patients operated on for gastric or duodenal ulcer. To put these various findings into perspective, however, gastric cancer accounted for only 11 of the 97 excess deaths in our study whereas lung cancer accounted for 33.

Our study confirms a previously documented relation between gastric surgery and colorectal carcinoma.³ Smoking state may partly explain this association, at least for carcinoma of the rectum.⁹ A further possibility is that bile salt metabolites, which are formed in the stomach after operation,¹⁴ could have a promoting effect on colonic carcinoma.¹⁵ An abnormality of bile salt metabolism has been suggested as a cause of the increased incidence of colonic cancer after cholecystectomy.¹⁶

Unfortunately, smoking state was not fully recorded for all patients in our study either at the time of operation or subsequently, but we recently clinically reviewed 264 of the survivors. Of these, 75% had been smokers at the time of operation but only 45% were smokers at the time of review. Among those who died probably a similar proportion had been smokers at operation but fewer may have given up smoking afterwards, though this must remain speculative.

In conclusion, our study of long term survival of patients who had undergone vagotomy and drainage showed that they are subject to an increased mortality, at least as great as that in patients after gastrectomy. Although cancer of the stomach occurred in excess, lung cancer accounted for a larger proportion of the excess deaths. We suggest that when patients attend clinics for long term follow up after gastric surgery they should be carefully questioned and examined for smoking related diseases. Frequent chest radiography is advisable, but regular endoscopy in all patients after gastric surgery yields little benefit.

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Mammary skin oedema: a new prognostic indicator for breast cancer

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Abstract

Mammary skin thickening shown on the mammogram was measured in 220 patients with non-inflammatory breast cancer, and the mean skin oedema was derived by taking the mean of five measurements from separate sites on the breast (upper part, lower part, medial part, lateral part, and areola) after subtracting the corresponding figures from the opposite (normal) breast.

The prevalence of appreciable oedema (greater than 0.25 mm) was 70% for tumours less than 1 cm and 100% for tumours more than 3 cm in diameter. This measure of oedema correlated positively and significantly with tumour size and lymph node status. In a minimum of 60 months' follow up patients developing recurrence had

significantly higher oedema values. The amount of oedema also predicted recurrence better than lymph node status, tumour size, or tumour stage. Oedema and tumour size, information available preoperatively, provide a simple means of assessing prognosis before definitive treatment.

Introduction

Oedema of the mammary skin is well known to occur in the course of inflammatory carcinoma of the breast. Although it is often not visible to the naked eye, skin oedema is often present in non-inflammatory cancer and is clearly shown on xeromammograms. The clinical implications of skin oedema in non-inflammatory breast cancer have not been defined.

In the only study of skin oedema in non-inflammatory breast cancer we showed that the oedema could be measured accurately and reproducibly on xeromammograms and that it correlated significantly with other indices of the severity of the tumour such as clinical stage, size, lymph node status, and vascularity.¹ The amount of skin oedema also correlated well with prognosis over a follow up period of 7 to 70 months. This was not unexpected in view of the positive correlation of the amount of oedema with clinical and pathological prognostic indicators, but it was not clear whether this factor had an independent prognostic value, which could only be assessed over a longer period

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of follow up. This study has now been extended to a minimum follow up of five years and a maximum of 11 years to determine whether skin oedema is as valuable as other indices.

Patients and methods

Patients with breast cancer who presented to the breast clinic of the University Hospital of Wales, Cardiff, between 1972 and 1977 were studied. The follow up ranged from 60 months to 132 months, mean and standard deviation being 80 and 16 months. Those with stage IV cancer, previous breast operations, or other cancers were excluded. The diagnosis had been confirmed histopathologically in all patients. Patients were classified according to the TNM system. Treatment varied according to trial protocols in force at the particular time and included simple mastectomy, radical mastectomy, modified radical (Patey) mastectomy, and radiotherapy. Patients who underwent simple mastectomy had axillary sampling, but patients in this and the radiotherapy group in whom no axillary nodes were found were excluded from computations that included lymph node status.

The follow up data were recorded prospectively within the Cardiff breast clinic. The end point of the follow up was the first indication of treatment failure. Recurrences in the chest wall around the area of surgery or in the axilla were designated "local recurrences," while distant and supraclavicular recurrences were included in the "systemic recurrence" group. Patients developing local and systemic recurrences concurrently were included in the systemic group. Patients who died during follow up from disease other than breast cancer but in whom no definitive necropsy was carried out were included in the systemic recurrence group.

In brief, skin thickness was measured from mammograms or xero-mammograms with the help of an x ray viewing box, magnifying glass, and millimetre scale.¹ Measurements were made at five fixed points—over the upper and lower parts of the breast on lateral films, over the inner and outer parts of the breast on the craniocaudal films measured midway between the periphery of the breast and the nipple as seen on the mammogram, and at the areola measured 1.5 cm medially from the centre of the nipple on the craniocaudal films. Mirror image measurements of the contralateral normal breast skin were made and the difference in skin thickness between the two breasts was taken to represent the skin oedema. We found that we could detect reproducibly a difference in skin thickness of 0.25 mm on individual sites, so a difference equal to or greater than this was regarded as thickening. The greatest thickening occurred in the skin of the areola and on lower and inner parts of the breast, except when the growth was in the lower outer quadrant, when the lower part of the breast showed greater thickening than the areola and inner parts ($p < 0.05$). To remove this variable of distribution we derived the mean amount of skin oedema for each patient by taking the mean of the five skin thickness measurements (on the upper, lower, inner, outer parts and areolar skin) of the tumorous breast. Mean skin oedema was correlated with the type and time interval of recurrence within well defined clinical groups of patients.

For this study patients were classified according to the TNM classification based on clinical staging. When the prognostic value of skin oedema was compared with lymph node status, however, only patients with histologically confirmed axillary nodes (172 patients) were included.

Because the distribution of oedema was highly skewed, non-parametric methods of analysis were chosen,² except for the discriminant analysis, in which a log transformation was chosen. Discriminant function analysis was performed by the direct method for oedema; for tumour size and lymph node status; and for all three variables in turn to compare the prognostic information these contained. The effect of oedema on recurrence rate, including time to recurrence, was assessed using the log rank test.

Results

A total of 220 patients were studied (table I). All the patients were followed up for at least 60 months, and recurrence status was defined as that recorded at 60 months. The patients were divided into three subgroups—no recurrence, local recurrence, and systemic recurrence—on the basis of the type of recurrence first noted. Table II shows the method of treatment, type of recurrence, time to first recurrence, and mean skin oedema in each group. Highly significant differences were present in skin thickening among the three recurrence groups (Kruskal-

TABLE I—Distribution of TNM stage and recurrence. Results are numbers of patients

TNM stage	Recurrence group			Total
	No recurrence	Local recurrence	Systemic recurrence	
T ₀ N ₀	8	0	0	8
T ₀ N ₁	1	0	1	2
T ₁ N ₀	44	11	4	59
T ₁ N ₁	4	2	1	7
T ₂ N ₀	33	11	15	59
T ₂ N ₁	9	6	11	26
T ₃ N ₀	6	6	13	25
T ₃ N ₁	1	9	24	34
Total	106	45	69	220

TABLE II—Treatment method, time to recurrence, and mean oedema measurement in recurrence groups. Results are numbers of patients

Treatment	Recurrence group			Total
	No recurrence	Local recurrence	Systemic recurrence	
Radical or Patey mastectomy	31	4	18	53
Simple mastectomy	68	30	28	126
Radiotherapy	7	11	23	41
Total	106	45	69	220
Time to recurrence (months (SD))				
		26 (16)	20 (12)	
Mean skin oedema (mm) (SD)				
	1.19 (1.01)	3.74 (3.84) ($p < 0.001$)	5.27 (5.30) ($p < 0.001$)

No of patients	0-1 mm	1.1-2 mm	2.1-3 mm	3.1-4 mm	>4 mm
83	83	77	76	70	68
66	66	66	65	63	61
50	49	44	37	34	32
32	32	32	29	29	29
31	29	26	24	18	17
14	13	11	11	11	11
16	15	11	10	8	7
7	7	6	6	6	5
40	34	23	17	12	11
7	4	1	1	1	1

FIG 1—Percentage of patients free of recurrence related to mean skin oedema alone. Patient numbers in each group are shown underneath graph.

Wallis test: $\chi^2 = 66.38$; $df = 2$; $p < 0.001$). Among patients developing recurrence the oedema was greater in those with systemic recurrence than in those with local recurrence, the difference being significant by the Mann-Whitney test ($p < 0.05$).

PROGNOSTIC SIGNIFICANCE OF OEDEMA

Figure 1 shows patients divided into five groups according to their mean skin oedema (0-0.1 mm, 1.1-1.3 mm, 2.1-3 mm, 3.1-4 mm, and more than 4.1 mm) without regard to the size of the tumour or axillary lymph node status. The log rank test showed a highly significant association of the degree of skin thickening with the recurrence rate ($\chi^2 = 72.17$; $p < 0.001$).

PROGNOSTIC SIGNIFICANCE IN RELATION TO TUMOUR SIZE

The prevalence of skin oedema, which ranged from 0.25 mm to 10 mm, was 71% in those with tumours of 0-1 cm, 92% in those with tumours of 1.1-2 cm, and 94% in those with tumours of 2.1-3 cm. All tumours over 3 cm were associated with measurable skin thickening. The Spearman rank correlation of oedema with tumour size was 0.55 ($p < 0.001$) based on all patients, and was similar and reached significance in the no recurrence (0.40; $p < 0.001$), local recurrence (0.31; $p < 0.05$), and systemic recurrence (0.56; $p < 0.001$) groups. Kruskal-Wallis analysis of variance on ranks showed that oedema

FIG 2—Value of data available before operation—mean skin oedema and tumour size—in predicting recurrence. This figure shows only 182 of the 220 patients: in 38 patients the tumour size was recorded as T₁ or T₂, instead of in centimetres; they were excluded from those aspects of analysis in which size was critical and hence have been excluded from this figure.

FIG 3—Percentage of patients free of recurrence related to mean skin oedema in (a) those without lymph node disease and (b) those with lymph node disease.

varied highly significantly among the three recurrence groups ($\chi^2 = 66.38$; $df = 2$; $p < 0.001$), being greatest in the systemic recurrence group and lowest in those without recurrence (table III). A corresponding two way analysis showed a similar, though somewhat reduced, effect when tumour size was held constant ($\chi^2 = 21.54$; $p < 0.001$); it was similar in all six tumour size groups and reached 0.05

significance in three (1.1-2 cm, 4.1-5 cm, and > 5 cm). Thus the oedema provided prognostic information as well as that given by tumour size alone.

Tumour size and mean skin oedema are two elements of information that are available before any operative procedure has been performed. The prognostic value of this information is presented in fig 2. Irrespective of tumour size, an oedema of less than 1.5 mm carried a high likelihood of freedom from recurrence, while oedema of over 3 mm carried an equally high likelihood of recurrence. Further information on the probability of recurrence with oedema between these two limits was obtained by combining oedema with tumour size, providing a valuable guide to prognosis at the time of planning treatment.

PROGNOSTIC SIGNIFICANCE IN RELATION TO LYMPH NODE STATUS

One hundred and seventy nine of the 220 patients underwent simple or Halsted-Patey mastectomy. In 172 of these cases axillary lymph node status had been confirmed histologically: in 103 there was no lymph node disease, and in 69 axillary lymph nodes were affected. Fig 3 shows the chance of freedom from recurrence in relation to axillary lymph node status.

In those with no lymph node disease 26% of women with oedema of

TABLE III—Mean skin oedema (and standard deviation) related to size of tumour in three recurrence groups. Numbers of patients in each group are shown in *italics*

Tumour size (cm)	Recurrence group			Total
	No recurrence	Local recurrence	Systemic recurrence	
0-1	0.59 (0.62) 29	1.31 (1.46) 4	1.0	0.68 (0.76) 34
2	1.34 (1.17) 31	2.27 (1.40) 12	2.53 (1.70) 8	1.75 (1.39) 51
3	1.30 (0.89) 27	3.71 (3.58) 7	2.67 (3.37) 16	2.07 (2.51) 50
4	1.93 (0.87) 7	4.56 (5.29) 9	5.78 (6.13) 8	4.20 (4.88) 24
5	1.69 (1.27) 9	4.04 (3.20) 6	4.91 (3.53) 19	3.90 (3.27) 34
>5	1.42 (0.38) 3	5.14 (3.77) 7	9.61 (6.67) 17	7.55 (6.28) 27

0-1 mm developed recurrence, 36% of those with 1.1-3 mm of oedema, and 72% of those with more than 3 mm of oedema. The difference was statistically significant ($\chi^2 = 11.09$; $p < 0.01$). The relative recurrence rates in each group compared with that in the total group were 0.64, 0.90, and 2.41 respectively in 0-1, 1.1-3, and > 3 mm skin oedema groups ($\chi^2 = 13.02$; $p < 0.01$).

Similar figures for patients with lymph node disease were 50%, 68%, and 100% for oedema of 0-1, 1.1-3, and >3 mm respectively ($\chi^2=13.34$; $p<0.01$) with relative recurrence rates of 0.53, 0.94, and 1.91 ($\chi^2=13.37$; $p<0.01$).

PROGNOSTIC SIGNIFICANCE OF OEDEMA COMBINED WITH TUMOUR SIZE AND LYMPH NODE STATUS

Discriminant function analysis was used to assess the relative contributions of oedema, tumour size, and lymph node status to prognosis. Oedema was transformed to $\log(\text{mean skin oedema} + \frac{1}{2})$ for this purpose to help the values conform to a normal distribution. The mean discriminant scores were 0.62, 0.92, and 1.06 respectively for tumour size together with lymph node status, $\log(\text{mean skin oedema} + \frac{1}{2})$, and all three variables together. In separating those with no recurrence from those with systemic occurrence the three scores were 1.16, 1.31, and 1.54. Hence, oedema was rather better at discriminating than the tumour size and histological lymph node status together, though the combination of all three, not surprisingly, was better still.

CORRELATION OF OEDEMA WITH LATE TREATMENT FAILURE

Among the 106 patients who were free of recurrence at 60 months outcome was assessed during further follow up to a maximum of 132 months: five developed a new primary carcinoma in the second breast, three died without any evidence of breast cancer, two developed systemic recurrence, and three developed local recurrence. Mean skin oedema in the five patients who developed recurrence did not differ from that in the total recurrence free group.

Discussion

The clinical behaviour of breast cancer may be correlated with several prognostic factors in relation to the outcome of treatment. Already there are epidemiological, histological, hormonal, biochemical, and clinical prognostic factors, including the site and size of the tumour and presence or absence of axillary lymph node disease,^{3,4} yet it remains difficult to predict the prognosis in an individual patient. The variations in surgical treatment of breast cancer cause added problems in prognostic formulas based on retrospective studies. Axillary lymph node status is recognised as the most important single prognostic factor in the management of breast cancer,⁴ but McNeil and Hanley have drawn attention to the problems of evaluating prognosis on the basis of a single factor and the danger of assuming the independent significance of such factors.⁵

Haybittle *et al* devised a prognostic index in a homogeneous group of patients with breast cancer treated by simple mastectomy.⁶ This prognostic index was more accurate than axillary

lymph node disease and size alone in their patients. Evaluation and use of this prognostic index, however, required information on tumour size, axillary lymph node status (sometimes difficult to ascertain in patients treated by simple mastectomy or radiotherapy), grade of tumour, and oestrogen receptor status. It is therefore not available before treatment and cannot be used as a basis for selecting treatment. The mammogram is a routine examination for breast cancer so that the mean skin oedema measurement is always available. Since skin oedema, tumour size, and the likelihood of axillary lymph node disease increase as breast cancer progresses, skin oedema would be expected to correlate with axillary lymph node status and tumour size. Thus to be of prognostic value skin oedema measurement should provide information over and above that given by the tumour size and lymph node status. We have shown that it does and that oedema may be combined with tumour size to provide a simple means of assessing prognosis before deciding which treatment is appropriate to the individual patient.

On the whole treatment failure occurred often in patients with more than 2.0 mm of mean skin oedema, but those with more than 4.0 mm of skin thickening invariably developed recurrences. More pertinently, for tumours smaller than 2 cm the presence of skin oedema was a poor prognostic sign and in tumours larger than 5 cm absence of oedema carried a relatively favourable prognosis.

This relation between skin oedema and prognosis now needs to be confirmed in relation to any specific treatment policy by study of large homogeneous groups being treated by a particular therapeutic regimen. If our results are confirmed for specific treatment groups, it might lead to a position analogous to that in melanoma: the thickness of the skin over a breast tumour could have as great an impact on management as tumour thickness has with melanoma of the skin.

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THE MOUTH, AND ITS DISEASES—Whosoever would keep their mouth, or tongue, or nose, or eyes, or ears, or teeth, from pain or infirmities, let them often use sneezing, and such gargarisms as they were instructed in a preceding chapter; for, indeed, most of the infirmities, if not all, which infest those parts, proceed from rheum. *For extreme heat of the Mouth*—Take Rib-wort, and boil it in red Wine, and hold the decoction as warm in your mouth as you can endure it. *For a Canker in the Mouth*—Wash the mouth often with Verjuice. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)

GLUTINATIVE MEDICINES—That is the true cure of an ulcer which joins the mouth of it together. That is a glutinative medicine, which couples together by drying and binding, the sides of an ulcer before brought together. These require a greater drying faculty than the former, not only to consume what flows out, but what remains liquid in the flesh, for liquid flesh is more subject to flow abroad than stick to together. The time of using them, any body may know without

teaching, viz when the ulcer is cleansed and filled with flesh, and such symptoms as hinder are taken away. For many times ulcers must be kept open that the sanies, or fords that lie in them may be purged out, whereas of themselves they would heal before. Only beware, lest by too much binding you cause pain in tender parts. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)

FOR THE EARS, AND THEIR IMPEDIMENTS—*For pain in the Ears*—Drop a little oil of sweet Almonds into the ear, and it easeth the pain instantly. (and yet oil of bitter Almonds is our doctor's common remedy.) *For an imposthume in the Ear*—Boil some milk, and put it into a stone pot with a narrow mouth, and hold the sore ear over the pot whilst the milk is very hot, that the vapour of the milk may ascend into the ear: this is an often approved remedy to take away the pain, and break the imposthume. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)