A NOVEL APPROACH FOR LOCAL TREATMENT OF BREAST CANCER

DISSERTATION FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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DEDICATED TO

MY FATHER

DR. SHARAD G. VAIDYA

AND

MY MOTHER

DR. NIRMALA S. VAIDYA

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Abstract

Early local recurrence of breast cancer most commonly (over 90%) occurs at the site of the primary tumour. This is true whether or not radiotherapy is given and irrespective of the margin status. Whole-organ analysis of mastectomy specimens on the other hand, reveals that 63% of breasts harbour occult cancer foci and 80% of these are situated remote from the index quadrant. Therefore, these occult cancer foci may be clinically irrelevant and it may not be necessary to treat the whole breast with radiotherapy. This 6-wks long course of post-operative radiotherapy after breast conserving therapy is not only inconvenient and costly, but may cause many women from geographically remote areas to choose mastectomy. Targeted Intraoperative radiotherapy (TARGIT) to the peri-tumoural area alone might provide adequate local control. 'Intrabeam' (*PeC*) is a portable electron-beam driven device that can deliver therapeutic radiation (soft x-rays) in 20-30 minutes within a standard operating theatre environment. The pliable breast tissue - the target - is wrapped around a spherical applicator - the source - providing truly conformal radiotherapy. The prescribed dose is 5 & 20Gy at 1cm and 0.2cm respectively, from the tumour bed. The biologically effective dose is 7-53Gy for $\alpha/\beta=10$ and 20-120Gy for $\alpha/\beta=1.5$. In our pilot study of 26 patients (age 30-80 years, T=0.42-4.0cm), we replaced the routine post-operative tumour bed boost with targeted intra-operative radiotherapy. There have been no major complications and no patient has developed local recurrence, although the median follow-up time is short at 34 months. The cosmetic outcome is satisfying to both the patient and the clinician. Having established the feasibility, acceptability and safety in the pilot study, we started in March 2000, a randomised trial that compares TARGIT with conventional post-operative radiotherapy for infiltrating duct carcinomas, with local recurrence and cosmesis as the main outcome measures. Patient accrual in this trial has been excellent and it has attracted several international collaborative groups. If proven effective, TARGIT could eliminate the need for post-operative radiotherapy potentially saving time, money and breasts.

CHAPTER 2

Multicentricity of breast cancer: Whole organ analysis and clinical implications

Introduction

William Halsted's paradigm of systematic centrifugal spread of breast cancer was the prevalent consensus for nearly 50 years. However, the fact that many of his patients, even when nodes were not involved died from breast cancer, in spite of having had a 'curative operation to remove the tumour from its roots', led many researchers, Bernard Fisher in particular, to seek alternative theories to explain the natural history of breast cancer, and suggest that less mutilating operations might have similar outcomes especially in terms of survival. In the mid-20th century, the science of randomised clinical trials was developing fast and people started contemplating testing the hypothesis that less radical surgery would have equivalent survival outcome to the more radical approach.

Around the time when the conservative breast surgery was being tested in clinical trials, many studies tried to explore the reasons for recurrence of breast cancer. Several autopsy studies since the 1970s revealed that multiple occult cancers were not uncommon in thyroid and in the prostates of elderly men. A remarkable autopsy study from Denmark [Nielsen et al., 1987] was reported in 1987. These investigators studied 110 women who had died of medico-legal causes. They simulated a bilateral modified radical mastectomy and then studied the specimens exhaustively. The whole breast was sectioned and examined. They studied some 60,000 paraffin blocks. The median age of these women who had mostly died of accidental causes was 39 years. Even then 20% of the breast specimens revealed microscopic breast carcinoma. This was mostly *in situ* carcinoma but 10% of these were invasive cancers. The proportion of women rose to 1/3rd in the above 50 age group. Clearly, most of these occult cancers would not have surfaced in these women's lifetimes. From population studies, it can be estimated that more than only about a quarter of these occult lesions would go on to become clinically overt cancers.

Many studies have investigated the multicentric nature of breast cancer in mastectomy specimens ([Qualheim and Gall, 1957],[Gallager HS and Martin, 1969], [Hutter and Dim, 1971], [Shah et al., 1973], [Rosen et al., 1975], [Lagios, 1977], [Westman-Naeser et al., 1981], [Sarnelli and Squartini, 1986], [Spinelli et al., 1992], [Anastassiades et al., 1993]). Although some of these studies ([Gallager HS and Martin, 1969], [Hutter and Dim, 1971], [Lagios, 1977]) used radiography, it was Egan ([Egan et al., 1969], [Egan, 1982]) who standardised the "correlated pathological-radiological" method of whole organ analysis which provides optimum sampling of breast tissue. The incidence of multicentricity found in these studies have varied from 18%, when 1-2 random samples from each quadrant are examined ([Spinelli et al., 1992]), to 69% when 5mm sections of whole breast are examined using the Egan's method ([Egan, 1982]). The principal aim of all these studies has been to find the incidence of multicentric foci (MCF) in the breast. Holland et al [Holland et al., 1985]in their landmark paper addressed the additional issue of distribution of MCF in terms of their distances from the primary tumour. They showed that MCF were within 2 cm of the tumour edge in 53% patients and within 4cm in

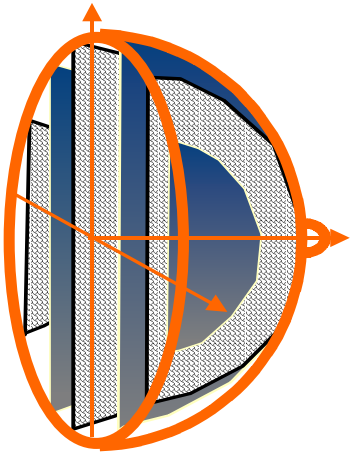
90% of patients. The findings expressed in this manner gave an impression that most MCF are present close to the tumour.

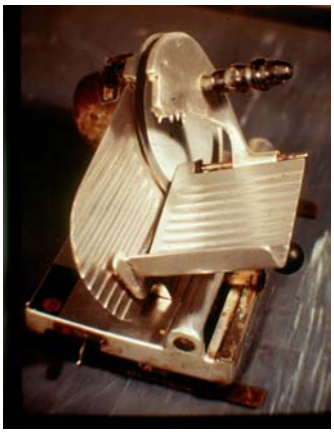
We studied the spatial relationship within the breast of multicentric foci (MCF) with respect to the primary tumour in 30 patients using the Egan's technique. We used two new approaches to this problem and investigated the spatial distribution not only in one dimension in terms of distances from the primary tumour, but also in two- and three-dimensional analysis within the respective breast specimen, viz., 1) We plotted the relative distribution of MCF and the primary tumour within the 4 breast quadrants and 2) we calculated the volume of breast tissue that would be required to be surgically excised, expressed as a percent of the total breast volume, to include all MCF in each breast. Since we analysed the spatial distribution of all lesions, we chose not to differentiate between multicentric and multifocal lesions [Holland et al., 1990].

Method

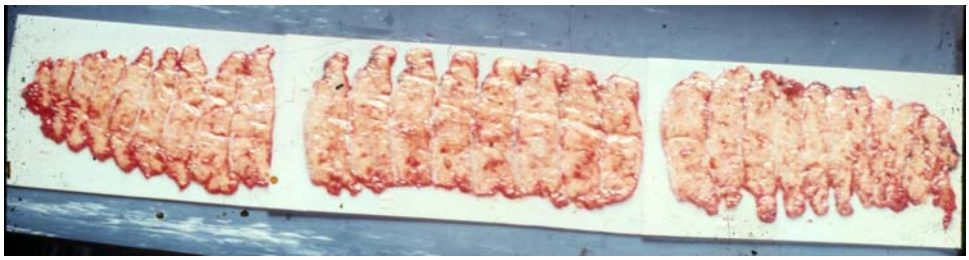
Thirty modified radical mastectomy specimens were studied. All patients had their diagnosis established by fine needle aspiration cytology with the primary tumour in situ. The patients had opted for modified radical mastectomy after all available surgical options including conservative surgery had been explained to them. The specimens were studied using the Egan's correlated pathologic-radiological method which involves freezing, slicing, radiography, grossing and microscopy ([Egan et al., 1969], [Egan, 1982]). The superior and lateral margins of the breast specimen and the 6'o clock position were marked with ink. Axillary tissue was excised and processed separately for dissection of axillary lymph nodes, so that the patient's definitive treatment was not delayed. The breast specimen was placed in a tray, covered with silver foil and kept in a -80°C freezer for 4-24 hours. A transverse line across the nipple was marked to indicate the plane of x-axis.

The breast was sliced using a ham slicer. 5mm thick slices were cut in saggital plane starting from the medial side. The slices were laid on acrylic sheets and were radiographed with a mammography machine (100 mA and 22 kV) using high quality mammography plates. The radiologist examined the mammograms and marked any suspicious areas.





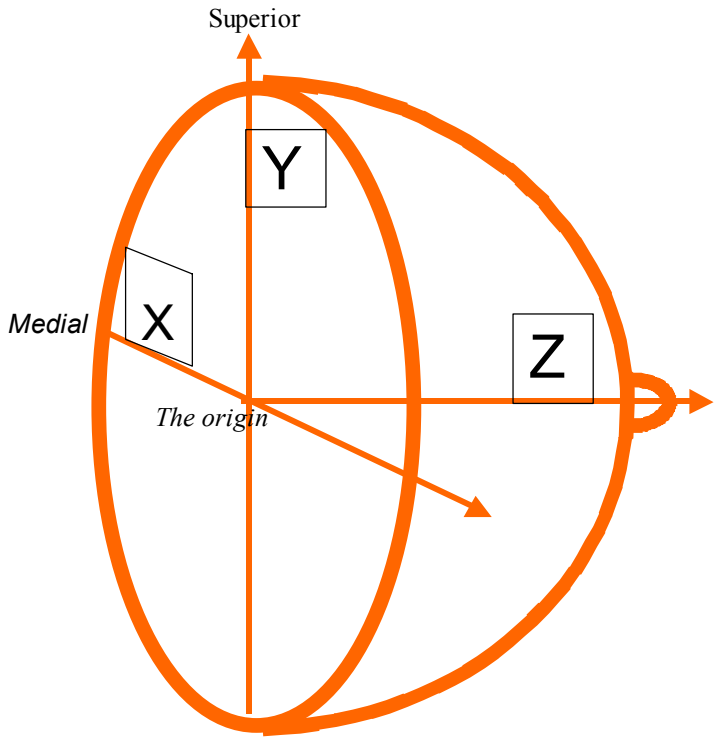
Grossing
The breast specimen was grossed into 5 mm saggital slices



5mm slices of a mastectomy specimen

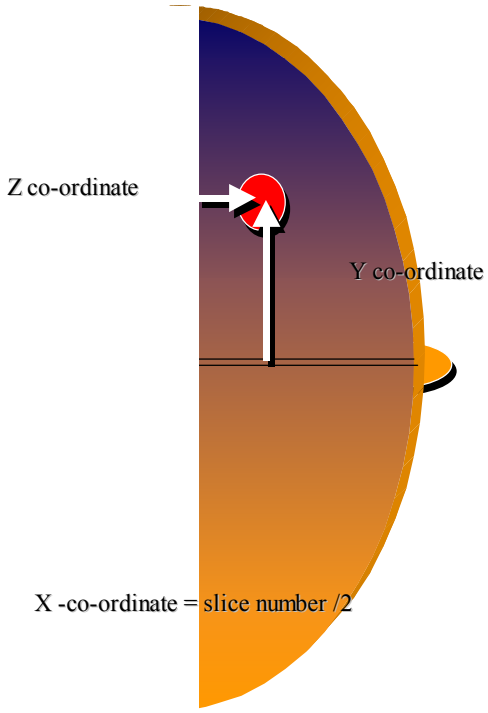
Breast slices and mammogram of slices
(not the same patient)

Gross examination of the slices was then carried out. In every slice, areas that looked or felt suspicious to palpation, and those marked on radiographs, were excised. These suspicious areas were fixed in formalin, embedded in paraffin and studied microscopically. The following lesions were considered as significant: a focus showing ductal hyperplasia with atypia (ADH), ductal carcinoma in situ (DCIS), infiltrating duct carcinoma (IDC), atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS) and infiltrating lobular carcinoma (ILC). The analysis for spatial distribution as described below was repeated after exclusion of ADH, ALH and LCIS.



Orientation in Space
Breast was considered to be a hemisphere and the point on the base of the breast immediately deep to the nipple was considered the origin. X-axis was in the medial to lateral direction, y-axis from inferior to superior direction and z-axis from the base to nipple.

For orientation in space, the point on the base of the breast directly below the nipple was considered the origin of the frame of reference. The horizontal line from medial to lateral side across the nipple projection was called x-axis; the vertical line from inferior to superior edge across the nipple-projection was called y-axis; and the line from the origin to nipple was called z-axis. All measurements were made in centimetres. The slice through nipple was numbered 0; the medial slices were numbered -1, -2, -3... and the lateral slices +1, +2, +3... .



Orientation in space
Determination of co-ordinates on each slice

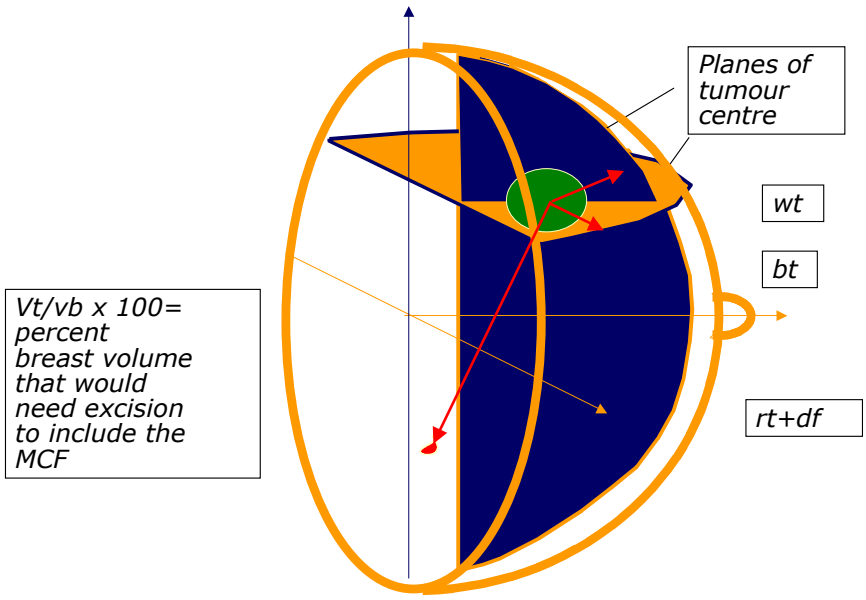
The x-, y- and z co-ordinates of centre of each suspicious MCF were then measured. Since each slice was 0.5 cm thick, the slice number divided by 2 was equal to the x co-ordinate in cm. The y and z co-ordinates were measured on each slice. The radius of the tumour and all the 3 co-ordinates of the tumour centre were also measured. These co-ordinates indicated the position within the breast of MCF and the primary tumour. We then calculated The following calculations were made:

1) distances of MCF from the tumour edge, 2) the relative distribution of primary tumour and MCF in the 4 quadrants of the breast, and, 3) percent breast volume that would be required to be excised to include all MCF. The Microsoft Excel Ver. 5.0 computer programme was used for the above calculations. We wish to point out that the last two methods of analysis are novel and not attempted by previous investigators.

1) Distance of each MCF from edge of tumour was calculated using the formula:

$$df = \sqrt{(xf-xt)^2 + (yf-yt)^2 + (zf-zt)^2} - rt$$

(df = Distance of each MCF from the edge of the tumour, xf, yf, zf = the co-ordinates of the MCF, xt, yt, zt = the co-ordinates of tumour centre and rt = the radius of the tumour)



Volume calculations: Once the co-ordinates of each MCF and each tumour was known, the proportional volume of breast tissue that would be required to be excised so that all MCF are included (Vt) was calculated. We expressed the latter as percent of total breast volume.

The following formulae were used for this calculation:

2) The relative distribution of the MCF and primary tumour in the four quadrants of the breast were calculated and plotted in two dimensions using the x and y co-ordinates.

3) For each case, the total breast volume (Vb) and the volume of breast tissue that would be required to

Total volume of breast	Vb = 2/3 x Π x h/2 x b/2 x w
Breast volume that would be required to be excised to include the farthest MCF	Vt = 4/3 x Π x (rt +df) x (ht) x (bt)
The percentage of breast volume that would be required to be excised to include all MCF	=Vt / Vb x 100

[h= Vertical height, b= Horizontal width and w= Depth of the breast at nipple, ht and bt = the height and breadth of the breast at the site of the tumour or (rt + df) whichever is smaller]

Statistical analysis was done using Chi-square test and standard tests for correlation and regression.

Most mastectomies, all the pathological specimen handling, its design and actual performance (except microscopy), data

collection and analysis was performed by the author.

Results

The patients' ages ranged from 28 to 72 years (mean 49 years). 20 patients were post-menopausal and 10 were pre-menopausal. The mean breast dimensions were: height: 15cm (range 9.5 - 18.5cm), breadth: 13cm (range 10 - 17cm) and depth: 4.5cm (range 3 - 5.5cm). Mean tumour size was 2.98cm (range 1.5 - 5cm). Mean breast volume was 458cc (range 164 - 747cc). We calculated that if the tumours were excised with a 0.5 cm margin, the excised tissue would constitute on an average 9% of the total breast volume. This suggested that, on average, the patients included in the study would have been suitable for conservative surgery, although that was not the entry criteria for the study and in fact, 3 patients' tumours were 4cm diameter and one was 5cm diameter; these would not have been suitable for breast conserving surgery.

A total of 667 blocks were prepared from the 30 breast specimens. Nineteen breasts were found to harbour MCF. A total of 54 multicentric foci (MCF) were detected. There were 21 foci of hyperplasia without atypia, which were not included for analysis. Of the 54 MCF, 18 (33%) were detected by radiography, and 28 (52%) were detected by gross inspection and palpation and 8 (15%) by both.

Of the 30 primary tumours, 27 were infiltrating duct carcinomas (IDC) and 3 were infiltrating lobular carcinomas (ILC). Of the 54 MCF, 4 were ADH, 16 were DCIS, 17 were IDC, 11 were LCIS and 6 were ILC. There were no foci showing ALH. Of 36 MCF with IDC as primary, 35 were ductal in origin and 1 was ILC. Of 18 MCF with ILC as primary, 16 were lobular in origin and 2 were ADH. The most malignant histological type of MCF in each breast is given in the Table 1. The histological type of MCF (whether infiltrating or in-situ) was not related to its distance from the edge of primary tumour nor to the percent volume of breast tissue that would be required to be excised to include the MCF.

Table 1: The Most adverse histological type of MCF in Infiltrating duct and in infiltrating lobular carcinomas

Primary tumour	The most adverse histological type of MCF				
	IDC	ILC	DCIS	LCIS	Nil
IDC (27)	9	1	6	-	11
ILC (3)	-	2	-	1	-

IDC= Infiltrating Duct Carcinoma, ILC= Infiltrating Lobular Carcinoma, DCIS= Ductal carcinoma in situ, LCIS= Lobular carcinoma in situ, MCF=Multicentric focus

We investigated whether MCF were generated by lymphatic embolization from the primary tumour. Lymphatic emboli were present within the primary tumour in 3 of the 27 primary IDCs. However, only 1 out of these 3 breast specimens harboured an MCF, and this too was a focus of DCIS. On the other hand, none of the 9 specimens that had IDC as MCF had lymphatic emboli in the primary tumour, suggesting that MCF were not emboli from the primary tumour but rather were independent malignant foci. In addition, in our analysis of spatial distribution in three dimensions as given below, we did not find any evidence of communications between the primary tumour and MCF.

Distance calculation: We found that 53% of patients had all MCF within 2cm; 67% within 3cm, 80% of within 4cm and 90% within 5cm. Thus, MCF would be left behind in 47% of the patients if the primary tumour were to be excised with a 2cm margin; in 33% with a 3cm margin and in 20% with a 4cm margin and 10% with a 5cm margin. These findings are similar to those observed by Holland et al, 1985 (Table 2).

Table 2: Percent patients in whom MCF would be left behind with increasing excision margin of primary tumour

Excision margin of primary tumour	% patients in whom MCF would be left behind	
	Holland et al, 1985	Present series
2 cm	42%	47%
3 cm	17%	33%
4 cm	10%	20%
5cm	-	10%

Relative Distribution of MCF and Primary tumour: On calculating the relative distribution of MCF and primary tumour within the 4 quadrants of the breast, we found that while the primary tumour was most common in the upper outer quadrant, MCF were widely distributed in all the 4 quadrants of the breast.

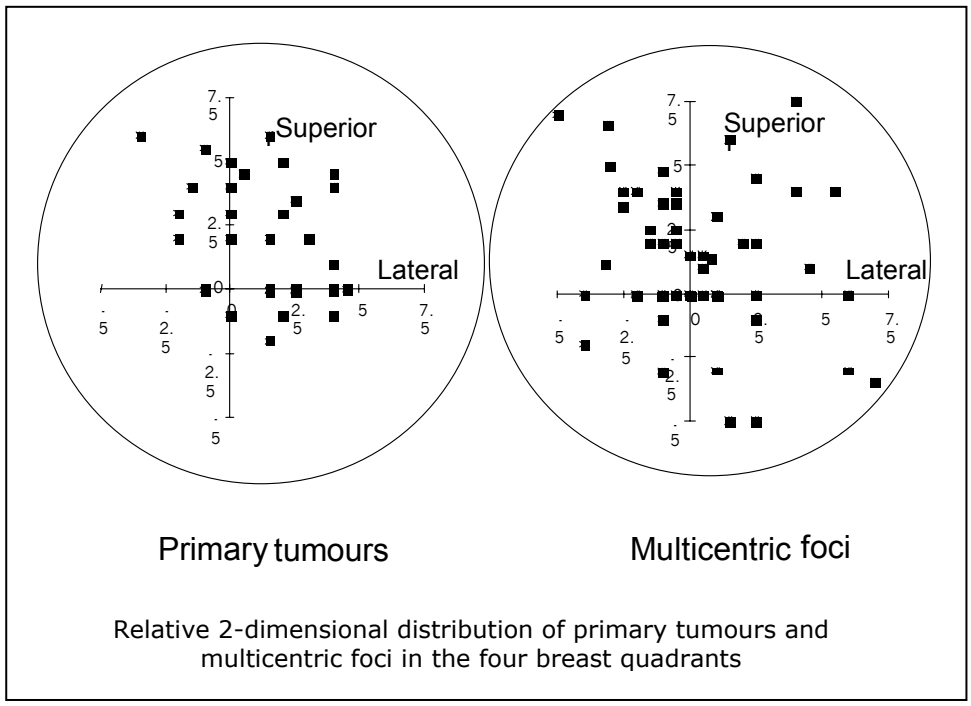
When considered in terms of conventional quadrants, out of the 19 cases that harboured MCF, 14 had MCF outside the index quadrant (a 90° sector of breast which had the primary tumour in its centre).

The distribution of the primary tumour and MCF in the 4 quadrants was statistically significantly different (Chi sq. =8.65, p =0.034) (Table 3).

Table 3: Relative Distribution of primary tumour and MCF in breast quadrants

Quadrant	Primary tumour	MCF
Upper outer	14	13
Upper inner	5	16
Lower outer	10	14
Lower inner	1	11

The distribution of primary tumour and MCF in the 4 breast quadrants of the breast was significantly different. Chi-square = 8.65 p=0.034.



Relative 2-dimensional distribution of primary tumours and multicentric foci in the four breast quadrants

Volume calculation: We calculated the proportion of patients in whom MCF would be left behind with increasing volume of breast tissue excised with the tumour (expressed as percent of total breast volume). When all patients were considered, 18/30 (60%) had MCF beyond 10% of the breast volume, 15/30 (50%) had MCF beyond 25% of the breast volume (a quadrant), and 7/30 (23%) had MCF beyond 50% of total breast volume (Table 4).

Table 4: Percent patients in whom MCF would be left behind with increasing volume of breast tissue excised.

% of total breast volume excised	% patients in whom MCF would be left behind
10% (~lumpectomy)	60%
25% (~quadrantectomy)	50%
50%	23%

However, when only those breasts which actually harboured MCF were considered, then 95% of breasts (18/19) had MCF beyond 10%, 79% of breasts (15/19) had MCF beyond 25% (a quadrant), and 37% of breasts (8/19) had MCF beyond 50% of breast volume including the tumour. Of the 15 cases that had MCF beyond the index quadrant, 7 were infiltrating, (5 IDC + 2 ILC), 7 were in-situ (6 DCIS + 1 LCIS) and 1 was ADH. The discrepancy (14 vs. 15) between the results of analysis in 2- and 3-dimensions is related to the fact that in one case the MCF was within the anatomical quadrant as conventionally defined in two dimensions, but was beyond 25% breast volume which included the primary tumour.

We then calculated the distribution of the 54 MCF found in the study within increasing volumes of breast tissue around the tumour. Tables 5 and 6 show these distributions for primary IDC and primary ILC tumours, respectively. They show that the number of MCF contained within 10%, 11-25%, 26-50% and >50% of the breast volumes around the tumour were similar, indicating that MCF are scattered throughout the breast. The histological type of MCF (non-infiltrating or infiltrating) also had similar distributions within increasing volumes of breast tissue around the tumour. After exclusion of ADH and LCIS, these results remained unchanged. Atypical Lobular Hyperplasia (ALH) was not detected in any of the sections.

Table 5: Number of MCF contained within increasing volumes of breast tissue around the tumour, in 27 cases with primary IDC

% breast volume around the tumour	MCF contained within that breast volume				
	Total No.	Histological type of MCF			
		ADH	DCIS	IDC	ILC
≤10%	8	-	5	3	-
11-25%	10	-	4	5	1
26-50%	13	1	5	7	-
>50%	5	1	2	2	-

Table 6: Number of MCF contained within increasing volumes of breast tissue around the tumour, in 3 cases with primary ILC.

% breast volume around the tumour	MCF contained within that breast volume			
	Total No.	Histological type of MCF		
		ADH	LCIS	ILC
≤10%	6	-	5	1
11-25%	2	-	1	1
26-50%	6	1	5	-
>50%	4	1	-	3

ADH= Ductal Hyperplasia with Atypia, DCIS= Ductal carcinoma *in situ*, ILCS= Lobular carcinoma *in situ*, IDC= Infiltrating Duct Carcinoma, ILC= Infiltrating Lobular Carcinoma, MCF=Multicentric focus

In breast specimens that had IDC as primary tumour, presence of multicentricity was related to tumour size. Four out of 12 breast specimens with tumours < 3cm harboured MCF, while 12 out of 15 breast specimens with tumours ≥ 3cm harboured MCF (p=.02). However, the actual number of MCF present in each breast or their distance from the edge of the primary tumour were not related to the tumour size. The volume of breast, expressed as percent of the total breast volume, which would be required to be excised to remove all MCF, also did not correlate with the size of primary tumour. MCF were present beyond 25% of breast volume including the tumour in 7/15 breasts with primary tumour <3cm and in 8/15 breasts with primary tumour ≥ 3cm. There was no relationship between nodal status, age or menopausal status of the patient and MCF (their presence, actual number, distance from tumour edge, or, the percent volume of breast tissue that would be required to be excised to include it with the excision of primary).

Discussion

We found that 63% of our patients harboured multicentric foci in addition to the primary tumour. This incidence is similar to that found by other workers using the Egan's technique (Lagios [Lagios, 1977], n=211: 56%, Egan [Egan, 1982], n=118: 69% and Holland [Holland et al., 1985], n=282: 63%). Although in our study, breast specimens with primary tumours ≥3cm were more likely to harbour MCF than those with smaller tumours (p=0.02), there was no relationship between the tumour size and either the number of MCF or their distances from the tumour edge. When calculated according to breast volumes, there was no correlation between tumour size and the volume of breast tissue that would need to be surgically excised to include all MCF (expressed as % of total breast volume). There was no relationship between the histological type of MCF (whether infiltrating or in-situ) and the distance of MCF from the tumour edge or percent volume of breast tissue that would be required to be excised to include the MCF with the primary tumour (tables 5 and 6). Age or menopausal status of the patient were not related to the presence, number or distance of MCF from the tumour edge.

It is noteworthy that although radiography detected 33% of the MCF, they were missed in 52% of cases. Our findings regarding the distribution of MCF around the primary tumour, expressed as distances from the tumour edge, are similar to that of Holland et al, [Holland et al., 1985](Table 2). We found that 53% of patients had MCF within 2cm, 80% of within 4cm and 90% within 5cm of the tumour edge. The difference between our study and that of Holland et al (1985), however, lies in the fact that the latter group did not take the size of the breast into account, and expressed the distribution of MCF in only one dimension. Expressed in this way, in one dimension, an impression is created that MCF are mostly present around the primary tumour. Our approach to the analysis in 2- and 3-dimensions makes the following novel observations. 1) The relative distribution of primary tumour and MCF in the 4 breast quadrants was significantly different (p=0.034). We found that the primary tumour was more common in the upper outer quadrant while MCF were widely distributed in all 4 quadrants,

suggesting that MCF are widely scattered throughout the breast. 2) When the 19 breasts that actually harboured MCF were considered, in as many as 79% (15/19) MCF were present beyond 25% of breast volume including the tumour (index quadrant). When all patients were considered, half (15/30) harboured MCF beyond the index quadrant. Thus, even if a quadrant were excised, 50% of patients would still have MCF left behind.

The above findings are at variance with the suggestion made by Holland et al that MCF are present in the index quadrant in close proximity of the primary tumour in 90% of cases and therefore could be responsible for local recurrence. Is our sample size of too small and our findings a result of play of chance? Let the hypothesis be, as has been suggested by Holland et al (1985) that in 90% of cases MCF are contained within the index quadrant. If this hypothesis were true, then 25% of breast volume including the tumour would contain all MCF in 90% of breast specimens. Thus, we should have found all MCF within 25% of breast volume in 27 of the 30 (90%) breast specimens. In actual fact, we found that all MCF were contained in the index quadrant in only 15 of 30 (50%) breast specimens. The probability of our finding being due to play of chance is 1 in 1500 (27:3 vs. 15:15, chi sq. =11.4, p=0.0007).

Our finding that MCF lie beyond the index quadrant in 50% of breast specimens may have implications for breast conservation therapy (BCT). In large series of breast conservation studies, it has been seen that >90% of early breast recurrences occur in the quadrant that harboured the primary tumour ([Harris et al., 1981], [Clark et al., 1982], [Schnitt et al., 1984], [Clarke et al., 1985], [Kurtz et al., 1989b], [Boyages et al., 1990], [Fowble et al., 1990], [Fisher et al., 1992], [Clark et al., 1992], [Veronesi et al., 1993]). This is true whether or not radiotherapy is given ([Clark et al., 1992]). If recurrences were to arise from MCF, then we would expect 50% of recurrences to occur in other quadrants. Since this is not the case, we conclude that early recurrences do not arise from MCF. Therefore, MCF in the index breast should behave in a fashion similar to putative MCF present in the opposite breast. This is borne out by the fact that recurrence rate in the remaining quadrants of the index breast is identical to that in the opposite breast (1% per year in both cases,[Kurtz et al., 1989a]). We believe that recurrences in the index quadrant arise from a) the original primary tumour cells left behind, b) a new disease arising as a result of chromosomal instability, or c) from circulating metastatic cancer cells lodging in the highly vascular bed of the excised tumour. The latter is supported by the fact that patients who have local relapse in the breast after BCT have a relatively poor prognosis ([Fisher et al., 1991b], [van Dongen et al., 1992]).

In any case, if multicentric foci (MCF) do not give rise to breast recurrence then why should we treat them with either mastectomy or whole breast radiotherapy? It is as necessary or as unnecessary as treating the contralateral breast! It appears that local treatment of breast cancer could probably suffice to be truly local- at and around the site of the primary tumour!

Summary

We studied the spatial relationship within the breast between multicentric foci (MCF) and the primary tumour in 30 modified radical mastectomy specimens using Egan's correlated pathological-radiological method using 5mm slices of the whole breast. The relative positions within the breast of the primary tumour and MCF were used to calculate the relative distribution of primary tumour and MCF in the 4 quadrants of the breast and the percent breast volume that would be required to be excised to include all MCF. Nineteen (63%) breasts harboured MCF. The relative distribution of primary tumour and MCF in the 4 breast quadrants was significantly different (p=0.034). MCF were present beyond the index quadrant (25% of breast volume including the tumour) in as many as 79% (15/19) of breasts that harboured MCF; and, in half the cases (15/30) when all breasts were considered. This is in variance with the suggestion put forward previously that MCF are contained within the index quadrant in 90% of cases. Although the number of patients in the present series is small, the probability of our finding being due to play of chance is 1 in 1500. In large series of breast conservation studies >90% of early breast recurrences have been found to occur in the index quadrant. Our finding, that in half the patients (15/30) MCF are present in quadrants other than the index quadrant, suggests that MCF do not give rise to early breast recurrence.