in the treatment of cancer, the breast is one of the sites in which the best results are obtained. When the incidence of cancer in each anatomical site is considered, it is probable that approximately one quarter of all cases of cancer in women occurs in the breast.

The average age in the following series of cases was 55.5 years, so that not only is the incidence high, but the disease appears at a comparatively early age. The youngest patient was twenty-four years old.

Difficulty of Comparison of Results from Different Methods of Treatment.—It is extremely difficult to determine accurately the results obtained from the various methods employed in the treatment of carcinoma of the breast. Many tables of figures have been published, but these merely indicate the survival-rates of the cases accepted as suitable for a particular method of treatment. By careful selection of cases it is a simple matter to produce good results by any method which the author has devised or chooses to advocate. Such figures are of little help when one wishes to determine the value of a particular method of treatment applied to *all cases* of cancer occurring in the breast. Such difficulties will not be overcome until the results, obtained from the application of one method of treatment to all cases occurring in a large population unit, are compared with the results of a different method applied to all cases in another large

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unit of population, it being clearly understood that no cases—even untreated cases—are excluded from the total on which the percentage success is based. The future regionalisation of medical services may, therefore, play an important part, not only in providing complete and efficient treatment for the population, but also in enabling us to evaluate the advantages or disadvantages of the various methods of treatment at present employed in a manner not hitherto possible. Under existing conditions, and when surgery is the only method of treatment employed, it is probable that not more than 20 per cent. of all cases of cancer of the breast (treated and untreated) coming to a large general hospital survive five years.

In any one centre the problem is somewhat less complex and the difficulties of selection can, to some extent, be overcome. Comparison of results may be made, provided that all cases are divided into groups according to the stage of advancement of the disease at the time treatment is undertaken. Cases in the same stage of advancement may then be compared with reasonable accuracy. The method of staging adopted for this paper is that suggested by Dr Ralston Paterson of Manchester, and is as follows :—

Stage I.—The growth is confined to the breast. Involvement of the skin directly over and in continuity with tumour does not affect staging, provided that the area involved is small in relation to the size of the breast.

Stage II.—As Stage I, but there are palpable mobile glands in the axilla.

Stage III.—The growth is extending beyond the *corpus mammae* as shown by :

- (a) The skin is invaded or fixed over an area large in relation to the size of the breast.
- (b) The tumour is fixed to underlying muscle. Axillary glands may or may not be palpable, but if glands are present they must be mobile.

Stage IV.—The growth has extended beyond the breast area, as shown by :

- (a) Fixation or matting of axillary glands indicating extension outside the capsule.
- (b) Complete fixation of tumour to chest wall.
- (c) Secondaries in supraclavicular glands.

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- (d) Secondaries in skin wide of tumour.
- (e) Secondaries in opposite breast.
- (f) Distant secondaries, *e.g.* bone, liver, lung, etc.

Paget's Disease of the nipple is accepted as a primary duct carcinoma and regarded as Stage I unless palpable glands are present.

Total Cases.—For the period 1930 to 1942 there are available in the Radiotherapy Department the records of 1879 cases of carcinoma of the breast. When these cases are arranged according to the above method of staging the findings are as follows:—

TABLE I
Carcinoma Breast—1930 to 1942

Year.	Stage I.	Stage II.	Stage III.	Stage IV.	Recurrent Carcinomata.	Unstaged.	Total.
1930	33	18	17	1	3	0	72
1931	21	22	21	6	2	0	72
1932	31	12	28	1	6	0	78
1933	19	20	37	8	5	3	92
1934	34	14	30	19	14	1	112
1935	34	22	15	39	14	3	127
1936	39	16	23	28	20	1	127
1937	50	19	32	36	32	2	171
1938	48	17	29	38	27	1	160
1939	45	24	27	42	31	3	172
1940	50	39	31	40	13	2	175
1941	69	49	42	66	25	2	253
1942	83	53	42	76	14	0	268
Total . .	556	325	374	400	206	18	1879
Per cent. of total . .	30%	17%	20%	21%	11%	1%	100%

Up till 1935 untreated and incompletely treated cases were not fully recorded.

The group termed "recurrent carcinomata" indicates cases treated outside the centre and only referred to the centre after recurrence has taken place.

The "unstaged" group refers to cases treated outside the centre and still remaining free from recurrence, but referred to the centre for observation. This group also includes a few cases in which insufficient information was available to permit of staging.

Methods of Treatment selected for Comparison.—The primary object of this paper is to demonstrate the effect produced by post-operative radiotherapy. It is necessary, therefore, to select two groups of cases—those treated by operation alone, and those treated by operation and post-operative radiotherapy. A certain standard must be laid down for each group and the standard selected was as follows :—

Operation Alone.—All cases must have been treated by radical excision of the breast, and cases in which the operation was less extensive were excluded. To permit of fair comparison with the next group post-operative deaths were also excluded.

Operation and Post-operative Radiotherapy.—In this group cases having less extensive operations, such as simple mastectomy and even local removal of the tumour from the breast, were included provided that a full course of radiotherapy was given subsequently. Full treatment by radiotherapy was considered to be the delivery of a minimum dose of not less than 3500 r. in three weeks to the chest wall and to the whole length of the chain of glands from the axilla to the supraclavicular region on the affected side. In the majority of cases a minimum dose of 4500 r. was delivered to this area in a period of four weeks.

It was found that no useful purpose was served by making a comparison of the cases in Stage IV, for no matter what method of treatment was used, nearly all the cases died in the first few years. In any case, in a high proportion of cases the disease was so advanced that no treatment was given at all, or else the treatment was on a purely palliative basis and was designed to relieve pain and to diminish the extent of ulceration.

Basis of Comparison.—The commonly selected basis of comparison in carcinoma of any site is the five-year survival-rate. On such a basis progress must, however, be slow because of the delay which must occur before the results are available. Accordingly an attempt was made to obtain a more rapid means of evaluation, and it was found that if a patient remained free from recurrence for a period of three years that she was likely to be alive at the end of five years. The following figures show how remarkably the two sets of figures agree.

It must be emphasised that the symptom-free rate is used in a special sense and is taken to indicate that the patient was symptom free for three years, and not merely symptom-free at the end of this period. The three-year symptom-free rate has certain advantages over the five-year survival-rate, as is shown

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by the following example. Case 1794 had a radical excision of the breast on 30.5.36. In 1937 the patient developed several recurrences on the chest wall. On 3.8.37 these recurrences were

TABLE II

Comparison of Three-Year Symptom-Free Rate and Five-Year Survival-Rate (1930 to 1937 Cases)

	No. of Cases.	Three-Year Symptom-Free Rate.	Five-Year Survival-Rate.
		Per Cent.	Per Cent.
Stage I . . .	247	54	52
Stage II . . .	136	34	34
Stage III . . .	183	20	20
Total . . .	566	38	37

treated by means of X-rays and the patient is still alive and free from disease. The patient was thus alive at the end of five years, but could scarcely be considered to be alive as the result of operation alone. By means of the three-year symptom-free rate this case would be recorded as a surgical failure, while the five-year survival-rate actually indicates the case as a surgical success. The example also demonstrates that only the first-planned treatment can be usefully analysed. The five-year symptom-free rate would be a still more valuable means of assessment, but as the number of patients treated by post-operative radiotherapy five years ago is small, the three-year symptom-free rate, as defined, has been selected as the basis of comparison.

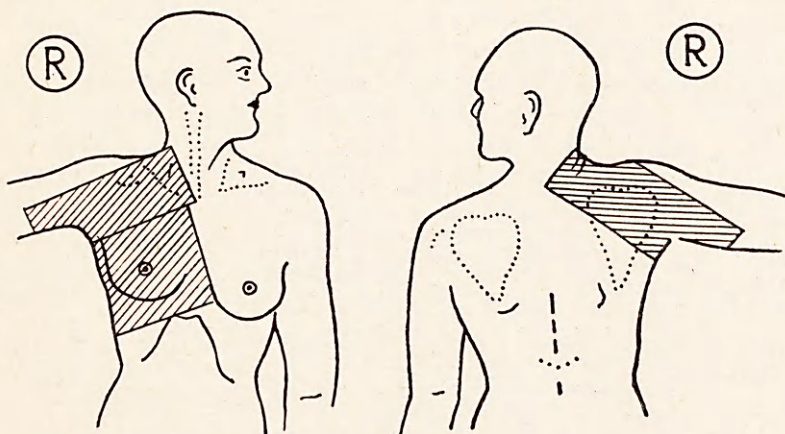
Recurrence - Rate in the "Treatable Area." — Before passing to the consideration of the three-year symptom-free rates, it is of interest to try to visualise the possible affects produced by post-operative radiotherapy.

Successful treatment of a patient by radical surgery alone implies complete removal of all disease locally from the chest wall and from the axilla, and also implies that malignant cells have not been disseminated beyond this area. Failure to cure the patient may be due to malignant cells having been left behind locally or to distant dissemination.

The area treated by radiotherapy, in this series of cases to be discussed, is more extensive than the area treated by radical surgery, and includes not only the chest wall and the axilla but also the supraclavicular region. This more extensive area will

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be referred to subsequently as the "treatable area." It will be obvious immediately that radiotherapy can only influence



results in so far as it can destroy cells left behind in the "treatable area," and that it cannot influence results if the disease has spread beyond the "treatable area."

TABLE III

New Recurrences in the "Treatable Area" expressed as a Percentage of the Total Cases Treated One, Two and Three Years Ago

			Number of Cases.			Percentage.		
			One Year.	Two Years.	Three Years.	One Year.	Two Years.	Three Years.
Stage I	Radical Surgery	Recurrences	22	9	7	Per Cent.	Per Cent.	Per Cent.
		Total Cases	165	163	153	13.3	5.5	4.6
	Surgery plus Radiotherapy	Recurrences	4	3	1	2.0	2.3	1.1
		Total Cases	202	132	93			
Stage II	Radical Surgery	Recurrences	18	5	6	21.4	6.0	7.5
		Total Cases	84	83	80			
	Surgery plus Radiotherapy	Recurrences	6	7	2	4.3	8.0	3.8
		Total Cases	139	87	52			
Stage III	Radical Surgery	Recurrences	30	5	2	28.0	4.7	2.0
		Total Cases	107	107	101			
	Surgery plus Radiotherapy	Recurrences	4	6	1	3.6	8.8	2.1
		Total Cases	110	68	48			

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The first point to be determined, therefore, is how often are malignant cells left behind in the "treatable area" after the radical operation. It is, of course, quite impossible to determine this point directly, but some indication of its frequency may be deduced by noting how often recurrences become manifest at a later date in this area. By the same means the effectiveness of post-operative radiotherapy may be determined.

The recurrence-rates in the "treatable area" after radical surgery alone are high in all three stages. It is important to bear in mind that the method of staging is not that usually employed—namely the Steintal method. In the Steintal method cases are only placed in Stage I provided that there is no involvement of the skin and provided that the axillary glands on histological examination were free from secondary deposits.

TABLE IV

Comparison of Results between Radical Surgery and Surgery plus Post-Operative Radiotherapy

			Number of Cases.			Percentage Symptom-Free.		
			One Year.	Two Years.	Three Years.	One Year.	Two Years.	Three Years.
Stage I	Radical Surgery	Symptom-Free Total Cases .	124 165	107 163	83 153	75	66	54
	Surgery plus Radiotherapy	Symptom-Free Total cases .	180 202	103 132	71 93	89	78	76
Stage II	Radical Surgery	Symptom-Free Total Cases .	52 84	35 83	22 80	62	42	28
	Surgery plus Radiotherapy	Symptom-Free Total Cases .	116 139	57 87	31 52	83	66	60
Stage III	Radical Surgery	Symptom-Free Total Cases .	50 107	31 107	21 101	47	29	21
	Surgery plus Radiotherapy	Symptom-Free Total cases .	93 110	37 68	21 48	85	54	44

Dr A. C. Aitken has kindly examined the figures in this table and is satisfied that the difference in the results is statistically significant.

If the cases had been staged by the Steintal method the number of cases in Stage I would have been approximately half that

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included in the above clinical Stage I, and the number of recurrences would have been considerably less in this stage. (Of 215 cases in clinical Stage I, 49 per cent. were found to have involvement of the axillary glands on histological examination.)

The Symptom-Free Rates in Stages I, II and III. The reduction in the local recurrence-rate is considerable in all stages, and it is, therefore, to be expected that post-operative radiotherapy should result in an increase in the three-year symptom-free rate.

The results in Table IV at the three-year period are what might be expected from a study of the total recurrence-rates in Table III.

TABLE V

Recurrence-Rates in the "Treatable Area" and Symptom-Free Rates

		Total Recurrence-Rate at Three Years.	Symptom-Free Rate at Three Years.
		Per Cent.	Per Cent.
Stage I	Radical Surgery	23·4	54
	Surgery plus Radiotherapy	5·4	76
	Difference	18·0	22
Stage II	Radical Surgery	34·9	28
	Surgery plus Radiotherapy	16·1	60
	Difference	18·8	32
Stage III	Radical Surgery	34·7	21
	Surgery plus Radiotherapy	14·5	44
	Difference	20·2	23

In the above table the difference in the total recurrence-rates in three years bears some relationship to the difference in the symptom-free rates obtained by the two methods of treatment.

The Symptom-Free Rates with and without Involvement of the Axillary Glands.—The Steintal method of staging has already been mentioned, and it was noted that this method of staging was dependent on the histological examination of the axillary glands. The effect of secondary involvement of the axillary glands is considerable, and it was thought advisable to re-group the cases in the above three clinical stages into two groups—those without histological involvement of the axillary glands and those with involvement—and to compare again the results from radical surgery alone and from surgery combined with post-operative radiotherapy. Unfortunately histological examination of the axillary glands was not always carried out, and the number of cases available for comparison is smaller.

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The recurrence-rates in the "treatable area," the symptom-free rates in each stage and the symptom-free rates according to

TABLE VI

Comparison of Results between Radical Surgery and Surgery plus Post-Operative Radiotherapy
Stages I, II and III. Axillary Glands Histologically Examined

			Number of Cases.			Percentage Symptom-Free.		
			One Year.	Two Years.	Three Years.	One Year.	Two Years.	Three Years.
						Per Cent.	Per Cent.	Per Cent.
Glands Histologically Negative	Radical Surgery	Symptom-Free Total Cases .	65 79	53 78	42 74	82	68	57
	Surgery plus Radiotherapy	Symptom-Free Total Cases .	85 87	58 64	39 43	98	91	91
Glands Histologically Involved	Radical Surgery	Symptom-Free Total Cases .	77 143	52 141	33 135	54	37	24
	Surgery plus Radiotherapy	Symptom-Free Total Cases .	160 197	85 151	50 100	81	56	50

whether the axillary glands were involved or not, all show that effective post-operative radiotherapy results in considerably improved symptom-free rates and, therefore, in higher five-year survival-rates. Up until 1941 the decision to treat or not to treat cases by post-operative radiotherapy, rested with the surgeon in charge of the case, and it may be assumed that there was no selection of early cases for radiotherapy. If anything, the reverse was the case. A further point in demonstrating that the better results in the surgery plus radiotherapy group were not obtained by selection is the fact that the results obtained in all cases in Stage I, II and III have improved since the present method of radiotherapy was introduced in 1935.

The improvement in the three-year symptom-free rates is sufficiently great to show that the use of post-operative radiotherapy has, in fact, led to better results and proves, too, that the improvement shown in Tables IV and VI was not obtained by selection.

It should be noted, too, that only 45 per cent. of the total cases in the period 1935 to 1939 received full post-operative

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radiotherapy. Since 1939 (*i.e.* the period 1940 to 1942), 95 per cent. of all cases in Stages I, II and III have received

TABLE VII

*Comparison of Results between the periods 1930 to 1934 and 1935 to 1939.
All Cases in Stages I, II and III (Post-Operative Deaths excluded)*

		Three-Year Symptom-Free Rates.		Percentage of Cases receiving Full Post- Operative Radio- therapy, 1935 to 1939.
		1930 to 1934.	1935 to 1939.	
Stage I	Total Cases	131	201	Per Cent.
	Symptom-Free	53 per cent.	62 per cent.	45
Stage II	Total Cases	80	94	
	Symptom-Free	26 per cent.	40 per cent.	52
Stage III	Total Cases	120	114	
	Symptom-Free	19 per cent.	32 per cent.	41
Stages I, II and III	Total Cases	331	409	
	Symptom-Free	34 per cent.	49 per cent.	45

full post-operative radiotherapy, so that in the future still greater improvement may be expected.

Present Methods.—The difference in the symptom-free rates when the glands are histologically involved suggests that, as shown in Table VI, post-operative radiotherapy may be relied upon to destroy the malignant cells left behind in the axilla, for the results are almost twice as high when post-operative radiotherapy was given.

Complete removal of secondarily involved axillary glands by surgery is never an easy matter, and even with the greatest care malignant cells may be left behind in the wound. Following the operation considerable serous exudate pours into the area, and as this exudate is absorbed malignant cells may escape to distant sites and may, therefore, spread beyond the "treatable area." When distant dissemination has thus occurred post-operative radiotherapy is rendered ineffective.

Consequent upon these observations it was agreed that, for a time at least, the breast alone should be removed by surgery and that the axilla should not be dissected, and that all cases so treated surgically should have a full course of radiotherapy. It is still much too early to evaluate the results, and the following one-year symptom-free rates are put forward with some hesitation.

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Should this method of treatment prove no more effective than the radical operation combined with radiotherapy, it would still be preferable because the patient has much less subsequent disability and the post-operative mortality is reduced. (The

TABLE VIII

Comparison between Radical Surgery Alone, Radical Surgery plus Post-Operative Radiotherapy and Simple Mastectomy plus Post-Operative Radiotherapy. Symptom-Free Rates at the end of One Year

		Radical Surgery.	Radical Surgery plus Radiotherapy.	Simple Mastectomy plus Radiotherapy.
Stage I	Total Cases	165	109	93
	Symptom-Free one year	124	94	86
	Percentage	75	86	92
Stage II	Total Cases	84	85	54
	Symptom-Free one year	52	72	43
	Percentage	62	85	80
Stage III	Total Cases	107	62	48
	Symptom-Free one year	50	52	41
	Percentage	47	84	85

death of a patient within one month from the time of the operation has been accepted as the definition of a post-operative death.) With the radical operation the post-operative mortality is probably as high as 5 per cent., while with simple mastectomy the post-operative mortality is of the order of 1 per cent. or less. In the ultimate analysis of any group of cases the post-operative mortality must be taken into account, and the results would actually be better in the case of simple mastectomy provided that the symptom-free rates, as obtained above, were the same.

The method is still on trial, and it would seem advisable that it should not be generally adopted in other centres until the results of the investigation are available. It is, of course, very important that this method should not be adopted in centres in which effective post-operative radiotherapy is not available.

Stage IV Cases.—So far this stage has not been considered in any detail. The table on p. 204 shows the survival-rates obtained.

Some of these cases have had a full course of post-operative radiotherapy but, as might be expected, the influence of radiotherapy is negligible, because almost all the cases already had

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distant metastases well beyond the "treatable area." Many of the cases in this group had no treatment at all, and were admitted to medical wards in a moribund state or with jaundice, pleural

TABLE IX

Stage IV. Net Survival-Rate (1930 to 1941)

	One Year Alive.	Two Years Alive.	Three Years Alive.	Four Years Alive.	Five Years Alive.
Total	307	244	205	164	128
Alive	125	33	14	4	2
Percentage Alive . . .	41	14	7	2	2

effusions, skeletal metastases, etc. It is impossible, meantime, to visualise how the results may be improved once the disease has reached this stage of advancement.

The Necessity for Early Diagnosis and Treatment.— If progress is to be made in the treatment of carcinoma of the breast as a whole, then patients must be treated before they reach this stage. It should be noted from Table I that no fewer than 21 per cent. of all the cases referred to the centre were in this advanced category. What is the explanation of the delay in treatment? This can be resolved into two main causes, the delay due to the patient and the delay due to the present medical outlook and organisation. Information is now being collected on these points, and the following table shows that a considerable proportion of the delay is due to the medical profession and to the existing medical organisation.

TABLE X

Cancer of the Breast

	Delay before Treatment is Undertaken.			Percentage of Cases Treated in Less than Three Months.
	Average Total Delay.	Average Medical Delay.	Average Patients' Delay.	
Stage I	6.2 months	3.0 months	3.2 months	Stage I 60
Stage II	7.7 "	3.5 "	4.2 "	Stage II 51
Stage III	11.7 "	6.0 "	5.7 "	Stage III 32
Stage IV	13.1 "	4.9 "	8.2 "	Stage IV 25
All Stages	9.4 "	4.1 "	5.3 "	

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Owing to the teaching of the past and to the fact that it is impossible for the average general practitioner to gain adequate experience in the diagnosis of cancer of the breast, it far too often happens that the early case is wrongly diagnosed as a cyst, a simple tumour, or an area of chronic mastitis. Textbooks all too often describe only the advanced stages of the disease, and it is common to find, prominently displayed, a long list of differential diagnoses so set out as to indicate that a differential diagnosis is possible in all cases. It cannot be too strongly emphasised that, in many cases, the features of an early cancer of the breast are identical with those of a cyst or simple tumour. In the early stages a carcinoma is a mobile tumour within the breast and there is no enlargement of the axillary lymph nodes. Differential diagnosis with any degree of certainty is only possible when the cancer has reached an advanced stage. The diagnosis of cancer of the breast is, therefore, histological in the early stage of the disease—the stage at which treatment gives highly successful results.

Any tumour of the breast must be regarded as carcinoma until it is removed and histologically proven otherwise. The age of the patient is not always a reliable guide, for in this series one in every twelve patients were found to be under forty years of age. To wait till the period of clinical certainty is reached, when the disease shows all the so-called classical signs of its presence, is perhaps of value so far as the signing of the death certificate is concerned, but it is of little value to the patient. A diagnosis must be made at the curative stage and not at the pre-death-certificate stage if better results are to be obtained in cancer of the breast as a whole. It follows, too, that the existing organisation for treatment must be altered so that hospital waiting-lists for malignant disease are abolished. Until this is possible it is important that early cases should be given preference in admission, and that preference should not be given to the late cases as so often happens at present.

So far as the patient's delay is concerned, I feel sure that this will become less as soon as the public come to realise that cancer of the breast can be cured in a high proportion of cases. Reorientation of the medical outlook in the direction indicated above, and the better results consequent upon this, will do much to diminish the patient's delay, because the fear which exists at present as to the ultimate outcome will no longer be justified.

Under present conditions the public is justified in being

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afraid of the outcome when a diagnosis of cancer is made, for of the 2000 cases of cancer in all sites occurring per 1,000,000 of the population, 1700 die of cancer. The medical outlook must first change before propaganda to the public is introduced, because if patients did seek advice at an earlier stage, in many cases they would be assured that the condition was not serious, and because they naturally wish to believe this, they might not seek advice again till an even later stage than at present. As in cancer so in other diseases, early diagnosis and treatment are of paramount importance, and every effort must be made to bring this about in the near future. It cannot be too strongly emphasised that there is no credit attached to the making of a diagnosis when all the classical signs and symptoms are present and that such a diagnosis is nearly always a "pre-death-certificate diagnosis."

Provided that patients do come to be treated earlier, I see no reason why, at the very least, one out of every two of all cases of cancer of the breast (all four stages) should not be permanently cured. It is important to realise that this high figure is easily obtainable with the methods of treatment at present available (surgery and radiotherapy).

Summary

1. Of the women who develop cancer, one in four develops the disease in the breast.

2. In this series the average age of the patient when treated was 55.5 years.

3. Under existing conditions, and when surgery is the only method of treatment available, probably not more than one in five of *all cases* of cancer of the breast survive five years.

4. The three-year symptom-free rate (as defined) is not only a reliable guide to the five-year survival-rate, but its adoption permits of progress being made more rapidly.

5. A total of 1879 cases has been analysed, and in the operable group (stages I, II and III) effective post-operative radiotherapy, by destroying cells left behind in the "treatable area," results in much higher three-year symptom-free rates in all three stages.

6. Post-operative radiotherapy is still effective when the disease has spread to the axillary glands, but is of no value so far as survival-rate is concerned if the disease has spread to distant sites.

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7. Simple mastectomy combined with post-operative radiotherapy as a method of improving results and as a means of diminishing disability is on trial.

8. Survival to five years in the advanced (Stage IV) group is so low as to be accidental, irrespective of the method of treatment employed.

9. The delay which occurs between the time the patient first notices "something wrong" and treatment is on an average nine months, and much of the delay is due to the present outlook and organisation in medical practice.

10. Treatment before the stage of clinical certainty is reached is strongly advocated if further progress is to be made. At the early highly curable stage a clinical differential diagnosis should not be attempted. Excision and histological examination is the only reliable means of diagnosis.

11. If medical delay is eliminated, the cure of at least one out of every two of all cases of cancer of the breast is easily possible with methods of treatment at present available. When such results can be published, it is doubtful if any other form of propaganda to the public will be required.

In conclusion, I would like to express again my gratitude to the Surgical Staff for their very friendly and very helpful co-operation in this work. Without their co-operation the investigation would not have been possible and, while I have had the honour of reading the paper, I trust it will be appreciated that it is read on behalf of the Surgical Staff as well as on behalf of the Staff of the Radiotherapy Department.

I must also refer to further help. The number of cases investigated was almost two thousand, and in the extraction of the above information the records had to be examined many times. I have been fortunate in having secretarial assistance provided by means of a grant made available by Professor Learmonth from the Wilkie Research Fund.