Papers and Originals

Results of Treatment of Breast Cancer at Aberdeen Royal Infirmary 1940-55

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Over 16 years ago a survey of the results of treatment for cancer in this region (Philip, 1949) made apparent the need for evaluation of our policy for breast cancer, which was treated mainly by radical surgery, with or without postoperative radiotherapy, and it was concluded that the treatment of operable breast cancer should not be resolved into fixed terms of surgery and radiotherapy. In planning treatment for a particular case the size and position of the growth, its extent so far as this could be assessed clinically, the age and general condition of the patient, and the existence of concomitant disease should each play a part. No significant improvement in our survival rate for the disease has been achieved by this policy except in so far as hormone therapy has been effective in dragging many terminal cases over the arbitrary five-year line. Nevertheless, it was thought that a report of the results of that treatment policy might be of some general interest.

The records of 1,335 patients were examined individually and Table I shows their clinical staging, method of treatment, and five-year survival rates. The follow-up is incomplete for nine patients beyond the five-year line—from periods varying between 5.5 and 13 years—and one patient has been excluded from the survey because she could not be traced at the end of two years after treatment. Some patients treated over 20 years ago are still alive and on the follow-up register. The clinical staging used for the series is the one usually referred to as the "Manchester" method.

TABLE I.—*Survival-rate Figures by Staging and Method of Treatment, 1940–55*

Treatment	Stage	No.	Alive at 5 Years	Unstaged	Alive at 5 Years
Radical mastectomy	I	111	68	1	1
	II	72	36		
	III	22	5		
	IV	8	1		
Radical mastectomy +X.R.T.	I	109	59	8	0
	II	148	80		
	III	62	15		
	IV	20	2		
Local mastectomy	I	27	10	1	1
	II	15	3		
	III	22	2		
	IV	11	1		
Local mastectomy +X.R.T.	I	151	106	2	0
	II	130	55		
	III	78	24		
	IV	29	1		
X.R.T.	I	3	1		
	II	9	5		
	III	43	8		
	IV	78	4		
*Modified radical mastectomy	I	4	3		
	II	3	3		
	III	2	1		
Modified radical mastectomy +X.R.T.	I	19	16	1	0
	II	13	6		
	III	6	1		
	IV	1	0		
Local excision	I	3	2		
	II	2	1		
	III	3	0		
	IV	2	0		
Local excision +X.R.T.	I	12	9		
	III	1	0		
	IV	1	0		
Seen only	I	10	2		
	II	5	0		
	III	14	3		
	IV	73	1		
Total		1,322	534	13	2

Absolute five-year survival rate = 40%.
*Pectoral muscles not removed.

1. Clinical Staging

Table II shows the clinical staging and five-year survival rates for the series; 63% were in the stage I and stage II groups. Of 449 stage I cases the axillary nodes were subsequently found to be invaded in 91—an error of 20% in the clinical stage I group. Of 397 stage II cases the axillary nodes were found to be free of secondary disease on histological examination in 60—an error of 15%.

TABLE II.—*Clinical Staging, with Average Length of History, of* 1,335 *Patients with Breast Cancer,* 1940–55

Stage	No. of Cases	No. Alive at Five Years	Survival %	No. of Cases where Length of History was Recorded	Average Length of History (Months)
I	449	276	61·4	422	6·95
II	397	189	47·6	373	10·6
III	253	59	23·3	231	15·37
IV	223	10	4·4	204	17·55
Unstaged	13	2	15·4	11	10
Total	1,335	536	40·1	1,241	11·38

The significant point is that one out of five patients in the clinical stage I group had the disease in the axillary nodes at the time of diagnosis, and this figure takes no account of possible internal mammary-node involvement or of distant metastases.

Operability Rates.—The operability rate of the 1930–9 series was contrasted with a 10-year period in the present series, and a rise of 15% in the latter probably reflects an increasing awareness by the public of the possible significance of a lump in the breast, leading more patients to report earlier, and has some bearing also on increased five-year survival rates.

Clinical Staging Related to Delay.—The average length of history (Table II) bore some relation to the "clinical" staging of the disease at the time of diagnosis; stage I, 6.95 months; stage II, 10.6 months; stage III, 15.37 months; and stage IV, 17.55 months. Nevertheless, there were marked differences in the length of history given by patients in the same clinical staging. In Table IV it will be seen that 34 patients out of 422 in the stage I category gave a history varying from 18 months to over three years. With each decade there was an increase in the difference between the length of history for stage I and

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stage IV cases. This may mean that in younger patients the interval before a growth reached stage IV was much shorter than in older patients, or that older patients survive in stage IV for a longer period of time before seeking treatment than those in the younger age groups.

Clinical Staging Related to Age Groups.—The records were examined to see whether age had any bearing on the likely clinical staging at the time the patients sought treatment, and Table III shows the number of patients in each stage for each decade. Up to the age of 50 approximately 70% of the cases in each decade were clinically staged I or II, but after the age of 50 there was a gradual decline in the proportion of operable cases with each decade.

Age and Length of History.—Table III shows that the average duration of symptoms in each stage and for all cases registered tended to increase until the end of the seventh decade, after which the curve rose more steeply.

Conclusion.—Over the entire series clinical staging bore some but no constant relation to delay and to age groups.

II. Five-year Survival Rates

In the series of 1,335 patients treated in 1940–55 the absolute five-year survival rate was 40%. When assessed at intervals during the period under review the five-year absolute survival rates were: 1940–4 35%, 1945–9 38%, 1950–5 43%. These figures compare with 28% from an earlier series treated here in 1930–6.

Since 1936 the absolute five-year survival rate increased by something like 15%, but most of this increase appeared over 15 years ago. The increase was due, in some measure at least, to the higher operability rate, partly to ancillary aids in treatment such as blood transfusion, to improvements in anaesthesia, to antibiotics, and in later years to hormone therapy. The increase in five-year survival rates therefore owes little to technical advances in treatment by themselves if we argue that we are now treating patients at an earlier stage in the natural history of the disease. For example, the rise in operability rate is mainly due to the increased incidence of stage I and stage II cases at the time of treatment, and there is a general relation between staging and length of history, though admittedly this is by no means constant, and we get many patients in a particular clinical staging, with each one giving a different length of history before treatment. This can lead to ambiguity both in the interpretation of survival rates and in the effectiveness of the treatment adopted.

Suppose two patients, A and B, develop the disease simultaneously and that both survive for the same length of time thereafter, say six years. If A delays two years before treatment and then lives for four years she is excluded from the five-year survivors, whereas B accepting treatment after only one year's delay is included in the five-year survival-rate figures, though she has the same total period as A, and these patients may actually be in the same clinical stage group at the time of treatment.

If applied to the aggregate, however, these considerations do not make a significant difference to the ultimate results, and advantage for total survival time remains with the stage I group (see Table V).

Hormone ablative procedures, apart from an occasional ovariectomy, did not come into general use until after the period covered by the survey, so that their effect on the five-year rate is not as yet apparent.

All that we can expect so far, then, is that approximately one of every two patients we see with breast cancer will be alive at

TABLE III.—*Clinical Staging Related to Age Groups*, 1940–55

Age Group	Total No. of Cases					Average Duration of Symptoms (Months)					Percentage in Stages I and II
	I	II	III	IV	Unstaged	I	II	III	IV	Unstaged	
20–29	3 (0)			1 (0)		4			4		75
30–39	36 (3)	27 (3)	13 (1)	12 (1)		5·86	4·48	12·75	6·04		71·6
40–49	118 (2)	108 (4)	44 (2)	36 (1)	4 (1)	6·94	8·86	8·84	9·77	2·83	72·9
50–59	104 (6)	90 (3)	51 (5)	55 (2)	4 (0)	5·63	10·46	9·33	13·99	8·37	63·8
60–69	117 (6)	109 (5)	75 (8)	66 (4)	2 (0)	7	9·76	16·42	17·18	18	61·2
70–79	58 (7)	50 (6)	56 (4)	40 (7)	3 (1)	7·12	20·64	20·27	34·76	16	52·4
80+	13 (3)	10 (1)	12 (1)	12 (4)		22·95	9·97	41	22·25		48
N.K.		3 (2)	2 (1)	1 (0)			3	1	36		50
Total	449 (27)	397 (24)	253 (22)	223 (19)	13 (2)						

Figures in parentheses indicate number of patients where length of history was not recorded.

TABLE IV.—*Length of History (Delay) and Five-year Survival Rates*, 1940–55

Delay*	All Cases												Cases Submitted to Radical Measures Only											
	Total		Stage I		Stage II		Stage III		Stage IV		Unstaged		Total		Stage I		Stage II		Stage III		Stage IV		Unstaged	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1/12 or less (a)	223		115		67		20		20		1		189		103		64		13		9		1	
(b)	122	54·7	78	67·8	37	55·2	5	25	2	10	—	0	115	60·8	74	71·8	36	56·2	4	30·7	1	11·1	—	0
1/12 to 3/12 (a)	319		127		113		41		35		3		263		115		107		30		9		3	
(b)	135	42·3	70	55·1	55	48·6	8	19·5	1	2·8	1	33·3	126	47·9	64	55·6	54	50·4	6	20	1	11·1	1	33·3
3/12 to 6/12 (a)	221		70		69		42		38		2		176		66		67		32		8		2	
(b)	88	39·8	40	57·1	40	57·9	8	19	—	0	—	0	85	48·3	39	59	40	59·7	6	18·7	—	0	—	0
6/12 to 1 year (a)	242		69		63		65		44		1		178		63		53		42		17		1	
(b)	85	35·1	46	66·6	26	41·2	10	15·4	3	6·8	—	0	74	41·6	43	68·2	23	43·4	8	19	—	0	—	0
1 year to 18/12 (a)	52		7		14		17		12		2		31		6		13		9		2		2	
(b)	17	32·7	6	85·7	5	35·7	6	35·3	—	0	—	0	13	41·9	5	83·3	4	30·8	4	44·4	—	0	—	0
18/12 to 2 years (a)	73		15		19		17		20		2		49		12		16		12		6		2	
(b)	27	37	11	73·3	8	42·1	6	35·3	2	10	—	0	24	49	10	83·3	7	43·7	5	41·6	2	33·3	—	0
2 to 3 years (a)	46		8		10		12		16		—		26		4		9		9		4		0	
(b)	15	32·6	5	62·5	4	40	6	50	—	0	—	0	11	42·3	3	75	3	33·3	5	55·5	—	0	—	0
3 years + (a)	65		11		18		17		19		—		36		7		17		11		2		—	
(b)	23	35·4	3	27·3	9	50	9	52·9	2	10·5	—	0	17	47·2	1	14·3	9	52·9	7	63·6	—	0	—	0
N.K. (a)	94		27		24		22		19		2		52		18		20		12		1		1	
(b)	24	25·5	17	62·9	5	20·8	1	4·5	—	0	1	50	18	34·6	13	72·2	4	20	1	8·3	—	0	—	0
Total (a)	1,335		449		397		253		223		13		1,000		394		366		170		58		12	
(b)	536	40·1	276	61·4	189	47·6	59	23·3	10	4·4	2	15·4	483	48·3	252	63·9	180	49·1	46	27	4	7	1	8·3

* (a) = Patients. (b) = No. alive at five years.

the end of five years. The picture as it applies to 10 and to 15 years is referred to below.

Can we look for any common denominator on which treatment policy might be founded, by an appraisal of different factors which from time to time have been accepted as having a bearing on the five-year prognosis? The influence of delay, age groupings, general histological features of the primary growth, and differing modalities in treatment were considered separately in relation to five-year survival rates, and with the following results.

Effect of Delay (Length of History) on Five-year Survival Rates

Patients tend to underestimate rather than overestimate the duration of a lump in the breast, but the length of history has been taken as that recorded in the case notes. Delay intervals have been divided into eight separate groups: (1) less than one month, (2) one to three months, (3) three to six months, (4) six to 12 months, (5) 12 to 18 months, (6) 18 months to two years, (7) two to three years, (8) over three years. Table IV indicates the five-year survival rates as related to these intervals of delay for all cases seen and also for those subjected to radical measures.

In the group subjected to radical treatment there would appear to be advantage to those patients reporting with a history of one month or less, and a little to those reporting up to six months from discovery of the tumour; otherwise the five-year survival rate did not seem to be particularly affected by delay, even up to periods of over three years. If we consider all cases, whether treated or not, the same general picture is presented, so we may conclude that, in general terms, after the lapse of one month increasing delay by itself is not of much import in relation to five-year survival rates, unless it is associated with advanced clinical staging.

For example, should a growth still be staged I after two years' delay the patient stands a good chance of being alive at the end of five years from treatment, and to a lesser extent this holds for more advanced cases. The reverse is also true. If a growth has progressed to stage IV in a short period of time the prognosis will be much poorer than for one that has done so only after a long interval. Table V shows the five-year rate for patients in each stage (from a 10-year period) set against the combined preoperative and postoperative length of history. It also shows the average total survival times for each staging. The increase in the five-year rate when worked out in this way gives approximately 7% for stages I, II, and III and about 13% for stage IV of the total cases in the survey (see Table II).

Bearing of Age on Five-year Survival Rates

In the older age groups intercurrent disease must play an increasingly important part in reducing the five-year survival rate. On the other hand, operative risk is not the hazard it was and more elderly patients are being subjected to curative treatment. Certainly our results suggest that up to the age of 70 no great significance could be attached to age in relation to five-year survival rates, except for the 40–49 group, where possibly the effect of the menopause was beneficial. In the 40–49 age group the five-year survival rate was 63% of the series of operable cases as compared with 58% for both the 30–39 and the 50–59 age groups; and this finding we accept as statistically significant. ($\chi^2(7)=25.1$. $P<0.001$.) After the age of 70 a progressive reduction occurred in the survival rates, which is what one might expect from advancing age and concomitant disease.

TABLE V.—*Five-year Survival Rates in Terms of Survival from Date of Earliest Sign or Symptom* (1943–1952)

Stage	No. of Cases	No. Alive at Five Years	Survival %	Average Total Survival Period
All Cases (Five-year survival rate = 47·89%)				
Stage I ..	285	194	68·07	104·13
„ II ..	256	138	53·9	84·99
„ III ..	156	49	31·41	52·9
„ IV ..	147	26	17·68	35·27
Unstaged ..	10	2	20	40·8
Radical (Five-year survival rate = 54·36%)				
Stage I ..	254	179	70·47	107·06
„ II ..	242	133	54·96	87·16
„ III ..	109	39	35·78	58·74
„ IV ..	49	8	16·32	39·65
Unstaged ..	10	2	20	40·8
Non-radical (Five-year survival rate = 25·26%)				
Stage I ..	31	15	48·38	80·14
„ II ..	14	5	35·71	47·39
„ III ..	47	10	21·27	39·35
„ IV ..	98	18	18·36	33·07

Histological Type Related to Five-year Survival Rates

The cases subjected to radical treatment were divided into arbitrary groups according to the pathology if noted: (1) intraduct carcinoma; (2) adenocarcinoma; (3) spheroidal-cell, encephaloid, anaplastic carcinoma; and (4) colloid or mucoid carcinoma.

Survival-rate figures at five years are shown for those patients in the stage I and II groups (Table VI). As might be expected, the survival rate was high for intraduct carcinoma. If the growth was predominantly spheroidal-celled, anaplastic, or encephaloid the five-year survival rate was much lower than for intraduct cancer but 8% higher than for scirrhous cancer.

TABLE VI.—*Histological Type and Five-year-Survival Rates*

Histological Type	Stage I			Stage II			Stages I and II		
	No.	Alive at 5 Years	%	No.	Alive at 5 Years	%	No.	Alive at 5 Years	%
Carcinoma with intraductal element still obvious ..	42	32	76	15	12	80	57	44	77
Adenocarcinoma	16	8	50	9	4	44	25	12	48
Scirrhous carcinoma ..	70	43	61	50	15	30	120	58	48
Spheroidal cell, encephaloid, anaplastic ..	255	157	61	249	128	51	504	285	56
Others	11	8	73	16	9	56	27	17	63

Treatment Methods and Five-year Survival Rates

During the period covered by the survey there were five modalities in the treatment of operable breast cancer. It is difficult, and perhaps pointless, to attempt to define clinical considerations which conditioned the selection of each particular method. It would be fair to say that "personal conviction" based on clinical experience, and training, were in large measure responsible for individual preferences in treatment. It is certainly true that operation alone, as practised in earlier years, was a more radical procedure than that obtaining today, but it is also true that the radical operation was in some instances carried out in earlier years for certain stage III cases for which it would not be considered now.

From 1944 onwards a modified radical mastectomy had some measure of support, entailing axillary dissection but leaving the pectoral muscles behind.

With improved radiotherapeutic technique the morbidity associated with radiation became less, and therapy became more generally acceptable, so that preoperative irradiation was increasingly employed for patients in the stage III group who might subsequently be submitted to mastectomy.

The use of local mastectomy and *x*-ray therapy in the series increased from 15% in 1940–4 to 32% in 1950–5, whereas the rate for radical mastectomy fell from 30% to 14% in the same periods.

Five-year survival rates for all cases treated by radical measures are as shown in Table VII, and, separately, those in the stage I and

TABLE VII.—*Five-year-survival Rates for All Cases Treated by Radical Measures*

Method of Treatment	No. of Cases	No. Alive at Five Years	Survival Rate (%)	Stages I and II Only	Stages I and II Only	Stages I and II Only (%)
Radical mastectomy ..	223	118	53	190	110	58
„ +X.R.T. „	387	179	46	289	161	56
Local mastectomy +X.R.T.	390	186	48	281	161	57

II groups only. Where curative treatment is concerned, and when all cases are taken together, the advantage was to radical mastectomy alone, but this difference may not be significant, because the group of cases receiving irradiation may have included a proportion of cases with the disease locally advanced or in the medial part of the breast.

It must be concluded, however, that for breast cancer there was no significant difference between the five-year survival rates for the three main modalities in treatment which we have employed. It is still our policy to plan treatment on an individual basis, but in its application to the aggregate it is realized that even at its most effective such a policy is unlikely to produce a rise in the absolute five-year survival rates which could be regarded as significant.

Survival Rate for Patients given Palliative Treatment Only

It is of interest that where local treatment alone was used (local mastectomy, local excision, local excision + *x*-ray therapy, or *x*-ray therapy alone) for 233 patients 47 (20%) were alive at five years, and of 102 patients who had no surgical or radiation treatment six survived for five years after diagnosis.

Ten- and Fifteen-year Survival Rates

Up to ten-year survival-rate figures are shown for cases registered between 1940 and 1951 inclusive, and up to 15-year survival rates for those patients seen up to the end of 1940 (Table VIII).

Incidence of Scar Recurrence after Treatment

In this report the "scar" is defined as the area outlined by the breast flaps and the axillary bed, and the records of 951 patients subjected to "radical" measures are presented. Three main modalities in treatment were used—radical mastectomy, radical mastectomy and *x*-ray therapy, and local mastectomy followed by *x*-ray therapy. The recurrence rate for each method of treatment is shown in Table IX. In addition, the scar-recurrence rate for stage II cases is presented separately because it seems that conditions when treatment was applied by differing techniques show their closest approximation in this group.

TABLE IX.—*Incidence of Scar Recurrence After Different Modalities in Treatment*

Method of Treatment	No.	Rec. Rate (%)	No. of Stage II Cases	Rec. Rate for Stage II Cases Only (%)
Radical mastectomy ..	214	15	72	10
" +X.R.T. "	347	18	148	17
Local mastectomy +X.R.T.	390	18	130	18

The figures show apparent advantage to radical mastectomy alone, but it should be observed that the cases so treated were in the main those most suited for the operation, usually fit patients with the disease either central or in the outer part of the breast, and to this extent they represent a selected group. On the same count it would be illogical to blame the higher recurrence rate in those patients who had irradiation to a lowering of local tissue resistance after such therapy. If in fact the difference shown is meaningful the explanation may lie in the greater preponderance of local advancement in those cases given *x*-ray therapy as part of their planned treatment.

It must be accepted, however, that all three curative treatment methods were subject to scar recurrence to an average degree of 17%. In approximately one out of every five or six patients the disease was not eradicated from those areas in which treatment was specifically designed to do so. It is seldom that any such recurrence can be treated successfully, and this must at once reduce the potential cure rate in operable cases, quite apart from the possibility of death from distant metastases or intercurrent disease.

TABLE X.—*Incidence of Pulmonary Metastases and Skeletal Metastases Recorded at Follow-up Clinics*

Method of Treatment	No. Treated	Developed Pulmonary Metastases		Developed Skeletal Metastases	
		No.	%	No.	%
Radical mastectomy	214	32	15	40	19
" +X.R.T. " ..	347	72	21	117	34
Local mastectomy +X.R.T. ..	390	72	18	95	24
Total	951	176	18	252	26

TABLE VIII.—*Five-, 10-, and 15-year Survival Rates for 349 Patients who Received Radical Treatment in 1940–46, and Five- and 10-year Survival Rates for 710 Patients who Received Radical Treatment in 1940–51*

Method of Treatment	No.	1940–6			No.	1940–51	
		Alive at 5 Years	Alive at 10 Years	Alive at 15 Years		Alive at 5 Years	Alive at 10 Years
Radical mastectomy, including modified radical mastectomy	100	43 (43%)	22 (22%)	14 (14%)	171	83 (48%)	44 (26%)
" " +X.R.T.	169	68 (40%)	44 (26%)	38 (22%)	300	133 (44%)	88 (29%)
Local mastectomy + X.R.T	80	41 (51%)	27 (34%)	20 (25%)	239	103 (43%)	71 (30%)
Total	349	152 (43%)	93 (27%)	72 (21%)	710	319 (45%)	203 (29%)

Metastases.—Table X shows the incidence of metastases developing in the lungs and skeleton after treatment by surgery and/or irradiation. Of 951 patients 18% developed pulmonary metastases and 26% skeletal secondaries.

Palliative Measures Subsequent to the Initial Planned Treatment

Out of 930 patients with the disease in stages I, II, or III at the time of diagnosis and initial treatment there were 307 (33%) who required subsequent treatment for local recurrence or metastases, and 14% of the whole series had treatment by

TABLE XI.—*Incidence of Recurrent Disease and the Palliative Treatment Given After Initial Curative Treatment*

Treatment	Stage	X.R.T.	Ovariectomy	Ovariectomy + Adrenalectomy	Hypophysectomy	Surg.	Oestrogen Therapy	Androgen Therapy	Two or More Methods	Alkylating Agents	Totals	All Cases Totals
Rad. mast.	I	17				1	2	4	14		38	111
	II	9					3		5		17	72
	III	2						2	1		5	22
Rad. mast. +X.R.T.	I	11					7	2	13	1	34	109
	II	1	1	3			15	2	18		40	148
	III	5					6	5	18		34	62
Loc. mast. +X.R.T.	I	6		2	1	5	4	5	14		37	151
	II	6				1	14	7	25		53	130
	III	5		2		1	9	3	13		33	78
Mod. rad. mast.	I								1		1	4
	II						2				2	3
	III										0	2
Mod. rad. mast. +X.R.T.	I	1						1			2	19
	II	1	1				1	1	3		7	13
	III						3		1		4	6
Total ..		64	2	7	1	8	66	32	126	1	307	930

two or more methods (Table XI). These figures do not include patients who had less than radical treatment initially, nor any who were in the stage IV category when first seen.

It will be observed that considerable use was made of sex hormones in treatment, oestrogens being given mainly for soft-tissue recurrent and metastatic disease, whereas androgen therapy was used for skeletal secondaries. Oestrogens were avoided for patients who were not at least six to eight years beyond the menopause, but androgens were used, apparently with safety, for any age group. The greatest success from oestrogen therapy lay with elderly patients at an average dosage of 1 mg. of ethinyloestradiol t.d.s. Androgen therapy varied from oral administration of testosterone to intramuscular injection of long-acting testosterone esters, but all of them produced virilism and hirsuties, often to a distressing degree. This complication of course does not occur so often since the introduction of Durabolin (nandrolone phenylpropionate) and Decadurabolin (nandrolone decanoate).

X-ray therapy alone was employed for 21% of the re-treated cases, sometimes for local recurrence, but more often for skeletal metastases. Its value mainly lay in the treatment of osteolytic rather than osteoplastic deposits, and, unless metastatic lesions appeared rapidly at other sites, therapy often relieved symptoms for upwards of months at a time. Most cases required admission to hospital during treatment, but a number were treated as outpatients.

Hormone ablative procedures were not in general use during the period covered by this survey and are not discussed.

Morbidity after Curative Treatment

The records of 68 patients were studied in respect of shoulder-joint disability and arm oedema. For each patient the type of operation, delay in healing, period of drainage and immobilization, position and mobility of the scar, resultant swelling, stiffness and pain, late skin effects, limitation of movement, and, in some cases, tissue pressures were recorded.

Shoulder-joint Disability.—This occurred most commonly after the radical operation, especially if this had been followed by *x*-ray therapy, but it also arose in some patients treated by local mastectomy and *x*-ray therapy and in those treated by radiation alone. The disability ranged from slight to severe, and in its worst form developed to "frozen shoulder." Three main factors predisposed to the disability:

1. A scar so placed as to "bowstring" the axilla.
2. Periarticular adhesions. These follow on the diminished range of movement produced by a badly positioned scar, but can occur quite apart from this, owing to lack of supervision in the immediate postoperative period—a failure to encourage active movements within a reasonable interval after operation.
3. The production of a dense bed of scar tissue such as may follow a very radical axillary dissection, perhaps in some cases also with damage to the neurovascular bundle in the subscapular region. It is apparent that each modality in treatment is possible without resultant limitation of shoulder-joint movement if the operative technique is correct, with skin-grafting in the "skin-short" case as described by Riddell (1950), and by the institution of postoperative exercises controlled by a physiotherapist.

Arm Oedema.—This complication occurred, at least to a minor degree, in most patients subjected to radical mastectomy. Severe oedema was distressing and incapacitating, and resulted from scarring of the main lymphatic trunks and compression of the great veins by fibrous tissue. A number of cases were also due to residual disease in the subclavian lymphatic vessels. In the series of 68 cases reviewed there was slight to marked oedema in 70% of the patients who had radical mastectomy, in 42% of those who had a modified radical procedure, but in only 28% of those treated by local mastectomy and *x*-ray therapy. In the early part of the interval covered by the series it was often the practice to remove the clavicular head of the pectoralis major, and it is certain that this procedure was an important contributory cause of postmastectomy oedema. In "pitting" oedema severe enough to be painful and incapacitating considerable relief was obtained by the subcutaneous insertion of nylon tubing from the arm down to the iliac region, a measure which provides a channel whereby the pent-up lymph is transferred to a new absorption area. With oedema due to residual disease in the axillary or subclavian lymphatics, symptomatic relief was obtained by scarifying the arm, a measure which does not require anaesthesia because the skin is taut and relatively insensitive. Relief of pain and reduction of the swelling was rapid and lasted for upwards of a week at a time and could be repeated as often as required in the terminal stage of the disease.

Pain.—A number of patients complained of subjective symptoms such as hyperaesthesia over the breast area, pain in the shoulder joint, and sometimes pain with an ulnar distribution in the hand. A few of the last-mentioned developed marked ulnar neuritis, sometimes apparently from scar compression of the brachial plexus, and in others the result of metastatic disease in the supraclavicular region.

Posture.—Patients tended to adopt a characteristic posture unless they were given a prosthesis to mask the defect on the side of the operation, and we found it desirable to provide this as soon as the wound and/or the radiation reaction had soundly healed.

Radiation Morbidity.—In some earlier cases of the series radionecrosis was not uncommon and could appear up to many years after treatment. This was a particularly intractable complication, sometimes responding to conservative treatment, but only after many months, and always apt to recur. The worst cases called for plastic procedures. Some degree of pneumonitis may be evident after irradiation. Severe damage to the lung parenchyma seldom arose, but if it occurred it caused symptoms varying from an irritable non-productive cough to dyspnoea. Irradiation fractures of ribs did not cause more than a temporary upset lasting for a few weeks, but irradiation fracture of the humerus, fortunately a rare complication, caused a great deal of distress to the patient until false joint formation took place.

Discussion

With many of the presently held concepts of breast cancer their acceptance over the years has established them almost as "facts" to which most treatment planning subscribes, and it is desirable that we should from time to time reappraise the evidence on which these concepts are founded, and, on those issues, reaffirm or modify our treatment policy.

1. Significance of Clinical Staging

The International Union Against Cancer (1959) recommended a five-year clinical trial of what is termed the T.N.M. method of clinical staging. This is a distinct advance on those systems previously in use, but let us not ignore the point that it cannot define the extent of the disease; in this it must often be quite inaccurate. This degree of inaccuracy is perhaps of little consequence in cancer of skin and lip, etc., but not when applied to the more unpredictable high-risk cancers of the breast and cervix. Tumours in the latter situations form metastases much more readily than the former, and the margin of error between the clinical staging and actual extent of the disease must always be that much greater, so that any tendency for treatment policy to be rigidly defined on a basis of clinical staging is a retrograde step with implications which we must guard against.

Figures published on the basis of clinical staging may indicate that x% of the cases had no evidence of nodal metastases: this does not mean that the regional nodes were not involved ; they may have been found to be so at operation, or on histological examination, or at necropsy. Unless this fact is appreciated, or specifically stressed, it is easy for one to get the impression that in those particular cases the disease was confined to the primary site at the time of operation. The composite picture for cancer in most situations is therefore unrealistic, as it is defined and presented by clinical staging. It must be accepted, however, that clinical staging is the only method which can be applied uniformly to the disease irrespective of the treatment carried out.

2. Evaluation of Survival Rates

The realistic index for comparing results between centres is not the survival rate applied to various clinical stages but the absolute survival rate—that is, the figure for all cases registered, whether treated or not—and this figure should be considered in relation to the annual incidence of new cancer cases expected from the population served by the centre. For example, a centre registering fewer stage IV cases could record a higher cure rate for cancer than another recording more stage IV cases, because of more comprehensive registration. These opinions do not of course contradict the value of survival rates reported by different centres for the disease in its operable phase.

3. Autonomy in Breast Cancer

It has been held generally that the disease can be cured only if it is confined to the breast at the time of treatment and perhaps also in a few cases where it has spread to the axillary nodes. To accept the theory of complete autonomy for untreated cancer or for cancer beyond the confines of the breast at the time of treatment calls for all emphasis on early diagnosis as the critical factor in prognosis. To this end much thought is being directed to intelligently planned educative measures, supported by adequate bed accommodation, to preclude delay in treatment. Park and Lees (1951) concluded that it had not been proved that the survival rate for cancer of the breast, with the use of the five-year survival rate as an index, was affected by treatment at all, and held that the evidence strongly suggested that treatment was quite ineffectual in reducing the incidence of death from metastatic spread. They are convinced that if treatment is in any way effective the effectiveness cannot be greater than that required to increase the overall five-year rate by more than 5 to 10%. On the other hand, Bloom *et al.* (1962), in a closely reasoned report, came to the conclusion that treatment does in fact increase the survival rate in all three grades of malignancy as judged by the five-, 10-, and 15-year survival from the onset of symptoms, the most striking difference being seen in patients with tumours of high-grade malignancy.

Collectively, the evidence in support of both general and local resistance in the host to the spread of cancer is sufficiently arresting to warrant a more imaginative and explorative treatment policy based on the concept of breast cancer as a disease process which is already leaking neoplastic cells into the circulation at the time of its diagnosis as a clinical stage I growth. For a time the tide of the disease may be stemmed by some positive reaction on the part of the host ; otherwise the existence of the dormant cancer cell presenting as a metastasis many years after the apparently successful removal of the primary lesion cannot be explained. Surely this must be the most important single factor in determining prognosis ? If this is agreed, it follows that there may be two points in the treatment of breast cancer where one might boost such resistance: (1) at the time of operation by measures directed against the free cancer cell, and (2) when metastases begin to appear at the point when host resistance is failing.

"Early" Growth

Early diagnosis has been regarded as of paramount importance to the treatment and potential cure of cancer, yet there is no clear interpretation of what the term "early" signifies.

(*a*) *Length of History.*—Bloom (1950) has shown that this cannot be consistently correlated with the prognosis, though some meaning did appear when he correlated length of history and degree of histological differentiation of the tumour with the prognosis, but this latter quality can be assessed adequately only subsequent to operation. There is now general acceptance of the point that with the highly anaplastic lesion immediate treatment may not make all that difference to the prognosis, and delay in the less vicious type of lesion may not completely defeat the patient's chance of cure. Whatever the overall influence of a short history on the absolute survival rate in breast cancer, it stands to reason that the longer a patient with a low-grade carcinoma delays before seeking treatment the greater will be the likelihood of metastases and the less likely will be her chance of survival after radical treatment. If this is so, then public education in breast cancer, directed towards getting all patients to seek treatment immediately, will at least benefit some of the aggregate.

(*b*) *Locally Confined Lesion.*—In breast cancer the interval between the appearance of the disease and its dissemination is more unpredictable than it is for many other forms of cancer, and the clinical estimate of the degree of spread just so much more unreliable. We have only to compare our assignment of breast cancers to stage I with the ultimate survival rate after radical treatment to get some conception of the fallacy of attempting to gauge accurately the degree of spread by clinical findings and the histological extent of the local lesion.

(*c*) *Size of Tumour.*—McWhirter (1957) has drawn attention to the correlation between the size of the tumour in centimetres and the five-year survival rate. We should look beyond this fixed point in time and ask whether there is a constant relation between tumour size at the time of treatment and the rate of cure. Kreyberg and Christiansen (1953) reported that even the smallest carcinomas, those of the size of a pea or a bean, had a fatal outcome in four out of ten cases when followed up over 10 to 20 years, and they also showed that nearly two-thirds of the patients had metastases when arriving for treatment. Bloom (1950) investigated the five-year survival rate analysed according to size and histological grade of malignancy and concluded that only with tumours of intermediate malignancy could size be directly related to the five-year survival rate.

To sum up, we cannot uniformly equate any single quality such as a short history, a clinically localized lesion, or actual size with the prognosis, and the precise definition of what constitutes an "early" growth still eludes us.

Appraisal of Different Modalities in Treatment

The merits of any single method in the treatment of cancer should be judged on its effectiveness when applied to the disease in its operable phase, and in breast cancer this is for the growth in the clinical stages I and II, and ? early stage III category. The probability of cure is not very high for those in the stage III group, however, and non-existent for those in stage IV, so that an evaluation of curative treatment in the more advanced cases has little meaning.

At present there are several methods in use for the radical treatment of breast cancer, each one meeting with its greatest success if applied to the disease when this is confined to the breast or, at any rate, when it has not progressed beyond its lymphatic barrier. A great deal of clinical emotion has resulted from conflicting claims made for different modalities in treatment, and this storm, which is now abating, will leave in its trail an embarrassed silence when it is realized that the ultimate survival rate from each method is not appreciably different

from the others. This impasse in the cure rate of the disease will nevertheless continue if we remain hypnotized by the primary growth and the axilla. There are of course many grounds on which the value of a particular policy can be challenged, and it is right that we should argue the treatment of the local field, however widely we may plan to cast our net in the future. With these premises in mind, what are the arguments for and against the different methods at present employed ?

1. Radical Mastectomy

It is not possible to diagnose true stage I breast cancer before operation. Moreover, subsequent failure by the pathologist to demonstrate invasion of the axillary nodes does not definitely establish the staging as I, because he cannot be expected to examine serial sections of all lymphatic tissue and nodes removed at operation, nor can we be confident that the internal mammary nodes are free of disease even when the lesion lies in the outer quadrant of the breast. At the very least, for the purpose of treatment planning, we should assume that the disease has progressed to stage II.

Setting aside for the moment the postulate that the host may not be entirely defenceless against wider dissemination, it is accepted that radical mastectomy alone has produced high five-year survival rates in the hands of many surgeons. This figure is highest for those patients in whom no secondary disease has been detected histologically in the axillary nodes. Furthermore, the five-year survival rate for those patients whose axillary nodes are involved, though less than for stage I, is not inconsiderable. This tailing off in the case of the stage II group does not necessarily condemn the radical procedure as ineffectual in clearing the disease from the axilla, because this feature may be conditioned by dissemination beyond the operative field before treatment. Nevertheless, radical mastectomy can rarely, if indeed ever, confer any practical advantage for those lesions occupying the inner part of the breast, because of their high incidence of internal mammary-node involvement. Its employment for any stage III case can seldom be justified, and of course it has no meaning for the stage IV group.

In some patients, probably not a large number, the disease is of a radioresistant character, and for these radical mastectomy must offer the greatest chance of cure, but unfortunately this type of lesion cannot be recognized clinically.

The main objections to the radical operation usually quoted are shoulder-joint disability and arm oedema, both of which are minimal with careful operative technique and postoperative supervision. It might be mentioned also that less radical surgical techniques combined with radiotherapy are by no means devoid of morbidity.

2. Irradiation Alone

Radium therapy was used alone or in association with surgery for some patients in this centre up to 1936, and, though it produced some five-year survivors, it was soon given up because of its morbidity—radionecrosis of skin and ribs, brachial neuritis, and sometimes haemorrhage.

X-ray therapy can apparently inactivate some breast cancers. More often than not its success when used alone lies in surrounding viable tumour tissue with a dense bed of fibrous tissue ; it probably prolongs the patient's life, but not because it cures the disease. In association with radical surgery it has been indicated in several publications as increasing the five-year survival rate to a significant degree. Here, again, this effect may not always be due to sterilization of tumour residue in the breast or axilla, but because it extends the treatment field to include the supraclavicular nodes, and, less effectively, the parasternal lymphatics on the affected side, and it is not irrational to postulate that some of its effect may be on free circulating tumour cells in the blood stream. *X*-ray therapy alone, as a preoperative measure in early stage III cases, has generally been regarded as the treatment of choice for patients in this category, and, used alone for late stage III and for stage IV cases, is an accepted method of palliation.

3. Local Mastectomy and X-ray Therapy

If any centre were to be restricted to a single method of treatment, then this technique could be regarded as the one most generally applicable. It is a technique whose effectiveness has been both overrated and underestimated over the same period in time. In this centre its value has always been recognized, but its selection in planned treatment for individual patients has been through regard to such characteristics as tumour size and site, plus the general condition and age of the patient. We are concerned with claims made for this treatment mainly as they apply to patients in the clinical stage I and stage II groups, though it has a very considerable value indeed for more-advanced cases. The claim put forward in its support for stage I cases is that local mastectomy (by definition of stage I breast cancer) must remove all the disease, and therefore a radical operation is not required. Unfortunately, as we have seen, the clinical estimate is so often in error that the axilla is also treated by irradiation. The Edinburgh School advocates leaving the pectoral fascia behind unless the growth is adherent to it, but we know that normally breast elements frequently penetrate the fascia to extend into the underlying muscle, so that local mastectomy under those circumstances may not completely remove the breast. It could be argued, of course, that efficient postoperative irradiation should deal effectively with this residue and sterilize any tumour left behind.

As regards the axilla, Professor McWhirter (1955) is of the opinion that the axillary nodes are at least as easily, if not more easily, sterilized by irradiation therapy than the primary breast cancer. In this centre we have on occasion found it necessary to carry out an axillary dissection after efficiently performed local mastectomy and *x*-ray therapy. It has been suggested (McWhirter, 1954) that in some centres this could follow faulty technique, or have arisen in cases where the nodes have been reinfected from an incompletely removed primary lesion, and that where viable cells are found in such nodes it is doubtful if the histologist attempted to distinguish between cells just viable and cells capable of division. All these postulates are reasonable, but in our own cases there did not appear to be any residual primary growth. The technique, which was that devised by the Edinburgh School, was efficient. However, the nodes were progressively enlarging, and therefore residual cells were capable of division.

Taken overall, the effectiveness of local mastectomy and *x*-ray therapy has been proved ; it has a low morbidity, and when it is generally applied the published absolute five-year survival rate is of the order of 42%.

4. Radical Mastectomy and Postoperative Radiotherapy

Paterson and Marion Russell (1959) reported the result of a clinical trial based on random selection and designed to attempt an objective assessment of the actual value of radiotherapy when given after radical mastectomy: a total number of 1,461 cases were covered by this study, and the trial was divided into two series which cannot be summated, as distinctly different methods of postoperative radiotherapy were employed in the treated cases. In the first period the main irradiated area was the operation flap and the axilla (quadrate series 720 cases). In the second period the radiation was primarily directed towards the axilla, the supraclavicular area, and the parasternal region (peripheral series of 741 cases).

Two groups of patients are contrasted in each series. One group had immediate treatment on orthodox lines ; in the other no immediate treatment was given but the patients were treated only if the need arose. It was stressed that the contrast was not between prophylactic radiotherapy and no radiotherapy, but between radiotherapy immediately after operation and careful follow-up, with the object of providing radical treatment if recurrence or metastases appeared. No statistically significant differences were established in the crude mortality rate at five years between groups of cases treated prophylactically on orthodox lines and cases "watched" and treated only on need. An apparent minor advantage to the "watched" policy seemed to be demonstrated for the surgical stage I cases and for younger women. Investigation of the incidence of local recurrence showed that prophylactic irradiation had been effective in the treated area, but that subsequent purposive treatment eventually evened out the situation to a large extent. Analysis of distant (blood-borne) metastases showed in general remarkable similarity of incidence, but a possible increased incidence in liver metastases in the irradiated cases.

A somewhat different picture is presented in an article by Professor Watson (1959). Using radical mastectomy followed by *x*-ray therapy for operable cases, he reports a five-year absolute survival rate of 52%—a 10% increase over the similar rate for the Edinburgh technique.

It is difficult to resolve apparently conflicting findings in published reports. Are they possibly related to an increase in the percentage of stage I cases over the years ? Are we now treating a larger number of "early" cases, or is the character of the disease itself changing ? Arguments in favour of postoperative *x*-ray therapy after radical mastectomy have been advanced on several counts, but its effectiveness must leave grave doubts in our minds in view of Paterson's studies, and it does not lessen the validity of his deductions to postulate that as the operation becomes less radical so the value of postoperative radiotherapy must increase. It remains to be seen whether supervoltage therapy can improve the cure rate to a significant degree, but on technical and other grounds it does not seem likely that it will.

Ovarian Ablation

Smithers (1952) referred to trends in the survival rates for breast cancer among patients in the middle age group and he suggests that alterations in the hormone balance at the natural menopause may exert a beneficial effect on patients who have already developed breast cancer, but should the growth occur at or just after the menopause the prognosis is slightly but significantly worse.

McWhirter (1957) reported the result of a trial of ovarian irradiation as part of the first planned treatment in patients with clinical stage I and II cancer subjected to local mastectomy and adequate *x*-ray therapy. No difference in the percentage five-year survival rates were found between those having ovarian irradiation and those not. It is conceded, however, that ovarian irradiation may be less effective than oophorectomy.

Paterson and Russell (1959) carried out a clinical trial of simple ovarian irradiation for breast cancer, and concluded that the overall results at three, five, and seven years show apparent advantage to ovarian irradiation at statistical levels just short of 1:20 conventional index. They also concluded that the differences are demonstrable in stage I cases and in postmenopausal women. Analysis of the incidence of recurrence and metastases seemed to suggest some degree of inhibition of those sequelae in the radiated cases.

On the available evidence we must accept ovariectomy or ovarian irradiation as conferring benefit on many premenopausal and menopausal patients.

Chemotherapy as Part of the Planned Treatment in the Operable Case

Until recently our sole method of treatment for the potentially curable case has been surgery and radiotherapy. Little more can be expected from alteration or extension of present surgical techniques ; possibly more may be gained from radiotherapy, not through further developments for its local application, or by more powerful apparatus than is currently in use, but through procedures likely to increase the sensitivity of the tumour (Hodnett, 1963), or, less likely, by the utilization of radioactive isotopes (Horwitz, 1960). Meantime chemotherapy provides an additional measure in treatment which permits us for the first time to think in terms of attacking the disease beyond the regional confines of the breast and its lymphatic bed. Though the present stage in its development must be compared to that obtaining for radiotherapy in the early 1930s, already it has established itself as more applicable than the latter to certain forms of advanced cancer, and there would appear also to be a logical case for its integration in treatment of the disease in its operable phase. The use of chemotherapy in breast cancer should not be opposed on the grounds of its present empiricism, but its acceptance must be for reasons which equate with our basic concept of the disease process.

We have no measure of iatrogenic influence in the production of metastases through spread of the disease during examination of the tumour and subsequently during operative or radiation procedures. By themselves, these factors may not be of particular significance, but they are possibilities. Apart from these abstract considerations it is now well known that free cancer cells can be demonstrated in the peripheral blood of many patients with "solid" cancers, and several laboratory methods have been devised for their study. Moore *et al.* (1960) reported an incidence of positive findings in 78% of patients with lung cancer, in 53% of patients with stomach cancer, and in 33% of those with colorectal cancer. They also observed a decrease in tumour cells in the peripheral blood after cancer chemotherapy. It is likely that these findings also apply to breast cancer in some degree.

Chemotherapeutic agents have a temporary effect in many cases of advanced breast cancer, and it seems logical to consider whether the unestablished free cell in the peripheral blood may be even more sensitive to their action. At the same time, if these agents are used as maintenance therapy for long intervals after operation, is it possible that they may have a delayed effect on marrow function of which we are as yet unaware ? We must also ask ourselves whether such agents carry some risk of lowering general or local resistance to the tumour. If we are prepared to accept these hazards as a calculated risk at present, and because we cannot expect the absolute five-year survival rate to exceed something of the order of 50% by conventional methods, it would now seem logical to integrate chemotherapy in treatment policy for the operable case on the basis of a controlled clinical trial at an interregional level. Ancillary to this, and in association with pathology departments, further studies of the biological action of these agents on the tumour cell should be intensified.

Summary

A report of the results of treatment for breast cancer at Aberdeen Royal Infirmary from 1940 to 1955 is presented.

With certain qualifications, the earlier the disease is diagnosed the more effective is treatment likely to prove, and therefore, in a limited form, public education in breast cancer has a claim for support.

There seems to be little advantage held by any one treatment modality over others when that modality is uniformly applied. On the other hand, each method has some claim for its selection when particular conditions exist to sustain that choice.

Ovarian ablation is accepted as of value in certain age groups.

The potential role of chemotherapy in operable breast cancer is discussed.

I have to thank my colleagues in the Royal Infirmary, Aberdeen, for permission to use their case records in the preparation of this paper, and especially Dr. Roy Weir for his guidance and comment on the statistics.

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Selective Lymphopenia in Man after Intralymphatic Injection of Radioactive ^{131}I Lipiodol

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There are several problems associated with the homotransplantation of tissue in man, not least of which is the homograft rejection mechanism. Certainly with kidney transplantation the technical problems of implantation appear subservient to those concerned with the rejection phenomenon.

The role of lymphocytes in this immune response is not fully understood, but there is ample evidence of their special importance (Woodruff, 1960). Loss of lymphocytes from the thoracic duct in rats resulted in severe depression or abolition of the primary immune response (McGregor and Gowans, 1963), and multiple methods of producing lymphocyte reduction have been used as a means of prolonging homograft survival in both experimental animals and man.

Over the past four years we have been particularly interested in the treatment of melanoma with endolymphatic ^{131}I Lipiodol. Before this period lymph-node metastases from melanoma had been treated with endolymphatic ^{198}Au (Jantet *et al.*, 1964).

Complete records have been made in a series of 50 patients who received endolymphatic ^{131}I therapy for melanoma. These investigations included preoperative and postoperative leucocyte estimations. It was noted in our early investigations that the endolymphatic therapy in the range of dosages used did not depress the total leucocyte count markedly, though this did occur in the occasional patient. However, of more significance was the feature that in several patients a *relative and absolute lymphopenia occurred.*

This paper is concerned with a detailed analysis of these patients, with particular reference to the achievement of a relative and absolute lymphocyte depression after endolymphatic therapy.

Treatment Policy for Melanoma

Our therapeutic approach to the patient with malignant melanoma is to follow the initial wide excision of the primary lesion with endolymphatic therapy via the lymphatics draining the site of excision. The endolymphatic treatment is usually given three weeks after the time of excision, though when the diagnosis is assured synchronous treatment is occasionally given.

Should the lymph nodes be clinically and radiologically negative then this plan of action is usually regarded as sufficient, and the patient is subsequently followed carefully in the outpatient department. In some patients node dissections have been made at varying intervals after endolymphatic treatment. Microscopical examination often reveals total destruction of lymph nodes in this group (see Fig. 1).

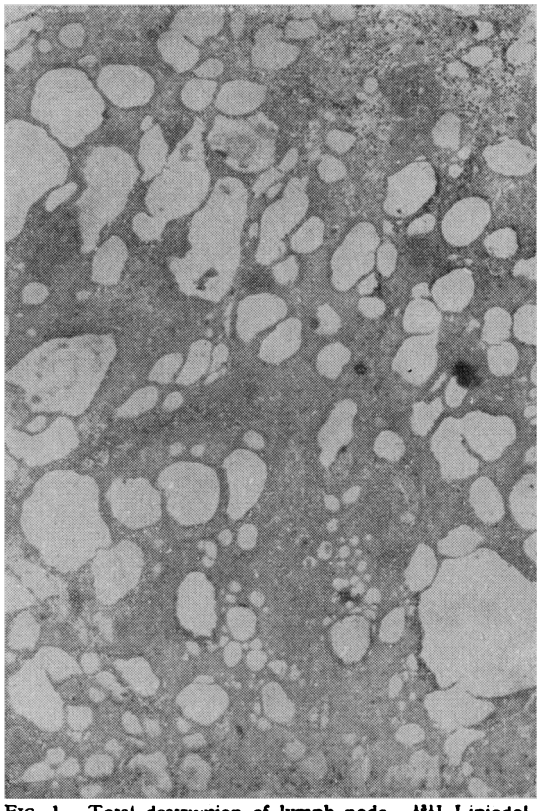

FIG. 1.—Total destruction of lymph node. ^{131}I Lipiodol represented by vacuolated spaces. Married woman. Melanoma of leg treated with endolymphatic ^{131}I Lipiodol after wide excision of primary tumour. Lymph nodes in inguinal region removed six weeks later.

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