a second response with the addition of 4OHA to LHRH agonist therapy [11]. We have also shown that 4OHA is effective in primary breast cancer and acceptable as adjuvant therapy over 18 months given as 250 mg intramuscularly every 2 weeks [12].

Future studies need to determine whether 40HA, when used following tamoxifen therapy, is of value in extending survival in patients with primary breast cancer.

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Variations in Breast Cancer Management Between a Teaching and a Non-teaching District

Ian Basnett, Mike Gill and Jeffrey S. Tobias

We compared the management and outcome of 999 women with breast cancer presenting between 1982 and 1986 at two centres in a region, one in a teaching district. A comparison was also made with relevant research and The Kings Fund Consensus Statement. The centres frequently differed markedly in the investigations done, diagnostic procedures, histology reporting, axillary sampling, and in the treatment given, also differing from the Consensus with no trend towards it. Survival was better at the teaching centre, both disease-free (N.S.) and overall [odds ratio 1.46 (1.16–1.84) $P = 0.0009$ unadjusted]. This should be interpreted cautiously as the median follow-up time was relatively short and the study was non-randomised. We conclude that how women with breast cancer are managed is determined as much by where they are referred as by scientific evidence. This indicates the need to introduce standards and protocols into business plans, making audit and service specifications easier.
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INTRODUCTION

MANY PREVIOUS studies have documented variations in both management and outcome in a variety of cancers [1–5]. Such differences clearly raise questions about both the cost and effectiveness of the treatment. In breast cancer doubts persist about the best forms of management. However, there are some areas where established standards do exist and departures from them are of interest.

We compared the management and outcome of women with breast cancer at two centres where radiotherapy and chemotherapy were available, one in an urban teaching district (T) comprising two hospitals, the other a rural non-teaching district, some 60 miles away (NT). The null hypothesis was that there would be no difference between them. We used accepted research and consensus statements as benchmarks for comparison. The King's Fund consensus conference [6] is the most

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relevant to practice in this country, and although it reported at the end of the period covered by this study, its statement was based on earlier research. A recent study [7] had demonstrated considerable departures from the consensus, so it was not our expectation that either centre would completely conform, particularly in the earlier years, but we were especially interested in how the districts moved towards it, if at all.

The comparison of services against established standards of treatment is fundamental to audit. Our study aimed to indicate some areas where such audit might be routinely performed.

PATIENTS AND METHODS

Women with primary breast cancer whose initial management was at one of the above two centres between 1982 and 1986 inclusive, were retrospectively identified using hospital activity analysis data, the Thames Cancer Registry and, where available, hospital pathology and diagnostic registers. A reorganisation of medical records led to data for 1983 and 1984 being incomplete in district T and hence subject to systematic bias [8]. They were therefore excluded, as were private patients and women with lymphomas and sarcomas.

The data were obtained from the hospital records using a standard proforma, entered onto computer, checked and analysed using SPSS-PC+ and BMDP. As well as overall comparisons between the two centres the data were analysed by individual year, thus any trends in rates could be detected. Because of the absence of 1983/84 data for district T, trends could bias overall comparisons. This was checked for by comparing individual years and excluding 1983/84 data for both centres. The survival and disease-free interval analysis used a Cox proportional hazards model, fitting age, stage, year, operation done and district of treatment. It was assumed that the risk was log-linear. Other analyses were performed using the χ^2-test, Fisher's exact test and the t-test (using log-transformed data where the distribution was not normal).

Stage was assigned on the basis of all available data, whether pre- or postoperative, and by the tumour–node–metastasis system [9].

Table 1. *Year of diagnosis, age and stage at presentation by centre, % (n)*

Year of diagnosis	District NT (*n*)	District T (*n*)
1982	21 (119)	38 (167)
1983	20 (115)	—
1984	19 (109)	—
1985	19 (107)	33 (143)
1986	20 (113)	29 (126)
≤ 50 years	22 (125)	25 (110)
50–74 years	53 (300)	59 (258)
≥ 75 years	25 (138)	17 (68)
Stage		
1	28 (155)	18 (79)
2	46 (257)	47 (203)
3	4 (20)	13 (55)
4	14 (79)	19 (82)
Unknown	9 (52)	4 (17)
Total	100 (563)	101 (436)

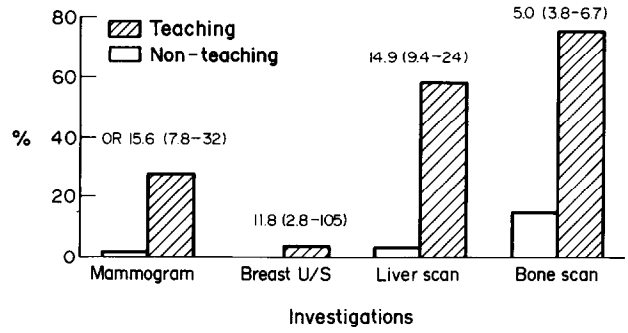

Fig. 1. Proportion of women having investigations by centre. OR = Odds ratio of teaching/non-teaching (95% confidence interval).

RESULTS

During the study period 563 patients were identified in the district NT and 436 in district T. The age and stage distribution of the two groups is described in Table 1. It was stable over the 5 years.

Women were increasingly more likely to have an isotopic bone scan, liver scan, breast ultrasound or mammography in district T (Fig. 1), though the diagnostic yield was lower: for example 1 in 10 bone scans were positive, compared with 1 in 4 in district NT.

In both centres the technique used most frequently to obtain a tissue diagnosis was excision biopsy, although the rate decreased in district NT (79–43%:$P < 0.0001$). Cytology rates (using fine-needle aspiration technique) increased in district T from 9 to 44% by 1986. Use of Trucut declined. In contrast district NT's Trucut biopsy rates rose from 11 to 50% ($P < 0.0001$).

Completeness of excision was mentioned in 79% (277) of histology reports in district T and only 11% (49) in district NT, (95% CI for difference:63–73%). Of these (for stages 1 and 2 only), 17% ($n = 38$) reported incomplete excision in district T and 33% ($n = 11$) in district NT (95% CI for difference: < 0–33%).

More surgeons were responsible for the care of women with breast cancer in district T (maximum 14 per year), compared with district NT (maximum 8 per year). The mean number of surgeons per 100 women per year was 7.57 in district T, 6.22 in NT.

Rates of axillary sampling or clearance are shown in Table 2. The differences persist when women with clinical evidence of axillary involvement are excluded.

Radiotherapy was used much less in district NT and there was no trend with time. By contrast in district T there was an increase in its use from 53% of women to 74% by 1986 ($P = 0.0051$). It was used much more frequently amongst women having lumpectomies or wide excisions in comparison with women undergoing mastectomies in both centres (district NT 69 vs. 35%:95% CI for difference:23–43%, district T 82 vs. 46%:95% CI for difference:27–46%, both $P < 0.0001$). The number of radiotherapy visits in the first year for those surviving at least a year was significantly higher in district T, (mean 23 vs. 15:95% CI for difference:6.2–8.9%, $P < 0.001$). This difference persisted for all stages.

More chemotherapy was used in district T, and in contrast to district NT, with an upward trend throughout the study period (3–13%, $P < 0.002$). The use of chemotherapy according to node status is described in Table 3.

Table 2. Women undergoing axillary surgery as a proportion of those undergoing any surgery by stage, % (n)

Stage	Those having axillary sampling/clearance: District NT (n)	District T (n)	Difference (95% CI)
1	66 (89)*	37 (29)*	29 (15 to 41)
2	75 (173)†	49 (95)†	26 (16 to 34)
3	87 (13)	75 (33)	12 (−10 to 31)
4	58 (15)	58 (18)	0 (−26 to 25)
1,2,3 < 50 years age	72 (74)*	42 (40)*	30 (17 to 43)
1,2,3 = or ≥ 50 years age	71 (201)‡	53 (117)‡	18 (11 to 28)
Total	71 (301)§	51 (178)§	20 (14 to 27)

* $P < 0.03$; † $P < 0.01$; ‡ $P < 0.05$; and § $P < 0.0001$.

Endocrine therapy rates increased amongst those aged over 50 years in both centres (district NT 40–79%, district T 38–88%: both $P < 0.0001$).

11% of women in district NT and 13% in district T were entered into trials. The proportion increased with time in district T, (19% by 1986). More who were treated with chemotherapy in district NT were entered into a formal multicentre trial [86 ($n = 25$) vs. 53% ($n = 19$):95% CI for difference:13–54%, $P < 0.01$). In district T the proportion fell significantly from 80% in 1982 to 25% in 1986 ($P < 0.02$).

Recurrences were more frequently at a distant metastatic site in women in district T (75 vs. 55% of recurrences:95% CI for difference:9–31%) but more frequently in the contralateral breast in those in district NT (10 vs. 4%:95% CI for difference:0.8–12%). Local recurrence rates varied little between the two districts (36%, NT vs. 35%, T). The disease-free interval was longer at district T than district NT, but only significantly so when adjustment is made for operation and stage (Table 4) or stage alone.

Table 3. The proportion of women with non-metastatic disease undergoing chemotherapy by node status and age group (n). In each cell the percentages refer to the proportion of women in that category who underwent chemotherapy, % (n)

Node status	District	Age group: ≤ 49 years	50–74 years
Node-positive	NT	3 (3)	6 (6)
	T	6 (1)	5 (3)
Node-negative	NT	9 (4)	10 (11)
	T	0 (0)	0 (0)
No axillary surgery	NT	3 (1)	0 (0)
	T	27 (15)	5 (5)

There was 1 case in the 50–74 year age group in district NT where chemotherapy was administered but it was not known whether axillary surgery had been performed.
No women aged over 74 with non-metastatic disease had chemotherapy.

Table 4. Relative odds of relapse and death at district NT

	Odds of relapse	Odds of death
Unadjusted	1.25 (0.99–1.59) $P = 0.064$	1.46 (1.16–1.84) $P = 0.0009$
Adjusting for age	—	1.40 (1.10–1.76) $P = 0.0052$
Adjusting for age and stage	—	1.74 (1.34–2.27) $P = < 0.00001$
Adjusting for operation	1.20 (0.90–1.56) $P = 0.22$	—
Adjusting for operation and stage	1.45 (1.09–1.90) $P = 0.0092$	—

(95% CI in brackets.)
For the odds of relapse age made very little difference (and is not included in the table), while stage was the most important variable. The effect of operation was significant, favouring lumpectomies.
For the odds of death operation had no effect and is therefore not included in the table.

For women who relapsed, the approaches were similar except for the use of chemotherapy, which was more frequently employed in district T (23 vs. 12%:95% CI for difference:0.6–19%).

In both centres survival slightly improved with time, although not significantly so, and introducing year of diagnosis into the Cox model did not substantially alter the results. The operation done had no effect on survival.

DISCUSSION

This study has demonstrated some remarkable differences in management and outcome between the two centres, and also from agreed standards. Clearly these have implications for the cost and effectiveness of the services.

The absence of data in 1983 and 1984 in district T is a potential source of bias. Where there was a trend with time in one or both centres, which would affect overall comparisons between centres, this has been discussed.

Women attending the teaching centre were younger overall and there were less in stage 1 (Table 1). However, the relatively small numbers of women allocated to stage 3 in district NT suggest that staging was incomplete amongst women with local spread. These differences do not account for the very large differences in approach to investigation and treatment, as Fig. 1 and Tables 2, 3, 5 and 6 indicate.

The very much higher proportions of women undergoing liver scans, bone scans and mammograms in district T have profound cost implications. Their use may reflect their availability and local interest, but of bone scans, for example, the King's Fund Consensus Statement [6] says ".... isotope scanning is not usually necessary". The value of their routine use is doubted [10, 11]:it has been suggested they have a role in tumours larger than 2 cm or more advanced stages [12–16]. In district T the proportion of women having a bone scan was the same irrespective of the tumour size or stage.

Approaches to tissue diagnosis differed. The Consensus view was that only for a minority of women will an open surgical biopsy be required [6]. The increasing use of cytology in district T or Trucut in district NT began to have this effect, although more so in district NT.

The very high proportion of cases, particularly in district NT (89%) where no mention was made in the histology report about

Table 5. Treatment by age, % (n)

	District	Age Group < 50 years	⩾ 50–74 years	⩾ 75 years	Total
Surgery	NT	91 (114)	87 (260)	51 (70)	79 (444)
	T	95 (104)	82 (212)	54 (36)	81 (352)
RT	NT	61 (76)	45 (135)*	18 (24)	42 (236)
	T	73 (81)	69 (176)*	25 (18)	63 (274)
CT	NT	7 (9)*	6 (18)	1 (2)	5 (29)
	T	17 (18)*	7 (18)	0 (0)	8 (36)
ET	NT	38 (48)	46 (138)*	71 (98)	51 (284)
	NT	36 (40)	58 (148)	82 (55)	56 (243)
Total	NT	22 (125)	53 (300)	25 (138)	100 (563)
	T	25 (110)	59 (258)	17 (68)	436 (563)

* $P < 0.001$.

the completeness of the excision, seems a far from ideal policy. In the absence of data about completeness for many cases, it is difficult to draw firm conclusions about the proportion that are reported to be incompletely excised. However, the relatively high proportions found, with no other explanation, are noteworthy.

The finding that so many surgeons were involved, particularly in district T, suggests that a better service could be offered by streamlining the organisation and investing overall responsibility for clinical management in one individual, as recommended by the Consensus [6].

Axillary sampling has received a great deal of attention of late [17–20] and the Consensus supported its use [6]. Its value derives from persisting doubt as to the net benefit of adjuvant therapy in node-negative women [21]. The teaching centre operated very much less on the axilla than the non-teaching centre, contrary to the expectations of previous authors [17]. It has been suggested that axillary surgery is only required in approximately 20% of women [22]; this is on the basis that chemotherapy is only useful in premenopausal women and amongst the youngest of them there is evidence that disease-free interval is prolonged even in the node-negative group [23–25]. In line with this policy in district T, amongst those under 50, chemotherapy was used almost exclusively in women who had not had axillary surgery (Table 3). However, axillary surgery was performed nearly as frequently as in older women (Table 2), even if women with clinical evidence of node involvement are excluded.

Table 6. Treatment by stage, % (n)

	District	Stage 1	2	3	4	?
Surgery	NT	92 (142)	93 (239)	80 (16)	33 (26)	40 (21)
	T	99 (78)	95 (193)	80 (44)	38 (31)	35 (6)
RT	NT	34 (53)†	51 (131)‡	50 (10)	37 (29)‡	25 (13)
	T	62 (49)†	68 (138)‡	60 (33)	59 (48)‡	24 (4)
CT	NT	7 (10)	6 (16)	0 (0)	4 (3)*	0 (0)
	T	9 (7)	6 (13)	7 (4)	15 (12)*	0 (0)
ET	NT	43 (66)	43 (111)	60 (12)	77 (61)	65 (34)
	T	49 (39)	48 (90)	66 (36)	76 (62)	47 (8)
Total	NT	28 (155)	46 (257)	4 (20)	14 (79)	9 (52)
	T	18 (79)	47 (203)	13 (55)	19 (82)	4 (17)

* $P < 0.05$; † $P < 0.02$; and ‡ $P < 0.01$.

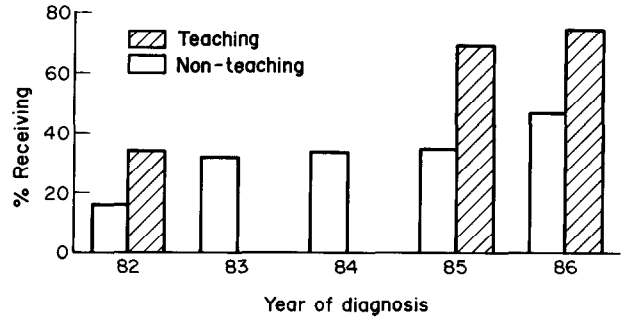

Fig. 2. Lumpectomies as a proportion of operations by centre. χ^2 for T, $P < 0.001$; NT, $P < 0.02$.

The evidence that mastectomy has no advantage in relapse-free survival and overall survival, when compared with more local excision followed by radiotherapy [6, 26, 27] has been incorporated into clinical practice more slowly in district NT (Fig. 2).

The higher proportions of women receiving radiotherapy (after lumpectomies and mastectomies) as well as longer courses, suggest that a different policy is being applied in district T. The Royal College of Radiologists' study[4] documented wide variations between regions and clinicians in the number of treatment fractions used for a variety of specific clinical situations (including breast cancer), although the total dose given was often similar. This study has documented differences within a region which raise questions of efficacy and cost both for the NHS and the women concerned.

Distict T's greater use of tamoxifen in those over 50 is more in line with the research evidence [6], though in both centres more than a third of women aged less than 50 also received tamoxifen, despite less ample support from trials at the time these women were treated [21].

Chemotherapy increases relapse-free survival in women under 50, though it remains to be demonstrated that it increases overall survival in the absence of positive nodes [6, 21]. In line with this, in district T chemotherapy was used twice as frequently in those less than 50 years, and at a higher rate by 1986 than 1982, but the nodal status was usually unknown. In contrast the approach in district NT was influenced much less by age and its use diminished with time, though women with positive axillary nodes were marginally more likely to have treatment.

The low proportion of women entered into clinical trials was disappointing, particularly as it fell with time amongst those receiving chemotherapy in district T. There was no in-house trial to explain this. As the Consensus [6] concludes, "Advances in knowledge are likely to continue to come from properly controlled trials of different treatments."

Both the longer length of stay in district T in 1982 and that in district NT in 1985 and 1986 (Fig. 3), will have had profound

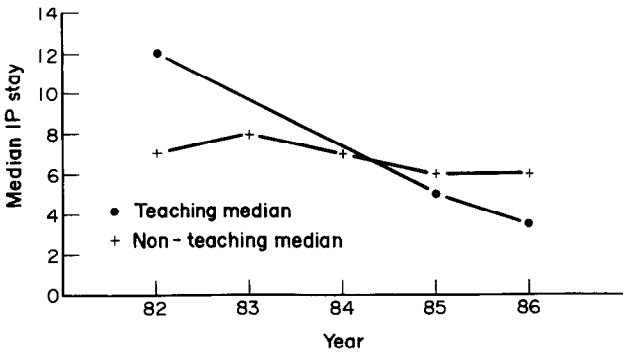

Fig. 3. Median in-patient (IP) days by year by centre.

implications for the cost and quality of the service. The significantly better survival and a trend towards a better disease-free interval seen in district T (Table 4), should be treated with caution. The study has the limitations of being retrospective and non-randomised. Staging was not done in a standard fashion in both centres, and the median follow-up time was relatively short (3.2 years in district NT and 2.6 in district T). No measurement was possible of social class or other possible confounders. Disease-free interval is not a well-defined outcome and recurrence was not searched for in a standard fashion. In our view this study does not allow a firm conclusion that survival and possible disease-free interval advantage was the result of a particular feature of management, or that it will be sustained. However, in the context of such huge differences in management, this difference may lend weight to the argument that cancer registries should be used as a tool for audit [5].

The study has demonstrated some marked, although historical, differences from accepted practice in both centres. We have highlighted a number of areas where practice might routinely be compared against accepted standards and thereby audited. We would suggest these include: the number of surgeons managing women with breast cancer, preoperative investigations, including tissue diagnosis techniques, the sort of surgery performed, i.e. mastectomies vs. lumpectomies and whether axillary sampling and clearance are performed, and the policies for the administration of chemotherapy, endocrine therapy and radiotherapy, and the median in-patient stay.

This study's focus reflects what can be gleaned from hospital notes. The above list of items for audit is not intended to be exhaustive. The time elapsed between presentation to GP and diagnosis, access to a breast counsellor, and palliative care arrangements are but three of many issues we have not yet studied.

Clinical decisions will involve a wide range of considerations including patient preferences. However, management would undoubtedly be strengthened by the presence of protocols based on sound scientific evidence, and performance should be audited against those protocols. As well as being essential information for clinicians, purchasers, general practitioners and women will want to know what the treatment protocols are and that local performance is audited against them.

It is recognised that consensus conferences may lead to clinicians considering changes in their behaviour but that they are unlikely to effect rapid change in practice without other incentives [28]. It is to be hoped that the contracting mechanism will make it possible for purchasers to insist on the inclusion of treatment protocols in business plans in the future. This may act as the extra incentive required to effect changes in practice [29]. By specifying for the latest accepted standards in cancer treatment, and asking for treatment to be audited against them, standards should be improved. However, such are the competing clinical and financial priorities, this will take commitment from those providing medical advice to the contracting process.

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Serum Vanillylmandelic Acid/Homovanillic Acid Contributes to Prognosis Estimation in Patients with Localised but not with Metastatic Neuroblastoma

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In 211 patients with neuroblastoma, serum vanillylmandelic acid (VMA) and homovanillic acid (HVA) levels were determined and correlated to stage, histological differentiation, ferritin, neuron-specific enolase, lactate dehydrogenase (LDH) and outcome. Elevated serum VMA and/or HVA levels were found 16% less frequently than elevated urine levels. The incidence of the elevated serum levels increased with stage (stages I–III 58%, IV 78%, IVS 100%). Increased VMA/HVA ratios were not associated with a higher grade of tumour differentiation. Serum ferritin and neuron-specific enolase showed no correlation, and LDH a borderline non-random correlation with the serum catecholamine metabolites. Using age-related reference values a quotient of serum VMA/HVA ($P = 0.061$)< 0.7 indicated a poorer event-free survival (48 ± 10%) than ratios ≥ 0.7 (event-free survival 81 ± 6%) for children with localised neuroblastoma ($P = 0.0004$). No correlation with prognosis was detected for patients with stage IV and stage IVS disease. We conclude that serum VMA and HVA determinations may be useful as tumour markers for 71% of neuroblastoma patients, and aid in estimating the prognosis in children with localised disease.
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INTRODUCTION

THE DETERMINATION of the two major catecholamine metabolites vanillylmandelic acid (VMA) and homovanillic acid (HVA) in urine has been widely recognised as a valuable tool for diagnosis and response evaluation [1–5] as well as a tumour marker for possible early detection in a mass screening programme [6, 7]. The degree of biochemical tumour maturation indicated by the VMA/HVA ratio in urine has been thought to show prognostic information when comparing those data with histological differentiation patterns [8–11], DNA ploidy [12] and N-*myc* amplification [13, 14]. Recently serum determinations of VMA and HVA have become available [15, 16], considerably facilitating disease monitoring because of their independence of 24 h urine collection. Here we report the prognostic impact of initial serum VMA and HVA levels in 211 neuroblastoma patients and their relationship to other prognostic factors.

PATIENTS AND METHODS

Serum samples of 211 neuroblastoma patients were obtained for VMA and HVA determinations at diagnosis. 97 children had localised disease (stages I–III according to Evans), 93 patients metastatic neuroblastoma (stage IV) and 21 infants stage IVS. The 211 patients with known serum VMA and HVA values were compared with 357 patients of the same trial in whom those data were not available (total 568 patients). We found no differences with respect to stage, age at diagnosis, incidences of abnormal lactate dehydrogenase (LDH) and ferritin levels, surgical resectability, histological grade and survival parameters [event-free survival (EFS), survival (S)], indicating that the group investigated here was representative of the total group. The children were treated according to the German cooperative trials NB 82 and NB 85 [17]. No differences in EFS were

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